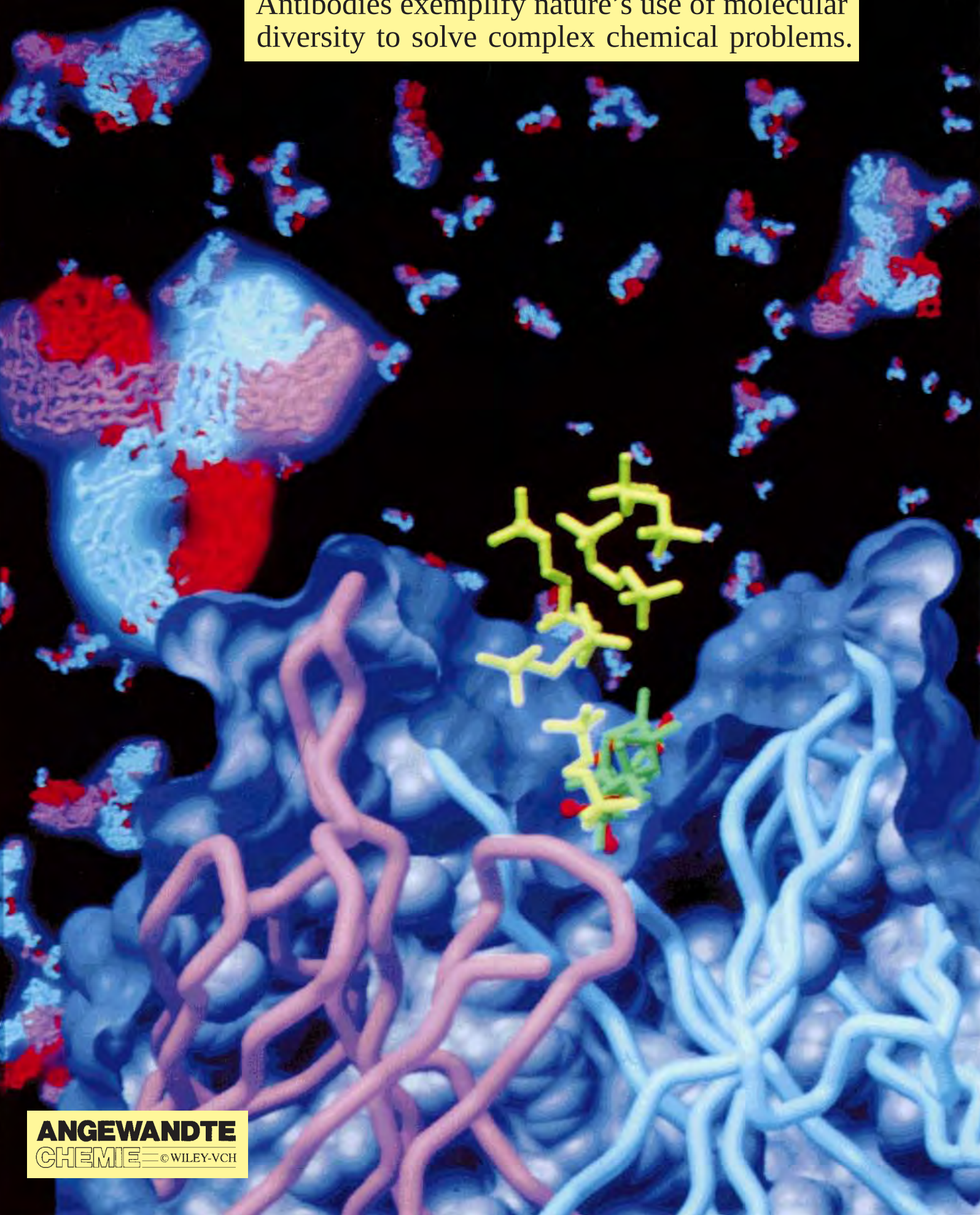


Antibodies exemplify nature's use of molecular diversity to solve complex chemical problems.



Generating New Molecular Function: A Lesson from Nature

David R. Liu and Peter G. Schultz*

As the focus in molecular synthesis shifts increasingly from structure to function, more efficient strategies must be developed to generate molecules with defined biological, chemical, or physical properties. Nature has produced molecules with a wide number of complex biological functions by synthesizing large, diverse collections or libraries of chemical structures and

screening or selecting for a desired function. This same approach is now being applied in conjunction with the tools and principles of chemistry, biology, and physics to generate synthetic molecules with novel or enhanced properties, ranging from biological catalysts and bioactive small molecules to luminescent metal oxides. Analysis of the structures and properties of these

molecules, together with the wealth of related information produced in these experiments, is leading to an increased understanding of the relationship between molecular structure and function.

Keywords: combinatorial chemistry • materials science • nucleic acids • proteins • synthetic methods

1. Introduction

Our ability to create new molecular structures with novel physical, chemical, or biological properties has had a major impact on many fields of science including the biomedical sciences, chemistry, and solid-state physics. Examples range from the synthesis of antibiotics and genes to photoresists and high-temperature superconductors. As the structural and functional complexity of target molecules increases, our ability to define the precise structural requirements that result in a desired set of properties becomes increasingly limited. This in turn leads to a large increase in the number of molecules that must be iteratively synthesized and tested to identify those structures with a desired function—a time- and resource-intensive process. Among the strategies being developed to meet the challenges created by the ever growing need for molecules with new or enhanced properties are a number of biologically inspired approaches. The latter derive from our recognition that nature has produced an impressive array of complex molecular structures and assemblies with functions ranging from gene regulation and signal transduction to photosynthesis and protein biosynthesis. As we begin to understand the structures and molecular mechanisms involved in these processes, we can combine these biological

insights, as well as the processes themselves, with the tools of the physical sciences to create new molecules with functions found neither in nature nor the laboratory.

One such example of this synergy between chemistry and biology is the development and application of combinatorial strategies. This approach, in which large, diverse collections, or “libraries”, of molecules are generated and subsequently screened or selected for novel functions, stems from the combinatorial processes in nature. For example, both the humoral and cellular arms of the immune system have developed highly sophisticated combinatorial genetic mechanisms for generating molecular diversity and selecting receptors that can recognize foreign antigens with high affinity and selectivity. The mechanisms of these processes are relatively well understood.^[1–3] The three-dimensional framework of the antibody molecule consists of two polypeptide chains (heavy (H) and light (L)) containing six loops on an eight-stranded β -sheet framework.^[4] This structure is assembled from four different gene segments, variable (V), diversity (D), joining (J), and constant (C), each of which can be chosen from a number of distinct genes. The combinatorial association of V, D, and J gene segments with additional junctional diversity occurring at the V_L-J_L , V_H-D , and $D-J_H$ joining regions leads to a structurally diverse population of germ-line antibodies (Figure 1). After a “lead” antibody structure is selected from this pool based on its ability to bind a foreign substance, its affinity is increased as the immune response proceeds by somatic mutation. This process, which alters bases throughout the DNA sequences encoding the variable region, results in additional diversity. Thus, in its most basic form, the combinatorial process involves the synthesis of large numbers of distinct structures around a central frame-

[*] P. G. Schultz, D. R. Liu
Howard Hughes Medical Institute
and
Department of Chemistry
University of California, Berkeley
Berkeley, CA 94720–1460 (USA)
Fax: (+1) 510-643-6890
E-mail: pgschultz@lbl.gov

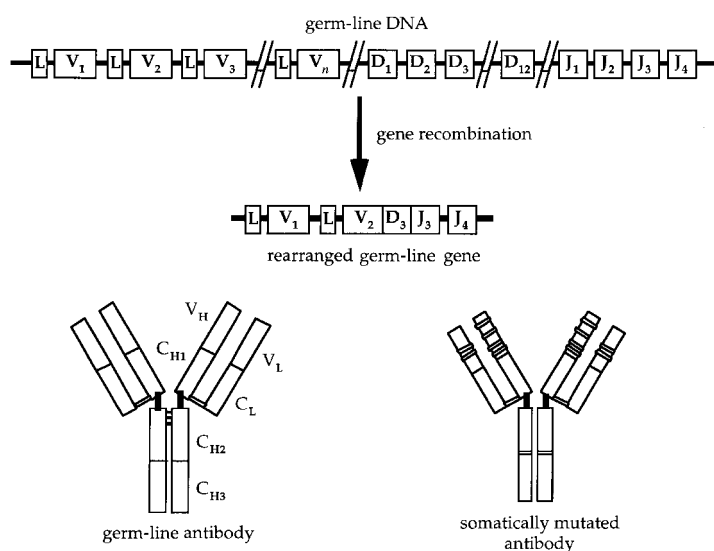


Figure 1. Combinatorial association of V, D, and J genes to form an antibody molecule.

work from sets of building blocks. The choice of framework structure and building blocks is best made based on empirical and theoretical models at hand. Those structures with a desired function then are identified and further optimized by repeated rounds of screening or selection and mutation.

This combinatorial approach is applicable to any molecular structure that can be assembled either in a stepwise or concerted fashion from a set of molecular precursors, and where a screen or selection for a desired function exists. This includes oligomeric molecules such as nucleic acids and

peptides, nonpolymeric molecules such as natural products, or even solid-state materials such as superconductors or polymers. To illustrate the utility and scope of this new synthetic strategy, as well as the challenges that remain, a number of examples, both from our laboratory and many others, will be described. These applications cover a broad spectrum, ranging from biological catalysis and drug discovery to materials science.

2. Protein and Polypeptide Protein Diversity

2.1. Immunological Diversity and Catalytic Antibodies

The notion that natural immunological diversity can be used to generate novel chemical function was first illustrated with the generation of catalytic antibodies.^[5–7] Immunological diversity is clonally selected on a time scale of weeks (in contrast to evolutionary diversity), and is thus “programmable” in the laboratory setting. However, binding affinity rather than catalytic activity serves as the basis for antibody selection, and therefore mechanistic principles such as selective binding and stabilization of the transition state must be used to generate catalytic antibodies. For example, to generate an antibody that catalyzes the insertion of a metal ion into porphyrin (the last chemical step in heme biosynthesis), antibodies were generated against *N*-methylprotoporphyrin (**1**). This molecule mimics the putative transition state, a conformationally distorted porphyrin ring, of the metalation reaction. An antibody specific for **1** catalyzes the insertion of metal ion into mesoporphyrin with rates similar to that of the

Peter G. Schultz did his undergraduate and graduate work at the California Institute of Technology. His thesis work resulted in the first synthetic molecules that sequence-selectively cleave DNA. In 1985, after postdoctoral studies at the Massachusetts Institute of Technology, he joined the faculty of the University of California at Berkeley, where he is currently Professor of Chemistry, a Principal Investigator at Lawrence Berkeley National Laboratory and an Investigator of the Howard Hughes Medical Institute. His research—which spans the interface of biology, chemistry, and materials science—includes a) the development of catalytic antibodies; b) the application of molecular diversity to problems in biomolecular recognition and catalysis, drug discovery, and materials science; c) the development of methods for incorporating unnatural amino acids selectively into proteins; and d) most recently single-molecule biological imaging. He was a founding scientist of Affymax Research Institute and is a cofounder of Symyx Technologies. His awards include the Waterman Award of the National Science Foundation, membership in the National Academy of Sciences, and the 1994 Wolf Prize in Chemistry. Recently, he became a Professor of Chemistry at the Scripps Research Institute, and has been named as the director of the new Novartis Institute for Functional Genomics in San Diego. This review is based on his opening lecture at the 36th IUPAC Congress in Geneva in the summer of 1997.



P. G. Schultz



D. R. Liu

David R. Liu was born in Riverside, California in 1973. He received his B. A. in chemistry from Harvard University in 1994, where he conducted research on steroid biosynthesis under the guidance of Professor E. J. Corey. Presently he is a graduate student in Professor Schultz's group at the University of California, Berkeley, and investigates in vitro and in vivo methods for the site-specific incorporation of unnatural amino acids into proteins.

natural biosynthetic enzyme, ferrochelatase.^[8] Resonance Raman studies revealed that both the enzyme and antibody facilitate the reaction by distorting the planar porphyrin substrate, which is consistent with the proposed reaction mechanism. This distortion involves doming of the porphyrin ring in the case of the enzyme, and for the antibody an up-down distortion mimicking that in *N*-methylmesoporphyrin^[9] (Figure 2). Crystallographic analysis of the antibody·*N*-methylprotoporphyrin complex has revealed the structural basis for this distortion, and shown that somatic mutations in response to **1** play an important mechanistic role.^[10]

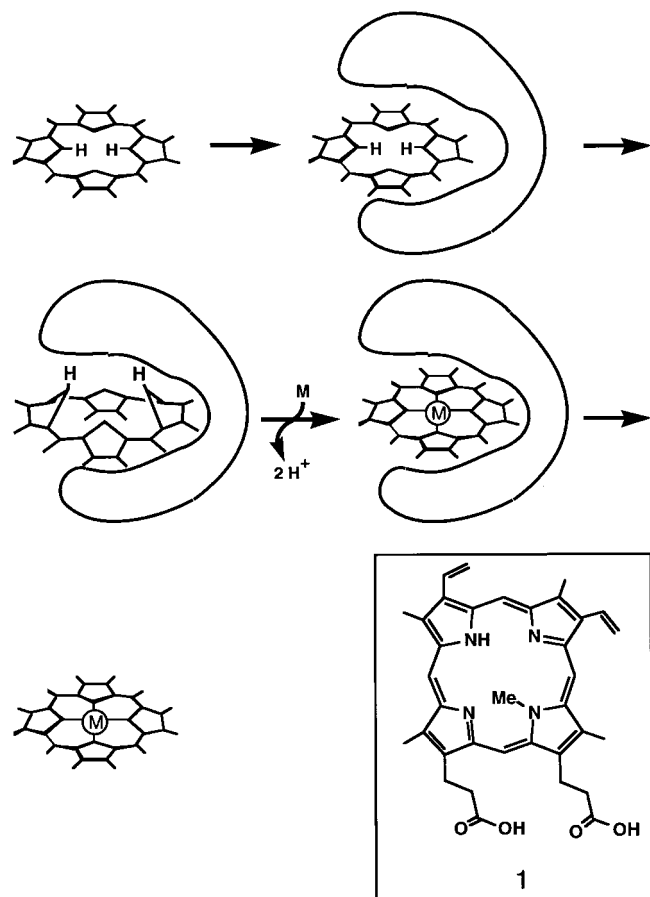


Figure 2. Representation of *N*-methyl protoporphyrin (**1**) distortion induced by an antibody with ferrochelatase activity.^[10]

A second example involves a transesterification reaction catalyzed by an antibody generated against a phosphonate diester transition state analogue.^[11] The antibody catalyzes the corresponding acyl transfer reaction of thymidine and an alanyl ester with an effective molarity of $3 \times 10^4 \text{ M}$ ($(k_{\text{cat}}/K_{\text{m}})/k_{\text{uncat}} \approx 10^8$). Moreover, the antibody does not catalyze acyl transfer to water. NMR studies of the Michaelis complex suggest that the high catalytic efficiency and selectivity of this antibody result largely from an optimal orientation of the acyl donor and nucleophile in the antibody active site, reflecting the orientation of the phosphonate moiety in the hapten.^[12] Thus, by selecting the natural diversity of the immune system on the basis of mechanistic criteria (for example, distortion of a planar porphyrin ring or proximity of reactive groups), it is possible both to generate antibodies with enzyme-like properties as well as to test basic principles of enzymic catalysis.

Other approaches have been developed to generate catalytic antibodies including covalent catalysis, proximity effects, and general acid–base catalysis.^[7] In addition, strategies have been developed to directly select immunological diversity for catalytic function both in vivo and in vitro. Such approaches have been used to generate antibodies that catalyze a wide array of enzymic and nonenzymic reactions. These include stereoselective redox reactions, pericyclic reactions, rearrangement and acyl transfer reactions, as well as a number of “difficult” chemical transformations including kinetically disfavored exo-Diels–Alder and anti-Baldwin cyclization reactions.^[13] A recent example involved the generation of an aldolase antibody by means of a mechanism-based selection with a hapten capable of forming a covalent bond with active-site lysine residues. The catalytic efficiency and stereoselectivity of this antibody are remarkably similar to those of Class I aldolase enzymes.^[14] Catalysis proceeds through imine formation between the ketone substrate and the ϵ -amino group of an active site-lysine residue, followed by enamine formation, condensation with an aldehyde, and subsequent hydrolysis to give the aldol product—a mechanism similar to that of the enzyme. At the same time the antibody tolerates a remarkably broad range of substrate structures (Figure 3) and thus represents one of the most general stereoselective catalysts to date for carbon–carbon bond formation.^[15] This example beautifully illustrates the catalytic potential of immunological diversity that can be harnessed with proper chemical instruction.

The characterization of catalytic antibodies also provides important new insights into the evolution of binding and catalytic function, as well as the combinatorial processes of the immune system itself. For example, structural and mechanistic analyses of antibody-catalyzed oxy-Cope rearrangement and Diels–Alder reactions have illustrated a number of mechanisms whereby binding energy can be used to affect the stereoelectronics of pericyclic reactions.^[16–18] Detailed biophysical and structural studies have also been carried out to examine the affinity maturation of an esterolytic antibody generated against a nitrophenyl phosphonate transition state analogue. Nine somatic mutations resulted in a catalytic antibody that binds hapten with 35 000-fold greater affinity than its germ-line precursor. In contrast to the affinity-matured antibody, which binds hapten in a “lock-and-key” fashion, the germ-line antibody can adopt more than one combining site conformation. Both antigen binding and somatic mutation stabilize the conformation with optimal hapten complementarity (Figure 4). This result suggests that conformational diversity (a key element of Pauling’s chemical instruction model of antibody specificity) may play an important role in expanding the binding potential of the primary immune response.^[19–21] This study further showed that the binding and catalytic properties of the antibody are greatly affected by mutations distant from the bound ligand, an important lesson for those involved in efforts to modify protein function. The study of catalytic antibodies has also provided insights into the structural basis for the polyspecificity of families of germ-line antibodies, another factor that likely contributes to the remarkable binding potential of the primary antibody repertoire.^[17] Thus, by generating new

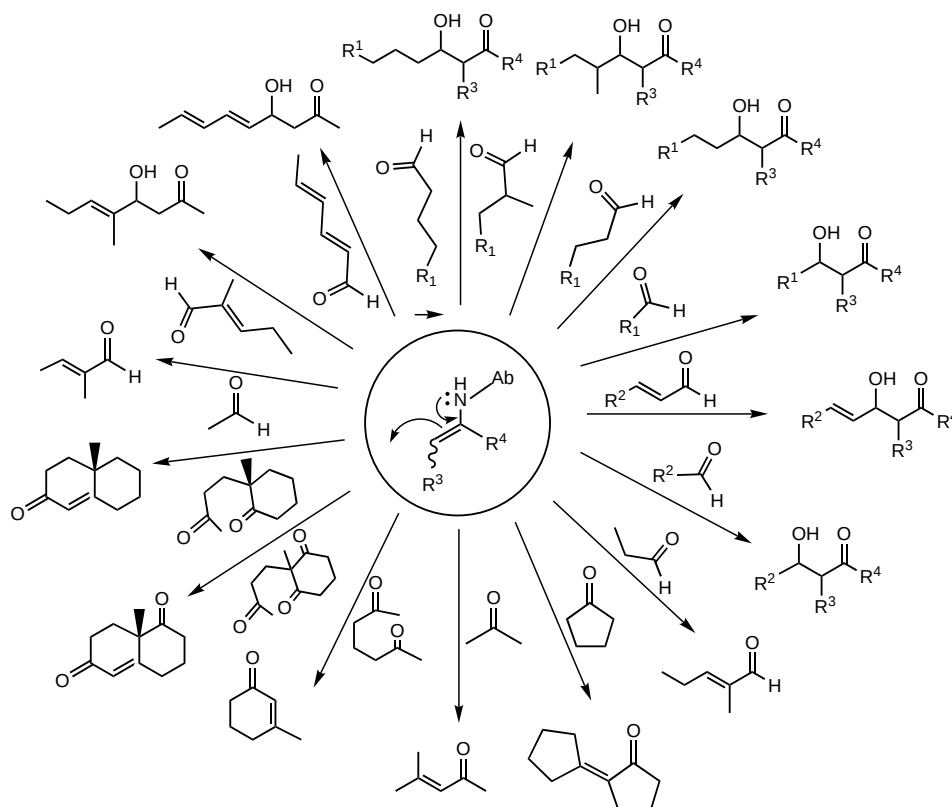


Figure 3. Schematic representation of an antibody (Ab) aldolase with broad substrate specificity.^[14] Shown in the sphere is the covalent enamine intermediate that is formed from the ketone substrate and the ϵ -amino group of an active-site lysine residue.

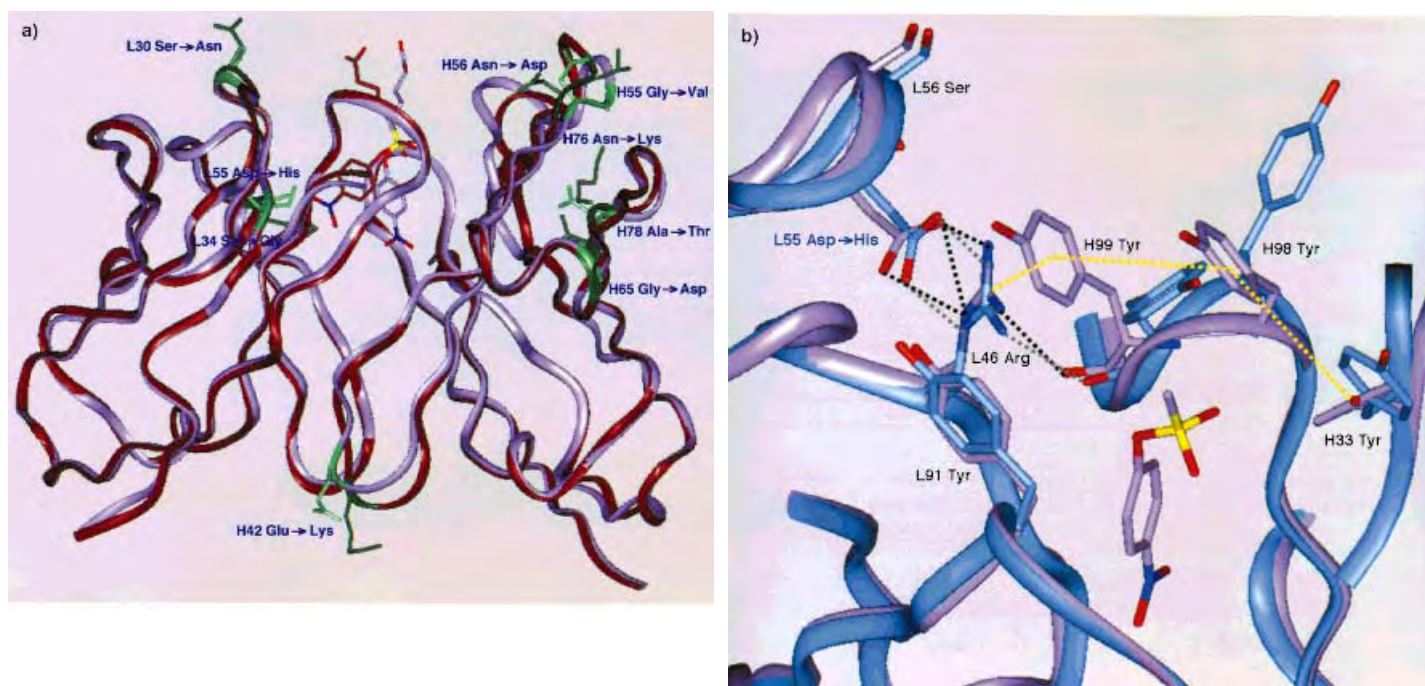


Figure 4. Conformational diversity in an antibody esterase. Whether the amino acid belongs to a heavy or light chain is indicated with the letter H or L before the sequence number. a) Superposition of the germ-line Fab-hapten complex (Fab = antigen-binding fragment of an antibody; purple) and the affinity-matured Fab-hapten complex (red). Somatic mutated residues (X $\rightarrow$ Y) are shown in green. b) Superposition of the structures of the germ-line Fab domain without hapten (blue) and the germ-line Fab-hapten complex (purple). Gray dotted lines denote hydrogen bonds in the structure of the germ-line Fab without hapten, while black dotted lines denote hydrogen bonds in the germ-line Fab-hapten complex.^[19] Yellow dotted lines show the formation of a "double T-stack" arrangement between the side chains of three tyrosine residues.

functions from antibody diversity, new insights are being gained into the relationship between structure and function in the immune system itself.

Researchers have expanded upon the natural diversity generated by the immune system. In 1989 a novel vector system based on the bacteriophage lambda was used to

express a synthetic combinatorial library of Fab fragments of the mouse antibody repertoire in *Escherichia coli*.^[22] This system allowed rapid and easy identification of monoclonal Fab fragments that bind a given antigen, in a form suitable for genetic manipulation. For example, monoclonal Fab fragments against a transition state analogue hapten were generated using this technique.

Phage display,^[23–26] in which a peptide or protein is expressed on the surface of filamentous phage, as well as other schemes linking the polypeptide chain to the encoding DNA,^[27–29] have also proven to be very powerful techniques for generating diversity in vitro. By mutagenizing codons randomly or at specific sites in a gene with synthetic oligonucleotides, libraries of greater than 10^8 different polypeptide sequences can be generated and expressed on the phage surface. Subsequent screening by affinity-based techniques using immobilized ligands, followed by elution of bound phage, amplification, and additional rounds of screening can lead to the isolation of high-affinity receptors or ligands. The identity of a particular member of the library is determined by sequencing the phage DNA.

With phage display techniques, synthetic combinatorial libraries of antibody genes from multiple species (including human), or from large synthetic repertoires of antibody encoding genes, have been expressed on phage as single-chain Fv or Fab fragments (Figure 5).^[30, 31] High-affinity antibodies have been isolated that bind a wide variety of small ligands and macromolecules including viral and tumor antigens, and that catalyze a number of chemical reactions.^[24, 32] More recently, methods have been developed that allow the direct chemical selection of catalysts from phage displayed Fab libraries.^[33] For example, an antibody glycosidase was isolated using a mechanism-based inhibitor that produced a reactive quinone methide, resulting in the covalent trapping of catalytic clones onto a solid support for further rounds of amplification and selection. In vitro methods for generating antibody diversity may become as important as hybridoma technology in the development of monoclonal antibodies for diagnostic, therapeutic, and chemical applications. Phage display methods are also being used to identify other protein frameworks, such as the loops of four-helix bundle proteins, which when randomized might function as miniantibodies.^[34]

Most recently, we have developed a general scheme for the in vitro evolution of protein catalysts that directly links substrate turnover to a selective advantage in a biologically amplifiable system.^[35] Substrate is covalently and site-specifically attached by a flexible tether to the pIII coat protein of a filamentous phage that also displays the protein catalyst. Intramolecular conversion of substrate into product provides a basis for isolating active catalysts from a library of proteins, either by

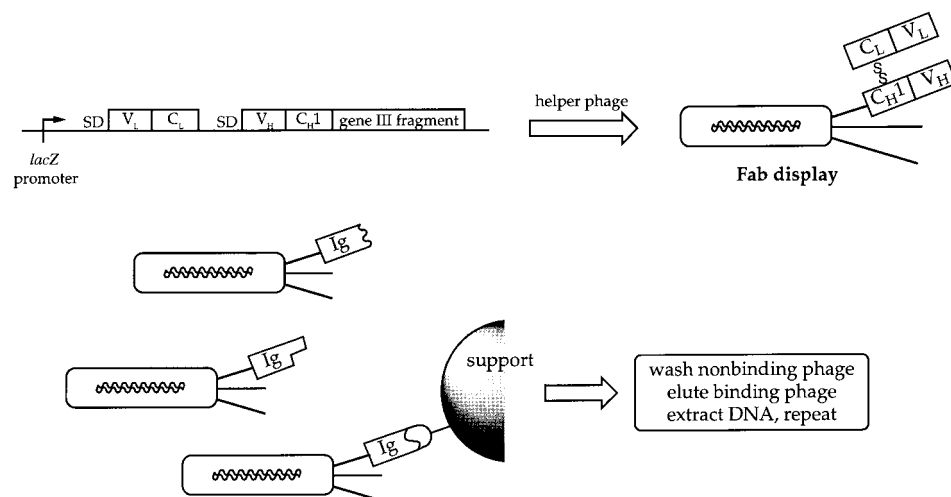


Figure 5. Phage display and screening of an antibody library. SD = Shine–Dalgarno sequence (ribosome binding site on prokaryotic mRNA); Ig = immunoglobulin domain.

release or attachment of the phage to a solid support, or by the capture of the product by a product-specific antibody (Figure 6). This methodology was developed using the enzyme staphylococcal nuclease (SNase) as a model. Phage

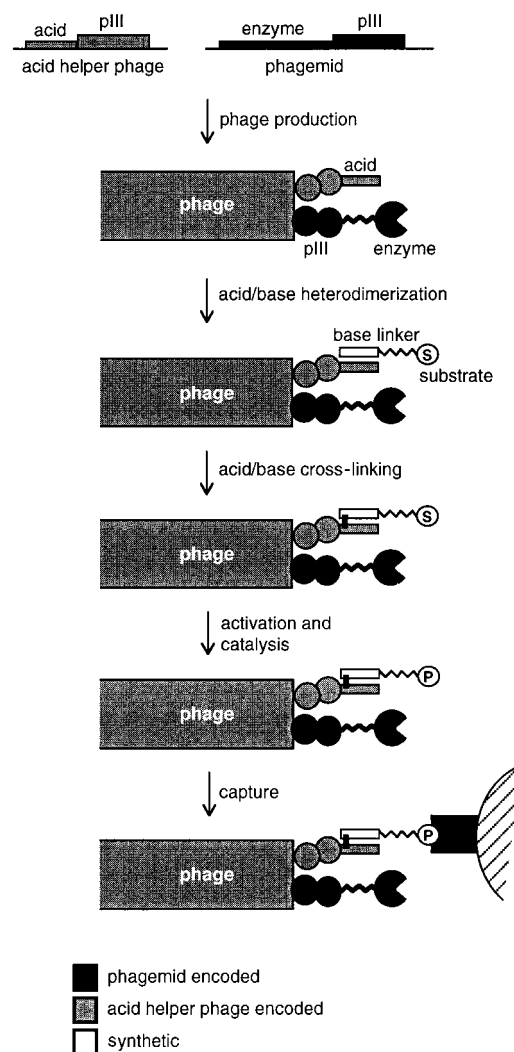


Figure 6. A general scheme for the in vitro evolution of protein catalysts.

displaying SNase can be enriched up to 1000-fold in a single step from a librarylike ensemble of phage displaying non-catalytic proteins. Additionally, this approach should allow one to functionally clone natural enzymes based on their ability to catalyze specific reactions (for example, glycosyl transfer, sequence-specific proteolysis or phosphorylation, polymerization), rather than their sequence or structural homology to known enzymes.

2.2. Peptide Diversity

Libraries of linear and cyclic peptides displayed on phage have been used to identify high-affinity, selective ligands which bind a range of biological receptors including antibodies, enzymes, lectins, cell surface receptors, signal transduction proteins, and even nucleic acids.^[24] One of the most impressive examples was the isolation of a disulfide-bonded cyclic peptide containing 14 amino acids with the consensus sequence YXCXXGPXTWXCXP (where X can be several amino acids), that binds and activates the receptor for the cytokine erythropoietin (EPO).^[36] The successful isolation of this peptide required both variations in the stringency of the screening (by varying binding avidity and elution conditions) and the generation and screening of libraries derived from low-affinity peptides. The isolated peptide binds the extracellular domain of the EPO receptor (EPOR) with an IC_{50} of roughly $0.2\mu M$, and stimulates erythropoiesis in mice through a signaling pathway that appears to be identical to that induced by the natural ligand. The molecular basis for the agonist activity of this peptide was determined by analysis of the three-dimensional crystal structure of the complex of EPOR and a related 20 amino acid peptide (Figure 7).^[37] The

EPOR, suggests that peptides may be able to recapitulate many of the other functions of larger proteins.

Another interesting application of phage display techniques is the determination of substrate specificities of proteases by screening peptide libraries with an assay based on peptide hydrolysis.^[38] In this case the amino terminal domain of the pIII protein of filamentous phage is fused to a tag by a randomized peptide linker. Phage are then bound to an affinity support specific for the tag. Upon protease treatment, phage displaying peptides that are good substrates are cleaved from the support. After several rounds of binding, proteolysis, and amplification, sensitive and resistant substrate sequences were identified for the proteases subtilisin BPN' and factor X_a . Peptide libraries presented on phage have also been panned directly against cells to identify peptide sequences that bind and/or enter specific cell types. These peptides may ultimately provide the basis for intravenously delivered gene therapy vectors^[39] or tissue-specific therapeutic agents.^[40]

2.3. Evolving Protein Function

The natural rate of genetic diversification by point mutation can be increased with UV, chemical, or enzymatic mutagenesis, or genetic methods such as the use of mutator strains. Proteins with random mutations generated by these methods can be subjected to an appropriate screen or selection to isolate mutants with altered properties. For example, these methods have been used to change the substrate specificity of β -galactosidase,^[41] ribitol dehydrogenase,^[42] and alkylamidases.^[43]

More recently, a number of highly efficient methods have been developed for generating larger and more diverse libraries of mutants including cassette mutagenesis,^[44, 45] error-prone polymerase chain reaction (PCR),^[46] and the technique of DNA shuffling.^[47, 48] These methods have accelerated our ability to carry out artificial evolution by introducing diversity at a higher rate, and have been used to modify the stability, catalytic activity, and specificity of proteins.^[49–54] In particular, DNA shuffling mimics the combinatorial processes of the immune system and natural evolution by combining both random point mutagenesis of a gene with in vitro homologous recombination to generate libraries of structurally diverse mutants (Figure 8). This approach allows one to more efficiently search large sequence spaces for mutations that lead to additive or even cooperative enhancements in binding or catalytic function. When directly compared with processes such as error-prone PCR that iteratively build up beneficial mutations without recombination, DNA shuffling has yielded evolved proteins with higher desired activities in fewer rounds of selection.^[47] DNA shuffling has been used to enhance the properties of a number of proteins including glycosidases, β -lactamases, antibodies, green fluorescent protein (GFP), and growth factors.^[48] For example, three cycles of DNA shuffling and two cycles of backcrossing (recombination with the wild-type gene) with selection on increasing concentrations of the antibiotic cefotaxime resulted in a β -lactamase with six mutations which conferred to the cell a 32000-fold higher resistance to the antibiotic.^[47] The mutations, like the somatic mutations in affinity-matured

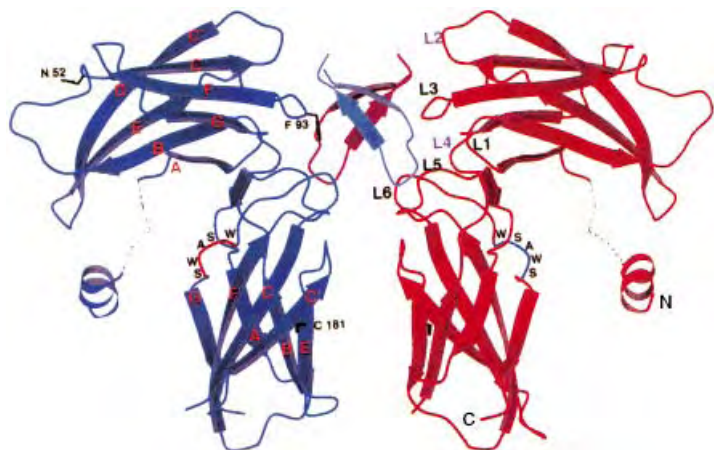


Figure 7. Complex of a 20-residue peptide isolated from a phage peptide library with the extracellular domain of the EPO receptor.^[37]

structure reveals that the peptide forms a dimer consisting of a four-stranded, anti-parallel β -pleated sheet and two type I β turns. The peptide induces an almost perfect twofold dimerization of the receptor through a combination of hydrophobic and hydrogen-bonding interactions with segments of four loop regions of EPOR. The successful isolation of this novel peptide, which may define a minimal epitope for activation of

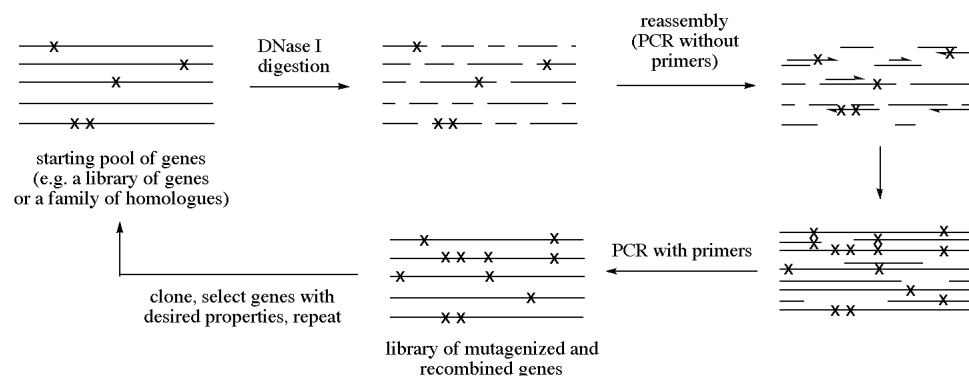


Figure 8. DNA shuffling involves random fragmentation of a gene into discrete fragments, reassembly of these fragments by PCR without primers, final PCR amplification with primers, and cloning of the mutated and recombined genes.^[47]

antibodies, are distributed throughout the protein, making the rational design of the mutant proteins difficult, if not impossible.

Recently, the technique of DNA shuffling has been applied to the evolution of an “orthogonal” suppressor tRNA and aminoacyl-tRNA synthetase pair that may allow one to site-specifically incorporate into proteins in vivo amino acids with novel structural or electronic properties not specified in the genetic code.^[55] The orthogonal suppressor tRNA was constructed by introducing eight mutations into tRNA_{2^{Gln}} based on analyses of the X-ray crystal structure of the GlnRS–tRNA_{2^{Gln}} complex (GlnRS = glutaminyl-tRNA aminoacyl synthetase) and previous biochemical data. The resulting tRNA satisfies the minimal requirements for the delivery of an unnatural amino acid: It is not acylated by any endogenous *E. coli* aminoacyl-tRNA synthetase, including GlnRS, and it functions efficiently in protein translation. Repeated rounds of DNA shuffling and oligonucleotide-directed mutagenesis were then used to generate a large library of directed and random mutants of GlnRS. This library was selected for mutant enzymes that efficiently acylate the engineered tRNA with glutamine in vivo, based on suppression of an amber codon (termination codon UAG) in the *lacZ* gene (Figure 9). With this approach an “orthogonal” mutant GlnRS/tRNA pair has been generated that functions in vivo. Currently, DNA shuffling and cassette mutagenesis are being used to

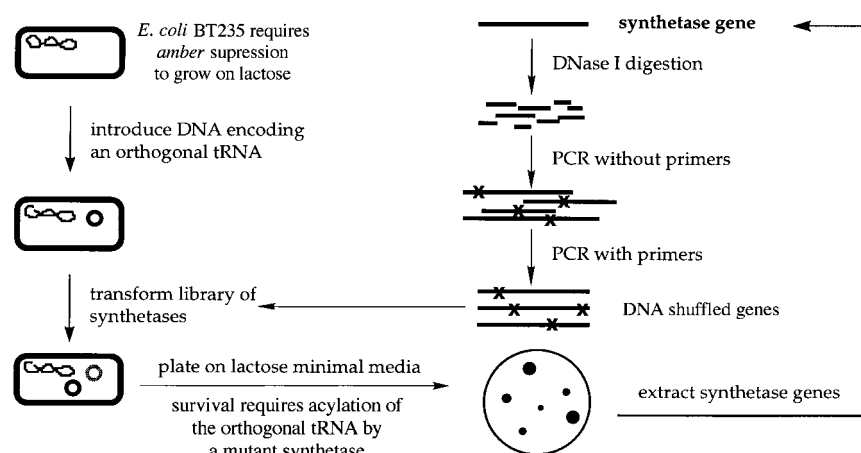


Figure 9. Selection of an orthogonal GlnRS/tRNA pair from a library of GlnRS mutants.^[55]

select for synthetase mutants that acylate orthogonal tRNAs with novel amino acids.^[56] Clearly, both structural information and diversity play a critical role in the design of these experiments.

A variety of other proteins with modified binding affinities and specificities, including growth hormones^[57] and DNA-binding proteins,^[58–60] have been isolated from large libraries of mutants. For example, the zinc finger DNA-binding motif of Zif268 pro-

tein has been expressed on filamentous phage, and libraries of mutants have been selected against duplex DNA sequences containing wild-type and mutant binding sites.^[61] This approach has resulted in the generation of a DNA-binding peptide comprising three zinc fingers that binds to a unique nine base pair region of a BCR-ABL fusion oncogene with a dissociation constant K_d of 6.2×10^{-7} M. Its binding affinities for genomic BCR and C-ABL sequences (which differ by as little as one base pair) differ by an order of magnitude. Binding of the peptide to the target oncogene in transformed cells in vitro resulted in blockage of transcription. Techniques other than phage display can also be used to generate DNA-binding proteins with altered specificities. For example, helix-turn-helix and leucine zipper proteins with novel specificities have been generated from large libraries of mutants using selections based on interference with transcription of antibiotic resistance genes.^[62, 63] Studies of this sort are also helping to define the recognition codes between the amino acid sequences of DNA-binding proteins and their cognate recognition sites.

Large libraries of mutant proteins have also been used to investigate the factors that influence the structure and stability of specific protein folds. For example, cassette mutagenesis has been used to randomly alter seven residues in the hydrophobic core of the N-terminal domain of phage λ repressor.^[64] By selecting for functional repressors (phage-

resistant transformants), it was shown that many different sequences can form a stable core. The main determinant of whether a particular sequence is compatible with the wild-type fold was hydrophobicity, although the van der Waals volume of the core and steric interactions between residues also limited the number of functional sequences. More recently, the sequence determinants that dictate the four helix bundle structure have been investigated.^[65] A library of cytochrome *b*₅₆₂ mutants was generated in which amino acids at defined positions were replaced with any of the hydrophobic amino acids Phe, Leu, Ile, Met, or Val, or any of the

hydrophilic amino acids Glu, Asp, Lys, Asn, Gln, or His to generate a binary pattern of nonpolar and polar amino acids. Bacterial expression of soluble, protease-resistant protein was assayed spectrophotometrically by monitoring heme absorbance. It was found that 29 of 48 sequences examined expressed protein that was both soluble and resistant to intracellular degradation. Two proteins that were characterized by urea denaturation experiments were stabilized by 3.7 and 4.4 kcal mol⁻¹ relative to the unfolded form. A similar strategy has been applied to a random sequence of 80 to 100 amino acids consisting of Gln, Leu, and Arg. Bacterial expression of these “QLR proteins” revealed that 5% of the sequences were expressed at readily detectable levels. Several of the characterized proteins possessed features of native proteins such as α -helical content and highly cooperative folding, suggesting that folded proteins occur frequently in libraries of random amino acid sequences.^[66]

The relationship between protein sequence and structure has also been examined using libraries created neither in vivo nor in vitro, but rather by computational methods. Recently, a design algorithm based on chemical potential functions and stereochemical constraints was used to search 1.9×10^{27} amino acid sequences for those that adopt a β - α - β zinc finger motif. The resulting designed sequence (FSF-1) possesses little or no identity to any known protein sequence. The synthesis and subsequent NMR spectroscopic investigation of FSF-1 in solution revealed a compact structure in excellent agreement with the design target. This experiment demonstrates the potential power of computational methods to screen combinatorial libraries ten or more orders of magnitude larger than any created in the laboratory.^[67]

3. Nucleic Acid Diversity

Combinatorial methods have played an important role in investigating the scope of nucleic acid function and its possible role in the prebiotic world. In these experiments libraries containing up to 10^{15} random single-stranded RNA or DNA sequences are generated using a combination of chemical synthesis, PCR, and runoff transcription (in the case of RNA).^[68–71] These libraries are then selected for individual molecules that either 1) bind specific ligands using affinity-based methods or 2) carry out specific chemical transformations using in vitro selections or screenings. Amplification of an enriched population of binders or catalysts is followed by subsequent rounds of selection. With these techniques, nucleic acids have been generated that selectively bind small molecules, proteins, and nucleic acids; and catalyze a number of reactions ranging from phosphoryl and acyl transfer reactions to metalation and pericyclic reactions.

3.1. Selecting for Binding Function

Single-stranded RNA and DNA oligomers (or aptamers) have been isolated from large, random oligonucleotide libraries that selectively bind a wide array of molecules including T4DNA polymerase, human immunodeficiency

virus (HIV), HIV Rev protein, thrombin, amino acids, organic dyes, and cofactors.^[68, 69, 72–78] For example, by screening a library of 10^{13} transcripts with ATP immobilized on agarose, an RNA was isolated that binds adenosine with a dissociation constant K_d of $0.7 \mu\text{M}$.^[74] The solution structure of a 40 nucleotide RNA containing the consensus ATP-binding motif complexed with AMP (which binds with affinity similar to that of ATP) has been determined by NMR spectroscopy.^[79] The AMP molecule is bound in a “GNRA-like” hairpin fold^[80] with the intercalated adenine involved in an A·G mismatch pair and the 2' and 3' hydroxyl groups of the ribose sugar forming hydrogen bonds to the RNA. The binding of AMP was shown to induce a conformational transition in the ATP binding site on the RNA. RNA aptamers have also been isolated from oligonucleotide libraries that bind the purine theophylline with high affinity ($K_d = 0.1 \mu\text{M}$). These aptamers do not bind appreciably to caffeine ($K_d = 3500 \mu\text{M}$), which differs from theophylline by only a methyl group at nitrogen atom N7.^[81] Experiments of this sort demonstrate that RNA, like proteins, can bind a wide array of small molecules with extremely high specificity, by a combination of van der Waals packing, hydrogen-bonding, and electrostatic interactions.

Aptamers have also been isolated that bind selectively to macromolecules, including proteins and nucleic acids. For example, single-stranded RNAs have been isolated that bind sequence-selectively to duplex DNA through the formation of triple-helical structures involving Hoogsteen base pairs.^[82] Single-stranded DNAs have been isolated that bind to thrombin through the formation of a highly conserved guanine-rich structure of 14–17 nucleotides. In this case the binding affinity was 25–200 nM, and several aptamers inhibited thrombin-catalyzed fibrin clot formation in vitro at nanomolar concentrations.^[77]

3.2. RNA Catalysis

The earliest use of in vitro selection schemes to isolate RNAs with novel phenotypes from pools of mutants were those of Spiegelman et al.^[83] In these experiments Q β replicase, a template-specific RNA-directed polymerase, was used in a Darwinian selection system to isolate a structured RNA that had reduced affinity for the intercalating dye ethidium bromide. The mutant arose by sequential mutation during the course of the experiments, and was not a preexisting variant of the original RNA pool.

The use of in vitro selections to isolate RNAs with novel catalytic activities has involved either libraries generated by mutagenesis of naturally occurring ribozymes, or synthetic libraries of randomized RNA sequences. For example, the *Tetrahymena* group I ribozyme has been used as a starting point to isolate a new ribozyme that cleaves DNA.^[70, 71] The selection required the ribozyme to complete a phosphorylation reaction with an alternative DNA substrate that results in the addition of nine bases to the 3'-terminal hydroxyl group of the ribozyme (Figure 10). This 3'-terminal extension permits successful annealing of an amplification primer necessary to complete the cycle of selection. With a much larger pool of mutants (10^{13}), variants were isolated that catalyze the

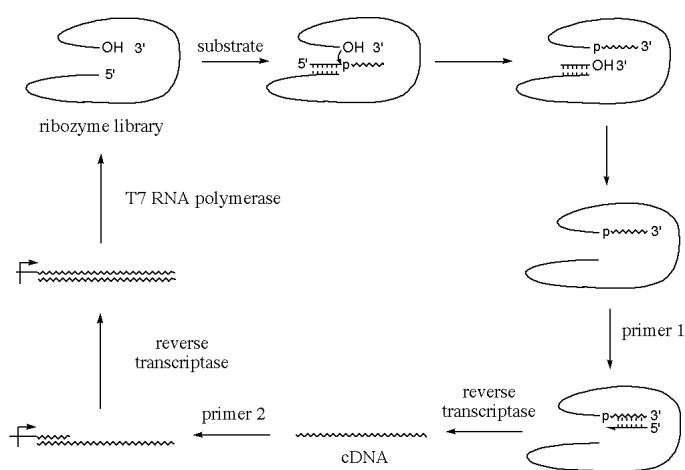


Figure 10. Selection of a *Tetrahymena* ribozyme mutant that uses an alternative DNA substrate.^[70, 71] Wavy lines represent DNA strands.

reaction under physiological conditions at a rate up to 65 times faster than the wild-type ribozyme. Other selection schemes using naturally occurring ribozymes have yielded RNAs with self-copying functions^[84] and altered metal requirements.^[85]

One of the most impressive examples of the selection of RNA catalysts from complex libraries of random sequences was the isolation of a RNA ligase that can act as a RNA polymerase.^[86, 87] Beginning with a pool of approximately 10^{15} distinct transcripts, iterative rounds of amplification and selection were carried out based upon the ability of the ribozyme to ligate its own 5'-terminal triphosphate group to a substrate oligonucleotide containing a 5' "tag" (Figure 11). A ribozyme that catalyzes 3',5'-phosphodiester bond formation with k_{cat} greater than 1 s^{-1} was isolated;^[86, 87] when fused to a template strand, this RNA ligase was shown to catalyze RNA primer extension by up to six nucleotides in a template-directed fashion.^[88] Nucleotides complementary to the template

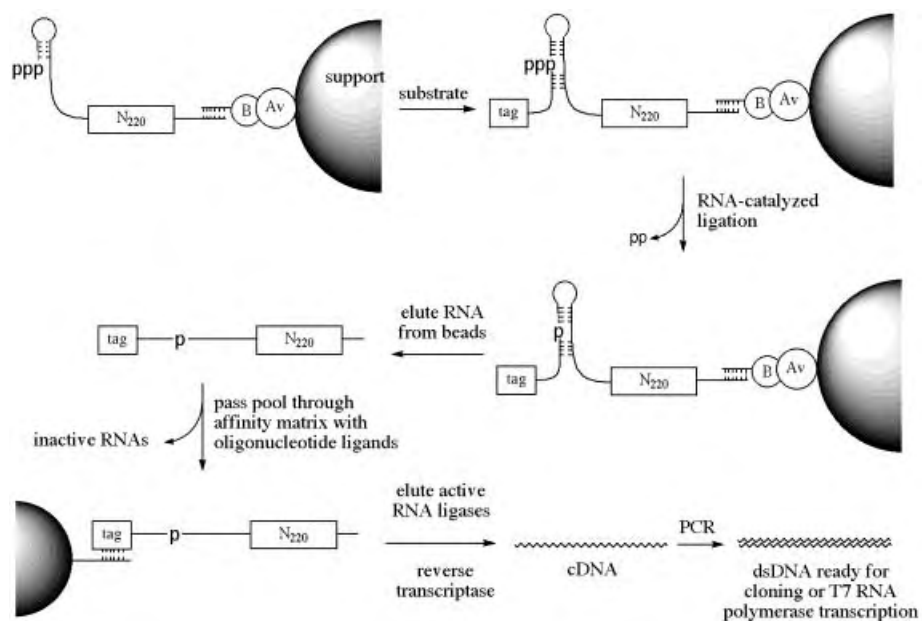


Figure 11. Selection scheme for generation of an RNA ligase.^[86, 87] Biotin and avidin are represented by B and Av, respectively.

are added up to 1000 times more efficiently than mismatched oligonucleotides. Although a number of obstacles remain to generate an RNA replicase (for example, strand separation after polymerization, nonspecific binding of template and primer, and sequence fidelity) these experiments illustrate the potential to evolve RNAs that catalyze reactions which may have been required in the prebiotic world.

Selections and affinity-based methods have also been used to expand the scope of RNA-catalyzed reactions to other classes of reactions including isomerization, carbon-carbon bond forming, metalation, and alkylation reactions. For example, by exploiting the same notions of transition state theory that were used in the initial generation of catalytic antibodies, an RNA was isolated that catalyzes the isomerization of a bridged biphenyl substrate to its diastereomer (Figure 12).^[89] In this case a library of 10^{13} random RNA

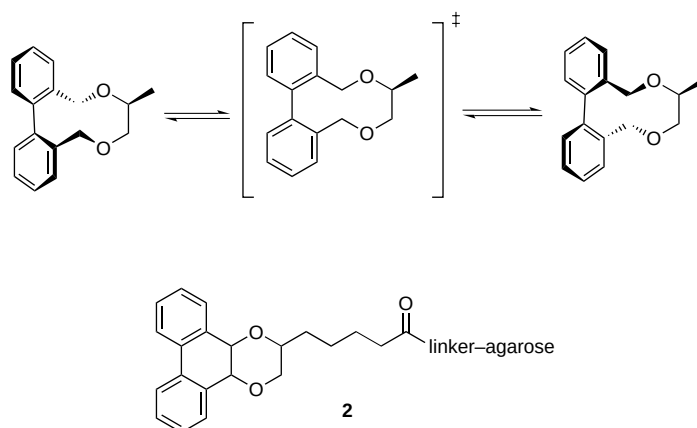


Figure 12. Atropisomerization between diastereoisomeric 1,1'-biphenyls. Structure **2** is an analogue of the transition state for this reaction.^[89]

molecules was screened based on binding affinity to the planar biphenyl transition state analogue **2** immobilized on a solid support. A similar approach has been used to generate single-stranded RNAs and DNAs that catalyze porphyrin metalation.^[90, 91] More recently, selections based on covalent linkage of a ribozyme to a solid support have been used to generate RNAs that catalyze a Diels-Alder reaction between a diene and dienophile.^[92]

3.3. Other Applications

Many other novel uses of nucleic acid libraries continue to appear including in vivo applications. One such example involves the use of genomic expression libraries for immunization, a technique that makes use of genetic immunization (immunization with the gene encoding the protein antigen rather than the protein itself) and the fact that

all antigens of a pathogen are encoded in its DNA.^[93] Indeed, it has been shown that even partial expression libraries made from the DNA of *Mycoplasma pulmonis*, a natural pathogen in rodents, provide protection against challenges from the pathogen. Libraries of nucleic acids have also been used in vivo to identify cis-acting sequences that lead to localization of RNAs in the nucleus of *Xenopus laevis* oocytes.^[94] Clearly, libraries of nucleic acids, like those of peptides and proteins, will find many applications in the search for new biological and chemical functions, and in our efforts to better understand complex biological processes.

4. Diversity in Chemical Synthesis

The biosynthetic machinery used by living cells to generate diverse populations of molecules is limited to specific classes of chemical structures including oligomeric molecules such as polypeptides, oligonucleotides, and polysaccharides, and a variety of natural products such as the polyketides. Moreover, these structures are generated from restricted sets of building blocks. The development of methods for generating large, diverse populations of synthetic molecules has extended the scope of this approach to new classes of molecules with a broader range of chemical, biological, and physical properties.

4.1. Approaches to Synthetic Diversity

Virtually all of the efforts aimed at generating and screening large populations of synthetic diversity are based on the method of solid-phase synthesis developed by Merrifield.^[95] The initial work focused on polypeptides, which can be rapidly assembled by iterative chemical synthesis from a diverse set of commonly occurring and unnatural amino acids. Methods were first developed that simply involved the simultaneous synthesis of multiple discrete peptide sequences using either polyacrylic acid grafted polyethylene pins arranged in microtiter format,^[96] or later resins sealed in porous polypropylene bags (the “tea bag” technique).^[97]

These experiments were followed by efforts aimed at generating more diverse populations of molecules by connecting sets of building blocks in all possible combinations, again mimicking the combinatorial strategies used by nature to efficiently generate molecular diversity. These methods involve either the generation of spatially separated libraries of molecules, or mixtures of resins each containing a discrete structure or small number of related structures. One example of the former approach involves the “mimotope” strategy in which peptides are again synthesized on pins, but in this case by randomly incorporating residues from mixtures of activated amino acids to give all peptide sequences.^[98, 99] Two positions in a peptide containing n residues are then iteratively defined by multipin synthesis of 400 discrete mixtures, each containing all possible $(n-2)$ peptide sequences with one of the 400 possible pairs of the common L-amino acids defined. This technique has been used in conjunction with ELISA (enzyme-linked immunosorbent assay) screening methods to identify peptides that selectively bind antibodies and other receptors.

A second method for the spatially addressable synthesis of combinatorial libraries makes use of photolithography together with solid-phase synthesis to generate high-density, combinatorial arrays of peptides on a glass substrate.^[100, 101] By illuminating specific regions of the glass substrate containing growing peptide chains, in which the terminal amino group is protected with a photolabile group, the spatial distribution of individual amino acid coupling steps can be controlled (Figure 13). With n binary masks in which half of the

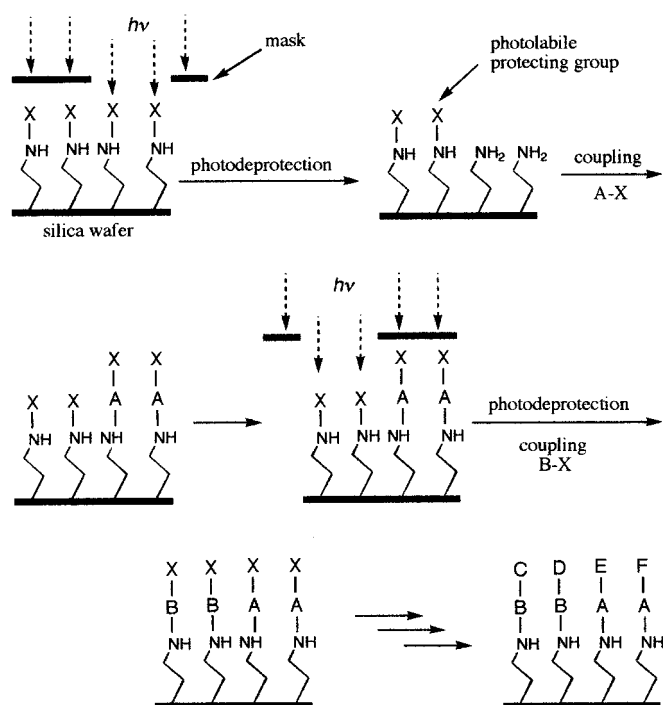


Figure 13. Light-directed synthesis of combinatorial arrays.

surface is photolyzed during each coupling step, 2^n compounds can be synthesized. The sequence of masks and coupling steps defines the identity of the peptide at each site. Binding of fluorescently labeled receptors to the surface is detected by fluorescence emission. Although this technique was developed for peptide synthesis, it has proven to be most useful for generating high-density arrays of oligonucleotides (see below).

Another approach that has been used to generate combinatorial libraries of peptides is the split synthesis method.^[102–104] This technique involves dividing the resin support into n equal fractions, coupling each fraction with a single activated monomer (or in some cases, a small number of monomers), and then recombining the fractions (Figure 14). Iteration for x cycles leads to a stochastic population of n^x peptides. This approach has been used in conjunction with the “tea bag” technique and beaded resins equipped with non-cleavable linkers to generate large combinatorial libraries of up to 50 million different sequences. However, since mixtures of resins are generated, this technique also requires methods to identify the sequence of a high-affinity ligand isolated from an affinity-based assay.

A number of strategies have been developed to determine the identity of a peptide ligand isolated from pools of random

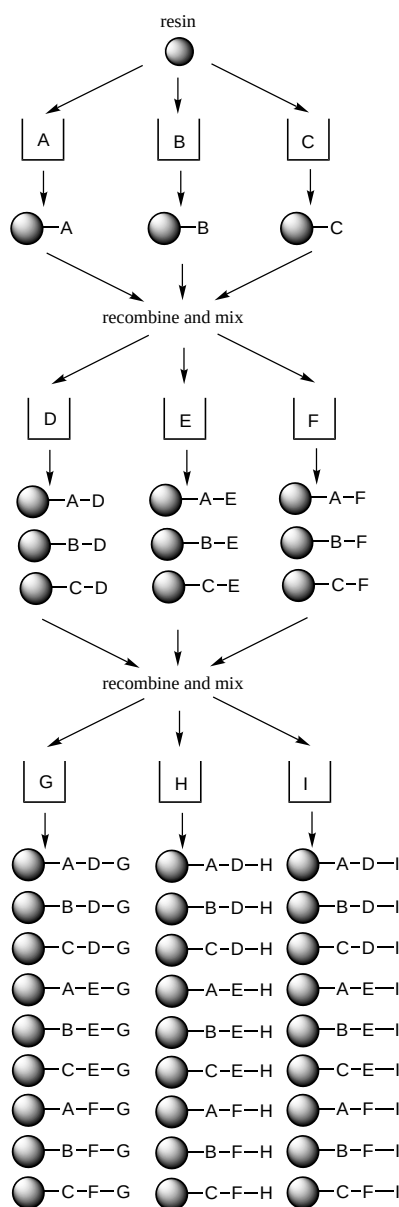


Figure 14. Preparation of a combinatorial library by the split synthesis method.

sequences. These include methods based on the iterative “mimotope” deconvolution strategy described above,^[105] as well as direct Edman peptide microsequencing, which can be used with beads containing 80–100 pmol of peptide.^[106] Mass spectrometry can also be used to identify the sequence of a peptide, if in each step of the synthesis a small fraction of the growing polypeptide chain is capped, resulting in a small amount of truncated chain at each step in the synthesis of the full length peptide.^[107]

More recently, a number of methods have been developed for generating libraries of peptides on resin beads in which each bead is attached to a molecular “tag” that allows rapid and sensitive identification of the associated polypeptide.^[108–111] The tags are attached to the bead coincident with each monomer coupling step. Consequently, they must be stable under the conditions of polymer synthesis and deprotection, their attachment must not interfere with the synthesis

of the polypeptide, and they must have high information content that can be detected with high sensitivity. A number of tagging techniques have been developed (Figure 15), including the use of oligonucleotide tags that can be detected by PCR amplification and DNA sequencing,^[109] and a set of related halocarbon tags that can be separated and detected by electron capture capillary gas chromatography.^[111] The high detection sensitivity of both these tags should facilitate the synthesis of increasingly diverse chemical libraries.

The techniques described above have been used to identify natural and unnatural polypeptides that bind a host of molecules including antibodies, enzymes, and receptors.^[24] For example, antimicrobial peptides with activities against both gram-positive and gram-negative bacteria have been generated.^[112] The binding specificities of synthetic steroid- and macrocycle-based hosts for peptide ligands have also been determined.^[113–115] In addition, these techniques have been used to analyze protein–protein interactions involved in cellular processes.^[116] In one such study, two different SH3 domains conjugated to fluorescein were used to screen a peptide library for ligands that possessed affinity for SH3 domains. Analysis of the resulting sequences suggested a set

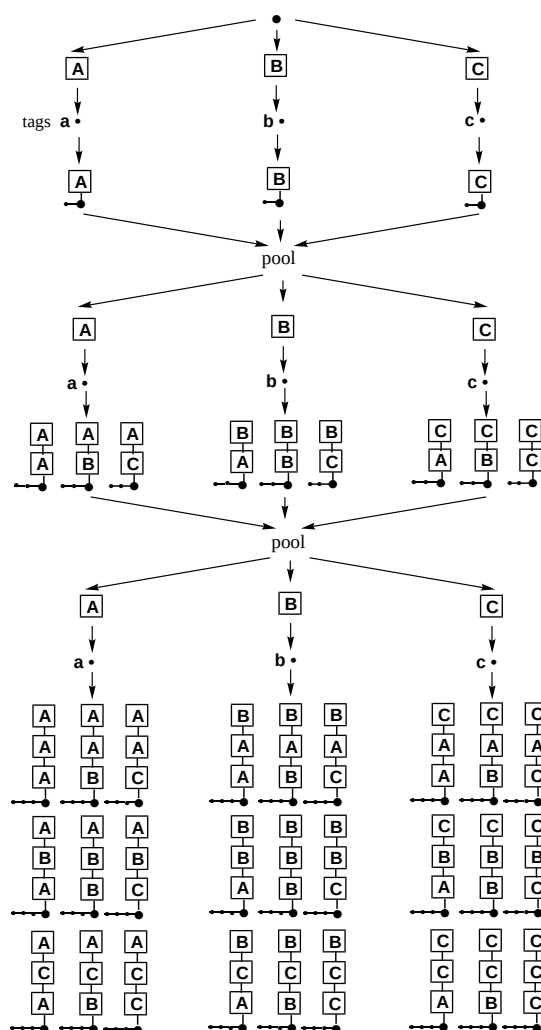


Figure 15. The use of molecular tags to identify members of a library.^[108–111]

of rules governing SH3–ligand interactions, and subsequent structural studies revealed a detailed mode of ligand binding by the SH3 domain.^[116]

4.2. Extension to Other Polymeric and Nonpolymeric Frameworks

Molecular diversity has also been used to explore the chemical and biological properties of heteropolymers composed of building blocks other than amino acids. These unnatural polymeric frameworks may have novel properties such as improved pharmacokinetic properties (including membrane permeability and biological stability) that increase bioavailability, or altered conformational or hydrogen-bonding properties that provide insights into biomolecular structure and folding. A number of novel “unnatural biopolymers” have been generated including oligocarbamates,^[117] peptoids,^[118, 119] oligoureas,^[120–122] oligopyrrolinones,^[123] oligoazatides,^[124] oligosulfonamides,^[125] and β -peptides.^[126–128] Because these oligomeric compounds can be assembled from a set of diverse building blocks, large molecular libraries can be rapidly generated and screened for desired properties. For example, oligocarbamates consisting of a chiral ethylene backbone with a variety of side chains linked through relatively rigid carbamate groups have been efficiently synthesized by the stepwise coupling of N-protected amino-*p*-nitrophenyl carbonate monomers. The monomers in turn are readily derived from the corresponding amino acids (Figure 16).^[117] Libraries of these molecules have been generated, and high-affinity selective ligands have been identified that bind antibodies and integrin receptors.^[111, 129] Libraries of polypeptoids,^[118, 119] a polypeptide backbone composed of N-substituted glycine units, have also been

generated. Peptoids have been identified that selectively bind the α -adrenergic receptor and a number of enzymes.^[118] Efforts are ongoing to determine the conformational and pharmacological properties of these molecules.

The application of combinatorial approaches to creating nonpolymeric small molecules came with the realization that many such molecules can also be synthesized by the iterative stepwise addition of building blocks on a solid support. The most notable early example was that of the combinatorial synthesis of a library of 1,4-benzodiazepines,^[130, 131] a pharmacophore common to a wide variety of clinically important therapeutic agents. A library of approximately 2000 structurally diverse 1,4-benzodiazepine derivatives containing a variety of chemical functionalities including amides, carboxylic acids, amines, phenols, and indoles was constructed by multipin synthesis from three components: 2-aminobenzophenones, amino acids, and alkylating agents (Figure 17). Ligands that selectively bind p60src, a cholecystokinin A receptor, and DNA-binding antibodies have been isolated from this library.

Combinatorial libraries for a large number of small organic molecules have since been generated including β -turn mimetics,^[132] hydantoins,^[133] protease inhibitors,^[134] pyrrolidines,^[135] β -lactams,^[136] and tyrosine kinase inhibitors.^[137] In addition, a library of 1300 di- and trisaccharides was recently synthesized on beads and screened against *Bauhinia purpurea* lectin conjugated to a reporter enzyme.^[138] Two ligands were isolated that bound to the lectin more tightly than the natural ligand. Similar approaches provide promising routes to the identification of carbohydrate-based ligands for other receptors.

Finally, considerable effort is also being focused on the development of new solid-phase synthetic methodologies for generating small-molecule libraries,^[139, 140] as well as theoretical and empirical methods for library design. For example, the structure-based design of nonpeptide libraries containing the hydroxyethylamine pharmacophore of pepstatin yielded potent inhibitors ($K_i = 9$ – 15 nM) of cathepsin D.^[141] Clearly, the use of libraries of synthetic oligomeric and nonpolymeric molecules will continue to have a significant impact on the pharmaceutical industry.

4.3. Natural Products

Not only can chemical synthesis be used to generate libraries of small organic molecules, recently it has been shown that the biosynthetic machinery of cells can be exploited to produce libraries of natural products such as the polyketides, which include the well-known antibiotics erythromycin, avermectin, and spiramycin.^[142] These compounds are synthesized by modular polyketide synthases (PKSs), large multi-functional enzyme assemblies that

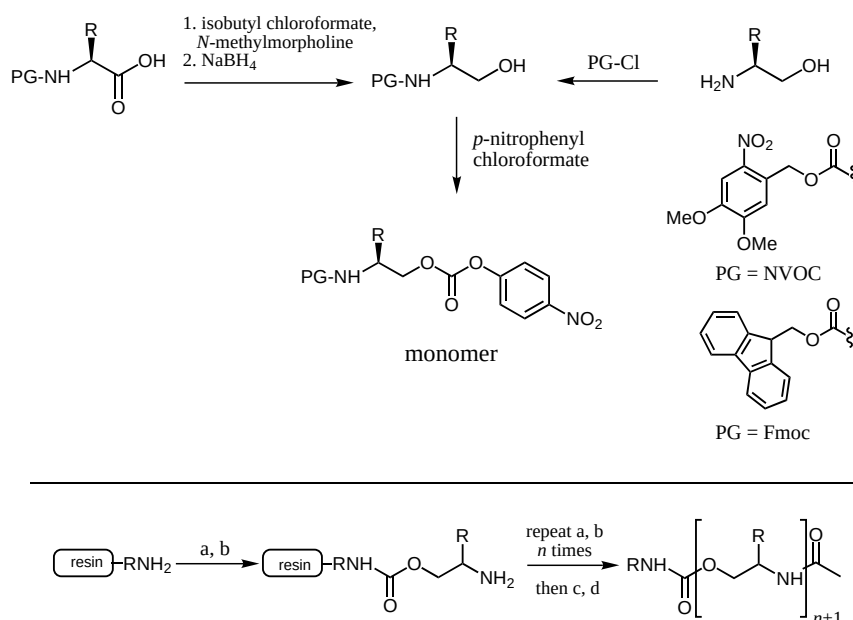


Figure 16. Synthesis of oligocarbamates from amino acid starting materials.^[117] a) Monomer, 1-hydroxy-1*H*-benzotriazole (HOBt), diisopropylethylamine, N-methylpyrrolidine (NMP); b) piperidine, NMP; c) acetic anhydride, pyridine; d) trifluoroacetic acid (TFA), CH₂Cl₂. PG = protecting group, NVOC = nitroveratrylmethoxycarbonyl, Fmoc = 9-fluorenylmethoxycarbonyl.

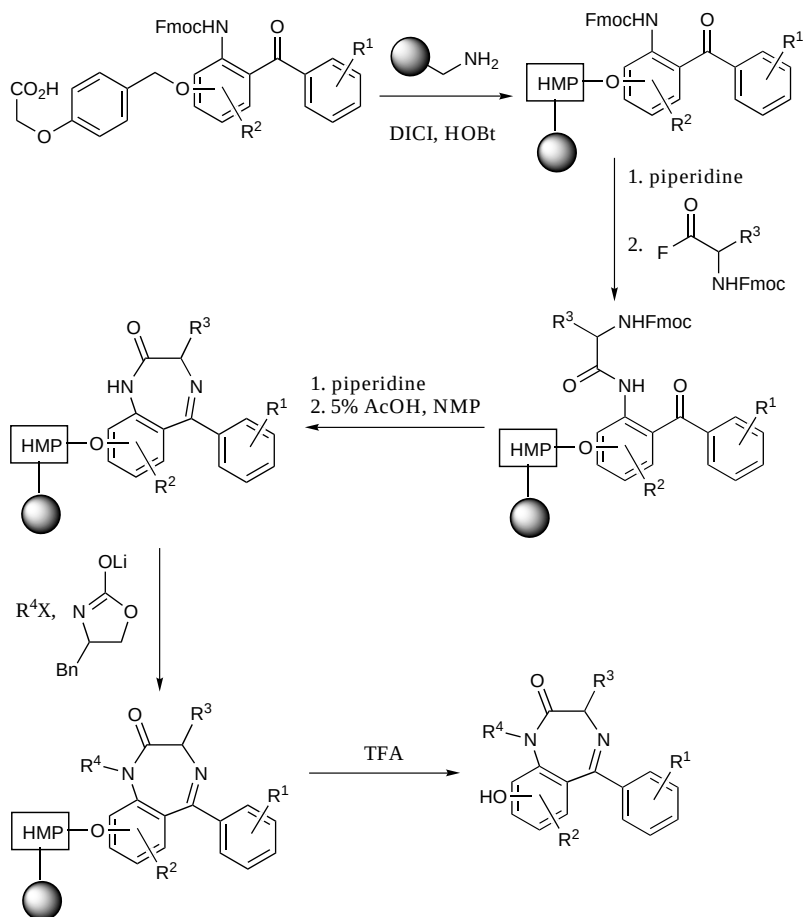


Figure 17. Synthesis of a library of 1,4-benzodiazepines on solid support.^[130] Bn = benzyl, DICl = diisopropylcarbodiimide, HMP = 4-(hydroxymethyl)phenoxyacetic acid.

catalyze the stepwise biosynthesis of these natural products.^[143, 144] These modules encode sets of enzymes (ketosynthases, acyl transferases, ketoreductases, dehydratases, and enoyl reductases) that processively carry out rounds of polyketide chain elongation with concomitant alterations in oxidation level and stereochemistry after each elongation step. Deleting individual modules, altering the specificity of individual enzymes in a module, or adding new enzymatic activities results in the synthesis of a large number of different macrolides.^[142] Most recently, it has been shown that exogenous addition of synthetic diketide mimics to deoxyerythronolide B synthase containing a genetic block in the KS-1 gene results in the synthesis of a novel polyketide containing the synthetic building block (Figure 18).^[145] As more nontemplated biosynthetic pathways are isolated and characterized (e.g., cyclic peptides, ene-diyne, and bleomycins) and our ability to manipulate their function increases, this approach is likely to provide an increasingly diverse collection of chemical structures to screen for novel biological properties.

4.4. Genomics

Combinatorial synthetic methods have also found important applications in genomics. For example, the photolithographic chemical synthesis methods developed for peptides

have made it possible to synthesize spatially addressable, high-density arrays of oligonucleotides of known sequence.^[146, 147] This technique has been used to generate more than 260 000 specifically chosen oligonucleotide probes (in an area of about 6.5 cm²) that hybridize to all open reading frames (ORFs) in the yeast genome (twenty 25-mers complementary to segments within each ORF; Figure 19).^[148] With this array one can monitor the expression levels of nearly all yeast genes in a quantitative, sensitive, and highly reproducible fashion due to the redundancy in the detection and analysis of the data. Arrays of this sort are likely to have a major impact on our ability to analyze the information content of genomic DNA, including mismatch scanning, homology comparisons, and the detection of genetic differences between strains. Other parallel, high-throughput methods have also been developed for generating oligonucleotide arrays,^[149–156] including spotting methods with presynthesized oligonucleotides.^[157]

A recent example demonstrates how combinatorial libraries of small molecules, structural information, and oligonucleotide arrays can be used synergistically to identify and characterize selective kinase inhibitors.^[158] A combinatorial library of 2,6,9-trisubstituted purines was generated based on structural analysis of the novel binding mode of the purine olomoucine to the ATP binding pocket

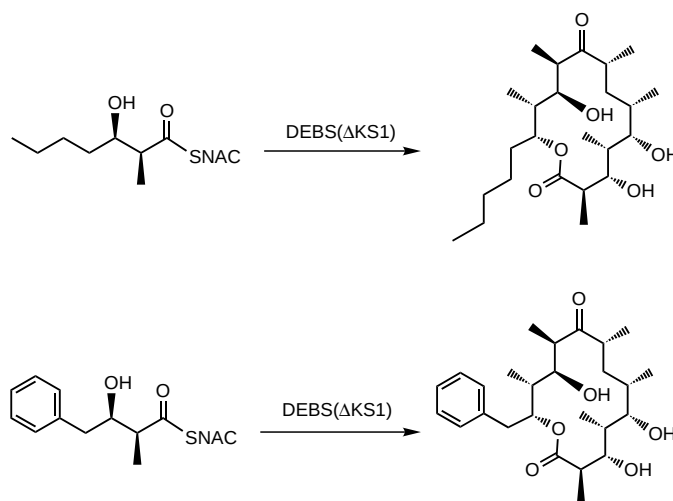


Figure 18. Precursor-directed biosynthesis of novel polyketides containing synthetic building blocks.^[145] NAC = *N*-acetylcysteamine, DEBS = deoxyerythronolide B synthase.

of the cell cycle kinase CDK2.^[159, 160] By iterating chemical library synthesis and biological screening, high-affinity, selective inhibitors of human CDK2/cyclin A and yeast *cdc28* kinases were identified. The CDK2/cyclin A kinase inhibitors include compounds that selectively inhibit the growth of colon



Figure 19. Fluorescence image of an array of oligonucleotide probes following hybridization of a fluorescently labeled RNA sample prepared from mRNA extracted from yeast cells.

cancer cell lines. The structural basis for the affinity and selectivity of these purine derivatives was determined by analysis of the three-dimensional crystal structure of their complex with CDK2, providing a basis for further enhancing the affinity and selectivity of the compounds. The cellular effects of this class of compounds were further examined and compared to those of the CDK2 inhibitor flavopiridol, as well as to those arising from mutations in *cdc28* itself, by monitoring changes in mRNA expressions levels for all genes in treated cells of *Saccharomyces cerevisiae* using high-density oligonucleotide probe arrays.^[148, 161] In particular, of the 105 transcripts that changed greater than threefold in response to both compounds (335 for the purine and 267 for flavopiridol) only seven were down regulated, all of which were associated with progression of the cell cycle. These experiments also began to delineate other common effects of these compounds on cellular metabolism, stress response, signaling, and growth, as well as reveal significant differences in the effects of flavopiridol and the purine, despite their apparent *in vitro* selectivity for CDKs. Information of this sort may, in general, be useful in comparing compounds prior to clinical studies or in identifying targets whose inhibition might potentiate the effects of a primary drug. Moreover, the use of gene expression profiles together with multiple copy overexpression libraries^[162] may allow one to rapidly identify the targets of compounds with interesting biological activities isolated from phenotypic screening of whole cells. The combined use of chemical libraries, novel *in vitro* and cellular screens,^[163–165] and genomics is likely to provide important new insights into complex cellular processes.

5. Materials Science

The most recent application of combinatorial approaches has been to solid-state and materials science. The properties of many functional materials, such as high-temperature superconductors, heterogeneous catalysts, ferroelectric materials, magnets, and even structural materials such as alloys arise from complex interactions involving the host structure, dopants, defects, and interfaces, all of which are highly

dependent on composition and processing. Unfortunately, the current level of theoretical and empirical understanding does not generally allow one to predict the structures and resulting properties of these materials.^[166] The situation is further complicated by the complex compositions of many modern materials (four or more elements) and the fact that materials synthesis, unlike organic synthesis, is generally not a kinetically controlled process. Given approximately 60 elements in the periodic table that can be used to make compositions consisting of three, four, five, or even six elements, the universe of possible new compounds with interesting physical and chemical properties remains largely uncharted. Combinatorial methods should make it possible to rapidly synthesize, process, and analyze large libraries (hundreds to hundreds of thousands of members) of inorganic and organic materials and devices. This may lead to significant increases both in the efficiency of materials discovery and optimization, and in our information base relating materials structure and properties.

5.1. Synthesis and Screening

The first application of combinatorial methods to materials science involved the synthesis of libraries of thin-film copper oxides containing high-temperature superconductors.^[167] Libraries designed to explore many different materials compositions were synthesized by sequentially sputtering precursors at different sites on a substrate using a series of precisely positioned shadow masks (Figure 20). Low-temperature annealing followed by high-temperature processing resulted in formation of superconducting thin films. More recently, quaternary and shutter masking systems, together with photolithographic masking techniques and pulsed laser deposition, have made possible the synthesis of high-quality, diverse thin-film libraries of some 1000 to 10000 samples on an area of about 6.5 cm².^[168–170] Solution-based methods have also been applied to materials library synthesis. For example, scanning fluid delivery stems (inkjets) have been used to rapidly and accurately deliver nanoliter volumes of precursor solutions to generate libraries of metal oxides and organic polymers.^[171, 171] Processing conditions play an important role in determining materials properties, and it is important to include these variables in the design of a materials library. Identical libraries synthesized simultaneously can be processed under different conditions to enhance diversity. Gradient temperature ovens have been used to identify optimal processing conditions for a library of metal oxides; similarly, it may be possible to vary oxygen partial pressure by introducing oxygen on one side of the chip.^[173]

A number of detection systems have been developed to date for screening materials libraries for optical, electronic, magnetic, or chemical properties of interest.^[173] Optical imaging systems have been used to evaluate libraries of photoluminescent materials. For example, a scanning spectrophotometer and CCD array detectors (CCD = charge-coupled device) were used to evaluate the photon output and chromaticity of each member in phosphor libraries upon excitation with monochromatic UV light.^[168, 169] A novel

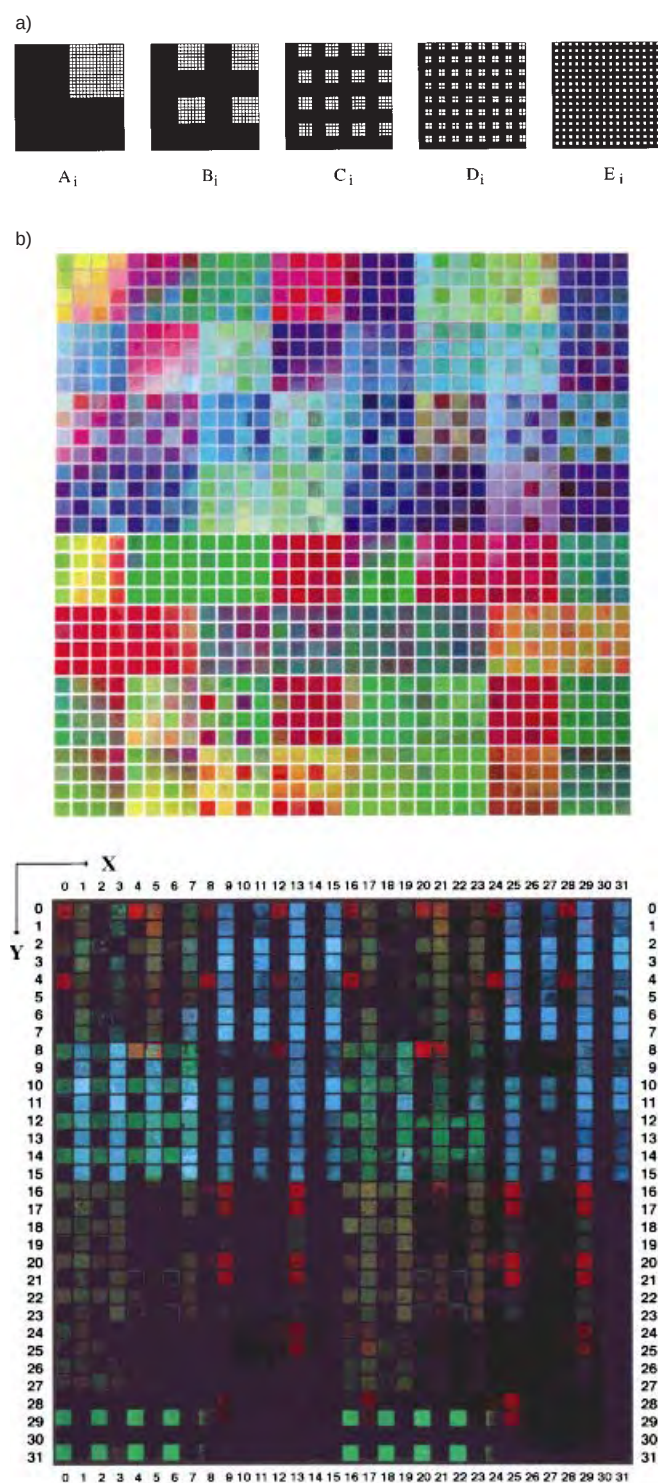


Figure 20. a) In the quaternary masking scheme, deposition is carried out using a series of n different masks which subdivide the substrate into a series of nested quadrants. Each mask is used in four sequential deposition steps with a 90° rotation of the mask in each step, generating up to 4^n compositions in $4n$ deposition steps. b) Photograph of the 1024-membered library (deposited on a Si substrate with an area of $2.54 \times 2.54 \text{ cm}^2$) under ambient light (top) and UV irradiation (bottom).

scanning-tip microwave near-field microscope (STMNM) has been developed to nondestructively measure dielectric constant and tangent loss of a library of ferroelectric materials with submicron spatial resolution and high sensitivity (Fig-

ure 21).^[170, 174] More recently, X-ray microbeam techniques with a spot size of $3 \times 20 \mu\text{m}^2$ have been used to characterize the composition and structure of samples in thin-film libraries.^[175] Infrared imaging thermography has been used to qualitatively evaluate catalyst performance in a small member library of hydrogen oxidation catalysts,^[176] and mass spec-

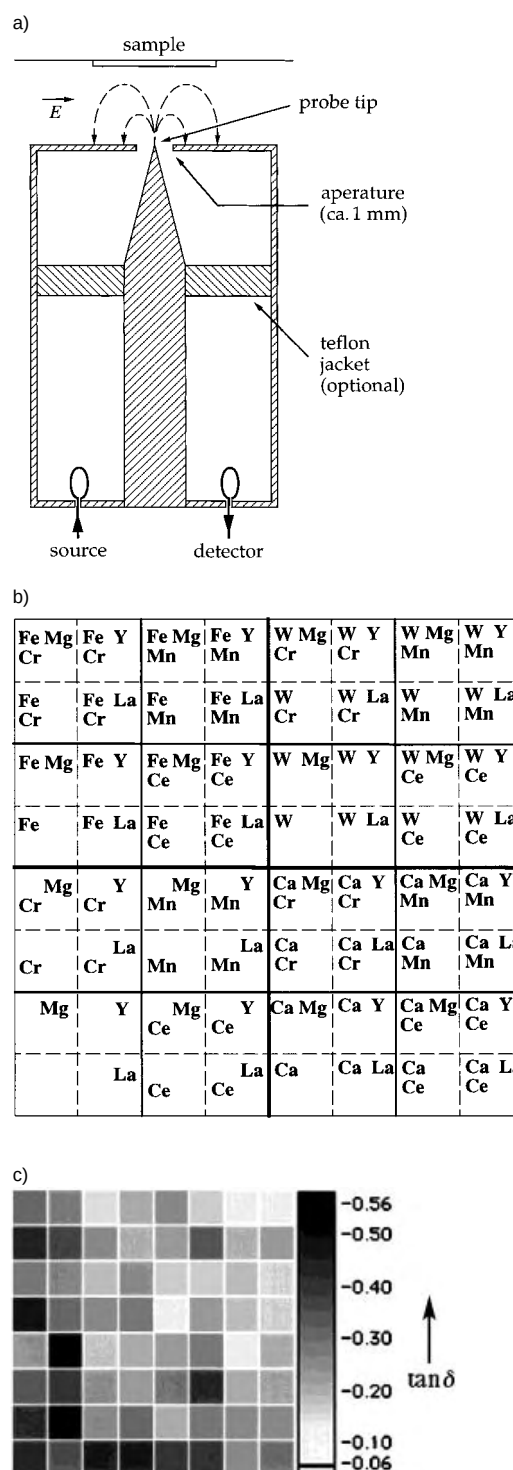


Figure 21. a) Schematic representation of a scanning tip microwave near-field microscope for analyzing ferroelectric and dielectric libraries. b) Composition of a region of a BaTiO_3 ferroelectric library with dopants indicated. c) Image of tangent loss ($\tan \delta$) from this library obtained with the near-field scanning microwave microscope.^[174]

trometry has been used to rapidly screen a library of oxidation catalysts with high sensitivity.^[177] Magneto-optical detectors are being developed to image libraries of magnetic materials, and many other detector systems can be envisaged to measure a range of material properties (IR and Raman spectroscopy, surface plasma resonance, nanoindentation, light scattering, and polarized light microscopy).

5.2. Applications

Although there remains a great deal of work to be done in developing methods for the combinatorial synthesis, processing, and detection of materials libraries, a number of applications of this approach has already been reported. Combinatorial approaches have been used to identify a class of cobalt oxide magnetoresistive materials of the form $(\text{La}_{0.88}\text{S}_{0.12})\text{CoO}_3$.^[178] Magnetoresistance was found to increase as the size of the dopant ion increased, in contrast to Mn-containing compounds, in which the magnetoresistive effect increases as the size of the alkaline earth ion decreases. Combinatorial methods have also been applied to the optimization and identification of luminescent materials. Recently, two novel blue phosphorescent compounds, SrCeO_4 ^[179] and $\text{Gd}_3\text{Ga}_5\text{O}_{12}/\text{SiO}_x$,^[168] were discovered in combinatorial libraries. Similar approaches have also been applied to ferroelectric materials where the effects of transition metal dopants on the dielectric constant and tangent loss of a library of thin films of $(\text{Ba}_x\text{Sr}_{1-x})\text{TiO}_3$ were determined.^[170] Combinatorial methods are likely to have a significant impact on catalysis and polymer chemistry, and the first attempts to apply combinatorial methods in this area have already surfaced.^[173–176, 180–182] It may also be possible to generate combinatorial libraries of entire devices such as capacitors or electroluminescent displays.^[183]

6. Conclusion

The development of strategies for generating large diverse libraries of biomolecules, small organic molecules, and solid-state materials, together with novel screens and selections for specific biological, chemical, or physical properties, is having an enormous impact on science. These approaches are significantly increasing the rate and efficiency with which the scientific method can be used both to identify molecules with novel properties and to understand the structural basis for their function. Clearly, many challenges lie ahead including 1) improved theoretical and computational methods for designing libraries and analyzing the output of library experiments; 2) the development of methods for increasing library size (especially for polypeptides, proteins, and synthetic molecules); 3) high-throughput screens for a broader range of biological (cellular), chemical, and physical properties; 4) extension of biological selections and amplification to synthetic diversity; and 5) further engineering improvements in miniaturization and robotics. Nonetheless, molecular

diversity has already been exploited to produce a large number of molecules with functions that would have been difficult and, in many cases, impossible to realize using more traditional synthetic approaches.

A portion of this work was supported by the Department of Energy, the National Institutes of Health, and the Office of Naval Research. D.R.L. would like to acknowledge a predoctoral fellowship from the Howard Hughes Medical Institute. P.G.S. is a Howard Hughes Medical Institute Investigator and W. M. Keck Foundation Investigator.

Received: February 18, 1998

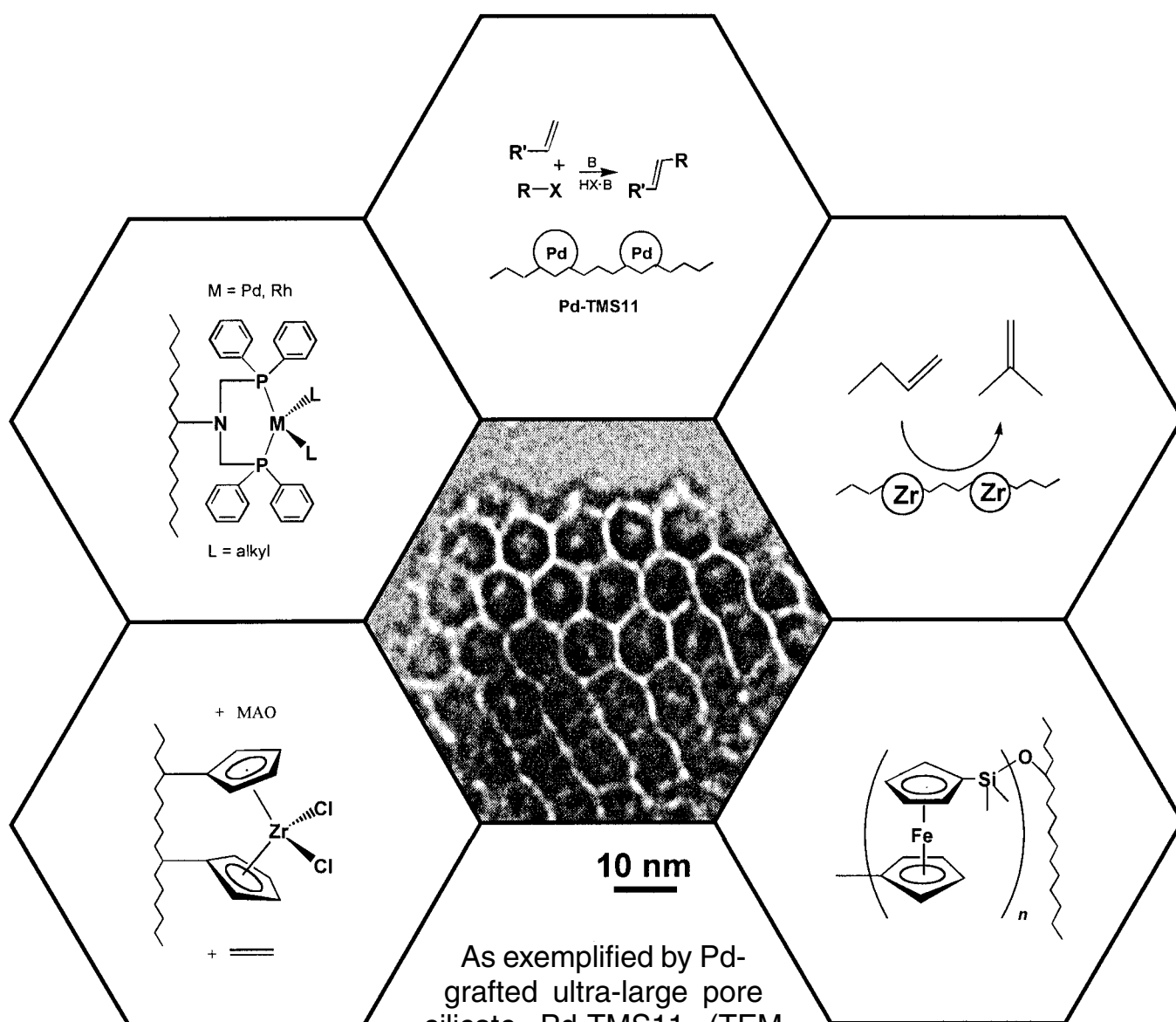
Revised version: July 15, 1998 [A274IE]

German version: *Angew. Chem.* **1999**, *111*, 36–56

- [1] F. M. Burnet, *The Clonal Selection Theory of Acquired Immunity*, Vanderbilt University Press, Nashville, TN, **1959**, p. 53.
- [2] D. W. Talmage, *Science* **1959**, *129*, 1649.
- [3] S. Tonegawa, *Nature* **1983**, *302*, 57.
- [4] D. R. Davies, S. Chacto, *Acc. Chem. Res.* **1993**, *26*, 421.
- [5] S. J. Pollack, J. W. Jacobs, P. G. Schultz, *Science* **1986**, *234*, 1570.
- [6] A. Tramontano, K. D. Janda, R. A. Lerner, *Science* **1986**, *234*, 1566.
- [7] P. G. Schultz, R. A. Lerner, *Science* **1995**, *269*, 1835.
- [8] A. G. Cochran, P. G. Schultz, *Science* **1990**, *249*, 781.
- [9] M. E. Blackwood, Jr., T. S. Rush III, F. Romesberg, P. G. Schultz, T. G. Spiro, *Biochemistry* **1998**, *37*, 779.
- [10] F. E. Romesberg, B. D. Santarsiero, B. Spiller, J. Yin, D. Barnes, P. G. Schultz, R. C. Stevens, *Biochemistry* **1998**, *37*, 14404.
- [11] J. R. Jacobsen, J. R. Prudent, L. Kockersperger, S. Yonkovich, P. G. Schultz, *Science* **1992**, *256*, 365.
- [12] E. Driggers, P. G. Schultz, unpublished results.
- [13] P. G. Schultz, R. A. Lerner, *Acc. Chem. Res.* **1993**, *26*, 391–395.
- [14] C. F. Barbas III, A. Heine, G. Zhong, T. Hoffmann, S. Gramatikova, R. Bjornestedt, B. List, J. Anderson, E. A. Stura, I. A. Wilson, *Science* **1997**, *278*, 2085–2092.
- [15] G. F. Zhong, T. Hoffmann, R. A. Lerner, S. Danishefsky, C. F. Barbas III, *J. Am. Chem. Soc.* **1997**, *119*, 8131–8132.
- [16] H. D. Ulrich, E. Mundorff, B. D. Santarsiero, E. M. Driggers, R. C. Stevens, P. G. Schultz, *Nature* **1997**, *389*, 271–275.
- [17] F. E. Romesberg, B. Spiller, P. G. Schultz, R. C. Stevens, *Science* **1998**, *279*, 1929–1933.
- [18] A. Heine, E. A. Stura, J. T. Yli-Kauhaluoma, C. Gao, Q. Deng, B. R. Beno, K. N. Houk, K. D. Janda, I. A. Wilson, *Science* **1998**, *279*, 1934.
- [19] G. J. Wedemayer, P. A. Patten, L. H. Wang, P. G. Schultz, R. C. Stevens, *Science* **1997**, *276*, 1613–1756.
- [20] P. A. Patten, N. S. Gray, P. L. Yang, C. B. Marks, G. J. Wedemayer, J. J. Boniface, R. C. Stevens, P. G. Schultz, *Science* **1996**, *271*, 1086.
- [21] G. J. Wedemayer, L. H. Wang, P. A. Patten, P. G. Schultz, R. C. Stevens, *J. Mol. Biol.* **1997**, *268*, 390.
- [22] W. D. Huse, L. Sastry, S. A. Iverson, A. S. Kang, M. Alting-Mees, D. R. Burton, S. J. Benkovic, R. A. Lerner, *Science* **1989**, *246*, 1275–1281.
- [23] S. Cwirla, E. A. Peters, R. W. Barrett, W. J. Dower, *Proc. Natl. Acad. Sci. USA* **1990**, *87*, 6378–6382.
- [24] M. A. Gallop, R. W. Barrett, W. J. Dower, S. P. A. Fodor, E. M. Gordon, *J. Med. Chem.* **1994**, *37*, 1233–1251.
- [25] J. K. Scott, C. P. Smith, *Science* **1990**, *249*, 386–390.
- [26] J. J. Delvin, L. C. Panganiban, P. E. Delvin, *Science* **1990**, *249*, 404–406.
- [27] M. G. Cull, J. F. Miller, P. J. Schatz, *Proc. Natl. Acad. Sci. USA* **1992**, *89*, 1865–1869.
- [28] L. C. Mattheakis, R. Bhatt, W. J. Dower, *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 9022.
- [29] R. W. Roberts, J. W. Szostak, *Proc. Natl. Acad. Sci. USA* **1997**, *94*, 12297–12302.
- [30] A. S. Kang, C. F. Barbas, K. D. Janda, S. J. Benkovic, R. A. Lerner, *Proc. Natl. Acad. Sci. USA* **1991**, *88*, 4363–4366.
- [31] J. McCafferty, A. D. Griffiths, G. Winter, D. J. Chiswell, *Nature* **1990**, *348*, 552–554.

- [32] K. D. Janda, C. H. Lo, T. Li, C. F. Barbas III, P. Wirsching, R. A. Lerner, *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 2532.
- [33] K. D. Janda, L.-C. Lo, C.-H. Lo, M.-M. Sim, R. Wang, C.-H. Wong, R. A. Lerner, *Science* **1997**, *275*, 945–948.
- [34] J. Ku, P. G. Schultz, *Proc. Natl. Acad. Sci. USA* **1995**, *92*, 6552.
- [35] H. Pedersen, S. Holder, D. S. Sutherlin, U. Schwitter, D. S. King, P. G. Schultz, *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 10523.
- [36] N. C. Wrighton, F. X. Farrell, R. Chang, A. K. Kashyap, F. P. Barbone, L. S. Mulcahy, D. L. Johnson, R. W. Barrett, L. K. Jolliffe, W. J. Dower, *Science* **1996**, *273*, 458–463.
- [37] O. Livnah, E. A. Stura, D. L. Johnson, S. A. Middleton, L. S. Mulcahy, N. C. Wrighton, W. J. Dower, L. K. Jolliffe, I. A. Wilson, *Science* **1996**, *273*, 464.
- [38] D. J. Matthews, J. A. Wells, *Science* **1993**, *260*, 1113–1117.
- [39] M. A. Barry, W. J. Dower, S. A. Johnston, *Nat. Med.* **1996**, *2*, 299–305.
- [40] M. Barinaga, *Science* **1998**, *279*, 323–324.
- [41] B. G. Hall, *Biochemistry* **1981**, *20*, 4042–4049.
- [42] M. S. Neuberger, B. S. Hartley, *J. Gen. Microbiol.* **1981**, *122*, 181–191.
- [43] A. Paterson, P. H. Clarke, *J. Gen. Microbiol.* **1979**, *114*, 75–85.
- [44] J. Reidhaar-Olson, J. Bowie, R. M. Breyer, J. C. Hu, K. L. Knight, W. A. Lim, M. C. Mossing, D. A. Parsell, K. R. Shoemaker, R. T. Sauer, *Methods Enzymol.* **1991**, *208*, 564–586.
- [45] J. A. Wells, M. Vasser, D. B. Powers, *Gene* **1985**, *34*, 315.
- [46] R. C. Caldwell, G. F. Joyce, *PCR Methods Appl.* **1992**, *2*, 28–33.
- [47] W. P. C. Stemmer, *Nature* **1994**, *370*, 389–391.
- [48] P. A. Patten, R. J. Howard, W. P. C. Stemmer, *Curr. Opin. Biol.* **1997**, *8*, 724–733.
- [49] C. Ho, M. Jasin, P. Schimmel, *Science* **1985**, *229*, 389.
- [50] A. R. Oliphant, K. Struhl, *Proc. Natl. Acad. Sci. USA* **1989**, *86*, 9094.
- [51] H. Liao, T. McKensie, R. Hageman, *Proc. Natl. Acad. Sci. USA* **1986**, *83*, 576.
- [52] J. F. Reidhaar-Olson, R. T. Sauer, *Science* **1988**, *241*, 53.
- [53] J. C. Moore, F. H. Arnold, *Nat. Biotechnol.* **1996**, *14*, 458.
- [54] K. W. Munir, D. C. French, L. A. Loeb, *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 4012.
- [55] D. R. Liu, T. J. Magliery, M. Pasternak, P. G. Schultz, *Proc. Natl. Acad. Sci. USA* **1997**, *94*, 10092–10097.
- [56] D. R. Liu, M. Pasternak, P. G. Schultz, unpublished results.
- [57] S. Bass, R. Green, J. A. Wells, *Proteins: Struct. Funct. Genet.* **1990**, *8*, 309–314.
- [58] Y. Choo, A. Klug, *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 1163–1167.
- [59] E. J. Rebar, C. O. Pabo, *Science* **1994**, *263*, 671–673.
- [60] A. C. Jamieson, S.-H. Kim, J. A. Wells, *Biochemistry* **1994**, *33*, 5689–5695.
- [61] Y. Choo, I. Sánchez-García, A. Klug, *Nature* **1994**, *372*, 642–645.
- [62] L. Huang, T. Sera, P. G. Schultz, *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 3969–3973.
- [63] T. Sera, P. G. Schultz, *Proc. Natl. Acad. Sci. USA* **1996**, *93*, 2920–2925.
- [64] W. A. Lim, R. T. Sauer, *Nature* **1989**, *339*, 31–36.
- [65] S. Kamtekar, J. M. Schiffer, H. Xiong, J. M. Babik, M. H. Hecht, *Science* **1993**, *262*, 1680–1685.
- [66] A. R. Davidson, R. T. Sauer, *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 2146–2150.
- [67] B. I. Dahiyat, S. L. Mayo, *Science* **1997**, *278*, 82–87.
- [68] A. D. Ellington, J. W. Szostak, *Nature* **1990**, *346*, 818–822.
- [69] C. Tuerk, L. Gold, *Science* **1990**, *249*, 505–510.
- [70] D. L. Robertson, G. F. Joyce, *Nature* **1990**, *344*, 467.
- [71] A. A. Beaudry, G. F. Joyce, *Science* **1992**, *257*, 635.
- [72] C. Tuerk, S. MacDougall, L. Gold, *Proc. Natl. Acad. Sci. USA* **1992**, *89*, 6988.
- [73] D. P. Bartel, M. L. Zapp, M. R. Green, J. Szostak, *Cell* **1991**, *67*, 529.
- [74] M. Sassanfar, J. W. Szostak, *Nature* **1993**, *364*, 550–553.
- [75] M. Famulok, J. W. Szostak, *J. Am. Chem. Soc.* **1992**, *114*, 3990.
- [76] G. J. Connell, M. Illangsekare, M. Yarus, *Biochemistry* **1993**, *32*, 5497.
- [77] L. Bock, L. Griffin, J. Latham, E. Vermaas, J. Toole, *Nature* **1992**, *355*, 564–566.
- [78] A. D. Ellington, J. W. Szostak, *Nature* **1992**, *355*, 850.
- [79] F. Jiang, R. A. Kumar, R. A. Jones, D. J. Patel, *Nature* **1996**, *382*, 183–186.
- [80] C. R. Woese, S. Winker, R. R. Gutell, *Proc. Natl. Acad. Sci. USA* **1990**, *87*, 8467–8471.
- [81] R. D. Jenison, S. C. Gill, A. Pardi, B. Polisky, *Science* **1994**, *263*, 1425–1429.
- [82] D. Pei, H. D. Ulrich, P. G. Schultz, *Science* **1991**, *253*, 1408–1411.
- [83] I. Haruna, S. Spiegelman, *Science* **1965**, *150*, 886.
- [84] R. Green, *Science* **1992**, *258*, 1910–1915.
- [85] N. Lehman, G. F. Joyce, *Nature* **1993**, *361*, 182–185.
- [86] D. P. Bartel, J. W. Szostak, *Science* **1993**, *261*, 1411–1418.
- [87] E. H. Ekland, J. W. Szostak, D. P. Bartel, *Science* **1995**, *269*, 364–370.
- [88] E. H. Ekland, D. P. Bartel, *Nature* **1996**, *382*, 373–376.
- [89] J. R. Prudent, T. Uno, P. G. Schultz, *Science* **1994**, *264*, 1924–1927.
- [90] M. M. Conn, J. R. Prudent, P. G. Schultz, *J. Am. Chem. Soc.* **1996**, *118*, 7012–7013.
- [91] Y. Li, D. Sen, *Nat. Struct. Biol.* **1996**, *3*, 743–747.
- [92] T. M. Tarasow, S. L. Tarasow, B. E. Eaton, *Nature* **1997**, *389*, 54–57.
- [93] M. A. Barry, W. C. Lai, S. A. Johnston, *Nature* **1995**, *377*, 632–635.
- [94] C. Grimm, E. Lund, J. E. Dahlberg, *EMBO J.* **1997**, *16*, 793–806.
- [95] R. B. Merrifield, *J. Am. Chem. Soc.* **1963**, *85*, 2149–2154.
- [96] H. M. Geysen, R. H. Meloen, S. J. Barteling, *Proc. Natl. Acad. Sci. USA* **1984**, *81*, 3998–4002.
- [97] R. A. Houghten, *Proc. Natl. Acad. Sci. USA* **1985**, *82*, 5131–5135.
- [98] H. M. Geysen, S. J. Rodda, T. J. Mason, G. Tribbick, P. G. Schoofs, *J. Immunol. Methods* **1987**, *102*, 259–274.
- [99] H. M. Geysen, S. J. Rodda, T. J. Mason, *Mol. Immunol.* **1986**, *23*, 709–715.
- [100] S. P. A. Fodor, J. L. Read, M. C. Pirrung, L. Stryer, A. T. Lu, D. Solas, *Science* **1991**, *251*, 767.
- [101] J. W. Jacobs, S. P. A. Fodor, *Trends Biotechnol.* **1994**, *12*, 19–26.
- [102] A. Furka, F. Sebestyen, M. Asgedom, G. Dibo, *Int. J. Pept. Protein Res.* **1991**, *37*, 487–493.
- [103] K. S. Lam, S. E. Salmon, E. M. Hersh, V. J. Hruby, W. M. Kazmierski, R. J. Knapp, *Nature* **1991**, *354*, 82–84.
- [104] R. A. Houghten, C. Pinilla, S. E. Blondelle, J. R. Appel, C. T. Dooley, J. H. Cuervo, *Nature* **1991**, *354*, 84–86.
- [105] C. Pinilla, J. R. Appel, P. Blanc, R. A. Houghten, *Biotechniques* **1992**, *13*, 901–905.
- [106] K. S. Lam, V. J. Hruby, M. Lebl, R. J. Knapp, W. M. Kazmierski, E. M. Hersh, S. E. Salmon, *Bioorg. Med. Chem. Lett.* **1993**, *3*, 419–424.
- [107] G. P. Smith, D. A. Schultz, J. E. Ladbury, *Gene* **1993**, *128*, 37–42.
- [108] S. Brenner, R. A. Lerner, *Proc. Natl. Acad. Sci. USA* **1992**, *89*, 5181–5183.
- [109] M. N. Needels, D. G. Jones, E. H. Tate, G. L. Heinkel, L. M. Kochersperger, W. J. Dower, R. W. Barrett, M. A. Gallop, *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 10700–10704.
- [110] V. Nikolaiev, A. Stierandova, V. Krchnak, B. Sekigmann, K. S. Lam, S. E. Salmon, M. Lebl, *Pept. Res.* **1993**, *6*, 161–170.
- [111] M. H. J. Ohlmeyer, R. N. Swanson, L. W. Dillard, J. C. Reader, G. Asouline, R. Kobayashi, M. Wigler, W. C. Still, *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 10922–10926.
- [112] R. A. Houghten, J. R. Appel, S. E. Blondelle, J. H. Cuervo, C. T. Dooley, C. Pinilla, *Biotechniques* **1992**, *13*, 412–421.
- [113] M. Torneiro, W. C. Still, *J. Am. Chem. Soc.* **1995**, *117*, 5887–5888.
- [114] S. S. Yoon, W. C. Still, *Tetrahedron* **1995**, *51*, 567–578.
- [115] A. Borchardt, W. C. Still, *J. Am. Chem. Soc.* **1994**, *116*, 373–374.
- [116] J. K. Chen, S. L. Schreiber, *Angew. Chem.* **1995**, *107*, 1041; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 953–969.
- [117] C. Y. Cho, E. J. Moran, S. R. Cherry, J. C. Stephans, S. P. A. Fodor, C. L. Adams, A. Sundaram, J. W. Jacobs, P. G. Schultz, *Science* **1993**, *261*, 1303–1305.
- [118] R. J. Simon, R. S. Kania, R. N. Zuckermann, V. D. Huebner, D. A. Jewell, S. Banville, S. Ng, L. Wang, S. Rosenberg, C. K. Marlowe, *Proc. Natl. Acad. Sci. USA* **1992**, *89*, 9367–9371.
- [119] R. N. Zuckermann, E. J. Martin, D. C. Spellmeyer, G. B. Stauber, K. R. Shoemaker, J. M. Kerr, G. M. Figliozzi, D. A. Goff, M. A. Siana, R. J. Simon, *J. Med. Chem.* **1994**, *37*, 2678–2685.
- [120] J. S. Nowick, N. A. Powell, E. J. Martinez, E. M. Smith, G. Noronha, *J. Org. Chem.* **1992**, *57*, 3763–3765.
- [121] K. Burgess, J. Ibarzo, D. S. Linthicum, D. H. Russell, H. Shin, A. Shitangkoon, R. Totani, A. J. Zhang, *J. Am. Chem. Soc.* **1997**, *119*, 1556–1564.
- [122] J.-M. Kim, T. E. Wilson, T. C. Norman, P. G. Schultz, *Tetrahedron Lett.* **1996**, *37*, 5305–5308.

- [123] A. B. Smith, T. P. Keenan, R. C. Holcomb, P. A. Sprengeler, M. C. Guzman, J. L. Wood, P. J. Carroll, R. Hirschmann, *J. Am. Chem. Soc.* **1992**, *114*, 10672–10674.
- [124] H. Han, K. D. Janda, *J. Am. Chem. Soc.* **1996**, *118*, 2539–2544.
- [125] C. Gennari, B. Salom, D. Potenza, A. Williams, *Angew. Chem.* **1994**, *106*, 2181; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2067–2069.
- [126] M. Hagihara, N. J. Anthony, T. J. Stout, J. Clardy, S. L. Schreiber, *J. Am. Chem. Soc.* **1992**, *114*, 6568–6570.
- [127] D. H. Appella, L. A. Christianson, D. A. Klein, D. R. Powell, X. Huang, J. J. Barchi, S. H. Gellman, *Nature* **1997**, *387*, 381–384.
- [128] J. L. Matthews, M. Overhand, F. N. M. Kühnle, P. E. Ciceri, D. Seebach, *Liebigs Ann.* **1997**, 1371–1379.
- [129] C. Y. Cho, R. S. Youngquist, S. J. Paikoff, M. H. Beresini, A. R. Hebert, C. W. Liu, D. E. Wemmer, T. Keough, P. G. Schultz, *J. Am. Chem. Soc.* **1998**, in press.
- [130] B. A. Bunin, J. A. Ellman, *J. Am. Chem. Soc.* **1992**, *114*, 10997–10998.
- [131] B. A. Bunin, M. J. Plunkett, J. A. Ellman, *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 4708–4712.
- [132] A. A. Virgilio, A. A. Bray, W. Zhang, L. Trinh, M. Snyder, M. M. Morrissey, J. A. Ellman, *Tetrahedron* **1997**, *53*, 6635–6644.
- [133] S. H. De Witt, J. S. Kiely, C. J. Stankovic, M. C. Schroeder, D. M. Cody, M. R. Pavia, *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 6909–6913.
- [134] D. A. Campbell, J. C. Bermak, T. S. Burkoth, D. V. Patel, *J. Am. Chem. Soc.* **1995**, *117*, 5381–5382.
- [135] M. M. Murphy, J. R. Schullek, E. M. Gordon, M. A. Gallop, *J. Am. Chem. Soc.* **1995**, *117*, 7029–7030.
- [136] B. Ruhland, A. Bhandari, E. M. Gordon, M. A. Gallop, *J. Am. Chem. Soc.* **1996**, *118*, 253–254.
- [137] J. Green, *J. Org. Chem.* **1995**, *60*, 4287–4290.
- [138] R. Liang, L. Yan, J. Loebach, M. Ge, Y. Uozumi, K. Sekanina, N. Horan, J. Gildersleeve, C. Thompson, A. Smith, *Science* **1996**, *274*, 1520–1522.
- [139] P. H. H. Hermkens, H. C. J. Ottenheijm, D. Rees, *Tetrahedron* **1996**, *52*, 4527–4554.
- [140] P. H. H. Hermkens, H. C. J. Ottenheijm, D. Rees, *Tetrahedron* **1997**, *53*, 5643–5678.
- [141] E. K. Kick, D. C. Roe, A. G. Skillman, G. Liu, T. J. A. Ewing, Y. Sun, I. D. Kuntz, J. A. Ellman, *Chem. Biol.* **1997**, *4*, 297–307.
- [142] C. Khosla, *Chem. Rev.* **1997**, *97*, 2577–2590.
- [143] J. Cortes, S. F. Haydock, G. A. Roberts, D. J. Bevirt, P. F. Leadlay, *Nature* **1990**, *348*, 176–178.
- [144] S. Donadio, M. J. Staver, J. B. McAlpine, S. J. Swanson, L. Katz, *Science* **1991**, *252*, 675–679.
- [145] J. R. Jacobsen, C. R. Hutchinson, D. E. Cane, C. Khosla, *Science* **1997**, *277*, 367–369.
- [146] A. C. Pease, D. Solas, E. J. Sullivan, M. T. Cronin, C. P. Holmes, S. P. A. Fodor, *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 5022–5026.
- [147] M. S. Chee, X. Huang, R. Yang, E. Hubbell, A. Berno, D. Stern, J. Winkler, D. J. Lockhart, M. S. Morris, S. P. A. Fodor, *Science* **1996**, *274*, 610–614.
- [148] L. Wodicka, H. Dong, M. Mittman, M.-H. Ho, D. J. Lockhart, *Nat. Biotechnol.* **1997**, *15*, 1359–1367.
- [149] M. D. Adams, J. M. Kelley, J. D. Gocayne, M. Dubnick, M. H. Polymeropoulos, H. Xiao, C. R. Merrill, A. Wu, B. Olde, R. F. Moreno, A. R. Kerlavage, W. R. McCombie, J. C. Venter, *Science* **1991**, *252*, 1651–1656.
- [150] G. G. Lennon, H. Lehrach, *Trends Genet.* **1991**, *7*, 314–317.
- [151] P. Liang, A. B. Pardee, *Science* **1992**, *257*, 967–971.
- [152] K. Okubo, N. Hori, R. Matoba, T. Niiyama, A. Fukushima, Y. Kojima, K. Matsubara, *Nat. Genet.* **1992**, *2*, 173–179.
- [153] S. Meier-Ewert, E. Maier, A. Ahmadi, J. Curtis, H. Lehrach, *Nature* **1993**, *361*, 375–376.
- [154] V. E. Velculescu, L. Zhang, B. Vogelstein, K. W. Kinzler, *Science* **1995**, *270*, 484–487.
- [155] N. Zhao, H. Hashida, N. Takahashi, Y. Misumi, Y. Sakaki, *Gene* **1995**, *156*, 207–213.
- [156] C. Nguyen, D. Rocha, S. Granjeaud, M. Baldit, K. Bernard, P. Naquet, B. R. Jordan, *Genomics* **1995**, *29*, 207–216.
- [157] M. Schena, D. Shalon, R. W. Davis, P. O. Brown, *Science* **1995**, *270*, 467–470.
- [158] N. S. Gray, L. Wodicka, A.-M. Thunnissen, T. C. Norman, S. Kwon, F. H. Espinoza, D. O. Morgan, G. Barnes, S. LeClerc, L. Meijer, S.-H. Kim, D. J. Lockhart, P. G. Schultz, *Science* **1998**, *281*, 533–538.
- [159] N. S. Gray, S. Kwon, P. G. Schultz, *Tetrahedron Lett.* **1997**, *38*, 1161–1164.
- [160] T. C. Norman, N. S. Gray, J. T. Koh, *J. Am. Chem. Soc.* **1996**, *118*, 7430–7431.
- [161] J. L. DeRisi, V. R. Iyer, P. O. Brown, *Science* **1997**, *278*, 680–686.
- [162] D. Hirata, K. Yano, T. Miyakawa, *Mol. Gen. Genet.* **1994**, *242*, 250.
- [163] G. Zlokarnik, P. A. Negulescu, T. E. Knapp, L. Mere, N. Burres, L. Feng, M. Whitney, K. Roemer, R. Y. Tsien, *Science* **1998**, *279*, 84–88.
- [164] S. D. Liberles, S. T. Diver, D. J. Austin, S. L. Schreiber, *Proc. Natl. Acad. Sci. USA* **1997**, *94*, 7825–7830.
- [165] E. J. Licitra, J. O. Liu, *Proc. Natl. Acad. Sci. USA* **1996**, *93*, 12817–12821.
- [166] F. J. DiSalvo, *Science* **1990**, *247*, 649.
- [167] X.-D. Xiang, X. Sun, G. Briceño, Y. Lou, K.-A. Wang, H. Chang, W. G. Wallace-Freedman, S.-W. Chen, P. G. Schultz, *Science* **1995**, *268*, 1738–1740.
- [168] J. X. Wang, *Science* **1998**, in press.
- [169] E. Danielson, J. H. Golden, E. W. McFarland, C. M. Reaves, W. H. Weinberg, X. D. Wu, *Nature* **1997**, *389*, 944.
- [170] H. Chang, C. Gao, I. Takeuchi, Y. Yoo, J. Wang, P. G. Schultz, X.-D. Xiang, *Appl. Phys. Lett.*, submitted.
- [171] X. Sun, K.-A. Wang, Y. Yoo, W. G. Wallace-Freedman, C. Gao, X.-D. Xiang, P. G. Schultz, *Adv. Mater.* **1998**, *9*, 1046.
- [172] R. Nielsen, personal communication, **1997**.
- [173] P. G. Schultz, X.-D. Xiang, *Curr. Opin. Solid State Mater. Sci.* **1998**, in press.
- [174] Y. Lu, T. Wei, F. Duewer, Y. Lu, N. B. Min, P. G. Schultz, X.-D. Xiang, *Science* **1997**, *276*, 2004.
- [175] E. D. Isaacs, M. Kao, G. Aeppli, X.-D. Xiang, X. Sun, P. G. Schultz, M. A. Marcus, G. S. I. Cargill, R. Haushalter, *Appl. Phys. Lett.*, in press.
- [176] F. C. Moates, M. Somani, J. Annamalai, J. T. Richardson, *Ind. Eng. Chem. Res.* **1996**, *35*, 4801.
- [177] H. Weinberg, personal communication, **1998**.
- [178] G. Briceño, H. Chang, P. G. Schultz, X.-D. Xiang, *Science* **1995**, *270*, 273–275.
- [179] H. Weinberg, *Science* **1998**, in press.
- [180] C. L. Hill, R. D. Gall, *J. Mol. Catal. A* **1996**, *114*, 103.
- [181] S. Brocchini, K. James, V. Tangpasuthadol, J. Kohn, *J. Am. Chem. Soc.* **1997**, *119*, 4553.
- [182] T. A. Dickinson, D. R. Walt, J. While, J. S. Kauer, *Anal. Chem.* **1997**, *69*, 3413.
- [183] I. Takeuchi, H. Weinberg, unpublished results.



As exemplified by Pd-grafted ultra-large pore silicate Pd-TMS11 (TEM image presented above), supramolecular-templated mesoporous materials find many uses, for example (starting at the left and going clockwise) in polymerization, for immobilization of well-defined homogeneous catalysts, in Heck catalysis, in acid catalysis, and as an encapsulation host for ferrocenyl units.

Synthesis and Applications of Supramolecular-Templated Mesoporous Materials**

Jackie Y. Ying,* Christian P. Mehnert, and Michael S. Wong

Research in supramolecular-templated mesoporous materials began in the early 1990s with the announcement of MCM-41 and the M41S family of molecular sieves. These materials are highly unusual in their textural characteristics: uniform pore sizes greater than 20 Å, surface areas in excess of 1000 m² g⁻¹, and long-range ordering of the packing of pores. The mesoporous materials are derived with supramolecular assemblies of surfactants, which template the inorganic components

during synthesis. Many researchers have since exploited this technique of supramolecular templating to produce materials with different compositions, new pore systems, and novel properties. This article reviews the current state of the art in mesoporous materials research in three general areas: synthesis, catalytic properties, and other applications that take advantage of bulk morphologies. Various mechanisms formulated to explain the formation of mesostructures are discussed

in the context of compositional control. The catalytic applications of mesoporous materials are examined, with a significant fraction based on recent patent literature. Other directions in the utilization of mesoporous materials are also presented.

Keywords: amphiphiles • heterogeneous catalysis • mesoporosity • molecular sieves • template synthesis

1. Introduction

Only six years have passed since the exciting discovery of the novel family of molecular sieves called M41S was reported by the researchers at Mobil Research and Development Corporation.^[1] These mesoporous (alumino)silicate materials, with well-defined pore sizes of 15–100 Å, break past the pore-size constraint (<15 Å) of microporous zeolites. The extremely high surface areas (>1000 m² g⁻¹) and the precise tuning of pore sizes are among the many desirable properties that have made such materials the focus of great interest. The M41S materials also ushered in a new approach in materials synthesis where, instead of the use of single molecules as templating agents (as in the case of zeolites), self-assembled molecular aggregates or supramolecular assemblies are employed as the structure-directing agents. Various aspects of M41S and related mesoporous materials have been reviewed by Brinker (recent advances in porous inorganic materials),^[2] Vartuli et al. (synthesis of the M41S family),^[3] Stucky et al. (biomimetic synthesis of mesoporous materials),^[4] Raman et al. (porous silicates templated by surfactants and organo-

silicate precursors),^[5] Antonelli and Ying (mesoporous transition metal oxide (TMS) family),^[6] Behrens (mesoporous transition metal oxides),^[7] Zhao et al. (aluminosilicate MCM-41),^[8] and Sayari (catalytic applications of MCM-41).^[9] Here we review the current state of mesoporous materials research from the standpoint of compositional control. The synthesis of not only (alumino)silicate M41S materials but also transition metal doped and pure transition metal oxide mesoporous materials is addressed. After discussion of the major synthesis routes and mechanisms of formation, the applications of these materials are surveyed, with particular emphasis on heterogeneous catalysis.

Inorganic solids that contain pores with diameters in the size range of 20–500 Å are considered mesoporous materials, according to IUPAC definition. Examples of mesoporous materials include M41S, aerogels, and pillared layered structures, as listed in Table 1.^[10] In this paper, we will focus only on “mesoporous materials” that have been prepared by supramolecular templating, such as M41S. The demarcation at 20 Å between the micropore and mesopore regimes is convenient, in that all zeolites and related zeotypes are microporous; however, some types of the supramolecular-templated structures can be microporous (see Section 2.4). Mesoporous materials derived by means of surfactant templating are occasionally called “zeolites” and described as “crystalline” materials in reference to their long-range ordering of the pore packing. Such references are not correct, as the pore walls of these materials are amorphous and lack long-range order.

[*] Prof. J. Y. Ying, Dr. C. P. Mehnert, M. S. Wong
Department of Chemical Engineering
Massachusetts Institute of Technology
Cambridge, MA 02139 (USA)
Fax: (+1) 617-258-5766
E-mail: jyying@mit.edu

[**] A list of abbreviations is provided in the Appendix.

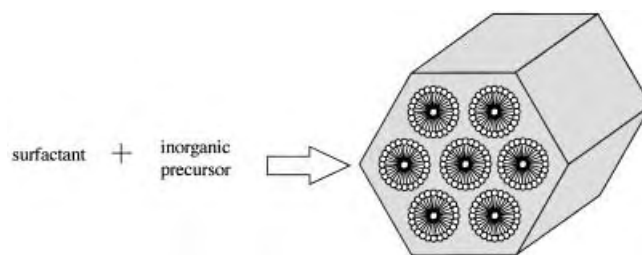
Table 1. Pore-size regimes and representative porous inorganic materials.

Pore-size regimes	Definition	Examples	Actual size range
macroporous	> 500 Å	glasses	> 500 Å
mesoporous	20–500 Å	aerogels	> 100 Å
		pillared layered clays	10 Å, 100 Å ^[a]
		M41S	16–100 Å
microporous	< 20 Å	zeolites, zeotypes	< 14.2 Å
		activated carbon	6 Å

[a] Bimodal pore-size distribution.

2. Mechanisms of Mesosstructure Formation

There have been a number of models proposed to explain the formation of mesoporous materials and to provide a rational basis for the various synthesis routes. On the most common level, these models are predicated upon the presence of surfactants in a solution to guide the formation of the inorganic mesostructure from the solubilized inorganic precursors (Scheme 1). Surfactants contain a hydrophilic head



Scheme 1. Schematic representation of the general formation of MCM-41 from inorganic precursors and organic surfactants.

group and a long hydrophobic tail group within the same molecule and will self-organize in such a way as to minimize contact between the incompatible ends. How the inorganic precursor interacts with the surfactant is the issue whereby the models diverge; the type of interaction between the surfactant and the inorganic precursor will be seen as a significant difference among the various synthesis routes, the formation models, and the resulting classes of mesoporous materials.

Jackie Y. Ying was born in Taiwan and raised in Singapore. She graduated *summa cum laude* from The Cooper Union in 1987, and completed her Ph.D. degree as an AT&T Bell Laboratories Scholar at Princeton University in 1991. She was a NSF-NATO Postdoctoral Fellow and Alexander von Humboldt Research Fellow at the University of Saarland with Prof. H. Gleiter, and she currently holds the St. Laurent Associate Professorship at the Chemical Engineering Department

of the Massachusetts Institute of Technology. Her research is focused on the synthesis of nanostructured inorganic materials for catalytic, membrane, and advanced ceramic applications. She is the author of over eighty publications, and the recipient of the American Ceramic Society Ross C. Purdy Award, David and Lucile Packard Fellowship, National Science Foundation and Office of Naval Research Young Investigator Awards, Camille Dreyfus Teacher-Scholar Award, Royal Academy of Engineering ICI Faculty Fellowship, and American Chemical Society Faculty Fellowship Award in Solid-State Chemistry. She serves on the Board of Directors of the Alexander von Humboldt Association of America as well as the editorial boards of several journals.



J. Y. Ying



C. P. Mehnert



M. S. Wong

Christian P. Mehnert studied chemistry at the Technische Universität München (1985–1992). During this time he carried out research with Dr. D. O'Hare at Oxford University (1990) and Prof. J. Lewis at Cambridge University (1991), before he completed his research thesis which focused on the synthesis of new aminocarbyne complexes of chromium with Prof. W. A. Herrmann and Prof. A. C. Filippou (1992). He then moved to England, where he became a graduate student at Oxford University with Prof. M. L. H. Green to work on the synthesis of new organometallic complexes with metal vapor synthesis techniques and the investigation of the reaction chemistry of highly Lewis acidic perfluorinated borane complexes. After receiving his doctorate (D.Phil.) as a student at Balliol College (1996), he moved to the United States and joined Prof. J. Y. Ying's laboratory at the Massachusetts Institute of Technology as a postdoctoral research associate. The area of his current research is the synthesis and application of new nanostructured materials for catalysis, with a special focus on the incorporation of organometallic catalysts into mesoporous molecular sieves.

Michael S. Wong is a Ph.D. student in Chemical Engineering at the Massachusetts Institute of Technology. He received a B.S. degree in Chemical Engineering from the California Institute of Technology (1990–1994) and a M.S. degree in Chemical Engineering Practice from the Massachusetts Institute of Technology (1997). His research interests include the synthesis and characterization of nanostructured zirconia-based material for acid catalytic applications.

2.1. Pure Silicate Composition

2.1.1. Liquid Crystal Templating Mechanism

The original M41S family of mesoporous molecular sieves was synthesized, in general, by the combination of appropriate amounts of a silica source (e.g. tetraethylorthosilicate (TEOS), Ludox, fumed silica, sodium silicate), an alkyltrimethylammonium halide surfactant (e.g. cetyltrimethylammonium bromide (CTAB)), a base (e.g. sodium hydroxide or tetramethylammonium hydroxide (TMAOH)), and water. Aluminosilicate M41S was synthesized by the addition of an aluminum source to the synthesis mixture. The mixture was aged at elevated temperatures ($\geq 100^\circ\text{C}$) for 24 to 144 hours, which resulted in a solid precipitate. The organic–inorganic mesostructured product was filtered, washed with water, and air-dried. The product was calcined at about 500°C under a flowing gas to burn off the surfactant, to yield the mesoporous material.

A “liquid crystal templating” (LCT) mechanism was proposed by the Mobil researchers, based on the similarity between liquid crystalline surfactant assemblies (i.e., lyotropic phases) and M41S.^[1] The common traits were the mesostructure dependence on the hydrocarbon chain length of the surfactant tail group,^[11] the effect of variation of the surfactant concentrations, and the influence of organic swelling agents. With MCM-41 (which has hexagonally packed cylindrical mesopores) as the representative M41S material, two mechanistic pathways were postulated by the Mobil researchers (Scheme 2):

- 1) The aluminosilicate precursor species occupied the space between a preexisting hexagonal lyotropic liquid crystal (LC) phase and deposited on the micellar rods of the LC phase.
- 2) The inorganics mediated, in some manner, the ordering of the surfactants into the hexagonal arrangement.

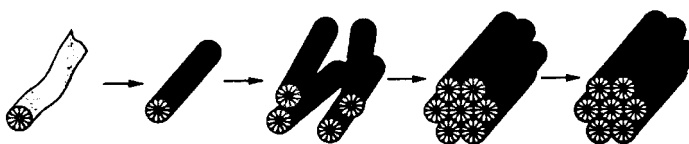
In either case, the inorganic components (which were negatively charged at the high pH values used) preferentially interacted with the positively charged ammonium head groups of the surfactants and condensed into a solid, continuous framework. The resulting organic–inorganic mesostructure could be alternatively viewed as a hexagonal array of surfactant micellar rods embedded in a silica matrix; removal of the surfactants produced the open, mesoporous MCM-41 framework. It is now known that pathway 1 did not take place because the surfactant concentrations used were

far below the critical micelle concentration (CMC) required for hexagonal LC formation.^[12] This mechanistic pathway was shown possible recently under different synthesis conditions (see Section 2.1.5).

The second mechanistic pathway of LCT was vaguely postulated as a cooperative self-assembly of the ammonium surfactant and the silicate precursor species below the CMC. It has been known that no preformed LC phase was necessary for MCM-41 formation but, to date, the actual details of MCM-41 formation have not yet been fully agreed upon. Several mechanistic models have been advanced which share the basic idea that the silicate species promoted LC phase formation below the CMC.

2.1.1.1. Silicate Rod Assembly

Davis and co-workers^[13] found that the hexagonal LC phase did not develop during MCM-41 synthesis, based on *in situ* ^{14}N NMR spectroscopy. They proposed that, under the synthesis conditions reported by Mobil, the formation of MCM-41 began with the deposition of two to three monolayers of silicate precursor onto isolated surfactant micellar rods (Scheme 3). The silicate-encapsulated rods were randomly

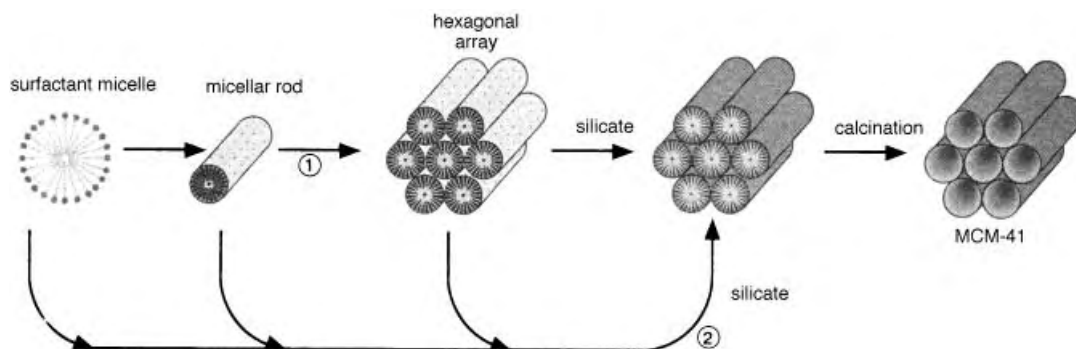


Scheme 3. Assembly of silicate-encapsulated rods (adapted from ref. [13]).

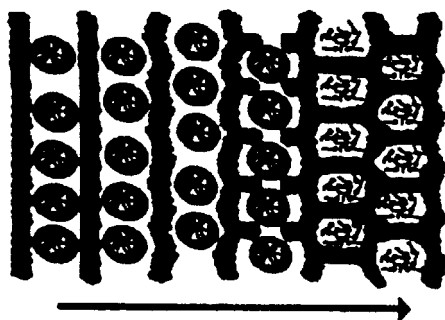
ordered, eventually packing into a hexagonal mesostructure. Heating and aging then completed the condensation of the silicates into the as-synthesized MCM-41 mesostructure.

2.1.1.2. Silicate Layer Puckering

Instead of the formation of silicate-covered micellar rods, Steel et al.^[14] postulated that surfactant molecules assembled directly into the hexagonal LC phase upon addition of the silicate species, based on ^{14}N NMR spectroscopy. The silicates were organized into layers, with rows of the cylindrical rods intercalated between the layers (Scheme 4). Aging the



Scheme 2. Two possible pathways for the LCT mechanism.^[1b]

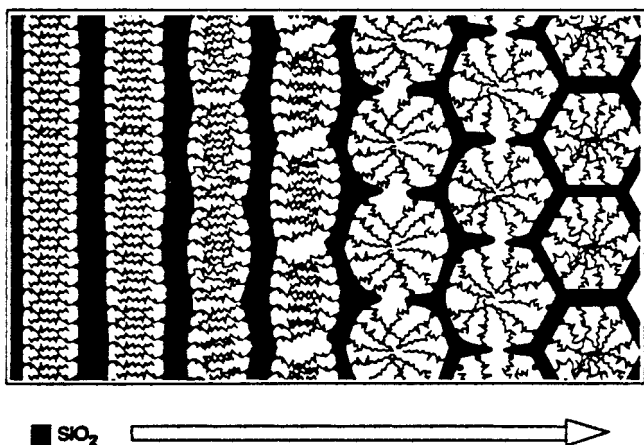


Scheme 4. Puckering of silicate layers in the direction shown (adapted from ref. [14]).

mixture caused the layers to pucker and collapse around the rods, which then transformed into the surfactant-containing MCM-41 hexagonal-phase mesostructure.

2.1.1.3. “Charge Density Matching”

A “charge density matching” mechanistic model was proposed by Monnier et al.^[15] and Stucky et al.^[16] and suggested that MCM-41 could be derived from a lamellar phase. The initial phase of the synthesis mixture was layered (as detected by X-ray diffractometry (XRD)), and was formed from the electrostatic attraction between the anionic silicates and the cationic surfactant head groups (Scheme 5).

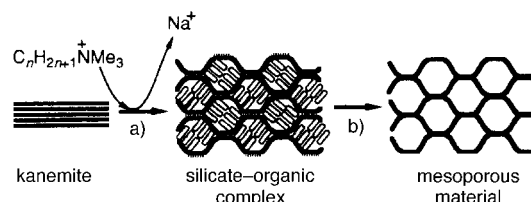


Scheme 5. Curvature induced by charge density matching.^[15] The arrow indicates the reaction coordinate.

As the silicate species began to condense, the charge density was reduced. Accompanying this process, curvature was introduced into the layers to maintain the charge density balance with the surfactant head groups, which transformed the lamellar mesostructure into the hexagonal mesostructure.

2.1.1.4. “Folding Sheets”

The lamellar-to-hexagonal phase motif also appeared in materials called FSM prepared from the intercalation of the ammonium surfactant in kanemite, a type of hydrated sodium silicate composed of single-layered silica sheets.^[17] After the surfactants were ion-exchanged into the layered structure, the silicate sheets were thought to fold around the surfactants and condense into a hexagonal mesostructure (Scheme 6). The

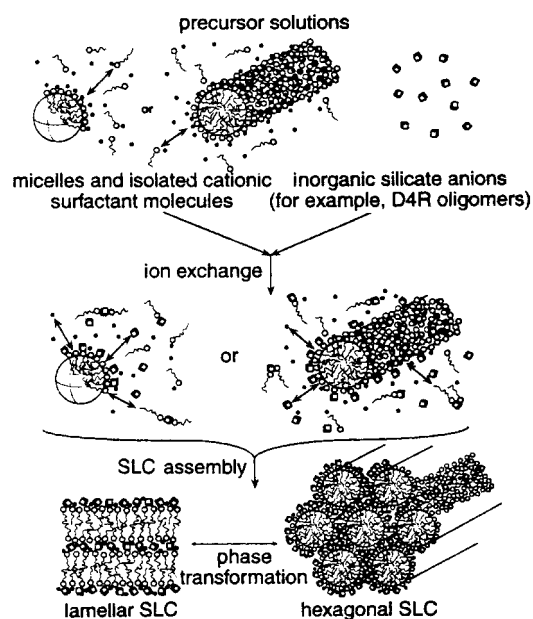


Scheme 6. Folding of silicate sheets around intercalated surfactant molecules.^[17b] a) Ion exchange, b) calcination.

final product was claimed to be very similar to MCM-41, with no resemblance to the original kanemite structure. However, Vartuli et al.^[12] found that the layered structures were still retained in the kanemite-derived mesoporous materials.

2.1.1.5. “Silicatropic Liquid Crystals”

Under synthesis conditions that prevented condensation of the silicate species, such as low temperatures and high pH (≈ 14), a true cooperative self-assembly of the silicates and surfactants was found possible. Firouzi et al.^[18] conclusively showed, through ^2H and ^{29}Si NMR spectroscopy, and neutron scattering, that a micellar solution of CTAB transformed to a hexagonal phase in the presence of silicate anions; this was consistent with the effect of electrolytes on micellar phase transitions.^[19] The silicate anions ion-exchanged with the surfactant halide counterions, to form a “silicatropic liquid crystal” (SLC) phase that involved silicate-encrusted cylindrical micelles (Scheme 7). The SLC phase exhibited behavior



Scheme 7. Formation of a silicatropic liquid crystal phase.^[18]

very similar to typical lyotropic systems, except that the surfactant concentrations were much lower and the silicate counterions were reactive.^[20] Heating the SLC phase caused the silicates to condense irreversibly into MCM-41.

Firouzi and co-workers^[18, 20] also demonstrated that in addition to the charge balance requirement (i.e., electrostatic interaction) there was preferential bonding of the ammonium

head group to multi-charged D4R (double four-ring, $[\text{Si}_8\text{O}_{20}]^{8-}$) silicate anions under the high pH conditions. The interaction was so strong that an alkyltrimethylammonium surfactant solution could force a silicate solution that did not contain D4R oligomers to re-equilibrate and form D4R species. It was suggested that this behavior came from the closely matched projected areas of a D4R anion and an ammonium head group (0.098 nm^2 vs. 0.094 nm^2) and the correct distribution of charges on the projected surfaces.

Fyfe and Fu^[21] were able to prepare mesostructured silicates with D4R silicates. Combination of the D4R precursors with cetyltrimethylammonium chloride (CTAC) surfactants produced mesostructured precipitates. Control of the condensation of the silicates within the mesostructure by acidic vapor treatment led to the observation of cubic, lamellar, and hexagonal phases as intermediate transformation phases (see Section 2.1.3).

2.1.1.6. Silicate Rod Clusters

The previous theories have regarded the formation of MCM-41 as a series of events that occur homogeneously throughout an aqueous solution. Recent work has shown that MCM-41 might be formed heterogeneously. Regev^[22] found evidence for MCM-41 intermediate structures in the form of clusters of rodlike micelles “wrapped” by a coating of silicate through low-temperature transmission electron microscopy (TEM) and small-angle X-ray scattering. The clusters of elongated micelles were found before precipitation occurred. As the reaction progressed, Regev proposed, the silicate species diffused to and deposited onto the individual surfaces of the micelles within the cluster; the clusters of elongated micelles eventually became clusters of silicate-covered micelles. Thus, the clusters of micelles served as nucleation sites for MCM-41 formation.

2.1.2. Generalized Liquid Crystal Templating Mechanism: Electrostatic Interaction

A generalized mechanism of formation based on the specific type of electrostatic interaction between a given inorganic precursor I and surfactant head group S was proposed by Huo and co-workers.^[23] Based on the nomenclature, pathway 2 of the original LCT mechanism (Scheme 2), which involved anionic silicate species and cationic quaternary ammonium surfactant, could be categorized as the S^+I^- pathway. By extension, the other charge-interaction pathways are S^-I^+ , $S^+X^-I^+$ (X^- is a counteranion), and $S^-M^+I^-$ (M^+ is a metal cation). This classification system is useful, especially when other types of inorganic–organic interactions are considered (Figure 1). The success of the cooperative templating model, referred to here as the generalized LCT mechanism (Scheme 8), was illustrated by the diverse compositions of organic–inorganic mesostructures found possible (see Section 2.3.1). As for silicate mesostructures, Huo and co-workers^[23] found them possible through the $S^+X^-I^+$ pathway. By operating below the isoelectric point of silica ($\text{pH} \approx 2$) under acidic conditions, the silicate species were cationic (I^+). The same ammonium surfactant S^+ could be used as a

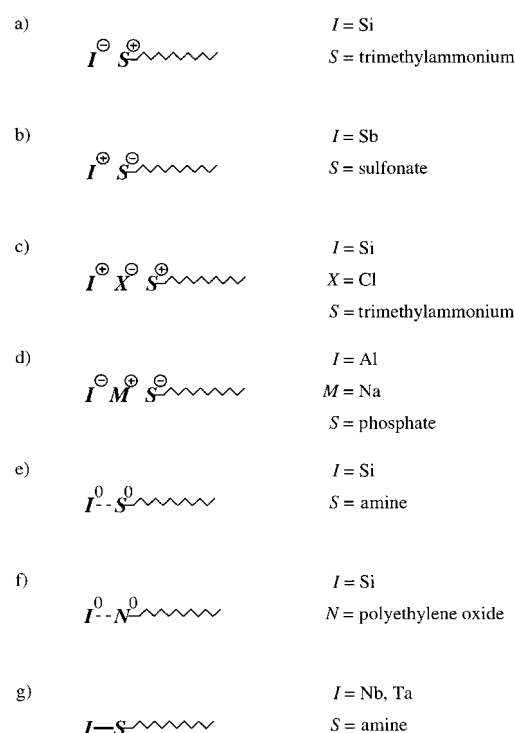
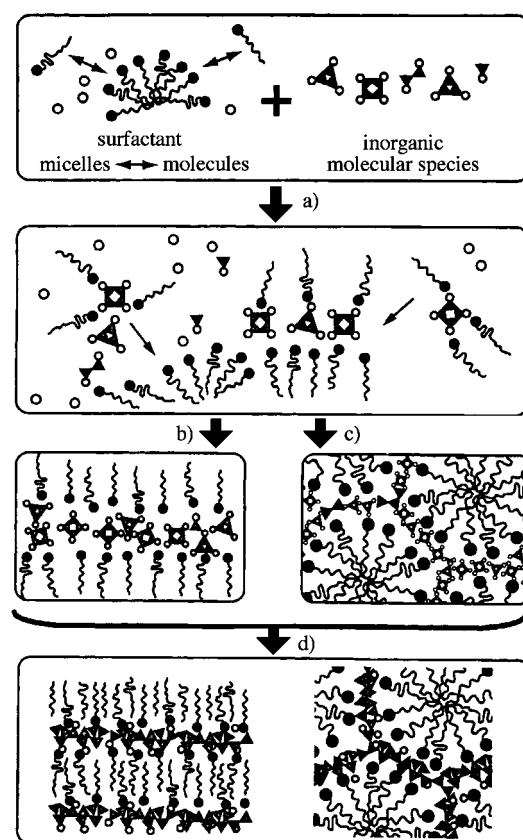


Figure 1. Schematic representation of the various types of inorganic–surfactant head group interactions: electrostatic: a) S^+I^- , b) S^-I^+ , c) $S^+X^-I^+$, and d) $S^-M^+I^-$; hydrogen bonding: e) S^0I^0 and f) N^0I^0 ; and covalent bonding: g) $S-I$.



Scheme 8. Cooperative templating of the generalized LCT mechanism.^[23b] a) Cooperative nucleation; b), c) liquid crystal formation with molecular inorganic compounds; d) inorganic polymerization and condensation.

templating agent but the halide counteranion X^- became involved through this pathway as it served to buffer the repulsion between the I^+ and S^+ by means of weak hydrogen-bonding forces. The resulting materials are known as “acid-prepared mesostructures” or APM materials.

2.1.3. Formation of Non-Hexagonal Mesophases

There are two synthesis routes for the derivation of silicate mesoporous molecular sieves of various mesophases: the basic route (S^+I^-) and the acidic route ($S^+X^-I^+$). Synthesized in basic medium, the M41S family is made up of three well-defined mesostructures: MCM-41, MCM-48, and MCM-50^[24] (Table 2, Figure 2). MCM-41 has a hexagonally packed array

Table 2. Mesophases of silicate molecular sieves and governing synthesis parameters.

Name	Mesophase	Space group	Parameter
MCM-41 ^[1, 24]	hexagonal ^[a]	$p6m$	$[\text{surfactant}]/[\text{Si}] < 1$
MCM-48 ^[1, 24]	cubic	$ Ia\bar{3}d$	$[\text{surfactant}]/[\text{Si}] = 1 - 1.5$
MCM-50 ^[1, 25]	lamellar	$p2$	$[\text{surfactant}]/[\text{Si}] = 1.2 - 2$
SBA-1 ^[23, 26]	cubic	$Pm\bar{3}n$	$g = 1/3^{[b]}$
SBA-2 ^[29]	hexagonal ^[c]	$P6_3/mmc$	$g < 1/3^{[b]}$
SBA-3 ^[26]	hexagonal ^[a]	$p6m$	$g = 1/2^{[b]}$

[a] Two-dimensional array. [b] $g = V/a_0l$. [c] Three-dimensional array.

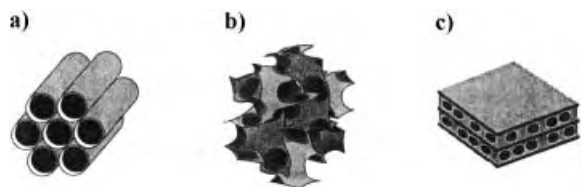


Figure 2. Illustrations of mesoporous M41S materials: a) MCM-41, b) MCM-48, and c) MCM-50.^[3]

of noninterconnecting cylindrical pores. The structure of MCM-48 belongs to the cubic space group $Ia\bar{3}d$. The structure can be thought of as two intertwined networks of spherical cages separated by a continuous silicate framework. MCM-50 contains a lamellar structure in the uncalcined form; a mesoporous pillared layered material results when the surfactant is removed after post-treatment with TEOS.^[25] Vartuli et al.^[24] found that the surfactant:silicon molar ratio was the key synthesis parameter that determined the mesophase (Table 2). At ratios approaching 2:1, a “cubic octamer” structure was formed. The uncondensed material was composed of D4R silicate anions complexed with the surfactant; this molecular compound further supports the preferential binding of D4R silicates with ammonium surfactants.

Through the acidic route, APM materials termed SBA have been synthesized.^[26] SBA-1 is cubic (space group $Pm\bar{3}n$, Figure 3),^[23, 26] but not bicontinuous as in MCM-48 ($Ia\bar{3}d$); SBA-3 (space group $p6m$) is the APM mesostructural analogue of MCM-41. The acid-derived materials have thicker pore walls and a framework charge different from the base-derived mesoporous materials, due to the different precipitation conditions and charge balance requirements. For example, the overall framework charge of SBA-3 was slightly positive and so the surfactant and counterion species (S^+X^-)

could be removed in ethanol under reflux. In contrast, the inorganic framework of MCM-41 was negatively charged and the surfactants could be washed out only with acidic alcohol under reflux.

Another aspect of mesophase formation is the manner in which the surfactant tail groups pack in the material. Huo et al.^[26] applied the concept of an effective surfactant packing parameter g ($g = V/a_0l$) used for lyotropic LC phases to the silicate mesophases.^[28] The packing parameter can be used to predict the phase of a given LC system as a first approximation; it is affected by the overall volume V of the surfactant, the effective head group area a_0 , and the surfactant chain length l . Huo et al.^[29] exploited this concept with the use of gemini surfactants (two ammonium surfactant molecules covalently linked through the head groups) to create SBA-2. The space group of SBA-2 is $P6_3/mmc$. Its structure consists of a hexagonal close-packed (hcp) array of spheres; the spheres can be thought of as spherical micelles. This structure is not found in the traditional LC systems. The preparation of MCM-48 ($Ia\bar{3}d$) was also demonstrated by adjustment of g with alcohol addition to the synthesis mixture^[30] or with mixed cationic-anionic surfactants.^[31]

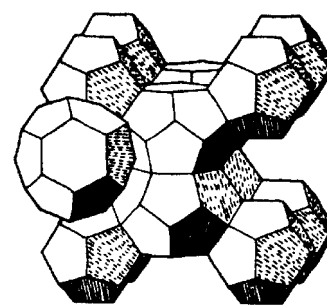


Figure 3. The $Pm\bar{3}n$ cubic phase, in which the polyhedra represent micelles.^[27]

2.1.4. Hydrogen-Bonding Interaction

Tanev and Pinnavaia^[32] showed that mesoporous silica could be prepared by the hydrogen-bonding interaction of an alkylamine (S^0) head group and hydroxylated TEOS (I^0 ; Figure 1 e). The materials lacked long-range ordering of pores and had higher amounts of interparticle mesoporosity, because the long-range effects of the electrostatic interaction that would normally control the packing of micellar rods were absent. This neutral templating synthesis route produced mesoporous silicates with thicker walls and higher thermal stability compared to the LCT-derived silicates.^[33] The silicate framework in the resulting mesophase was neutrally charged, so the surfactants could be removed by solvent extraction. Tanev and Pinnavaia^[34] further exploited the S^0I^0 route by the use of double-headed alkylamines (α,ω -dialkylamine) to create porous lamellar mesostructures.

Another hydrogen-bonding synthesis route used surfactants with a polyethylene oxide head group (Figure 1 f).^[35] Because the length of the head group and that of the tail group could be adjusted, pores as large as 58 Å could be synthesized without the use of swelling agents. The polyethylene oxide head group is nonionic (N^0), unlike the amine head group (S^0) which is uncharged and can be ionized. The nonionic route (N^0I^0) seemed to provide greater pore ordering than the neutral route (S^0I^0), but still lacked long-range hexagonal packing order. The pores were more “wormlike” than rodlike cylinders.

2.1.5. True Liquid Crystal Templating Mechanism

By operating in the liquid crystal phase region of a polyethylene oxide surfactant solution, Attard et al.^[36] showed that monolithic mesoporous silicates could be prepared. Tetramethylorthosilicate (TMOS) was gelled in the LC solution with removal of the LC-destabilizing methanol, to produce a hexagonal mesophase; the $1a\bar{3}d$ and layered phases were found possible also, depending on the chain length of the tail group. This synthesis approach could be considered a true LCT route, which supports the viability of pathway 1 of the originally proposed LCT mechanism for MCM-41 (Scheme 2).^[1b] In this method of preparation, the organic–inorganic interaction was less important than the actual presence of a LC phase. Göltner and co-workers^[37] showed that amphiphilic diblock copolymers (with a polyethylene oxide head group and a polystyrene tail group) could also be used as templates to create crack-free monoliths of mesoporous silica.

2.1.6. Formation of Other Mesophases

Mesoporous silicates with pore systems not as well-defined as those of the M41S and SBA materials could result when an additional salt is added to the synthesis mixture. The structures of these materials deviate from the ideal hexagonal pore packing of MCM-41, as detected through XRD and TEM. The long-range ordering of the materials is not definitive proof for “better” materials, however. McGrath et al.^[38] showed that a “sponge” phase (L_3) of mesoporous silicates could be induced by the use of cetylpyridinium bromide surfactant, hexanol co-surfactant, sodium chloride, and water as precursors. After the addition of TMOS and aging, the solution gelled into a monolithic form. The L_3 phase exists in lyotropic surfactant solutions but has no long-range ordering (Figure 4). Because of the special characteristics of the L_3 phase (which can be thought of as a random, bicontinuous cubic phase), the pore volume of the material could be controlled simply with the amount of water in solution, and surfactant removal was not required for mesoporosity.

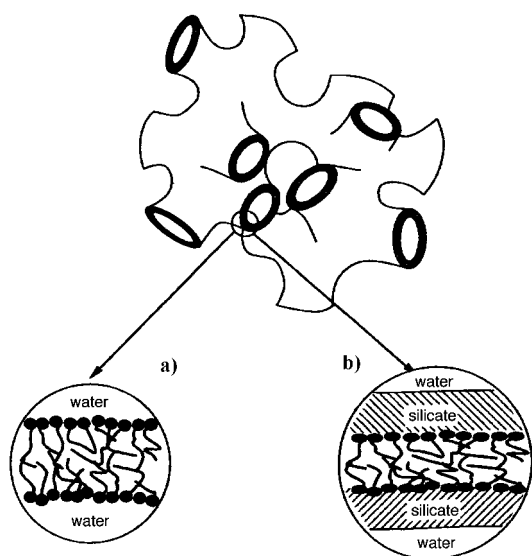


Figure 4. The silicate framework separates the water from the surfactants in the L_3 phase.^[38]

In another approach, Ryoo and co-workers^[39] added ethylenediaminetetraacetic acid (EDTA) to a high pH synthesis mixture, to create a hydrothermally stable mesoporous silicate with a highly branched network of pores similar to the L_3 surfactant phase (termed KIT-1). It was proposed that the EDTA polyacid salt caused the transformation of the hexagonal phase to the L_3 -like mesophase.^[39] For these disordered mesoporous materials, at least one strong XRD peak could still be detected in the low-angle region.

2.2. Doped Silicate Compositions

The interest in doping mesoporous silicates with metals lies primarily in the development of catalytically active materials. The incorporation of a metal is seemingly straightforward in light of the various mechanistic pathways, but the amount of dopant incorporation, the reproduction of the mesophase that is obtained in the pure silica system and the stability of the resulting mesoporous material cannot be predicted. In the original Mobil recipe, tetrahedrally coordinated aluminum atoms could be substituted isomorphously for silicon atoms in the MCM-41 framework as in the case for zeolites, but the degree of substitution depended on the aluminum precursor and method of preparation.^[40, 45] The highest amount of aluminum that could be incorporated into the framework without formation of octahedrally coordinated aluminum (which does not belong to the framework) was reported to be about 9 mol %.^[45] Fu et al.^[46] reported the incorporation of up to 50 mol % Al into MCM-41 by means of special aluminosilicate ions ($[Al_4Si_4(OH)_8O_{12}]^{4-}$) with a similar cubelike structure as D4R silicates; however, the resulting materials showed little resemblance to MCM-41 and dealumination was reported. Ryoo et al.^[40] showed that aluminum could be added to the synthesis mixture and be incorporated into MCM-41 even after the precipitation of the pure mesostructured silicate.

There are numerous reports that concern the doping of MCM-41 with a variety of metals (Table 3); the doped MCM-41 materials have been primarily used for catalytic applications (see Section 3.1). The amorphous silicate framework of MCM-41 could accept metal dopants other than aluminum but beyond a certain limit, the stability of the calcined material would become affected. Thus, the reported levels of doping for calcined MCM-41 were usually low, at most 1–2 mol %. The small amounts of metals that could be incorporated contrasted that of aluminum, probably due to the ease of substitution of the latter (which has a similar cation size and same coordination state as Si) into the silicate framework. Tuel and Gontier^[52] showed that much higher loadings of tetrahedrally coordinated trivalent metal cations were possible through the “neutral” S^0I^0 route, rather than the electrostatic approach. The incorporation levels were apparently highly dependent on the synthesis route and sensitive to the pH of the synthesis mixture. Most doped MCM-41 materials were prepared under basic pH conditions (S^+I^-), whereas one set was prepared under acidic conditions ($S^+X^-I^+$)^[56] with low incorporation levels (Table 3). In contrast, Wong et al. showed that MCM-41 type materials could be doped with very high

Table 3. Reports of dopant incorporation in silicate M41S materials.

Authors	Metal dopant	Si/dopant molar ratio	Synthesis route ^[a]
Beck et al. ^[1b]	Al	15	S^+I^-
Corma et al. ^[41]	Ti	56	S^+I^-
Reddy et al. ^[42]	V	60	S^+I^-
Tanev et al. ^[43]	Ti	100 ^[b]	S^0I^0
Sayari et al. ^[44]	B	6.25 ^[b]	S^+I^-
Luan et al. ^[45]	Al	10	S^+I^-
Fu et al. ^[46]	Al	≈ 1 ^[b]	S^+I^-
Zhao, Goldfarb ^[47]	Mn	11	S^+I^-
Abdel-Fattah, Pinnavaia ^[48]	Sn	99	S^0I^0
Cheng et al. ^[49]	Ga	30	S^+I^-
Cheng, Klinowski ^[50]	Ga, Al	57, 57	S^+I^-
Koyano, Tatsumi ^[51]	Ti	80	S^+I^- (MCM-48)
Tuel, Gontier ^[52]	Al	6	S^0I^0
	Ga	31	S^0I^0
	Fe	55	S^0I^0
	B	17	S^0I^0
Tuel et al. ^[53]	Zr	17	S^0I^0
Ulagappan, Rao ^[54]	Cr	30 ^[b]	S^+I^-
Zhang, Pinnavaia ^[55]	Ti	50 ^[b]	S^+I^- (MCM-48)
	Cr	50 ^[b]	S^+I^- (MCM-48)
	V	50 ^[b]	S^+I^- (MCM-48)
Zhang et al. ^[56]	Ti	277, 76	$S^+X^-I^+$, S^0I^0
	V	434, 131	$S^+X^-I^+$, S^0I^0
	Cr	163, 70	$S^+X^-I^+$, S^0I^0
	Mn	3332, 118	$S^+X^-I^+$, S^0I^0
	Mo	95, 199	$S^+X^-I^+$, S^0I^0
Echchahed et al. ^[57]	Fe	40	S^+I^- (MCM-48)
He et al. ^[58]	Fe	52	S^0I^0
Jones et al. ^[59]	Zr	25	S^+I^-
Zhang, Ying ^[60]	Nb	10	S^+I^-
Wong et al. ^[61]	Zr	5	$S^+X^-I^+$

[a] MCM-41 structure, unless otherwise noted. [b] Molar ratio values of precursor mixture, not of calcined materials.

loadings of zirconium (≈17 mol %) through the $S^+X^-I^+$ route.^[61] Zhang and Ying^[60] found that up to 10 mol % Nb could be introduced into MCM-41 at high pH, which could then be used to anchor amine-substituted porphyrin molecules^[151] (see Section 3.3).

2.3. Non-Silicate Compositions

2.3.1. Generalized Liquid Crystal Templating Mechanism—Early Efforts

The first foray into mesostructured materials of non-silicate compositions started with the generalized LCT mechanism of Huo and co-workers.^[23] Mesostructured oxides were found possible for such metals as Sb, Fe, Zn, Pb, W, and Mo.^[23, 62] However, most mesophases were layered and did not yield porous materials when the surfactants were removed. The few hexagonal phases derived underwent mesostructure collapse upon surfactant removal (either by solvent extraction or by calcination) probably due to the lack of complete condensation of the inorganic framework.

2.3.2. A Modified Sol–Gel Method

Our laboratory's initial research efforts led to the first reported synthesis of mesoporous transition metal oxides.^[63] Mesoporous titanium oxide was obtained with titanium ethoxide

as the metal precursor since, like other transition metal alkoxides, it is highly reactive in the presence of water. Left uncontrolled, titanium alkoxide would react and form an insoluble titanium oxide gel precipitate. Antonelli and Ying reasoned that if the hydrolysis and condensation rates were controlled with a chelating agent such as acetylacetone, titanium isopropoxide could form mesostructured titania in the presence of a surfactant solution.^[63] This “modified sol–gel method” was successful in yielding the mesoporous materials, with the resulting product characterized with XRD, nitrogen adsorption and TEM. Surfactants with head groups that could interact with the titanium alkoxide led to titania mesostructures, and the phosphate surfactants were preferred for their thermal stability to 100 °C during aging. The resulting mesoporous materials were termed TMS1 (Tech molecular sieves). Though not quite as well-defined in its long-range hexagonal packing order as the MCM-41 silicates, Ti-TMS1 still possessed a narrow pore-size distribution and a high surface area of about 200 m² g^{−1}.

2.3.3. Ligand-Assisted Templating: Covalent Interactions

In a different synthesis approach, our laboratory has successfully derived mesoporous niobium oxide (Nb-TMS1) and tantalum oxide (Ta-TMS1) molecular sieves without the addition of chelating agents.^[64–66] Instead of relying on charge interaction, the surfactants were pretreated with the metal alkoxides in the absence of water to form metal-ligated surfactants. The highest quality materials came from the use of amine surfactants, due to the strong affinity for nitrogen–metal bond formation between the surfactant head group and the niobium or tantalum alkoxide precursor. Upon addition to the alkoxide–surfactant solution, water acted as both a solvent and a reactant, to initiate surfactant self-assembly and alkoxide hydrolysis/condensation, respectively. In this ligand-assisted templating (LAT) approach, control of mesostructure phases was found possible by adjustment of the metal/surfactant ratio, and led to a family of mesoporous transition metal oxides analogous to the M41S family of aluminosilicates (Table 4).

Table 4. Mesophases of niobium oxide molecular sieves.

Name	Mesophase	Space group	Parameter
Nb-TMS1 ^[64]	hexagonal ^[a]	$p6m$	[surfactant]/[Nb] < 1.25
Nb-TMS2 ^[65]	hexagonal ^[b]	$P6_3/mmc$	[surfactant]/[Nb] = 1.5
Nb-TMS3 ^[65]	cubic	$Pm\bar{3}n$	[surfactant]/[Nb] = 1 ^[c]
Nb-TMS4 ^[65]	lamellar	$p2$	[surfactant]/[Nb] = 2

[a] Two-dimensional array. [b] Three-dimensional array. [c] Prepared by vapor diffusion of water into synthesis mixture.

Our laboratory has also extended the LAT approach to synthesize mesoporous zirconium oxide, Zr-TMS.^[67] Zr-TMS was derived with very high surface areas (as high as 560 m² g^{−1}) from zirconium *n*-propoxide and phosphate surfactant, though not with a well-defined mesoporous phase. Wong and Ying were able to show that surface areas, pore sizes, and pore volumes could be controlled in accordance with the chain lengths of templating alkylphosphate molecules (for carbon number *n* = 4–16).^[68] As in the case of Ti-

TMS1, some phosphate head groups remained in the material after calcination, which could be exploited for acid catalysis (see Section 2.3.4.3). The interactions between zirconium alkoxide and various anionic and nonionic amphiphiles were explored;^[68] the covalency of the interaction was deduced from NMR spectroscopic studies and the templating of Zr-TMS by short-chained amphiphilic molecules (see Section 2.4).

2.3.4. Other Compositions

Before we developed the modified sol–gel and LAT routes, we too began with the electrostatic approach in the attempt to prepare mesoporous transition metal oxides. Many of our attempts resulted in non-mesoporous amorphous oxides, in spite of the careful control of pH, aging temperature and period, and choice of metal-surfactant ratios and precursor salts. The generalized LCT mechanism could be used to explain the formation of mesostructures but, unfortunately it could not be used a priori to predict mesostructure formation, given a metal salt and a surfactant precursor.

For many mesostructured metal oxides prepared through an electrostatic approach via the generalized LCT pathway, the isolated mesostructured products were uncondensed transition metal salts and were unstable upon surfactant removal. Stein et al.^[69] found this to be the case for tungstate ($[\text{H}_2\text{W}_{12}\text{O}_{40}]^{6-}$) and niobotungstate ($[\text{Nb}_x\text{W}_{6-x}\text{O}_{19}]^{(2+x)-}$, $x = 2-4$) Keggin ions, as did others, including Janauer et al.^[70] (W, Mo, V) and Luca and co-workers^[71] (V). Suib and co-workers found that mesoporous manganese oxides (termed MOMS) could be synthesized by adjustment of the oxidation state of the Mn-containing precursor.^[72, 73] The pore structure of the resulting materials was less well-defined after calcination than that of mesoporous MCM-41 and TMS1. Interestingly, the framework walls were crystalline, and the material exhibited semiconducting properties.

2.3.4.1. Alumina

Bagshaw and Pinnavaia^[74] used polyethylene oxide surfactants in the N^0I^0 nonionic route to template mesoporous alumina (termed MSU). The materials contained wormlike pore channels with surface areas of greater than $400 \text{ m}^2 \text{ g}^{-1}$. Vaudry et al.^[75] synthesized mesoporous alumina with higher surface areas ($710 \text{ m}^2 \text{ g}^{-1}$). Carboxylate surfactants were used as the templates but the average pore sizes could not be tailored by variation of surfactant chain lengths; an LCT mechanism (S^-I^+ pathway) was not apparent. Yada et al.^[76] found that careful control of pH led to the preparation of mesoporous alumina (with the retention of the main XRD peak) by the S^-I^+ route.

2.3.4.2. Aluminophosphates and Vanadophosphates

There have been attempts to extend the surfactant templating synthesis technique to aluminophosphates. Lamellar aluminophosphates were prepared.^[77, 78] Vesicular templating of the inorganic components was proposed to explain the formation of inorganic–organic bilayers organized as cylinders,^[79] and particles patterned like exoskeletons of radiolarian organisms.^[80]

Fluoride ions were used in the synthesis mixture as mineralizing agents by Feng et al.^[81] to produce layered, hexagonal, and cubic phases of aluminophosphates. The mesostructures were unstable to calcination, however. Hexagonally packed mesoporous aluminophosphates were obtained by Zhao et al.^[82] by the use of TMAOH to carefully control the pH. Chakraborty et al.^[83] were able to substitute silicon atoms into mesostructured aluminophosphates, where upon calcination, mesoporous silicoaluminophosphates were obtained.

Vanadium phosphorus oxides (VPO) are useful as selective oxidation catalysts, and mesoporous VPO synthesis has been attempted by several groups.^[84, 85] Mesostructured VPO materials were found possible, but accounts on surfactant removal either indicated collapse of the mesostructure^[84] or provided insufficient information on the mesoporosity.^[85]

2.3.4.3. Zirconia

Zirconium oxide is an interesting material catalytically and much effort has been devoted to the generation of a mesoporous form. Hudson and Knowles^[86] used alkyltrimethylammonium halide to template zirconium hydroxide to produce pure zirconia with a high surface area. The templating effect was not seen in this synthesis, which resulted in broad pore-size distributions. A “scaffolding” mechanism was proposed in which the occluded surfactant basically acted as a filler to prevent the zirconia framework from collapsing during heat treatment. Reddy and Sayari^[87] found that a zirconium oxide mesostructure could be produced with zirconium sulfate as the inorganic precursor in a $S^+X^-I^+$ synthesis route. The material was found to collapse upon calcination. Ciesla et al.^[88] and Liu et al.^[89] found that by ion-exchanging the occluded sulfate counteranions with phosphates, a microporous zirconium oxo-phosphate could be obtained. Ciesla et al.^[88] also found that a microporous zirconium oxide stabilized with sulfates could be produced by use of a different precursor, for example a zirconium *n*-propoxide at low pH. A microporous oxide form of hafnium, a heavier congener of zirconium, was derived similarly.^[90]

Pure zirconium oxide is a weakly acidic catalyst and is not useful for reactions that demand strong acidity. To increase acidic strength, modification of the pure zirconium oxide with anions or metal dopants is required. Mesoporous phosphated zirconium oxide, a moderately acidic material, was prepared through a one-pot synthesis with zirconium *n*-propoxide and alkylphosphates.^[67, 68] The phosphate groups that remained after calcination enhanced the thermal stability (as in the case of microporous zirconium oxo-phosphates), and increased the acidic strength of the zirconia framework.

2.3.4.4. Metal Sulfides

A few examples of mesostructured metal sulfides have been reported. Stupp and co-workers^[91] used a polyethylene oxide surfactant with a cadmium salt solution to obtain a hexagonal mesophase. The material was then exposed to hydrogen sulfide gas, which converted the cadmium salt to cadmium sulfide. Li et al.^[92] derived a lamellar tin sulfide material with CTAB and tin chloride as precursors, and sodium sulfide as

the reducing agent. Surfactant removal was not possible from the CdS materials and probably not possible from the SnS₂ layered mesostructures.

2.3.4.5. Other Examples

Zhao and Goldfarb^[93] reported the use of non-amphiphilic compounds to template oxides of magnesium and zinc into lamellar mesostructures. Disodium chromoglycate and flufenamic acid compounds self-assembled into a lyotropic chromonic phase and interacted with the metal precursor by means of S^+I^- electrostatic attraction. Self-assembly occurred with the flat aromatic molecules containing edgewise polar groups, which differed from the amphiphilic molecules normally used.

Attard et al.^[94] templated platinum salts with the hexagonal phase of polyethylene oxide surfactants, and reduced the mesostructure (with hydrazine hydrate or less noble metals) to give mesoporous platinum metal with an average pore size of 30 Å. The mesoporous platinum did not possess a long-range hexagonal packing of the pores.

2.4. Control of Pore Sizes

There is no energetic limitation to the pore sizes possible in microporous and mesoporous silicates, as shown by Navrotsky et al.^[95] It was found that MCM-41 and zeolites are only slightly less stable relative to the thermodynamically stable phase of silica, α -quartz, which suggests that the only limitation to the synthesis of porous structures is to find the appropriate kinetic pathways. In this respect, it may be easier to synthesize amorphous mesoporous MCM-41-like materials with smaller pores, rather than crystalline microporous zeolites with larger pores.

Sun and Ying^[96] were able to control pore sizes between 5 Å and 20 Å by the use of short-chain alkylamines as supramolecular templates, allowing for systematic bridging of the mesoporous and microporous regimes. This work demonstrated for the first time that non-zeolitic microporous materials (TMS5) could be synthesized by supramolecular templating of small molecules, and could be composed of pure niobia. The amphiphilic molecules with a hydrocarbon chain length of n less than eight are normally too small to self-assemble in an aqueous solution and would be expected to behave as molecular templating agents (as in zeolite synthesis). However, the ligand-assisted templating technique provided a shielding effect by the inorganic components on the amphiphile head groups in such a way as to favor self-assembly versus solubilization of the templating agents. Thus, supramolecular templating was successfully extended to the systematic synthesis of microporous materials. This approach was further modified by Sun and Ying to produce microporous Nb-TMS6 with use of α,ω -dialkylamines.^[97]

The use of short-chained amphiphiles has also led to the systematic derivation of micropores in zirconium oxide. Wong and Ying^[68] used short-chained alkylphosphates to produce high surface area porous zirconium oxides modified by surface phosphate groups.

At the other end of the pore-size spectrum, hexagonally ordered mesoporous silicates with pores as large as 300 Å (SBA-15) were found possible by researchers at the University of California at Santa Barbara.^[98] Nonionic triblock copolymers (polyethylene oxide/polypropylene oxide/polyethylene oxide) were used under acidic conditions (pH $\approx$ 1), and the templating was thought to occur through both electrostatic and hydrogen-bonding interactions.

3. Catalytic Applications

The unique physical properties of MCM-41 have made these materials highly desirable for catalytic applications. The extremely high specific surface areas are conducive to high catalytic activity. The large pore size (relative to that of microporous zeolites) allows for the fixation of large active complexes, reduces diffusional restriction of reactants, and enables reactions involving bulky molecules to take place. In spite of the one-dimensionality of its pore channels, MCM-41 has been the main focus of catalytic studies (rather than the other M41S mesoporous structures) because of its ease of preparation.

The first catalytic studies with mesoporous molecular sieves focused on metal-substituted MCM-41 materials in which the active species were incorporated into the silicate matrix. The reactions studied were mainly oxidation reactions and acid catalysis. The next stage of development of MCM-41-based catalysts involved the deposition of heteroatoms onto the surface of the mesoporous framework. Since then, a wide variety of applications have been established and the field is still expanding rapidly. More recently, research has been devoted to the fixation of catalytically active complexes onto the walls of the MCM-41 porous framework to combine the advantages of homogeneous catalysis with a heterogeneous catalyst support. Although extensive research efforts have been undertaken to explore the catalytic applications of modified MCM-41 materials, industrial use has so far been limited. Only a longer time frame will reveal if commercial applications of these systems will become feasible.

3.1. Metal-Substituted Mesoporous Molecular Sieves

3.1.1. Oxidation Reactions

Titanium silicate materials with MFI or MEL zeolite structure types (e.g. TS-1 or TS-2) have been investigated as olefin epoxidation catalysts.^[99] Although zeolites such as TS-1 showed very high catalytic activity and selectivity, they could only be effective in the oxidation of small molecules. Larger molecules like cyclohexene were excluded from catalytic conversion due to the rather small pore size of the TS-1 material (5.3×5.5 Å). Consequently, a considerable amount of research was dedicated to the preparation of titanium-containing zeolites with large pores. The synthesis of a titanium-substituted β zeolite with BEA structure (7.6×6.4 Å) enabled the epoxidation of long-chain aliphatic olefins.

To catalyze bulkier substrates, it would be critical to develop molecular sieves with even larger pore sizes.

Soon after the Mobil announcement of the M41S materials, the synthesis of MCM-41 doped with titanium was reported simultaneously by two groups. Corma et al.^[41] prepared Ti-MCM-41 with ionic surfactants under hydrothermal condition, while Tanev et al.^[43] synthesized Ti-HMS with neutral primary amine surfactants in a room-temperature preparation. Both synthesis procedures led to the incorporation of catalytically active titanium sites into the mesoporous silicate matrix without significantly affecting the surface area and pore size, although the Ti-HMS material contained more interparticle mesoporosity.

Comparison study^[41] of Ti-MCM-41 with Ti- β zeolite and Ti-ZSM-5 showed a higher catalytic activity for the former in the epoxidation of norbornene with *tert*-butyl hydroperoxide (TBHP) as oxidant. In the evaluation of the Ti-HMS catalyst,^[43] the sterically more demanding substrate 2,6-di-*tert*-butylphenol (2,6-DTBP) was investigated. The aromatic compound was selectively oxidized to the corresponding quinone with H₂O₂. This study further illustrated that Ti-HMS gave a higher conversion rate than Ti-MCM-41 in the oxidation of 2,6-DTBP. The authors suggested that due to the exceptionally high textural mesoporosity of the catalyst, Ti-HMS has less diffusional limitation than Ti-MCM-41 and therefore superior catalytic activity for the oxidation of large organic substrates.

A further study on the selective oxidation of large organic molecules was undertaken by Reddy et al.^[42] By the substitution of vanadium into the porous framework of MCM-41 through hydrothermal synthesis, they were able to prepare a highly active and selective catalyst for the partial oxidation of cyclododecane and 1-naphthol with H₂O₂ as oxidant. The same group also prepared a vanadium-containing mesoporous material, V-HMS, by a room-temperature synthesis route.^[100] The resulting catalyst was evaluated for the oxidation of 2,6-DTBP with either H₂O₂ or TBHP. Compared to the Ti-HMS described earlier,^[43] the V-HMS material showed higher catalytic activity for this reaction.

Gontier and Tuel^[101] reported the successful application of transition metal (Ti and V) substituted mesoporous and microporous molecular sieves for the liquid-phase oxidation of aniline. Although conventional oxidation catalysts like TS-1 and ZSM-48 exhibited good activity, the reaction was limited by pore diffusion of products and reactants in the zeolites. By the use of ultra-large pore materials like the doped MCM-41, diffusion limitation was overcome and higher catalytic activities were observed.

Tuel et al.^[53] showed that zirconium-containing mesoporous MCM-41 could be synthesized with hexadecylamine surfactant and zirconium isopropoxide at room temperature. The resulting material, designated Zr-MS, showed similar catalytic activity in the oxidation of aniline as the titanium-containing mesoporous material. However, it gave higher selectivity for alcohol in the epoxidation of norbornylene.

An interesting approach was undertaken by Vankelecom et al.^[102] which involved the incorporation of Ti-MCM-41 catalyst into a partially polymerized polymethylsiloxane matrix. Catalytic results for the epoxidation of *cis*-cyclooctene

with TBHP suggested an even higher conversion for the polymer-embedded Ti-MCM-41 than the free catalyst. This example illustrated that a combination of membrane technique and materials design could have a significant impact in the development of future catalyst technology. Although a variety of MCM-41 materials containing early transition metals has been prepared and investigated for oxidation catalysis, their activities were lower than the existing zeolite systems. In order to make a real impact in the area of oxidation catalysis, new systems must be as active as TS-1 materials while providing a mesoporous structure.

3.1.2. Acid-Catalyzed Reactions

The cracking activity and hydrothermal stability of aluminum-substituted MCM-41 materials were investigated by Corma et al.^[103] It was shown that the activity of MCM-41 for a reaction catalyzed by strong acid sites, such as *n*-heptane cracking, was much lower than that of an ultra-stabilized Y (USY) zeolite, and similar to that of amorphous aluminosilicate. However, in the case of gasoil cracking, the greater accessibility of the large molecules to acid sites in MCM-41 relative to USY made the difference in activity much smaller between these two catalysts. In order to simulate fluidized catalytic cracking conditions, MCM-41 was steam treated. The resulting material showed a collapse of the porous structure, and the gasoil cracking activity was greatly diminished. The steam-treated MCM-41 was a much less active catalyst than steam-treated amorphous aluminosilicate.

An investigation of the hydrocracking abilities of aluminum-substituted MCM-41 for larger size molecules was carried out by Reddy and Song.^[104, 105] Significant catalytic activity was obtained with 1,3,5-triisopropylbenzene (TIPB), to form mainly mono- and di-substituted isopropylbenzene. A conversion as high as 100% was achieved for the hydrocracking of TIPB by loading the MCM-41 aluminosilicate with platinum metal.

Extensive studies on cracking^[106–112] and hydrocracking^[113–119] over MCM-41 were undertaken by the Mobil researchers, but no commercial use has been established yet. An interesting approach was described by Degnan et al.^[116] that combined modified MCM-41 materials with zeolites to give a mixed hydroprocessing catalyst. In this catalyst, MCM-41 provided an ultra-high surface area supporting the metal components (Ni/W or Pt) for hydrogenation reactions, while the zeolite provided the acidic functionality required for cracking. The resulting catalyst exhibited good activities in both hydrogenation and cracking, and could be used in fuel hydrocracking processes, especially where high conversion levels were desired.

An application of aluminum-containing MCM-41 was reported by Aguado et al.,^[120] which showed the conversion of low-density polyethylene (LDPE) to hydrocarbon feedstock. Cracking of polyolefins typically involves solid acid catalysts, such as amorphous aluminosilicates and zeolites. Due to the bulky nature of the polymeric feedstock, catalytic activity has been mainly governed and limited by the catalyst pore size. Consequently, despite its lower aluminum content, aluminosilicate MCM-41 was found to be more active for LDPE cracking than amorphous aluminosilicate, due to its

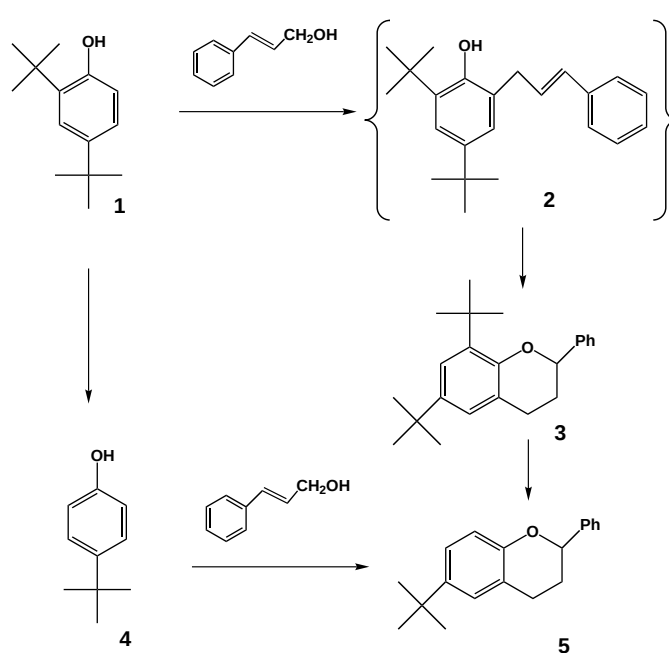
greater mesoporosity. Although the reaction was hindered by its small pore size (≈ 5.5 Å), ZSM-5 showed the highest activity for the LDPE cracking since, in the earlier reaction stages, only acid sites located on or near the external surface were involved. The superior activity of ZSM-5 compared to MCM-41 was attributed to the higher acid strength of ZSM-5. However, the product distribution obtained with MCM-41 consisted of more liquid hydrocarbons in the range of gasoline and middle distillates with lower aromatic content relative to amorphous aluminosilicate and ZSM-5. This example showed quite nicely that even though MCM-41 materials could not compete in catalytic activity, they could produce new product distributions (i.e., favorable selectivity) that could be useful towards existing processes.

The application of aluminosilicate MCM-41 as a catalyst in the production of acetals was reported by Climent et al.,^[121] and it represented a good example where the moderate acidity and the mesoporous structure of MCM-41 were well utilized. These acetal compounds are interesting for use in pharmaceuticals and as fragrances in perfumes and detergents. MCM-41 was shown to be an active and selective catalyst for the acetalization of aldehydes. For small aldehyde reactant molecules, zeolites were found to be more active than mesoporous MCM-41. However, when reactants larger than 7 Å were involved, geometrical constraints did not allow them to diffuse into the microporous framework of zeolites. The ultra-large pores of MCM-41 made this material more attractive for the acetalization of many fine chemicals.

Tetrahydropyranylation of alcohols and phenols represents a common synthetic tool to protect the hydroxyl functionality in peptide, nucleotide, carbohydrate and steroid chemistry. Kloetstra and van Bekkum^[122] used aluminosilicate MCM-41 as a mild and efficient acid catalyst for the tetrahydropyranylation of primary, secondary, and tertiary alcohols and phenols. It was also shown that aluminosilicate MCM-41 provided excellent catalytic activity and selectivity with respect to bulky substrates like cholesterol, superior to the current commercial heterogeneous aluminosilicate catalysts.

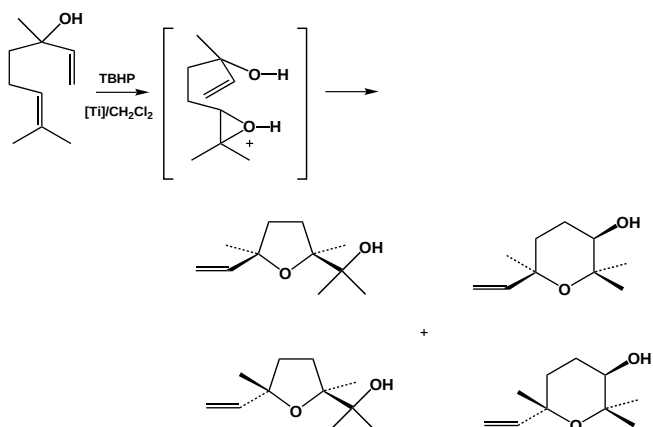
The application of aluminosilicate MCM-41 as acid catalyst for Friedel–Crafts alkylation was reported by Armengol et al.^[123] In this study, the bulky substrate 2,4-di-*tert*-butylphenol (2,4-DTBP, **1**) was alkylated with cinnamyl alcohol, to give a mixture of **3** and **4** together with minor amounts of **5** (Scheme 9). The formation of dihydrobenzopyran **3** was attributed to an intramolecular ring closure of the primary cinnamylphenol **2** that arose from the Friedel–Crafts alkylation of phenol **1**. The formation of **4** and **5** was suggested to be based on acid-catalyzed dealkylation, which has been frequently observed for *tert*-butyl-substituted aromatic compounds. MCM-41 was shown to give higher yields of **3** than conventional catalysis with sulfuric acid or amorphous aluminosilicate. No reaction occurred over acid faujasites (HY) and only very little activity was noted for steam-treated HY zeolite.

Alkylation reactions of naphthalene, paraffin, and benzene with short- and long-chain olefins were also examined over MCM-41.^[124–127] MCM-41 was found to be less reactive than ZSM-5 in the synthesis of ethylbenzene, but it yielded more polyalkylated products than the latter.



Scheme 9. Alkylation of 2,4-DTBP with cinnamyl alcohol over aluminosilicate MCM-41.

By introducing titanium into the framework of aluminosilicate MCM-41, a bifunctional catalyst was prepared by Corma et al.^[128] for the conversion of linalool into cyclic furan and pyran hydroxyl ethers (Scheme 10). The authors



Scheme 10. Conversion of linalool into cyclic furan and pyran hydroxyl ethers with Ti-MCM-41 ([Ti]).

postulated that epoxidation took place over the titanium sites, and acid-catalyzed intramolecular ring opening of the epoxide then occurred by the 3-hydroxyl group. The conversion for this reaction was as high as 80 % with the Ti-MCM-41 material. In comparison, titanium-modified zeolite β gave somewhat lower conversion. Although Ti- β zeolite usually exhibited higher activity than Ti-MCM-41 in epoxidation reactions, Ti-MCM-41 provided greater activity in this case, possibly due to increased diffusion of reagents through its larger pores.

Deviating from the typical aluminosilicate compositions, phosphated mesoporous zirconium oxide (Zr-TMS) was developed for mild acid catalysis.^[67, 68] The Zr-TMS material

was found to be active for the gas-phase double-bond isomerization of 1-butene at temperatures of 100–350 °C. The material should also be useful for other types of reactions that require moderate acidity, and was seen as an improvement over crystalline layered zirconium phosphates for acid catalytic applications.

3.1.3. Hydroxylation Reactions

The catalytic hydroxylation of benzene to phenol over a variety of transition metal substituted mesoporous molecular sieves was reported by Zhang et al.^[56] Ti-, V-, Cr-, Mo-, and Mn-substituted MCM-41 and HMS silicates (with typical transition metal contents of 0.2–1.5 wt %) were prepared by electrostatic and neutral templating pathways, and examined for the peroxide hydroxylation of benzene. All materials were catalytically active, and in particular the Ti-HMS material gave $\approx 100\%$ selectivity at low conversion. In a further study by the same group,^[55] transition metal (Ti, V, Cr) substituted cubic-phased MCM-48 mesoporous silicates were prepared by hydrothermal synthesis, and successfully applied for the selective peroxide oxidation of styrene and methyl methacrylate to benzaldehyde and methyl pyruvate, respectively.

3.1.4. Polymerization Reactions

In a study by Abdel-Fattah and Pinnavaia,^[48] tin-substituted mesoporous silicate was prepared by neutral amine surfactant assembly of silicon and tin(IV) alkoxides at ambient temperature. The resulting material was successfully applied to lactide ring-opening polymerization. Sn-HMS yielded higher conversion than tin-doped silica and pure tin oxide. Compared to homogeneous catalysts, Sn-HMS improved the average molecular weight and polydispersity of polymers produced, possibly by imposing steric constraints on the propagating polymer chain with its ordered pore structure, and by minimizing “back-biting” and intermolecular transesterification reactions.

3.2. Metal-Deposited Mesoporous Silicates

One of the earliest catalytic applications of MCM-41 involved supported NiMo in gasoil hydrocracking.^[103] The molybdenum and nickel components were introduced by the incipient wetness impregnation technique, followed by calcination. Despite a loading of 12 wt % MoO₃ and 3 wt % NiO, the surface area of the MCM-41 support was only slightly reduced. The NiMo-MCM-41 catalyst showed a higher hydrodesulfurization and hydrodenitrogenation activity than NiMo loaded on USY or amorphous aluminosilicate. The better performance of NiMo-MCM-41 was attributed to the mesoporous structure and the high surface area that provided access to bulky molecules and a high dispersion of active metal components.

The application of modified MCM-41 material in the reduction of nitrogen oxides (NO_x) from emission gases has been reported by Beck et al.^[129] The molecular sieves were used as a framework for the deposition of vanadium and

titanium oxides. It was found that the modified MCM-41 material exhibited higher activity for NO_x reduction by ammonia than vanadium oxide and titanium oxide loaded amorphous silica gel.

Another interesting application of modified MCM-41 material was reported by Kresge et al.^[130] for the demetalation of hydrocarbon feedstock. MCM-41 was loaded with MoO₃ and NiO by impregnation. This catalyst showed a high efficiency for the removal of iron and nickel, and was also active for arsenic removal and desulfurization.

For the oligomerization of α -olefins, Pelrine and co-workers^[131, 132] reported the use of chromium-modified MCM-41 material. The metal component was introduced through impregnation, followed by calcination to give chromia-loaded MCM-41. Prior to polymerization experiments, the material was activated by carbon monoxide to reduce the chromium to a lower valence state. Oligomerization of 1-decene over this catalyst produced a wide variety of lubricants with higher viscosity values than those obtained with chromia on silica.

The use of nickel-impregnated MCM-41 aluminosilicate for oligomerization of olefins was reported by Bhore et al.^[133] Compared to zeolites with medium pore sizes, the impregnated MCM-41 material showed higher activity and greater selectivity for the formation of trimers and tetramers of propylene. Furthermore, they offered control over the degree of branching through variation of the reaction conditions.

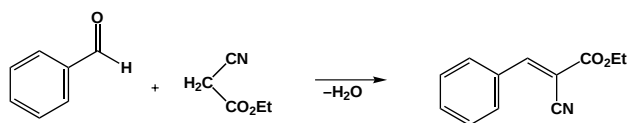
The isomerization of *n*-hexane with platinum-modified MCM-41 aluminosilicate was reported by Del Rossi et al.^[134] The platinum precursor [Pt(NH₃)₄Cl₂] was introduced by ion exchange, and the material was then calcined. Although platinum on amorphous SiO₂-Al₂O₃ showed a slightly higher conversion of *n*-hexane than Pt-MCM-41, the selectivity for isohexane was significantly higher over Pt-MCM-41 with its uniform pore structure.

Borghard et al. investigated the hydrogenation of benzene to cyclohexane, and showed that Pd-impregnated MCM-41 has higher activity than palladium supported on other materials.^[135] The enhanced reactivity was attributed to the higher surface area and pore volume of the MCM-41 support.

An alternative approach in acid catalysis was described by Kresge et al.^[136] Instead of modification of the silicate framework of MCM-41 with trivalent cations (e.g. Al³⁺) to generate Brønsted acid sites, they deposited heteropolymetallic acids inside the porous framework. Although heteropolymetallic acids have very strong acid sites, their surface areas are rather small. By utilizing supports with high surface areas, acid site dispersion was achieved. The catalyst was prepared by loading the mesoporous material with phosphotungstic acid (H₃PW₁₂O₄₀) with the incipient wetness method, and was investigated for four different paraffin substrates. In *n*-butane conversion, isobutane was obtained with a selectivity exceeding 80%, which was substantially higher than that achieved over ZSM-5. For the conversion of *n*-hexane, the heteropolymetallic acid loaded MCM-41 exhibited higher activity (with comparable selectivity), compared to Pt-MCM-41. The excellent activity was attributed to the high dispersion of the heteropolymetallic acid on MCM-41.

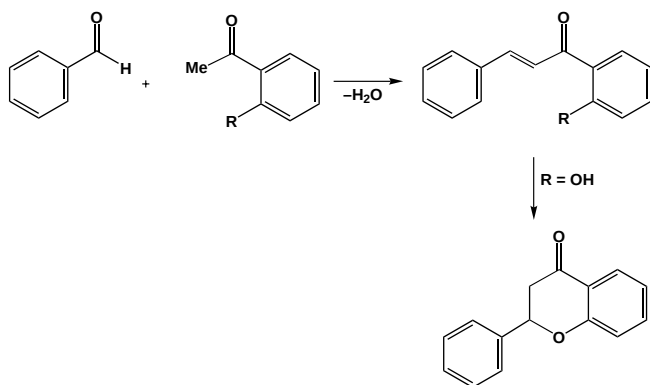
Aluminosilicate MCM-41 materials cation-exchanged with sodium and cesium have been successfully used for the base-

catalyzed Knoevenagel condensation.^[137] The reaction of benzaldehyde and ethyl cyanoacetate in aqueous solution in the presence of Na-MCM-41 (Scheme 11) led to a conversion



Scheme 11. Base-catalyzed Knoevenagel condensation over MCM-41 cation-exchanged with sodium and cesium.

of about 90 % within three hours with almost 100 % selectivity. In contrast, the same reaction in boiling ethanol led to the acetalization of benzaldehyde due to the presence of residual acid sites. Furthermore, both H-MCM-41 and Na-MCM-41 catalyzed the condensation of benzaldehyde with acetophenone to yield chalcone. They were also successfully employed for aldol condensations with bulky ketones. In addition, if an α -hydroxyl group was present on the benzophenone, an intramolecular Michael addition giving flavanone would follow the aldol condensation (Scheme 12).



Scheme 12. Aldol condensation between benzaldehyde and acetophenone, followed by a Michael addition to give flavone, over H-MCM-41 and Na-MCM-41.

One of the first examples of the deposition of active metal oxide sites on MCM-41 through the fixation of organometallic complexes onto the inside walls of MCM-41 was reported by Maschmeyer et al.^[138] Treatment of the porous MCM-41 material with a solution of $[(C_5H_5)_2TiCl_2]$ in the presence of NEt_3 anchored the titanocene complex through oxygen atoms onto the pore surface. Calcination under a stream of oxygen removed the cyclopentadienyl ligand and generated an active epoxidation catalyst. The resulting system showed good activity, and was particularly useful in the conversion of bulky substrates, which could have access to the active centers inside the ultra-large pores. With the same approach, vanadium-grafted^[139] and manganese-grafted^[140] MCM-41 materials were derived

and their applications as oxidation catalysts were demonstrated.

A major drawback of the “wet” impregnation method is the undesired cluster growth during the deposition of the active species. In order to overcome this problem and to ensure a high dispersion of active species, a new methodology, termed vapor grafting, was developed by Ying and Mehnert.^[141] By use of volatile organometallic precursors, it was possible to deposit active species in a highly dispersed and uniform fashion throughout the entire porous system of MCM-41 (Figure 5). The resulting variety of metal and metal oxide

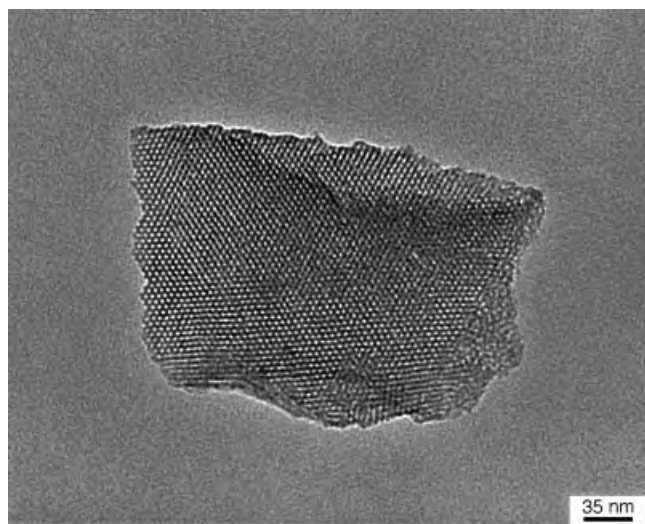
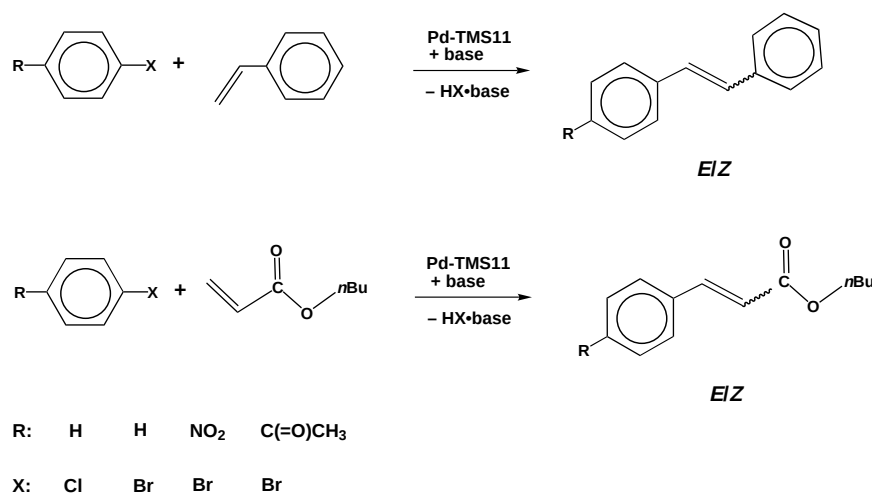


Figure 5. TEM image of the palladium-grafted mesoporous silicate material Pd-TMS11.^[142]

grafted mesoporous materials (termed TMS11) presented an attractive combination of ultra-high catalyst dispersion and tunable pore sizes (15–100 Å). The Pd-TMS11 material^[142, 143] was conveniently prepared by vacuum sublimation of $[CpPd(\eta^3-C_3H_5)]$ through the hexagonally packed MCM-41 mesopores, followed by reduction under hydrogen. Investigation of Pd-TMS11 for carbon–carbon coupling reactions (Heck reaction, Scheme 13) showed that its catalytic activity was superior to that of other heterogeneous Heck catalysts



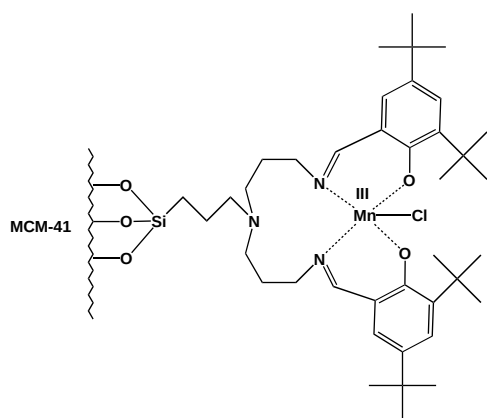
Scheme 13. Carbon–carbon coupling reactions catalyzed by mesoporous Pd-TMS11 material.

and even surpassed that of many homogeneous catalysts. This heterogeneous Heck catalyst demonstrated how bulky substrates could be effectively and selectively coupled to an even larger molecule inside the mesoporous framework. The highly dispersed Pd-grafted catalyst provided a less expensive and more thermally robust alternative to homogeneous Pd complexes.

3.3. Organometallic Complexes Anchored to Mesoporous Silicates

An early example for the anchoring of an organometallic complex onto the porous walls of aluminosilicate MCM-41 was reported by Liu et al.^[144] They treated ion-exchanged MCM-41 with phenanthrolineiron(II) chloride and were able to immobilize the complex. The resulting material was investigated for the oxidation of phenol with H_2O_2 as the oxidant. A higher activity was obtained with the immobilized iron complex than for the free iron complex. However, a significant amount (9.5%) of leaching was noted in the former, which could be overcome when the transition metal complexes were anchored onto the walls of MCM-41 with an organic linker.

Sutra and Brunel^[145] treated MCM-41 material with $(\text{MeO})_3\text{Si}(\text{CH}_2)_3\text{Cl}$, which generated surface-bound 3-chloropropylsilane moieties that could be allowed to react with bis-3-(3,5-di-*tert*-butylsalicylideneaminopropyl)amine, to yield surface-bound Schiff base ligands (Scheme 14). The metal was



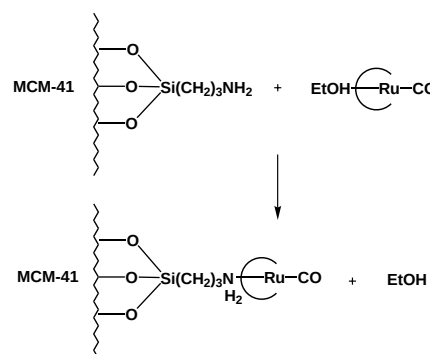
Scheme 14. Surface-fixated Schiff base ligand with coordinated manganese for epoxidation reactions.

then introduced by means of a solution of $[\text{Mn}^{\text{II}}(\text{acac})_2]$ (acac = acetylacetonate) in methanol. Air oxidation of the solution gave the final Mn^{III} complex. The immobilization of such epoxidation catalysts offered the advantage of easy separation and the potential of increased selectivity with the well-defined pore structure of the support material.

Surface-immobilized manganese–triazacyclononane complexes have also been developed for epoxidation catalysis.^[146] By anchoring 1,4,7-triazacyclononane on glycidylated MCM-41, followed by the introduction of the manganese metal, a catalyst with remarkable epoxidation activity and high selectivity for styrene and cyclohexene was achieved.

Cobalt(II) complexes have been immobilized onto the inside walls of ethylenediamine-grafted mesoporous materials.^[147] For the functionalization of the support, the surface-bound silanol groups were allowed to react with alkoxy-silyl compounds that possessed donor amine groups to produce chelating ligands that were then used in the complexation of metal ions such as Co^{II} . The ability of the cobalt–amine complexes to form reversible dioxygen adducts was also demonstrated and might be useful to some biological reactions.

Although numerous efforts have focused on the fixation of metalloporphyrins, as in the elegant work of Herron and co-workers^[148, 149] who reported the entrapment of phthalocyanine within large pore zeolites, turnover frequency and selectivity were rather poor. More recently, the encapsulation of ruthenium porphyrins in modified MCM-41 was reported by Liu et al.^[150] In this work, the surface of MCM-41 was treated with 3-aminopropyltriethoxysilane to provide a two-electron donor anchor (NH_2 group) to which the ruthenium porphyrin was attached (Scheme 15). The catalyst derived was



Scheme 15. Surface-immobilized ruthenium porphyrin complex on MCM-41.

investigated for the oxidation of olefins, giving turnover numbers that were 20–40 times higher than that for the free porphyrin. Also of interest was the observation that in the oxidation of *cis*-stilbene with the modified MCM-41 material, the major product was *trans*-stilbene oxide. In contrast, oxidation of *cis*-stilbene catalyzed by free ruthenium porphyrin gave a 1:1 mixture of *cis*- and *trans*-stilbene oxides. The high selectivity to *trans*-stilbene oxide was attributed to the steric constraint imposed by the straight channels of the MCM-41 support. This example demonstrated nicely the potential of mesoporous materials in size- and shape-selective catalysis.

An alternative approach in the anchoring of metalloporphyrin onto the inside walls of mesoporous MCM-41 has been developed by Zhang et al.^[151] with amine-substituted porphyrin systems. The active complex was attached by means of a covalent interaction between the amine terminal groups of the complex and the niobium dopants in the support matrix. Such ligation ensured that the active sites would not undergo self-oxidation. Excellent cyclohexane hydroxylation and cyclohexene epoxidation activities have been obtained with this catalyst system, and the material could be recycled for

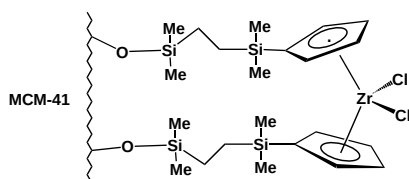
repeated use without loss of activity or leaching of porphyrin complexes.

An interesting approach was taken by O'Brien et al.,^[152] whereby the MCM-41 material was modified with ferrocenyl end groups attached to the silicate surface. By means of the ring-opening reaction of the strained metallocenophane $[\text{Fe}\{(\eta\text{-C}_5\text{H}_4)_2\text{SiMe}_2\}]$, it was possible to anchor ferrocenyl units inside the pore channels of MCM-41. This fixation reaction demonstrated the potential of these mesoporous molecular sieves as a matrix for the encapsulation of defined organometallic complexes.

A further example for the attachment of a well-defined cobalt oxide species was reported by Maschmeyer et al.^[153] They investigated the selective oxidation of cyclohexane to cyclohexanone using a cobalt complex that was bound either directly to a hydroxyl group of the MCM-41 surface or to a surface-anchored spacer compound which contained a carboxylic acid group. The evaluation of the catalysts showed that the directly anchored complex had a lower conversion than the complex that was attached through the spacer. Although this catalyst system exhibited only mediocre activity (12% conversion after 24 hours), no leaching of the cobalt cluster was apparent. The high stability against leaching was attributed to the anchoring of the cluster to the functionalized MCM-41 surface.

Two independent groups have reported the preparation of MCM-41 grafted with methylalumoxane (MAO) for use as support for catalysts in Ziegler–Natta polymerization.^[154, 155] The immobilization of homogeneous metallocene catalysts onto support materials has been of great interest since fixation of the polymerization catalysts to a surface might enable polymers to be replicated with higher density and larger particle size than those produced by unsupported homogeneous catalysts. In the catalyst preparation by Tudor and O'Hare,^[155] dehydrated MCM-41 material was first treated with an excess of MAO, and then with the chiral polymerization catalyst *rac*-ethenebis(indenyl)zirconium dichloride. It was found that the polypropylene produced by the metallocene-grafted MCM-41 was fourfold higher in number-averaged molecular weight and has higher isotacticity and melting point than that produced by the homogeneous catalyst.

An alternative approach in the fixation of polymerization catalysts has been developed by immobilizing zirconocene complexes^[156] that have modified cyclopentadienyl ligands. These zirconocene complexes could be conveniently anchored onto the walls of MCM-41 materials through their siloxy groups (Scheme 16). This catalyst system showed remarkable reactivity for ethylene polymerization; however, low activity was observed for propylene polymerization.



Scheme 16. Zirconocene complex anchored on the MCM-41 surface.

4. Other Applications

4.1. Thin Films and Membranes

In addition to catalytic applications, the well-defined mesoporous M41S family of materials also offer interesting potential for use in membrane separation, adsorption, and electronic/optical applications. For membrane applications, it is important to be able to process mesoporous structures in the form of defect-free, oriented thin films. Synthesis of ordered films of hexagonally packed mesoporous silica was first reported by Yang et al., who used an acidic aqueous mixture of cationic CTAC surfactant and TEOS.^[157] Thin films (0.2–1.0 μm) could be grown from the bottom side of a cleaved mica substrate held horizontally in the synthesis vessel. Mesoporosity of the thin films became accessible upon calcination, and TEM revealed that the pore channels ran predominantly parallel to the mica surface. The formation of the oriented mesoporous silica films was thought to begin with nucleation which involved silica-surfactant-mica interfacial interactions that facilitated the assembly of silica-surfactant micellar seeds on the mica. A later study by Yang et al.^[158] showed that ordered mesoporous films could be grown without a solid substrate by surfactant templating at the interface between air and water. These continuous films were believed to be formed through a dual-templating role of the surfactants. The authors suggested that the surfactant overstructure at the air–water interface and the micellar aggregates in solution interacted collectively with the soluble silicate building blocks to polymerize mesostructured silicates as free-standing films.

Aksay et al.^[159] showed that continuous mesostructured silica films could be grown on many substrates, with the corresponding structure determined by the specifics of the substrate–surfactant interaction. For example, not only the hydrophilic surface of mica but hydrophobic surfaces such as graphite could be used as binding sites for the silica–surfactant micellar precursor species to orient a hexagonal phase of mesostructured silica in the form of a continuous thin film. This study presented XRD results that illustrated epitaxial alignment of the adsorbed surfactant layer with crystalline mica and graphite substrates. The presence of significant strain in the mesostructured silica overlayer was verified, and as the films grew thicker, accumulated strain was released, which resulted in the growth of hierarchical structures from the ordered film.

By slow evaporation of a sol mixture containing TMOS, two equivalents of water, CTAC, and a mineral acid, Ogawa^[160] prepared a self-supporting transparent film of hexagonal-phase mesostructured silica. Transparency was retained after calcination, but the author did not discuss the orientation of the hexagonally packed pores or the retention of crack-free films.

For many potential applications, such as membranes for biomolecular separations and sensors for large molecules, it would be particularly useful to have the axis of the pore channel oriented vertically (instead of parallel) with respect to the solid substrate or liquid surface. The use of external forces to influence the ordering of pores in mesoporous films

has been examined recently. Hillhouse et al.^[161] have prepared hexagonally packed mesoporous silica layers on glass substrates in a continuous flow cell, and showed that an external flow field could induce a preferred orientation for film formation. Tolbert et al.^[162] demonstrated that the application of a strong magnetic field (11.7 T) could force the long-range orientational ordering of the pores in MCM-41 during the co-assembly process.

Lu et al.^[163] found that oriented mesostructured films could be obtained by dip-coating substrates with dilute precursor sols. Slow evaporation of the solvent in the entrained solution drove the surfactant concentration past the CMC, and the co-assembly of the silicate and surfactant into a well-defined mesostructure. Depending on the initial surfactant concentration, mesostructured films with hexagonal, cubic, and layered phases could be prepared. With calcination, supported mesoporous films of the two-dimensional hexagonal phase (with pore channels parallel to the air–solid interface) and a mixed cubic and three-dimensional hexagonal phase were obtained. The mixed-phase film contained three-dimensional pore channels accessible from the air–solid interface. Lu and co-workers further reported the in situ study of the lamellar → cubic → hexagonal mesostructure phase transformations. Whereas Lu et al.^[163] used CTAB as the templating surfactant, Tolbert et al.^[164] employed a gemini surfactant to prepare a mesoporous silicate film with the three-dimensional $P6_3/mmc$ mesophase structure.^[26, 29]

4.2. Hollow Tubules and Other Bulk Morphologies

The processing of mesoporous materials into designed bulk morphologies is not limited to thin films. Lin and Mou^[165] have found that hollow tubules of 0.3–3 μm in diameter could be produced by careful control of the surfactant–water content and the rate of silica condensation at high pH values. The wall of these tubules consisted of coaxial cylindrical MCM-41 mesopores. It was proposed that solvent-separated multilayers of periodic hexagonal MCM-41 silicates could be formed and further “bent” into hollow microtubules with the nanochannels constituting the walls of these tubules. The hierarchical order of this “tubules-within-a-tubule” organization is similar in nature to that of the frustules of marine diatoms, and may find applications in catalysis, separation technologies, and optoelectronics.

While MCM-41 synthesis typically resulted in precipitated powders, Huo et al.^[166] demonstrated that mesoporous silica could be produced in the form of marblelike spheres of about 1 mm in diameter. The authors prepared a basic CTAB solution and slowly added tetrabutylorthosilicate (TBOS) while stirring; the stirring speed controlled the size of the spheres. The surfactant was removed by calcination to yield smaller-diameter spheres of mesoporous silica. The authors suggested that the formation of the spheres was based on an emulsion synthesis, wherein the mixture of butanol (from hydrolyzed TBOS) was stabilized by the CTAB surfactant. The use of microemulsions was shown earlier in the formation of mesoporous silicate spherical shells by Schacht et al.^[167]

MCM-41 powders typically have little form, because of the uncontrolled precipitation of these materials. Exceptions have illustrated the hexagonal habit of MCM-41^[1b] and Nb-TMS1.^[65] Interesting particle morphologies of APM materials (mesoporous silicates prepared under acidic conditions) were demonstrated by Ozin and co-workers.^[168] The materials were synthesized under very low pH conditions and high dilution of TEOS and surfactant. These extreme synthesis conditions prevented uncontrolled precipitation of the mesostructured silicates, which allowed for high-curvature particles to nucleate and grow.

4.3. Other Templated Mesostructures and Hierarchical Structures

In the synthesis of MCM-41, ordered arrangements of mesoporous channels were produced in silica-based materials upon surfactant removal. The resulting pore sizes were governed by the diameter of the templating micelles, and have been limited to ≤ 30 nm. Recently, Davis et al.^[169] showed that a bacterial superstructure, which consisted of a thread of coaligned multicellular filaments of *Bacillus subtilis*, could be used to extend the length scale of inorganic materials patterning. Ordered macroporous fibers of either amorphous silica or MCM-41 mesostructured silica were obtained by template-directed mineralization of the interfilament spaces, followed by removal of organic material by calcination. The resulting inorganic structures consisted of a macroporous framework of 0.5 μm wide channels with curved walls of either amorphous or mesoporous silica, 50–200 nm in thickness. This work illustrated how supramolecular and supercellular templates might be combined for the fabrication of inorganic materials with hierarchical structures.

The concept of supramolecular templating was also extended to porous silicates with a layered structure.^[34, 170] Galarneau et al.^[170] showed that mesoporosity could be introduced into layered silicate clays by a gallery-template synthesis, which extended the range of pore sizes possible in pillared layered silicates (from spacings of < 10 Å to 14–22 Å). A cationic ammonium surfactant was used to swell a silicate clay before shorter chained alkylamines and TEOS were added; the organic components were later removed by calcination to yield porous clay heterostructures (PCH). The templating organics not only swelled the layers for the TEOS to pillar, but also controlled the spacing between the pillars within the galleries, an advantage not offered by traditional pillaring methods. Although the resulting materials did not resemble the typical M41S-type mesoporous materials, this approach could be applied to other classes of layered materials, such as zirconium phosphates.

4.4. Adsorbents

Beside catalysis and membrane separation, a major potential application of mesoporous materials lies in adsorbents. The huge pore volume and the compositional flexibility of MCM-41 type materials can be widely exploited for selective

adsorption of gases and liquids, and binding of metals. For example, Ioneva et al.^[171] have shown that adsorptive storage of methane in silicate-based MCM-41 was possible at 25 °C up to 6.9 MPa. An increase in methane storage could be attained with increasing surface area per unit volume of adsorbent. MCM-41 allowed for a 75 % improvement in the methane storage density over that of the compressed gas at 3.45 MPa. It also has higher total storage capacities for argon, nitrogen and light hydrocarbon vapors than typical microporous sorbents. In some applications, such as methane adsorption, pores smaller than 20 Å might be desirable for optimization of the gas affinity.

Mesoporous materials are also being used by Mitsubishi Heavy Industries, Ltd.^[172] for a volatile organic compounds (VOC) recovery process. The high surface area of mesoporous aluminosilicates can be utilized to adsorb VOC at room temperature with great capacity. The saturated sorbent can be reactivated with hot air (120–150 °C) and the recovered VOC can be concentrated by 3–10 times. This process does not require the use of steam for adsorbent reactivation, and is flexible for recovery of various kinds of VOC. Izumi^[172] has demonstrated that mesoporous materials can out-perform leading zeolite sorbents in the adsorption of methyl ethyl ketone by about twofold for a high SiO₂/Al₂O₃ ratio. The acidic, low-temperature synthesis developed also holds promise for the manufacture of mesoporous materials at a lower cost than high-silica zeolites.

For effective binding of heavy metals, Feng et al.^[173] have functionalized the surface of mesoporous silicate supports with a monolayer of tris(methoxy)sulfanylpropylsilane molecules with thiol terminal groups. This strategy enabled mercury, silver, and lead ions to be proficiently adsorbed from tainted water so that the samples were rendered clean enough to drink. The adsorptive power of this new material was more than an order of magnitude higher than that of conventional sorbents. The sorbent was highly selective for certain metals; metal ions such as sodium, barium, and zinc were not taken up. It was also reusable; treatment of the mercury-loaded material with concentrated HCl would release the mercury, and the sorbent remained functional after multiple cycles. This example represented a powerful application of functionalized mesoporous materials as a selective sorbent with ultra-high surface activity.

4.5. Hosts for Quantum Structures

The well-defined mesoporous structure of M41S materials can be used as hosts for quantum semiconductor structures of low dimensionality. The cylindrical channels of the mesoporous structure of MCM-41 allow for matrix-mediated synthesis of molecular wires and quantum wires, and the silicate-based framework can provide electrical isolation of the conducting wires. Wu and Bein^[174] have reported the adsorption of aniline and its polymerization in the pores of a transition metal containing mesoporous MCM-41 host. The resulting polyaniline filaments encapsulated in the 3 nm wide pore channels showed significant low-field conductivity,

which indicated that they still supported mobile charge carriers.

Leon et al.^[175] have demonstrated the feasibility of filling the mesopores with a semiconductor. Using vapor phase epitaxy, germanium filaments were deposited in the pore channels whereby surface hydroxyls acted as anchor points for seeding the nucleation of semiconductor clusters. The Ge crystallites took the shape and periodicity of the mesopores of the silicate matrix. While only some of the pores were filled and more complete semiconductor loading awaits future development, such fabrication techniques are promising towards generating quantum wire and dot arrays with high packing density.

For device fabrication, it would be of interest to derive the host inorganic materials in the form of thin films (instead of particulates), with ordered mesopores preferably oriented perpendicular to the plane of the films. It would also be important for many applications to achieve the quantum wires as continuous, single crystals.^[176] This area of research holds a great deal of potential for significant technological impact, and may capitalize on the pore-size tunability of well-defined MCM-41 mesostructures for unique quantum confinement effects.

5. Summary and Outlook

The field of heterogeneous catalysis has benefited tremendously from the research in supramolecular-templated mesoporous materials and will continue to grow, especially with the development of materials of new compositions and surface modifications. The potential of mesoporous materials as catalysts has already been demonstrated in a number of areas, but only time will tell if these novel materials will find widespread commercial applications. Research in the preparation of materials that contain both surfactant-templated mesoporosity and controlled bulk features has just begun, and it remains to be seen if these systems can be developed for macrostructure-dependent applications, such as membrane separations. In spite of the large amount of synthesis work done already, relatively little research has been devoted to further elucidate the mechanisms of formation for the variety of mesostructures. Insights on self-assembly mechanisms will be useful towards expanding our capability to derive systematically tuned pore dimensions which span the microporous, mesoporous and macroporous regimes. Hierarchical mesostructures possessing patterned features on different length scales processed in the desired bulk morphologies also await further development as unique multifunctional devices.

Appendix

Abbreviations of mesoporous materials, proposed mechanisms, and substrates.

APM	acid-prepared mesostructures
CMC	critical micelle concentration
CTAB	cetyltrimethylammonium bromide
CTAC	cetyltrimethylammonium chloride

D4R	double four-ring
FSM	mesoporous materials prepared from kanemite
<i>g</i>	effective surfactant packing parameter
<i>I</i>	inorganic precursor
L_3	“sponge” mesopore phases
LAT	ligand-assisted templating
LC	liquid crystal
LCT	liquid crystal templating
M^+	metal cation
M41S	family of mesoporous materials
MCM-41	hexagonal mesoporous phase
MCM-48	cubic mesoporous phase
MCM-50	lamellar mesoporous phase
MOMS	mesoporous manganese oxides
MSU	mesoporous alumina phases
N^0	nonionic head group
<i>S</i>	surfactant head group
SBA	mesoporous materials derived by the APM method
SLC	silicatropic liquid crystal
TBOS	tetrabutylorthosilicate
TEOS	tetraethylorthosilicate
TMAOH	tetramethylammonium hydroxide
TMOS	tetramethylorthosilicate
TMS	mesoporous transition metal oxides (Tech molecular sieves)
X^-	counteranion

We acknowledge the financial support of the National Science Foundation and the David and Lucile Packard Foundation.

Received: December 1, 1997

Revised version: July 15, 1998 [A262IE]

German version: *Angew. Chem.* **1999**, *111*, 58–82

- [1] a) C. T. Kresge, M. E. Leonowicz, W. J. Roth, J. C. Vartuli, J. S. Beck, *Nature* **1992**, *359*, 710–712; b) J. S. Beck, J. C. Vartuli, W. J. Roth, M. E. Leonowicz, C. T. Kresge, K. D. Schmitt, C. T.-W. Chu, D. H. Olson, E. W. Sheppard, S. B. McCullen, J. B. Higgins, J. L. Schlenker, *J. Am. Chem. Soc.* **1992**, *114*, 10834–10843; c) C. T. Kresge, M. E. Leonowicz, W. J. Roth, J. C. Vartuli (Mobil Oil Corp.), US-A 5098 684, **1992** [*Chem. Abstr.* **1992**, *117*, 72621].
- [2] C. J. Brinker, *Curr. Opin. Solid State. Mater. Sci.* **1996**, *1*, 798–805.
- [3] J. C. Vartuli, C. T. Kresge, W. J. Roth, S. B. McCullen, J. S. Beck, K. D. Schmitt, M. E. Leonowicz, J. D. Lutner, E. W. Sheppard in *Advanced Catalysts and Nanostructured Materials: Modern Synthesis Methods* (Ed.: W. R. Moser), Academic Press, New York, **1996**, pp. 1–19.
- [4] G. D. Stucky, Q. Huo, A. Firouzi, B. F. Chmelka, S. Schacht, I. G. Voigt-Martin, F. Schüth in *Progress in Zeolite and Microporous Materials, Studies in Surface Science and Catalysis, Vol. 105* (Eds.: H. Chon, S.-K. Ihm, Y. S. Uh), Elsevier, Amsterdam, **1997**, pp. 3–28.
- [5] N. K. Raman, M. T. Anderson, C. J. Brinker, *Chem. Mater.* **1996**, *8*, 1682–1701.
- [6] D. M. Antonelli, J. Y. Ying, *Curr. Opin. Coll. Interf. Sci.* **1996**, *1*, 523–529.
- [7] P. Behrens, *Angew. Chem.* **1996**, *108*, 561–564; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 515–518.
- [8] X. S. Zhao, G. Q. Lu, G. J. Millar, *Ind. Eng. Chem. Res.* **1996**, *35*, 2075–2090.
- [9] A. Sayari, *Chem. Mater.* **1996**, *8*, 1840–1852.
- [10] P. Behrens, *Adv. Mater.* **1993**, *5*, 127–132.
- [11] J. S. Beck, J. C. Vartuli, G. J. Kennedy, C. T. Kresge, W. J. Roth, S. E. Schramm, *Chem. Mater.* **1994**, *6*, 1816–1821.
- [12] J. C. Vartuli, C. T. Kresge, M. E. Leonowicz, A. S. Chu, S. B. McCullen, I. D. Johnson, E. W. Sheppard, *Chem. Mater.* **1994**, *6*, 2070–2077.
- [13] C.-Y. Chen, S. L. Burkett, H.-X. Li, M. E. Davis, *Microporous Mater.* **1993**, *2*, 27–34.
- [14] A. Steel, S. W. Carr, M. W. Anderson, *J. Chem. Soc. Chem. Commun.* **1994**, 1571–1572.
- [15] A. Monnier, F. Schüth, Q. Huo, D. Kumar, D. Margolese, R. S. Maxwell, G. D. Stucky, M. Krishnamurty, P. Petroff, A. Firouzi, M. Janicke, B. F. Chmelka, *Science* **1993**, *261*, 1299–1303.
- [16] G. D. Stucky, A. Monnier, F. Schüth, Q. Huo, D. Margolese, D. Kumar, M. Krishnamurty, P. Petroff, A. Firouzi, M. Janicke, B. F. Chmelka, *Mol. Cryst. Liq. Cryst.* **1994**, *240*, 187–200.
- [17] a) T. Yanagisawa, T. Shimizu, K. Kuroda, C. Kato, *Bull. Chem. Soc. Jpn.* **1990**, *63*, 988–992; b) S. Inagaki, Y. Fukushima, K. Kuroda, *J. Chem. Soc. Chem. Commun.* **1993**, 680–682; c) Y. Fukushima, S. Inagaki, *Mater. Sci. Eng. A* **1996**, *217–218*, 116–118.
- [18] A. Firouzi, D. Kumar, L. M. Bull, T. Besier, P. Sieger, Q. Huo, S. A. Walker, J. A. Zasadzinski, C. Glinka, J. Nicol, D. Margolese, G. D. Stucky, B. F. Chmelka, *Science* **1995**, *267*, 1138–1143.
- [19] S. Ikeda in *Surfactants in Solution, Vol. 2* (Eds.: K. L. Mittal, B. Lindman), Plenum, New York, **1984**, pp. 825–840.
- [20] A. Firouzi, F. Atef, A. G. Oertli, G. D. Stucky, B. F. Chmelka, *J. Am. Chem. Soc.* **1997**, *119*, 3596–3610.
- [21] C. A. Fyfe, G. Fu, *J. Am. Chem. Soc.* **1995**, *117*, 9709–9714.
- [22] O. Regev, *Langmuir* **1996**, *12*, 4940–4944.
- [23] a) Q. Huo, D. I. Margolese, U. Ciesla, P. Feng, T. E. Gier, P. Sieger, R. Leon, P. M. Petroff, F. Schüth, G. D. Stucky, *Nature* **1994**, *368*, 317–321; b) Q. Huo, D. I. Margolese, U. Ciesla, D. G. Demuth, P. Feng, T. E. Gier, P. Sieger, A. Firouzi, B. F. Chmelka, F. Schüth, G. D. Stucky, *Chem. Mater.* **1994**, *6*, 1176–1191.
- [24] J. C. Vartuli, K. D. Schmitt, C. T. Kresge, W. J. Roth, M. E. Leonowicz, S. B. McCullen, S. D. Hellring, J. S. Beck, J. L. Schlenker, D. H. Olsen, E. W. Sheppard, *Chem. Mater.* **1994**, *6*, 2317–2326.
- [25] J. C. Vartuli, C. T. Kresge, W. J. Roth, S. B. McCullen, J. S. Beck, K. D. Schmitt, M. E. Leonowicz, J. D. Lutner, E. W. Sheppard in *Proceedings of the 209th ACS National Meeting, Division of Petroleum Chemistry* **1995**, pp. 21–25.
- [26] Q. Huo, D. I. Margolese, G. D. Stucky, *Chem. Mater.* **1996**, *8*, 1147–1160.
- [27] V. Luzzati, R. Vargas, P. Mariani, A. Gulik, H. Delacroix, *J. Mol. Biol.* **1993**, *229*, 540–551.
- [28] J. N. Israelachvili, *Intermolecular and Surface Forces*, 2nd ed., Academic Press, London, **1992**, pp. 366–394.
- [29] Q. Huo, R. Leon, P. M. Petroff, G. D. Stucky, *Science* **1995**, *268*, 1324–1327.
- [30] a) J. M. Kim, S. K. Kim, R. Ryoo, *Chem. Commun.* **1998**, 259–260; b) K. W. Gallis, C. C. Landry, *Chem. Mater.* **1997**, *9*, 2035–2038.
- [31] F. Chen, L. Huang, Q. Li, *Chem. Mater.* **1997**, *9*, 2685–2686.
- [32] P. T. Tanev, T. J. Pinnavaia, *Science* **1995**, *267*, 865–867.
- [33] P. T. Tanev, T. J. Pinnavaia, *Chem. Mater.* **1996**, *8*, 2068–2079.
- [34] P. T. Tanev, T. J. Pinnavaia, *Science* **1996**, *271*, 1267–1269.
- [35] S. A. Bagshaw, E. Prouzet, T. J. Pinnavaia, *Science* **1995**, *269*, 1242–1244.
- [36] G. S. Attard, J. C. Glyde, C. G. Göltner, *Nature* **1995**, *378*, 366–368.
- [37] a) C. G. Göltner, M. Antonietti, *Adv. Mater.* **1997**, *9*, 431–436; b) C. G. Göltner, S. Henke, M. C. Weissenberger, M. Antonietti, *Angew. Chem.* **1998**, *110*, 633–636; *Angew. Chem. Int. Ed.* **1998**, *37*, 613–616.
- [38] K. M. McGrath, D. M. Dabbs, N. Yao, I. A. Aksay, S. M. Gruner, *Science* **1997**, *277*, 552–556.
- [39] a) R. Ryoo, J. M. Kim, C. H. Ko, C. H. Shin, *J. Phys. Chem.* **1996**, *100*, 17718–17721; b) R. Ryoo, J. M. Kim, C. H. Shin, J. Y. Lee in *Progress in Zeolite and Microporous Materials, Studies in Surface Science and Catalysis, Vol. 105* (Eds.: H. Chon, S.-K. Ihm, Y. S. Uh), Elsevier, Amsterdam, **1997**, pp. 45–52.
- [40] R. Ryoo, C. H. Ko, R. F. Howe, *Chem. Mater.* **1997**, *9*, 1607–1613.
- [41] A. Corma, M. T. Navarro, J. Pérez Pariente, *J. Chem. Soc. Chem. Commun.* **1994**, 147–148.
- [42] K. M. Reddy, I. Moudrakovski, A. Sayari, *J. Chem. Soc. Chem. Commun.* **1994**, 1059–1060.
- [43] P. T. Tanev, M. Chibwe, T. J. Pinnavaia, *Nature* **1994**, *368*, 321–323.
- [44] A. Sayari, C. Danumah, I. L. Moudrakovski, *Chem. Mater.* **1995**, *7*, 813–815.

- [45] Z. Luan, C.-F. Cheng, W. Zhou, J. Klinowski, *J. Phys. Chem.* **1995**, 99, 1018–1024.
- [46] G. Fu, C. A. Fyfe, W. Schwieger, G. T. Kokotailo, *Angew. Chem.* **1995**, 107, 1582–1585; *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 1499–1502.
- [47] D. Zhao, D. Goldfarb, *J. Chem. Soc. Chem. Commun.* **1995**, 875–876.
- [48] T. M. Abdel-Fattah, T. J. Pinnavaia, *Chem. Commun.* **1996**, 665–666.
- [49] C.-F. Cheng, H. He, W. Zhou, J. Klinowski, J. A. S. Gonçalves, L. F. Gladden, *J. Phys. Chem.* **1996**, 100, 390–396.
- [50] C.-F. Cheng, J. Klinowski, *J. Chem. Soc. Faraday Trans.* **1996**, 92, 289–292.
- [51] K. A. Koyano, T. Tatsumi, *Chem. Commun.* **1996**, 145–146.
- [52] A. Tuel, S. Gontier, *Chem. Mater.* **1996**, 8, 114–122.
- [53] A. Tuel, S. Gontier, R. Teissier, *Chem. Commun.* **1996**, 651–652.
- [54] N. Ulagappan, C. N. R. Rao, *Chem. Commun.* **1996**, 1047–1048.
- [55] W. Zhang, T. J. Pinnavaia, *Catal. Lett.* **1996**, 38, 261–265.
- [56] W. Zhang, J. Wang, P. T. Tanev, T. J. Pinnavaia, *Chem. Commun.* **1996**, 979–980.
- [57] B. Echchahed, A. Moen, D. Nicholson, L. Bonneviot, *Chem. Mater.* **1997**, 9, 1716–1719.
- [58] N.-Y. He, J.-M. Cao, S.-L. Bao, Q.-H. Xu, *Mater. Lett.* **1997**, 31, 133–136.
- [59] D. J. Jones, J. Jiménez-Jiménez, A. Jiménez-López, P. Maireles-Torres, P. Olivera-Pastor, E. Rodríguez-Castellón, J. Rozière, *Chem. Commun.* **1997**, 431–432.
- [60] L. Zhang, J. Y. Ying, *AIChE J.* **1997**, 43, 2793–2801.
- [61] M. S. Wong, H. C. Huang, J. Y. Ying, unpublished results.
- [62] U. Ciesla, D. Demuth, R. Leon, P. Petroff, G. Stucky, K. Unger, F. Schüth, *J. Chem. Soc. Chem. Commun.* **1994**, 1387–1388.
- [63] D. M. Antonelli, J. Y. Ying, *Angew. Chem.* **1995**, 107, 2202–2206; *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 2014–2017.
- [64] D. M. Antonelli, J. Y. Ying, *Angew. Chem.* **1996**, 108, 461–464; *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 426–430.
- [65] D. M. Antonelli, A. Nakahira, J. Y. Ying, *Inorg. Chem.* **1996**, 35, 3126–3136.
- [66] D. M. Antonelli, J. Y. Ying, *Chem. Mater.* **1996**, 8, 874–881.
- [67] M. S. Wong, D. M. Antonelli, J. Y. Ying, *Nanostr. Mater.* **1997**, 9, 165–168.
- [68] M. S. Wong, J. Y. Ying, *Chem. Mater.* **1998**, 10, 2067–2077.
- [69] A. Stein, M. Fendorf, T. P. Jarvie, K. T. Mueller, A. J. Benesi, T. E. Mallouk, *Chem. Mater.* **1995**, 7, 304–313.
- [70] G. G. Janauer, A. Doble, J. Guo, P. Zavalij, M. S. Whittingham, *Chem. Mater.* **1996**, 8, 2096–2101.
- [71] a) V. Luca, D. J. MacLachlan, J. M. Hook, R. Withers, *Chem. Mater.* **1995**, 7, 2220–2223; b) V. Luca, J. M. Hook, *Chem. Mater.* **1997**, 9, 2731–2744.
- [72] J. Luo, S. L. Suib, *Chem. Commun.* **1997**, 1031–1032.
- [73] Z.-R. Tian, W. Tong, J.-Y. Wang, N.-G. Duan, V. V. Krishnan, S. L. Suib, *Science* **1997**, 276, 926–930.
- [74] S. A. Bagshaw, T. J. Pinnavaia, *Angew. Chem.* **1996**, 108, 1180–1183; *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 1102–1105.
- [75] F. Vaudry, S. Khodabandeh, M. E. Davis, *Chem. Mater.* **1996**, 8, 1451–1464.
- [76] M. Yada, M. Machida, T. Kijima, *Chem. Commun.* **1996**, 769–770.
- [77] A. Sayari, I. Moudrakovski, J. S. Reddy, C. I. Ratcliffe, J. A. Ripmeester, K. F. Preston, *Chem. Mater.* **1996**, 8, 2080–2088.
- [78] A. Sayari, V. R. Karra, J. S. Reddy, I. L. Moudrakovski, *J. Chem. Soc. Chem. Commun.* **1996**, 411–412.
- [79] A. Chenite, Y. Le Page, V. R. Karra, A. Sayari, *J. Chem. Soc. Chem. Commun.* **1996**, 413–414.
- [80] S. Oliver, A. Kuperman, N. Coombs, A. Lough, G. A. Ozin, *Nature* **1995**, 378, 47–50.
- [81] P. Feng, Y. Xia, J. Feng, X. Bu, G. D. Stucky, *Chem. Commun.* **1997**, 949–950.
- [82] D. Zhao, Z. Luan, L. Kevan, *Chem. Commun.* **1997**, 1009–1010.
- [83] B. Chakraborty, A. C. Pulikottil, S. Das, B. Viswanathan, *Chem. Commun.* **1997**, 911–912.
- [84] T. Abe, A. Taguchi, M. Iwamoto, *Chem. Mater.* **1995**, 7, 1429–1430.
- [85] T. Doi, T. Miyake, *Chem. Commun.* **1996**, 1635–1636.
- [86] M. J. Hudson, J. A. Knowles, *J. Mater. Chem.* **1996**, 6, 89–95.
- [87] J. S. Reddy, A. Sayari, *Catal. Lett.* **1996**, 38, 219–223.
- [88] U. Ciesla, S. Schacht, G. D. Stucky, K. K. Unger, F. Schüth, *Angew. Chem.* **1996**, 108, 597–600; *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 541–543.
- [89] P. Liu, J. S. Reddy, A. Adnot, A. Sayari, *Mater. Res. Soc. Symp. Proc.* **1996**, 431, 101–106.
- [90] P. Liu, J. Liu, A. Sayari, *Chem. Commun.* **1997**, 577–578.
- [91] a) P. V. Braun, P. Osenar, S. I. Stupp, *Nature* **1996**, 380, 325–328; b) V. Tohver, P. V. Braun, M. U. Pralle, S. I. Stupp, *Chem. Mater.* **1997**, 9, 1495–1498.
- [92] J. Li, L. Delmotte, H. Kessler, *Chem. Commun.* **1996**, 1023–1024.
- [93] D. Zhao, D. Goldfarb, *Chem. Mater.* **1996**, 8, 2571–2578.
- [94] G. S. Attard, C. G. Göltner, J. M. Corker, S. Henke, R. H. Templer, *Angew. Chem.* **1997**, 109, 1372–1374; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 1315–1317.
- [95] A. Navrotsky, I. Petrovic, Y. Hu, C.-Y. Chen, M. E. Davis, *J. Non-Cryst. Solids* **1995**, 192&193, 474–477.
- [96] T. Sun, J. Y. Ying, *Nature* **1997**, 389, 704–706.
- [97] T. Sun, J. Y. Ying, *Angew. Chem.* **1998**, 110, 690–693; *Angew. Chem. Int. Ed.* **1998**, 37, 664–667.
- [98] D. Zhao, J. Feng, Q. Huo, N. Melosh, G. H. Fredrickson, B. F. Chmelka, G. D. Stucky, *Science* **1998**, 279, 548–552.
- [99] I. W. C. E. Arends, R. A. Sheldon, M. Wallau, U. Schuchardt, *Angew. Chem.* **1997**, 109, 1190–1211; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 1144–1163.
- [100] J. S. Reddy, A. Sayari, *J. Chem. Soc. Chem. Commun.* **1995**, 2231–2232.
- [101] S. Gontier, A. Tuel, *J. Catal.* **1995**, 157, 124–132.
- [102] I. Vankelecom, K. Vercruysse, N. Moens, R. Parton, J. S. Reddy, P. Jacobs, *Chem. Commun.* **1997**, 137–138.
- [103] A. Corma, A. Martinez, V. Martinez-Soria, J. B. Monton, *J. Catal.* **1995**, 153, 25–31.
- [104] K. M. Reddy, C. Song, *Catal. Lett.* **1996**, 36, 103–109.
- [105] K. M. Reddy, C. Song, *Catal. Today* **1996**, 31, 137–144.
- [106] B. A. Aufdembrink, A. W. Chester, J. A. Herbst, C. T. Kresge (Mobil Oil Corp.), US-A 5258114, **1993** [*Chem. Abstr.* **1991**, 115,-139158].
- [107] J. S. Beck, D. C. Calabro, S. B. McCullen, B. P. Pelrine, K. D. Schmitt, J. C. Vartuli (Mobil Oil Corp.), US-A 5200058, **1993** [*Chem. Abstr.* **1991**, 115, 139158].
- [108] N. A. Bhole, Q. N. Le, G. H. Yokomizo (Mobil Oil Corp.), US-A 5134243, **1992** [*Chem. Abstr.* **1993**, 118, 106144].
- [109] Q. N. Le, R. T. Thomson, G. H. Yokomizo (Mobil Oil Corp.), US-A 5134241, **1992** [*Chem. Abstr.* **1992**, 117, 237023].
- [110] Q. N. Le, R. T. Thomson, G. H. Yokomizo (Mobil Oil Corp.), US-A 5134242, **1992** [*Chem. Abstr.* **1993**, 118, 172297].
- [111] Q. N. Le, R. T. Thomson (Mobil Oil Corp.), US-A 5232580, **1993** [*Chem. Abstr.* **1993**, 119, 52652].
- [112] Q. N. Le, R. T. Thomson (Mobil Oil Corp.), US-A 5191144, **1993** [*Chem. Abstr.* **1993**, 119, 31334].
- [113] T. F. Degnan, Jr., K. M. Keville, D. O. Marler, D. N. Mazzone (Mobil Oil Corp.), US-A 5281328, **1994** [*Chem. Abstr.* **1993**, 119, 31376].
- [114] M. R. Apelian, T. F. Degnan, Jr., D. O. Marler, D. N. Mazzone (Mobil Oil Corp.), US-A 5227353, **1993** [*Chem. Abstr.* **1993**, 119, 31331].
- [115] M. R. Apelian, T. F. Degnan, Jr., D. O. Marler, D. N. Mazzone (Mobil Oil Corp.), US-A 5264116, **1993** [*Chem. Abstr.* **1993**, 119, 31355].
- [116] T. F. Degnan, Jr., K. M. Keville, M. E. Landis, D. O. Marler, D. N. Mazzone (Mobil Oil Corp.), US-A 5183557, **1993** [*Chem. Abstr.* **1993**, 119, 31376].
- [117] T. F. Degnan, Jr., K. M. Keville, M. E. Landis, D. O. Marler, D. N. Mazzone (Mobil Oil Corp.), US-A 5290744, **1994** [*Chem. Abstr.* **1993**, 119, 31376].
- [118] D. O. Marler, D. N. Mazzone (Mobil Oil Corp.), US-A 5288395, **1994** [*Chem. Abstr.* **1993**, 119, 31354].
- [119] D. O. Marler, D. N. Mazzone (Mobil Oil Corp.), US-A 5277792, **1994** [*Chem. Abstr.* **1993**, 119, 31355].
- [120] J. Aguado, D. P. Serrano, M. D. Romero, J. M. Escola, *Chem. Commun.* **1996**, 725–726.
- [121] M. J. Climent, A. Corma, S. Iborra, M. C. Navarro, J. Primo, *J. Catal.* **1996**, 161, 783–789.
- [122] K. R. Kloetstra, H. van Bekkum, *J. Chem. Res.* **1995**, 26–27.
- [123] E. Armengol, M. L. Cano, A. Corma, H. Garcia, M. T. Navarro, *J. Chem. Soc. Chem. Commun.* **1995**, 519–520.
- [124] Q. N. Le (Mobil Oil Corp.), US-A 5191134, **1993** [*Chem. Abstr.* **1993**, 118, 212647].

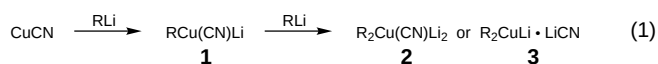
- [125] T. F. Degnan, Jr., K. J. Del Rossi, A. Huss, Jr. (Mobil Oil Corp.), US-A 5191148, **1993** [*Chem. Abstr.* **1993**, *118*, 256987].
- [126] T. F. Degnan, Jr., K. J. Del Rossi, A. Husain, A. Huss, Jr., US-A 5191147, **1993** [*Chem. Abstr.* **1993**, *119*, 163816].
- [127] Q. N. Le (Mobil Oil Corp.), US-A 5118894, **1992** [*Chem. Abstr.* **1992**, *117*, 153192].
- [128] A. Corma, M. Iglesias, F. Sanchez, *J. Chem. Soc. Chem. Commun.* **1995**, 1635–1636.
- [129] J. S. Beck, R. F. Socha, D. S. Shihiba, J. C. Vartuli (Mobil Oil Corp.), US-A 5143707, **1992** [*Chem. Abstr.* **1993**, *118*, 26784].
- [130] C. T. Kresge, M. E. Leonowicz, W. J. Roth, J. C. Vartuli, K. M. Keville, S. S. Shih, T. F. Degnan, Jr., F. G. Dwyer, M. E. Landis (Mobil Oil Corp.), US-A 5183561, **1993** [*Chem. Abstr.* **1991**, *115*, 139158].
- [131] B. P. Pelrine, K. D. Schmitt, J. C. Vartuli (Mobil Oil Corp.), US-A 5105051, **1992** [*Chem. Abstr.* **1992**, *117*, 154327].
- [132] B. P. Pelrine, K. D. Schmitt, J. C. Vartuli (Mobil Oil Corp.), US-A 5270273, **1993** [*Chem. Abstr.* **1994**, *120*, 303101].
- [133] N. A. Bhore, I. D. Johnson, K. M. Keville, Q. N. Le, G. H. Yokomizo (Mobil Oil Corp.), US-A 5260501, **1993** [*Chem. Abstr.* **1992**, *117*, 237023].
- [134] K. J. Del Rossi, G. H. Hatzikos, A. Huss, Jr. (Mobil Oil Corp.), US-A 5256277, **1993** [*Chem. Abstr.* **1993**, *119*, 31332].
- [135] W. S. Borghard, C. T. Chu, T. F. Degnan, Jr., S. S. Shih (Mobil Oil Corp.), US-A 5264641, **1993** [*Chem. Abstr.* **1994**, *120*, 133915].
- [136] C. T. Kresge, D. O. Marler, G. S. Rav, B. H. Rose (Mobil Oil Corp.), US-A 5366945, **1994** [*Chem. Abstr.* **1995**, *122*, 110416].
- [137] K. R. Klotstra, H. van Bekkum, *J. Chem. Soc. Chem. Commun.* **1995**, 1005–1006.
- [138] T. Maschmeyer, F. Rey, G. Sankar, J. M. Thomas, *Nature* **1995**, *378*, 159–162.
- [139] R. Neumann, A. M. Khenkin, *Chem. Commun.* **1996**, 2643–2644.
- [140] R. Burch, N. Cruise, D. Gleeson, S. C. Tsang, *Chem. Commun.* **1996**, 951–952.
- [141] J. Y. Ying, C. P. Mehnert (Massachusetts Institute of Technology), US Patent pending, **1997**.
- [142] C. P. Mehnert, J. Y. Ying, *Chem. Commun.* **1997**, 2215–2216.
- [143] C. P. Mehnert, D. Weaver, J. Y. Ying, *J. Am. Chem. Soc.*, in press.
- [144] C. Liu, X. Ye, Y. Wu, *Catal. Lett.* **1996**, *36*, 263–266.
- [145] P. Sutra, D. Brunel, *Chem. Commun.* **1996**, 2485–2486.
- [146] Y. V. S. Rao, D. E. De Vos, T. Bein, P. A. Jacobs, *Chem. Commun.* **1997**, 355–356.
- [147] J. F. Diaz, K. J. Balkus, Jr., F. Bedioui, V. Kurshev, L. Kevan, *Chem. Mater.* **1997**, *9*, 61–67.
- [148] N. Herron, G. D. Stucky, C. A. Tolman, *J. Chem. Soc. Chem. Commun.* **1986**, 1521–1522.
- [149] N. Herron, *Inorg. Chem.* **1986**, *25*, 4714–4723.
- [150] C.-J. Liu, S.-G. Li, W.-Q. Pang, C.-M. Che, *Chem. Commun.* **1997**, 65–66.
- [151] L. Zhang, T. Sun, J. Y. Ying, **1997**, unpublished results.
- [152] S. O'Brien, J. Tudor, S. Barlow, M. J. Drewitt, S. J. Heyes, D. O'Hare, *Chem. Commun.* **1997**, 641–642.
- [153] T. Maschmeyer, R. D. Oldroyd, G. Sankar, J. M. Thomas, I. J. Shannon, J. A. Klepetko, A. F. Masters, J. K. Beattie, C. R. A. Catlow, *Angew. Chem.* **1997**, *109*, 1713–1716; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1639–1642.
- [154] Y. S. Ko, T. K. Han, J. W. Park, S. I. Woo, *Macromol. Rapid Commun.* **1996**, *17*, 749–750.
- [155] J. Tudor, D. O'Hare, *Chem. Commun.* **1997**, 603–604.
- [156] C. P. Mehnert, B. L. Lungwitz, D. Seyferth, J. Y. Ying, **1997**, unpublished results.
- [157] H. Yang, A. Kuperman, N. Coombs, S. Mamiche-Afara, G. A. Ozin, *Nature* **1996**, *379*, 703–705.
- [158] H. Yang, N. Coombs, I. Sokolov, G. A. Ozin, *Nature* **1996**, *381*, 589–592.
- [159] I. Aksay, M. Trau, S. Manne, I. Honma, N. Yao, L. Zhou, P. Fenter, P. M. Eisenberger, S. M. Gruner, *Science* **1996**, *273*, 892–898.
- [160] M. Ogawa, *Chem. Commun.* **1996**, 1149–1150.
- [161] W. Hillhouse, T. Okubo, J. W. van Egmond, M. Tsapatsis, *Chem. Mater.* **1997**, *9*, 1505–1507.
- [162] J. Tolbert, A. Firouzi, G. D. Stucky, B. F. Chmelka, *Science* **1997**, *278*, 264–268.
- [163] Y. Lu, R. Ganguli, C. A. Drewien, M. T. Anderson, C. J. Brinker, W. Gong, Y. Guo, H. Soyez, B. Dunn, M. H. Huang, J. I. Zink, *Nature* **1997**, *389*, 364–368.
- [164] S. H. Tolbert, T. E. Schäffer, J. Feng, P. K. Hansma, G. D. Stucky, *Chem. Mater.* **1997**, *9*, 1962–1967.
- [165] H.-P. Lin, C.-Y. Mou, *Science* **1996**, *273*, 765–768.
- [166] Q. Huo, J. Feng, F. Schüth, G. D. Stucky, *Chem. Mater.* **1997**, *9*, 14–17.
- [167] S. Schacht, Q. Huo, G. Voigt-Martin, G. D. Stucky, F. Schüth, *Science* **1996**, *273*, 768–771.
- [168] a) H. Yang, N. Coombs, G. A. Ozin, *Nature* **1997**, *386*, 692–695; b) G. A. Ozin, H. Yang, I. Sokolov, N. Coombs, *Adv. Mater.* **1997**, *9*, 662–667.
- [169] S. A. Davis, S. L. Burkett, N. H. Mendelson, S. Mann, *Nature* **1997**, *385*, 420–423.
- [170] A. Galarneau, A. Barodawalla, T. J. Pinnavaia, *Nature* **1995**, *374*, 529–531.
- [171] M. A. Ioneva, G. K. Newman, J. H. Harwell, *AIChE Symp. Ser.* **1995**, *91*(309), 40–48.
- [172] J. Izumi, *Mitsubishi VOC Recovery Process*, Mitsubishi Heavy Industries, Ltd., **1996**.
- [173] a) X. Feng, G. E. Fryxell, L.-Q. Wang, A. Y. Kim, J. Liu, K. M. Kemner, *Science* **1997**, *276*, 923–926; b) J. Liu, X. Feng, G. E. Fryxell, L.-Q. Wang, A. Y. Kim, M. Gong, *Adv. Mater.* **1998**, *10*, 161–165.
- [174] C.-G. Wu, T. Bein, *Chem. Mater.* **1994**, *6*, 1109–1112.
- [175] R. Leon, D. Margolese, G. Stucky, P. M. Petroff, *Phys. Rev. B* **1995**, *52*, 2285–2288.
- [176] Z. Zhang, J. Y. Ying, M. S. Dresselhaus, *J. Mater. Res.* **1998**, *13*, 1745–1748.

New Results Regarding the Structure and Reactivity of Cyanocuprates— The End of an Old Controversy

Norbert Krause*

History

Organocopper reagents play a prominent role among the many organometallic compounds which can be used for the selective formation of C–C bonds.^[1] Monoorganocopper compounds RCu and cuprates R₂CuLi are usually prepared by transmetalation of organolithium or Grignard reagents with copper(I) salts. In 1981, Lipshutz et al.^[2] described for the first time cyanocuprates which were formed by reaction of copper(I) cyanide with one or two equivalents of RLi. These reagents seemed to differ considerably in terms of stability and reactivity (in Michael additions and substitution reactions) from the so-called Gilman cuprates R₂CuLi · LiX (X = Cl, Br, I) which are prepared from copper(I) halides. Lipshutz et al. explained these findings by postulating that the cyano group is bound to the copper center. Accordingly, the reaction of CuCN with one equivalent of RLi would lead to the copper species RCu(CN)Li (**1**) which was designated as a “lower-order” cyanocuprate; after addition of a second equivalent of RLi, the cyanocuprate R₂Cu(CN)Li₂ (**2**) would be formed [Eq. (1)]. In contrast to the monoanionic cuprates R₂CuLi,



which can be described in ionic form as [R₂Cu][−] + Li⁺, the latter species would exist as an dianionic cuprate ([R₂Cu(CN)]^{2−} + 2Li⁺) with three organic groups bound to the copper. Lipshutz designated these reagents as “higher-order” cyanocuprates.^[2, 3]

The structural assignment for the “lower-order” species **1** was confirmed by different spectroscopic experiments. The most convincing proof is the coupling between the cyanide ligand and methyl group (²J ≈ 22 Hz) observed by Bertz^[4] in the ¹³C NMR spectrum of the labeled cuprate MeCu(¹³CN)Li; of course, such a coupling can only be observed when *both* groups are bound to the copper atom. In contrast to this, the question whether cyanocuprates with a 2:1 stoichiometry exist as “higher-order” species **2** or rather as “cyano-Gilman”

cuprates **3** in their thermodynamically most stable form has been a matter of controversy since 1990, the protagonists being B. H. Lipshutz (“If the cyano ligand is not on copper, then where is it?”) and S. H. Bertz (“It’s on lithium!”). The controversy started with different interpretations of the ¹³C NMR data of several cuprates prepared from CuI or CuCN^[5, 6] and the observation that no coupling occurs between the alkyl groups and the cyanide ligand in cyanocuprates with 2:1 stoichiometry which had been prepared from Cu¹³CN.^[4] Other arguments for and against “higher-order” cyanocuprates have already been summarized.^[1] Here, it should only be mentioned that EXAFS and XANES spectra^[7] as well as ab initio calculations^[8] all point towards “cyano-Gilman” reagents **3** as most stable species wherein the cyanide is not bound to copper but rather to the lithium ions. This interpretation is also in accordance with recent NMR-spectroscopical studies of Bertz et al.^[9] and Berger et al.^[10]

Still, the most convincing structural proof is the determination of solid-state structures by X-ray analysis. The groups of Boche^[11] and van Koten^[12] now independently report the crystal structures of cyanocuprates with 2:1 stoichiometry which settle the question of the thermodynamically most stable form of these reagents unambiguously. Additionally, new results concerning the reactivity of these organocopper compounds also allow conclusions about the kinetically active species.

Structure

Based on their experience with C,N-chelating aminoaryl ligands, Kronenburg, Jastrzebski, Spek, and van Koten^[12] solved the X-ray crystal structure of the cyanocuprate [(2-(Me₂NCH₂)C₆H₄CH₂)₂CuLi₂(CN)(THF)₄]_∞ (**4**). In the solid state, the cuprate exists as a polymeric zigzag chain with alternating Ar₂Cu[−] and Li–CN–Li⁺ ions (Figure 1); the lithium ions reach the ideal coordination number 4 by additional coordination to two THF molecules and an amino group. The carbon and nitrogen atoms of the cyano groups cannot be differentiated in the X-ray analysis; the Li–C and Li–N bond lengths are 204.5 pm. As found frequently in solid-state structures of organocuprates,^[13] also **4** contains a linear arrangement of the anionic Ar₂Cu[−] fragments.

At first glance, the X-ray crystal structure of the alkylcyanocuprate [*t*Bu₂CuLi₂(CN)(THF)(pmdeta)] (**5**;

[*] Prof. Dr. N. Krause
Lehrstuhl für Organische Chemie II der Universität
D-44221 Dortmund (Germany)
Fax: (+49) 231-755-3884
E-mail: nkrause@pop.uni-dortmund.de

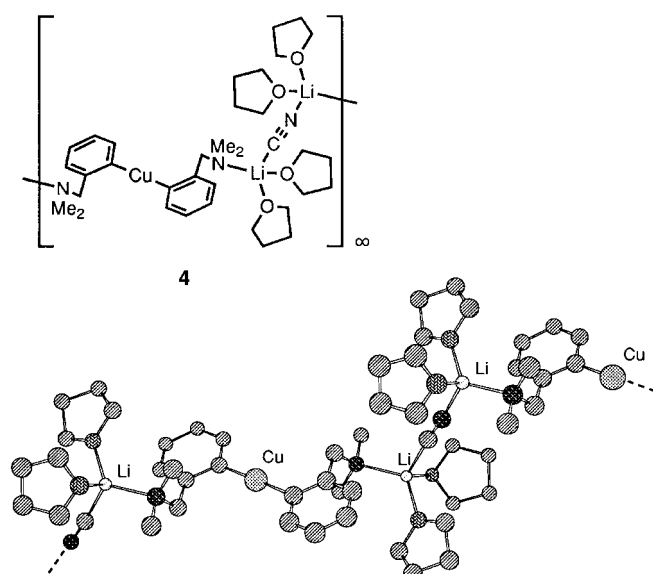


Figure 1. Part of the solid-state structure of the "cyano-Gilman" cuprate **4** (hydrogen atoms omitted for clarity).^[12]

pmdeta = pentamethyldiethylenetriamine) (Figure 2) obtained by Boche, Bosold, Marsch, and Harms^[11] seems to be rather different with respect to that of **4**, but it does indeed bear the *same structural features*. Also here, a linear cuprate anion and an almost linear Li-CN-Li⁺ ion are found which, however, are completely separated from each other. The

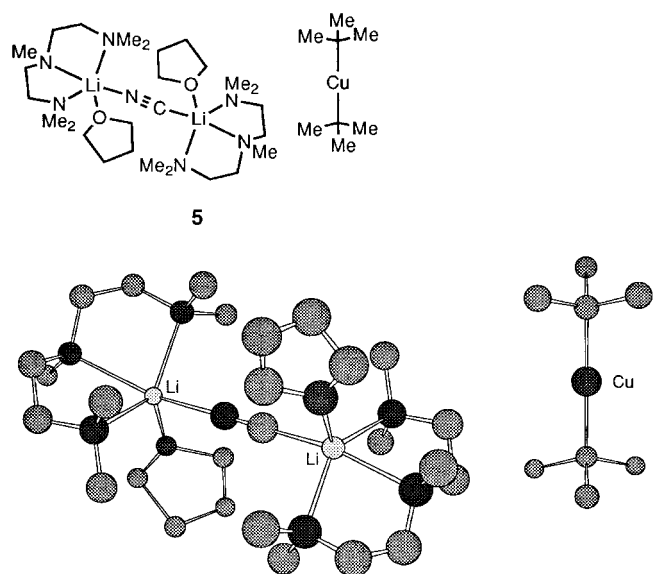


Figure 2. Solid-state structure of the "cyano-Gilman" cuprate **5** (hydrogen atoms and a disorder of the *tert*-butyl groups omitted).^[11]

reason is that the lithium ions in **5** are coordinated to pmdeta ligands instead of the covalently bound amino groups of **4**; additionally, each lithium ion is coordinated to a THF molecule. Again, it is not possible to differentiate the carbon and nitrogen atoms of the cyanide; the length of the Li-C and Li-N bonds (210.5 pm) is very similar to that found for **4**. Both structures exhibit a high affinity of CN⁻ for lithium ions; in the case of **5**, the cyanide is still attached to the Li⁺ ions

although the latter has already reached the coordination number 4 by binding to pmdeta and THF.

Based on these structures, the question of the thermodynamically most stable form of the reagents prepared from two equivalents of RLi and one equivalent of CuCN can be answered clearly in favor of the "cyano-Gilman" cuprates; the resemblance of structural details of **4** and **5** is particularly striking. This statement applies *a priori* only for the structure in the solid state. However, several experimental findings indicate that the cyanocuprates exist also in solution mainly as "cyano-Gilman" cuprates **3** and not as "higher-order" species **2**. In addition to the numerous spectroscopical studies mentioned above, this notion is also supported by additional investigations carried out by van Koten et al.^[12] with **4**. This cuprate is highly soluble in THF, and the determination of the aggregation state by cryoscopy revealed that it exists as a monomeric species in this solvent. The analogous observation had already been made for the cyanocuprates R₂CuLi · LiCN with R = Me and Ph, and this can be explained in terms of contact-ion pairs with "cyano-Gilman" structure (linear R-Cu-R unit with Li-CN-Li bridge).^[14] In the case of the *tert*-butyl cuprate *t*Bu₂CuLi · LiCN, the cryoscopic determination of the aggregation state hinted at the existence of equilibria between different species.^[14a]

At this point it should be mentioned that Boche et al. did not only determine the solid-state structure of the "cyano-Gilman" cuprate **5**, but also the first structure of a "lower-order" cyanocuprate of type **1**, that is the *tert*-butyl cuprate [*t*BuCu(CN)Li(OEt₂)₂]_∞ (**6**; Figure 3).^[11] In accordance with the solution studies mentioned above, a Cu-CN bond was found also in the solid state.^[15]

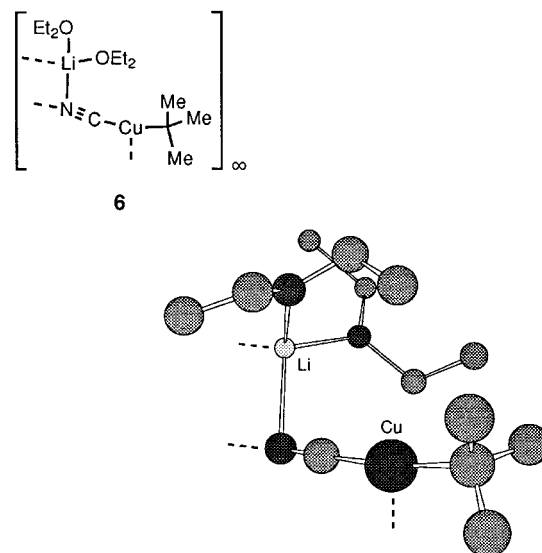


Figure 3. Part of the solid-state structure of the "lower-order" cyanocuprate **6** (hydrogen atoms omitted for clarity).^[11]

Reactivity

In organometallic chemistry one often finds that the thermodynamically most stable species of a given reagent is not the kinetically active one. Of course, this can only occur if there is a fast equilibrium between different species, and the

existence of such equilibria has indeed been proven spectroscopically for several organocuprates.^[1] In the case of the cyanocuprates of 2:1 stoichiometry there might be an equilibrium between the thermodynamically more stable “cyano-Gilman” reagent **3** and the “higher-order” cuprate **2**; because of its (formal) dianionic character, the latter should be much more reactive towards electrophiles. The actual existence of such an equilibrium, however, has not been proven to date. Therefore, one may ask if there is really a noticeable difference in reactivity between cyanocuprates and classical monoanionic Gilman cuprates prepared from copper(I) halides.

The original postulate of the “higher-order” cyanocuprate structure was based on the observance of much higher yields in substitution reactions when CuCN was used instead of other copper sources for the preparation of the cuprate.^[2, 3] Conclusions from yields on reactivities, however, can only be made when the reactions are carried out under identical conditions (solvent, temperature, concentrations etc.). Recent studies of this kind were reported by Bertz et al.;^[8c] they revealed only small differences in reactivity between classical cuprates and “cyano-Gilman” reagents. This finding is in accordance with new kinetic measurements; for example, the 1,4-addition of Me₂CuLi·LiI to 4,4-dimethyl-2-cyclohexenone at –59 °C in diethyl ether takes place about five times faster than that of Me₂CuLi·LiCN.^[16]

Even these results do not allow an unambiguous decision for “cyano-Gilman” cuprates **3** or “higher-order” cyanocuprates **2** as reactive species. However, it seems reasonable to assume that the “cyano-Gilman” species is the kinetically active one for those transformations which show only a small reactivity difference since a dianionic cuprate should exhibit a drastically increased reactivity. The only difference between the Gilman reagents R₂CuLi·LiX (X = Cl, Br, I) and R₂CuLi·LiCN would then be the cation ((Li·X·Li)⁺ vs. (Li·CN·Li)⁺), whereas the cuprate anion [R₂Cu][–] would be identical. The experimentally observed small reactivity differences could then be explained in terms of a (slightly) different electrophilic activation of the substrate^[1] by the respective cation. Here, it may also be important whether the reactive cuprate species exists as a solvent-separated ion pair (such as **4** and **5**) or rather as a contact ion pair, consisting of [R₂Cu][–] and (Li₂X)⁺ ions. The former assumption would be in accordance with the observation that enantioselective 1,4-additions of chirally modified cuprates RCu(L*)Li take place with high stereoselectivities only when “soft” sulfur or phosphorus nucleophiles (which are bound to the copper center) are used as chiral ligands L*.^[17] In contrast to this, “hard” amide or alcoholate ligands which bind to the lithium ions give only low enantioselectivities in most cases, presumably because the chiral ligand is too far away from the reaction center in these cases (cf. **5**).

Is there still a “chance” for “higher-order” cyanocuprates? In spite of the overwhelming evidence in favor of “cyano-Gilman” reagents as thermodynamically most stable and kinetically most active species, it is still impossible to answer the question definitely with “no”. After all, the final product

of all reactions of “cyano-Gilman” reagents is the “lower-order” cyanocuprate RCu(CN)Li, that is a Cu–CN bond is indeed formed at some point during the transformation! Moreover, there are certain reactions which can only be carried out with the cyanocuprates R₂CuLi·LiCN formed from CuCN, but not with classical Gilman reagents R₂CuLi·LiX (X = Br, I).^[18] Therefore, the final answer to the question has to await further kinetic and spectroscopic studies.

German version: *Angew. Chem.* **1998**, *110*, 83–85

Keywords: cuprates • kinetics • reactivity • structure elucidation

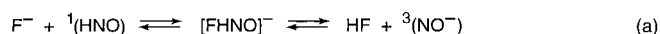
- [1] Recent review: N. Krause, A. Gerold, *Angew. Chem.* **1997**, *109*, 194–213; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 186–204.
- [2] B. H. Lipshutz, R. S. Wilhelm, D. M. Floyd, *J. Am. Chem. Soc.* **1981**, *103*, 7672–7674. The first cyanocuprate with 1:1 stoichiometry was reported by: J.-P. Gorlier, L. Hamon, J. Levisalles, J. Wagnon, *J. Chem. Soc. Chem. Commun.* **1973**, 88.
- [3] Reviews: a) B. H. Lipshutz, *Synthesis* **1987**, 325–341; b) B. H. Lipshutz, *Synlett* **1990**, 119–128; c) B. H. Lipshutz, S. Sengupta, *Org. React.* **1992**, *41*, 135–631; d) B. H. Lipshutz in *Organometallics in Synthesis* (Ed.: M. Schlosser), Wiley, Chichester, **1994**, pp. 283–382; e) B. H. Lipshutz in *Advances in Metal-Organic Chemistry* (Ed.: L. S. Liebeskind), JAI Press, Greenwich, **1995**, Vol. 4, pp. 1–64.
- [4] S. H. Bertz, *J. Am. Chem. Soc.* **1991**, *113*, 5470–5471.
- [5] S. H. Bertz, *J. Am. Chem. Soc.* **1990**, *112*, 4031–4032.
- [6] B. H. Lipshutz, S. Sharma, E. L. Ellsworth, *J. Am. Chem. Soc.* **1990**, *112*, 4032–4034.
- [7] a) T. Stemmler, J. E. Penner-Hahn, P. Knochel, *J. Am. Chem. Soc.* **1993**, *115*, 348–350; b) T. M. Barnhart, H. Huang, J. E. Penner-Hahn, *J. Org. Chem.* **1995**, *60*, 4310–4311; c) T. L. Stemmler, T. M. Barnhart, J. E. Penner-Hahn, C. E. Tucker, P. Knochel, M. Böhme, G. Frenking, *J. Am. Chem. Soc.* **1995**, *117*, 12489–12497.
- [8] a) J. P. Snyder, D. P. Spangler, J. R. Behling, B. E. Rossiter, *J. Org. Chem.* **1994**, *59*, 2665–2667; b) J. P. Snyder, S. H. Bertz, *J. Org. Chem.* **1995**, *60*, 4312–4313; c) S. H. Bertz, G. Miao, M. Eriksson, *Chem. Commun.* **1996**, 815–816.
- [9] S. H. Bertz, J. P. Snyder, K. Nilsson, Ö. Davidsson, *Angew. Chem.* **1998**, *110*, 327–331; *Angew. Chem. Int. Ed.* **1998**, *37*, 314–317.
- [10] T. A. Mobley, F. Müller, S. Berger, *J. Am. Chem. Soc.* **1998**, *120*, 1333–1334.
- [11] G. Boche, F. Bosold, M. Marsch, K. Harms, *Angew. Chem.* **1998**, *110*, 1779–1781; *Angew. Chem. Int. Ed.* **1998**, *37*, 1684–1686.
- [12] C. M. P. Kronenburg, J. T. B. H. Jastrzebski, A. L. Spek, G. van Koten, *J. Am. Chem. Soc.* **1998**, *120*, 9688–9689.
- [13] G. van Koten, S. L. James, J. T. B. H. Jastrzebski in *Comprehensive Organometallic Chemistry II*, Vol. 3 (Ed.: E. W. Abel, F. G. A. Stone, G. Wilkinson), Pergamon, Oxford, **1995**, pp. 57–133.
- [14] a) A. Gerold, J. T. B. H. Jastrzebski, C. M. P. Kronenburg, G. van Koten, N. Krause, *Angew. Chem.* **1997**, *109*, 778–780; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 755–757; b) H. Huang, C. H. Liang, J. E. Penner-Hahn, *Angew. Chem.* **1998**, *110*, 1628–1630; *Angew. Chem. Int. Ed.* **1998**, *37*, 1564–1566.
- [15] Recently, another solid state structure of a “lower-order” cyanocuprate with similar structural features was reported: C.-S. Hwang, P. P. Power, *J. Am. Chem. Soc.* **1998**, *120*, 6409–6410.
- [16] N. Krause, J. Canisius, unpublished results.
- [17] a) B. L. Feringa, M. Pineschi, L. A. Arnold, R. Imbos, A. H. M. de Vries, *Angew. Chem.* **1997**, *109*, 2733–2736; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2620–2623; b) N. Krause, *Angew. Chem.* **1998**, *110*, 295–297; *Angew. Chem. Int. Ed.* **1998**, *37*, 283–285.
- [18] B. H. Lipshutz, K. Siegmann, E. Garcia, F. Kayser, *J. Am. Chem. Soc.* **1993**, *115*, 9276–9282, and references therein.

Interspin Crossing and Reactivity

Dietmar A. Plattner*

The discussion of reaction mechanisms and pathways is usually based on a single potential energy surface: starting from the reactant minimum the reactive system moves through a transition state and proceeds further to intermediates and/or product minima. Although this concept represents only one aspect of chemical reactivity, it has proven to be a useful tool in rationalizing the greater part of reactions. The success of this concept and its justification, especially in organic chemistry, lies in the fact that organic species generally possess low-spin ground states, and their reactions proceed on a single energy surface (single-state reactivity). Nevertheless, the simple example of the stability of many organic compounds with regard to ground-state triplet O_2 should always remind us of the important consequences of spin states on reactivity. Reactions that involve a change in the spin state and thus occur on two or more potential energy surfaces (and are therefore nonadiabatic processes^[1]) have received much attention in recent years. A number of reactions in organic, inorganic, and organometallic chemistry, in which two states of different multiplicities determine the minimum-energy reaction pathway (two-state reactivity), have been confirmed by experimental and computational studies, and it is the aim of the present article to highlight those efforts.

Gas-phase ion chemistry provides a powerful tool for the study of intermediates that are too reactive for a solution-phase characterization. Moreover, information about the intrinsic reactivity of the molecule or reactive system in question is obtained in the gas phase, unperturbed by effects of solvents or aggregation phenomena. Recently, two experimental gas-phase studies have confirmed the possibility of a spin-forbidden proton-transfer reaction, that is, a protonation during which a spin change occurs. The first reaction under consideration is the protonation of F^- by HNO [Eq. (a)]^[2].



The energetics of the ground-state reaction, that is, the reaction with ${}^1HNO$, are known from the heats of formation of the ions and molecules (Figure 1). The reaction is exothermic by 8 kcal mol⁻¹ and leads to ${}^3(NO^-)$, since ${}^1(NO^-)$ is not a bound state. In the study of Brauman and co-workers, the nature of the intermediate complex $[FHNO]^-$ and its reactivity were addressed. $[FHNO]^-$ was synthesized by the reaction of F^- with neopentyl nitrite and then treated with a variety of neutral molecules. The reaction products

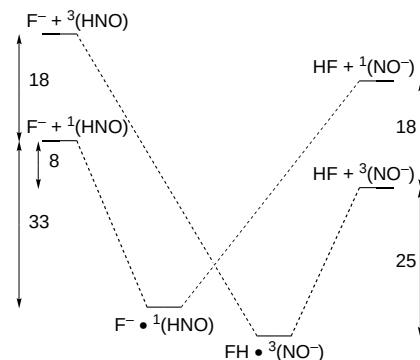
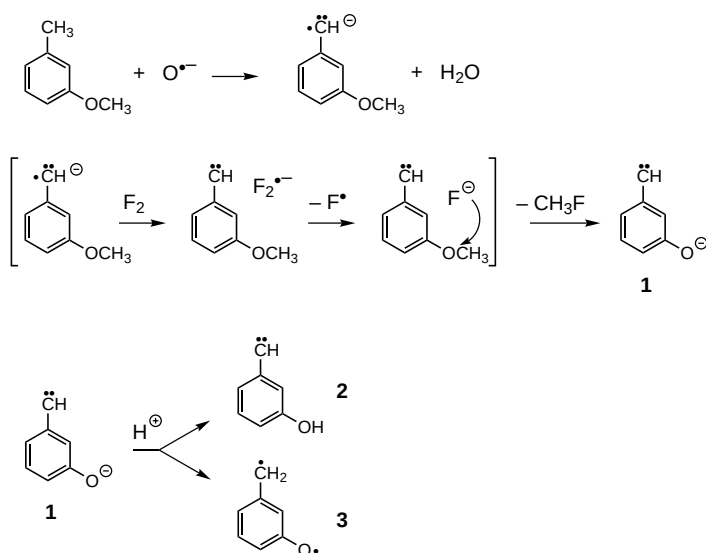


Figure 1. Schematic potential energy diagram for reaction (a). The relative energies are given in kcal mol⁻¹.

were monitored in a Fourier transform mass spectrometer. Reactions with alcohols and HCN give F^- transfer, which indicates the structure of the complex is $F^- \cdot HNO$. On the other hand, reaction with NO gives N_2O_2 , and the reactions with SF_6 , O_2 , and SO_2 lead to electron and/or HF transfer as would be expected for the triplet $FH \cdot {}^3(NO^-)$. This dual reactivity is attributed to efficient spin change. The structure of the intermediate complex was assigned by electron photo-detachment in an ICR spectrometer. The spectrum shows an onset at about 29 kcal mol⁻¹, which indicates the structure of $[FHNO]^-$ to be $FH \cdot {}^3(NO^-)$ as opposed to $F^- \cdot HNO$. This result is also consistent with high-level ab initio calculations. The calculations show $FH \cdot {}^3(NO^-)$ to be 5 kcal mol⁻¹ more stable, with the singlet and triplet curves crossing about 3 kcal mol⁻¹ above the singlet minimum. The energy required to reach the curve crossing region is quite low, and—according to the calculations—binding of an alcohol molecule brings the energy of the singlet surface below that of the triplet, which seems to facilitate the spin change in this system.

An example of an organic conjugate acid–base pair with different spin multiplicities was studied by Hu, Hill, and Squires.^[3] They synthesized a so-called distonic^[4] carbene ion, that is, a species where the charged and the carbenic moieties are formally separate, in a flowing afterglow-triple-quadrupole apparatus by the reaction sequence shown in Scheme 1. The chemical reactivity of the (3-oxyphenyl)methylene anion **1** is indicative of a singlet ground state: the ion reacts with NO_2 to yield the 3-oxybenzaldehyde anion, abstracts sulfur from CS_2 and COS , and undergoes cycloadditions with electron-deficient olefins. Calculations at the B3LYP/cc-pVTZ level also predict a singlet ground state for **1**, with the lowest triplet 3 kcal mol⁻¹ higher in energy, but a triplet ground state for the conjugate acid **2** with a singlet–triplet gap of 6.4 kcal mol⁻¹ (the protonation at the oxygen atom is kinetically favored with respect to carbon protonation to give **3**). The proton affinity of **1** was determined experimentally by collision induced dissociation (CID) of clusters with different phenols to be 343.0 ± 0.5 kcal mol⁻¹, which is in excellent

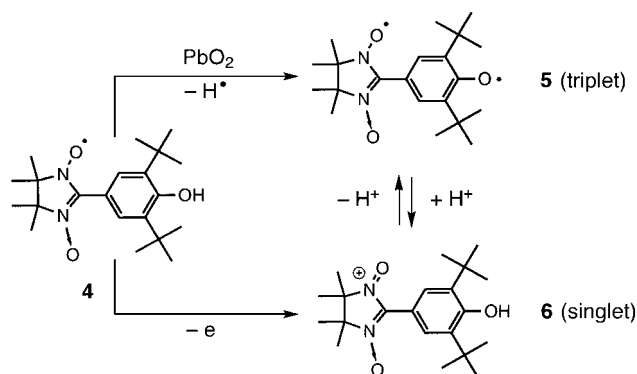
[*] Dr. D. A. Plattner
Laboratorium für Organische Chemie der
Eidgenössischen Technischen Hochschule (ETH) Zürich
Universitätsstrasse 16, CH-8092 Zürich (Switzerland)
Fax: (+41) 1-632-1280
E-mail: plattner@org.chem.ethz.ch



Scheme 1. Synthesis of the distonic carbene ion **1** and the subsequent protonated products as an example of an organic acid–base pair with interspin crossing.

agreement with the calculated value for a S→T proton transfer. These results suggest that the spin barrier for the proton transfer in the cluster of **1** with the phenol must be small and that intersystem crossing is an efficient process.

Another example of an organic acid–base pair with different spin multiplicities was recently described by Sawaki et al.^[5] The cross-conjugated phenoxy-nitronyl nitroxide biradical **5**, prepared by PbO₂ oxidation of the corresponding phenol-substituted radical **4** (Scheme 2), has a triplet ground state according to ESR spectroscopy. Upon protonation the closed-shell cation **6** is formed, which can also be prepared independently by one-electron oxidation of **4**. Thus, the spin state of the system can be controlled by altering the pH of the solution. This observation may lead to applications as pH sensors that respond to changes in magnetic properties.



Scheme 2. Another example of an organic acid–base pair with interspin crossing.

From recent experimental and computational studies, two-state reactivity also accounts for the notorious elusiveness of C₂O₂ (ethylenedione).^[6] Singlet C₂O₂ is of course a classic example of an unbound species, a consequence of the extraordinary large singlet–triplet gap of CO

(139.1 kcal mol^{−1}^[7]). Ab initio calculations predict triplet C₂O₂ (³Σ_g[−]) to be thermochemically stable with respect to the spin-allowed dissociation into CO (¹Σ_g⁺) and CO (³Π) (Figure 2).^[8, 9] A “complete” mass spectrometric study was performed to elucidate the stability of triplet C₂O₂:^[8] all possible neutralization–reionization and charge-reversal experiments were conducted starting from C₂O₂⁺⁺ and C₂O₂^{−−}, respectively. In no case was it possible to obtain a recovery signal in a neutralization–reionization experiment. On the other

hand, charge reversal is quite an efficient process in this experimental setup. The energetics of the charge-reversal experiment suggest that the appearance of the recovery signal is a result of a double electron transfer in a single collision (with Xe) and rule out a two-step mechanism. Stepwise electron transfer, however, would be expected to be observed if the neutral C₂O₂ molecule were to have a lifetime above 30 ns. The successful charge-reversal experiments also rule out Franck–Condon effects as the reason for the failure to observe neutral C₂O₂. These results suggest that triplet ethylenedione is an intrinsically unstable molecule. The mechanism proposed to account for the short lifetime of C₂O₂ is outlined in Figure 2: the bound triplet state proceeds via efficient curve crossing from the triplet to the singlet surface followed by fast dissociation. Support for this view comes from the location of the minimum-energy crossing point (MECP) of the two surfaces and the calculation at the MP2/cc-pVDZ level of theory of the magnitude of the spin-orbit coupling element *H*_{SO} at the MECP. The structure of the MECP is fairly close to that of the triplet minimum, and its energy is only about 3 kcal mol^{−1} above the triplet minimum (Figure 2).^[10] The low-lying MECP is mainly responsible for the very short lifetime of triplet C₂O₂, which is estimated to be in the low nanosecond regime.

A similar combined experimental/theoretical approach was taken by the Schwarz group to establish the mechanism of the unimolecular decay of the triplet methoxy cation.^[11] Two pathways have so far been proposed in the literature: a) a stepwise reaction, namely a hydrogen shift concurrent with spin change to form ¹(CH₂OH⁺), which then eliminates H₂ [Eq. (b)];^[12] and b) a concerted pathway that involves simultaneous spin change and [1,1] elimination of H₂ from ³(CH₃O⁺) [Eq. (c)].^[13] The kinetic isotope effect observed in

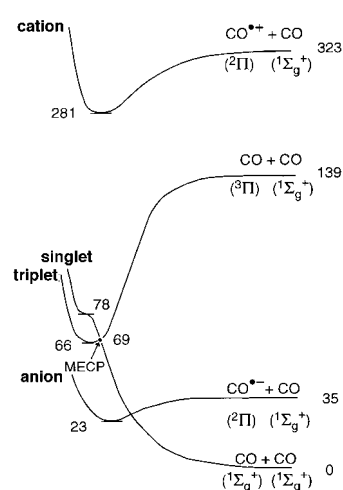
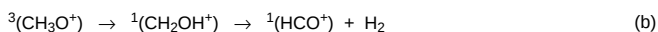


Figure 2. Schematic representation of the potential energy surfaces of the cationic, neutral, and anionic states of C₂O₂. The energies shown [kcal mol^{−1}] were obtained from calculations at the CCSD(T) level of theory.

the MS experiments for the decay of $^3(\text{CH}_2\text{DO}^+)$ is not consistent with a stepwise mechanism. Instead, the $[\text{H}_2]/[\text{HD}]/[\text{D}_2]$ branching ratio is indicative of the concerted pathway. The calculated location of both MECPs and the calculation of the spin–orbit coupling constant H_{SO} for both reactions indicate that the concerted mechanism is somewhat favored over the stepwise pathway.

The importance of spin state for the reactivity of organometallic compounds has been the subject of controversy for a long time, but it has only recently become feasible to study this problem quantitatively. It has long been recognized that different coordinatively unsaturated organometallic fragments display highly variable reactivities. For example, pulsed UV photolysis of $[\text{Fe}(\text{CO})_5]$ leads to the formation of the unsaturated species $[\text{Fe}(\text{CO})_x]$ ($x=2-4$), which show quite different reactivities in the recombination reaction with CO.^[14, 15] While the reactions of $[\text{Fe}(\text{CO})_2]$ and $[\text{Fe}(\text{CO})_3]$ with CO proceed at near gas kinetic rates, the reaction of $[\text{Fe}(\text{CO})_4]$ is about three orders of magnitude slower, with an activation energy of about 2.5 kcal mol⁻¹.^[15] This unexpected behavior was explained by the spin change in the reaction since ground-state $[\text{Fe}(\text{CO})_4]$ is high spin (triplet^[16]), whereas ground-state $[\text{Fe}(\text{CO})_5]$ is low spin. Significant spin changes also occur in the sequential addition of CO to Mn^+ to form $[\text{Mn}(\text{CO})_6]^+$, and the CO exchange rates of the unsaturated fragments were discussed in terms of the requirements for spin conservation in ligand exchange reactions.^[17, 18]

While “spin-blocking” in typical organometallic two-electron reactions has often been claimed to explain unusual reactivity (for a recent example see ref. [19]), no barrier has been observed in ligand-binding reactions that convert 16e ground-state triplet complexes to diamagnetic 18e singlet products.^[20, 21] Speculation regarding the spin-forbiddenness of certain organometallic reactions remains difficult to justify without benefit of reliable information on the exact value of the energy difference between the ground and lowest excited state and the energy required to reach the curve crossing point(s). Recently, the significance of two-state reactivity for organometallic reactions was addressed quantitatively. During the last decade, the dependence of reactivity of bare transition metal cations on the spin state has been demonstrated in a series of cleverly devised experiments.^[22, 23] For example, Fe^+ in the quartet excited state (^4F) is about 70 times more reactive than the sextet ground state (^6D) in the reaction with H_2 . It is no exaggeration to claim that in atomic transition metal ion chemistry each electronic state is potentially a different chemical.

The state-specific reactivity of metal–oxo complexes has received much attention recently. At the beginning of this development is the finding that OsO^+ and FeO^+ can activate CH_4 , a process of utmost importance for the functionalization of hydrocarbons.^[24–27] Subsequently, the reaction of FeO^+ with H_2 was studied and was found to have a surprisingly low efficiency. Although an exothermic, spin-allowed process, the reaction is very inefficient and occurs only once in every 100–1000 collisions.^[28, 29] This unexpected behavior stimulat-

ed a series of experimental and computational studies directed at the elucidation of the electronic structures and gas-phase reactivities of late, first-row transition metal oxide cations MO^+ ($\text{M}=\text{Mn}, \text{Fe}, \text{Co}, \text{Ni}, \text{Cu}$).^[30–34] Two recent computational studies have proven the validity of the two-state reactivity scheme for metal–oxo cations. Danovich and Shaik calculated the amount of spin–orbit coupling along the pathway for the reaction $\text{FeO}^+ + \text{H}_2 \rightarrow \text{Fe}^+ + \text{H}_2\text{O}$.^[33] The low-energy path involves two spin-inversion junctions between the sextet and quartet series: one near the FeO^+/H_2 cluster at the entrance channel, and one near the $\text{Fe}^+/\text{H}_2\text{O}$ cluster at the exit channel. The spin–orbit coupling matrix elements are relatively large at the entrance channel, and they decrease steadily along the insertion pathway, going to nearly zero at the exit channel between the ^6D ground state and the ^4F excited state. The overall reaction efficiency is found to be limited by the spin–orbit coupling at the spin-inversion junctions, which is in good agreement with the experimental data by Schwarz and Armentrout.^[28, 29] A similar picture has been derived from hybrid Hartree–Fock/density functional calculations (B3LYP) on the system $\text{MO}^+ + \text{CH}_4$ ($\text{M}=\text{Fe}, \text{Mn}, \text{Co}$).^[34] In the case of FeO^+ and CoO^+ , a low-energy reaction pathway is opened by a crossing of the sextet and quartet surfaces at the entrance channel, that is, between the reactant complex $\text{OM}^+(\text{CH}_4)$ and the transition state of the insertion step (Figure 3). It is important to note that $\text{HO}-\text{M}^+-\text{CH}_3$ is not formed by a mechanism that involves direct hydrogen abstraction by MO^+ , but that CH_4 is activated through the simultaneous formation of $\text{M}-\text{C}$ as well as $\text{M}-\text{H}$ bonds. Another crossing occurs in the exit channel when $\text{M}^+(\text{CH}_3\text{OH})$ dissociates. The situation is different for MnO^+ , where only one surface crossing occurs in the exit channel between the high-spin septet and the low-spin quintet surface. The energies obtained for the transition states compare very well with experimentally reported reaction efficiencies and product branching ratios, which thus suggests that two-state reactivity is indeed operative in these reactions.

The two-state reactivity paradigm was recently applied to the hydroxylation of alkanes by cytochrome P-450.^[35] The detailed mechanism of alkane hydroxylation by cytochro-

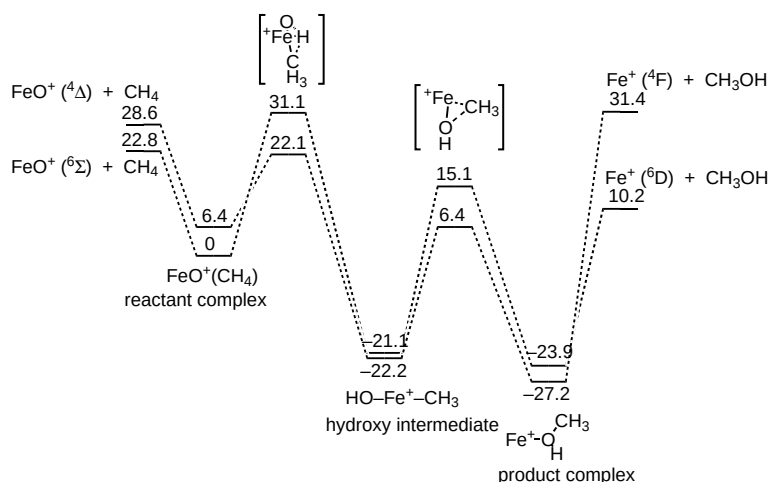
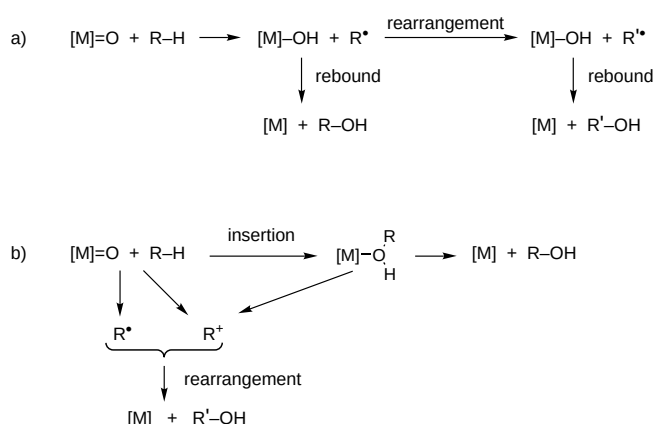


Figure 3. Schematic potential energy diagram for the reaction $\text{FeO}^+ + \text{CH}_4 \rightarrow \text{Fe}^+ + \text{CH}_3\text{OH}$ in the sextet and quartet states. Relative energies are given in kcal mol⁻¹.

meP-450 is still the subject of much debate, which has been further stimulated by the recent experiments by Newcomb and co-workers^[36] (Scheme 3): the rebound mechanism



Scheme 3. a) The rebound mechanism for alkane hydroxylation by cytochrome P-450; b) the concerted oxene-insertion mechanism proposed by Newcomb and co-workers.

(Scheme 3a), which involves the formation of alkyl radicals, is not entirely consistent with the lifetimes of the putative radical intermediates. Newcomb has therefore suggested a concerted oxene-insertion mechanism where the occurrence of radicals and carbocations is the result of a minor pathway (Scheme 3b). The problem with the latter mechanism is that the ferryl complex (bare FeO^+ as well as the FeO moiety in the active form of cytochrome P-450) has a high-spin ground state that does not react with C–H or C–C bonds in a concerted manner,^[37] but favors stepwise reactions such as hydrogen abstraction. The low-spin state, on the other hand, is prone to concerted mechanisms with only a low barrier to the insertion product $R-Fe^+-OH$, which, in addition, is also more stable than the high-spin analogue. However, initial excitation is not necessary in order to switch to the low-spin surface. Two-state reactivity will be operative if spin inversion occurs on the way to the intermediate, and the reaction efficiency is then determined by the probability of spin inversion at the crossing junction. The amount of concerted versus radical mechanism in this mechanistic scheme is simply modulated by the spin-inversion probability.

Two-state reactivity is a governing factor in many reactions when the adjacency of excited-state surfaces makes it necessary to expand the single-surface representation. The transition probability between the surfaces of different multiplicities is of the same fundamental importance as are transition structures, their entropic requirements, and the associated barrier heights in the classical kinetic model. In the future, new experimental examples of two-state reactivity will undoubtedly emerge, which will highlight the need for a deeper understanding and more precise calculations of spin-inversion probabilities in polyatomic molecules in order to establish this concept alongside the classical reactivity paradigms.

German version: *Angew. Chem.* **1999**, *111*, 86–90

Keywords: gas-phase chemistry • ion chemistry • mass spectrometry • spin-forbidden reactions

- [1] D. R. Yarkony, *J. Phys. Chem.* **1996**, *100*, 18612–18628.
- [2] G. A. Janaway, M. Zhong, G. G. Gatev, M. L. Chabinyc, J. I. Brauman, *J. Am. Chem. Soc.* **1997**, *119*, 11697–11698.
- [3] J. Hu, B. T. Hill, R. R. Squires, *J. Am. Chem. Soc.* **1997**, *119*, 11699–11700.
- [4] B. F. Yates, W. J. Bouma, L. Radom, *J. Am. Chem. Soc.* **1984**, *106*, 5805–5808; B. F. Yates, W. J. Bouma, L. Radom, *Tetrahedron* **1986**, *42*, 6225–6234.
- [5] K. Ishiguro, M. Ozaki, N. Sekine, Y. Sawaki, *J. Am. Chem. Soc.* **1997**, *119*, 3625–3626.
- [6] G. Maier, M. Naumann, H. P. Reisenauer, J. Eckwert, *Angew. Chem.* **1996**, *108*, 1800–1801; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1696–1697.
- [7] G. Herzberg, *Molecular Spectra and Molecular Structure, Vol. I: Spectra of Diatomic Molecules*, Krieger, Malabar, **1989**.
- [8] D. Schröder, C. Heinemann, H. Schwarz, J. N. Harvey, S. Dua, S. J. Blanksby, J. H. Bowie, *Chem. Eur. J.* **1998**, *4*, 2550–2557.
- [9] Ethylenedithione ($S=C=C=S$) and ethenonethione ($O=C=C=S$) have been detected by neutralization–reionization mass spectrometry: D. Sülzle, H. Schwarz, *Angew. Chem.* **1988**, *100*, 1384–1386; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1337–1339; D. Sülzle, J. K. Terlouw, H. Schwarz, *J. Am. Chem. Soc.* **1990**, *112*, 628–630. C_2OS has recently been characterized by matrix isolation experiments: G. Maier, H. P. Reisenauer, R. Ruppel, *Angew. Chem.* **1997**, *109*, 1972–1973; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1862–1864.
- [10] For a detailed description and justification of the computational procedure employed, theoretically interested readers are referred to: J. N. Harvey, M. Aschi, H. Schwarz, W. Koch, *Theor. Chem. Acc.* **1998**, *99*, 95–99.
- [11] M. Aschi, J. N. Harvey, C. A. Schalley, D. Schröder, H. Schwarz, *Chem. Commun.* **1998**, 531–532.
- [12] M. M. Bursey, J. R. Hass, D. J. Harvan, C. E. Parker, *J. Am. Chem. Soc.* **1979**, *101*, 5485–5489; P. C. Burgers, J. L. Holmes, *Org. Mass Spectrom.* **1984**, *19*, 452–456; S.-C. Kuo, Z. Zhang, R. B. Klemm, J. F. Liebman, L. J. Stief, F. L. Nesbitt, *J. Phys. Chem.* **1994**, *98*, 4026–4033.
- [13] D. R. Yarkony, *J. Am. Chem. Soc.* **1992**, *114*, 5406–5411.
- [14] A. J. Ouderkirk, P. Wermer, N. L. Schultz, E. Weitz, *J. Am. Chem. Soc.* **1983**, *105*, 3354–3355.
- [15] T. A. Seder, A. J. Ouderkirk, E. Weitz, *J. Chem. Phys.* **1986**, *85*, 1977–1986.
- [16] T. J. Barton, R. Grinter, A. J. Thomson, B. Davies, M. Poliakoff, *J. Chem. Soc. Chem. Commun.* **1977**, 841–842.
- [17] D. V. Dearden, K. Hayashibara, J. L. Beauchamp, N. J. Kirchner, P. A. M. van Koppen, M. T. Bowers, *J. Am. Chem. Soc.* **1989**, *111*, 2401–2409.
- [18] The bond strengths of transition metal–carbonyl ion complexes have been discussed with regard to spin changes: L. S. Sunderlin, D. Wang, R. R. Squires, *J. Am. Chem. Soc.* **1993**, *115*, 12060–12070; P. B. Armentrout, *Acc. Chem. Res.* **1995**, *28*, 430–436.
- [19] R. R. Schrock, K.-Y. Shih, D. A. Dobbs, W. M. Davis, *J. Am. Chem. Soc.* **1995**, *117*, 6609–6610.
- [20] A. H. Janowicz, H. E. Bryndza, R. G. Bergman, *J. Am. Chem. Soc.* **1981**, *103*, 1516–1518.
- [21] J. L. Detrich, O. M. Reinaud, A. L. Rheingold, K. H. Theopold, *J. Am. Chem. Soc.* **1995**, *117*, 11745–11748.
- [22] P. B. Armentrout, *Science* **1991**, *251*, 175–179.
- [23] J. C. Weisshaar, *Acc. Chem. Res.* **1993**, *26*, 213–219.
- [24] K. K. Irikura, J. L. Beauchamp, *J. Am. Chem. Soc.* **1989**, *111*, 75–85.
- [25] D. Schröder, H. Schwarz, *Angew. Chem.* **1990**, *102*, 1468–1469; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1433–1434.
- [26] D. Schröder, A. Fiedler, J. Hrusak, H. Schwarz, *J. Am. Chem. Soc.* **1992**, *114*, 1215–1222.
- [27] H. Schwarz, *Angew. Chem.* **1991**, *103*, 837–838; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 820–821.
- [28] D. Schröder, A. Fiedler, M. F. Ryan, H. Schwarz, *J. Phys. Chem.* **1994**, *98*, 68–70; D. Schröder, H. Schwarz, D. E. Clemmer, Y.-M. Chen, P. B.

- Armentrout, V. I. Baranov, D. K. Böhme, *Int. J. Mass Spectrom. Ion Proc.* **1997**, 161, 175–191.
- [29] D. E. Clemmer, Y.-M. Chen, F. A. Khan, P. B. Armentrout, *J. Phys. Chem.* **1994**, 98, 6522–6529.
- [30] Y.-M. Chen, D. E. Clemmer, P. B. Armentrout, *J. Am. Chem. Soc.* **1994**, 116, 7815–7826.
- [31] A. Fiedler, D. Schröder, S. Shaik, H. Schwarz, *J. Am. Chem. Soc.* **1994**, 116, 10734–10741.
- [32] S. Shaik, D. Danovich, A. Fiedler, D. Schröder, H. Schwarz, *Helv. Chim. Acta* **1995**, 78, 1393–1407.
- [33] D. Danovich, S. Shaik, *J. Am. Chem. Soc.* **1997**, 119, 1773–1786.
- [34] K. Yoshizawa, Y. Shiota, T. Yamabe, *J. Am. Chem. Soc.* **1998**, 120, 564–572.
- [35] S. Shaik, M. Filatov, D. Schröder, H. Schwarz, *Chem. Eur. J.* **1998**, 4, 193–199.
- [36] M. Newcomb, M.-H. Le Tadic, D. A. Putt, P. F. Hollenberg, *J. Am. Chem. Soc.* **1995**, 117, 3312–3313; M. Newcomb, M.-H. Le Tadic-Biadatti, D. L. Chestrey, E. S. Roberts, P. F. Hollenberg, *J. Am. Chem. Soc.* **1995**, 117, 12085–12091; S.-Y. Choi, P. E. Eaton, P. F. Hollenberg, K. E. Liu, S. J. Lippard, M. Newcomb, D. A. Putt, S. P. Upadhyaya, Y. Xiong, *J. Am. Chem. Soc.* **1996**, 118, 6547–6555; P. H. Toy, M. Newcomb, P. F. Hollenberg, *J. Am. Chem. Soc.* **1998**, 120, 7719–7729.
- [37] The comparison of the MO diagram for FeO^+ with the electronic configuration of the triplet ground state of O_2 reveals that both molecules exhibit a similar bonding situation (see ref. [31]). Ground-state triplet oxygen reacts with closed-shell molecules through radical mechanisms, whereas the first excited state $^1\Delta_g$ readily undergoes concerted reactions such as cycloadditions.

Parent Substances of Inorganic Chemistry: Homoleptic Pnictogenyl Compounds of Group 14, $\text{E}(\text{ZR}_2)_4$

Norbert W. Mitzel*

A new parent substance of inorganic nonmetal chemistry has been prepared and structurally characterized: the simplest compound containing a SiP_4 unit, tetraphosphanylsilane, $\text{Si}(\text{PH}_2)_4$.^[1] Driess and Monsé achieved the synthesis of this compound by treating lithium tetraphosphanylalanate, $\text{Li}[\text{Al}(\text{PH}_2)_4]$, with SiCl_4 ; Boese and Bläser have grown a single crystal at low temperatures and determined its structure (Figure 1). Thus, $\text{Si}(\text{PH}_2)_4$ is the first example of the successful synthesis of an $\text{E}(\text{ZH}_2)_4$ compound ($\text{E} = \text{C}, \text{Si}, \text{Ge}, \text{Sn}, \text{Pb}$; $\text{Z} = \text{N}, \text{P}, \text{As}, \text{Sb}, \text{Bi}$), that is an EZ_4 fragment without organic substituents. $\text{Ge}(\text{PH}_2)_4$ was also prepared, but was so far only

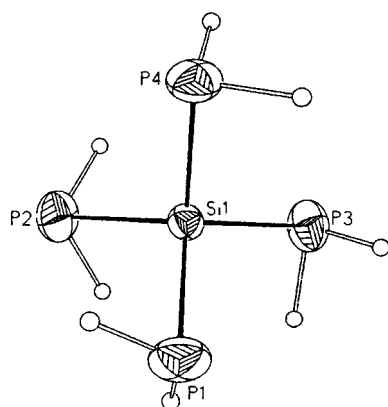


Figure 1. Molecular structure of $\text{Si}(\text{PH}_2)_4$.

[*] Dr. N. W. Mitzel
Anorganisch-chemisches Institut der
Technischen Universität München
Lichtenbergstrasse 4, D-85747 Garching (Germany)
Fax: (+49) 89-289-13125
E-mail: n.mitzel@lrz.tum.de

detected by means of GC/MS analysis. The simplest representative of an $\text{Si}-\text{P}$ compound, H_3SiPH_2 , had already been prepared in 1955 by G. Fritz,^[2] while $\text{HSi}(\text{PH}_2)_3$ was described in 1968.^[3]

The synthesis of compounds without organic substituents is of importance because their existence allows conclusions to be drawn regarding the inherent stability of the core structure and allows an assessment of the influence of the stabilization by more or less space-filling organic substituents, which is important for the synthesis of derivatives. Moreover, since in most cases direct comparisons with the results of high-level quantum chemical calculations is only possible for the simplest unsubstituted systems, such studies serve to confirm theoretical methods and allow for their further development.

Recently the research on $\text{E}(\text{ZR}_2)_4$ compounds was intensified. On the one hand, attempts were made to apply such compounds as precursors for new IV/V materials, on the other to provide representative objects for structural studies. The presence of four donor centers in these molecules makes them attractive as ligands for complex chemistry and for the design of supramolecular aggregates.

Many compounds of the type $\text{E}(\text{ZR}_2)_4$ are unknown. Despite numerous attempts, no synthetic pathway to a neutral compound $\text{C}(\text{PR}_2)_4$ has been found. The same applies for analogous compounds of arsenic, antimony, and bismuth. Some silicon phosphanides have been prepared, for example, tetrakis(*tert*-butyl)-1,2,4,5-tetraphosphasilaspiro[2.2]pentane.^[4] Compounds with SiAs_4 , SiSb_4 , and SiBi_4 units, however, have not been documented so far. $\text{Sn}(\text{SbPh}_2)_4$ is known as an example from tin chemistry.^[5]

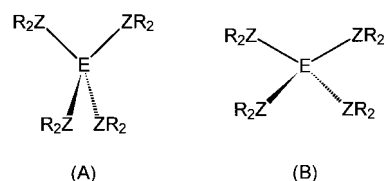
The only class of compounds with numerous members in this context are the element amides, while compounds containing CN_4 units are rare, but of actual interest. Plenty

of data have been reported for tetraaminosilanes,^[6] -germanes, and -stannanes.^[7]

However, even with these classes of compounds the simplest representatives $\text{E}(\text{NH}_2)_4$ are as yet unknown, which is paralleled by the chemistry of the hydroxides $\text{E}(\text{OH})_4$: only $\text{Si}(\text{OH})_4$ is existent in dilute aqueous solutions.

Structural Chemistry of the Compounds $\text{E}(\text{ZR}_2)_4$

The structures of compounds of the type $\text{E}(\text{ZR}_2)_4$ are not yet satisfactorily understood. All the homoleptic element amides show distinct deviations from an ideal tetrahedral geometry at the central atom. In this context two of the N-E-N angles are markedly compressed, while four of them are widened (Scheme 1 A), or the inverse case is observed with two larger and four smaller angles (Scheme 1 B). Examples of



Scheme 1.

this include $\text{C}(\text{NMe}_2)_4$ ^[8] and $\text{Si}(\text{NHMe})_4$.^[9] A parallel situation is observed for the homoleptic element alkoxides such as $\text{Si}(\text{OCHMe}_2)_4$.^[10] These findings cannot be attributed to packing effects in crystal lattices, as the deviations are also predicted for $\text{C}(\text{NMe}_2)_4$ and $\text{Si}(\text{NH}_2)_4$ by density functional theory (DFT) calculations^[11] and have been found in experimentally determined gas-phase structures of $\text{C}(\text{OMe})_4$ ^[12] and $\text{Si}(\text{OMe})_4$.^[13]

Very recently Gillespie et al. have attempted again to explain these anomalies^[14] and thus to extend the VSEPR model.^[15] In this context they quote the distortions of the electron densities at the ligand atoms (Z in this case). If closely packed about the central atoms E, halogen ligands with rotational symmetry lead to ideally tetrahedral molecules EX_4 . In contrast, the electron density at nitrogen or oxygen in OR and NR_2 ligands is not rotationally symmetrical, thus leading to a ligand radius that is dependent on orientation. Consequently, the nonbonding distances $\text{O} \cdots \text{O}$ and $\text{N} \cdots \text{N}$ are dependent on the orientation of the ligands R. Closest packing of these unsymmetrical ligands thus leads to different angles O-E-O and N-E-N about the central atoms.

The structural elucidation of $\text{Si}(\text{PH}_2)_4$ is important in this context because the results show distinctly smaller deviations from tetrahedral symmetry than the comparable silicon amides. In fact $\text{Si}(\text{PH}_2)_4$ has an almost ideal tetrahedral geometry at silicon. It might be speculated whether the small hydrogen atoms are completely immersed in the electron cloud of the relatively large phosphorus atom; that is the phosphorus atom in the PH_2 ligand is effectively still rotationally symmetrical or its ligand radius is not orientation-dependent. A closest packing of such ligands about a silicon center leads then to an almost tetrahedral structure. The very low rotational barrier about the Si-P bond can be rationalized in exactly the same way. Is it possible that it turns out that

the elements of the first period are an exception to the rule of otherwise almost symmetrical ligand radii?

Precursors for IV/V Materials

There are numerous interesting materials comprising elements of Groups 14 and 15. Some have already found broad technical application, others are under development or have not been synthesized to date, but are very promising candidates. Of the nitride materials silicon nitride is the most important and among the precursors tested for the chemical vapor deposition of silicon nitride are compounds of the type $\text{Si}(\text{NR}_2)_4$.^[16]

Reports about the nitrides of the heavier elements of Group 14 are comparatively rare (Ge/N ;^[17] Sn/N ;^[18]), but there are still huge efforts to prepare carbon nitride C_3N_4 ,^[19] for which a hardness greater than that of diamond was predicted. However, so far no unequivocal report about a phase C_3N_4 has appeared. It is only in surface science that there are some reports about the existence of C_3N_4 phases as thin layers.^[20] Attempts to develop precursors for this material have also included the synthesis of $\text{C}(\text{NR}_2)_4$ compounds.^[8]

Silicon/phosphorus phases are promising materials for applications in micro- and optoelectronic devices such as heterojunction bipolar transistors, photovoltaic cells, sensors, and light-emitting diodes.^[21] Materials under consideration have compositions from single-crystalline p-doped silicon up to phosphorus-rich amorphous phases, the properties of which can be tuned by varying the Si/P ratio. Compounds like $\text{Si}(\text{PH}_2)_4$ are naturally interesting precursors for the preparation of such phases and the search for new Si/P materials is still uncovering new phases such as Si_2P_5 .^[22]

The most recent reports about the successful preparation of $\text{Si}(\text{PH}_2)_4$ show how important it is to reinvestigate the development of synthetic pathways to the missing members of parent substances of inorganic molecular chemistry. The absence of stabilizing organic substituents in particular make such compounds desirable for studying their fundamental properties but also for hightech applications.

German version: *Angew. Chem.* **1999**, *111*, 91–92

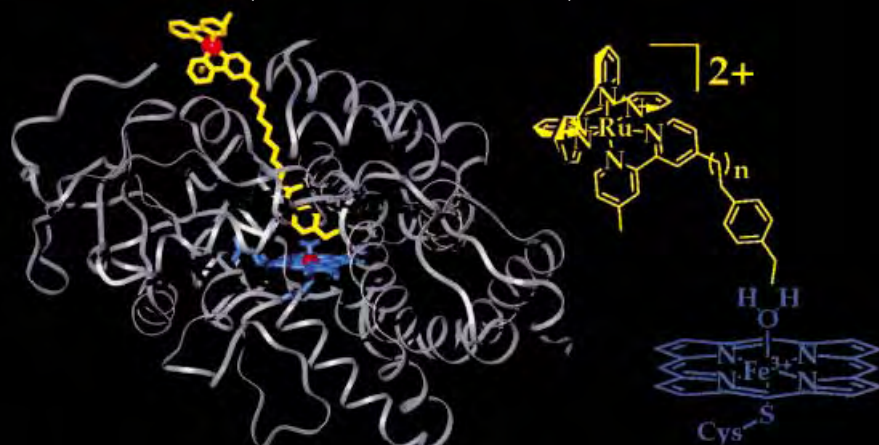
Keywords: germanium • materials science • phosphanes • silanes • silicon

- [1] M. Driess, C. Mosé, R. Boese, D. Bläser, *Angew. Chem.* **1998**, *110*, 2389–2391; *Angew. Chem. Int. Ed.* **1998**, *37*, 2257–2259.
- [2] G. Fritz, *Z. Anorg. Allg. Chem.* **1955**, *280*, 332–345.
- [3] A. D. Norman, *J. Am. Chem. Soc.*, **1968**, *90*, 6556–6557.
- [4] K.-F. Tebbe, T. Heinlein, M. Feher, *Z. Kristallogr.* **1985**, *172*, 89–90.
- [5] H. Schumann, T. Oestermann, M. Schmidt, *J. Organomet. Chem.* **1967**, *8*, 105–110.
- [6] G. Huber, A. Jockisch, H. Schmidbaur, *Eur. J. Inorg. Chem.* **1998**, 107–112.
- [7] M. F. Lappert, P. P. Power, A. R. Sanger, R. C. Srivastava *Metal and Metalloid Amides*, Ellis Horwood, Chichester, **1980**.
- [8] A. Jockisch, H. Schmidbaur, *Chem. Ber.* **1997**, *130*, 1739–1744.
- [9] H. Andersch, M. Jansen, *Acta Crystallogr. Sect. C* **1990**, *46*, 1985–1986.
- [10] N. W. Mitzel, A. J. Blake, D. W. H. Rankin, *J. Am. Chem. Soc.* **1997**, *119*, 4143–4148.

- [11] K. Albert, N. Rösch, *Chem. Ber.* **1997**, *130*, 1745–1749.
- [12] F. C. Mijlhoff, H. J. Geise, E. J. M. van Schaick, *J. Mol. Struct.* **1974**, *20*, 393–401.
- [13] L. H. Boonstra, F. C. Mijlhoff, G. Renes, A. Spelbos, I. Hargittai, *J. Mol. Struct.* **1975**, *28*, 129–139.
- [14] a) R. J. Gillespie, I. Bytheway, E. A. Robinson, *Inorg. Chem.* **1998**, *37*, 2811–2825.
- [15] R. J. Gillespie, E. A. Johnson, *Angew. Chem.* **1996**, *108*, 539–560; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 495–514.
- [16] R. D. Gordon, D. M. Hofmann, K. Riaz, *Chem. Mater.* **1990**, *2*, 480–489.
- [17] G. A. Johnson, V. J. Kapoor, *J. Appl. Phys.* **1991**, *69*, 3616–3622.
- [18] D. M. Hoffman, P. Rangarajan, S. D. Athavale, D. J. Economou, J. R. Liu, Z. S. Zheng, *J. Vac. Sci. Technol. A* **1995**, *13*, 820–825.
- [19] W. Schnick, *Angew. Chem.* **1993**, *105*, 1649–1650; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1580–1581.
- [20] S. Vepřek, J. Weidmann, F. Glatz, *J. Vac. Sci. Technol. A* **1995**, *13*, 2914–2919.
- [21] X.-H. Li, J. R. A. Carlsson, S. F. Gong, H. T. G. Hentzell, *J. Appl. Phys.* **1994**, *76*, 5179–5184.
- [22] J. R. A. Carlsson, L. D. Madsen, M. P. Johansson, L. Hultman, X.-H. Li, H. T. G. Hentzell, L. R. Wallenberg, *J. Vac. Sci. Technol. A* **1997**, *15*, 394–401.

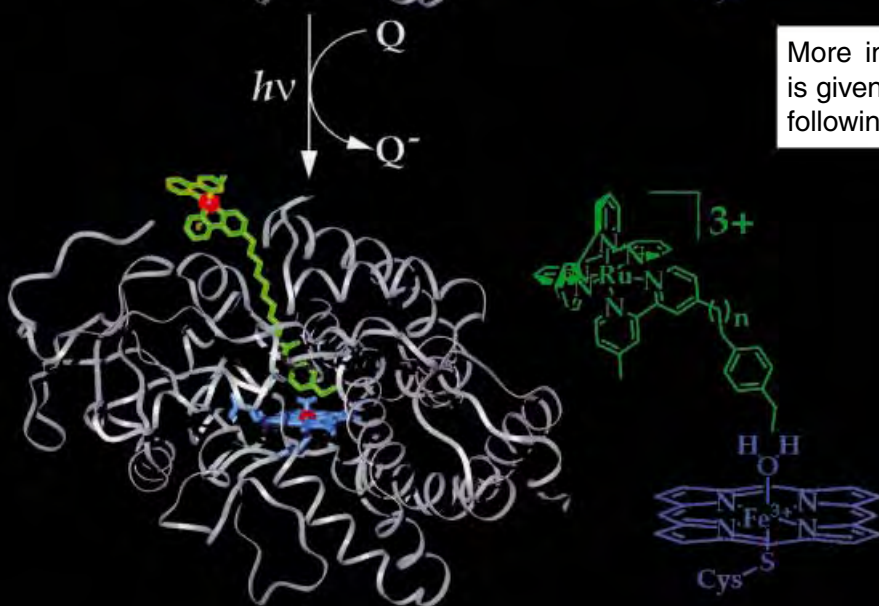
Conjugates of protein substrates and photoactive redox agents permit reduction or oxidation of buried protein active sites (oxidation is shown):

Protein binding of the sensitizer-linked substrate (SLS)

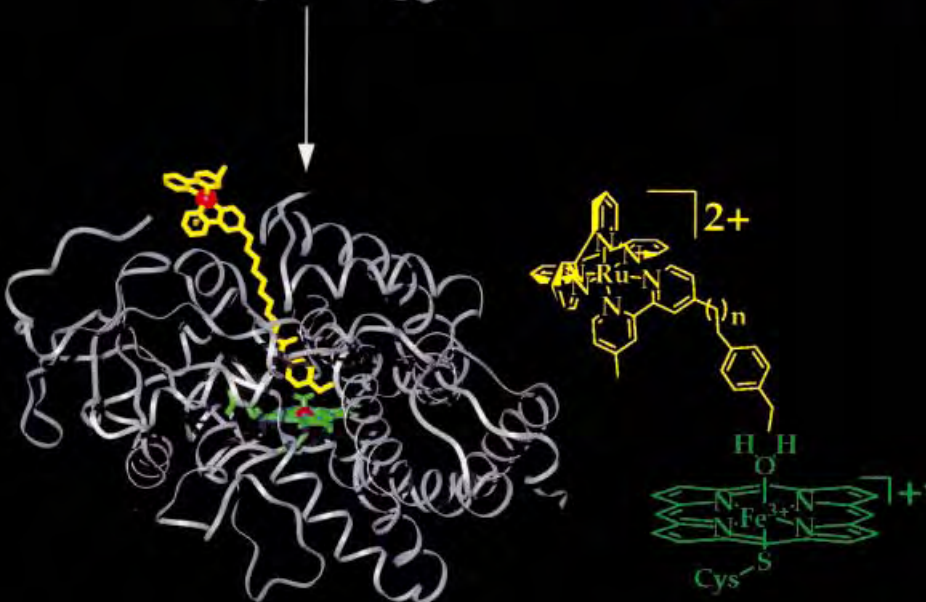


More information is given on the following pages.

Irradiation followed by excited state quenching (by Q) to generate an oxidized SLS



Subsequent electron transfer forms the oxidized active site



Substrates for Rapid Delivery of Electrons and Holes to Buried Active Sites in Proteins**

Jonathan J. Wilker, Ivan J. Dmochowski,
John H. Dawson, Jay R. Winkler,* and Harry B. Gray*

Rigorous characterization of metalloenzyme oxidation states is essential to understanding metabolic processes at a molecular level. Reactive intermediates in enzymatic catalysis are of special interest, but they are frequently too short-lived to be examined directly. A case in point is the high-valent heme that is believed to be a catalytic intermediate in the oxygenation reactions of cytochrome P450_{cam} (P450);^[1, 2] this oxidant has eluded detection thus far, raising questions concerning its role in the catalytic cycle.^[1–3]

We have shown previously that reactive high-valent hemes of peroxidases can be prepared in solutions containing photogenerated ruthenium–diimine complexes as oxidizing agents.^[4, 5] Our attempts to use the same approach with P450 have not met with success, however, owing in part to the inefficiency of electron transfer (ET) between external redox agents and a deeply buried heme. We have now developed a powerful photochemical method for the delivery of electrons and holes to buried redox sites. By tethering a Ru photosensitizer to a protein substrate, we have succeeded in reducing the P450 heme much more rapidly than has been possible previously, and we have also generated a hitherto unobserved oxidized state of the enzyme. The strategy of linking sensitizers to substrates opens the door to exploration of reactive redox states in enzyme interiors.

The photosensitizer [Ru(bpy)₃]²⁺ (bpy = 2,2′-bipyridine) is linked through a hydrocarbon chain to a species with high affinity for the P450 heme pocket: imidazole (Im), adamantane (Ad), or ethylbenzene (EB).^[6] Imidazole ligates the heme iron center directly,^[7] whereas adamantane^[8] and ethylbenzene^[9] bind strongly to the hydrophobic cavity of the active site (Figure 1). Adamantanone displaces ligated water from the enzyme active site [P_{Cys}Fe^{III}(OH₂)] (P_{Cys} is the protoporphyrin IX of P450 which is ligated through the thiolate group of a cysteine residue), to yield five-coordinate [P_{Cys}Fe^{III}].^[10] Binding of ethylbenzene, in contrast, leaves the six-coordinate resting state relatively unperturbed.

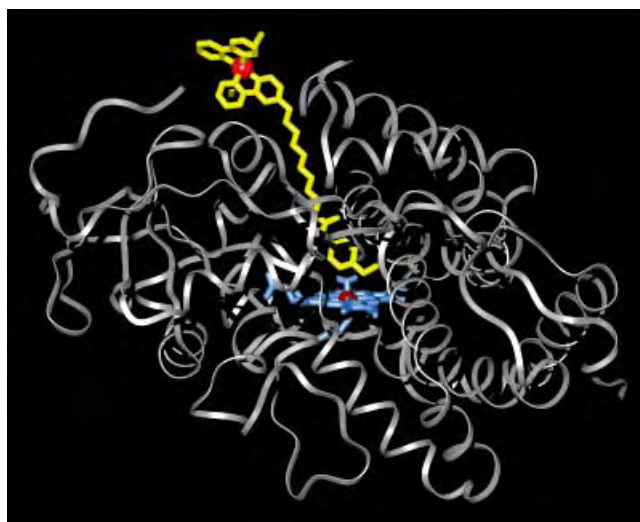
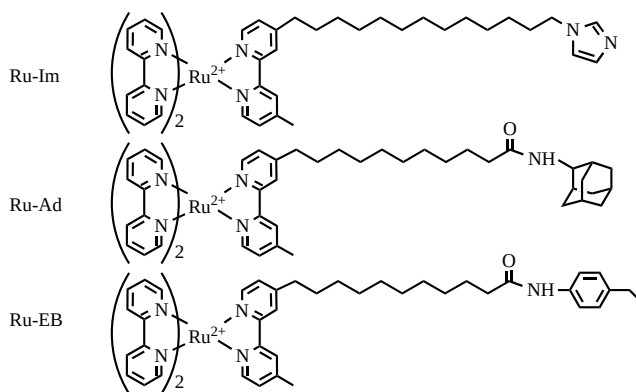


Figure 1. View of the (Ru-EB)–P450 complex with the Ru-EB alkyl chain placed in the channel to which the substrate has access (modeled from the crystal structure of P450: T. L. Poulos, *Methods Enzymol.* **1991**, 206, 11–30). The hydrocarbon chain and protein substrate provide a well-coupled pathway for electron tunneling between the Ru and the heme. Energy minimization of (Ru-EB)–P450 was not performed.

Addition of stoichiometric amounts of Ru-Ad to ferric P450 shifts the Soret absorption maximum from 417 to 415 nm and creates a shoulder at 391 nm, indicating binding of the adamantyl moiety in the heme region.^[11] This peak shift is attributed to lengthening of the Fe^{III}–OH₂ bond or partial displacement of water from the [P_{Cys}Fe^{III}(OH₂)] resting state, both of which accompany the binding of adamantyl compounds in the heme cavity.^[12] In addition to this absorbance change, there is a decrease in the lifetime of the excited state of Ru-Ad (Ru^{II*}-Ad).^[13] The normally monophasic luminescence decay profile of Ru^{II*}-Ad ($k_1 = 2.2 \times 10^6 \text{ s}^{-1}$) becomes biphasic ($k_1 = 2.2 \times 10^6 \text{ s}^{-1}$, $k_2 = 7.7 \times 10^6 \text{ s}^{-1}$) in the presence of P450, with the faster phase accounting for 77% of Ru^{II*} decay. We attribute the rapid luminescence decay (k_2) to (Ru-Ad)–P450 interactions; the dissociation constant K_D is $0.69 \mu\text{M}$ for the complex formed between Ru-Ad and P450.^[14]

The Soret absorption maximum of ferric P450 in the presence of equimolar amounts of Ru-Im shifts from 417 to 420 nm, indicating binding of the imidazole ligand to the heme iron center.^[7] Luminescence decay of the (Ru^{II*}-Im)–P450 complex is biphasic ($k_1 = 2.2 \times 10^6 \text{ s}^{-1}$, $k_2 = 7.0 \times 10^6 \text{ s}^{-1}$).

[*] J. R. Winkler, H. B. Gray, J. J. Wilker, I. J. Dmochowski
Beckman Institute
California Institute of Technology
Pasadena, CA 91125 (USA)
Fax: (+1) 626-449-4159
E-mail: winklerj@cco.caltech.edu
hgcm@cco.caltech.edu

J. H. Dawson
Department of Chemistry and Biochemistry
University of South Carolina, Columbia, SC (USA).

[**] We are indebted to M. C. Lamczyk for growing cells containing enzyme, S. G. Sligar for providing a P450 vector, and S. J. Lippard for insightful discussions. I.J.D. is a predoctoral trainee under the National Institutes of Health Biotechnology Grant GM08346. H.B.G. thanks Balliol College and the Inorganic Chemistry Laboratory, University of Oxford, for providing a stimulating environment during 1997–1998. This work was supported by the National Institutes of Health (DK19038) and the National Science Foundation (CHE9508533, CHE9807150).

Approximately 68 % of $\text{Ru}^{\text{II}*}$ decay occurs by the faster phase (k_2); $K_D = 1.5 \mu\text{M}$ for $(\text{Ru-Im})-\text{P450}$.

A 1:1 mixture of Ru-EB and P450 does not display an altered Soret absorption maximum; however, $\text{Ru}^{\text{II}*}\text{-EB}$ is quenched in the presence of P450 . The faster of two decay processes ($k_1 = 2.2 \times 10^6 \text{ s}^{-1}$, $k_2 = 1.2 \times 10^7 \text{ s}^{-1}$) accounts for 70 % of $\text{Ru}^{\text{II}*}\text{-EB}$ decay, indicating $K_D = 1.0 \mu\text{M}$ for the $(\text{Ru-EB})-\text{P450}$ complex. Addition of excess camphor ($K_D \approx 1 \mu\text{M}^{[2]}$) to $(\text{Ru-EB})-\text{P450}$ displaces the Ru-linked substrate, as judged by an increased contribution of the slower luminescence decay process (k_1). We conclude that all three sensitizer-linked substrates bind tightly to the active site of P450 .

Laser excitation of $\text{Ru}^{\text{II}}\text{-Im}$ followed by reductive quenching with *para*-methoxy-*N,N*-dimethylaniline (*p*-MDMA)^[15] yields a powerful reductant, $\text{Ru}^{\text{I}}\text{-Im}$ ($E^0 = -1.24 \text{ V}$ versus the normal hydrogen electrode (NHE)).^[16, 17] In the presence of P450 , $\text{Ru}^{\text{I}}\text{-Im}$ is converted rapidly into $\text{Ru}^{\text{II}}\text{-Im}$. Concomitant with this oxidation of Ru^{I} is reduction of the heme group, as evidenced by a shift of the Soret band from 420 to 445 nm.^[7, 18] The rate constant k_{ET} for $\text{Ru}^{\text{I}} \rightarrow \text{Fe}^{\text{III}}$ electron transfer is $2 \times 10^4 \text{ s}^{-1}$ (Figure 2). Similar kinetics ($k_{\text{ET}} = 2 \times 10^4 \text{ s}^{-1}$) are observed upon reductive quenching of the

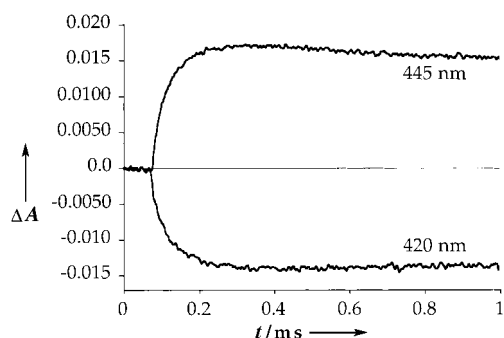


Figure 2. Plot of change in absorbance ΔA versus time t for the reaction of $\text{Ru}^{\text{I}}\text{-Im}$ with P450 ($10 \mu\text{M}$ ruthenium complex, $10 \mu\text{M}$ enzyme, 20 mM *p*-MDMA).

$(\text{Ru}^{\text{II}*}\text{-EB})-\text{P450}$ complex; a shift of the Soret band from 417 to 390 nm results from the $\text{Ru}^{\text{I}} \rightarrow \text{Fe}^{\text{III}}$ reaction. Reductive quenching of the $(\text{Ru}^{\text{II}*}\text{-Ad})-\text{P450}$ complex yields spectroscopic changes comparable to those seen for $(\text{Ru}^{\text{II}*}\text{-EB})-\text{P450}$. This blue-shifted Soret band indicates that the reduction product is the previously unobserved $[\text{P}_{\text{Cys}}\text{Fe}^{\text{II}}(\text{OH}_2)]^-$ form of P450 .^[19] Further confirmation of heme reduction is the production of $[\text{P}_{\text{Cys}}\text{Fe}^{\text{II}}(\text{CO})]^-$ ($\lambda_{\text{max}} = 448 \text{ nm}$) upon steady-state visible irradiation of $(\text{Ru}^{\text{II}}\text{-EB})-\text{P450}$ in the presence of *p*-MDMA and carbon monoxide. The relatively high rate of heme reduction in the photogenerated $(\text{Ru}^{\text{I}}\text{-EB})-\text{P450}$ complex shows that a direct bond to the iron center is not required for efficient Ru–heme electronic coupling. Indeed, electron tunneling to the P450 active site through Ru-linked ethylbenzene is over two orders of magnitude faster than reduction by putidaredoxin ($k \approx 50 \text{ s}^{-1}$), a natural redox partner.^[20]

The efficient coupling of the sensitizer-linked substrate to the heme can be exploited to generate a

high-valent state of the enzyme. Oxidative quenching of the photoexcited species $\text{Ru}^{\text{II}*}\text{-EB}$ by $[\text{CoCl}(\text{NH}_3)_5]^{2+}$ yields $\text{Ru}^{\text{III}}\text{-EB}$, a strong oxidant ($E^0 = 1.26 \text{ V}$ vs. NHE).^[4, 17] The $(\text{Ru}^{\text{III}}\text{-EB})-\text{P450}$ complex undergoes rapid heme-to- Ru^{III} electron transfer ($k_{\text{ET}} = 6 \times 10^3 \text{ s}^{-1}$), yielding an oxidized product with a Soret peak at 390 nm (Figure 3). This absorption change is not

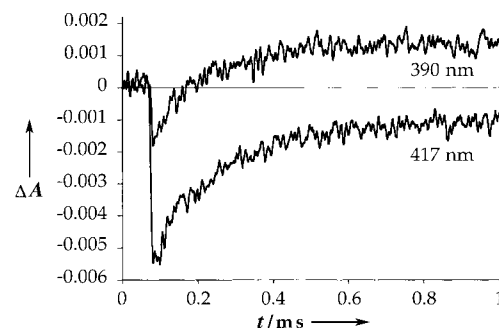


Figure 3. Plot of change in absorbance ΔA versus time t for the reaction of $\text{Ru}^{\text{III}}\text{-EB}$ with P450 ($10 \mu\text{M}$ ruthenium complex, $10 \mu\text{M}$ enzyme, 5 mM $[\text{CoCl}(\text{NH}_3)_5]^{2+}$).

observed upon laser photolysis of the $(\text{Ru}^{\text{II}}\text{-EB})-\text{P450}$ complex in the absence of $[\text{CoCl}(\text{NH}_3)_5]^{2+}$. The oxidized species could be the porphyrin π -cation radical $[\text{P}_{\text{Cys}}^+\text{Fe}^{\text{III}}(\text{OH}_2)]^+$ or the Fe^{IV} species $[\text{P}_{\text{Cys}}\text{Fe}^{\text{IV}}(\text{OH}_2)]^+$. The blue-shifted Soret band in the spectrum of the oxidized heme is in accordance with the formulation of a radical;^[21] indeed, porphyrin π -cation radicals often display Soret bands that are blue-shifted with respect to those of resting hemes.^[22–24]

By employing sensitizer-linked substrates, we have prepared new oxidized and reduced states of P450 (Figure 4).

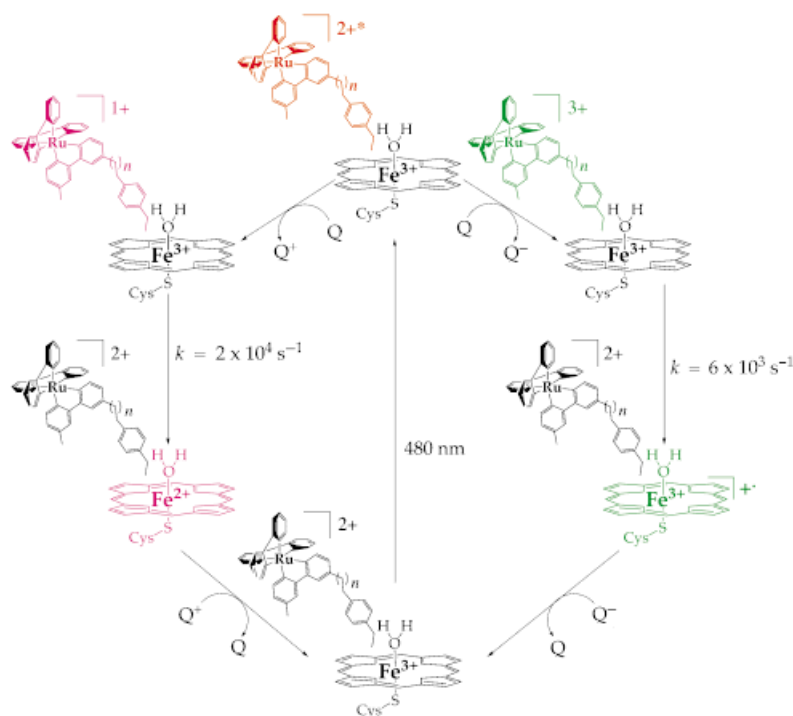


Figure 4. Schematic representation of the flash/quench reaction sequence for the preparation of new redox states in the $(\text{Ru-EB})-\text{P450}$ complex. Q = quenching agent.

These flash/quench methods provide a wide time window to study highly reactive forms of the enzyme. Both $[P_{\text{Cys}}\text{Fe}^{\text{II}}(\text{OH}_2)]^-$ and $[P_{\text{Cys}}^+\text{Fe}^{\text{III}}(\text{OH}_2)]^+$ are formed in about 0.1 ms and persist for approximately 100 ms. Improved design of sensitizers, quenchers, linkers, and substrates may lead to even faster electron and hole injection into P450 and other redox-active enzymes.

Received: July 31, 1998 [Z 12231 IE]
German version: *Angew. Chem.* **1999**, *111*, 94–96

Keywords: electron transfer • heme proteins • metallo-enzymes • ruthenium • sensitizers

- [1] M. Sono, M. P. Roach, E. D. Coulter, J. H. Dawson, *Chem. Rev.* **1996**, *96*, 2841–2887.
- [2] E. J. Mueller, P. J. Loida, S. G. Sligar in *Cytochrome P450. Structure, Mechanism, and Biochemistry* (Ed: P. R. Ortiz de Montellano), Plenum, New York, **1995**, pp. 83–124.
- [3] L.-L. Wong, *Curr. Opin. Chem. Biol.* **1998**, *2*, 263–268.
- [4] J. Berglund, T. Pascher, J. R. Winkler, H. B. Gray, *J. Am. Chem. Soc.* **1997**, *119*, 2464–2469.
- [5] D. W. Low, J. R. Winkler, H. B. Gray, *J. Am. Chem. Soc.* **1996**, *118*, 117–120.
- [6] The synthesis of Ru-EB is typical: Reaction of thionyl chloride with 10-bromodecanoic acid, followed by addition of 4-ethylaniline, gives the corresponding amide. Addition of the amide to a solution of 4,4'-dimethyl-2,2'-bipyridine and lithium diisopropylamide yields the derivatized bpy, which was allowed to react with $[\text{RuCl}_2(\text{bpy})_2]$ to give Ru-EB.
- [7] J. H. Dawson, L. A. Anderson, M. Sono, *J. Biol. Chem.* **1982**, *257*, 3606–3617.
- [8] R. E. White, M. B. McCarthy, K. D. Egeberg, S. G. Sligar, *Arch. Biochem. Biophys.* **1984**, *228*, 493–502.
- [9] D. Filipovic, M. D. Paulsen, P. J. Loida, S. G. Sligar, R. L. Ornstein, *Biochem. Biophys. Res. Commun.* **1992**, *189*, 488–495.
- [10] R. Raag, T. L. Poulos, *Biochemistry* **1991**, *30*, 2674–2684.
- [11] All studies were performed under an argon atmosphere with 10 μM ruthenium complex, 10 μM enzyme in 100 mM potassium chloride, and 20 mM potassium phosphate buffer (pH 7.4) at room temperature.
- [12] T. L. Poulos, J. Cupp-Vickery, H. Li in ref. [2], pp. 125–150.
- [13] Excitation at 480 nm (20-ns pulse width); the experimental setup has been described.^[5]
- [14] Shifts of Soret bands resulting from addition of the ruthenium complexes to P450 are small. Competitive binding assays of camphor and Ru-Ad with P450 by Soret absorption shifts yielded $K_D = 0.68 \mu\text{M}$.
- [15] G. A. Mines, M. J. Bjerrum, M. G. Hill, D. R. Casimiro, I.-J. Chang, J. R. Winkler, H. B. Gray, *J. Am. Chem. Soc.* **1996**, *118*, 1961–1965.
- [16] Reductive quenching of $[\text{Ru}^{\text{II}}(\text{bpy})_3]^{2+}$ yields a ruthenium complex containing a coordinated bpy anion radical, $[\text{Ru}^{\text{II}}(\text{bpy})_2(\text{bpy}^{\cdot-})]^+$: K. Kalyanasundaram, *Photochemistry of Polypyridyl and Porphyrin Complexes*, Academic Press, London, **1992**, p. 108. $[\text{Ru}^{\text{II}}(\text{bpy})_2(\text{bpy}^{\cdot-})]^+$ is designated as Ru^I.
- [17] Reduction potentials are given for $[\text{Ru}(\text{bpy})_3]^{2+}$ (ref. [16], p. 144). The E^0 values of derivatives with substrate-terminated hydrocarbon chains should be similar.
- [18] J. H. Dawson, L. A. Andersson, M. Sono, *J. Biol. Chem.* **1983**, *258*, 13637–13645.
- [19] The $[P_{\text{His}}\text{Fe}^{\text{II}}(\text{OH}_2)]$ form of myoglobin exhibits a Soret band that is blue-shifted by 15 nm with respect to that of $[P_{\text{His}}\text{Fe}^{\text{II}}]$: D. C. Lamb, V. Prusakov, N. Engler, A. Ostermann, P. Schellenberg, F. G. Parak, G. U. Nienhaus, *J. Am. Chem. Soc.* **1998**, *120*, 2981–2982. Typical bulk reduction of P450 results in five-coordinate $[P_{\text{Cys}}\text{Fe}^{\text{II}}]$ with a Soret peak at 408 nm. The product of $[P_{\text{Cys}}\text{Fe}^{\text{III}}(\text{OH}_2)]$ reduction by Ru^I-EB displays a Soret peak at 390 nm.
- [20] M. J. Hintz, D. M. Mock, L. L. Peterson, K. Tuttle, J. A. Peterson, *J. Biol. Chem.* **1982**, *257*, 14324–14332.

- [21] The cysteine thiolate ligand could stabilize an Fe^{IV} state of P450. Hydrogen bonding to this thiolate (T. L. Poulos, B. C. Finzel, A. J. Howard, *J. Mol. Biol.* **1987**, *195*, 687–700), however, decreases the donor strength. Although the reaction product of iodosobenzene and P450 exhibits a Soret band at 393 nm (R. C. Blake II, M. J. Coon, *J. Biol. Chem.* **1989**, *264*, 3694–3701), the Soret band of chloroperoxidase is red-shifted upon ferryl formation: R. Nakajima, I. Yamazaki, B. W. Griffi, *Biochem. Biophys. Res. Commun.* **1985**, *128*, 1–6). The blue-shifted Soret band exhibited by the heme in the oxidized (Ru-EB)–P450 complex is not unlike that of P420, a common P450 decomposition product: S. A. Martinis, S. R. Blank, L. P. Hager, S. G. Sligar, G. H. B. Hoa, J. J. Rux, J. H. Dawson, *Biochemistry* **1996**, *35*, 14530–14536. Formation of P420, however, is largely irreversible, whereas oxidized (Ru-EB)–P450 returns to the resting state without appreciable decomposition.
- [22] P. Gans, G. Buisson, E. Duee, J.-C. Marchon, B. S. Erler, W. F. Scholz, C. A. Reed, *J. Am. Chem. Soc.* **1986**, *108*, 1223–1234.
- [23] R. H. Felton, G. S. Owen, D. Dolphin, J. Fajer, *J. Am. Chem. Soc.* **1971**, *93*, 6332–6334.
- [24] A. Wolberg, J. Manassen, *J. Am. Chem. Soc.* **1970**, *92*, 2982–2991.

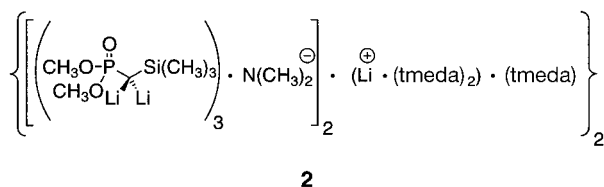
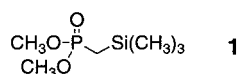
Structural Investigation of a Dilithiated Phosphonate in the Solid State

Jürgen F. K. Müller,* Markus Neuburger, and Bernhard Spingler

The structural determination of reaction intermediates in organophosphonate anion chemistry has been stimulated by the extraordinary synthetic utility of these reagents.^[1] A great body of information about the solid-state and solution structures of phosphorus-stabilized anions has been collected during recent years, and include lithiated phosphonates,^[2] phosphinoxides,^[3] phosphonamides, and thiophosphonamides.^[4] Even though a more detailed picture of the characteristics was achieved, and important conclusions about the related reactivity were drawn, there some open questions still remain. For example, a general problem in the reactions of such monolithiated reagents with electrophiles occurs when more acidic products are formed. This usually leads to the formation of unwanted side products. To overcome this limitation, an attractive strategy that takes advantage of a dianionic intermediate has been developed.^[5] Dicarbaniions have already been used in several cases as supernucleophiles, and even in asymmetric reactions.^[6] Despite the synthetic value of these reagents, there is still a demand for more information about the structures.^[6], 7] Our interest in the study of such dilithiophosphonates is an extension of our work in the development and application of chiral substituted dianions.^[6] Here we present the first solid-state structure of a geminal dilithiated phosphonate.

[*] Dr. J. F. K. Müller, M. Neuburger, B. Spingler
Institut für Anorganische Chemie der Universität
Spitalstrasse 51, CH-4056 Basel (Switzerland)
Fax: (+41) 61-267-10-18
E-mail: muellerju@ubaclu.unibas.ch

Treatment of a clear solution of **1** in tmeda (*N,N,N',N'*-tetramethyl-1,2-ethane diamine) at -78°C with 2.5 equivalents of *n*BuLi in hexane gave a yellow–green solution from



which yellow crystals were obtained after 24 h at room temperature. These crystals decomposed during storage for longer periods and were pyrophoric upon exposure to moist air. The lithium cluster **2** crystallizes in the space group $P\bar{1}$ as a hexameric aggregate, which consists of six dilithiated phosphonate units and two molecules of dimethylamide.^[8] In addition, two Li^+ ions are coordinated by four tmeda ligands in a distorted tetrahedral fashion, which balances the remaining two negative charges (Figure 1). The core of the aggregate

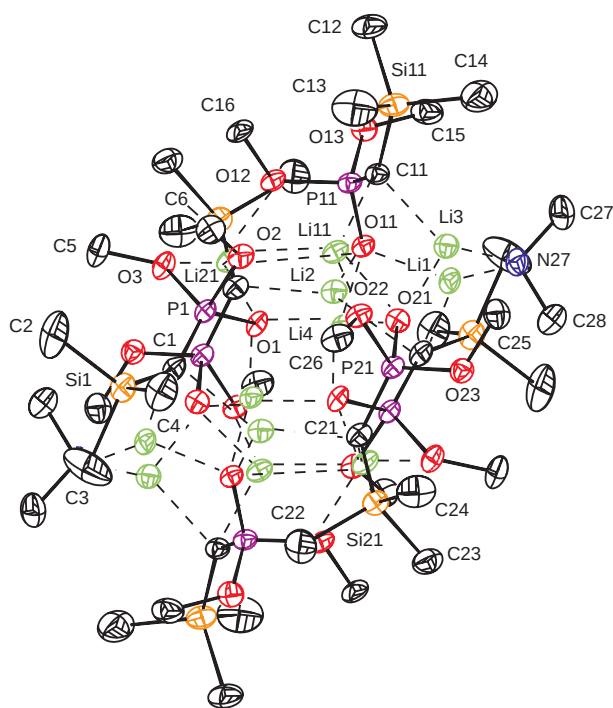


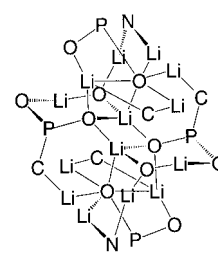
Figure 1. Molecular structure of **2** in the crystal. All hydrogen atoms, two tmeda molecules, and two $[\text{Li}(\text{tmeda})_2]^+$ complexes are omitted for clarity. The thermal ellipsoids are drawn at the 30% probability level.

is characterized by a Li–O–Li–O four-membered ring that contains the crystallographic inversion center. Such a structural motif has been found to be an essential feature in such monolithiated phosphonates that do not contain C–Li bonds.^[2] Up to six six-membered rings (Li4–O11–Li1–C1–P1–

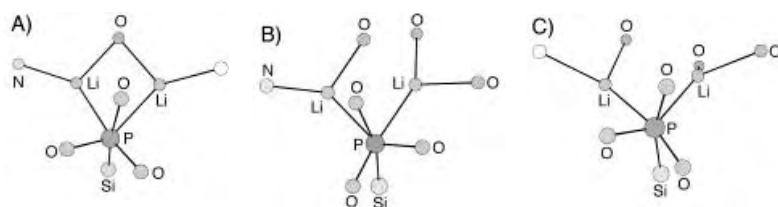
O1, Li4–O11–Li2–C1–P1–O1, O1–Li2–C21–P21–O21–Li4, Li1–O11–Li4–O21–Li3–N27, Li4–O21–Li11–O2–P1–O1, and Li2–O11–P11–O12–Li21–C21) are fused to opposite sides of the central four-membered ring (Scheme 1), to form an overall puckered-ladder structure, which is known for certain lithium siloxides.^[9]

There are three different dilithiated carbon atoms in the asymmetric unit, each connected to two Li^+ ions and distinctly pyramidalized. These geminal bound Li^+ ions coordinate in a similar fashion to a neighboring phosphonate oxygen atom to form C–Li–O–Li four-membered ring motifs. However, they differ in their detailed coordination mode: Li3 and Li21 show heteroatom coordination (N,O versus O,O), whereas the others have one additional C–Li bond and a Li–N or Li–O contact. In the second case, one Li^+ ion bridges two different dimetalated carbon atoms and leads to a O1–Li21–C21–Li2–C1–Li1–N27 zig-zag chain. The Li^+ ion in the bridging position complements its three-coordination by complexation to a phosphonate oxygen atom. A similar three-coordination is found for Li1 and Li3. Another unusual coordination mode is found for Li21, which is surrounded by an array of four oxygen atoms and one dianionic carbon atom, which leads to a distorted trigonal bipyramidal geometry. The incorporation of lithium dimethylamide into the aggregate arises from the use of an excess of *n*BuLi in tmeda, which leads to the decomposition products *N,N*-dimethylvinylamine and lithium dimethylamide at elevated temperatures.^[10] However, lithium dimethylamide is essential for the formation of the aggregate, because it acts as a bridge between the trigonal coordinated Li1 and Li3 atoms. The Li–C bond lengths (2.13(1)–2.28(1) Å) are similar to those in monolithiated phosphonates, which have Li–C bond lengths of 2.21–2.26 Å.^[2] The Li–O bond lengths within each C–Li–O–Li chelate (1.95(1)–2.85(1) Å) are significantly longer than those within the $(\text{Li}–\text{O})_2$ core (1.895(9) and 1.903(9) Å, respectively). A striking feature is the extremely short P–C bonds (1.587(6), 1.604(5), and 1.619(6) Å) compared to neutral (1.80 Å) and monolithiated phosphonates (ca. 1.68 Å).^[2] This additional contraction can be explained with the threefold and/or fourfold Li^+ ion coordination of each phosphonate oxygen atom and the additional complexation of the methoxy groups to one Li^+ ion, which leads to an increased coulombic attraction of the negatively charged $\text{C}^{(a)}$ atom.^[6, 7] A closer look along the C–P bonds demonstrates that the phosphonate oxygen atoms adopt a *gauche* conformation between the geminal Li^+ ions, which clearly indicates a significant degree of pyramidalization (Scheme 2). This view is supported by the examination of the dihedral angles (Li21–C21–P21–O21 25.7° , Li2–C21–P21–O21 65.2° , Li2–C1–P1–O1 27.4° , Li1–C1–P1–O1 48.8° , Li11–C11–P11–O11 58.1° , and Li3–C11–P11–O11 19.7°).

The question remains, how does the organization of such a highly aggregated species occur? The foundation of this



Scheme 1. Schematic representation of the central Li–O–Li–O four-membered ring in **2**. Tmeda, methyl, methoxy, and trimethylsilyl groups have been omitted for clarity; only selected connectivities are shown.



Scheme 2. Newman projections along the P1–C1 (A), P11–C11 (B), and P21–C21 bonds (C) in **2**.

aggregate seems to be the central $(\text{Li}-\text{O})_2$ core, which is related to the fundamental structural unit that is derived from several monolithiophosphonates. Based on this, we conclude that after the formation of the typical four-membered rhomboid motif, the incorporation of the second lithium ion affects only the aggregation sphere outside of the $(\text{Li}-\text{O})_2$ core. This is supported by the fact that nearly every available coordination partner is linked to at least one lithium ion, except the phosphonate oxygen atoms in the center, which leads finally to this hexameric aggregate. However, it is interesting to note in this context that, despite the large excess of tmeda no such ligand has been incorporated within the aggregate as a coordination partner.^[11]

Experimental Section

2: A solution of **1** (236 mg, 1.2 mmol) in tmeda (2 mL) was treated with *n*BuLi in hexane (1.2 mL, 2.48 M, 3 mmol) at -78°C . After 24 h at room temperature yellow crystals of **2** formed, which were suitable for X-ray analysis (211 mg, 63%).

Received: August 25, 1998 [Z 12326 IE]
German version: *Angew. Chem.* **1999**, *111*, 97–99

Keywords: aggregation • dianions • lithium • phosphorus • solid-state structures

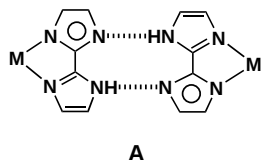
- [1] a) L. Horner, H. Hoffmann, H. G. Wippel, *Chem. Ber.* **1958**, *91*, 61–63; b) W. S. J. Wadsworth, W. D. Emmons, *J. Am. Chem. Soc.* **1961**, *83*, 1733–1738; c) B. E. Maryanoff, A. B. Reitz, *Chem. Rev.* **1989**, *89*, 863–927; d) J. Clayden, S. Warren, *Angew. Chem.* **1996**, *108*, 261–291; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 241–270.
- [2] a) W. Zarges, M. Marsch, K. Harms, F. Haller, G. Frenking, G. Boche, *Chem. Ber.* **1991**, *124*, 861–866; b) S. E. Denmark, K. A. Swiss, P. C. Miller, S. R. Wilson, *Heteroatom Chem.* **1998**, *9*, 209–218.
- [3] a) S. E. Denmark, K. A. Swiss, S. R. Wilson, *Angew. Chem.* **1996**, *108*, 2686–2688; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2515–2517; b) J. E. Davies, R. P. Davies, L. Dunbar, P. R. Raithby, M. G. Russell, R. Snaith, S. Warren, A. E. H. Wheatley, *Angew. Chem.* **1997**, *109*, 2428–2430; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2334–2335.
- [4] a) S. E. Denmark, R. L. Dorow, *J. Am. Chem. Soc.* **1990**, *112*, 864–866; b) S. E. Denmark, P. C. Miller, S. R. Wilson, *J. Am. Chem. Soc.* **1991**, *113*, 1468–1470; c) S. E. Denmark, K. A. Swiss, S. R. Wilson, *J. Am. Chem. Soc.* **1993**, *115*, 3826–3827; d) M. Kranz, S. E. Denmark, K. A. Swiss, S. R. Wilson, *J. Org. Chem.* **1996**, *61*, 8551–8563.
- [5] a) B. Iorga, F. Eymery, P. Savignac, *Tetrahedron Lett.* **1998**, *39*, 3693–3696; b) C. M. Thomson in *Dianion Chemistry in Organic Synthesis*, CRC Press, Boca Raton, FL, USA, **1994**, pp. 1–250.
- [6] a) S. Brenner, M. Bovete, *Tetrahedron* **1975**, *31*, 153–158; b) E. M. Kaiser, J. D. Petty, P. L. A. Knutson, *Synthesis* **1977**, 509–550; c) C. J. Kowalsky, M. L. O'Dowd, M. C. Burke, K. W. Fields, *J. Am. Chem. Soc.* **1980**, *102*, 5411–5412; d) H.-H. Vogt, R. Gompper, *Chem. Ber.* **1981**, *114*, 2884–2897; e) D. Seebach, M. Pohmakotr, *Tetrahedron* **1981**, *37*, 4047–4058; f) J. Vollhardt, H.-J. Gais, L. Lukas, *Angew. Chem.* **1985**, *97*, 607–609; *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 608–610; g) H.-J. Gais, J. Vollhardt, *Tetrahedron Lett.* **1988**, *29*, 1529–1532; h) A. Maercker, M. Theis *Top. Curr. Chem.* **1987**, *138*, 1–62; i) F. Caturia, C. Nájera, *Tetrahedron Lett.* **1996**, *37*, 2833–2836; j) P. Bonete, C. Nájera, *Tetrahedron* **1996**, *52*, 4111–4122; k) I. Marek, J.-F. Normant, *Chem. Rev.* **1996**, *96*, 3241–3267; l) J. F. K. Müller, M. Neuburger, M. Zehnder, *Helv. Chim. Acta* **1997**, *80*, 2182–2190.
- [7] a) H.-J. Gais, J. Vollhardt, H. Günther, D. Moskau, H. J. Lindner, S. Braun, *J. Am. Chem. Soc.* **1988**, *110*, 978–980; b) G. Boche, *Angew. Chem.* **1989**, *101*, 186–306; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 277–297; W. Zarges, M. Marsch, K. Harms, G. Boche, *Chem. Ber.* **1989**, *122*, 1307–1311.
- [8] X-ray crystal data for **2**: $\text{C}_{38}\text{H}_{99}\text{Li}_7\text{N}_7\text{O}_9\text{P}_3\text{Si}_3$, $M_r = 1024.01$, triclinic, space group $P\bar{1}$, $a = 4.359(4)$, $b = 14.555(4)$, $c = 16.465(5)$ Å, $\alpha = 78.02(3)^\circ$, $\beta = 71.00(2)^\circ$, $\gamma = 77.33(2)^\circ$, $V = 3139.7(16)$ Å³, $Z = 2$, $F(000) = 1112$, $\rho_{\text{calcd}} = 1.08$ Mg m^{−3}, $\mu = 1.79$ cm^{−1}, crystal dimensions = $0.3 \times 0.4 \times 0.5$ mm, $T = 193$ K, radiation $\text{CuK}\alpha$ ($\lambda = 1.54180$ Å), scan type $\omega/2\theta$, $\theta_{\text{max}} = 74.33^\circ$, no. of measured reflections = 10510, no. of independent reflections = 10170, no. of reflections in refinement = 6117, $I > 3.00\sigma(I)$, no. of parameters = 660, $R = 0.0792$, $R_w = 0.0955$, weighting scheme $w(1 - (\delta F/6\sigma F)^2)$, $\Delta\rho = 0.45/-1.10$ e Å^{−3}, $R = \sum ||F_o| - |F_c|| / \sum |F_o|$, $R_w = \{\sum (|F_o| - |F_c|)^2 / \sum F_o^2\}^{1/2}$. A crystal of **2** was stuck with perfluoropolyether to a glass fibre and mounted on the diffractometer. Unit cell parameters were determined by careful centering of 21 independent strong reflections with $11 \leq \theta \leq 20^\circ$. Data collection was carried out on an Enraf–Nonius CAD4 diffractometer equipped with a graphite monochromator, and 10510 reflections with $2.88 \leq \theta \leq 74.33^\circ$ were measured, three of which, monitored every 2 h, showed an intensity loss of 24.60%. The usual corrections were applied. Absorption correction was carried out with φ scans (minimum and maximum transmission: 0.51/1.00). The structure was solved by direct methods with the program SIR92.^[12] An anisotropic least squares full matrix refinement was carried out on all non-hydrogen atoms with the program CRYSTALS.^[13] The positions of the hydrogen atoms were determined geometrically. The disordered tmeda ligand was refined with appropriate restraints. Chebyshev polynomial weights were used to complete the refinement.^[14] Scattering factors were taken from the International Tables, Vol. IV, Table 2.2B. Crystallographic data (excluding structure factors) for the structure reported in this publication have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-102686. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [9] a) M. B. Hursthouse, M. A. Hossain, M. Motevalli, M. Sanganee, *J. Organomet. Chem.* **1990**, *381*, 293–297; b) F. Pauer, P. P. Power in *Lithium Chemistry* (Eds.: A. M. Sapse, P. von R. Schleyer), Wiley, New York, **1995**, pp. 295–392.
- [10] G. G. Eberhardt, W. A. Butte, *J. Org. Chem.* **1964**, *29*, 2928–2932.
- [11] D. B. Collum, *Acc. Chem. Res.* **1992**, *25*, 448–454.
- [12] A. Altomare, G. Cascarano, G. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli, *J. Appl. Crystallogr.* **1994**, *27*, 435–435.
- [13] D. J. Watkin, R. J. Carruthers, P. Betteridge, *Crystals*, Chemical Crystallography Laboratory, Oxford, **1985**.
- [14] J. R. Carruthers, D. J. Watkin, *Acta Crystallogr. Sect. A* **1979**, *35*, 698–699.

Cation-Dependent Formation of Superstructures by One-Pot Self-Organization of Hydrogen-Bonded Nickel Complexes**

Makoto Tadokoro,* Kiyoshi Isobe, Hidehiro Uekusa, Yuji Ohashi, Jiro Toyoda, Koji Tashiro, and Kazuhiro Nakasuji*

The unique strength, directionality, and complementarity of noncovalent interactions such as hydrogen bonding and coordination bonding play a central role in the creation of a variety of molecular architectures for molecular self-assembly and recognition in chemical, physical, and biological sciences.^[1, 2] The building blocks possessing such noncovalent interaction sites can produce one-, two-, and three-dimensional molecular arrangements with long-range order.^[3–5] Control of such multidimensional molecular arrangements is essential for progressing crystal engineering and in constructing the desired molecular-based materials.^[6–8] We have designed a new anionic building block, a tris(biimidazolato)-nickel(II) complex, in which the three strong, π -conjugated biimidazolato ligands each provide one complementary hydrogen-bonding site. We now report the construction of four types of hydrogen-bonded and coordination-bonded molecular architectures of nickel(II) ions, biimidazolato ligands, and counter cations.

Since 2,2'-biimidazole (H_2bim) is a bidentate chelating ligand with multiple proton-donor sites, it can coordinate to a transition metal in three reversible protonated and deprotonated modes: neutral (H_2bim), monoanionic ($Hbim^{-1}$), and dianionic (bim^{-2}).^[9] The mono-deprotonated ligand ($Hbim^{-1}$) can form both a complementary binary $NH\cdots N$ -type hydrogen bond and a coordination bond with metal ions (see structure **A**).^[10]



A

In this study, we have found that simple one-pot procedures^[11] of mixing the nickel(II) ions, $Hbim^{-1}$, and counter cations produces four types of hydrogen-bonded crystals (**1–4**) based on arrangements of the $[Ni(Hbim)_3]^{-}$ building blocks

(Figure 1). Figures 2 and 3 show the schematic drawings and crystal structures of the four types of molecular arrangements.

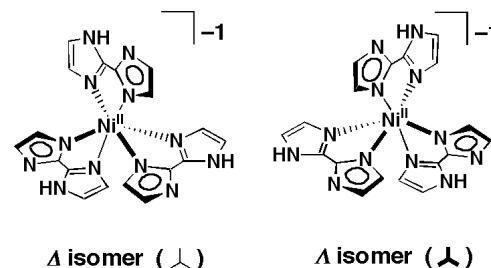


Figure 1. Δ and Λ isomers of the building block $[Ni(Hbim)_3]^{-}$.

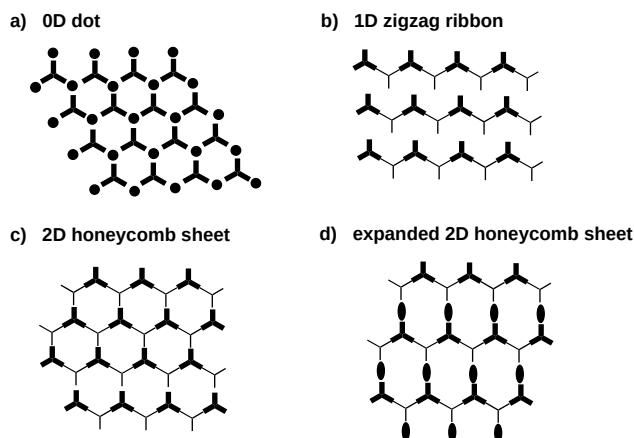


Figure 2. Schematic representations of the hydrogen-bonded networks of $[Ni(Hbim)_3]^{-}$ building blocks for **1–4** (a–d). Water molecules (●) and free 2,2'-biimidazole (■) also function as intermediate spacers.

As a common feature, all the structures contain the anionic building block $[Ni(Hbim)_3]^{-}$, in which the central Ni^{II} atom is coordinated by three bidentate $Hbim^{-1}$ ligands through the lone pairs of the imine nitrogen atoms in the imidazole rings. The $Ni-N$ bond lengths are in the range of 1.96(3)–2.19(2) Å. The building block has approximate D_3 symmetry; both the Δ and Λ isomers are illustrated in Figure 1.

Structure **1**^[12a] contains tetramethylammonium as the counter cation (Figures 2a, 3a). Although there is no hydrogen bonding between the ligands of the $[Ni(Hbim)_3]^{-}$ building blocks, the units are connected by hydrogen bonding through water molecules to make a sheet arrangement along the ab plane (Figure 2a): The length of the hydrogen bonds between the oxygen atoms of the water molecules and the nitrogen atoms of the $Hbim^{-1}$ ligands are 2.753(4) and 2.756(4) Å. The water molecules themselves form a 1D columnar structure along the c axis. A single sheet consists of only one of the two optical isomers (Δ or Λ). The whole structure is formed by an alternate stacking of the Δ and Λ sheets along the c axis, and the NMe_4^+ counter cations occupy the cavity formed between three $[Ni(Hbim)_3]^{-}$ building blocks in a sheet.

Structure **2**^[12b] contains tetra(n -propyl)ammonium as the counter cation (Figures 2b, 3b). Of the three hydrogen-bonding sites in the building block, the one oriented along the b axis is blocked by hydrogen bonding with a methanol molecule. The other two sites are linked by complementary

[*] Prof. M. Tadokoro, Prof. K. Isobe
Graduate School of Science
Osaka City University
Sumiyoshi-ku, Osaka 558-8585 (Japan)
Fax: (+81) 6-605-2522
E-mail: tadokoro@sci.osaka-cu.ac.jp

Prof. K. Nakasuji, Dr. J. Toyoda, Prof. K. Tashiro
Graduate School of Science
Osaka University
Toyonaka, Osaka 560-0043 (Japan)
Fax: (+81) 6-850-5392
E-mail: nakasuji@chem.sci.osaka-u.ac.jp

Dr. H. Uekusa, Prof. Y. Ohashi
Faculty of Science
Tokyo Institute of Technology O-okayama (Japan)

[**] This work was supported by a Grant-in-Aid for Scientific Research (no. 10146103) on Priority Areas from the Ministry of Education, Science and Culture, Japan. The authors thank the Analytical Center, Osaka City University, for the use of a four-circle single-crystal X-ray diffractometer and for an elemental analysis.

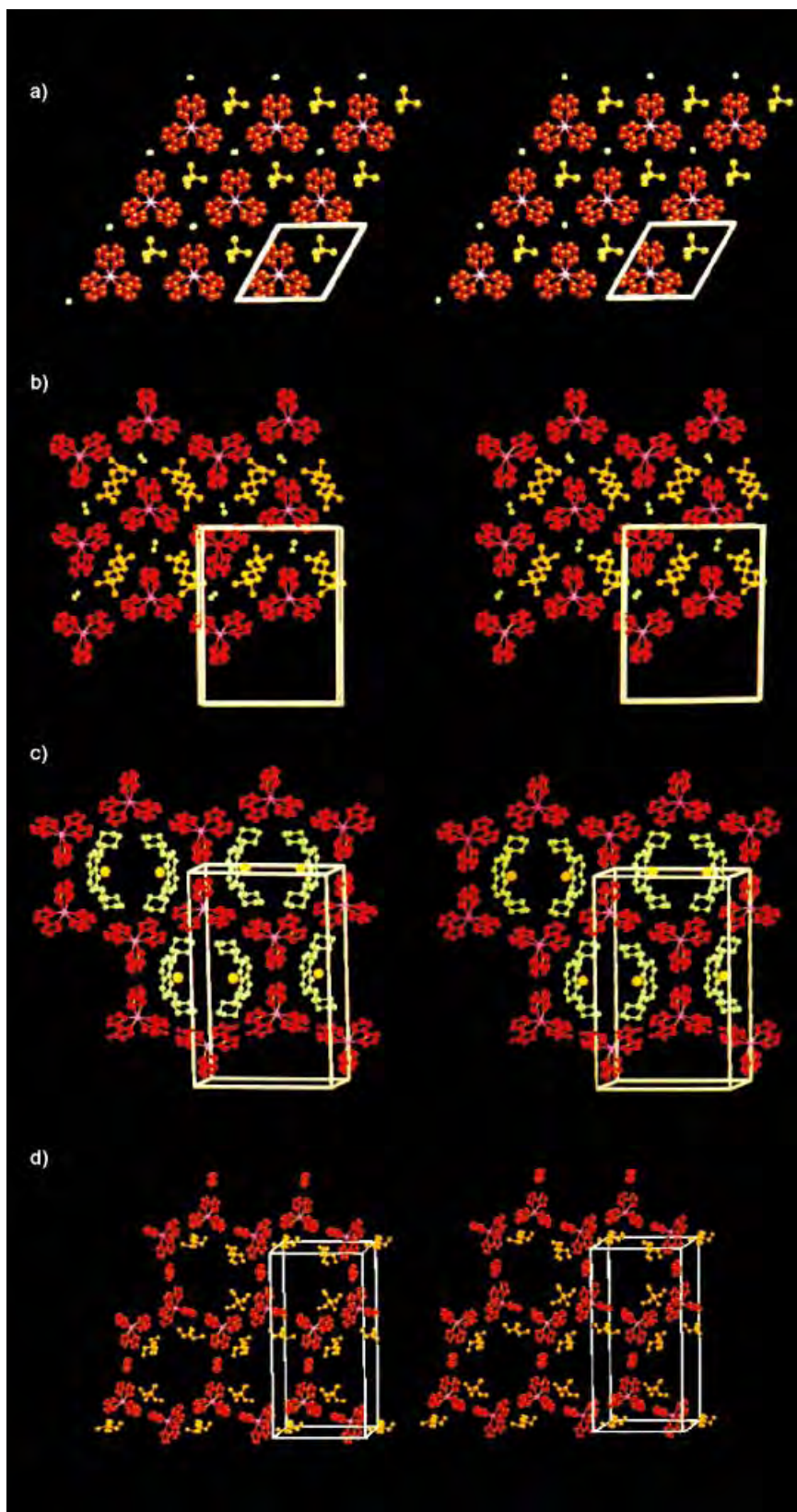


Figure 3. Arrangement of the $[\text{Ni}(\text{Hbim})_3]^-$ building blocks in the crystal structures (stereoviews): a) "Zero-dimensional" dot structure without complementary hydrogen bonds between the ligands in $[\text{NMe}_4][\text{Ni}(\text{Hbim})_3]$ (**1**), as viewed along the c axis. b) One-dimensional zigzag ribbon structures in $[\text{NnPr}_4][\text{Ni}(\text{Hbim})_3]$ (**2**), as viewed along the c axis. c) Double-channel structures built up by two-dimensional honeycomb sheets in $[\text{K}(\text{DCH}[18]\text{crown-6})][\text{Ni}(\text{Hbim})_3]$ (**3**). The inner channels (yellow) are constructed by K^+ -crown ether complexes, and the outer channels (red) are constructed by the $[\text{Ni}(\text{Hbim})_3]^-$ building blocks to form a microporous crystal. d) Two-dimensional expanded honeycomb sheet structure in $[\text{NEt}_4][\text{Ni}(\text{Hbim})_3]_2(\text{H}_2\text{bim})$ (**4**), as viewed along the a axis. The free neutral H_2bim ligands connect zigzag ribbons through complementary hydrogen bonds to form an expanded sheet structure along the bc plane.

binary $\text{NH}\cdots\text{N}$ hydrogen bonds to produce a 1D zigzag ribbon structure along the a axis (Figure 2b); the ribbon is made up of alternating Δ and Λ isomers of the building block. The $\text{N}\cdots\text{N}$ distances of intermolecular hydrogen bonds are 2.70(2), 2.76(3), 2.89(2), and 2.91(1) Å. The NnPr_4^+ counter cations occupy the cavity formed between the ribbons.

Structure **3**^[12c] contains potassium *cis-syn-cis*-dicyclohexano-[18]crown-6 ($[\text{K}(\text{DCH}[18]\text{crown-6})]^+$) as the counter cation (Figures 2c, 3c). The characteristic feature is that **3** has a microporous structure with a double-channel system (Figure 3c). All three ligands of the $[\text{Ni}(\text{Hbim})_3]^-$ building blocks form complementary intermolecular hydrogen bonds. Interactions of two of the hydrogen-bonding sites result in a 1D hydrogen-bonded zigzag ribbon as for **2**. Then, the ribbons are connected to each other through the remaining hydrogen-bonding site to form 2D honeycomb sheets along the ab plane in which each hexagon is made up of alternating Δ and Λ optical isomers of $[\text{Ni}(\text{Hbim})_3]^-$ (Figure 2c). The sheets are stacked along the c axis in such a way that $[\text{Ni}(\text{Hbim})_3]^-$ units of the same chirality are above each other in the outer channels formed (Figure 4a). The $\text{N}\cdots\text{N}$ distances of intermolecular hydrogen bonds are 2.737(9) and 2.74(1) Å. The inner channels are formed by stacking of two $[\text{K}(\text{DCH}[18]\text{crown-6})]^+$ cations facing each other along the c axis. The channel contains methanol and water molecules that are involved in hydrogen bonding.

Structure **4**^[12d] contains tetraethylammonium as the counter cation (Figures 2d, 3d). This crystal structure shows an unprecedented example of a 3D supra-cross-catenated self-organization based on hydrogen-bonded networks of the anionic $[\text{Ni}(\text{Hbim})_3]^-$ building blocks (Figures 4b, c). The crystal has four structural characteristics. First, there is a 1D zigzag ribbon

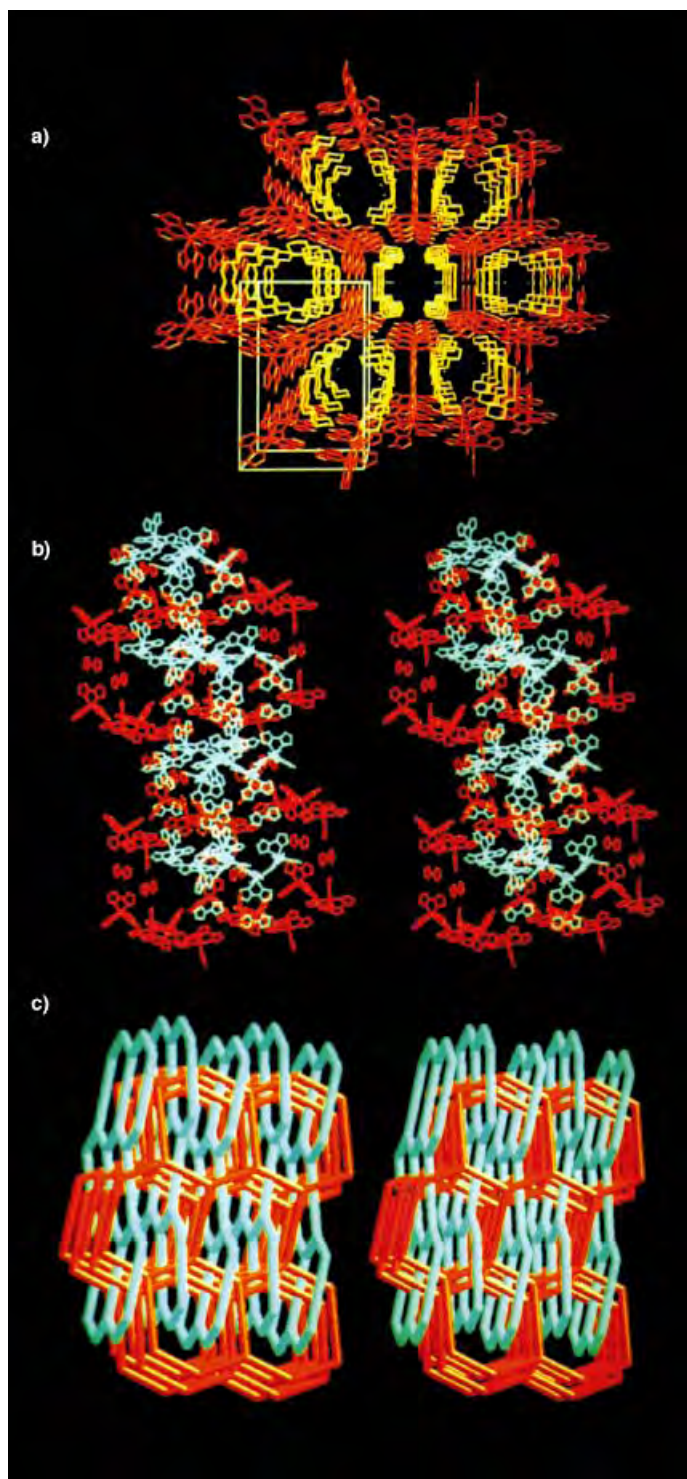


Figure 4. Representations of the final crystal structures for **3** and **4**. a) A perspective view of the microporous structure with a double channel formed by $[\text{Ni}(\text{Hbim})_3]^-$ building blocks and K^+ -crown ether complexes for **3**. b) A part of the polycatenate network for **4** (stereoview) c) Schematic drawing of the polycatenate network for **4** (stereoview): The straight lines represent the distance between nickel ions in two $[\text{Ni}(\text{Hbim})_3]^-$ building blocks connected by hydrogen bonds. A double-interlocking polycatenate structure is formed by two sets of stacked honeycomb sheets (red and blue) that are perpendicular to each other.

arrangement of the anions similar to that in **2**; the distances of hydrogen bonds between the building blocks are 2.77(1), 2.78(1), 2.82(1), and 2.84(1) Å. Second, free neutral H_2bim

ligands connect the 1D ribbons by complementary hydrogen bonding to form an expanded 2D honeycomb sheet along the bc plane; the $\text{N}\cdots\text{N}$ distances of the hydrogen bonds are 2.70(1), 2.76(1), and 2.84(1), 2.88(1) Å. Third, two sets of honeycomb sheets that are perpendicular to each other interpenetrate to construct a double-interlocking catenate structure. Finally, the catenated structure is arranged in 3D to form an infinite interlocking cross-catenated structure (Figure 4c).

The production of the four types of molecular architectures by the one-pot molecular self-organization of the anionic building blocks evolves from three fundamental factors: 1) the presence of three complementary binary hydrogen-bonding sites, 2) the occurrence of Δ and Λ optical isomers of the anionic nickel building blocks, and 3) the identity of the counter cations. Therefore, our results suggest that the mode of self-organization can be controlled by varying the kind of counter cation, although at this stage the cation specificity is difficult to predict. With a systematic approach, we have succeeded in the organization of $[\text{Ni}(\text{Hbim})_3]^-$ building blocks to microporous crystals of type **3** with double channels and crystals of type **4** with double-interlocking chains as polycatenate structures. These created crystals are involved in the construction of organic zeolites^[13] and superstructures for supramolecular chemistry.^[14] Our further study will be aimed at finding the mutual relationship between the building blocks and the kinds or shapes of counter cations for hydrogen-bonded superstructures. Thus, the cations play an important role in the prediction of crystal structures and the rationalization of the crystal structure engineering in this systems. In addition, the introduction of paramagnetic metal ions and transition metal chromophores into the system of the hydrogen-bonded extended arrays may lead to a new material with interesting magnetic and electronic properties.

Experimental Section

1: A suspension of H_2bim (0.4 g, 3 mmol) and $\text{Me}_4\text{NOH} \cdot 5\text{H}_2\text{O}$ (0.42 g, 2.2 mmol) in methanol (60 mL) was added to a 28% NaOMe solution in methanol (5 mL) and heated under reflux until the ligand had dissolved. A solution of $\text{Ni}(\text{ClO}_4) \cdot 6\text{H}_2\text{O}$ (0.36 g, 1 mmol) in methanol (40 mL) was added dropwise, and the mixture was heated under reflux for 15 min. The insoluble components were removed by filtration, and the filtrate was allowed to stand at room temperature. After renewed filtration of white precipitate, blue prisms were obtained from the filtrate after several weeks. Elemental analysis calcd for $[\text{NMe}_4][\text{Ni}(\text{Hbim})_3] \cdot 2\text{H}_2\text{O}$ ($\text{C}_{22}\text{H}_{31}\text{N}_{13}\text{NiO}_2$): C 46.50, H 5.50, N 32.04; found: C 46.98, H 5.09, N 32.36; IR (KBr): $\tilde{\nu} = 2620$ (br, $\nu(\text{NH})$), 1899 cm^{-1} (br, $2\gamma(\text{NH})$).

Crystals **2–4** were obtained by a method similar to that of **1**, except that different counter cations were used. **2:** Elemental analysis calcd for $[\text{NnPr}_4][\text{Ni}(\text{Hbim})_3] \cdot \text{MeOH}$ ($\text{C}_{31}\text{H}_{47}\text{N}_{13}\text{NiO}$): C 55.04, H 7.00, N 26.92; found: C 54.51, H 6.53, N 27.34; IR (KBr): $\tilde{\nu} = 2844$ (br, $\nu(\text{NH})$), 1912 cm^{-1} (br, $2\gamma(\text{NH})$). **3:** Elemental analysis calcd for $[\text{K}(\text{DCH}[18]\text{crown-6})][\text{Ni}(\text{Hbim})_3] \cdot 0.5\text{H}_2\text{O}$ ($\text{C}_{38}\text{H}_{52}\text{N}_{12}\text{KNiO}_{6.5}$): C 50.90, H 6.07, N 18.74; found: C 50.85, H 5.86, N 18.77 (sample dried under vacuum for 6 h at 100°C); IR (KBr): $\tilde{\nu} = 2513$ (br, $\nu(\text{NH})$), 1902 cm^{-1} (br, $2\gamma(\text{NH})$). **4:** Elemental analysis calcd for $[\text{NEt}_4]_2[[\text{Ni}(\text{Hbim})_3]_2(\text{H}_2\text{bim})] \cdot \text{MeOH} \cdot \text{H}_2\text{O}$ ($\text{C}_{59}\text{H}_{82}\text{N}_{30}\text{Ni}_2\text{O}_2$): C 52.07, H 6.07, N 30.88; found: C 52.02, H 6.16, N 30.32; IR (KBr): $\tilde{\nu} = 2811$ (br, $\nu(\text{NH})$), 1912 cm^{-1} (br, $2\gamma(\text{NH})$).

Received: July 27, 1998 [Z12213IE]
German version: *Angew. Chem.* **1999**, *111*, 102–106

Keywords: crystal engineering • hydrogen bonds • N ligands • nickel • supramolecular chemistry

- [1] J.-M. Lehn, *Supramolecular Chemistry*, VCH, Weinheim, 1995.
- [2] a) G. M. Whitesides, J. P. Mathias, C. T. Seto, *Science* **1991**, 254, 1312–1319; b) J. Rebek, Jr., *Angew. Chem.* **1990**, 102, 261–272; *Angew. Chem. Int. Ed. Engl.* **1990**, 29, 245–255.
- [3] a) S. Subramanian, M. J. Zaworotko, *Coord. Chem. Rev.* **1994**, 137, 357–401; b) O. Ermer, *J. Am. Chem. Soc.* **1988**, 110, 3747–3754.
- [4] a) M. C. Etter, *Acc. Chem. Res.* **1990**, 23, 120–126; b) C. B. Aakeröy, K. R. Seddon, *Chem. Soc. Rev.* **1993**, 26, 397–407.
- [5] I. Weissbuch, R. P. Biro, M. Lahav, L. Leiserowitz, *Acta Crystallogr. Sect. B* **1995**, 51, 115–148.
- [6] a) G. R. Desiraju, *Crystal Engineering: The Design of Organic Solids*, Elsevier, Amsterdam, 1989; b) G. R. Desiraju, *Angew. Chem.* **1995**, 107, 2541–2558; *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 2311–2327.
- [7] J. C. MacDonald, G. M. Whitesides, *Chem. Rev.* **1994**, 94, 2383–2420.
- [8] a) M. J. Zaworotko, *Chem. Soc. Rev.* **1994**, 137, 283–288; b) A. D. Burrows, C.-W. Chan, M. M. Chowdhry, J. E. McGrady, D. M. P. Mingos, *Chem. Soc. Rev.* **1995**, 138, 329–339.
- [9] S. W. Kaiser, R. B. Saillant, W. M. Butler, P. G. Rasmussen, *Inorg. Chem.* **1976**, 15, 2681–2687.
- [10] M. Tadokoro, J. Toyoda, K. Isobe, T. Itoh, A. Miyazaki, T. Enoki, K. Nakasuiji, *Chem. Lett.* **1995**, 613–614.
- [11] M. M. Chowdhry, D. M. P. Mingos, A. J. P. White, D. J. Williams, *Chem. Commun.* **1996**, 899–900.
- [12] Crystal structure determinations. General: Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-103363–103366. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk). a) Crystal data for **1**: $C_{22}H_{31}O_2N_{13}Ni_2$, $M_r = 568.27$, trigonal, space group $P\bar{3}$ (no. 147), $a = 11.167(2)$, $c = 13.206(4)$ Å, $V = 1426.1(3)$ Å³, $Z = 2$, $\rho_{\text{calcd}} = 1.323$ g cm⁻³, $F(000) = 596$, 106 parameters; $R_1 = 0.060$, $R_w = 0.080$, GOF = 1.55 for all 1613 data ($I > 3\sigma(I)$); max./min. residual electron density: 0.79/–0.36 e Å⁻³. Diffractometer: Rigaku AFC5R; $\mu(\text{MoK}\alpha) = 7.24$ cm⁻¹; Lp correction; 3094 reflections collected; the structure was solved with the program PATTY, and refined with the program DIRDIF92; reflections were refined based on F_o by full-matrix least squares. b) Crystal data for **2**: $C_{62}H_{94}O_2N_{26}Ni_2$, $M_r = 1353.00$, orthorhombic, space group $Pca2_1$ (no. 29), $a = 18.667(2)$, $b = 23.7236(8)$, $c = 16.786(1)$ Å, $V = 7433.6(8)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 1.209$ g cm⁻³, $F(000) = 2880$, 829 parameters; $R_1 = 0.065$, $R_w = 0.079$, GOF = 1.63 for all 2803 data ($I > 3\sigma(I)$); max./min. residual electron density: 0.44/–0.27 e Å⁻³. Diffractometer: Nonius CAD4; $\mu(\text{CuK}\alpha) = 10.90$ cm⁻¹; Lp correction; 7729 reflections collected; the solution was solved with the program SAPI91, and refined with the program DIRDIF94; reflections were refined based on F_o by full-matrix least squares. c) Crystal data for **3**: $C_{41}H_{67}O_{11}N_{12}NiK$, $M_r = 1001.85$, monoclinic, space group $C2/m$ (no. 12), $a = 19.077(3)$, $b = 29.074(3)$, $c = 9.769(3)$, $\beta = 110.39(2)^\circ$, $V = 5078(1)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 1.310$ g cm⁻³, $F(000) = 2128$, 287 parameters; $R_1 = 0.057$, $R_w = 0.073$, GOF = 1.77 for all 1484 data ($I > 3\sigma(I)$); max./min. residual electron density 0.29/–0.29 e Å⁻³. Diffractometer: Rigaku AFC7R; $\mu(\text{CuK}\alpha) = 18.38$ cm⁻¹; Lp correction; 4004 reflections collected; the structure was solved with the program PATTY, and refined with the program DIRDIF94; reflections were refined based on F_o by full-matrix least squares. d) Crystal data for **4**: $C_{60}H_{84}O_2N_{30}Ni_2$, $M_r = 1374.92$, tetragonal, space group $P4_12_1$ (no. 92), $a = 19.061(1)$, $c = 38.474(2)$ Å, $V = 13977(1)$ Å³, $Z = 8$, $\rho_{\text{calcd}} = 1.307$ g cm⁻³, $F(000) = 5808$, 778 parameters; $R_1 = 0.075$, $R_w = 0.109$, GOF = 1.83 for all 3213 data ($I > 3\sigma(I)$); max./min. residual electron density 0.80/–0.36 e Å⁻³. Diffractometer: Rigaku AFC7R; $\mu(\text{CuK}\alpha) = 11.89$ cm⁻¹; Lp correction; 5374 reflections collected; the structure was solved with the program SHLXS86, and refined with the program DIRDIF94; reflections were refined based on F_o by full-matrix least squares.
- [13] J. S. Moore, S. Lee, *Chem. Ind.* **1994**, 556–560.
- [14] L. Carlucci, G. Ciani, D. M. Proserpio, A. Sironi, *J. Am. Chem. Soc.* **1995**, 117, 4562–4569.

Bioaffinity NMR Spectroscopy: Identification of an E-Selectin Antagonist in a Substance Mixture by Transfer NOE**

Dirk Henrichsen, Beat Ernst, John L. Magnani, Wei-Tong Wang, Bernd Meyer,* and Thomas Peters*

Leukocytes play a central role in the body's resistance to tissue lesions and microbial infections. So to be able to exercise their defense function, they must selectively enter the area of the affected tissue. The first step in this inflammatory cascade is the cytokine-induced expression of P-selectin and E-selectin, which, located on the surface of endothelial cells, interact specifically with ligands on leukocyte surfaces. With E-selectin this is the ESL–1 ligand, with P-selectin the PSGL–1 ligand.^[1] The specific interactions between selectins and ligands first initiate a “rolling” of the leukocytes, which leads to further specific interactions with other membrane proteins and, ultimately, to leukocyte migration into the affected tissue. In pathological situations such as myocardial infarction, transplantation, or rheumatoid arthritis, suppression of the inflammatory cascade is desirable. Considerable effort has therefore been expended on the preparation of potent P- and E-selectin antagonists.^[2] In the case of E-selectin, the bioactive conformation of the sialyl Lewis^x mimetic **2** was recently elucidated by transfer NOE experiments.^[3] It emerged that the bioactive conformation of this antagonist has much in common with that of the sialyl Lewis^x **1** (see Scheme 1).^[4]

As always in the search for active compounds, the search for sialyl Lewis^x mimetics requires screening procedures that allow the rapid identification of lead compounds. A procedure we have described recently, “bioaffinity NMR spectroscopy”, is based on the selective detection of transfer NOEs (trNOEs).^[5] It makes use of the observation that small molecules (relative molecular mass up to about 2 kDa) exhibit strong negative trNOEs when bound to receptor proteins, and can thus be differentiated from nonbinding molecules with weak positive NOEs. Isotope labeling of the

- [*] Prof. Dr. B. Meyer
Institut für Organische Chemie der Universität Hamburg
Martin-Luther-King-Platz 6, D-20146 Hamburg (Germany)
Fax: (+49) 40-4123-2878
E-mail: bernd.meyer@sg1.chemie.uni-hamburg.de
- Prof. Dr. T. Peters, Dipl.-Chem. D. Henrichsen
Institut für Chemie der Medizinischen Universität
Ratzeburger Allee 160, D-23538 Lübeck (Germany)
Fax: (+49) 451-500-4241
E-mail: tp@chemie.mu-luebeck.de
- Prof. Dr. B. Ernst^[+]
Novartis Pharma AG, Basel (Switzerland)
Dr. J. L. Magnani, Dr. W.-T. Wang
GlycoTech Corp., Rockville, MD (USA)

[+] Present Address:
Universität Basel, Institut für Pharmazie
Basel (Switzerland)

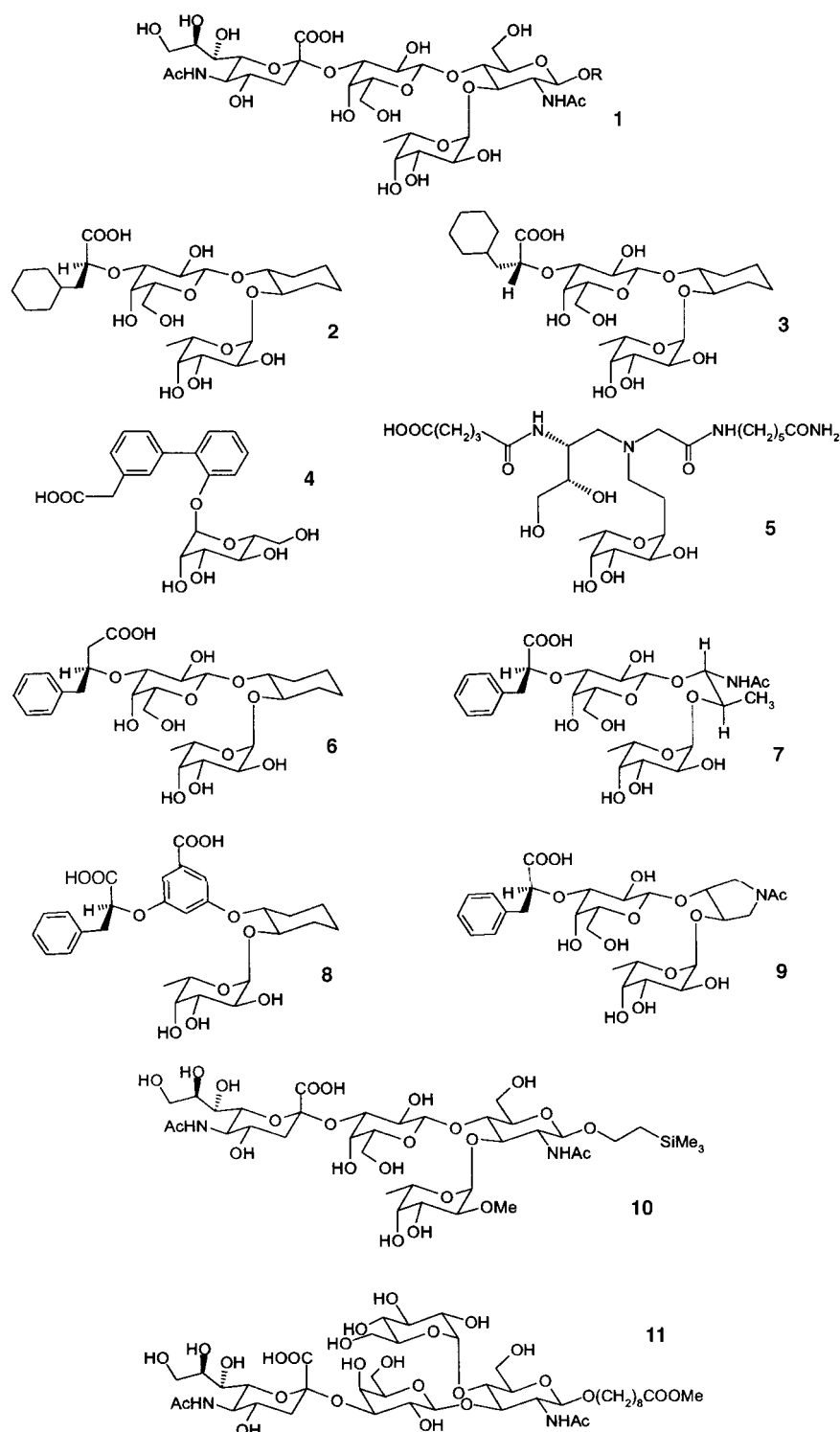
[**] This work was supported by BMBF (FKZ 031161 and 0311395), the Deutschen Forschungsgemeinschaft (Sonderforschungsbereich 470, Teilprojekt B3), and the Fonds der Chemischen Industrie. We thank Dr. T. Keller and Dr. G. Wolff (Bruker Analytik GmbH, Rheinstetten) for excellent support.

protein is not necessary, nor is there any limitation to the relative molecular mass of the receptor protein. Lead compounds in pharmacological research ideally have relative molecular masses below 1 kDa, and they are therefore, in principle, readily identifiable by the cited procedure. Since trNOEs are ideally suited to the analysis of bioactive conformations,^[6] the analysis of the bioactive conformations of ligands in compound mixtures should also be possible.

Another procedure that has been introduced recently for small proteins (<30 kDa) is based on ligand-induced changes in ¹⁵N chemical shifts of amino acids at the binding site measured by ¹⁵N HSQC spectroscopy.^[7] However, we were unable to use this method since recombinant E-selectin, which is present as an IgG chimera, has a relative molecular mass of about 220 kDa, which is well outside the range accessible to ¹⁵N HSQC spectroscopy.

Here we show that bioactive components can be identified by bioaffinity NMR spectroscopy, even if structurally related ligands are present in a library. The compound library selected consisted of ten compounds (**2–11**, Scheme 1), seven of which have a basic structure derived from a Lewis^a or Lewis^x pattern (**2, 3, 6, 7, 9–11**). The tetrasaccharides **10** and **11** are sialyl Lewis^x and sialyl Lewis^a tetrasaccharide derivatives with only minor structural differences. Compound **10** differs from sialyl Lewis^x **1** only in that the 2-hydroxyl functional group of L-fucose is replaced by a methoxy group. The sialyl Lewis^a derivative **11** contains an L-galactose group in place of the L-fucose group. Compounds **4**,^[8] **5**, and **8** are further simplified sialyl Lewis^x mimetics that contain merely the fucose residue and the carboxyl group of the natural product **1** as potential active groups.

The NOESY spectra of this ligand library were measured at several temperatures. It emerged that a few ligands showed weak negative NOEs at room temperature, but most exhibited the weak positive NOEs that are typical of low molecular weight compounds. No negative NOEs were observed at 310 K, so at this temperature a clear differentiation between trNOES (negative value) and NOEs (positive value) was possible. As expected, the NOESY spectrum of the compound mixture exhibited a complex signal pattern that precluded identification of individual components (Figure 1, left).



Scheme 1. Schematic drawings of compounds **2–11** present in the compound library compared with the sialyl Lewis^x base structure **1**.

In the trNOE experiments, recombinant E-selectin/hIgG was deglycosylated enzymatically, since it was known that the signals of covalently bound sialyl *N*-acetylglucosamine chains interfere with trNOE measurements.^[4] Treatment with glycopeptidase F (PNGase F) and neuraminidase from *Clostridium perfringens* reduced the fraction of covalently bound carbohydrate to about one-sixth of the original value. More than

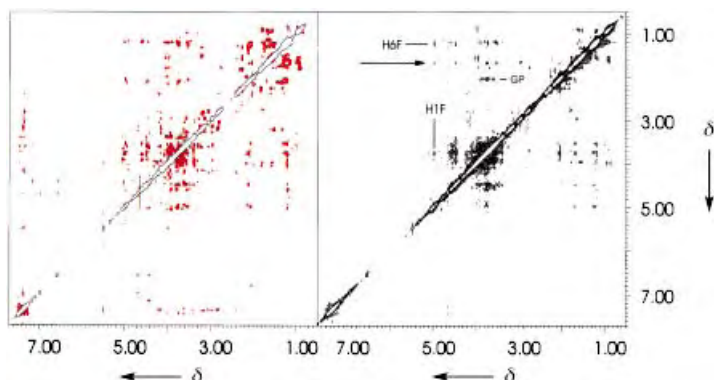


Figure 1. Left: 2D NOESY spectrum of the compound mixture in D₂O at 310 K. The mixing time was 900 ms. Only positive NOEs (red) appeared. Right: 2D trNOESY spectrum of the compound mixture in the presence of E-selectin at a mixing time of 300 ms and a temperature of 310 K. A spin lock filter^[10] of 15 ms was used. The molar ratio of binding sites to ligands was 1:15 (see Experimental Section). The cross signals shown are negative (trNOEs) and can be assigned to the bioactive component **2**. Only negative cross signals (black) are illustrated. Cross signals that are caused by spin diffusion are indicated with an arrow. GP indicates the signals of the glycan moiety of E-selectin.

90% of the sialic acid residues were removed. A final treatment with β -galactosidase from *E. coli* reduced E-selectin activity by about 90%, so further deglycosylation was not possible. The NOESY spectra of the deglycosylated E-selectin showed that the normally intense ¹H NMR signals of the sialic acid residues have almost disappeared, whereas the *N*-acetylglucosamine signals still represented a disruptive factor.

The trNOESY spectra of the ligand library at different levels of excess relative to deglycosylated E-selectin were measured at 310 K. This was to ensure that favorable ratios were present for the detection of potential trNOES of components that were present in the mixture at varying concentrations. The ratios were 5:1, 8:1, 12:1, 15:1, and 20:1, and in all cases trNOEs were observed. The ratio of 15:1 emerged as the most favorable (maximum trNOEs).

A comparison of the NOESY spectrum of the free library (Figure 1, left) with that of the trNOESY of the library in the presence of E-selectin (Figure 1, right) shows that the majority of cross signals in the trNOESY spectrum is absent (under these experimental conditions they appeared as weak positive NOEs, and thus could be readily differentiated from the strong negative trNOEs). For example, no trNOEs are observed in the region of the chemical shifts of the aromatic protons, so that compounds **4** and **6–9** are eliminated as bioactive compounds. The typical signal patterns for *N*-acetylneuraminic acid residues, for example the cross signals between the geminal protons on C3 of the *N*-acetylneuraminic acid units, are also absent. Thus, **10** and **11** were also rejected as bioactive compounds. Compound **5**, which contains L-fucose as a C-glycosidic linkage, is characterized by the presence of 13 CH₂ groups. In the trNOESY spectrum there is, however, no sign of this number of CH₂ groups. Therefore, the trNOESY cross signal pattern observed is assigned to either **2** or **3**. Both are derived from the natural sialyl Lewis^x structure **1**, in which the *N*-acetylglucosamine residue is replaced by a cyclohexanediol ring (Cyc), and the *N*-

acetylneuraminic acid by a cyclohexyllactic acid residue (Lact). In **2** the cyclohexyllactic acid has an *S* configuration, and in **3** an *R* configuration. A differentiation between these two compounds was not possible on the basis of the trNOE cross signal pattern. A comparison of the NOESY spectra was necessary, which demonstrated that **2** was the active component, as will be discussed in more detail in the following.

A complete assignment of the ¹H NMR signals for the sialyl Lewis^x mimetic **2** has already been made,^[3] and the bioactive conformation was determined by trNOE experiments. Therefore, in the following only the assignment of a number of the more important signals will be discussed briefly. Figure 2 illustrates the sections from the NOESY (left) and trNOESY (right) spectra that are especially characteristic for the bioactive compound **2**. There are a series of interglycosidic trNOEs between the cyclohexanediol ring (Cyc) on the one

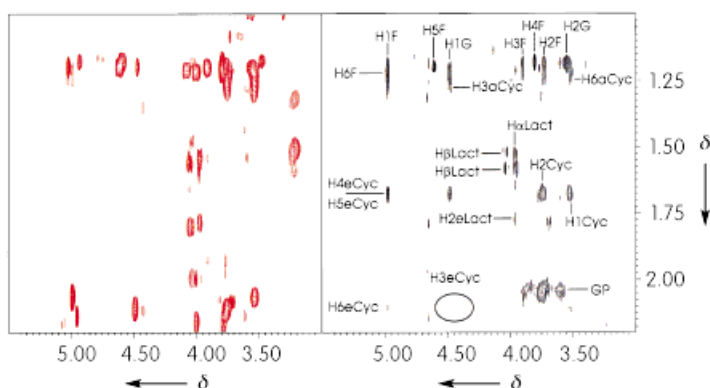


Figure 2. Left: section from the 2D NOESY spectrum in Figure 1. Right: section from the 2D trNOESY spectrum in Figure 1. The typical cross signal patterns for **2** are clearly recognizable, and several of them are labeled. Interglycosidic trNOEs between the anomeric protons of fucose and galactose and the cyclohexane ring lie under these cross signals. The encircled region indicates the extinction of an interglycosidic trNOE by superimposition with positive NOEs of the free library (see text).

hand, and fucose (F) and galactose (G) on the other, a number of which are labeled in Figure 2. Starting from H1^G, there are, for example, interglycosidic trNOEs to H3a^{Cys}, H4a^{Cys}, H4e^{Cys}, and H5e^{Cys}, of which the latter three are caused by spin diffusion in the cyclohexane ring. The interglycosidic trNOE between H2^G and H6^F is also unambiguously recognizable. A further characteristic trNOE between H4^{Lact} and H3^G is also observed (not shown in the section in Figure 2). Other typical cross signals for **2** are observed within the cyclohexane ring as well as the cyclohexyllactic acid residue, as is illustrated in Figure 2. Starting from H1^F, there are interglycosidic trNOEs to H6a^{Cyc}, H6e^{Cyc}, H4a^{Cyc}, H4e^{Cyc}, H5e^{Cyc}, and H3a^{Cyc}. Since only the effects towards H6a^{Cyc} and H6e^{Cyc} may be considered to be “direct” trNOEs, a high fraction of spin diffusion is also present here. The cross signal for the connectivity between H1^F and the protons H4e^{Cyc} and H5e^{Cyc}, which is transmitted by spin diffusion, lies on a trace of further cross signals (this is labeled by an arrow in Figure 1, right), which is almost exclusively attributable to spin diffusion. This becomes clear from a comparison with the NOESY spectrum of the free library (Figure 2, left), since there these cross signals are absent. Equally, the fact that all protons of fucose show

intraglycosidic trNOEs to the C6 methyl group of fucose is attributable to spin diffusion (Figure 2, right). Whereas spin diffusion is a disadvantage for the structural characterization of biological macromolecules, here it greatly simplifies unambiguous assignment of the bioactive component **2**. However, superposition of positive NOE and negative trNOE cross signals also lead to extinction of one interglycosidic NOE, namely, that between H1^G and H3e^{Cyc} (encircled region in Figure 2, right).

The trace of cross signals labeled "GP" in Figures 1 and 2 is not observed for the free library. These are signals which must be assigned to the *N*-acetyl groups of the covalently bound *N*-acetylglucosamine residues in E-selectin. This becomes immediately clear by comparison with a NOESY spectrum of E-selectin. Apparently, the spin lock pulse^[10] that is applied at the beginning of the t_1 evolution period during the measurement of the trNOESY spectra effectively filters the interfering protein signals, but not, however, the signals of the mobile, covalently bound carbohydrate chains. This effect may be used directly to observe carbohydrate chains of glycoproteins selectively, but here it is undesirable.^[11]

Overall the NMR experiments show that the library contains only one component with binding activity towards E-selectin, namely, compound **2**. Generally it may be said that identification of ligands with dissociation constants K_D in the range 10^{-7} to 10^{-3} is possible with bioaffinity NMR spectroscopy. In conclusion, it should also be mentioned that derivative **4**, which has been described as a potential E-selectin mimetic,^[8] shows no trNOEs. The same applies to compound **5**, which is closely related to fucopeptides, for which good binding activity was reported.^[2d] In spite of the structural similarity, no trNOEs were observed for **5**. Thus, the K_D values of **4** and **5** must be greater than 10^{-3} m.

To verify our results, we carried out independent ELISA activity measurements.^[12] These confirm the results of our trNOE experiments.^[13]

In total, the investigations show that the bioaffinity NMR procedure we have recently described^[5] is well suited for the identification of bioactive components, even where significant structural similarities lead to extensive signal overlap. In contrast to current procedures, bioaffinity NMR spectroscopy has a number of advantages which should be highlighted: 1) Separation of the components of a library or, in general, of any mixture prior to activity tests is not necessary. 2) Small amounts of protein suffice since the ligands are added in a 10- to 20-fold excess. 3) The protein tested can be used for further tests after dialysis. 4) Neither the protein nor the ligand must be immobilized. 5) The procedure may be used in competitive experiments and, in particular, the investigation of allosteric effects.

Experimental Section

Recombinant E-selectin/hIgG was obtained as previously described;^[4a] compounds **2–11** were synthesized.^[14]

Deglycosylation of E-selectin/hIgG with PNGase F and neuraminidase: E-selectin/hIgG (10 mg, 1.75 mg per mL phosphate buffered solution (PBS)) was adjusted to pH 8.6. PNGase F (Sigma, G-8031; 40 units, 200 μ L) was added, and the mixture was incubated for 16 h at 37 °C. Deglycosylation was followed by gel filtration chromatography and SDS-PAGE.

When conversion was complete, separation was achieved with a Sephacryl S-400 column in PBS at pH 7.4. Incubation with agarose-immobilized neuraminidase from *Clostridium perfringens* was carried out by the same method at pH 4.5 and 37 °C. The activity was tested against HSA-coupled sialyl Lewis^a (HSA = human serum albumine).

For NMR investigations, E-selectin/hIgG (2.5 mg, 11.25 nmol) was dialyzed against deuterated imidazole (100 mM) and CaCl₂ (1 mM) in D₂O at pH 7.4 and concentrated to a sample volume of 0.5 mL with Centricon YM-50 (Amicon). Compounds **2–11** were present in the mixture in the following amounts: **2** (M_{rel} = 600.64) 1.66 μ mol, **3** (M_{rel} = 600.64) 1.91 μ mol, **4** (M_{rel} = 412.38) 3.12 μ mol, **5** (M_{rel} = 614.63) 2.74 μ mol, **6** (M_{rel} = 586.6) 0.99 μ mol, **7** (M_{rel} = 592.58) 1.66 μ mol, **8** (M_{rel} = 590.54) 1.76 μ mol, **9** (M_{rel} = 623.59) 1.84 μ mol, **10** (M_{rel} = 957.0) 1.25 μ mol, **11** (M_{rel} = 1037.05) 1.205 μ mol. The compound mixture was used to prepare the following E-selectin:ligand mole ratios (each E-selectin/hIgG chimera contains two binding sites for ESL – 1): 1:5, 1:8, 1:12, 1:15, 1:20. The data for the ligands relate in each case to compound **11**.

All spectra were measured on a Bruker DRX 500 NMR spectrometer (500.13 MHz). The phase-sensitive 2D NOESY spectra of the substance mixture were measured at 300 or 310 K with 512 increments in t_1 (TPPI), each with 32 scans of 2 K data points in t_2 . The spectral width was 10 ppm in both dimensions. Prior to the Fourier transformation, the data matrix was zero-filled to 2 K $\times$ 1 K data points. For measurement of the 2D trNOESY spectra of the compound library in the presence of E-selectin, a spin lock pulse (3.2 kHz) of 15 ms duration was applied after the first $\pi/2$ pulse.^[10] A total of 48 scans per t_1 increment was recorded.

Received: August 5, 1998 [Z12253]

German version: *Angew. Chem.* **1999**, *111*, 106–110

Keywords: compound libraries • NMR spectroscopy • oligosaccharides • selectins

- [1] a) M. P. Bevilacqua, S. Stengelin, M. A. Gimbrone, Jr., B. Seed, *Science* **1989**, *243*, 1160–1165; b) L. A. Lasky, *Science* **1992**, *258*, 964–969; c) A. Levinovitz, J. Muhloff, S. Isenmann, D. Vestweber, *J. Cell. Biol.* **1993**, *121*, 449–459; d) M. Lenter, A. Levinovitz, S. Isenmann, D. Vestweber, *J. Cell. Biol.* **1994**, *125*, 471–481; e) K. L. Moore, N. L. Stults, S. Diaz, D. F. Smith, R. D. Cummings, A. Varki, R. P. McEver, *J. Cell. Biol.* **1992**, *118*, 445–456.
- [2] a) H. C. Kolb, B. Ernst, *Pure Appl. Chem.* **1997**, *69*, 1879–1884; b) H. C. Kolb, B. Ernst, *Chem. Eur. J.* **1997**, *3*, 1571–1578; c) K. E. Norman, G. P. Anderson, H. C. Kolb, K. Ley, B. Ernst, *Blood* **1998**, *91*, 475–483; d) T. F. Lampe, G. Weitz-Schmidt, C.-H. Wong, *Angew. Chem.* **1998**, *110*, 1761–1764; *Angew. Chem. Int. Ed.* **1998**, *37*, 1707–1711; e) T. Uchiyama, V. P. Vassilev, T. Kajimoto, W. Wong, H. Huang, C.-H. Wong, *J. Am. Chem. Soc.* **1995**, *117*, 5395–5396; f) E. E. Simanek, G. J. McGarvey, J. A. Jablonowski, C.-H. Wong, *Chem. Rev.* **1998**, *833*–862.
- [3] W. Jahnke, H. C. Kolb, M. J. J. Blommers, J. L. Magnani, B. Ernst, *Angew. Chem.* **1997**, *109*, 2715–2719; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2603–2607.
- [4] a) K. Scheffler, B. Ernst, A. Katopodis, J. L. Magnani, W.-T. Wang, R. Weisemann, T. Peters, *Angew. Chem.* **1995**, *107*, 2034–2037; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1841–1844; b) K. Scheffler, J.-R. Brisson, R. Weisemann, J. L. Magnani, W.-T. Wang, B. Ernst, T. Peters, *J. Biomol. NMR* **1997**, *9*, 423–436; c) R. M. Cooke, R. S. Hale, S. G. Lister, G. Shah, M. P. Weir, *Biochemistry* **1994**, *33*, 10591–10596; d) L. Poppe, G. S. Brown, J. S. Philo, P. V. Nikrad, B. H. Shah, *J. Am. Chem. Soc.* **1997**, *119*, 1727–1736.
- [5] a) B. Meyer, T. Weimar, T. Peters, *Eur. J. Biochem.* **1997**, *246*, 705–709; b) T. Peters, B. Meyer, DE-B 19649359, **1996**.
- [6] a) H. N. B. Moseley, W. Lee, C. Arrowsmith, N. R. Krishna, *Biochemistry* **1997**, *36*, 5239–5299; b) H. N. B. Moseley, E. V. Curto, N. R. Krishna, *J. Magn. Reson. B* **1995**, *108*, 243–261; c) F. Ni, *Prog. NMR Spectrosc.* **1994**, *26*, 517–606; d) T. Peters, B. M. Pinto, *Curr. Opin. Struct. Biol.* **1996**, *6*, 710–720.
- [7] a) S. B. Shuker, P. J. Hajduk, R. P. Meadows, S. W. Fesik, *Science* **1996**, *274*, 1531–1534; b) H. Kessler, *Angew. Chem.* **1997**, *109*, 857–859; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 829–831.

- [8] T. P. Kogan, B. Dupré, K. M. Keller, I. L. Scott, H. Bui, R. V. Market, P. J. Beck, J. A. Voytus, B. M. Reville, D. Scott, *J. Med. Chem.* **1995**, 38, 4976–4984.
- [9] a) J. Fejzo, W. M. Westler, J. L. Markley, S. Macura, *J. Am. Chem. Soc.* **1992**, 114, 1523–1524; b) C. Zwahlen, S. J. F. Vincent, L. D. Bari, M. H. Levitt, G. Bodenhausen, *J. Am. Chem. Soc.* **1994**, 116, 362–368; c) S. J. F. Vincent, C. Zwahlen, G. Bodenhausen, *J. Biomol. NMR* **1996**, 7, 169–172; d) S. J. F. Vincent, C. Zwahlen, C. B. Post, J. W. Burgner, G. Bodenhausen, *Proc. Natl. Acad. Sci. USA* **1997**, 94, 4383–4388.
- [10] T. Scherf, J. Anglister, *Biophys. J.* **1993**, 64, 754–761.
- [11] D. Henrichsen, I. Brockhausen, H. Schachter, T. Peters, *Glycoconjugate J.*, submitted.
- [12] The method for the E-selectin bioassay is found in reference 17 in: G. Thoma, J. L. Magnani, R. Öhrlein, B. Ernst, F. Schwarzenbach, R. O. Duthaler, *J. Am. Chem. Soc.* **1997**, 119, 7414–7415.
- [13] Sialyl Lewis^x tetrasaccharide **1** was used as reference for the ELISA tests. Its relative IC₅₀ was adjusted to 1 mM (the absolute values lie between 0.9 and 1.5 mM). The sialyl Lewis^x mimetic **2** exhibits a relative IC₅₀ of 0.09 mM.^[2a] A relative IC₅₀ of 0.66 mM has been reported for **4**,^[8] however, in the ELISA test it exhibits a relative IC₅₀ of >10 mM and is therefore classified as inactive. The remaining components of the compound library, **3** and **5–11**, with relative IC₅₀ values of >10 mM, are also regarded as inactive.
- [14] B. Ernst, unpublished results.

Discovery of Peptide–Zirconium Complexes That Mediate Phosphate Hydrolysis by Batch Screening of a Combinatorial Undecapeptide Library**

Albrecht Berkessel* and David A. Héroult

*Dedicated to Professor Bernt Krebs
on the occasion of his 60th birthday*

The search for new low-molecular weight catalysts is one of the most fascinating fields of contemporary organic chemistry. One source of inspiration is the spatial arrangement of functional groups in the active site of enzymes, that is the design and synthesis of enzyme models.^[1, 2] Many enzymes harbor a metal ion in the active site. The success in modeling a metalloenzyme—and in constructing a novel metal catalyst in general—heavily relies on the matching of the ligand(s) with the central metal ion and with the substrate. Although this problem is widely recognized, it was only recently that parallel ligand synthesis and rapid screening methods were introduced to the field of catalyst research.^[3–6]

Herein, we describe our approach to artificial hydrolase activity which consists of a) the split-mix synthesis^[7] of a ligand library containing 625 solid-phase-bound undecapeptides, b) complexing of the ligand library with Lewis acidic

transition metals, and c) screening of the library with chromogenic test substrates. As it turned out, solid-phase-bound undecapeptides ligands could be identified that mediate the hydrolysis of phosphates. The sequences of the most active (and inactive) peptides were determined by means of Edman degradation, and the catalytic activity or inactivity could be confirmed in homogeneous solution.

The general structure of our ligand library is shown in Figure 1. Initially Fmoc-L-Phe was attached to TentaGel S–NH₂ by using PyBOP as the coupling agent (Fmoc = 9-fluorenylmethoxycarbonyl).^[8] After splitting the polymer



Figure 1. General structure of the undecapeptide library. PEG = polyethylene glycol.

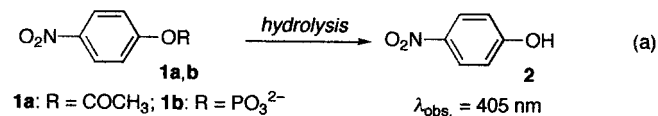
into five fractions, the second amino acid was introduced. After this step L-Arg, L-His, L-Tyr, L-Trp, or L-Ser was found at position X. After pooling the fractions, the spacer Gly was added twice. Seven more coupling steps, including three split-mix additions of X and a final deprotection protocol completed the synthesis. In other words, the 625 polymer-bound undecapeptides thus produced contain four variable positions separated by three spacers Gly–Gly and occupied by L-Arg, L-His, L-Tyr, L-Trp, or L-Ser in a combinatorial fashion. Arginine was chosen because a typical motif encountered, for example, in the X-ray crystal structures of staphylococcal nuclease^[9] and other enzymes that catalyze phosphoryl transfer,^[10] is the activation of the anionic phosphate moiety towards nucleophilic attack by water by ion-pair formation with the cationic guanidinium moiety. This structural theme has inspired a lot of work aimed at catalytically active mono- and bis-guanidinium receptors, which serve as enzyme models for the hydrolysis of phosphoric esters.^[11, 12] The imidazole moiety of histidine is a ligand for numerous transition metal ions in metalloenzymes, as is tyrosine.^[12, 13] It was hoped that the electron-rich indole system of tryptophan would display π – π stacking interactions with the aromatic esters that were envisaged as test substrates. Finally, the hydroxy group of serine might serve as the acceptor for an acyl/phosphoryl group in a transesterification reaction.^[11–12]

Our approach to the simulation of hydrolase activity bears some resemblance to the work of Zouhair Atassi and Manshour, which was aimed at the active sites of serine esterases and proteases.^[14, 15] The components of the catalytic triad (Asp-His-Ser) were scaffolded onto cyclic 29-mer peptides, separated by Gly spacers, and designed to reproduce the spatial arrangement of the catalytically active functional groups in the enzymes' active sites. Unfortunately, the remarkable activities and selectivities reported by Zouhair Atassi and Manshour could not be reproduced by others.^[16] Most likely, the 29-mers do not adopt the conformation in which the catalytic triad is in the desired orientation.^[16] Instead of merely matching structures, our approach includes the combinatorial shuffling of functional groups plus the restriction of conformational mobility by addition of metal ions that are expected to coordinate the peptides (see below).

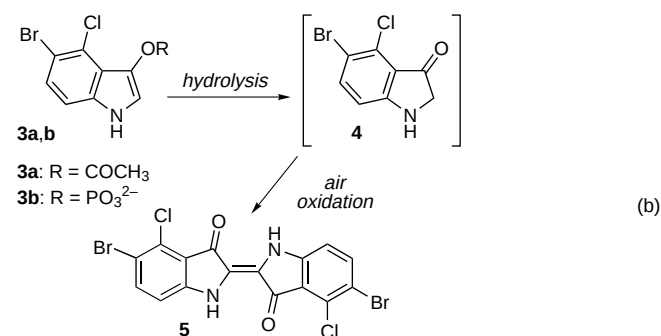
[*] Prof. Dr. A. Berkessel, Dr. D. A. Héroult
Institut für Organische Chemie der Universität
Greinstrasse 4, D-50939 Köln (Germany)
Fax: (+49) 221-470-5102
E-mail: berkessel@uni-koeln.de

[**] This work was supported by the Fonds der Chemischen Industrie. The authors wish to thank the BASF AG, in particular Dr. H. Platsch, T. Brugger, and W. Weishaar, for carrying out the Edman degradations.

To screen the library for hydrolase activity we employed chromogenic test substrates. Upon hydrolysis, standard substrates like *para*-nitrophenyl esters **1a** and **1b** liberate *para*-nitrophenol (**2**) [Eq. (a)], which can be easily determined



quantitatively by UV/Vis spectroscopy. However, since **2** is a freely diffusible species, the information on which polymer bead(s) it was formed, is lost. We therefore turned our attention to the 3-hydroxyindolyl derivatives **3a, b** [Eq. (b)]:^[17] When the ester functions are hydrolyzed, the



resulting indoxyl derivative **4** is oxidized in the aerated solution to afford the turquoise and insoluble indigo dye **5**. In the screening experiments, 1 mM solutions of Cu²⁺, Zn²⁺, Fe³⁺, Co³⁺, Eu³⁺, Ce⁴⁺, or Zr⁴⁺ (or without metal salts) were added to about 2500 of the polymer beads in EPPS buffer at pH 5.6.^[18] Activity was found with the 3-hydroxyindolyl phosphate **3b** in the presence of Zr⁴⁺: In this assay, about 20 of the about 2500 beads showed the typical turquoise color of the indigo dye **5** (Figure 2a). The three most intensively colored beads were isolated and subjected to Edman degradation, together with two control beads that did not show an indigo stain at all. The sequences found are listed in Figure 3. The top sequence **A** in Figure 3 is the one determined from the most deeply stained bead in the assay.^[19] This peptide **A** was re-synthesized first in polymer-bound form as described above. When the TentaGel beads carrying **A** were exposed to the Zr⁴⁺ ion and the substrate **3b**, they all turned deeply turquoise (Figure 2b). Alternatively, when the control sequence **D** was re-synthesized on solid support and subjected to the same assay conditions, none of the beads adopted a turquoise stain (Figure 2c).

Next, the catalytic activity of the peptide **A** and the inactivity of peptide **D** were probed in homogeneous solution. For this purpose, the peptides were synthesized on Wang resin and cleaved off. In fact, when the test substrate **3b** was exposed to peptide **A** in the presence of Zr⁴⁺, the hydrolysis of **3b** was nicely indicated by the precipitation of the indigo dye **5**, whereas no significant hydrolysis occurred when **D** was employed. Since the low solubility of **5** prohibited a quantitative assessment of the kinetic parameters of the hydrolysis,

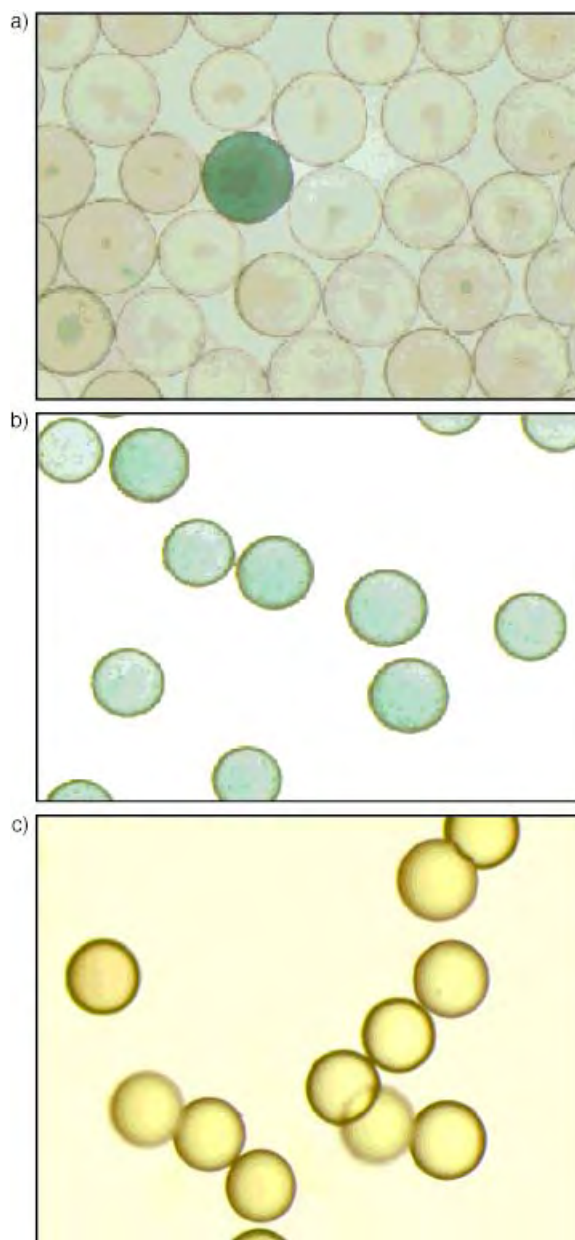


Figure 2. TentaGel beads exposed to Zr⁴⁺ and **3b**, carrying the following undeca-peptides: a) library; b) sequence **A**; c) sequence **D**.

Active sequences:

- H₂N-Ser-Gly-Gly-His-Gly-Gly-Arg-Gly-Gly-His-Phe-CO₂H **A**
H₂N-Ser-Gly-Gly-Ser-Gly-Gly-Ser-Gly-Gly-His-Phe-CO₂H **B**
H₂N-Ser-Gly-Gly-Arg-Gly-Gly-His-Gly-Gly-His-Phe-CO₂H **C**

Inactive sequences:

- H₂N-Trp-Gly-Gly-Arg-Gly-Gly-Trp-Gly-Gly-Arg-Phe-CO₂H **D**
H₂N-Arg-Gly-Gly-Ser-Gly-Gly-Arg-Gly-Gly-Trp-Phe-CO₂H **E**

Figure 3. Hit and control sequences found by screening of the undeca-peptide library with Zr⁴⁺ and **3b**.

we resorted to *para*-nitrophenyl phosphate (**1b**). The results are depicted in Figure 4 (see Experimental Section for conditions): When incubated with Zr⁴⁺ and the control peptide **D**, only a very slow liberation of *para*-nitrophenol

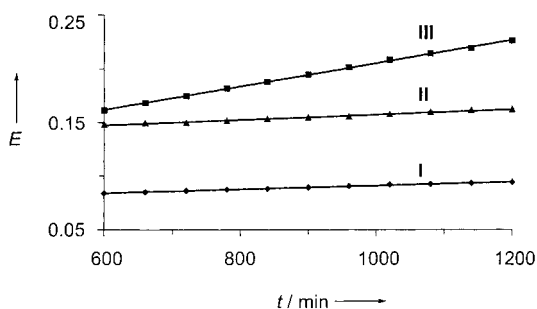


Figure 4. UV/Vis monitoring of the hydrolysis of **1b** (20°C, 67 mM MES-buffer,^[20] pH = 5.4, λ_{obs} = 405 nm). Trace I: **1b** (3.3 mM); trace II: **1b** (3.3 mM); ZrCl₄ (1.7 mM), peptide **D** (1.7 mM); trace III: **1b** (3.3 mM), ZrCl₄ (1.7 mM), peptide **A** (1.7 mM).

(2) was observed. The rate of hydrolysis in the presence of **D** is virtually the same as that of the background hydrolysis of *para*-nitrophenyl phosphate (**1b**; Figure 4, traces II and I, respectively). In contrast, in the presence of the peptide **A**, the hydrolysis of *para*-nitrophenyl phosphate (**1b**) proceeded about five times faster (Figure 4, trace III).^[21] Interestingly, rapid hydrolysis of phosphates was recently reported for Zr⁴⁺ alone and in the presence of amino or hydroxy ligands.^[22, 23]

In summary, we have combinatorially synthesized a library of 625 undecapeptides. On-bead screening of this library with the test substrates **3a,b** in the presence of a variety of transition metal ions enabled the identification of members of this library that—in combination with Zr⁴⁺—mediate phosphate hydrolysis. The activity (and inactivity of the control peptides) was not an exclusive feature of the polymer-bound state, but was also reproduced in homogenous solution when the peptides were cleaved off the resin. The inactivity of the combination Zr⁴⁺/control peptide **D** suggests that our combinatorial approach apparently identified peptide ligands that do not totally prevent binding/activation of the anionic phosphate to the positively charged zirconium cation (cleavage of the neutral ester **3a** was not observed). This is an important starting point for the further development of ligands that allow Zr⁴⁺ to perform phosphate hydrolysis in biological matrices. We presently do not attempt to explain the activity of, for example, **A** and the inactivities of **D** and **E** on the basis of their mere sequences—the absence of structural data for the peptide–zirconium complexes of **A–C** (and **D,E**, respectively) precludes a sound rationalization. Nevertheless, it is interesting to note, for example, that the inactive sequences **D** and **E** carry two positive charges (2 × Arg), whereas **A** and **C** carry one arginine residue and **B** none at all. Possibly, the combination of histidine as a neutral Zr⁴⁺-binding motif^[24] and serine as the phosphate acceptor may be seen as the common feature of the active sequences **A–C**. To the best of our knowledge, this is the first case of a truly combinatorial approach to the discovery of a well defined metal–ligand system: The ligand diversity was generated in a combinatorial manner, the active members of the library were selected by bulk screening of the library, and the structures of the hits (and controls) were analyzed subsequently.

Experimental Section

Microscopy was done using a Zeiss Axioplan 2 microscope, equipped with a MC-3250 CCD-camera and KS 100 software for video processing. Peptide sequences were determined from single beads using an Applied Biosystems Procise 494 Protein Sequencer. TentaGel S–NH₂ resin was purchased from Rapp Polymere, Tübingen, 5-bromo-4-chloroindolyl butyrate (**3a**) and 5-bromo-4-chloroindolyl phosphate (**3b**) from Molecular Probes Europe BV, Leiden, The Netherlands. Peptide synthesis was performed on TentaGel S–NH₂ following a standard procedure consisting of the repetition of the following four steps: 1) Coupling with 2 equiv of an Fmoc-protected L-amino acid by using 2 equiv of PyBOP^[8] in 3% *N*-methylmorpholine in absolute DMF; 2) washing with absolute DMF; 3) deprotection with 20% piperidine in absolute DMF; 4) washing with absolute DMF. The efficiencies of the coupling steps were determined by UV/Vis spectroscopic quantification of the subsequent deprotections. After the last cycle, the resins were treated with TFA/EtSH/DMS/phenol 80:10:5:5 (TFA = trifluoroacetic acid, DMS = dimethyl sulfide). In the split-mix synthesis of the library, the coupling of the functional amino acids **X** was carried out in five separate reactors, using Fmoc-L-Arg(Pmc), Fmoc-L-Trp, Fmoc-L-His(Trt), Fmoc-L-Ser(*t*Bu) and Fmoc-L-Tyr(*t*Bu), respectively. For the addition of the Gly units, the resins were pooled in one reactor.

Screening: The resin (5 mg, ca. 2500 beads, corresponding to ca. 1.2 μmol peptide) was treated with 1 mL of a 1 mM solution of 5-bromo-4-chloroindolyl butyrate (**3a**) or 5-bromo-4-chloroindolyl phosphate (**3b**) in EPPS buffer (10 mM, pH 5.6) and 1 mL of 1 mM solutions of the following salts in EPPS buffer (10 mM, pH 5.6): CuCl₂, FeCl₃·6H₂O, ZnCl₂, EuCl₃·6H₂O, ZrCl₄, (NH₄)₂Ce(NO₃)₆, and Na₂[Co(NO₂)₆]. In an additional experiment, buffer was added without a metal salt. The turquoise stain of the indigo dye **5** developed exclusively in the assay using 5-bromo-4-chloroindolyl phosphate (**3b**), and only in the presence of Zr⁴⁺. About 20 stained beads were found after incubation for one day at about 20°C. The three most deeply stained beads were selected, together with two control beads that did not show any stain. Edman degradation afforded the sequences **A–C** and **D,E**, respectively. For experiments in homogeneous solution, the peptides **A** and **D** were synthesized on Wang resin by the above Fmoc-technique and cleaved off the solid support by treatment with TFA. The kinetic runs shown in Figure 4 were carried out in a Beckman DU-640 spectrophotometer at 20°C and at a total sample volume of 3 mL. In the case of peptide **A** (Figure 4, trace III), 20 h reaction time corresponded to about 7% conversion of *para*-nitrophenyl phosphate (**1b**). The degree of conversion was determined by calibration using *para*-nitrophenol (**2**). Extinction/time profiles were monitored for up to two days and remained linear ($\rho \geq 0.998$) during this period of time. In multiple experiments, slopes were reproduced within ± 5%.

Received: August 5, 1998 [Z12255 IE]
German version: *Angew. Chem.* **1999**, *111*, 99–102

Keywords: combinatorial chemistry • enzyme mimetics • hydrolyses • peptides • transition metals

- [1] R. Breslow, *Acc. Chem. Res.* **1995**, *28*, 146–153.
- [2] a) A. J. Kirby, *Angew. Chem.* **1996**, *108*, 770–790; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 705–724; b) Y. Murakami, J. Kikuchi, Y. Hiseada, O. Hayashida, *Chem. Rev.* **1996**, *96*, 721–758.
- [3] L. C. Hsieh-Wilson, X.-D. Xiang, P. G. Schultz, *Acc. Chem. Res.* **1996**, *29*, 164–170.
- [4] a) S. J. Taylor, J. P. Morken, *Science* **1998**, *280*, 267–270; b) K. D. Shimizu, B. M. Cole, C. A. Krueger, K. W. Kuntz, M. L. Snapper, A. H. Hoveyda, *Angew. Chem.* **1997**, *109*, 1782–1785; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1704–1707; c) B. M. Cole, K. D. Shimizu, C. A. Krueger, J. P. A. Harrity, M. L. Snapper, A. H. Hoveyda, *Angew. Chem.* **1996**, *108*, 1776–1779; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1668–1671; d) S. R. Gilbertson, X. Wang, *Tetrahedron Lett.* **1996**, *37*, 6475–6478; e) K. Burgess, H.-J. Lim, A. M. Porte, G. A. Sulikowski, *Angew. Chem.* **1996**, *108*, 192–194; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 192–194.

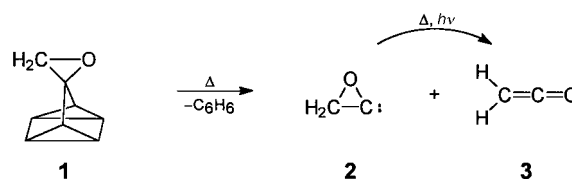
- 35, 220–222; f) G. Liu, J. A. Ellman, *J. Org. Chem.* **1995**, *60*, 7712–7713.
- [5] For an approach to phosphatase activity by grafting catalytically active groups onto polyallylamine and complexation with metal ions, see ref. [6].
- [6] F. M. Menger, A. V. Eliseev, V. A. Migulin, *J. Org. Chem.* **1995**, *60*, 6666–6667.
- [7] a) K. S. Lam, M. Lebl, V. Krchnák, *Chem. Rev.* **1997**, *97*, 411–448; b) F. Balkenhohl, C. von dem Bussche-Hünnefeld, A. Lansky, C. Zechel, *Angew. Chem.* **1996**, *108*, 2436–2488; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2288–2337; c) A. Furka, F. Sebestyén, M. Asgedom, G. Dibó, *Int. J. Pept. Protein Res.* **1991**, *37*, 487–493; d) R. A. Houghten, C. Pinilla, S. E. Blondelle, J. R. Appel, C. T. Dooley, J. H. Cuervo, *Nature* **1991**, *354*, 84–86; e) K. S. Lam, S. E. Salmon, E. M. Hersh, V. J. Hruby, W. M. Kazmiersky, R. J. Knapp, *Nature* **1991**, *354*, 82–84.
- [8] PyBOP: benzotriazol-1-yloxy-tripyrrolidinophosphonium hexafluorophosphate; J. Coste, D. Le-Nguyen, B. Castro, *Tetrahedron Lett.* **1990**, *31*, 205–208.
- [9] a) F. A. Cotton, E. E. Hazen, Jr., M. J. Legg, *Proc. Natl. Acad. Sci. USA* **1979**, *76*, 2551–2555; b) P. W. Tucker, E. E. Hazen, Jr., F. A. Cotton, *Mol. Cell. Biochem.* **1979**, *23*, 67–86.
- [10] N. Sträter, W. N. Lipscomb, T. Klabunde, B. Krebs, *Angew. Chem.* **1996**, *108*, 2158–2191; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2024–2055.
- [11] a) M.-S. Muche, M. W. Göbel, *Angew. Chem.* **1996**, *108*, 2263–2265; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2126–2129; b) V. Jubian, A. Veronese, R. P. Dixon, A. D. Hamilton, *Angew. Chem.* **1995**, *107*, 1343–1345; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1237–1239; c) D. M. Perreault, L. A. Cabell, E. V. Anslyn, *Bioorg. Med. Chem.* **1997**, *5*, 1209–1220; d) T. Oost, M. Kalesse, *Tetrahedron* **1997**, *53*, 8421–8438; e) R. Hettich, H.-J. Schneider, *J. Am. Chem. Soc.* **1997**, *119*, 5638–5647; f) P. Hurst, B. K. Takasaki, J. Chin, *J. Am. Chem. Soc.* **1996**, *118*, 9982–9983.
- [12] D. M. Perreault, E. V. Anslyn, *Angew. Chem.* **1997**, *109*, 470–490; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 432–451.
- [13] a) S. J. Lippard, J. M. Berg, *Principles of Bioinorganic Chemistry*, University Science Books, Mill Valley, USA, **1994**; b) J. Reedijk in *Bioinorganic Catalysis* (Ed.: J. Reedijk), Dekker, New York, USA, **1993**, pp. 1–10.
- [14] M. Zouhair Atassi, T. Manshour, *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 8282–8286.
- [15] Examples of designed catalytically active peptides: a) K. Johnsson, R. K. Allemann, H. Widmer, S. A. Benner, *Nature* **1993**, *365*, 530–532; b) K. S. Broo, H. Nilsson, J. Nilsson, A. Flodberg, L. Baltzer, *J. Am. Chem. Soc.* **1998**, *120*, 4063–4068.
- [16] a) B. W. Matthews, C. S. Craik, H. Neurath, *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 4103–4105; b) D. R. Corey, M. A. Phillips, *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 4106–4109; c) J. A. Wells, W. J. Fairbrother, J. Otowski, M. Laskowski, Jr., J. Burnier, *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 4110–4114.
- [17] Commercially available from Molecular Probes Europe BV, Leiden, The Netherlands.
- [18] EPPS: 3-[4-(2-hydroxyethyl)-1-piperazino]propanesulfonic acid. The polymer (ca. 5 mg, ca. 1.2 μmol peptide) was incubated with the metal salt (1 μmol) and the test substrates **3a,b** (1 μmol).
- [19] To exclude sequence-specific adsorption effects, the following control experiments were carried out: a) The hydroxyindolyl phosphate **3b** was hydrolyzed enzymatically and oxidized to the indigo dye **5** in an aerated solution of alkaline phosphatase from *bovine intestinal mucosa* (EC 3.1.3.1; Sigma; 20 U mg^{-1}). Exposure of about 2500 beads of the undecapeptide library to the resulting deeply colored suspension did not afford stained beads. b) When TentaGel S-NH₂ was swollen in an aqueous solution of the above alkaline phosphatase, exposure to the reagent **3b** resulted in a deep turquoise stain of all beads.
- [20] MES: 2-morpholinoethanesulfonic acid.
- [21] Mixtures of L-Arg, L-His, and L-Ser of equivalent concentrations did not effect an acceleration.
- [22] a) R. Ott, R. Krämer, *Angew. Chem.* **1998**, *110*, 2064–2067; *Angew. Chem. Int. Ed.* **1998**, *37*, 1957–1960; b) R. A. Moss, J. Zhang, K. G. Raghunathan, *Tetrahedron Lett.* **1998**, *39*, 1529–1532.

- [23] Uncomplexed Zr^{4+} as the cause of the observed acceleration appears very unlikely according to the following control experiments: At constant Zr concentration, a duplication of the peptide concentration does not result in a decrease of the rate of hydrolysis. On the other hand, at constant peptide concentration, an increase of the Zr concentration results in an increase of the rate of hydrolysis. Complex formation is furthermore indicated by resonance shifts observed in the NMR spectra of peptide **A** upon addition of Zr^{4+} .
- [24] R. C. Fay in *Comprehensive Coordination Chemistry*, Vol. 3 (Eds.: G. Wilkinson, R. D. Gillard, J. A. McClaverty), Pergamon, Oxford, **1987**, p. 363–451.

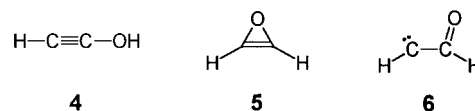
Oxiranylidene**

Günther Maier,* Hans Peter Reisenauer, and Michael Cibulka

Fourteen years ago we could generate cyclopropenylidene by high vacuum flash pyrolysis of a quadricyclane derivative, synthesized by Hoffmann et al.,^[1] and identify it spectroscopically in a rare gas matrix.^[2] This was the starting point for intensive studies on the C_3H_2 potential-energy surface.^[3] Consequently we tried to synthesize oxiranylidene (**2**) by using the quadricyclane derivative **1** as a precursor. This compound in particular was used because Hoffmann and Schüttler^[4] had detected ketene (**3**) on thermolysis of **1** in an earlier experiment. The question as to whether oxiranylidene (**2**) is the primary product of this reaction could not be answered at that time. It was logical to resume the search for **2**



with techniques available today (high vacuum flash pyrolysis in combination with matrix-isolation). This was especially tempting because of the great theoretical interest in oxiranylidene (**2**). Ab initio calculations predict that it should be a minimum on the $\text{C}_2\text{H}_2\text{O}$ potential-energy surface with a considerable energy barrier to isomerization.^[5, 6] Therefore it should be possible to detect **2** in a cryogenic matrix. Herein we show that besides ketene (**3**) and ethynol (**4**),^[7] oxiranylidene (**2**) is indeed an observable $\text{C}_2\text{H}_2\text{O}$ species.



[*] Prof. Dr. G. Maier, Dr. H. P. Reisenauer, Dipl.-Chem. M. Cibulka
Institut für Organische Chemie der Universität
Heinrich-Buff-Ring 58, D-35392 Giessen (Germany)
Fax: (+49) 641-99-34309

[**] This work was supported by the Fonds der Chemischen Industrie and the Deutsche Forschungsgemeinschaft.

If one pyrolyzes polycycle **1** under high vacuum (quartz tube: diameter 8 mm; heating zone 5 cm; approximately 10^{-5} mbar; 500°C) and deposits the resulting products together with nitrogen or argon as the matrix material on a cold (10 K) CsI window, the absorptions listed in Table 1 in addition to those of benzene and ketene (**3**) can be found in the IR

Table 1. Observed IR absorptions (N_2 matrix, 10 K; relative intensities in parentheses) and calculated vibrational spectra (MP2/6-311++G**, B3LYP/6-311++G**) of oxiranylidene (**2**).

	Type	$\tilde{\nu}_{\text{N}_2, \text{exp}}$ [cm^{-1}]	$\tilde{\nu}_{\text{calcd}}$ [cm^{-1}] (MP2)	$\tilde{\nu}_{\text{calcd}}$ [cm^{-1}] (B3LYP)
ν_7	a''	CH_2 str.	—	3313 (7)
ν_1	a'	CH_2 str.	—	3189 (2)
ν_2	a'	ring def.	1470.8 (46)	1554 (61)
		+ CH_2 scis.		1528 (73)
ν_3	a'	CH_2 scis.	1375.1 (50)	1438 (55)
		+ ring def.		1417 (64)
ν_8	a''	CH_2 rock.	—	1139 (3)
ν_4	a'	CH_2 wag.	1078.5 (16)	1118 (38)
		+ ring def.		1094 (42)
ν_9	a''	CH_2 twist	—	902 (4)
ν_5	a'	ring def.	830.1 (100)	860 (100) ^[a]
		+ CH_2 wag.		838 (61)
ν_6	a'	ring def.	778.1 (29)	815 (59)
				823 (100) ^[b]

[a] Absolute intensity: 52 km mol^{-1} . [b] Absolute intensity: 53 km mol^{-1} .

spectrum. The bands are sharp in solid nitrogen, but split in argon because of matrix effects. Their intensity depends on the conditions of the pyrolysis and is highest if a temperature is chosen under which some starting material is still detectable in the condensate. When the temperature is raised up to 600°C the absorptions listed in Table 1 diminish and those of ketene (**3**) become enlarged. The bands of **2** also decrease if the matrix-isolated pyrolysate is irradiated ($\lambda = 313 \text{ nm}$), while the absorptions of **3** grow simultaneously. These observations and the good agreement between the experimental and the calculated (MP2/6-311++G**, B3LYP/6-311++G**) spectrum (Table 1, Figure 1) confirm that the thermal cleavage of polycycle **1** leads, as expected, to oxiranylidene (**2**). The five fundamental vibrations with the highest calculated intensities are observed. No weak CH stretching vibrations at about 3000 cm^{-1} were detectable. Oxiranylidene (**2**) is converted into ketene (**3**) either under the conditions of the pyrolysis or on irradiation of the matrix after the thermolysis of **1**. The calculated IR spectrum for the singlet ground state **S-2** corresponds well with the experimental one. In contrast, the expected IR spectrum for the triplet carbene **T-2** looks quite different (Figure 1).

The structural elucidation of oxiranylidene (**2**) is confirmed by the result of the flash pyrolysis of the precursor $[\text{D}_2]\text{1}$ ^[9] with a deuterated three-membered ring. Again the experiment is in good agreement with the calculations (Table 2, Figure 2). The surprising splitting of the strongest band in the IR spectrum of $[\text{D}_2]\text{2}$ into two signals of nearly the same intensity at 1419.4 and 1400.6 cm^{-1} is the result of a Fermi resonance of the fundamental vibration ν_2 with the overtone of the fundamental vibration ν_6 of $[\text{D}_2]\text{2}$ at 706.3 cm^{-1} .

The UV spectrum of the matrix-isolated pyrolysis products shows a weak, structureless band at $\lambda_{\text{max}} = 324 \text{ nm}$. It is very

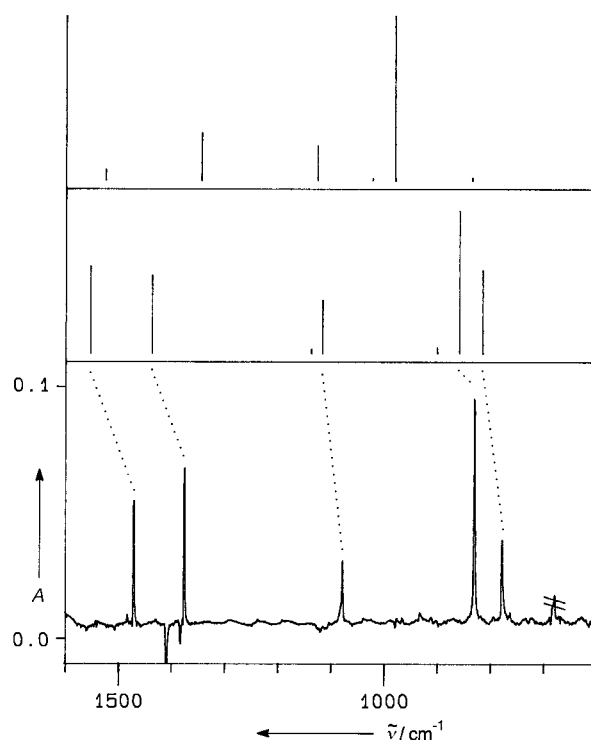


Figure 1. Selected region of the experimental (N_2 matrix, 10 K, bottom) and calculated (MP2/6-311++G**, middle) IR spectrum of oxiranylidene (**S-2**), as well as the calculated IR spectrum (MP2/6-311++G**, top) of triplet oxiranylidene **T-2**. The experimental spectrum is a difference spectrum of the photoisomerization $\text{2} \rightarrow \text{3}$ (the bands with positive values diminish upon irradiation).

Table 2. Observed IR absorptions (N_2 matrix, 10 K; relative intensities in parentheses) and calculated vibrational spectra (MP2/6-311++G**, B3LYP/6-311++G**) of $[\text{D}_2]$ oxiranylidene ($[\text{D}_2]\text{2}$).

	Type	$\tilde{\nu}_{\text{N}_2, \text{exp}}$ [cm^{-1}]	$\tilde{\nu}_{\text{calcd}}$ [cm^{-1}] (MP2)	$\tilde{\nu}_{\text{calcd}}$ [cm^{-1}] (B3LYP)
ν_7	a''	CD_2 str.	—	2474 (8)
ν_1	a'	CD_2 str.	—	2307 (2)
$\nu_2/2\nu_6$	a'	ring def.	1419.4 (85) ^[a]	1489 (100) ^[b]
		+ CD_2 scis.		1467 (100) ^[c]
$\nu_2/2\nu_6$	a'		1400.6 (81) ^[a]	
ν_3	a'	CD_2 scis.	1050.2 (21)	1090 (9)
ν_4	a'	CD_2 wag.	960.3 (57)	1001 (38)
		+ ring def.		974 (37)
ν_8	a''	CD_2 rock.	—	868 (4)
ν_5	a'	ring def.	780.1 (100)	811 (42)
ν_6	a'	CD_2 wag.	706.3 (94)	722 (56)
ν_9	a''	CD_2 twist	—	687 (5)
				673 (4)

[a] Fermi resonance $\nu_2/2\nu_6$. [b] Absolute intensity: 57 km mol^{-1} . [c] Absolute intensity: 67 km mol^{-1} .

likely that oxiranylidene (**2**) is responsible for this absorption, because it vanishes in the previously mentioned photoisomerization $\text{2} \rightarrow \text{3}$, which is fastest with light of wavelength $\lambda = 313 \text{ nm}$, slower with $\lambda = 254 \text{ nm}$, and is not observed at all at $\lambda \geq 366 \text{ nm}$.

The investigation of oxiranylidene (**2**) was of interest to us also because of our earlier attempts^[10] on matrix isolation of oxirene (**5**).^[11] If **2** behaved as a normal alkylcarbene with an α -hydrogen atom, a 1,2-hydrogen migration to give oxirene (**5**) should occur easily.^[12] However, this reaction cannot be observed.

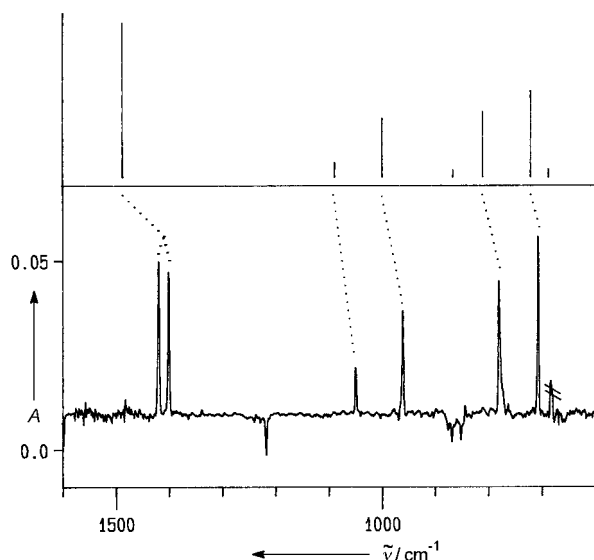


Figure 2. Selected region of the experimental (N_2 matrix, 10 K, bottom) and the calculated (MP2/6-311++G**, top) IR spectrum of $[D_2]$ oxiranylidene (S - $[D_2]2$). The experimental spectrum is a difference spectrum of the photoisomerization $[D_2]2 \rightarrow [D_2]3$ (the bands with positive values diminish upon irradiation).

Altogether the experiments and theoretical predictions give a consistent picture.^[5, 6] In order to be able to compare the relevant stationary points, they were again calculated on the B3LYP/6-311++G** level of theory^[8] (Scheme 1). The following conclusions can be drawn: a) The C_2H_2O isomer that is next highest in energy to ethynol (**4**)^[7] (relative energy: 37.2 kcal mol⁻¹) was found with oxiranylidene (**2**) (relative energy on the level of theory used: 66.7 kcal mol⁻¹). b) Unlike formylcarbene (**6**) oxiranylidene (**2**) has a singlet ground state. c) The energy barrier for the ring-opening $2 \rightarrow 3$ is 30.6 kcal mol⁻¹ lower than the barrier for a 1,2-hydrogen migration. The transition state $TS(2 \rightarrow 3)$ of the former reaction looks like a $CH_2 \cdot CO$ complex.^[13] The TS of the energetically disfavored reaction path $2 \rightarrow 6$ leads to formylcarbene (**6**) rather than oxirene (**5**).^[6b] d) There seems to be no chance to generate C_2H_2O species other than **3**, **4**, and **2**. Even if **S-6** was formed from **S-2** it should react to ketene (**3**) via $TS(6 \rightarrow 3)$ nearly without any activation and hence compete with the conversion into the ground state **T-6**.^[6b] The widely discussed formylcarbene/oxirene isomerization^[6, 10–12] is also believed not to be observable experimentally, even if oxirene (**5**) is, in contrast to earlier calculations,^[6] a true minimum.^[14] The energy difference between oxirene (**5**), formylcarbene (**S-6**), and the transition state, which links **5** and **S-6**, is so small that isomerization to ketene (**3**) will occur immediately.

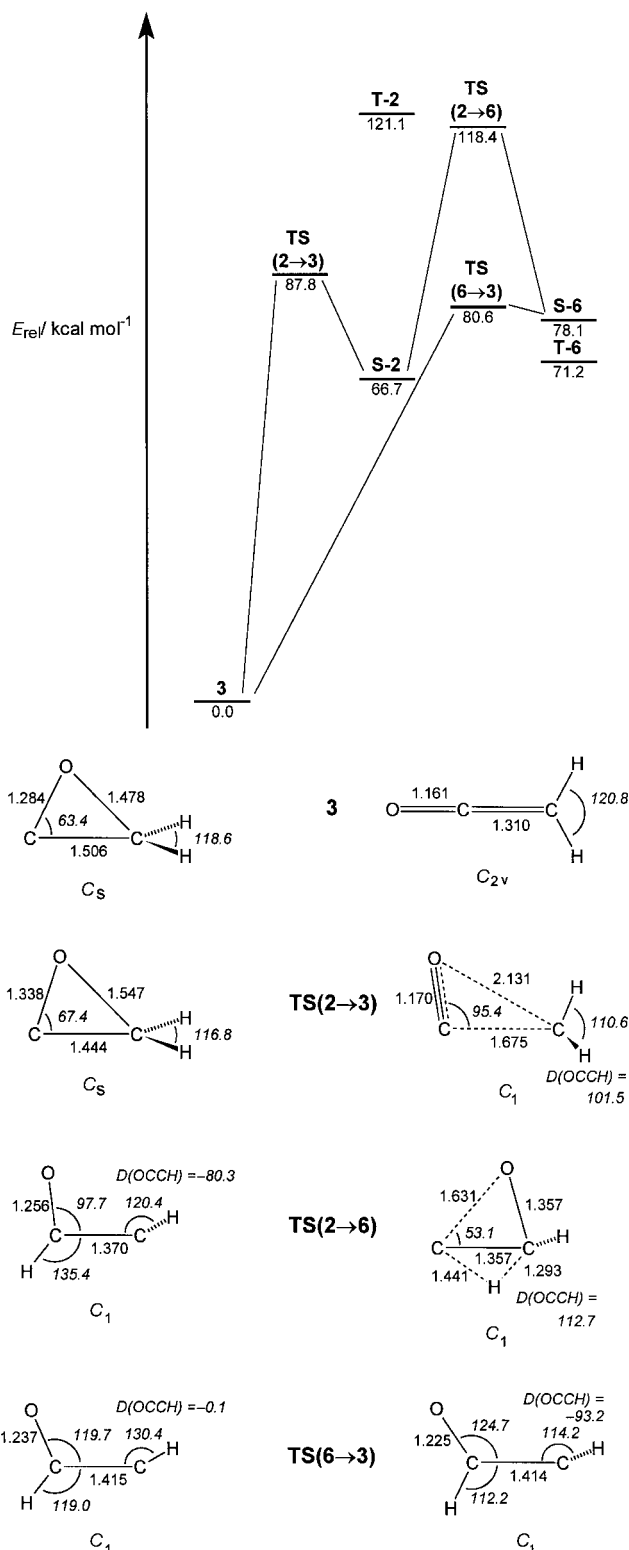
Received: July 27, 1998 [Z.122051E]

German version: *Angew. Chem.* **1999**, *111*, 110–113

Keywords: ab initio calculations • carbenes • isomerizations • matrix isolation • photochemistry

[1] A. Riemann, R. W. Hoffmann, J. Spanget-Larsen, R. Gleiter, *Chem. Ber.* **1985**, *118*, 1000–1007.

[2] H. P. Reisenauer, G. Maier, A. Riemann, R. W. Hoffmann, *Angew. Chem.* **1984**, *96*, 596; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 641.



Scheme 1. Calculated (B3LYP/6-311++G**) relative energies (including zero point vibrational energies) and structures of relevant C_2H_2O minima and related transition structures **TS**. Distances in Å, angles in degrees (italic; D = dihedral angle).

[3] a) G. Maier, H. P. Reisenauer, W. Schwab, P. Čársky, B. A. Hess, Jr., L. J. Schaad, *J. Am. Chem. Soc.* **1987**, *109*, 5183–5188; b) G. Maier, H. P. Reisenauer, W. Schwab, P. Čársky, V. Špirko, B. A. Hess, Jr., L. J. Schaad, *J. Chem. Phys.* **1989**, *91*, 4763–4773; see also c) G. Maier, T. Preiss, H. P. Reisenauer, *Chem. Ber.* **1994**, *127*, 779–782; d) G. Maier,

- T. Preiss, H. P. Reisenauer, B. A. Hess, Jr., L. J. Schaad, *J. Am. Chem. Soc.* **1994**, *116*, 2014–2018.
- [4] R. W. Hoffmann, R. Schüttler, *Chem. Ber.* **1975**, *108*, 844–855.
- [5] We thank Prof. E.-U. Würthwein, Universität Münster, for drawing our attention to this fact in 1993 (MP2/6–31G** calculations, unpublished results).
- [6] a) K. Tanaka, M. Yoshimine, *J. Am. Chem. Soc.* **1980**, *102*, 7655–7662; b) W. J. Bouma, R. H. Nobes, L. Radom, C. E. Woodward, *J. Org. Chem.* **1982**, *47*, 1869–1875; c) M. Yoshimine, *J. Chem. Phys.* **1989**, *90*, 378–385.
- [7] R. Hochstrasser, J. Wirz, *Angew. Chem.* **1989**, *101*, 183–185; *Angew. Chem. Int. Ed. Engl.* **1989**, *26*, 805.
- [8] Gaussian 94, Revision B.1, M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. Keith, G. A. Petersson, J. A. Montgomery, K. Raghavachari, M. A. Al-Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, J. Cioslowski, B. B. Stefanov, A. Nanayakkara, M. Challacombe, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. Defrees, J. Baker, J. P. Stewart, M. Head-Gordon, C. Gonzalez, J. A. Pople, Gaussian, Inc., Pittsburgh PA, **1995**.
- [9] The isotopomer [D₂]**1** was prepared according to ref. [4] from quadricyclanone and nonadeuterotrimethylsulfoxonium chloride.
- [10] a) G. Maier, H. P. Reisenauer, T. Sayrac, *Chem. Ber.* **1982**, *115*, 2192–2201; b) G. Maier, H. P. Reisenauer, T. Sayrac, *Chem. Ber.* **1982**, *115*, 2202–2213.
- [11] For a review on the oxirene problem, see a) E. Lewars, *Chem. Ber.* **1983**, *83*, 519–534; see also b) E. Lewars, *J. Mol. Struct. (Theochem)* **1996**, *360*, 67–80, and references therein; c) G. Maier, C. Schmidt, H. P. Reisenauer, E. Endlein, D. Becker, J. Eckwert, B. A. Hess, Jr., L. J. Schaad, *Chem. Ber.* **1993**, *126*, 2337–2352; reference [6].
- [12] W. Sander, G. Bucher, S. Wierlacher, *Chem. Rev.* **1993**, *93*, 1583–1621.
- [13] If CH₂ is replaced by SiH₂ the CO complex H₂Si·CO is calculated to be the global minimum on the CH₂OSi potential-energy surface and can be isolated in a cryogenic matrix: G. Maier, H. P. Reisenauer, H. Egenolf in *Organosilicon Chemistry IV – From Molecules to Materials* (Eds: N. Auner, J. Weis), VCH, Weinheim, in press.
- [14] G. Vacek, J. M. Galbraith, Y. Yamaguchi, H. F. Schaefer III, R. H. Nobes, A. P. Scott, L. Radom, *J. Phys. Chem.* **1994**, *98*, 8660–8665.

Isonitroso Hydrogen (Hydroxy Nitrene, HON)**

Günther Maier,* Hans Peter Reisenauer, and Michael De Marco

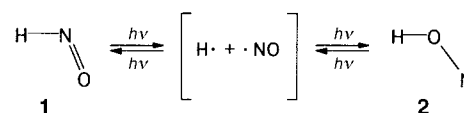
Dedicated to Professor Heinrich Nöth on the occasion of his 70th birthday

The importance of nitroso hydrogen HNO (**1**) for combustion, atmospheric chemistry, astrophysics, and particularly theoretical chemistry is demonstrated in a multitude of papers published on this topic.^[1] According to the results of some theoretical studies the existence of isonitroso hydrogen HON (**2**) besides HNO (**1**) is anticipated, but to the best of our knowledge there is no experimental evidence for that. Herein we describe the first matrix isolation and IR-spectroscopic

identification of isonitroso hydrogen (**2**) in solid argon at 10 K.

For the generation of HON (**2**) the same method can be used, which was employed by Jacox and Milligan 15 years ago to produce and to identify HNO (**1**) IR spectroscopically in an argon matrix.^[2] Thus, hydrogen atoms are generated by exposing a H₂/Ar mixture to a microwave discharge and deposited together with a NO/Ar mixture on a 10 K cold spectroscopic window. Under these conditions a NO radical and a hydrogen atom can recombine to form HNO (**1**). In the meantime we know that HON (**2**) is also generated within this process in a small amount. Alternatively one can produce the same products by passing a mixture of NO, H₂, and argon (ratio: 1:2:250) or of H₂, N₂, O₂, and argon (ratio: 4:1:1:500) through a microwave discharge.

Independent of the chosen method of generation we found strong IR absorptions of HNO (**1**) and small bands, which we assign to HON (**2**). The identification of **2** is based mainly on the investigation of the photochemistry of the already known HNO (**1**) isomer. Moreover, further products (NH, N₂O, N₂O₂, N₂O₃, HNO₂, NO₂, OH, H₂O, HO₂, CO, CO₂) could be observed in various amounts. In analogy with the photoisomerization of nitrosyl cyanide (ONCN) to isonitrosyl cyanide (NOCN),^[3] the thermodynamically more stable nitroso hydrogen (**1**) was converted into the less stable isonitroso hydrogen (**2**). During irradiation of HNO (**1**) in solid argon at 10 K with monochromatic light of the wavelength $\lambda = 313$ nm, the HNO bands at 2715.1, 1562.2, and 1504.3 cm⁻¹ decrease, while two new absorptions arise at 3467.2 and 1095.6 cm⁻¹, which we assign to HON (**2**). At the same time the NO band (1871.4 cm⁻¹) increases. If the wavelength is changed to $\lambda = 254$ nm the HON absorptions decrease, while the HNO bands increase. During this second irradiation the NO band continues to grow. All these observations point to a photochemical equilibrium between HNO (**1**) and HON (**2**), which is presumably reached by the



dissociation of the two isomers into NO radicals and H atoms. The position of the equilibrium depends on the wavelength of light used for the irradiation. The increase of the NO concentration during the photoisomerization is caused by cage escape of H atoms, which are rather mobile even at 10 K in solid argon.^[4]

Irradiation with very short (248, 193, 185 nm) and long (> 330 nm) wavelengths does not lead to any observable isomerization. The identification of isonitroso hydrogen (**2**) is based essentially on the comparison of the experimental and calculated IR spectra. Figure 1 shows a difference spectrum, which documents the photoisomerization between **1** and **2**. Furthermore the corresponding calculated IR spectra (Gaussian package of programs)^[5] are included for comparison. In addition the D- (Figure 2) and ¹⁵N-isotopomers of HON (**2**) have been investigated. All results (BLYP^[6] and QCISD/6-311++G**) are compiled in Table 1.

[*] Prof. Dr. G. Maier, Dr. H. P. Reisenauer, Dipl.-Chem. M. De Marco
Institut für Organische Chemie der Universität
Heinrich-Buff-Ring 58, D-35392 Giessen (Germany)
Fax: (+49) 641-99-34309

[**] This work was supported by the Fonds der Chemischen Industrie and the Deutsche Forschungsgemeinschaft.

Table 1. Experimental ($[\text{cm}^{-1}]$, argon matrix, 10 K) and calculated vibrational spectra (BLYP and QCISD/6-311++G**) of four isotopomers of HON (relative intensities are given in parentheses).

	Type ^[a]			HON	HO ¹⁵ N	DON	DO ¹⁵ N
ν_1	A'	OH str	exp.	3467.2 (19)	3466.4 (19)	2563.6 (28)	2564.6 (20)
			calcd ^[b]	3479.8 (27)	3479.8 (27)	2532.8 (30)	2532.8 (31)
			calcd ^[c]	3780.3 (42)	3780.3 (44)	2751.9 (42)	2751.9 (43)
ν_2	A'	NO str	exp.	— ^[d]	— ^[d]	1149.0 (100)	1127.9 (100)
			calcd ^[b]	1157.7 (0)	1145.7 (0)	1092.2 (100) ^[i]	1071.6 (100) ^[k]
			calcd ^[c]	1232.1 (1)	1222.4 (5)	1171.1 (100) ^[j]	1149.2 (100) ^[l]
ν_3	A'	bend	exp.	1095.6 (100)	1085.6 (100)	868.8 (79)	867.2 (74)
			calcd ^[b]	1030.2 (100) ^[e]	1020.7 (100) ^[g]	815.2 (70)	813.6 (72)
			calcd ^[c]	1142.5 (100) ^[f]	1129.1 (100) ^[h]	895.8 (81)	893.9 (52)

[a] str=stretching vibration, bend=bending vibration. [b] BLYP/6-311++G**. [c] QCISD/6-311++G**. [d] Not measurable due to too low intensity. [e] Absolute intensity: 163 km mol^{-1} . [f] Absolute intensity: 177 km mol^{-1} . [g] Absolute intensity: 160 km mol^{-1} . [h] Absolute intensity: 168 km mol^{-1} . [i] Absolute intensity: 76 km mol^{-1} . [j] Absolute intensity: 95 km mol^{-1} . [k] Absolute intensity: 73 km mol^{-1} . [l] Absolute intensity: 93 km mol^{-1} .

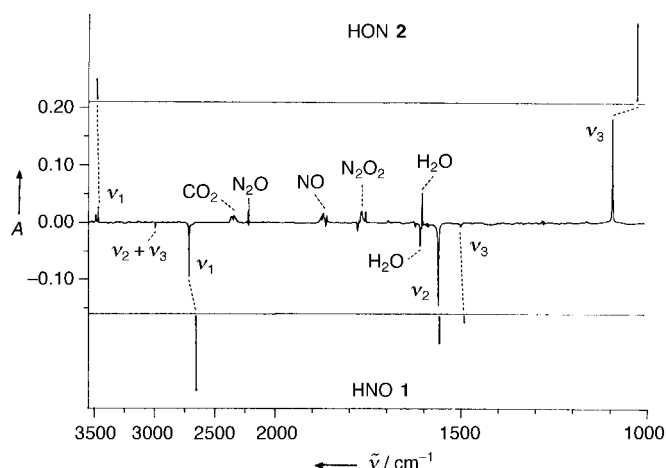


Figure 1. Calculated (BLYP/6-311++G**) and experimental IR spectra of HNO (**1**) and HON (**2**). Theoretical spectrum for HON (**2**) at the top and for HNO (**1**) at the bottom. Difference spectrum (Ar matrix, 10 K) of the photochemical isomerization of **1** to **2** in the middle. The investigated matrix was produced by cocondensation of a mixture of NO/Ar (ratio: 4:1000) with H atoms, which were generated by microwave discharge of a mixture of H_2/Ar (ratio: 8:1000).

For the triatomic bent molecule HON (**2**), as well as for HNO (**1**), three IR active fundamental vibrations are expected. However, for isomer **2** due to the low intensity of the NO stretching vibration (ν_2), which is coupled with the HON bending mode (ν_3), only two absorptions could be observed. They are attributed to the bending mode (ν_3 ; 1095.6 cm^{-1}), which is mixed with the NO stretching vibration (ν_2) and the OH stretching vibration (ν_1 ; 3467.2 cm^{-1}). The calculated IR spectrum of DON predicts an increase of the intensity of the now uncoupled NO stretching vibration. Indeed, three new bands were observed during the photoisomerization of DNO, which we assign to the bending mode (ν_3 ; 868.8 cm^{-1}), the NO stretching vibration (ν_2 ; 1149.0 cm^{-1}), and the OD stretching vibration (ν_1 ; 2563.6 cm^{-1}) of DON ([D]**2**) (Figure 2). The comparison of the calculated and experimental band shifts of the isotopomers HON, HO¹⁵N, DON, and DO¹⁵N (Table 1) are in good agreement again. The spectra of DON and DO¹⁵N are particularly informative because all three fundamental vibrations are observable.

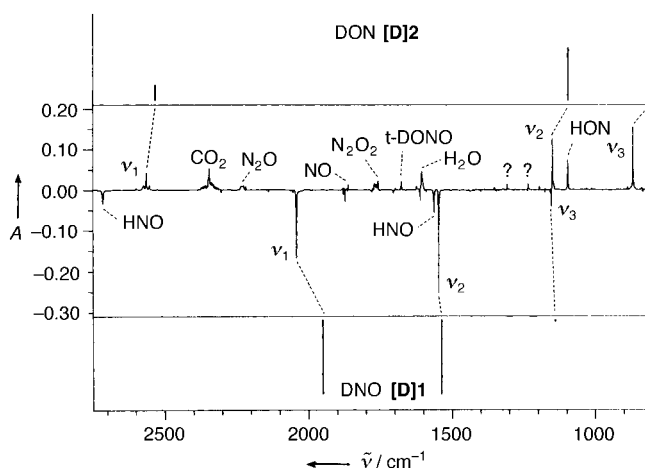


Figure 2. Calculated (BLYP/6-311++G**) and experimental IR spectra of DNO ([D]**1**) and DON ([D]**2**). Theoretical spectrum for DON ([D]**2**) on the top and for DNO ([D]**1**) at the bottom. Difference spectrum (Ar matrix, 10 K) of the photochemical isomerization of [D]**1** to [D]**2** in the middle. The investigated matrix was produced by cocondensation of a mixture of NO/Ar (ratio: 4:1000) with D atoms, which were generated by microwave discharge of a mixture of D_2/Ar (ratio: 8:1000).

How does the UV/Vis spectrum of **2** look? During irradiation of HNO (**1**) with light of the wavelength $\lambda = 313$ nm one observes the decrease of its characteristic sharp bands at 688, 709, and 761 nm,^[7] new absorptions in the range between 230 and 1100 nm cannot be detected. Nevertheless, **2** must absorb below 300 nm, since this compound is photochemically stable against irradiation with wavelengths above 300 nm, but, irradiation with $\lambda = 254$ nm light causes isomerization to **1**.

What is the multiplicity of the ground state of isonitroso hydrogen (**2**)? Calculation of the potential energy surface of the system HNO/HON shows a singlet ground state for HNO (**1**), which is also the global minimum.^[1, 8] However, for HON (**2**) a triplet ground state is predicted. The energy gap between singlet and triplet of approximately 20 kcal mol^{-1} supports the assumption that under our conditions the triplet ground state of **2** is present. Indeed, the experimental IR spectrum fits much better to the calculated spectrum of the triplet molecule (see ref. [8] and our own calculations).^[9] Thus, the isomerization of HNO to HON involves a change of multiplicity. Calculations reported by Guadagnini et al.^[8] correspond with

results from our experiment in so far as the dissociation to H and NO is lower in energy than a cyclic transition state for the direct reaction of **1** to **2** on the singlet as well as the triplet potential-energy surface.

What can we say about the geometry of **2**? The calculations^[8] reveal a typical O–H bond length for isonitroso hydrogen (**2**) ($d = 0.984 \text{ \AA}$; $\text{trans-HONO: } d(\text{OH}) = 0.98 \text{ \AA}$). The N–O bond length ($1.323 \text{ \AA}$) is very long and lies between a double ($\text{trans-HONO: } d(\text{N=O}) = 1.20 \text{ \AA}$) and a single bond ($\text{trans-HONO: } d(\text{N–O}) = 1.46 \text{ \AA}$). These structural data of isonitroso hydrogen (**2**) express the character of a nitrene. In other words: This molecule should be regarded as “hydroxy nitrene”.

Received: July 27, 1998 [Z 12206 IE]
German version: *Angew. Chem.* **1999**, *111*, 113–115

Keywords: ab initio calculations • isomerizations • matrix isolation • nitrenes • photochemistry

- [1] D. H. Mordant, H. Flöthmann, M. Stumpf, H.-M. Keller, C. Beck, R. Schinke, K. Yamashita, *J. Chem. Phys.* **1997**, *107*, 6603–6615, and references therein.
- [2] M. E. Jacox, D. E. Milligan, *J. Mol. Spectrosc.* **1973**, *48*, 536–559.
- [3] G. Maier, H. P. Reisenauer, J. Eckwert, M. Naumann, M. De Marco, *Angew. Chem.* **1997**, *109*, 1785–1787; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1707–1709.
- [4] K. H. Gödderz, N. Schwentner, M. Chergui, *J. Chem. Phys.* **1996**, *105*, 451–458.
- [5] Gaussian 94, Revision B.1: M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. Keith, G. A. Petersson, J. A. Montgomery, K. Raghavachari, M. A. Alalam, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, J. Cioslowski, B. B. Stefanov, A. Nanayakkara, M. Challacombe, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. Derees, J. Baker, J. P. Stewart, M. Head-Gordon, C. Gonzales, J. A. Pople, Gaussian Inc., Pittsburgh, PA, USA, **1995**.
- [6] Review: L. J. Bartolotti, U. Flurchick, *Rev. Comput. Chem.* **1996**, *7*, 187–216.
- [7] G. W. Robinson, M. McCarty, Jr., *Can. J. Phys.* **1958**, *63*, 1590–1591.
- [8] R. Guadagnini, G. C. Schatz, S. P. Walch, *J. Chem. Phys.* **1995**, *102*, 774–783.
- [9] In principle it should be possible to verify the triplet multiplicity of the HON ground state by ESR spectroscopy. However, since the relevant signal is expected to lie outside the range of our ESR spectrometer, we have not carried out measurements.

Palladium-Mediated Dynamic Kinetic Resolution: Stereoselective Synthesis of Vicinal Diamines**

Gregory R. Cook,* P. Sathya Shanker, and
Ketheeswaran Pararajasingham

The palladium-catalyzed allylic substitution reaction has emerged as a powerful methodology in organic synthesis.^[1] The stereoselective variants have focussed primarily on enantioselective processes which utilize chiral ligands and achiral substrates.^[2] When chiral substrates are used, the configuration of the allylic leaving group controls the configuration of the product through a double inversion mechanism. In contrast, little attention has been paid to diastereoselectivity in the nucleophilic addition to π -allyl palladium complexes with an adjacent stereocenter,^[2–4] and a study of the asymmetric induction by acyclic substrates in intermolecular reactions has not been previously reported.^[5] For stereocenters outside of the allyl framework to control the addition of a nucleophile, the palladium complex must be able to undergo rapid allyl inversion (Figure 1). Our interest in dynamic transition metal complexes^[6] has led us to probe the diastereoselectivity in such a system, and our results are reported herein. This process constitutes an example of palladium-mediated dynamic kinetic resolution.^[3b, 7]

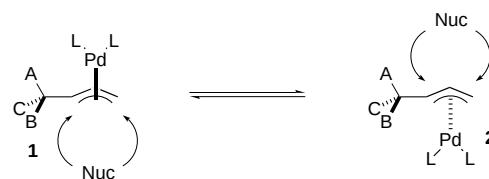


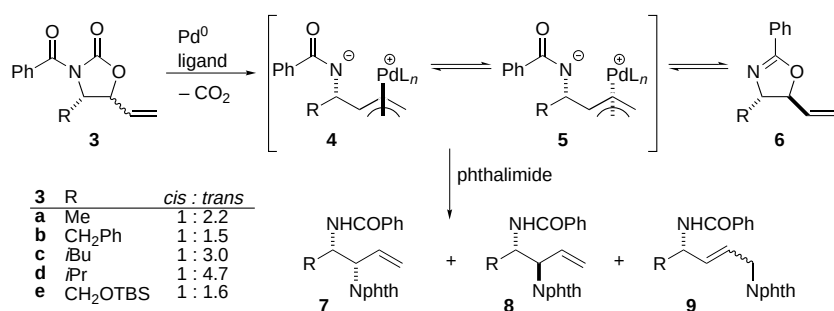
Figure 1. Selectivity issues in dynamic diastereomeric complexes (see text for details).

Several issues of regio- and stereoselectivity need to be addressed when considering the allylic substitution reaction. The palladium-catalyzed reaction usually favors addition at the less substituted terminus. For complexes **1** and **2** (Figure 1), this mode of reactivity must be reversed in order to generate a new stereocenter. While many allyl complexes are configurationally stable, rapid equilibration is common, and this usually results in loss of allyl stereochemistry. For selectivity in a diastereoselective process, such as described here, the rate of π -allyl inversion relative to the rate of nucleophilic addition is important (Figure 1).

We have shown^[6] that chiral 5-vinyloxazolidinones **3** derived from α -amino acids react with palladium(0) catalysts to afford 5-vinyloxazolines **6** by oxidative insertion, loss of CO_2 , and subsequent cyclization at the amide oxygen atom (Scheme 1). The oxazoline products were obtained with

[*] Prof. G. R. Cook, P. S. Shanker, K. Pararajasingham
Department of Chemistry
North Dakota State University
Fargo, ND 58105 (USA)
Fax: (+1) 701-231-8831
E-mail: grcook@plains.nodak.edu

[**] We thank the National Science Foundation (OSR 9452892) and North Dakota State University for support of this project.



Scheme 1. Palladium(0)-mediated synthesis of chiral vicinal diamines from chiral oxazolidinones. phth = phthalimidyl, TBS = *tert*-butyldimethylsilyl.

enhanced diastereomeric ratios, which suggested that the intermediate π -allyl palladium complexes **4** and **5** were undergoing rapid equilibration. Oxazolines **6** were also ionized by the palladium catalyst and were in equilibrium with **4** and **5**, thus giving rise to thermodynamically controlled product ratios. We reasoned that these dynamic intermediates could be trapped with external nitrogen-containing nucleophiles under kinetic control to afford chiral diamines **7** and/or **8**.

The oxazolidinones **3a–e** were prepared as mixtures of diastereomers from α -amino acids as previously described.^[6] The allylic substitution with phthalimide as the nucleophile was investigated, and the results are described in Table 1.

Table 1. Dynamic kinetic resolution of chiral 5-vinyloxazolidinones **3**.^[a]

Entry	Substrate	Ligand	Reaction time [h]	1,2:1,4 (7+8:9)	<i>syn:anti</i> (7:8)	Yield [%] (combined)
1	3a	dppe	20	5.5:1	97:3	97
2	3a	dppp	2	6.0:1	95:5	92
3	3a	dppb	1	6.0:1	94:6	98
4	3a	dppf	0.5	7.0:1	93:7	97
5	3b	dppp	1.5	1.6:1	97:3	98
6	3c	dppp	2	3.2:1	> 99:1	91
7	3d	dppp	2	7.9:1	> 99:1	99
8	3e	dppb	5	3.6:1	> 99:1	98

[a] All reactions were run at 25 °C with 1 mol % of the Pd dimer catalyst and 4 mol % of the ligand in THF. Isomer ratios were determined by NMR spectroscopy.

Table 2. Influence of chiral ligands on regio- and diastereoselectivity.^[a]

Entry	Substrate	Ligand	Reaction time [min]	1,2:1,4 (7+8:9)	<i>syn:anti</i> (7:8)	1,2 ^[b]	1,4 ^[b]	Yield [%] combined ^[c]
1	3a	(<i>R</i>)-BINAP	30	3:1	88:12	71	25	99
2	3a	(<i>S</i>)-BINAP	30	1.5:1	96:4	— ^[d]	— ^[d]	99
3	3b	(<i>R</i>)-BINAP	20	20:1	> 99:1	90	5	98
4	3b	(<i>S</i>)-BINAP	30	3:1	98:2	— ^[d]	— ^[d]	99
5	3b	(<i>R</i>)-Tol-BINAP	10	19:1	> 99:1	91	5	98
6	3b	(<i>S</i>)-Tol-BINAP	30	3.5:1	98:2	— ^[d]	— ^[d]	99
7	3c	(<i>R</i>)-BINAP	20	3.4:1	> 99:1	77	22	99
8	3c	(<i>S</i>)-BINAP	20	2.2:1	> 99:1	— ^[d]	— ^[d]	99
9	3d	(<i>R</i>)-BINAP	20	10:1	> 99:1	81	9	89
10	3d	(<i>S</i>)-BINAP	20	10:1	> 99:1	— ^[d]	— ^[d]	89
11	3e	(<i>R</i>)-Tol-BINAP	20	6.5:1	> 99:1	81	12	94
12	3e	(<i>S</i>)-Tol-BINAP	20	1:1	> 99:1	— ^[d]	— ^[d]	92

[a] All reactions were run at 25 °C with 1 mol % of the Pd dimer catalyst and 4 mol % of the ligand in THF. Isomer ratios were determined by NMR spectroscopy. [b] Determined after chromatographic separation. [c] Determined before chromatographic separation. [d] Not determined. BINAP = 2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl; Tol-BINAP = 2,2'-bis(di-*p*-tolylphosphanyl)-1,1'-binaphthyl.

Treatment of **3a** with 1 mol % of $[(\pi\text{-C}_3\text{H}_5)\text{-PdCl}]_2$, 4 mol % of bis(diphenylphosphanyl)ethane (dppe), and phthalimide with catalytic amounts of potassium phthalimide in THF at room temperature afforded, after 20 hours, a mixture of *syn*- and *anti*-1,2-diamine isomers (**7a:8a** = 97:3) and the 1,4-diamine regioisomer **9a**. We were delighted to find the ratio of regioisomers was 5.5:1 favoring the 1,2-isomer. The use of 1,1'-bis(diphenylphosphanyl)propane (dppp) or 1,1'-bis(diphenylphosphanyl)butane (dppb) as ligand led to decreased diastereoselectivity with the same level of regioselectivity

(Table 1, entries 2 and 3). The rate of these reactions was notably faster, affording complete conversion in two hours or less as compared to dppe. The ligand 1,1'-bis(diphenylphosphanyl)ferrocene (dppf) gave the best regioselectivity and the lowest diastereoselectivity for substrate **3a** (entry 4).

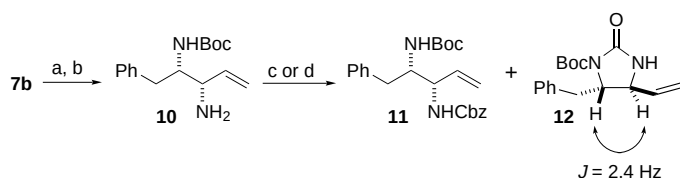
As the size of the substituent at the stereogenic center was increased, selectivities also increased. Under the standard conditions with dppp as ligand, the phenylalanine-derived substrate **3b** led to diamine products with good diastereoselectivity (97:3); however, the regioselectivity dropped significantly (entry 5). Changing from a benzyl group to an isobutyl group (**3c**) to an isopropyl group (**3d**) resulted in higher regio- and diastereoselectivity (entries 5–7). In the latter two cases, the *syn* product was the only diastereomer detectable by ¹H NMR spectroscopy. The serine-derived substrate also afforded excellent diastereoselectivity. The yield of purified product in all cases was greater than 90%.

The influence of chiral ligands in the allylic amination was explored with binaphthyl-based ligands. The results of this study are summarized in Table 2. Although the selectivities for reactions of the methyl substrate **3a** were lower with chiral ligands than with achiral ligands, an interesting trend for positive (matched) and negative influences (mismatched) was observed (entries 1 and 2). While the (*R*)-BINAP ligand was matched for regioselectivity (3:1 versus 1.5:1), the (*S*)-BINAP ligand was matched for diastereoselectivity (96:4 versus 88:12). The diastereoselectivity was controlled by the substrate, not the ligand, as the *syn* product was obtained in both

cases. With all other substrates, the regioselectivity was also matched with the *R* ligand, and selectivities in general were better than with achiral ligands. The benzyl substrate **3b** afforded the best result, with (*R*)-BINAP giving rise to excellent regioselectivity (20:1): **7b** was formed as a single diastereomer detectable by ¹H NMR spectroscopy (entry 3). (*R*)-Tol-BINAP performed equally well in the amination reaction (entry 5). Interestingly, the *S* ligand gave lower regio- and diastereoselectivity for substrate **3b**.

While a steric effect on the selectivities was also observed when the chiral ligands were utilized (compare entries 7 and 9), the benzyl derivative **3b** did not follow the same trend as in the previous experiments with achiral ligands. The role of the benzyl group in obtaining high regioselectivity is not clear. Electronic effects in the interaction of the aromatic system with the BINAP ligand may be attenuating the steric effects that are present; however, the nature of this interaction is not obvious. With oxazolidinones **3b–e**, the substrate control of diastereoselectivity was essentially complete, affording *syn*-diamine derivatives as the only detectable 1,2-products.

Elaboration of the diamine derivative **7b** was readily accomplished (Scheme 2). Protection with the *tert*-butoxycarbonyl (Boc) group followed by selective hydrazinolysis to remove the phthalimide and benzoyl groups afforded the



Scheme 2. a) Boc₂O, DMAP; b) H₂NNH₂/H₂O, MeOH, 89% (over two steps); c) CbzCl, Et₃N, 14% (**11**) and 38% (**12**); d) CbzCl, NaOH (aq.), 85% (only **11**). Cbz = benzyloxycarbonyl, DMAP = 4-dimethylaminopyridine.

monoprotected diamine **10** in high yield. Initial attempts to protect the free amine with a carbobenzoxy group by reaction with CBzCl and triethylamine resulted in a low yield of **11** accompanied by the cyclic urea **12**. The yield of **11** could be increased to 85% with no formation of **12** by utilizing aqueous NaOH as the base. The relative configuration of **7b** was established by comparison of the proton coupling constants of **12** with known cyclic ureas.^[8] The stereochemical assignment was further confirmed by independent preparation of the minor diastereomer **8b**.^[9]

We have established a new palladium-mediated process for dynamic kinetic resolution which affords a facile method for the preparation of enantio- and diastereomerically pure *syn*-1,2-diamines. Vicinal diamines have well-documented utility as chiral auxiliaries and chiral ligands.^[10] In addition, unusual diamino acids are emerging as important components of new protease inhibitors.^[11]

Experimental Section

7b (representative procedure): Oxazolidinone **3b** (345 mg, 1.123 mmol), (*R*)-BINAP (28 mg, 0.094 mmol), phthalimide (182 mg, 1.236 mmol), potassium phthalimide (21 mg, 0.112 mmol), and [(*π*-C₃H₅)PdCl]₂ (4.1 mg, 0.011 mmol) were placed in a test tube that was sealed with a

rubber septum. The tube was evacuated and flushed with nitrogen three times. THF (4 mL) was added, and the reaction was stirred at ambient temperature for 20 min (until thin-layer chromatography (TLC) indicated consumption of the starting material). The solution was filtered through a small plug of silica gel, washed with ethyl acetate/dichloromethane (1/1, 10 mL), and concentrated to afford **7b** (single diastereomer) and **9b** (*cis:trans* = 1:1) as a 20:1 mixture (452 mg, 1.101 mmol, 98% combined yield). The regioisomers were readily separated on silica gel (200–400 mesh, 20→40% (v/v) ethyl acetate in hexanes) to afford pure **7b** (414 mg, 1.008 mmol) in 90% yield and **9b** (24 mg, 0.058 mmol, *cis:trans* = 1:1) in 5% yield.

7b: White solid, m.p. 126–128 °C; [α]_D²⁵ = –55.8° (*c* = 2.18, MeOH); ¹H NMR (400 MHz, CDCl₃): δ = 8.16 (d, *J* = 8.6 Hz, 1H), 7.74–7.91 (m, 6H), 7.41–7.52 (m, 3H), 7.12–7.24 (m, 5H), 6.08 (ddd, *J* = 16.4, 10.5, 5.6 Hz, 1H), 5.0–5.22 (m, 4H), 2.96 (dd, *J* = 14.2, 6.1 Hz, 1H), 2.79 (dd, *J* = 14.2, 7.5 Hz, 1H); ¹³C NMR (100.5 MHz, CDCl₃): δ = 169.0, 166.9, 137.0, 134.6, 134.4, 132.6, 131.6, 131.5, 129.3, 128.7, 128.6, 127.1, 126.8, 123.8, 118.0, 55.7, 52.6, 38.7; IR (neat): $\tilde{\nu}$ = 3352, 1771, 1709, 1647, 1532, 1356 cm^{–1}; elemental analysis calcd: C 76.08, H 5.40, N 6.82; found: C 76.05, H 5.42, N 7.00.

Received: May 29, 1998 [Z11920IE]

German version: *Angew. Chem.* **1999**, *111*, 226–228

Keywords: allyl complexes • aminations • diamines • palladium • stereoselective synthesis

- [1] For recent reviews, see a) S. A. Godleski in *Comprehensive Organic Synthesis*, Vol. 4 (Eds.: B. M. Trost, I. Fleming, M. F. Semmelhock), Pergamon, Oxford, **1991**, p. 585; b) L. Hegedus in *Organometallics in Synthesis* (Ed.: M. Schlosser), Wiley, New York, **1994**, pp. 385–459; c) *Palladium Reagents and Catalysis* (Ed.: J. Tsuji), Wiley, New York, **1995**.
- [2] For reviews on asymmetric palladium-catalyzed allylic substitutions, see a) O. Reiser, *Angew. Chem.* **1993**, *105*, 576; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 547; b) B. M. Trost, D. L. VanVranken, *Chem. Rev.* **1996**, *96*, 395; c) C. G. Frost, J. Howarth, J. M. J. Williams, *Tetrahedron: Asymmetry* **1992**, *3*, 1089; d) G. Consiglio, R. M. Waymouth, *Chem. Rev.* **1989**, *89*, 257.
- [3] The influence of chiral nucleophiles on diastereoselectivity has been reported. For recent examples, see a) M. E. Humphries, B. P. Clark, J. M. J. Williams, *Tetrahedron: Asymmetry* **1998**, *9*, 749; b) B. M. Trost, T. L. Calkins, C. Oertelt, J. Zambrano, *Tetrahedron Lett.* **1998**, *39*, 1713.
- [4] Asymmetry in the allylic substrate adjacent to the π -allyl complex has only been investigated in the context of intramolecular cyclizations or intermolecular reactions with cyclic substrates. For recent examples, see a) J. Pohlmann, C. Sabater, H. M. R. Hoffmann, *Angew. Chem.* **1998**, *110*, 656; *Angew. Chem. Int. Ed.* **1998**, *37*, 633; b) R. G. P. Gatti, A. L. E. Larsson, J.-E. Bäckvall, *J. Chem. Soc. Perkin Trans. 1* **1997**, 577; c) V. K. Aggarwal, N. Monteiro, G. J. Tarver, R. McCague, *J. Org. Chem.* **1997**, *62*, 4665; d) B. M. Trost, *Science* **1991**, *254*, 1471; e) E. Keinan, Z. Roth, *Isr. J. Chem.* **1990**, *30*, 305; f) B. M. Trost, *Angew. Chem.* **1989**, *101*, 1199; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1173.
- [5] Recently an example of an adjacent stereocenter influencing the stereoselective formation of a π -allyl palladium complex was reported: V. Atlan, S. Racouchot, M. Rubin, C. Bremer, J. Ollivier, A. de Meijere, J. Salaün, *Tetrahedron: Asymmetry* **1998**, *9*, 1131.
- [6] G. R. Cook, P. S. Shanker, *Tetrahedron Lett.* **1998**, *39*, 3405.
- [7] a) For a recent review on dynamic kinetic resolutions, see R. Noyori, M. Tokunaga, M. Kitamura, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36; for recent examples, see b) R. Prétôt, A. Pfaltz, *Angew. Chem.* **1998**, *110*, 337; *Angew. Chem. Int. Ed.* **1998**, *37*, 323; c) M. T. Reetz, K. Schimossek, *Chimia* **1996**, *50*, 668; d) T. Hayashi, H. Iwamura, Y. Uozumi, Y. Matsumoto, F. Ozawa, *Synthesis* **1994**, 526; e) T. Hayashi, H. Iwamura, M. Naito, Y. Matsumoto, Y. Uozumi, M. Miki, K. Yanagi, *J. Am. Chem. Soc.* **1994**, *116*, 775.
- [8] A. M. Doherty, B. E. Kornberg, M. D. Reily, *J. Org. Chem.* **1993**, *58*, 795.

- [9] Partial hydrolysis of oxazoline **6b** of known configuration^[6] followed by a Mitsunobu reaction with phthalimide afforded a diamine derivative which correlated spectroscopically to the minor isomer **8b**.
- [10] a) Y. L. Bennani, S. Hanessian, *Chem. Rev.* **1997**, 97, 3161; b) H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, 94, 2483; c) A. Togni, L. M. Venanzi, *Angew. Chem.* **1994**, 106, 517; *Angew. Chem. Int. Ed. Engl.* **1994**, 33, 497.
- [11] a) D. M. Jones, J. Sueiras-Diaz, M. Szelke, B. J. Leckie, S. R. Beattie, J. Morton, S. Neidle, R. Kuroda, *J. Peptide Res.* **1997**, 50, 109; b) R. H. Bradbury, J. E. Rivett, *J. Med. Chem.* **1991**, 34, 151.

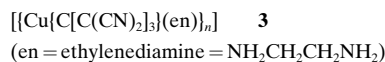
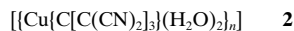
Novel Infinite Three-Dimensional Networks with Highly Conjugated Polynitrile Ligands: Syntheses, Crystal Structures, and Magnetic Properties of $[\text{Cu}\{\text{C}[\text{C}(\text{CN})_2\}_3(\text{H}_2\text{O})_2\}_n$ and $[\text{Cu}\{\text{C}[\text{C}(\text{CN})_2\}_3(\text{en})\}_n$ ($\text{en} = \text{NH}_2\text{CH}_2\text{CH}_2\text{NH}_2$)

Smaïl Triki, Jean Sala Pala,* Marc Decoster, Philippe Molinié, and Loïc Toupet

Many cyanocarbon and cyanocarbanion derivatives are distinguished by unusual physical properties that are attractive for potential applications, for example as organic metals and molecular ferromagnets.^[1] As recently noted^[2] solids that contain transition metal cations and polycyano units can be grossly divided into two categories: one in which the ligand is σ bonded to the cation, and one which contains stacked anionic organic systems, which are usually obtained from electron acceptors such as tetracyanoethylene (TCNE) and 7,7,8,8-tetracyano-*p*-quinodimethane (TCNQ). As part of our investigations into the first class we described recently the intriguing three-dimensional polymeric structure of the silver complex with the cyanocarbon ligand $[\{\text{C}(\text{CN})_2\text{C}(\text{CN})\}_2\text{N}]^-$.^[3] We were thus interested in novel polymeric solids based on transition metal cations and such highly conjugated polynitrile anions that present a plurality of cyano groups juxtaposed in such a way that they cannot all coordinate to the same metal cation.

Our objective is to examine the ability of these organic ligands to create a range of two- or three-dimensional polymeric metallacycle networks. This study will therefore contribute to the understanding of properties of molecular systems, such as binary metal/TCNX ($\text{X} = \text{E}, \text{Q}$) compounds, which present fascinating properties,^[1, 2] but for which the detailed structures are as yet unknown. We focus here on the use of the symmetrical 2-dicyanomethylene-1,1,3,3-tetracya-

nopropanediide anion $[\text{C}\{\text{C}(\text{CN})_2\}_3]^{2-}$ (**1**) with copper(II) ions; several studies of the chemical and physical properties of this anion have been reported,^[4] but as far as we know no crystal structure of solids containing a transition metal cation σ bonded to this ligand has been reported. We report here the syntheses, crystal structures, and preliminary magnetic properties of compounds **2** and **3**, which have unprecedented three-dimensional polymeric networks.



X-ray analyses^[5] of **2** and **3** show they have polymeric structures based on networks of octahedrally coordinated Cu^{II} centers linked by $[\text{C}\{\text{C}(\text{CN})_2\}_3]^{2-}$ ligands (Figures 1a and 2a). In both structures, each $[\text{C}\{\text{C}(\text{CN})_2\}_3]^{2-}$ ligand acts in a polybridging mode with four of its six nitrogen atoms bound to four different copper cations. Each metal cation in complex **2** has a pseudo-octahedral *trans*- CuO_2N_4 environment with four nitrogen atoms from four different organic ligands and two oxygen atoms from the water molecules (Figure 1a). While the bond angles around the Cu atom only deviate moderately from 90° , the Cu–N bond lengths of the perfectly planar CuN1N2N1N2 unit are significantly different (1.978(5) and 2.051(5) Å). The most important distortion of the octahedron corresponds to an elongation along the pseudo fourfold axis with a Cu–O bond length of 2.191(5) Å.

The molecular unit from which the molecular arrangement can be easily described is the 12-membered metallacycle **A** ($\text{Cu} \cdots \text{Cu}$ 7.026 Å) (Figure 1a). These metallacycles are connected to each other through Cu atoms to give the first monodimensional chain **Ch1** (**A-A-A-A**), which runs along the $[-110]$ direction (Figure 1b). Such infinite units form eclipsed stacks parallel to the $[100]$ direction and separated by 8.108 Å. Furthermore, each metallacycle **A** is laterally connected to two metallacycles **A'** by two organic ligands; this affords a second monodimensional chain **Ch2** (**A'-A'-A'-A'**) that is crystallographically equivalent to **Ch1** chain but runs orthogonally (along the $[110]$ direction). This generates the three-dimensional structure represented in Figure 1b.

In complex **3** each Cu atom presents a CuN_4N_2 distorted octahedral coordination with four nitrogen atoms from four organic ligand and two nitrogen atoms from a classical bidentate en ligand. The Cu^{II} coordination octahedron is much more severely distorted here than in complex **2**. Whilst the CuN2N5N7N8 fragment is planar within ± 0.03 Å and presents almost equivalent Cu–N bond lengths (1.977(4) and 1.980(4) Å from the polynitrile ligand; 2.008(4) and 2.013(5) Å from the en ligand), the two *trans*-CuN1 and CuN6 bonds are much longer (2.437(5) and 2.449(5) Å, respectively). The extended molecular structure of complex **3** represented in Figure 2b is very similar to that of complex **2** described above; the main difference lies in the absence of the monodimensional chain observed in **2**; the fictive chain is destroyed by the coordination of the bidentate en ligand. This leads to linear successions along the $[101]$ direction of metallacycles fairly similar to those described in complex **2**;

[*] Prof. J. Sala Pala, Dr. S. Triki, Dr. M. Decoster
UMR CNRS 6521, Université de Bretagne Occidentale
F-29285 Brest-Cedex (France)
Fax: (+33) 2-98-01-61-65
E-mail: jean.sala@univ-brest.fr
Dr. P. Molinié
UMR CNRS 6502, Université de Nantes
F-44072 Nantes-Cedex (France)
Dr. L. Toupet
UMR CNRS 6626, Université de Rennes I
F-35042 Rennes-Cedex (France)

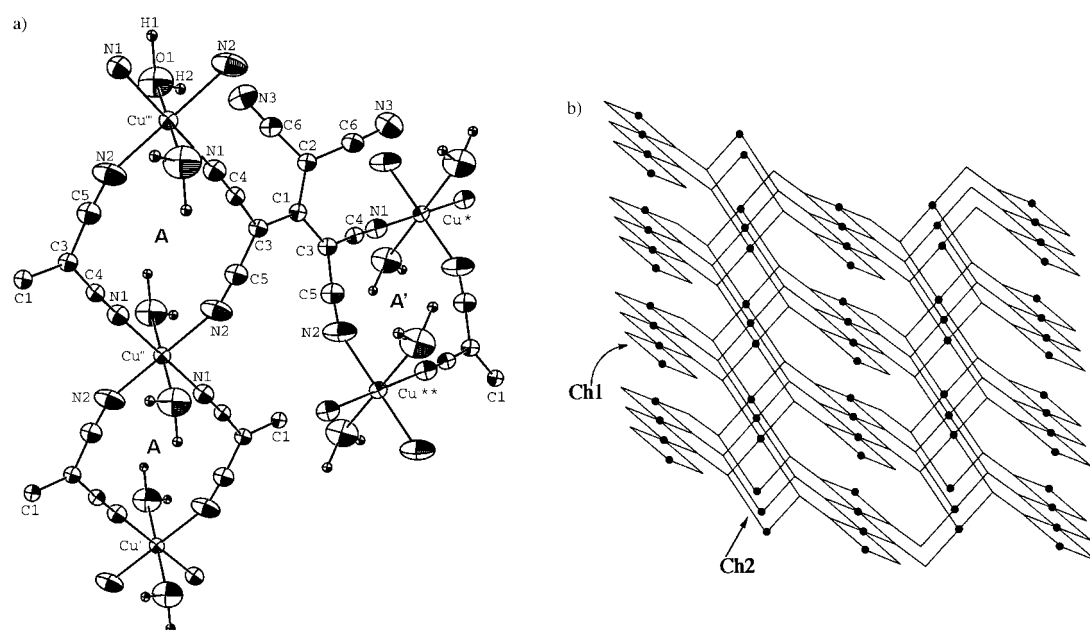


Figure 1. Complex **2**: a) Perspective view showing the polybridging $(\mu_4-\eta^4)$ ligand geometry, the copper environment, and the two metallacycles **A** and **A'**. Selected distances [Å]: C1–C2 1.41(1), C1–C3 1.424(6), C4–N1 1.136(7), C5–N2 1.140(8), C6–N3 1.138(8). Copper positions: Cu' $(-\frac{1}{2}, \frac{1}{2}, \frac{1}{2})$; Cu'' $(0, 0, \frac{1}{2})$; Cu''' $(\frac{1}{2}, -\frac{1}{2}, \frac{1}{2})$; Cu* $(-\frac{1}{2}, -\frac{1}{2}, 1)$; Cu** $(0, 0, 1)$. b) Schematic representation of the extended structure to show the two infinite monodimensional chains, **Ch1** and **Ch2**, which run orthogonally along the $[-110]$ and $[110]$ directions, respectively. The water molecules are omitted and only the C3 atom of the organic ligands is represented for clarity.

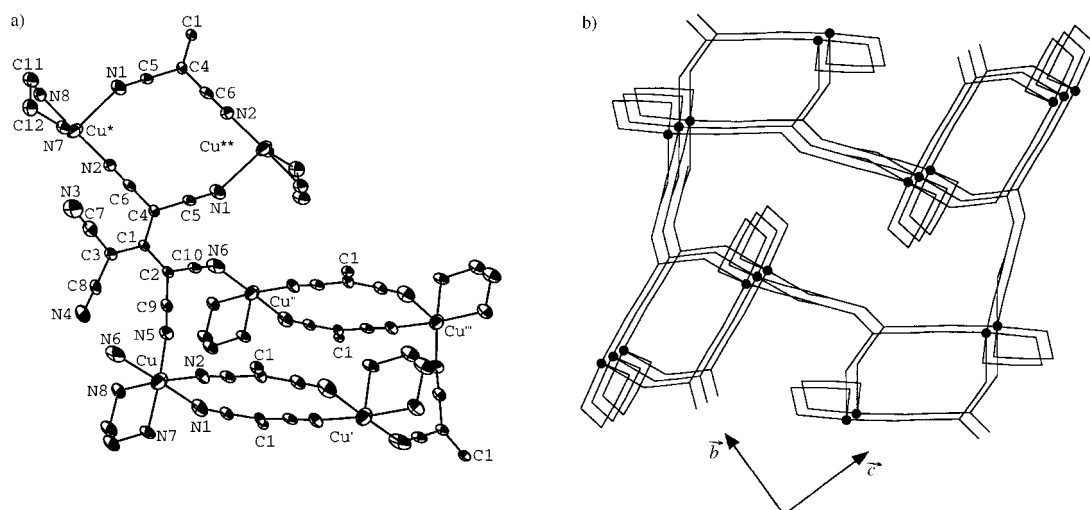


Figure 2. Complex **3**: a) Perspective view that shows the polybridging $(\mu_4-\eta^4)$ ligand geometry and the copper environment. Selected distances [Å]: C5–N1 1.144(6), C6–N2 1.146(6), C7–N3 1.146(7), C8–N4 1.158(7), C9–N5 1.142(6), C10–N6 1.148(6), C1–C2 1.424(6), C1–C3 1.412(6), C1–C4 1.419(6). Symmetry code of copper positions: Cu' $= -x, -y, -z$; Cu'' $= -1+x, y, z$; Cu''' $= -1-x, -y, -z$; Cu* $= -\frac{1}{2}+x, \frac{1}{2}-y, \frac{1}{2}+z$; Cu** $= -\frac{1}{2}-x, \frac{1}{2}+y, \frac{1}{2}-z$. b) Schematic representation of the extended structure to show the 12-membered metallacycles and the bidentate en ligand. Only the two coordinated C(CN)₂ arms of the organic ligands are represented for clarity.

the intra-metallacycle Cu...Cu distances of 7.434 Å is longer than that observed in complex **2**. As in the first complex (**2**), the metallacycles stack in an eclipsed way along the $[100]$ direction with an inter-planar distance of 7.214 Å. In both complexes, as in previously studied derivatives,^[4, 6] the $[\text{C}[\text{C}(\text{CN})_2]_3]^{2-}$ unit has a propeller-shaped geometry of approximate D_3 symmetry since the axis that passes through the central carbon atom appears as a pseudo threefold axis. The three C(CN)₂ arms are tilted out of the plane that contains the four central carbon atoms; the mean tilt angle is

slightly greater in **2** ($26.9(1)^\circ$) than in **3** ($22.7(7)^\circ$). These values are of the same order of magnitude as that observed in the calcium derivative (24°).^[6]

The magnetic behavior of complex **2** follows a Curie–Weiss law with $\theta = 0.8$ K, which indicates the presence of a weak ferromagnetic exchange interaction between copper(II) ions. This observation is confirmed by the $\chi_M T$ versus T plot, which shows an increase in $\chi_M T$ below 50 K to 0.54 emu K mol⁻¹ at 4 K (Figure 3). Complex **3** follows a Curie law with $C = 0.40$ emu K mol⁻¹ (Figure 3). The weak ferromagnetic behav-

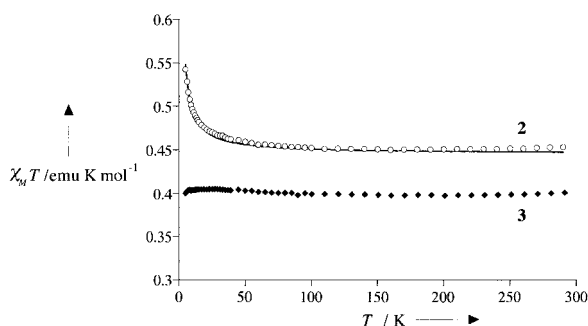


Figure 3. Variable-temperature magnetic data for **2** and **3**. The solid line represents the best fit obtained with the parameters reported in the text.

ior obtained for **2** can be explained on the basis of the structural results by intra-chain interaction between neighboring copper cations in the metallacycles. A further analysis was then restricted to the one-dimensional model; the experimental data were fitted by using the empirical expression proposed by Baker^[7, 8] for ferromagnetic one-dimensional isotropic Heisenberg chains with $S = 1/2$. The solid curve in Figure 3 represents the best fit for the experimental data obtained with $J = 0.6$ K and $g = 2.18$ (from deconvolution of the powder EPR spectra from reference [9]: $g_x = 2.095$, $g_y = 2.180$, $g_z = 2.260$).

The polycyanocarbanion $[\text{C}(\text{CN})_2]_3^{2-}$ appears to have a sophisticated bridging mode toward copper cations but structural comparison with uncoordinated $[\text{C}(\text{CN})_2]_3^{2-}$ anions shows that the coordination does not greatly affect the geometry of this moiety. Extension of this study to other polynitrile anions and to other magnetic metal cations is in progress to obtain a more unified view of the bonding/electronic structure relationship in these highly conjugated systems. This might lead to a rationale of their properties of interest: electronic delocalization within the ligand, conduction, and magnetism.

Experimental Section

2: A hot solution of $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ (340 mg, 2 mmol) in water (50 mL) was added to a hot solution of $\text{K}_2[\text{C}(\text{CN})_2]_3 \cdot \text{H}_2\text{O}$ ^[10] (600 mg, 2 mmol). The mixture was refluxed for about 30 minutes and then maintained at room temperature. The black prismatic crystals were filtered, and recrystallized from hot water. Yield approximately 80%. IR (KBr): $\tilde{\nu} = 2240$ (sh), 2220 (s), 2200 (s), 2180 cm^{-1} (sh).

3: A solution of ethylenediamine (60 mg, 1 mmol) and $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ (170 mg, 1 mmol) in water (40 mL) was added to a solution of monohydrated potassium salt of $\text{K}_2[\text{C}(\text{CN})_2]_3 \cdot \text{H}_2\text{O}$ (300 mg, 1 mmol) in water (40 mL). The green product was filtered, and recrystallized from hot water. Yield approximately 90%. IR (KBr): $\tilde{\nu} = 3420$ (w), 3350 (w), 3270 (sh), 3250 (s), 3150 (w), 2240 (sh), 2220 (s), 2200 (s), 2180 cm^{-1} (sh).

Physical measurements: IR spectra were recorded in the range 4000–200 cm^{-1} on a Perkin–Elmer 1430 spectrometer with samples prepared as KBr pellets. The magnetic susceptibility measurements were performed at 0.1 T between 5 and 300 K with a SQUID magnetometer “MPMS-5” from Quantum Design Corporation. The X-band ESR spectra were performed on a Bruker ER 200D-SRC spectrometer in the range 100–360 K. The molar susceptibility was corrected from the sample holder and diamagnetic contributions of all atoms.

Received: June 10, 1998 [Z119741E]

German version: *Angew. Chem.* **1999**, *111*, 155–158

Keywords: copper • magnetic properties • metallacycles • polymers • structure elucidation

- [1] See for example J. S. Miller, A. J. Epstein, W. M. Reiff, *Chem. Rev.* **1988**, *88*, 201–220; J. S. Miller, A. J. Epstein, W. M. Reiff, *Science* **1988**, *240*, 40–47; J. M. Manriquez, T. Y. Gordon, R. S. McLean, *Science* **1991**, *252*, 1415–1417; R. Kato, H. Kobayashi, A. Kobayashi, *J. Am. Chem. Soc.* **1989**, *111*, 5224–5232.
- [2] K. R. Dunbar, *Angew. Chem.* **1996**, *108*, 1769–1771; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1659–1661.
- [3] M. Decoster, J. E. Guerschais, Y. Le Mest, J. Sala Pala, S. Triki, L. Toupet, *Polyhedron* **1996**, *15*, 195–202.
- [4] D. A. Long, W. O. George, *Spectrochim. Acta* **1963**, *19*, 1717–1729; S. Sakanoue, N. Yasuoka, M. Kakudo, N. Kasai, *Bull. Chem. Soc. Jpn.* **1971**, *44*, 1–8; K. Nakamura, Y. Kai, N. Yasuoka, N. Kasai, *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3300–3303; H. Yamochi, T. Tsuji, G. Saito, T. Suzuki, *Synth. Met.* **1988**, *27*, A479–A484; M. D. Ward, J. C. Calabrese, *Organometallics* **1989**, *8*, 593–602; J. S. Miller, D. A. Dixon, J. C. Calabrese, C. Vazquez, P. J. Krusic, M. D. Ward, E. Wasserman, R. L. Harlow, *J. Am. Chem. Soc.* **1990**, *112*, 381–398; H. Yamochi, T. Nakamura, G. Saito, T. Kikuchi, S. Sato, K. Nozawa, M. Kinoshita, T. Sugano, F. Wudl, *Synth. Met.* **1991**, *42*, 1741–1744.
- [5] Crystal structure analysis: **2**: Black prisms: $0.05 \times 0.07 \times 0.08 \text{ mm}^3$, Enraf–Nonius CAD4 diffractometer, with graphite monochromatized $\text{MoK}\alpha$ radiation ($\lambda(\text{MoK}\alpha) = 0.71073 \text{ \AA}$), $M_r = 303.7 \text{ g mol}^{-1}$, monoclinic, space group $C2/c$, $a = 8.108(3)$, $b = 11.477(4)$, $c = 12.466(6) \text{ \AA}$, $\beta = 94.15(3)^\circ$, $V = 1157 \text{ \AA}^3$, $Z = 4$, $\rho_{\text{calcd}} = 1.74 \text{ g cm}^{-3}$, $\mu = 18.97 \text{ cm}^{-1}$, $F(000) = 604$, $T = 294 \text{ K}$, $R_{\text{int}} = 0.014$, 769 observed reflections ($I > 3\sigma(I)$). **3**: Green prisms: $0.15 \times 0.15 \times 0.20 \text{ mm}^3$, $M_r = 327.8 \text{ g mol}^{-1}$, monoclinic, space group $P2_1/n$, $a = 7.214(5)$, $b = 13.418(2)$, $c = 14.154(4) \text{ \AA}$, $\beta = 94.00(4)^\circ$, $V = 1367 \text{ \AA}^3$, $Z = 4$, $\rho_{\text{calcd}} = 1.593 \text{ g cm}^{-3}$, $\mu = 16.06 \text{ cm}^{-1}$, $F(000) = 660$, $T = 294 \text{ K}$, $R_{\text{int}} = 0.033$, 1253 observed reflections ($I > 3\sigma(I)$). The structures were solved by direct methods and successive Fourier difference syntheses, and were refined by weighted anisotropic full-matrix least-squares methods. The hydrogen atoms of both structures were observed in the Fourier difference syntheses and refined isotropically to give $R = 0.039$, $R_w = 0.045$, $\Delta\rho_{\text{max}} = 0.84 \text{ e \AA}^{-3}$, and $\text{GOF} = 1.129$ for **2**; $R = 0.028$, $R_w = 0.031$, $\Delta\rho_{\text{max}} = 0.278 \text{ e \AA}^{-3}$, and $\text{GOF} = 1.29$ for **3**. Further details on the crystal structure investigations may be obtained from the Fachinformationszentrum Karlsruhe, D-76344 Eggenstein-Leopoldshafen, Germany (fax: (+49) 7247-808-666, on quoting the depository numbers CSD-408624 and -408625).
- [6] D. A. Bekoe, P. K. Gantzel, K. N. Trueblood, *Acta Crystallogr.* **1967**, *22*, 657–665.
- [7] G. A. Baker, G. S. Rushbrooke, H. E. Gilbert, *Phys. Rev.* **1964**, *135*, A1272–A1277.
- [8] To the best of our knowledge no analytical expression has yet been proposed for a uniform ferromagnetic copper(II) chain. The fit of the experimental data for **2** was performed with the expression given in Equation (1) with $N = 1 + 5.7979916x + 16.902653x^2 + 29.376885x^3 + 29.832959x^4 + 14.036918x^5$, $D = 1 + 2.7979916x + 7.0086780x^2 + 8.6538644x^3 + 4.5743114x^4$ and $x = J/kT$

$$\chi_M = \frac{N g^2 \beta^2}{4 k T} \left[\frac{N}{D} \right]^{2/3} \quad (1)$$
- [9] T. P. Nguyen, M. Giffard, P. Molinié, *J. Chem. Phys.* **1994**, *100*, 8340–8346.
- [10] W. J. Middleton, US 2766246, Oct. 9, 1956 [*Chem. Abstr.* **1957**, *51*, P11372]; W. J. Middleton, E. L. Little, D. D. Coffman, V. A. Engelhardt, *J. Am. Chem. Soc.* **1958**, *80*, 2795–2806; in these references the reaction of $\text{Ba}[\text{C}(\text{CN})_2]_3 \cdot 6\text{H}_2\text{O}$ with hydrated $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ affords $\text{Cu}[\text{C}(\text{CN})_2]_3 \cdot 0.5\text{H}_2\text{O}$; we found it more convenient to prepare complex **2** by the reaction of $\text{K}_2[\text{C}(\text{CN})_2]_3$ with hydrated CuCl_2 in water since 1) isolation and purification of the $[\text{C}(\text{CN})_2]_3^{2-}$ anion is easier as the potassium salt than as the barium salt and 2) problems that arise from the possible co-precipitation of the copper complex and barium sulfate are avoided.

Dynamics of Ligated Water Molecules in Oxo-Centered Trinuclear Carboxylates: An Incoherent Inelastic Neutron Scattering Study**

John A. Stride, Upali A. Jayasooriya,* and Jürgen Eckert

Oxo-centered trinuclear transition metal complexes of the general formula $[M_3O(L)_6(L_t)_3]$, where L a bidentate bridging ligand and L_t a terminal ligand, have provided an important template to study a range of fundamental chemical and physical phenomena.^[1] Of particular interest is the mechanism of electron transfer for the mixed-valent members of this family of complexes. Much effort has therefore been spent on obtaining a detailed understanding of the potential energy surfaces of these materials by measuring the low-lying magnetic and vibrational transitions. The most difficult part of assigning the vibrations of these compounds up to now has been for those vibrations of water molecules, when present as terminal ligands L_t and as water of crystallization. Here we illustrate a technique which consists of inelastic neutron scattering spectroscopy of isotopically diluted species which substantially simplifies the assignments of vibrations of such strongly hydrogen bonded systems.

The first compound of this family of compounds to be discovered was the chromium acetate complex $[Cr_3O(CH_3CO_2)_6(H_2O)_3]Cl \cdot 5H_2O$ (CRAC), and it is the most studied member.^[2–7] A fairly detailed crystal structure of CRAC was reported by Chang and Jeffreys,^[8] where CRAC was shown to crystallize in the orthorhombic space group $P2_12_12$ with four molecules per unit cell in sites of C_1 symmetry. This determination was of low accuracy and was unable to discriminate effectively between the noncoordinated water molecules and the counterions, and therefore arrived at the conclusion that these units were extensively and mutually disordered. A recent accurate redetermination of this crystal structure^[9] clearly shows the chloride ions to be well-defined with no disorder between the chloride ions and the water molecules. Phase transitions were also reported at temperatures of 211.4 to 215.5 K, and established by anomalies in specific heat^[10] and by NMR data. X-ray diffraction showed the low-temperature space group to be $P2_12_12_1$, with the unit cell doubled in size along the *c* axis. Although the low-

temperature structure has still not been determined completely, it is known to contain equal numbers of two crystallographically nonequivalent sets of trimer complex ions. Sorai et al.^[10] found that the low-temperature specific heat could best be interpreted by assuming that one of the two sets of compounds is significantly more distorted than the other. Ferguson and Güdel^[11] came to the same conclusion from electronic spectroscopy, and Jayasooriya et al.^[12] from neutron magnetic scattering.

Mixed-valent and mixed-metal compounds of this class have the general formula of $A_2^{III}B^{II}O$ for the central triangular unit; the unique ion B may be of the same or of a different metallic element to A. The vibrational and magnetic studies of these compounds highlight the marked distortion of the central oxygen bonding geometry.^[13, 14] No structural data on the aquo complexes are available, possibly because they are normally difficult to crystallize.

The vibrational spectra of the trinuclear carboxylate complexes have been the subject of a number of studies.^[13, 15, 16] The complexity of the molecules results in a large number of normal modes, and the detailed assignment by the semi-empirical force-field approach is nontrivial.^[17] However isotopic substitution studies have resulted in many useful assignments. Of particular interest is the recognition of the vibrations of the central oxygen atom and the use of these vibrations to probe the electron transfer properties of the mixed-valent compounds.

Despite these compounds being extensively characterized by a host of techniques, attempts at determining the strength of the bonding interaction between a metal ion and a terminal water ligand have never been successful. Previous efforts to assign the metal–water stretching modes in the vibrational spectra of these compounds have been thwarted by the interference of strong overlapping carboxylate bands, both in the IR and Raman spectra.^[15]

This problem can be overcome by the use of incoherent inelastic neutron scattering spectroscopy (IINS). The intensities of energy transfers in this technique are determined by the neutron scattering cross-section of the atoms and their amplitudes of motion in the normal mode of relevance to the transition. Hydrogen, being the lightest element and also possessing the largest incoherent scattering cross-section (almost one order of magnitude larger than that for any other element), therefore dominates IIN spectra of hydrogen-containing molecules. Further, deuterium-substitution studies are of particular interest. In addition to the frequency shifts to lower energies as observable with IR and Raman spectroscopies, one would also notice an almost complete disappearance of the mode of interest, due to the very low incoherent scattering cross-section of deuterium, thus potentially leading to reliable assignments. Previous attempts at measuring the metal–water vibrational modes by IINS were unsuccessful due to the presence of a strong hydrogen-bonding network of both coordinated and uncoordinated water molecules in the solid.^[15] A broad envelope of features between about 400 and 800 cm^{-1} , due to the hydrogen-bonding network, was observed, and no detailed assignments of the ligated water vibrations were possible. Here we report an experiment where an isotope dilution technique was used to decouple the O–H

[*] Dr. U. A. Jayasooriya, Dr. J. A. Stride⁽⁺⁾

School of Chemical Sciences
University of East Anglia
Norwich NR4 7TJ (UK)
Fax: (+44) 1603-259-396
E-mail: u.jayasooriya@uea.ac.uk

Dr. J. Eckert
LANSCE, Los Alamos National Laboratory, New Mexico (USA)

[+] Present address:

BENSCE, Hahn-Meitner-Institut, D-14109 Berlin (Germany)

[**] Funding of this research by the SERC, UK, and a studentship to J.A.S. are gratefully acknowledged. This work has benefited from the use of facilities at the Los Alamos neutron scattering center, and neutron user facility funded as such by the DOE/Office of Basic Energy Science. We also thank Dr Roderick Cannon for useful discussions.

vibrations from the broad features of the network of hydrogen bonds, which includes the water of crystallization. By using an almost fully deuterated sample (ca. 5% H) the broad envelopes of bands found in the fully protonated compounds were almost totally removed from the IIN spectra, thus giving better access to $\nu(\text{M}-\text{OH}_2)$ vibrations.

The IIN spectra were collected at about 20 K on the Filter Difference Spectrometer (FDS)^[18] at LANSCE (Los Alamos, New Mexico, USA) with a usable spectral window of approximately about 75–3500 cm^{-1} . The spectra were gathered using the Be filter detector, and a numerical method of Mezei and Vorderwisch^[19, 20] was applied to filter out the long time of flight tails in the spectra and thus increase the spectral resolution. However, the reliable spectral range in the reported spectra is only that below about 1500 cm^{-1} due to insufficient counting statistics.

Samples were prepared by literature methods^[15] and characterized by elemental analysis and IR spectroscopy. The synthetic methods used for the mixed-metal compounds studied here have been shown to produce stoichiometric compounds.^[15, 21]

An important complication to be expected with IINS in comparison to IR and Raman spectroscopies is the possible observation of overtone and combination bands and the accompaniment of external modes with each internal mode, which is dependent on the strength of such a coupling. Therefore, we provide an assignment based on a comparison of the spectra of all the isotopomers, which is facilitated by a spectral deconvolution.

The IIN spectrum of $[\text{Cr}_3\text{O}(\text{CH}_3\text{CO}_2)_6(\text{H}_2\text{O})_3]\text{Cl} \cdot 5\text{H}_2\text{O}$ (CRACHH) is shown in Figure 1a. The spectrum is dominated by a broad feature stretching from about 400 to 800 cm^{-1} , which is due to the water molecules of crystallization. Standing out above this broad envelop are at least four features. Other strong features are found around 1000 cm^{-1} , and there are a number of peaks below 400 cm^{-1} . The partially deuterated sample $[\text{Cr}_3\text{O}(\text{CD}_3\text{CO}_2)_6(\text{H}_2\text{O})_3]\text{Cl} \cdot 5\text{H}_2\text{O}$ (CRACDH) gave a spectrum in which the latter features were of much lower intensity (Figure 2), indicating the acetate group motion in these normal modes. What are left behind are the very intense broad features due to the vibrations involving the water molecules. By using D_2O and CH_3COOH in the synthesis, the compound $[\text{Cr}_3\text{O}(\text{CH}_3\text{CO}_2)_6(\text{D}_2\text{O})_3]\text{Cl} \cdot 5\text{D}_2\text{O}$ (CRACHD) was produced, whose IIN spectrum (Figure 1b) shows the absence of the broad peaks due to H_2O vibrations which dominated the other spectra. This spectrum clearly shows the acetate modes as relatively sharp features at about 272, 342, 395, 550, 595, 710, 800, and 1010 cm^{-1} , which correspond well to some of the peaks in the fine structure observed on top of the broad water feature in the spectrum of CRACHH (Figure 1a).

The IIN spectrum of the fully deuterated compound, $[\text{Cr}_3\text{O}(\text{CD}_3\text{CO}_2)_6(\text{D}_2\text{O})_3]\text{Cl} \cdot 5\text{D}_2\text{O}$ (CRACDD) is shown in Figure 1d. The most intense peak is a relatively sharp feature around 500 cm^{-1} . Other peaks are observed at about 380, 621, 700, 860, and 970 cm^{-1} , and are clearly due to the vibrations of the residual protons (see below). The present investigation will be confined mainly to the modes of ligated water, as these were the least understood prior to this study. The IIN

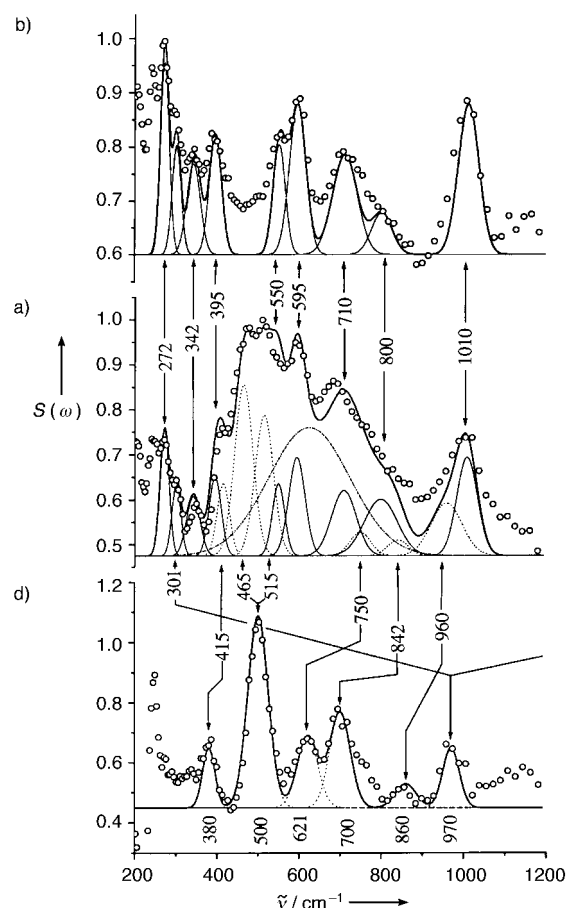


Figure 1. IIN spectra of b) CRACHD, a) CRACHH, and d) CRACDD taken at 20 K showing the shift in peak positions with isotopic substitution. The spectra are numbered in this unconventional manner to correspond with the spectra in Figures 4 and 5; that is, the degree of deuteration for the isotopic variants is similar in each series a, b, and d. Spectral deconvolutions are provided to clarify the assignments proposed. $S(\omega)$ = inelastic scattering intensity (in arbitrary units), $\tilde{\nu}$ = neutron energy loss.

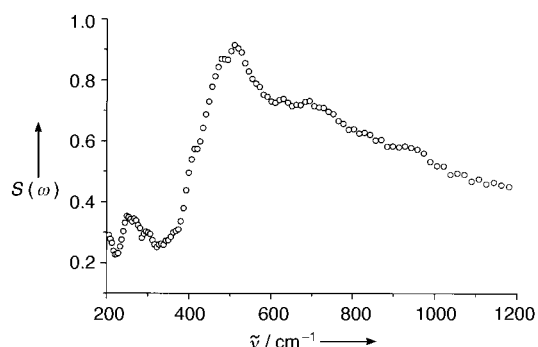


Figure 2. IIN spectrum of CRACDH taken at 20 K. As far as the degree of deuteration of the complex is concerned, the spectrum corresponds to Figures 4c and 5c. $S(\omega)$ = inelastic scattering intensity (in arbitrary units), $\tilde{\nu}$ = neutron energy loss.

spectroscopy is applied here to a sample containing a few HOD molecules in a D_2O host matrix. Therefore, the vibrational interactions across the hydrogen-bonded water network are sufficiently disrupted to justify treatment of the H vibrations of the HOD molecules as localized modes. The spectra obtained from such isotopically dilute samples can be understood by considering the evolution of the normal modes

of vibration (Figure 3) from their respective internal modes. Let us consider the ligated water first. The normal modes $\nu_s(\text{HOH})$ and $\nu_{as}(\text{HOH})$ are in-phase and out-of-phase combinations of the OH stretching internal modes. In HOD, this mixing will mainly disappear, leaving an OH stretching mode with a frequency almost half-way between those of

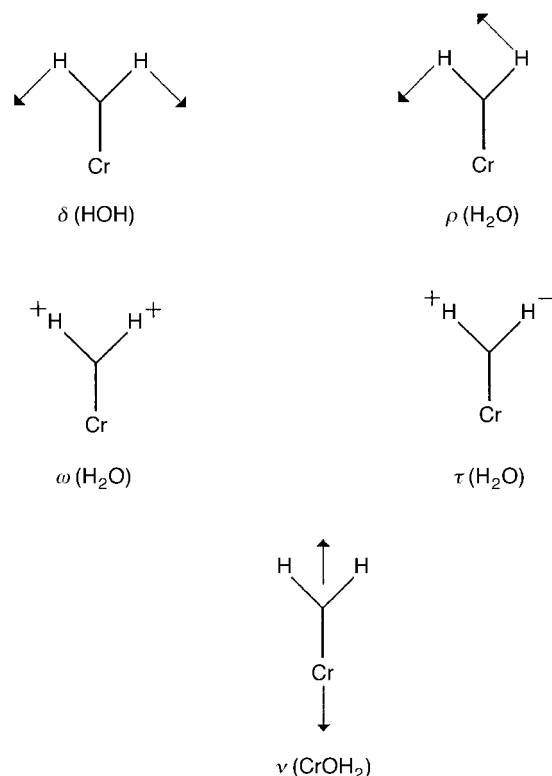


Figure 3. Vibrational normal modes of coordinated water in CRAC expected to appear above about 250 cm^{-1} .

$\nu_s(\text{HOH})$ and $\nu_{as}(\text{HOH})$, and an O–D stretching mode at almost $1/\sqrt{2}$ times the isolated O–H frequency. These modes appear at higher frequencies and will not be discussed further. A similar line of argument could be used to predict the outcome for the pair of in-plane OH deformations, the scissoring mode $\delta(\text{HOH})$ and the rocking mode $\rho(\text{HOH})$, as well as the pair of out-of-plane deformations, the wag $\omega(\text{HOH})$ and the twist $\tau(\text{HOH})$. In summary, the effect of going from HOH to HOD will broadly bring about the replacement of each of these pairs of frequencies for HOH by a band approximately half-way between them, due to the now isolated O–H bond normal mode, and another band shifted by approximately $1/\sqrt{2}$ in frequency from it due to the O–D bond vibration. However, the latter mode will be of very reduced intensity in the IIN spectrum due to the very low incoherent neutron scattering cross-section of deuterium when compared to hydrogen. The remaining internal mode of ligated water, the Cr–OH₂ stretching mode, will be expected to show behavior different to the above, with a relatively small shift corresponding to the change in relative ligand mass in going from 18 (H₂O) to 19 (HOD). Similarly, the librational modes of the water molecules of crystallization

will show small shifts due to the change in moment of inertia with this isotopic modification.^[22, 23]

The ¹H contamination of the D₂O molecules of the CRACDD and CRACHD samples was around 5%. Considering the respective neutron scattering cross-sections for H and D, a vibrational mode of the H–O bonds in these compounds will be expected to be about four to eight times the intensity of the corresponding mode of the D–O bonds. The statistical probability of finding any H₂O units in this matrix is negligible, and so the vibrations of the HOD features are expected to dominate the IIN spectrum of this material, in spite of the high isotopic dilution of ¹H. The deuterium content of the acetate methyl groups is better than 99.9% for CRACDH and CRACDD.

The spectra of CRACHH, CRACHD, and CRACDD are collected together in Figure 1, in order to highlight the relative changes in intensity associated with the isotopic substitutions and thus to clarify the assignment proposed. Let us consider the spectrum of CRACHH first (Figure 1a). The acetate vibrations are assigned by comparison with the spectrum of CRACHD (Figure 1b), that is, to bands at about 1010, 800, 710, 595, 550, 395, 342, and 272 cm^{-1} . The assignment of the vibrations of the water molecules is best started using the spectrum of CRACDD (Figure 1d). The dominant features in this spectrum are expected to be due to the hydrogenic modes in residual HOD species. The vibrational modes of HOD expected to appear in the region of 300–1200 cm^{-1} in this spectrum are the following: The in-plane and out-of-plane motions of the O–H bond in HOD molecules ligated to the Cr atoms, the Cr–OHD stretching mode, and the three librations R, W, and T of the HOD molecules of crystallization. The X-ray diffraction study of Anson et al.^[9] does not provide accurate information on the detailed structure of the water molecules. However, it is unlikely that the different molecules of water of crystallization are distinguishable within the resolution of this inelastic neutron scattering experiment. Therefore six vibrational modes are expected in this frequency range, as was experimentally observed (Figure 1d).

The in-plane deformation of the O–H bond in ligated HOD, which is predicted to be half-way in frequency between the modes $\delta_{\text{sym}}(\text{HOH})$ (ca. 1650 cm^{-1}) and $\rho(\text{HOH})$ of the ligated water molecule, is assignable to the highest wavenumber band in this region at about 970 cm^{-1} . This in turn provides the assignment of a wavenumber of approximately 290 cm^{-1} in the spectrum of CRACHH to the rocking mode of the HOH ligand. Band overlap makes this assignment difficult, and a wavenumber of 301 cm^{-1} is therefore tentatively assigned to this mode. Of the bands left to be assigned in the spectrum of Figure 1d, that at about 500 cm^{-1} is clearly of greatest intensity. An inelastic neutron scattering study of a single crystal of barium chlorate hydrate by Thaper et al.^[23] shows the intensities of the R, W, and T modes of a water molecule of crystallization to be of similar intensity, suggesting similar amplitudes of proton motion for all of these modes. Further, the Cr–OHD stretching mode is expected to show a band of low intensity because the hydrogen motion in this mode is determined by the motion of the oxygen atom on which the hydrogen rides. This therefore provides the assignment of the relatively strong band at about 500 cm^{-1} to the

out-of-plane deformation of the O–H bond in the Cr–OHD unit. It is very reasonable to expect a large amplitude of hydrogen motion for such a mode, and hence the large IINS intensity. Following our previous reasoning, the bands at around 465 and 515 cm^{−1} in the spectrum of CRACHH (Figure 1a) are assigned to the twist and wag of the HOH ligand. Of the remaining four bands, the lowest frequency band at approximately 380 cm^{−1} is most reasonably assigned to the Cr–OHD stretching mode. The possible mixing of this mode with the OH out-of-plane deformation mode, which gives the strongest peak in this spectral region, provides a mechanism for intensity enhancement. The effect of such mixing is more evident in the case of the mixed-valent compounds to be discussed later. The corresponding assignment in the spectrum of CRACHH (Figure 1a) is to the shoulder at about 415 cm^{−1}. The remaining three bands around 621, 700, and 860 cm^{−1} in the spectrum of CRACDD (Figure 1d) are assigned to the librations of water molecules of crystallization. With the present data it is not possible to make a more detailed assignment of these librations. The isotopic shifts expected for these modes are reported by Tayal et al.^[22] Assuming an HOH angle of 116° and an assignment of the HOD vibrations R, T, and W to the peaks at about 621, 700, and 860 cm^{−1}, respectively, in the spectrum of CRACDD leads to the prediction of peaks at about 750, 842, and 960 cm^{−1} for the corresponding librations of the HOH molecules of crystallization in CRACHH. There is substantial neutron scattering intensity corresponding to the latter frequencies in the spectrum of CRACHH. The IINS intensity envelope due to hydrogen-bonding effects and the translational modes of the water molecules of crystallization are empirically modeled by an intense broad band at approximately 625 cm^{−1} in the spectrum of CRACHH. The final assignments are summarized in Tables 1 and 2.

Spectra of the isotopic variants of two mixed-metal complexes [Fe^{III}Mn^{II}O(CH₃CO₂)₆(H₂O)₃]·3H₂O (FeMn) and

Table 1. Vibrational assignments in the region between 240 and 1100 cm^{−1} in the spectra of CRAC, FeMn, and FeCo containing either H₂O (a; Figures 1a, 4a, and 5a) or D₂O (b; Figures 1b, 4b, and 5b) as ligands and molecules of crystallization. The estimated relative intensities are given in parenthesis.

CRAC		FeMn		FeCo		Assignment
(a)	(b)	(a)	(b)	(a)	(b)	
1010 (25)	1010 (25)	1007 (24)	1007 (24)	1005 (25)	1005 (25)	acetate
960 (20)						W (H ₂ O of cryst.)
842 (4)						T (H ₂ O of cryst.)
800 (23)	800 (7)	790 (10)		790 (10)		acetate
750 (6)						R (H ₂ O of cryst.)
710 (20)	710 (12)	715 (30)	715 (30)	715 (28)	715 (28)	acetate
625 (130)		650 (55)		660 (60)		H-bonded water background
595 (20)	595 (15)	590 (27)	590 (26)	595 (27)	595 (27)	acetate
550 (11)	550 (7)	507 (18)	507 (23)	510 (22)	510 (22)	acetate
515 (32)		515 (12)		515 (12)		τ/ω (H ₂ O–Cr)
465 (39)		465 (9)		465 (9)		ω/τ (H ₂ O–Cr)
415 (11)		420 (5)		420 (5)		ν (Cr–OH ₂)
395 (12)	395 (7)	390 (10)	390 (11)	390 (12)	400 (12)	acetate
342 (10)	345 (6)	335 (7)	335 (8)	320 (9)	330 (9)	acetate
301 (8)	298 (6)	297 (5)	297 (6)	295 (5)	295 (5)	overlapping ρ (H ₂ O–Cr) and acetate
272 (14)	272 (8)	272 (8)	272 (10)	272 (10)	272 (10)	acetate

Table 2. Vibrational assignments in the region between 240 and 1100 cm^{−1} in the spectra of fully deuterated CRAC (CRACDD, Figure 1d), FeMn (Figure 4d), and FeCo (Figure 5d). The estimated relative intensities are given in parenthesis.

CRACDD	FeMn	FeCo	Assignment
970 (10)	970 (10)	990 (9)	ligand O–H in-plane deformation
860 (5)	815 (5)	805 (28)	W (HDO of cryst.)
700 (20)	700 (20)	690 (16)	T (HDO of cryst.)
621 (15)	615 (12)	628 (18)	R (HDO of cryst.)
500 (40)	500 (45)	500 (65)	ligand O–H out-of-plane-deformation
380 (7.5)			ν (Cr–OHD)
	325 (4)	328 (11)	ν (Fe–OHD)
	385 (7.5)		ν (Mn–OHD)
		395 (11)	ν (Co–OHD)

[Fe^{III}Co^{II}O(CH₃CO₂)₆(H₂O)₃]·3H₂O (FeCo) are shown in Figures 4 and 5. These sets of spectra are similar to each other, as would be expected from their molecular formulae. A comparison of these spectra with those of CRAC (Figures 1 and 2) shows the largest differences to be between the spectral regions showing vibrations of the water of crystallization. This

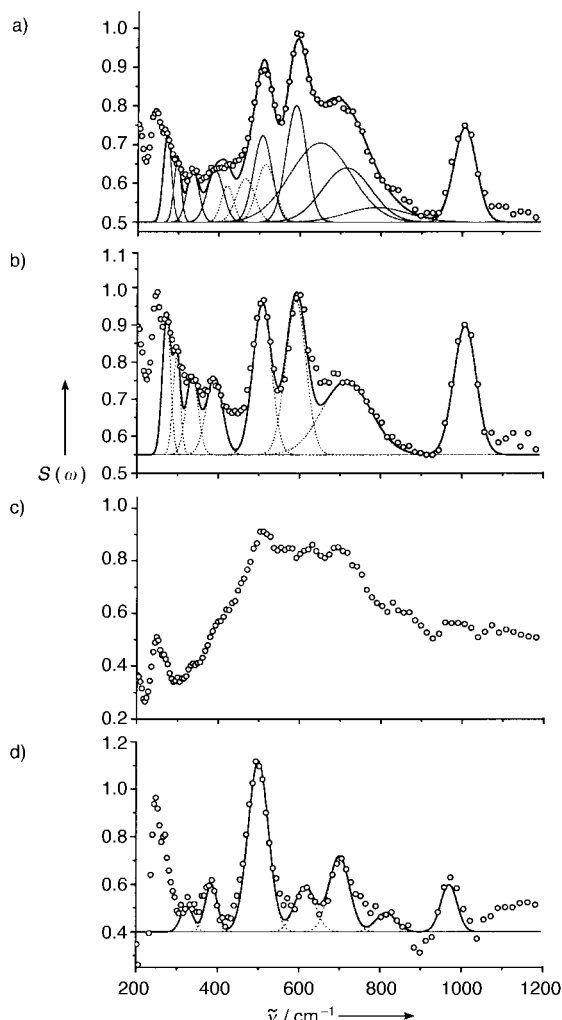


Figure 4. IIN spectra of a) [Fe₂MnO(CH₃CO₂)₆(H₂O)₃]·3H₂O, b) [Fe₂MnO(CH₃CO₂)₆(D₂O)₃]·3D₂O, c) [Fe₂MnO(CD₃CO₂)₆(H₂O)₃]·3H₂O, and d) [Fe₂MnO(CD₃CO₂)₆(D₂O)₃]·3D₂O taken at 20 K. S(ω)=inelastic scattering intensity (in arbitrary units), $\tilde{\nu}$ =neutron energy loss.

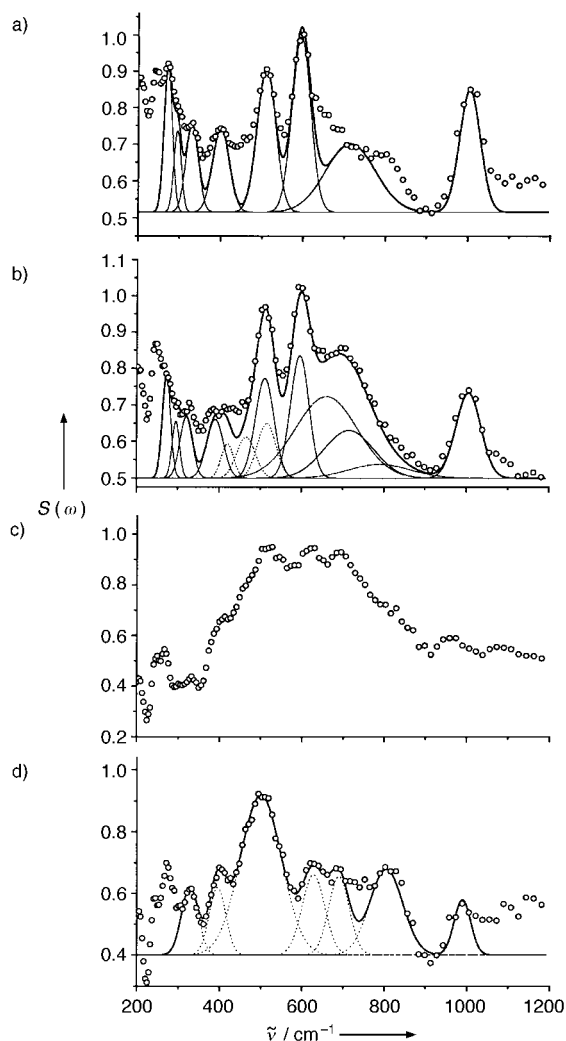


Figure 5. IIN spectra of a) $[\text{Fe}_2\text{CoO}(\text{CH}_3\text{CO}_2)_6(\text{H}_2\text{O})_3] \cdot 3\text{H}_2\text{O}$, b) $[\text{Fe}_2\text{CoO}(\text{CH}_3\text{CO}_2)_6(\text{D}_2\text{O})_3] \cdot 3\text{D}_2\text{O}$, c) $[\text{Fe}_2\text{CoO}(\text{CD}_3\text{CO}_2)_6(\text{H}_2\text{O})_3] \cdot 3\text{H}_2\text{O}$, and d) $[\text{Fe}_2\text{CoO}(\text{CD}_3\text{CO}_2)_6(\text{D}_2\text{O})_3] \cdot 3\text{D}_2\text{O}$ taken at 20 K. $S(\omega)$ = inelastic scattering intensity (in arbitrary units), $\tilde{\nu}$ = neutron energy loss.

observation is compatible with the different numbers of molecules of water of crystallization found in these compounds, five per formula unit in CRAC compared to three in the mixed-metal compounds.

In Figures 4 and 5, a comparison between spectra a and b provides assignments of bands to acetate modes. These bands are at similar frequencies for both FeMn and FeCo (Table 1). The most significant difference between these bands and those assigned to acetate modes in CRAC is the shift of the band at about 550 cm^{-1} for CRAC to approximately 507 and 510 cm^{-1} for FeMn and FeCo, respectively. This is the spectral region where $\text{M}-\text{O}_{\text{acetate}}$ stretching modes are expected to appear, and is therefore likely to be due to the two types of metal–acetate bonds present in these compounds.

Just as was found with the CRAC spectra, the vibrations of the water molecules are best assigned using the fully deuterated compounds. The IIN spectra of the fully deuterated variants of FeMn and FeCo are shown in Figures 4d and 5d, where the prominent features are those due to the

approximately 5% residual protons in the samples. The spectrum of fully deuterated FeMn (Figure 4d) is directly assigned by comparison with that of CRACDD (Figure 1d). The only significant difference between these spectra is the metal–water stretch, which for the former appears to be split into two peaks of unequal intensity at about 385 and 325 cm^{-1} . The band at 385 cm^{-1} , which is more intense, suggests an assignment to the stretching modes of the two $\text{Fe}-\text{OH}_2$ bonds, while the weaker band at 325 cm^{-1} corresponds to the stretching of the single $\text{Mn}-\text{OH}_2$ bond. However, the possibility exists that the cause of increased intensity of the former band may not be the multiplicity of bonds, but intensity stealing from the strong out-of-plane deformation at about 500 cm^{-1} through mode mixing.

In spite of poor statistics, the spectrum of fully deuterated FeCo (Figure 5d) could also be assigned by comparison with the spectrum of CRACDD (Figure 1d), the difference being the possible assignment of the $\text{Fe}-\text{OH}_2$ stretch to that band at 395 cm^{-1} and the $\text{Co}-\text{OH}_2$ stretching mode to 328 cm^{-1} . Here again a mixing of internal modes with the out-of-plane deformation may be the cause of the stronger intensity of the former band.

The above assignments for the metal–water stretching modes in FeMn and FeCo give the same frequency of about 325 cm^{-1} for the $\text{Mn}-\text{OH}_2$ and $\text{Co}-\text{OH}_2$ vibrations (that is, involving two different metals), while two different frequencies are assigned to the $\text{Fe}-\text{OH}_2$ vibration in the two compounds. If intensity stealing through mode mixing is assumed, the more reasonable assignment of a single frequency for the $\text{Fe}-\text{OH}_2$ bond stretching modes for the two compounds become acceptable. Further, the latter assignment is consistent with the studies reported for the metal–water stretching modes of a number of hexaquo complexes.^[24] The value for $\nu(\text{Co}^{\text{II}}-\text{OH}_2)$ is greater than that for $\nu(\text{Mn}^{\text{II}}-\text{OH}_2)$ and $\nu(\text{Fe}^{\text{II}}-\text{OH}_2)$; this reflects the relative bond strengths for the transition metals in octahedral environments and may be a consequence of the ligand field stabilization energy, analogous to that found by Jenkins and Lewis^[25] in their study of Ni^{II} , Fe^{II} , and Zn^{II} hexaquo ions in simple salts. It is interesting to note the substantially larger widths of the peaks in the spectra of FeCo, for example the out-of-plane OH deformation at about 500 cm^{-1} in the spectrum in Figure 5d, compared to the spectra of the other two compounds. This may be another indication of a larger difference in bond strengths between $\text{Fe}-\text{OH}_2$ and $\text{Co}-\text{OH}_2$ than between $\text{Fe}-\text{OH}_2$ and $\text{Mn}-\text{OH}_2$. Poor spectral statistics prevent any firm conclusions.

Here we have illustrated the use of an isotopic dilution technique in inelastic neutron scattering spectroscopy to simplify assignment of a complicated hydrogen-bonded molecular system. The trimeric complexes studied were found to have lower metal–water stretching frequencies and bond strengths (even after taking the involvement of the metal ions in the vibrational modes into consideration) than their respective monomeric complexes. This parallels the observations of longer bond lengths for $\text{Mn}-\text{OH}_2$ bonds in the trimeric complexes compared to the monomeric analogues, thus confirming the *trans* effect of the central oxygen atom. The method of assignment reported here should be of general

applicability to vibrational assignments of systems where there is extensive hydrogen bonding.

Received: April 14, 1998

Revised version: September 17, 1998 [Z11717IE]

German version: *Angew. Chem.* **1999**, *111*, 172–177

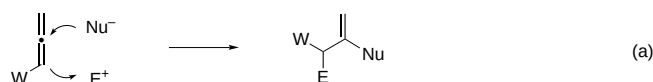
Keywords: aquo complexes • hydrogen bonds • isotope effects • neutron scattering • vibrational spectroscopy

- [1] R. D. Cannon, R. P. White, *Prog. Inorg. Chem.* **1988**, *36*, 195.
- [2] A. Werner, *Ber. Dtsch. Chem. Ges.* **1908**, *41*, 3447.
- [3] R. F. Weinland, *Chem. Ztg.* **1908**, *32*, 812.
- [4] R. F. Weinland, *Ber. Dtsch. Chem. Ges.* **1908**, *41*, 3236.
- [5] L. A. Welo, *Phys. Rev.* **1928**, *32*, 320.
- [6] L. A. Welo, *Philos. Mag.* **1928**, *6*, 481.
- [7] B. N. Figgis, G. B. Robertson, *Nature* **1965**, *205*, 694.
- [8] S. C. Chang, G. A. Jeffreys, *Acta Crystallogr. Sect. B* **1970**, *26*, 673.
- [9] C. E. Anson, J. P. Bourke, R. D. Cannon, U. A. Jayasooriya, M. Molinier, A. K. Powell, *Inorg. Chem.* **1997**, *36*, 1265.
- [10] M. Sorai, M. Tachiki, H. Suga, S. Seki, *J. Phys. Soc. Jpn.* **1971**, *30*, 750.
- [11] J. Ferguson, H. U. Güdel, *Chem. Phys. Lett.* **1972**, *17*, 547.
- [12] U. A. Jayasooriya, R. D. Cannon, R. P. White, J. A. Stride, R. Grinter, G. J. Kearley, *J. Chem. Phys.* **1993**, *98*, 9303.
- [13] L. Meesuk, U. A. Jayasooriya, R. D. Cannon, *J. Am. Chem. Soc.* **1987**, *109*, 2009; R. P. White, J. A. Stride, S. K. Bollen, N. C. Sa-Ard, G. J. Kearley, U. A. Jayasooriya, R. D. Cannon, *J. Am. Chem. Soc.* **1993**, *115*, 7778.
- [14] A. B. Blake, A. Yavari, W. E. Hatfield, C. N. Sethulekshmi, *J. Chem. Soc. Dalton Trans.* **1985**, 2509.
- [15] R. P. White, N. C. Sa-Ard, S. K. Bollen, R. D. Cannon, U. A. Jayasooriya, S. T. Robertson, U. Steigenberger, J. Tomkinson, *Spectrochim. Acta A* **1990**, *46*, 673.
- [16] M. K. Johnson, D. B. Powell, R. D. Cannon, *Spectrochim. Acta A* **1981**, *37*, 995.
- [17] A. Triantafillou, Ph.D. Thesis, University of East Anglia, **1993**.
- [18] A. D. Taylor, E. J. Wood, J. A. Goldstone, J. Eckert, *J. Nucl. Instr. Meth.* **1984**, *221*, 408.
- [19] F. Mezei, P. Vorderwisch, *Physica B* **1989**, *156*, 678.
- [20] D. S. Sivia, P. Vorderwisch, R. N. Silver, *J. Nucl. Instr. Meth. A* **1990**, *290*, 492.
- [21] J. B. Vincent, *Inorg. Chem.* **1994**, *33*, 5604.
- [22] V. P. Tayal, B. K. Srivastava, P. Khandelwal, *Appl. Spec. Rev.* **1980**, *16*, 43.
- [23] C. L. Thaper, B. A. Dasannacharya, A. Sequeira, P. K. Iyengar, *Solid State Commun.* **1970**, *8*, 497.
- [24] S. P. Best, J. K. Beattie, R. S. Armstrong, *J. Chem. Soc. Dalton Trans.* **1992**, 299.
- [25] T. E. Jenkins, J. Lewis, *Spectrochim. Acta A* **1981**, *37*, 47.

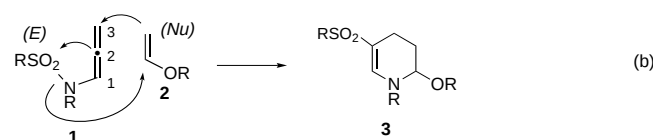
Efficient Entry to Tetrahydropyridines: Addition of Enol Ethers to Allenesulfonamides Involving a Novel 1,3-Sulfonyl Shift**

Yoshikazu Horino, Masanari Kimura, Yoshinori Wakamiya, Toshiya Okajima, and Yoshinao Tamaru*

Owing to the ground-state strain and the allylic stabilization of the resultant carbanion, allenes bearing electron-withdrawing substituents (W) are highly reactive toward nucleophilic addition at the central sp carbon atom [Eq. (a)].^[1] Nucleophilic addition to the terminal sp² carbon atom of



allenes, on the other hand, takes place with difficulty^[2] owing to the lack of a substituent to stabilize the developing anionic charge on the central carbon atom.^[3] Here we report that enol ethers **2** assist *N*-allenesulfonamides **1** to undergo a novel 1,3-shift of the sulfonyl group and eventually furnish tetrahydropyridines **3** in good to excellent yields [Eq. (b)]. The reaction



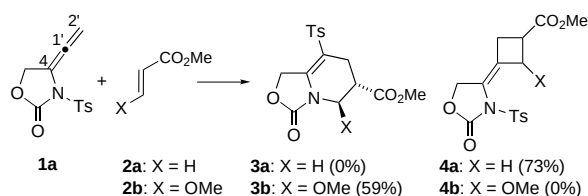
is triggered most likely by nucleophilic attack of **2** at the terminal carbon atom of the allenic C2–C3 double bond, activated through space by the nearby sulfonyl group ($\pi_{C-C}^* - \sigma_{N-S}^*$ interaction).

As reported recently from our laboratories,^[4] 4-vinylidene-1,3-oxazolidin-2-one **1a**, when heated with electron-deficient or conjugated alkenes (e.g., styrene, 1,3-butadienes) at 70–100 °C, undergoes a facile [2+2] cycloaddition reaction via a concerted [$\pi_{2s} + \pi_{2s} + \pi_{2s}$] Hückel transition state to provide cyclobutane derivatives **4** in excellent yields. For example, **1a** reacts with methyl acrylate (**2a**) to provide **4a**, which can be isolated in 73 % yield (Scheme 1). We were pleasantly surprised to find that methyl β -methoxyacrylate ((*E*)-**2b**) reacted in a completely different manner than **2a** (Scheme 1): When a mixture of **1a** (0.5 mmol) and (*E*)-**2b** (20 mmol) was

[*] Prof. Dr. Y. Tamaru, Y. Horino, Dr. M. Kimura, Y. Wakamiya
Department of Applied Chemistry, Faculty of Engineering
Nagasaki University
1-14 Bunkyo-machi, Nagasaki 852–8521 (Japan)
Fax: (+81)958-47-9008
E-mail: tamaru@net.nagasaki-u.ac.jp

Dr. T. Okajima
Department of Chemistry, Faculty of Culture and Education
Saga University
1 Honjo, Saga 840–8502 (Japan)

[**] We thank Mr. Y. Ohhama (NMR facility) and Mrs. J. Nagaoka (X-ray facility) for their splendid technical assistance. Financial support by the Ministry of Education, Science, Sports and Culture, Japanese Government, is gratefully acknowledged.



Scheme 1. Reaction of **1a** with electron-deficient alkenes.

heated at 70 °C for 23 h under N₂, **1a** underwent a unique skeletal rearrangement to selectively provide bicyclic tetrahydropyridine derivative *trans*-**3b** (isolated in 59% yield).

The expected [2+2] addition product **4b** was not detected at all. The formation of *trans*-**3b** apparently indicates that N–SO₂ bond cleavage and migration of the sulfonyl group from nitrogen to carbon C1' (1,3-sulfonyl shift) take place.

As summarized in Table 1, enol ethers, encompassing acyclic (**2b–d**, **2i**) and cyclic aldehyde enol ethers (**2e–g**) as well as acyclic (**2k**) and cyclic keto-enol ethers (**2h**, **2j**), all behaved in a similar manner and provided **3** exclusively. All the products were characterized by IR, ¹H NMR (400 MHz), and ¹³C NMR spectroscopy (100 MHz), high-resolution mass spectrometry, and/or elemental analyses. The structures of **3f** and **3j** were determined unequivocally by X-ray crystallographic analyses, which revealed that the alkoxy substituents at C2 occupy a quasi-axial position of the tetrahydropyridine ring in order to avoid steric and electrostatic repulsions with the carbonyl oxygen atom of the oxazolidinone unit).

Among the results in Table 1, the following points deserve comment: First, it is known that furan tends to act as a 4π component and undergo Diels–Alder reaction with allenes.^[5] However, in the present reaction it served as a dienol ether. It reacted presumably as a nucleophile at the 2-position to give **3g** selectively (run 5), a regioisomer that differs from the other compounds **3** with respect to the position of the oxygen atom on the tetrahydropyridine ring (C3–O for **3g**, otherwise C2–O). Second, despite severe repulsion^[6] between the oxazolidinone carbonyl moiety and C2 substituents, geminally C2-disubstituted **3** (e.g., **3h**, **3k**, and **3l**) are obtained in excellent yields. Finally, the reaction is highly stereoselective, providing the products with retention of configuration of the starting alkenes: (*Z*)-**2d** (*E:Z* = 1:17)

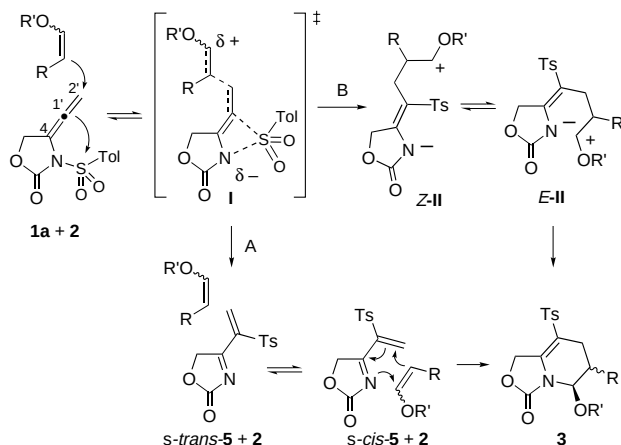
gave *cis*-**3d** exclusively (run 2). The C2–OMe_{ax}/C3–phenyl_{eq} structure was deduced from the 400-MHz ¹H NMR spectrum (³*J*(C2H_{eq}–C3H_{ax}) = 2.2, ³*J*(C3H_{ax}–C4H_{ax}) = 13.4, ³*J*(C3H_{ax}–C4H_{eq}) = 3.7 Hz), and large increments in the area intensity of C2H_{eq} (14%) and C4H_{eq} (11%) by irradiation of the signal for C3H_{ax}.^[7] Similarly, (*E*)-**2b** (*E:Z* > 99:1) gave rise to *trans*-**3b** (Scheme 1) and *trans*-**3j** (run 8 and Figure 1) exclusively. In contrast, lower stereoselectivity was observed for the reaction of (*Z*)-**2i** (*E:Z* = 1:10, run 7), where a mixture of *cis*-**3i** and *trans*-**3i** in a ratio of 4:1 resulted. No epimerization at C2 of **3i** was observed during purification of the reaction mixture by column chromatography over silica gel.

Table 1. Novel addition–cyclization reaction of 4-vinylidene-1,3-oxazolidin-2-ones **1a–c** and enol ethers **2**.

Run	1	2	Reaction conditions ^[a] T[°C]/t[h]	Products (yield[%]) ^[b]
1			100/8	 3c (92)
2	1a		80/24	 3d (75)
3	1a		100/24	 3e , n = 1 (75)
4	1a		80/12	 3f , n = 2 (89)
5	1a		80/48	 3g (60)
6	1a		70/6	 3h (88) ^[c]
7			80/33	 3i (90) ^[d]
8	1b		70/15	 3j (72)
9	1b		80/85	 3k (66)
10			70/45	 3l (74)

[a] A mixture of **1** (0.5 mmol) and **2** [**2b** (10 mmol, *E:Z* > 99:1), **2c** (50 mmol in 1 mL of dioxane), **2d** (10 mmol, *E:Z* = 1:17; recovered **2d**: *E:Z* = 1.3:1), **2e** (40 mmol in 1 mL of dioxane), **2f** (10 mmol in 1 mL of dioxane), **2g** (10 mmol in 1 mL of dioxane in a sealed tube), **2h** (5 mmol in 0.4 mL of dioxane), **2i** (5 mmol, *E:Z* = 1:10, in 1 mL of dioxane; recovered **2i**: *E:Z* = 1:2), **2j** (10 mmol), or **2k** (40 mmol in 0.5 mL of dioxane)] was heated under N₂. [b] Yields of isolated spectroscopically homogeneous **3**. [c] Combined yield of isolated **3h** (59%) and its desilylated OH derivative (29%). [d] *trans*-**3i**:*cis*-**3i** = 1:4.

Two reasonable pathways accounting for the selective formation of **3** are shown in Scheme 2.^[8] In the transition state **I**, electron density is pushed into the sulfonamide moiety through the C1'–C2' double bond, and the N–S bond is weakened. At the same time, electron density is drawn away from the carbamate by conjugation through the C4–C1' double bond. This allows the 1,3-sulfonyl shift^[9, 10] and hence the isomerization of **1a** to *s-trans*-1-azabutadiene **5** (path A). Compound **2** is itself restored by *E*–*Z* isomerization. Indeed, **2d** and **2i** isomerized during the reaction with **1**, and were



Scheme 2. Two possible pathways for the selective formation of tetrahydropyridines **3**.

recovered as mixtures with *E*:*Z* ratios of 1.3:1 (run 2) and 1:2 (run 7), respectively. In the absence of **1**, no isomerization of **2d** and **2i** was observed. In the absence of **2**, **1b** remained intact and was recovered quantitatively (in dioxane at 80 °C, 24 h). In contrast, **1a** readily isomerized even at 60 °C and gave 3-tosyl-4-vinyl-4-oxazolin-2-one (by a 1,3-H shift) in varying yields (15–50 %, in dioxane, 10 h)^[11] and decomposed completely at 80 °C (24 h) to give an intractable tarry mixture. Thus, **1** promotes the isomerization of **2**, and **2** stimulates the 1,3-sulfonyl shift of **1** (to give intermediate **5**^[12]) rather than the 1,3-H shift. The thus-formed **5** is expected to be highly reactive toward hetero-Diels–Alder reaction with enol ethers^[13] and would readily react with (*Z*)-**2** (rather than with (*E*)-**2**, probably owing to steric reasons) to furnish *cis*-2,3-disubstituted **3**^[14] either exclusively (run 2) or selectively (run 7).

Path B might contribute to some extent, especially for the reactions with enol ethers (e.g., ketone enol ethers and furans^[15]) that are highly electron-donating and able to stabilize zwitterionic species of type **II**.

In conclusion, we have demonstrated that allenessulfonamides **1a–c** undergo a novel cyclization reaction with a variety of enol ethers **2** to provide bi-, tri-, and tetracyclic tetrahydropyridines **3** in good to excellent yields. The reaction most likely proceeds by an enol ether promoted isomerization of **1** to **5**, which then undergoes hetero-Diels–Alder reaction with **2** (see Scheme 2). Reactions of **1** with electron-rich alkenes (enamines, allylsilanes, allylstannanes) and soft Lewis bases (phosphanes, low-valent transition metals) are under intensive study.

Experimental Section

Run 8 from Table 1: A mixture of **1b** (0.5 mmol, *R*_f = 0.57, hexane/ethyl acetate 2/1 v/v)^[14] and **2b** (10 mmol, *E*:*Z* > 99:1, Aldrich) was heated at 70 °C for 15 h under N₂, after which excess **2b** was removed in vacuo. The resultant sticky mixture was purified by column chromatography over silica gel (hexane/ethyl acetate 4/1 v/v) and then recrystallized from CH₂Cl₂/hexane to give **3j** in 72 % yield: *R*_f = 0.63 (hexane/ethyl acetate 2/1 v/v); m.p. 193.0–193.5 °C; IR (KBr): $\tilde{\nu}$ = 1800 (s), 1720 (s), 1640 cm^{−1} (s); ¹H NMR (400 MHz, CDCl₃, TMS): δ = 1.94 (s, 3H), 1.99 (s, 3H), 2.45 (s, 3H), 2.52 (dd, *J* = 5.7, 16.5 Hz, 1H, C4H_{ax}), 2.66 (ddd, *J* = 1.1, 2.2, 16.5 Hz, 1H, C4H_{eq}), 2.99 (dt, *J* = 5.7, 2.2 Hz, 1H, C3H_{eq}), 3.42 (s, 3H), 3.45 (s, 3H), 5.39 (dd, *J* = 1.1, 2.2 Hz, 1H, C2H_{eq}), 7.35 (d, *J* = 8.4 Hz, 2H), 7.75 (d, *J* = 8.4 Hz, 2H); correct elemental analysis (C,H,N,S).

Received: June 18, 1998

Revised version: August 24, 1998 [Z12008 IE]

German version: *Angew. Chem.* **1999**, *111*, 123–126

Keywords: allenes • cyclizations • oxazolidinones • 1,3-sulfonyl shift • tetrahydropyridines

- [1] W. T. Brady in *The Chemistry of Ketenes, Allenes and Related Compounds, Part I* (Ed.: S. Patai), Wiley, Chichester, **1980**, pp. 302–303; M. E. Jung in *Comprehensive Organic Synthesis, Vol. 4* (Eds.: B. M. Trost, I. Fleming, M. F. Semmelhack), Pergamon, Oxford, **1991**, pp. 53–58; B. B. Snider, E. Ron, *J. Org. Chem.* **1986**, *51*, 3643–3652; K. Hayakawa, M. Takewaki, I. Fujimoto, K. Kanematsu, *J. Org. Chem.* **1986**, *51*, 5100–5105; K. Banert, C. Toth, *Angew. Chem.* **1995**, *107*, 1776–1778; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1627–1629; G. Zhu, Z. Chen, Q. Jiang, D. Xiao, P. Chao, X. Zhang, *J. Am. Chem. Soc.* **1997**, *119*, 3836–3837; J.-T. Chen, R.-H. Hsu, A.-J. Chen, *J. Am. Chem. Soc.* **1998**, *120*, 3243–3244.
- [2] S. Araki, H. Usui, M. Kato, Y. Butsugan, *J. Am. Chem. Soc.* **1996**, *118*, 4699–4700; H. Urabe, T. Takeda, D. Hideura, F. Sato, *J. Am. Chem. Soc.* **1997**, *119*, 11 295–11 305.
- [3] For the electrophilic addition to the central carbon of allenes followed by nucleophilic addition to the terminal carbon atom, see W. Smadja, *Chem. Rev.* **1983**, *83*, 263–320; D. J. Pasto, *Tetrahedron* **1984**, *40*, 2805–2827; B. M. Trost, V. J. Gerusz, *J. Am. Chem. Soc.* **1995**, *117*, 5156–5157; K. Okuro, H. Alper, *J. Org. Chem.* **1997**, *62*, 1566–1567; A. S. K. Hashmi, T. L. Ruppert, T. Kröfel, J. W. Bats, *J. Org. Chem.* **1997**, *62*, 7295–7304; M. Al-Masum, Y. Yamamoto, *J. Am. Chem. Soc.* **1998**, *120*, 3809–3810.
- [4] M. Kimura, Y. Wakamiya, Y. Horino, Y. Tamaru, *Tetrahedron Lett.* **1997**, *38*, 3963–3966; M. Kimura, Y. Horino, Y. Wakamiya, T. Okajima, Y. Tamaru, *J. Am. Chem. Soc.* **1997**, *119*, 10 869–10 870.
- [5] K. Kanematsu, I. Kinoyama, *J. Chem. Soc. Chem. Commun.* **1992**, 735–736; A. Padwa, M. Meske, S. S. Murphree, S. H. Watterson, Z. Ni, *J. Am. Chem. Soc.* **1995**, *117*, 7071–7080; R. L. Elliott, N. H. Nicholson, F. E. Peaker, A. K. Takle, C. M. Richardson, J. W. Tyler, J. White, M. J. Pearson, D. S. Eggleston, R. C. Haltiwanger, *J. Org. Chem.* **1997**, *62*, 4998–5016.
- [6] R. W. Hoffmann, *Angew. Chem.* **1992**, *104*, 1147–1157; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1124–1134.
- [7] Similar coupling patterns and nOes were observed for *cis*-**3f** and *cis*-**3i**. See the Experimental Section for the characteristic coupling patterns that *trans*-**3** displays.
- [8] A radical mechanism involving homolytic N–S bond cleavage may be ruled out based on the fact that methanesulfonamide **1c** (run 10, Table 1) shows reaction features similar to those of toluenesulfonamides **1a**, **b**: B. Quiclet-Sire, S. Z. Zard, *J. Am. Chem. Soc.* **1996**, *118*, 1209–1210; S. Kim, J.-Y. Yoon, *J. Am. Chem. Soc.* **1997**, *119*, 5982–5983, and references therein.
- [9] A similar four-membered cyclic transition state has been proposed for the 1,3-shift of chlorine in chlorocarbonylketene: J. Finnerty, J.

- Andraos, Y. Yamamoto, M. W. Wong, C. Wentrup, *J. Am. Chem. Soc.* **1998**, *120*, 1701–1704.; see also H. Bibas, M. W. Wong, C. Wentrup, *Chem. Eur. J.* **1997**, *3*, 237–248, and references therein.
- [10] To the best of our knowledge, this is the first example for the displacement of nitrogen from sulfonamide by a nucleophilic carbon atom. For displacement of nitrogen by a nucleophilic oxygen atom, see D. L. Comins, A. Dehghani, *Tetrahedron Lett.* **1992**, *33*, 6299–6302; Z. Xu, X. Lu, *Tetrahedron Lett.* **1997**, *38*, 3461–3464. The sulfonamide N–SO₂ bond is so strong that it must be cleaved under rather harsh conditions: D. J. Ramon, G. Guillena, D. Seebach, *Helv. Chim. Acta* **1996**, *79*, 875–894. Other modifications of N–SO₂ bond cleavage: S. M. Weinreb, D. M. Demko, T. A. Lessen, *Tetrahedron Lett.* **1986**, *27*, 2099–2102; T. Fukuyama, C.-K. Jow, M. Cheung, *Tetrahedron Lett.* **1995**, *36*, 6373–6374; C. Huart, L. Ghosez, *Angew. Chem.* **1997**, *109*, 627–629; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 634–636.
- [11] Thiophene failed to react with **1a** to furnish **3**. Instead, 4-vinyl-4-oxazolin-2-one (product of a 1,3-hydrogen shift) was provided in 88 % yield (**1a**/thiophene = 1/100 mol/mol, 80 °C, 11 h).
- [12] No trace of **5** was detected when run 8 of Table 1 was monitored by ¹H NMR spectroscopy and HPLC. There were only very small amounts of impurities; 20, 29, and 51 % conversions after 2, 4, and 9 h at 70 °C, respectively.
- [13] D. L. Boger in *Comprehensive Organic Synthesis*, Vol. 5 (Eds.: B. M. Trost, I. Fleming, L. A. Paquette), Pergamon, Oxford, **1991**, pp. 470–507; L. F. Tietze, G. Ketschau, *Top. Curr. Chem.* **1997**, *189*, 1–120.
- [14] T. Bando, H. Harayama, Y. Fukazawa, M. Shiro, K. Fugami, S. Tanaka, Y. Tamaru, *J. Org. Chem.* **1994**, *59*, 1465–1474.
- [15] We thank the referee who pointed out the possibility that **3g** might be formed by the Diels–Alder addition of furan (4π) and the vinyl group of **5** and subsequent 1-aza-Cope rearrangement.

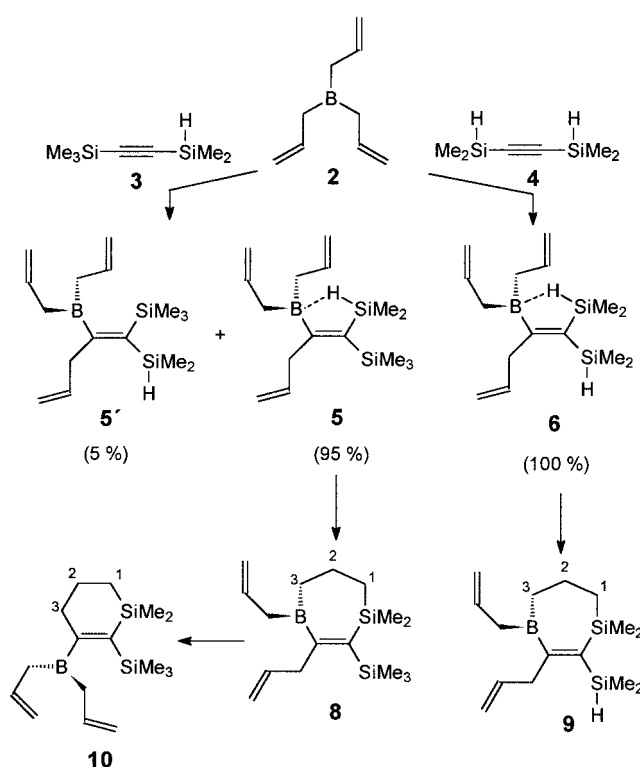
The First Si–H–B Bridge: Combination of 1,1-Organoboration and Hydrosilylation**

Bernd Wrackmeyer,* Oleg L. Tok, and Yuri N. Bubnov

The enormous synthetic potential of organoboron^[1] and organosilicon compounds^[2] is well documented. However, the combination of reactive species from both areas has not been studied extensively.^[3–6] 1-Alkynylsilanes are known to react with diorganoboron hydrides by 1,2-hydroboration^[4] and also by cleavage of the Si–C_{sp} bond, depending on the reaction conditions.^[5] 1,1-Organoboration of 1-alkynylsilanes takes

place if they are treated with triorganoboranes such as triethylborane (**1**) and heated up to 100 °C.^[3c, 6] Boron compounds containing silyl groups with Si–H functionalities have received even less attention so far.

We have now observed that the reaction conditions for 1,1-organoboration can be much milder (room temperature, 0.5–1 h) if triallylborane (**2**), instead of **1**, and 1-alkynylsilanes with Si–H bonds, for example dimethylsilyl(trimethylsilyl)ethyne (**3**) and bis(dimethylsilyl)ethyne (**4**), are used. In the reaction products, the mutual positions of silyl and boryl groups at the C=C bond rouses in particular two questions: 1) Does the presence of the neighboring three-coordinate boron atom induce Si–H bond activation, or in other words, is there a Si–H–B bridge? 2) Are there further reactions between the Si–H functionalities and the C=C double bonds of the allyl groups? The answer to both questions is yes, as shown in Scheme 1.



Scheme 1. Reactions of triallylborane **2** with the 1-alkynylsilanes **3** and **4**.

The spectroscopic data of all compounds discussed here are summarized in Table 1. The presence of a Si–H–B bridge in **5** and **6** is reflected unequivocally by ¹H, ¹¹B, and ²⁹Si NMR and IR spectroscopic data. The ¹H NMR signal of the hydrogen atom in the bridge is broad, it is shifted to high field by about 1.5 ppm with respect to resonances for “normal” Si–H groups (for example, the second Me₂SiH group in **6**), and it is shifted further to high field at lower temperature (–30 °C; Δδ = –0.3). The ¹¹B nuclear shielding is increased by about 20 (**6**) or 30 ppm (**5**) when compared with derivatives without a Si–H–B bridge. The ²⁹Si nuclear shielding is decreased by 34 (**6**; Figure 1) or 44 ppm (**5**) already at room temperature, and it decreases further at lower temperature (**5** (–30 °C): δ²⁹Si =

[*] Prof. Dr. B. Wrackmeyer
Laboratorium für Anorganische Chemie der Universität
D-95440 Bayreuth (Germany)
Fax: (+49) 921-552157
E-mail: b.wrack@uni-bayreuth.de
Dr. O. L. Tok, Prof. Dr. Yu. N. Bubnov
INEOS, Russian Academy of Sciences, Moscow (Russia)

[**] Support of this work by the Volkswagen-Stiftung, the Deutsche Forschungsgemeinschaft, and the Fonds der Chemischen Industrie is gratefully acknowledged.

Table 1. ^1H (500 MHz, CDCl_3 , $J(\text{H,H})/\text{Hz}$), ^{13}C (125.8 MHz, CDCl_3 , $J(\text{Si,C})/\text{Hz}$), ^{29}Si (99.4 MHz, CDCl_3 , $J(\text{Si,Si})/\text{Hz}$), and ^{11}B NMR data (160.5 MHz, CDCl_3) for compounds **5**–**10**.

5: $\delta(^1\text{H}) = 0.17$ (s, 9H, Me_3Si , 6.5[Si]), 0.32 (d, 6H, Me_2Si , 6.5[Si], 3.0), 1.82 (dd, 2H, CH_2B , 15.3, 6.8), 2.00 (dd, 2H, CH_2B , 15.3, 8.4), 2.76 (br, 1H, SiH, 129.1[Si]), 3.03 (dt, 2H, CH_2 , 7.2, 1.3(t)), 4.82 (ddt, 2H, *cis*- CH_2 , 10.2, 2.3, 1.2), 4.84 (ddt, 2H, *trans*- CH_2 , 16.9, 2.3, 1.5), 5.01 (ddt, 1H, *cis*- CH_2 , 9.9, 1.8, 1.2), 5.04 (ddd, 1H, *trans*- CH_2 , 17.1, 3.4, 1.7), 5.74 (ddt 1H, $-\text{CH}=\text{}$, 17.1, 9.9, 7.2), 5.91 (dddd, 2H, $-\text{CH}=\text{}$, 16.9, 10.2, 8.4, 6.8); $\delta(^{13}\text{C}) = -0.4$ (Me_2Si , 49.3), 1.4 (Me_3Si , 50.8), 32.6 (br, CH_2B), 42.9 (CH_2), 112.3 ($\text{CH}_2=\text{B}$), 116.1 ($\text{CH}_2=\text{}$), 136.1 ($-\text{CH}=\text{}$), 136.7 (56.5), 138.9 ($-\text{CH}=\text{B}$), 186.5 (br, $=\text{C}-\text{B}$); $\delta(^{29}\text{Si}) = -12.1$ (Me_3Si , 10.0), 12.6 (Me_2HSi , 10.0, $^2\Delta^{10/11}\text{B}(^{29}\text{Si}) = -46$ ppb); $\delta(^{11}\text{B}) = 51.6$

6: $\delta(^1\text{H}) = 0.22$ (d, 6H, Me_2Si , 6.7[Si], 3.8), 0.27 (d, 6H, Me_2Si , 6.4[Si], 3.4), 2.05 (br, 4H, CH_2B), 3.08 (dt, 2H, CH_2 , 7.2, 1.4 (t)), 3.18 (br, 1H, *cis*-SiH, 146.0[Si]), 4.37 (sept, 1H, *trans*-SiH, 186.0[Si], 3.8), 4.85 (ddd, 2H, *cis*- CH_2 , 10.1, 1.4, 1.4), 4.88 (ddd, 2H, *trans*- CH_2 , 17.4, 1.4, 1.4), 5.02 (ddd, 1H, *cis*- CH_2 , 9.8, 1.8, 1.2), 5.06 (ddd, 1H, *trans*- CH_2 , 16.9, 3.5, 1.7), 5.75 (ddd, 1H, $-\text{CH}=\text{}$, 16.9, 9.8, 7.2), 5.92 (m, 2H, $-\text{CH}=\text{}$); $\delta(^{13}\text{C}) = -2.1$ (Me_2Si , 50.4), -1.3 (Me_2Si , 49.6), 33.8 (br, CH_2B), 42.2 (CH_2), 112.9 ($\text{CH}_2=\text{}$), 116.3 ($\text{CH}_2=\text{B}$), 134.1 (56.1), 135.8 ($\text{CH}=\text{}$), 137.8 ($\text{CH}=\text{B}$), 185.5 (br, $=\text{C}-\text{B}$); $\delta(^{29}\text{Si}) = -31.0$ (Me_2HSi , 11.0), 3.2 (Me_3Si , 11.0, $^2\Delta^{10/11}\text{B}(^{29}\text{Si}) = -75$ ppb); $\delta(^{11}\text{B}) = 64.3$

7: $\delta(^1\text{H}) = 0.16$ (s, 9H, Me_3Si), 0.25 (d, 6H, Me_2Si), 0.95 (m, 9H, CH_3), 1.21 (q, 4H, CH_2 , 7.8), 2.23 (q, 2H, CH_2 , 7.6), 3.21 (br, 1H, SiH, 150.9); $\delta(^{13}\text{C}) = -1.1$ (Me_3Si , 49.7), 1.8 (Me_3Si , 50.2), 10.2 (CH_3), 13.5 (CH_3), 19.1 (br, CH_2), 30.7 (CH_2), 133.8 ($=\text{C}-\text{Si}$, 56.5), 191.5 (br, $=\text{C}-\text{B}$); $\delta(^{29}\text{Si}) = -1.1$ (Me_2Si , 10.8, $^2\Delta^{10/11}\text{B}(^{29}\text{Si}) = -50$ ppb), -12.2 (Me_2Si , 10.8); $\delta(^{11}\text{B}) = 69.4$

8: $\delta(^1\text{H}) = 0.14$ (s, 9H, Me_3Si , 7.0[Si]), 0.18 (s, 6H, Me_2Si), 0.60 (dd, 2H, H-1, 6.7[Si]), 1.39 (dd, 2H, H-3, 6.6), 1.77 (m, 2H, H-2), 2.23 (d, 2H, CH_2B , 7.5), 3.26 (dt, 2H, CH_2 , 6.6, 1.5), 4.80–5.07 (m, 4H, $=\text{CH}_2$), 5.65–6.00 (m, 2H, $=\text{CH}-$); $\delta(^{13}\text{C}) = 0.6$ (Me_3Si , 49.7), 3.0 (Me_2Si , 50.2), 18.2 (C-2), 19.5 (C-1, 49.8), 29.6 (br, C-3), 36.3 (br, CH_2B), 42.9 (CH_2), 112.3 ($=\text{CH}_2$), 113.9 ($=\text{CH}_2$), 136.0 ($=\text{CH}-$), 136.6 ($=\text{CH}-$), 154.9 ($=\text{C}-\text{Si}$), 179.8 (br, $=\text{C}-\text{B}$); $\delta(^{29}\text{Si}) = -9.4$ (Me_3Si , 8.2), -4.3 (Me_2Si , 8.2); $\delta(^{11}\text{B}) = 80.5$

9: $\delta(^1\text{H}) = 0.10$ (s, 6H, Me_2Si), 0.28 (d, 6H, Me_2HSi , 4.1), 0.65 (dd, 2H, CH_2 -1, 7.3, 6.7), 1.41 (t, 2H, CH_2 -3, 6.6), 1.79 (m, 2H, CH_2 -2), 2.24 (d, 2H, CH_2B , 7.8), 3.31 (dt, 2H, CH_2 , 6.7, 1.4), 4.39 (sept, 1H, SiH, 4.1), 4.90–5.05 (m, 6H, CH_2), 5.72 (ddt, 1H, $-\text{CH}=\text{}$, 16.9, 10.4, 6.6), 5.95 (m, 1H, $-\text{CH}=\text{B}$); $\delta(^{13}\text{C}) = -1.5$ (SiMe_2H , 49.7), 0.9 (SiMe_2 , 50.6), 18.7 (C-2), 18.7 (C-1, 49.8), 30.3 (br, C-3), 36.0 (br, CH_2B), 42.8 (CH_2), 114.1 ($=\text{CH}_2\text{B}$), 116.3 ($=\text{CH}_2$), 135.7 ($=\text{CH}-$), 136.5 ($=\text{CH}-$), 143.6 ($=\text{C}-\text{Si}$, 51.9), 180.4 (br, $=\text{C}-\text{B}$); $\delta(^{29}\text{Si}) = -28.4$ (Me_2HSi , 7.7), -5.00 (Me_2Si , 7.7); $\delta(^{11}\text{B}) = 81.7$

10: $\delta(^1\text{H}) = 0.03$ (s, 9H, Me_3Si), 0.23 (s, 6H, Me_2Si), 0.69 (dd, 2H, H-1, 6.7), 1.70 (m, 2H, H-2), 1.80 (dd, 2H, H-3, 6.7, 5.2), 2.23 (d, 4H, CH_2B , 7.5), 4.89–5.00 (m, 4H, $=\text{CH}_2$), 5.91 (ddt, 2H, $=\text{CH}-$, 17.8, 9.6, 7.5); $\delta(^{13}\text{C}) = 1.4$ (Me_2Si , 50.3), 1.5 (Me_3Si , 49.6), 13.6 (C-1, 50.4), 21.1 (C-2), 31.4 (C-3), 34.0 (br, CH_2B), 113.9 ($=\text{CH}_2$), 136.1 ($=\text{CH}-$), 145.1 ($=\text{C}-\text{Si}$, 51.9), 181.7 (br, $=\text{C}-\text{B}$); $\delta(^{29}\text{Si}) = -16.2$ (Me_3Si , 7.0), -6.0 (Me_2Si , 7.0); $\delta(^{11}\text{B}) = 76.9$

+18.0). This is in contrast to the finding for Zr-H-Si interactions,^[7d] where the ^{29}Si shielding increases significantly, possibly as a result of Si–Zr bonding. The magnitude of the coupling constant $|^1J(^{29}\text{Si},^1\text{H})|$ is significantly reduced (by ca. 40 to 55 Hz; e.g. **6**: $^1J(^{29}\text{Si},^1\text{H}) = 146$ Hz for the Si-H-B bridge and 186 Hz for the Me_2SiH group in *trans* position with respect to the boryl group), which is typical of Si–H activation and has been found for many transition metal complexes of silanes.^[7] ^{11}B decoupling does not significantly sharpen the $^1\text{H}(\text{Si-H-B})$ resonance since scalar $^{11}\text{B}-^1\text{H}$ coupling is averaged by fast ^{11}B quadrupolar relaxation (the line widths of the ^{11}B NMR signals exceed 300 Hz). There is an unprecedented isotope-induced shift $^2\Delta^{10/11}\text{B}(^{29}\text{Si})$ in the ^{29}Si NMR spectra (**5**: -46 ppb, **6**: -75 ppb; confirmed by measurement at two different field strengths), transmitted through the Si-H-B

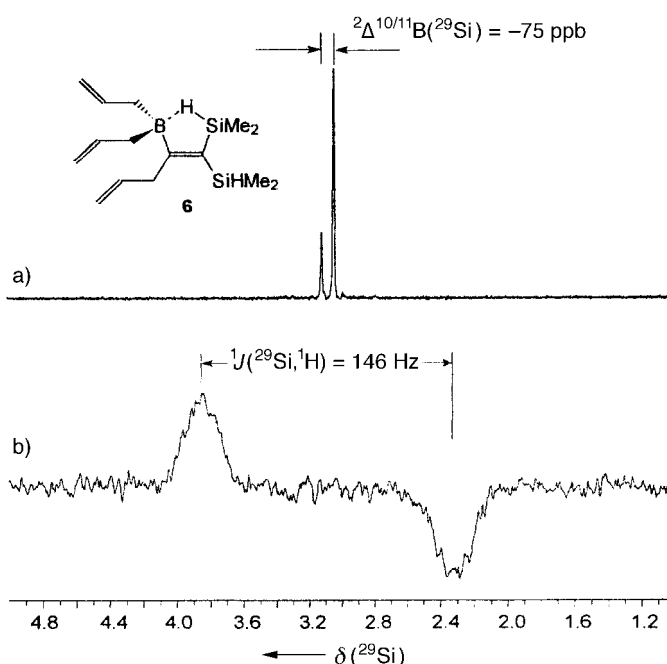
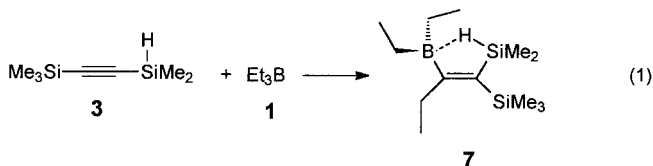


Figure 1. Sections of the ^{29}Si NMR spectra of **6** (99.4 MHz, the portions shown contain the signals for silicon atoms involved in the Si-H-B bridge). a) INEPT spectrum based on $^1J(^{29}\text{Si},^1\text{H}) = 150$ Hz, refocused, ^1H -decoupled; the isotope-induced chemical shift $^2\Delta^{10/11}\text{B}(^{29}\text{Si})$ is shown. b) INEPT spectrum based on $^1J(^{29}\text{Si},^1\text{H}) = 150$ Hz, ^1H -coupled.

bridge (Figure 1). In the IR spectrum of **5**, the band observed at 1905 cm^{-1} for $\nu(\text{Si-H})$ is at markedly lower wavenumber than for the stretching vibrations of terminal Si-H groups (e.g. **3**: $\tilde{\nu}(\text{Si-H}) = 2146\text{ cm}^{-1}$).

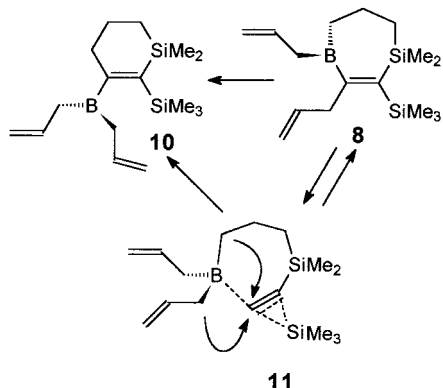
The product **7** obtained from the reaction of an excess of **1** with **3** [Eq. (1); no reaction at room temperature; heating for 10 h in boiling chloroform is required] has the same stereochemistry as **5**. The NMR spectroscopic properties of **7** (Table 1) are similar to those of **5** and **6**. This means that there



is also a Si-H-B bridge in **7**, although the ^{11}B and ^{29}Si NMR data as well as the value of 2055 cm^{-1} for the $\tilde{\nu}(\text{Si-H})$ suggest that the bridge is somewhat weaker. Interestingly, all physical data of a comparable tin compound indicate negligible Sn-H-B interactions.^[8]

After 24–48 h at room temperature in CDCl_3 , compounds **5** and **6** have undergone further transformations. Thus, the new seven-membered heterocycles **8** and **9** (Table 1) are formed as the result of intramolecular hydrosilylation. These are rare examples of hydrosilylation taking place under extremely mild conditions without a catalyst. It is conceivable that the Si-H-B bridge is a prerequisite for this process (it should be noted that hydrosilylation of the C-allyl substituent does not take place in **6**). Compound **9** can be distilled and isolated as a colorless, extremely air-sensitive liquid. In

contrast, **8** undergoes further rearrangement to give the six-membered heterocycle **10**. This can be explained as the result of 1,1-deorganoboration^[3c] followed by 1,1-organoboration after which both allyl groups remain at the boron atom (Scheme 2). Intermediates of the type **11** are rather short-lived, whereas comparable derivatives with tin^[9] or lead^[10] instead of silicon have been isolated and fully characterized.



Scheme 2. Proposed mechanism for the 1,1-deorganoboration and 1,1-organoboration of **8** to **10** via the short-lived intermediate **11**.

In summary, firm evidence for the presence of the Si-H-B bridge in **5** and **6** has been found. This kind of interaction will explain in particular intramolecular reactions of boron compounds which contain silyl groups with Si-H functionalities, and it will stimulate investigations in this field. First examples of novel routes to heterocycles have already been observed here in the attempt to combine 1,1-allylboration and hydrosilylation.

Received: August 5, 1998 [Z.122521E]
German version: *Angew. Chem.* **1999**, *111*, 214–217

Keywords: boron • hydrosilylations • NMR spectroscopy • organoborations • silicon

- [1] a) R. Köster, *Methoden Org. Chem. (Houben-Weyl)* 4th ed. 1982–1984, Vol. 13/3a–c; b) A. Pelter, K. Smith, H. C. Brown, *Borane Reagents*, Academic Press, London, **1988**; c) D. S. Matteson, *Synthesis* **1989**, 973–985.
- [2] a) E. W. Colvin, *Silicon in Organic Synthesis*, Academic Press, London, **1988**; b) M. Lalonde, T. H. Chan, *Synthesis* **1985**, 817–845; c) N. Auner, J. Weis, *Organosilicon Chemistry*, VCH, Weinheim, **1994**; d) N. Auner, J. Weis, *Organosilicon Chemistry II*, VCH, Weinheim, **1995**.
- [3] a) R. Köster, *Pure Appl. Chem.* **1977**, *49*, 765–789; b) N. S. Hosmane in *The Borane, Carborane, Carbocation Continuum* (Ed: J. Casanova), Wiley, New York, **1998**, pp. 397–423; c) B. Wrackmeyer, *Coord. Chem. Rev.* **1995**, *143*, 125–156; d) D. Seiferth, K. Büchner, W. S. Rees, Jr., W. M. Davis, *Angew. Chem.* **1990**, *102*, 911–913; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 918–920; e) N. Metzler, M. Denk, *Chem. Commun.* **1996**, 2657–2658.
- [4] a) J. A. Soderquist, J. Rivera, A. Negron, *J. Org. Chem.* **1989**, *54*, 4051–4055; b) J. A. Soderquist, H. C. Brown, *J. Org. Chem.* **1980**, *45*, 3571–3578; c) K. Uchida, K. Utimoto, H. Nozaki, *J. Org. Chem.* **1976**, *41*, 2941–2942; d) K. Uchida, K. Utimoto, H. Nozaki, *Tetrahedron* **1977**, *33*, 2987–2992.
- [5] a) R. Köster, G. Seidel, B. Wrackmeyer, *Angew. Chem.* **1994**, *106*, 2380–2382; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2294–2296; b) R.

- Köster, G. Seidel, R. Boese, B. Wrackmeyer, *Z. Naturforsch. B* **1995**, *50*, 439–447.
- [6] a) B. Wrackmeyer, *J. Chem. Soc. Chem. Commun.* **1988**, 1624–1626; b) R. Köster, G. Seidel, B. Wrackmeyer, *Chem. Ber.* **1989**, *122*, 1825–1850; c) R. Köster, G. Seidel, J. Süß, B. Wrackmeyer, *Chem. Ber.* **1993**, *126*, 1107–1114; d) B. Wrackmeyer, H. E. Maisel, J. Süß, W. Milius, *Z. Naturforsch. B* **1996**, *51*, 1320–1324; e) B. Wrackmeyer, H. E. Maisel, W. Milius, *Chem. Ber.* **1997**, *130*, 1349–1352.
- [7] a) J. J. Schneider, *Angew. Chem.* **1996**, *108*, 1132–1139; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1068–1076; b) U. Schubert, *Adv. Organomet. Chem.* **1990**, *30*, 151–187; c) W. A. Herrmann, N. W. Huber, J. Behm, *Chem. Ber.* **1992**, *125*, 1405–1407; d) L. J. Procopio, P. J. Carroll, D. H. Berry, *J. Am. Chem. Soc.* **1994**, *116*, 177–185.
- [8] S. Kersch, B. Wrackmeyer, *Z. Naturforsch. B* **1987**, *42*, 1047–1049.
- [9] a) B. Wrackmeyer, G. Kehr, R. Boese, *Angew. Chem.* **1991**, *103*, 1374–1376; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1370–1372; b) B. Wrackmeyer, S. Kundler, R. Boese, *Chem. Ber.* **1993**, *126*, 1361–1370; c) B. Wrackmeyer, S. Kundler, W. Milius, R. Boese, *Chem. Ber.* **1994**, *127*, 333–342.
- [10] B. Wrackmeyer, K. Horchler, R. Boese, *Angew. Chem.* **1989**, *101*, 1563–1565; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1500–1501.

Synthesis of Mono- and Di(oxopyrri)porphyrins: A New Approach through Ring Enlargement with Diazomethane**

Andrei N. Kozyrev, James L. Alderfer, Thomas J. Dougherty, and Ravindra K. Pandey*

The past decade has seen increasing attention being paid to the synthesis of novel porphyrinoid aromatic compounds. A large number of these macrocyclic structures, including “expanded porphyrins”, has been reported recently.^[1] The interest in cyclic polypyrrole systems and their heteroanalogues is based on their potential application as photosensitizers in the treatment of cancer by photodynamic therapy, and as highly selective catalysts and organic electrical conductors.^[1]

The simplest expanded porphyrins known are homoporphyrins containing an extra carbon atom in their structure. This class of porphyrins was first reported by Callot and co-workers.^[2] Homoporphyrins that are expanded at *meso* positions are nonaromatic and unstable, although the related metal complexes were found to be quite stable.^[3] The insertion of a carbonyl group between the α - and β -pyrrole

[*] Dr. R. K. Pandey, Dr. A. N. Kozyrev, Dr. T. J. Dougherty
Chemistry Section, Photodynamic Therapy Center
Department of Radiation Biology, Roswell Park Cancer Institute
Buffalo, NY 14263 (USA)
Fax: (+1) 716-845-8920
E-mail: pdt.ctr@3101med.buffalo.edu
Dr. J. L. Alderfer
Molecular and Cellular Biophysics, Roswell Park Cancer Institute
Buffalo, NY 14263 (USA)

[**] This work was supported by the research grants funded by Mallinckrodt Medical Inc., St. Louis (USA), the National Institutes of Health (CA 55791), and the Oncologic Foundation of Buffalo (USA). Partial support to the NMR facility by the NIH (CA-16056) is also acknowledged.

carbon atoms produced stable and fully aromatic homoporphyrinones containing a pyridine unit. The first synthesis of this type of porphyrin was presented by Bonnett and co-workers in 1993.^[4] More recently, Lash reported^[5] the synthesis of a similar semiquinone "oxobenziporphyrin" structure by a [3+1] approach,^[6] and subsequently extended these studies to the pyridone system, which he termed "oxypyriporphyrin".^[7] These novel 18- π -electron aromatic porphyrinoids exhibit spectroscopic properties similar to porphyrin-type systems, notably a significantly red shifted Soret band. Sessler and co-workers^[8] have also shown that nonaromatic calix[4]pyrroles can also be converted into nonaromatic calix[4]pyridines by the insertion of dichlorocarbene into the pyrrole fragment.

The successful synthesis of verdinochlorins^[9] by the reaction of 13²-oxypyropheophorbide *a* with diazomethane prompted us to explore the utility of this methodology for porphyrin derivatives with one or more dioxopyrrole rings. We anticipated that a similar reaction with dioxo- and tetraoxo-TPP derivatives (TPP = *meso*-tetraphenylporphyrin) as substrates would yield the corresponding mono- and di(oxopyri)porphyrins, which are otherwise difficult to synthesize.

In our attempts to prepare these compounds, 2,3-dioxo-*meso*-tetraphenylchlorin (TPC, **1**; see Scheme 1) was prepared from the corresponding *vic*-dihydroxy analogue with the procedures reported by Dolphin and Bruckner^[10] and Crossley et al.^[11] A similar approach was followed to convert 2,3,17,18-tetrahydroxy-tetraphenyl-bacteriochlorin (TTPBC) into the tetraone **2** (see Scheme 3). These compounds have been previously synthesized by Crossley and co-workers,^[12, 13] and have been used successfully as building blocks for the construction of linear polyporphyrin arrays and photosynthetic models.^[14]

The reaction of **1** with a large excess of diazomethane gave a mixture of three compounds (Scheme 1), which were separated by chromatography on silica gel and identified by

protons of the epoxymethylene group. Because of the asymmetry of the molecule, each β -pyrrole proton appeared as an individual doublet in the low-field region.^[15]

Analysis by LR-MS of the two polar, red-brown bands gave identical molecular ion peaks at m/z 672, which indicates the insertion of two CH₂ units into the molecule. The NMR spectra of these compounds showed a distinctive singlet for the protons of the methoxy groups at $\delta = 3.85$ (minor product) and $\delta = 3.39$ (major product) along with a singlet which integrated for one proton. This is strong evidence for the presence of a methoxypyridinone ring in each isomer. The minor isomer (12%), with the methoxy group signal shifted down field by the deshielding effect of neighboring carbonyl functionality, was identified as 2-oxo-2^a-methoxy-*meso*-tetraphenylpyriporphyrin (**4**; Scheme 1). This assignment was unambiguously confirmed by ¹H NMR 2D ROESY experiments, which showed a strong through-space interaction of the 2^a-methoxy protons and the hydrogen atom at position 3. The latter also showed clear interactions with the *ortho* and *meta* protons of the neighboring 5-phenyl substituent. Again, owing to asymmetry in the molecule, each pyrrole β -proton appeared as a well-resolved doublet in the region of $\delta = 8.4$ –8.6. The resonances of the *ortho* and most of the *meta* hydrogen atoms of the phenyl group were also surprisingly well resolved, which provided the opportunity for a complete assignment of all the resonances.^[16]

On the basis of the 2D ROESY NMR data, the structure of the major isomer, which is obtained from the most polar band (78% yield), was identified as 3-methoxy-2-oxo-*meso*-tetraphenylpyriporphyrin (**5**; Scheme 1). The spectrum exhibited a strong through-space interaction between the 3-methoxy group and the *ortho* and *meta* protons of the neighboring 5-phenyl ring, and gave a classic example of a nearest neighbor stepwise assignment of all NMR signals.^[17] Selected NOE connectivities are shown in Figure 1. The UV/Vis spectra of oxopyriporphyrins **4** and **5** exhibited red-shifted, Soret-type absorptions at 450 and 444 nm, respectively.

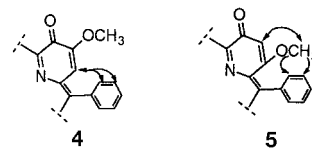
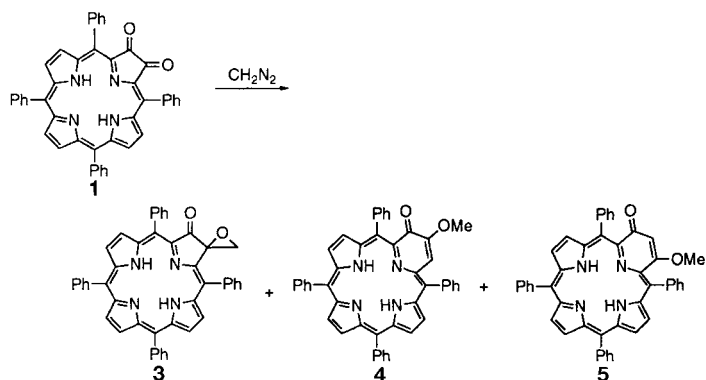


Figure 1. Selected NOE connectivities for oxopyriporphyrins **4** and **5**.

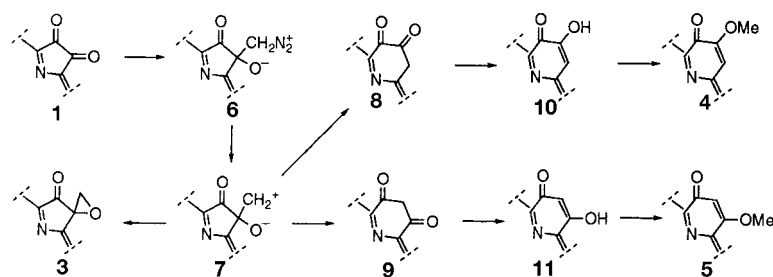
The mechanism of the formation of compounds **3**–**5** is consistent with that reported for reactions of diazoalkanes with electron-deficient cyclic ketones.^[18] Nucleophilic attack of diazomethane on **1** produces the reactive species **7**, which can either generate the epoxide **3** or rearrange into ring-expanded products **8** and **9** (Scheme 2). The remarkable difference in the respective yields of these ring-expanded compounds (ca. 1:7) can be explained by the higher polarization of the 2-oxo group. Enolization of the activated methylene groups in **8** and **9** leads to the formation of the hydroxypyridinones **10** and **11**, which on reaction with a second molecule of diazomethane afford methoxy derivatives **4** and **5**, respectively.

The ring-enlargement reaction was extended to tetraoxo-bacteriochlorin (**2**). Owing to its highly electron deficient nature, it reacted immediately with diazomethane to give a mixture of three orange-brown products (Scheme 3), which

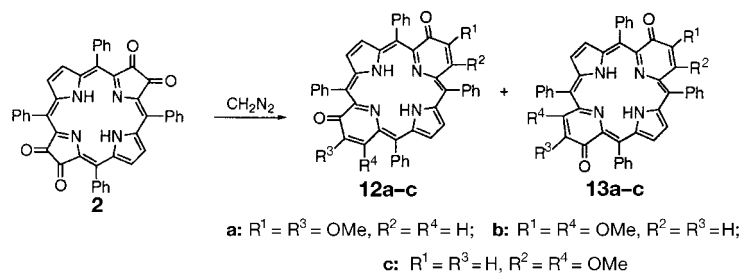


Scheme 1. Synthesis of epoxychlorin **3** and mono(oxopyri)porphyrins **4** and **5**.

mass spectrometry and ¹H NMR spectroscopy. The fastest moving, green band (7%) was identified as 2-oxo-3-epoxymethylene-TPC (**3**; low-resolution mass spectrometry (LRMS): m/z 658). The NMR spectrum showed a characteristic pair of AB doublets at $\delta = 3.78$ for the nonequivalent



Scheme 2. A possible mechanism for the formation of epoxy- and oxopyrporphyrins.



Scheme 3. Synthesis of di(oxopyr)porphyrins **12** and **13**.

were separated by chromatography on silica gel and purified by preparative thin-layer chromatography (TLC). Each component gave the molecular ion peak $[M+1]^+$ at m/z 732, which indicated the formation of two opposed methoxypyrindione units. The ^1H NMR spectrum of the least polar band (18%) exhibited a singlet for the methoxy groups at $\delta = 3.9$, and on the basis of our assignments for **4**, it was identified as a mixture of the isomeric di(oxopyr)porphyrins **12a** and **13a**, with methoxy substituents at the 2^a- and 17^a-positions. The second band (31%), whose ^1H NMR spectrum showed two well-separated methoxy group singlets at $\delta = 3.9$ and 3.4, was found to be a mixture of isomers **12b** and **13b**. Similarly, the most polar band (47%), with a distinctive methoxy group singlet at $\delta = 3.3$ in the ^1H NMR spectrum, was identified as a mixture of **12c** and **13c**. All di(oxopyr)porphyrins showed resonances for β -pyrrole protons in the low-field region ($\delta = 8.5$ – 8.7), which indicated that in spite of the presence of two pyridinone units, the molecule still retains aromaticity and a strong ring current. The tendency of these compounds to aggregate^[7] and their existence as isomeric mixtures made it difficult to assign the individual low-field resonances, which were observed as several groups of multiplets. Attempts to separate the individual isomers by column chromatography were unsuccessful. The UV/Vis spectra of these novel oxopyrporphyrins showed a significant shift of the Soret-type band centered at 490 nm and weak absorptions at 560 and 660 nm. Currently, these novel homoporphyrins are being evaluated for their photophysical properties and photosensitizing efficacy, and these results will be published elsewhere.

Received: July 1, 1998 [Z12082IE]

German version: *Angew. Chem.* **1999**, *111*, 169–171

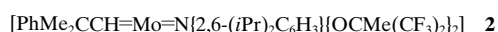
Keywords: diazomethane • homoporphyrins • insertions • porphyrinoids

- [1] a) A. Jasat, D. Dolphin, *Chem. Rev.* **1997**, *97*, 2267, and references therein; b) J. L. Sessler, A. K. Burrell, *Top. Curr. Chem.* **1991**, *161*, 177.
- [2] a) H. J. Callot, T. Tschamber, *J. Am. Chem. Soc.* **1975**, *97*, 6175; b) H. J. Callot, E. Schaeffer, *J. Org. Chem.* **1977**, *42*, 1567; c) H. J. Callot, E. Schaeffer, *Tetrahedron* **1978**, *34*, 2295.
- [3] P. A. Liddell, K. R. Gerzevske, J. J. Lin, M. M. Olmstead, K. M. Smith, *J. Org. Chem.* **1993**, *58*, 6681.
- [4] K. P. Adams, R. Bonnett, P. J. Burke, A. Salgano, M. A. Valles, *J. Chem. Soc. Chem. Commun.* **1993**, 1860; see also A. R. Adams, R. Bonnett, P. J. Burke, A. Salgano, M. A. Valles, *J. Chem. Soc. Perkin Trans. 1* **1997**, 1769.
- [5] T. D. Lash, *Angew. Chem.* **1995**, *107*, 2703; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2533.
- [6] T. D. Lash, *Chem. Eur. J.* **1996**, *2*, 1197, and references therein.
- [7] T. D. Lash, S. T. Chaney, *Chem. Eur. J.* **1996**, *2*, 944; see also T. Schonemeier, E. Breitmeier, *Synthesis* **1997**, 273. According to IUPAC rules the ketone functionality should be indicated with oxo- and oxy-.
- [8] J. L. Sessler, V. Karl, P. A. Gale, P. Anzenbacher, Jr., K. Jursikova, V. Lynch, *Chem. Commun.* **1998**, 9.
- [9] A. N. Kozyrev, J. L. Alderfer, T. J. Dougherty, R. K. Pandey, *Chem. Commun.* **1998**, 1083.
- [10] C. Bruckner, D. Dolphin, *Tetrahedron Lett.* **1995**, *36*, 3295.
- [11] M. J. Crossley, P. L. Burn, S. J. Langford, S. M. Pyke, A. G. Stark, *J. Chem. Soc. Chem. Commun.* **1991**, 1567.
- [12] M. J. Crossley, L. G. King, *J. Chem. Soc. Chem. Commun.* **1985**, 920.
- [13] M. J. Crossley, L. J. Govenlock, J. K. Prashar, *J. Chem. Soc. Chem. Commun.* **1995**, 2379.
- [14] K. A. Jolliffe, T. D. M. Bell, K. P. Ghiggino, S. J. Langford, M. N. Paddon-Row, *Angew. Chem.* **1998**, *110*, 960; *Angew. Chem. Int. Ed.* **1998**, *37*, 916.
- [15] Selected spectroscopic data for **8**: ^1H NMR (400 MHz, CDCl_3): $\delta = -0.8$ (brs, 1H, NH), -0.2 (brs, 1H, NH), 3.78 (AB, 2H, 3-OCH₃), 7.72–7.78 (m, 18H), 7.82 (d, $J = 6.8$ Hz, 1H), 8.40 (d, $J = 6.8$ Hz, 1H), 8.46 (d, $J = 4.9$ Hz, 2H), 8.52 (d, $J = 4.8$ Hz, 1H), 8.64 (d, $J = 4.8$ Hz, 1H), 8.79 (d, $J = 4.8$ Hz, 1H), 9.21 (d, $J = 4.8$ Hz, 1H); UV/Vis (CH_2Cl_2): λ_{max} [nm] (ϵ [$\text{M}^{-1}\text{cm}^{-1}$]) = 429 (118000), 588 (13900), 588 (9500); LR-MS: m/z (%): 669.2 (100, $[M+1]^+$), 569 (9), 433 (23), 419 (34).
- [16] Spectroscopic data for **9**: ^1H NMR (400 MHz, CDCl_3): $\delta = -1.5$ (brs, 2H, NH), 3.85 (s, 3H, 2^a-OMe), 7.60 (dt, $J = 6.7, 5.4$ Hz, 2H, *meta* H of 20-Ph), 7.71 (t, $J = 6.9$ Hz, 2H, *meta* H of 5-Ph), 7.72 (t, $J = 6.8$ Hz, 2H, *meta* H of 10-Ph), 7.72–7.76 (m, 6H, *para* H of Ph and *meta* H of 15-Ph), 7.88 (s, 1H, 3-H), 8.05 (d, $J = 6.8, 2.6$ Hz, 2H, *ortho* H of 5-Ph), 8.12 (dd, $J = 6.9, 1.8$ Hz, 2H, *ortho* H of 10-Ph), 8.16 (dd, $J = 6.1, 2.6$ Hz, 2H, *ortho* H of 15-Ph), 8.24 (d, $J = 6.7$ Hz, 2H, *ortho* H of 20-Ph), 8.39 (d, $J = 5.4$ Hz, 1H, 7-H), 8.49 (s, 2H, 12-H and 13-H), 8.52 (d, $J = 1.8$ Hz, 2H, 17-H and 18-H), 8.56 (d, $J = 5.4$ Hz, 1H, 8-H); UV/Vis (CH_2Cl_2): λ_{max} [nm] (ϵ [$\text{M}^{-1}\text{cm}^{-1}$]) = 450 (126000), 549 (14000), 588 (9500); LR-MS (%): $m/z = 673.3$ (100, $[M+1]^+$), 595 (8), 433 (43).
- [17] Spectroscopic data for **10**: ^1H NMR (400 MHz, CDCl_3): $\delta = -1.5$ (brs, 2H, NH), 3.39 (s, 3H, 3-OMe), 6.83 (s, 1H, 2^a-H), 7.60 (t, $J = 5.4$ Hz, 2H, *meta* H of 20-Ph), 7.62 (m, 2H, *para* H of 5-Ph and of 20-Ph), 7.63 (t, $J = 6.9$ Hz, 2H, *meta* H of 5-Ph), 7.70 (t, $J = 6.8$ Hz, 2H, *meta* H of 15-Ph), 7.71 (m, 2H, *para* H of 10-Ph and of 15-Ph), 7.72 (t, $J = 6.4$ Hz, 2H, *meta* H of 10-Ph), 7.95 (dd, $J = 6.4, 2.6$ Hz, 2H, *ortho* H of 20-Ph), 8.05 (d, $J = 6.9$ Hz, 2H, *ortho* H of 5-Ph), 8.08 (dd, $J = 6.8, 2.1$ Hz, 2H, *ortho* H of 15-Ph), 8.11 (dd, $J = 6.4$ Hz, $J = 2.5$ Hz, 2H, *ortho* H of 10-Ph), 8.35 (d, $J = 5.3$ Hz, 1H, 7-H), 8.37 (d, $J = 5.6$ Hz, 1H, 18-H), 8.49 (s, 2H, 12-H and 13-H), 8.53 (d, $J = 5.6$ Hz, 1H, 17-H), 8.56 (d, $J = 5.3$ Hz, 1H, 8-H); UV/Vis (CH_2Cl_2): λ_{max} [nm] (ϵ [$\text{M}^{-1}\text{cm}^{-1}$]) = 444 (123000), 543 (15500), 624 (8500); LR-MS: m/z (%): 673.3 (100, $[M+1]^+$), 595 (12), 469 (23).
- [18] H. Zollinger, *Azo and Diazo Chemistry. Aliphatic and Aromatic Compounds*, Interscience, New York, **1961**.

Diastereoselective Ring Closing Metathesis Reactions: Synthesis of Bicyclic Diallyl Alcohols and Ethers**

Mark Lautens* and Gregory Hughes

In recent years there has been a surge of interest in ring closing metathesis (RCM) reactions as a consequence of the development of well-defined metal alkylidene catalysts that display a wide range of functional group tolerance.^[1] By far the two most widely employed catalysts are **1** (Cy = cyclohexyl) developed by Grubbs et al.^[2] and **2** developed by Schrock et al.^[3]

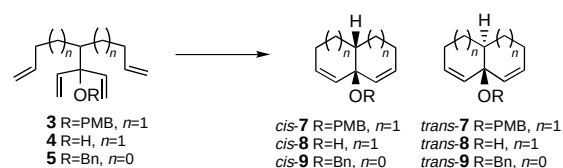


We now report a group-selective activation followed by a diastereoselective RCM (DSRCM) reaction to provide convenient access to a new class of bicyclic diallyl alcohols with a σ plane of symmetry that is not readily accessible by conventional approaches. When we began this investigation the diastereoselectivity of RCM reactions had not been explored. Very recently Blechert et al. reported a DSRCM reaction that gave five membered heterocycles in which they observed a reversal in the sense of the diastereoselectivity on switching from catalyst **1** to **2**, but noted complete loss of selectivity in their attempts to form six membered rings.^[4] In addition to this report, there have been some examples of diastereomeric mixtures whose components cyclize at different rates.^[5]

Our studies were conducted with tetraenes of general structure **A** (Scheme 1). Initial metal alkylidination at olefin *a* in preference to *b* would be expected upon treatment with **1** or **2** on the basis of literature reports, which suggests that the

presence of substituents α to an olefin hinders its participation in the RCM reaction.^[6] After the formation of a metal carbene at olefin *a*, the molecule can cyclize in one of two ways to give either triene **B** or **C**. In the event that **B** is initially formed it could eventually yield **C** by reacting with the catalyst to reform the alkylidene first generated by reaction of **A** with **1** or **2**. Triene **C** could then undergo a second RCM reaction to give bicyclo[4.4.0]decadiene **D**. We anticipated by analogy to the fully saturated decalin systems that *trans*-fused **D** would be thermodynamically preferred. If all the steps shown in Scheme 1 were reversible then a thermodynamic mixture of *cis* and *trans* decalins would be expected. Subsequent sigmatropic rearrangement of **D** to give **E** would provide an efficient entry into the tetrahydronaphthalene skeleton found in the HMG CoA reductase inhibitor (+)-mevinolin.

Our initial investigations (Scheme 2) have provided some surprising results, which are highlighted in Table 1. When tetraene **3** was treated with three mol % of **1** in CH_2Cl_2 at



Scheme 2. Formation of bicyclic dienes from tetraenes. PMB = *p*-methoxybenzyl, Bn = benzyl. See Table 1 for the conditions.

Table 1. RCM reactions of tetraene substrates.

Entry	Starting material	Product	Conditions ^[a] [mol %, h]	<i>cis:trans</i>	Yield [%]
1	3	7	A ^[b] (12, 20)	8:1	80
2	3	7	B (12, 20)	8:1	82
3	4	8	A (10, 2.5)	1:2.8	84
4	5	9	A ^[b] (4, 20)	^[c]	81
5	5	9	B (4, 2)	^[c]	66

[a] Reaction conditions: A: 0.1 M in CH_2Cl_2 , cat. = **1**, 23 °C; B: 0.1 M in C_6H_6 , cat. = **2**, 23 °C; [b] Under an ethylene atmosphere. [c] Only the *cis* bicyclic product was observed, see text.

23 °C for three hours cycloheptene **6** (Figure 1) was isolated as the major product in 70 % yield.^[7] This suggests that the substituents α to olefin *b* are more influential than ring size in determining the type of cyclization that will occur first. However, treatment of **3** or **6** with 10–12 mol % of **1** at 23 °C for 20 h under an atmosphere of ethylene gave bicyclic product **7** in good yield as an 8:1 mixture of diastereoisomers (Table 1, entry 1). Furthermore, contrary to our initial expectations, the *cis* isomer was formed preferentially.^[8] Treatment of **3** with **2** in C_6H_6 at 23 °C gave essentially the same result (entry 2). When the free alcohol **4** was treated with **1** (10 mol %) a 2.8:1 mixture of diastereomers was formed in good yield, with the *trans* isomer now pre-

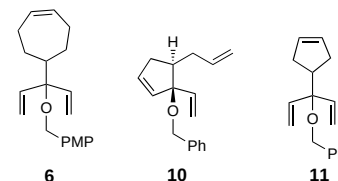
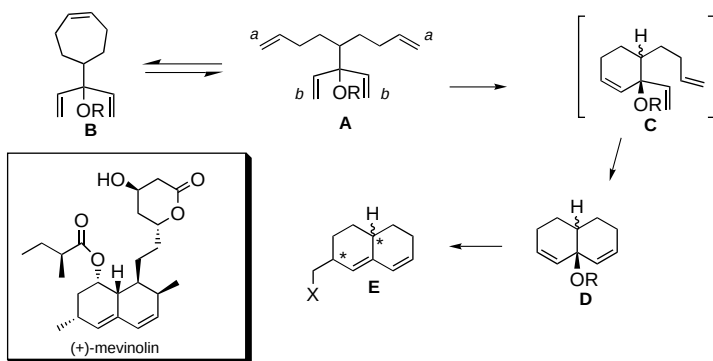


Figure 1. Intermediates and by-products of tetraene metathesis. PMP = *p*-methoxyphenyl.



Scheme 1. Strategy for stereoselective preparation of bicyclic dienes.

[*] Prof. Dr. M. Lautens, G. Hughes
Department of Chemistry, University of Toronto
Toronto, Ontario M5S 3H6 (Canada)
Fax: (+1) 416-978-6083
E-mail: mlautens@alchemy.chem.utoronto.ca

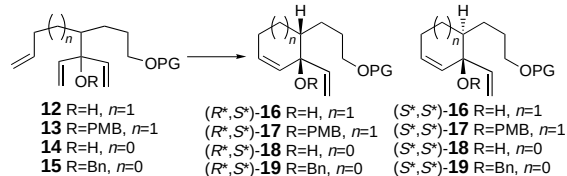
[**] M.L. thanks the Merck Frosst Centre for Therapeutic Research and NSERC Canada for support of this work. G.H. thanks NSERC for a predoctoral fellowship.

Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.

dominating (entry 3).^[8] The use of ethylene presumably facilitates the formation of the more reactive methylenide catalyst.^[2,9]

To evaluate the thermodynamic preference for *cis* versus *trans* decalins of this type, ab initio calculations on the two possible isomers were carried out. At the 3-21G* level the two isomers appear to have essentially the same ground-state energy, differing by less than 0.4 J mol⁻¹, which suggests that the formation of *cis*-decalin is a kinetic outcome and that at least one of the steps in the reaction sequence prior to the final bond formation is irreversible. The preparation of [3.3.0] bicyclic compounds was also examined. When tetraene **5** was treated with four mol % of **1** for 20 h the *cis* isomer of **9** was formed in 81 % yield, along with 12 % of the monocycle **10** (Figure 1), whose formation appears to be irreversible. This triene is unlikely to cyclize to give an extremely strained *trans* bicyclo[3.3.0]octadiene. Again, lower catalyst loadings and shorter reaction times gave a symmetrical triene **11** (Figure 1).

We also prepared trienes **12–15** (Scheme 3) to gain insight into the inherent diastereoselectivity in the first cyclization (Table 2).^[7] A 2.8:1 mixture of diastereomers was obtained in



Scheme 3. Formation of vinyl cycloalkenes from trienes. See Table 2 for the conditions.

Table 2. RCM reactions of triene substrates.

Entry	Starting material	Product	Conditions ^[a] [mol %, h]	<i>R*, S*, S*, S*</i>	Yield [%]
1	12 ^[b]	16 ^[b]	A (12, 5)	1:2.8	80
2	13 ^[b]	17 ^[b]	A (3, 3)	6.1:1	96
3	13 ^[b]	17 ^[b]	B (6, 1.5)	7.8:1	86
4	14 ^[c]	18 ^[c]	A (6, 1.5)	1:1	65
5	15 ^[c]	19 ^[c]	A (3, 1)	8.0:1	99
6	15 ^[c]	19 ^[c]	B (6, 0.5)	1.7:1	94

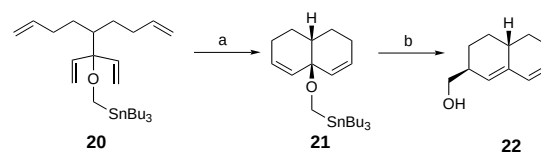
[a] Reaction conditions: A: 0.1 M in CH₂Cl₂, cat. = **1**, 23 °C; B: 0.1 M in C₆H₆, cat. = **2**, 23 °C. [b] PG = *t*BuPh₂Si. [c] PG = *t*BuMe₂Si.

good yield, with (*S*, S**)-**16** favored (entry 1)^[8] upon treatment of free alcohol **12** with catalyst **1**. When *p*-methoxybenzyl ether **13** was treated with **1** the formation of cyclohexene (*R*, S**)-**17** was preferred by a ratio of 6.1:1 (entry 2). Treatment with **2** gave slightly higher levels of selectivity (7.8:1; entry 3).

Trienes that lead to vinylcyclopentene derivatives were also examined. Treatment of free alcohol **14** with **1** yielded a 1:1 mixture of diastereomers (entry 4) in moderate yield and treatment of benzyl ether **15** with **1** gave cyclopentene **19** in excellent yield as an 8.0:1 mixture, with (*R*, S**)-**19** favored (entry 5). In contrast to the formation of six membered rings, treatment of **15** with **2** resulted in a decrease in diastereoselectivity, although the *R*, S** diastereomer was still favored by a ratio of 1.7:1 (entry 6).

In light of our interest in the conversion of diallylic ethers into conjugated dienes we carried out a study of the feasibility

of the [2,3] Wittig rearrangement in this ring system (Scheme 4).^[10] When the [4.4.0] system **21** was treated with *n*BuLi the Wittig rearrangement occurred to give the primary alcohol **22** in 67 % yield along with 17 % of the product that arises from a [1,2] Wittig rearrangement.



Scheme 4. Sigmatropic rearrangement of the bicyclo[4.4.0]decadiene **21**. a) **1** (12 mol %), CH₂Cl₂, reflux, 7 h, 86 %; b) *n*BuLi (1.2 equiv), HMPA (4.0 equiv), THF, -78 °C, 10 min, 67 %. HMPA = hexamethylphosphoramide.

In conclusion, we have developed a group and diastereoselective RCM approach to a novel class of bicyclic diallylic alcohols and ethers. While the cyclization of tetraenes initially gives symmetrical trienes of type **B**, longer reaction times lead selectively to the *cis* isomer of the bicyclic dienes with a σ plane of symmetry. We have also demonstrated that it is possible to rearrange a bicyclo[4.4.0] product to give conjugated dienes. Our current efforts are directed toward the examination of enantioselective methods for the conversion of the diallyl-ethers into chiral and enantiomerically enriched bicyclic dienes.

Experimental Section

Typical procedure for the stereoselective ring closing metathesis of a tetraene as exemplified by formation of *cis*-**9** (Table 1, entry 4): Compound **1** (12 mg, 0.015 mmol) was added to a solution of **5** (100 mg, 0.372 mmol) in CH₂Cl₂ (4 mL) at 23 °C. The resulting solution was stirred under an ethylene atmosphere for 20 h before PPh₃ (14 mg, 0.053 mmol) was added, and the mixture concentrated in vacuo. Purification by flash chromatography (2 % diethyl ether/hexane) on triethylamine-washed silica gel yielded 64 mg (81 %) of *cis*-**9** as a colorless oil. *R_f* = 0.11 (2 % diethyl ether/hexane); ¹H NMR (400 MHz, CDCl₃) δ = 2.06–2.15 (m, 2 H; allylic), 2.81–2.91 (m, 3 H; allylic and C₃CH), 4.42 (s, 2 H; benzylic), 5.83 (dt, ³J(H,H) = 6, 2 Hz, 2 H; olefinic), 5.92 (dt, ³J(H,H) = 6, 2 Hz, 2 H; olefinic), 7.21–7.26 (m, 1 H; aromatic), 7.28–7.35 (m, 4 H; aromatic); ¹³C NMR (neat) $\bar{\nu}$ = 3053, 2919, 2848, 1497, 1448, 1378, 1349, 1216, 1139, 1099, 1028, 991, 733, 697 cm⁻¹; HR-MS (C₁₅H₁₆O, *M*⁺): calcd: 212.1201; found: 212.1196.

Received: June 26, 1998 [Z12061IE]
German version: *Angew. Chem.* **1999**, *111*, 160–162

Keywords: bicycles • homogeneous catalysis • metathesis • rearrangements

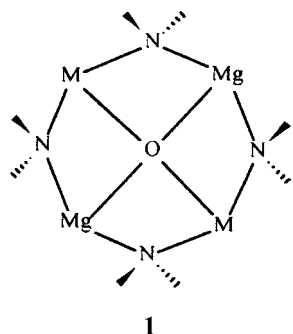
- [1] For several recent reviews, see a) R. H. Grubbs, S. Chang, *Tetrahedron* **1998**, *54*, 4413–4450; b) M. S. Schuster, S. Blechert, *Angew. Chem.* **1997**, *109*, 2124–2145; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2036–2056; c) A. Fürstner, *Top. Catal.* **1997**, *4*, 285–299; d) S. K. Armstrong, *J. Chem. Soc. Perkin Trans. 1* **1998**, 371–388; e) R. H. Grubbs, S. J. Miller, G. C. Fu, *Acc. Chem. Res.* **1995**, *28*, 446–452; f) R. H. Grubbs, S. H. Pine in *Comprehensive Organic Synthesis*, Vol. 5 (Ed.: B. M. Trost), Pergamon, New York, **1991**, pp. 1115–1127.
- [2] P. Schwab, R. H. Grubbs, J. W. Ziller, *J. Am. Chem. Soc.* **1996**, *118*, 100–110.
- [3] R. R. Schrock, J. S. Murdzek, G. C. Bazan, J. Robbins, M. DiMare, M. O'Regan, *J. Am. Chem. Soc.* **1990**, *112*, 3875–3886.

- [4] C. M. Huwe, J. Velder, S. Blechert, *Angew. Chem.* **1996**, *108*, 2542–2544; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2376–2378.
- [5] a) B. Schmidt, T. Sattelkau, *Tetrahedron* **1997**, *53*, 12991–13000; b) S. J. Miller, R. H. Grubbs, *J. Am. Chem. Soc.* **1995**, *117*, 5855–5856; c) S. J. Miller, S.-H. Kim, Z.-R. Chen, R. H. Grubbs, *J. Am. Chem. Soc.* **1995**, *117*, 2108–2109.
- [6] A. Fürstner, K. Langemann, *J. Org. Chem.* **1996**, *61*, 3942–3943.
- [7] Tetraenes **3–5** and trienes **12–15** were prepared efficiently from dimethyl malonate by dialkylation and Krapcho decarboxylation followed by addition of two equivalents of vinylcerium and protection of the resulting tertiary diallylic alcohol. See supporting information for a detailed description of the starting material preparations.
- [8] The ratio of diastereomers was measured by ^1H NMR spectroscopy. See supporting information for the reactions carried out to prove the stereochemistry.
- [9] J. P. A. Harrity, M. S. Visser, J. D. Gleason, A. H. Hoveyda, *J. Am. Chem. Soc.* **1997**, *119*, 1488–1489.
- [10] a) H. Priepke, R. Brückner, *Chem. Ber.* **1990**, *123*, 153–168; b) W. C. Still, *J. Am. Chem. Soc.* **1978**, *100*, 1481–1487; c) W. C. Still, A. Mitra, *J. Am. Chem. Soc.* **1978**, *100*, 1927–1928.

Mixed-Metal Sodium–Magnesium Macrocyclic Amide Chemistry: A Template Reaction for the Site Selective Dideprotonation of Arene Molecules

David R. Armstrong, Alan R. Kennedy, Robert E. Mulvey,* and René B. Rowlings

In a new development in s block chemistry, we recently reported the first examples of mixed-metal (Group 1/Group 2) cationic ring systems with anionic oxo or peroxy cores.^[1]

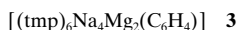
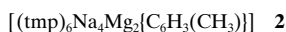


Eight-membered macrocyclic amides, their basic motif, **1** (shown with an oxo core), consists of alternating nitrogen and metal atoms, two lithium or two sodium atoms combined with two magnesium atoms. The nitrogen atoms belong to sterically encumbered hexamethyldisilazide (HMDS) or 2,2,6,6-tetramethylpiperidine (TMP) ligands.

This new class of compound can be regarded as antithetical “crown ether” complexes, where the host–guest (Lewis acid/Lewis base) positions have been reversed relative to those in conventional crown ether complexes: as such, they can be likened to the mercuracarborands pioneered by Hawthorne et al.^[2] Here, in another link to crown ether chemistry, we reveal that a larger twelve-

membered ($\text{N}_6\text{Na}_4\text{Mg}_2$) cationic ring system can be prepared. From the perspective of the number of metal centers in the ring, if the former macrocyclic amides prompt comparisons with [12]crown-4, then this new type can be compared to [18]crown-6. Most interestingly of all, the hexanuclear metallic ring acts as a host to the selectively dideprotonated arene molecules $[\text{C}_6\text{H}_3(\text{CH}_3)]^{2-}$ (from toluene) or $\text{C}_6\text{H}_4^{2-}$ (from benzene). The formation of these dianions suggests a template reaction is in operation.

Complexes **2** and **3** can be prepared easily and reproducibly from a 1:1:3 molar ratio of $n\text{BuNa}$, Bu_2Mg , and TMPH in



hydrocarbon media, to which the appropriate arene is added in excess. Attempts to prepare them from a 2:1:3 molar ratio of reactants matching the stoichiometry in the crystalline products, are hampered by solubility problems at the amine addition step.

Disregarding the methyl substituent of the dimetalated toluene, the molecular structures of **2** and **3** are essentially equivalent.^[3] Figure 1 shows **2** viewed from above the macrocycle, while Figure 2 shows an alternative side view of **3**. Notable features include: a) the severely puckered $\text{N}_6\text{Na}_4\text{Mg}_2$ ring possesses crystallographic inversion symmetry; b) the arene molecules lie almost orthogonal to the mean plane of this ring; c) the metalation sites of the toluene dianion (2,5-

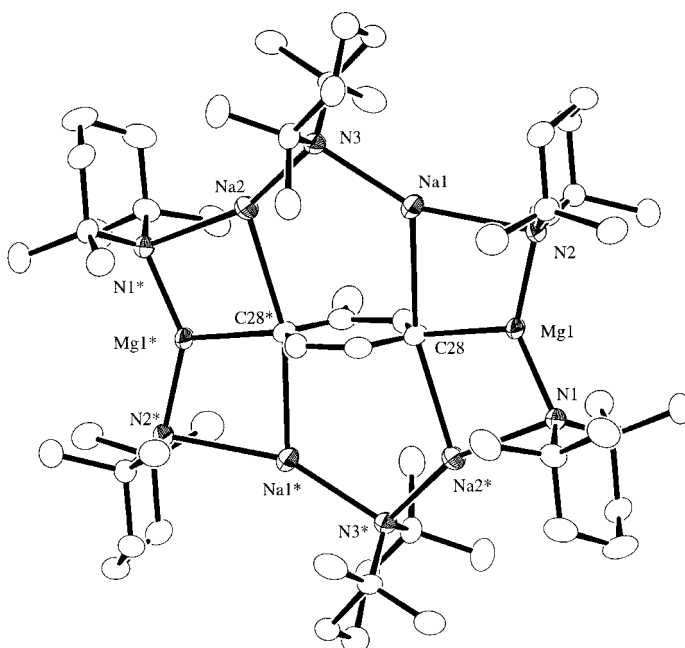


Figure 1. Molecular structure of **2** without hydrogen atoms and disorder component. Selected bond lengths [Å] and angles [°]: Na1–N2 2.626(2), Na1–N3 2.393(2), Na1–C28 2.691(2), Na2–N3 2.350(2), Na2–N1* 2.596(2), Na2–C28* 2.682(2), Mg1–N1 2.048(2), Mg1–N2 2.051(2), Mg1–C28 2.200(2); N2–Na1–N3 156.25(6), N2–Na1–C28 80.18(6), N3–Na1–C28 123.31(7), N3–Na2–N1* 160.54(6), N3–Na2–C28* 116.54(7), N1*–Na2–C28* 82.36(6), N1–Mg1–N2 142.85(7), N1–Mg1–C28 109.75(7), N2–Mg1–C28 107.32(7), Na1–C28–Na2* 164.17(9), Na1–C28–Mg1 83.38(7), Na2*–C28–Mg1 80.93(7), C29–C28–C30* 113.3(2). * = 1 – x, 1 – y, 1 – z.

[*] Prof. R. E. Mulvey, Dr. D. R. Armstrong, Dr. A. R. Kennedy, R. B. Rowlings
Department of Pure and Applied Chemistry
University of Strathclyde
Glasgow, G1 1XL (UK)
Fax: (+44) 141-552-0876
E-mail: r.e.mulvey@strath.ac.uk

[**] This work was supported by the UK Engineering and Physical Science Research Council.

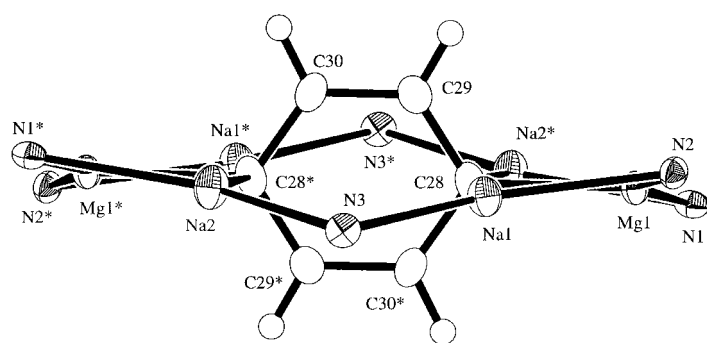


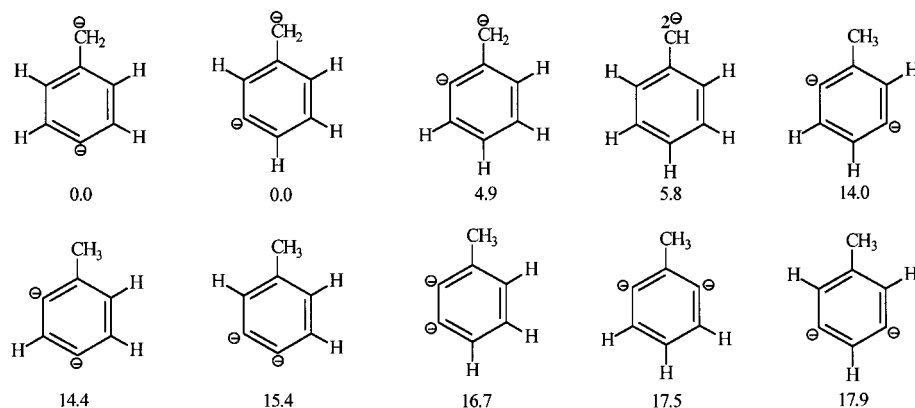
Figure 2. Side view of the molecular structure of **3** without amide carbon and hydrogen atoms. Selected bond lengths [Å] and angles [°]: Na1–N2 2.603(4), Na1–N3 2.387(4), Na1–C28 2.689(5), Na2–N3 2.350(4), Na2–N1* 2.591(4), Na2–C28* 2.676(5), Mg1–N1 2.049(4), Mg1–N2 2.037(4), Mg1–C28 2.192(5); N2–Na1–N3 157.4(1), N2–Na1–C28 80.2(1), N3–Na1–C28 122.1(1), N3–Na2–N1* 159.9(1), N3–Na2–C28* 117.6(1), N1*–Na2–C28* 81.8(1), N1–Mg1–N2 143.8(2), N1–Mg1–C28 108.8(2), N2–Mg1–C28 107.4(2), Na1–C28–Na2* 164.6(2), Na1–C28–Mg1 82.9(1), Na2*–C28–Mg1 81.7(1), C29–C28–C30* 112.7(4). * = 1 – x, 1 – y, 1 – z.

positions) are the same as those of the benzene dianion (1,4-positions); d) the two missing C–H σ bonds of each arene have been replaced by two C–Mg σ bonds; and e) these same C atoms each engage in π interactions with two Na⁺ ions that lie above and below the aromatic ring. The similarity between **2** and **3** extends to their respective dimensions. Significantly, the N–Na bond lengths within the NaNa units (mean over the two structures, 2.370 Å) are on average 0.234 Å shorter than those in the NaMg units (mean 2.604 Å). This is primarily a consequence of the large difference in the endocyclic bond angles at N (that is, mean 101.5° for N3 and 87.1° for N1/N2). The former bond lengths lie in the range of those found in the cyclic trimeric polymorph of [(Me₃Si)₂NNa]₃ (2.358–2.394 Å),^[4] while the latter compare well with those in [(hmds)₄Na₂Mg₂(O₂)_x(O)_y] (mean 2.572 Å). There is also good agreement between the N–Mg bond lengths (mean 2.046 Å) and exocyclic N–Mg–N bond angles (mean 143.3°) with corresponding values in [(hmds)₄Na₂Mg₂(O₂)_x(O)_y] (2.051 Å and 141.6°). The C–Mg bonds are slightly shorter (mean 2.196 Å) than those in polymeric [(Ph₂Mg)_∞] (2.261 Å),^[5] which has four-coordinate Mg centers (cf. three-coordinate here). These complete the distorted trigonal-planar Mg geometry. The same geometry is apparent at the Na center (range of summed bond angles 359.3–359.7°), confirming that the N–Na–N units are coplanar with the metalated C atoms to maximize C–Na π interactions. This is reflected by a mean distance of 2.684 Å, which places them toward the lower limit of interactions of this type (approximate range 2.6–3.2 Å) as presently recorded in the Cambridge Structural Database.^[6]

Metalation of toluene by reagents such as BuLi/TMEDA^[7] or BuNa^[8] predominantly yields the resonance-stabilized

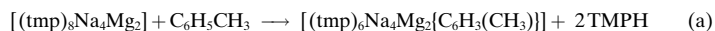
benzyl carbanion, the thermodynamically favored product. Kinetic control can bring about ring metalation, though generally only to a minor extent. It is therefore noteworthy that the toluene ring fragment in **2** is deprotonated at the diagonal *ortho*–*meta* positions and that the methyl group remains intact. While it is known that a complex mixture of polyolithiated species is generated on treating toluene with excess BuLi/TMEDA,^[9] significantly an *ortho*–*meta* dilithiated species is not among them. As a normal metalation would produce a benzyl group, the novel *ortho*–*meta*-directed metalation in **2** can be attributed to a special ring template effect. To give an estimation of the power of this effect, we have performed geometry-optimized ab initio MO calculations^[10] (at the B3LYP/6-311G (d,p) level)^[11] on the ten possible isomers formed when toluene is deprotonated twice (Scheme 1). These reveal that an energy deficit of 14.0 kcal mol^{−1} has to be overcome if the experimentally observed isomer is to be preferred to the most stable one (methyl-*para* or methyl-*meta* deprotonated) in a thermodynamically controlled reaction.

Clearly, on this evidence, the cationic ring of **2** or **3**, or more precisely its immediate precursor of unknown structure, must



Scheme 1. Relative energies of toluene-based dianions in kcal mol^{−1}.

possess exceptional proton abstraction capabilities, well beyond that of conventional magnesium amides. Presumably the precursor is (tmp)₈Na₄Mg₂, which must lose two ligands on reaction with the arene to give amine as a by-product [Eq. (a)].



Studies are in hand to examine whether the ring template effect^[12] can overturn the normal reactivity patterns of other core guest molecules. Anion-exchange possibilities are also under investigation.

Experimental Section

2 and **3**: Preparations were performed in Schlenk tubes under dry argon. To a mixture of *n*-butylsodium (10 mmol) and dibutylmagnesium (10 mmol) in hydrocarbon media, was added 2,2,6,6-tetramethylpiperidine (30 mmol). The cloudy solution produced was filtered through Celite. Addition of the appropriate arene in excess (5 mL) caused an immediate precipitation of a solid. This crude product was recrystallized from the same arene (50 mL),

in which it is only partially soluble. Colorless crystals of **2** or **3** were obtained by leaving the hot filtrates to cool on the bench. Yield of crystalline material (first batches) 26% and 27%, respectively; m.p. 180 °C (decomp) and 175 °C (decomp), respectively. Satisfactory C,H,Mg,N,Na analyses were obtained for both compounds.

Received: August 11, 1998 [Z122731E]
German version: *Angew. Chem.* **1999**, *111*, 231–233

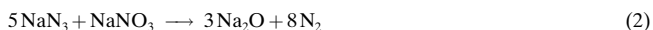
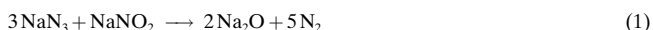
Keywords: alkali metals • alkaline earth metals • amides • arenes • macrocycles • template synthesis

A New and Simple Route to Alkali Metal Oxometalates**

Dieter Trinschek and Martin Jansen*

*Dedicated to Professor Edgar Niecke
on the occasion of his 60th birthday*

The alkali metal oxides are the strongest oxide bases available; the basicity increases from Li₂O to Cs₂O. Accordingly these exhibit pronounced reactivity in solid-state reactions to give ternary oxides. In particular, systematic research by Hoppe et al. has revealed that the cations in such ternary alkali metal oxometalates exhibit an extraordinarily wide variety of valence, structural chemistry, and physical properties. Insulators as well as ionic or metallic conductors, maximum (e.g. K₂FeO₄,^[1] K₆Co₂O₇^[2]) or minimum oxidation states (K₃FeO₂,^[3] Cs₃AuO^[4]), unusually low (K₂NiO₂^[5]) or high (Na₃NO₄^[6]) coordination numbers, and last but not least special coordination geometries (Na₄FeO₃,^[7] KCoO₂^[8]) are found in this class of compounds. However, the synthesis of these materials can be a rather tedious and difficult task. In particular, for the heavier alkali metals the procedure includes preparation and purification of the metals, their oxidation with molecular oxygen to oxides, peroxides, or hyperoxides with a well-defined composition. All preparative work including weighing and homogenizing the starting components must be performed under strictly inert conditions. Additional problems arise from the fact that the commonly used crucibles are attacked by the alkali metal oxides more or less severely. Finally, the reaction parameters must be chosen very carefully. In this paper we present a considerably simplified and generally applicable new route to multinary alkali metal oxometalates, which circumvents most of the difficulties noted above. The approach is based on the reaction of sodium azide with sodium nitrite or sodium nitrate, first described by Zintl and Baumbach^[9] [Eq. (1) and (2)]:



This particular method has not been generally accepted for the preparation of sodium oxide itself, because the components often react in an unforeseeable way, with a tendency to explode, which agrees with our own experiences. However, the reaction always proceeds in a controlled manner, if the starting materials already contain the particular oxide for the synthesis of the alkali metal oxometalate thus diluting the azide/nitrate mixture, and if the reaction is conducted in a closed container. Under these conditions the evolving N₂ can

- [1] A. R. Kennedy, R. E. Mulvey, R. B. Rowlings, *Angew. Chem.* **1998**, *110*, 3321; *Angew. Chem. Int. Ed.* **1998**, *37*, 3180.
- [2] M. F. Hawthorne, Z. Zheng, *Acc. Chem. Res.* **1997**, *30*, 267.
- [3] Crystal data: General: All measurements were made at 123 K on a Rigaku AFC7S diffractometer by using MoK_α radiation (λ = 0.71069 Å), scan method ω. Intensities were corrected for Lp effects only. Structures were solved by direct methods^[13] and refined on F using full-matrix least-squares.^[14] Details given for **2** with **3** in parentheses. C₆₁H₁₁₄Mg₂N₆Na₄ (C₆₀H₁₁₂Mg₂Na₄): 0.7 × 0.4 × 0.4 (0.4 × 0.15 × 0.12) mm³, monoclinic, P2₁/n, a = 15.277(2) (15.206(2)), b = 8.213(2) (8.175(3)), c = 25.541(6) (25.524(3)) Å, β = 94.277(14) (93.855(10))°, V = 3195(1) (3165(1)) Å³, ρ_{calcd} = 1.11 (1.11) g cm⁻³, μ = 0.105 (0.106) mm⁻¹, 2θ_{max} = 55 (45)°, 8128 (4674) data measured, 7844 (4490) unique, R_m = 0.021 (0.039). H atoms were placed in calculated positions and all other atoms were treated anisotropically. R = 0.0441 (0.0623), R_w = 0.0550 (0.0655), GOF = 1.66 (1.40) based on 4770 (2899) observations with I > 2σ(I), max/min residual electron density = 0.66/−0.31 (0.34/−0.28). Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-102591 and CCDC-102592. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [4] J. Knizek, I. Krossing, H. Nöth, H. Schwenk, T. Seifert, *Chem. Ber.* **1997**, *130*, 1053.
- [5] P. R. Markies, G. Schat, O. S. Akkerman, F. Bickelhaupt, W. J. J. Smeets, P. van der Sluis, A. L. Spek, *J. Organomet. Chem.* **1990**, *393*, 315.
- [6] F. H. Allen, O. Kennard, *Chem. Des. Autom. News* **1993**, *8*, 31.
- [7] A. J. Chalk, T. J. Hoogeboom, *J. Organomet. Chem.* **1968**, *11*, 615.
- [8] C. D. Broaddus, *J. Am. Chem. Soc.* **1966**, *88*, 4174.
- [9] R. West, P. C. Jones, *J. Am. Chem. Soc.* **1968**, *90*, 2656.
- [10] A. D. McLean, G. S. Chandler, *J. Chem. Phys.* **1980**, *72*, 5639.
- [11] A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648.
- [12] For examples of other metal-based ring systems made by a template approach see: R. W. Saalfrank, I. Bernt, E. Uller, F. Hampel, *Angew. Chem.* **1997**, *109*, 2596; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2482.
- [13] SIR: M. C. Burla, M. Camalli, G. Cascarano, C. Giacovazzo, G. Polidori, R. Spagna, D. Viterbo, *J. Appl. Crystallogr.* **1989**, *22*, 389.
- [14] SHELXL-97: G. M. Sheldrick, Universität Göttingen, Germany, **1997**.

[*] Prof. Dr. M. Jansen, Dr. D. Trinschek
Max-Planck-Institut für Festkörperforschung
Heisenbergstrasse 1, 70506 Stuttgart (Germany)
Fax: (+49) 711-689-1502
E-mail: hamilton@vsibml.mpi-stuttgart.mpg.de

[**] This work was funded by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

moderate the reaction by increasing the nitrogen partial pressure.

The cylindrical reaction container (Figure 1) is equipped with squeeze seals. While the body is made of 9S29 K steel, the inlay consists of special metals according to the requirements of the chemical system under study (Cu, Au, Pt, Ni, Fe in most cases).^[*] Although squeeze seals, which are less efficient than self-sealing systems (Bridgman seals), withstand the internal pressure to a certain degree, they let the nitrogen formed during the reaction escape safely.

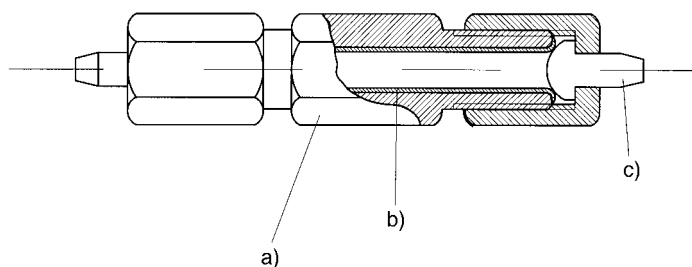
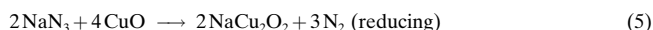
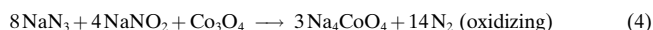
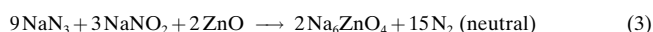


Figure 1. Construction of the crucible for the experiments. a) crucible (steel); b) inlay (e.g. copper); c) stopper (e.g. copper).

The process steps are always the same, independent of the particular system under investigation. The weighed mixture of starting materials consisting of the alkali metal azide, alkali metal nitrite, or alkali metal nitrate, and a selected binary oxide as the reaction partner are thoroughly mixed and homogenized. This is normally achieved by wet grinding (acetone, ethanol) in a planet-ball-mill. After removal of the solvent the starting mixture is dried and then put into the crucible, which is sealed after having replaced the air with nitrogen or argon. The temperature schedule applied has to be optimized for each system. However, it has proved to be advantageous to keep the heating rate low ($2\text{--}5\text{ K h}^{-1}$) at the decomposition temperature (ranging from 300 to 350°C) of the particular alkali metal azide.

The main advantage of the presented synthesis route is the simplification of the preparative work and the wide variety of systems that can be tackled. In addition to acid–base reactions without oxidation or reduction, it is also possible to perform redox reactions with simultaneous reduction or oxidation of the counteraction. The examples ([Eq. (3)–(5)] : see also Table 1) show that only the azide/nitrate or azide/nitrite ratio needs to be varied to obtain the desired result.



In most cases, the novel synthesis route yields the same ternary oxides of the alkali metals as those obtained from the direct reaction of the alkali metal oxides. However, in some cases the products are different. For instance, Na_3NO_4 has not

[*] Since the mixture of the azides and nitrates of K, Rb, and Cs frequently melts, in these cases we use vertically arranged crucibles of corundum or silver.

Table 1. Examples of reactions for the preparation of alkali metal oxometalates and alkali metal orthonitrates.

Compound	Reaction	Conditions $T[^\circ\text{C}]/t[\text{h}]$
Na_2ZnO_2 ^[12]	$3\text{NaN}_3 + \text{NaNO}_2 + 2\text{ZnO} \rightarrow 2\text{Na}_2\text{ZnO}_2 + 5\text{N}_2$	390/20
$\text{t-Na}_2\text{Zn}_2\text{O}_3$ ^[13]	$3\text{NaN}_3 + \text{NaNO}_2 + 4\text{ZnO} \rightarrow 2\text{Na}_2\text{Zn}_2\text{O}_3 + 5\text{N}_2$	650/50 ^[a]
$\text{Na}_{10}\text{Zn}_4\text{O}_9$ ^[14]	$15\text{NaN}_3 + 5\text{NaNO}_2 + 8\text{ZnO} \rightarrow 2\text{Na}_{10}\text{Zn}_4\text{O}_9 + 25\text{N}_2$	500/50
Na_4SiO_4 ^[15]	$3\text{NaN}_3 + \text{NaNO}_2 + \text{SiO}_2 \rightarrow \text{Na}_4\text{SiO}_4 + 5\text{N}_2$	500/50
Na_4TiO_4 ^[16]	$3\text{NaN}_3 + \text{NaNO}_2 + \text{TiO}_2 \rightarrow \text{Na}_4\text{TiO}_4 + 5\text{N}_2$	450/50
NaTiO_2 ^[17]	$\text{NaN}_3 + \text{TiO}_2 \rightarrow \text{NaTiO}_2 + 3/2\text{N}_2$	900/18
Na_3InO_4 ^[18]	$15\text{NaN}_3 + 5\text{NaNO}_2 + 2\text{In}_2\text{O}_3 \rightarrow 4\text{Na}_3\text{InO}_4 + 25\text{N}_2$	475/50
NaCuO ^[19]	$2\text{NaN}_3 + 2\text{CuO} \rightarrow 2\text{NaCuO} + 3\text{N}_2$	550/80
NaCu_2O_2 ^[20]	$2\text{NaN}_3 + 4\text{CuO} \rightarrow 2\text{NaCu}_2\text{O}_2 + 3\text{N}_2$	625/50
Na_4CoO_4 ^[21]	$8\text{NaN}_3 + 4\text{NaNO}_2 + \text{Co}_3\text{O}_4 \rightarrow 3\text{Na}_4\text{CoO}_4 + 14\text{N}_2$	550/20
Na_3NO_3 ^[10]	$4\text{NaN}_3 + 2\text{NaNO}_3 \rightarrow 2\text{Na}_3\text{NO}_3 + 6\text{N}_2$	400/24
K_3NO_3 ^[11]	$4\text{KN}_3 + 2\text{KNO}_3 \rightarrow 2\text{K}_3\text{NO}_3 + 6\text{N}_2$	420/24
KCuO ^[22]	$\text{KNO}_2 + 3\text{KN}_3 + 2\text{Cu}_2\text{O} \rightarrow 4\text{KCuO} + 5\text{N}_2$	460/48
NaNiO_2 ^[23]	$\text{NaN}_3 + \text{NaNO}_2 + 2\text{NiO} \rightarrow 2\text{NaNiO}_2 + 2\text{N}_2$	650/10 ^[b]
CsCuO ^[24]	$2\text{CsN}_3 + 2\text{CuO} \rightarrow 2\text{CsCuO} + 3/2\text{N}_2$	400/24
Cs_2ZnO_2 ^[25]	$5\text{CsN}_3 + \text{CsNO}_3 + 3\text{ZnO} \rightarrow 3\text{Cs}_2\text{ZnO}_2 + 8\text{N}_2$	410/24
Cs_2NiO_2 ^[5]	$5\text{CsN}_3 + \text{CsNO}_3 + 3\text{NiO} \rightarrow 3\text{Cs}_2\text{NiO}_2 + 8\text{N}_2$	420/50
Rb_2NiO_2 ^[5]	$5\text{RbN}_3 + \text{RbNO}_3 + 3\text{NiO} \rightarrow 3\text{Rb}_2\text{NiO}_2 + 8\text{N}_2$	420/48
RbCuO ^[26]	$2\text{RbN}_3 + 2\text{CuO} \rightarrow 2\text{RbCuO} + 3/2\text{N}_2$	450/50
Li_2NiO_2 ^[27]	$5\text{LiN}_3 + \text{LiNO}_3 + 3\text{NiO} \rightarrow 3\text{Li}_2\text{NiO}_2 + 8\text{N}_2$	450/50
LiCuO ^[22]	$2\text{LiN}_3 + 2\text{CuO} \rightarrow 2\text{LiCuO} + 3/2\text{N}_2$	450/50
LiTiO_2 ^[28]	$\text{LiN}_3 + \text{TiO}_2 \rightarrow \text{LiTiO}_2 + 3/2\text{N}_2$	820/5 ^[b]
LiTi_2O_4 ^[29]	$\text{LiN}_3 + 2\text{TiO}_2 \rightarrow \text{LiTi}_2\text{O}_4 + 3/2\text{N}_2$	820/5 ^[b]

[a] Sample was quenched. [b] Reaction time in days.

been available by the azide/nitrate route so far. Evidently, the oxide basicity of the alkali metal oxides is not fully reached. On the other hand, this method presents a way to obtain new sodium zincates that could not be synthesized by the traditional route in spite of intensive efforts. The reason might be that the starting materials are more efficiently homogenized, and that the in situ generated alkali metal oxide is highly reactive. How elegantly this azide/nitrate route works becomes evident when using it for the preparation of the alkali metal orthonitrates:^[10, 11] the only preparative step is to mix the appropriate amounts of the alkali metal nitrites, which are easily available and stable in air, with the respective azides and to start the reaction. Batches of several grams of starting materials yield very pure products.

In conclusion, the new synthesis route for the preparation of ternary alkali metal oxometalates presented herein combines several favorable aspects: general applicability for different chemical systems, the starting materials are easy to handle, and, finally, the alkali metal oxide is generated in situ in a highly reactive form.

Received: July 23, 1998

Revised version: September 4, 1998 [Z10722IE]

German version: *Angew. Chem.* **1999**, *111*, 234–235

Keywords: alkali metals • metal oxides • oxidations • reductions • solid-state syntheses

[1] B. Hefnerich, K. Lang, *Z. Anorg. Allg. Chem.* **1950**, 263, 169.

[2] M. Jansen, R. Hoppe, *Z. Anorg. Allg. Chem.* **1974**, 409, 152.

[3] F. Bernhardt, R. Hoppe, *Z. Anorg. Allg. Chem.* **1993**, 619, 969.

[4] C. Feldmann, M. Jansen, *Z. Anorg. Allg. Chem.* **1995**, 621, 201.

[5] H. Rieck, R. Hoppe, *Z. Anorg. Allg. Chem.* **1973**, 400, 311.

[6] M. Jansen, *Angew. Chem.* **1979**, 91, 762; *Angew. Chem. Int. Ed. Engl.* **1979**, 18, 698.

[7] H. Rieck, R. Hoppe, *Naturwissenschaften* **1974**, 61, 126.

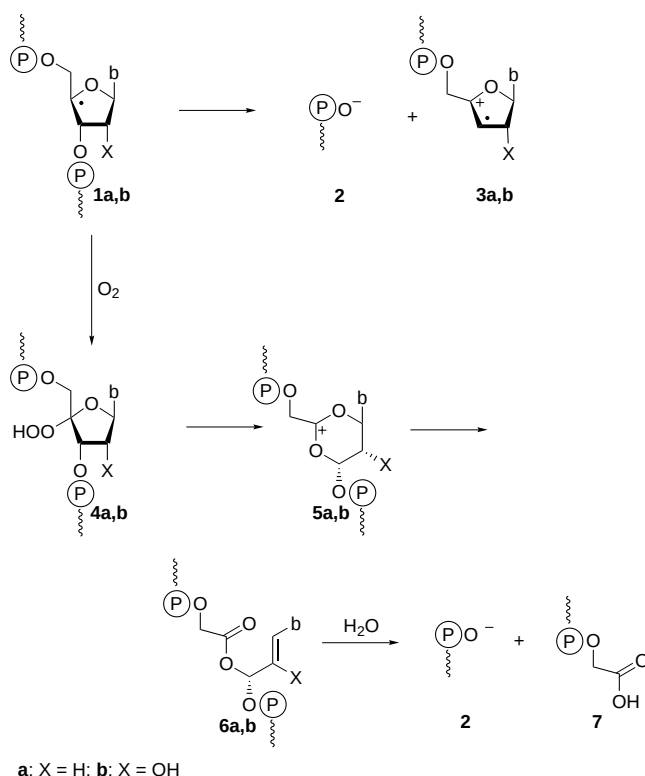
- [8] M. Jansen, R. Hoppe, *Z. Anorg. Allg. Chem.* **1975**, 417, 31.
 [9] E. Zintl, H. H. von Baumbach, *Z. Anorg. Allg. Chem.* **1931**, 198, 88.
 [10] H. Klassen, R. Hoppe, *Z. Anorg. Allg. Chem.* **1983**, 497, 70.
 [11] M. Jansen, B. Wolf, *Z. Anorg. Allg. Chem.* **1983**, 497, 65.
 [12] D. Trinschek, M. Jansen, *Z. Naturforsch. B* **1996**, 51, 711.
 [13] D. Trinschek, M. Jansen, *Z. Naturforsch. B* **1996**, 51, 917.
 [14] D. Trinschek, M. Jansen, *Z. Anorg. Allg. Chem.* **1996**, 622, 245.
 [15] M. G. Barker, P. G. Gadd, *J. Chem. Res. Synop.* **1981**, 274.
 [16] J. Kissel, R. Hoppe, *Z. Anorg. Allg. Chem.* **1990**, 582, 103.
 [17] P. Hagenmuller, A. Lecerf, M. Onillon, *C. R. Hebd. Seances Acad. Sci. Ser. B* **1962**, 255, 928.
 [18] G. Wagner, R. Hoppe, *Z. Anorg. Allg. Chem.* **1987**, 549, 15.
 [19] R. Hoppe, K. Hestermann, F. Schenk, *Z. Anorg. Allg. Chem.* **1969**, 367, 275.
 [20] G. Tams, H. Müller-Buschbaum, *J. Alloys Compd.* **1992**, 189, 241.
 [21] M. Jansen, *Z. Anorg. Allg. Chem.* **1975**, 417, 35.
 [22] H. Klassen, R. Hoppe, *Z. Anorg. Allg. Chem.* **1982**, 485, 101.
 [23] L. D. Dyer, B. S. Borie, G. P. Smith, *J. Am. Chem. Soc.* **1954**, 76, 1499.
 [24] K. Hestermann, R. Hoppe, *Z. Anorg. Allg. Chem.* **1969**, 367, 249.
 [25] K.-R. Wambach, R. Hoppe, *Z. Anorg. Allg. Chem.* **1978**, 444, 30.
 [26] R. Hoppe, K. Hestermann, F. Schenk, *Z. Anorg. Allg. Chem.* **1969**, 367, 275.
 [27] H. Rieck, R. Hoppe, *Z. Anorg. Allg. Chem.* **1972**, 372, 193.
 [28] T. Hewston, B. Chamberland, *J. Phys. Chem. Solids* **1988**, 75, 332.
 [29] P. Lambert, M. Morrison, P. Edwards, *J. Solid State Chem.* **1988**, 75, 332.

Differences Between 4'-RNA and 4'-DNA Radicals during Anaerobic and Aerobic Strand Cleavage**

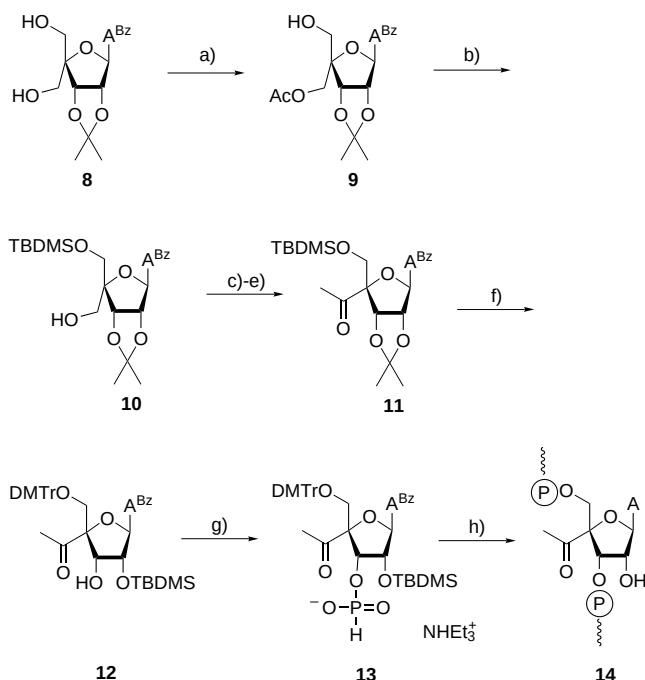
Harald Strittmatter, Adrian Dussy, Urs Schwitter, and Bernd Giese*

The mechanism of DNA strand cleavage by 4'-DNA radicals has been elucidated to a large extent in recent years.^[1] Under anaerobic conditions a spontaneous strand cleavage takes place whereby a heterolytic C,O bond scission at C3' leads to the 5'-phosphate **2** as the stable cleavage product (Scheme 1). In the presence of O₂ the 4'-DNA radical **1a** is converted first into hydroperoxide **4a**, then to cation **5a**, which after β -elimination (**5a** $\rightarrow$ **6a**) and subsequent hydrolysis leads to the stable cleavage products 5'-phosphate **2** and 3'-phosphoglycolate **7**.

The mechanism of the corresponding RNA cleavage, however, has been hardly investigated. Nevertheless, studies by Hecht^[2] have shown that bleomycin, which generates 4'-nucleotide radicals, cleaves RNA slower than DNA. Since bleomycin binds better to t-RNA^[3] than to DNA, the difference in cleavage efficiency might be explained by a difference in the reactivity of the 4'-oligonucleotide radical **1a** relative to **1b**. In order to prove this we have synthesized oligonucleotide **14** in which one ribonucleotide carries an acetyl group at position C4' (Scheme 2). In analogy to the



Scheme 1. Nucleotide strand cleavage by 4'-radicals under anaerobic and aerobic conditions. b = nucleobase. wavy line = nucleotide strand.



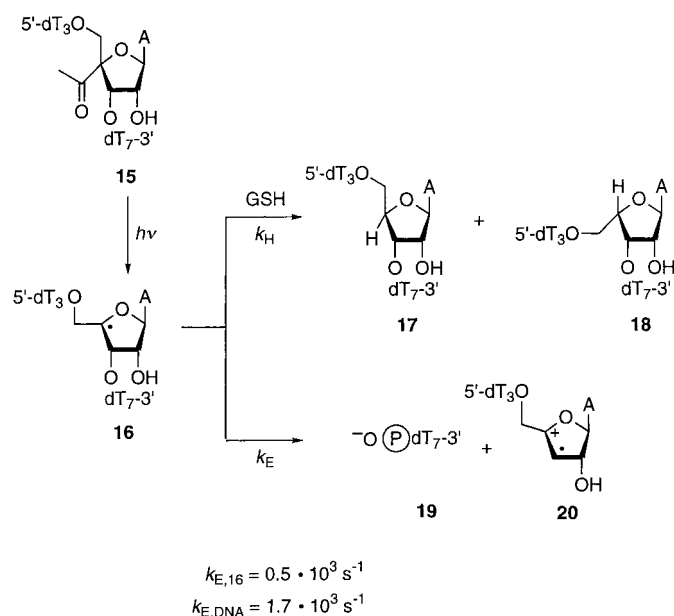
Scheme 2. Synthesis of 4'-acetylated RNA. a) MeC(OMe)₃, camphorsulfonic acid, 20 °C; HOAc, 0 °C, 42 %; in the second diastereomer (formed in 41 % yield) the acetyl group was cleaved off to reform nucleoside **8**; b) TBDMSO, imidazole, 40 °C; NaOMe, 20 °C, 5 min, 72 %; c) Dess-Martin periodinane, 80 %; d) MeMgCl, 93 %; e) Dess-Martin periodinane, 85 %; f) CF₃CO₂H; TBDMSO; CF₃CO₂H; DMTrCl; 68 %; g) PCl₃, 1,2,4-triazole; Me₃NH⁺ HCO₃⁻; 78 %; h) DNA synthesizer. A^{Bz} = benzyladenine, DMTr = 4,4'-dimethoxytrityl, dT = 2'-deoxyriboylthymine, TBDMS = *tert*-butyldimethylsilyl.

[*] Prof. Dr. B. Giese, Dipl.-Chem. H. Strittmatter, Dipl.-Chem. A. Dussy, Dr. U. Schwitter
 Institut für Organische Chemie der Universität
 St. Johannis-Ring 19, CH-4056 Basel (Switzerland)
 Fax: (+41) 61-267-1105
 E-mail: giese@ubaclu.unibas.ch

[**] This work was supported by the Swiss National Science Foundation.

photolysis experiments that were carried out with 4'-acylated deoxyribonucleotides^[4] compound **14** is a precursor of 4'-ribonucleotide radicals **1b**.

The synthesis starts from the known compound **8**^[5] and essentially follows the synthetic route that was worked out for the corresponding modified deoxyribonucleotides (Scheme 2).^[6] The 2',5'-protected phosphite **13** was used so that the oligonucleotide synthesis could be performed on a solid support.^[7] The rate of the spontaneous strand cleavage was measured by photolysis of the modified oligomer **15** to the 4'-RNA radical **16**, which was then trapped with an excess of glutathione diethyl ester (GSH; Scheme 3). The ratio of the rate constants k_H/k_E was obtained from the dependence of the product mixture (**17**+**18**)/**19** on the GSH concentration.^[8] With the rate of hydrogen abstraction $k_H = 1.0 \cdot 10^7 \text{ M}^{-1}\text{s}^{-1}$ ^[9] the rate of cleavage k_E of the 4'-ribonucleotide radical **16** was determined as $0.5 \cdot 10^3 \text{ s}^{-1}$. The cleavage rate of the corresponding 4'-DNA radical at $k_E = 1.7 \cdot 10^3 \text{ M}^{-1}\text{s}^{-1}$ was more than three times faster.^[10]

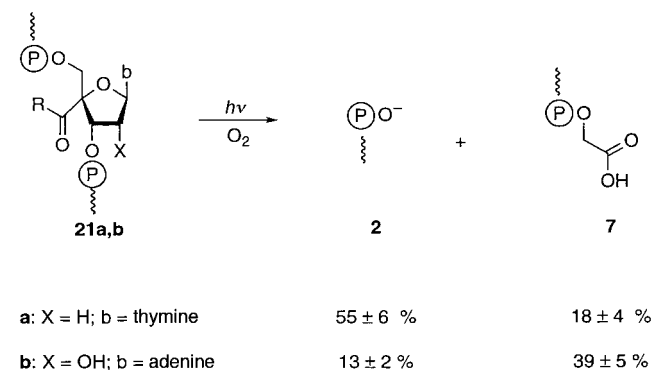


Scheme 3. Determination of the relative rate constants of the photo-induced strand cleavage. A = adenine.

This decrease in the rate of cleavage of 4'-ribonucleotide radicals can be interpreted by a destabilizing effect of the additional OH group on the radical cation **20**. Nevertheless, this effect is very small and we assume that the oligomeric radical cation is probably so well solvated by water molecules that the introduction of a 2'-OH group exerts only a slight destabilizing effect on the transition state of the reaction.^[11]

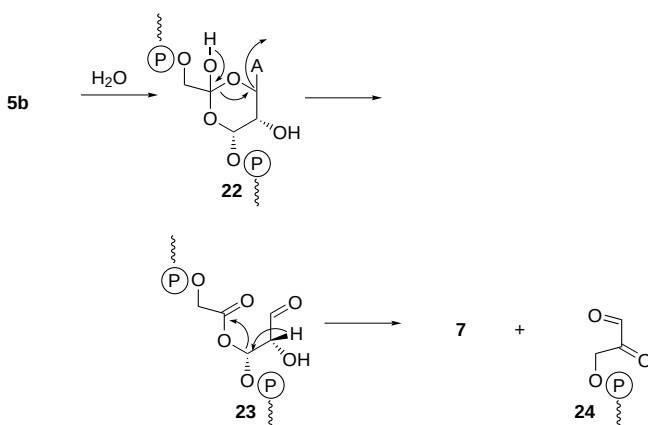
Experiments carried out under aerobic conditions, in which the hydroperoxides **4a, b** are intermediates,^[4a] should also be influenced by the presence of an additional 2'-OH group. Stubbe et al.^[12] have shown that the deoxyribonucleotide cation **5a**, formed by a Criegee rearrangement, opens the ring stereoselectively (**5a**→**6a**), whereby only the *pro-R* proton at C2' of **5a** is cleaved (Scheme 1). In the ribonucleotide this position is occupied by the OH group, so that the elimination

step (**5b**→**6b**) should be slowed down. Our experiments have now shown that the introduction of the 2'-OH group has a strong influence on the product composition obtained by aerobic cleavage. Whereas oligodeoxyribonucleotide **21a** yields preferentially the 5'-phosphate **2**, the 3'-phosphoglycolate **7** was obtained as the major product from ribonucleotide **21b** (Scheme 4).^[13] The preferred formation of 5'-phosphate **2**



Scheme 4. Difference in the product composition after aerobic photolytic strand cleavage.

from deoxyribonucleotides is in accordance with the Stubbe mechanism^[12] where intermediate **6a** cleaves the 5'-phosphate **2** in an S_N1 reaction (Scheme 1). The 3'-phosphoglycolate **7** is formed later on in the reaction pathway and thus is obtained in lower yield. In the ribose system **5b** the 2'-OH group slows down the elimination step (**5b**→**6b**) so that cation **5b** can be trapped by water in a competing reaction (**5b**→**22**). Fragmentation (**22**→**23**) and subsequent elimination (**23**→**7**+**24**) then leads to 3'-phosphoglycolate **7** as the cleavage product (Scheme 5). This additional pathway in RNA offers a possible explanation for the preferred formation of 3'-phosphoglycolate **7** during the aerobic strand cleavage of 4'-ribonucleotide radical **1b**.^[14]



Scheme 5. Trapping of cation **5b** by water, and subsequent fragmentation and elimination to give **7**.

The 2'-OH group in ribonucleotides influences the rate of the spontaneous cleavage of 4'-ribonucleotide radicals and changes the product composition under aerobic cleavage. Both effects originate from the retardation of reaction steps

1 → **2** + **3** and **5** → **6**, respectively, during RNA strand cleavage. Whereas the 2'-OH group accelerates the ionic cleavage of RNA relative to DNA,^[15] it slows down the radical-induced RNA strand cleavage.

Received: August 7, 1998 [Z 12265 IE]
German version: *Angew. Chem.* **1999**, *111*, 238–240

Keywords: DNA cleavage • nucleotides • radical ions • RNA

- [1] Review: W. K. Pogozelski, T. D. Tullius, *Chem. Rev.* **1998**, *98*, 1089.
- [2] a) S. M. Hecht, *Bioconjugate Chem.* **1994**, *5*, 513; b) S. M. Hecht, *Polynucleotide Cleavage and the Expression of Antitumor Activity by Bleomycin* (Ed.: S. M. Hecht), Kluwer Academic, Dordrecht, **1996**, p. 77.
- [3] C. E. Holmes, S. M. Hecht, *J. Biol. Chem.* **1993**, *268*, 25909.
- [4] a) B. Giese, X. Beyrich-Graf, P. Erdmann, M. Petretta, U. Schwitter, *Chem. Biol.* **1995**, *2*, 367; b) A. Marx, M. P. MacWilliams, T. A. Bickle, U. Schwitter, B. Giese, *J. Am. Chem. Soc.* **1997**, *119*, 1131.
- [5] R. Youssefyeh, D. Tegg, J. H. Verheyen, G. H. Jones, G. H. Moffat, *Tetrahedron Lett.* **1977**, *18*, 435.
- [6] The stereochemistry at C4' of nucleotide **11** was determined by NOE experiments. A medium-sized NOE effect was observed between 5'-H and 3'-H, a small NOE effect between C4'-(acetoxymethyl) and 1'-H, as well as between the methyl group of the acetate and one of the methyl groups of the isopropylidene protecting group.
- [7] Phosphite **13** was activated with pivaloyl chloride, subsequently coupled with the oligonucleotide bound to the solid phase, and the oligonucleotide synthesis was finally performed with a synthesizer.
- [8] An aqueous solution (100 µL) containing the modified oligonucleotide (about 0.3 nmol) and GSH (10–70 nmol) was irradiated for 5 min under argon (Osram 500 W, 320 nm filter, 30°C). The product separation was performed by HPLC on a reversed-phase column and the product analysis was done by MALDI-TOF MS. The relative ratio of the competing reaction rates k_H/k_E was determined from the ratio of products (**17** + **18**)/**19** and the glutathione concentration, see B. Giese, A. Dussy, E. Meggers, M. Petretta, U. Schwitter, *J. Am. Chem. Soc.* **1997**, *119*, 11130.
- [9] C. Tronche, F. N. Martinez, J. H. Horner, M. Newcomb, M. Senn, B. Giese, *Tetrahedron Lett.* **1996**, *37*, 5845.
- [10] These experiments were carried out as described in ref. [8].
- [11] In model studies with noncharged phosphate triesters in alcoholic solutions the effect of the 2'-OH group is considerably larger: D. Crich, X. Mo, *J. Am. Chem. Soc.* **1997**, *119*, 245. This shows how risky it is to extrapolate results obtained from model reactions with small molecules in organic solvents to explain biomolecules in water.
- [12] a) S. Ajmera, J. C. Wu, L. Worth, Jr., L. E. Rabow, J. Stubbe, J. W. Kozarich *Biochemistry* **1986**, *25*, 6586; b) G. H. McGall, L. E. Rabow, G. W. Ashley, S. H. Wu, J. W. Kozarich, J. Stubbe *J. Am. Chem. Soc.* **1992**, *114*, 4958.
- [13] The aqueous solution (200 µL) containing the modified oligonucleotide **21a** (5'-dCGCGT*TACTGCT-3') or **21b** (5'-d[TCTC]A*d[C-TAACTA]-3') (0.3 nmol) as well as GSH (about 75 nmol) was saturated with O₂. After photolyzing for 5–10 min (Osram 500 W, 320 nm filter, 25°C) the products were separated by HPLC on a reversed-phase column and the peaks were analyzed by MALDI-TOF MS. The compounds 5'-phosphate **2** and 3'-phosphoglycolate **7** were obtained in all experiments together with 2–8% of 3'-phosphate.
- [14] The preferred formation of 3'-phosphoglycolate **7** can also be explained by the Burger mechanism in which the cleavage of intermediate **6a** in DNA leads preferentially to **7**, see R. M. Burger, *Chem. Rev.* **1998**, *98*, 1153.
- [15] Review: B. N. Trawick, A. T. Daniher, J. K. Bashkin, *Chem. Rev.* **1998**, *98*, 939.

UF³⁺—A Thermochemically Stable Diatomic Trication with a Covalent Bond**

Detlef Schröder,* Martin Diefenbach, Thomas M. Klapötke, and Helmut Schwarz*

Dedicated to Professor Heinrich Nöth on the occasion of his 70th birthday

The chemistry and physics of multiply charged ions are attracting ongoing attention. One particular aspect concerns the quest for diatomic, thermochemically stable polycations. Here, thermochemical stability refers to a situation in which the polycation state ABⁿ⁺ is lower in energy than the dissociated fragments due to charge separation, that is A⁽ⁿ⁻¹⁾⁺ + B⁺. Since the ionization energies (IEs)^[1] of mono-cations AB⁺ are often much larger than those of the separated neutral atoms, IE(A) and IE(B), respectively, many diatomic dications are not thermochemically stable. Nevertheless, a number of thermochemically stable, diatomic dications have recently been studied by theoretical and experimental means.^[2] For diatomic trications, however, the energetic situation is even worse, because triple ionization of neutrals often requires enormous amounts of energy such that Coulomb explosion according to reaction (1) is energetically favorable.^[3]



First-principle considerations predict the existence of thermochemically stable diatomic trications for rare gas (Rg) complexes of metals M for which IE(M²⁺) is smaller than IE(Rg). For example, ThHe³⁺ should be stable with respect to charge separation according to reaction (1), simply because IE(Th²⁺) (18.3 eV) is smaller than IE(He) (24.5 eV); in fact, even the existence of ThHe⁴⁺ has been suggested.^[4] However, such highly charged rare-gas complexes offer limited conceptual insight into bonding principles because they are expected to have mostly electrostatic character.

In contrast, we are focussing on the generation of multiply charged molecules having well-defined covalent bonds in which for a diatomic trication it is the A³⁺–B bond energy which locates the ABⁿ⁺ ground state below the A⁽ⁿ⁻¹⁾⁺ + B⁺ asymptote.^[5] In this respect the UFⁿ⁺ (n = 1–3) cations deem promising, because the combination of uranium and fluorine appears as a good candidate with respect to thermochemical stability (Table 1). Thus, the ionization energies of uranium are moderate,^[6] while fluorine is the most electronegative element with a rather high IE (17.4 eV) and a pronounced

[*] Dr. D. Schröder, Prof. Dr. H. Schwarz
Dipl.-Chem. M. Diefenbach
Institut für Organische Chemie der Technischen Universität
Strasse des 17. Juni 135, D-10623 Berlin (Germany)
Fax: (+49)30-314-21102
Prof. Dr. T. M. Klapötke
Institut für Anorganische Chemie der Universität
Meiserstrasse 1, D-80333 München (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft, the Volkswagen-Stiftung, and the Fonds der Chemischen Industrie.

Table 1. Ground state electronic configurations, total energies [Hartree], adiabatic and vertical ionization energies [eV] of UF^{n+} ions ($n = 1-3$) and the corresponding atomic fragments.

		Config. ^[a]	E_{tot}	IE_a ^[b]	IE_v ^[b]
UF^{+} ^[c]	quintet	$(\sigma^2\sigma^2\pi^4\sigma^1\pi^1\delta^1\phi^1)$	-575.18535	12.01	12.04
UF^{2+} ^[c]	quartet	$(\sigma^2\sigma^2\pi^4\pi^1\delta^1\phi^1)$	-574.74414	21.85	22.01
UF^{3+} ^[c]	triplet	$(\sigma^2\sigma^2\pi^4\delta^1\phi^1)$	-573.94109		
U^+	quartet	$(7s^25f^3)$	-475.31115	11.82	
U^{2+}	quintet	$(5f^3)$	-474.87671	19.08	
U^{3+}	quartet	$(5f^3)$	-474.17571	32.32	
F^-	singlet	$(2s^22p^6)$	-99.74954	3.32 ^[d]	
F	doublet	$(2s^22p^5)$	-99.62761	17.27	
F^+	triplet	$(2s^22p^4)$	-98.99301		

[a] Only the occupations of the valence orbitals are given. Assuming ground states with maximal orbital momentum, these are ^5I for UF^+ , ^4I for UF^{2+} , and ^3H for UF^{3+} . [b] Ionization into the next charge state, that is $\text{A}^{n+} \rightarrow \text{A}^{(n+1)+}$. [c] Optimized bond lengths: 1.98 Å for UF^+ , 1.94 Å for UF^{2+} and 1.85 Å for UF^{3+} . [d] This entry corresponds to the electron affinity (EA).

tendency to form strong, significantly polarized covalent bonds to many metals.

A convenient route to generate multiply charged ions is provided by charge-stripping (CS) mass spectrometry^[7] in which mass-selected precursor cations are further ionized in high-energy collision experiments. For example, charge-stripping of UF^+ yields appreciable amounts of the UF^{2+} dication according to reaction (2), occurring in a collision with the target gas T.



The energy balance of reaction (2) is equal to the vertical ionization energy (IE_v) of the projectile ion. To a first approximation, this quantity can be measured by the kinetic energy loss of the dication beam; this quantity is usually referred to as the Q_{min} value.^[8] Accordingly, the energy-resolved CS spectrum of UF^+ gives $Q_{\text{min}} \approx \text{IE}_v(\text{UF}^+) = 11.8 \pm 0.5$ eV. This result agrees quite nicely with the theoretically predicted value of $\text{IE}_v(\text{UF}^+) = 12.04$ eV (Table 1). Using the almost negligible difference between the vertical and adiabatic ionization energies (IE_a), together with complementary thermochemical information,^[1] we conclude that UF^{2+} has a dissociation energy $D(\text{U}^{2+} - \text{F}) = 6.5$ eV and is stable towards Coulomb explosion into U^+ and F^+ by as much as 12.0 eV. Thus, not unexpectedly UF^{2+} adds to the series of thermochemically stable diatomic dications among the binary element fluorides.^[2]

In the same manner, UF^{3+} is accessible by subjecting mass-selected UF^{2+} to a CS experiment according to reaction (3). In



addition, UF^{3+} formed by electron ionization of gaseous UF_6 in the ion source was subjected to a charge-exchange (CE) experiment in which the trication is collided with a target gas to afford mono- and dications, respectively. Along with U–F bond cleavage to afford the U^{3+} fragment, the CE mass spectrum of mass-selected UF^{3+} (m/z 85.7) displays signals at m/z 126.5 and 257, respectively (Figure 1). In conjunction with the fragmentation pattern, these signals unambiguously confirm the identity of UF^{3+} as a genuine diatomic trication.

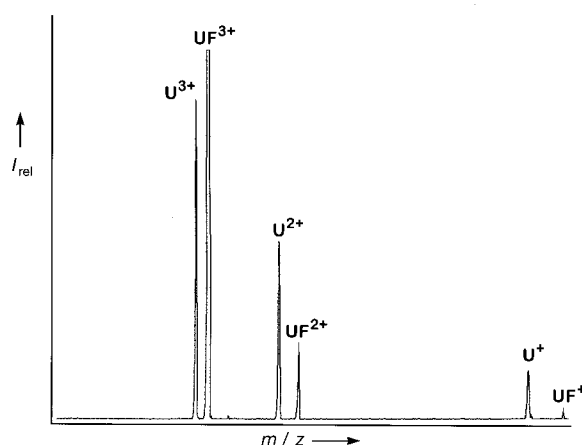


Figure 1. Charge-exchange mass spectrum of mass-selected UF^{3+} using neon as collision gas. In addition to fragmentation of the trication to afford $\text{U}^{3+} + \text{F}$, significant peaks due to the dicationic species U^{2+} and UF^{2+} as well as the corresponding monocations U^+ and UF^+ are observed. Note that the precursor UF^{3+} beam is off-scale (cut off at about 10% intensity).

Further, $Q_{\text{min}}(\text{UF}^{3+})$ is determined as 22.7 ± 1.0 eV by energy-resolved charge stripping.^[9] Assuming that $Q_{\text{min}} \approx \text{IE}_v$, this experimental number is again in good agreement with the calculated values of $\text{IE}_v(\text{UF}^{2+}) = 22.01$ eV and $\text{IE}_a(\text{UF}^{2+}) = 21.85$ eV, respectively (Table 1).

The key issue is the thermochemical stability of UF^{3+} trication. To our surprise, the higher ionization energies of the uranium atom are ill-defined. Thus, a recent compilation of Liu et al.^[6] quotes several experimental values for $\text{IE}(\text{U}^+)$ such as 11.07, 11.45, and 11.59 eV, while for $\text{IE}(\text{U}^{2+})$ the discrepancy between the experimental values is even larger, that is 17.73, 17.92, and 19.8 eV. In their detailed theoretical study, Liu et al. predict $\text{IE}(\text{U}^+) = 12.00$ eV and $\text{IE}(\text{U}^{2+}) = 18.62$ eV at the ACPF level of theory. Our less sophisticated CCSD(T) approach yields $\text{IE}(\text{U}^+) = 11.82$ eV and $\text{IE}(\text{U}^{2+}) = 19.08$ eV which is in acceptable agreement with the ACPF results. It appears premature, however, to adopt either of these values uncritically, because the spread of the experimental data is most likely due to systematic rather than statistical errors, and the computational approaches do not explicitly consider the appreciable spin-orbit coupling of uranium, but rather treat it in a state-averaged manner. As far as our calculations of UF^{n+} are concerned a further complication arises from the fact that the four uncoupled electrons in UF^+ , three in UF^{2+} , and two in UF^{3+} give rise to a vast manifold of low-lying electronic states with different occupations of the more or less nonbonding 5f orbitals. For the time being, we will not dwell on these aspects any further and shall simply rely on the theoretical data due to the reasonable agreement of the calculated and measured ionization energies for UF^{n+} ($n = 1, 2$).

Accordingly, not only UF^{2+} , but also UF^{3+} is predicted to be a thermochemically stable polycation with $D(\text{U}^{3+} - \text{F}) = 3.7$ eV and $D(\text{U}^{2+} - \text{F}^+) = 1.9$ eV, respectively (Figure 2). Hence, it is the favorable U – F interaction which brings the trication below the asymptote for Coulomb explosion to yield $\text{U}^{2+} + \text{F}^+$, that is the covalent bonding in the trication compensates for $\text{IE}(\text{U}^{2+}) > \text{IE}(\text{F})$. Besides this mere energetic

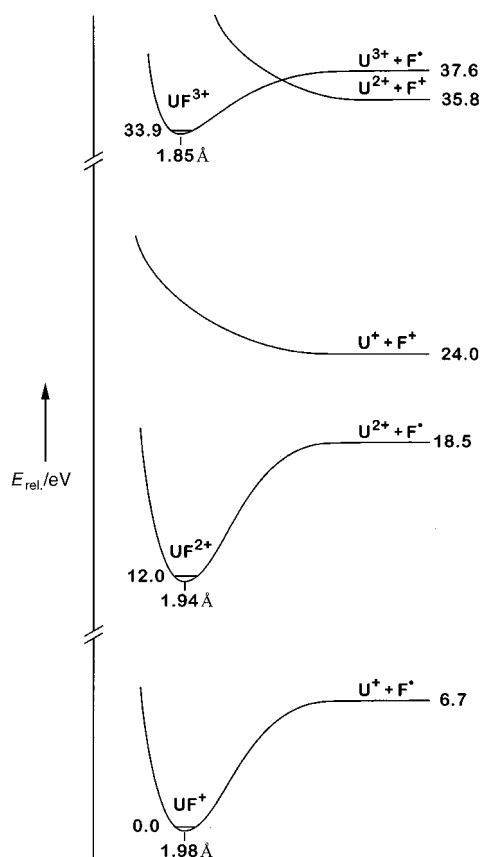


Figure 2. Schematic energy diagram for UF^{n+} ions ($n=1-3$) and the associated dissociation asymptotes. Note that the energy axis (in eV) is not proportional.

analysis, covalent bonding in the trication is also implied by the formal charge on uranium which amounts to 3.4 in the trication as compared to 2.6 in the di- and 1.6 in the monocation, respectively. Thus, even in UF^{3+} trication, fluorine acts as a strongly electron-withdrawing ligand which further increases the charge on uranium.

Finally, let us address an apparent discrepancy of the calculated and experimental thermochemistry of UF^{n+} ($n=1-3$). Thus, for the monocation our calculations predict $D(\text{U}^+-\text{F})=6.7$ eV, while a value of 4.9 ± 0.5 eV has been derived in an early guided-ion beam study from the threshold of about 1.4 eV associated with reaction (4).^[10]



Although the experimental approach used in this earlier study was not that advanced as nowadays,^[11] we will not doubt the threshold measurement in itself. However, recent experimental and theoretical studies indicate that formal F-atom transfer to a metal cation is associated with a considerable barrier due to the electron-transfer harpoon-like mechanism involved.^[12, 13] Thus, the experimental value derived from reaction (4) may better be regarded as a lower limit for $D(\text{U}^+-\text{F})$ which is consistent with the calculated figure.

In conclusion, UF^{3+} is predicted as the first diatomic trication whose thermochemical stability is due to covalent

bonding in the triply charged state. Nevertheless, this deduction relies on the computed ionization energies of uranium. Hence, a more accurate experimental evaluation of these fundamental quantities is very much indicated. In turn, future theoretical approaches need to explicitly incorporate spin-orbit effects for an accurate energetic description of coordinatively unsaturated uranium compounds such as UF^{n+} ($n=1-3$).

Experimental and Computational Procedures

The experiments were performed with a modified VG ZAB/HF/AMD 604 four-sector mass spectrometer of BEBE configuration (B stands for magnetic and E for electric sectors), which has been described elsewhere.^[14] UF^{n+} ions ($n=1-3$) were generated by electron ionization (electron energy 50–100 eV) of gaseous UF_6 . After acceleration by a 8 kV voltage, the ions of interest were mass-selected using B(1)E(1) at a mass resolution of $m/\Delta m \approx 4000$. The charge-stripping experiments^[15] of monocations were performed by colliding the ions with oxygen (50–80 % transmission, T); for charge stripping of dications, helium and neon were used as collision gases.^[5] $Q_{\min}$ values were determined by energy scans with E(1) for B(1) mass-selected species at energy resolutions of $E/\Delta E \approx 6000$. As references for the calibration of the energy scale, we applied the commonly used toluene standard^[8] assuming $Q_{\min}=15.7$ eV for the transition $\text{C}_7\text{H}_8^+ \rightarrow \text{C}_7\text{H}_8^{2+}$. Due to hardware limitations of the A/D interface, the $Q_{\min}$ values were acquired as single-scans with an x/y recorder in order to achieve maximal energy resolution; indications for the presence of electronically excited precursor ions were not observed in the charge-stripping experiments.^[15, 16] The other spectra were accumulated and on-line processed with the AMD/Intetra data system; five to 50 spectra were averaged to improve the signal-to-noise ratio.

Within the scope of a conceptual description of UF^{n+} ($n=1-3$), a complete coverage of all possible states at a highly correlated level is simply too demanding. As a compromise, we have determined the low-lying electronic states using the ADF program package^[17] at the non-local spin density level (VWN exchange-correlation functional with Becke88/Perdew86 gradient corrections). A first-order treatment of relativity was achieved by inclusion of scalar relativistic effects by means of a Pauli–Hamiltonian. The inner 78 electrons ($[\text{Xe}] 5d^{10} 4f^{14}$) of uranium and the two 1s electrons of fluorine were treated with the frozen-core approximation, while triple- ζ basis sets were used for the remaining valence electrons. Each configuration arising from distribution of the uncoupled electrons into the nonbonding 5f orbitals has been examined, and the U–F distances were optimized separately. This procedure leads to a manifold of low-lying configurations, e.g. 22 quintet and triplet states of UF^+ within 2 eV. Then, the lowest roots (< 0.35 eV) were examined further using the restricted open-shell coupled cluster method CCSD(T) as implemented in MOLPRO 96.^[18] For each species, the minimum geometry was re-optimized. In these calculations, we employed the quasi-relativistic effective 60-core electron pseudo potential and the associated (12s11p10d8f)/[8s7p6d4f] valence basis set by Küchle et al.^[19] which was augmented by two g-type polarization functions (exponents: 1.2649 and 0.5060).^[20] For fluorine, the aug-cc-pVTZ basis set was used.^[21] Except for the 1s electrons of fluorine, the 5s, 5p, and 5d electrons of uranium, all valence electrons were correlated in the calculations.

Received: July 29, 1998 [Z12217IE]

German version: *Angew. Chem.* **1999**, *111*, 206–209

Keywords: ab initio calculations • dications • trications • uranium

[1] Unless mentioned otherwise, all auxiliary thermochemical data are taken from: S. G. Lias, J. E. Bartmess, J. F. Liebman, J. L. Holmes, R. D. Levin, W. G. Mallard, *J. Phys. Chem. Ref. Data* **1988**, *17*, Suppl. 1. Part of the compilation is available in the internet, see: <http://webbook.nist.gov/chemistry>.

- [2] For a survey, see: M. Kolbuszewski, J. S. Wright, R. J. Buenker *J. Chem. Phys.* **1995**, *102*, 7519.
- [3] Only a very few diatomic trications have been studied so far; for recent theoretical studies and leading references P. J. Bruna, J. S. Wright, *J. Phys. B* **1993**, *26*, 1819; R. C. Mahwhinney, P. J. Bruna, F. Grein, *J. Phys. B* **1995**, *28*, 4015. For metastable X_2^{3+} ($X = \text{Cl}, \text{Br}, \text{I}$), see: H. Stapelfeldt, E. Constant, M. Y. Ivanov, D. R. Matusek, J. S. Wright, P. B. Corkum, *Phys. Rev. Lett.* **1998**, *81*, 2217.
- [4] M. Hotokka, T. Kindstedt, P. Pykkö, B. O. Roos, *Mol. Phys.* **1984**, *52*, 23.
- [5] D. Schröder, J. N. Harvey, H. Schwarz, *J. Phys. Chem. A* **1998**, *102*, 3639.
- [6] Unlike most other elements, the higher ionization energies of uranium are not known precisely; for a survey, see: W. Liu, W. Küchle, M. Dolg, *Phys. Rev. A* **1998**, *58*, 1103.
- [7] T. Ast, *Adv. Mass Spectrom. A* **1980**, *8*, 555.
- [8] K. Lammertsma, P. von R. Schleyer, H. Schwarz, *Angew. Chem.* **1989**, *101*, 1313; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1321.
- [9] The increased error in the Q_{min} value of the dication is mostly due to some uncertainties with respect to the adequate calibration Scheme to be applied, for a discussion see ref. [5].
- [10] P. B. Armentrout, J. L. Beauchamp *J. Phys. Chem.* **1981**, *85*, 4103.
- [11] P. B. Armentrout, B. L. Kickel, in *Organometallic Ion Chemistry* (Ed. B. S. Freiser), Kluwer, Dordrecht, **1996**, p. 1.
- [12] H. H. Cornehl, G. Hornung, H. Schwarz *J. Am. Chem. Soc.* **1996**, *118*, 9960.
- [13] J. N. Harvey, D. Schröder, W. Koch, D. Danovich, S. Shaik, H. Schwarz *Chem. Phys. Lett.* **1997**, *278*, 391.
- [14] R. Srinivas, D. Sülzle, T. Weiske, H. Schwarz *Int. J. Mass Spectrom. Ion Processes* **1991**, *107*, 368; R. Srinivas, D. Sülzle, W. Koch, C. H. DePuy, H. Schwarz *J. Am. Chem. Soc.* **1991**, *113*, 5970.
- [15] T. Ast, C. J. Proctor, C. J. Porter, J. H. Beynon, *Int. J. Mass Spectrom. Ion Phys.* **1981**, *40*, 111; C. J. Proctor, C. J. Porter, T. Ast, J. H. Beynon, *Int. J. Mass Spectrom. Ion Phys.* **1982**, *41*, 251; C. J. Porter, C. J. Proctor, T. Ast, J. H. Beynon, *Int. J. Mass Spectrom. Ion Phys.* **1982**, *41*, 265; M. Rabrenovic, T. Ast, J. H. Beynon, *Int. J. Mass Spectrom. Ion Processes* **1984**, *61*, 31.
- [16] For an example, see: C. Heinemann, D. Schröder, H. Schwarz *J. Phys. Chem.* **1995**, *99*, 16195.
- [17] Amsterdam density functional (ADF), version 2.3.0, Theoretical Chemistry, Vrije Universiteit, Amsterdam, see: G. te Velde, E. J. Baerends *J. Comp. Phys.* **1992**, *99*, 84.
- [18] MOLPRO 96.4 is a package of ab initio programs written by H.-J. Werner and P. J. Knowles with contributions from: J. Almlöf, R. D. Amos, M. J. O. Deegan, S. T. Elbert, C. Hampel, W. Meyer, K. Peterson, R. Pitzer, A. J. Stone, and P. R. Taylor.
- [19] W. Küchle, M. Dolg, H. Stoll, H. Preuss *J. Chem. Phys.* **1994**, *100*, 7535.
- [20] H. H. Cornehl, C. Heinemann, J. Marcalo, A. Pires de Matos, H. Schwarz, *Angew. Chem.* **1996**, *108*, 950; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 891.
- [21] R. A. Kendall, T. H. Dunning, Jr., R. J. Harrison *J. Chem. Phys.* **1992**, *96*, 6769.

Rational Synthesis of Stable Channel-Like Cavities with Methane Gas Adsorption Properties: $[\{\text{Cu}_2(\text{pzdc})_2(\text{L})\}_n]$ (pzdc = pyrazine-2,3-dicarboxylate; L = a Pillar Ligand)**

Mitsuru Kondo, Takashi Okubo, Akiko Asami, Shin-ichiro Noro, Tomomichi Yoshitomi, Susumu Kitagawa,* Tomohiko Ishii, Hiroyuki Matsuzaka, and Kenji Seki

The synthesis and characterization of coordination networks with channel structures that provide new sizes, shapes, and chemical environments are of great current interest.^[1–5] This is not only because of their intriguing structural diversity, but also because of their potential for applications in molecular adsorption, ion exchange, and heterogeneous catalysis.^[2, 6–10] However, the synthesis of such functional porous networks is often unsuccessful, because of the formation of an interpenetrating structure, which provides only small-sized channels or none at all.^[1, 11–17] Another reason could be the deformation of the channel structure on the removal of the included guest molecules.

Although several porous structures have been reported, the methods for synthesizing stable porous networks are still in their infancy. Some successful examples of multidimensional networks that have been synthesized and structurally characterized to date are: $[\{\text{M}_2(4,4'\text{-bpy})_3(\text{NO}_3)_4\}_n]$ ($\text{M} = \text{Co}, \text{Ni}, \text{Zn}$; 4,4'-bpy = 4,4'-bipyridine),^[18] $[\{\text{Ag}(\text{teb})(\text{CF}_3\text{SO}_3)\}_n]$ (teb = 1,3,5-tris(3-ethynylbenzonitrile)benzene),^[19] $[\{\text{Zn}_2(\text{btc})(\text{NO}_3) \cdot (\text{H}_2\text{O})(\text{C}_2\text{H}_5\text{OH})_5\}_n]$ (btc = 1,3,5-benzenetricarboxylate),^[1] and $[\{\text{Zn}_3(\text{bdc})_3 \cdot 2\text{CH}_3\text{OH}\}_n]$ (bdc = 1,4-benzenedicarboxylate).^[20]

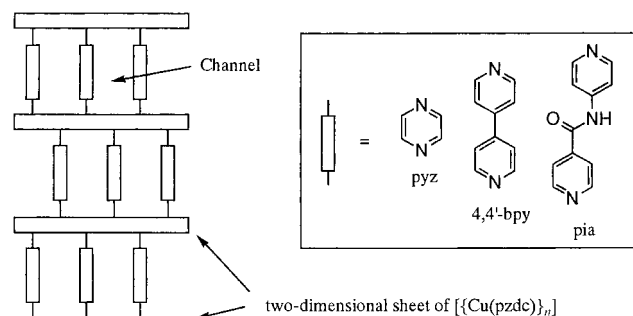
It has been demonstrated that the pillared-layer structure is effective for the construction of three-dimensional networks with large channels.^[21] Although this type of network has been investigated in the hydrogen-bonded assembly of organic molecules, the organic pillared-layer structures obtained are unstable in the absence of included guest molecules.^[21, 22] In comparison, coordination networks give more stable struc-

[*] Prof. Dr. S. Kitagawa, Dr. M. Kondo
Department of Synthetic Chemistry and Biological Chemistry
Graduate School of Engineering, Kyoto University
Yoshida, Sakyo-ku, Kyoto 606–8501 (Japan)
Fax: (+81) 75-753-4979
E-mail: kitagawa@sbchem.kyoto-u.ac.jp
T. Okubo, A. Asami, S. Noro, T. Yoshitomi, Dr. T. Ishii,
Dr. H. Matsuzaka
Department of Chemistry, Graduate School of Science
Tokyo Metropolitan University
Minami-ohsawa Hachioji, Tokyo 192–0397 (Japan)
K. Seki
Energy Conversion and
Storage Technology Applied Research Center
Research and Development Department, Osaka Gas Co., Ltd.
Torishima, Konohana-ku, Osaka 554-0051 (Japan)

[**] This work was supported by the Kao Foundation for Arts and Science and a Grant-in-Aid for Scientific Research from the Japanese Ministry of Education, Science and Culture.

 Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.

tures.^[22] We have developed a new method for synthesizing stable pillared-layer structures using coordination networks (Scheme 1), and have succeeded in the syntheses of porous



Scheme 1. Schematic representation of the pillared-layer structures of $[[\text{Cu}_2(\text{pzdc})_2(\text{L})] \cdot x\text{H}_2\text{O}]_n$. pzdc = pyrazine-2,3-dicarboxylate; 1: L = pyz, $x = 2$; 2: L = 4,4'-bpy, $x = 5$; 3: L = pia, $x = 5$.

materials with various new channel properties. Complex **1** was prepared by the reaction of $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ with Na_2pzdc and pyrazine in water. The crystal structure of this complex was determined by X-ray crystallography, and Figure 1 shows the ORTEP drawing around the Cu^{II} center; three carboxylate oxygen atoms, one nitrogen atom of pzdc, and one nitrogen atom of pyrazine form a distorted square-pyramidal geometry around the Cu^{II} atom.

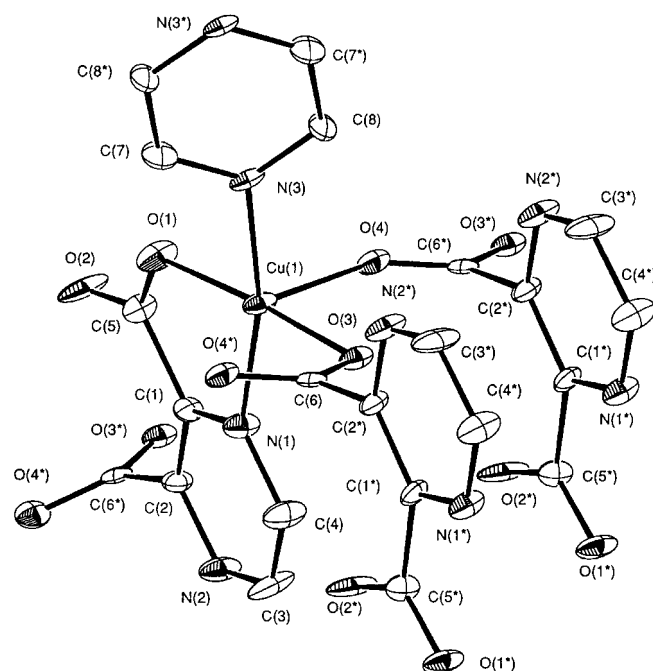


Figure 1. ORTEP drawing of the structure of **1** around the Cu center (30% probability ellipsoids). Hydrogen atoms are omitted for clarity. Selected bond lengths [Å] and angles [°]: Cu(1)–N(1) 1.99(1), Cu(1)–N(3) 2.04(1), Cu(1)–O(1) 1.947(9), Cu(1)–O(3) 1.973(8), Cu(1)–O(4) 2.21(1); N(1)–Cu(1)–N(3) 167.8(5), N(1)–Cu(1)–O(1) 81.9(4), N(1)–Cu(1)–O(3) 95.9(4), N(1)–Cu(1)–O(4) 86.8(4), N(3)–Cu(1)–O(1) 91.0(4), N(3)–Cu(1)–O(3) 90.6(4), N(3)–Cu(1)–O(4) 103.2(4), O(1)–Cu(1)–O(3) 176.0(4), O(1)–Cu(1)–O(4) 90.4(4), O(3)–Cu(1)–O(4) 92.9(4).

This complex consists of a two-dimensional sheet of $[[\text{Cu}(\text{pzdc})]_n]$ and pillar pyrazine ligands that bridge each sheet. The pzdc unit links the three Cu^{II} atoms; one nitrogen atom from pzdc and one oxygen atom from the carboxylate group chelate with the Cu^{II} atom, while each oxygen atom of the other carboxylate group forms a monodentate ligand with two Cu^{II} atoms. The remaining nitrogen atom from pzdc does not associate with any other atoms. As a result, an extended neutral two-dimensional sheet is formed in the ac plane (Figure 2). The sheet has a puckered structure with a thickness of about 7.5 Å; it has no large cavities, and forms no interpenetrating networks.

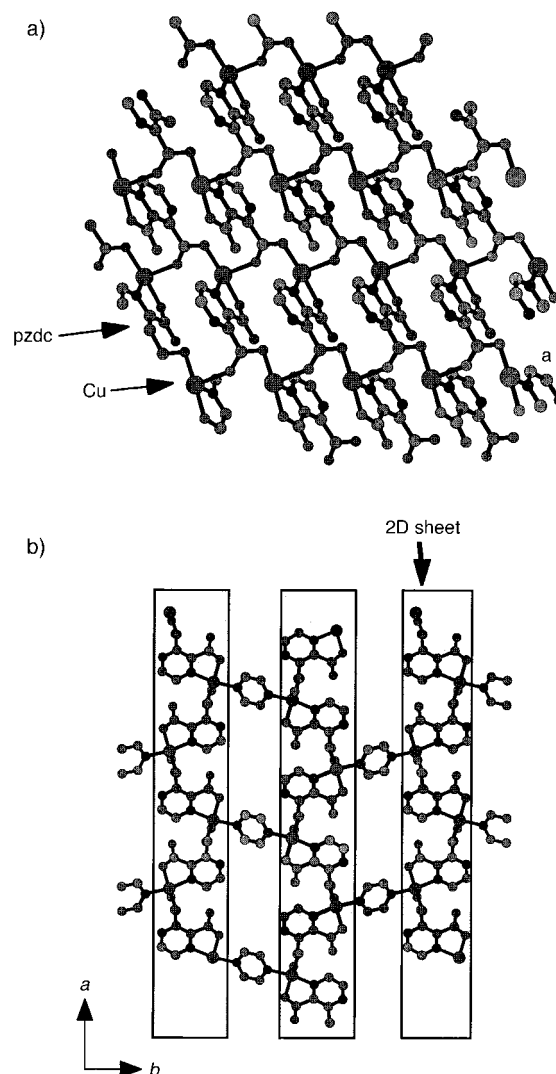


Figure 2. a) View of the two-dimensional sheet. b) Crystal structure of **1** along the c axis. Solvent water molecules and hydrogen atoms are omitted for clarity.

Coordination of the pyz ligands to the Cu^{II} atoms provides a pillared-layer structure, in which each two-dimensional sheet is separated by about 3 Å (Figure 2b). The regular arrangement of the pillar ligands along the a axis with spacings of 11 Å creates extended channels along the c axis with dimensions of about 4×6 Å.^[23] These channels are occupied by water molecules which are linked with carboxylate oxygen

atom (O(2)) through a hydrogen-bonding interaction (O(5)–O(2) 2.91(1) Å).

The dimensions and characteristics of channel structures of this network are apparently controllable depending on the kinds of pillar ligands used. This new adaptable structure prompted us to construct coordination networks with new channel properties in which sizes and chemical environments could be varied. For this purpose, two pillar ligands, 4,4'-bpy and pia were selected; the former provides larger pore sizes, while the latter creates larger channels with specific hydrogen bonding interaction sites for guest molecules. These two complexes were successfully synthesized by using similar procedures for the preparation of **1**, and obtained as microcrystals. The formation of similar pillared-layer networks was confirmed by elemental analyses and X-ray powder diffraction (XRPD) patterns, whose shifts of the (0*n*0) reflections demonstrate the elongated *b* axes of **2** (29.0 Å) and **3** (32.6 Å) compared with that of **1** (19.849(2) Å). These observations are in agreement with the expected elongation of the corresponding pillar ligands. From these results, the channel dimensions of **2** and **3** are estimated to be about 9 × 6 Å and 10 × 6 Å, respectively.

In order to examine the thermal stability of these porous networks, thermal gravimetric (TG) analyses and measurements of the XRPD patterns were carried out. The TG curve of **1** illustrates release of the included water molecules up to 100 °C, followed by release of ligand molecules from 260 to 310 °C. No chemical decomposition was observed between 100 and 260 °C. The structure of this stable phase was studied by measuring the XRPD pattern at 100 °C under reduced pressure. Figure 3 shows the observed XRPD patterns compared with the simulated powder pattern obtained upon removal of water from the single-crystal model of **1**. The good agreement of the peaks in both diagrams demonstrates that

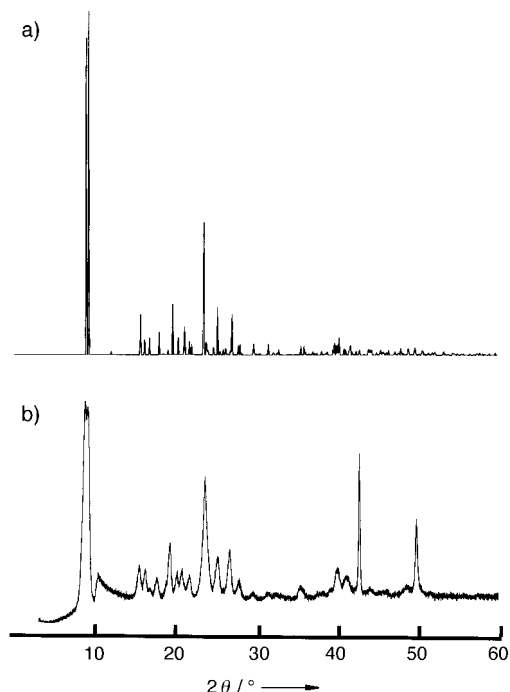


Figure 3. a) Simulated and b) experimental X-ray powder diffraction diagrams of **1** after removal of water.

the porous network is retained in this phase, indicating that porosity is retained in the absence of the included guest molecules. Similar stability was also observed for complexes **2** and **3**.

In order to examine the porous functionality of these synthetic materials, their methane adsorption capabilities were measured. Gas adsorption activity is one of the most attractive properties of porous materials such as zeolites.^[24–26] Figure 4 displays the results of the adsorption activity experiments of anhydrous complexes **1–3**, which were obtained by

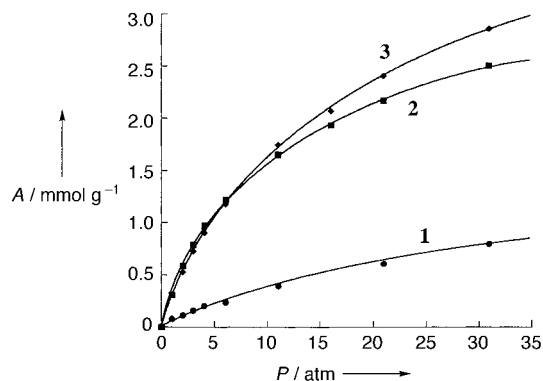


Figure 4. Adsorption isotherms for **1–3** obtained with CH₄ between 1 and 36 atm. *A* = absolute adsorption [mmol g^{−1}].

drying under vacuum with methane between 1 and 31 atm. A rapid increase in the amount of adsorbed gas is shown by an increase in pressure of up to 5 atm, which represents the diffusion of methane into the channels. These isotherms are of type I according to the IUPAC classification.^[27] Approximately 0.8 mmol, 2.5 mmol, and 2.9 mmol of methane were adsorbed per 1.0 g of anhydrous samples of **1**, **2**, and **3**, respectively, at a pressure of 31 atm. The increased methane adsorption activity for **2** and **3** compared to that of **1** is consistent with the larger channel sizes of these complexes. This activity is comparable to that of zeolites^[28, 29] and a stable porous network of [M₂(4,4'-bpy)₃(NO₃)₄] (M = Co, Ni, Zn),^[18] which we reported recently.

Experimental Section

Synthesis of **1**: Na₂pzdc (0.21 g, 1.00 mmol) in H₂O (20 mL) was slowly added to the H₂O solution (20 mL) containing Cu(ClO₄)₂ · 6 H₂O (0.37 g, 1.00 mmol) and pyz (1.0 g, 12.5 mmol). The blue microcrystals obtained were collected by filtration, and dried under reduced pressure for 2 h. Yield 0.26 g (90 %). Elemental analysis calcd for C₁₆H₁₂Cu₂N₆O₁₀ (%): C 33.40, H 2.10, N 14.61; found: C 32.78, H 1.57, N 14.34.

Complexes **2** and **3** were prepared analogously in EtOH/H₂O (1/1) media. **2**: Elemental analysis calcd for C₂₂H₂₂Cu₂N₆O₁₃ (%): C 37.45, H 3.14, N 11.91; found: C 37.44, H 3.30, N 11.67. **3**: Elemental analysis calcd for C₂₃H₂₃Cu₂N₇O₁₄ (%): C 36.90, H 3.10, N 13.10; found: C 37.63, H 3.20, N 12.23.

X-ray structure determination of **1**: All measurements were made on a Rigaku AFC7R diffractometer with graphite-monochromated MoK_α radiation and a 12 kW rotating anode generator. The unit cell constant was obtained from a least-squares refinement using the setting angles of 25 carefully centered reflections with 2θ values in the range of 20.03° < 2θ < 24.34°. The structure was solved by direct methods and refined by the block-diagonal least-squares method. Hydrogen atoms except for those in water molecules were placed at calculated positions, but their parameters

were not refined. The final refinements were carried out using full-matrix least-squares techniques for non-hydrogen atoms. All calculations were performed using the TEXSAN crystallographic software package of Molecular Structure Corporation. Crystal data: $C_{16}H_{12}Cu_2N_6O_{10}$, $M_r = 575.40$, orthorhombic, space group $P2_1/c$, $a = 4.693(3)$, $b = 19.849(2)$, $c = 11.096(2)$ Å, $\beta = 96.90(2)^\circ$, $V = 1026.1(6)$ Å³, $Z = 2$, $\rho_{\text{calcd}} = 1.862$ g cm⁻³, $\lambda(\text{MoK}\alpha) = 0.71069$ Å, $F(000) = 576$, $\mu(\text{MoK}\alpha) = 21.43$ cm⁻¹, $T = 25^\circ\text{C}$, $2\theta_{\text{max}} = 55.1^\circ$, 2447 reflections measured, 934 observed ($I > 2.00\sigma(I)$), number of parameters 155; $R = 0.062$, $R_w = 0.062$. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-103110. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Gas adsorption measurements: The adsorption isotherms of CH₄ gas were measured according to the reported procedure.^[18, 24, 25] The apparatus was equipped with a Cahn R-100 electrobalance contained within a SUS steel pressure chamber which was connected with two separate lines for evacuation and adsorbate gas pressurization. Prior to adsorption measurement, in order to remove the solvated water molecules, the sample (50–80 mg) was dried under reduced pressure at 25 °C until no further weight loss was observed. The adsorbate CH₄ was dosed into the adsorption chamber, then the change of the weight of the sample was monitored. The entire adsorption isotherms were determined by increasing the adsorbate gas pressure to a maximum of 31 atm.

Received: June 2, 1998

Revised version: August 24, 1998 [Z11933IE]

German version: *Angew. Chem.* **1999**, *111*, 190–193

Keywords: copper • crystal engineering • gas adsorption • microporosity • solid-state structures

- [1] O. M. Yaghi, C. E. Davis, G. Li, H. Li, *J. Am. Chem. Soc.* **1997**, *119*, 2861–2868.
- [2] O. M. Yaghi, H. Li, T. L. Groy, *J. Am. Chem. Soc.* **1996**, *118*, 9096–9101.
- [3] O. M. Yaghi, G. Li, H. Li, *Nature* **1995**, *378*, 703–706.
- [4] C. Janiak, *Angew. Chem.* **1997**, *109*, 1499–1502; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1431–1434.
- [5] S. Kawata, S. Kitagawa, H. Kumagai, C. Kudo, H. Kamesaki, T. Ishiyama, R. Suzuki, M. Kondo, M. Katada, *Inorg. Chem.* **1996**, *35*, 4449–4461.
- [6] M. A. Withersby, A. J. Blake, N. R. Champness, P. Hubberstey, W.-S. Li, M. Schröder, *Angew. Chem.* **1997**, *109*, 2421–2423; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2327–2329.
- [7] O. M. Yaghi, H. Li, *J. Am. Chem. Soc.* **1995**, *117*, 10401–10402.
- [8] S. Subramanian, M. J. Zaworotko, *Angew. Chem.* **1995**, *107*, 2295–2297; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2127–2129.
- [9] O. M. Yaghi, H. Li, *J. Am. Chem. Soc.* **1996**, *118*, 295–296.
- [10] M. Fujita, Y. J. Kwon, S. Washizu, K. Ogura, *J. Am. Chem. Soc.* **1994**, *116*, 1151–1152.
- [11] O. M. Yaghi, G. Li, *Angew. Chem.* **1995**, *107*, 232–234; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 207–209.
- [12] L. Carlucci, G. Ciani, D. M. Proserpio, A. Sironi, *J. Chem. Soc. Chem. Commun.* **1994**, 2755–2756.
- [13] L. R. MacGillivray, S. Subramanian, M. J. Zaworotko, *J. Chem. Soc. Chem. Commun.* **1994**, 1325–1326.
- [14] P. C. M. Duncan, D. M. L. Goodgame, S. Menzer, D. J. Williams, *Chem. Commun.* **1996**, 2127–2128.
- [15] L. Carlucci, G. Ciani, D. M. Proserpio, A. Sironi, *J. Am. Chem. Soc.* **1995**, *117*, 12861–12862.
- [16] B. F. Hoskins, R. Robson, *J. Am. Chem. Soc.* **1990**, *112*, 1546–1554.
- [17] R. W. Gable, B. F. Hoskins, R. Robson, *J. Chem. Soc. Chem. Commun.* **1990**, 1677–1678.
- [18] M. Kondo, T. Yoshitomi, K. Seki, H. Matsuzaka, S. Kitagawa, *Angew. Chem.* **1997**, *109*, 1844–1846; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1725–1727.

- [19] D. Venkataraman, G. B. Gardner, S. Lee, J. S. Moore, *J. Am. Chem. Soc.* **1995**, *117*, 11600–11601.
- [20] H. Li, C. E. Davis, T. L. Groy, D. G. Kelley, O. M. Yaghi, *J. Am. Chem. Soc.* **1998**, *120*, 2186–2187.
- [21] V. A. Russell, C. C. Evans, W. Li, M. D. Ward, *Science* **1997**, *276*, 575–579.
- [22] S. C. Zimmerman, *Science* **1997**, *276*, 543–544.
- [23] The cavity sizes are estimated from the van der Waals radii of constituent atoms.
- [24] J. L. Zuech, A. L. Hines, E. D. Sloan, *Ind. Eng. Chem. Process Des. Dev.* **1983**, *22*, 172–174.
- [25] S.-Y. Zhang, O. Talu, D. T. Hayhurst, *J. Phys. Chem.* **1991**, *95*, 1722–1726.
- [26] T. C. Golden, S. Sircar, *J. Colloid Interface Sci.* **1994**, *162*, 182–188.
- [27] IUPAC, *Pure. Appl. Chem.* **1985**, *57*, 603–619.
- [28] Zeolites 13X and 5A adsorb 2.3 mmol g⁻¹ and 2.8 mmol g⁻¹ of CH₄ at 30 atm, respectively.
- [29] L. Mentastay, A. M. Woestyn, G. Zgrablich, *Adsorp. Sci. Technol.* **1994**, *11*, 123–133.

Formation of Supramolecular Polymers from Homoditopic Molecules Containing Secondary Ammonium Ions and Crown Ether Moieties**

Nori Yamaguchi and Harry W. Gibson*

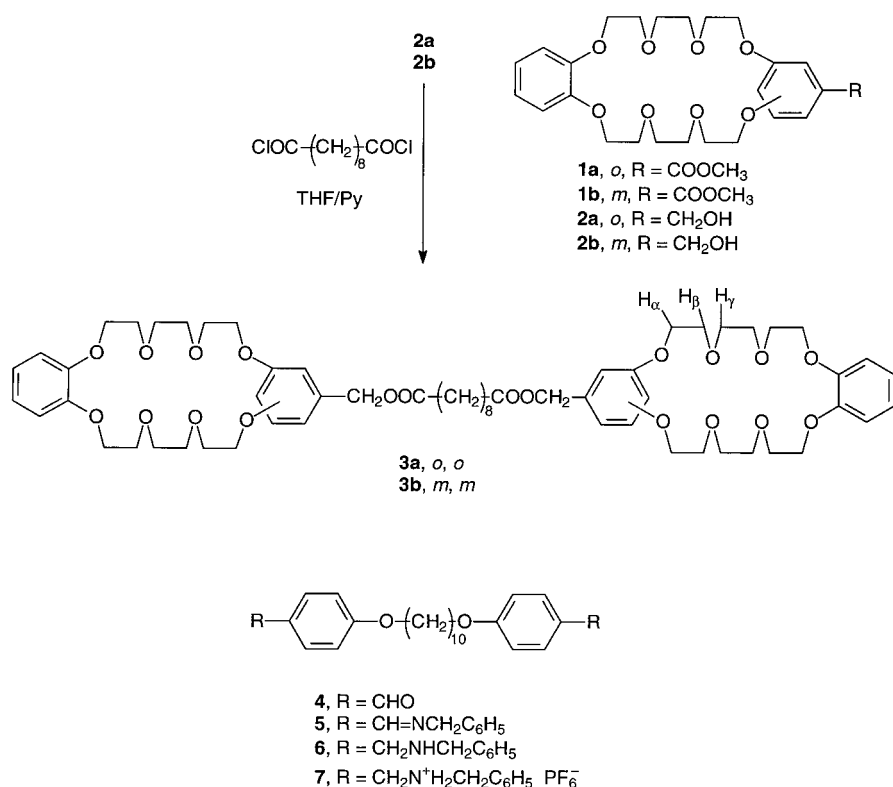
Chemists are extending the concept of self-organizing noncovalent interactions into the field of material science to control and engineer linear and network supramolecular polymers.^[1] Such interactions permit reversibility in the polymeric materials at the molecular level to afford thermodynamically controlled suprastructures.^[2] This factor is advantageous for producing polymers with the potential for commercial use, since kinetically induced defects in conventional covalently bonded polymers are irreversible.

Strong associations between self-organizing building blocks promote the construction of well-defined supramolecular polymeric materials with properties comparable to covalent polymers.^[3] This prompted us to utilize a simple system with dibenzylammonium hexafluorophosphate and dibenzo-[24]crown-8 (DB24C8) units, between which the association constant is desirably high ($K_a = 2.7 \times 10^4 \text{ M}^{-1}$ in [D₃]chloroform at 25 °C).^[4] Association of homoditopic molecules that contain such complimentary units spontaneously leads to reversible chain extension in 1:1 stoichiometric solutions to form linear supramolecular polymers based on pseudorotaxane formation.

The synthetic methodologies employed for the homoditopic molecules are depicted in Scheme 1 and the constructions

[*] Prof. H. W. Gibson, N. Yamaguchi
Department of Chemistry
Virginia Polytechnic Institute and State University
Blacksburg, Virginia, 24061 (USA)
Fax: (+1) 540-231-8517
E-mail: hwgibson@vt.edu

[**] This work was supported by the National Science Foundation (CHE95-21738). The authors thank Prof. H. Marand for his helpful discussions on the thermal analyses of the supramolecular polymers. Mass spectra were provided by the Washington University Mass Spectrometry Resource, an NIH Research Resource (Grant No. P41RR0954).



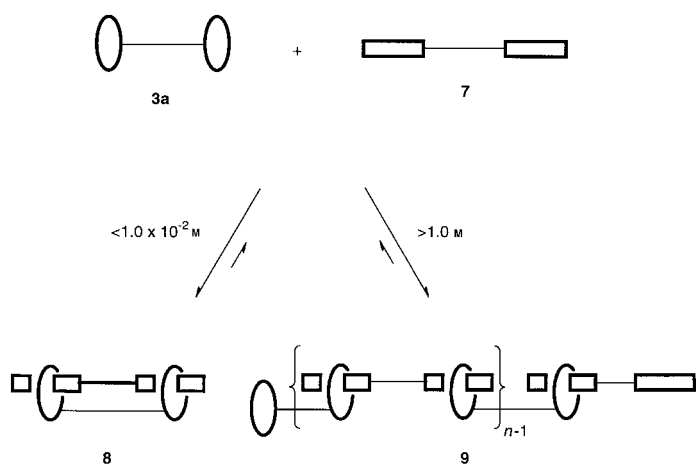
Scheme 1. Syntheses of **3a**, **3b**, and **7**.

of self-organized supramolecules are illustrated in Scheme 2. The ¹H NMR spectrum of an equimolar solution of **3a** and **7** in [D₆]acetone/[D₃]chloroform (1/1) at 22 °C showed three

adopted by **8**. A series of 1.0×10^{-2} M solutions of **7** were prepared with non-stoichiometric amounts of **3a** (from 2.0×10^{-2} to 8.0×10^{-2} M) and the ¹H NMR spectra were recorded at 22 °C (Figure 2) so that the two sets of signals could be assigned properly. An increase in the concentration of **3a** with respect to **7** shifts the complexation equilibrium toward the formation of the 1:2 complex **7**:(**3a**)₂, which emulates the repeating sequence in **9**. Since the signals at $\delta = 4.53$ and 4.63 become more intense while the signals at $\delta = 4.45$ and 4.74 become less intense as the concentration of **3a** increases the former (inner) signals correspond to the benzylic protons of complexed **7** in the linearly linked chain **9** and the latter (outer) signals to those in the 1:1 cyclic dimer **8**.

The ¹H NMR spectra (Figure 1) recorded at different concentrations of equimolar solutions of **3a** and **7** in [D₆]acetone/[D₃]chloroform (1/1) at 22 °C revealed that both the ratio of **8**:**9** and the extent of aggregation in **9**

are concentration dependent. At lower equimolar concentrations (less than 1.0×10^{-2} M) the ¹H NMR spectra revealed more intense signals for complexed **7** in the cyclic dimer **8** than



Scheme 2. Illustration of the construction of the supramolecules **8** and **9** from **3a** and **7**.

sets of signals for the benzylic protons of **7** (Figure 1 d).^[5] Two of these can be attributed to the signals for complexed **7** while the other set corresponds to the signals for uncomplexed **7** based on the argument of slow exchange on the ¹H NMR time scale. The two sets of signals for complexed **7** arise from two different pseudorotaxane structures, the cyclic dimer **8** and linear chain **9**. The chemical shifts of the signals for complexed **7** in the 1:1 cyclic dimer **8** are unique from those in the linearly linked chain **9** as a consequence of the discrete geometry

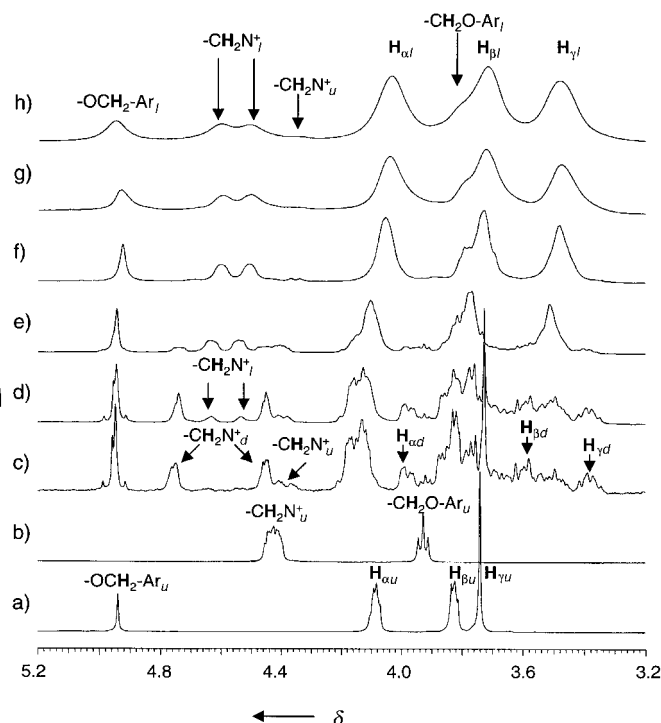


Figure 1. The stacked ¹H NMR spectra (400 MHz, [D₆]acetone/CDCl₃ (1/1), 22 °C) of solutions of **3a** and **7** at various concentrations: a) 1.0×10^{-2} M, b) $0/1.0 \times 10^{-2}$ M, and equimolar solutions c) 1.0×10^{-3} M, d) 1.0×10^{-2} M, e) 0.10 M, f) 0.50 M, g) 1.0 M, and h) 2.0 M. The three sets of signals are for uncomplexed **3a** and **7** (*u*), **8** (*d*), and **9** (*l*).

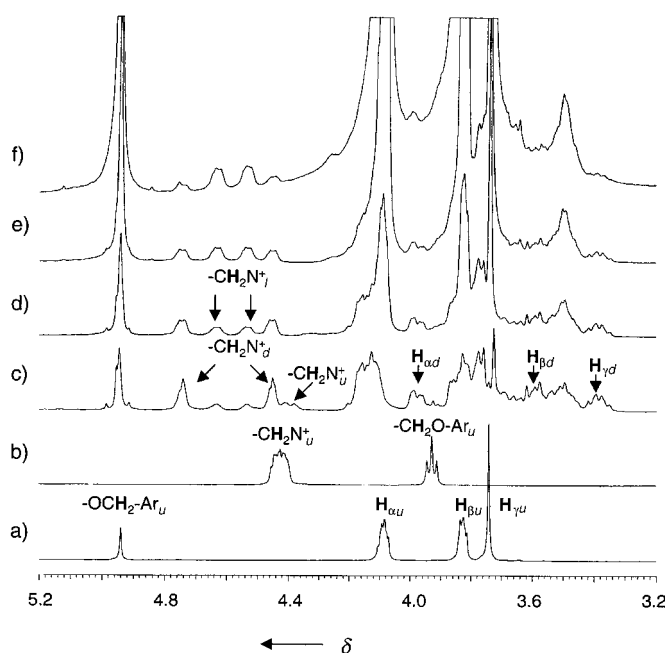


Figure 2. The stacked ^1H NMR spectra (400 MHz, $[\text{D}_6]\text{acetone}/[\text{D}_3]\text{chloroform}$ (1/1), 22°C) of solutions of **3a** and **7** at a) $1.0 \times 10^{-2}/0\text{M}$, b) $0/1.0 \times 10^{-2}\text{M}$, c) $1.0 \times 10^{-2}/1.0 \times 10^{-2}\text{M}$, d) $2.0 \times 10^{-2}/1.0 \times 10^{-2}\text{M}$, e) $4.0 \times 10^{-2}/1.0 \times 10^{-2}\text{M}$, f) $8.0 \times 10^{-2}/1.0 \times 10^{-2}\text{M}$. The three sets of signals are for uncomplexed **3a** and **7** (**u**), **8** (**d**), and **9** (**l**).

in the linear chain **9**. For instance, 72 and 66% of each homoditopic molecule are consumed to form the 1:1 cyclic dimer **8** in 1.0×10^{-3} and $1.0 \times 10^{-2}\text{M}$ equimolar solutions at 22°C , respectively (Table 1). The NOESY spectrum of the $1.0 \times 10^{-3}\text{M}$ equimolar solution recorded at 22°C showed a through-space interaction between the protons of the methylene units of corresponding homoditopic molecules **3a** and **7**, which indicated the presence of the 1:1 cyclic dimer **8**. In contrast, the signals for the 1:1 cyclic dimer are no longer observed (Figure 1h) at the highest equimolar concentration we examined (2.0M), which indicated its absence.^[6] Since the concentrations of the end groups in the supramolecular polymers **9** are readily determined by integration of the signal for uncomplexed **7** in the ^1H NMR spectra, one can estimate

Table 1. Percentages of ammonium ion moieties in dimer **8** and supramolecular polymer **9**, and the average number of repeat units n in **9**.^[a]

Equimolar conc. [M]	% 7 in 8 at $22/-40^\circ\text{C}$	% uncomplexed 7 at $22/-40^\circ\text{C}$	$n^{[c]}$ at $22/-40^\circ\text{C}$	$M_n^{[d]}$ [kDa] at $22/-40^\circ\text{C}$
2.0	0/- ^[b]	5.5/- ^[b]	9.1/- ^[b]	18/- ^[b]
1.0	3.4/- ^[b]	6.4/- ^[b]	7.5/- ^[b]	15/- ^[b]
0.50	12/15	7.9/5.1	5.6/8.3	11/16
0.10	23/27	20/5.4	1.9/6.8	3.8/13
0.01	66/81	16/4.3	1.1/2.2	2.2/4.4
0.001	72/94	20/2.3	0.70/1.3	1.4/2.6

[a] Calculated from the ^1H NMR spectra of equimolar solutions ($[\text{D}_6]\text{acetone}/[\text{D}_3]\text{chloroform}$, 1/1) of **3a** and **7** at various concentrations and temperatures. [b] The ^1H NMR spectra of the 2.0 and 1.0M equimolar solutions recorded at lower temperatures exhibited severe signal broadening, which prevented accurate signal integration. [c] For the determination of n see reference [7]. [d] The number average molecular weight (M_n) of the aggregate was calculated from the following equation; $M_n = n \times 1980\text{ Da}$ (repeat unit mass).

the average molecular weight of the linearly linked chain **9** at a given concentration (Table 1).^[7] For instance, in the 1.0M equimolar solution $M_n = 15\text{ kDa}$ ($n = 7.5$), while the 2.0M equimolar solution^[8] gives an even higher molecular weight of 18 kDa ($n = 9.1$). Substantially broadened signals (Figures 1g and 1h) strongly support the formation of large supramolecular polymers **9** in solution.^[9]

The plot of reduced viscosity η_{red} versus concentration of equimolar solutions of **3a** and **7** in chloroform/acetone (1/1) at 22°C is nonlinear (Figure 3b), which reflects the increase in size of the supramolecular polymer **9** with concentration, as

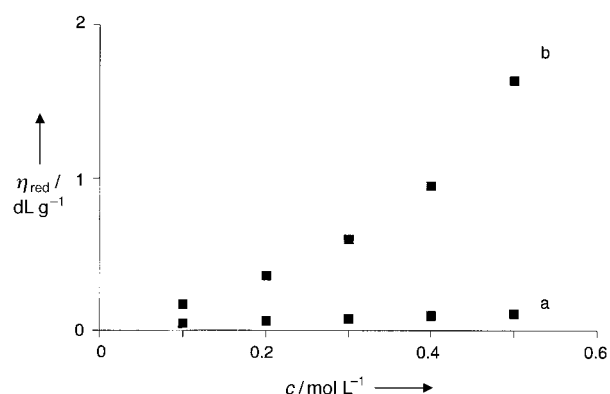


Figure 3. Reduced viscosity η_{red} as a function of concentration c in acetone/chloroform (1/1) at 22°C for a) **3b** and **7** and b) **3a** and **7**.

shown by the ^1H NMR data. In fact the viscosities of 1.0 and 2.0M equimolar solutions were too high to measure by this method. On the other hand, a completely different solution viscosity profile was observed for equimolar solutions of **3b**, a constitutional isomer of **3a**, and **7** (Figure 3a). It should be noted that the ^1H NMR spectrum of an equimolar solution of **1b** and dibenzylammonium hexafluorophosphate in the same solvent system displayed no sign of complexation.^[10] A straight line with a small slope (Figure 3a) is consistent with the ^1H NMR observation that there is no complexation between **3b** and **7** in solution. It also indicates that the ionic strength per se has a negligible effect on viscosity under these experimental conditions. Therefore, the sharp increase in viscosity at higher concentrations (Figure 3b) is reflective of the aggregation between **3a** and **7**, which produces structures of large hydrodynamic volume, namely, **9**.

Solid samples prepared by freeze-drying^[11] the 1.0×10^{-2} , 0.10 , and 0.50M equimolar solutions of **3a** and **7** in acetone/chloroform (1/1) were analyzed by differential scanning calorimetry (DSC).^[12] The M_n value of the supramolecular polymer **9** and the abundance of the 1:1 cyclic dimer **8** in each sample were estimated from low temperature ^1H NMR spectra (Table 1).^[13] The DSC thermograms for the 0.10 and 0.50M materials were entirely different from those observed for the pure, crystalline homoditopic molecules **3a** and **7**. As a result of self-organization amorphous polymers **9** with glass transition temperatures T_g above 50°C were formed for the 0.10 and 0.50M samples (57 and 59°C , respectively). From end-group analysis the 0.10 and 0.50M materials contained supramolecular polymers **9** of $M_n = 13$ and 16 kDa , respectively (Table 1). The polymers became rubberlike materials

above T_g and thus they may be processable. A high degree of crystallinity was observed by optical microscopy in the case of the $1.0 \times 10^{-2} \text{ M}$ sample (81% cyclic dimer **8**, Table 1). Presumably, compactness and the semi-rigid nature of **8** allow stable packing in the crystal lattice.^[14]

It is noteworthy that flexible, creasable, amorphous, and transparent films can be cast from 1:1 stoichiometric solutions of **3a** and **7**. Such properties can only result from entanglement of linearly connected macro-sized aggregates. Similarly, since a polymer structure of high molecular weight is necessary for fiber formation,^[15] the scanning electron microscope images (Figure 4) of a rodlike fiber with a regular diameter of $10 \mu\text{m}$ drawn from a concentrated equimolar solution of **3a** and **7** in acetone/chloroform (1/1) indicate a high degree of the linear chain extension in **9**.

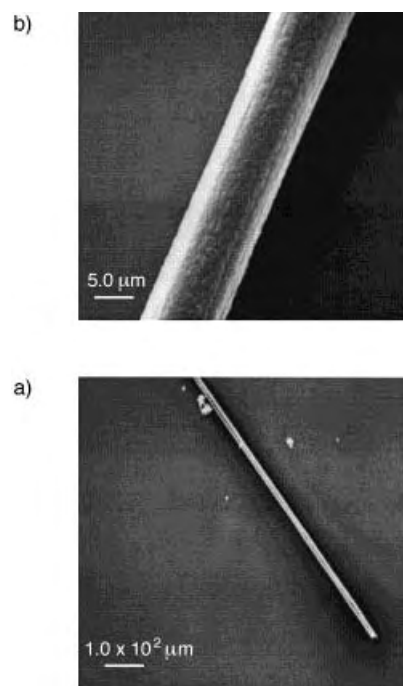


Figure 4. Longitudinal views of scanning electron micrographs of a fiber pulled from a concentrated ($>2.0 \text{ M}$) acetone/chloroform (1/1) equimolar solution of **3a** and **7**; a) low resolution, b) high resolution.

In summary, the 1:1 cyclic dimer complex **8** is preferentially formed in dilute equimolar solutions ($<1.0 \times 10^{-2} \text{ M}$), while linear chain extension to **9** is observed almost exclusively in concentrated equimolar solutions ($>1.0 \text{ M}$). The solution behavior of the self-organized supramolecules **9** was characteristic of large aggregates as demonstrated by the viscosity experiments. The solid state samples prepared by freeze-drying 0.10 and 0.50 M equimolar solutions showed that the supramolecules **9** are amorphous polymers. The preparation of films and fibers corroborates the polymeric nature of the self-organized suprastructures **9**.

Experimental Section

General procedure for **2a** and **2b**: Compounds **1a** and **1b**^[16] were reduced with LAH in THF, followed by standard isolation and recrystallization from EtOH.

2a: 92% yield, m.p. $82-84^\circ\text{C}$. ^1H NMR (400 MHz, $[\text{D}_3]\text{chloroform}$, 22°C): $\delta = 3.83$ (8H, s), 3.91 (8H, t, $J = 4.4 \text{ Hz}$), $4.13-4.17$ (8H, m), 4.58 (2H, s), $6.82-6.90$ (7H, m); MS (FAB): m/z : $478.3 [M]^+$; HR-MS (FAB): calcd for $[M]^+ \text{C}_{25}\text{H}_{34}\text{O}_9$: 478.2203 ; found: 478.2200 ; elemental analysis calcd for $\text{C}_{25}\text{H}_{34}\text{O}_9$: C 62.73 , H 7.17 ; found: C 62.61 , H 7.15 .

2b: 83% yield, m.p. $78-80^\circ\text{C}$. ^1H NMR (400 MHz, $[\text{D}_3]\text{chloroform}$, 22°C): $\delta = 3.72$ (8H, s), 3.81 (8H, m), 4.14 (8H, m), 4.58 (2H, d, $J = 6.4 \text{ Hz}$), 6.52 (2H, d, $J = 1.6 \text{ Hz}$), 6.61 (1H, t, $J = 1.6 \text{ Hz}$), $6.88-6.93$ (4H, m); MS (FAB): m/z : $478.3 [M]^+$; HR-MS (FAB): calcd for $[M]^+ \text{C}_{25}\text{H}_{34}\text{O}_9$: 478.2203 ; found: 478.2183 ; elemental analysis calcd for $\text{C}_{25}\text{H}_{34}\text{O}_9$: C 62.73 , H 7.17 ; found: C 62.58 , H 7.17 .

General procedure for **3a** and **3b**: Sebacyl chloride was condensed with **2** (2.00 equiv) in pyridine (2.20 equiv) and anhydrous THF at 40°C , followed by standard isolation and recrystallization from EtOH.

3a: 80% yield, m.p. $120-122^\circ\text{C}$. ^1H NMR (400 MHz, $[\text{D}_3]\text{chloroform}$, 22°C): $\delta = 1.23-1.27$ (8H, m), 1.57 (4H, m), 2.31 (4H, t, $J = 8.0 \text{ Hz}$), 3.83 (8H, s), 3.91 (8H, t, $J = 4.0 \text{ Hz}$), 5.00 (4H, s), 6.82 (1H, d, $J = 8.0 \text{ Hz}$), $6.85-6.91$ (6H, m); MS (FAB): m/z : $1123.2 [M+H]^+$; HR-MS (FAB): calcd for $[M]^+ \text{C}_{60}\text{H}_{82}\text{O}_{20}$: 1122.5399 ; found: 1122.5374 ; elemental analysis calcd for $\text{C}_{60}\text{H}_{82}\text{O}_{20}$: C 64.14 , H 7.36 ; found: C 64.10 , H 7.40 .

3b: 90% yield, m.p. $78-80^\circ\text{C}$. ^1H NMR (400 MHz, $[\text{D}_3]\text{chloroform}$, 22°C): $\delta = 1.25-1.29$ (8H, m), 1.63 (4H, m), 2.33 (4H, t, $J = 8.0 \text{ Hz}$), 3.72 (8H, s), 3.82 (4H, t, $J = 4.0 \text{ Hz}$), 3.85 (4H, t, $J = 4.0 \text{ Hz}$), 4.15 (8H, t, $J = 4.0 \text{ Hz}$), 5.00 (4H, s), 6.48 (2H, d, $J = 1.6 \text{ Hz}$), 6.66 (1H, t, $J = 1.6 \text{ Hz}$), $6.87-6.92$ (4H, m); MS (FAB): m/z : $1123.2 [M+H]^+$; HR-MS (FAB): calcd for $[M]^+ \text{C}_{60}\text{H}_{82}\text{O}_{20}$: 1122.5399 ; found: 1122.5372 ; elemental analysis calcd for $\text{C}_{60}\text{H}_{82}\text{O}_{20}$: C 64.14 , H 7.36 ; found: C 64.06 , H 7.29 .

5: Condensation of **4**^[17] and benzylamine (2.00 equiv) in refluxing toluene afforded an off-white solid, 4.56 g , 88% yield, m.p. $105-107^\circ\text{C}$. ^1H NMR (400 MHz, $[\text{D}_3]\text{chloroform}$, 22°C): $\delta = 1.34$ (8H, s), 1.46 (4H, m), 1.79 (4H, m), 3.99 (4H, t, $J = 6.4 \text{ Hz}$), 4.79 (4H, s), 6.92 (4H, d, $J = 8.8 \text{ Hz}$), $7.24-7.34$ (10H, m), 7.72 (4H, d, $J = 8.8 \text{ Hz}$), 8.31 (2H, s); MS (FAB): m/z : $561.5 [M+H]^+$; HR-MS (FAB): calcd for $\text{C}_{38}\text{H}_{44}\text{N}_2\text{O}_2$ ($[M+H]^+$): 561.3481 ; found: 561.3474 ; elemental analysis calcd for $\text{C}_{38}\text{H}_{44}\text{N}_2\text{O}_2$: C 81.39 , H 7.91 ; found: C 81.28 , H 7.86 .

6: Reduction of **5** in MeOH with NaBH_4 (2.00 equiv) gave an off-white solid, 3.12 g , 93%, m.p. $64-66^\circ\text{C}$. ^1H NMR (400 MHz, $[\text{D}_3]\text{chloroform}$, 22°C): $\delta = 1.34$ (8H, s), 1.46 (4H, m), 1.78 (4H, m), 3.75 (4H, s), 3.80 (4H, s), 3.95 (4H, t, $J = 6.4 \text{ Hz}$), 6.86 (4H, d, $J = 8.8 \text{ Hz}$), 7.25 (4H, d, $J = 8.8 \text{ Hz}$), $7.26-7.34$ (10H, m); MS (FAB): m/z : $565.5 [M+H]^+$; HR-MS (FAB): calcd for $\text{C}_{38}\text{H}_{48}\text{N}_2\text{O}_2$ ($[M+H]^+$): 565.3794 ; found: 565.3790 ; elemental analysis calcd for $\text{C}_{38}\text{H}_{48}\text{N}_2\text{O}_2$: C 80.81 , H 8.57 ; found: C 80.68 , H 8.47 .

7: A solution of **6** in MeOH was treated with excess 2 M HCl. The solvent was removed to give an off-white solid, which was then suspended in acetone and aqueous NH_4PF_6 added until complete dissolution occurred. The solvent was evaporated and the resulting solid was washed thoroughly with H_2O to afford an off-white solid, 2.90 g , 87% yield, m.p. 150°C (decomp). ^1H NMR (400 MHz, $[\text{D}_6]\text{acetone}$, 22°C): $\delta = 1.34$ (8H, s), 1.45 (4H, m), 1.76 (4H, m), 4.01 (4H, t, $J = 6.4 \text{ Hz}$), 4.58 (4H, s), 4.61 (4H, s), 6.99 (4H, d, $J = 8.8 \text{ Hz}$), $7.45-7.58$ (10H, m), 7.50 (4H, d, $J = 8.8 \text{ Hz}$); MS (FAB): m/z : $711.6 [M - \text{PF}_6]^+$; HR-MS (FAB): calcd for $\text{C}_{38}\text{H}_{50}\text{N}_2\text{O}_2 \cdot \text{PF}_6$ ($[M - \text{PF}_6]^+$): 711.3514 ; found: 711.3528 ; elemental analysis calcd for $\text{C}_{38}\text{H}_{50}\text{N}_2\text{O}_2 \cdot \text{P}_2\text{F}_{12}$: C 53.27 , H 5.88 ; found: C 53.17 , H 5.81 .

Received: July 8, 1998 [Z12119IE]

German version: *Angew. Chem.* **1999**, *111*, 195–199

Keywords: crown compounds • homoditopic molecules • noncovalent interactions • self-organization • supramolecular chemistry

[1] J.-M. Lehn, *Supramolecular Chemistry*, VCH, Weinheim, **1995**, pp. 139–197.

[2] a) Y. Ducharme, J. D. Wuest, *J. Org. Chem.* **1988**, *53*, 5789–5791; b) T. Kato, J. M. J. Fréchet, *J. Am. Chem. Soc.* **1989**, *111*, 8533–8534; c) Y.-L. Chang, M.-A. West, F. W. Fowler, J. W. Lauher, *J. Am. Chem. Soc.* **1993**, *115*, 5991–6000; d) J.-M. Lehn, *Makromol. Chem. Macromol.*

- Symp. **1993**, 69, 1–17; e) C. Hilger, M. Dräger, R. Stadler, *Macromolecules* **1992**, 25, 2498–2501; f) P. Bladon, A. C. Griffin, *Macromolecules* **1993**, 26, 6604–6610; g) L. M. Wilson, *Macromolecules* **1994**, 27, 6683–6686; h) C. B. St. Pourcain, A. C. Griffin, *Macromolecules* **1995**, 28, 4116–4121.
- [3] a) R. P. Sijbesma, F. H. Beijer, L. Brunsveld, B. J. B. Folmer, J. H. K. K. Hirschberg, R. F. M. Lange, J. K. L. Lowe, E. W. Meijer, *Science* **1997**, 278, 1601–1604; b) F. H. Beijer, H. Kooijman, A. L. Spek, R. P. Sijbesma, E. W. Meijer, *Angew. Chem.* **1998**, 110, 79–82; *Angew. Chem. Int. Ed.* **1998**, 37, 75–78.
- [4] P. R. Ashton, P. J. Campbell, E. J. T. Chrystal, P. T. Glink, S. Menzer, D. Philp, N. Spencer, J. F. Stoddart, P. A. Tasker, D. J. Williams, *Angew. Chem.* **1995**, 107, 1997–2001; *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 1865–1869.
- [5] Based on the assumption that the complexation at the ammonium ion moieties of **7** are independent of each other the association constant for pseudorotaxane formation between the ammonium ion moieties of **7** and DB24C8 in [D₆]acetone/[D₃]chloroform (1/1) at 22 °C was calculated as $3.5 \times 10^2 \text{ M}^{-1}$ by single point measurement (slow exchange) by using ¹H NMR spectroscopy.
- [6] The NOESY spectra of 1:1 stoichiometric solutions of **3a** and **7** could not be recorded at concentrations greater than 1.0 M because of overloading of the analogue to digital converter.
- [7] The average molecular weight of **9** was calculated on the assumption that the cyclic oligomers such as 2:2 and 3:3 complexes were absent. It is noteworthy that linear polymerization is highly favored over cyclization at high solution concentrations (for example, 1.0 M). For reviews on cyclization versus linear polymerization, see a) G. Odian, *Principles of Polymerization*, 3rd ed., Wiley, New York, **1991**, p. 73; b) S. C. Hamilton, J. A. Semlyen, *Polymer* **1997**, 38, 1685–1691. Therefore, the assumption of the absence of the oligomeric cyclic complexes is valid in the more concentrated solutions. The percentage of ammonium ion units *l* in **9** is equal to 100 minus the percentage of ammonium ion units *d* in **8** ($l + d = 100$). The ratio of the percentage of ammonium ion units *l* in **9** to the percentage of uncomplexed ammonium ion units *u* is equal to $2n$ ($n = \text{degree of aggregation}$). Thus, this equation yields $n = (100\% - d/2u)$. From the *n* value and the repeat unit mass (1980 Da) the number average molar mass M_n of **9** was calculated.
- [8] A mixture of acetone/chloroform (1/1) was added to a flask containing **3a** (1.1233 g) and **7** (0.8568 g) until complete dissolution occurred. The solution was slowly concentrated and vacuum dried to afford **9**, which was then diluted with acetone/chloroform (1/1) to 0.50 mL.
- [9] Similar effects have been observed in a supramolecule assembled from a heteroditopic precursor. See N. Yamaguchi, D. S. Nagvekar, H. W. Gibson, *Angew. Chem.* **1998**, 110, 2518–2520; *Angew. Chem. Int. Ed.* **1998**, 37, 2361–2364.
- [10] The ¹H NMR spectrum of a 1:1 stoichiometric solution of **1b** and dibenzylammonium hexafluorophosphate at $1.0 \times 10^{-2} \text{ M}$ in [D₆]acetone/[D₃]chloroform (1/1) did not show extra sets of signals from slow exchange or changes in the chemical shifts from fast exchange. The *m*-phenylene linkage prevents pseudorotaxane formation in solution.
- [11] The solutions were frozen at –93 °C with an acetone–ethanol/liquid nitrogen bath and the solvents were removed under high vacuum to give yellow–orange solids.
- [12] To eliminate sample history the freeze-dried samples were initially heated to 100 °C and cooled to 30 °C at the rate of 10 °C min^{–1}. They were then heated at 10 °C min^{–1} and the DSC thermograms were recorded.
- [13] The ¹H NMR spectra of equimolar solutions of **3a** and **7** at 1.0×10^{-2} , 0.10, and 0.50 M in [D₆]acetone/[D₃]chloroform (1/1) were essentially unchanged from –40 to –60 °C. Below this temperature the ¹H NMR spectra of the solutions were unable to be recorded because of partial freezing of the solvents. Thus, M_n values of the freeze-dried (–93 °C) samples were estimated by simple integration of relevant signals of the spectra recorded at –40 °C.
- [14] A similar dimeric cyclic species has recently been reported: P. R. Ashton, I. Baxter, S. J. Cantrill, M. C. T. Fyfe, P. T. Glink, J. F. Stoddart, A. J. P. White, D. J. Williams, *Angew. Chem.* **1998**, 110, 1344–1347; *Angew. Chem. Int. Ed.* **1998**, 37, 1294–1297.
- [15] It must be noted that these fibers were formed in a manner analogous to that used for covalently bonded macromolecules (dry spinning: H. R. Allcock, F. W. Lampe, *Contemporary Polymer Chemistry*, 2nd ed., Prentice-Hall, New Jersey, **1990**, pp. 508–511) and not by gelation in a poor solvent, which has also yielded fibers by self-organization: a) C. F. van Nostrum, S. J. Picken, A.-J. Schouten, R. J. M. Nolte, *J. Am. Chem. Soc.* **1995**, 117, 9957–9965; b) M. de Loos, J. van Esch, I. Stokroos, R. M. Kellogg, B. L. Feringa, *J. Am. Chem. Soc.* **1997**, 119, 12675–12676; c) N. Kimizuka, S. Fujikawa, H. Kuwahara, T. Kunitake, A. Marsh, J.-M. Lehn, *J. Chem. Soc. Chem. Commun.* **1995**, 2103–2104. Linear hydrogen-bonded supramolecular aggregates have been formed into fibers from the molten state.^[2f–h] For a review on fiber theory, see H. L. Needles, *Handbook of Textile Fibers, Dyes, and Finishes*, Garland STPM, New York, **1981**, pp. 1–27.
- [16] N. Yamaguchi, L. M. Hamilton, H. W. Gibson, *Angew. Chem.* **1998**, 110, 3463–3466; *Angew. Chem. Int. Ed.* **1998**, 37, No. 23.
- [17] J.-P. Leblanc, H. W. Gibson, *Tetrahedron Lett.* **1992**, 33, 6295–6298.

Cleavage of Palladium Metallacycles by Acids: A Probe for the Study of the Cyclometalation Reaction**

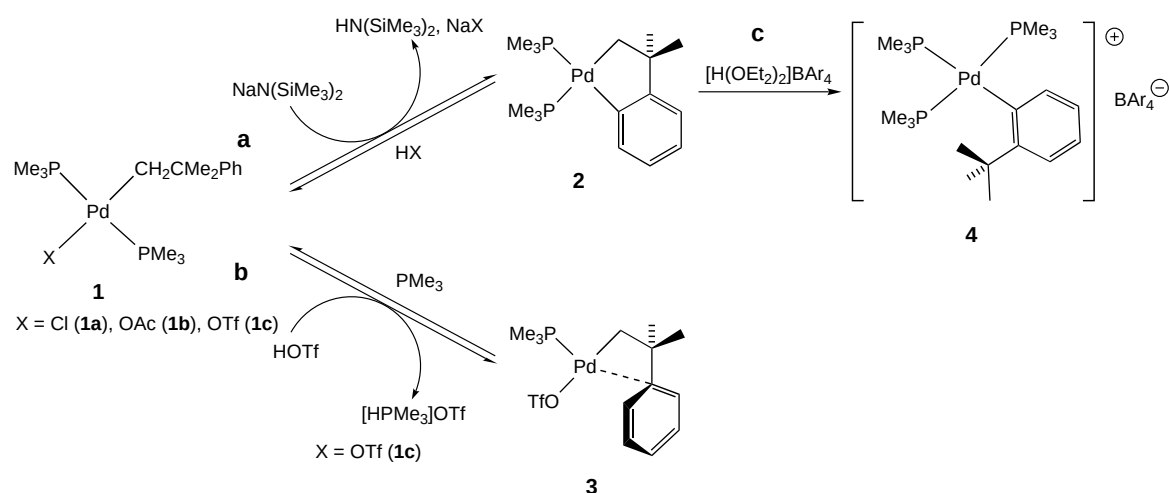
Juan Cámpora,* Jorge A. López, Pilar Palma,* Pedro Valerga, Edzard Spillner, and Ernesto Carmona*

The cyclometalation reaction^[1] constitutes one of the first known examples of C–H bond activation, which is a major achievement of organometallic chemistry.^[2] Of particular interest is the cyclometalation of a pendant aromatic ring, a process that constitutes a good model for C–H activation and has in addition led to many useful synthetic applications.^[3–6]

Despite the number of studies devoted to this transformation,^[7] contemporary work continues to provide important mechanistic information.^[1a] A recent account by Canty and van Koten has pointed out the formal relationship that may be established between the cyclometalation reaction and the protonation of M–CH₃ and M–C₆H₅ bonds,^[8] as well as the possible intermediary role of arenonium ions in both processes.^[8, 9] Here we provide experimental evidence in support

[*] Dr. J. Cámpora, Dr. P. Palma, Prof. Dr. E. Carmona, Dr. J. A. López, E. Spillner
Departamento de Química Inorgánica
Instituto de Investigaciones Químicas
Universidad de Sevilla—
Consejo Superior de Investigaciones Científicas
C/ Américo Vespucio s/n., Isla de la Cartuja, E-41092 Sevilla (Spain)
Fax: (+34)95-4460565
E-mail: guzman@cica.es
Dr. Pedro Valerga
Departamento de Ciencia de Materiales,
Ingeniería Metalúrgica y Química Inorgánica
Facultad de Ciencias, Universidad de Cádiz
Apdo 40, E-11510 Puerto Real, Cádiz (Spain)

[**] Financial support from the Dirección General de Investigación Científica y Técnica (Project PB96-0824) and Junta de Andalucía is gratefully acknowledged. J.A.L. thanks the CONACYT and the University of Guanajuato (Mexico) for a studentship. E.S. was an Erasmus student in our laboratory from the University of Hamburg. We thank Professors M. Brookhart and R. A. Andersen for helpful discussions during their sabbatical stays in our laboratory as Iberdrola Visiting Professors. Thanks are also given to Iberdrola for making their stay possible.



Scheme 1.

of this proposal by: 1) the synthesis of the palladacycle **2** (Scheme 1) by the base-induced metalation of the neophyl derivatives $\text{trans-[Pd(CH}_2\text{CMe}_2\text{Ph)X(PMe}_3)_2\text{]}$ ($\text{X} = \text{Cl}$, **1a**; OAc , **1b**; OTf , **1c**) and 2) the study of the reverse reaction, namely the protonation of **2** to produce compounds of types **1** and **3** or the aryl derivative $[\text{Pd(C}_6\text{H}_4\text{-}o\text{-CMe}_3\text{)(PMe}_3)_3]\text{BAR}_4$ (**4**, $\text{Ar} = 3,5\text{-C}_6\text{H}_3(\text{CF}_3)_2$, Scheme 1). As discussed below one of the intermediates in our system is a cationic species **B** (Scheme 2), in which the highly electrophilic palladium center is stabilized by an auxiliary π, η^1 interaction with the *ipso* carbon atom of the phenyl group.^[10]

In contrast with the behavior exhibited by the analogous Ni^{II} and Pt^{II} neophyl derivatives, which convert readily into the corresponding metallacycles,^[7c, 11a] the bis(alkyl) complex $[\text{Pd(CH}_2\text{CMe}_2\text{Ph)}_2(\text{PMe}_3)_2]$ fails to give a product of this kind,^[11b] even though related palladacyclic species can be easily prepared.^[12] Nonetheless, metallacycle **2** can be formed by treatment of the neophyl complexes **1** with a strong base such as $\text{NaN(SiMe}_3)_2$ (Scheme 1, reaction a). This method parallels the previously reported synthesis of other related palladium metallacycles.^[12] The cyclometalation reaction can be readily reversed by treating **2** with stoichiometric amounts of HX ($\text{X} = \text{Cl}$, OAc , HTfO) to give **1**. This regioselectivity is the same as that found in the analogous Ni metallacycle.^[11a] The triflate complex **1c** is very labile and, whereas it has been fully characterized in solution, it could not be isolated in pure, crystalline form. If two equivalents of triflic acid (HOTf) are used, high yields of the crystalline complex **3** are obtained along with $[\text{HPMe}_3]\text{OTf}$ (Scheme 1, reaction b). This latter transformation can also be reversed; the addition of PMe_3 to solutions of **3** regenerates the neophyl compound **1c**.

The structure proposed for **3** on spectroscopic grounds has been confirmed by X-ray studies. Figure 1 shows an ORTEP view of one of the two crystallographically independent molecules of **3** that are contained in the unit cell.^[13] The most interesting aspect of this highly distorted square-planar structure is undoubtedly the coordination mode of the neophyl ligand. The Pd-CH_2 bond has a normal length (ca. $2.02 \text{ \AA}$) but the neophyl backbone bends in such a way that the phenyl ring comes close to the Pd atom (Figure 1, Table 1).

Thus, the relatively short $\text{Pd-C}_{\text{ipso}}$ distance of about $2.38 \text{ \AA}$ is indicative of a π -bonding interaction. Since the *ortho* carbon atoms are farther apart (the shortest $\text{Pd-C}_{\text{ortho}}$ distances being $2.61(2)$ and $2.53(1) \text{ \AA}$ in the two independent molecules, respectively), the coordination of the ring can be described as approximately π, η^1 . This is in accord with a similar observation by Falvello, Forniés, and co-workers in the complex $\text{cis-[Pd(C}_6\text{F}_5)_2(\text{NMe}_2\text{CH}_2\text{C}_6\text{H}_5)]$,^[10a] although for other related Pd-arene complexes π, η^2 coordination of the arene ligand has been proposed.^[10c,d]

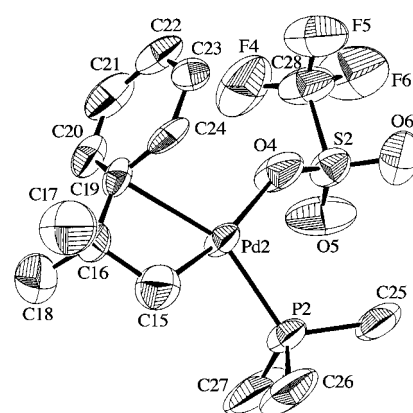


Figure 1. ORTEP representation of one of the two crystallographically independent molecules of **3**.

Table 1. Selected bond lengths [$\text{\AA}$] and angles [$^\circ$] for **3**.

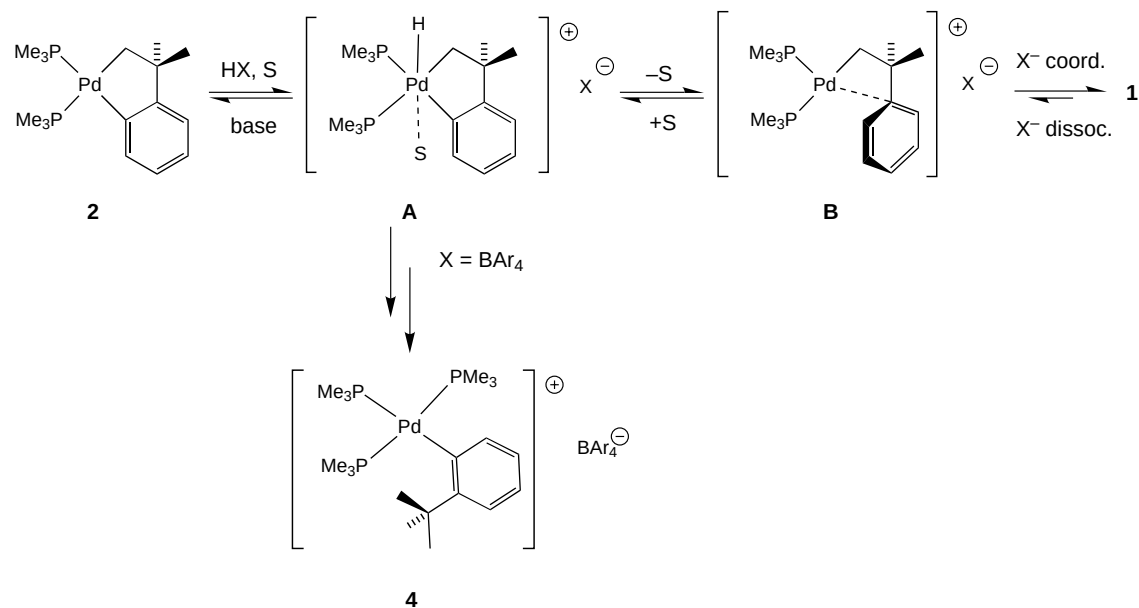
Molecule A		Molecule B	
Pd1-P1	2.233(4)	Pd2-P2	2.232(4)
Pd1-O1	2.21(1)	Pd2-O4	2.16(1)
Pd1-C1	2.02(2)	Pd2-C15	2.01(2)
Pd1-C5	2.38(1)	Pd2-C19	2.39(1)
P1-Pd1-O1	99.7(3)	P2-Pd2-O4	99.9(3)
P1-Pd1-C1	90.2(5)	P2-Pd2-C15	90.9(5)
P1-Pd1-C5	153.8(4)	P2-Pd2-C19	154.0(4)
O1-Pd1-C1	170.0(5)	O4-Pd2-C15	169.2(6)
O1-Pd1-C5	104.6(4)	O4-Pd2-C19	104.6(5)
C1-Pd1-C5	65.4(6)	C15-Pd2-C19	64.9(6)

The formation of **3** is particularly noteworthy because π -arene complexes have been proposed to be intermediates in the activation of aromatic C–H bonds by Pd and other metals.^[14] The recent observation by Cheng and co-workers of the cyclometalation of a neutral palladium π -arene complex by treatment with sodium hydroxide in the presence of PPh_3 ,^[1m] seems to indicate the intermediacy of this type of complex in the cyclometalation reaction. Unfortunately, direct cyclometalation of **3** by bases under the experimental conditions used by Cheng et al. has proved meaningless, because the π -arene interaction is readily cleaved by added PMe_3 .^[15] Nevertheless, **3** is a robust compound that can be dissolved in CD_3OD without decomposition.^[16] No H–D exchange, in the *ortho* positions of the phenyl ring could be detected after three days at room temperature (or 6 h at 60°C) in this solvent, which suggests these protons are not labile.

At variance with the protonations described above, the reaction of the metallacycle **2** with one equivalent of $[\text{H}(\text{OEt}_2)_2]\text{BAR}_4$ ^[17] ($\text{Ar} = 3,5\text{-C}_6\text{H}_3(\text{CF}_3)_2$) in Et_2O (-40°C , then warmed to room temperature) leads to the aryl derivative **4**, in 42% yield (Scheme 1, reaction c), together with some as yet unidentified products. The nature of **4** would appear to suggest a different regioselectivity for the protonation reaction, namely proton attack at the sp^3 alkyl carbon atom. However, carrying out the reaction in CH_2Cl_2 at -40°C or, alternatively, treating the $[\text{Pd}(\text{CH}_2\text{CMe}_2\text{Ph})\text{X}(\text{PMe}_3)_2]$ complexes **1a** or **1c** with NaBAR_4 , also in CH_2Cl_2 at low temperature, allows the isolation of a colorless complex **B** (Scheme 2, $\text{X} = \text{BAR}_4$). This complex has spectroscopic properties related to those of **3**, which is indicative of a π, η^1 -arene coordination ($^{31}\text{P}\{^1\text{H}\}$ NMR: AX spin system, $\delta_{\text{A}} = -1.8$, $\delta_{\text{X}} = -31.1$, $^2J_{\text{AX}} = 37$ Hz; $^{13}\text{C}\{^1\text{H}\}$ NMR: $\delta = 33.5$ (dd, $^2J_{\text{CP}} = 65$, 8 Hz, Pd–CH₂), 123.5 (dd, $^2J_{\text{CP}} = 12$, 4 Hz, C_{ipso}). Dissolution of **B** in Et_2O or THF results in formation of the above-mentioned mixture of **4** plus unidentified products. On the

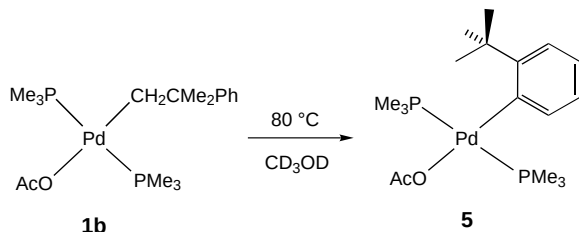
basis of these data we propose that the protonation occurs also at the aryl carbon atom to give initially compound **B** (that is, the kinetic product, see below) and that **B** subsequently isomerizes by a solvent-assisted rearrangement of the neophyl ligand (Scheme 2). We are not aware of a similar role of the solvent in related isomerizations of $\text{M}-\text{CH}_2\text{CMe}_2\text{C}_6\text{H}_5$ moieties.^[11e, 18–20]

We have been unable to obtain experimental evidence for the formation of intermediate **A** (Scheme 2), hence its participation in the proposed reaction pathway remains speculative. However it appears reasonable on chemical grounds and moreover its formulation is in agreement with recent results on organopalladium(IV) and hydridoplatinum(IV) chemistry.^[8, 9, 21] As a consequence of the higher kinetic barrier to the reorientation of the strongly directional sp^3 orbital of the alkyl PdCH₂ carbon atom relative to the sp^2 aryl carbon atom, to form the C–H bond,^[22] hydrogen transfer to the aryl carbon atom is expected to be kinetically more favorable. This would yield the cationic species **B**, perhaps with participation of an arenonium ion or an agostic intermediate (not illustrated in Scheme 2).^[9, 21] Coordination of X^- would convert **B** into compounds **1** but if X^- is a noncoordinating anion, for example BAR_4^- , **B** could reverse to the purported Pd^{IV} hydride **A** in a process that seems to require the presence of Et_2O or THF as a weakly coordinating solvent. Eventually, complex **A** could undergo the kinetically less-favorable 1,2 hydrogen shift to the sp^3 -hybridised alkyl site, followed by phosphane substitution to give compound **4**. There are still some aspects of these transformations that are only partially understood and the overall process of Scheme 2 may be mechanistically more complex than depicted. However in agreement with the above hypothesis, treatment of **2** with $[\text{HPMe}_3]\text{BAR}_4$ in CH_2Cl_2 gives $[\text{Pd}(\text{CH}_2\text{CMe}_2\text{Ph})(\text{PMe}_3)_3]\text{BAR}_4$, which converts cleanly into **4** after heating at 60°C for three hours. A similar isomerization of the neophyl ligand occurs when **1b** is heated at 80°C in CD_3OD for three



Scheme 2.

hours, with the aryl compound *trans*-[Pd(C₆H₄-*o*-CMe₃)(OAc)(PMe₃)₂] (**5**) being formed in good yield. Only 10% isomerization is observed after three hours in C₆D₆ under the same reaction conditions.



In closing, some comments on the chemical significance of the cationic species **B** seem appropriate. As noted above, **B** is involved as an intermediate in both the cyclometalation and the isomerization of the neophyl ligand although the additional participation in the key C–H bond activation reaction of an arenonium ion or an agostic intermediate appears likely. The lability of **B** contrasts with the relative inertness of the neutral triflate complex **3**. This observation suggests that a positive charge at the Pd center may be needed to achieve the metalation of the pendant aromatic ring. In other words, anion dissociation rather than phosphane dissociation could be required for the activation of the C–H bond in compounds of type **1**. This proposal is in agreement with previous findings on somewhat related reactions.^[23] Moreover, it is in accord with our failure to cyclometalate the bis(alkyl) complex [Pd(CH₂CMe₂Ph)₂(PMe₃)₂].^[11e]

Experimental Section

2 and 3: The metallacyclic precursor **2** was prepared by treating a solution of complex **1a** (0.21 g, 0.5 mmol) in THF (30 mL) at –50 °C with NaN(SiMe₃)₂ (0.85 mL, 0.6 M solution in toluene, 0.5 mmol) and was isolated as white crystals (ca. 40% yield) from its solutions in diethyl ether or diethyl ether/petroleum ether mixtures. Elemental analysis calcd for C₁₆H₃₀P₂Pd: C 49.18, H 7.68; found: C 49.22, H 7.56; ¹H NMR (CD₂Cl₂, 20 °C): δ = 2.20 (dd, 2H, ³J_{HP} = 8.8, 5.7 Hz, CH₂); ³¹P{¹H} NMR (CD₂Cl₂, 20 °C) AX spin system, δ_A = –22.9, δ_X = –27.9, J_{AX} = 23 Hz; ¹³C{¹H} NMR (CD₂Cl₂, 20 °C): δ = 52.5 (dd, ²J_{CP} = 95, 9 Hz, CH₂), 169.2 (dd, ²J_{CP} = 123, 14 Hz, C_q arom.). A solution of HOTf in Et₂O (3.8 mL, 0.53 M, 2 mmol) was added dropwise to a cold solution (–80 °C) of a pure, crystalline sample of this compound (0.39 g, 1 mmol) in Et₂O (40 mL). The mixture was stirred for 2.5 h at room temperature, the solvent evaporated under vacuum, and the residue extracted with Et₂O. The white precipitate of HPMe₃⁺TfO[–] was separated by filtration, and the solution concentrated and cooled overnight at –20 °C. The product was isolated as colorless crystals (290 mg, 75%). Elemental analysis calcd for C₁₄H₂₂F₃O₃PSPd: C 36.18, H 4.77; found: C 36.34, H 4.60; ¹H NMR (CD₂Cl₂, 20 °C): δ = 1.46 (d, 2H, ³J_{HP} = 5.6 Hz, CH₂); ³¹P{¹H} NMR (CD₂Cl₂, 20 °C): δ = –2.85 s; ¹³C{¹H} NMR (CD₂Cl₂, 20 °C): δ = 24.3 (d, ²J_{CP} = 4 Hz, CH₂), 121.8 (d, ²J_{CP} = 13 Hz, C_q arom.), 123.2 (s, 2 CH arom.), 131.2 (s, 1 CH arom.), 132.3 (s, 2 CH arom.).

4: A solution of compound **2** (0.1 g, ca. 0.25 mmol) in Et₂O (40 mL) was cooled at –40 °C, and treated with [H(OEt)₂]₂BAR₄ (0.25 g, 0.25 mmol) dissolved in Et₂O (10 mL). The mixture was stirred for 1 h at room temperature. The solvent was then removed in vacuo, and the residue extracted with Et₂O (30 mL). The volume was reduced to approximately one half and petroleum ether added until the solution became slightly cloudy. After cooling the mixture at –20 °C overnight, the product was collected as colorless crystals, which were filtered, washed with petroleum ether, and dried (140 mg, 42%). Elemental analysis calcd for C₃₁H₃₂BF₂₄P₃Pd: C 46.02, H 3.94; found: C 46.37, H 3.88; ¹H NMR (CD₂Cl₂, 20 °C): δ = 1.44 (s, 9H, CMe₃); ³¹P{¹H} NMR (CD₂Cl₂, 20 °C) AX₂

spin system, δ_A = –27.6, δ_X = –17.2, J_{AX} = 44 Hz; ¹³C{¹H} NMR (CD₂Cl₂, 20 °C): δ = 33.0 (s, CMe₃), 36.9 (s, CMe₃), 151.7 (d, ²J_{CP} = 107 Hz, C_q arom.).

Received: May 5,

Revised version: July 31, 1998 [Z11819IE]

German version: *Angew. Chem.* **1999**, *111*, 199–203

Keywords: C–H activation • metallacycles • palladium • pi interactions • protonations

- a) A. D. Ryabov, *Chem. Rev.* **1990**, *90*, 403; b) G. R. Newkome, W. E. Puckett, V. K. Gupta, *Chem. Rev.* **1986**, *86*, 451; c) G. E. Kiefer, *Chem. Rev.* **1986**, *86*, 151; d) I. Omae, *Chem. Rev.* **1989**, *93*, 155; for recent examples of cyclometalation reactions, see e) T. Hascall, V. Murphy, G. Parkin, *Organometallics* **1996**, *15*, 3910; f) N. S. Radu, S. L. Buchwald, S. Berk, C. J. Burns, *Organometallics* **1996**, *15*, 3913; g) R. H. Zambrano, P. R. Sharp, C. L. Barnes, *Organometallics* **1995**, *14*, 3607; h) R. Bosque, C. López, J. Sales, P. Tramuns, X. Solans, *J. Chem. Soc. Dalton Trans.* **1995**, 2445; i) J. C. Jeffrey, E. Schatz, E. H. Tilley, M. D. Ward, *J. Chem. Soc. Dalton Trans.* **1995**, 825; j) P. W. Jennings, L. L. Johnson, *Chem. Rev.* **1994**, *94*, 2241; k) M. Catellani, G. P. Chiusoli, *Gazz. Chim. Ital.* **1993**, *123*, 1; l) M. Catellani, M. C. Fagnola, *Angew. Chem.* **1994**, *106*, 2559; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2421; m) C. Liu, C. S. Li, C. H. Cheng, *Organometallics* **1994**, *13*, 18.
- a) A. E. Shilov, G. B. Shul'pin, *Chem. Rev.* **1997**, *97*, 2879; b) B. A. Arndtsen, R. G. Bergman, T. A. Morley, T. H. Peterson, *Acc. Chem. Res.* **1995**, *28*, 154.
- a) A. J. Canty, *Acc. Chem. Res.* **1992**, *25*, 83; b) A. J. Canty in *Comprehensive Organometallic Chemistry II. Vol. 9* (Eds: E. W. Abel, F. G. A. Stone, G. Wilkinson), Pergamon, Oxford, **1995**, p. 225.
- a) R. F. Heck, *Palladium Reagents in Organic Chemistry*; Academic Press, London, **1985**; b) J. Vicente, J. A. Abad, J. Gil-Rubio, *Organometallics* **1996**, *15*, 350; c) U. Aulwurm, J. V. Melchinger, H. Kisch, *Organometallics* **1995**, *14*, 3385; d) J. Spencer, M. Pfeffer, N. Krystakis, J. Fischer, *Organometallics* **1995**, *14*, 2214, and references therein.
- a) E. Lindner, *Adv. Heterocyclic Chem.* **1986**, *39*, 237; b) D. S. Chappell, D. J. Cole-Hamilton, *Polyhedron* **1982**, *1*, 739; c) G. Ingrosso in *Reactions of Coordinated Ligands* (Ed.: P. S. Braterman), Plenum, New York, **1986**, p. 639; d) I. Ojima, M. Tzamarioudaki, Z. Li, R. J. Donovan, *Chem. Rev.* **1996**, *96*, 635.
- Applied Homogeneous Catalysis with Organometallic Compounds* (Eds: B. Cornelis, W. A. Herrmann), VCH, Weinheim, **1996**.
- a) W. Parshall, *Acc. Chem. Res.* **1970**, *3*, 139; b) R. Di Cosimo, S. S. Moore, A. F. Sowinski, G. M. Whitesides, *J. Am. Chem. Soc.* **1982**, *104*, 124; c) D. C. Griffiths, G. B. Young, *Organometallics* **1989**, *8*, 875. d) A. D. Ryabov, I. K. Sakodinskaya, A. K. Yatsimirsky, *J. Chem. Soc. Dalton Trans.* **1985**, 2629; e) H. L. Holcomb, S. Nakanishi, T. C. Flood, *Organometallics* **1996**, *15*, 4228.
- A. J. Canty, G. van Koten, *Acc. Chem. Res.* **1995**, *28*, 406.
- a) D. M. Grove, G. van Koten, J. N. Louwen, J. G. Noltes, A. L. Spek, H. J. C. Ubbels, *J. Am. Chem. Soc.* **1982**, *104*, 6609; b) J. Terhijden, G. van Koten, I. C. Vinke, A. L. Spek, *J. Am. Chem. Soc.* **1985**, *107*, 2891.
- a) L. R. Falvello, J. Forníes, R. Navarro, V. Sicilia, M. Tomás, *J. Chem. Soc. Dalton Trans.* **1994**, 3143; b) J. Forníes, B. Menjón, N. Gómez, M. Tomás, *Organometallics* **1992**, *11*, 1187; c) C. S. Li, C. H. Cheng, S. L. Wang, *J. Chem. Soc. Chem. Commun.* **1991**, 710; d) E. Wehman, G. van Koten, T. B. H. Jastrzbeski, H. Ossor, M. Pfeffer, *J. Chem. Soc. Dalton Trans.* **1988**, 2975.
- a) E. Carmona, E. Gutiérrez-Puebla, J. M. Marín, A. Monge, M. Paneque, M. L. Poveda, C. Ruiz, *J. Am. Chem. Soc.* **1989**, *111*, 2883; b) M. C. Nicasio, PhD thesis, Universidad de Sevilla, **1993**.
- a) D. J. Cárdenas, C. Mateo, A. M. Echevarren, *Angew. Chem.* **1994**, *106*, 2529; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2445; b) C. Mateo, D. J. Cárdenas, C. Fernández-Rivas, A. M. Echevarren, *Chem. Eur. J.* **1996**, *2*, 1596.
- Crystallographic data for **3**: a yellow irregular crystal of PdC₁₄H₂₂F₃O₃PS having approximate dimensions of 0.26 × 0.15 × 0.34 mm was mounted in a glass capillary under argon. All measurements were performed on a Rigaku AFC6S diffractometer with

graphite monochromated Mo K_{α} radiation; $M_r = 464.76$; triclinic, space group $P1$ (no. 2), $a = 11.428(3)$, $b = 17.336(4)$, $c = 10.439(5)$ Å, $\alpha = 98.11(3)$, $\beta = 104.13(3)$, $\gamma = 106.02(2)^\circ$, $V = 1879(2)$ Å ^{3} , $\rho_{\text{calc}} = 1.643$ g cm $^{-3}$, $F(000) = 936$, $T = 293$ K, ($\lambda = 0.71069$ Å), $\mu(\text{MoK}_{\alpha}) = 12.0$ cm $^{-1}$, scan = $\omega/2\theta$, scan rate = 8.0° min (in ω ; 3 scans), scan width ($1.10 + 0.30 \tan \theta$), $2\theta_{\text{max}} = 50.1^\circ$. Of the 5734 reflections measured through a detector aperture 6.0 mm horizontal and 6.0 mm vertical, 5455 were unique ($R_{\text{int}} = 0.120$). A decay correction was applied following the intensities of three standard reflections measured after every 100 reflections (-6.80% during data collection). The absorption correction was negligible and it was not applied. The data were corrected for Lorentz and polarization effects. A structural solution was found by direct methods (Patterson method, MITHRIL program).^[24] The least-squares refinement was performed for a total of 415 parameters with 2976 reflections ($I > 3\sigma(I)$); minimization function: $\sum w(|F_o| - |F_c|)^2$, with least-squares weights: $4F_o^2/\sigma^2(F_o^2)$, p factor = 0.03. The non-hydrogen atoms were anisotropically refined and the hydrogen atoms were included at idealized positions and they were not refined. $R_F = 0.060$, $R_w = 0.070$, GOF = 2.03, maximum shift/error: 7.26. Accurate cell dimensions were obtained by least-squares refinement of 25 reflections ranged $13.40 < 2\theta < 16.44^\circ$. All calculations were performed on a VAX 3520 station at the Servicio Central de Ciencias y Tecnología de la Universidad de Cádiz. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-101361. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

- [14] a) W. D. Jones, F. J. Feher, *Acc. Chem. Res.* **1989**, 22, 91; b) M. R. Chin, L. Dong, S. B. Duckett, M. G. Partridge, W. D. Jones, R. N. Perutz, *J. Am. Chem. Soc.* **1993**, 115, 7685.
- [15] Compound **3** reacts rapidly with one equivalent of PMe_3 to give **1b**.
- [16] The $^{13}\text{C}\{^1\text{H}\}$ NMR spectra of **3** in CD_2Cl_2 and CD_3OD are very similar. Since the signal assigned to the Pd-bonded aromatic quaternary carbon atom appears in both cases as a doublet ($^2J_{\text{CP}} = 7$ Hz) the π, η^1 arene interaction seems to be maintained in methanol.
- [17] a) L. K. Johnson, S. Mecking, M. Brookhart, *J. Am. Chem. Soc.* **1996**, 118, 267; b) C. M. Killian, L. K. Johnson, M. Brookhart, *Organometallics* **1997**, 16, 2005.
- [18] S. I. Black, G. B. Young, *Polyhedron* **1984**, 8, 585.
- [19] a) R. F. Heck, *J. Organomet. Chem.* **1982**, 37, 389; b) B. A. Markies, P. Wijkens, H. Kooijman, A. Spek, J. Boersma, G. van Koten, *J. Chem. Soc. Chem. Commun.* **1992**, 1420.
- [20] a) D. C. Griffiths, L. G. Joy, A. C. Skapski, D. J. Wilkes, G. B. Young, *Organometallics* **1986**, 5, 1744; b) M. E. Cucciolto, A. de Rienzi, F. Ruffo, D. Tesauro, *J. Chem. Soc. Dalton Trans.* **1998**, 1675.
- [21] a) A. F. H. J. van der Ploeg, G. van Koten, K. Vrieze, A. L. Spek, *Inorg. Chem.* **1982**, 21, 2014; b) J. E. Kickham, S. J. Loeb, *Organometallics* **1995**, 14, 3584.
- [22] M. J. Calhorda, J. M. Brown, N. A. Cooley, *Organometallics* **1991**, 10, 1431; b) P. M. Maitlis, H. C. Long, R. Quyoum, M. L. Turner, Z.-Q. Wang, *Chem. Commun.* **1996**, 1.
- [23] F. Kawataka, Y. Yoshito, I. Shimizu, A. Yamamoto, *Organometallics* **1994**, 13, 3517.
- [24] G. J. Gilmore, *J. Appl. Crystallogr.* **1984**, 17, 42–46.

Spin-Orbit Coupling versus the VSEPR Method: On the Possibility of a Nonplanar Structure for the Super-Heavy Noble Gas Tetrafluoride (118)F $_4$ **

Clinton S. Nash and Bruce E. Bursten*

The discovery of the super-heavy elements 110, 111, and 112 by Armbruster and co-workers during the 1990s^[1] has stimulated new interest in the properties and chemistry of newly discovered elements.^[2,3] Elements 110, 111, and 112 complete the 6d block of the periodic table. The next elements likely to be discovered are the representative 7p block elements, those with atomic numbers 113–118. The last of these, element 118, is predicted to be a noble gas with a closed-shell $7s^2 6d^{10} 7p^6$ electron configuration. As such, its properties are expected to resemble those of the heavy noble gases Xe and Rn, which are known to form compounds with electronegative elements such as F.^[4]

The correct prediction of the structures of noble gas compounds was one of the great successes of the valence-shell electron-pair repulsion (VSEPR) model of Gillespie and Nyholm, in both its original^[5] and more-refined current^[6] formulations. This simple and pedagogically useful model correctly predicted that NgF_2 and NgF_4 (Ng = noble gas) should adopt linear and square-planar molecular geometries, respectively, based on trigonal-bipyramidal and octahedral electron-pair geometries. Herein, we will focus on the noble gas tetrafluorides XeF_4 , which is known,^[7] RnF_4 , which has not been characterized definitively,^[8] and (118)F $_4$. Our interest in the bonding in compounds of the super-heavy elements stems in part from the huge spin-orbit effects exhibited by these elements by virtue of their large atomic numbers.^[9] These relativistic effects can have a remarkable influence on the properties of atoms and compounds of these elements. For example, Kaldor et al. have used relativistic coupled cluster calculations to predict that relativistic stabilization of the 8s orbital causes the element 118 to have a small electron affinity, making it unique among the noble gases.^[10] We have recently predicted that spin-orbit effects will cause the super-heavy hydrogen halide H(117) to have an unusually long and strong bond.^[11] Here we will report that the influence of spin-orbit effects on the bonding in (118)F $_4$ is so great as to favor a non-VSEPR tetrahedral structure for this molecule.

[*] Prof. B. E. Bursten

Department of Chemistry, The Ohio State University
Columbus, OH 43210 (USA)
Fax: (+1) 614-688-3306
E-mail: bursten.1@osu.edu

Dr. C. S. Nash
The Glenn T. Seaborg Institute for Transactinium Science
Lawrence Livermore National Laboratory
Livermore, CA 94550 (USA)
Fax: (+1) 925-422-3610
E-mail: nash6@llnl.gov

[**] This work was supported by the Division of Chemical Sciences, US Department of Energy (Grant DE-FG02-86ER13529), by the Ohio Supercomputer Center, and by the National Energy Research Supercomputer Center. We are grateful to W. C. Ermler, D. C. Hoffman, R. M. Pitzer, and P. Schwerdtfeger for helpful comments.

Correlated electronic structure calculations on XeF_4 , RnF_4 , and $(118)\text{F}_4$ have been carried out using the relativistic configuration interaction (RCI) method with the explicit inclusion (or exclusion) of a spin-orbit operator.^[12] The Ng–F bond length was optimized by single-point calculations under the constraint of either a square-planar (D_{4h}) or tetrahedral (T_d) geometry. The results of these calculations are summarized in Table 1. Like other recent relativistic studies of

Table 1. Relative minimum energies and optimized Ng–F bond lengths from the relativistic configuration interaction calculations on XeF_4 , RnF_4 , and $(118)\text{F}_4$, without and with spin-orbit (SO) effects.

Molecule	Geometry	Without SO effects		With SO effects	
		$E^{[a]}$ [eV]	Ng–F [Å]	$E^{[a]}$ [eV]	Ng–F [Å]
XeF_4	D_{4h}	0.0	1.95	0.0	1.95
	T_d	5.66		4.96	
RnF_4	D_{4h}	0.0	2.04	0.0	2.05
	T_d	4.92		2.56	
$(118)\text{F}_4$	D_{4h}	0.0	2.13	0.24	2.15
	T_d	4.25		0.0	2.14

[a] The relative energy of the higher energy geometry is evaluated at the optimized Ng–F distance of the lower energy geometry.

XeF_4 ,^[15, 16] our RCI calculations on XeF_4 greatly favor the experimentally observed square-planar geometry for this molecule. The calculated equilibrium Xe–F bond length, 1.95 Å, is in excellent agreement with the value obtained from neutron diffraction (1.951 Å)^[17] and with that recently determined by high-resolution IR spectroscopy (1.935 Å).^[16] At a bond length of 1.95 Å, the tetrahedral structure of XeF_4 lies roughly 5 eV higher in energy than the square-planar structure. We find a similar result for RnF_4 : A square-planar structure with a Rn–F bond length of 2.05 Å is predicted, and the tetrahedral structure is about 2.5 eV higher in energy at this bond length. The bond length we predict for RnF_4 is close to the 2.025 Å bond length predicted by Dolg et al.^[18] For both XeF_4 and RnF_4 , the tetrahedral structure is considerably higher in energy than the square-planar structure over the entire range of bond lengths examined, both with and without the inclusion of spin-orbit coupling.

Without spin-orbit coupling, the RCI calculations on $(118)\text{F}_4$ predict a square-planar structure, like that of XeF_4 and RnF_4 , with a (118)–F bond length of 2.13 Å (Table 1). The tetrahedral structure is more than 4 eV higher at this bond length and is markedly higher in energy than the square-planar surface at all bond lengths examined (Figure 1). A separate SCF RECP geometry optimization under C_{2v} symmetry was used to sample the continuum of structures from square-planar (D_{4h}) to disphenoidal (sawhorse) (C_{2v}) to tetrahedral (T_d) under a common symmetry. In spite of the lowered symmetry constraints, these calculations also converged to a square-planar structure with a bond length of 2.124 Å. Clearly, in the absence of spin-orbit coupling, $(118)\text{F}_4$ adopts the geometry predicted by the VSEPR method.

The inclusion of spin-orbit coupling in the calculations on $(118)\text{F}_4$ drastically changes the situation, as shown in Figure 1. The potential energy surfaces for the tetrahedral and square-

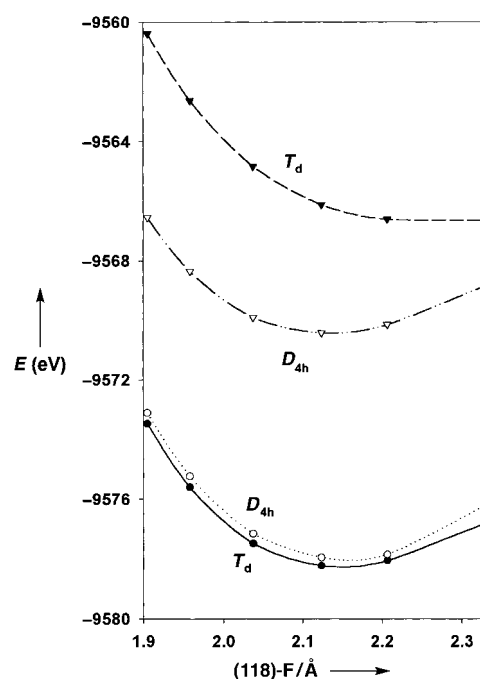


Figure 1. RCI energies of the $(118)\text{F}_4$ molecule as a function of (118)–F bond length under square-planar (D_{4h}) and tetrahedral (T_d) symmetry, without (∇ and $\triangledown$, respectively) and with ($\circ$ and $\bullet$, respectively) spin-orbit coupling.

planar structures are nearly coincident; the tetrahedral structure is lower in energy by a small amount (< 0.5 eV) at all bond lengths examined. The (118)–F bond lengths are calculated to be nearly the same in both geometries, namely 2.14 Å and 2.15 Å in the tetrahedral and square-planar geometries, respectively. We believe that our choice of configurations in these RCI calculations is such that the closeness in energy of these two surfaces is likely to remain even with the inclusion of more electron correlation. These results suggest a slight preference for a tetrahedral structure for $(118)\text{F}_4$ or, at minimum, an essentially nonrigid structure. Interestingly, a single-point RCI calculation in a C_{2v} geometry intermediate between the optimized tetrahedral and square-planar geometries gave a slightly higher energy than either of the higher symmetry structures.

In the VSEPR model, the square-planar geometry of NgF_4 molecules is attributed to the presence of six electron-pair domains, four of which are used to make Ng–F bonds. The results in Figure 1 clearly show that spin-orbit effects are responsible for the prediction of a non-VSEPR tetrahedral geometry for $(118)\text{F}_4$. Because spin-orbit coupling destroys the separation between spatial and spin coordinates, it is difficult to provide a simple orbital-based explanation for this apparently exceptional geometry. The most ready explanation involves the response of the valence atomic orbitals of (118) to the spin-orbit operator, which we have explored by using the atomic Dirac–Hartree–Fock relativistic calculations^[19] that are summarized in Table 2. The 7s orbital of (118) undergoes its expected large energetic stabilization and radial contraction upon the inclusion of relativistic effects. Further, spin-orbit coupling dramatically splits the (118) 7p orbitals into lower energy $7p_{1/2}$ and higher energy $7p_{3/2}$ spinors. The

Table 2. Nonrelativistic Hartree–Fock and relativistic Dirac–Hartree–Fock orbital eigenvalues (ϵ) and radial expectation values ($\langle r \rangle$) for the ns and np orbitals of Rn and (118).

Element Rn			Element 118		
Orbital	ϵ [eV]	$\langle r \rangle$ [Å]	Orbital	ϵ [eV]	$\langle r \rangle$ [Å]
nonrelativistic			nonrelativistic		
6s	–23.78	1.14	7s	–21.06	1.28
6p	–11.65	1.35	7p	–10.73	1.49
relativistic			relativistic		
6s _{1/2}	–29.19	1.02	7s _{1/2}	–36.25	0.96
6p _{1/2}	–14.71	1.19	7p _{1/2}	–20.29	1.09
6p _{3/2}	–10.45	1.37	7p _{3/2}	–8.25	1.58

7p_{1/2} spinors are stabilized by 12 eV and radially contracted by 0.5 Å relative to the 7p_{3/2} spinors. As is evident in Table 2, these effects are much greater in (118) than for the corresponding orbitals in Rn. The large relative stabilization and radial contraction of the 7s_{1/2} and 7p_{1/2} spinors of (118) essentially make them unavailable for bonding interactions with the F atoms. Thus, the four electrons that can be described by these spinors are rendered as stereochemically inactive “inert pairs”.^[9c] From the point of view of the VSEPR model, the number of electron-pair domains has been reduced from six to four, consistent with a tetrahedral geometry within that model. The generation of inert pairs in conjunction with the expected large radius of (118) are consistent with our prediction that the tetrahedral and square-planar forms of (118)F₄ are practically isoenergetic, a remarkable consequence of large spin-orbit coupling.

Received: July 20, 1998 [Z 12183 IE]

German version: *Angew. Chem.* **1999**, *111*, 115–117

Keywords: electronic structure • noble gases • spin-orbit coupling • transuranium elements • VSEPR model

- [1] a) S. Hofmann, V. Ninov, F. P. Hessberger, P. Armbruster, H. Folger, G. Muenzenberg, H. J. Schoett, A. G. Popeko, A. V. Yerebin, *Z. Phys. A* **1996**, *354*, 229; b) P. Armbruster, *Bull. Soc. Fr. Phys.* **1996**, *107*, 6.
- [2] Examples: a) V. Pershina, *Chem. Rev.* **1996**, *96*, 1977; b) M. Jacoby, *Chem. Eng. News* **1998**, *76*(12), 48–54.
- [3] Nomenclature: For unnamed elements, the atomic symbol is represented as (atomic number), such as (118).
- [4] *Noble-Gas Compounds* (Ed.: H. H. Hyman), University of Chicago Press, Chicago, **1963**.
- [5] R. J. Gillespie, R. S. Nyholm, *Q. Rev. Chem. Soc.* **1957**, 339.
- [6] R. J. Gillespie, *Angew. Chem.* **1996**, *108*, 539; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 495.
- [7] P. Laszlo, G. J. Schrobilgen, *Angew. Chem.* **1988**, *100*, 495; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 479.
- [8] a) V. V. Avrorin, R. N. Krasikova, V. D. Nefedov, M. A. Toropova, *Radiokhimiya* **1981**, *23*, 879; b) L. Stein, *Inorg. Chem.* **1984**, *23*, 3670.
- [9] Reviews of relativistic effects: a) K. S. Pitzer, *Acc. Chem. Res.* **1979**, *12*, 271; b) P. Pyykkö, J.-P. Desclaux, *Acc. Chem. Res.* **1979**, *12*, 276; c) P. Pyykkö, *Chem. Rev.* **1988**, *88*, 563; d) W. C. Ermler, R. B. Ross, P. A. Christiansen, *Adv. Quantum Chem.* **1988**, *19*, 139; e) M. Pepper, B. E. Bursten, *Chem. Rev.* **1991**, *91*, 719; f) K. Balasubramanian, *Relativistic Effects in Chemistry, Part A: Theory and Techniques*, Wiley, New York, **1997**.
- [10] E. Eliav, U. Kaldor, Y. Ishikawa, P. Pyykkö, *Phys. Rev. Lett.* **1996**, *77*, 5350.
- [11] C. S. Nash, B. E. Bursten, unpublished results.

- [12] Computational details: RCI calculations were carried out using Pitzer's modification of the COLUMBUS quantum-chemistry suite to allow inclusion of a spin-orbit potential.^[13] Core electrons were replaced with shape-consistent relativistic effective core potentials (RECPs), which include spin-orbit operators.^[14] The valence basis set consisted of (6p6sd1f) Gaussians contracted to [5p5sd1f]. The active space in the spin-orbit CI calculations consisted of single excitations of 24 electrons in 12 doubly occupied molecular orbitals into 14 virtual orbitals. Selected double excitations were also included in the active set. A typical calculation involved 3876 configurations and 24657 determinants under T_d symmetry and 1548 configurations and 9633 determinants under D_{4h} . Complete computational details will be given elsewhere.^[11]
- [13] a) R. Shepard, I. Shavitt, R. M. Pitzer, D. C. Comeau, M. Pepper, H. Lischka, P. G. Szalay, R. Ahlrichs, F. B. Brown, J. G. Zhao, *Int. J. Quantum Chem. Symp.* **1989**, *22*, 149; b) A. Chang, R. M. Pitzer, *J. Am. Chem. Soc.* **1989**, *111*, 2500.
- [14] a) R. B. Ross, J. M. Powers, T. Atashroo, W. C. Ermler, L. A. LaJohn, P. A. Christiansen, *J. Chem. Phys.* **1990**, *93*, 6654, **1994**, *101*, 10198; b) C. S. Nash, B. E. Bursten, W. C. Ermler, *J. Chem. Phys.* **1997**, *106*, 5133.
- [15] a) J. Styszynski, G. L. Malli, *Int. J. Quantum Chem.* **1995**, *55*, 227; b) J. Styszynski, X. Cao, G. L. Malli, L. Visscher, *J. Comput. Chem.* **1997**, *18*, 601.
- [16] H. Bürger, S. Ma, J. Breidung, W. Thiel, *J. Chem. Phys.* **1996**, *104*, 4945.
- [17] J. H. Burns, P. A. Agron, H. A. Levy, *Science* **1963**, *139*, 1208.
- [18] M. Dolg, W. Kuchle, H. Stoll, H. Preuss, P. Schwerdtfeger, *Mol. Phys.* **1991**, *74*, 1265.
- [19] J. P. Desclaux, *At. Data Nucl. Data Tables* **1973**, *12*, 311.

A New Type of Metal-Organic Large-Pore Zeotype**

David M. L. Goodgame,* David A. Grachvogel, and David J. Williams*

The great industrial importance of zeolites, particularly in the petrochemicals industry, has fuelled the continuing interest in the synthesis and applications of new types of zeolites and related microporous materials (zeotypes). Particularly attractive avenues of further exploration include the incorporation of redox-active metals into such frameworks to provide novel heterogeneous catalytic systems^[1] and the formation of zeotypes comprising microporous metal-organic ligand coordination arrays.^[2] The latter approach offers, in principle, an extensive capability of custom-designing frameworks to gain better control of the pore sizes and shapes, whilst also permitting the incorporation of a wide range of metal ions, either as part of the framework or in the form of an

[*] Prof. D. M. L. Goodgame, Prof. D. J. Williams, D. A. Grachvogel
Chemistry Department
Imperial College of Science
Technology and Medicine
London SW7 2AY (UK)
Fax: (+44) 171-594-5804
E-mail: d.goodgame@ic.ac.uk

[**] This work was supported by the Engineering and Physical Sciences Research Council. The University of London Intercollegiate Research Service is thanked for the provision of facilities for solid-state NMR spectroscopy.

Table 2. Nonrelativistic Hartree–Fock and relativistic Dirac–Hartree–Fock orbital eigenvalues (ϵ) and radial expectation values ($\langle r \rangle$) for the ns and np orbitals of Rn and (118).

Element Rn			Element 118		
Orbital	ϵ [eV]	$\langle r \rangle$ [Å]	Orbital	ϵ [eV]	$\langle r \rangle$ [Å]
nonrelativistic			nonrelativistic		
6s	–23.78	1.14	7s	–21.06	1.28
6p	–11.65	1.35	7p	–10.73	1.49
relativistic			relativistic		
6s _{1/2}	–29.19	1.02	7s _{1/2}	–36.25	0.96
6p _{1/2}	–14.71	1.19	7p _{1/2}	–20.29	1.09
6p _{3/2}	–10.45	1.37	7p _{3/2}	–8.25	1.58

7p_{1/2} spinors are stabilized by 12 eV and radially contracted by 0.5 Å relative to the 7p_{3/2} spinors. As is evident in Table 2, these effects are much greater in (118) than for the corresponding orbitals in Rn. The large relative stabilization and radial contraction of the 7s_{1/2} and 7p_{1/2} spinors of (118) essentially make them unavailable for bonding interactions with the F atoms. Thus, the four electrons that can be described by these spinors are rendered as stereochemically inactive “inert pairs”.^[9c] From the point of view of the VSEPR model, the number of electron-pair domains has been reduced from six to four, consistent with a tetrahedral geometry within that model. The generation of inert pairs in conjunction with the expected large radius of (118) are consistent with our prediction that the tetrahedral and square-planar forms of (118)F₄ are practically isoenergetic, a remarkable consequence of large spin-orbit coupling.

Received: July 20, 1998 [Z12183IE]

German version: *Angew. Chem.* **1999**, *111*, 115–117

Keywords: electronic structure • noble gases • spin-orbit coupling • transuranium elements • VSEPR model

- [1] a) S. Hofmann, V. Ninov, F. P. Hessberger, P. Armbruster, H. Folger, G. Muenzenberg, H. J. Schoett, A. G. Popeko, A. V. Yerebin, *Z. Phys. A* **1996**, *354*, 229; b) P. Armbruster, *Bull. Soc. Fr. Phys.* **1996**, *107*, 6.
- [2] Examples: a) V. Pershina, *Chem. Rev.* **1996**, *96*, 1977; b) M. Jacoby, *Chem. Eng. News* **1998**, *76*(12), 48–54.
- [3] Nomenclature: For unnamed elements, the atomic symbol is represented as (atomic number), such as (118).
- [4] *Noble-Gas Compounds* (Ed.: H. H. Hyman), University of Chicago Press, Chicago, **1963**.
- [5] R. J. Gillespie, R. S. Nyholm, *Q. Rev. Chem. Soc.* **1957**, 339.
- [6] R. J. Gillespie, *Angew. Chem.* **1996**, *108*, 539; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 495.
- [7] P. Laszlo, G. J. Schrobilgen, *Angew. Chem.* **1988**, *100*, 495; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 479.
- [8] a) V. V. Avrorin, R. N. Krasikova, V. D. Nefedov, M. A. Toropova, *Radiokhimiya* **1981**, *23*, 879; b) L. Stein, *Inorg. Chem.* **1984**, *23*, 3670.
- [9] Reviews of relativistic effects: a) K. S. Pitzer, *Acc. Chem. Res.* **1979**, *12*, 271; b) P. Pyykkö, J.-P. Desclaux, *Acc. Chem. Res.* **1979**, *12*, 276; c) P. Pyykkö, *Chem. Rev.* **1988**, *88*, 563; d) W. C. Ermler, R. B. Ross, P. A. Christiansen, *Adv. Quantum Chem.* **1988**, *19*, 139; e) M. Pepper, B. E. Bursten, *Chem. Rev.* **1991**, *91*, 719; f) K. Balasubramanian, *Relativistic Effects in Chemistry, Part A: Theory and Techniques*, Wiley, New York, **1997**.
- [10] E. Eliav, U. Kaldor, Y. Ishikawa, P. Pyykkö, *Phys. Rev. Lett.* **1996**, *77*, 5350.
- [11] C. S. Nash, B. E. Bursten, unpublished results.

- [12] Computational details: RCI calculations were carried out using Pitzer's modification of the COLUMBUS quantum-chemistry suite to allow inclusion of a spin-orbit potential.^[13] Core electrons were replaced with shape-consistent relativistic effective core potentials (RECPs), which include spin-orbit operators.^[14] The valence basis set consisted of (6p6sd1f) Gaussians contracted to [5p5sd1f]. The active space in the spin-orbit CI calculations consisted of single excitations of 24 electrons in 12 doubly occupied molecular orbitals into 14 virtual orbitals. Selected double excitations were also included in the active set. A typical calculation involved 3876 configurations and 24657 determinants under T_d symmetry and 1548 configurations and 9633 determinants under D_{4h} . Complete computational details will be given elsewhere.^[11]
- [13] a) R. Shepard, I. Shavitt, R. M. Pitzer, D. C. Comeau, M. Pepper, H. Lischka, P. G. Szalay, R. Ahlrichs, F. B. Brown, J. G. Zhao, *Int. J. Quantum Chem. Symp.* **1989**, *22*, 149; b) A. Chang, R. M. Pitzer, *J. Am. Chem. Soc.* **1989**, *111*, 2500.
- [14] a) R. B. Ross, J. M. Powers, T. Atashroo, W. C. Ermler, L. A. LaJohn, P. A. Christiansen, *J. Chem. Phys.* **1990**, *93*, 6654, **1994**, *101*, 10198; b) C. S. Nash, B. E. Bursten, W. C. Ermler, *J. Chem. Phys.* **1997**, *106*, 5133.
- [15] a) J. Styszynski, G. L. Malli, *Int. J. Quantum Chem.* **1995**, *55*, 227; b) J. Styszynski, X. Cao, G. L. Malli, L. Visscher, *J. Comput. Chem.* **1997**, *18*, 601.
- [16] H. Bürger, S. Ma, J. Breidung, W. Thiel, *J. Chem. Phys.* **1996**, *104*, 4945.
- [17] J. H. Burns, P. A. Agron, H. A. Levy, *Science* **1963**, *139*, 1208.
- [18] M. Dolg, W. Kuchle, H. Stoll, H. Preuss, P. Schwerdtfeger, *Mol. Phys.* **1991**, *74*, 1265.
- [19] J. P. Desclaux, *At. Data Nucl. Data Tables* **1973**, *12*, 311.

A New Type of Metal-Organic Large-Pore Zeotype**

David M. L. Goodgame,* David A. Grachvogel, and David J. Williams*

The great industrial importance of zeolites, particularly in the petrochemicals industry, has fuelled the continuing interest in the synthesis and applications of new types of zeolites and related microporous materials (zeotypes). Particularly attractive avenues of further exploration include the incorporation of redox-active metals into such frameworks to provide novel heterogeneous catalytic systems^[1] and the formation of zeotypes comprising microporous metal-organic ligand coordination arrays.^[2] The latter approach offers, in principle, an extensive capability of custom-designing frameworks to gain better control of the pore sizes and shapes, whilst also permitting the incorporation of a wide range of metal ions, either as part of the framework or in the form of an

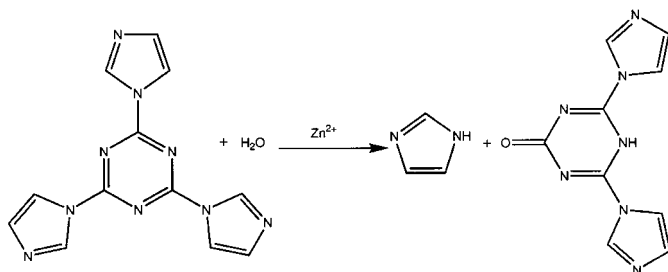
[*] Prof. D. M. L. Goodgame, Prof. D. J. Williams, D. A. Grachvogel
Chemistry Department
Imperial College of Science
Technology and Medicine
London SW7 2AY (UK)
Fax: (+44) 171-594-5804
E-mail: d.goodgame@ic.ac.uk

[**] This work was supported by the Engineering and Physical Sciences Research Council. The University of London Intercollegiate Research Service is thanked for the provision of facilities for solid-state NMR spectroscopy.

included catalytic unit (the “ship in a bottle” approach). The inclusion of features leading to chiral selectivity in catalytic processes also presents an extremely desirable, albeit challenging, goal.

There are, however, some serious problems that can vitiate the development of genuinely useful metal-organic zeotypes. These include, *inter alia*: a) the potential problem of organic matrix instability under the operating conditions that may be required for effective catalysis or separation process activity; b) the tendency of more flexible crystal lattices to “self-fill” any large potential “boxlike” cavities; c) the avoidance of the formation of such cavities by multiple three-dimensional (3D) lattice interpenetration.^[3] Additionally, the cavities may be largely or completely occupied by counterions and/or solvent molecules, though the problem of solvent inclusion may not prevent zeotype usefulness if the solvent molecules can be removed without significant structural change leading to major loss of zeotype porosity. We report here an example of a novel, large-pore metal-organic zeotype which manages to circumvent, at least to a significant extent, most of these problems.

When equimolar amounts of zinc bromide and 2,4,6-tri(1-imidazolyl)-1,3,5-triazine (timt) were mixed in *N,N*-dimethylformamide (DMF) at room temperature a colorless crystalline solid was formed. X-ray structural examination^[4] of the crystals obtained revealed that the reaction results in the conversion of timt to 4,6-di(1-imidazolyl)-1,3,5-triazine-2-one (Hdimto) (Scheme 1) which, in its deprotonated form, gives the complex $[\text{Zn}(\text{dimto})_2]_n \cdot x(\text{DMF})$ (**1**). The same product was also formed when zinc bromide was replaced by zinc chloride or zinc iodide.



Scheme 1. Metal-catalyzed conversion of timt to dimto.

The anion of the 4,6-di(1-imidazolyl)-1,3,5-triazine-2-one molecule acts as a trinucleating ligand, binding to the metal ions through the two available imidazole nitrogen atoms and the carbonyl oxygen atom (Figure 1). These units self-assemble to form nearly planar tapes mutually inclined by 79° and joining at the zinc centers. Each dimto ligand is coplanar to within 0.19 Å, with the zinc atom bound to the oxygen atom lying within the plane, whilst those bonded to the nitrogen atoms lie 0.42 Å above and below the plane. The symmetry at each zinc center is D_2 , the Zn–O and Zn–N distances being 2.116(5) and 2.138(5) Å, respectively; the angular departures from octahedral symmetry are less than 1°. An unusual feature of the ligand coordination is the Zn–O–C angle of 180°.^[5]

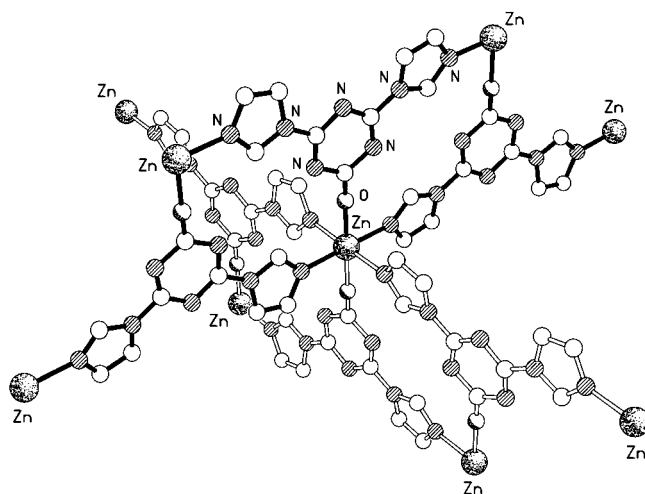


Figure 1. The coordination environment at one of the Zn centers in the solid-state structure of **1** showing the intersection of two approximately orthogonally oriented segments of the continuous tapes.

The motif illustrated in Figure 1 extends in three dimensions to form a set of contiguous boxlike units (Figure 2). The Zn ⋯ Zn separations around the equatorial belt of each box are 13.08 Å, the inter-Zn–Zn vector angles being 79/101° (see above). Each unit contains voids which interconnect to form

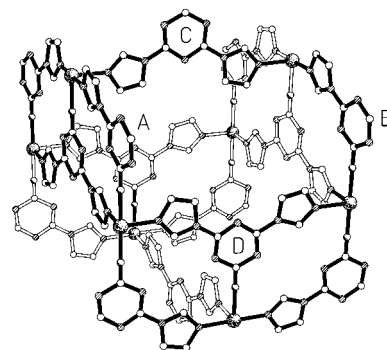


Figure 2. One of the boxlike units that extend to form the continuous three-dimensional network of **1**.

sinuous channels that extend in three dimensions. The windows into each of these channels are bounded by the ligands containing the triazine rings indicated A–D in Figure 2. Allowing for the van der Waals radii, the approximate window size is 9.6 × 5.5 Å. Figure 3 depicts a view of this porous structure viewed down the crystallographic 101 direction. A particularly important feature of this material is that, because of the uncharged nature of this array, there are no counterions to obstruct the pores.

Because of the very open nature of the $[\text{Zn}(\text{dimto})_2]_n$ framework, at least some of the DMF molecules of solvation occluded in the lattice are lost on removal of the solid from solution and it is therefore difficult to obtain either a reproducible or a precise value for the DMF:Zn ratio from the X-ray study or from elemental analysis results. Thermogravimetric analysis measurements indicate a typical DMF:Zn ratio of about 6, and show that there is complete desolvation by about 170 °C. The desolvated lattice is then

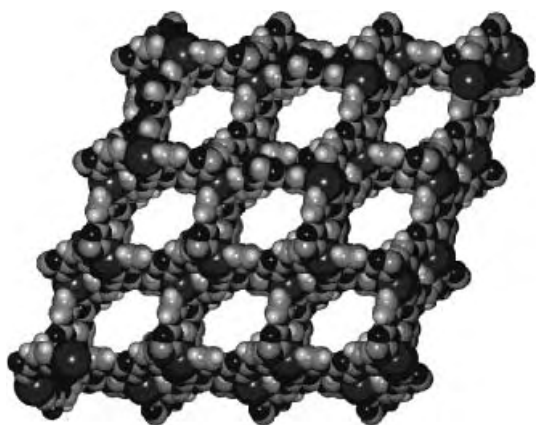


Figure 3. Space-filling representation of the solid-state structure of **1**, showing the large pores that extend through the structure.

thermally stable to about 300 °C after which gradual decomposition occurs. Desolvation can also be easily achieved at room temperature by immersing the solid in a more volatile small molecule solvent such as acetonitrile (which causes exchange of the included solvent molecules—see below), filtering off the solid, and then simply applying a vacuum to remove the occluded acetonitrile. X-ray powder patterns of the solvent-free matrix obtained by desolvation at room temperature show that there is no significant change in the structure. Even after direct thermal removal of the less volatile guests such as DMF (at about 140 °C) the gross lattice integrity appears to be retained.^[6]

The sizes of the cavities and access channels in **1** offer appreciable potential for guest molecule uptake and this is under examination. The diamagnetism of the host $[\text{Zn}(\text{dim-to})_2]_n$ lattice permits the application of a particularly favorable way of studying the inclusion of guest molecules by means of solid-state magic angle spinning (MAS) NMR spectroscopy. This is illustrated in Figure 4 which shows the ^{13}C MAS spectrum of the desolvated lattice and the analogous spectra of samples containing DMF or ethanol molecules, respectively.

The formation of this type of large-pore metal-organic zeotype is not restricted to zinc as the linking metal ion, as we have obtained, and structurally characterized, an analogous compound with manganese(II), thus demonstrating the feasibility of incorporating potentially redox-active metal centers into the lattice framework. This fact, when taken in conjunction with the size of the lattice cavities, the fundamental difference in the nature of the cavity “walls” as compared with the aluminosilicate zeolites, the absence of counterions, and a reasonable thermal stability, make these, and related, materials exciting new candidates for examination of their potential utility in, for example, catalysis or separation processes.

Experimental Section

Large colorless crystals of **1** formed over a two-day period from a solution containing zinc bromide (45 mg, 0.2 mmol) and 2,4,6-tri(1-imidazolyl)-1,3,5-triazine (56 mg, 0.2 mmol) in DMF (4 mL). Yield 70 % (based on Zn^{2+}). Once separated from the mother liquor the crystals were sensitive to partial loss of the included DMF of solvation. The solid-state CP/MAS

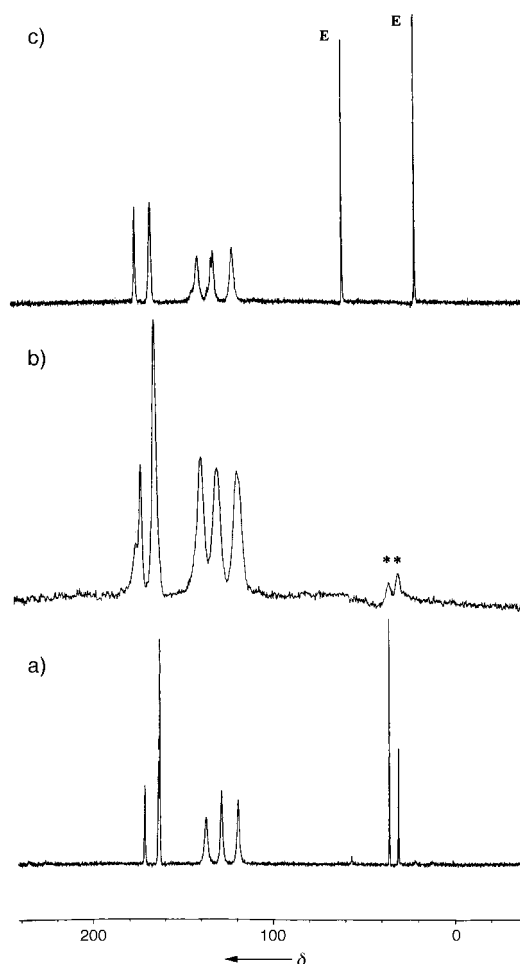


Figure 4. ^{13}C MAS NMR spectra of a) compound **1**, peaks at $\delta = 30.57$, 35.49 , and 163.25 are due to the ^{13}C NMR resonances of DMF; b) compound **1** after almost complete removal of the included DMF (the peaks marked * are due to small residual amounts of DMF); c) a sample of **1** in which the DMF has been replaced by ethanol (the ^{13}C NMR resonances of ethanol are marked E).

^{13}C NMR spectra were recorded at 75.5 MHz (7.05 T) on a Bruker MSL300 spectrometer and a standard Bruker magic angle sample spinning (MAS) probe with double-bearing rotation mechanism. The samples were studied at ambient probe temperature as polycrystalline powders in zirconia rotors (7 mm external diameter) and MAS frequencies between 4 and 5 kHz (with stability better than about ± 10 Hz) were used. The ^{13}C chemical shifts are given relative to tetramethylsilane.

Received: July 20, 1998 [Z12178IE]
German version: *Angew. Chem.* **1999**, *111*, 217–219

Keywords: microporosity • solid-state structures • supramolecular chemistry • zeolite analogues • zinc

- [1] I. W. C. E. Arends, R. A. Sheldon, M. Wallau, U. Schuchardt, *Angew. Chem.* **1997**, *109*, 1190–1211; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1144–1163.
- [2] a) C. Janiak, *Angew. Chem.* **1997**, *109*, 1499–1502; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1431–1434, and references therein; b) Subsequent to the submission of this communication, Yaghi and co-workers reported a microporous framework comprising zinc centers bonded to 1,4-benzenedicarboxylate anions, H. Li, M. Eddaoudi, T. L. Groy, O. M. Yaghi, *J. Am. Chem. Soc.* **1998**, *120*, 8571–8572.

- [3] For a recent comprehensive review of lattice interpenetration see: S. R. Batten, R. Robson, *Angew. Chem.* **1998**, *110*, 1558–1595; *Angew. Chem. Int. Ed.* **1998**, *37*, 1460–1494.
- [4] Crystal data for **1**: $C_{18}H_{12}N_{14}O_2Zn_6C_3H_7NO$, $M_r = 960.36$, clear octahedron, $0.30 \times 0.23 \times 0.20$ mm, orthorhombic, space group *Fddd*, $a = 16.638(5)$, $b = 20.198(3)$, $c = 26.273(3)$ Å³, $V = 8829(3)$ Å³, $Z = 8$, $\rho_{\text{calc}} = 1.445$ g cm⁻³, $\mu(\text{CuK}\alpha) = 1.400$ mm⁻¹, $F(000) = 4032$. Siemens P4 diffractometer, graphite-monochromated $\text{CuK}\alpha$ radiation, ω scans, $T = 293$ K. Of 1650 independent reflections measured ($2\theta < 120^\circ$), 1156 had $I_0 > 2\sigma(I_0)$ and were considered observed. The structure was solved by direct methods and the non-hydrogen atoms were refined anisotropically. The hydrogen atoms were placed in calculated positions, assigned isotropic thermal parameters $U(\text{H}) = 1.2U_{\text{eq}}(\text{C})$ and allowed to ride on their parent carbon atoms. Refinement was by full-matrix least-squares based on F^2 to give $R_1 = 0.0767$, and $wR_2 = 0.2143$. Computations were carried out with the SHELXTL 5.03 program package. The included DMF solvent was distributed randomly throughout the channels in the structure and no realistic atom positions could be fitted to the weak diffuse areas of residual electron density. The value of about six DMF molecules per zinc atom given in the empirical formula was deduced from the TGA measurements and the corresponding values of calculated density, μ , and $F(000)$ reflect this figure. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-102315. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [5] A search of the April 1998 release of the Cambridge Crystallographic Database revealed only three other examples of a linear M-O-C arrangement out of a total of 1787 hits.
- [6] A substantial portion of the powder pattern of the heated sample comprises an amorphous “hump” but with the principal lines of the host structure clearly visible.

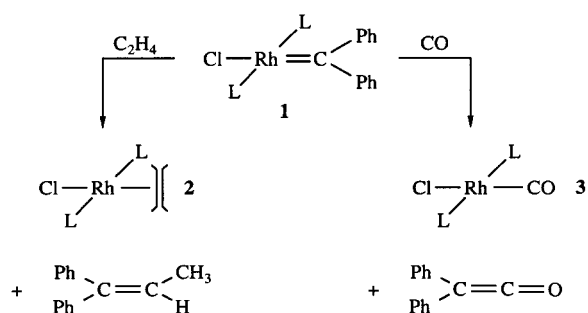
The First Example of Linkage-Isomeric Ketene Metal Complexes**

Elke Bleuel, Matthias Laubender,
Birgit Weberndörfer, and Helmut Werner*

*Dedicated to Professor Otto J. Scherer
on the occasion of his 65th birthday*

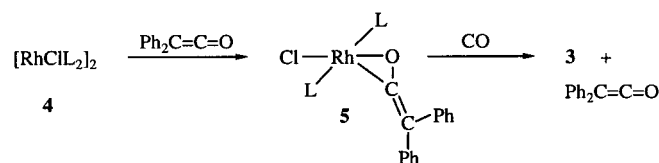
In the course of investigations on the reactivity of carbenerhodium complexes *trans*-[RhCl(=CR')(L)₂] (R' = aryl; L = PR₃, AsR₃, SbR₃) we recently observed^[1] that these compounds react smoothly with olefins, CO, and isocyanides by C–C coupling. While the reaction of **1** with ethene affords **2** exclusively 1,1-diphenylpropene (and *not* 1,1-diphenylcyclopropane), treatment of **1** with CO forms the carbonyl complex **3** and diphenylketene (Scheme 1).^[1, 2]

Since it is known from the work by the groups of Herrmann, Cutler, Roper, and others that reactions of both metal carbonyls with diazoalkanes and of metal carbenes with CO under pressure lead to ketene complexes,^[3] we were inter-



Scheme 1. L = PiPr₃.

ested to find out whether the metal-assisted formation of Ph₂C=C=O from **1** and CO occurs via the intermediate *trans*-[RhCl(Ph₂C=C=O)(PiPr₃)₂]. Attempts to detect such a compound by controlled addition of CO to a solution of **1** in C₆D₆ or CDCl₃ failed. Therefore we chose a different synthetic route for our target, the square-planar ketenerhodium complex, and treated the chloro-bridged binuclear compound **4**^[4] with diphenylketene. In benzene at room temperature complex **5** (Scheme 2) is readily formed and, after removal of the



Scheme 2. L = PiPr₃.

solvent, is isolated as a red-brown solid in almost quantitative yield. The coordination of diphenylketene through the C=O and not the C=C bond, which was already indicated by the spectroscopic data,^[3c] was confirmed by an X-ray crystal structure analysis (Figure 1).^[5] The coordination geometry around the rhodium atom is distorted square-planar, the bond angle P1-Rh-P2 of 168.41(4)° thereby deviates considerably from the ideal value of 180°. We assume that this is due to the repulsion between the isopropyl and phenyl groups. Moreover, a remarkable feature is that in contrast to Cl-Rh-Cl (146.32(1)°) the axis Cl-Rh-O (177.25(9)°) is nearly linear and thus unsymmetrical bonding of the C=O unit to the metal center results. Compared to other $\eta^2(\text{C}, \text{O})$ -diphenylketene complexes,^[6] the distance O–Cl in **5** is significantly shorter which points to a reduced degree of π -back bonding from the rhodium center to the π^* orbital of the C=O moiety. In view of the presence of the electron-rich [RhCl(PiPr₃)₂] fragment this observation is really surprising.

The ketene complex **5**, which is thermally remarkably stable, reacts with CO under normal pressure to yield quantitatively the rhodium carbonyl compound *trans*-[RhCl(CO)(PiPr₃)₂]^[7] and diphenylketene. Upon treatment of **5** with C₆H₇K in THF a substitution of chloride for indenyl does not occur. However, the desired ligand exchange can be carried out if compound **5** is transformed in the initial step with one equivalent of AgPF₆ to an intermediate with the supposed composition *trans*-[Rh(Ph₂C=C=O)(PiPr₃)₂-(O=CMe₂)]PF₆, which subsequently reacts in situ with

[*] Prof. Dr. H. Werner, Dipl.-Chem. E. Bleuel,
Dipl.-Chem. M. Laubender, Dipl.-Chem. B. Weberndörfer
Institut für Anorganische Chemie der Universität
Am Hubland, D-97074 Würzburg (Germany)
Fax: (+49)931-888-4605
E-mail: helmut.werner@mail.uni-wuerzburg.de

[**] This work was supported by the Deutsche Forschungsgemeinschaft (SFB 347), the Fonds der Chemischen Industrie, and the BASF AG.

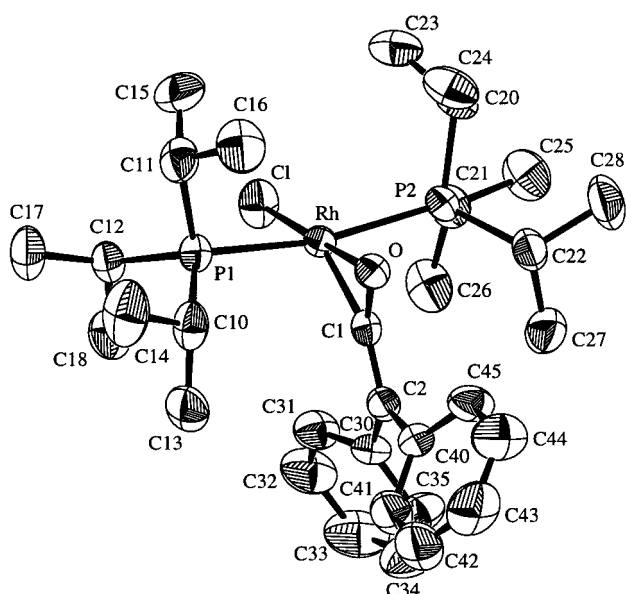


Figure 1. Molecular structure of **5** (thermal ellipsoids with 50% probability). Selected bond lengths [Å] and angles [°]: Rh–O 2.090(3), Rh–C1 1.971(4), Rh–C1 2.298(1), Rh–P1 2.382(1), Rh–P2 2.369(1), C1–O 1.264(5), C1–C2 1.349(6); P1–Rh–P2 168.41(4), Cl–Rh–O 177.25(9), Cl–Rh–C1 146.32(1), P1–Rh–C1 90.02(4), P2–Rh–C1 90.28(4), P1–Rh–O 88.37(8), P2–Rh–O 90.85(8), Rh–O–C1 66.8(2), Rh–C1–C2 144.0(3), O–C1–C2 138.9(4).

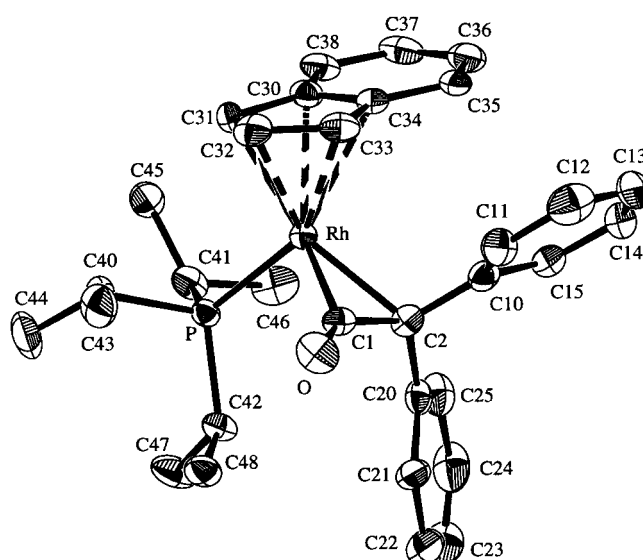
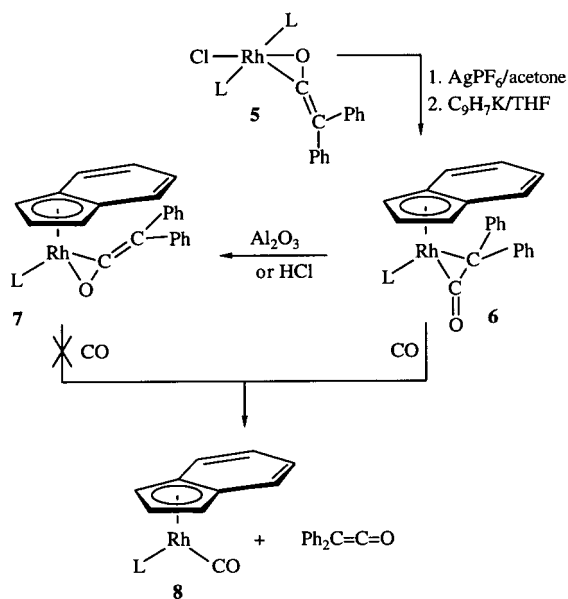


Figure 2. Molecular structure of **6** (thermal ellipsoids with 50% probability). Selected bond lengths [Å] and angles [°]: Rh–C1 1.936(5), Rh–C2 2.180(5), Rh–P 2.321(1), Rh–C30 2.461(5), Rh–C31 2.263(5), Rh–C32 2.242(4), Rh–C33 2.271(5), Rh–C34 2.451(5), O–C1 1.208(4), C1–C2 1.467(5); P–Rh–C1 98.1(2), P–Rh–C2 103.9(1), Rh–C1–O 139.6(4), Rh–C2–C1 60.4(2), C1–Rh–C2 41.2(2), O–C1–C2 142.0(5).



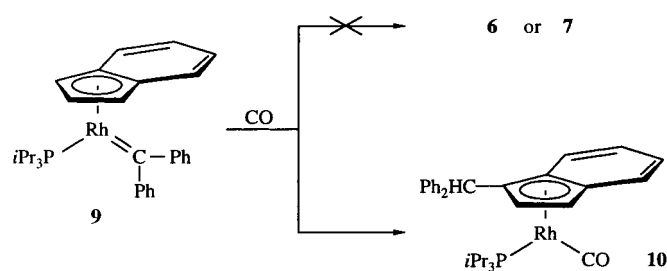
Scheme 3. L = $\text{P}(\text{iPr})_3$.

$\text{C}_9\text{H}_7\text{K}$ to give the indenyl complex **6** (Scheme 3). By using this method, **6** can be isolated in 86% yield. Spectroscopic data reveal that the conversion of **5** to **6** is accompanied by a change of the coordination mode of the ketene ligand from $\eta^2(\text{C},\text{O})$ to $\eta^2(\text{C},\text{C})$. The IR spectrum of **6** displays an absorption at 1777 cm^{-1} for the $\text{C}=\text{O}$ stretch (**5**: $\tilde{\nu}(\text{C}=\text{O}) = 1590\text{ cm}^{-1}$) and the ^{13}C NMR spectrum a doublet of doublets at $\delta = 227.7$ for the $\text{C}=\text{C}=\text{O}$ and a doublet at $\delta = 19.5$ for the $\text{C}=\text{C}=\text{O}$ carbon atom (**5**: $\delta = 167.4$ (dt) and 123.9 (s)). The X-ray crystal structure analysis of **6** confirms the proposed linkage isomerization of the metal-bound ketene (Figure 2).

The C1–C2 bond is longer and the C1–O bond shorter than in **5**. The difference of the Rh–C1 bond length in **5** and **6** is quite small and also the bond angle O–C1–C2 is almost identical in both complexes. The indenyl ligand in **6** is unsymmetrically linked (i.e. approaching η^3 coordination) to the metal, as was also found in other rhodium complexes of the general composition $[(\text{C}_9\text{H}_7)\text{RhL}_2]$ and $[(\text{C}_9\text{H}_7)\text{RhL}(\text{L}')]^{[8]}$.

Although compound **6** is thermally stable up to 137°C , upon treatment with acidic Al_2O_3 or with a solution of HCl in benzene it rapidly rearranges to the isomeric complex **7**. The isomerization, which can be monitored by the change of color from orange-red to orange, is confirmed by the spectroscopic data. Characteristic features for **7** are the position of the $\tilde{\nu}(\text{C}=\text{O})$ stretching frequency at 1598 cm^{-1} (see for comparison the data for **5** and **6**) and the chemical shift of the signals for the carbon atoms of the $\text{C}=\text{C}=\text{O}$ unit at $\delta = 223.0$ and 130.2 . With regard to the reactivity, compounds **6** and **7** differ insofar as the $\eta^2(\text{C},\text{C})$ -bonded isomer reacts instantaneously with CO to yield the carbonylrhodium complex **8** (plus diphenylketene), while the $\eta^2(\text{C},\text{O})$ -bonded isomer is completely inert toward carbon monoxide (C_6H_6 , 25°C , 1 bar, 5 days).

The attempt to generate either compound **6** or **7** by metal-assisted C–C coupling from the carbene complex **9** (recently prepared in our laboratory)^[8d] and CO led to a surprising result. Instead of a coupling of the CPh_2 moiety with CO, after attack of CO at the metal center a migration of the carbene to the indenyl ligand takes place, which is accompanied by an insertion of CPh_2 into one of the C–H bonds of the five-membered ring of C_9H_7 . The structure of **10** (Scheme 4) has been confirmed by X-ray crystallography.^[9] Complex **9** thus behaves differently to the corresponding cyclopentadienyl



Scheme 4.

analogue $[(\eta^5\text{-C}_5\text{H}_5)\text{Rh}(\text{C}=\text{CPh}_2)(\text{PiPr}_3)]$ which reacts with CO to give $[(\eta^5\text{-C}_5\text{H}_5)\text{Rh}(\text{CO})(\text{PiPr}_3)]$ and diphenylketene.^[1b]

With the synthesis and the characterization of compounds **6** and **7** we have shown for the first time that linkage isomerism exists also among ketene transition metal complexes. Up to now examples for this type of isomerism were known mainly for metal compounds containing NO_2^- , NCS^- , and triazole derivatives as ligands,^[10] the stability of the respective isomers could usually be predicted by the hard/soft acid/base (HSAB) concept.^[11] Since only a conversion of **6** to **7** but not in the reverse direction takes place, we assume that the $\eta^2(\text{C},\text{O})$ -bonded isomer is thermodynamically more stable. We are now attempting to prepare rhodium and iridium complexes with different configurations as well as oxidation states of the metal using not only $\text{Ph}_2\text{C}=\text{C}=\text{O}$ but also other ketenes as ligands in an effort to establish under which circumstances the $\eta^2(\text{C},\text{O})$ - or the $\eta^2(\text{C},\text{C})$ -coordination mode of a particular ketene is preferred.

Experimental Section

5: A solution of **4** (238 mg, 0.26 mmol) in benzene (5 mL) was treated with diphenylketene (88 μL , 0.52 mmol) and stirred for 5 min at room temperature. The solvent was removed in vacuo, the red-brown solid was washed twice with pentane (10 mL) and dried; yield 296 mg (87 %); m.p. 110 °C (decomp); IR (C_6H_6): $\tilde{\nu}(\text{C}=\text{C}=\text{O}) = 1590\text{ cm}^{-1}$; ^1H NMR (200 MHz, C_6D_6):^[12] $\delta = 8.76, 7.66, 7.39\text{--}6.98$ (all m, C_6H_5), 2.33 (m, PCHCH_3), 1.19 (dvt, $N = 13.5$, $^3J(\text{H},\text{H}) = 6.8\text{ Hz}$, PCHCH_3); $^{13}\text{C}\{^1\text{H}\}$ NMR (50.3 MHz, C_6D_6): $\delta = 167.4$ (dt, $^1J(\text{Rh},\text{C}) = 19.5$, $^2J(\text{P},\text{C}) = 4.9\text{ Hz}$, $\text{C}=\text{C}=\text{O}$), 138.4, 137.6, 130.2, 129.4, 129.1, 128.9, 128.7, 128.3, 127.8, 127.6 (all s, C_6H_5), 123.9 (s, $\text{C}=\text{C}=\text{O}$), 22.2 (vt, $N = 19.5\text{ Hz}$, PCHCH_3), 19.6, 19.3 (both s, PCHCH_3); ^{31}P NMR (81.0 MHz, C_6D_6): $\delta = 32.5$ (d, $^1J(\text{Rh},\text{P}) = 108.3\text{ Hz}$).

6: A solution of **5** (117 mg, 0.18 mmol) in acetone (10 mL) was treated dropwise with a solution of AgPF_6 (45 mg, 0.18 mmol) in acetone (10 mL). A change of color from red-brown to orange occurred and a white flocky precipitate of AgCl was formed. After the reaction mixture had been stirred for 5 min at room temperature, the solution was filtered. The filtrate was dried in vacuo and the residue was dissolved in THF (10 mL). The solution was treated with $\text{C}_6\text{H}_7\text{K}$ (139 mg, 0.90 mmol) and stirred for 30 min. After the solvent had been removed, the residue was extracted with pentane (50 mL). The extract was filtered, the filtrate was concentrated to about 10 mL and then stored for 12 h at 0 °C. Orange-red crystals were formed which were washed with small quantities of pentane and dried in vacuo; yield 89 mg (86 %); m.p. 137 °C (decomp); IR (C_6H_6): $\tilde{\nu}(\text{C}=\text{C}=\text{O}) = 1777\text{ cm}^{-1}$; ^1H NMR (200 MHz, C_6D_6):^[13] $\delta = 7.59, 7.12\text{--}6.75$ (both m, C_6H_5 and $\text{H}^{4,7}$ of indenyl), 6.07 (dt, $^2J(\text{Rh},\text{H}) = ^3J(\text{H},\text{H}) = 2.8\text{ Hz}$, H^2 of indenyl), 4.58 (m, $\text{H}^{1,3}$ of indenyl), 1.23 (sept (br), $^3J(\text{H},\text{H}) = 7.2\text{ Hz}$, PCHCH_3), 0.85 (dd, $^3J(\text{P},\text{H}) = 13.4$, $^3J(\text{H},\text{H}) = 7.2\text{ Hz}$, PCHCH_3); $^{13}\text{C}\{^1\text{H}\}$ NMR (100.6 MHz, C_6D_6): $\delta = 227.7$ (dd, $^1J(\text{Rh},\text{C}) = 22.9$, $^2J(\text{P},\text{C}) = 5.1\text{ Hz}$, $\text{C}=\text{C}=\text{O}$), 142.3, 140.3, 133.1, 128.4, 128.3, 128.1, 128.0, 127.2, 126.0, 125.4, 124.9, 123.8 (all s, C_6H_5), 122.3, 122.2, 119.9, 119.0 (all s, $\text{C}^{4,7}$ of indenyl), 115.8 (s, $\text{C}^{8,9}$ of indenyl), 99.4 (d, $^1J(\text{Rh},\text{C}) = 6.4\text{ Hz}$, C^2 of indenyl), 68.5 (s (br), C^1 , C^3 of indenyl), 27.1 (d, $^1J(\text{P},\text{C}) = 19.1\text{ Hz}$, PCHCH_3), 20.2 (s,

PCHCH_3), 19.5 (d, $^1J(\text{Rh},\text{C}) = 3.8\text{ Hz}$, $\text{C}=\text{C}=\text{O}$); ^{31}P NMR (81.0 MHz, C_6D_6): $\delta = 52.8$ (d, $^1J(\text{Rh},\text{P}) = 197.1\text{ Hz}$).

7: A solution of **6** (74 mg, 0.13 mmol) in benzene (5 mL) was treated with a 0.36 M solution of HCl (833 μL , 0.30 mmol) in benzene and stirred for 5 min at room temperature. The solvent was removed in vacuo, the residue was dissolved in pentane (5 mL), and the solution stored for 24 h at 0 °C. Orange crystals were formed which were washed with small quantities of pentane and dried in vacuo; yield 69 mg (93 %); m.p. 122 °C (decomp); IR (C_6H_6): $\tilde{\nu}(\text{C}=\text{C}=\text{O}) = 1598\text{ cm}^{-1}$; ^1H NMR (400 MHz, C_6D_6): $\delta = 7.89, 7.45\text{--}6.66$ (both m, C_6H_5 and $\text{H}^{4,7}$ of indenyl), 5.85 (m, H^2 of indenyl), 5.28, 5.00 (both m, $\text{H}^{1,3}$ of indenyl), 2.23 (m, PCHCH_3), 0.86 (dd, $^3J(\text{P},\text{H}) = 13.1$, $^3J(\text{H},\text{H}) = 7.2\text{ Hz}$, PCHCH_3), 0.82 (dd, $^3J(\text{P},\text{H}) = 14.4$, $^3J(\text{H},\text{H}) = 7.3\text{ Hz}$, PCHCH_3); $^{13}\text{C}\{^1\text{H}\}$ NMR (100.6 MHz, C_6D_6): $\delta = 223.0$ (dd, $^1J(\text{Rh},\text{C}) = 32.6$, $^2J(\text{P},\text{C}) = 7.1\text{ Hz}$, $\text{C}=\text{C}=\text{O}$), 141.1, 140.5 (both s, C_6H_5), 130.2 (s, $\text{C}=\text{C}=\text{O}$), 129.4, 129.2, 129.0, 128.3 (all s, C_6H_5), 128.2 (s, $\text{C}^{8,9}$ of indenyl), 127.6, 127.4, 126.7, 126.6 (all s, C_6H_5), 123.2, 120.5 (both s, $\text{C}^{4,7}$ of indenyl), 104.7 (d, $^3J(\text{Rh},\text{C}) = 5.7\text{ Hz}$, C^5 or C^6 of indenyl), 82.0 (m, C^2 of indenyl), 77.4 (s, C^5 or C^6 of indenyl), 62.9 (d, $^1J(\text{Rh},\text{C}) = 9.5\text{ Hz}$, $\text{C}^{1,3}$ of indenyl), 25.0 (d, $^2J(\text{P},\text{C}) = 19.1\text{ Hz}$, PCHCH_3), 19.6, 19.1 (both s, PCHCH_3); ^{31}P NMR (162.0 MHz, C_6D_6): $\delta = 49.8$ (d, $^1J(\text{Rh},\text{P}) = 162.8\text{ Hz}$).

10: A slow stream of CO was passed through a solution of **9** (98 mg, 0.18 mmol) in pentane (10 mL) for 30 s at -78°C . Upon warming the mixture to room temperature, the color of the deep green solution brightened. The solution was stirred for 30 min, the solvent was removed, and the residue was dissolved in pentane (3 mL), which was saturated with CO. After the solution had been stored for 3 d at -18°C , an orange-yellow solid precipitated which was washed with small quantities of pentane (-10°C) and dried in vacuo; yield 81 mg (79 %); m.p. 56 °C; IR (C_6H_{14}): $\tilde{\nu}(\text{CO}) = 1944\text{ cm}^{-1}$; ^1H NMR (400 MHz, C_6D_6): $\delta = 7.69, 7.24\text{--}6.89$ (both m, C_6H_5 and $\text{H}^{4,7}$ of indenyl), 6.06 (d, $^3J(\text{Rh},\text{H}) = 3.2\text{ Hz}$, CHPh_2), 5.83 (m, H^2 of indenyl), 4.82 (d, $^2J(\text{Rh},\text{H}) = 3.2\text{ Hz}$, H^3 of indenyl), 1.72 (sept (br), $^3J(\text{H},\text{H}) = 7.2\text{ Hz}$, PCHCH_3), 0.84 (dd, $^3J(\text{P},\text{H}) = 14.4$, $^3J(\text{H},\text{H}) = 7.2\text{ Hz}$, PCHCH_3), 0.81 (dd, $^3J(\text{P},\text{H}) = 14.0$, $^3J(\text{H},\text{H}) = 7.2\text{ Hz}$, PCHCH_3); $^{13}\text{C}\{^1\text{H}\}$ NMR (100.6 MHz, C_6D_6): $\delta = 196.0$ (dd, $^1J(\text{Rh},\text{C}) = 89.0$, $^2J(\text{P},\text{C}) = 21.6\text{ Hz}$, $\text{Rh}-\text{CO}$), 144.3, 144.0, 130.4, 128.9, 128.5, 128.1, 126.5, 126.4 (all s, C_6H_5), 122.9, 121.2 (both s, $\text{C}^{4,7}$ of indenyl), 119.3 (s, C^8 or C^9 of indenyl), 118.6 (s, C^5 or C^6 of indenyl), 117.6 (s, C^8 or C^9 of indenyl), 117.3 (s, C^5 or C^6 of indenyl), 98.5 (dd, $^2J(\text{Rh},\text{C}) = 5.2$, $^3J(\text{P},\text{C}) = 1.7\text{ Hz}$, CHPh_2), 97.3 (dd, $^1J(\text{Rh},\text{C}) = 13.0$, $^2J(\text{P},\text{C}) = 3.8\text{ Hz}$, C^1 of indenyl), 72.3 (d, $^1J(\text{Rh},\text{C}) = 3.3\text{ Hz}$, C^2 of indenyl), 51.0 (d, $^1J(\text{Rh},\text{C}) = 1.5\text{ Hz}$, C^3 of indenyl), 28.0 (d, $^1J(\text{P},\text{C}) = 21.2\text{ Hz}$, PCHCH_3), 19.8, 19.7 (both s, PCHCH_3); ^{31}P NMR (162.0 MHz, C_6D_6): $\delta = 74.3$ (d, $^1J(\text{Rh},\text{P}) = 194.7\text{ Hz}$).

Received: August 31, 1998 [Z12352IE]

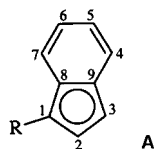
German version: *Angew. Chem.* **1999**, *111*, 222–225

Keywords: carbene complexes • indenyl complexes • ketene complexes • linkage isomerism • rhodium

- [1] a) P. Schwab, N. Mahr, J. Wolf, H. Werner, *Angew. Chem.* **1993**, *105*, 1498–1500; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1480–1482; b) H. Werner, *J. Organomet. Chem.* **1995**, *500*, 331–336.
- [2] H. Werner, P. Schwab, E. Bleuel, N. Mahr, P. Steinert, J. Wolf, *Chem. Eur. J.* **1997**, *3*, 1375–1384.
- [3] Übersichten: a) W. A. Herrmann, *Angew. Chem.* **1978**, *90*, 855–868; *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 800–813; b) M. A. Gallop, W. R. Roper, *Adv. Organomet. Chem.* **1986**, *25*, 121–198; c) G. L. Geoffroy, S. L. Bassner, *Adv. Organomet. Chem.* **1988**, *28*, 1–83.
- [4] a) Isolation: H. Werner, J. Wolf, A. Höhn, *J. Organomet. Chem.* **1985**, *287*, 395–407; b) Strukturanalyse: P. Binger, J. Haas, G. Glaser, R. Goddard, C. Krüger, *Chem. Ber.* **1994**, *127*, 1927–1929.
- [5] Data for the X-ray structure analyses: **5**: Crystals from pentane at 0 °C, $\text{C}_{32}\text{H}_{52}\text{ClO}_2\text{Rh}$ (653.04); crystal size $0.2 \times 0.15 \times 0.1\text{ mm}$; triclinic, space group $P\bar{1}$ (no. 2), $a = 8.7233(4)$, $b = 11.0994(8)$, $c = 18.725(1)\text{ Å}$, $\alpha = 93.249(5)$, $\beta = 103.280(5)$, $\gamma = 107.901(6)^\circ$, $Z = 2$, $V = 1663.2(2)\text{ Å}^3$, $\rho_{\text{calcd}} = 1.304\text{ g cm}^{-3}$; $T = 293(2)\text{ K}$; $2\theta = 48^\circ$; 5595 reflections measured, 5207 were unique ($R_{\text{int}} = 0.0227$) and 4037 observed ($I > 2\sigma(I)$); Enraf-Nonius CAD4 diffractometer, $\text{MoK}\alpha$ radiation ($\lambda = 0.71073\text{ Å}$), graphite-monochromated, zirconium filter (factor 15.4); L_p and

empirical absorption corrections (Ψ scan, min. transmission 94.56 %). The structure was solved by direct methods and refined with the full-matrix, least-squares method; $R_1=0.0398$, $wR_2=0.0729$ (for 4037 reflections with $I>2\sigma(I)$), $R_1=0.0626$, $wR_2=0.0859$ (for all 5207 data); data-to-parameter ratio 15.04; residual electron density $+0.349/-0.343$ e $\text{\AA}^{-3}$. **6**: crystals from pentane at 0 °C, $\text{C}_{32}\text{H}_{38}\text{OPRh}$ (572.50); crystal size $0.4 \times 0.3 \times 0.2$ mm; monoclinic, space group $P2_1/c$ (no. 14), $a=9.753(3)$, $b=13.384(4)$, $c=20.914(6)$ Å, $\beta=95.998(14)^\circ$, $Z=4$, $V=2714.9(14)$ Å³, $\rho_{\text{calcd.}}=1.401$ g cm⁻³; $T=173(2)$ K; $2\theta=50^\circ$; 3569 reflections measured, 3473 were unique ($R_{\text{int}}=0.0328$) and 2619 observed ($I>2\sigma(I)$); Enraf-Nonius CAD4 diffractometer, $\text{MoK}\alpha$ radiation ($\lambda=0.71073$ Å), graphite-monochromated, zirconium filter (factor 16.4); Lp and empirical absorption corrections (Ψ scan, min. transmission 96.85 %). The structure was solved by direct methods and refined with the full-matrix, least-squares method; $R_1=0.0348$, $wR_2=0.0604$ (for 2619 reflections with $I>2\sigma(I)$), $R_1=0.0602$, $wR_2=0.0683$ (for all 3473 data); data-to-parameter ratio 10.24; residual electron density $+0.239/-0.240$ e $\text{\AA}^{-3}$. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-102818 (**5**) and CCDC-102919 (**6**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

- [6] a) S. Gambarotta, M. Pasquali, C. Floriani, A. Chiesi-Villa, C. Guastini, *Inorg. Chem.* **1981**, 20, 1173–1178; b) R. Birk, H. Berke, H.-U. Hund, G. Huttner, L. Zsolnai, L. Dahlenburg, U. Behrens, T. Sielisch, *J. Organomet. Chem.* **1989**, 372, 397–410; c) P. Hofmann, L. A. Perez-Moya, O. Steigelmann, J. Riede, *Organometallics* **1992**, 11, 1167–1176; d) A. Antiñolo, A. Otero, M. Fajardo, C. Lopez-Mardomingo, D. Lucas, Y. Mugnier, M. Lanfranchi, M. A. Pellinghelli, *J. Organomet. Chem.* **1992**, 435, 55–72; e) D. B. Grotjahn, H. C. Lo, *Organometallics* **1995**, 14, 5463–5465; f) R. Flügel, O. Gevert, H. Werner, *Chem. Ber.* **1996**, 129, 405–410.
- [7] a) C. Busetto, A. D'Alfonso, F. Maspero, G. Perego, A. Zazzetta, *J. Chem. Soc. Dalton Trans.* **1977**, 1828–1834; b) K. Wang, G. P. Rosini, S. P. Nolan, A. S. Goldman, *J. Am. Chem. Soc.* **1995**, 117, 5082–5088.
- [8] a) G. G. Aleksandrov, Y. T. Struchkov, V. S. Khandkarova, S. P. Gubin, *J. Organomet. Chem.* **1970**, 25, 243–247; b) P. Caddy, M. Green, E. O'Brien, L. E. Smart, P. Woodward, *Angew. Chem.* **1977**, 89, 671–672; *Angew. Chem. Int. Ed. Engl.* **1977**, 16, 648–649; c) T. B. Marder, J. C. Calabrese, D. C. Roe, T. H. Tulip, *Organometallics* **1987**, 6, 2012–2014; d) E. Bleuel, Diplomarbeit, Universität Würzburg, **1996**.
- [9] M. Laubender, Dissertation, Universität Würzburg, unpublished.
- [10] L. H. Gade, *Koordinationschemie*, WILEY-VCH, Weinheim, **1998**, chapter 7.
- [11] a) R. G. Pearson, *J. Am. Chem. Soc.* **1963**, 85, 3533–3539; b) H. Werner, *Chem. Unserer Zeit* **1967**, 1, 135–139; c) R. G. Pearson, *J. Chem. Educ.* **1968**, 45, 581–587; R. G. Pearson, *J. Chem. Educ.* **1968**, 45, 643–648.
- [12] Abbreviations used: vt=virtual triplet, dvt=doublet of virtual triplets, $N=^3J(\text{P,H})+^5J(\text{P,H})$ or $^1J(\text{P,C})+^3J(\text{P,C})$.
- [13] For the numbering of the indenyl carbon (and corresponding hydrogen) atoms see formula **A**.

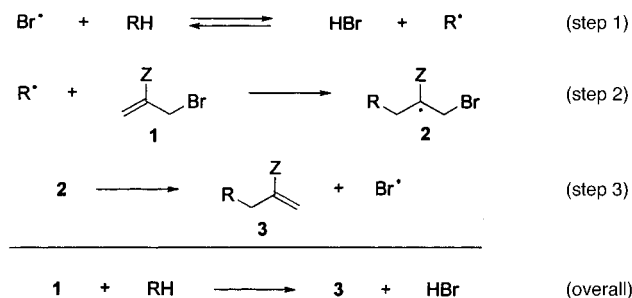


Functionalization of Hydrocarbons by a New Free Radical Based Condensation Reaction**

James. M. Tanko* and Mitra Sadeghipour

There is increased awareness of the need to develop new chemical reactions and processes which avoid the use or generation of toxic and/or environmentally threatening materials. Herein we report a newly developed reaction in which a C–H bond of a hydrocarbon is converted into a C–C bond by transfer of an allyl group ($\text{R–H} \rightarrow \text{R–C=C}$). This process is especially attractive because (unlike other procedures which effect this conversion) the transformation is accomplished in a single step and does not require strongly acidic or basic reaction conditions, or the use of heavy metals.

The proposed mechanism of this reaction is depicted in Scheme 1. Abstraction of hydrogen from R–H (by $\text{Br}^\bullet$) yields $\text{R}^\bullet$, which subsequently adds to the C=C bond of a substituted allyl bromide (**1**). Adduct radical **2** undergoes β cleavage to yield product **3** and regenerate $\text{Br}^\bullet$. Each step depicted in Scheme 1 is well documented in the literature: A bromine atom exhibits high selectivity in hydrogen atom abstractions (step 1),^[1] and is especially reactive towards benzylic hydrogen atoms (for example in the Ziegler bromination).^[2] Allyl bromides have been shown to be effective chain transfer reagents in free radical polymerizations, essentially by steps identical to 2 and 3.^[3]



Scheme 1. Mechanism of the proposed allyl transfer reaction.

To test whether this chemistry could be coupled as shown in Scheme 1 to “invent” a viable synthetic process, we examined the reaction of several allyl bromides with toluene and cumene (Table 1). Overall, mass balances for these reactions were high, and good to excellent yields were obtained, especially when the allyl bromide possesses a radical-stabilizing substituent (e.g., $\text{Z} = \text{Ph}$, CO_2Et , or CN). To confirm the role of $\text{Br}^\bullet$ as the chain carrier in this reaction, a series of competition experiments were performed pitting PhCH_3

[*] Prof. J. M. Tanko, M. Sadeghipour
Department of Chemistry
Virginia Polytechnic Institute and State University
Blacksburg, VA 24061-0212 (USA)
Fax: (+1) 540-231-3255
E-mail: jtanko@vt.edu

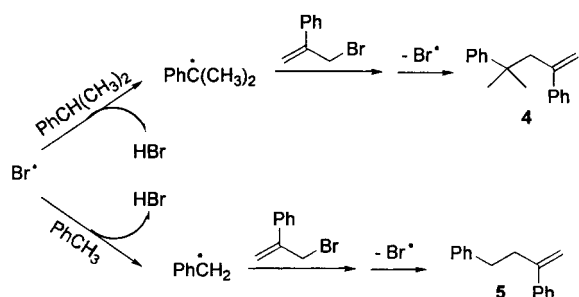
[**] Financial support from the National Science Foundation (CHE-9524986) is acknowledged and appreciated.

Table 1. Reactions of alkylarenes with substituted allyl bromides.

R	Z	A ^[a] [mmol]	B [mmol]	Initiator ^[b]	T [°C]	t [h]	HBr trapping reagent ^[c]	Yield [%]
H	H	47	0.69	DTBPO	120	94	1,2-epoxybutane	33
H	Ph	47	0.72	DTBPO	120	93	K ₂ CO ₃	82
H	Ph	2.8 ^[d]	0.72	DTBPO	120	93	K ₂ CO ₃	24
CH ₃	Ph	36	0.72	DTBPO	120	93	K ₂ CO ₃	100
CH ₃	Ph	1.4 ^[d]	0.72	(<i>t</i> BuO) ₂	120	93	K ₂ CO ₃	66
H	CO ₂ Et	47	0.77	(PhCO ₂) ₂	80	40	K ₂ CO ₃	47
CH ₃	CO ₂ Et	36	0.77	DTBPO	120	94	K ₂ CO ₃	48
H	CN	38	0.77	(PhCO ₂) ₂	80	2	1,2-epoxybutane	66
CH ₃	CN	29	0.77	DTBPO	120	2	1,2-epoxybutane	80

[a] Neat, when not stated otherwise. [b] 20 mol %. [c] 1.1 equiv. [d] In 5 mL of benzene.

against PhCH(CH₃)₂ for Br[•] generated by reaction with a) α-(bromomethyl)styrene (α-BMS, Scheme 2) and b) molecular bromine.



Scheme 2. Competition experiments to establish Br[•] as the chain carrier.

The results (Table 2) reveal that for reactions of α-BMS, the ratio of products formed from the tertiary and primary radicals (*r*(3°/1°)) decreases with increasing concentration of the HBr scavenger (1,2-epoxybutane), and levels off to a value of 25 at high concentrations. This variation in selectivity is readily explained by the fact that hydrogen abstractions by Br[•] are reversible,^[4] and at high scavenger concentrations the reverse reaction is effectively eliminated. The fact that *r*(3°/1°) observed for α-BMS is identical to that observed for the free radical bromination of these substrates with Br₂ confirms the role of Br[•] as chain carrier in accordance with Scheme 1.

Relative rate constants *k*_{rel} for the addition of PhCH₂[•] to several allyl bromides (Scheme 1, step 2: R[•] = PhCH₂[•]) were

Table 2. Observed selectivity in the reaction of toluene and cumene with α-(bromomethyl)styrene (α-BMS) and Br₂.

Br [•] source	1,2-epoxybutane [equiv]	<i>r</i> (3°/1°) ^[a] (80 °C)
α-BMS	0.05	50
α-BMS	0.10	48
α-BMS	0.50	34
α-BMS	1.10	25
α-BMS	2	25
Br ₂	1.1	26

[a] For α-BMS: *r*(3°/1°) = (yield(4)/yield(5)) × 3; for Br₂: *r*(3°/1°) = (yield(PhCBr(CH₃))/yield(PhCH₂Br)) × 3.

also determined from competition experiments at 80 °C: *k*_{rel} = 180 (Z = CN) > 110 (Z = CO₂Et) > 65 (Z = Ph) > 1.0 (Z = H). The observed substituent effect is very similar to that reported by Fischer et al. for addition of PhCH₂[•] to substituted alkenes.^[5]

Although the reactivity order is the same, additions of benzyl radical to CH₂=C(Z)CH₂Br are much less sensitive to the nature of the substituent Z. A plot of lg(*k*_{rel}) for the addition of benzyl radical to substituted allyl bromides versus lg(*k*_{C=C}) yields a line whose slope (*m* = 0.49) is considerably less than unity. The diminished sensitivity to the effect of substituent Z in radical additions to CH₂=C(Z)CH₂Br may be an indication that the resulting β-bromo radical adduct is stabilized by Br, presumably by bridging.^[6] Further work is needed to confirm this hypothesis.

Kinetic chain lengths (i.e., rate of product formation relative to rate of initiator disappearance (d[product]/dt)/(-2d[In₂]/dt))^[7] were determined by monitoring product yields as a function of time. The profile for reaction of toluene (38 mmol, neat) with α-BMS (0.56 mmol) initiated by 20 % di-*tert*-butyl peroxide (DTBPO) at 120 °C is depicted in Figure 1. The initial chain length for this reaction was high (400), and a

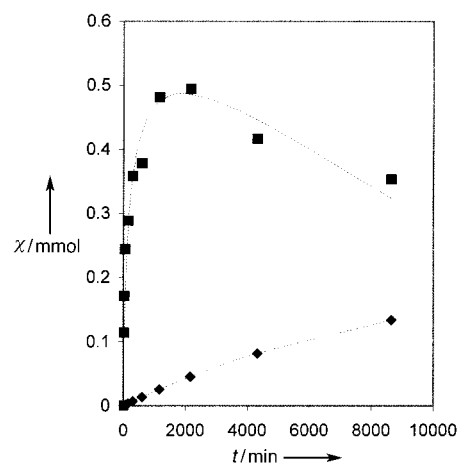


Figure 1. Amount x of product (■) and initiator radical In[•] produced (♦) in the reaction of toluene (38 mmol, neat) and α-(bromomethyl)styrene (0.56 mmol) initiated by di-*tert*-butyl peroxide at 120 °C.

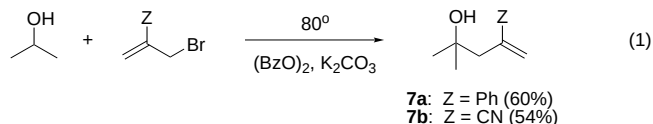
90 % yield of product was obtained within 24 hours (note that the half-life $t_{1/2}$ for DTBPO at 120 °C is 10³ min). At longer reaction times, the yield of the product decreased because the C=C bond of the product is also susceptible to radical addition. At longer reaction times, **6** was detected as a by-product by GC/MS analysis.

Similar results were obtained for other systems (Table 3). Generally, the effect of substituent Z on the chain length tends to parallel the reactivity of the allyl bromide towards PhCH₂· (i.e., Z = CN ≥ CO₂Et > Ph > H), and the chain lengths for PhCH₃ are greater than for PhCH(CH₃)₂. These observations suggest that the addition of the benzylic radical to the C=C bond is likely the rate-determining step of this reaction.^[8]

Table 3. Initial chain lengths for reaction of alkylarenes (neat) with allyl bromides (120 °C, (tBuO)₂ as initiator).

Z	R	Initial chain length	Z	R	Initial chain length
H	H	10	Ph	CH ₃	60
Ph	H	400	CO ₂ Et	CH ₃	60
CO ₂ Et	H	800	CN	CH ₃	400
CN	H	700			

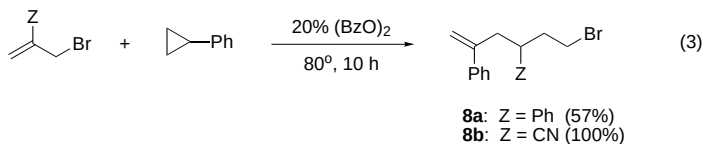
This reaction was extended to other substrates possessing reactive C–H bonds (e.g., secondary alcohols).^[9] Reaction of *i*PrOH (1.56 M) with α-BMS (0.14 M) in benzene produces the tertiary alcohol **7a** in 60 % yield [Eq. (1)]. A similar reaction of *i*PrOH (2.0 M) with α-bromoacrylonitrile (0.2 M) results in a 54 % yield of **7b**.



Finally, Br· is also known to be reactive towards cyclopropanes, yielding ring-opened products by an S_H2 process: Br· attack occurs at the least-hindered carbon atom of the cyclopropane (with inversion of configuration) to provide the most stable radical [Eq. (2)].^[10]



Reaction of phenylcyclopropane (32 mmol, neat) with α-BMS (0.56 mmol) results in a 57 % yield of 6-bromo-2,4-diphenylhex-1-ene [**8a**, Eq. (3)], with 43 % of the starting



material remaining unchanged. In benzene (0.72 mmol of α-BMS and 7.2 mmol of C₆H₅-c-C₃H₅ in 4 mL of solvent), the yield decreases to 42 % (44 % unchanged starting material).

Similar reaction of phenylcyclopropane (32 mmol, neat) with α-bromoacrylonitrile (0.77 mmol) produces **8b** in quantitative yield. In benzene (1 mmol of α-bromoacrylonitrile and 10 mmol of phenylcyclopropane in 3.7 mL of benzene), the yield decreased to 85 %). This reaction of an allyl bromide with a cyclopropane is especially attractive in that it provides a simple one-step synthesis of Δ⁵-hexenyl bromides, which are excellent precursors for the formation of five- and six-membered rings by radical reactions with R₃MH (M = Ge, Sn, Si).^[11]

In summary, a new reaction has been developed for the allylation of a hydrocarbon (and other substrates) by a free radical chain process involving a bromine atom. This reaction is unique in that it accomplishes this transformation in a single step in an environmentally benign manner, thereby demonstrating that “green chemistry” does not necessarily mean that high reaction yields and selectivities have to be compromised.

Experimental Section

In a typical procedure, the hydrocarbon, allyl bromide, the initiator, the solvent (if used), and an HBr scavenger (e.g., K₂CO₃ or epoxide) were combined in a 30-mL pressure tube. The resulting mixture was deoxygenated (three cycles of freeze-pump-thaw) and placed in a heated oil bath. Afterward, the reaction mixture was filtered, washed with saturated NaHCO₃, and concentrated. The crude product was further purified by either preparative TLC or HPLC. All products were fully characterized by IR, UV, ¹H NMR, and ¹³C NMR spectroscopy, mass spectrometry, and either elemental analysis or high-resolution mass spectrometry. Typical reaction conditions and quantities of materials are summarized in Table 1.

Received: July 9, 1998 [Z12122IE]
German version: *Angew. Chem.* **1999**, *111*, 219–222

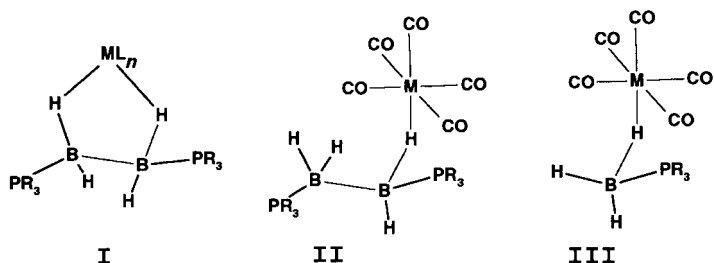
Keywords: bromine • C–C coupling • radical reactions • radicals • reaction mechanisms

- [1] S. S. Friedrich, E. C. Friedrich, L. J. Andrews, R. M. Keefer, *J. Org. Chem.* **1969**, *34*, 900; G. A. Russell, K. A. Desmond, *J. Am. Chem. Soc.* **1963**, *85*, 3139; G. A. Russell in *Free Radicals, Vol. I* (Ed.: J. K. Kochi), Wiley, New York, **1973**, pp. 275–331.
- [2] L. Poutsma, *Free Radicals, Vol. II* (Ed.: J. K. Kochi), Wiley, New York, **1973**, pp. 159–229.
- [3] G. F. Meijjs, E. Rizzardo, S. H. Thang, *Polymer Bulletin* **1990**, *24*, 501.
- [4] D. D. Tanner, N. Wada, *J. Am. Chem. Soc.* **1975**, *97*, 2190.
- [5] M. Walbinder, J.-Q. Wu, H. Fischer, *Helv. Chim. Acta* **1995**, *78*, 910.
- [6] P. S. Skell, J. G. Traynham, *Acc. Chem. Res.* **1984**, *17*, 160.
- [7] J. H. Espenson, *Chemical Kinetics and Reaction Mechanisms*, McGraw Hill, New York, **1981**, pp. 134–146.
- [8] Rate constants for addition of benzyl radical to substituted alkenes are on the order 10²–10³ M^{−1} s^{−1}.^[5] The rate constants for abstraction of a hydrogen atom from toluene is on the order of 10⁵ M^{−1} s^{−1} (based upon an activation energy of 7.6 kcal mol^{−1} and lg(A) = 13.5 (cm³ mol^{−1} s^{−1})); H. R. Anderson, Jr., H. A. Scheraga, E. R. VanArtsdalen, *J. Chem. Phys.* **1953**, *21*, 1258.
- [9] R. J. Kolt, D. D. M. Wayner, D. Griller, *J. Org. Chem.* **1989**, *54*, 4259.
- [10] K. J. Shea, P. S. Skell, *J. Am. Chem. Soc.* **1973**, *95*, 6728; D. E. Applequist, L. F. McKenzie, *J. Org. Chem.* **1976**, *41*, 2262.
- [11] a) J. Luszyk, B. Maillard, S. Deycard, D. A. Lindsay, K. U. Ingold, *J. Org. Chem.* **1987**, *52*, 3509; b) D. J. Hart, *Science* **1984**, *223*, 883; c) W. R. Dolbier, X. X. Rong, *J. Org. Chem.* **1996**, *61*, 4824; d) B. Giese, B. Kopping, *Tetrahedron Lett.* **1989**, *30*, 681; e) C. Chatgililoglu, *Acc. Chem. Res.* **1992**, *25*, 188.

[8,8- η^2 -{ η^2 -(BH₃)Ph₂PCH₂PPh₂}-*nido*-8,7-RhSB₉H₁₀]: A Rhodathiaborane with a Novel Bidentate Chelating Ligand**

Ramón Macías, Nigam P. Rath, and Lawrence Barton*

Although the B-H-M bridging bond is a common structural motif in the coordination and organometallic chemistry of boranes,^[1] interactions of this nature are commonly found when the borane ligands are anionic species, for example, Cu(PPh₂Me)₃BH₄ and [BH₄Cr(CO)₄]⁻, in which a BH₃·H⁻ adduct coordinates to the metal moiety through a single B-H-Cu bond^[2] or two B-H-Cr bonds,^[3] respectively. Compounds in which a neutral borane adduct coordinates to a metal center are less common. Examples exist in which the neutral 1,2-(PMe₃)₂·B₂H₄ acts as a bidentate chelating ligand towards ZnCl₂,^[4] Ni(CO)₂,^[5] or M(CO)₄,^[6] (I; M = Cr, Mo, W). In related Cr and W complexes, 1,2-(PMe₃)₂·B₂H₄^[6] or BH₃·PMe₃^[7] coordinates through a single B-H-M bond (II and III). Herein we describe some novel chemistry involving the



[8,8-(PPh₂)₂-*nido*-8,7-RhSB₉H₁₀] 1

[8,8-(η^2 -dppm)(η^1 -dppm)-*nido*-8,7-RhSB₉H₁₀] 2

unsaturated eleven-vertex cluster **1**.^[8] When treated with bis(diphenylphosphanyl)methane (dppm) **1** affords the saturated rhodathiaborane **2**, which contains a bidentate and a monodentate dppm ligand. Cluster **2** was obtained as a yellow crystalline solid in 48% yield and identified by high-resolution mass spectrometry, multinuclear NMR spectroscopy, and a single-crystal structure determination (Figure 1).

The existence of the dangling phosphane ligand in **2** suggested that it might be amenable to further reactions analogous to [(PPh₃)₂(CO)OsB₄H₈(BH₂·dppp)] (dppp = bis(diphenylphosphanyl)propane), for which reactions of the

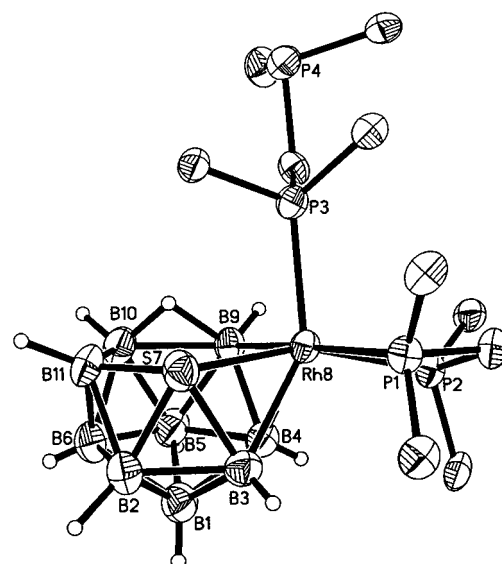


Figure 1. Projection of the molecular structure of **2**. Ellipsoids are drawn at the 50% probability level. Selected interatomic distances [Å] and angles [°]: Rh8-S7 2.370(2), Rh8-P1 2.393(2), Rh8-P2 2.295(2), Rh8-P3 2.411(2), Rh8-B9 2.280(9), Rh8-B3 2.251(10), Rh8-B4 2.235(10); P1-Rh8-P2 71.3(7), P1-Rh8-S7 96.34(8), P1-Rh8-B9 174.4(2), P3-Rh8-S7 97.24(7), P2-Rh8-P3 103.44(7), Rh8-P2-C13 96.1(3), P1-C13-P2 96.0(4).

free phosphane were observed.^[9] Accordingly, reaction of a 20-fold excess of BH₃·THF with **2** in CH₂Cl₂ at room temperature afforded the new rhodathiaborane **3** as an air-

[8,8-(Ph₂PCH₂PPh₂BH₃)-*nido*-8,7-RhSB₉H₁₀] 3

[8,8-(dppe)-*nido*-8,7-RhSB₉H₁₀] 4

stable orange crystalline solid in 71% yield. It was characterized by multinuclear NMR spectroscopy, elemental analysis, mass spectrometry, and a crystal structure determination (Figure 2).

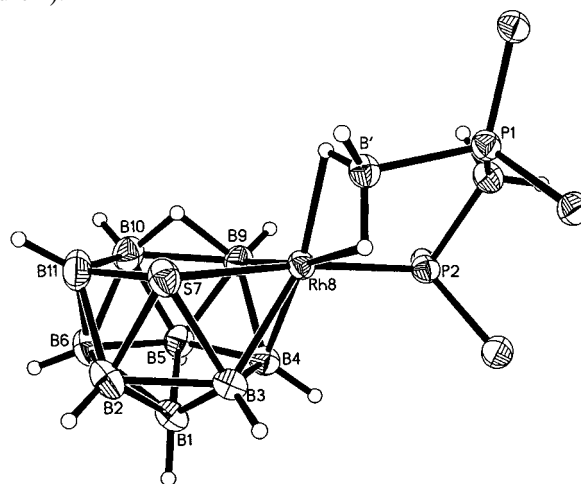


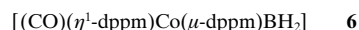
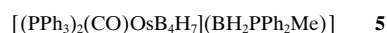
Figure 2. Projection of the molecular structure of **3**. Ellipsoids are drawn at the 50% probability level. Selected interatomic distances [Å] and angles [°]: Rh8-S7 2.3658(5), Rh8-P2 2.2803(5), Rh8-B' 2.323(2), Rh8-B3 2.195(2), Rh8-B4 2.193(2), Rh8-B9 2.174(2), B9-B10 1.848(4), B10-B11 1.855(4), B2-B3 1.891(4); the other boron-boron distances are in the range of 1.725(4)–1.804(4); P2-Rh8-S7 172.92(2), P2-Rh8-B9 92.40(7), B'-Rh8-S7 93.46(6), P2-Rh8-B' 88.36(6), Rh8-B'-P1 112.40(11), Rh8-P2-C1 108.74(7), P1-C1-P2 111.75(11), B9-Rh8-S7 90.42(7).

[*] Prof. L. Barton, Dr. R. Macías, Prof. N. P. Rath
Department of Chemistry
University of Missouri-St. Louis
St. Louis, MO 63121 (USA)
Fax: (+1) 314-516-5342
E-mail: lbarton@jinx.umsf.edu

[**] We acknowledge support from the Missouri Research Board and the Petroleum Research fund of the American Chemical Society. We thank Dr. David W. Berberich of Mallinckrodt Inc. and Professor Michael Gross of the Washington University Mass Spectrometry NIH Research Resource (Grant. No. P41RR094) for the mass spectra.

Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.

The molecular structure of **3** can be described as an eleven-vertex *nido*-rhodathiaborane with a unique exopolyhedral ligand that chelates the rhodium atom through a phosphane group and a borane unit. The BH₃ end of this ligand can be regarded by itself as a neutral adduct of BH₃ that coordinates to the rhodium atom in a bidentate fashion through two three-center, two-electron Rh-H-B bonds. The bond lengths in the rhodathiaborane cage are within the ranges found for **2** and for other related metallathiaboranes;^[8, 10] the Rh8–S7 distance of 2.3658(5) Å is close to those of **2** and the dppe derivative **4**^[10] (dppe = Ph₂P(CH₂)₂PPh₂), but shorter than that of **1**.^[8] The P2–Rh8–B' chelate angle of **3** is 88.36(6)°, close to the value of 84.22(6)° found in **4**, but significantly larger than the corresponding chelate angle P1–Rh8–P2 of 71.45(98)° in the precursor **2**. The P1–B' bond length of **3** is 1.921(2) Å, essentially the same value as is found in the dangling PPh₂MeBH₂ group of **5**^[11] and for the Co–BH₂–PPh₂ interaction of the bridged cobaltaborane **6**,^[12] which also contains a



dangling phosphane. The Rh8–B' bond length of 2.323(2) Å in **3** lies above the average value of 2.238 Å for rhodaboranes, but within the range of 1.951–2.477 Å so far reported.^[13] The hydrogen atoms were refined successfully; the geometry around the BH₃ group is approximately tetrahedral.

The course of the reaction in which **3** is formed is not clear at this time. However, it is likely that the large excess of BH₃·THF displaces the dangling dpmm ligand in **2** as Ph₂PCH₂PPh₂(BH₃)₂ (also isolated from the reaction mixture)^[14] and inserts into the Rh–P bond of the Rh(dpmm) chelate to give the title compound. Conversely, BH₃ may remove the chelating ligand as dpmm(BH₃)₂ and add to the dangling end of the monodentate dpmm. The NMR data for **3** are consistent with the molecular structure described above. The ¹¹B NMR spectrum consists of ten broad signals in the range from δ = +17.2 to –31.2. The peak at δ = –24.1 shows coupling to a phosphorous atom and is assigned to the BH₃ group (B' in Figure 2). All terminal hydrogen atoms were related to their corresponding boron atoms by selective ¹H{¹¹B} decoupling experiments. The signal of the bridging hydrogen atom on the B9–B10 edge appears at δ = –1.37. The ³¹P{¹H} spectrum shows a sharp doublet of doublets, which is assigned to the PPh₂ group *trans* to the sulfur atom, and a very broad signal for the phosphorous atom directly bound to the BH₃ unit. At room temperature, the three hydrogen atoms of the BH₃ group are equivalent on the NMR time scale and give rise to a broad single peak at δ = +0.85. As the temperature is lowered this peak broadens and finally splits into three signals. This indicates that the BH₃ group is fluxional in solution, most likely undergoing rotation about the B–P bond (Δ*G*[‡] ≈ 37 kJ mol^{–1}).

The resemblance of the NMR data of the BH₃ group to those of a pure borane adduct suggests that the BH₃–P interaction in **3** is best described as an adduct that coordinates to a rhodium center through two three-center, two-electron bonds. In terms of a metal complex, **3** could be formally

regarded as an 18-electron species with bonding vectors towards the sulfur atom, the B4–B3 and B9–B4 edges of the cluster, the phosphane group, and the BH₃ unit; the novel exopolyhedral ligand PPh₂CH₂PPh₂BH₃ acts as a six-electron donor. Alternatively, **3** can be regarded as a saturated rhodathiaborane that conforms to the polyhedral skeletal electron pair theory description for an eleven-vertex *nido* cluster.^[15]

In conclusion, **3** is the first polyhedral borane derivative in which a BH₃ adduct coordinates to a metal center in a bidentate fashion through the hydrogen atoms. We are currently investigating the reactivity of **3** and of related species.

Experimental Section

2: PPh₂CH₂PPh₂ (51 mg, 0.133 mmol) was added to a solution of **1** (32 mg, 0.042 mmol) in CH₂Cl₂. The bright red solution turned immediately bright yellow. The reaction mixture was stirred at room temperature under nitrogen. After 40 min the solvent was evaporated under vacuum. The yellow residue was subjected to thin layer chromatography (TLC) with CH₂Cl₂/pentane (3/2) as mobile phase, which gave rise to separation of **2** as a yellow component with *R*_f = 0.4 (20 mg, 0.02 mmol, 48 %). ¹H{¹¹B} NMR (500 MHz, CD₂Cl₂, 25 °C): δ = 7.80–6.52 (m, 40H, C₆H₅), 3.85 (s, 1H, BH), 3.74 (s, 1H, BH), 3.27 (d, *J* = 23 Hz, 1H, BH), 2.83 (d, *J* = 12 Hz, 1H, BH), 2.11 (s, 1H, BH), 1.71 (s, 1H, BH), 1.68 (s, 2H, BH), 1.10 (s, 1H, BH), –4.38 (s, 1H, μ-H); ¹H{³¹P} NMR (500 MHz, CD₂Cl₂, 25 °C): δ = 4.29, 4.18 (both pairs of AB d, ²*J*(H,H) = 14 Hz, 2H, CH₂), 3.58, 2.83 (each d, ²*J*(H,H) = 16 Hz, 2H, CH₂); ¹¹B NMR (160.5 MHz, CD₂Cl₂, 25 °C): δ = 14.7 (vbr, 1B, BH), 8.1 (vbr, 3B, BH), 1.2 (vbr, 1B, BH), –13.5 (vbr, 1B, BH), –14.9 (d, ¹*J*(H,B) = 126 Hz, 1B, BH), –19.0 (d, ¹*J*(H,B) = 126 Hz, 1B, BH), –29.2 (vbr, 1B, BH); ³¹P NMR (202.5 MHz, CD₂Cl₂, 25 °C): δ = 15.2 (dt, ¹*J*(P,Rh) = 126 Hz, ²*J*(P,P) = 26 Hz), –7.7 (ddd, ¹*J*(P,Rh) = 122, ²*J*(P,P) = 13 and 63 Hz), –26.9 (d, ²*J*(P,P) = 31 Hz), –42.9 (brtd, ¹*J*(P,Rh) + ²*J*(P,P) ≈ 68, ²*J*(P,P) ≈ 26 Hz); HR-MS (FAB Kratos MS-50, 3-NBA/Ar gas): *m/z* calcd for C₃₀H₅₂B₉P₄RhS: 1010.2633 [*M*⁺ – H₂]; found: 1010.2632.

3: A 20-fold excess of BH₃·THF (0.34 mmol) was added to a solution of **2** (17 mg, 0.017 mmol) in CH₂Cl₂. The resulting orange solution was stirred at room temperature under nitrogen for 20 h. The solvent was removed in vacuum, and the resulting yellow residue was subjected to TLC with CH₂Cl₂/pentane (3/2) as eluent. Two components were isolated: yellow and UV-active bands with *R*_f = 0.4 and 0.5, respectively. Slow diffusion of pentane into a solution of the yellow component in CH₂Cl₂ yielded air-stable orange crystals of **3** (7.4 mg, 0.012 mmol, 71 %). ¹H{¹¹B} NMR (500 MHz, CD₂Cl₂, –80 °C): δ = 7.80–6.52 (m, 20H, C₆H₅), 4.19 (s, 1H, BH), 3.58 (s, 1H, BH), 3.12 (s, 1H, BH), 2.91 (brs, 1H, BH₃), 2.73 (brd, *J* = 17 Hz, 1H, BH), 2.47 (s, 1H, BH), 1.53 (s, 1H, BH), 1.18 (s, 2H, BH), 1.09 (s, 1H, BH), –0.24 (brs, 1H, BH₃), –0.52 (brs, 1H, BH₃), –1.39 (s, 1H, μ-H); ¹H{³¹P} NMR (500 MHz, CD₂Cl₂, 25 °C): δ = 3.06, 3.36 (each d, ²*J*(H,H) = 15 Hz, 2H, CH₂); ¹¹B{¹H} NMR (160.5 MHz, CD₂Cl₂, 25 °C): δ = 17.2 (vbrs, 1B, BH), 13.1 (brs, 1H, BH), 10.8 (s, 1B, BH), 5.1 (s, 1B, BH), 1.9 (s, 1B, BH), –14.3 (s, 1B, BH), –19.1 (s, 1B, BH), –19.6 (s, 1B, BH), –24.1 (brd, ¹*J*(B,P) = 17 Hz, 1B, BH₃), –31.2 (brs, 1B, BH); ³¹P NMR (202.5 MHz, CD₂Cl₂, –50 °C): δ = 49.3 (dd, ¹*J*(P,Rh) = 151, ²*J*(P,P) = 6 Hz), 14.43 (vbr, 1P, PBH₃); elemental analysis: calcd: C 46.88, H 5.51; found: C 46.65, H 5.41; LR-MS (Finnegan TSQ-700, ESI, CHCl₃/TFA): *m/z* 644 [*M*⁺]; parent envelope pattern conforms to values calculated from isotopic abundances.

Crystal data were collected for both compounds on a Siemens CCD area detector single-crystal X-ray diffractometer with ω scans. Data reduction and structure solutions were carried out with the SAINT and SHELXTL software packages, respectively. Least square refinements were performed with SHELXTL-97. Absorption correction was applied to the data by equivalent reflections (SADABS).

2: C₁₀₂H₁₁₄B₁₈Cl₄OP₈S₂Rh₂, *M*_r = 2210.01, triclinic, space group *P* $\bar{1}$, *a* = 13.6177(1), *b* = 18.8835(2), *c* = 22.6213(2) Å, *α* = 102.61, *β* = 92.675(1), *γ* = 103.587(1)°, *V* = 5488.30(9) Å³, ρ_{calcd} = 1.337 Mg m^{–3}, *Z* = 2,

$\mu(\text{Mo}_{\text{K}\alpha}) = 0.599 \text{ mm}^{-1}$, $T = 223(2) \text{ K}$. A total of 19166 ($R_{\text{int}} = 0.100$) independent reflections were collected up to $2\theta_{\text{max}} = 55.00^\circ$. The final $\omega R(F^2)$ for all unique reflections was 0.2162 with a conventional $R(F)$ of 0.08123 for 19166 reflections with $I > 2\sigma(I)$ and 1259 parameters. The molecule crystallizes with two molecules of CH_2Cl_2 and a molecule of H_2O in the lattice. The unit cell contains two unique molecules of the metallaborane, only one of which is shown in Figure 1 without solvent molecules.

3: $\text{C}_{25}\text{H}_{35}\text{B}_{10}\text{P}_2\text{RhS}$, $M_r = 640.54$, monoclinic, space group $P2_1/n$, $a = 13.2721(1)$, $b = 11.5727(1)$, $c = 19.9181(2) \text{ \AA}$, $\beta = 94.898(1)^\circ$, $V = 3048.13(5) \text{ \AA}^3$, $\rho_{\text{calc}} = 1.396 \text{ Mg m}^{-3}$, $Z = 4$, $\mu(\text{Mo}_{\text{K}\alpha}) = 0.750 \text{ mm}^{-1}$, $T = 223(2) \text{ K}$. A total of 6964 ($R_{\text{int}} = 0.07$) independent reflections were collected up to $2\theta_{\text{max}} = 55.00^\circ$. The final $\omega R(F^2)$ for all unique reflections was 0.0597 with a conventional $R(F)$ of 0.0303 for 6943 reflections with $I > 2\sigma(I)$ and 492 parameters.

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-103258 and 103259 for **2** and **3**, respectively. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Received: June 22, 1998 [Z12027IE]
German version: *Angew. Chem.* **1999**, *111*, 203–206

Keywords: boron • clusters • P ligands • rhodium

- [1] R. N. Grimes in *Metal Interactions with Boron Clusters* (Ed.: R. N. Grimes), Plenum Press, New York, **1982**, chap. 7, pp. 269–319.
- [2] F. Takusagawa, A. Fumigalli, T. F. Koetzle, S. G. Shore, T. Schmitkons, A. V. Fratini, K. W. Morse, C.-Y. Wei, R. Bau, *J. Am. Chem. Soc.* **1981**, *103*, 5165–5171.
- [3] M. Y. Darensbourg, R. Bau, M. W. Mark, R. R. Burch, Jr., J. C. Deaton, S. Slater, *J. Am. Chem. Soc.* **1982**, *104*, 6961–6969.
- [4] S. A. Snow, M. Shimoi, C. D. Ostler, B. K. Thompson, G. Kodama, R. W. Parry, *Inorg. Chem.* **1984**, *23*, 511–512.
- [5] S. A. Snow, G. Kodama, *Inorg. Chem.* **1985**, *24*, 795–796.
- [6] K. Katoh, M. Shimoi, H. Ogino, *Inorg. Chem.* **1992**, *31*, 670–675.
- [7] M. Shimoi, K. Katoh, M. Uruichi, S. Nagai, H. Ogino in *Current Topics in the Chemistry of Boron*, Vol. 143 (Ed.: G. W. Kabalka), Royal Society of Chemistry, Cambridge, **1994**, pp. 293–296.
- [8] G. Ferguson, M. C. Jennings, A. L. Lough, S. Coughlan, T. R. Spalding, J. D. Kennedy, X. L. R. Fontaine, B. Štíbr, *J. Chem. Soc. Chem. Commun.* **1990**, 891–894.
- [9] P. McQuade, R. L. Thomas, H. Fang, N. P. Rath, L. Barton, *Abstr. Pap. 6th Boron-USA Workshop* (Athens, GA, USA) **1998**.
- [10] G. M. Rosair, A. J. Welch, A. S. Weller, *Acta Crystallogr. Sect. C* **1996**, *52*, 3020–3024.
- [11] L. Barton, J. Bould, H. Fang, K. Hupp, N. P. Rath, C. Gloeckner, *J. Am. Chem. Soc.* **1997**, *119*, 631–632.
- [12] D. J. Elliot, C. J. Levy, R. J. Puddephatt, D. G. Holah, A. N. Hughes, V. R. Magnuson, I. M. Moser, *Inorg. Chem.* **1990**, *29*, 5014–5015.
- [13] Cambridge Structural Database, QUEST-3D query, with the Rh–B distance in the fragment Rh–B–H constrained to be between 1.8 and 2.5 Å.
- [14] $[\text{Ph}_2\text{PCH}_2\text{PPh}_2(\text{BH}_3)_2]$: ^1H (^{11}B) NMR (299.9 MHz, CDCl_3 , 25°C): $\delta = 7.66$ – 7.34 (m, 20H, C_6H_5), 3.24 (t, $^2J(\text{H,P}) = 17.0 \text{ Hz}$, 2H, CH_2), 0.92 (d, $^2J(\text{H,P}) = 15.6 \text{ Hz}$, 6H, BH_3); ^{11}B NMR (96.2 MHz, CDCl_3 , 25°C): $\delta = -37.1$; ^{31}P NMR (121.4 MHz, CDCl_3 , 25°C): $\delta = 15.2$.
- [15] K. Wade, *Adv. Inorg. Chem. Radiochem.* **1976**, *18*, 1–66.

Insect Desaturases as Unique Analytical Tools To Unravel the Stereochemical Course of the Reduction of Vicinal Ditosylates with Lithium Aluminum Deuteride**

Isabel Navarro, Gemma Fabrias,* and Francisco Camps

The biosynthetic pathways of lepidopteran sex pheromones involve the action of rather unusual desaturases, among which the Δ^{11} -acyl-CoA desaturases are the most common ones.^[1] As part of our ongoing studies on the determination of the stereospecificity of fatty acyl desaturases from insects, we have recently demonstrated that in the moth, *Spodoptera littoralis*, formation of (*E*)-11-tetradecenoic acid takes place by stereospecific removal of the *pro*-(*R*) C11-H and the *pro*-(*S*) C12-H from myristic acid.^[2] In contrast, desaturation of myristic acid to (*Z*)-11-tetradecenoic acid occurs by stereospecific cleavage of *pro*-(*R*) C11-H and *pro*-(*R*) C12-H, in agreement with the previously reported stereospecificities of the related (*Z*)-11-palmitoyl CoA^[3] and (*Z*)-9-stearoyl-CoA desaturases.^[4–6]

To continue our investigations, we required an expeditious procedure for the synthesis of *vic*-dideuterated, enantiomerically pure fatty acids.^[7] In this context, we thought that asymmetric olefin dihydroxylation followed by tosylation and reduction of the resulting ditosylate with lithium aluminum deuteride might be an appropriate method. However, a recent report on the occurrence of anchimeric effects in the nucleophilic substitution of a *vic*-dimesylate^[8] suggested that the stereochemical outcome of the above procedure might be not so straightforward as anticipated. Thus, the evaluation of the stereochemical course of the proposed synthetic pathway was a complex issue, since the determination of the relative stereochemistry of deuterium atoms in the resulting *vic*-dideuterated fatty acids is very cumbersome by current analytical methods.

To solve this problem, we applied the above synthetic procedure to the preparation of a *vic*-dideuterated fatty acid suitable as substrate for a desaturase of known stereospecificity so that the result of the enzymatic reaction would reveal the relative configuration of the vicinal deuterium atoms in the probe. Since the stereochemical courses of both (*Z*)- and (*E*)-11 desaturations of myristic acid in *S. littoralis* is known,^[2] the mass of the most abundant isotopomer of both (*Z*)- and (*E*)-11-tetradecenoic acids formed in pheromone glands of insects incubated with both the racemic mixtures of the diastereomers of [11,12,13,13,14,14,14- $^2\text{H}_7$]myristic acid

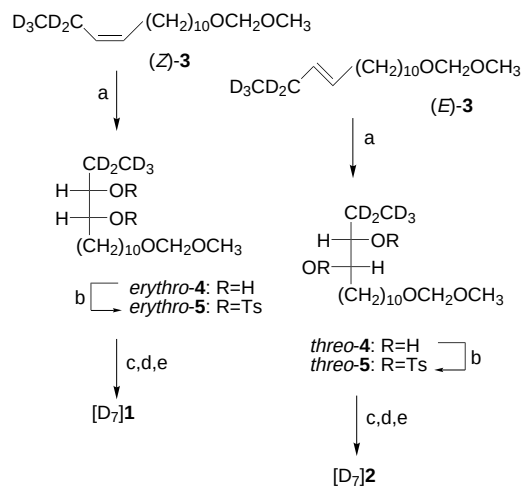
[*] Dr. G. Fabrias, Dr. I. Navarro, Prof. Dr. F. Camps
Department of Biological Organic Chemistry (CID-CSIC)
Jordi Girona 18-26, E-08034-Barcelona (Spain)
Fax: (+349) 3-2045904
E-mail: gfdqob@cid.csic.es

[**] This work was supported by Comisión Asesora de Investigación Científica y Técnica (grant AGF 98-0844), Comissionat per a Universitats i Recerca from the Generalitat de Catalunya (grant GRQ 93-8016) and SEDQ S.A.

Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.

([D₇]1 and [D₇]2) would reveal the relative configuration of the deuterium atoms at C11 and C12 in both tracers.

According to Scheme 1, racemic [D₇]1 and [D₇]2 were obtained by dihydroxylation of (*Z*)- and (*E*)-3 catalyzed by OsO₄ in the presence of *N*-methylmorpholine *N*-oxide,^[9] followed by tosylation of the formed *erythro*- and *threo*-4



Scheme 1. a) *N*-methylmorpholine *N*-oxide, OsO₄, *t*BuOH, acetone (*erythro*-4, 71%; *threo*-4, 65%); b) TsCl, pyridine, then column chromatography (*erythro*-5, 23%; *threo*-5, 22%); c) LiAlD₄, Et₂O, reflux; d) HCl, MeOH; e) CrO₃, H₂SO₄, H₂O ([D₇]1, 50% from *erythro*-5, [D₇]2, 37% from *threo*-5).

diols, respectively, with tosyl chloride and pyridine.^[10] Reduction of *erythro*- and *threo*-5 tosylates with lithium aluminum deuteride,^[11] followed by deprotection and oxidation afforded the expected probes [D₇]1 and [D₇]2, respectively, in 5–8% overall yields. These probes were then administered to the pheromone glands as dimethyl sulfoxide solutions (0.1 μL, 10 mg mL⁻¹). Fatty acid methyl esters were obtained by base-catalyzed methanolysis of pheromone gland lipidic extracts, and analyses were performed by GC-MS as previously reported^[12] by using a SGE BP-20 capillary column (30 m × 0.20 mm) programmed from 60 °C to 150 °C at 2 °C min⁻¹ and then to 260 °C at 7 °C min⁻¹ after an initial delay of 2 min. The selected ion-monitoring mode of the corresponding molecular

ions for the possible isotopomers was used. The results of the deuterium-labeling experiments are depicted in Figure 1. In these experiments, the most abundant isotopomer of (*Z*)-11-tetradecenoic acid formed from [D₇]1 was that with six deuterium atoms (*m/z* 246, methyl ester). In the light of these results, taking into account that the (*Z*)-11 desaturation proceeds with elimination of C11-H and C12-H of the same configuration,^[2] we concluded that the relative spatial location of deuterium atoms in [D₇]1 was *threo*. Likewise, the most abundant isotopomer of (*Z*)-11-tetradecenoic acid formed from [D₇]2 was that with seven deuterium atoms (*m/z* 247, methyl ester). A molecular ion was also detected at *m/z* 245, corresponding to the compound with five deuterium atoms arising from the loss of two deuterium atoms from the probe; however, its abundance was lower than that of the ion at *m/z* 247 because of a primary isotope effect.^[13] These data indicated that C11-D and C12-D in [D₇]2 adopt an

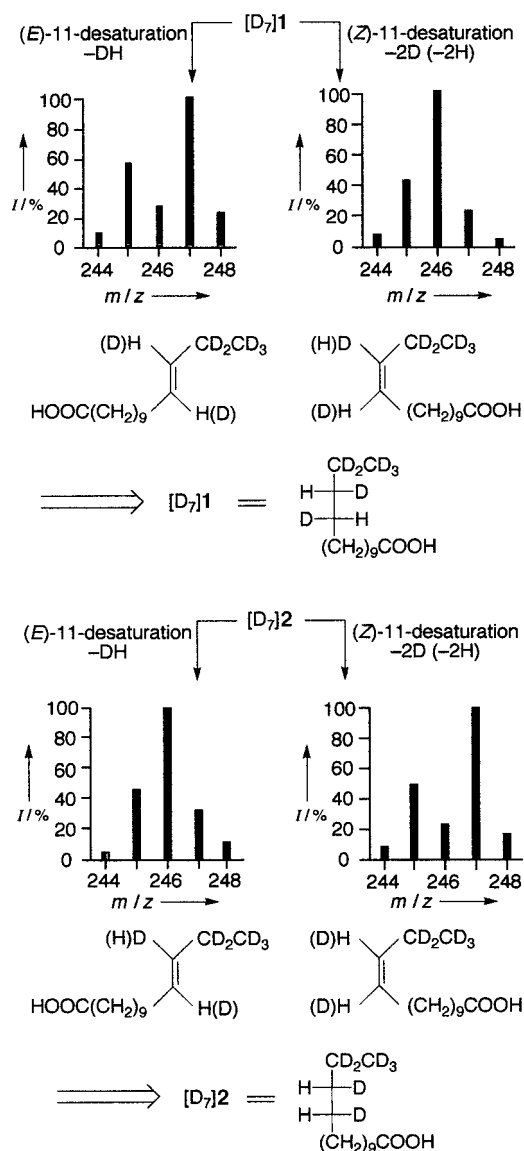
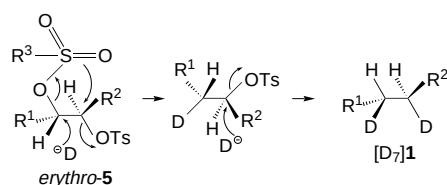


Figure 1. Relative intensities of isotopomers of (*Z*)- and (*E*)-11-tetradecenoic acids, analyzed as methyl esters, formed in pheromone glands incubated with [D₇]1 and [D₇]2. Percentages correspond to the average mol % of three or four independent experiments performed with groups of five glands. Standard deviations were less than 5 % of the mean values in all cases.

erythro configuration. In agreement with these results and with the stereospecificity reported for the formation of (*E*)-11-tetradecenoic acid,^[2] the main isotopomer of this acid formed from the probe [D₇]1 was that with seven deuterium atoms, whereas the compound with six deuterium atoms was mainly formed from probe [D₇]2. Therefore, these results clearly showed that a configurational change occurred during the reduction step of Scheme 1. The possibility that this change occurred at either the dihydroxylation or the tosylation reactions is highly unlikely, since both catalytic olefin dihydroxylation with OsO₄ and formation of tosyl esters are well established reactions.

As exemplified for *erythro*-5 ditosylate (Scheme 2), a plausible explanation for the observed unexpected result would involve the S_N2 substitution of one tosylate group by a deuteride ion with concomitant displacement of the vicinal



Scheme 2.

tosylate group by the leaving tosyl ester group, thus causing an inversion of configuration at this site. A second inversion at this C atom would then occur by substitution of the remaining tosyl group by a further deuteride ion. The extent of the reduction also occurring through the a priori expected mechanism has not been quantified, but the fact that the proportion of isotopomers of both methyl (*Z*)- and (*E*)-11-tetradecenoate formed from both **[D₇]**1 and **[D₇]**2 are similar to those formed from the same probes obtained by direct deuteration of the olefins^[2] indicates that the unexpected mechanism largely predominated over the expected one. As mentioned above, a similar reaction has been reported by Lin and Shi^[8] in the nucleophilic substitution of a 1,2-dimesylate (mesylate = methanesulfonate) with a tosylamine. However, the occurrence of this anchimeric effect is not apparently general. For instance, a cyclic vicinal dimesylate reacts with sodium azide to give the corresponding vicinal diazido derivative arising from single S_N2 displacements at both carbon atoms.^[14] Likewise, ditosylates *erythro*- and *threo*-5 (Scheme 1) react with CsF in polyethyleneglycol to give the corresponding *erythro*- and *threo*-difluorides, respectively.^[15]

In summary, we have demonstrated the usefulness of enzymatic reactions as analytical tools to evidence configurational changes not detectable by current analytical techniques. Finally, our results prove that care must be taken when introducing deuterium labeling by reduction of *vic*-ditosylates (and probably other related sulfonate esters) with lithium aluminum deuteride if the configuration of the final products is important.

Received: June 22, 1998 [Z 120301E]

German version: *Angew. Chem.* **1999**, *111*, 121–123

Keywords: deuterations • fatty acids • reaction mechanisms

- [1] W. L. Roelofs, L. Bjostad, *Bioorg. Chem.* **1984**, *12*, 279–298.
- [2] I. Navarro, I. Font, G. Fabrias, F. Camps, *J. Am. Chem. Soc.* **1997**, *119*, 11 335–11 336.
- [3] W. Boland, C. Frossl, M. Schottler, M. Toth, *J. Chem. Soc. Chem. Commun.* **1993**, 1155–1157.
- [4] G. J. Schroeffer, K. Bloch, *J. Biol. Chem.* **1965**, *240*, 54–63.
- [5] H. G. Enoch, A. Catala, P. Strittmatter, *J. Biol. Chem.* **1976**, *251*, 5095–5103.
- [6] P. H. Buist, D. M. Marecak, *J. Am. Chem. Soc.* **1992**, *114*, 5073–5080.
- [7] For an enzymatic synthesis of enantiomerically pure *vic*-dideuterated palmitic acids see: C. Frossl, W. Boland, *Tetrahedron* **1993**, *49*, 6613–6618.
- [8] G.-Q. Lin, Z.-K. Shi, *Tetrahedron* **1997**, *53*, 1369–1382.
- [9] V. VanRheenen, R. C. Kelly, D. Y. Cha, *Tetrahedron Lett.* **1976**, *23*, 1973–1976.
- [10] K. B. Wirberg, J. G. Pfeiffer, *J. Am. Chem. Soc.* **1970**, *11*, 553–564.
- [11] H. C. Brown, S. Krishnamurthy, *J. Org. Chem.* **1980**, *54*, 849–856.
- [12] T. Martinez, G. Fabrias, F. Camps, *J. Biol. Chem.* **1990**, *265*, 1381–1387.
- [13] P. H. Buist, B. Behrouzian, *J. Am. Chem. Soc.* **1996**, *118*, 6295–6296.
- [14] M. Torneiro, W. C. Still, *Tetrahedron* **1997**, *53*, 8739–8750.
- [15] J. Navarri, MsD thesis, University of Barcelona (Spain), **1998**.

Insertion of O₂ into a Chromium–Phenyl Bond: Mechanism of Formation of the Paramagnetic d² Oxo Complex [Tp^{tBu,Me}Cr^{IV}(O)OPh]**

Alexandra Hess, Markus R. Hörz, Louise M. Liable-Sands, Danielle C. Lindner, Arnold L. Rheingold, and Klaus H. Theopold*

The oxidative functionalization of organic molecules utilizing dioxygen as a reagent remains one of the major challenges for research in catalysis.^[1] The ready availability of O₂ and the absence of environmentally harmful by-products are among the attractive features of such processes. Fundamental studies of the role of transition metals in catalytic oxidation must naturally include investigations of the reaction pathways of organometallic molecules with O₂. In this context, the insertion of O₂ into metal–carbon bonds is a reaction of central importance. Despite its significance, only relatively few mechanistic studies of this transformation are available.^[2] Herein we report an investigation of the reaction of O₂ with a tris(pyrazolyl)borate chromium phenyl complex, which ultimately yields a phenoxide.

Exposure of a cold (–45 °C) solution in pentane of [Tp^{tBu,Me}CrPh]^[3] (**1**; Tp^{tBu,Me} = hydrotris(3-*tert*-butyl-5-methylpyrazolyl)borate) to an excess of O₂ led to a rapid color change from blue to red. Upon warming to ambient temperature the color of the solution changed again, from red to brown, and workup of the reaction mixture provided the complex [Tp^{tBu,Me}Cr(O)OPh] (**2**), which could be isolated in moderate yield (48 %; see Scheme 1). The molecular structure of **2** has been determined by X-ray diffraction,^[4] and the result is shown in Figure 1. Despite the steric hindrance of the Tp^{tBu,Me} ligand, which has earned it the title “tetrahedral enforcer”,^[5] **2** exhibits a five-coordinate chromium atom in a trigonal-bipyramidal configuration. The apparent product of the incorporation of one equivalent of O₂, **2** exhibits an equatorial oxo ligand and an axial phenoxide moiety, which formally results from the insertion of an oxygen atom into the erstwhile chromium–carbon bond. The oxidation state of chromium in the new complex is +IV (d²); hence, **2** is chemically related to oxo complexes of the type [(porphyrinato)Cr^{IV}(O)].^[6] However, in contrast to the latter and as indicated by its isotropically shifted and broadened ¹H NMR resonances, **2** is paramagnetic, and its effective magnetic moment in the solid state ($\mu_{\text{eff}}(293 \text{ K}) = 2.6(1) \mu_{\text{B}}$) is consistent with two unpaired electrons. Paramagnetism of a d² mono-oxo complex is rather unusual.^[7] We suggest that both frontier orbitals (i.e., d_{xz} and d_{yz}; the *z* axis is along N(3)–Cr–O(2)) are

[*] Prof. Dr. K. H. Theopold, A. Hess, M. R. Hörz, L. M. Liable-Sands, Dr. D. C. Lindner, Prof. Dr. A. L. Rheingold
Department of Chemistry and Biochemistry
Center for Catalytic Science and Technology
University of Delaware
Newark, DE 19716 (USA)
Fax: (+1) 302-831-6335
E-mail: theopold@udel.edu

[**] This research was supported by grants from the U. S. National Science Foundation and the U. S. Department of Energy. We thank Applied Systems Inc. for the donation of a ReactIR 1000 instrument.

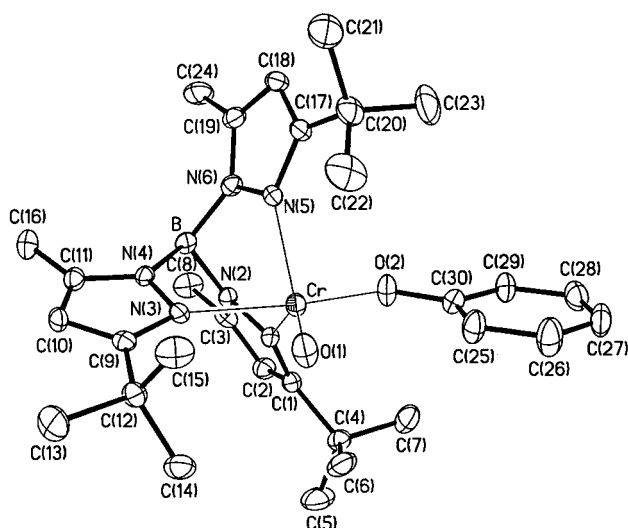


Figure 1. The molecular structure of trigonal-bipyramidal **2**. Selected interatomic distances [Å] and angles [°]: Cr–O(1) 1.576(3), Cr–O(2) 1.844(3), Cr–N(1) 2.097(4), Cr–N(3) 2.191(4), Cr–N(5) 2.099(4); Cr–O(2)–C(30) 136.7(3), O(1)–Cr–O(2) 103.8(2), O(1)–Cr–N(1) 130.2(2), O(1)–Cr–N(3) 87.9(2), O(1)–Cr–N(5) 128.7(2), O(2)–Cr–N(1) 89.7(2), O(2)–Cr–N(3) 168.2(2), O(2)–Cr–N(5) 90.7(2), N(1)–Cr–N(3) 81.46(14), N(1)–Cr–N(5) 98.1(2), N(3)–Cr–N(5) 82.95(14).

destabilized by competitive π donation from the oxo and the phenoxo ligands, respectively; apparently the resulting split in their degeneracy does not suffice to enforce spin pairing.

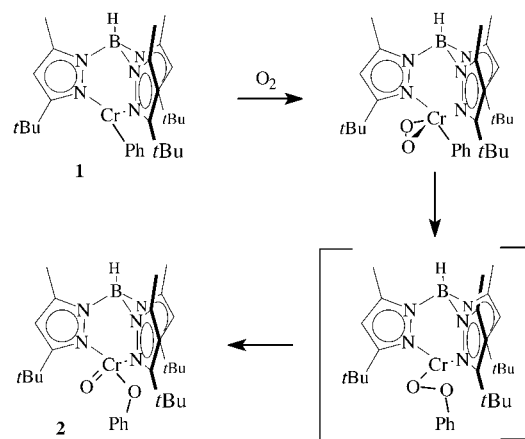
The spectroscopic characterization of **2** is in accordance with its solid-state structure. Specifically, its IR spectrum (KBr pellet) exhibited a strong band at 922 cm^{-1} , assigned as $\nu_{\text{Cr}=\text{O}}$, which was shifted to 884 cm^{-1} upon substitution by ^{18}O . The ^1H NMR spectrum ($[\text{D}_8]\text{toluene}$, room temperature) showed three broad resonances ($\delta = 17.5$ (9H), 9.4 (27H), and 1.5 (3H)) due to the protons of the $\text{Tp}^{\text{tBu,Me}}$ ligand, indicating fluxionality of the five-coordinate molecule. This rearrangement can be slowed on the time scale of the NMR experiment by cooling the sample below 180 K. For the identification of the less intense resonances of the phenoxide ligand, deuterium labeling proved indispensable.^[8] The ^2H NMR spectrum of $[\text{Tp}^{\text{tBu,Me}}\text{Cr}(\text{O})\text{OC}_6\text{D}_5]$ ($[\text{D}_5]$ -**2**) revealed three reasonably sharp resonances at $\delta = 17.4$ (2D), -31.7 (1D), and -33.6 (2D). In the ^1H NMR spectrum of **2** the first of these was obscured by a Tp ligand resonance, and the latter two were not resolved due to the greater line width of ^1H resonances of paramagnets. All resonances exhibited the expected temperature dependence (i.e., $\delta_{\text{iso}} \propto 1/T$).

Important questions concerning the formation of **2** include the nature of the intermediate observed at low temperature and the detailed mechanism of the oxygen insertion. A dioxygen adduct ($[\text{Tp}^{\text{tBu,Me}}\text{Cr}(\text{O}_2)\text{Ph}]$), a phenyl peroxide ($[\text{Tp}^{\text{tBu,Me}}\text{Cr}(\text{OOPh})]$), or a dioxo phenyl complex resulting from oxidative addition of O_2 to Cr^{II} ($[\text{Tp}^{\text{tBu,Me}}\text{Cr}(\text{O})_2\text{Ph}]$) are among the possible candidates for the intermediate. We sought to address this question by in situ IR spectroscopy. Exposure of a stirred, cold (-78 to -50°C) solution in toluene of **1** (ca. 0.5 M) to O_2 led to a gradual replacement of the characteristic signals of the starting material with a new set of bands. The absence of any strong bands attributable to

$\nu_{\text{Cr}=\text{O}}$ ($\approx 920 \text{ cm}^{-1}$) or $\nu_{\text{C}=\text{O}}$ ($\approx 1280 \text{ cm}^{-1}$) was notable. Repe-
tition of the experiment with $^{18}\text{O}_2$ afforded a spectrum that was indistinguishable except for the position of one resonance, which had been shifted from 1027 cm^{-1} (^{16}O) to 969 cm^{-1} (^{18}O). Based on these observations we propose that the first observable intermediate of the reaction of **1** with O_2 is a Cr^{III} superoxo complex, that is, $[\text{Tp}^{\text{tBu,Me}}\text{Cr}(\text{O}_2)\text{Ph}]$.^[9] The well-known preference of Cr^{III} for octahedral coordination and the similarity in the vibrational spectra to that of $[\text{Tp}^{\text{tBu,Me}}\text{Co}(\text{O}_2)]$ suggests that the superoxo ligand may well be coordinated in the side-on fashion ($\eta^2\text{-O}_2$),^[10] although the more common end-on coordination ($\eta^1\text{-O}_2$) is also possible. Upon warming of the solution of $[\text{Tp}^{\text{tBu,Me}}\text{Cr}(\text{O}_2)\text{Ph}]$ to room temperature, its IR spectrum was smoothly transformed into that of **2**, ruling out the intervention of another spectroscopically observable intermediate.

The reaction of metal–alkyl complexes with O_2 may proceed by a radical chain process, involving an $\text{S}_{\text{H}}2$ displacement of $\text{R}^\bullet$ by $\text{ROO}^\bullet$, rather than an intramolecular insertion of O_2 into the $\text{M}–\text{R}$ bond.^[2a–d] To distinguish between these two pathways, we have performed a crossover experiment. When an equimolar solution of $[\text{Tp}^{\text{tBu,Me}}\text{CrC}_6\text{D}_5]$ and $[\text{Tp}^{\text{tBu}}\text{CrC}_6\text{H}_5]$ was allowed to react with O_2 , ^2H NMR analysis of the product mixture showed the presence of $[\text{Tp}^{\text{tBu,Me}}\text{Cr}(\text{O})\text{OC}_6\text{D}_5]$ as the only major deuteriated product. Specifically, only a very small amount of the crossover product—that is, $[\text{Tp}^{\text{tBu}}\text{Cr}(\text{O})\text{OC}_6\text{D}_5]$ (which was independently prepared and characterized spectroscopically)—was detected; the latter is thought to result from a slow scrambling process occurring in the starting mixture. This observation indicates that the insertion of O_2 , starting from the adduct $[\text{Tp}^{\text{tBu,Me}}\text{Cr}(\text{O}_2)\text{Ph}]$, proceeds in an intramolecular fashion.

Based on the observations summarized above we propose a mechanism for the reaction of **2** with O_2 (Scheme 1). The postulated phenylperoxo intermediate resulting from inser-



Scheme 1. Proposed mechanism for the formation of **2** from **1** and O_2 .

tion of O_2 into the $\text{Cr}–\text{Ph}$ bond was not observed directly and is inferred. However, several factors militate against a pathway involving its possible alternative, that is, $[\text{Tp}^{\text{tBu,Me}}\text{Cr}(\text{O})_2\text{Ph}]$. First, the coordination of three independent ligands to a transition metal in addition to the $\text{Tp}^{\text{tBu,Me}}$ ligand is unprecedented, due to the steric demand of the

latter.^[11] Furthermore, its stable cyclopentadienyl analogue [Cp*Cr(O)₂Me] does not rearrange to [Cp*Cr(O)OMe].^[12] In general, the migratory insertion of oxo ligands into metal–carbon single bonds appears to be an unfavorable process.^[13] It is unlikely to be kinetically competent to explain the ready transformation of **1** into **2**.

The isolation of **2** extends the scarce tris(pyrazolyl)borate chemistry of chromium to its relatively rare +IV oxidation state. It also demonstrates that there exist facile intramolecular pathways for the oxygenation of metal–carbon σ bonds by migratory insertion of O₂. Such transformations may serve as individual steps in metal-catalyzed oxidations of organic molecules by air.

Experimental Section

All experiments were carried out under exclusion of air and moisture with inert atmosphere glove box, Schlenk, or high vacuum line techniques.

2: A solution of **1** (0.50 g, 0.91 mmol) in pentane (50 mL) was charged into a glass ampoule equipped with a Teflon stopcock. After the solution was cooled to –45 °C, the ampoule was evacuated and then filled with dry O₂. The color of the solution changed immediately from blue to red. After the solution was stirred for 0.5 h, it was allowed to warm to room temperature, whereupon it turned brown. The solvent was evaporated, and the solid residue was recrystallized from Et₂O at –30 °C to yield light brown crystals of **2** (0.254 g, 48 %). M.p. 98 °C; ¹H NMR (250 MHz, [D₆]benzene, 25 °C): δ = 17.5 (br, 9H), 9.4 (br, 27H), 1.5 (br, 3H), –35.4 (br, 3H); IR (KBr): $\tilde{\nu}$ = 3053, 2961, 2545, 1587, 1543, 1478, 1424, 1350, 1282, 1261, 1194, 1070, 1024, 922, 866, 292, 659 cm^{–1}; UV/Vis (Et₂O): λ_{max} (ϵ) = 415 nm (1730); μ_{eff} (25 °C) = 2.6(1) μB ; elemental analysis for C₃₀H₄₅BCrN₆O₂: calcd (found): C 61.64 (61.38), H 7.76 (7.02).

The in-situ IR spectroscopic monitoring of the reaction of **1** with O₂ was carried out with an Applied Systems Inc. ReactIR 1000 instrument, equipped with a DiComp probe. The probe was inserted directly into a cooled (–78 °C initially) solution of **1** in toluene (0.5 M). Spectra were acquired at 4-cm^{–1} resolution, and a background spectrum of toluene was subtracted.

Received: June 23, 1998 [Z12034IE]

German version: *Angew. Chem.* **1999**, *111*, 126–128

Keywords: chromium • insertions • O–O activation • oxygenations • tripodal ligands

- [1] a) R. A. Sheldon, J. K. Kochi, *Metal-Catalyzed Oxidations of Organic Compounds*, Academic Press, New York, **1981**; b) *3rd World Congress on Oxidation Catalysis* (Eds.: R. K. Grasselli, S. T. Oyama, A. M. Gaffney, J. E. Lyons), Elsevier, Amsterdam, **1997**.
- [2] a) J. K. Kochi, *Organometallic Mechanisms and Catalysis*, Academic Press, New York, **1978**, pp. 517–522; b) T. P. Blackburn, J. A. Labinger, J. Schwartz, *Tetrahedron Lett.* **1975**, 3041–3044; c) D. A. Ryan, J. A. Espenson, *J. Am. Chem. Soc.* **1979**, *101*, 2488–2489; d) T. V. Lubben, P. T. Wolczanski, *J. Am. Chem. Soc.* **1987**, *109*, 424–435; e) A. Van Asselt, M. S. Trimmer, L. M. Henling, J. E. Bercaw, *J. Am. Chem. Soc.* **1988**, *110*, 8254–8255; f) G. Parkin, J. E. Bercaw, *J. Am. Chem. Soc.* **1989**, *111*, 391–393.
- [3] J. L. Kersten, R. R. Kucharczyk, G. P. A. Yap, A. L. Rheingold, K. H. Theopold, *Chem. Eur. J.* **1997**, *3*, 1668–1674.
- [4] Crystal data for **2** (C₃₀H₄₅BCrN₆O₂): monoclinic, *P*₂/c, *a* = 10.7379(2), *b* = 18.9283(5), *c* = 15.5552(1) Å, β = 90.508(1)°, *V* = 3161.5(1) Å³, *Z* = 4, *T* = 223(2) K, ρ_{calcd} = 1.228 g cm^{–3}; of 10 127 reflections collected, 4572 were independent and 2593 observed; 364 parameters, SHELXTL software (Version 5.03), *R*(*F*) = 0.0658, *R*(*wF*) = 0.1137 [*I* > 2 σ (*I*)], 4 ≤ 2 θ ≤ 57°. The data were collected on a Siemens P4 diffractometer equipped with a SMART/CCD detector. No absorption correction was required. The hydrogen atom on boron was

located from the difference map, the thermal parameter was fixed and the coordinates were allowed to refine. All other hydrogen atoms were treated as idealized contributions. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-101985. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

- [5] S. Trofimenko, J. C. Calabrese, J. S. Thompson, *Inorg. Chem.* **1987**, *26*, 1507–1514.
- [6] a) J. R. Budge, B. M. K. Gatehouse, M. C. Nesbit, B. O. West, *J. Chem. Soc. Chem. Commun.* **1981**, 370–372; b) J. W. Buchler, K. L. Lay, L. Castle, V. Ullrich, *Inorg. Chem.* **1982**, *21*, 842–844; c) J. T. Groves, Jr., W. J. Kruper, R. C. Haushalter, W. M. Butler, *Inorg. Chem.* **1982**, *21*, 1363–1368.
- [7] a) J. M. Mayer, *Comments Inorg. Chem.* **1988**, *8*, 125–135; b) for an exception, see S. Sarkar, B. Sharma, R. C. Maurya, S. C. Chaurasia, *Indian J. Chem. Sect. A* **1977**, *15*, 747–747.
- [8] N. Hebenanz, F. H. Köhler, F. Scherbaum, B. Schlesinger, *Magn. Reson. Chem.* **1989**, *27*, 798–802.
- [9] M. H. Dickmann, M. T. Pope, *Chem. Rev.* **1994**, *94*, 569–584.
- [10] J. W. Egan, Jr., B. S. Haggerty, A. L. Rheingold, S. C. Sendlinger, K. H. Theopold, *J. Am. Chem. Soc.* **1990**, *112*, 2445–2446.
- [11] N. Kitajima, W. B. Tolman, *Prog. Inorg. Chem.* **1995**, *43*, 419–531.
- [12] S.-K. Noh, R. A. Heintz, B. S. Haggerty, A. L. Rheingold, K. H. Theopold, *J. Am. Chem. Soc.* **1992**, *114*, 1892–1893.
- [13] S. N. Brown, J. M. Mayer, *J. Am. Chem. Soc.* **1996**, *118*, 12119–12133.

A Novel Highly Charged (+12) Anion Receptor That Encapsulates Simultaneously NO₃[–] and PF₆[–] Ions**

Ralf-Dieter Schnebeck, Eva Freisinger, and Bernhard Lippert*

Recently we described a molecular triangle, [(en)Pt(bpz)₃](NO₃)₆, consisting of three (en)Pt^{II} entities (en = ethylenediamine) and three 2,2′-bipyrazine (bpz) ligands that bridge metals through N(4) and N(4′).^[1] In this compound the pyrazine rings adopt a transoid arrangement and are markedly twisted. We have now found that addition of chelating metal entities, for example (en)Pd^{II}, to this compound causes rotation of a pyrazine ring about the central C(2)–C(2′) bond and coordination of the heterometal atom at the N(1) and N(1′) positions. The hexanuclear cation formed in the presence of (en)Pd^{II} has a charge of +12 and exhibits a high affinity for anions. The X-ray crystal structure of [(en)Pt(bpz)₃](NO₃)₄(PF₆)₈ (**1**) confirms the simultaneous encapsulation of NO₃[–] and PF₆[–] ions in the cavity of

[*] Prof. Dr. B. Lippert, Dipl.-Chem. R.-D. Schnebeck, Dipl.-Chem. E. Freisinger
Fachbereich Chemie der Universität Dortmund
Otto-Hahn-Strasse 6, D-44227 Dortmund (Germany)
Fax: (+49) 231-755-3797
E-mail: lippert@pop.uni-dortmund.de

[**] This work was supported by the Fonds der Chemischen Industrie. We thank R. K. O. Sigel for the introduction in the association constant determination.

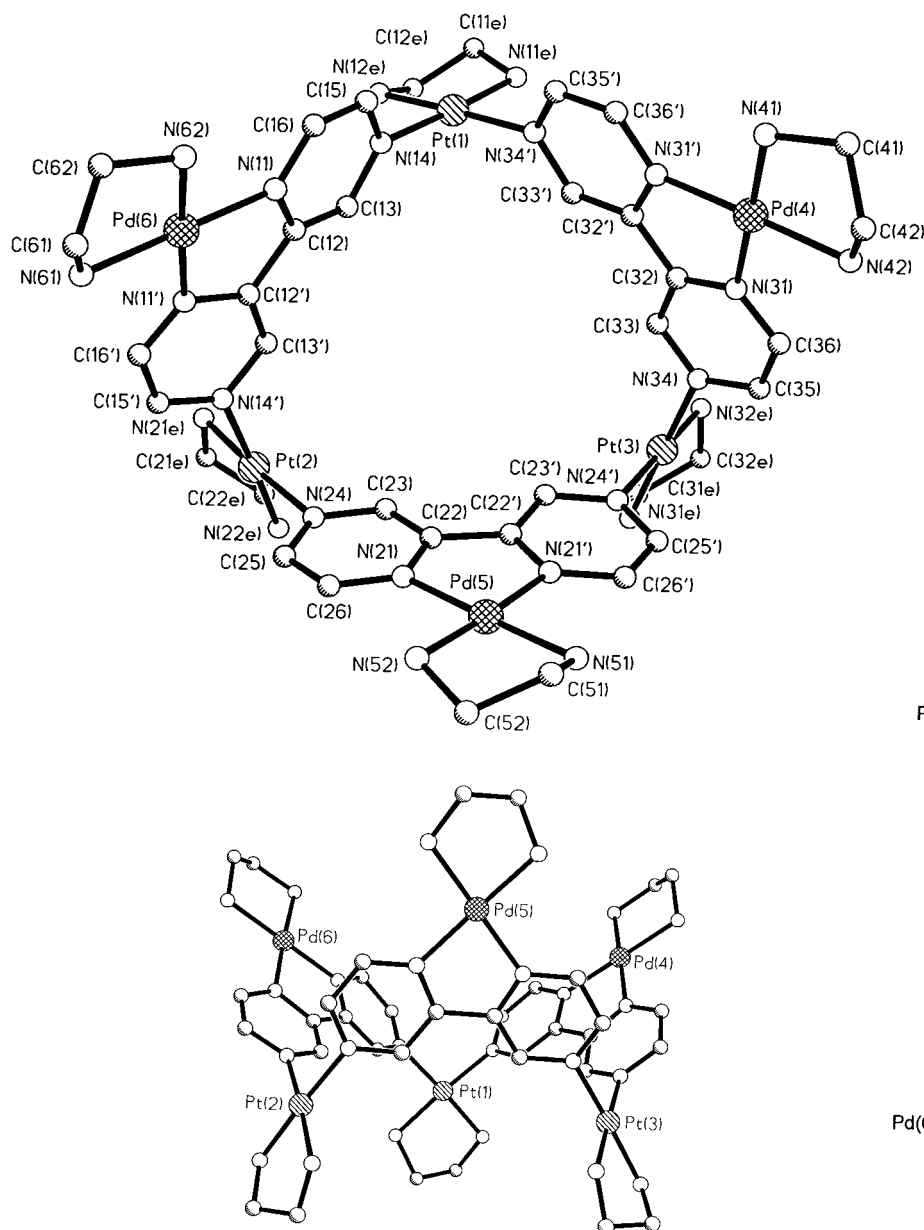


Figure 1. Top view (top) and side view (bottom) of the cation of **1**.

the cation. In solution a host–guest interaction between the cation of **1** and PF_6^- as well as other anions has been observed.

Figure 1 gives two different views of the cation of **1**.^[2] The six metal atoms form the corners of a compressed, distorted trigonal antiprism. While the three Pt atoms form an equilateral triangle with side lengths of 7.88(1) Å, the Pd triangle is considerably larger and nearly isosceles (8.39(1), 8.55(1), 9.77(1) Å). The six Pt–Pd distances are about 6.82(1) Å.

The topology of the starting material $[(\text{en})\text{Pt}(\text{bpz})_3](\text{NO}_3)_6$ changes dramatically as a consequence of $(\text{en})\text{Pd}^{\text{II}}$ coordination (Figure 2): The molecular triangle is converted into a calixarene-like structure. The results of the X-ray crystal structure determination and NMR solution studies confirm that **1** is capable of encapsulating anions. The structure reveals that a nitrate ion is located in the center of the Pt triangle (Figure 3); the oxygen atoms of the nitrate ion point towards the Lewis acidic Pt atoms. As a consequence

each Pt atom has a square-pyramidal coordination sphere (Pt–O 3.49(1), 3.26(1), 3.39(1) Å). We have observed similar Pt–O distances previously.^[7] Furthermore a PF_6^- ion is located in the center of the trigonal antiprism on top of the NO_3^- ion (Figure 4). Three corners of the PF_6^- octahedron point towards the Pt atoms (Pt–F 3.87(1), 4.61(1), 4.42(1) Å), while the others are orientated towards the Pd atoms (Pd–F 3.88(1), 3.39(1), 4.31(1) Å). The distances between the oxygen atoms of the NO_3^- ion and the fluorine atoms of the PF_6^- ion are between 3.15(1) and 3.53(1) Å, with a P3–N10 distance of 4.240(8) Å. The anions are not disordered.

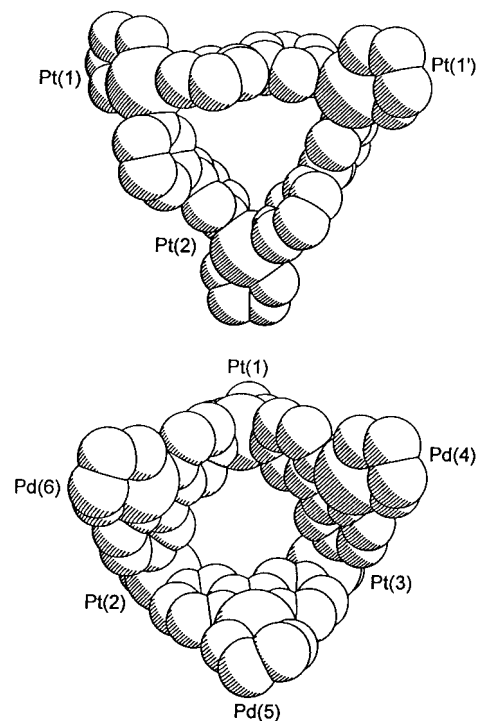


Figure 2. Space-filling models of cations of the trinuclear starting material $[(\text{en})\text{Pt}(\text{bpz})_3](\text{NO}_3)_6$ (top) and of the hexanuclear product **1** (bottom).

The association constant (K_{ass})^[8, 9] has been determined for PF_6^- by NMR spectroscopic investigations. The H(3) and H(3') proton resonances are shifted by about $\Delta\delta = 0.27$ to higher field upon addition of NH_4PF_6 to the pure hexanuclear nitrate salt **1***, whereas the signals of the other aromatic protons are virtually unaffected (max. shifts $\Delta\delta = 0.03$). The ^{19}F NMR signal of NH_4PF_6 , which is a doublet as a consequence of coupling between the ^{19}F and the ^{31}P nuclei, undergoes a downfield shift upon addition NH_4PF_6 to the pure nitrate salt **1***. With an excess of the PF_6^- ion, the signal shifts back to highfield. The maximum effect ($\Delta\delta = 0.36$, after addition of 4–5 equivalents of PF_6^-) is not very pronounced

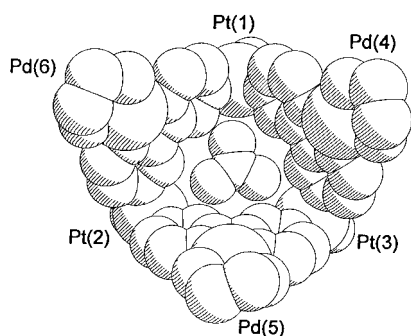


Figure 3. Space-filling model of the cation **1** with an NO_3^- ion at the bottom of the calixarene-like structure.

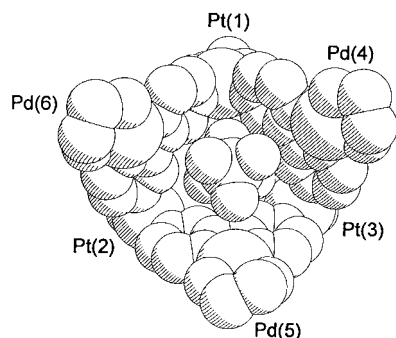


Figure 4. Space-filling model of the encapsulation of the PF_6^- ion in $[(\text{en})\text{Pt}(\text{bpz})\text{Pd}(\text{en})]_3(\text{NO}_3)_{11}^+$. The NO_3^- ion is omitted for clarity.

due to signal averaging between free and encapsulated anion. In the ^{31}P NMR spectrum, the septet shifts by about $\Delta\delta = 0.62$ to higher field as compared to free PF_6^- ions, after addition of one equivalent of NH_4PF_6 to **1***. A further increase in the concentration of PF_6^- ions causes the ^{31}P NMR signal to shift to the value of the free PF_6^- ion in D_2O . By analogy with the crystal structure we suggest that also in solution the PF_6^- ion is encapsulated over the Pd_3 plane. The NMR studies can, however, not confirm an encapsulation of the nitrate anion in solution.

The association constant calculated for PF_6^- from ^1H NMR data was $10.6 \pm 3.9 \text{ M}^{-1}$ (standard deviation 3σ). In comparison to other systems with host–guest interactions, this value seems to be small,^[10] but it has to be taken into consideration that association constants in water are generally considerably lower than those measured in a nonpolar solvent. In water there is clearly competition between the solvent and the host. Measurements in nonpolar solvents could not be performed due to solubility problems; however, we believe that here the association constant is considerably higher.

^1H NMR experiments with other anions confirm that **1*** is also a receptor for the tetrahedral anions ClO_4^- , BF_4^- , and SO_4^{2-} . The comparison of the determined association constants (Table 1) clearly reveals that the binding of SO_4^{2-} is very strong ($255.8 \pm 57.3 \text{ M}^{-1}$). In contrast to the anions PF_6^- , ClO_4^- , and BF_4^- , H(3) and H(3') protons are downfield shifted in the presence of SO_4^{2-} . The difference in the NMR spectra may indicate another mode of encapsulation of the SO_4^{2-} ion in **1***. One possibility would be an association over the Pt_3 plane and a replacement of NO_3^- ions. Sodium-3-(trimethylsilyl)propanesulfonate (TSP) gives no indication of any host–guest

Table 1. Association constants K_{ass} .

Anions	$K_{\text{ass}} [\text{M}^{-1}] \pm 3\sigma$
PF_6^-	10.6 ± 3.9
ClO_4^-	9.6 ± 4.5
BF_4^-	4.1 ± 1.1
SO_4^{2-}	255.8 ± 57.3
TSP	0.0

interaction. No association constants could be determined for PtCl_4^{2-} , PdCl_4^{2-} , PtCl_6^{2-} and SiF_6^{2-} because of solubility problems.

Anion receptors are a field of great current interest.^[11] Receptors for nitrate and phosphate ions are very important because of their role in environmental pollution.^[12] Among the various approaches for recognition and complexation there are also those that take advantage of electrostatic, Lewis acidic, and coordinative interactions between anionic guests and hosts containing metal entities.^[13] In the present case of the simultaneous encapsulation of NO_3^- and PF_6^- ions there appears to be a combination of the first two mentioned interactions in operation. In order to find out if **1** is a sensor for these anions further experiments are necessary.

Experimental Section

1: $[(\text{en})\text{PdCl}_2]$ (44.2 mg, 0.186 mmol) was suspended in water (10 mL) and stirred for 4 h at room temperature with AgNO_3 (60.1 mg, 0.354 mmol). After removal of AgCl by filtration and addition of $[(\text{en})\text{Pt}(\text{bpz})]_3(\text{NO}_3)_6$ ^[11] (100 mg, 0.0581 mmol) to the filtrate, the mixture was stirred for 2 h at room temperature. The orange reaction mixture was filtered and NH_4PF_6 (140 mg, 0.86 mmol) was added. Yellow-orange **1**·5 H_2O was isolated in 63 % yield after 2 d at 4 °C. Satisfactory elemental analysis for $\text{Pt}_3\text{Pd}_3\text{N}_{28}\text{C}_{36}\text{H}_{76}\text{O}_{17}\text{P}_8\text{F}_{48}$; ^1H NMR (200 MHz, D_2O , TSP): $\delta = 2.96$ (s, 8H; CH_2), 8.86 (d, $^3J = 3.4$ Hz, 2H; aromatic), 9.76 (d, $^3J = 3.9$ Hz, 2H; aromatic), 10.39 (s, 2H; aromatic); ^{195}Pt NMR (43 MHz, D_2O): $\delta = -2726$ (PtN_4).

1*: The pure nitrate hexanuclear compound **1*** was prepared in an analogous manner to **1** in solution except for the addition of NH_4PF_6 . Compound **1*** was identified by NMR spectroscopy: ^1H NMR (200 MHz, D_2O , TSP): $\delta = 2.97$ (s, 8H; CH_2), 8.83 (d, $^3J = 3.4$ Hz, 2H; aromatic), 9.79 (d, $^3J = 3.9$ Hz, 2H; aromatic), 10.66 (s, 2H; aromatic); ^{195}Pt NMR (43 MHz, D_2O): $\delta = -2719$ (PtN_4).

Received: March 25, 1998

Revised version: September 21, 1998 [Z11637IE]

German version: *Angew. Chem.* **1999**, *111*, 235–238

Keywords: anion recognition • host–guest chemistry • palladium • platinum

[1] R.-D. Schnebeck, L. Randaccio, E. Zangrando, B. Lippert, *Angew. Chem.* **1998**, *110*, 128; *Angew. Chem. Int. Ed.* **1998**, *37*, 119.

[2] Crystal structure analysis of **1**: $\text{C}_{36}\text{H}_{66}\text{O}_{12}\text{N}_{28}\text{P}_8\text{F}_{48}\text{Pd}_3\text{Pt}_3 \cdot 5\text{H}_2\text{O}$ ($M_r = 3237.48$); monoclinic; space group $P2(1)/c$; $a = 17.002(3)$, $b = 22.837(5)$, $c = 22.763(5)$ Å, $\beta = 93.91(3)^\circ$, $V = 8817.7(31)$ Å³, $Z = 4$, $\rho_{\text{calc}} = 2.439 \text{ g cm}^{-3}$, $F(000) = 6192$, $\mu = 5.661 \text{ mm}^{-1}$, 10265 observed reflections with $F_o > 4\sigma(F_o)$, $R_1 = 0.0484$, $wR_2 = 0.0958$, $S = 1.169$, max./min. residual electron density $1.33/-1.24 \text{ e Å}^{-3}$, Enraf-Nonius Kappa CCD diffractometer,^[3] $\text{MoK}\alpha$ radiation ($\lambda = 0.71069$ Å), graphite monochromator, absorption correction: considered in SCALE-PACK,^[4] correction for Lorentzian and polarization effects,^[4] The structure was solved by the Patterson method,^[5] and refined by the least-squares method,^[6] fluorine atoms of four PF_6^- ions in the lattice (P(5)–P(8)) were treated isotropically because they were disordered.

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-101228. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

- [3] NONIUS BV, KappaCCD package, Delft, Netherlands.
- [4] Z. Otwinowsky, W. Minor, "Processing of X-ray Diffraction Data Collected in Oscillation Mode" in *Methods Enzymol.* **1996**, 276, 307.
- [5] SHELXS-86: G. M. Sheldrick, *Acta Crystallogr. Sect. A*, **1990**, 46, 467.
- [6] G. M. Sheldrick, SHELXL-93, program for crystal structure refinement, Universität Göttingen, Germany, **1993**.
- [7] C. Meiser, B. Song, E. Freisinger, M. Peilert, H. Sigel, B. Lippert, *Chem. Eur. J.* **1997**, 3, 388.
- [8] Association constant: The ^1H NMR spectra were measured at constant temperature (20°C) and constant pD (2.9). The salts were added to the pure nitrate complex **1*** with increasing concentrations (0.5–10 equiv; 0.01–0.02 M) in three independent measurements for each salt (NH_4PF_6 , NaClO_4 , NaBF_4 , and Na_2SO_4). The association constants were determined according to ref. [9] with a nonlinear least-squares method. The individual results did not differ from each other within the error limits. K_{ass} (standard deviation 3σ) is the weighted mean of the results of the three independent measurements.
- [9] H. Sigel, K. H. Scheller, V. M. Rheinberger, B. E. Fischer, *J. Chem. Soc. Dalton Trans.* **1980**, 1022.
- [10] P. D. Beer, *Acc. Chem. Res.* **1998**, 31, 71.
- [11] F. P. Schmidtchen, M. Berger, *Chem. Rev.* **1997**, 97, 1609, and references therein.
- [12] a) C. F. Mason, *Biology of Freshwater Pollution*, 2nd ed., Longman: Harlow, U. K., 2nd ed. **1991**; b) R. G. Gymer *Chemistry: An Ecological Approach*, Harper and Row, New York, **1973**.
- [13] a) A. P. Bisson, V. M. Lynch, M.-K. C. Monahan, E. V. Anslyn, *Angew. Chem.* **1997**, 109, 2435; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 2340; b) P. L. Jones, K. J. Byrom, J. C. Jeffery, J. A. McCleverty, M. D. Ward, *Chem. Commun.* **1997**, 1361; c) S. Warzeska, R. Krämer, *Chem. Commun.* **1996**, 499; d) K. T. Holman, M. M. Halihan, J. W. Steed, *J. Am. Chem. Soc.* **1996**, 118, 9567; e) M. Staffilani, K. S. B. Hancock, J. W. Steed, K. T. Holman, J. L. Atwood, R. K. Juneja, R. S. Burkhalter, *J. Am. Chem. Soc.* **1997**, 119, 6324; f) M. Fujita, *J. Synth. Org. Chem. Jpn.* **1996**, 54, 953, and references therein.

[{Mn(salen)CN} $_n$]: The First One-Dimensional Chain with Alternating High-Spin and Low-Spin Mn^{III} Centers Exhibits Metamagnetism**

Naohide Matsumoto,* Yukinari Sunatsuki, Hitoshi Miyasaka, Yuzo Hashimoto, Dominique Luneau, and Jean-Pierre Tuchagues*

Of the few low-spin manganese(III) complexes,^[1–3] the majority contain five or six cyano ligands.^[1] Manganese(III) complexes with one or two cyano ligands are generally high spin:^[4] monocyano manganese(III) porphyrins,^[4a] discrete five-coordinate manganese species with L-Mn-CN coordination^[4b] (L = tetradentate salen-type ligand; H_2salen = bis(salicylidene)ethylenediamine), and heterometallic species with Fe-CN-Mn(L)-NC repeat units.^[4c, d] However, low-spin Mn^{III} is present in dicyanomanganese(III) porphyrins.^[2] Finally, [Mn(trp)]^[5] (trp = tris[1-(2-azoly)-2-azabuten-4-yl]amine) is the only manganese(III) complex known to exhibit a thermally induced $S = 1 \leftrightarrow S = 2$ spin crossover. In this complex, the ligand field generated by the three pyrrole and three imine N centers of trp is sufficiently strong to yield a Δ parameter close to the spin-pairing energy. The strong ligand field which stabilizes low-spin Mn^{III} in dicyanomanganese(III) porphyrins is probably provided by C-bonded cyano ligands in addition to the four pyrrole N donors. In this context, the question of whether the presence of two C-bonded cyanide ligands is sufficient to stabilize low-spin Mn^{III} in an octahedral coordination environment is of utmost interest. This will determine whether molecular magnetic materials can be built from a single Mn^{III} paramagnetic component.

The simplest way to obtain an NC-Mn-CN pattern is to induce CN[−] bridging of [Mn^{III}L]⁺ cations (L = planar tetradentate ligand). The reaction of an aqueous solution of NaCN with a methanolic solution of [Mn(salen)(H₂O)]ClO₄ yields red-brown microcrystals of [{Mn(salen)CN} $_n$] (**1**), a new type of one-dimensional coordination polymer which contains alternating $S = 1$ and $S = 2$ Mn^{III} spin states and exhibits

[*] Prof. N. Matsumoto, Dr. Y. Sunatsuki, Dr. H. Miyasaka

Department of Chemistry, Faculty of Science
Kumamoto University
Kurokami 2-39-1, Kumamoto 860-8555 (Japan)
Fax: (+81)96-342-3390
E-mail: naohide@aster.sci.kumamoto-u.ac.jp

Prof. J.-P. Tuchagues
Laboratoire de Chimie de Coordination du CNRS
UPR 8241, 205 route de Narbonne, 31077 Toulouse Cedex (France)
Fax: (+33)561 553003
E-mail: tuchague@lcc-toulouse.fr

Prof. Y. Hashimoto
Department of Physics, Fukuoka University of Education
Akama 729, Fukuoka 811-41 (Japan)

Dr. D. Luneau
CEA-Département de Recherche Fondamentale sur la Matière Condensée
SCIB-Laboratoire de Chimie de Coordination (URA CNRS 1194)
38054 Grenoble Cédex 9 (France)

[**] This work was supported by the Monbusho International Scientific Research Program ("Joint Research" no. 10044089) and by a Grant-in-Aid for Scientific Research on Priority Areas (no. 10149101, "Metal-assembled Complexes").

metamagnetism. Compound **1** is structurally reminiscent of the one-dimensional “shish kebab” coordination polymers with porphyrins or phthalocyanines as equatorial ligands and diverse polyatomic axial bridges.^[6]

The asymmetric unit of **1**^[7] (Figure 1) contains two Mn^{III} ions with similar N₂O₂ equatorial coordination environments provided by salen ligands. However, all four distances between MnA and the donor atoms of salen A are larger

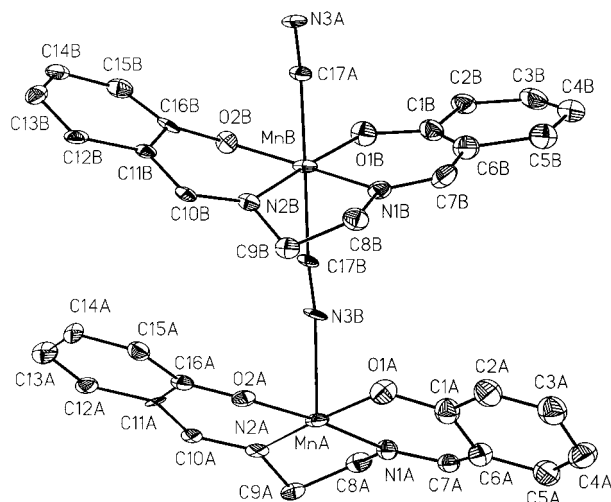


Figure 1. Perspective view of complex **1** (hydrogen atoms are omitted for clarity). Selected bond distances [Å] and angles [°]: MnA–O1A 1.92(2), MnA–O2A 1.89(2), MnA–N1A 1.94(2), MnA–N2A 1.97(2), MnA–N3B 2.25(3), MnA–N3A' 2.34(3), MnB–O1B 1.90(2), MnB–O2B 1.86(2), MnB–N1B 1.92(2), MnB–N2B 1.91(2), MnB–C17A 2.06(3), MnB–C17B 2.13(3); MnA–N3A'–C17A' 143(2), MnA–N3B–C17B 147(3), MnB–C17A–N3A 170(3), MnB–C17B–N3B 165(3) (the prime indicates atoms that are related by $x, y-1, z$ symmetry).

than the corresponding distances between MnB and salen B (av MnA–L^A 1.93 Å; av MnB–L^B 1.90 Å). The cyanide nitrogen atoms N3B and N3A' are the axial ligands of MnA, while the cyanide carbon atoms C17A and C17B are axially coordinated to MnB. The MnA–N3B (2.25(3) Å) and MnA–N3A' distances (2.34(3) Å) are close to those reported for bonds between high-spin Mn^{III} and cyanide ligands (2.290(5)–2.415(5) Å).^[4c–e] The MnB–C17A (2.06(3) Å) and MnB–C17B distances (2.13(3) Å) are similar to those of low-spin Mn^{III} to cyanide bonds (1.940(15)–2.056(27) Å)^[1] and shorter than the only known distance between high-spin Mn^{III} and cyanide (2.190(3) Å).^[4b] Comparison of the MnA–N3B–C17B (147(3)°) and MnA–N3A'–C17A' angles (143(2)°) with MnB–C17A–N3A (170(3)°) and MnB–C17B–N3B (165(3)°) also reveals different ligand environments of MnA and MnB and clearly indicates the high- and low-spin nature of their respective d⁴ systems. The MnA–MnB distance is 5.115(6) Å.

The asymmetric units are linked together through CN[–] bridges into infinite one-dimensional chains with alternating high- and low-spin [Mn^{III}salen]⁺ complex cations along the *b* axis (Figure 2). The closest contacts (3.18(6) Å) between adjacent chains involve the aromatic C3A atoms, which are related by the $1-x, -1-y, -z$ symmetry. The shortest distance between Mn ions of adjacent chains (7.215(8) Å) involves MnA and MnB ($1-x, -1/2+y, 1/2-z$). No π -

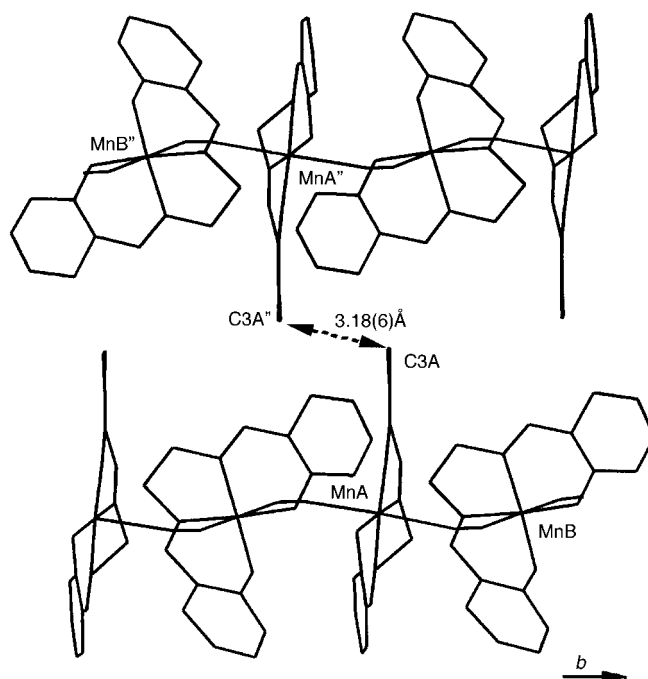


Figure 2. Perspective view of **1** emphasizing the closest contacts between aromatic C3A carbon atoms of adjacent chains, which are related by $1-x, -1-y, -z$ symmetry.

stacking interactions between aromatic rings of adjacent 1D chains are evident.

The magnetic susceptibility of **1** was measured in the temperature range of 2–300 K with a SQUID susceptometer in an applied magnetic field of 500 Oe. The plots of the effective magnetic moment μ_{eff} versus temperature *T* and of the reciprocal magnetic susceptibility χ_{A}^{-1} versus *T* are shown in Figure 3. The μ_{eff} value of 4.09 μ_{B} at room temperature is consistent neither with the spin-only value for high-spin Mn^{III} (4.89 μ_{B} for $S=2$) nor with the spin-only value for low-spin

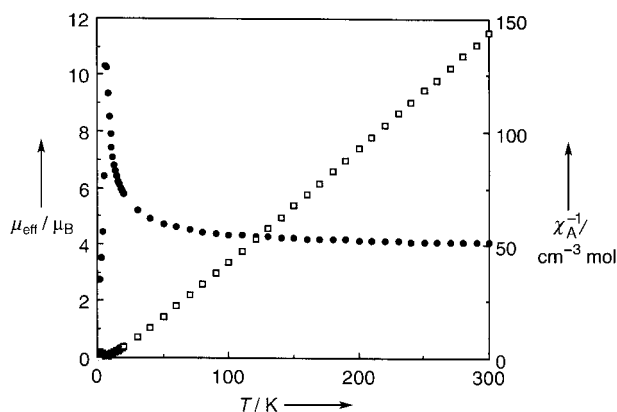


Figure 3. Plots of effective magnetic moment μ_{eff} and the reciprocal magnetic susceptibility χ_{A}^{-1} of **1** as a function of temperature *T*.

Mn^{III} (2.83 μ_{B} for $S=1$). On lowering the temperature, μ_{eff} increases over the whole temperature range 300–6 K, smoothly from 300 to 25 K, and then sharply reaching a maximum value of 10.3 μ_{B} at 6 K. Finally, μ_{eff} decreases to 2.75 μ_{B} at 2 K. The χ_{A}^{-1} versus *T* plot obeys a Curie–Weiss law

with a positive θ constant of 5.6 K. The positive Weiss constant and the increase in μ_{eff} over the entire range 300–6 K is typical of a ferromagnetic coupling between adjacent Mn^{III} ions along the chains.^[8] The abrupt increase in μ_{eff} between 25 and 6 K suggests the onset of magnetic ordering in the chains, and the decrease below 6 K suggests the operation of long-range weak antiferromagnetic interactions through interchain contacts between the salen ligands and/or the zero-field splitting (ZFS) of the anisotropic high-spin Mn^{III} ion. The field-dependent magnetization was measured up to 50 kOe at 2 and 6 K with a SQUID susceptometer, and up to 120 kOe at 4.2 K with a flux magnetometer by using conventional pulse techniques (Figure 4). The curve at 2 K (below the Néel temperature) has the sigmoidal shape expected for a metamagnet: The magnetization first increases slowly with increasing H due to antiferromagnetic interchain interactions,

Experimental Section

1: $[\text{Mn}(\text{salen})(\text{H}_2\text{O})]\text{ClO}_4$ was prepared by reaction of $\text{Mn}^{\text{III}}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$ with salen H_2 and NaClO_4 in methanol (1:1:1 molar ratio, 0.5 mmol in 20 mL). Reaction of an aqueous solution of NaCN (0.5 mmol in 5 mL) with a methanolic solution of $[\text{Mn}(\text{salen})(\text{H}_2\text{O})]\text{ClO}_4$ (0.5 mmol in 20 mL) at room temperature for 10 min yielded **1** as red-brown microcrystals, which were collected by suction filtration. Complex **1** is insoluble in common organic solvents. Slow interdiffusion of a solution of $[\text{Mn}(\text{salen})(\text{H}_2\text{O})]\text{ClO}_4$ in DMF/MeOH (1/1) and an aqueous solution of NaCN yielded single crystals of **1** in the form of very thin red-brown platelets. Elemental analysis calcd for $\text{C}_{17}\text{H}_{14}\text{N}_6\text{O}_4\text{Mn}$: C 58.80, H 4.06, N 12.10; found: C 58.66, H 4.10, N 12.11; IR (KBr): $\bar{\nu}_{\text{CN}} = 2110\text{ cm}^{-1}$.

Received: June 2, 1998

Revised version: September 3, 1988 [Z11935 IE]

German version: *Angew. Chem.* **1999**, *111*, 137–139

Keywords: magnetic properties • manganese • N ligands • O ligands

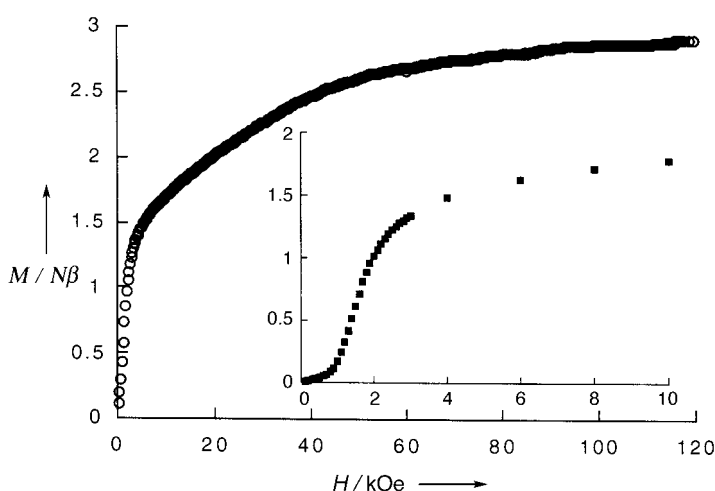


Figure 4. Plot of magnetization M of **1** as a function of the applied magnetic field H at 4.2 K ($\circ$) up to 120 kOe, and at 2 K ($\blacksquare$) up to 10 kOe (inset).

then increases abruptly for a phase transition to a ferromagnetic state, and finally reaches a saturation magnetization plateau of $2.83\text{--}2.91\text{ }N\beta$ at $85\text{--}120\text{ kOe}$. The large magnetic field required to reach saturation may be due to the ZFS of high-spin Mn^{III} . The saturation magnetization value of about $3N\beta$ implies that the compound has an average of three unpaired electrons per Mn center. This unusual magnetic behavior can be rationalized on the basis of the molecular structure: 1) The complex is a mixed-spin system consisting of uniformly distributed high-spin ($S=2$) and low-spin ($S=1$) Mn^{III} ions; indeed, the μ_{eff} value of $4.09\text{ }\mu_{\text{B}}$ at room temperature agrees with the spin-only value of $4.0\text{ }\mu_{\text{B}}$ derived by assuming a magnetically dilute system with high- and low-spin Mn^{III} species ($g=2$) in a 1:1 ratio. 2) The saturation magnetization for such a system is expected to be $M_s = N\beta g(S_1 + S_2)/2 = 3N\beta$ per Mn center. 3) The ferromagnetic interactions operate between high-spin and low-spin Mn^{III} species through CN bridges within the chains, and the antiferromagnetic interactions operate between Mn^{III} ions of adjacent chains, probably by means of electrostatic interactions between the salen ligands; the result is a metamagnetic character.

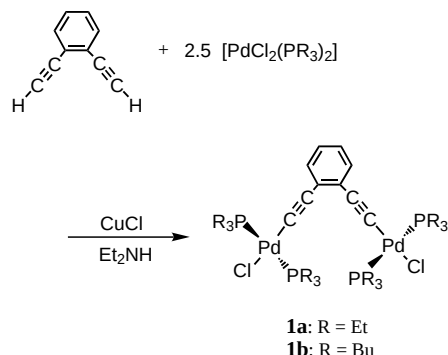
- [1] a) M. P. Gupta, H. J. Milledge, A. E. McCarthy, *Acta Crystallogr. Sect. B* **1974**, *30*, 656; b) D. Babel, *Z. Naturforsch. B* **1984**, *39*, 880; c) H. K. Saha, *Sci. Cult.* **1961**, *27*, 582; d) R. F. Ziolo, R. H. Stanford, G. R. Rossman, H. B. Gray, *J. Am. Chem. Soc.* **1974**, *96*, 7910.
- [2] A. P. Hansen, H. M. Goff, *Inorg. Chem.* **1984**, *23*, 4519.
- [3] a) J. T. Landrum, K. Hatano, W. R. Scheidt, C. A. Reed, *J. Am. Chem. Soc.* **1980**, *102*, 6729; b) P. Basu, A. Chakravorty, *Inorg. Chem.* **1992**, *31*, 4980; c) S. Ganguly, S. Karmakar, A. Chakravorty, *Inorg. Chem.* **1997**, *36*, 116.
- [4] a) B. B. Wayland, L. W. Olson, Z. U. Siddiqui, *J. Am. Chem. Soc.* **1976**, *98*, 94; b) N. Matsumoto et al., unpublished results; c) H. Miyasaka, N. Matsumoto, H. Okawa, N. Re, E. Gallo, C. Floriani, *Angew. Chem.* **1995**, *107*, 1565; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1446; d) H. Miyasaka, N. Matsumoto, H. Okawa, N. Re, E. Gallo, C. Floriani, *J. Am. Chem. Soc.* **1996**, *118*, 981; e) N. Re, E. Gallo, C. Floriani, H. Miyasaka, N. Matsumoto, *Inorg. Chem.* **1996**, *35*, 6004.
- [5] P. G. Sim, E. Sinn, *J. Am. Chem. Soc.* **1980**, *103*, 241.
- [6] C.-T. Chen, K. S. Suslick, *Coord. Chem. Rev.* **1993**, *128*, 293.
- [7] Crystal data for **1** ($\text{C}_{34}\text{H}_{28}\text{N}_6\text{O}_4\text{Mn}_2$): $M_r = 694.50$, red-brown platelet ($0.05 \times 0.05 \times 0.01\text{ mm}$), monoclinic, space group $P2_1/c$, $a = 11.2454(8)$, $b = 10.2320(7)$, $c = 26.850(2)\text{ Å}$, $\beta = 98.138(2)^\circ$, $V = 3058.4(4)\text{ Å}^3$, $Z = 4$, $\rho_{\text{calcd}} = 1.508\text{ g cm}^{-3}$, $\mu(\text{Mo K}\alpha) = 8.76\text{ cm}^{-1}$. Data were collected at 193 K on a Siemens SMART CCD area detector system equipped with a normal focus molybdenum-target X-ray tube operated at 2 kW. A total of 1321 data frames were obtained with a narrow-frame method with 0.3° scan width, 60 s exposure time per frame, and a 5.922 cm crystal-to-detector distance. The data were processed with the SAINT reduction and SADABS absorption programs^[9] to give a total of 8742 reflections ($3.06 \leq 2\theta \leq 40.0^\circ$), of which 2850 were independent ($R_{\text{int}} = 0.0916$, $R(\sigma) = 0.1202$) and 1631 with $I > 2\sigma(I)$ were used to solve the structure with SHELXTL.^[9] Crystals of **1** were very thin, weakly diffracting, and gave low-resolution data, and the refinement on F^2 converged to relatively high final R values: $R1 = 0.1063$, $wR2 = 0.3572$ (all data), $\text{GOF} = 1.280$. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-101380. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [8] N. Re, E. Gallo, C. Floriani, H. Miyasaka, N. Matsumoto, *Inorg. Chem.* **1996**, *35*, 5964.
- [9] SAINT, Version 4.050, **1992–1995**, and SHELXTL, Version 5.030, **1994**, Siemens Analytical X-ray Instruments.

A Novel Organometallic Macrocycle Composed of a Tetranuclear Palladium Acetylide**

Kiyotaka Onitsuka, Shin Yamamoto, and Shigetoshi Takahashi*

Macrocyclic compounds, which are a fundamental two-dimensional system of molecular networks, have attracted much attention due to their novel properties.^[1] Recently, there has been growing interest in macrocycles composed of transition metal complexes and bipyridine ligands.^[2] Their structures are strongly influenced by the structure of the bridging ligands and of the metal species. We have been investigating organometallic networks composed of transition metal acetylides,^[3] since multinuclear acetylides have potential applications in materials science owing to their characteristic properties such as electronic interaction between metal atoms through bridging acetylide ligands.^[4] Here we present a novel macrocyclic multinuclear acetylide complex, the structure of which is determined by the geometry of the bridging ligands and by the steric demand of the phosphane ligands. Although there are a few reports on macrocycles with a metal–acetylide bond,^[5] multinuclear complexes are quite rare.^[6]

Treatment of *o*-diethynylbenzene^[7] with 2.5 equivalents of [PdCl₂(PEt₃)₂] in the presence of a CuCl catalyst in diethylamine at room temperature gave the dipalladium complex **1a** in 62 % yield [Eq. (1)]. The tri-*n*-butylphosphane analogue **1b**



was prepared by a similar reaction in 81 % yield. These complexes were fully characterized by spectroscopy. To obtain information on the geometry of the two palladium moieties and *o*-diethynylbenzene ring, an X-ray crystallographic analysis was performed on **1a** (Figure 1).^[8] The two acetylene groups are slightly bent away from each other due to steric repulsion between the two bulky Pd moieties. The Pd–C and C≡C bond lengths and the bond angles are similar to those of

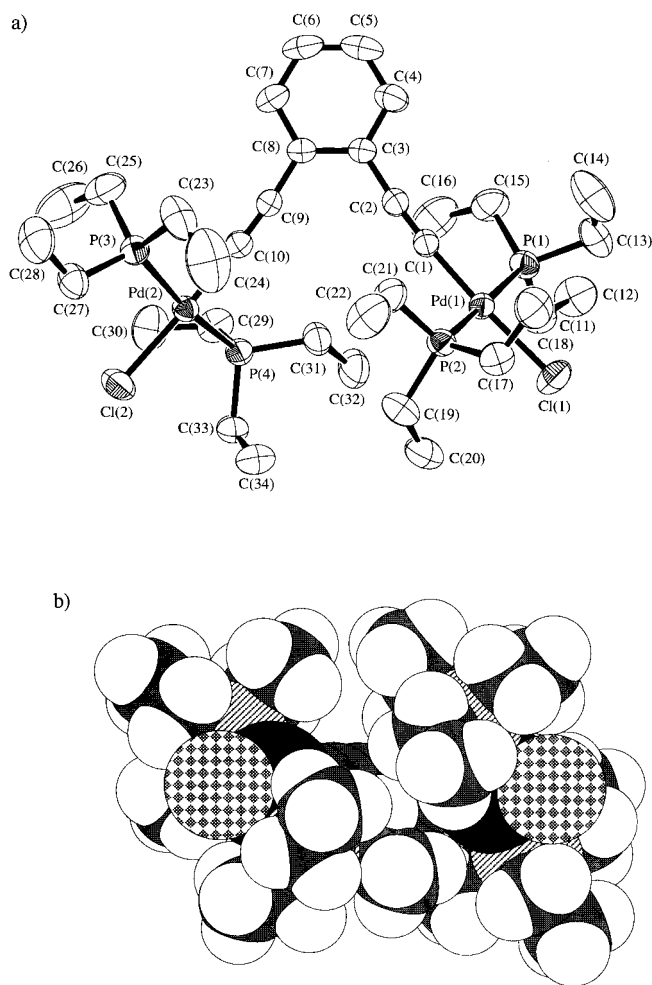


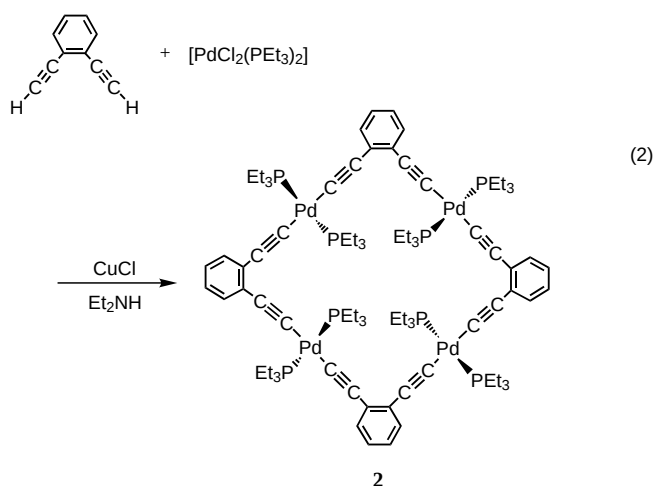
Figure 1. Molecular structure of **1a**. a) ORTEP plot (top view). Hydrogen atoms are omitted for clarity. Selected bond lengths [Å] and angles [°]: Pd(1)–C(1) 1.951(3), Pd(2)–C(10) 1.956(4), C(1)–C(2) 1.192(5), C(9)–C(10) 1.195(5); Cl(1)–Pd(1)–C(1) 175.8(1), P(1)–Pd(1)–P(2) 176.16(4), Cl(2)–Pd(2)–C(10) 178.0(1), P(3)–Pd(2)–P(4) 169.58(4), Pd(1)–C(1)–C(2) 175.1(3), C(1)–C(2)–C(3) 175.1(4), C(2)–C(3)–C(8) 122.5(3), C(3)–C(8)–C(9) 121.1(3), C(8)–C(9)–C(10) 175.8(4), Pd(2)–C(10)–C(9) 176.1(3). b) Space-filling representation (side view).

other palladium acetylide complexes.^[9] The noteworthy structural feature of **1a** is that the two palladium coordination planes are twisted out of the C₆H₄ plane of *o*-diethynylbenzene in the same direction to minimize steric repulsion between the triethylphosphane ligands. The dihedral angles are 55.1 and 46.8°.^[3b, 5a, 9a, 10]

When *o*-diethynylbenzene was treated with an equimolar amount of [PdCl₂(PEt₃)₂] under similar conditions [Eq. (2)], the oligomeric complex **2** was formed along with small amounts of polymeric complexes, as confirmed by gel permeation chromatography.^[11] Purification by column chromatography on alumina followed by recrystallization from CH₂Cl₂/hexane gave pale yellow crystals of **2** in 33 % yield. Formation of M–C bonds was indicated by a characteristic band for ν(C≡C) of palladium acetylides at 2088 cm^{–1} in the IR spectrum of **2**. Although **2** is an oligomer, its NMR spectra show simple patterns. For example, the ³¹P NMR spectrum exhibits a singlet at δ = 19.3, and single sets of signals for the acetylenic and aromatic carbon atoms were observed in the

[*] Prof. Dr. S. Takahashi, Dr. K. Onitsuka, S. Yamamoto
The Institute of Scientific and Industrial Research
Osaka University, Mihogaoka, Ibaraki
Osaka 567-0047 (Japan)
Fax: (+81) 6-879-8459
E-mail: takahashi@sanken.osaka-u.ac.jp

[**] This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas (no. 10149228 “Metal-assembled Complexes”) from the Ministry of Education, Science, Sports and Culture.



^{13}C NMR spectrum. These spectroscopic data suggest that **2** is a macrocyclic complex. Elemental analysis gave the composition $(\text{C}_{22}\text{H}_{34}\text{P}_2\text{Pd})_n$, which also suggests a macrocyclic structure. Since the angle between two acetylene groups in *o*-diethynylbenzene is 60° , we assumed that **2** would be trinuclear.^[2, 12] However, the average molecular weight of **2** determined by vapor pressure osmometry was 1850, which corresponds to a tetranuclear complex. Finally, the tetranuclear, macrocyclic structure of **2** was confirmed by an X-ray structural analysis (Figure 2).^[13] The molecule of **2** has D_{2d} symmetry in the solid state. The macrocyclic skeleton of palladium atoms, acetylide groups, and aromatic rings lies

almost in a plane. The Pd–C bonds are slightly longer than those of **1a** due to the larger *trans* influence of an alkynyl group relative to a chloride ligand. The coordination plane of the Pd center forms dihedral angles of 63.9° and 69.6° with the C_6H_4 plane, which are larger than those of **1a**. The ethyl groups of the phosphane ligands are directed into the center of the macrocycle (Figure 3), so that there is no significant space for the inclusion of organic guest molecules.

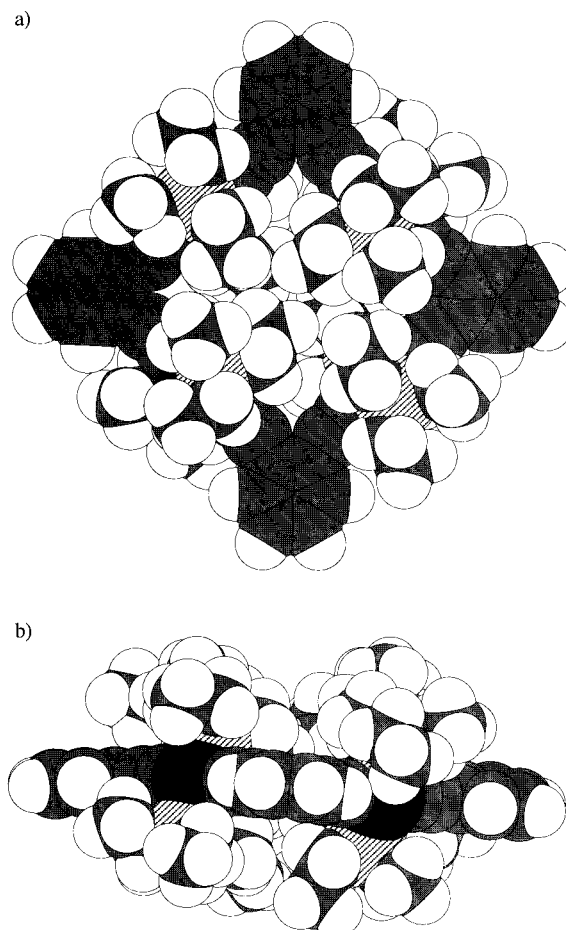


Figure 3. Space-filling representation of **2**. a) Top view. b) Side view.

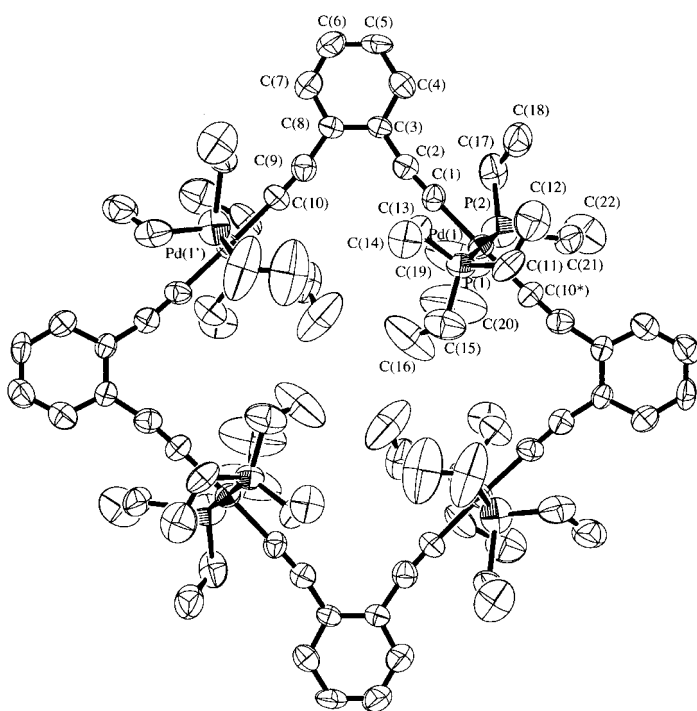


Figure 2. ORTEP plot of the molecular structure of **2**. Hydrogen atoms are omitted for clarity. Selected bond lengths [Å] and angles [°]: Pd(1)–C(1) 1.996(8), Pd(1)–C(10*) 2.013(8), C(1)–C(2) 1.22(1), C(9)–C(10) 1.18(1); P(1)–Pd(1)–P(2) 176.82(9), C(1)–Pd(1)–C(10*) 177.6(3), Pd(1)–C(1)–C(2) 178.2(7), C(1)–C(2)–C(3) 170.7(8), C(2)–C(3)–C(8) 122.7(7), C(3)–C(8)–C(9) 123.1(7), C(8)–C(9)–C(10) 171.1(9), Pd(1)–C(10)–C(9) 177.1(3).

The molecular structure provides information on the selective formation of **2**. In each $\text{Pd}(\text{PEt}_3)_2(o\text{-C}\equiv\text{CC}_6\text{H}_4\text{C}\equiv\text{C})\text{-Pd}(\text{PEt}_3)_2$ moiety, the two coordination planes are twisted out of the C_6H_4 plane in the same direction to avoid steric interactions, as is observed in **1a**. Consequently, the P–Pd–P axes are inclined alternately in opposite directions with respect to the macrocycle, and the triethylphosphane ligands on one side of the macrocycle plane are alternately situated on the outside and inside of the macrocycle. Therefore, the number of palladium atoms in the macrocycle must be even. Because dinuclear and hexanuclear macrocycles are highly strained, the tetranuclear complex **2** with minimum strain is selectively formed.

Treatment of *o*-diethynylbenzene with an equimolar amount of $[\text{PdCl}_2(\text{PnBu}_3)_2]$ did not give a macrocycle, but a mixture of linear oligomeric complexes owing to the slightly

larger steric bulk of tri-*n*-butylphosphane relative to triethylphosphane.

We have demonstrated a novel route to a macrocycle with palladium acetylide units in the backbone. We are currently investigating the extension of this method to the formation of macrocycles with other bridging acetylide ligands.

Experimental Section

1a: A mixture of *o*-diethynylbenzene (126 mg, 1 mmol) and [PdCl₂(PEt₃)₂] (1.034 g, 2.5 mmol) in diethylamine (50 mL) in the presence of CuCl (ca. 2 mol %) was stirred at room temperature for 18 h. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on alumina with CH₂Cl₂ as eluent. Recrystallization from CH₂Cl₂/hexane gave pale yellow crystals (544 mg, 62 %). IR (KBr): $\tilde{\nu}$ = 2114 cm⁻¹ (C≡C); ¹H NMR (400 MHz, CDCl₃): δ = 7.22 (dd, *J* = 5.8, 3.5 Hz, 2H), 6.99 (dd, *J* = 5.8, 3.5 Hz, 2H), 2.00–1.93 (m, 24H), 1.19 (dt, *J* = 16.6, 8.0 Hz, 36H); ¹³C NMR (100 MHz, CDCl₃): δ = 138.3, 127.9, 124.9, 107.0 (t, *J*_{PC} = 5.8 Hz), 98.2 (t, *J*_{PC} = 16.5 Hz), 15.4 (vt, *N* = 14.1 Hz), 8.43; ³¹P NMR (162 MHz, CDCl₃): δ = 18.2; satisfactory elemental analysis.

2: An equimolar mixture of *o*-diethynylbenzene and [Pd(PEt₃)₂Cl₂] was treated as for **1a** to give pale yellow crystals in 33 % yield. IR (KBr): $\tilde{\nu}$ = 2088 cm⁻¹ (C≡C); ¹H NMR (400 MHz, CDCl₃): δ = 7.23 (dd, *J* = 5.9, 3.4 Hz, 8H), 6.99 (dd, *J* = 5.9, 3.4 Hz, 8H), 2.05–2.00 (m, 48H), 1.21 (dt, *J* = 16.3, 8.0 Hz, 72H); ¹³C NMR (100 MHz, CDCl₃): δ = 132.4, 128.6, 124.0, 114.2 (t, *J*_{PC} = 17.4 Hz), 111.1 (t, *J*_{PC} = 3.7 Hz), 17.2 (vt, *N* = 14.1 Hz), 8.9; ³¹P NMR (162 MHz, CDCl₃): δ = 19.3; satisfactory elemental analysis.

Received: June 23, 1998 [Z120401E]
German version: *Angew. Chem.* **1999**, *111*, 129–131

Keywords: alkyne complexes • macrocycles • metallacycles • palladium

- [1] Recent reviews: a) *Comprehensive Supramolecular Chemistry* (Eds.: J. L. Atwood, J. E. D. Davies, D. D. MacNicol, F. Vögtle, K. S. Suslick), Pergamon, Oxford, **1996**; b) J.-M. Lehn, *Supramolecular Chemistry, Concepts and Perspectives*, VCH, Weinheim, **1995**.
- [2] Recent reviews: a) M. Fujita, K. Ogura, *Bull. Chem. Soc. Jpn.* **1996**, *69*, 1471; b) P. J. Stang, B. Olenyuk, *Acc. Chem. Res.* **1997**, *30*, 502.
- [3] a) N. Hagihara, K. Sonogashira, S. Takahashi, *Adv. Polym. Sci.* **1981**, *41*, 149; b) N. Ohshiro, F. Takei, K. Onitsuka, S. Takahashi, *Chem. Lett.* **1996**, 871; c) K. Onitsuka, Y. Harada, F. Takei, S. Takahashi, *Chem. Commun.* **1998**, 643.
- [4] H. Lang, *Angew. Chem.* **1994**, *106*, 569; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 547, and references therein.
- [5] a) R. Faust, F. Diederich, V. Gramlich, P. Seiler, *Chem. Eur. J.* **1995**, *1*, 111; b) D. Zhang, D. B. McConville, C. A. Tessier, Y. J. Youngs, *Organometallics* **1997**, *16*, 824; c) J. J. Pak, T. J. R. Weakley, M. M. Haley, *Organometallics* **1997**, *16*, 4505.
- [6] L. G. Mackay, H. L. Anderson, J. K. M. Sanders, *J. Chem. Soc. Perkin Trans. I* **1995**, 2269.
- [7] S. Takahashi, Y. Kuroyama, K. Sonogashira, N. Hagihara, *Synthesis* **1980**, 627.
- [8] Crystallographic data for **1a**: C₃₄H₆₄Cl₂P₄Pd₂ (*M*_r = 592.54), monoclinic, space group *P*₂₁/*c* (no. 14), *a* = 17.681(2), *b* = 11.080(1), *c* = 22.446(2) Å, β = 103.810(8)°, *V* = 4270.3(7) Å³, *Z* = 4, ρ_{calcd} = 1.369 g cm⁻³, $\mu(\text{MoK}\alpha)$ = 11.38 cm⁻¹, *T* = -75 °C, $\omega/2\theta$ scans, $6 < 2\theta < 60^\circ$, *R* = 0.035 and *R*_w = 0.054 for 379 parameters against 8528 reflections with *I* > 3.0σ(*I*) out of 13341 unique reflections by full-matrix least-squares method, GOF = 1.12.^[13b]
- [9] a) U. Behrens, K. Hoffmann, *J. Organomet. Chem.* **1977**, *129*, 273; b) K. Onitsuka, H. Ogawa, T. Joh, S. Takahashi, Y. Yamamoto, H. Yamazaki, *J. Chem. Soc. Dalton Trans.* **1991**, 1531.
- [10] U. Behrens, K. Hoffmann, J. Kopf, J. Morits, *J. Organomet. Chem.* **1976**, *117*, 91.
- [11] R. Nast, V. Pank, *J. Organomet. Chem.* **1977**, *129*, 265.

- [12] a) F. Diederich, Y. Rubin, *Angew. Chem.* **1992**, *104*, 1123; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1101; b) M. M. Haley, *Synlett* **1998**, 557.
- [13] a) Crystallographic data for **2**: C₈₈H₁₃₆P₈Pd₄ (*M*_r = 1867.43), tetragonal, space group *P*₄₂/*n* (no. 86), *a* = 18.429(4), *c* = 14.440(4) Å, *V* = 4904(1) Å³, *Z* = 2, ρ_{calcd} = 1.264 g cm⁻³, $\mu(\text{MoK}\alpha)$ = 8.90 cm⁻¹, *T* = -75 °C, $\omega/2\theta$ scans, $6 < 2\theta < 55^\circ$, *R* = 0.068 *R*_w = 0.110 for 244 parameters against 2711 reflections with *I* > 3.0σ(*I*) out of 4573 unique reflections by full-matrix least-squares method, GOF = 1.24. b) Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-101 904 (**1a**) and CCDC-101 905 (**2**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Completely Regioselective Synthesis of Directly Linked *meso,meso* and *meso,β* Porphyrin Dimers by One-Pot Electrochemical Oxidation of Metalloporphyrins**

Takuji Ogawa,* Yoshihiro Nishimoto, Naoya Yoshida, Noboru Ono, and Atsuhiko Osuka*

Porphyrin dimers have been attracting considerable attention as biomimetic models of photosynthetic systems, and as photonic materials and functional molecular devices.^[1–7] Since the type of bond connecting the porphyrin rings influences the electronic communication in the dimer, a variety of porphyrin arrays has been explored.^[8–10] Directly linked porphyrin arrays are one interesting class of these compounds, because of the strong interaction between the two porphyrin rings.^[1, 7, 11–14]

We previously reported that electrochemical oxidation has an advantage over silver salt oxidation for obtaining directly linked *meso,meso* porphyrins, since the former method can be

- [*] Prof. Dr. T. Ogawa, Y. Nishimoto
Institute for Fundamental Research of Organic Chemistry
Kyushu University
Hakozaki, Higashi-ku, Fukuoka 812-81 (Japan)
Fax: (+81) 92-642-4224
E-mail: ogawat@ms.ifoc.kyushu-u.ac.jp
- Prof. Dr. A. Osuka, N. Yoshida
Department of Chemistry, Graduate School of Science
Kyoto University
CREST, Japan Science and Technology Corporation (JST)
Sakyo-ku Kyoto 606-01 (Japan)
- Prof. Dr. N. Ono
Department of Chemistry, Faculty of Science
Ehime University, Matsuyama 790 (Japan)

[**] Work at Kyushu University was partly supported by the Nishida Memorial Foundation for Fundamental Organic Chemistry. Work at Kyoto University was partly supported by Grants-in Aid for Scientific Research (no. 08874074) from the Ministry of Education, Science, Sports and Culture of Japan and by the Tokuyama Science Foundation.

Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author. The following data are available as supporting information: a preliminary X-ray crystal structure of **10**, the ROESY NMR spectrum of **11**, and cyclic and differential-pulse voltammograms of **2**, **4**, **5**, **8**, **10**, **11**, and **13–15**.

applied to a wider range of substrates.^[15] To determine the scope and limitations of the electrochemical method, we performed the reaction using a variety of metalloporphyrins that were unsubstituted at the *meso* position, and discovered a surprising dependence of the coupling product on the metal incorporated in the porphyrin ring. When electrolyzed, magnesium(II) (**1**) and zinc(II) 5,15-di(3,5-di-*tert*-butylphenyl)-porphyrin (**2**) produced the corresponding directly linked *meso,meso* dimers shown in Table 1.^[15] In contrast, the copper(II) (**3**), palladium(II) (**4**), and nickel(II) porphyrins (**6**)

Table 1. Electrochemical reactions of metal 5,15-di(3,5-di-*tert*-butylphenyl)porphyrins.

Metal ion	E_{ox} [mV] ^[a] vs. AgNO ₃ /Ag	monomer	Yield [%] ^[b] <i>meso,meso</i> dimer	<i>meso,β</i> dimer
Mg ²⁺	355	34.4 ^[c]	9.2 ^[c]	0.0
Zn ²⁺ ^[d]	540	44.0	20.7	0.0
Cu ²⁺	716	64.6	trace	4.3
Pd ²⁺	750	60.2	0.0	9.2
2H ⁺	765	95.5	trace	2.5
Ni ²⁺	780	70.8	0.0	19.1

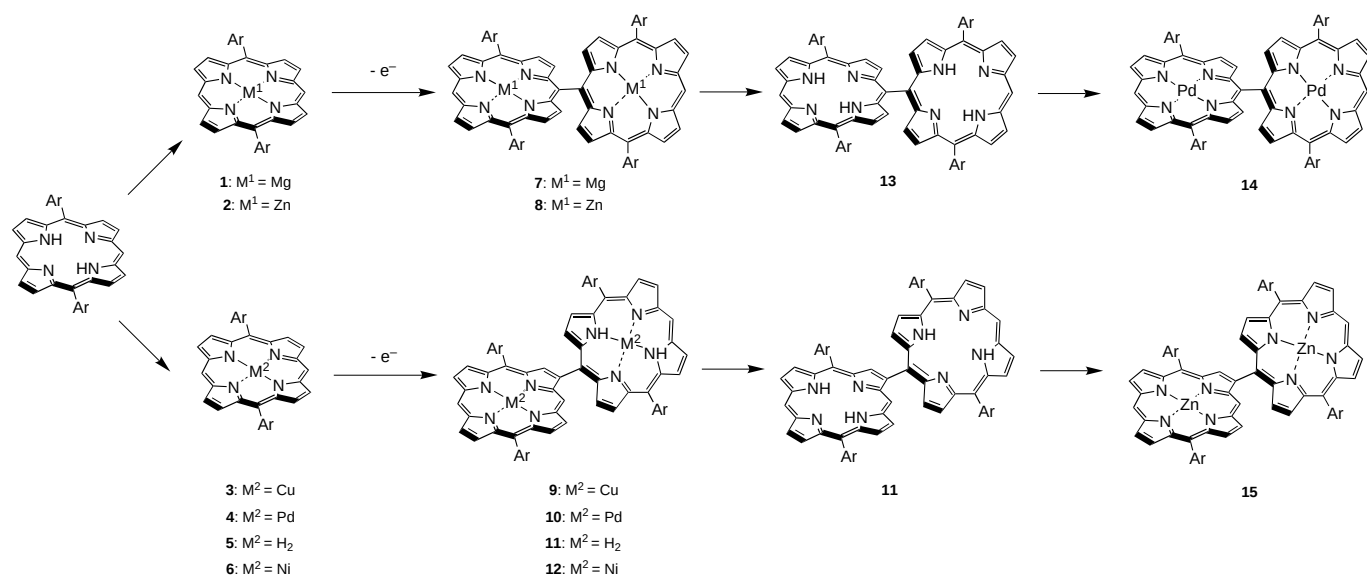
[a] The electrochemical reactions were performed in benzonitrile at the first oxidation potentials cited here. [b] Yields given are for isolated products. The electricity passed was roughly 1.7 equiv of that required for the starting porphyrin. [c] The yields of isolated products were relatively low because of the difficult separation of the products from the electrolyte since the products have similar polarity to the electrolyte. [d] Data from ref. [15]; about 2.5 equiv of the electricity were used.

as well as the free porphyrin base (**5**) produced the corresponding directly linked *meso,β* dimers exclusively (Table 1, Scheme 1). In all the reactions, trace amounts of higher coupling products were detected, although full identifications of these products have not yet been performed. The structures of these unforeseen *meso,β* products were confirmed by FAB mass spectrometry and ¹H NMR and ROESY NMR spectroscopy as well as high-resolution FAB-MS of the metal-free dimer (**11**).

The ¹H NMR spectrum of the products clearly indicated a nonsymmetrical structure. The presence of four singlet peaks in the aromatic region is consistent only with the *meso,β* dimer structure. Of the two possible isomers of the *meso,β* dimers, that depicted in Scheme 1 is consistent with the ROESY NMR spectrum.

The proposed mechanism for the reaction involves the loss of a single electron by the metalloporphyrin followed by nucleophilic attack by a neutral metalloporphyrin. According to the four-orbital model,^[16] when a porphyrin is oxidized to its radical cation, one of the closer orbitals, either A_{1u} or A_{2u}, becomes the magnetic orbital. The orbital involved depends on both the substrates and the central metals.^[17] Gouterman et al. reported that Pd^{II}-TPP and Cu^{II}-TPP (TPP = tetraphenylporphyrin) favor A_{1u} cation radicals, while Zn^{II}-TPP and H₂-TPP favor A_{2u} cation radicals.^[18] Cation radicals in the A_{1u} state will attack the neutral porphyrin at *meso* positions, which are the most nucleophilic carbon atoms, through their β positions. This leads to the formation of *meso,β* porphyrin dimers. Similarly, cation radicals in the A_{2u} state produce *meso,meso* porphyrin dimers. This mechanism is consistent with our results, except for the reaction of **5**. It is worthy to note that the regioselectivity is nearly complete and quite contrasting (*meso,meso* coupling for **1** and **2** and *meso,β* coupling for **4** and **6**). According to Gouterman, the free porphyrin base should favor the A_{2u} cation radical state (*meso*-dominant) over the zinc porphyrin. However, **5** produced *meso,β* dimer **11**, while **2** produced *meso,meso* dimer **8**. A possible interpretation of this result is that the cation radical of the free porphyrin base rapidly loses a proton from an NH group, giving rise to a neutral radical with A_{2u} symmetry. The radical either picks up one hydrogen atom to reform the original porphyrin, or attacks another neutral porphyrin to produce a directly linked *meso,β* dimer. The observed low efficiency of **5** (Table 1) seems to be consistent with this mechanism.

The absorption and fluorescence spectra of the zinc diporphyrins **8** and **15** are shown in Figure 1. The *meso,β*-



Scheme 1. Electrochemical syntheses of the *meso,meso*- and *meso,β*-linked porphyrin dimers **7–15**. Ar = 3,5-di-*tert*-butylphenyl.

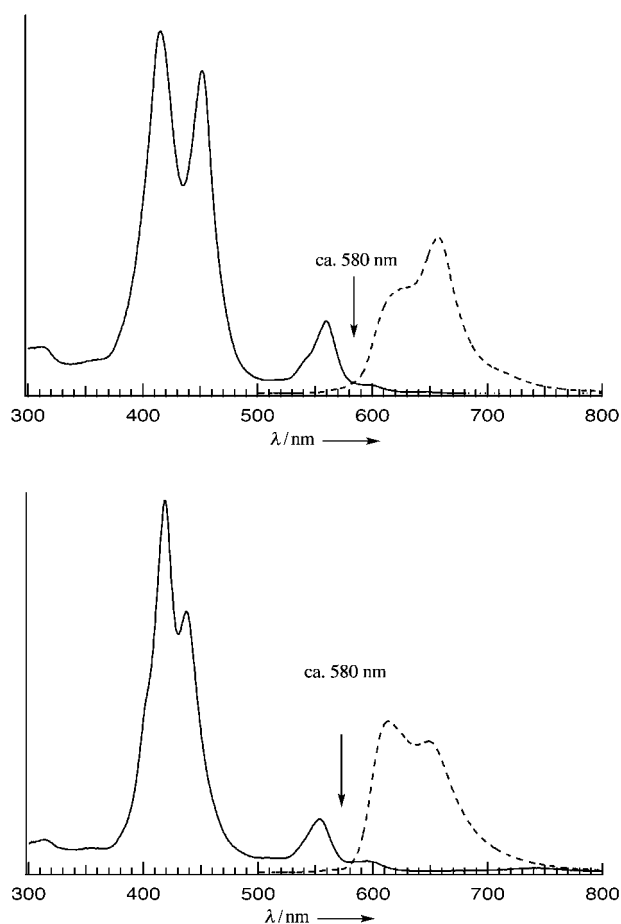


Figure 1. The electronic absorption (—) and emission spectra (---) of the *meso*, β dimer–Zn complex **15** (bottom) and the *meso*,*meso* dimer–Zn complex **8** (top).

linked diporphyrin **15** displays split Soret bands due to the exciton coupling, but its exciton coupling energy (ca. 1265 cm^{-1}) is smaller than that of the *meso*,*meso*-linked diporphyrin **8** (2100 cm^{-1}). In the both cases, the two porphyrin rings are nearly orthogonal, leading to relatively small exciton coupling energies regardless of the direct linkage of the porphyrin. The spectral changes in the Q-band region are also weaker for **15** than for **8**. The energies of the S_1 state estimated on the basis of the absorption and fluorescence spectra are 2.03 and 2.05 eV for **8** and **15**, respectively, and thus smaller than that of reference monomer **2** (2.13 eV). The fluorescence spectra of **8** and **15** are both red-shifted compared with that of **2**, and the shape of the spectra of **15** is more similar to that of **2**. The fluorescence quantum yields of **8** and **15** determined in THF relative to Zn–TPP (0.030) are 0.025 and 0.043, respectively, and the fluorescence lifetime determined by the single photon counting technique are 1.92 and 1.97 ns for **8** and **15**, respectively. Therefore, it may be concluded that the S_1 state of the these directly linked diporphyrins are not so strongly perturbed.

Cyclic and differential-pulse voltammograms have been measured for the monomer porphyrins as well as the *meso*,*meso*-, and *meso*, β -linked diporphyrins to clarify the electronic communications between the two porphyrin rings. For both the free porphyrin base and the palladium porphyr-

ins, the first oxidation potential of the monomeric porphyrins split into two separate waves in the dimeric porphyrins. The separation of the peaks is larger in the *meso*,*meso* dimers than those in the *meso*, β dimers (**5**: 760 mV, **11**: 760 and 800 mV, **13**: 780 and 930 mV, **4**: 800 mV, **10**: 860 and 980 mV, **14**: 860 and 1040 mV). Although the zinc dimers **8** and **15** do not show apparent separation of the oxidation waves, the peaks of the *meso*,*meso* dimer **8** at 560 and 910 mV are broader than the corresponding peaks of **15**.

Since the splitting is caused by the Coulomb interaction between the positive charge in one porphyrin ring of the monocation radical generated in the first oxidation and the electron to be extracted from another porphyrin ring in the second oxidation,^[11] it will depend both on the distance between the two porphyrin rings and on the molecular orbital distribution in each of the rings. The distance between the centers of the porphyrin rings in the *meso*, β dimer was determined to be $8.74\text{ \AA}$ from a preliminary X-ray crystallographic analysis, and that of the *meso*,*meso* dimer was estimated to be about $8.34\text{ \AA}$ from a semiempirical molecular orbital optimization. Thus in all cases the splitting of the *meso*,*meso* dimers with shorter distances between the two rings was larger than that of the *meso*, β dimers. The dependence of the splittings on the central metals may be ascribed to the different distribution of the molecular orbitals.

This electrochemical method is a new, simple way to produce directly linked *meso*,*meso* and *meso*, β porphyrin arrays, which should permit control of the electronic interactions and thus physical properties of multiporphyrin assemblies. Incorporation of these directly linked diporphyrin units into more elaborate photosynthetic models is our next target.

Experimental Section

Typical procedure for the electrochemical dimerization: Porphyrin **6** (200 mg, 0.27 mmol) was electrolyzed in dry benzonitrile (200 mL) in a single cell with tetrabutylammonium perchlorate (0.05 M) as the electrolyte, a platinum net ($1.8 \times 2.4\text{ cm}$) as the counter electrode, and a platinum net ($3 \times 4\text{ cm}$) as the working electrode; the electricity used was 0.55 mF. The porphyrin products were purified by being passed through an alumina and then a silica gel chromatography column, and isolated by preparative-scale HPLC with a gel-permeation chromatography column (GPC-HPLC) to give the *meso*, β -linked dimer **12** and the recovered monomer **6** in yields of 19.1 and 70.8%, respectively. It was possible to utilize open-column gel-permeation chromatography with Bio-Beads S-X1 (BIO-RAD) and chloroform as the eluent instead of GPC-HPLC in the final separation.

12: $^1\text{H NMR}$ (500 MHz, $[\text{D}_6]\text{acetone}$): $\delta = 1.51$ (m, 72H, *t*Bu-H), 7.35 (d, $J = 2.0\text{ Hz}$, 4H, Ar-2,6-H), 7.87 (m, 4H, Ar-2,6-H), 7.95 (d, $J = 1.5\text{ Hz}$, 2H, Ar-4-H), 8.34 (d, $J = 1.5\text{ Hz}$, 2H, Ar-4-H), 8.75 (d, $J = 5.0\text{ Hz}$, 1H, β -H), 8.77 (d, $J = 5.0\text{ Hz}$, 2H, β -H), 8.80 (d, $J = 5.0\text{ Hz}$, 1H, β -H), 8.96 (d, $J = 4.5\text{ Hz}$, 2H, β -H), 8.99 (d, $J = 5.0\text{ Hz}$, 1H, β -H), 9.01 (d, $J = 5.0\text{ Hz}$, 2H, β -H), 9.20 (d, $J = 4.5\text{ Hz}$, 1H, β -H), 9.43 (m, 4H, β -H), 9.50 (d, $J = 5.0\text{ Hz}$, 1H, β -H), 9.79 (s, 1H, *meso*-H), 10.25 (s, 1H, *meso*-H), 10.32 (s, 1H, *meso*-H); FAB MS: m/z : 1485.6 (calcd for $\text{C}_{96}\text{H}_{102}\text{N}_8\text{Ni}_2$: 1484.7); UV/Vis (CHCl_3): $\lambda_{\text{max}} = 410.8, 525.0\text{ nm}$.

9: An NMR spectrum could not be measured because of the paramagnetism of Cu^{II} . FAB MS: m/z : 1494.8 (calcd for $\text{C}_{96}\text{H}_{102}\text{N}_8\text{Cu}_2$: 1494.7); UV/Vis (CHCl_3): $\lambda_{\text{max}} = 412.0, 493.0, 538.4\text{ nm}$. The dimer was demetallated with 10% $\text{H}_2\text{SO}_4/\text{CF}_3\text{COOH}$ ^[7] to give the free base *meso*, β dimer **11** in a yield of 65%.

10: $^1\text{H NMR}$ (500 MHz, CDCl_3): $\delta = 1.48$ (s, 18H, *t*Bu-H), 1.49 (s, 18H, *t*Bu-H), 1.494 (s, 18H, *t*Bu-H), 1.495 (s, 18H, *t*Bu-H), 7.75 (m, 4H, Ar-2,6-H),

8.03 (d, $J = 2.0$ Hz, 4H, Ar-2,6-H), 8.17 (t, $J = 1.8$ Hz, 2H, Ar-4-H), 8.37 (d, $J = 1.5$ Hz, 2H, Ar-4-H), 8.62 (d, $J = 4.5$ Hz, 1H, β -H), 8.81 (d, $J = 5.0$ Hz, 2H, β -H), 8.82 (d, $J = 4.5$ Hz, 1H, β -H), 8.96 (d, $J = 5.0$ Hz, 2H, β -H), 9.08 (d, $J = 5.0$ Hz, 3H, β -H), 9.25 (d, $J = 5.0$ Hz, 1H, β -H), 9.33 (d, $J = 4.5$ Hz, 2H, β -H), 9.34 (d, $J = 4.5$ Hz, 1H, β -H), 9.40 (d, $J = 5.0$ Hz, 1H, β -H), 9.78 (s, 1H, *meso*-H), 9.88 (s, 1H, *meso*-H), 10.31 (s, 1H, *meso*-H), 10.35 (s, 1H, *meso*-H); FAB MS: m/z : 1581.1 (calcd for $C_{96}H_{102}N_8Pd_2$: 1580.6); UV/Vis ($CHCl_3$): $\lambda_{max} = 414.0, 522.2, 549.2, 681.2$ nm.

11: ^1H NMR (500 MHz, $CDCl_3$): $\delta = -2.69$ (s, 1H, N-H), -2.53 (s, 1H, N-H), -2.50 (s, 2H, N-H), 1.49 (s, 18H, *t*Bu-H), 1.50 (s, 18H, *t*Bu-H), 1.506 (s, 18H, *t*Bu-H), 1.512 (s, 18H, *t*Bu-H), 7.76 (m, 4H, Ar-2,6-H), 8.07 (d, $J = 2.0$ Hz, 2H, Ar-2,6-H), 8.09 (t, $J = 1.5$ Hz, 2H, Ar-2,6-H), 8.19 (t, $J = 1.5$ Hz, 2H, Ar-4-H), 8.44 (d, $J = 2.0$ Hz, 2H, Ar-4-H), 8.66 (d, $J = 4.5$ Hz, 1H, β -H), 8.84 (d, $J = 4.5$ Hz, 2H, β -H), 8.88 (d, $J = 4.5$ Hz, 1H, β -H), 8.98 (d, $J = 5.0$ Hz, 2H, β -H), 9.11 (d, $J = 4.5$ Hz, 1H, β -H), 9.13 (d, $J = 4.5$ Hz, 2H, β -H), 9.36 (d, $J = 4.5$ Hz, 1H, β -H), 9.41 (d, $J = 4.5$ Hz, 1H, β -H), 9.42 (d, $J = 4.5$ Hz, 2H, β -H), 9.55 (d, $J = 4.5$ Hz, 1H, β -H), 9.81 (s, 1H, *meso*-H), 9.96 (s, 1H, *meso*-H), 10.33 (s, 1H, *meso*-H), 10.40 (s, 1H, *meso*-H); HR FAB MS: m/z : 1371.8608 (calcd for $C_{96}H_{107}N_8$: 1371.8619); UV/Vis ($CHCl_3$): $\lambda_{max} = 414.8, 431.6, 514.4, 545.6, 583.6$ nm.

13: ^1H NMR (500 MHz, $CDCl_3$): $\delta = -2.31$ (s, 4H, N-H), 1.46 (s, 72H, *t*Bu-H), 7.72 (t, $J = 1.8$ Hz, 4H, Ar-4-H), 8.08 (d, $J = 5.0$ Hz, 4H, β -H), 8.10 (d, $J = 1.8$ Hz, 8H, Ar-2,6-H), 8.66 (d, $J = 5.0$ Hz, 4H, β -H), 9.10 (d, $J = 5.0$ Hz, 4H, β -H), 9.42 (d, $J = 5.0$ Hz, 4H, β -H), 10.34 (s, 2H, *meso*-H); HR FAB MS: m/z : 1370.8542 (calcd for $C_{96}H_{106}N_8$: 1370.8540); UV/Vis ($CHCl_3$): $\lambda_{max} = 412.6, 446.6, 520.0, 589.8, 647.0$ nm.

Received: July 10, 1998 [Z 12125 IE]

German version: *Angew. Chem.* **1999**, *111*, 140–142

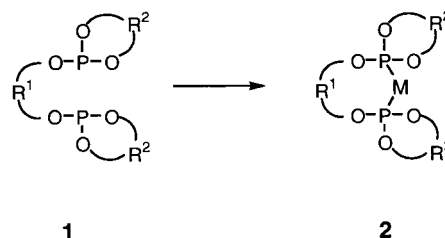
Keywords: electrochemistry • porphyrinoids • synthetic methods

New Diphosphite Ligands for Catalytic Asymmetric Hydrogenation: The Crucial Role of Conformationally Enantiomeric Diols

Manfred T. Reetz* and Torsten Neugebauer

Dedicated to Reinhard W. Hoffman
on the occasion of his 65th birthday

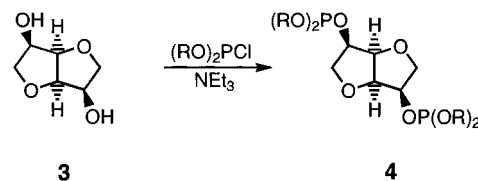
Many chiral diphosphanes^[1] and diphosphinites^[2] have been synthesized as ligands for enantioselective transition metal catalyzed hydrogenations. On the other hand, little is known about chelating, chiral diphosphites as ligands in asymmetric hydrogenations,^[3] although such ligands are increasingly being used in other transition metal catalyzed reactions such as hydrocyanations, hydroformylations, and hydrosilylations.^[4] The availability of many enantiomerically pure diols allows the production of electron-deficient, bidentate phosphite ligands. Topologically different possibilities arise, for example the use of chiral or achiral diols HO-R¹-OH and HO-R²-OH as the backbone or as a component of two P/O heterocycles, as is schematically represented in **1** and **2**. If the backbone is chiral, defined



- [1] M. O. Senge, W. W. Kalisch, K. Ruhlandt-Senge, *Chem. Commun.* **1996**, 2149–2150.
- [2] L. Ruhlmann, A. Giraudeau, *Chem. Commun.* **1996**, 2007–2008.
- [3] A. Giraudeau, L. Ruhlmann, L. E. Kahel, M. Gross, *J. Am. Chem. Soc.* **1996**, *118*, 2969–2979.
- [4] A. Osuka, S. Marumo, N. Mataga, S. Taniguchi, T. Okada, I. Yamazaki, Y. Nishimura, T. Ohno, K. Nozaki, *J. Am. Chem. Soc.* **1996**, *118*, 155–168.
- [5] A. Osuka, S. Nakajima, T. Okada, S. Taniguchi, K. Nozaki, T. Ohno, I. Yamazaki, Y. Nishimura, N. Mataga, *Angew. Chem.* **1996**, *108*, 98–101; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 92–95.
- [6] A. P. H. Schenning, F. B. G. Benneker, H. P. M. Geurts, X. Y. Liu, R. J. M. Nolte, *J. Am. Chem. Soc.* **1996**, *118*, 8549–8552.
- [7] K. Susumu, T. Shimidzu, K. Tanaka, H. Segawa, *Tetrahedron Lett.* **1996**, *37*, 8399–8402.
- [8] S. Prathapan, T. E. Johnson, J. S. Lindsey, *J. Am. Chem. Soc.* **1993**, *115*, 7519–7520.
- [9] V. S.-Y. Lin, S. G. Dimagno, M. J. Therien, *Science* **1994**, *264*, 1105–1111.
- [10] V. S.-Y. Lin, M. J. Therien, *Chem. Eur. J.* **1995**, *1*, 645–651.
- [11] J. Y. Becker, D. Dolphin, J. B. Paine, T. Wijesekera, *J. Electroanal. Chem.* **1984**, *164*, 335–346.
- [12] M. R. Wasielewski, D. G. Johnson, M. P. Niemczyk, I. G. L. Gaines, M. P. O'Neil, W. A. Svec, *J. Am. Chem. Soc.* **1990**, *112*, 6482–6488.
- [13] K. Susumu, Dissertation, Kyoto University (Japan), **1996**.
- [14] A. Osuka, H. Shimidzu, *Angew. Chem.* **1997**, *109*, 93–95; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 135–137.
- [15] T. Ogawa, Y. Nishimoto, N. Yoshida, N. Ono, A. Osuka, *Chem. Commun.* **1998**, 337–338.
- [16] M. Gouterman, *The Porphyrins, Vol. III*, Academic Press, New York, **1978**.
- [17] C. M. Barzilay, S. A. Sibilia, T. G. Spiro, Z. Gross, *Chem. Eur. J.* **1995**, *1*, 222–231.
- [18] P. J. Spellane, M. Gouterman, A. Antipas, S. Kim, Y. C. Liu, *Inorg. Chem.* **1980**, *19*, 386–391.

local chirality in the P/O heterocycle of the transition metal catalyst **2** may be possible even when seemingly achiral diols such as *meso*-1,2-cyclohexanediol^[5] or diphenol serve as the second component. In such cases the catalyst exists in the form of three rapidly interconverting conformational diastereomers, one of which could kinetically control the reaction. It is therefore possible that the conformationally enantiomeric diols in the P/O heterocycle play a crucial role in determining the direction as well as the extent of enantioselectivity in hydrogenation reactions.^[6] Herein we describe the first examples of such a phenomenon.

As the chiral diol for the backbone we chose the easily accessible and commercially available *C*₂-symmetric 1,4:3,6-dianhydro-D-mannite (**3**),^[7] which exhibits a vaultlike geom-



[*] Prof. M. T. Reetz, Dipl.-Chem. T. Neugebauer
Max-Planck-Institut für Kohlenforschung
Kaiser-Wilhelm-Platz 1, D-45470 Mülheim an der Ruhr (Germany)
Fax: (+49) 208-306-2985
E-mail: reetz@mpi-muelheim.mpg.de

Table 1. Synthesis of the chelating ligands **4**.

(RO) ₂ PCl	Chelating ligand	Yield [%]
	4a	62
	4b	87
	4c	96
	4d	99
	4e	89
	4f	99
	4g	86

etry with two hydroxyl groups on the concave side. Reactions with chlorophosphoric acid diaryl ester (2 equiv each) provide access to many different ligands of type **4** (Table 1).

The Rh-catalyzed hydrogenation of dimethyl itaconate (**5**) was examined as the model reaction (Table 2). When the ligand **4a** with two achiral β -naphthoxy residues at each phosphorus center is used, the reactions at room temperature provide (*S*)-**6** with an *ee* value of only 21%. Clearly, the transfer of the chiral information present in the backbone of the catalyst onto the product is inefficient. The catalysts derived from ligands **4b** and **4c** which contain (*S*)- and (*R*)-binaphthol, respectively, in the P/O heterocycle behave differently. The *ee* values of 88% and 95% attained for (*S*)- and (*R*)-**6**, respectively, prove that the chirality in the P/O heterocycles is decisive and that the *R*-selective combination **3**/(*R*)-binaphthol is the matched case.^[8] This is no contradiction to the fact that the rhodium catalyst from **4a** is weakly

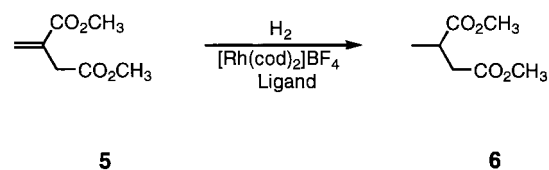


Table 2. Enantioselective hydrogenation of **5** and **8**.

Ligand ^[a]	Substrate	<i>T</i> [°C]	Conversion [%]	<i>ee</i> [%]	Config.
4a ^[b]	5	20	65	21.0	(<i>S</i>)- 6
4b ^[c]	5	20	> 99	87.8	(<i>S</i>)- 6
4c ^[c]	5	20	> 99	94.5	(<i>R</i>)- 6
4c	5	−10	> 99	96.2	(<i>R</i>)- 6
4d ^[c]	5	20	74	38.9	(<i>S</i>)- 6
4e	5	20	> 99	96.8	(<i>R</i>)- 6
4e	5	−10	> 99	98.2	(<i>R</i>)- 6
4f ^[d]	5	20	24	5.2	(<i>R</i>)- 6
4g	5	20	> 99	49.3	(<i>R</i>)- 6
4a	8	20	66	43.8	(<i>S</i>)- 9
4b	8	20	77	23.2	(<i>S</i>)- 9
4c	8	20	> 99	88.8	(<i>R</i>)- 9
4e	8	20	> 99	80.7	(<i>R</i>)- 9

[a] General conditions: substrate:catalyst (s:c) = 1000:1; *t* = 20 h; ligand:rhodium = 1:1. [b] s:c = 500:1. [c] The catalysis was carried out with preformed catalyst. [d] s:c = 250:1.

S-selective (21% *ee*), since the spatial position of the naphthyl groups in **4a** with respect to the catalytically active center is probably not fixed.

In the case of ligands with atropoisomeric biphenol units in the P/O heterocycle, three defined diastereomeric metal complexes are possible (*R/R*, *S/S*, and *R/S* combinations in the biphenol moieties) which can rapidly interconvert due to the energetically low barrier^[9] for rotation about the biaryl axis. In the case of the unsubstituted biphenol derivative **4d** an *ee* value of only 39% is reached in the production of (*S*)-**6**. In contrast, ligand **4e** with *ortho* methyl groups shows an entirely different behavior, leading almost exclusively to the *R* enantiomer (*ee* = 96–98%)! Evidently, one diastereomer of the three possible complexes determines the reaction. Under the assumption that the configurations of the binaphthol and the 2,2'-dihydroxy-3,3'-dimethyl-1,1'-biphenyl units in the respective catalysts induce the same direction of enantioselectivity, it can be concluded that the most active and therefore reaction-determining catalyst contains P/O heterocycles having the *R/R* configuration. Moreover, it was observed that hydrogenations with **4c** are significantly faster than those with **4b**, and that the most active catalyst is formed with **4e**.^[10] Therefore, pronounced in situ selection between conformationally diastereomeric catalysts take place in reactions based on **4e**.^[11] Interestingly, **4f** with sterically demanding *tert*-butyl groups leads to low activity as well as poor enantioselectivity.

Finally, **4g** was tested in the Rh-catalyzed hydrogenation. In this reaction (*R*)-**6** was obtained with an *ee* value of 50%. Thus, when going from **4d** to **4g**, reversal of the direction of enantioselectivity is effected while retaining the backbone diol **3**. In the case of **4g** several chiral conformers of the P/O heterocycle are possible which are in fast equilibrium. Force-field calculations of the P/O heterocycles with hydrogen bonded to the phosphorus centers as model compounds identified the enantiomeric structures **7a** and **7b** (Figure 1) to be equivalent energetic minima.^[12] In the metal complex, they therefore lead to local chirality close to the catalytically active center, as in the case of the catalyst based on **4e**. Similar effects were also observed in the hydrogenation of methyl *N*-

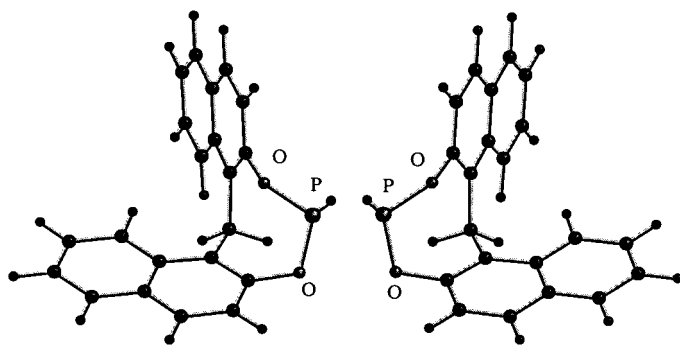
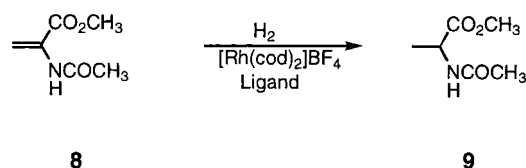


Figure 1. The enantiomers **7a** (left) and **7b** (right) generated from force-field calculations of the P/O-heterocycles with hydrogen at the phosphorus centers as model compounds.

acetamidoacrylate (**8**) with formation of the alanine derivative **9** (Table 1, cod = 1,5-cyclooctadiene).



In summary, we have described the first diphosphite ligands capable of inducing highly enantioselective hydrogenations. Significantly, the ligand **4e** with conformational flexibility in readily epimerizing diastereomeric P/O heterocycles proved superior to those with fixed chirality (binaphthol derivatives). This principle presents the opportunity to synthesize efficient ligands for asymmetric catalysis from chiral auxiliaries and suitable conformationally enantiomeric compounds. The advantage is that the chiral selectivity-determining ligand need not (and cannot) be separated into antipodes. Research concerning other substrates and the use of the ligands in other metal-catalyzed reactions is the subject of further investigations.

Experimental Section

4e: Under an inert atmosphere, the chlorophosphoric acid diaryl ester (0.408 g, 1.46 mmol) from 2,2'-dihydroxy-3,3'-dimethyl-1,1'-biphenyl was dissolved in THF (120 mL) and treated with triethylamine (0.40 mL, 2.9 mmol). To this slightly cloudy solution, **3** (0.107 g, 0.732 mmol) in THF (15 mL) was slowly added with stirring. After 3 h of stirring at room temperature, half of the solvent was removed under reduced pressure, the precipitate was removed by filtration, and all solvent was removed from the clear filtrate in vacuo. The yellow solid was dried under high vacuum. Yield: 0.41 g (89%). ^1H NMR (81 MHz, CDCl_3): δ = 134.4 (s).

Hydrogenations: In a Schlenk vessel, an aliquot (0.5 mL) of a 2×10^{-3} M solution of the ligand in CH_2Cl_2 is added to a 2×10^{-3} M solution of $[\text{Rh}(\text{cod})_2]\text{BF}_4$ in CH_2Cl_2 (0.5 mL) under inert conditions. The mixture is stirred for 5 min at room temperature. Subsequently, dimethyl itaconate (1.0 mmol) in CH_2Cl_2 (9.0 mL) is added, and the vessel is briefly evacuated and vented with H_2 three times in order to remove dissolved argon. The mixture is then hydrogenated (0.3 bar H_2) for 20 h at 20 °C. To remove the catalyst, the solution is placed on a short silica gel column and eluted with CH_2Cl_2 . Conversion and enantiomeric excess is determined by means of gas chromatography. The absolute configuration of the products was determined by comparison with a commercially available sample of dimethyl (*R*)-methylsuccinate.

Received: June 18, 1998 [Z12009IE]
German version: *Angew. Chem.* **1999**, *111*, 134–137

Keywords: asymmetric hydrogenations • chirality • homogeneous catalysis • P ligands • rhodium

- [1] a) H. Brunner, W. Zettelmeyer, *Handbook of Enantioselective Catalysis with Transition Metal Compounds*, Vol. I, II, VCH, Weinheim, **1993**; b) R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, **1994**.
- [2] a) A. S. C. Chan, W. Hu, C.-C. Pai, C.-P. Lau, *J. Am. Chem. Soc.* **1997**, *119*, 9570–9571; b) T. V. RajanBabu, T. A. Ayers, G. A. Halliday, K. K. You, J. C. Calabrese, *J. Org. Chem.* **1997**, *62*, 6012–6028; c) R. Selke, *J. Organomet. Chem.* **1989**, *370*, 249–256.
- [3] Brunner and Wink used chiral diphosphite ligands based on carbohydrates and tartaric acid derivatives in Rh-catalyzed hydrogenations and obtained *ee* values of 1–34%: a) H. Brunner, W. Pieronczyk, *J. Chem. Res. Synop.* **1980**, 76; b) D. J. Wink, T. J. Kwok, A. Yee, *Inorg. Chem.* **1990**, *29*, 5006–5008.
- [4] See, for example, a) M. J. Baker, P. G. Pringle, *J. Chem. Soc. Chem. Commun.* **1991**, 1292–1293; b) N. Sakai, K. Nozaki, K. Mashima, H. Takaya, *Tetrahedron: Asymmetry* **1992**, *3*, 583–586; c) T. J. Kwok, D. J. Wink, *Organometallics* **1993**, *12*, 1954–1959; d) B. Moasser, W. L. Gladfelter, *Inorg. Chim. Acta* **1996**, *242*, 125–136; e) G. J. H. Buisman, L. A. van der Veen, A. Klootwijk, W. G. J. de Lange, P. C. J. Kamer, P. W. N. M. van Leeuwen, D. Vogt, *Organometallics* **1997**, *16*, 2929–2939; f) R. Kadyrov, D. Heller, R. Selke, *Tetrahedron: Asymmetry* **1998**, *9*, 329–340; g) E. Yu. Zhorov, K. N. Gavrilov, V. A. Pavlov, A. T. Teleshev, É. E. Nifant'ev, E. I. Klabunovskii, *Izv. Akad. Nauk SSSR Ser. Khim.* **1990**, 1451–1452; h) J. Sakaki, W. B. Schweizer, D. Seebach, *Helv. Chim. Acta* **1993**, *76*, 2654–2665.
- [5] *meso* Compounds such as *cis*-1,2-dimethylcyclohexane exist in the form of two chiral conformational enantiomers that rapidly interconvert: E. L. Eliel, S. H. Wilen, L. N. Mander, *Stereochemistry of Organic Compounds*, Wiley, New York, **1994**.
- [6] A few examples of ligands with a chiral backbone and additional biphenol units which are not stereochemically fixed have recently been described for hydroformylations. However, the direction of asymmetric induction is determined exclusively by the chiral backbone.^[4e,f] See also K. Nozaki, N. Sakai, T. Nanno, T. Higashijima, S. Mano, T. Horiuchi, H. Takaya, *J. Am. Chem. Soc.* **1997**, *119*, 4413–4423.
- [7] a) P. Stoss, R. Hemmer, *Adv. Carbohydr. Chem. Biochem.* **1992**, *49*, 93–173; b) Bakos et al. synthesized the corresponding 2,5-bis(diphenylphosphino)idite from ditosylated 1,4:3,6-dianhydro-D-mannite by means of double nucleophilic substitution under inversion of configuration with lithium diphenylphosphide and used this nonchelating diphosphane in the asymmetric Rh-catalyzed hydrogenation (*ee* = 21–58%): J. Bakos, B. Heil, L. Marko, *J. Organomet. Chem.* **1983**, *253*, 249–252.
- [8] These results were obtained with preformed catalysts. If the hydrogenation is carried out with catalysts formed in situ, no differences in selectivity are observed. Both ligands lead to similarly high conversions and selectivities, the results for the *S*-selective ligand **4b** being subject to variation: **4b** (conversion 73–98%; *ee* = 89–95% (*S*)); **4c** (conversion > 99%; *ee* = 93.5% (*R*)). In contrast, the hydrogenation with **4e** leads to identical results with catalyst formed in situ and with preformed catalyst.
- [9] S. D. Pastor, S. P. Shum, R. K. Rodebaugh, A. D. Debellis, F. H. Clarke, *Helv. Chim. Acta* **1993**, *76*, 900–914.
- [10] Detailed kinetic studies are under way in cooperation with T. Rosner and D. Blackmond (Max-Planck-Institut für Kohlenforschung).
- [11] Low-temperature ^{31}P NMR studies of **4e** showed that three diastereomers occur. At room temperature the spectrum contains one single ^{31}P NMR signal.
- [12] The force-field calculations were carried out with the SYBYL program (Tripos Ass. Inc.). Other than the lowest energy pair of enantiomers **7a/7b**, no minimum was found for an achiral conformer. We thank Dr. K. Angermund for performing the calculations.

A Tricyclic, Organometallic Cage Molecule with a Tetraaminoethane Unit**

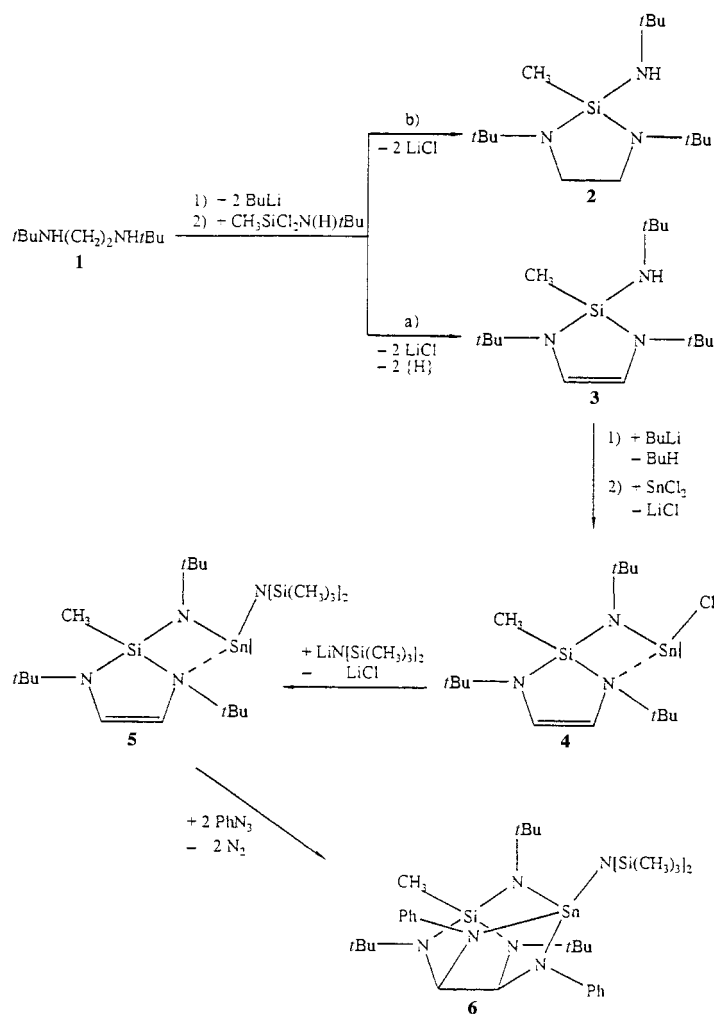
Michael Veith,* Bernhard Schillo, and Volker Huch

Dedicated to Professor Peter Jutzi
on the occasion of his 60th birthday

Organyl nitrenes, accessible by the thermal decomposition of organyl azides, are known to react readily with both carbon π bonds and carbene analogues of type R_2E ($E = Ge, Sn$),^[1, 2] yielding respectively cycloaminopropanes^[3] and germa- and stannazenes.^[4] Both types of product are reactive and are generally stable only under certain conditions (low temperature or sterically demanding ligands). Therefore, stannazenes with insufficient steric protection are known to react further with the organyl azide to form the corresponding stannatetrazoles.^[5] It seemed to us an attractive idea to combine within a single molecule both a reactive π bond and a stannylene unit, so as to trigger further reactions through steric immobilization of the two reaction centers, thereby leading perhaps to novel, otherwise inaccessible interatomic linkages. The strategy presented herein should also be transferable to other systems.

We selected the compound **5**, which contains both reaction centers and, as shown in Scheme 1, can be constructed by a multistep reaction sequence. In **5** the π system and the stannylene moiety are held together at a defined distance through the $-N(tBu)Si(Me)[tBuN-]_2$ group. In the synthesis of **5** the following should be noted: a) The ethylenediamine derivative **1** must undergo reaction with butyllithium and $Cl_2Si(Me)N(H)tBu$ in concentrated solution in order to obtain the 1,3-diaza-2-silacyclopentene **3**. b) If the reaction is carried out in a more dilute solution, the cyclopentane **2** is formed.^[6] The cause of the hydrogen abstraction from the ethylene moiety in the formation of **3** is unclear; similar behavior has been observed in other analogous reactions of ethylenediamines.^[7] Both spectroscopic data and X-ray crystallography confirm the presence of a $C=C$ bond in **3** (Figure 1).

Compound **3** can be converted by a classical reaction sequence into the tin(II) compound **4**, which is in turn converted into **5** through a $Cl/N(SiMe_3)_2$ exchange. We were able to obtain single crystals of **4**, and its crystal structure has been determined. As can be seen from Figure 2, the tin(II) atom is bonded to three different ligands—quadruply (N1) and triply coordinated nitrogen atoms (N2) and a chlorine atom. Two enantiomers of the compound crystallize together in a centrosymmetric crystal structure (with chirality centers at Si and N1 as well as at the Sn atom^[6]). The bond lengths and angles in **4** are within the expected range.^[8] The NMR spectra of **4** and **5** in solution show that the chirality centers in both compounds are clearly not stable towards intramolecular Lewis acid–base reactions in either compound. This can be



Scheme 1. a) Concentrated solution; b) dilute solution.

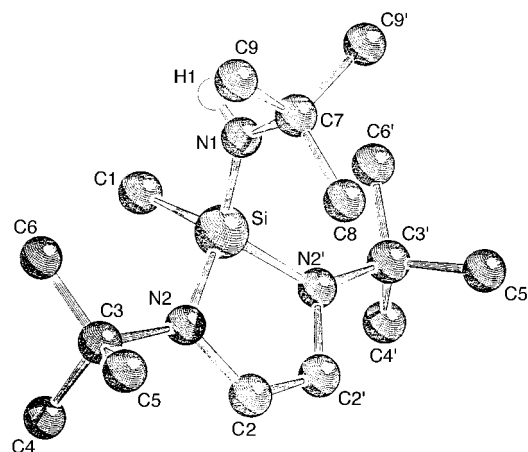


Figure 1. Ball-and-stick representation of the structure of **3** in the crystal.^[8] Important bond lengths [Å] and angles [°]: Si–N1 1.679(6), Si–N2 1.721(4), N2–C2 1.402(5), C2–C2' 1.310(9); N1–Si–N2 116.3(2), N2–Si–N2' 92.1(3), C2–N2–Si 109.4(3), C2'–C2–N2 114.6(2).

explained by the two nitrogen atoms of the enediamine moiety competing with each another for coordination to the metal atom (see the number of ^1H , ^{13}C , and ^{15}N signals (Experimental Section)). Moreover, the crystal structure

[*] Prof. Dr. M. Veith, Dipl.-Chem. B. Schillo, Dr. V. Huch
Institut für Anorganische Chemie der Universität
Postfach 15 11 50, D-66041 Saarbrücken (Germany)
Fax: (+49) 681-302-3995
E-mail: veith@rz.uni-sb.de

[**] This work was supported by the Fonds der Chemischen Industrie and by the Deutsche Forschungsgemeinschaft.

5: To a solution of **4** (2.97 g, 6.8 mmol) in benzene (20 mL) was added dropwise a solution of $\text{LiN}(\text{SiMe}_3)_2$ (1.14 g, 6.8 mmol) in benzene (30 mL). After being stirred for 14 h the mixture was filtered, and the solvent was condensed off. The yellow-brown oil obtained crystallized after 12 h. Recrystallization from hexane gave 2.37 g (62%) of light yellow crystals. Correct elemental analysis; ^1H NMR: $\delta = 0.50$ (s, 18H, $\text{N}(\text{SiMe}_3)_2$), 0.71 (s, 3H, SiMe), 1.13 (s, 18H, $\text{N}(\text{SiMe}_3)_2$), 1.28 (s, 9H, $\text{N}(\text{SiMe}_3)_2$), 5.67 (s, 2H, CH) $^3\text{J}(\text{H}, ^{117/119}\text{Sn}) = 5.6$ Hz; ^{13}C NMR: $\delta = 7.59$ (s, $\text{N}(\text{SiMe}_3)_2$), 9.21 (s, SiMe), 29.71 (s, $\text{NC}(\text{CH}_3)_3$), 35.50 (s, $\text{NC}(\text{CH}_3)_3$), 52.26 (s, $\text{NC}(\text{CH}_3)_3$), 54.74 (s, $\text{NC}(\text{CH}_3)_3$), 118.15 (s, CH); ^{15}N NMR: $\delta = -289.8$ (s, $\text{N}(\text{SiMe}_3)_2$); ^{29}Si NMR: $\delta = -15.70$ (s, SiMe), $^2\text{J}(\text{Si}, ^{117/119}\text{Sn}) = 20.6$ Hz, -0.77 (s, $\text{N}(\text{SiMe}_3)_2$), $^2\text{J}(\text{Si}, ^{117/119}\text{Sn}) = 54.4/19.2$ Hz; ^{119}Sn NMR: $\delta = 205.2$ (s, NSnN , $b_{1/2} = 774$ Hz).

6: To a solution of **5** (0.258 g, 0.459 mmol) in benzene (20 mL) was added dropwise phenyl azide (0.109 g, 0.919 mmol). The solution rapidly turned red with the evolution of gas. After the mixture was stirred for 2 h the solvent was removed, and the residue recrystallized from hexane to give 0.27 g (78%) of light yellow crystals. Correct elemental analysis; ^1H NMR: $\delta = 0.14$ (s, 18H, $\text{N}(\text{SiMe}_3)_2$), 0.77 (s, 3H, SiMe), 1.17 (s, 18H, $\text{N}(\text{SiMe}_3)_2$), 1.56 (s, 9H, $\text{N}(\text{SiMe}_3)_2$), 5.42 (s, 2H, CH, $^3\text{J}(\text{H}, ^{117/119}\text{Sn}) = 57.8/60.4$ Hz), 6.85–7.26 (m, 10H, C_6H_5); ^{13}C NMR: $\delta = 4.97$ (s, $\text{N}(\text{SiMe}_3)_2$), $^3\text{J}(\text{C}, ^{117/119}\text{Sn}) = 28.0$ Hz), 8.89 (s, SiMe), $^3\text{J}(\text{C}, ^{117/119}\text{Sn}) = 15.9$ Hz), 31.95 (s, $\text{NC}(\text{CH}_3)_3$), 36.92 (s, $\text{NC}(\text{CH}_3)_3$), $^3\text{J}(\text{C}, ^{117/119}\text{Sn}) = 15.3$ Hz), 52.48 (s, $\text{NC}(\text{CH}_3)_3$), 54.95 (s, $\text{NC}(\text{CH}_3)_3$), $^2\text{J}(\text{C}, ^{117/119}\text{Sn}) = 14.4$ Hz), 79.37 (s, CH, $^2\text{J}(\text{C}, ^{117/119}\text{Sn}) = 15.9$ Hz), 121.20 (s, NC_6H_5), $^5\text{J}(\text{C}, ^{117/119}\text{Sn}) = 4.7$ Hz), 125.57 (s, NC_6H_5), $^4\text{J}(\text{C}, ^{117/119}\text{Sn}) = 12.3$ Hz), 128.49 (s, NC_6H_5), 152.29 (s, NC_6H_5), $^2\text{J}(\text{C}, ^{117/119}\text{Sn}) = 8.3$ Hz); ^{15}N NMR: $\delta = -270.3$ (s, $\text{N}(\text{SiMe}_3)_2$), -294.9 (s, $\text{N}(\text{SiMe}_3)_2$), -336.2 (s, NC_6H_5); ^{29}Si NMR: $\delta = -8.33$ (s, SiMe), $^2\text{J}(\text{Si}, ^{117/119}\text{Sn}) = 22.4$ Hz), 8.37 (s, $\text{N}(\text{SiMe}_3)_2$), $^2\text{J}(\text{Si}, ^{117/119}\text{Sn}) = 28.0/7.4$ Hz); ^{119}Sn NMR: $\delta = -175.3$ (s, NSnN).

Received: June 29, 1998 [Z12063]

German version: *Angew. Chem.* **1999**, *111*, 131–134

Keywords: carbene analogues • cage compounds • multi-component reactions • nitrenes • nitrogen heterocycles

AED2 four circle diffractometer, $T = 293(2)$ K, $2.14 \leq \theta \leq 24.00^\circ$, 3230 symmetry-independent reflections, no restrictions, 194 parameters; for solution and refinement see details given for **3**, $R1 = 0.0395$, $wR2 = 0.0986$. **6:** $\text{C}_{33}\text{H}_{60}\text{N}_6\text{Si}_3\text{Sn}$, $M_r = 743.83$, monoclinic, space group $P2_1/c$, $a = 1856.4(4)$, $b = 1045.9(2)$, $c = 2196.3(4)$ pm, $\beta = 93.15(3)^\circ$, $V = 4258(2) \times 10^6$ pm³, $Z = 4$, $\rho_{\text{calcd}} = 1.160$ g cm⁻³, $F(000) = 1568$, Stoe-AED2 four circle diffractometer, $T = 293(2)$ K, $2.69 \leq \theta \leq 28.38^\circ$, 10050 symmetry-independent reflections ($R_{\text{int}} = 0.0504$), no restrictions, 388 parameters for solution and refinement see details given for **3**, $R1 = 0.0600$, $wR2 = 0.1831$. Crystallographic data (excluding structure factors) of the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-103341, 103342, and 103343. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

- [9] N. Li, S. Maluendes, R. H. Blessing, M. Dupuis, G. R. Moss, G. T. DeTitta, *J. Am. Chem. Soc.* **1994**, *116*, 6494.
- [10] W. M. Koppes, M. Chaykovsky, H. G. Adolph, R. Gilardi, C. George, *J. Org. Chem.* **1987**, *52*, 1113.
- [11] P. Böttcher, H. Buchkremer-Hermanns, W. Hönle, H. G. von Schnering, *Z. Kristallogr.* **1987**, *181*, 223.
- [12] D. S. C. Black, D. C. Craig, M. Kassiou, R. W. Read, *Aust. J. Chem.* **1991**, *44*, 143.
- [13] A. Batsanov, J. C. Cole, M. R. Crampton, J. Hamid, J. A. K. Howard, R. Millar, *J. Chem. Soc. Perkin Trans. 2* **1994**, 421.
- [14] J. L. Flippen-Anderson, M. Kony, I. J. Dagley, *Acta Crystallogr. Sect. C* **1994**, *50*, 974.
- [15] V. L. Himes, C. R. Hubbard, A. D. Mighell, A. J. Fatiadi, *Acta Crystallogr. Sect. B* **1978**, *34*, 3102.

N,N*-Phthaloylamino Acids as Chiral Auxiliaries in Asymmetric Mannich-Type Reactions*

Roland Müller, Helmut Goesmann, and Herbert Waldmann*

Dedicated to Professor Janos Rétey on the occasion of his 65th birthday

The Mannich reaction is one of the most important methods of organic synthesis. It provides a powerful tool for instance for the construction of β -amino ketones and β -amino acids that are versatile building blocks in the preparation of biologically important compounds^[1] and their analogues (for example β -peptides^[2]). Therefore, the development of methods that allow this transformation to be carried out asymmetrically is of great importance to organic synthesis, and diastereo-^[3] and enantioselective^[3a, 4] Mannich-type processes have attracted considerable attention. Herein we report that a very high level of stereoselectivity (diastereomeric ratio of

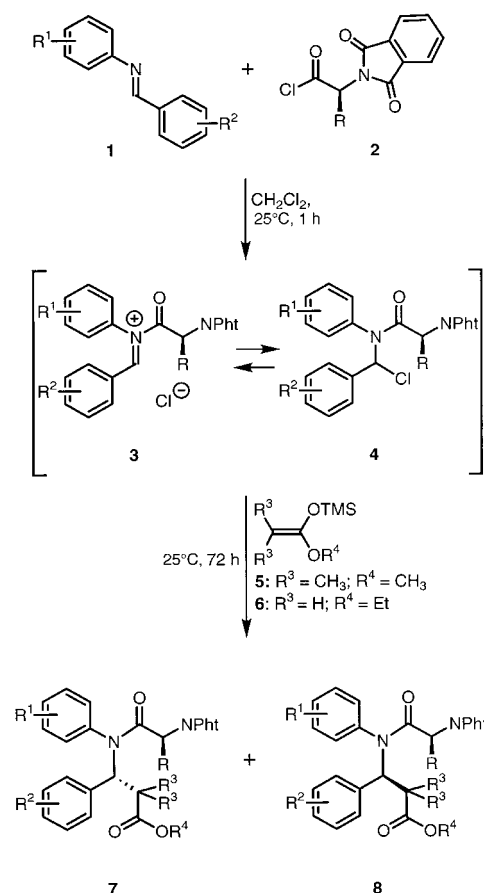
- [1] A. Hassner, *Methoden Org. Chem. (Houben-Weyl) 4th ed.* 1952–, Vol. E16a, **1990**, p. 1243.
- [2] W. P. Neumann, *Chem. Rev.* **1991**, *91*, 311.
- [3] K. Alder, F. H. Flock, A. Hausweiler, R. Roeber, *Chem. Ber.* **1954**, *87*, 1752.
- [4] a) M. Veith, S. Becker, V. Huch, *Angew. Chem.* **1990**, *102*, 186; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 216; b) A. Meller, G. Ossig, W. Maringgele, D. Stalke, R. Herbst-Irmer, S. Freitag, G. M. Sheldrick, *J. Chem. Soc. Chem. Commun.* **1991**, 1123; c) C. Glidewell, D. Lloyd, K. W. Lumbar, J. S. McKechnie, *J. Chem. Soc. Dalton Trans.* **1987**, 2981; d) W. Ando, T. Ohtaki, Y. Kabe, *Organometallics* **1994**, *13*, 434; e) G. Ossig, A. Meller, S. Freitag, R. Herbst-Irmer, *J. Chem. Soc. Chem. Commun.* **1993**, 497; f) T. Ohtaki, Y. Kabe, W. Ando, *Heteroatom Chem.* **1994**, *5*, 313.
- [5] a) W. P. Neumann, R. C. Obloh, *Bull. Soc. Chim. Belg.* **1991**, *100*, 145; b) H. Grützmacher, H. Pritzkow, *Angew. Chem.* **1991**, *103*, 976; *Angew. Chem. Int. Ed. Engl.* **1990**, *30*, 216; c) N. Wiberg, S. K. Vasisht, *Angew. Chem.* **1991**, *103*, 105; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 93.
- [6] M. Veith, A. Rammo, *Z. Anorg. Allg. Chem.* **1997**, 623, 861.
- [7] H. Schmidbaur, W. Hiller, A. Sladek, T. Schlosser, *Z. Naturforsch. B* **1994**, *49*, 1247.
- [8] Crystal structure analyses: **3**: $\text{C}_{15}\text{H}_{33}\text{N}_3\text{Si}$, $M_r = 283.53$, orthorhombic, space group $Pnma$, $a = 938.8(6)$, $b = 1693.0(14)$, $c = 1132.4(9)$ pm, $V = 1800(2) \times 10^6$ pm³, $Z = 4$, $\rho_{\text{calcd}} = 1.046$ g cm⁻³, $F(000) = 632$, Stoe-AED2 four circle diffractometer, $T = 193(2)$ K, $2.16 \leq \theta \leq 19.99^\circ$, 775 symmetry-independent reflections, no restrictions, 76 parameters; solved by direct methods (SHELXS86), refinement (SHELXL-93) with anisotropic temperature factors for all non-hydrogen atoms, hydrogen atoms located geometrically, $R_1 = 0.0557$, $wR_2 = 0.1442$. **4**: $\text{C}_{15}\text{H}_{32}\text{ClN}_3\text{SiSn}$, $M_r = 436.67$, monoclinic, space group $P2_1/n$, $a = 1125.7(12)$, $b = 1441.6(14)$, $c = 1273.7(11)$ pm, $\beta = 96.10(8)^\circ$, $V = 2055(4) \times 10^6$ pm³, $Z = 4$, $\rho_{\text{calcd}} = 1.411$ g cm⁻³, $F(000) = 896$, Stoe-

[*] Prof. H. Waldmann, Dipl.-Chem. R. Müller
Institut für Organische Chemie der Universität
Richard-Willstätter-Allee 2, D-76128 Karlsruhe (Germany)
Fax: (+49) 721-608-425
E-mail: waldmann@ochhades.chemie.uni-karlsruhe.de
Dr. H. Goesmann
Institut für Anorganische Chemie der Universität Karlsruhe

[**] This research was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

more than 99:1) is reached in Mannich-type reactions with *N,N*-phthaloylamino acids as removable chiral auxiliary groups.

If Schiff bases **1** are treated with *N,N*-phthaloyl-protected amino acid chlorides **2** and the silylketene acetals **5** or **6** at room temperature the *N*-acylated β -amino acid esters **7** and **8** are formed in a smooth reaction in moderate to high yields and with good to excellent diastereomer ratios (Scheme 1, Table 1). Presumably the reaction proceeds by the attack of



Scheme 1. Asymmetric Mannich reactions with *N,N*-phthaloylamino acids as the chiral auxiliaries.

the acid chlorides on the nitrogen atom of the C=N bond to give rise to *N*-acyliminium intermediates **3**, which are then attacked by the nucleophile **5** or **6** at the electrophilic carbon atom of the C=N bond. We assume that prior to the nucleophilic attack the *Z*-imines **1** are converted into the *E*-iminium salts **3** by the addition and re-elimination of the chloride ion, that is by intermediary formation of chloroalkylamides **4**.^[6] Unfavorable steric interactions between the amino acid side chain (or the *N*-phthaloyl (NPhT) group) and the aryl group linked to the imine carbon atom are thereby avoided (Scheme 1).

In a first series of experiments with the silylketene acetal **5** the factors that influence the efficiency of the stereoselection were determined. The stereoselectivity increases with an increase in the steric demand of the amino acid side chain, with Pht-alanine and Pht-valine being clearly less favorable auxiliaries than Pht-*tert*-leucine (Table 1, entries 1–3). The

Table 1. Results of the Mannich reactions with *N,N*-phthaloyl amino acids as chiral auxiliary groups to give the β -amino acid esters **7** and **8**.

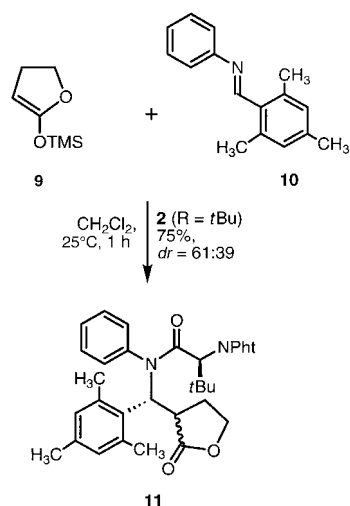
Entry	7	R	R ¹	R ²	R ³	R ⁴	Yield 7 : 8 ^[b] [%] ^[a]
1	a	CH ₃	H	H	Me	Me	67 78:22
2	b	<i>i</i> Pr	H	H	Me	Me	80 87:13
3	c	<i>t</i> Bu	H	H	Me	Me	54 93:7
4	d	<i>t</i> Bu	H	4-MeO	Me	Me	84 91:9
5	e	<i>t</i> Bu	H	2-MeO	Me	Me	91 92:8
6	f	<i>t</i> Bu	H	4-NMe ₂	Me	Me	91 91:9
7	g	<i>t</i> Bu	H	4-Cl	Me	Me	44 92:8
8	h	<i>t</i> Bu	H	2,4,6-Me ₃	Me	Me	46 > 99:1
9	i	<i>t</i> Bu	4-MeO	H	Me	Me	82 91:9
10	j	<i>t</i> Bu	2-MeO, 6-Me	H	Me	Me	50 ^[c] > 99:1
11	k	<i>t</i> Bu	2-MeO, 6-Me	4-MeO	Me	Me	75 ^[c] > 99:1
12	l	<i>t</i> Bu	2-MeO, 6-Me	2-MeO	Me	Me	59 ^[c] > 99:1
13	m	<i>t</i> Bu	2-MeO, 6-Me	4-Cl	Me	Me	17 ^[c] > 99:1
14	n	<i>t</i> Bu	2-MeO, 6-Me	H	H	Et	34 97:3
15	o	<i>t</i> Bu	2-MeO, 6-Me	4-MeO	H	Et	68 > 99:1
16	p	<i>t</i> Bu	2-MeO, 6-Me	2-MeO	H	Et	51 > 99:1

[a] All β -amino acid esters **7** and **8** were identified from 250 or 400 MHz ¹H NMR spectra (CDCl₃) and gave correct elemental analyses and/or high-resolution mass spectra. [b] Determined from the crude reaction mixture by HPLC. [c] **7j**: [α]_D²⁵ = –79.9 (*c* = 0.5, CHCl₃); **7k**: [α]_D²⁵ = –98.5 (*c* = 0.5, CHCl₃); **7l**: [α]_D²⁵ = –103.4 (*c* = 0.5, CHCl₃); **7m**: [α]_D²⁵ = –87.9 (*c* = 0.5, CHCl₃).

diastereomeric ratio is higher when the imine nitrogen atom carries an aromatic substituent than in the presence of an aliphatic residue. Thus, **7c**, which is derived from aniline, is obtained with an isomer ratio of 93:7 (Table 1, entry 3), but, if the corresponding imine obtained from benzylamine is employed the two diastereomers are formed in a ratio of only 83:17. Particularly striking is the observation that the stereoselectivity in the Mannich-type reaction increases sharply if either the aromatic group at the imine nitrogen or the carbon atom of the C=N bond carries *ortho* substituents. Thus, if the phenyl ring that stems from the aldehyde is *ortho*- or *para*-substituted, **7** and **8** are formed in ratios of 91:9 to 92:8, respectively (Table 1, entries 4–7). If however two *ortho*-substituents are present, the diastereomer ratio rises to greater than 99:1 (Table 1, entry 8). When the aniline phenyl ring has a *para*-methoxy substituent the two amino acid esters **7i** and **8i** are obtained in a ratio of 91:9 (Table 1, entry 9). However, if the aniline ring contains two *ortho* substituents the Mannich adducts are consistently formed in diastereomerically pure form (Table 1, entries 10–13; the second diastereomer could not be detected by 400 MHz NMR spectroscopy and by HPLC). Several substituted Schiff bases, as well as the imine derived from benzaldehyde itself, gave the desired Mannich adducts with diastereomer ratios greater than 99:1 (Table 1, entries 11–13).

The excellent diastereoselectivity observed in the reactions described above is not restricted to the use of silylketene acetal **5**. If nucleophile **6** is employed instead, the desired β -amino acid derivatives **7** are obtained with nearly complete diastereoselectivity as well (Table 1, entries 14–16). These results demonstrate that by proper choice of the aniline part of the Schiff base the steric course of the Mannich reactions investigated can be steered with complete selectivity.

In another experiment we have additionally employed silylketene acetal **9** in the Mannich-type reaction (Scheme 2).



Scheme 2. Asymmetric Mannich reaction of Schiff base **10** with silylketene acetal **9** and *N*-Pht-*t*Leu (**2**; R = *t*Bu) as the chiral auxiliary.

The addition of the carbon nucleophile **9** to the C=N bond once more proceeds exclusively from one face of the iminium intermediate (>99:1). However, the diastereomer ratio is only moderate.

The best results were obtained if the asymmetric Mannich reactions were run without any additional Lewis acid. Thus, if for instance titanium, tin, or boron Lewis acids were added to the reaction mixtures the desired Mannich adducts could not be isolated. Also, lowering the reaction temperature resulted in a reduced rate of reaction, but did not increase the stereoselectivity. The presence of the phthaloyl protecting group appears to be important. Only a low level of stereoselectivity was reached if *Z*-protected proline for instance was used as the chiral auxiliary (*Z* = benzyloxycarbonyl). In addition, *N,N*-phthaloylamino acid chlorides are not prone to racemization.^[5]

The relative configuration of the major diastereomers **7** was determined by crystal structure analysis of the Mannich adduct **7h**.^[7] Since **7h** contains an (*S*)- α -amino acid the configuration of the newly formed stereocenter in the β -amino acid part could be determined unambiguously.

To explain the high stereoselectivity attained through the Mannich reactions detailed above, we assume that the transformations proceed preferentially via transition states **A** (Figure 1). Here the two double bonds of the acyliminium structure are in a coplanar *E-trans* orientation. In this arrangement the stereogenic center of the amino acid part is closer to the imine carbon atom than in the analogous *E-cis* conformation, which explains the marked influence of the steric demand of the amino acid side chain on the stereoselectivity. Furthermore, by analogy to the preferred configuration of α,β -unsaturated amides,^[8] the two hydrogen atoms on the imine C=N bond and the amino acid α carbon atom point towards each other. In the corresponding *Z-trans* arrangement a less favorable interaction between the amino acid α hydrogen atom and the aromatic ring on the imine carbon atom would be encountered. The two aromatic rings lie close to each other in **A**, and it may be assumed that in order to minimize unfavorable steric interactions one of the

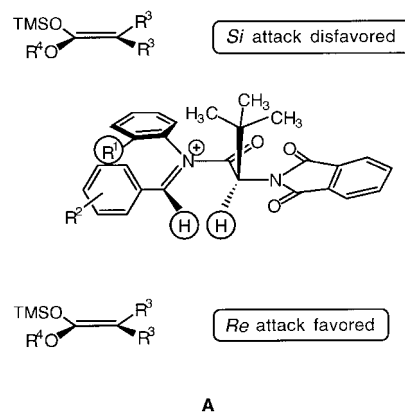
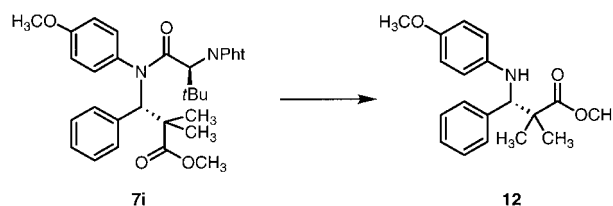


Figure 1. Possible transition state of the Mannich reaction.

two phenyl groups will be tilted away from the other and adopt a conformation in which the aromatic ring is perpendicular to the C=N group. This effect should be particularly pronounced if *ortho* substituents are present on the *N*-aryl group, which for steric and electronic reasons would preferably point away from the oxygen atom of the carbonyl group.

The chiral auxiliary can readily be removed from the Mannich adducts **7** by a simple two-step sequence. As shown in Scheme 3 for **7i**, first the phthaloyl group was cleaved off by partial reduction with NaBH_4 in a 2-propanol/water



Scheme 3. Removal of the chiral auxiliary from the Mannich adduct **7i**. Conditions: 1) NaBH_4 , *i*PrOH/ H_2O 7/1 then aqueous HCl, 80°C , 97%; 2) PhNCS, room temperature, then $\text{CF}_3\text{COOH}/\text{CH}_2\text{Cl}_2$ 1/5, heat, 84%.

mixture followed by acidic hydrolysis.^[9] The *N*-deprotected amino acid amide obtained thereby was then subjected to an Edman degradation^[10] to give the desired *N*-arylated β -amino acid ester **12** in high yield. The alkoxy substituted *N*-aryl group present in the Mannich adducts **7** can be cleaved off by oxidation with, for example, cerium ammonium nitrate.^[11] Thus, the phthaloyl group from **7j** was removed by the two-step sequence detailed above. Then the *ortho* methoxy-substituted *N*-aryl group was cleaved off by treatment with cerium ammonium nitrate to give the desired *N*-deprotected β -amino acid methyl ester in 52% yield. Its specific rotation ($[\alpha]_D^{25} = +34.7$; $c = 0.21$, 1M HCl) is in very good agreement with literature data $[\alpha]_D^{26} = +34.6$ ($c = 0.17$, 1M HCl).^[4c] and proves once more the absolute configuration of the Mannich adducts **7**.

In conclusion the results detailed above demonstrate that the steric course of the Mannich reaction can be directed efficiently by the use of *N,N*-phthaloylamino acids. Chiral β -amino acid esters can be obtained by this process with excellent stereoselectivity.

Experimental Section

A solution of *N*-Pht-*tert*-leucine chloride (1.2 mmol) in CH₂Cl₂ (3 mL) was added at 0 °C to a solution of the imine (1 mmol) in CH₂Cl₂ (2 mL). After the mixture was stirred for 30 min at room temperature it was again cooled to 0 °C, and the silylketene acetal (1.5 mmol) added. The reaction mixture was stirred and warmed to room temperature over 72 h, then CH₂Cl₂ (10 mL) was added. The solution was then extracted with a 10 % NaHCO₃ solution (10 mL) and a saturated NaCl solution (10 mL). The organic layer was dried with Na₂SO₄ and the solvent evaporated in vacuo. The products were isolated from the remaining residue by flash chromatography on silica gel with hexane/ethyl acetate mixtures as eluents. For yields and diastereomer ratios see Table 1.

7k: m.p. 146 °C; $[\alpha]_D^{25} = -98.5$ ($c = 0.5$ in CHCl₃); ¹H nmr (500 MHz, CDCl₃): $\delta = 0.65$ (s, 3H; CH₃, anisidine), 1.11 (s, 3H; *t*Bu), 1.16 (s, 3H; CH₃), 1.54 (s, 3H; CH₃), 3.60 (s, 3H; OCH₃), 3.67 (s, 3H; OCH₃), 3.95 (s, 3H; OCH₃), 4.34 (s, 1H; α H, *t*Leu), 6.08 (d, ³*J* = 8 Hz, 1H; α H, aryl), 6.44 (s, 1H; β H), 6.50 (d, ³*J* = 8 Hz, 2H; *m*H, aryl), 6.71–6.75 (br s, 2H; 3- and 5-H, anisidine), 6.86 (d, ³*J* = 8 Hz, 1H; α H, aryl), 7.08 (dd, ³*J*₁ = ³*J*₂ = 8 Hz, 1H; 4-H, anisidine), 7.51 (d, ³*J* = 7 Hz, 1H; α H, Pht), 7.61 (ddd, ³*J*₁ = ³*J*₂ = 7 Hz, ⁴*J* = 1 Hz, 1H, *m*H, Pht), 7.65 (ddd, ³*J*₁ = ³*J*₂ = 7 Hz, ⁴*J* = 1 Hz, 1H; *m*H, Pht), 7.74 (d, ³*J* = 7 Hz, 1H; α H, Pht); ¹³C nmr (125.8 MHz, CDCl₃): $\delta = 17.57$ ((CH₃)₂C), 21.34 ((CH₃)₂C), 24.40 (CH₃, anisidine), 27.86 (3-C, *t*Bu), 37.32 ((CH₃)₂C), 50.14 (*t*Bu), 51.69 (OCH₃), 54.69 (OCH₃), 54.92 (OCH₃), 58.41 (β -CH), 65.52 (α CH-*t*Leu), 109.50 (3-C, anisidine), 112.27 (*m*-C, aryl), 122.36 (5-C, anisidine), 122.71 (*o*-C, Pht), 122.95 (*o*-C, Pht), 127.11 (1-C, anisidine), 128.29 (6-C, anisidine), 129.12 (*o*-C, aryl), 130.68 (1-C, aryl), 132.29 (C, Pht), 133.53 (*m*-C, Pht), 133.85 (4-C, anisidine), 141.07 (C, Pht), 155.87 (*p*-C, aryl), 158.74 (4-C, anisidine), 166.27 (C(O), *t*Leu), 167.47 (2-C, C(O), Pht), 177.21 (CO₂CH₃); HR-MS: calcd for C₃₅H₄₀N₂O₇ [*M*⁺] 600.2836; found: 600.2823; elemental analysis calcd for C₃₅H₄₀N₂O₇: C 69.98, H 6.71, N 4.66; found: C 69.86, H 6.72, N 4.83.

Received: June 5, 1998

Supplemented version: September 30, 1998 [Z11953IE]

German version: *Angew. Chem.* **1999**, *111*, 166–169

Keywords: amino acids • asymmetric synthesis • chiral auxiliaries • Mannich reaction

- [4] a) E. J. Corey, C. P. Decicco, R. C. Newbold, *Tetrahedron Lett.* **1991**, 32, 5287–5290; b) K. Ishihara, M. Miyata, K. Hattori, T. Tada, H. Yamamoto, *J. Am. Chem. Soc.* **1994**, *116*, 10520–10524; c) H. Ishitani, M. Ueno, S. Kobayashi, *J. Am. Chem. Soc.* **1997**, *119*, 7153–7154; d) E. Hagiwara, A. Fujii, M. Sodeoka, *J. Am. Chem. Soc.* **1998**, *120*, 2474–2475.
- [5] a) J. Sheehan, D. W. Chapman, R. W. Roth, *J. Am. Chem. Soc.* **1952**, *74*, 3822–3825; b) C. R. Mc Arthur, P. M. Worster, A. U. Okon, *Synth. Commun.* **1983**, *13*, 311–318.
- [6] W. N. Speckamp, H. Hiemstra, *Tetrahedron* **1985**, *41*, 4367–4416.
- [7] The crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-101780. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [8] H. Waldmann, *Liebigs Ann. Chem.* **1990**, 671–680, and references therein.
- [9] J. O. Osby, M. G. Martin, B. Ganem, *Tetrahedron Lett.* **1984**, *25*, 2093–2096.
- [10] W. J. Mc Gahren, J. H. Martin, G. O. Morton, R. T. Hargreaves, R. A. Leese, F. M. Lovell, G. A. Ellestad, E. O'Brien, J. S. E. Holker, *J. Am. Chem. Soc.* **1990**, *112*, 1671–1684.
- [11] D. R. Kronenthal, C. Y. Han, M. K. Taylor, *J. Org. Chem.* **1982**, *47*, 2765–2768.

Tetrakis(2,4,6-triisopropylphenyl)diplumbene: A Molecule with a Lead–Lead Double Bond**

Martin Stürmann, Wolfgang Saak, Heinrich Marsmann, and Manfred Weidenbruch*

*Dedicated to Professor Helmut Werner
on the occasion of his 65th birthday*

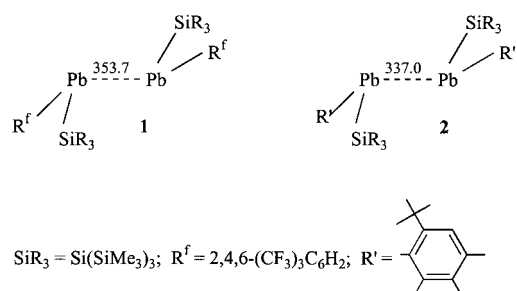
Disilenes, digermenes, and distannenes—compounds with Si–Si, Ge–Ge, and Sn–Sn double bonds—are now well-established molecules, and their properties have been summarized in several review articles.^[1, 2] They are usually prepared by the primary generation of the carbene analogues R₂E: (E = Si, Ge, Sn) and subsequent dimerization. Diplumbenes, molecules with a lead–lead double bond, were unknown until now. Furthermore, structurally characterized dialkyl-^[3, 4] and diarylplumbylenes (–plumbanediyls)^[5, 6] were reported for the first time in the past few years. The latter particles with electron sextets exist both in solution and in the crystal as monomers without noticeable Pb–Pb interactions.

- [1] a) M. Arend, B. Westermann, N. Risch, *Angew. Chem.* **1998**, *110*, 1096–1122; *Angew. Chem. Int. Ed.* **1998**, *37*, 1044–1070; b) E. F. Kleinmann in *Comprehensive Organic Synthesis*, Vol. 2 (Eds.: B. M. Trost, I. Fleming, C. H. Heathcock), Pergamon, Oxford, **1991**, pp. 893–952.
- [2] a) S. Krauthäuser, L. A. Christianson, D. R. Powell, S. H. Gellman, *J. Am. Chem. Soc.* **1997**, *119*, 11719–11720; b) D. Seebach, M. Overhand, F. N. M. Kühnle, D. Martini, L. Oberer, U. Hommel, H. Widmer, *Helv. Chim. Acta* **1996**, *79*, 913–941.
- [3] a) D. Enders, D. Ward, J. Arden, G. Raabe, *Angew. Chem.* **1996**, *108*, 1059–1062; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 981–984; b) M. Arend, N. Risch, *Angew. Chem.* **1995**, *107*, 2861–2864; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2861; c) H. Frauenrath, T. Arenz, G. Raabe, M. Zorn, *Angew. Chem.* **1993**, *105*, 74–76; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 83; d) D. A. Evans, F. Urpi, T. C. Somers, J. S. Clark, M. T. Bilodeau, *J. Am. Chem. Soc.* **1990**, *112*, 8215–8216; e) W. Oppolzer, R. Moretti, S. Thomi, *Tetrahedron Lett.* **1989**, *30*, 5603–5606; f) D. Seebach, C. Betschart, M. Schiess, *Helv. Chim. Acta* **1984**, *67*, 1593–1597; g) N. Risch, A. Esser, *Liebigs Ann. Chem.* **1992**, 233–237; h) K. Broadley, S. G. Davies, *Tetrahedron Lett.* **1984**, *25*, 1743–1744; i) W. Oppolzer, P. Schneider, *Helv. Chim. Acta* **1986**, *69*, 1817–1820; j) C. Gennari, I. Venturini, G. Gislón, G. Schimperna, *Tetrahedron Lett.* **1987**, 28, 227–230; k) H. Kunz, W. Pfengle, *Angew. Chem.* **1989**, *101*, 1041–1042; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1067; l) H. Kunz, D. Schanzenbach, *Angew. Chem.* **1989**, *101*, 1042–1043; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1068; m) H. Waldmann, M. Braun, M. Dräger, *Angew. Chem.* **1990**, *102*, 1445–1447; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1468; n) H. Waldmann, M. Braun, *J. Org. Chem.* **1992**, *57*, 4444–4451.

[*] Prof. Dr. M. Weidenbruch, Dipl.-Chem. M. Stürmann, Dipl.-Chem. W. Saak
Fachbereich Chemie der Universität
Carl-von-Ossietzky-Strasse 9–11, D-26111 Oldenburg (Germany)
Fax: (+1) 441-798-3352
Prof. Dr. H. Marsmann
Fachbereich Chemie der Universität (GH)
Warburger Strasse 100, D-33095 Paderborn (Germany)

[**] Compounds of Germanium, Tin, and Lead. Part 28. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. Part 27: M. Weidenbruch, U. Grobecker, W. Saak, E.-M. Peters, K. Peters, *Organometallics* **1998**, *17*, 5206.

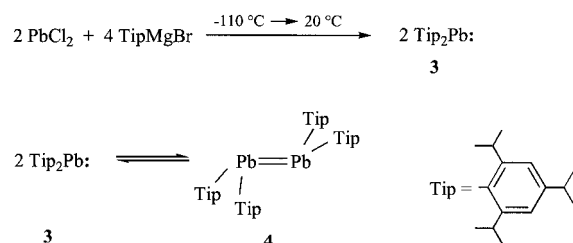
A first breakthrough in the field of lead–lead contacts between plumbylene molecules was achieved just recently with the isolation of the heteroleptic plumbylene dimer **1**, which exhibits a Pb–Pb separation of 353.7(1) pm and a *trans* bent angle of the substituents to the Pb–Pb vector of 40.8°.^[7] Since intramolecular interactions in **1** between the fluorine



atoms of the *ortho*-CF₃ groups and the lead atoms should weaken rather than favor a possible lead–lead bond,^[7] we prepared, by the same route, another heteroleptic plumbylene that exists in the solid state as the plumbylene dimer **2**. In comparison to **1**, **2** has a shorter lead–lead separation of 337.0(1) pm and a bending angle of 46.5°.^[8] However, the observed lead–lead distances in **2** and especially in **1** are still markedly longer than the value of 295–300 pm calculated for the parent compound H₂Pb=PbH₂.^[7, 9, 10]

As the choice of substituents seems to be of decisive importance for the formation of a lead–lead double bond, we turned our attention to the 2,4,6-triisopropylphenyl group (Tip), which was previously employed with success not only for the synthesis of the first tetrasilabuta-1,3-diene,^[11] but also in the generation of the as yet only distannene that does not dissociate into stannylene molecules in solution.^[12] The first attempt to prepare the plumbylene **3** was reported by Okazaki et al. Although these authors were able to demonstrate the existence of this particle in solution up to –40 °C by means of trapping reactions, they were only able to isolate the plumbanes Tip₃PbX (X = Br, I) as solids.^[13]

Reaction of the Grignard compound TipMgBr with lead(II) chloride at low temperature furnished a violet solution from which red crystals were isolated by rapid workup (Scheme 1). The product is light- and very air-sensitive and is thermally stable up to 75 °C. Spectral data recorded in the gas phase and



Scheme 1. Synthesis of **3** and dimerization of **3** to **4**.

in solution supported the presence of the plumbylene **3**, which exists for a short time in solution under strict exclusion of light up to 298 K. However, the absence of a signal in the ²⁰⁷Pb NMR spectra, recorded in the range between δ = 0 and 20000

at 233 and 253 K, as well as the temperature dependence of the ¹³C NMR signal for the *ipso*-carbon atoms, which exhibits a nonlinear shift to higher field on cooling from 298 (δ = 262.4) to 243 K (δ = 236.2), are suggestive of a possible equilibrium between **3** and the diplumbene **4**.^[14]

An X-ray crystallographic analysis of the red crystals (Figure 1)^[15] showed that the diplumbene **4** actually does exist in the solid state. The Pb–Pb bond length of

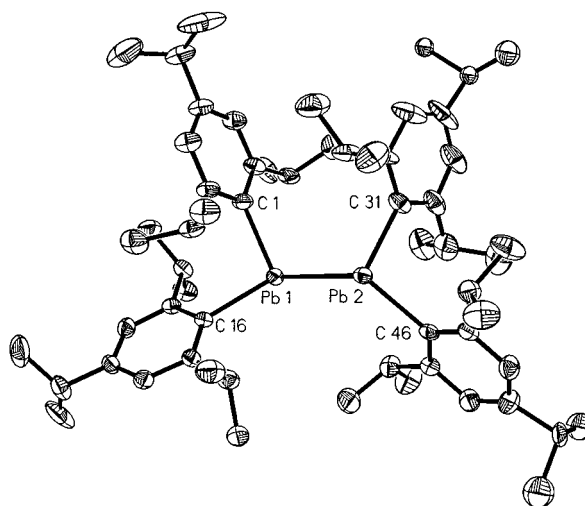


Figure 1. Structure of **4** in the crystal (hydrogen atoms omitted, ellipsoids represent the 50% probability level). Selected bond lengths [pm] and angles [°]: Pb1–Pb2 305.15(3), Pb1–C1 228.8(5), Pb1–C16 229.3(5), Pb2–C31 230.5(5), Pb2–C46 231.2(5); C1–Pb1–C16 97.8(2), C31–Pb2–C46 102.3(2), C1–Pb1–Pb2 100.5(1), C16–Pb1–Pb2 131.8(2), C31–Pb2–Pb1 99.6(1), C46–Pb2–Pb1 123.5(1).

305.15(3) pm is merely 5 to 10 pm longer than that calculated for H₂Pb=PbH₂. The folding angles of 43.9° and 51.2° are somewhat smaller than the theoretically calculated values of around 55°.^[7, 9, 10] Such deviations, which have also been observed in the distannenes,^[2] are possibly due to the replacement of hydrogen atoms in the parent compound by the bulky aryl groups. This may also be the reason for the only moderate torsion of 21.7° about the double bond.

With the synthesis of compound **4**, homonuclear double bonds between all elements of Group 14 have been realized for the first time. In contrast to C–C double bonds, the bonds between the heavier elements—especially in the case of lead—arise through a double donor–acceptor interaction between the respective doubly occupied 6s orbitals and the empty 6p orbitals of two singlet plumbylene molecules **3** (Figure 2). The low tendency for plumbylenes to undergo dimerization and the weakness of the resultant Pb–Pb double

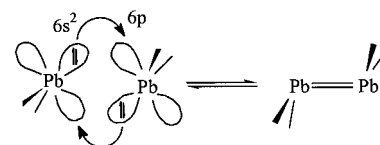


Figure 2. Orbital interactions in the formation of a diplumbene from two singlet plumbylenes.

bond may be due in part to the relativistic contraction of the 6s electron pairs, which are only available for bond formation to a limited extent.^[17] Furthermore, this mode of bond formation clearly demonstrates that the lengths of homonuclear double bonds between the heavier elements of Group 14 may well be in the same range as or even larger than the corresponding single bonds.

Experimental Section

At -110°C solid lead(II) chloride (5.6 g, 20 mmol) was added to a solution of the Grignard reagent TipMgBr , prepared from 1-bromo-2,4,6-triisopropylbenzene (11.44 g, 40.4 mmol) and magnesium (3.0 g, 123 mmol) in THF (100 mL), and the resultant mixture was warmed with vigorous stirring to room temperature within 20 min. The THF solvent was removed by distillation under vacuum, and the residue extracted with *n*-hexane (2×50 mL). After separation of the magnesium salts the violet solution was concentrated to a volume of 40 mL and allowed to crystallize at -50°C . Red crystals (5.8 g, 47%) of **4** were obtained: m.p. 75°C (decomp.). Spectroscopic data of **3** in solution: ^1H NMR (300 MHz, $[\text{D}_8]\text{toluene}$, 283 K): $\delta = 1.14$ (d, 24H, $^3J(\text{H,H}) = 6.7$ Hz), 1.23 (d, 12H, $^3J(\text{H,H}) = 6.9$ Hz, 2.72 (m, 2H), 2.82 (m, 4H), 7.68 (s, 4H); ^{13}C NMR (75 MHz, $[\text{D}_8]\text{toluene}$, 283 K): $\delta = 24.22, 24.37, 35.56, 36.28, 128.57, 147.45, 157.45, 255.62$ (ipso-C, $^1J(^{13}\text{C}, ^{207}\text{Pb}) = 1100$ Hz at 298 K); MS (CI, isobutane): m/z (%): 614 (100, M^+); UV/Vis (*n*-hexane): λ_{max} (ϵ) = 321, 385, 541 nm (960). Elemental analysis of **4** ($\text{C}_{60}\text{H}_{92}\text{Pb}_2$): found (calcd): C 58.57 (58.70), H 7.68 (7.55).

Received: August 26, 1998 [Z123391E]
German version: *Angew. Chem.* **1999**, *111*, 145–147

Keywords: carbene analogues • lead • main group elements • multiple bonds

- [12] S. Masamune, L. R. Sita, *J. Am. Chem. Soc.* **1985**, *107*, 6390; A. Schäfer, M. Weidenbruch, W. Saak, S. Pohl, H. Marsmann, *Angew. Chem.* **1991**, *103*, 873 and 978; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 834 and 962; M. Weidenbruch, A. Schäfer, H. Kilian, S. Pohl, W. Saak, H. Marsmann, *Chem. Ber.* **1992**, *125*, 563.
- [13] K. Shibata, N. Tokitoh, R. Okazaki, *Tetrahedron Lett.* **1993**, *34*, 1495; N. Tokitoh, N. Kano, K. Shibata, R. Okazaki, *Organometallics* **1995**, *14*, 3121.
- [14] Similar observations have been made for the ^{119}Sn signals of the equilibrium $2\text{R}_2\text{Sn} \rightleftharpoons \text{R}_2\text{Sn}=\text{SnR}_2$ ($\text{R} = 2\text{-}i\text{Bu-4,5,6-Me}_3\text{C}_6\text{H}$): M. A. DellaBonna, M. C. Cassani, J. M. Keates, G. A. Lawless, M. F. Lappert, M. Stürmann, M. Weidenbruch, *J. Chem. Soc. Dalton Trans.* **1998**, 1187.
- [15] a) Crystal structure analysis of **4**: STOE-IPDS diffractometer, MoK_α radiation, graphite monochromator. The reflections were recorded at 173 K from a shock-cooled crystal with dimensions $1.10 \times 0.44 \times 0.27$ mm³ under an inert oil to $2\theta_{\text{max}} = 52^{\circ}$. The structure was solved by direct methods (SHELXS-97) and refined by full-matrix least-squares techniques against F^2 (SHELXL-97).^[16] $\text{C}_{60}\text{H}_{92}\text{Pb}_2$, $M_r = 1227.72$, monoclinic, space group $\text{C}2/c$, $Z = 8$, $a = 4755.2(3)$, $b = 1375.24(6)$, $c = 1912.83(9)$ pm, $\beta = 101.155(6)^{\circ}$, $V = 12273(1) \times 10^6$ pm³, $\rho_{\text{calcd}} = 1.329$ g cm⁻³, $\mu = 5.511$ mm⁻¹; of 50232 measured reflections, 11197 were independent and 8498 observed for $I > 2\sigma(I)$. Hydrogen atoms were placed in calculated positions and refined with isotropic temperature factors; all other atoms were refined anisotropically. $R1 = 0.0290$, $wR2 = 0.0729$ (all data) for 553 parameters; max./min. residual electron density $1.070/-0.622$ e Å⁻³. b) Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-102629. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [16] G. M. Sheldrick, SHELXL-97, Program for crystal structure refinement, Universität Göttingen, Germany, **1997**.
- [17] P. Pykkö, *Chem. Rev.* **1988**, *88*, 563.

[1,3], [3,3], and [3,5] Sigmatropic Rearrangements of Esters Are Pseudopericyclic**

David M. Birney,* Xiaolian Xu, and Sihyun Ham

In 1969 the famous paper by Woodward and Hoffmann describing the conservation of orbital symmetry was published in this journal.^[1] All of the well-known rules regarding pericyclic reactions assume that there is a cyclic loop of interacting π orbitals. However, it is possible to have a pericyclic reaction in which this condition is not fulfilled, that is, in which there is *not* cyclic π overlap. The unique characteristics of these “pseudopericyclic” reactions^[2] have been described in detail elsewhere;^[3] they can be briefly summarized as follows: 1) These reactions have planar transition states, 2) they may have very low barriers if the

- [1] Reviews of disilenes: R. West, *Angew. Chem.* **1987**, *99*, 1231; *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 1202; G. Raabe, J. Michl in *The Chemistry of Organic Silicon Compounds, Part 2* (Eds.: S. Patai, Z. Rappoport), Wiley, Chichester, **1989**, p. 1015; T. Tsumuraya, S. A. Batcheller, S. Masamune, *Angew. Chem.* **1991**, *103*, 916; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 902; M. Weidenbruch, *Coord. Chem. Rev.* **1994**, *130*, 275; R. Okazaki, R. West in *Multiply Bonded Main Group Metals and Metalloids* (Eds.: R. West, F. G. A. Stone), Academic Press, San Diego, **1996**, p. 232.
- [2] Reviews on digermenes and distannenes: K. M. Baines, W. G. Stibbs in *Multiply Bonded Main Group Metals and Metalloids* (Eds.: R. West, F. G. A. Stone), Academic Press, San Diego **1996**, p. 275; M. Driess, H. Grützmacher, *Angew. Chem.* **1996**, *108*, 900; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 827.
- [3] $\text{Pb}[\text{CH}(\text{SiMe}_3)_2]_2$: synthesis: P. J. Davidson, M. F. Lappert, *J. Chem. Soc. Chem. Commun.* **1973**, 317; P. J. Davidson, D. H. Harris, M. F. Lappert, *J. Chem. Soc. Dalton Trans.* **1976**, 2268; structure: K. W. Klinkhammer, W. Schwarz, unpublished results. We thank Dr. Klinkhammer for advanced communication.
- [4] C. Eaborn, T. Ganicz, P. B. Hitchcock, J. D. Smith, S. E. Sözerli, *Organometallics* **1997**, *16*, 5621.
- [5] S. Brooker, J.-K. Buijink, F. T. Edelmann, *Organometallics* **1991**, *10*, 25.
- [6] R. S. Simons, L. Pu, M. M. Olmstead, P. P. Power, *Organometallics* **1997**, *16*, 1920.
- [7] K. W. Klinkhammer, T. F. Fässler, H. Grützmacher, *Angew. Chem.* **1998**, *110*, 114; *Angew. Chem. Int. Ed.* **1998**, *37*, 124.
- [8] M. Stürmann, M. Weidenbruch, K. W. Klinkhammer, F. Lissner, H. Marsmann, *Organometallics* **1998**, *17*, 4425.
- [9] G. Trinquier, *J. Am. Chem. Soc.* **1990**, *112*, 2130.
- [10] H. Jacobsen, T. Ziegler, *J. Am. Chem. Soc.* **1994**, *116*, 3667.
- [11] M. Weidenbruch, S. Willms, W. Saak, G. Henkel, *Angew. Chem.* **1997**, *109*, 2612; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2503.

[*] Dr. D. M. Birney, X. Xu, Dr. S. Ham
Department of Chemistry and Biochemistry
Texas Tech University
Lubbock, TX 79409-1061 (USA)
Fax: (+1) 806-742-1289
E-mail: vddmb@ttu.edu

[**] This work was supported by the Robert A. Welch Foundation.

Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.

geometries and the nucleophilic/electrophilic sites are favorable, and 3) no pseudopericyclic reaction can be forbidden by orbital symmetry. Figure 1 shows selected basis orbitals of esters. We recognized that this functional group is capable not

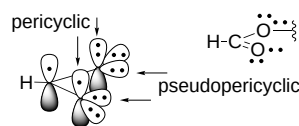


Figure 1. The π , σ , and lone pair basis orbitals of esters. If a reaction involves the π system it is pericyclic, but if the breaking bond and the lone pair do not overlap with the π system, the reaction is pseudopericyclic.

only of pericyclic reactions involving the π system, but also of pseudopericyclic reactions involving only the in-plane σ bond and the lone pairs. The results reported here are the first from an ongoing study of concerted reactions of esters.

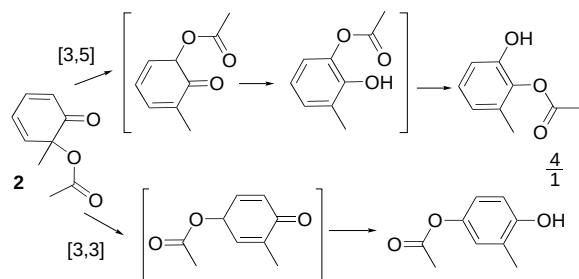
Experimental studies of sigmatropic rearrangements of allyl esters such as **1** [Eq. (1)] indicate a concerted

reaction with partial carbonium and carboxylate ion character.^[4] Recent ab initio^[5] and density functional theory (DFT) calculations^[6] found a chair and a flattened boat



transition state for this reaction. The chair geometry is similar to that of the Claisen rearrangement.^[7] The boat is lower in energy, and the partial bonds are nearly coplanar with the ester group. Zipse recognized that the geometry of this transition state “precludes efficient interaction of the formyl and allyl group π -systems as expected in [3,3]-sigmatropic rearrangements” and describes the reaction as an “intramolecular nucleophilic substitution reaction”. He did not generalize from this observation, but we anticipate that a [3,5] sigmatropic rearrangement with a pseudopericyclic geometry is also possible.

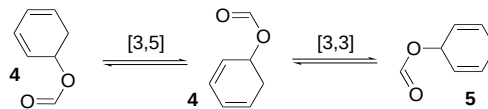
Indeed, in acyloxycyclohexadienones which can undergo both [3,3] and [3,5] sigmatropic rearrangements (e.g. **2**), the major products observed are from formal [3,5] rearrangements (Scheme 1).^[8] Tantalizingly, the authors suggested a concerted pathway. In a later review article, this mechanism was discounted; it was *assumed* that “concerted rearrangements of this type are not allowed by orbital symmetries”.^[9] We undertook the ab initio



Scheme 1.

study presented here with the expectation that the [3,5] sigmatropic rearrangement of esters would in fact be allowed by a pseudopericyclic pathway.^[10]

The rearrangements of 2,4-cyclohexadienyl formate (**4**, Scheme 2) were chosen as a model system for those in Scheme 1.^[13] The geometries of **4** and **5** were calculated, and



Scheme 2.

transition states (TSs) **6** and **7** for a [3,5] and a [3,3] sigmatropic rearrangement of **5** were located (Figure 2). The calculated barrier for the [3,3] rearrangement of **4** to **5** via the boat TS **7** is 38.3 kcal mol⁻¹. If the [3,3] rearrangement is allowed, then the conventional wisdom of the Woodward–Hoffmann rules leads us to expect a much higher barrier for the vinylogous [3,5] process. However, the TS **6** is pseudopericyclic, with the breaking and forming bonds in the plane of the formate (177.0°). And here is the surprise: The barrier calculated for this [3,5] rearrangement via **6** is 3.0 kcal mol⁻¹ lower in energy than that for the [3,3] rearrangement!

How can this be? Both the [3,3] and the [3,5] rearrangements are in fact orbital symmetry allowed, the latter because it is pseudopericyclic.^[3d] These are perhaps most easily

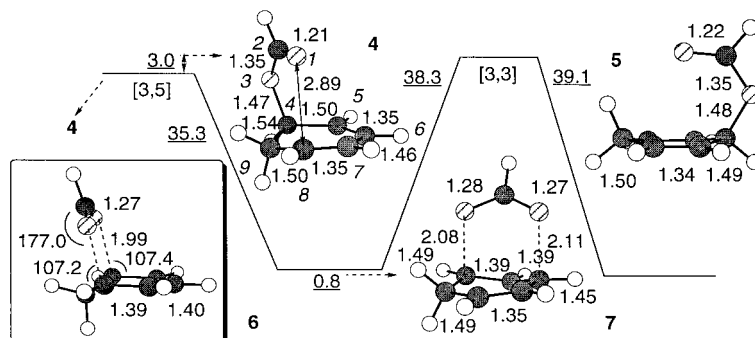


Figure 2. Relative energies (MP4/6-31G** + ZPE, underlined) [kcal mol⁻¹] and MP2/6-31G**-optimized geometries of **4** and **5** and transition states for the [3,5] and [3,3] sigmatropic rearrangement (**6** and **7**). Distances are in Å, angles between planes in degrees. Carbon and oxygen atom numbers are in italics.

understood in terms of the frontier molecular orbital interaction of a formate anion and either an allyl or a cyclohexadiene cation (Figure 3). The three HOMOs of the formate anion are the π_2 orbital and two linear combinations of oxygen lone pairs. The close spacing of these orbitals (0.6 eV) means that any one of them can have a stabilizing interaction with the LUMO of the cation.^[14] The π_2 orbital as well as the HOMO₋₂ are of the proper symmetry to interact with the LUMO of the allyl cation, while the HOMO₋₁ can interact with the LUMO of the cyclohexadienyl group.^[15]

The barrier for the [3,3] rearrangement of **4** to **5** might be expected to be lower because this reaction is slightly exothermic (0.8 kcal mol⁻¹), yet it is higher than for the

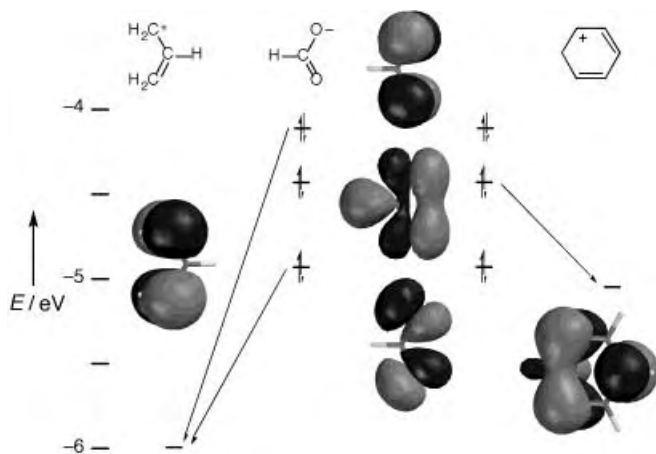
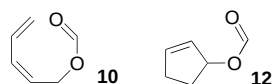


Figure 3. RHF/6-31G** orbitals of allyl cation (LUMO: -6.0 eV; MP2/6-31G** geometry), acetate anion (HOMO: -4.2 eV, HOMO $_{-1}$: -4.4 eV, HOMO $_{-2}$: -4.8 eV; geometry from **6**), and cyclohexadienyl cation (LUMO: -5.0 eV; geometry from **6**).

thermoneutral [3,5] rearrangement. Our experience suggests that the differences in barriers may reflect subtle differences in TS geometries.^[3d] Indeed, the [3,3] TS (**7**) is more distorted than the [3,5] TS (**6**). In **6**, the pentadienyl system is essentially planar, while in **7** it is significantly twisted. The facile downward bend of the C9 methylene group in **6** tips the p orbitals of C4 and C8 inwards, towards the ester oxygen atoms, which are closer together (2.31 Å) than these carbon atoms (2.47 Å). Also, in **6** the angle between the plane of the ester and the plane of the pentadienyl fragment is 107.4° , which is similar to the Burgi–Dunnitz trajectory for nucleophilic addition.^[17] We conclude that the geometry of TS **6** allows the better (pseudopericyclic) orbital overlap.

Since a radical pathway has been suggested,^[9a] we also calculated the energy of separated formyl (**8**) and cyclohexadienyl radicals (**9**; UMP2/6-31G**, admittedly not the best level for calculations of radicals). These are 92.9 kcal mol $^{-1}$ above the energy of TS **6** calculated at the MP2/6-31G** level. Alternatively, an estimate of 77 kcal mol $^{-1}$ for the formation of the radicals may be made from known bond dissociation energies and group additivities.^[18] Because the barriers are much lower, it is unlikely the radicals are involved.

In searching for a [3,5] sigmatropic rearrangement of a formate ester, we also considered the simplest system, the rearrangement of **10**. For this reaction, optimization of a TS constrained to C_s symmetry led not to a [3,5] rearrangement, but to **11**, which is a boat TS for a [3,3] rearrangement of **12**



(Figure 4). It is unlikely that **10** directly rearranges to **12** via this C_s -symmetrical TS since the thermal electrocyclic ring closure of the cyclopentadienyl fragment, if cationic, should be conrotatory (C_2). The boat (**11**) exhibits pseudopericyclic character; the angle between the planes of the formate and the partial bonds is 144.0° . This indicates participation of both the π_2 orbital and HOMO $_{-2}$ acetate orbitals.

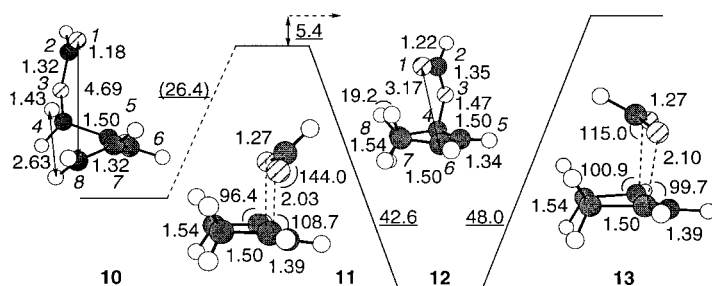


Figure 4. Relative energies (MP4/6-31G**) and MP2/6-31G**-optimized geometries of **11–13** as well as relative energy and geometry (RHF/6-31G*) of **10**. See Figure 2 for key.

A chair TS **13** was also located at the RHF/3-21G and MP2/6-31G** levels. Optimization at the RHF/6-31G** level led to the boat (**11**). The chair is 5.4 kcal mol $^{-1}$ higher in energy than the boat and is not pseudopericyclic; the angle between the formate and the partial bonds is only 115.0° . The angles between the partial bonds and the allyl moiety in **11** and **13** are 108.7 and 99.7° , respectively, and are also typical of those found in pericyclic reactions. The chair is apparently destabilized in part by steric crowding between the formate anion and the hydrogen atoms on C7 and C8; the angle between the C4–C6–C7–C8 plane and the partial bonds is 96.4° in **11**, but is opened to 100.9° in **13**.

It appears to us that the inside hydrogen atoms keep the ends of the pentadienyl system too far apart for the formate to bridge them in a [3,5] TS (O1–C8 4.69 Å in **10**). An obvious alternative was to consider the rearrangement of **15**, in which the ends of the pentadienyl system are bonded. However, only [3,3] TSs were found.^[19] The chair (**14**) and the boat TSs (**16**) both exhibit pseudopericyclic character, with angles of 141.5° and 150.7° , respectively, between the formate group and the partial bonds (Figure 5). The structures of **14** and **16** clearly show an isolated double bond between C7

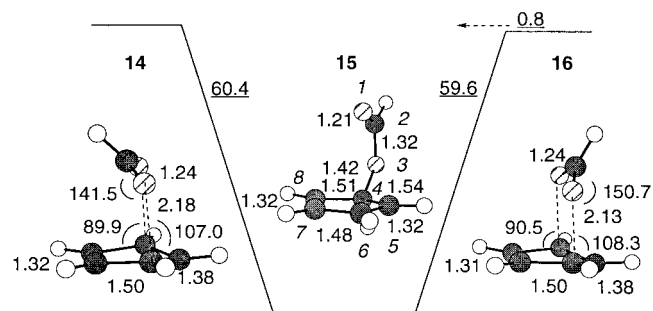
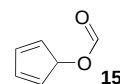
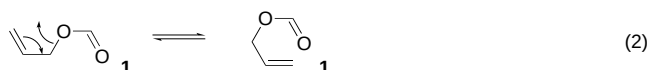


Figure 5. Relative energies and RHF/6-31G**-optimized geometries of **14–16**. See Figure 2 for key.

and C8 with single bonds to the allyl cation moiety (C4–C8). A [3,5] TS would have given more antiaromatic cation character to the cyclopentadienyl fragment as compared to **14** and **16**. The barriers to this rearrangement to **14** and **16** (60.4 and 59.6 kcal mol $^{-1}$, respectively) are significantly higher than for **12**, a clear manifestation of the antiaromaticity of the cationic cyclopentadienyl fragment.

At the suggestion of a referee, we also examined the [1,3] shift of allyl formate [**1**, Eq. (2)]. To the extent that the



breaking C–O bond and the oxygen lone pair are non-interacting, this reaction can also be pseudopericyclic. Alternatively, the HOMO₋₂ of one oxygen atom from the acetate can interact with the LUMO of the allyl cation (Figure 3). The TS for this reaction (**17**) is shown in Figure 6.^[20] The barrier of 64.8 kcal mol⁻¹ is approximately 20 kcal mol⁻¹ above that calculated for the [3,3] rearrangement.^[21]

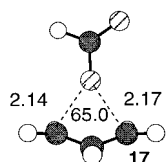


Figure 6. The geometry (MP2/6-31G**) of the transition state **17** for the [1,3] sigmatropic shift of allyl acetate. See Figure 2 for key.

Does this mean the reaction is forbidden? No! The strain energy of cyclobutane is estimated to be 24.9 kcal mol⁻¹ greater than in cyclohexane.^[22] Thus, the higher barrier can be understood to be simply a reflection of the additional strain in the four membered ring transition state for the allowed, pseudopericyclic [1,3] shift of allyl formate.

These transition states all show some transfer of charge to the formate moiety, in accord with experiment.^[4] The total RHF/6-31G**//MP2/6-31G** Mulliken charges on the formates increase from approximately –0.4 in the ground state molecules to –0.6 in the transition states. There does not seem to be a significant difference between the pericyclic and pseudopericyclic transition states, consistent with both reactions being allowed.

In conclusion, the pseudopericyclic [3,5] sigmatropic rearrangement of **4**, which had been thought to be forbidden, is in fact allowed and is favored by 3.0 kcal mol⁻¹ over the [3,3] rearrangement. A [3,5] rearrangement is not found for **10** because the reactive centers are too far apart. The [3,3] rearrangement is also favored in **15** since the cyclopentadienyl cation character of the [3,5] TS would be more antiaromatic. The [1,3] rearrangement of **1** via **17** is allowed, although the four membered ring transition state is strained. The facile [3,5] pseudopericyclic reaction of **4** suggests that whenever there are orthogonal π and/or nonbonding orbitals, the possibility of a pseudopericyclic reaction should be carefully considered.

Received: March 17, 1998

Revised version: August 24, 1998 [Z11596IE]

German version: *Angew. Chem.* **1999**, *111*, 147–150

Keywords: ab initio calculations • pericyclic reactions • rearrangements

[1] R. B. Woodward, R. Hoffmann, *Angew. Chem.* **1969**, *81*, 797; *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 781.

[2] J. A. Ross, R. P. Seiders, D. M. Lemal, *J. Am. Chem. Soc.* **1976**, *98*, 4325–4327.

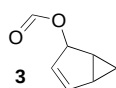
- [3] a) D. M. Birney, P. E. Wagnerseller, *J. Am. Chem. Soc.* **1994**, *116*, 6262–6270; b) P. E. Wagnerseller, D. M. Birney, D. Roy, *J. Am. Chem. Soc.* **1995**, *60*, 2853–2859; c) D. M. Birney, *J. Am. Chem. Soc.* **1996**, *61*, 243–251; d) D. M. Birney, S. Ham, G. R. Unruh, *J. Am. Chem. Soc.* **1997**, *119*, 4509–4517; e) S. Ham, D. M. Birney, *Tetrahedron Lett.* **1997**, *38*, 5925–5928.
- [4] a) W. J. Bailey, R. Barclay, Jr., *J. Org. Chem.* **1956**, *21*, 328–331; b) E. S. Lewis, J. T. Hill, E. R. Newman, *J. Am. Chem. Soc.* **1968**, *90*, 662–668.
- [5] Y. L. Pascal, J. Levisalles, J.-M. Normant, *Tetrahedron* **1993**, *49*, 7679–7690.
- [6] H. Zipse, *J. Chem. Soc. Perkin Trans. 2* **1996**, 1797–1800.
- [7] H. Y. Yoo, K. N. Houk, *J. Am. Chem. Soc.* **1997**, *119*, 2877–2884, and references therein.
- [8] E. Zbiral, F. Wessely, J. Jorg, *Monatsh. Chem.* **1961**, *92*, 654–666.
- [9] B. Miller in *Mechanisms of Molecular Migrations*, Vol. 1 (Ed.: B. S. Thyagarajan), Interscience, New York, **1968**, pp. 247–314; see in particular page 261. A radical mechanism was suggested instead. There is evidence for radical pathways in the formation of minor products in acetate eliminations: B. Shi, Y. Ji, H. A. Dabbagh, B. H. Davis, *J. Org. Chem.* **1994**, *59*, 845–849.
- [10] The ab initio molecular orbital calculations were carried out with the program Gaussian 94.^[11] Transition states showed a single imaginary frequency. The levels of theory used here give qualitatively correct results for allowed pericyclic and pseudopericyclic reactions.^[12] The relative energies discussed in the text are from the highest calculated level shown in Table 1. Full geometries and absolute energies are available in the supporting information.

Table 1. Calculated relative energies [kcal mol⁻¹], frequency minima $\tilde{\nu}$ [cm⁻¹], zero-point energies (ZPE) [kcal mol⁻¹], and Mulliken charges on the formate group. All calculations were carried out with the 6-31G** basis set and, unless otherwise indicated, at the MP2 level.

	Symmetry	RHF ^[a,b]	$\tilde{\nu}_{\min}$	ZPE	Formate charge ^[c]	$E(\text{MP2})$	$\Delta G(\text{MP2})$ ^[d]	$E(\text{MP4})$ ^[e]
1a	C _s	–0.2	44.2	61.2	–0.40	0.8	0.2	0.4 ^[f]
1b	C ₁	0.2	76.7	61.4	–0.40	0.2	0.0	0.1 ^[f]
1c	C ₁	0.0	84.7	61.5	–0.40	0.0	0.0	0.0 ^[f]
4	C ₁	1.8	72.7	87.6	–0.42	0.1	0.0	0.8
5	C ₁	0.0	101.9	87.6	–0.43	0.0	0.0	0.0
6	C _s	39.5	681.5i	86.7	–0.58	30.9	30.5	36.1
7	C ₁	40.7	524.0i	86.1	–0.66	36.2	35.3	39.1
8	C _s	–	635.5 ^[a]	13.9 ^[a]	0.0	–	–	–
9	C _{2v}	23.6 ^[a]	178.1 ^[a]	71.8 ^[a]	–	92.9 ^[a]	–	–
10	C ₁	15.3	42.9 ^[a]	87.3 ^[a]	–0.40 ^[a]	–	–	–
11	C _s	41.7	346.5i ^[a]	86.6 ^[a]	–0.63	39.3	–	42.6
12	C ₁	0.0	109.7 ^[a]	89.1 ^[a]	–0.43	0.0	–	0.0
13	C _s	– ^[h]	–	–	–0.63	43.2	–	48.0
14	C _s	60.4	558.7i ^[a]	70.4 ^[a]	–0.64 ^[a]	–	–	–
15	C ₁	0.0	84.3 ^[a]	72.9 ^[a]	–0.40 ^[a]	–	–	–
16	C _s	59.6	604.9i ^[a]	70.6 ^[a]	–0.65 ^[a]	–	–	–
17	C ₁	81.1	467.3i	59.0	–0.65	70.1	67.4	64.8 ^[f]

[a] RHF geometry. [b] With RHF ZPE correction, scaled by 0.9135.^[i] [c] Sum of RHF Mulliken charges on the formate group. [d] Relative free energy at 298 K, from unscaled MP2 vibrations. [e] MP4(SDQ,FC) energy, with MP2 ZPE correction, scaled by 0.9646.^[i] [f] MP4(SDTQ,FC) energy, with MP2 ZPE correction, scaled by 0.9646.^[i] [g] **8** + **9** relative to **5**. [h] The chair form could not be located at the RHF/6-31G** level. [i] J. A. Pople, A. P. Scott, M. W. Wong, L. Radom, *Isr. J. Chem.* **1993**, *33*, 345.

- [11] M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. Keith, G. A. Petersson, J. A. Montgomery, K. Raghavachari, M. A. Al-Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. Defrees, J. Baker, J. P. Stewart, M. Head-Gordon, C. Gonzalez, J. A. Pople, Gaussian, Inc., Pittsburgh PA, **1995**.
- [12] a) S. Ham, D. M. Birney, *J. Org. Chem.* **1996**, *61*, 3962–3968; b) D. M. Birney, X. Xu, S. Ham, X. Huang, *J. Org. Chem.* **1997**, *62*, 7114–7120.



- [13] A Nazarov-type cyclization to **3** would be possible in analogy to **10**, but would be disfavored by strain.
- [14] The near degeneracy of the HOMO₋₁ and HOMO₋₂ is a consequence of the weak interaction between the two oxygen lone pairs.
- [15] Subjacent orbital control of some forbidden hydrocarbon reactions has been proposed by Berson and Salem.^[16] The situation here is somewhat different in that the three HOMOs shown in Figure 3 are essentially noninteracting. Furthermore, the [3,3] and [3,5] rearrangements of **4** are both orbital symmetry allowed.
- [16] a) J. A. Berson, L. Salem, *J. Am. Chem. Soc.* **1972**, *94*, 8917–8918; b) J. A. Berson, R. W. Holder, *J. Am. Chem. Soc.* **1973**, *95*, 2037–2038.
- [17] H. B. Burgi, J. D. Dunitz, E. Shefter, *J. Am. Chem. Soc.* **1973**, *95*, 5065–5067.
- [18] T. H. Lowry, K. S. Richardson, *Mechanism and Theory in Organic Chemistry*, 3rd ed., Harper and Row, New York, **1987**, p. 839.
- [19] These structures were only optimized at the RHF/6-31G** level.
- [20] A second-order saddle point with C_s symmetry for this rearrangement has been calculated,^[5] but no TS was reported. The three lowest energy conformations of **1** were recalculated (**1a–c** in this work correspond to **5**, **3**, and **1**, respectively, in ref. [5]).
- [21] MP4/6-31G** + ZPE.^[5]
- [22] E. M. Engler, J. D. Andose, P. von R. Schleyer, *J. Am. Chem. Soc.* **1973**, *95*, 8005–8025.

Canted Ferromagnetism in a Ni^{II} Chain with a Single End-to-End Azido Bridge**

Chang Seop Hong and Youngkyu Do*

With regard to the factors that affect magnetic exchange pathways between paramagnetic centers, the proper choice of bridging ligands is of importance since they influence the magnetic strength and behavior of the molecules. The azido ligand has been widely utilized because its diverse binding modes lead to variations in the magnetic properties that depend on its orientation with respect to the magnetic centers.^[1] The structural variety of azido complexes spans from dinuclear,^[2] tetranuclear,^[3] cubane,^[4] one-dimensional,^[5] two-dimensional,^[6] to three-dimensional compounds.^[7] The coordination modes generally observed for the bridging azido group are end-on with ferromagnetic interaction and end-to-end with antiferromagnetic coupling. An example of end-to-end mode for an azido group with ferromagnetic coupling is still lacking, although such systems are favored according to theoretical calculations.^[5] Hence, it would be of interest to extend the studies on the magnetic properties of azido compounds by utilizing nonchelating capping ligands, which allow some freedom in the complexation process.^[8] We employed the nonchelating capping ligand 3(5-methyl-

pyrazole) to prepare new azido complexes. Here we report the synthesis, structure, and properties of a new one-dimensional compound $[\text{Ni}(\text{5-methylpyrazole})_4(\text{N}_3)]_n(\text{ClO}_4)_n \cdot n\text{H}_2\text{O}$ (**1**),^[9] the first ferromagnetic end-to-end azido complex involving spin canting.

A perspective view of the asymmetric unit and of one symmetry-related fragment of the chain complex **1** is shown in Figure 1. Crystallographic inversion centers are located at the

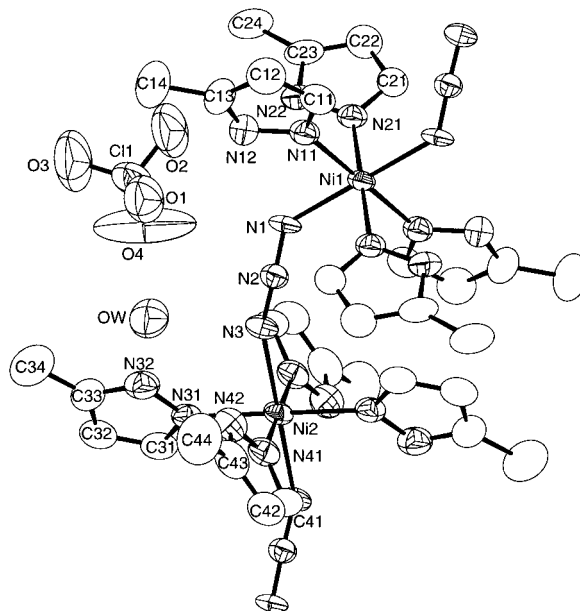


Figure 1. Perspective view of the asymmetric unit of **1** (50% thermal ellipsoids).

two nickel atoms, which have octahedral coordination environments. The nickel center Ni1 forms relatively uniform bonds to the surrounding nitrogen atoms (Ni1–N11 2.106(3), Ni1–N21 2.105(3), Ni1–N1 2.098(3) Å), while Ni2 has a more distorted geometry owing to a slight equatorial contraction and axial elongation (Ni2–N31 2.097(3), Ni2–N41 2.082(3), Ni2–N3 2.124(3) Å). The equatorial least-squares planes of the two Ni centers are not parallel and form a dihedral angle of 60.6°.

The bridging azido ligands link the nickel centers to form one-dimensional chains with a unique end-to-end coordination mode in which two neighboring nickel centers occupy *cis* positions with respect to the azido group. To our knowledge,^[5] this is the first example of a μ -azido nickel(II) complex with end-to-end coordination. The Ni1–N₃–Ni2 torsional angle of 75.7° is large for an azido nickel(II) compound.^[5] The unique coordination mode and the large torsional angle can be regarded as a manifestation of the structural freedom provided by the nonchelating capping ligands in the complexation process. The two Ni–N–N bond angles of the end-to-end azido group are different (Ni1–N1–N2 128.4(2), Ni2–N3–N2 146.1(3)°). The intrachain distance between the adjacent nickel centers is 5.717 Å, and the shortest interchain distance between nickel centers is 9.815 Å.

The magnetization *M* of **1** was measured in the temperature range 1.8–300 K at 100 G (Figure 2). Upon lowering the

[*] Prof. Y. Do, C. S. Hong
Department of Chemistry and Center for Molecular Science
Korea Advanced Institute of Science and Technology
Taejeon 305-701 (Korea)
Fax: (+82) 42-869-2810
E-mail: ykdo@single.kaist.ac.kr

[**] This research was supported by the Korea Science and Engineering Foundation and Samsung Advanced Institute of Technology. We thank Prof. Olivier Kahn for helpful discussions about magnetism.

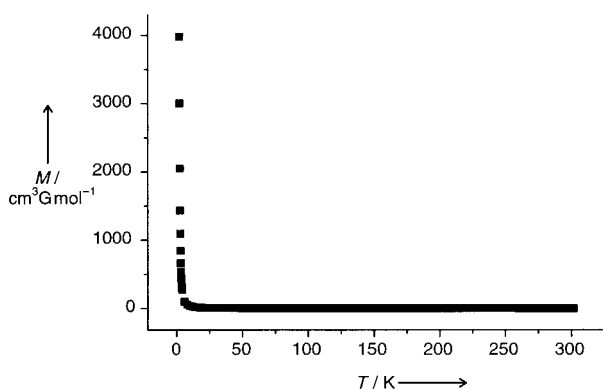


Figure 2. Plot of magnetization M versus temperature T for **1**.

temperature, the M value of $0.432 \text{ cm}^3 \text{ G mol}^{-1}$ at 300 K increases gradually to $98.42 \text{ cm}^3 \text{ G mol}^{-1}$ at 6 K and then rises sharply to $3980 \text{ cm}^3 \text{ G mol}^{-1}$ at 1.8 K, indicative of the onset of a long-range interaction in the lattice. Since the slope dM/dT is still increasing at the experimental temperature limit of 1.8 K; the critical temperature is probably slightly lower than 1.8 K. The magnetic properties of **1** can be interpreted by a Curie–Weiss law [$\chi_m = C/(T - \theta)$] in the temperature range 30–300 K. The best fit leads to $C = 1.244 \text{ cm}^3 \text{ K mol}^{-1}$ ($g = 2.23$) and $\theta = 11.1 \text{ K}$. By means of an infinite chain model,^[10] the magnetic parameters are estimated to be $g = 2.21$ and $J = 6.91 \text{ cm}^{-1}$. The positive J value suggests the presence of a ferromagnetic exchange interaction transmitted by the azido group. According to the literature criteria,^[5] the expected magnetic phenomenon for **1** would be antiferromagnetic ordering, since the Ni–N–N(azido) bond angles of $128.4(2)$ and $146.1(3)^\circ$ deviate from the value of around 164° , at which incidental orthogonality is achieved at a torsion angle of 0° . This apparently conflicts with the experimental observation of ferromagnetic behavior. We attempted to resolve this in terms of the large Ni–N₃–Ni torsional angle of 75.7° , which may minimize the antiferromagnetic contribution and favor a ferromagnetic interaction in chains of **1**.^[5, 11]

The magnetization M was measured with variation of the applied magnetic field H from 0 to 70 000 G (0–7 T) at 1.8 and 5 K (Figure 3). The experimental saturation value of $1.97 N\beta$ at 7 T does not reach the value of $gN\beta \approx 2.2 N\beta$ predicted by

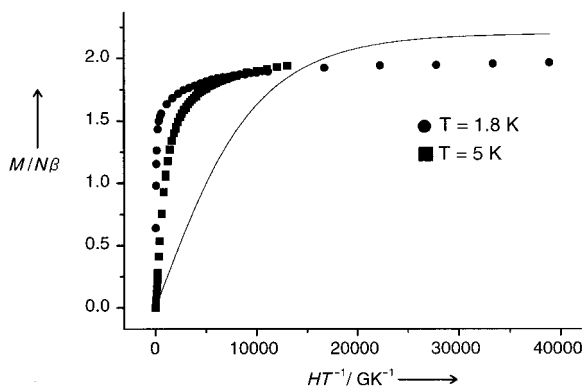


Figure 3. Plot of magnetization isotherms as a function of field strength (H/T) for **1** at 1.8 and 5 K. The solid line represents the Brillouin calculation for $S = 1$.

the Brillouin equation with $S = 1$ for noninteracting entities in a lattice.^[12] This indicates that the spin value of the Ni^{II} ion in the ground state is smaller than $S = 1$, and hence spin canting is operative in **1**. In addition, the abrupt approach of M to the saturation value at 1.8 K is reminiscent of a magnet.

Given a dihedral angle of 60.6° and a torsional angle of 75.7° , a possible pattern for spin canting can be suggested. Figure 4 illustrates spin canting in which the magnetic spins are coupled ferromagnetically but slightly tilted with respect to each other. This pattern requires no minimum valley in the $\chi_m T$ curve,^[13] as is observed for **1**, and is consistent with the experimental results displayed in Figures 2 and 3.



Figure 4. Schematic drawing of a possible spin canting pattern in **1**.

Experimental Section

1: To an aqueous solution (10 mL) of nickel perchlorate hexahydrate (0.50 mmol) was added neat 3(5)-methylpyrazole (2.0 mmol). After being stirred for 10 min, the resulting solution was treated dropwise with an aqueous solution of sodium azide (10 mL, 0.50 mmol). The pale green solution was filtered and the filtrate was left undisturbed. Well-shaped blue crystals of **1** formed (36% yield). Elemental analysis calcd for $\text{C}_{16}\text{H}_{26}\text{ClN}_{11}\text{NiO}_5$: C 35.16, H 4.79, N 28.19; found: C 35.15, H 4.94, N 28.56; IR: $\nu = 2092 \text{ cm}^{-1}$ ($\nu_a(\text{N}_3^-)$). The synthesis of the **1** requires not only use of the correct stoichiometry but also slow addition of an aqueous solution of sodium azide to the aqueous reaction mixture of Ni^{II} and 3(5)-methylpyrazole. Otherwise, the mononuclear compound $[\text{Ni}(\text{5-methylpyrazole})_4(\text{N}_3)_2]$ is formed.

Received: June 16, 1998

Revised version: August 24, 1998 [Z12000IE]

German version: *Angew. Chem.* **1999**, *111*, 153–155

Keywords: azides • magnetic properties • nickel • N ligands

- [1] J. Ribas, M. Monfort, I. Resino, X. Solans, P. Rabu, F. Maingot, M. Drillon, *Angew. Chem.* **1996**, *108*, 2671; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2520.
- [2] J. Ribas, M. Monfort, C. Diaz, C. Bastos, X. Solans, *Inorg. Chem.* **1993**, *32*, 3557.
- [3] J. Ribas, M. Monfort, R. Costa, X. Solans, *Inorg. Chem.* **1993**, *32*, 695.
- [4] M. A. Halcrow, J. C. Huffman, G. Christou, *Angew. Chem.* **1995**, *107*, 971; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 889.
- [5] a) A. Escuer, R. Vicente, J. Ribas, M. S. El Fallah, X. Solans, M. Font-Bardía, *Inorg. Chem.* **1994**, *33*, 1842; b) R. Vicente, A. Escuer, J. Ribas, M. S. El Fallah, X. Solans, M. Font-Bardía, *Inorg. Chem.* **1995**, *34*, 1278; c) J. Ribas, M. Monfort, B. K. Ghosh, R. Cortés, X. Solans, M. Font-Bardía, *Inorg. Chem.* **1996**, *35*, 864.
- [6] M. Monfort, J. Ribas, X. Solans, *J. Chem. Soc. Chem. Commun.* **1993**, 350.
- [7] F. A. Mautner, R. Cortés, L. Lezama, T. Rojo, *Angew. Chem.* **1996**, *108*, 96; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 78.
- [8] C. S. Hong, Y. Do, *Inorg. Chem.* **1997**, *36*, 5684.
- [9] X-ray structure analyses: Enraf-Nonius CAD4TSB diffractometer, MoK_α radiation, $\lambda = 0.71071 \text{ Å}$, Lorentz polarization, $\omega/2\theta$ scans. The structure was solved by direct methods with the SIR92 program and refined anisotropically for non-hydrogen atoms by full-matrix least-squares methods with SHELXS93. All hydrogen atoms were calculated at idealized positions and refined with an overall isotropic factor. Crystal data for **1** ($\text{C}_{16}\text{H}_{26}\text{ClN}_{11}\text{NiO}_5$): $M_r = 546.64$, space group $P2_1/n$, $a = 11.434(1)$, $b = 9.815(1)$, $c = 22.576(1) \text{ Å}$, $\beta = 102.68(1)^\circ$, $V =$

2471.8(3) Å³, $Z = 4$, $\rho_{\text{calc}} = 1.469 \text{ g cm}^{-3}$, $R1 = 0.048$ based on F , $wR2 = 0.133$ based on F^2 . Maximum and minimum heights in the final difference Fourier map are 0.578 and -0.378 e Å^{-3} . Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-101870. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

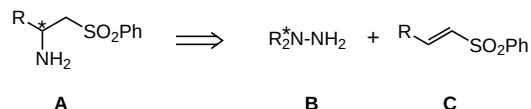
- [10] a) C. Dupas, J.-P. Renard, *J. Chem. Phys.* **1974**, *61*, 3871; b) fitting was attempted with the de Neef formula for ferromagnetic one-dimensional systems with $S = 1$ (A. Escuer, R. Vicente, M. S. El Fallah, X. Solans, M. Font-Bardía, *J. Chem. Soc. Dalton Trans.* **1996**, 1013), but was unsuccessful.
- [11] A. Escuer, R. Vicente, X. Solans, M. Font-Bardía, *Inorg. Chem.* **1994**, *33*, 6007.
- [12] R. L. Carlin, *Magnetochemistry*, Springer, New York, **1986**, p. 14.
- [13] S. Mitra, A. K. Gregson, W. E. Hatfield, R. R. Weller, *Inorg. Chem.* **1983**, *22*, 1729.

Enantioselective Synthesis of β -Amino Sulfones by aza-Michael Addition to Alkenyl Sulfones**

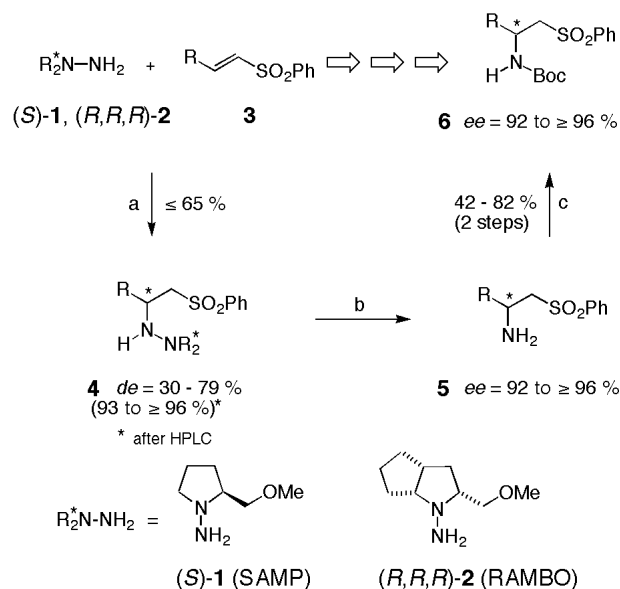
Dieter Enders,* Stephan F. Müller, and Gerhard Raabe

Dedicated to Professor Elias J. Corey
on the occasion of his 70th birthday

The use of sulfones in organic synthesis has become increasingly important in recent years. This has been due to versatile synthetic transformations involving sulfones, for example functionalization in the α position by electrophilic substitution, replacement of the sulfone group with other functional groups, and reductive cleavage of the sulfone group. Furthermore, α,β -unsaturated sulfones are excellent Michael acceptors and react with a number of carbon and heteroatom nucleophiles, such as alcohols, thiols, and amines.^[1] The aza-Michael addition involving C–N bond formation has proven to be a particularly useful synthetic tool.^[2] The conjugate addition of an enantiopure ammonia equivalent **B**, bearing a readily cleaved chiral auxiliary, to alkenyl sulfones **C** should provide a novel enantioselective access to synthetically valuable β -amino sulfones **A**.



Enantiopure β -amino sulfones play an important role in physiological processes.^[3] Additionally, they readily undergo electrophilic substitution in the α position and have, for instance, been used as intermediates in the synthesis of α -amino acids,^[4,5] amino alcohols,^[6] substituted uridines and adenosines,^[7] alkaloids,^[8] β -lactams,^[9] and nitrogen heterocycles.^[10,11] As early as the 1960s Stirling and McDowell investigated the kinetics of the intermolecular addition of achiral amines to alkenyl sulfones.^[12] Today, there exist several procedures for intramolecular^[6,8,13] and intermolecular^[7,10,11,14] aza-Michael additions to alkenyl sulfones. However, to our knowledge the enantioselective aza-Michael addition with a nitrogen nucleophile bearing chirality information, which may subsequently be cleaved, has not been described. We now report the synthesis of the title compounds by asymmetric conjugate addition with (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP, (*S*)-**1**)^[15] as a chiral ammonia equivalent; this species has already been proven to be of great value in asymmetric synthesis. As shown in Scheme 1,



Scheme 1. Enantioselective synthesis of β -amino sulfones by aza-Michael addition on alkenyl sulfones. a) 1.5 equiv of nitrogen nucleophile (*S*)-**1** or (*R,R,R*)-**2** per equiv of sulfone **3**, Yb(OTf)₃ (0.1 equiv), THF, room temperature (RT) for 20 d (procedure A) or heating at reflux for 3 d (procedure B); b) BH₃·THF (10.0 equiv, 1N in THF), THF, reflux, 5 h; HCl (4N), RT, 2 h; c) Boc₂O (10.0 equiv), Et₃N, MeOH, RT, 2 d. OTf = trifluoromethanesulfonate.

conjugate addition of (*S*)-**1** to (*E*)-alkenyl sulfones (*E*)-**3a–e** afforded Michael adducts (*R,S*)-**4a–e** in the presence of catalytic amounts of ytterbium trifluoromethanesulfonate (Yb(OTf)₃)^[16] in moderate chemical yields and with moderate to good diastereoselectivities. The epimers could be separated by preparative HPLC to yield virtually diastereomerically pure β -hydrazino sulfones (*R,S*)-**4a–e** ($de = 93$ to greater than 96% , Table 1). The absolute configuration of the newly formed stereogenic center of the major diastereomer was determined by X-ray structural analysis of crystalline (*R,S*)-**4b** (Figure 1).^[17,18]

[*] Prof. Dr. D. Enders, Dipl.-Chem. S. F. Müller, Dr. G. Raabe
Institut für Organische Chemie der Technischen Hochschule
Professor-Pirlet-Strasse 1, D-52074 Aachen (Germany)
Fax: (+49)241-888-8127
E-mail: enders@rwth-aachen.de

[**] This work was supported by the Deutsche Forschungsgemeinschaft (Leibniz prize and Sonderforschungsbereich 380) and by the Fonds der Chemischen Industrie. We thank the Degussa AG, BASF AG, Hoechst AG, Bayer AG, and Wacker Chemie for their donation of chemicals.

Table 1. Yields and diastereomeric excesses of β -hydrazino sulfones **4** prepared by conjugate addition of SAMP to (*E*)-alkenyl sulfones **3**.

Product	R ^[a]	Yield [%] ^[b]	Method	<i>de</i> [%] ^[c, d]
(<i>R,S</i>)- 4a	Et	42	A	64 (≥ 96)
(<i>R,S</i>)- 4a	Et	58	B	40 (≥ 96)
(<i>R,S</i>)- 4b	<i>i</i> Pr	25	A	79 (≥ 96)
(<i>R,S</i>)- 4b	<i>i</i> Pr	52	B	43 (≥ 96)
(<i>R,S</i>)- 4c	<i>i</i> Bu	34	A	54 (93)
(<i>R,S</i>)- 4c	<i>i</i> Bu	58	B	44 (93)
(<i>R,S</i>)- 4d	cHex ^[e]	6	A	61 (≥ 96)
(<i>R,S</i>)- 4d	cHex	35	B	50 (≥ 96)
(<i>R,S</i>)- 4e	BOM ^[f]	32	A	36 (≥ 96)
(<i>R,S</i>)- 4e	BOM	65	B	30 (≥ 96)

[a] 2-Aryl-substituted alkenyl sulfones are not suitable as Michael acceptors in the aza-analogous conjugate addition. [b] Yield of isolated **4**. The yield based on the conversion is usually 90–95%. [c] The *de* values were determined by ¹H NMR spectroscopy (Varian Gemini 300-MHz spectrometer). [d] The numbers in parentheses refer to the *de* value after resolution of the diastereomers by HPLC (SiO₂, diethyl ether/pentane 3/1). [e] cHex = cyclohexyl. [f] BOM = benzyloxymethyl.

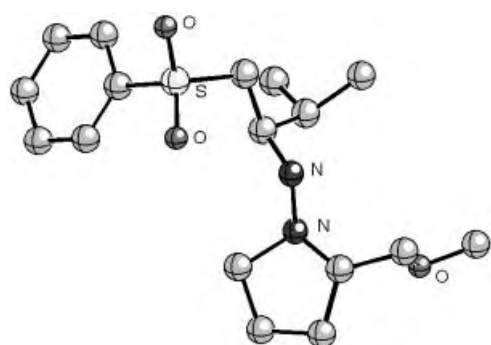


Figure 1. Structure of β -amino sulfone (*R,S*)-**4b**.^[19]

Alternatively, (*R,R,R*)-2-amino-3-methoxymethyl-azabicyclo[3.3.1]octane (RAMBO, (*R,R,R*)-**2**), first synthesized as its enantiomer SAMBO by Martens et al.,^[20] can be employed as the nitrogen nucleophile. This compound may be obtained by a five-step reaction sequence^[21] from the benzyl ester of (*R,R,R*)-2-azabicyclo[3.3.0]octane-3-carboxylic acid, a precursor to the angiotensin converting enzyme (ACE) inhibitor Ramipril from the Hoechst AG.^[22] With (*R,R,R*)-**2** as a nucleophile, considerably higher selectivities were obtained than with (*S*)-**1**. The separation of the diastereomers by means of HPLC was also feasible in this case (Table 2).

Table 2. Yields and diastereomeric excesses of β -hydrazino sulfones **4** prepared by conjugate addition of RAMBO to (*E*)-alkenyl sulfones **3** (procedure A).

Product	R ^[a]	Yield [%] ^[b]	<i>de</i> [%] ^[c, d]
(<i>S,R,R,R</i>)- 4a	Et	46	82 (≥ 96)
(<i>S,R,R,R</i>)- 4b	<i>i</i> Pr	21	≥ 96
(<i>S,R,R,R</i>)- 4c	<i>i</i> Bu	32	90 (≥ 96)
(<i>S,R,R,R</i>)- 4d	cHex	29	94
(<i>S,R,R,R</i>)- 4e	BOM	29	90
(<i>S,R,R,R</i>)- 4f	<i>n</i> Bu	45	86 (≥ 96)

[a] 2-Aryl-substituted alkenyl sulfones are not suitable as Michael acceptors in the aza-analogous conjugate addition. [b] Yield of isolated **4**. The yield based on the conversion is usually 90–95%. [c] The *de* values were determined by ¹H NMR spectroscopy (Varian Gemini 300-MHz spectrometer). [d] The numbers in parentheses refer to the *de* value after resolution of the diastereomers by HPLC (SiO₂, diethyl ether/pentane 3/1).

Reductive cleavage of the chiral auxiliary from β -hydrazino sulfones (*R,S*)-**4a–e** with BH₃·THF^[23] in refluxing THF afforded β -amino sulfones (*R*)-**5a–e** without racemization. Treatment with di-*tert*-butyldicarbonate (Boc₂O) and triethylamine in methanol gave the N-Boc-protected β -amino sulfones **6** (*ee* = 92 to greater than 96%) without prior purification of the amines **5** (Table 3). After N–N bond cleavage the chiral auxiliary (*S*)-2-methoxymethyl-pyrrolidine could be recovered as the N-Boc derivative and—after deprotection, nitrosation, and reduction—reused as a chiral ammonia equivalent.

Table 3. Yields, optical rotations, and enantiomeric excesses of N-Boc-protected β -amino sulfones **6**.

Product	R	Yield [%] ^[a]	$[\alpha]_D^{25}$ (c, CHCl ₃)	<i>ee</i> ^[b] [%]
(<i>R</i>)- 6a	Et	60	–2.1 (0.78)	≥ 96
(<i>R</i>)- 6b	<i>i</i> Pr	42	–12.9 (0.31)	≥ 96
(<i>R</i>)- 6c	<i>i</i> Bu	73	+7.1 (1.25)	92
(<i>R</i>)- 6d	cHex	58	–8.1 (0.16)	≥ 96
(<i>R</i>)- 6e	BOM	82	–9.7 (0.57)	≥ 96

[a] Yield determined over two steps. [b] The *ee* values were determined from the *de* values of the corresponding Mosher amides by ¹H NMR spectroscopy (Varian Gemini 300-MHz spectrometer).^[24]

Similarly, cleavage of the chiral auxiliary from β -hydrazino sulfones (*S,R,R,R*)-**4a–f** (Table 2) synthesized with (*R,R,R*)-**2** proceeded without racemization.^[25] By replacing SAMP by RAMBO, both enantiomers of the title compounds could be accessed.

In summary, the described asymmetric aza-Michael addition with C–N bond formation opens up an efficient approach to synthetically valuable and virtually enantiopure β -amino sulfones.^[26]

Experimental Section

4a–f: The alkenyl sulfone **3a–f** (5.0 mmol) was added dropwise to a solution of Yb(OTf)₃ (0.31 g, 0.50 mmol) in THF (10 mL) under an atmosphere of argon at room temperature. After the mixture was stirred for 15 min, the nitrogen nucleophile (*S*)-**1** or (*R,R,R*)-**2** (7.5 mmol) was added dropwise to the colorless to light yellow solution, and the mixture was stirred for 20 d at room temperature (procedure A) or 3 d under reflux (procedure B). The solution was then poured into pentane/diethyl ether (2/1, 150 mL) and filtered through celite. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography or HPLC (SiO₂, pentane/diethyl ether) to provide the major diastereomer. Products **4a–f** were isolated as colorless oils, and (*R,S*)-**4b** was obtained in crystalline form (m.p. 63 °C).

(*R*)-**5a–e:** The β -hydrazino sulfones (*R,S*)-**4a–e** (Table 1) were dissolved in THF (20 mL per mmol) under an atmosphere of argon. BH₃·THF (10 equiv, 1.0 N in THF) was added, and the reaction mixture was heated at reflux for 5 h. After the mixture had cooled to room temperature, hydrochloric acid (4 N, 3 mL per mmol) was slowly added and the solution was stirred for 2 h at room temperature. The solvent was evaporated under reduced pressure, and the residue was treated with a saturated aqueous solution of Na₂CO₃. The aqueous phase was extracted with dichloromethane/diethyl ether (3/1), and the combined organic layer was washed with brine. After drying of the solution over Na₂SO₄ the solvent was evaporated in vacuo. Without further purification, the crude product (*R*)-**5a–e** was subjected to reaction with Boc₂O or with (*R*)-Mosher's acid in order to determine the enantiomeric excess of the amine.

(*R*)-**6a–e**: The crude β -amino sulfones (*R*)-**5a–e** were dissolved in methanol (30 mL per mmol), and Boc_2O (10 equiv) and triethylamine (ca. 3 mL per mmol) were added at 0 °C. The reaction mixture was stirred for 2 d. The solvent was evaporated under reduced pressure, and the residue was diluted with diethyl ether. The mixture was washed with a saturated aqueous solution of NH_4Cl and then brine, and dried over MgSO_4 . The solvent was evaporated, and the products were purified by chromatography (SiO_2 , diethyl ether/pentane). The products (*R*)-**6a–e** were obtained as colorless solids.

Received: July 16, 1998 [Z12157IE]
German version: *Angew. Chem.* **1999**, *111*, 212–214

Keywords: aminations • asymmetric synthesis • chiral auxiliaries • Michael additions • sulfones

- [1] a) N. S. Simpkins in *Sulphones in Organic Synthesis, Tetrahedron Organic Chemistry Series, Vol. 10* (Eds.: J. E. Baldwin, P. D. Magnus), Pergamon, Oxford, **1993**; b) *The Chemistry of Functional Groups: The Chemistry of Sulphones and Sulphoxides*, (Eds.: S. Patai, Z. Rappoport, C. J. Stirling), Wiley, Chichester, **1988**; c) K. Schank, *Methoden Org. Chem. (Houben-Weyl)* **4th ed.** **1985**, Vol. E11/2, pp. 1132–1136; d) T. Durst in *Comprehensive Organic Chemistry, Vol. 3* (Eds.: D. H. R. Barton, W. D. Ollis), Pergamon, Oxford, **1979**, pp. 171–213; e) N. S. Simpkins, *Tetrahedron* **1990**, *46*, 6951–6984; f) L. Field, *Synthesis* **1978**, 713–740.
- [2] a) P. Perlmutter in *Conjugate Addition Reactions in Organic Synthesis, Tetrahedron Organic Chemistry Series, Vol. 9* (Eds.: J. E. Baldwin, P. D. Magnus), Pergamon, Oxford, **1992**; b) M. Schäfer, K. Drauz, M. Schwarm, *Methoden Org. Chem. (Houben-Weyl)* **4th ed.** **1995**, Vol. E21/5, pp. 5588–5642; c) D. Enders, H. Wahl, W. Bettray, *Angew. Chem.* **1995**, *107*, 527–529; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 453–457, and references therein.
- [3] a) D. Braghiroli, R. Avallone, M. D. Di Bella, *Tetrahedron: Asymmetry* **1997**, *8*, 2209–2213; b) H. Nakamura, H. Wu, J. Kobayashi, M. Kobayashi, Y. Ohizumi, Y. Hirata, *J. Org. Chem.* **1985**, *50*, 2494–2497; c) Y. Ichikawa, *Tetrahedron Lett.* **1988**, *29*, 4957–4958; d) B. Beagley, P. H. Crackett, R. G. Pritchard, R. J. Stoodley, *J. Chem. Soc. Perkin Trans. 1* **1990**, 773–781; e) Y. Girard, M. Larue, T. R. Jones, J. Rokach, *Tetrahedron Lett.* **1982**, *23*, 1023–1026.
- [4] R. Pauly, A. Sasaki, P. Portier, *Tetrahedron Lett.* **1994**, *35*, 237–240.
- [5] M. Hirama, H. Hioki, S. Ito, *Tetrahedron Lett.* **1988**, *29*, 3125–3128.
- [6] J. de Blas, J. C. Carretero, E. Dominguez, *Tetrahedron Lett.* **1994**, *35*, 4603–4606.
- [7] J. C. Wu, T. Pathak, W. Tong, J. M. Vial, G. Remaud, J. Chattopadhyaya, *Tetrahedron* **1988**, *44*, 6705–6722.
- [8] J. C. Carretero, R. G. Arrayas, J. Storch de Garcia, *Tetrahedron Lett.* **1997**, *38*, 8537–8540.
- [9] D. DiPietro, R. M. Borzilleri, S. M. Weinreb, *J. Org. Chem.* **1994**, *59*, 5856–5857.
- [10] D. A. Alonso, A. Costa, B. Mancheno, C. Najera, *Tetrahedron* **1997**, *53*, 4791–4814.
- [11] R. Giovannini, M. Petrini, *Synlett* **1997**, 90–92.
- [12] a) C. J. M. Stirling, S. T. McDowell, *J. Chem. Soc. B* **1967**, 343–348; b) C. J. M. Stirling, S. T. McDowell, *J. Chem. Soc. B* **1967**, 348–351.
- [13] H. Hirama, H. Hioki, S. Ito, C. Kubuto, *Tetrahedron Lett.* **1988**, *29*, 3121–3124.
- [14] A. Padwa, B. H. Norman, *J. Org. Chem.* **1990**, *55*, 4801–4807.
- [15] a) D. Enders in *Asymmetric Synthesis, Vol. 3* (Ed.: J. D. Morrison), Academic Press, Orlando, **1984**, pp. 275–339; b) D. Enders, P. Fey, H. Kipphardt, *Org. Synth.* **1987**, *65*, 173–182; c) D. Enders, P. Fey, H. Kipphardt, *Org. Synth.* **1987**, *65*, 183–202.
- [16] S. Matsubara, M. Yoshioka, K. Utimoto, *Chem. Lett.* **1994**, 827–830.
- [17] Crystal structure analysis of (*R,S*)-**4b** ($\text{C}_{17}\text{H}_{28}\text{O}_3\text{N}_2\text{S}$): orthorhombic, space group $P2_12_12_1$ (no. 19), $a = 8.2728(4)$, $b = 10.3874(5)$, $c = 22.205(1)$ Å, $V = 1908.14$ Å³, $Z = 4$, $M_{\text{calcd}} = 340.49$, $\rho_{\text{calcd}} = 1.185$ g cm⁻³. Crystals were obtained from dichloromethane/*n*-hexane, crystal dimensions ca. $0.3 \times 0.3 \times 0.3$ mm³, Enraf-Nonius CAD4 diffractometer, $\text{Cu}_{\text{K}\alpha}$ radiation (graphite monochromator, $\lambda = 1.54179$ Å). The structure was solved with direct methods (Gensin, Gentan, from Xtal3.2).^[18] Some of

the hydrogen positions could be localized, the remaining were calculated. Reflections observed [$I > 2\sigma(I)$]: 1826, parameters refined: 208; $R = 0.056$, $R_w = 0.046$; min./max. residual electron density $-0.4/+0.3$ e Å⁻³. The configuration at C8 was determined with respect to the known configuration at C3. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-102345. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

- [18] S. R. Hall, H. D. Flack, J. M. Stewart, *XTAL3.2 Reference Manual*, Universities of West Australia, Geneva, Maryland, Lamb, Perth, **1992**.
- [19] Software for preparing the ball-and-stick plot representation: Ball & Stick Version 2.2, A. Falk, N. Müller, G. Schoppel, L. Webb, Linz (Austria), Stafford (UK).
- [20] a) J. Martens, S. Lübben, *Liebigs Ann. Chem.* **1990**, 949–952; b) J. Wilken, C. Thorey, H. Gröger, D. Haase, W. Saak, S. Pohl, J. Muzart, J. Martens, *Liebigs Ann. Chem.* **1997**, 2133–2146, and references therein.
- [21] Preparation analogous to that of SAMP (*S*)-**1**.^[15]
- [22] V. Teetz, R. Geiger, R. Henning, H. Urbach, *Arzneim. Forsch.* **1984**, *34*, 1399–1401.
- [23] a) H. Feuer, F. Brown, *J. Org. Chem.* **1970**, *35*, 1468–1471; b) H. Susuki, S. Aoyagi, C. Kibayashi, *J. Org. Chem.* **1995**, *60*, 6114–6122; c) N. Yamazaki, H. Suzuki, S. Aoyagi, C. Kibayashi, *Tetrahedron Lett.* **1996**, *37*, 6161–6164; d) D. Enders, R. Lochtmann, *Synlett* **1997**, 355–357.
- [24] a) J. A. Dale, D. L. Dull, H. S. Mosher, *J. Org. Chem.* **1969**, *34*, 2543–2549; b) J. A. Dale, H. S. Mosher, *J. Am. Chem. Soc.* **1973**, *95*, 512–519.
- [25] The starting material for the synthesis of RAMBO—(*R,R,R*)-azabicyclo[3.3.0]octane-3-carboxylic acid benzyl ester hydrochloride, which was supplied by the Hoechst AG—showed an *ee* value of 80% (determined by ¹H NMR spectroscopy from the *de* value of the corresponding Mosher amide).
- [26] All new compounds showed suitable spectroscopic data (IR, MS, NMR) and correct elemental analysis or high-resolution mass spectra.

A Novel High-Nuclearity Luminescent Gold(I)–Sulfido Complex**

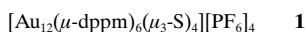
Vivian Wing-Wah Yam,* Eddie Chung-Chin Cheng, and Kung-Kai Cheung

There has been growing interest in the study of Cu^{I} , Ag^{I} , and Au^{I} complexes, and in particular polynuclear systems. This stems from the tendency of these metal ions to form clusters and aggregates as a result of weak metal–metal interactions^[1] and the recent demonstration that a number of these aggregates exhibit rich luminescence behavior.^[2] Recently, our group showed^[3] that unsubstituted chalcogenides, with their well-known ability to exhibit a variety of bridging

[*] Prof. V. W.-W. Yam, E. C.-C. Cheng, Dr. K.-K. Cheung
Department of Chemistry
The University of Hong Kong
Pokfulam Road, Hong Kong SAR (China)
Fax: (+852) 2857-1586
E-mail: wwyam@hkucc.hku.hk

[**] V.W.-W.Y. acknowledges financial support from the Research Grants Council and The University of Hong Kong. E.C.-C.C. acknowledges the receipt of a postgraduate studentship administered by The University of Hong Kong.

modes and unusual stereochemistries,^[4] could form soluble tetranuclear complexes of Cu^I and Ag^I with the formula [M₄(μ-dppm)₄(μ₃-E)]X₂ (M = Cu, Ag; E = S, Se, Te; X = PF₆, OTf; dppm = bis(diphenylphosphanyl)methane, Tf = trifluoromethanesulfonyl); all complexes were structurally characterized and shown to exhibit photophysical and photochemical properties. High-nuclearity chalcogenido clusters of Cu^I and Ag^I have also been reported by Fenske and co-workers.^[5] On the other hand, Au^I-sulfido complexes are comparatively rare,^[6] in particular those containing bridging phosphanes.^[6g, 7] Examples of Au^I-sulfido species with monodentate phosphanes include the well-known [S(AuPPh₃)₃]⁺,^[6b, c] and more recently [Au₄(μ₃-S)(PPh₃)₄]²⁺,^[6f] As the dppm ligand has a higher tendency to bind metal centers in a bridging rather than a chelating mode, it has been used in an attempt to synthesize polynuclear Au^I-chalcogenido complexes. Herein are reported the synthesis and structural characterization of **1**, a high-nuclearity luminescent Au^I-μ₃-sulfido complex with bridging dppm ligands.



Reaction of [Au₂Cl₂(dppm)]^[8] with H₂S in ethanol/pyridine, followed by removal of pyridinium chloride from the solid residue by washing with water, and subsequent metathesis reaction with NH₄PF₆ in methanol gave **1**. Recrystallization from acetone/diethyl ether afforded **1** as pale yellow crystals in 85% yield. The formulation of **1** was confirmed by elemental analyses, FAB and ESI mass spectrometry, and ¹H and ³¹P NMR spectroscopy.^[9]

The ³¹P{¹H} NMR spectrum of **1** at ambient temperature shows two singlets at δ = 28.2 and 29.8 in a ratio of 1:2, while three multiplets, which correspond to the methylene resonances of the dppm ligands, are observed in the ¹H NMR spectrum. The appearance of only two types of ³¹P signals and three types of methylene resonances suggests that **1** is fluxional in solution. It probably undergoes a ring flipping of the Au₂(μ-dppm) rings, as is commonly observed in other [M₂(μ-dppm)₂] systems.^[10] A proposed time-averaged structure of **1** in solution on the NMR time scale is depicted in Figure 1. The presence of local D_{2h} symmetry would account for the presence of two kinds of chemical environments for

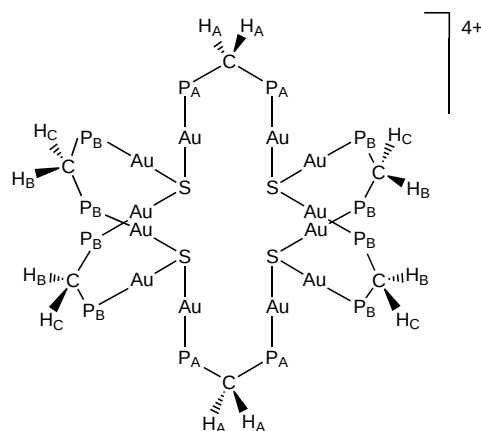


Figure 1. Proposed structure of the complex cation of **1** in solution on the NMR time scale.

the P atoms and three for the methylene protons (labeled P_A and P_B, and H_A, H_B, and H_C).

The structure of **1** in the solid state was established by X-ray crystallography (Figure 2).^[11] It consists of four Au₃S units linked together by six bridging dppm ligands to give a metallamacrobicyclic structure. A crystallographic center of inversion exists at the centroid of the four coplanar sulfur atoms.

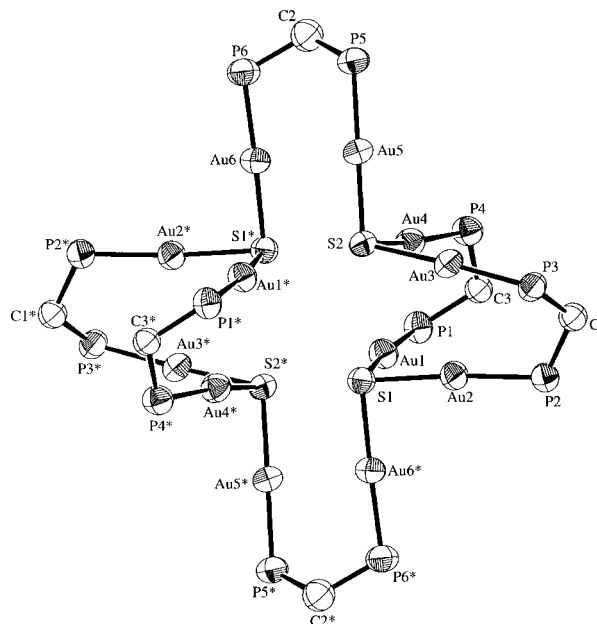


Figure 2. Crystal structure of the complex cation of **1**. Phenyl rings and hydrogen atoms have been omitted for clarity. Thermal ellipsoids are shown at the 50% probability level. Selected bond lengths [Å] and angles [°]: Au1–Au2 3.050(1), Au1–Au4 3.065(1), Au1–Au6* 3.342(1), Au2–Au3 3.176(1), Au2–Au6* 3.239(1), Au3–Au4 3.001(1), Au3–Au5 3.728(1), Au4–Au5 3.152(1), Au5–Au6 3.188(2), Au1–S1 2.334(5), Au2–S1 2.327(5), Au3–S2 2.319(5), Au4–S2 2.345(5), Au5–S2 2.309(5), Au6*–S1 2.297(5); Au1–S1–Au6* 92.4(2), Au1–S1–Au2 81.8(2), Au2–S1–Au6* 88.9(2), Au3–S2–Au4 80.1(2), Au3–S2–Au5 107.3(2), Au4–S2–Au5 85.2(2), S1–Au1–P1 170.8(2), S1–Au2–P2 175.5(2), S2–Au3–P3 177.5(2), S2–Au4–P4 168.1(2), S2–Au5–P5 176.8(2), S1–Au6*–P6* 175.3(2). Starred atoms have coordinates at 1 – x, 1 – y, – z.

The Au–S bond lengths are about 2.3 Å, which is in the range generally observed for Au^I-μ₃-sulfido complexes,^[6b, e, h] but longer than those found in μ₂-sulfido systems^[6d] and shorter than those in μ₄-sulfido systems.^[6f] Short intramolecular Au...Au contacts are present, and most are in the range of 3.001(1) to 3.342(1) Å. This is comparable to the intramolecular Au...Au distances observed in [S(AuPPh₃)₃]⁺PF₆ (3.071–3.409 Å)^[6b] and [(μ-Au₂dppf){S(Au₂dppf)}₂][OTf]₂ (2.905(2)–3.272(2) Å; dppf = bis(diphenylphosphanyl)ferrocene).^[7] An exceptionally long Au...Au distance of 3.728(1) Å is observed between Au3 and Au5. The Au–S–Au angles range from 80.1(2) to 107.3(2)°; most deviate from the 90° expected for bonding involving sulfur 3p orbitals. A smaller deviation of the Au–S–Au angle from 90° has been reported in Au^I-μ₃-sulfido systems containing monodentate phosphane ligands, such as [S(AuPPh₃)₃]⁺PF₆ (Au–S–Au 82.9(3)–95.0(3)°).^[6b] The presence of a long Au3–Au5 distance (3.728(1) Å) and a large Au3–S2–Au5 angle (107.3(2)°) may be a result of the steric demands of the dppm ligands. All the Au^I centers are two-

coordinate, and the P–Au–S angles range from 168.1(2) to 177.5(2)° and thus are slightly distorted from a linear coordination geometry. Similar deviation has also been observed in [S(AuPPh₃)₃][PF₆]^[6b] and [NEt₄]₂[S(AuC₆F₅)₃] · 0.5 MeC(O)Et.^[6h]

The UV/Vis spectrum of **1** in MeCN shows an intense absorption at 266 nm and an absorption shoulder at about 332 nm (Table 1). The intense absorption at 266 nm is

Table 1. Photophysical data for complex **1**.

λ_{abs} [nm] (ϵ)	Medium	T [K]	λ_{em} [nm]	τ_0 [μ s]
266 (94310)	MeCN	298	546	0.25 ± 0.02
332 (26150)	solid ^[a]	298	648	2.7 ± 0.2
	solid ^[a]	77	634	0.3 ± 0.02 ^[b]
	solid ^[a]	77	634	–

assigned to a dppm intraligand transition. The absence of the absorption shoulder in the spectra of [Au₂Cl₂(dppm)] and [Au₂(dppm)₂]²⁺ may suggest that it is characteristic of the Au^I–sulfido system. Unlike [S(AuPPh₃)₃]⁺, which only emits in the solid state at low temperature (λ_{em} = 640 nm, 77 K), excitation of **1** in the solid state and in solution at room temperature at wavelengths greater than 350 nm produce long-lived orange-red and green luminescence, respectively. The relatively long radiative lifetime in the microsecond range is suggestive of emission from a triplet state. With reference to previous spectroscopic work on related polynuclear d¹⁰ metal–chalcogenido complexes,^[3] the emission is tentatively assigned as derived from triplet states of a ligand-to-metal charge transfer (LMCT; S → Au) character that mix with metal-centered (ds/dp) states which are modified by Au^I...Au^I interactions.

Received: July 28, 1998

Revised version: September 17, 1998 [Z 122151E]

German version: *Angew. Chem.* **1999**, *111*, 193–195

Keywords: gold • luminescence • P ligands • S ligands

- [1] See, for example, a) D. M. P. Mingos, *J. Chem. Soc. Dalton Trans.* **1976**, 1163; b) A. Avdeef, J. P. Fackler, Jr., *Inorg. Chem.* **1978**, *17*, 2182; c) P. K. Mehrotra, R. Hoffmann, *Inorg. Chem.* **1978**, *17*, 2187; d) Y. Jiang, S. Alvarez, R. Hoffmann, *Inorg. Chem.* **1985**, *24*, 749; e) K. M. Merz, Jr., R. Hoffmann, *Inorg. Chem.* **1988**, *27*, 2120; f) H. Schmidbaur, *Chem. Soc. Rev.* **1995**, 391; g) P. Pyykkö, *Chem. Rev.* **1997**, *97*, 597.
- [2] a) P. C. Ford, A. Vogler, *Acc. Chem. Res.* **1993**, *26*, 220; b) F. Sabin, C. K. Ryu, P. C. Ford, A. Vogler, *Inorg. Chem.* **1992**, *31*, 1941; c) A. Vogler, H. Kunkely, *Chem. Phys. Lett.* **1988**, *150*, 135; d) V. W. W. Yam, K. K. W. Lo, W. K. M. Fung, C. R. Wang, *Coord. Chem. Rev.* **1998**, *171*, 17; e) B. C. Tzeng, C. K. Chan, K. K. Cheung, C. M. Che, S. M. Peng, *Chem. Commun.* **1997**, 135; f) C. K. Chan, K. K. Cheung, C. M. Che, *Chem. Commun.* **1996**, 227; g) V. W. W. Yam, W. K. M. Fung, K. K. Cheung, *Angew. Chem.* **1996**, *108*, 1213; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1100; h) C. M. Che, H. L. Kwong, C. K. Poon, V. W. W. Yam, *J. Chem. Soc. Dalton Trans.* **1990**, 3215; i) J. M. Forward, D. Bohmann, J. P. Fackler, Jr., R. J. Staples, *Inorg. Chem.* **1995**, *34*, 6330; j) M. N. I. Khan, C. King, D. D. Heinrich, J. P. Fackler, Jr., L. C. Porter, *Inorg. Chem.* **1989**, *28*, 2150; k) C. King, J. C. Wang, M. N. I. Khan, J. P. Fackler, Jr., *Inorg. Chem.* **1989**, *28*, 2145; l) M. N. I. Khan, J. P. Fackler, Jr., C. King, J. C. Wang, S. Wang,

- Inorg. Chem.* **1988**, *27*, 1672; m) M. Henary, J. I. Zink, *Inorg. Chem.* **1991**, *30*, 3111; n) J. C. Vickery, M. M. Olmstead, E. Y. Fung, A. L. Balch, *Angew. Chem.* **1997**, *109*, 1227; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1179.
- [3] a) V. W. W. Yam, W. K. Lee, T. F. Lai, *J. Chem. Soc. Chem. Commun.* **1993**, 1571; b) V. W. W. Yam, K. K. W. Lo, K. K. Cheung, *Inorg. Chem.* **1996**, *35*, 3459; c) V. W. W. Yam, K. K. W. Lo, C. R. Wang, K. K. Cheung, *Inorg. Chem.* **1996**, *35*, 5116; d) V. W. W. Yam, K. K. W. Lo, C. R. Wang, K. K. Cheung, *J. Phys. Chem. A* **1997**, *101*, 4666; e) V. W. W. Yam, K. K. W. Lo, *Comments Inorg. Chem.* **1997**, *19*, 209.
- [4] A. Müller, E. Diemann in *Comprehensive Coordination Chemistry*, Vol. 2 (Ed.: G. Wilkinson), Pergamon, Oxford, **1987**, p. 515.
- [5] See, for example, a) S. Dehnen, D. Fenske, A. C. Deveson, *J. Cluster Sci.* **1996**, *7*, 351; b) S. Dehnen, D. Fenske, *Chem. Eur. J.* **1996**, *2*, 1407; c) A. C. Deveson, S. Dehnen, D. Fenske, *J. Chem. Soc. Dalton Trans.* **1997**, 4491; d) J. F. Corrigan, D. Fenske, *Angew. Chem.* **1997**, *109*, 2070; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1981; e) J. F. Corrigan, D. Fenske, W. P. Power, *Angew. Chem.* **1997**, *109*, 1224; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1176.
- [6] a) C. Kowala, J. M. Swan, *Aust. J. Chem.* **1966**, *19*, 547; b) P. G. Jones, G. M. Sheldrick, E. Hädicke, *Acta Crystallogr. Sect. B* **1980**, *36*, 2777; c) H. Schmidbaur, A. Kolb, E. Zeller, A. Schier, H. Beruda, *Z. Anorg. Allg. Chem.* **1993**, *619*, 1575; d) C. Lensch, P. G. Jones, G. M. Sheldrick, *Z. Naturforsch. B* **1982**, *37*, 944; e) G. Marbach, J. Strähle, *Angew. Chem.* **1984**, *96*, 695; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 715; f) F. Canales, M. C. Gimeno, P. G. Jones, A. Laguna, *Angew. Chem.* **1994**, *106*, 811; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 769; g) S. Hofreiter, M. Paul, H. Schmidbaur, *Chem. Ber.* **1995**, *128*, 901; h) J. Vicente, M. T. Chicote, P. González-Herrero, C. Grünwald, P. G. Jones, *Organometallics* **1997**, *16*, 3381; i) F. Canales, C. Gimeno, A. Laguna, M. D. Villacampa, *Inorg. Chim. Acta* **1996**, *244*, 95.
- [7] F. Canales, M. C. Gimeno, A. Laguna, P. G. Jones, *J. Am. Chem. Soc.* **1996**, *118*, 4839.
- [8] H. Schmidbaur, A. Wohlleben, F. Wagner, O. Orama, G. Huttner, *Chem. Ber.* **1977**, *110*, 1748.
- [9] **1**: Elemental analysis calcd for **1** · 2H₂O (found): C 33.28 (33.03), H 2.53 (2.38); positive FAB-MS: m/z : 2545 [$M+2PF_6$]²⁺; positive ESI-MS: m/z : 1647 [$M+PF_6$]³⁺; ¹H NMR (300 MHz, [D₆]acetone, 298 K): δ = 3.58 (m, 4H, CH₂), 4.22 (m, 4H, CH₂), 4.86 (m, 4H, CH₂), 7.03–8.01 (m, 120H, Ph); ³¹P{¹H} NMR (202 MHz, [D₆]acetone, 298 K): δ = 28.2 (s, I = 1, dppm), 29.8 (s, I = 2, dppm).
- [10] a) C. T. Hunt, A. L. Balch, *Inorg. Chem.* **1981**, *20*, 2267; b) A. Blagg, A. T. Hutton, P. G. Pringle, B. L. Shaw, *J. Chem. Soc. Dalton Trans.* **1984**, 1815.
- [11] a) Crystal data for **1**: [C₁₅₀H₁₃₂P₁₂S₄Au₁₂][PF₆]₄ · 2CH₃OH · 6H₂O, M_r = 5550.25, monoclinic, space group $P2_1/n$ (no. 14), a = 16.336(6), b = 18.062(7), c = 31.982(7) Å, β = 90.30(4)°, V = 9154(5) Å³, Z = 2, ρ_{calcd} = 2.013 g cm^{−3}, $\mu(\text{MoK}\alpha)$ = 98.65 cm^{−1}, $F(000)$ = 5192, T = 301 K; R = 0.042, wR = 0.053 for 7165 reflections with $I > 3\sigma(I)$; Rigaku AFC7R diffractometer with graphite-monochromated MoK α radiation (λ = 0.71073 Å); ω – 2θ scan. The structure was solved by direct methods (SIR92^[11b]), expanded by Fourier methods, and refined by full-matrix least squares using the software package TeXsan^[11c] on a Silicon Graphics Indy computer. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-103033. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk); b) SIR92: A. Altomare, M. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli, *J. Appl. Crystallogr.* **1994**, *27*, 435; c) TeXsan: Crystal Structure Analysis Package, Molecular Structure Corporation, **1985** and **1992**.

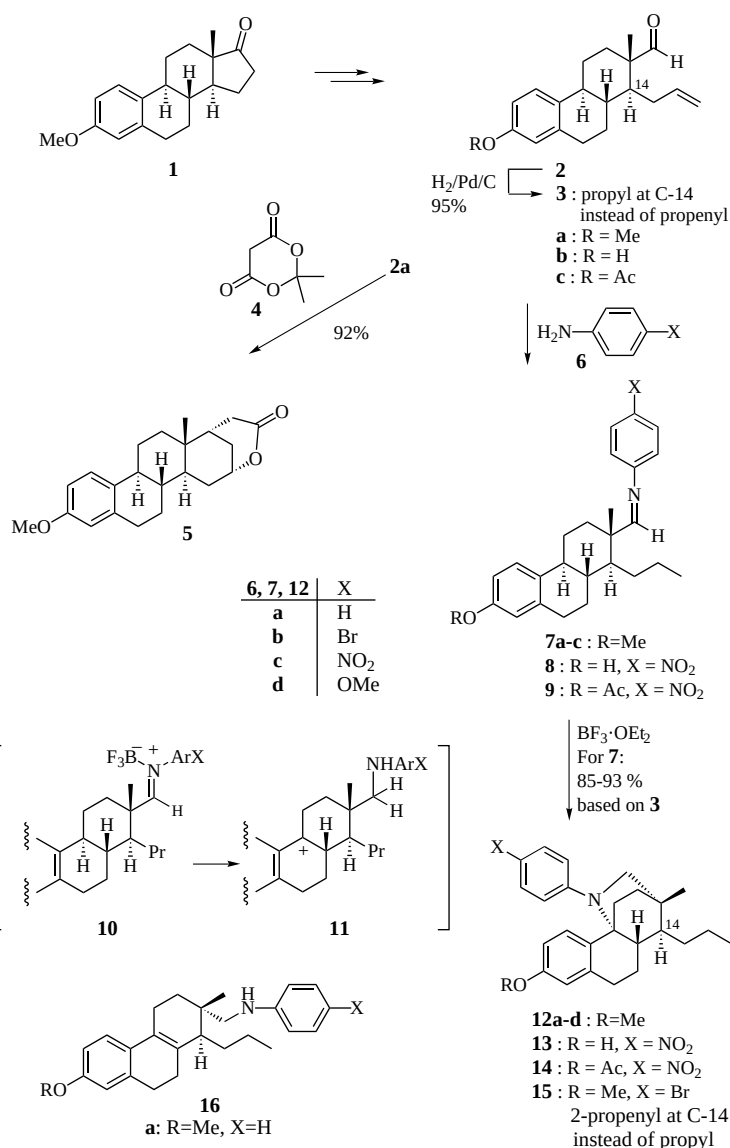
Synthesis of Unusual Bridged Steroid Alkaloids by an Iminium Ion Induced 1,5-Shift of a Benzylic Hydride**

János Wölfling, Éva Frank, Gyula Schneider,* and Lutz F. Tietze*

Dedicated to Professor Armin de Meijere on the occasion of his 60th birthday

A main principle in organic synthesis is the displacement of a suitable leaving group or the replacement of a hydrogen atom as a proton in α -position to an electron-withdrawing group. In addition, several examples of intramolecular free radical reactions at unactivated C–H bonds, such as the Barton reaction,^[1] are also known. In contrast, a cationic attack at a C–H bond with a hydride shift is rather uncommon. Here we describe a transformation of an iminium ion of a primary amine on a steroid skeleton to give the novel unusually bridged steroid alkaloids **12**–**14**; a reaction that presumably proceeds by a 1,5-hydride shift from a benzylic position to the iminium ion under formation of a carbocation that reacts with the resulting secondary amine.

Recently, we have developed the synthesis of D-homosteroid **5** by a domino Knoevenagel hetero Diels–Alder reaction^[2] of Meldrum's acid **4** and the steroid derivative **2a**,^[3] which was obtained from estrone 3-methyl ether **1** in four steps.^[4] In this sequence a 1-oxa-1,3-butadiene is formed as an intermediate. Similarly, 2-aza-1,3-butadienes can be synthesized by condensation of **2** with aniline derivatives which also undergo a hetero Diels–Alder reaction.^[2, 5] However, a completely different pathway dominates if one hydrogenates the propenyl side chain in **2a** first to give the aldehyde **3a**. Reaction of **3a** with aniline **6a** and its derivatives **6b** and **6c**, which contain an electron-withdrawing group in *para*-position, led to the imines **7a**–**c** which are rather unstable and difficult to isolate. Quite unexpectedly, treatment of crude **7a**–**c** with $\text{BF}_3 \cdot \text{OEt}_2$ in dichloromethane gave the novel unnatural bridged steroid alkaloids **12a**, **12b**, and **12c** in over 80% yield as single diastereomers. The reaction sequence can also be performed more efficiently as a



domino process^[6] to afford **12a**–**c** in 85–93% yield by preparing the imines in situ. In this way, we have also synthesized the imine **8**, which contains a hydroxyl group at C-3 of the steroid skeleton, and **9**, which contains an acetoxy group at C-3, starting from **6c** and the derivatives **3b** and **3c**, respectively, and treated them with $\text{BF}_3 \cdot \text{OEt}_2$. In the case of **8**, **13** was obtained in 63% yield together with some unsaturated material **16** within 6 h at room temperature, whereas in the case of **9** after reaction for 24 h at room temperature only 16% of the desired product **14** together with 56% of the starting material was isolated; a compound of type **16** was not found in the reaction of **9**. For the transformation of **3a** and **6c** we have also employed other Lewis acids and Brønsted acids such as AlCl_3 , SnCl_4 , SnMe_2Cl_2 , TiCl_4 , $\text{HBF}_4 \cdot \text{OEt}_2$, *p*-TsOH, and trimethylsilyl trifluoromethanesulfonate at room temperature for 24–48 h; however, the yields were much lower and the transformations less clean compared to the reactions with $\text{BF}_3 \cdot \text{OEt}_2$. Either the reaction did not proceed at all as in the case of SnMe_2Cl_2 or the unsaturated derivative **16** is the main compound, which is formed in a

[*] Prof. Dr. G. Schneider, Dr. J. Wölfling, Dipl.-Chem. É. Frank
 Institute of Organic Chemistry of József Attila University
 Dóm tér 8, H-6720 Szeged (Hungary)
 Fax: (+36) 62-454276
 E-mail: schneider@chem.u-szeged.hu

Prof. Dr. L. F. Tietze
 Institut für Organische Chemie der Universität
 Tammannstrasse 2, D-37077 Göttingen (Germany)
 Fax: (+49) 551-399476
 E-mail: ltietze@gwdg.de

[**] This work was supported by the Deutsche Forschungsgemeinschaft (SFB 416), the OTKA Grants (T016122 and F016119), and the Fonds der Chemischen Industrie. The authors thank for the Hungarian–German Intergovernmental S & T Cooperation Program (UNG-061-96).

consequential reaction from **12c** by elimination of the amino function. Thus, treatment of **12a** with $\text{BF}_3 \cdot \text{OEt}_2$ at room temperature for 24 h led to **16a** in 85 % yield. The structures of the steroid azacycles **12a–d**, **13**, and **14** were determined by NMR spectroscopy^[7] based on an X-ray crystal structure analysis of **15**.^[8]

We assume that during the reaction of the imines **7a–c**, **8**, and **9** with the Lewis acid $\text{BF}_3 \cdot \text{OEt}_2$ first an iminium ion **10** is formed. This undergoes a 1,5-hydride shift to give **11**, which contains a secondary amine moiety and a carbocation. A 1,2- or a 1,3-hydride shift is not observed, which was to be expected because of the higher activation energy of these rearrangements. Addition of the amino group to the carbocationic center in **11** then yields **12a–c**, **13**, or **14**. The proposed mechanism is consistent with the lower reactivity of **9** compared to that of **7** and **8**, which can easily be explained by a reduced stabilization of the intermediately formed benzylic cation **11**. This again is consistent with the observation that the *p*-methoxybenzyl group, which is used as a protecting group,^[9] can easily be removed by an oxidative hydride transfer by using cerium ammonium nitrate (CAN) or other oxidants, whereas a benzyl group without an electron-donating group does not undergo this reaction.

To the best of our knowledge the described domino process is a new type of transformation, though the opposite reaction, namely the formation of an iminium ion from an amine and a carbocation, is a well known process.^[10] In addition, examples of a formal insertion of an iminium ion derived from an oxime into a suitably oriented C–H bond have been described.^[11] According to the electrophilicity scale, which has recently been published by Mayr and Ofial,^[12] the iminium ion **10** is comparable with the tropylium cation and the phenyldiazonium ion. Therefore it is not unexpected that iminium ions obtained from **3a** and an aniline derivative containing an electron-donating group in *para* position such as **6d** gave the corresponding steroid alkaloids **12d** with only 2 % yield. Reactions of **3a** with *ortho*-substituted anilines did not lead to the desired products at all, presumably due to steric reasons.

Experimental Section

12a: A mixture of **3a** (298 mg, 1 mmol), freshly distilled aniline (0.9 mL, 1 mmol), and molecular sieves (4 Å, 150 mg) in dichloromethane (10 mL) was stirred under an argon atmosphere for 4 h at 40 °C. After filtration $\text{BF}_3 \cdot \text{OEt}_2$ (0.15 mL, 0.5 mmol) in dichloromethane (1 mL) was added slowly at room temperature, and stirring was continued for 12 h. After a addition of further $\text{BF}_3 \cdot \text{OEt}_2$ (0.15 mL, 0.5 mmol) in dichloromethane (1 mL) and stirring until completion (TLC), the reaction was quenched by adding ice-cold 1 N NaOH (30 mL). The organic phase was separated, the aqueous phase extracted with dichloromethane (3 × 30 mL), and the combined organic phases washed with brine and dried over Na_2SO_4 . Evaporation in vacuo and purification of the residue by chromatography (silica gel, *tert*-butyl methyl ether/petroleum ether = 1:4) afforded **12a** (319 mg, 85 %).

Received: March 30, 1998 [Z11662IE]
German version: *Angew. Chem.* **1999**, *111*, 151–152

Keywords: alkaloids • domino reactions • iminium ions • rearrangements • steroids

- [1] D. H. R. Barton, *Pure Appl. Chem.* **1968**, *16*, 1–15.
- [2] Reviews: a) L. F. Tietze, G. Kettischau, J. A. Gewert, A. Schuffenhauer, *Curr. Org. Chem.* **1998**, *2*, 19–62; b) L. F. Tietze, G. Kettischau, *Top. Curr. Chem.* **1997**, *189*, 1–101.
- [3] G. Schneider, S. Bottka, L. Hackler, J. Wölfling, P. Sohár, *Liebigs Ann. Chem.* **1989**, 263–267.
- [4] L. F. Tietze, J. Wölfling, G. Schneider, *Chem. Ber.* **1991**, *124*, 591.
- [5] J. Wölfling, É. Frank, Gy. Schneider, M. T. Bes, L. F. Tietze, *Synlett* **1998**, 1205–1206.
- [6] Reviews: a) L. F. Tietze, *Nachr. Chem. Techn. Lab.* **1997**, *45*, 1181; b) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 139–148; c) L. F. Tietze, U. Beifuss, *Angew. Chem.* **1993**, *105*, 137–169; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 131–163.
- [7] **12a:** M.p. 61–63 °C; $[\alpha]_D^{20} = +373.9$ (*c* = 1.0, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ = 0.92 (t, 3H, *J* = 7.2 Hz, 16a-H₃), 0.93 (s, 3H, 18-H₃), 1.10–1.95 (m, 11H), 2.52 (m, 1H), 2.85 (m, 2H, 6-H₂), 2.94 (dd, 1H, *J* = 9.4 Hz, *J* = 2.8 Hz, N-CH_{2,ax}), 3.52 (d, 1H, *J* = 9.4 Hz, N-CH_{2,eq}), 3.75 (s, 3H, 3-OMe), 6.31 (d, 2H, *J* = 8.3 Hz, 2'- and 6'-H), 6.52 (m, 2H, 2- and 4'-H), 6.64 (d, 1H, *J* = 2.6 Hz, 4-H), 6.86 (m, 3H, 1-, 3'- and 5'-H); ^{13}C NMR (100 MHz, CDCl_3) δ = 14.9 (C-16a), 22.3, 23.7 (C-18), 26.3, 28.6, 30.5, 33.4, 34.3, 35.0, 46.5 (C-14), 48.8 (C-8), 55.1 (3-OMe), 57.7 (C-9), 61.5 (N-CH₂), 111.8 (C-2), 113.2 (C-4), 116.9 (C-4'), 118.2 (2C, C-2' and C-6'), 127.6 (2C, C-3' and C-5'), 129.9 (C-1), 131.7 (C-10), 138.8 (C-5), 149.1 (C-1'), 158.1 (C-3). **12b:** M.p. 127–129 °C; $[\alpha]_D^{20} = +307.1$ (*c* = 1.0, CHCl_3). **12c:** Oil; $[\alpha]_D^{20} = +610.4$ (*c* = 1.0, CHCl_3).
- [8] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-102885. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [9] a) P. J. Kocienski, *Protecting Groups*, Thieme, Stuttgart, **1994**; b) T. W. Greene, P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 2nd ed., Wiley, Toronto, **1991**.
- [10] a) S. Laschat, *Liebigs Ann.* **1997**, 1–11; b) C. H. Heathcock, M. M. Hansen, R. B. Ruggeri, J. C. Kath, *J. Org. Chem.* **1992**, *57*, 2544–2553.
- [11] a) G. Neef, G. Michl, *Tetrahedron Lett.* **1991**, *32*, 5071–5072; b) P. T. Lansbury, Nitrenium Cations in *Nitrenes* (Ed.: W. Lowowski), Interscience, New York, **1970**, 404–419.
- [12] H. Mayr, A. R. Ofial, *Tetrahedron Lett.* **1997**, *38*, 3503–3506.

Peryleneimidazoloimides: Highly Fluorescent and Stable Replacements of Terrylenes**

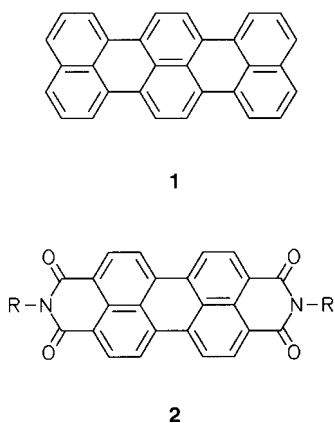
Heinz Langhals*, Harald Jaschke, Ulrike Ring, and Petra von Unold

Terrylene^[1] (**1**) is an important compound for physicochemical investigations,^[2] for example for single-molecule spectroscopy,^[3] because its UV/Vis absorption spectrum closely matches the operation region of the easily controllable rhodamine 6G dye laser (about 555–560 nm). The preparation of terrylene is however laborious, high purification very difficult, and the chemical persistency low. Moreover, the

[*] Prof. Dr. H. Langhals, Dr. H. Jaschke, Dr. U. Ring, Dr. P. von Unold
Institut für Organische Chemie der Universität
Karlstrasse 23, D-80333 Munich (Germany)
Fax: (+49) 89-5902-483
E-mail: langhals@lrz.uni-muenchen.de

[**] This work was financially supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. We thank Prof. T. Basché and Prof. C. Bräuchle for the single-molecule measurement.

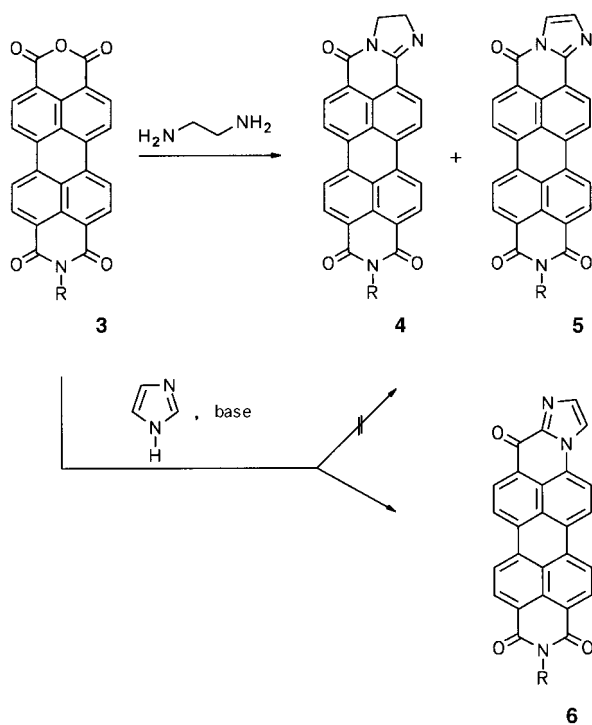
Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.



solubility is low, it has no anchor group for linkage to substrates and the fluorescence quantum yield Φ is only 45 %.^[4] An easily accessible replacement of terylene for the same spectral region would be of general interest and importance.

The perylene-3,4:9,10-bis(carboximide)s^[5] (perylenes dyes, **2**) are notable because of their high chemical and photochemical persistency, high fluo-

rescence quantum yields, and high molar absorptivities. However, their absorption spectra are more hypsochromic than **1**. We wanted to match the spectrum to **1** by replacement of one of the carbonyl groups of **2** ($R = \text{CH}(\text{C}_6\text{H}_{13})_2$) with a ketimine function through the condensation of an imidazole ring. Because the free *cis*-1,2-diaminoethylene is unknown we firstly condensed **3** with 1,2-diaminoethane to **4** so that **5** could be obtained by oxidation (Scheme 1). The latter reaction proved to be difficult because of the persistency of **4**. However, the condensation of **3** with 1,2-diaminoethane



Scheme 1. Syntheses of **4–6** ($R = \text{CH}(\text{C}_6\text{H}_{13})_2$).

forms an easily separable mixture of **4** and **5**. The ratio of **4** and **5** can be controlled by the amount of 1,2-diaminoethane used: 18 equivalents of 1,2-diaminoethane favors the formation of **4** (30 %; 39 % **5**), whereas 50 equivalents gave mainly **5** (75 %). We tried to avoid the separation of **4** and **5** by the in situ generation of an equivalent of *cis*-1,2-diaminoethylene

and its condensation with **3**. To this end, imidazole was treated with noncondensing amines such as 4-dimethylaminopyridine (DMAP^[6]) in the presence of **3**. Surprisingly, the reaction product was not **5**, but the isomer **6**. A reaction according to Regel's mechanism^[7–10] may be therefore responsible.

The exchange of a carbonyl group of **2** for the ketimine group in **4** causes a bathochromic shift (11 nm), which is increased (32 nm) by the extension of the π system in **5**, so that the working region of the laser is reached (Figure 1).

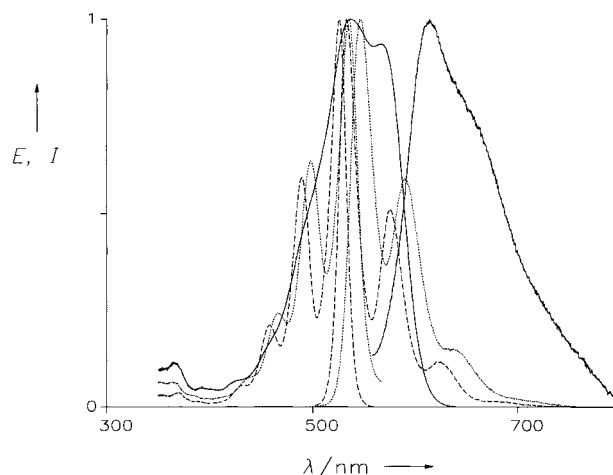


Figure 1. UV/Vis absorption and fluorescence spectra of **2** (---), **4** (···) (color coordinates: $x = 0.3646$, $y = 0.2817$, $Y = 65.24$, $T_{\min} = 0.1$, 2° , normlight C), and **5** (—) ($x = 0.3414$, $y = 0.1904$, $Y = 30.66$) in chloroform.

Dye **4** exhibits an intense fluorescence (97% quantum yield). However, the extension of the π system lowers the quantum yield (16%). The isomeric dye **6**, however, exhibits optimal properties such as a strong pink fluorescence with 84% quantum yield (in chloroform). Moreover, the absorption spectrum of **6** is nearly congruent with the spectrum of **1** (Figure 2) so that it is a replacement of terylene, but with better properties. The higher fluorescence quantum yield of **6**

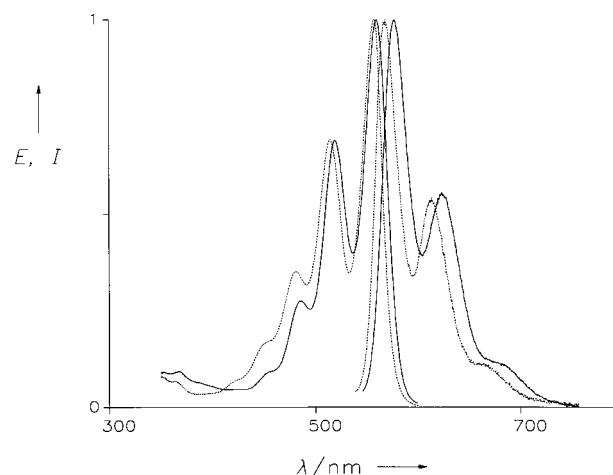


Figure 2. UV/Vis absorption and fluorescence spectra of **6** (—) (color coordinates: $x = 0.3452$, $y = 0.2343$, $Y = 50.55$, $T_{\min} = 0.1$, 2° , normlight C) compared to **1** (···) ($x = 0.3663$, $y = 0.2619$, $Y = 51.27$) in chloroform.

is remarkable as well as its high chemical and photochemical persistency.^[11] Moreover, further properties of **6** can be controlled by the substituent R. For example, **6a** exhibits a high solubility relative to **1** by the action of the "swallow-tail" substituent.^[12] On the other hand, R may contain, for example, an anchor group for the linkage of **6** to solid surfaces.

Compound **6** is a suitable dye for single-molecule spectroscopy (Figure 3). One observes for example a line with a half-width (FWHM) of 51 MHz in a polyethylene matrix, whereas a line with 39 MHz half-width was described for **1** in hexadecane.^[2] Further details of the spectroscopic investigations will be described elsewhere.^[13]

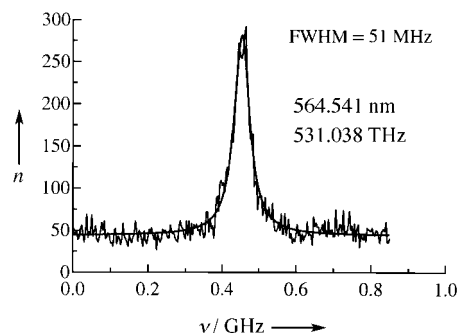


Figure 3. Single-molecule spectrum of **6** in a polyethylene matrix. Laser power 0.7 nW per 5-μm spot. Abscissa: laser detuning in GHz. Ordinate: counts in 90 ms.

Experimental Section

Condensation of **3a** with 1,2-diaminoethane: **3a** (100 mg, 0.17 mmol), 1,2-diaminoethane (0.20 mL, 3.0 mmol), and quinoline (10 mL) were heated at 180 °C for 2 h and poured while still warm into a mixture of ethanol (25 mL) and 2 N hydrochloric acid (50 mL). The violet precipitate was collected by vacuum filtration (D4 glass filter) after 1 h stirring for aging, dried (12 h, 100 °C), and purified by column chromatography (silica gel, chloroform/acetone 5/1). First fraction: 14 mg (7%) of 1,2-bis-[N-(1-hexylheptyl)perylene-3,4:9,10-bis(carboximide)s-N'-yl]ethane; R_f (silica gel, CHCl₃/acetone 5/1) = 0.94; elemental analysis calcd for C₇₆H₇₄N₄O₈ (1170.6): C 77.92, H 6.37, N 4.78; found: C 77.41, H 6.28, N 4.74. Second fraction: 40 mg (39%) of **5a**, m.p. 324 °C; R_f (silica gel, CHCl₃/acetone 5/1) = 0.49; IR (KBr): $\tilde{\nu}$ = 1697, 1658, 1593, 1349, 1282, 807, 741 cm⁻¹; UV/Vis(CHCl₃): $\lambda_{\max}$ (ϵ) = 568.6 nm (50420), 540.3 (53100), 427.1 (sh) (5540), 364.7 nm (9070 L mol⁻¹ cm⁻¹); fluorescence (CHCl₃) $\lambda_{\max}$ = 607, 654 nm (sh); Φ = 16% (c = 4.48 · 10⁻⁷ M in CHCl₃; **6a**: Φ = 84%, $\lambda_{\text{excit.}}$ = 537 nm);^[14] ¹H NMR (CDCl₃): δ = 8.61 (d, 1H, J = 8 Hz), 8.54 (s, 2H), 8.51 (d, 1H, J = 8 Hz), 8.47 (d, 1H, J = 8 Hz), 8.45 (d, 1H, J = 8 Hz), 8.42 (d, 1H, J = 8 Hz), 8.40 (d, 1H, J = 8 Hz), 7.78 (d, 1H, J = 1.7 Hz), 7.33 (d, 1H, J = 1.6 Hz), 5.11 (m_c, 1H), 2.21 (m_c, 2H), 1.83 (m_c, 2H), 1.26 (m, 16H), 0.77 (t, 6H, J = 5 Hz); ¹³C NMR (CDCl₃): δ = 158.5, 144.8, 132.5, 132.4, 131.3, 129.4, 126.8, 126.7, 125.8, 125.7, 123.8, 123.2, 122.6, 122.4, 122.2, 121.5, 115.2, 55.2, 32.4, 31.8, 29.3, 26.9, 22.6, 14.1; MS (70 eV): m/z (%): 596 (16), 595 (37) [M^+], 578 (5), 413 (100), 368 (9); elemental analysis calcd for C₃₉H₃₇N₃O₃ (595.7): C 78.63, H 6.26, N 7.05; found: C 78.49, H 6.05, N 7.13. Third fraction: yield 31 mg (30%) of **4a**, m.p. 308 °C; R_f (silica gel, CHCl₃/acetone 5/1) = 0.24; IR (KBr): $\tilde{\nu}$ = 2927, 1697, 1658, 1596, 1356, 1347, 809 cm⁻¹; UV/Vis (CHCl₃): $\lambda_{\max}$ (ϵ) = 536.2 (73290), 489.9 (46940), 467.1 (17870), 439.3 nm (sh) (5680 L mol⁻¹ cm⁻¹); fluorescence (CHCl₃): $\lambda_{\max}$ (I_{rel}) = 551 nm (1.00), 587 (0.59), 641 (0.14); Φ = 97% (c = 1.01 · 10⁻⁶ M in CHCl₃; **2a** Φ = 100%, $\lambda_{\text{excit.}}$ = 494 nm);^[14] ¹H NMR (CDCl₃): δ = 8.60 (m_c, 8H), 5.23 (m_c, 1H), 4.34 (d, 2H, J = 7.9 Hz), 4.27 (d, 2H, J = 7.8 Hz), 2.30 (m_c, 2H), 1.87 (m_c, 2H), 1.35 (m, 16H), 0.87 (t, 6H, J = 5 Hz); ¹³C NMR (CDCl₃): δ = 164.2, 163.4, 158.9, 153.6, 134.3, 134.0, 132.9, 132.0, 131.1, 130.5, 129.6, 129.3, 128.3, 126.5, 126.2, 125.7, 124.8, 122.9, 122.6, 121.9, 121.7,

121.6, 54.8, 54.3, 43.9, 32.4, 31.8, 29.3, 29.2, 27.1, 27.0, 22.6, 14.0; MS (70 eV): m/z (%): 597 (21) [M^+], 595 (29), 416 (31), 415 (66), 414 (79), 413 (100), 270 (20), 182 (30); elemental analysis calcd for C₃₉H₃₉N₃O₃ (597.8): C 78.29, H 6.52, N 7.03; found: C 77.95, H 6.55, N 6.93.

6a: Compound **3a** (250 mg, 0.436 mmol) and imidazole (1.00 g, 14.7 mmol) were homogenized (mortar). The mixture was heated at 170 °C for 3 h (autoclave) after the addition of 4-dimethylaminopyridine (1.06 g, 8.68 mmol). Ethanol (100 mL) and 2 N hydrochloric acid (150 mL) were added to the still warm (ca. 60 °C) mixture, which was then stirred for more than 1 h for aging. The black precipitate was collected by vacuum filtration and purified by column chromatography (silica gel, CHCl₃/acetone 5/1). Yield: 130 mg (51%) of **6a**, m.p. > 315 °C; R_f (silica gel, CHCl₃/acetic acid 20/1) = 0.21; IR (KBr): $\tilde{\nu}$ = 1697, 1653, 1592 cm⁻¹; UV/Vis (CHCl₃): $\lambda_{\max}$ (ϵ) = 561.5 (86800), 520.7 (60360), 486.7 nm (25050 L mol⁻¹ cm⁻¹); fluorescence (CHCl₃): $\lambda_{\max}$ (I_{rel}) = 575.5 nm (1.00), 616.5 (0.55), 682 (sh) (0.11); Φ = 84% (c = 1.11 · 10⁻⁶ M in CHCl₃; **2a**: Φ = 100%, $\lambda_{\text{excit.}}$ = 485 nm);^[14] ¹H NMR (CDCl₃): δ = 0.76 (t, 6H), 1.12–1.32 (m, 16H), 1.76–1.87 (m, 2H), 2.13–2.24 (m, 2H), 5.11 (m, 1H), 7.58 (d, 1H), 7.82 (d, 1H), 7.84 (d, 1H), 8.43 (d, 1H), 8.44 (d, 1H), 8.48 (d, 1H), 8.54 (d, 1H), 8.56 (d, 1H), 8.59 (d, 1H), 8.69 (d, 1H); ¹H NOESY NMR (CDCl₃): δ = (7.82, 7.84); ¹³C NMR (CDCl₃): δ = 13.96, 22.58, 27.02, 29.22, 31.79, 32.52, 54.90, 115.22, 115.50, 122.00, 122.67, 123.30, 123.36, 123.96, 125.92, 128.12, 128.25, 129.22, 129.61, 130.01, 130.23, 134.22, 134.52, 134.63, 135.69, 141.62, 171.65; MS (70 eV): m/z (%): 595 (24) [M^+], 415 (12), 414 (50), 413 (100), 85 (18), 83 (28); HR-MS calcd for C₃₉H₃₇N₃O₃: 595.2835; found 595.2825; elemental analysis calcd for C₃₉H₃₇N₃O₃: C 78.63, H 6.26, N 7.05; found: C 77.75, H 7.05, N 7.03.

Received: August 3, 1998 [Z12238IE]
German version: *Angew. Chem.* **1999**, *111*, 143–145

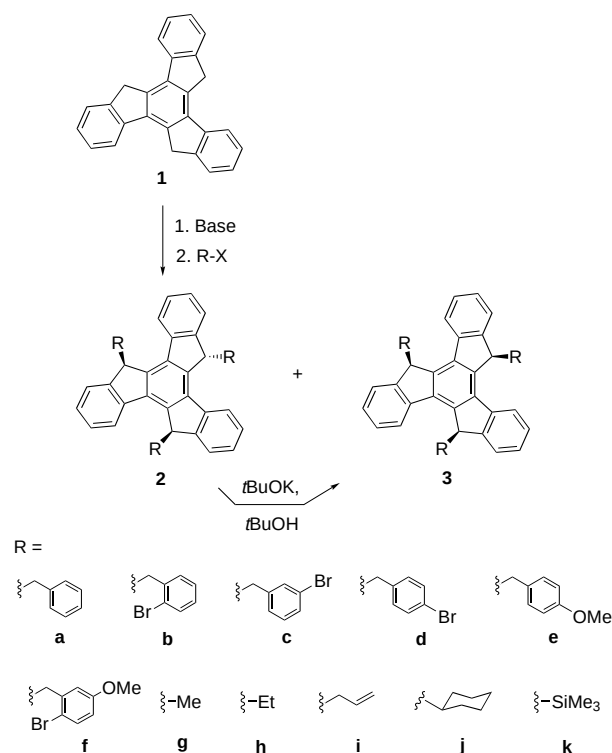
Keywords: dyes • fluorescence spectroscopy • imidazole • rearrangements

- [1] E. Clar, *Polycyclic Hydrocarbons*, Vol. 2, Academic Press, London **1964**, LCCCN 63–12392.
- [2] P. Tchenó, A. B. Myers, W. E. Moerner, *Chem. Phys. Lett.* **1993**, *213*, 325–332.
- [3] W. E. Moerner, T. Basché, *Angew. Chem.* **1993**, *105*, 537–557; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 457–476.
- [4] CHCl₃, $E_{\max}$ (557.5 nm) = 0.0621/1 cm, $\lambda_{\text{excit.}}$ = 491 nm.
- [5] For cyclic carboximide structures as structure elements of high stability and novel developments in perylene dye chemistry, see H. Langhals, *Heterocycles* **1995**, *40*, 477–500.
- [6] a) W. Steglich, G. Höfle, *Angew. Chem.* **1969**, *81*, 1001–1002, *Angew. Chem. Int. Ed. Engl.* **1969**, *12*, 918; b) G. Höfle, W. Steglich, H. Vorbrüggen, *Angew. Chem.* **1978**, *90*, 602–615, *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 569–583.
- [7] E. Regel, L. Eue, K.-H. Büchel (Bayer AG), DE-B 2043649, **1970** [*Chem. Abstr.* **1972**, *76*, 140809q].
- [8] E. Regel, K.-H. Büchel, *Justus Liebigs Ann. Chem.* **1977**, 145–158.
- [9] L. A. M. Bastiaansen, E. F. Godefroi, *J. Org. Chem.* **1978**, *43*, 1603–1604.
- [10] L. A. M. Bastiaansen, E. F. Godefroi, *Synthesis* **1978**, 675–676.
- [11] Solutions of **6** in chloroform can be irradiated with direct sunlight over several months without decomposition.
- [12] For the relationship between packing effects and solid-state fluorescence of dyes, see H. Langhals, S. Demmig, T. Potrawa, *J. Prakt. Chem.* **1991**, *333*, 733–748.
- [13] T. Basché, C. Bräuchle, H. Langhals, U. Ring, P. von Unold, H. Jaschke, unpublished results.
- [14] For convenient standards for measuring fluorescence quantum yields, see H. Langhals, see J. Karolin, L. B.-Å. Johansson, *J. Chem. Soc. Faraday Trans.* **1998**, *94*, 2919–2922.

syn-Trialkylated Truxenes: Building Blocks That Self-Associate by Arene Stacking**

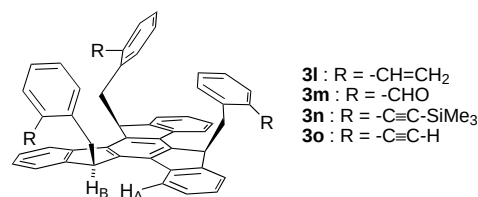
Óscar de Frutos, Berta Gómez-Lor, Thierry Granier, M. Ángeles Monge, Enrique Gutiérrez-Puebla, and Antonio M. Echavarren*

The development of a practical synthesis of bowl-shaped fragments of fullerenes^[1] would allow the construction of molecular cages with polycyclic aromatic walls which could encapsulate metal cations or small molecules.^[2] Truxene (**1**)^[3] could be used as a starting material for the synthesis of C₃ tripods by *syn* trialkylation.^[4] However alkylation of the red sodium trianion of **1** gave exclusively *anti* derivatives **2**.^[3a] We have now found that, contrary to intuition, *anti*-**2** could be isomerized to the more stable *syn*-trialkylated truxenes **3**, some of which self-associate tightly in solution.



Deprotonation of **1** with NaH (3.1 equiv, DMF, sonication, 4 °C, 45 min) followed by reaction with *o*-bromobenzyl bromide (3.5 equiv, 10 min) led exclusively to *anti* derivative **2b** (60–66 %). However, reaction of **1** with KH (3.1 equiv, THF, sonication, 4 °C, 15–30 min) or *n*BuLi (3.1 equiv, THF, –78 to –10 °C, 4 h) led to red solutions of the corresponding trianions, which reacted with a variety of alkyl halides to give 1:1 to 3:1 mixtures of *anti*- and *syn*-trialkylated derivatives from which the more insoluble *syn* derivatives **3** could be isolated by trituration with EtOAc (14–32 % yields). Notably, derivatives **2** could be almost quantitatively converted into **3** by heating with *t*BuOK (1 equiv, *t*BuOH, reflux, 12 h).^[5] Therefore, routine alkylation of **1** (*n*BuLi deprotonation) followed by base-catalyzed isomerization of the crude mixture of trialkylated products gave **3** in 59–79 % yields.^[6]

Functionalized truxenes **3** were easily obtained from the alkylated derivatives without significant isomerization to the *anti* isomers. Thus, Stille coupling of **3b** with vinyltributylstannane afforded **3l** (72 %),^[7] which was converted into the trialdehyde **3m** (98 %) by ozonolysis followed by treatment with PPh₃. On the other hand, palladium-catalyzed coupling of **3b** with (trimethylsilyl)ethynyltributylstannane^[8] gave trialkyne **3n** (55 %), which afforded **3o** (80 %) after treatment with K₂CO₃ in MeOH/THF.



The structure of **3b** was confirmed by single-crystal X-ray diffraction.^[9] After refinement in the triclinic cell (223 K), two enantiomers with different conformations are found in the unit cell (Figure 1). Both molecules show the benzyl groups approximately perpendicular to a slightly curved truxene skeleton. Molecules of **3b** pack in the crystal with a staggered face-to-face arrangement of their truxene moieties (distance between the faces 3.69–3.71 Å).^[10]

Truxenes **3** showed NMR data consistent with C₃ symmetry. Interestingly, the ¹H NMR chemical shifts in CDCl₃ were dependent on the concentration. The highest variations were observed for H_A and H_B, which moved upfield as the concentration increased (Figure 2). This suggested that truxenes **3** self-associate in this solvent.^[11] Assuming that the predominant association is due to a monomer–dimer equilibrium, the K_{assoc} values in Table 1 were determined. The highest K_{assoc} values were obtained for tribenzyltruxenes, while **3g–k** associate weakly. In fact, to the best of our knowledge, **3c** shows the highest K_{assoc} value determined for a self-association in solution which does not involve hydrogen bonds.^[11, 12] A van't Hoff analysis of K_{assoc} (CDCl₃) as a function of the temperature carried out on **3a** afforded ΔH = –5.9 ± 0.2 kcal mol^{–1} and ΔS = –8.4 ± 0.9 cal mol^{–1} K^{–1}, which indicates that the association is an enthalpically driven process.^[8] In contrast, no association was observed for the *anti* isomers **2** in CDCl₃.

[*] Prof. Dr. A. M. Echavarren, Ó. de Frutos, Dr. B. Gómez-Lor, Dr. T. Granier
 Departamento de Química Orgánica
 Universidad Autónoma de Madrid
 Cantoblanco, E-28049 Madrid (Spain)
 Fax: (+34) 91-3973966
 E-mail: anton.echavarren@uam.es

Dr. B. Gómez-Lor, Dr. M. A. Monge, Dr. E. Gutiérrez-Puebla
 Instituto de Ciencia de Materiales de Madrid, CSIC
 Cantoblanco, E-28049 Madrid (Spain).

[**] This work was supported by the DGICYT (project PB97–0002), the Ministerio de Educación y Cultura (Spain) for the award of a predoctoral fellowship and a postdoctoral contract to Ó. de F. and B.G.-L., respectively, and by the Schweizerische Nationalfonds for a postdoctoral fellowship to T.G. We also thank Prof. P. von R. Schleyer for a helpful comment.

Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.

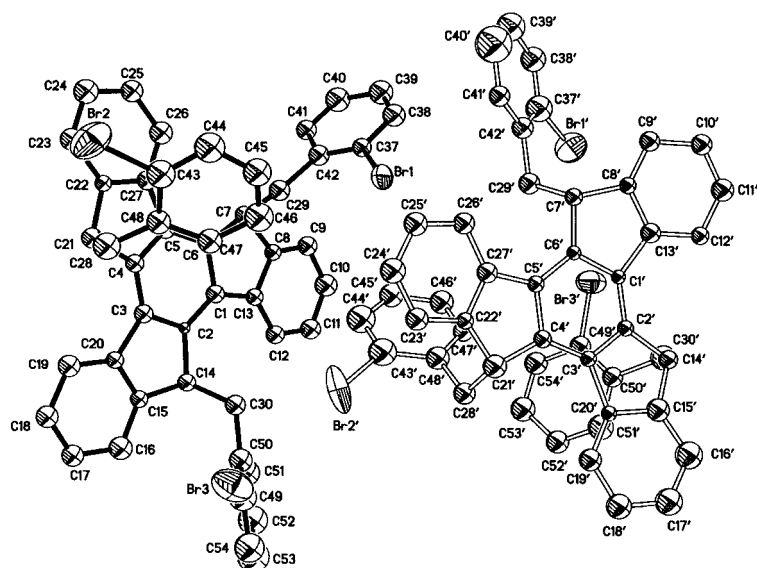


Figure 1. ORTEP diagram of the two independent conformers of **3b**.

Table 1. Association constants of truxenes **3a–i**, **3k**, **3m**, and **3n**.

Truxene	$K_{\text{assoc}} [\text{M}^{-1}]^{\text{a}}$	Truxene	$K_{\text{assoc}} [\text{M}^{-1}]^{\text{a}}$
3a	270	3g	9
3b	100	3h	8
3c	580	3i	10
3d	390	3k	2
3e	200	3m	180
3f	62	3n	200

[a] The constants were measured in CDCl_3 at 25 °C.

Alkylation of **1** with tribenzyl bromide **4**^[13] gave truxenephane **5** (66 %) yield.^[14, 15] X-ray diffraction shows that the distance between the centroids of the almost planar truxene (C1 to C6) and the parallel benzene ring (C31 to C36) is 3.36 Å (Figure 3a). Cyclophane **5** shows similar packing to that of **3b**; the truxene portions exhibit a distance between

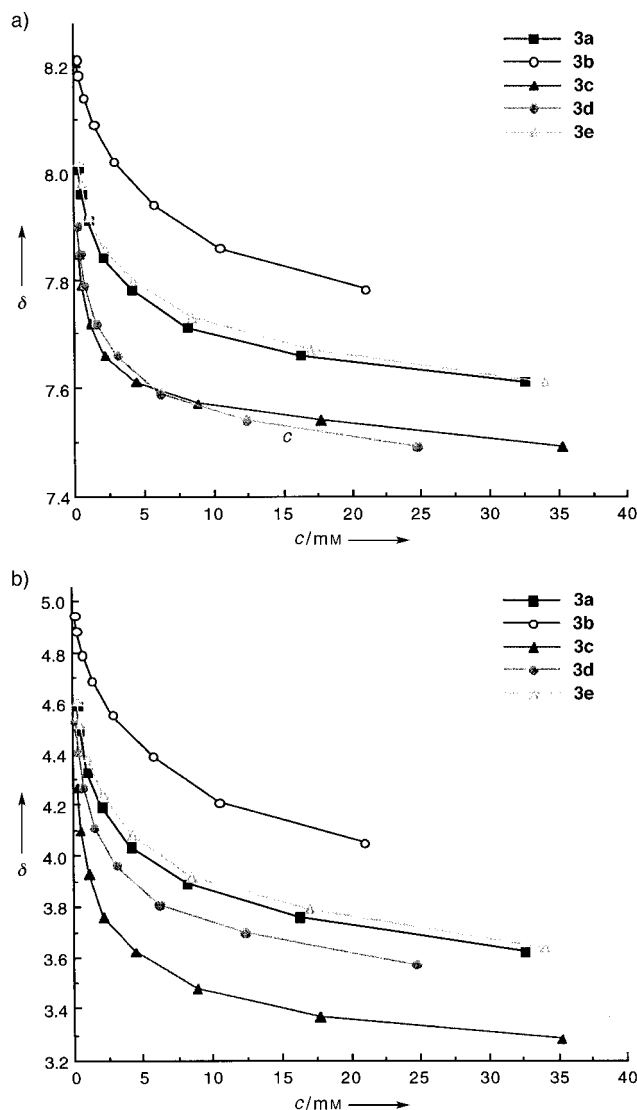


Figure 2. Chemical shifts H_A (a) and H_B (b) as a function of concentration for selected truxenes **3** (CDCl_3 , 24 °C; see structures **3i–3o** for hydrogen labeling).

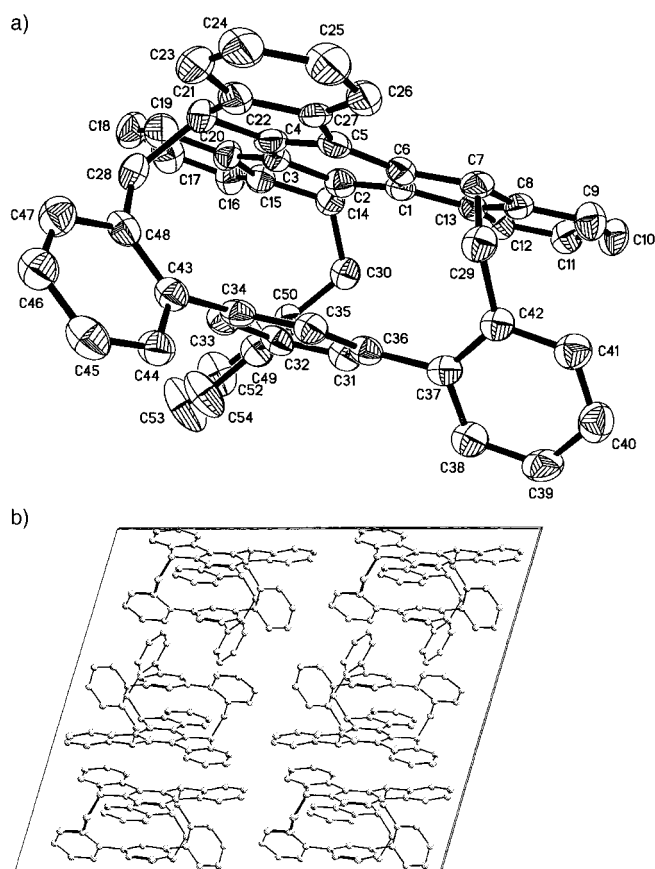
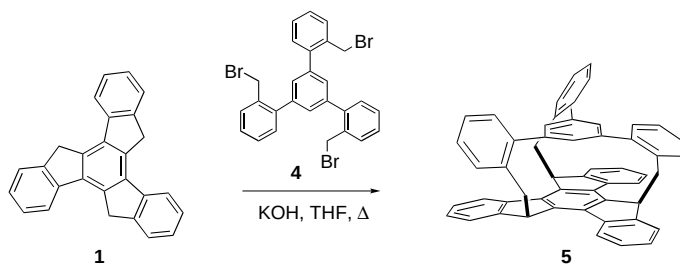
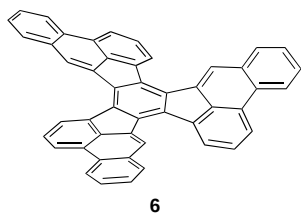


Figure 3. a) ORTEP diagram of **5**; b) crystallographic packing of **5**.

their centroids (atoms C1 to C6) of 3.70 Å (Figure 3b). Interestingly, the ^1H NMR spectrum of **5** in CDCl_3 does not change with concentration ($0.6\text{--}35 \times 10^{-3}\text{ M}$), which indicates that the association observed for **3** in solution is not a result of a truxene/truxene interaction. On the other hand, the significant shift observed for H_A and H_B (Figure 2) and the higher associations obtained for the benzyl derivatives suggest that the association in solution maximizes the aromatic interactions^[10, 11, 16] between the truxene portion of one molecule and the concave cavity of a second molecule.

The tris(*ortho*-bromobenzyl) derivatives **2b** and **3b** could be used for the synthesis of C_{48} hydrocarbon **6** by using the palladium-catalyzed intramolecular arylation reaction that we have used before for the preparation of benz[e]acephenanthrylenes and related polycyclic aromatic hydrocarbons.^[17] Interestingly, by using $\text{Pd}(\text{OAc})_2$ as the catalyst *syn*-**3b** cyclized more readily (DMF, 130 °C, 24 h) than its isomer **2b** (DMF or DMA, 36 h, 150–165 °C) to give **6** in good yields (71–79 %).



In summary, a variety of *syn*-trialkylated truxenes **3** can be readily synthesized in gram amounts from **1**. Some of these aromatic derivatives self-associate strongly in solution. A more extensive study of the arene stacking in these systems is in progress.^[18] Syntheses of higher analogues of **6** as well as efforts directed towards the preparation of large cyclophanes by dimerization of functionalized derivatives of **3b** (i.e., **3o**) and **3c** are underway.

Experimental Section

General procedure for the synthesis of *syn*-trialkylated truxenes **3:** To a mixture of **1** (1.5 mmol) in THF (50 mL) at -78°C was added *n*BuLi (3.1 equiv) and the mixture was slowly allowed to warm up to -10°C (4 h). The resulting red solution was treated with the electrophile (3.5 equiv) in THF (10 mL). After 30 min the mixture was diluted with EtOAc and washed with saturated aqueous NaCl solution, dried (Na_2SO_4), and evaporated. The residue was triturated with hexanes to yield a mixture of *anti*- and *syn*-trialkylated truxenes (3:1) as a pale yellow solid. The solid was heated under refluxing conditions with *t*BuOK (1 equiv) in *t*BuOH (30 mL) for 12 h. After being cooled, the mixture was partially evaporated, filtered, and the filtrate was evaporated. The residue was triturated with hexanes to give **3**. Further recrystallization from EtOH or toluene yielded pure compounds.

Truxenephane **5:** To a solution of **1** (137 mg, 0.4 mmol) in THF (80 mL) under refluxing conditions was added KOH (224 mg, 4 mmol). After being heated for 30 min, **4** (240 mg, 0.408 mmol) was added, and the mixture was heated for 2 h under refluxing conditions. After standard extractive workup, the residue was chromatographed (1:1 hexane/EtOAc) to give **5** (180 mg, 66 %) as a white solid, which was recrystallized from EtOH or MeCN: M.p. $> 300^\circ\text{C}$; ^1H NMR (500 MHz, CDCl_3): δ = 7.83 (d, J = 7.8 Hz, 3H), 7.42 (d, J = 7.1 Hz, 3H), 7.34 (d, J = 7.8 Hz, 3H), 7.27–7.24 (m, 3H), 7.12–7.08 (m, 6H), 6.95 (dt, J = 7.5, 1.3 Hz, 3H), 6.88 (s, 1H), 6.70 (dt, J = 7.6, 1.2 Hz, 3H), 5.05 (d, J = 14.1 Hz, 3H), 4.70 (d, J = 10.5 Hz, 3H), 3.74 (dd, J = 14.2, 10.7 Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ = 146.60, 142.92, 142.16, 141.50, 140.90, 137.34, 136.73, 134.41, 131.31, 128.73, 127.14, 126.88, 126.86, 126.69, 125.80, 122.34, 46.30, 33.87 (one C signal was not

observed); EI-MS: m/z (%): 684 (53) [M^+], 341 (100), 253 (10); elemental analysis calcd for $\text{C}_{54}\text{H}_{38} \cdot 0.5\text{EtOH}$ (%): C 93.31, H 5.55; found C 93.41, H 5.47.

Received: June 10, 1998

Revised version: October 5, 1998 [Z1971 IE]

German version: *Angew. Chem.* **1999**, *111*, 186–189

Keywords: cross-coupling • cyclophanes • hydrocarbons • palladium • stacking interactions

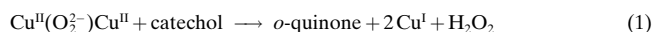
- [1] a) L. T. Scott, *Pure Appl. Chem.* **1996**, *68*, 291; b) P. W. Rabideau, A. Sygula, *Acc. Chem. Res.* **1996**, *29*, 235; c) Y. Rubin, *Chem. Eur. J.* **1997**, *3*, 1009.
- [2] Lead references on molecular capsules: a) J. M. Rivera, T. Martín, J. Rebek, *Science* **1998**, *279*, 1021; b) F.-Q. Liu, G. Harder, T. D. Tilley, *J. Am. Chem. Soc.* **1998**, *120*, 3271; c) E. V. Piatnitski, K. D. Deshayes, *Angew. Chem.* **1998**, *110*, 1022; *Angew. Chem. Int. Ed.* **1998**, *37*, 970; c) P. J. Stang, *Chem. Eur. J.* **1998**, *4*, 19; d) J. Yoo, D. J. Cram, *J. Am. Chem. Soc.* **1997**, *119*, 11796.
- [3] a) E. V. Dehmow, T. Kelle, *Synth. Commun.* **1997**, *27*, 2021; b) R. Seka, W. Kellermann, *Chem. Ber.* **1942**, *75*, 1730; c) F. S. Kipping, *J. Chem. Soc.* **1894**, 65, 272; d) J. Hausmann, *Chem. Ber.* **1889**, *22*, 2022.
- [4] Review on C_3 -symmetrical receptors: C. Moberg, *Angew. Chem.* **1998**, *110*, 260; *Angew. Chem. Int. Ed.* **1998**, *37*, 249.
- [5] a) Semiempirical calculations (PM3 Hamiltonian,^[5b] CS MOPAC Pro version) show that *syn*-trialkylated truxenes are more stable than the *anti* isomers ($\Delta\Delta H = 0.3$ (R = Me), 0.5 (R = cyclohexyl), 4.1 (R = *t*Bu) kcal mol⁻¹); b) J. J. P. Stewart, *J. Comput. Chem.* **1989**, *10*, 209. c) Attractive van der Waals interaction between the side chains may be responsible, at least in part, for the higher stability of the *syn*-trialkylated truxenes. For a discussion of this effect on the conformational equilibrium of 1,3,5-trialkylbenzenes: J. E. Anderson, V. Bru-Capdeville, P. A. Kirsch, J. S. Lomas, *J. Chem. Soc. Chem. Commun.* **1994**, 1077, and references therein.
- [6] *syn*-Truxenes **3f**, **3j**, and **3k** were obtained directly from **1** (*n*BuLi deprotonation) (30, 33, and 43 % yields, respectively). Alkylation of **1** with *p*-bromobenzyl bromide gave predominantly **2d** (68 %) which was isomerized with base to **3d** (61 % overall yield). For **2e**, best results were obtained by using KH as the base.
- [7] D. R. McKean, G. Parrinello, A. F. Renaldo, J. K. Stille, *J. Org. Chem.* **1987**, *52*, 422.
- [8] B. Gómez-Lor, A. M. Echavarren, A. Santos, *Tetrahedron Lett.* **1997**, *38*, 5347.
- [9] Crystal data for **3b**·0.5 MeCN: crystal dimensions $0.04 \times 0.12 \times 0.16\text{ mm}^3$, triclinic, space group *P1*, $a = 14.984(2)$, $b = 15.435(2)$, $c = 18.020(2)\text{ Å}$, $\alpha = 80.914(3)$, $\beta = 74.251(3)$, $\gamma = 66.706(2)^\circ$, $V = 3678.2(7)\text{ Å}^3$, $Z = 4$, $\rho_{\text{calcd}} = 1.545\text{ g cm}^{-3}$. Crystal data for **5**·0.5H₂O: crystal dimensions $0.10 \times 0.10 \times 0.20\text{ mm}^3$, triclinic, space group *P1*, $a = 11.037(1)$, $b = 13.154(1)$, $c = 15.440(1)\text{ Å}$, $\alpha = 67.227(2)$, $\beta = 69.677(2)$, $\gamma = 65.345(2)^\circ$, $V = 1831.7(3)\text{ Å}^3$, $Z = 2$, $\rho_{\text{calcd}} = 1.279\text{ g cm}^{-3}$. Equipment: CCD Siemens diffractometer (sealed tube, 2.4 kW), $\lambda(\text{Mo K}\alpha) = 0.71073\text{ Å}$. Data collections were performed at 223 K. Hemispheres of 8896 and 7535 data were collected at 223 K by 0.3° scans over 2θ ranges of $2.45\text{--}34.5^\circ$ and $2.25\text{--}42.0^\circ$ for **3b** and **5**, respectively; an empirical absorption correction from ϕ scans was applied to the data of **3b** ($\mu = 3.32\text{ mm}^{-1}$). Structural solutions by direct methods and least-squares refinements (based on F^2) were performed with SHELXTL (version 5.1994). Due to the instability and the poor diffraction spectrum of **3b**, the structure has been refined only isotropically (442 parameters/0 restraints); 3406 merged reflections converged at $R_1(F) = 0.13$, $\omega R_2(F^2) = 0.24$ for all data; $R_1(F) = 0.092$, $\omega R_2(F^2) = 0.21$ for observed data ($I > 2\sigma(I)$) GOF(F^2) = 1.013. Compound **5** was refined anisotropically (510 parameters/0 restraints); 3219 merged reflections converged at $R_1(F) = 0.094$, $\omega R_2(F^2) = 0.18$ for all data; $R_1(F) = 0.082$, $\omega R_2(F^2) = 0.18$ for observed data ($I > 2\sigma(I)$), GOF(F^2) = 1.120. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication nos. CCDC-101806 and CCDC-101807. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

- [10] Stacking of aromatic rings: G. V. Coates, A. R. Dunn, L. M. Henling, J. W. Ziller, E. B. Lobkovsky, R. H. Grubbs, *J. Am. Chem. Soc.* **1998**, *120*, 3641, and references therein.
- [11] a) A. S. Shetty, J. Zhang, J. S. Moore, *J. Am. Chem. Soc.* **1996**, *118*, 1019; b) Y. Tobe, N. Utsumi, A. Nagano, K. Naemura, *Angew. Chem.* **1998**, *110*, 1347; *Angew. Chem. Int. Ed.* **1998**, *37*, 1285.
- [12] For the self-association of porphyrins: R. J. Abraham, S. C. M. Fell, H. Pearson, K. M. Smith, *Tetrahedron* **1979**, *35*, 1759.
- [13] a) Prepared by coupling of 1,3,5-tribromobenzene with *o*-tolylboronic acid followed by benzyl bromination^[13b] of 1,3,5-tris(2-methylphenyl)benzene; b) M. J. Plater, M. Praveen, *Tetrahedron Lett.* **1997**, *38*, 1081.
- [14] G. J. Bodwell, *Angew. Chem.* **1996**, *108*, 2221; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2085.
- [15] The FAB mass spectra show complexation of cyclophane **5** with Ag⁺ (*m/z* 791) and Ag₂(OSO₂CF₃)⁺ (*m/z* 1049). For the silver ion extraction with cyclophanes: J. Gross, G. Harder, F. Vögtle, H. Stephan, K. Gloe, *Angew. Chem.* **1995**, *107*, 533; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 481.
- [16] C. A. Hunter, J. K. M. Sanders, *J. Am. Chem. Soc.* **1990**, *112*, 5525.
- [17] J. J. González, N. García, B. Gómez-Lor, A. M. Echavarren, *J. Org. Chem.* **1997**, *62*, 1286.
- [18] Liquid crystals based on truxenes: D. Sandström, M. Nygren, H. Zimmermann and A. Maliniak, *J. Phys. Chem.* **1995**, *99*, 6661, and references therein.

Reactivity of Peroxo- and Bis(μ -oxo)dicopper Complexes with Catechols**

Lisa M. Berreau, Samiran Mahapatra, Jason A. Halfen, Robert P. Houser, Victor G. Young, Jr., and William B. Tolman*

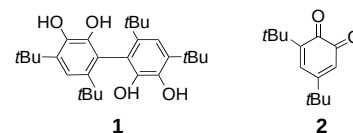
The aerobic oxidation of catechols to *o*-quinones mediated by copper ions is an important catalytic process in both synthetic and metalloprotein systems. Catechol oxidase^[1] and tyrosinase,^[2] both of which cycle through a (μ - η^2 : η^2 -peroxo)-dicopper active site intermediate, are capable of such catecholase activity, notwithstanding some controversy surrounding the involvement of discrete catechol intermediates in phenol oxidation by tyrosinase and model systems.^[3] Many mechanistic studies of catalytic catechol oxidation by dissolved copper complexes have appeared, with copper-dioxygen species often postulated as being responsible for formation of quinone and H₂O₂ in the key reaction step [Eq. (1)].^[4]



[*] Prof. W. B. Tolman, Dr. L. M. Berreau, Dr. S. Mahapatra, J. A. Halfen, R. P. Houser, Dr. V. G. Young, Jr.
Department of Chemistry and Center for Metals in Biocatalysis
University of Minnesota
207 Pleasant Street S.E., Minneapolis, MN 55455 (USA)
Fax: (+1) 612-624-7029
E-mail: tolman@chem.umn.edu

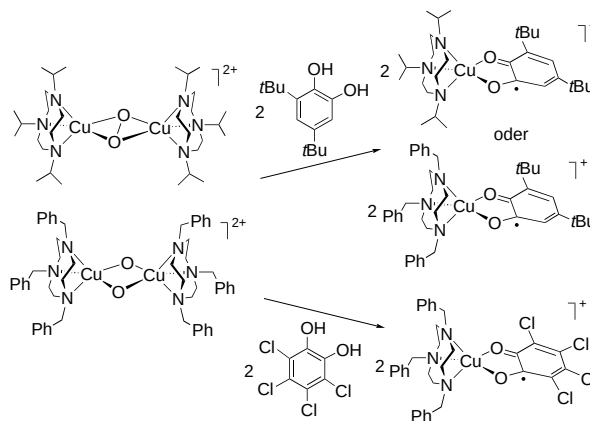
[**] We thank the National Institutes of Health (GM47365 and a postdoctoral fellowship to L.M.B.), the National Science Foundation (National Young Investigator Award to W.B.T.), the Alfred P. Sloan and Camille and Henry Dreyfus Foundations (fellowships to W.B.T.), and Unilever Corporation for financial support of this research. We also thank Professor Joel Miller and Jamie Manson (University of Utah) for magnetic measurements and helpful comments.

We have directly evaluated the feasibility of this transformation by examining the reaction of catechols with isolated (μ - η^2 : η^2 -peroxo)- and bis(μ -oxo)dicopper complexes^[5] relevant to the tyrosinase and catechol oxidase active site species. In the only other reported study of this type,^[6] a tris(pyrazolyl)hydroborate-capped (μ - η^2 : η^2 -peroxo)dicopper compound converted 3,5-di-*tert*-butylcatechol (dbcat) to the coupled product **1** under argon and to a mixture of **1** and the quinone **2** catalytically under O₂. Herein we report that instead of promoting these conversions or the reaction shown in Equation (1), complexes with isomeric [Cu(μ - η^2 : η^2 -O)₂]²⁺ and [Cu(μ -O)₂]²⁺ cores coordinated to amine macrocycles cleanly oxidize two equivalents of catechol to yield mono-copper-semiquinone complexes by a heretofore unreported synthetic route to such species (Scheme 1).



Addition of two equivalents of dbcat to solutions^[7] of orange [(Cu(L^{Bn3}))₂(μ -O)₂](SbF₆)₂ or red-brown [(Cu(L^{iPr3}))₂(μ - η^2 : η^2 -O)₂](O₃SCF₃)₂ in CH₂Cl₂ or THF at -80 °C caused bleaching of their respective optical absorption features (L^{R3} = *N,N,N*-trisubstituted 1,4,7-triazacyclononane). Upon subsequent warming and work-up, the deep green-brown complexes [Cu(L)(dbsq)]X (dbsq = 3,5-di-*tert*-butylsemiquinonato; L = L^{Bn3}, X = SbF₆; L = L^{iPr3}, X = O₃SCF₃) were isolated as crystalline solids in 93 % and 81 % yields, respectively. The complex [Cu(L^{Bn3})(Cl₄sq)]ClO₄ (Cl₄sq = 3,4,5,6-tetrachlorosemiquinonato) was prepared analogously (90 % yield of isolated product) from the ClO₄⁻ salt of the bis(μ -oxo)dicopper precursor and 3,4,5,6-tetrachlorocatechol monohydrate (Cl₄cat · H₂O). When <2.0 equivalents of dbcat were added to the bis(μ -oxo) compound, [Cu(L^{Bn3})(dbsq)]⁺ was generated in the corresponding substoichiometric amount and **1** or **2** were not produced (monitored by ¹H NMR spectroscopy).^[8]

The reaction products were identified as Cu^{II}-semiquinonato species on the basis of spectroscopic comparisons to previously reported examples,^[9] electrochemical properties, and X-ray crystallography. Notable diagnostic spectral features for the dbsq and Cl₄sq complexes include rich UV/Vis

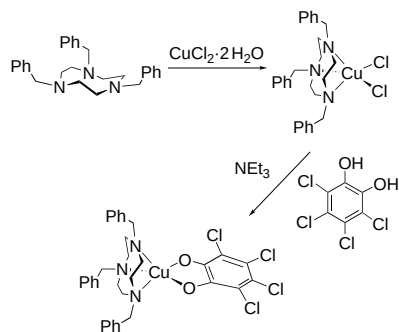


Scheme 1. Oxidation of catechol to monocopper semiquinone complexes.

spectra with a pattern of multiple intense CT bands akin to literature data^[9a-c] and EPR silence previously shown in a related complex^[9d] to result from large zero-field splitting in the ferromagnetically coupled Cu^{II}-semiquinonato spin system. Paramagnetism is revealed by room temperature magnetic susceptibility (for [Cu(L^{Bn3})(dbsq)]SbF₆, $\mu_{\text{eff}} = 2.8(1) \mu_{\text{B}}$, Evans method)^[10, 11] and large downfield-shifted signals for the dbsq ligand in the ¹H NMR spectrum of [Cu(L^{Bn3})(dbsq)]SbF₆ ($\delta = 32.2, 39.5, 59.0$, and 86.0). These signals were assigned by comparisons to the spectra of benzyl substituent deuterated and Cl₄sq analogues. Such paramagnetically shifted NMR spectral features have not been noted previously for compounds of this type.^[9] Also consistent with the Cu^{II}-semiquinonato formulation, [Cu(L^{Bn3})(dbsq)]SbF₆ shows reversible one-electron reduction ($E_{1/2} = -0.20$ V, $\Delta E_{\text{p}} = 80$ mV) and oxidation ($E_{1/2} = +0.80$ V, $\Delta E_{\text{p}} = 100$ mV) waves in its cyclic voltammogram indicative of stable Cu^{II}-catecholate and Cu^{II}-quinone/Cu^I-semiquinonato forms, respectively (data reported vs. SCE, 100 mV s⁻¹, Pt electrode, 25 °C, 0.2 M Bu₄NPF₆ in CH₂Cl₂). For the Cl₄sq analogue, both potentials are much higher, as expected, but the oxidation is irreversible ($E_{1/2} = +0.49$ V, $\Delta E_{\text{p}} = 80$ mV; $E_{\text{pa}} = +1.17$ V).

Definitive proof of the structural formulation of the reaction products was obtained by comparison of the X-ray structure of [Cu(L^{Bn3})(Cl₄sq)]ClO₄ to that of its reduced congener prepared independently, the Cu^{II}-catecholate complex [Cu(L^{Bn3})(Cl₄cat)]·CH₃CN (Scheme 2 and Figure 1).^[12-14] Both complexes exhibit square-pyramidal copper ion geometries ($\tau < 0.03$).^[15] A statistical analysis^[16] of the bond lengths associated with the bound Cl₄sq⁻ and Cl₄cat²⁻ ligands confirmed their indicated redox states ($\Delta = -0.9(1)$ and $-1.9(1)$, respectively, where values of -0 , -1 , or -2 indicate quinone, semiquinone, or catecholate levels).

Previously reported preparative routes to Cu^{II}-semiquinonato complexes include 1) reaction of dicopper(II) complexes with dbcat with generation of a Cu^I coproduct and 2) reduction of an *o*-benzoquinone by a Cu^I complex.^[9] Little mechanistic information is available for the reactions reported herein, but the existence of an intermediate (currently under investigation) is implicated by UV/Vis monitoring at -75 °C which showed bleaching of bis(μ -oxo)dicopper features *before* the appearance of final product Cu^{II}-semiquinonato absorptions that grew in only upon subsequent warming. The reactions we have discovered are new; indeed, we had anticipated conversion of catechols to *o*-benzoquinones with generation of bis(μ -hydroxo)dicopper(II) com-



Scheme 2. Synthesis of [Cu(L^{Bn3})(Cl₄cat)]·CH₃CN.

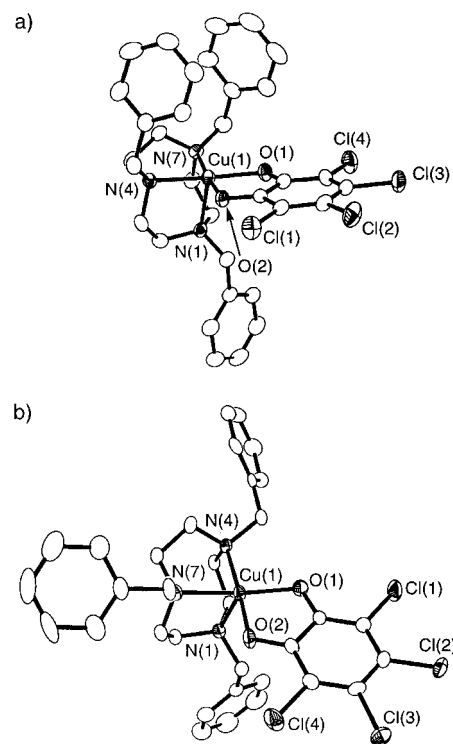


Figure 1. Representations of the X-ray crystal structures of a) the cationic portion of [Cu(L^{Bn3})(Cl₄sq)]SbF₆ and b) [Cu(L^{Bn3})(Cl₄cat)]·CH₃CN without the CH₃CN solvate molecule, showing non-hydrogen atoms as 30% and 50% thermal ellipsoids, respectively. Selected bond lengths [Å] and angles [°] for (a): Cu(1)–O(1) 1.989(4), Cu(1)–O(2) 2.001(4), Cu(1)–N(1) 2.203(4), Cu(1)–N(4) 2.028(4), Cu(1)–N(7) 2.024(4), O(1)–Cu(1)–O(2) 82.1(2); O(1)–Cu(1)–N(4) 174.0(2), N(7)–Cu(1)–O(2) 172.4(2), O(1)–Cu(1)–N(7) 96.2(2), O(2)–Cu(1)–N(4) 93.7, N(4)–Cu(1)–N(7) 87.4(2), O(1)–Cu(1)–N(1) 99.8(2), O(2)–Cu(1)–N(1) 101.0(2), N(7)–Cu(1)–N(1) 86.6(2), N(4)–Cu(1)–N(1) 85.2(2). Selected bond lengths [Å] and angles [°] for (b): Cu(1)–O(1) 1.940(4), Cu(1)–O(2) 1.915(4), Cu(1)–N(1) 2.254(4), Cu(1)–N(4) 2.058(4), Cu(1)–N(7) 2.079(4); O(1)–Cu(1)–O(2) 86.6(2), O(1)–Cu(1)–N(7) 168.3(2), O(1)–Cu(1)–N(4) 97.0(2), O(2)–Cu(1)–N(1) 98.2(2), N(4)–Cu(1)–N(1) 84.1(2), O(2)–Cu(1)–N(4) 174.8(2), O(2)–Cu(1)–N(7) 90.3(2), N(4)–Cu(1)–N(7) 85.4(2), O(1)–Cu(1)–N(1) 108.0(2), N(7)–Cu(1)–N(1) 83.6(2).

plexes on the basis of the propensity of the latter to be formed upon decomposition of (μ - η^2 : η^2 -peroxo)- and bis(μ -oxo)-dicopper compounds.^[7,17] Evidently, in the synthetic systems the mononuclear Cu^{II}-semiquinonato complexes are particularly stable thermodynamically. In contrast, the restrictive confines of the dicopper protein active sites of catechol oxidase or tyrosinase might be expected to inhibit the reaction pathway we have observed, leaving as a feasible enzymatic route the reaction of a single catechol with either a [Cu₂(μ - η^2 : η^2 -O₂)]²⁺ or a [Cu₂(μ -O)]²⁺ core to afford *o*-benzoquinone.^[19]

Experimental Section

Caution! Perchlorate salts of metal complexes with organic ligands are potentially explosive. Only small amounts of material should be prepared, and these should be handled with great care.

[Cu(L^{Bn3})(dbsq)]SbF₆: A solution of [(L^{Bn3}Cu)₂(μ -O)](SbF₆)₂ in CH₂Cl₂ (10 mL) at -80 °C was prepared as described previously (0.20 g, 0.27 mmol scale of Cu^I precursor).^[7b,c] After removal of excess dioxygen by purging N₂ at -80 °C for 10 min, a solution of dbcat (0.06 g, 0.27 mmol) in CH₂Cl₂

(≈ 0.5 mL) was added, resulting in an instantaneous color change from orange-brown to intense brown-green. The reaction mixture was stirred at -80°C for 30 min and then warmed to room temperature. After concentrating the solution to ≈ 2 mL by evaporation under vacuum, Et_2O (20 mL) was added to induce precipitation of a brown-green microcrystalline solid which was collected by filtration, washed with Et_2O , and air-dried. The product was obtained as dark brown-green crystals by diffusing Et_2O into a 1:1 $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$ solution at room temperature (0.23 g, 93 %). FT-IR (KBr): $\tilde{\nu} = 1476$ (C–O), 656 (SbF_6^-) cm^{-1} ; UV/Vis (CH_2Cl_2): $\lambda_{\text{max}}(\epsilon) = 382$ (2300), 441 (1400), 558 (720), 750 sh, 844 (340), 990 sh nm; EPR (CH_2Cl_2 , 77 K): silent; ^1H NMR (500 MHz, CD_2Cl_2 , 25°C): $\delta = 3.6$ (br, 12H), 8.1 (3H), 8.9 (6H), 12.2 (br, 6H), 32.2 (br, 9H), 39.5 (br, 1H), 59.0 (br, 9H), 86.0 (very br, 1H); ISP-MS (CH_2Cl_2): m/z (%): 682.4 (100) [M^+]; elemental analysis calcd for $\text{C}_{41}\text{H}_{33}\text{N}_3\text{O}_5\text{CuSbF}_6$ (%): C 53.64, H 5.82, N 4.58; found: C 53.07, H 5.76, N 4.54. Samples of $[\text{Cu}(\text{D}_{21}\text{L}^{\text{Bn}})(\text{dbsq})]\text{ClO}_4$ were prepared similarly starting with $[\text{Cu}(\text{D}_{21}\text{L}^{\text{Bn}})(\text{CH}_3\text{CN})]\text{ClO}_4$. FT-IR (KBr): $\tilde{\nu} = 1475$ (s, C–O), 1100 (vs, ClO_4^-), 624 (s, ClO_4^-) cm^{-1} ; EPR (CH_2Cl_2 , 77 K): silent; ^1H NMR (300 MHz, CD_2Cl_2 , 25°C): $\delta = 3.4$ (br, 12H), 32.4 (br, 9H), 39.8 (br, 1H), 59.5 (br, 9H), 86.0 (very br, 1H).

$[\text{Cu}(\text{L}^{\text{Bn}})(\text{Cl}_4\text{sq})]\text{ClO}_4$: This compound was prepared analogously to $[\text{Cu}(\text{L}^{\text{Bn}})(\text{dbsq})]\text{SbF}_6$, except by treating $[\{\text{Cu}(\text{L}^{\text{Bn}})_2(\mu\text{-O})_2\}(\text{ClO}_4)_2]$ with $\text{Cl}_4\text{cat} \cdot \text{H}_2\text{O}$ (0.24 g, 90 %). FT-IR (KBr): $\tilde{\nu} = 1498$ (s, C–O), 1451 (s, C–O), 1090 (vs, ClO_4^-), 624 (s, ClO_4^-) cm^{-1} ; UV/Vis (CH_2Cl_2): $\lambda_{\text{max}}(\epsilon) = 331$ (12400), 434 sh (3300), 444 (3400), 626 (1100), 988 (400) nm; EPR (CH_2Cl_2 , 77 K): silent; ^1H NMR (500 MHz, CD_2Cl_2 , 25°C): $\delta = 1.6$ (br, s, 12H), 8.1 (s, 3H), 9.0 (s, 6H), 12.8 (br, s, 6H); elemental analysis calcd for $\text{C}_{33}\text{H}_{33}\text{N}_3\text{O}_6\text{Cl}_5\text{Cu}$ (%): C 49.19, H 4.13, N 5.22; found: C 49.25, H 4.27, N 5.14.

$[\text{Cu}(\text{L}^{\text{Pr}})(\text{dbsq})]\text{CF}_3\text{SO}_3$: A deep red-brown solution of $[(\text{L}^{\text{Pr}}\text{Cu})_2(\mu\text{-}\eta^2\text{-O}_2)](\text{CF}_3\text{SO}_3)_2$ in CH_2Cl_2 (10 mL) at -80°C was prepared as described previously (0.13 g, 0.26 mmol scale of Cu^{I} precursor).^[7a] To this solution was added a solution of dtbc (0.057 g, 0.26 mmol) in CH_2Cl_2 (1 mL) which resulted in an instantaneous color change from red-brown to brown-green. After stirring at -80°C for 15 min, the solution was allowed to warm to room temperature and the solvent was removed under vacuum. Recrystallization of the resulting solid by pentane diffusion into a THF solution at room temperature resulted in the deposition of the product as brown-green crystals (0.142 g, 81 %). FT-IR (KBr): $\tilde{\nu} = 1476$ (s, C–O), 1226 (CF_3SO_3^-), 1151 (CF_3SO_3^-), 1030 (CF_3SO_3^-), 638 (CF_3SO_3^-) cm^{-1} ; EPR (1:1 CH_2Cl_2 /toluene, 77 K): silent; UV/Vis (CH_2Cl_2): $\lambda_{\text{max}}(\epsilon) = 380$ (2100), 444 (1450), 548 (730), 750 (350), 840 sh (330), 980 sh (200) nm; FAB-MS (MNBA): m/z (%): 538 (100) [$M - \text{CF}_3\text{SO}_3^+$]; elemental analysis calcd for $\text{C}_{40}\text{H}_{33}\text{N}_3\text{O}_5\text{F}_3\text{SCu}$ (%): C 52.35, H 7.76, N 6.10; found: C 52.10, H 7.66, N 6.00.

$[\text{Cu}(\text{L}^{\text{Bn}})(\text{Cl}_4\text{cat})] \cdot \text{CH}_3\text{CN}$: To a solution of L^{Bn} (0.20 g, 0.50 mmol)^[8] in CH_2Cl_2 (10 mL) was added a suspension of $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ (0.085 g, 0.50 mmol) in CH_2Cl_2 (10 mL). Addition of excess Et_2O (≈ 25 mL) to the resulting yellow-green solution induced deposition of a pale green microcrystalline product formulated as $\text{L}^{\text{Bn}}\text{CuCl}_2$ (0.22 g, 82 %). UV/Vis (CH_2Cl_2): $\lambda_{\text{max}}(\epsilon) = 396$ (1250), 710 (100) nm; EPR (CH_2Cl_2 , 77 K, 9.46 G Hz): $g_{\parallel} = 2.25$, $A_{\parallel} = 146$ G, $g_{\perp} = 2.04$; elemental analysis calcd for $\text{C}_{27}\text{H}_{33}\text{N}_3\text{CuCl}_2$ (%): C 60.89, H 6.25, N 7.89; found: C 60.33, H 6.27, N 7.75. To a solution of $\text{L}^{\text{Bn}}\text{CuCl}_2$ (0.15 g, 0.20 mmol) in CH_2Cl_2 (10 mL) was added $\text{Cl}_4\text{cat} \cdot \text{H}_2\text{O}$ (0.054 g, 0.20 mmol) and Et_3N (0.02 g, 0.20 mmol). The reaction mixture was stirred for 15 min during which time its green color slowly intensified. Addition of excess Et_2O resulted in the deposition of the product as green microcrystals (0.13 g, 89 %). X-ray quality crystals were obtained by slow evaporation of a $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{CN}$ solution. FT-IR (KBr): $\tilde{\nu} = 1462$ (vs, C–O) cm^{-1} ; UV/Vis (CH_2Cl_2): $\lambda_{\text{max}}(\epsilon) = 265$ (13000), 307 (7200), 485 (50), 634 (40), 990 (20) nm; EPR (CH_2Cl_2 /Toluene, 77 K, 9.44 G Hz): $g_1 = 2.24$, $g_2 = 2.05$, $g_3 = 2.01$, $A_1 = 177$ G; elemental analysis calcd for $\text{C}_{33}\text{H}_{36}\text{N}_4\text{O}_2\text{Cl}_4\text{Cu}$ (%): C 56.22, H 4.86, N 7.50; found: C 55.79, H 4.73, N 7.10.

Received: April 30, 1998

Revised version: September 10, 1998 [Z11800IE]

German version: *Angew. Chem.* **1999**, *111*, 180–183

Keywords: bioinorganic chemistry • copper • O ligands • oxidations • quinones

- [1] a) M. Tremolière, J. B. Bieth, *Phytochemistry* **1983**, *23*, 501; b) A. Rompel, H. Fischer, K. Büldt-Karentzopoulos, D. Meiwes, F. Zippel, H.-F. Nolting, C. Hermes, B. Krebs, H. Witzel, *J. Inorg. Biochem.* **1995**, *59*, 715; c) B. Krebs in *Bioinorganic Chemistry: An Inorganic Perspective of Life* (Ed.: D. P. Kessissoglou), Kluwer Academic, Dordrecht, **1995**, pp. 371–384; d) C. Eiken, F. Zippel, K. Büldt-Karentzopoulos, B. Krebs, *FEBS Lett.* **1998**, *436*, 293–299.
- [2] a) E. I. Solomon, U. M. Sundaram, T. E. Machonkin, *Chem. Rev.* **1996**, *96*, 2563–2605; b) A. Sánchez-Ferrer, J. N. Rodríguez-López, F. García-Cánovas, F. García-Carmona, *Biochim. Biophys. Acta* **1995**, *1247*, 1–11.
- [3] a) L. M. Sayre, D. V. Nadkarni, *J. Am. Chem. Soc.* **1994**, *116*, 3157–3158; b) M. Mauney, P. Capdevielle, *J. Mol. Cat. A* **1996**, *113*, 159–166.
- [4] For example, see: a) G. Speier, *J. Mol. Catal.* **1986**, *37*, 259–267; b) J.-P. Chyn, F. L. Urbach, *Inorg. Chim. Acta* **1991**, *189*, 157–163; c) J. Balia, T. Kiss, R. F. Jameson, *Inorg. Chem.* **1992**, *31*, 58–62; d) M. M. Rogic, M. D. Swerdloff, T. R. Demmin, in *Copper Coordination Chemistry: Biochemical & Inorganic Perspectives* (Eds.: K. D. Karlin, J. Zubieta), Adenine Press, New York, **1983**, pp. 259–279; e) F. Zippel, F. Ahlers, R. Werner, W. Haase, H.-F. Nolting, B. Krebs, *Inorg. Chem.* **1996**, *353*, 3409–3419; f) E. Monzani, L. Quinti, A. Perotti, L. Casella, M. Gullotti, L. Randaccio, S. Geremia, G. Nardin, P. Faleschini, G. Tabbi, *Inorg. Chem.* **1998**, *37*, 553–562; g) M. Kodera, H. Shimakoshi, Y. Tachi, K. Katayama, K. Kano, *Chem. Lett.* **1998**, 441–442; h) M. Réglier, C. Jorand, B. Waegell, *J. Chem. Soc. Chem. Commun.* **1990**, 1752–1755.
- [5] W. B. Tolman, *Acc. Chem. Res.* **1997**, *30*, 227–237.
- [6] N. Kitajima, T. Koda, Y. Iwata, Y. Moro-oka, *J. Am. Chem. Soc.* **1990**, *112*, 8833–8839.
- [7] a) S. Mahapatra, J. A. Halfen, E. C. Wilkinson, L. Que, Jr., W. B. Tolman, *J. Am. Chem. Soc.* **1994**, *116*, 9785–9786; b) J. A. Halfen, S. Mahapatra, E. C. Wilkinson, S. Kaderli, V. G. Young, Jr., L. Que, Jr., A. D. Zuberbühler, W. B. Tolman, *Science* **1996**, *271*, 1397–1400; c) S. Mahapatra, J. A. Halfen, E. C. Wilkinson, G. Pan, X. Wang, V. G. Young, Jr., C. J. Cramer, L. Que, Jr., W. B. Tolman, *J. Am. Chem. Soc.* **1996**, *118*, 11555–11574.
- [8] Treatment of THF solutions of $[(\text{Cu}(\text{L}^{\text{Bn}})_2)(\mu\text{-O})_2](\text{SbF}_6)_2$ (≈ 0.07 mm) that had been purged of excess O_2 with N_2 with 1.5, 1.0, or 0.5 equiv (per dicopper complex) of dbcat at -71°C followed by warming to ambient temperature produced $[\text{Cu}(\text{L}^{\text{Bn}})(\text{dbsq})]\text{SbF}_6$ [plus unidentified copper(II) products] in yields stoichiometrically consistent with the amount of dbcat introduced, as indicated by the intensity of the unique 454 (ϵ 1300 $\text{M}^{-1}\text{cm}^{-1}$) nm absorption band. Only a trace amount of **2** (<5 %) was detected after removal of solvent and ^1H NMR analysis of the Et_2O -extracted residue (even when only 0.5 equiv dbcat per dicopper complex was added).
- [9] a) J. S. Thompson, J. C. Calabrese, *Inorg. Chem.* **1985**, *24*, 3167–3171; b) J. S. Thompson, J. C. Calabrese, *J. Am. Chem. Soc.* **1986**, *108*, 1903–1907; c) C. Benelli, A. Dei, D. Gatteschi, L. Pardi, *Inorg. Chem.* **1990**, *29*, 3409–3415; d) A. Dei, D. Gatteschi, L. Pardi, A. L. Barra, L. C. Brunel, *Chem. Phys. Lett.* **1990**, *175*, 589–592; e) M. Ruf, B. C. Noll, M. D. Groner, G. T. Yee, C. G. Pierpont, *Inorg. Chem.* **1997**, *36*, 4860–4865.
- [10] We have been unable to interpret preliminary magnetic susceptibility data obtained (courtesy of Prof. J. Miller and J. Manson, University of Utah) for a powdered sample of $[\text{Cu}(\text{L}^{\text{Bn}})(\text{dbsq})]\text{SbF}_6$ (4.2–350 K, SQUID magnetometer), which showed an anomalously high μ_{eff} of $\approx 3.6 \mu_{\text{B}}$ at 300 K ($2.8 \mu_{\text{B}}$ at 5 K). Intermolecular magnetic interactions in this sample appear to be operative, but further experiments are necessary in order to fully analyze the system.
- [11] a) D. F. Evans, *J. Chem. Soc.* **1959**, 2003–2005; b) M. V. Baker, L. D. Field, T. W. Hambley, *Inorg. Chem.* **1988**, *27*, 2872–2876; c) W. L. Jolly, *The Synthesis and Characterization of Inorganic Compounds*, Waveland, Prospect Heights, IL, **1970**, pp. 369–374.
- [12] Crystal data for $[\text{Cu}(\text{L}^{\text{Bn}})(\text{Cl}_4\text{sq})]\text{ClO}_4$: $\text{C}_{33}\text{H}_{33}\text{N}_3\text{O}_6\text{Cl}_5\text{Cu}$, $M_r = 808.46$, crystal size $0.35 \times 0.30 \times 0.12$ mm, triclinic, space group $P\bar{1}$, $a = 10.181(2)$, $b = 10.638(2)$, $c = 16.529(3)$ Å, $\alpha = 77.80(3)$, $\beta = 86.91(3)$, $\gamma = 79.00(3)^\circ$, $V = 1717.5(6)$ Å³, $Z = 2$, $\rho_{\text{calcd}} = 1.563$ g cm^{-3} , $T = 293(2)$ K, radiation $\text{MoK}\alpha$ ($\lambda = 0.71073$ Å), 2θ max = 49.9° . Data were collected on an Enraf-Nonius CAD4 diffractometer and the structure was solved by direct methods using SHELXTL-Plus V5.0 on an SGI INDY R4400-SC computer. All non-hydrogen atoms were

refined with anisotropic displacement parameters. Hydrogen atoms were placed in calculated positions and refined as riding atoms with fixed isotropic displacement parameters. For 6017 independent reflections with $I > 2\sigma(I)$ and 433 parameters, $R1 = 0.058$ and $wR2 = 0.1181$.

- [13] Crystal data for $[\text{Cu}(\text{L}^{\text{Bn}})(\text{Cl}_4\text{cat})] \cdot \text{CH}_3\text{CN}$: $\text{C}_{35}\text{H}_{36}\text{N}_4\text{O}_2\text{Cl}_4\text{Cu}$, $M_r = 750.06$, crystal size $0.50 \times 0.35 \times 0.07$ mm, monoclinic, space group $P2_1/n$, $a = 9.802(2)$, $b = 27.759(5)$, $c = 13.049(2)$ Å, $\beta = 104.39(2)^\circ$, $V = 3439.2(1)$ Å³, $Z = 4$, $\rho_{\text{calc}} = 1.447$ g cm⁻³, $T = 173(2)$ K, radiation $\text{MoK}\alpha$ ($\lambda = 0.71073$ Å), 2θ max = 50.10° . Data were collected on Siemens SMART system and the structure was solved by direct methods using SHELXTL-Plus V5.0 on an SGI INDY R4400-SC computer. All non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were placed in calculated positions and refined as riding atoms with fixed isotropic displacement parameters. For 6038 independent reflections with $I > 2\sigma(I)$ and 444 parameters, $R1 = 0.0735$ and $wR2 = 0.1391$.
- [14] Further details of the crystal structure investigation(s) can be obtained from the Fachinformationszentrum Karlsruhe, D-76344 Eggenstein-Leopoldshafen, Germany (fax: (+49) 7247-808-666; e-mail: crysdata@fiz-karlsruhe.de), on quoting the depository numbers CSD-408633 and -408634.
- [15] A. W. Addison, T. N. Rao, J. Reedijk, J. von Rijn, G. C. Verschoor, *J. Chem. Soc. Dalton Trans.* **1984**, 1349–1356.
- [16] a) O. Carugo, C. B. Castellani, K. Djinić, M. Rizzi, *J. Chem. Soc. Dalton Trans.* **1992**, 837–841; b) O. Carugo, K. Djinić, M. Rizzi, C. B. Castellani, *J. Chem. Soc. Dalton Trans.* **1991**, 1551–1555.
- [17] S. Mahapatra, J. A. Halfen, W. B. Tolman, *J. Am. Chem. Soc.* **1996**, *118*, 11575–11586.
- [18] T. Beissel, B. S. P. C. D. Vedova, K. Wieghardt, R. Boese, *Inorg. Chem.* **1990**, *29*, 1736–1741.
- [19] Note added in proof (December 4, 1998): Semiquinone formation upon reaction of catechol with the $(\mu\text{-}\eta^2\text{-}\eta^2\text{-peroxo})\text{dicopper}$ core of *Octopus vulgaris* oxyhemocyanin was reported recently: B. Salvato, M. Santamaria, M. Beltamini, G. Alzuet, L. Casella, *Biochemistry* **1998**, *37*, 14065–14077.

Synthesis and Characterization of the Tetrahydroxyphosphonium Hexafluorometalates $\text{P}(\text{OH})_4^+\text{MF}_6^-$ ($\text{M} = \text{As}, \text{Sb}$)

Rolf Minkwitz* and Stefan Schneider

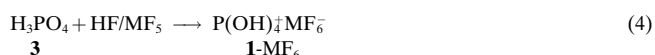
The existence of the tetrahydroxyphosphonium ion, $\text{P}(\text{OH})_4^+$ **1**, has been discussed for more than 60 years. The investigations were initiated by Hantzsch who erroneously postulated that nitracidium perchlorate, $(\text{HO})_2\text{NO}^+\text{ClO}_4^-$ **2**, was a product of the reaction of HNO_3 with HClO_4 , but which actually yielded a nitryl salt.^[1, 2] In 1937 Arlman studied the behavior of phosphorous acid, H_3PO_3 **3**, towards perchlorous acid on the assumption that **2** existed. He obtained a solid that he presumed had the formula $\text{P}(\text{OH})_4^+\text{ClO}_4^-$, in analogy to Hantzsch, but gave no evidence for the constitution.^[3] It was not until 1952 that the results were supported by Raman spectroscopic investigations.^[4] In the following years **1** was proved to exist also in HNO_3 , H_2SO_4 , FSO_3H , and superacidic $\text{FSO}_3\text{H}/\text{SbF}_5$ solutions, but it was not possible to isolate it.^[5–9] Finally, in 1995 **1** was assumed to be a structural element in a

modification of KH_2PO_4 , which was prepared at pH 10.^[10] The formation of **1** can nevertheless hardly be imagined under these conditions.

Phosphorus acids with the general composition H_3PO_n in hydrogen fluoride yield fluorophosphorane for $n = 2$ and 3 [Eqs. (1) and (2)] and in the case of **3** ($n = 4$) they yield monofluorophosphoric acid **4** and water [Eq. (3)].^[11, 12]



In the superacidic systems HF/MF_5 ($\text{M} = \text{As}, \text{Sb}$), which are suitable for the isolation of thermolabile salts,^[13–17] these acids show a differing reaction behavior. H_3PO_3 yields tetrafluorophosphorane [Eq. (2)] and hydronium salts.^[18] A hydronium salt, as well as **4**, can also be expected for an analogous reaction of **3**. However, in contrast to this expectation we find only a singlet at $\delta = -2.4$ ($\delta^1\text{H}$ 7.1)^[5–9] in the ³¹P NMR spectrum (in SO_2 at -40°C), and only the signals of the MF_6^- ions in the ¹⁹F NMR spectrum. It follows that the reaction with **3** does not proceed according to Equation (3) but yields **1-MF₆** [Eq. (4), $\text{M} = \text{As}, \text{Sb}$].



The presence of **1** in HF/MF_5 at -60°C can be directly proved as an intermediate in the reaction of **3** to **4**. Before **4** can be formed water has to be removed from **1**, which proceeds after a 1,3 proton transfer, for which a considerable energy barrier of 200 kJ mol⁻¹ was calculated.^[19]

With the HF/MF_5 system not only was proof for **1-MF₆** obtained but also its isolation and crystallization were achieved (Figure 1, Table 1). The crystal structural investigation shows that all P–O bond lengths (152.9(2) to 153.6(2) pm) are equivalent within the accuracy of the measurement. In comparison to **3** (154.7(4) to 155.1(4) pm) the bond lengths are shortened.^[20, 21] Compound **1** shows almost S_4 symmetry, with O–P–O angles between $101.2(1)^\circ$ and

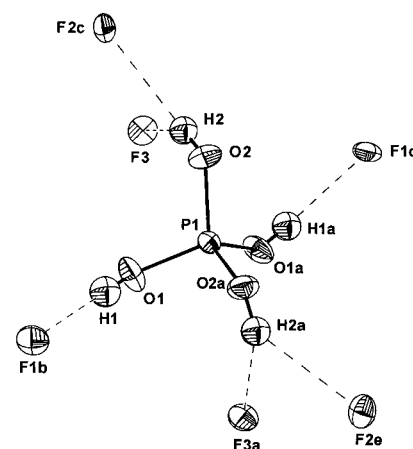


Figure 1. View of the structure of **1** showing the H...F contacts and atom labels. Selected bond lengths [pm]: F2c...H2 218(4), F3...H2 220(4), F1d...H1a 199(4), F2e...H2a 218(4), F3a...H2a 220(4), F1b...H1 199(4).

[*] Prof. Dr. R. Minkwitz, Dipl.-Chem. S. Schneider
Fachbereich Chemie der Universität
D-44221 Dortmund (Germany)
Fax: (+49) 0231-755-3797
E-mail: minkwitz@citrin.chemie.uni-dortmund.de

Table 1. Selected bond lengths [pm] and angles [°] of **1**-SbF₆. The atoms of the anions in Figure 1 are not completely shown.^[a]

Sb1–F1	189.4(1)	O1–P1–O2	114.2(1)
Sb1–F2	188.1(1)	O1a–P1–O2	112.3(1)
Sb1–F3	187.0(1)	O2–P1–O2a	101.2(1)
P1–O1	152.9(2)	F3–Sb1–F2	89.95(6)
P1–O2	153.6(2)	F3–Sb1–F1	89.80(6)
		F2–Sb1–F1	90.09(6)

[a] The standard deviations are valid for the last digit of the values. Symmetry operation: (a) = $-x, y, 0.5 - z$.

114.2(1)°. In the crystal the cations are situated on the twofold rotation axis and the anions located in an inversion center. Cations and anions are linked three-dimensionally by hydrogen bonds so that each cation is linked to six anions (Figure 2) through both simple and bifurcated hydrogen bonds. The H...F distances of the bifurcated hydrogen bonds (218(4) and 220(4) pm) are significantly longer than those of the simple hydrogen bonds (only 199(5) pm; Figure 1). This seems to be also reflected in the vibrational spectra (Figure 3, Table 2). The position and contour of the bands and lines depends on the influence of the crystal field. Relatively broad bands were measured in the IR spectra. In the Raman spectra two lines

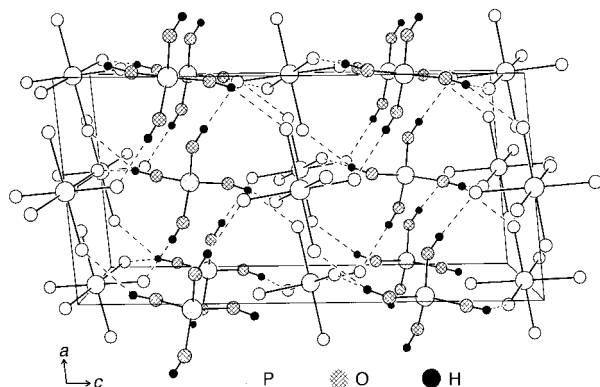


Figure 2. Section of the structure of **1**-SbF₆, showing the arrangement of the ions in the unit cell.

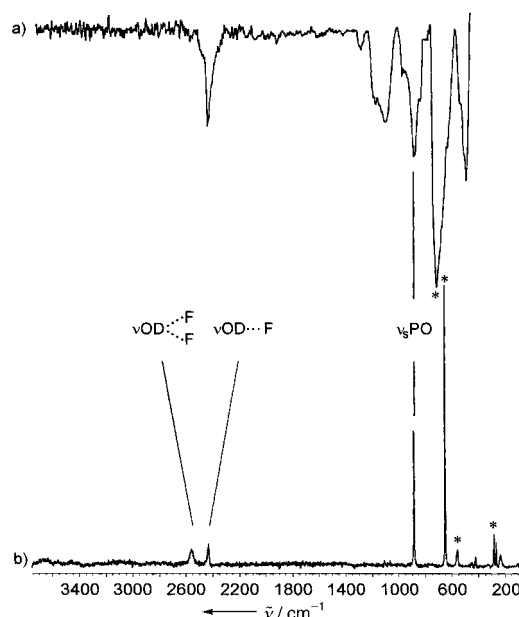


Figure 3. Solid state IR (a) and Raman spectrum (b) of P(OD)₄⁺-SbF₆⁻. Anion vibrations are marked by an *. IR spectrum was recorded at –40 °C (CsI plate) and the Raman spectrum at –78 °C.

with a separation of approximately 100 cm^{–1} that lie in the range of the stretching vibration of OH and OD, respectively, can be clearly distinguished. The different hydrogen bonds are responsible for these two lines, which was confirmed for **1**-SbF₆ by X-ray crystallography. The stretching vibrations of the hydroxyl groups with bifurcated hydrogen bonds can be found at the higher frequencies 3379/3372 cm^{–1} in P(OH)₄⁺ and at 2559/2551 cm^{–1} in P(OD)₄⁺. The vibrations of the OH and OD groups that contribute to simple hydrogen bonds are registered at 3262/3287 cm^{–1} and 2433/2428 cm^{–1}.

Experimental Section

H₃PO₄ **3** (Fluka >99%) was used without further purification. (Me₃SiO)₃PO (Fluka) was used for the preparation of the deuterated salts and the trimethylsilyl groups were removed as Me₃SiF. AsF₅ was prepared

Table 2. Vibrational frequencies [cm^{–1}]^[a] of P(OX)₄⁺MF₆[–] (M = AS, Sb; X = H, D) and assignments.^[a]

SbF ₆ [–]		P(OH) ₄ ⁺		AsF ₆ [–]		SbF ₆ [–]		P(OD) ₄ ⁺		AsF ₆ [–]		Tentative assignment	
Raman	IR	Raman	IR	Raman	IR	Raman	IR	Raman	IR	Raman	IR		
3379 (20)		3372 (34.3)				2559 (34.2)	2555 vw	2551 (22.9)	2549 vw			v	OX
3262 (32.8)	3270 b	3287 (21.4)	3281 b	2433 (33.0)	2430 s	2428 (35.6)	2430 b,s					v	OX
1112 (0.2)	1106 m	1109 (0.1)	1105 m	1114 (0.3)	1107 m	1111 (0.1)	1112 m					δ _{as}	POX
	1017 s		1011 s		1017 m		1012 m					δ _s	POX
896 (57.7)	893 m	894 (55.7)	893 m	891 (67.3)	887 s	895 (79.4)	887 s					v _s	PO
		591 (0.2)				588 (14.9)						δ	PO ₂
462 (4.7)		460 (1.5)				466 (0.9)						δ	PO ₂
		449 (3.8)		431 (7.5)	433 m	424 (10.2)	422 m,sh					τ _{as}	PO
		371 (10.4)				368 (7)						τ _{as}	PO ₂
		361 (4.7)				361 (9.1)						τ	PO
		330 (6.8)				307 (24.8)						δ _s	PO ₂
275 (25.7)				276 (22.4)								τ _s	PO ₂
	669 vs		703 vs		664 vs				703 vs			v	MF ₆ [–]
658 (100)		694 (100)		659 (100)		695 (100)							
574 (17.2)		571 (2.9)		567 (21.6)		562 (11.5)							
			396 s						98 s				
293 (9.8)		378 (6.2)		293 (14.5)		377 (14.1)							

[a] Relative intensity is shown in brackets; abbreviations: vw = very weak, w = weak, m = medium, s = strong, vs = very strong, b = broad, sh = shoulder.

by reaction of the elements and condensed fractionally, SbF_5 was fractionally distilled, and HF and DF were dried with fluorine.^[13]

MF_3 (M = As, Sb; 3 mmol) was dissolved in HF/DF (ca. 5 g) in a KEL-F reactor. After freezing the solution $\text{H}_3\text{PO}_4/(\text{Me}_3\text{SiO})_3\text{PO}$ (3 mmol) was added under inert gas (N_2) at -196°C . The reaction mixture was slowly warmed to -60°C and kept at this temperature until a clear solution formed. The excess of HF, DF, and Me_3SiF was subsequently removed at -60°C in a dynamic vacuum. $\text{P}(\text{OX})_3^+\text{MF}_6^-$ (X = H, D; M = As, Sb) remained as a colorless solid that was stable up to -10°C for M = As and -3°C for M = Sb.

Analytical instruments: Raman: Jobin–Yvon T64000, Ar^+ laser ($\lambda = 514.5\text{ nm}$) Spectra Physics; IR: Bruker IFS 113v; NMR: Bruker DPX300; X-ray diffractometer: Nonius Mach 3.

Received: June 19, 1998 [Z120131E]
German version: *Angew. Chem.* **1999**, *111*, 229–231

Keywords: IR spectroscopy • phosphonium salts • Raman spectroscopy • superacidic systems

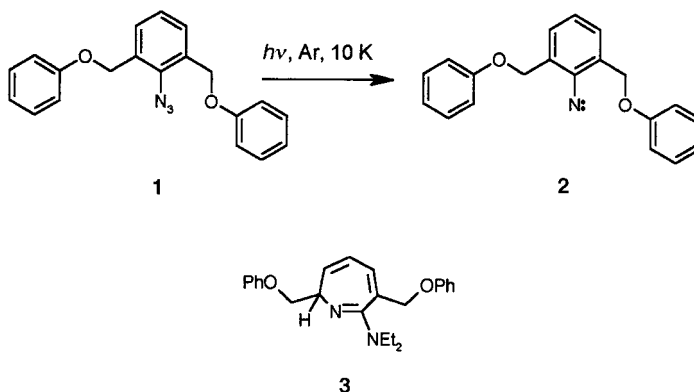
- [1] A. Hantzsch, *Chem. Ber.* **1925**, *58*, 941–961.
- [2] D. R. Goddard, E. D. Hughes, C. K. Ingold, *J. Chem. Soc. London* **1950**, 2559–2575.
- [3] E. J. Arlman, *Rec. Trav. Chim. Pays-Bas* **1937**, *56*, 919–922.
- [4] A. Simon, M. Weist, *Z. Anorg. Allg. Chem.* **1952**, *268*, 301–326.
- [5] C. C. Addison, J. W. Bailey, S. H. Bruce, M. F. A. Dove, R. C. Hibbert, N. Logan, *Polyhedron* **1983**, *2*, 651–656.
- [6] R. C. Hibbert, N. Logan, *J. Chem. Soc. Dalton Trans.* **1985**, 865–866.
- [7] R. J. Gillespie, R. Kapoor, E. A. Robinson, *Can. J. Chem.* **1966**, *44*, 1203–1210.
- [8] K. B. Dillon, T. C. Waddington, *J. Chem. Soc. A* **1970**, 1146–1150.
- [9] G. A. Olah, C. W. McFarland, *J. Org. Chem.* **1971**, *36*, 1374–1378.
- [10] M. Mathew, W. Wong-Ng, *J. Solid State Chem.* **1995**, *114*, 219–223.
- [11] R. R. Holmes, R. N. Storey, *Inorg. Chem.* **1966**, *5*, 2146–2151.
- [12] R. Schmutzler in *Advances in Fluorine Chemistry*, Vol. 5 (Eds.: M. Stacey, J. C. Tatlow, A. G. Sharpe), Butterworth, London **1965**, pp. 134–140.
- [13] R. Minkwitz, A. Kornath, W. Sawodny, *Angew. Chem.* **1992**, *104*, 648–649; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 643–644.
- [14] R. Minkwitz, A. Kornath, W. Sawodny, *Z. Anorg. Allg. Chem.* **1994**, *620*, 753–756.
- [15] R. Minkwitz, S. Schneider, M. Seifert, H. Hartl, *Z. Anorg. Allg. Chem.* **1996**, *622*, 1404–1410.
- [16] R. Minkwitz, S. Schneider, H. Preut, *Angew. Chem.* **1998**, *110*, 510–512; *Angew. Chem. Int. Ed.* **1998**, *37*, 494–496.
- [17] R. Minkwitz, H. Hartl, C. Hirsch, *Angew. Chem.* **1998**, *110*, 1776–1779; *Angew. Chem. Int. Ed.* **1998**, *37*, 1681–1684.
- [18] R. Minkwitz, S. Schneider, A. Kornath, *Inorg. Chem.* **1998**, *37*, 4662–4665.
- [19] S. Gevrey, A. Luna, V. Haldys, J. Tortajada, J.-P. Morizur, *J. Chem. Phys.* **1998**, *108*, 2458–2465.
- [20] Crystal structure analysis of 1-SbF₆: crystals obtained from HF solution, monoclinic, space group *C2/c* (No. 15), $a = 684.3(1)$, $b = 783.5(1)$, $c = 1426.6(2)\text{ pm}$, $\beta = 95.47(1)^\circ$, $Z = 4$, $V = 761.4(2) \times 10^6\text{ pm}^3$; $\rho_{\text{calc}} = 2.920\text{ g cm}^{-3}$, crystal dimensions: $0.22 \times 0.14 \times 0.14\text{ mm}^3$, $\text{MoK}\alpha$ radiation ($\lambda = 71.069\text{ pm}$), $2\theta/\omega$ scans, $2\theta_{\text{max}} = 65.0^\circ$, $T = 193\text{ K}$. Of the 2375 measured reflections, 1421 were independent, and 1134 were used in the refinement (σ to 2σ). L_p and absorption correction (ψ scans), $\mu(\text{MoK}\alpha) = 5.035\text{ mm}^{-1}$, min/max transmission 0.78/0.91, structure solution method: Patterson, difference-Fourier-synthesis; SHELXS-86, SHELXL-93, PARST, PLATON, MISSYM, 64 free parameters, hydrogen atoms determined and refined experimentally from ΔF , $R = 0.0206$, $wR = 0.0501$, $R = \sum ||F_o| - |F_c|| / \sum |F_o|$, refinement method: full matrix least-squares on F^2 ; min/max. residual electron density = $-1.073/0.501\text{ e \AA}^{-3}$. Further details on the crystal structure investigation may be obtained from the Fachinformationszentrum Karlsruhe, D-76344 Eggenstein-Leopoldshafen (fax: (+49) 7247-808-666; e-mail crysdata@fiz-karlsruhe.de), on quoting the depositary number CSD-408840.
- [21] R. H. Blessing, *Acta Crystallogr. Sect. B* **1988**, *44*, 334–340.

Photochemistry of *ortho*-Phenoxymethyl-Substituted Aryl Azides: A Novel Nitrene Rearrangement En Route to Isolable Iminoquinone Methides?*

Götz Bucher* and Hans-Gert Korth

Aryl azides show a fascinating and complex photochemistry, which only recently could be elucidated in detail.^[1–5] A singlet nitrene is formed as the primary reaction intermediate, which subsequently either adds intramolecularly to a neighboring C=C bond of the aromatic system,^[1, 2] or relaxes to the ground-state triplet nitrene via intersystem crossing (ISC). The efficiency of spin inversion depends, among others, on the temperature and on the substitution pattern. Low temperatures favor ISC, and 2,6-bisubstitution retards addition to the C=C bond for steric reasons.^[6] If only one *ortho* position is substituted, nitrene cycloaddition usually favors the unsubstituted side.^[6] In the course of our own studies on *ortho*-substituted aryl azides we have synthesized 2,6-bis(phenoxymethyl)-1-azidobenzene **1**, and we have investigated its photochemistry by means of product analysis and matrix isolation spectroscopy.

Photolysis of **1**, which was matrix isolated in Ar at 10 K, yielded a new product **2** (Scheme 1). The UV/Vis spectrum of **2** is typical of a triplet aryl nitrene with a weak band in the visible part of the spectrum that extends to 530 nm, and sharp



Scheme 1.

bands at 398, 296, and 288 nm (Figure 1). The infrared spectrum of **2** does not show bands that would be typical of products of nitrene rearrangement;^[7] for instance, there are no bands at about 1890 cm^{-1} (typical for a dihydroazepine^[2]). Photolysis of **1** is initially very efficient, but comes to a

[*] Dr. G. Bucher
Lehrstuhl OC II der Universität
Universitätsstrasse 150, D-44801 Bochum (Germany)
Fax: (+49) 234-709-4353
E-mail: goetz.bucher@orch.ruhr-uni-bochum.de
Dr. H.-G. Korth
Fachbereich 8—Chemie
Universität—Gesamthochschule Essen (Germany)

[**] G.B. thanks W. Sander for supporting this work. Financial support by the DFG and the Fonds der Chemischen Industrie is gratefully acknowledged.

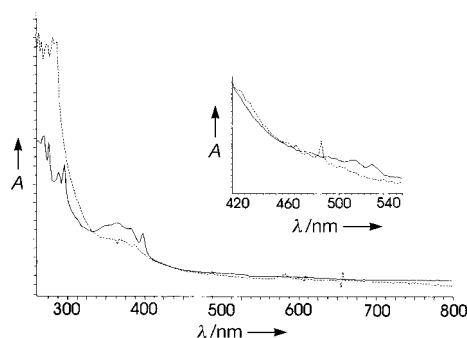


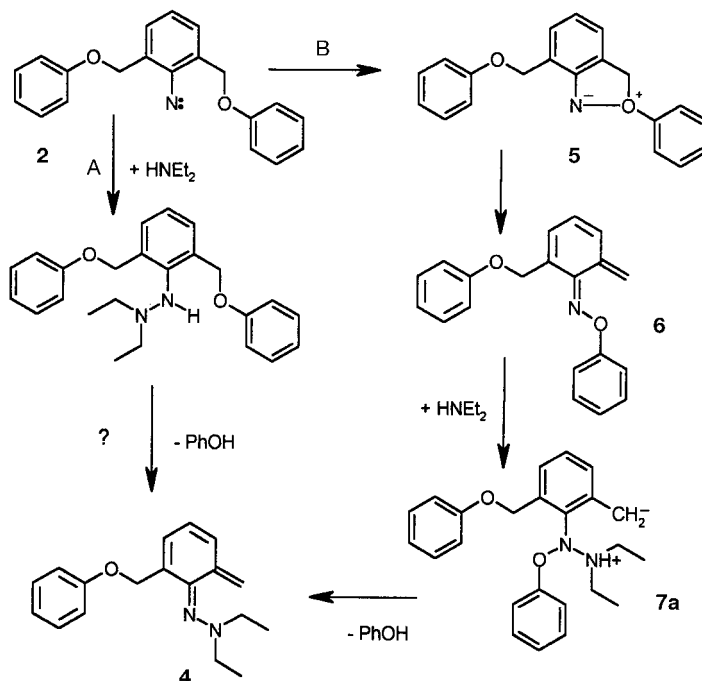
Figure 1. Solid line: UV/Vis spectrum of **2** obtained after photolysis (315 nm, 5 min) of **1** in an argon matrix at 10 K. Dashed line: UV/Vis spectrum obtained after photolysis (320 nm, 5 min) of **1** in glassy MTHF at 77 K. Inset: enlarged section between 420 and 540 nm. The spectrum obtained in MTHF at 77 K shows some sharp absorptions, which come from scattered light and are therefore artefacts.

standstill after a couple of minutes, presumably because of the filtering of light by **2**. Triplet nitrene **2** is essentially photo-stable at 10 K.^[8] Contrary to this stability at 10 K, **2** is formed only in minute amounts if **1** is photolyzed in glassy 2-methyltetrahydrofuran (MTHF) at 77 K. The UV/Vis spectrum of the photolysate does not show the characteristic broad absorption of **2** with maxima at 512 and 526 nm (Figure 1), and the EPR triplet resonance at 6705 G ($g = 1.0145$) has only a very weak intensity.^[9]

Photolysis (320 nm, 60 min) of **1** in CH_3CN /diethylamine (9/1) yielded 55% of a yellow product after purification by column chromatography. Mass spectrometric analysis showed that the product was not the expected azepine **3**. Evaluation of the spectroscopic data revealed instead that the *syn* isomer of 6-*exo*-methylene-2-phenoxyethyl-cyclohexa-2,4-diene-1-on-*N,N*-diethylhydrazone **4** had been formed (Table 1). Of particular diagnostic value were the resonances $\delta(^{13}\text{C}) = 113.093$, as well as $\delta(^1\text{H}) = 4.9369$ (dd, 1H) and 4.9105 (d,

1H). Their position and the fact that a GRAD-HMQC experiment showed cross peaks between these ^{13}C and ^1H resonances gave clear evidence for an *exo*-methylene group present in the molecule. The *syn* position of the diethylamino group, relative to the *exo*-methylene group, could be deduced from a NOESY experiment.

The iminoquinone methide **4** is a surprising product, whose formation necessitates the elimination of phenol. Two possible mechanisms for its formation will be briefly discussed (Scheme 2). In mechanism A the singlet nitrene inserts into



Scheme 2. Two routes to the formation of **4**.

the N–H bond of diethylamine. In a second step phenol is eliminated. However, **4** is formed almost exclusively. A ^1H NMR spectrum of the crude photolysate recorded after brief photolysis showed essentially only signals from **1** and **4**. Thus, any intermediary hydrazine derivative would have to be much shorter lived under the conditions of photolysis than **1**, which appears unlikely.^[10] The first excited singlet state of aryl nitrenes is an open-shell state ($\sigma_1\pi_1$), which shows a high reactivity towards intramolecular rearrangement, but is difficult to intercept intermolecularly. Perfluorinated aryl nitrenes represent the only exception to this rule.^[11] Photolysis of a series of 2-alkyl-substituted aryl azides did not lead to the formation of hydrazine derivatives,^[12] and thus such a reaction appears unlikely in the case of **1**.

The primary reaction step in mechanism B is the formation of an oxonium ylide **5** (which may represent a transition state as well), which ring-opens to

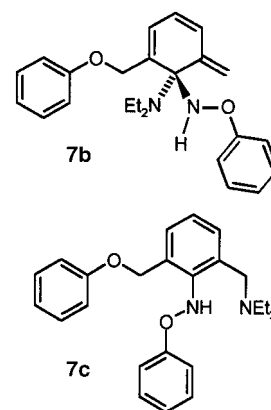
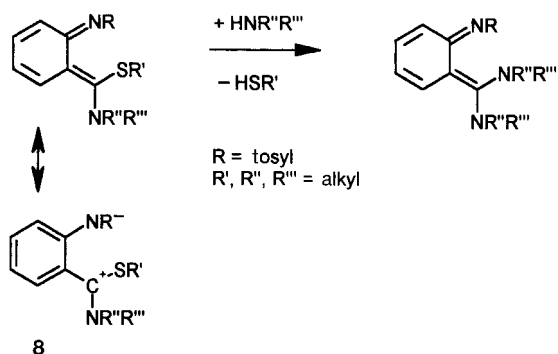


Table 1. NMR data for **4**.

$\delta(^{13}\text{C})$	Assign- ment ^[a,b]	Couples with ^[a,b]	$\delta(^1\text{H})$	Integral, multiplicity	J [Hz]
12.730	C14	H11	1.1033	6H, t	7.00
42.704	C13	H10	3.4504	4H, q	7.00
72.288	C5	H4	4.6722	2H, s	–
105.658	C7	H5	5.8169	1H, d	$J_{5,6} = 6.52$
113.093	C12	H8	4.9369	1H, d (dd?)	$J_{8,9} = 1.2$
		H9	4.9105	1H, d	(small)
115.168	C3	H3	6.9596	2H, d	$J_{2,3} = 7.52$
117.898	C9	H7	5.7774	1H, d	$J_{6,7} = 10.04$
120.399	C1	H1	6.8875	1H, t	$J_{1,2} = 7.16$
129.178	C2	H2	7.2287	2H, dd	$J_{2,3} = 7.52$
129.532	C8	H6	6.2007	1H, dd	$J_{5,6} = 6.54,$ $J_{6,7} = 10.04$
136.573	C10	–	–	–	–
148.484	C6	–	–	–	–
149.017	C11	–	–	–	–
159.081	C4	–	–	–	–

[a] Based on GRAD-HMQC, COSY, and NOESY determinations. [b] The numbering of the carbon atoms starts in the 4-position of the phenoxy substituent, and proceeds clockwise in the molecule (see Scheme 2). Thus, C5 corresponds to the benzylic carbon atom, C11 to the imino carbon atom, and C12 to the *exo*-methylene carbon atom. The numbering of the hydrogen atoms is organized analogously.

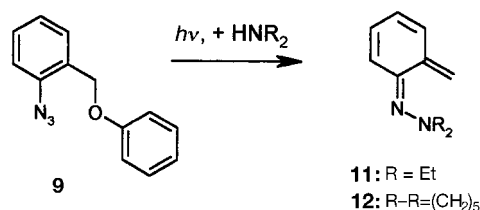
oxime **6**. Oxime **6** reacts with diethylamine to yield betaine **7a** (which may again be a transition state), which eliminates phenol to yield **4**. Alternatively, the reaction could also proceed via aminal **7b** or hydroxylamine **7c**. The mechanism via **7a** has some precedence in the literature: The reaction of iminoquinone methides **8** with secondary amines probably also proceeds via an addition–elimination-type mechanism (Scheme 3).^[13] In this case, however, the negative charge in the betain resides on a nitrogen atom, and it is stabilized by an electron-withdrawing tosyl group. The formation of **7c** seems to be the most plausible possibility. However, the question remains why this compound should so readily lose phenol.



Scheme 3. Substitution of **8** through an addition–elimination mechanism.

The first singlet excited state of nitrene **2** is of unusual reactivity even at 77 K. This is also revealed by the fact that only a single phenoxymethyl group *ortho* to the nitrene center is required to obtain iminoquinone methides. Photolysis of azide **9** in the presence of diethylamine or piperidine allows for the isolation of the quinoid compounds **10** and **11**, again in approximately 50 % yield (Scheme 4). As azepines are once again not formed as major products, the reaction that leads to **4** must have an activation barrier even lower than the very facile rearrangement to didehydroazepines.

The iminoquinone methides **4**, **10**, and **11** are isolable compounds of surprising stability (with half lives of the order of 24 h at ambient temperature and several weeks at -18°C). This observation is remarkable insofar as no isolable iminoquinone methides unsubstituted at the *exo*-methylene functionality had hitherto been known. Compounds of this type had up to now only been characterized by matrix isolation spectroscopy,^[14, 15] or they were trapped in solution by Diels–Alder reactions.^[16] The compounds **8** mentioned above bear donor substituents at the *exo*-methylene functionality as well as a tosyl acceptor substituent at the imino nitrogen atom, which results in push–pull stabilization.^[13] Compounds **4**, **10**,



Scheme 4.

and **11**, however, only have a single donor substituent at the imino nitrogen atom and are otherwise stabilized only by steric protection by the *syn*-diethylamino group.

Experimental Section

General: All NMR spectra were recorded on a 400 MHz spectrometer with CDCl_3 as the solvent. The matrix isolation arrangement has already been described.^[17] Photolyses at 77 K in glassy MTHF were performed with carefully degassed samples. The azides **1** and **9** were obtained from the corresponding aniline derivatives by diazotization and subsequent reaction with NaN_3 .

4 (analogously **10** and **11**): A solution of **1** (50 mg) in $\text{CH}_3\text{CN}/\text{HNEt}_2$ (9/1, 40 mL) was purged with Ar for 15 min and then irradiated at $\lambda = 320$ nm for 60 min. (Quartz tube, photoreactor 400 with a UV radiator at 320 nm, Grätzel, Karlsruhe, Germany). The solvent was then evaporated and the residue extracted with petroleum ether 60–80. The extract was purified by column chromatography (basic alumina, petroleum ether 60–80/triethylamine (98/2)) and **4** obtained as the first, yellow fraction. Additionally, some unphotolyzed **1** (20 mg) was recovered. Yield of **4**: 17 mg (55 % relative to starting material consumed). UV (in CH_3CN): λ_{max} (ϵ) = 299 (16475), 279 (17500), 272 (17675), 222 (51700), 198 (51875); MS: m/z : 282 [M^+], 189 [$M^+ - \text{PhO}$], 118, 110, 91, 65; HR-MS: calcd: 282.173214; found: 282.173401. IR (film): $\tilde{\nu}$ = 2975 (m), 2933 (m), 1601 (s), 1562 (vs), 1524 (vs), 1498 (s), 1460 (m), 1429 (m), 1363 (m), 1295 (m), 1246 (m), 1220 (m), 1132 (m), 1080 (w), 1052 (w), 753 cm^{-1} (s).

10: ^{13}C NMR: δ = 149.4886, 141.2475, 136.7158, 118.5160, 113.0524, 108.9593, 42.5190, 12.6428; ^1H NMR: δ = 7.049 (d, 1H), 6.204 (dd, 1H), 5.794 (d, 1H), 5.535 ("t", 1H), 4.933 (s, 1H), 4.909 (s, 1H), 3.447 (q, 4H), 1.108 (t, 6H); IR (film): $\tilde{\nu}$ = 2976 (s), 2936 (s), 2873 (m), 1642 (w), 1591 (m), 1554 (vs), 1512 (vs), 1460 (m), 1429 (s), 1380 (m), 1363 (s), 1322 (m), 1297 (s), 1276 (w), 1232 (vw), 1137 (w), 1079 (s), 1011 (w), 901 (w), 783 (w), 732 (w), 683 cm^{-1} (m); MS: m/z : 176 [M^+], 161, 147, 133, 120, 104, 94, 78, 65, 51.

11: ^{13}C NMR: δ = 150.2926, 141.1013, 136.2956, 119.1373, 113.3631, 109.5806, 46.6121, 25.4521, 24.7395; ^1H NMR: δ = 6.985 (d, 1H), 6.191 (dd, 1H), 5.779 (d, 1H), 5.542 (dd, 1H), 4.939 (dd, 1H), 4.898 (dd?, 1H), 3.558 (t, 4H), 1.60 (m, 2H), 1.53 (m, 4H); IR (film): 3013 (w), 2935 (s), 2855 (m), 1638 (w), 1590 (m), 1557 (vs), 1511 (vs), 1440 (s), 1368 (m), 1299 (s), 1280 (s), 1258 (w), 1238 (w), 1209 (s), 1130 (m), 1084 (m), 1062 (w), 1023 (m), 937 (w), 900 (m), 853 (w), 794 (w), 731 (w), 684 cm^{-1} (w); MS: m/z : 188 [M^+], 173, 159, 145, 131, 119, 104, 79, 51, 41.

Received: July 29, 1998 [Z12218IE]

German version: *Angew. Chem.* **1999**, *111*, 209–211

Keywords: iminoquinone methides • matrix isolation • nitrenes • rearrangements

- [1] E. Leyva, M. S. Platz, G. Persy, J. Wirz, *J. Am. Chem. Soc.* **1986**, *108*, 3783.
- [2] C. J. Shields, D. R. Chrisope, G. B. Schuster, A. J. Dixon, M. Poliakoff, J. J. Turner, *J. Am. Chem. Soc.* **1987**, *109*, 4723.
- [3] N. P. Gritsan, T. Yuzawa, M. S. Platz, *J. Am. Chem. Soc.* **1997**, *119*, 5059.
- [4] R. Born, C. Burda, P. Senn, J. Wirz, *J. Am. Chem. Soc.* **1997**, *119*, 5061.
- [5] W. L. Karney, W. T. Borden, *J. Am. Chem. Soc.* **1997**, *119*, 1378.
- [6] W. L. Karney, W. T. Borden, *J. Am. Chem. Soc.* **1997**, *119*, 3347.
- [7] IR bands assigned to the triplet nitrene **2** (Ar matrix, 10 K): $\tilde{\nu}$ = 1551 (m), 1515 (w), 1267 (m), 1250 (vs), 1240 (s), 1065 (w), 897 (w), 855 (w), 847 (w), 784 (s), 765 (s), 632 cm^{-1} (m).
- [8] Irradiation of **2** with a KrF excimer laser (248 nm) leads to the formation of bands at 2240 cm^{-1} , which may indicate a photochemical ring opening reaction.
- [9] The intensity of this transition proved to be independent of the solvent. EPR spectra recorded with polycrystalline hexafluorobenzene as the matrix material did not show more intense bands. For this reason the high reactivity observed for **2** (S_1) is probably not a consequence of reactions with the matrix material.

- [10] Preliminary calculations (PM3/RHF) indicate, that the elimination of phenol from the hydrazine derivative formed by insertion of **2** in the N–H bond of diethylamine should be distinctly endothermic (by about 24 kcal mol⁻¹). A thermal elimination of phenol, as suggested by a referee, therefore seems unlikely. Such a reaction should also preferentially yield the *anti* isomers of the iminoquinone methides.
- [11] H. Zhai, M. S. Platz, *J. Phys. Org. Chem.* **1996**, 10, 22.
- [12] R. J. Sundberg, S. R. Suter, M. Brenner, *J. Am. Chem. Soc.* **1972**, 94, 513.
- [13] R. Gompper, H. D. Lehmann, *Angew. Chem.* **1968**, 80, 38; *Angew. Chem. Int. Ed. Eng.* **1968**, 7, 74.
- [14] W. Sander, J. Morawietz, *Tetrahedron Lett.* **1993**, 34, 1913.
- [15] J. Morawietz, W. Sander, M. Träubel, *J. Org. Chem.* **1995**, 60, 6245.
- [16] Y. Ito, E. Nakajo, T. Saegusa, *Synth. Commun.* **1986**, 16, 1073.
- [17] W. W. Sander, *J. Org. Chem.* **1989**, 54, 333.

Formation and Structure of the First 7-Aza-1-phosphanorbornadiene Complex**

Udo Rohde, Frank Ruthe, Peter G. Jones, and Rainer Streubel*

Dedicated to Professor Edgar Niecke on the occasion of his 60th birthday

The chemistry of the norbornadienes (bicyclo[2.2.1]hepta-2,5-dienes) displays a variety of interesting aspects. One of these is the photochemical isomerization of norbornadienes to quadricyclanes^[1] and its catalytic reversal.^[2] Another is the synthesis, stability, and reactivity of heterocyclic analogues bearing a nitrogen or phosphorus atom at the 1- and/or 7-position (**I–III** in Figure 1); particularly noteworthy results from this area concern the differences in stability between 7-aza-^[3] and 7-phosphanorbornadienes (Type **II**),^[4] (the latter can be stabilized and isolated by coordination of the phosphorus to a metal^[5]), and catalytic reactions^[6] using 1-phosphanorbornadienes^[7] (Type **I**) as novel ligands.

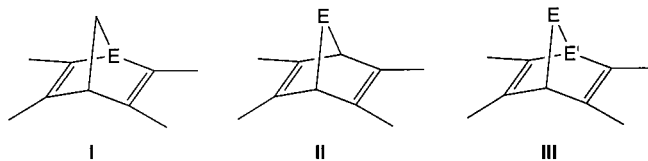


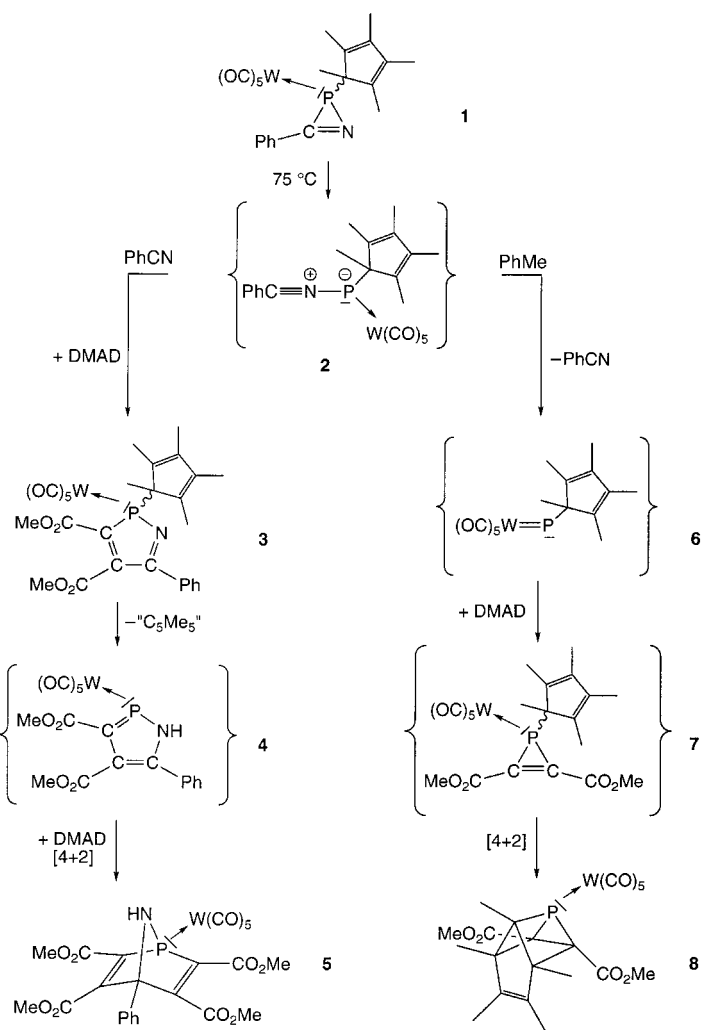
Figure 1. Heteronorborna-2,5-dienes **I–III** (exocyclic lines denote arbitrary substituents; E, E' = N, NR and/or P, PR).

[*] Priv.-Doz. Dr. R. Streubel, Dipl.-Chem. U. Rohde, Dipl.-Chem. F. Ruthe, Prof. Dr. P. G. Jones
Institut für Anorganische und Analytische Chemie
der Technischen Universität
Postfach 3329, D-38023 Braunschweig (Germany)
Fax: (+49) 531-391-5387
E-mail: r.streubel@tu-bs.de

[**] Chemistry of 2*H*-azaphosphirene complexes, Part 15. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. Part 14: R. Streubel, H. Wilkens, P. G. Jones, *Chem. Commun.* **1998**, 1761.

Here we report the synthesis and structural characterization of a tungsten complex of the novel 7-aza-1-phosphanorbornadiene ring system.^[8] This is formed by a trapping reaction of an intermediate, a PC₅Me₅-substituted nitrilium phosphane ylide tungsten complex,^[9] with dimethylacetylene dicarboxylate (DMAD) and subsequent reaction with DMAD, which leads to cleavage of an exocyclic P–C bond. We also present a highly efficient synthesis of a novel phosphorus–carbon cage compound.^[10]

If the 2*H*-azaphosphirene tungsten complex **1**^[11] is heated in benzonitrile at 75 °C in the presence of DMAD, the 2*H*-1,2-azaphosphole tungsten complex **3** is formed (Scheme 1); however, **3** ($\delta(^{31}\text{P}) = 119.1$, $^1J(^{31}\text{P}, ^{183}\text{W}) = 249 \text{ Hz}$ ^[9]) is not stable under these conditions, and undergoes cleavage of the exocyclic P–C bond (presumably by a radical mechanism) to form the transient intermediate 1*H*-1,2-azaphosphole complex **4**, which finally yields complex **5** by [4+2] cycloaddition with DMAD;^[7, 12, 13] the source of the H atom is still unclear. Since this reaction also provided a product with a ³¹P NMR resonance signal at high field, ($\delta(^{31}\text{P}) = -66.8$, ca. 10 %), we decided to repeat the reaction in toluene.^[9] This led, after formation of a short-lived intermediate ($\delta(^{31}\text{P}) = -100.1$) to benzonitrile and, as sole phosphorus-containing product, the



Scheme 1. Suggested reaction courses for the formation of complexes **5** and **8**.

complex **8**; our suggestion^[9] as to how **8** is formed is shown in Scheme 1. The complexes **5** and **8** are isolated by low-temperature chromatography and crystallization. The suggested structures of **5** and **8** are based on NMR-spectroscopic data in solution (Table 1) and MS data^[14] and are in both cases supported by X-ray structure analysis.^[15]

Table 1. Selected NMR-spectroscopic data of the complexes **5** and **8**.^[a]

5 : ¹³ C{ ¹ H} NMR: δ = 52.8 (s; OCH ₃), 53.0 (s; OCH ₃), 88.6 (d, <i>J</i> (P,C) = 5.4 Hz; C4), 126.1 (s; Ph), 129.0 (s; Ph), 129.6 (s; Ph), 132.5 (d, <i>J</i> (P,C) = 5.3 Hz; <i>i</i> -C(Ph)), 148.5 (d, <i>J</i> (P,C) = 13.3 Hz; C2/6), 162.3 (d, <i>J</i> (P,C) = 16.3 Hz; C3/5), 164.4 (d, <i>J</i> (P,C) = 9.7 Hz; C3/5-CO ₂ Me), 166.7 (d, ² <i>J</i> (P,C) = 2.1 Hz; C2/6-CO ₂ Me), 194.2 (d, ² <i>J</i> (P,C) = 8.2 Hz; <i>cis</i> -CO), 196.6 (d, ² <i>J</i> (P,C) = 32.9 Hz; <i>trans</i> -CO); ¹ H-NMR: δ = 3.72 (s, 6H; OCH ₃), 3.76 (d, ² <i>J</i> (P,H) = 5.1 Hz, 1H; NH), 3.85 (s, 6H; OCH ₃), 7.45 (m _c , 3H; H _{arom.}), 7.62 (m _c , 2H, H _{arom.})
8 : ¹³ C{ ¹ H} NMR: δ = 5.9 (d, ³ <i>J</i> (P,C) = 5.8 Hz; C8-CH ₃), 14.0 (s; C3/6-CH ₃), 14.1 (d, ⁴ <i>J</i> (P,C) = 2.6 Hz; C4/5-CH ₃), 52.1 (s; OCH ₃), 56.5 (d, ⁴ <i>J</i> (P,C) = 9.2 Hz; C3/6), 66.5 (d, <i>J</i> (P,C) = 32.2 Hz; C8), 70.4 (d, <i>J</i> (P,C) = 5.2 Hz; C2/7), 141.7 (d, <i>J</i> (P,C) = 10.4 Hz; C4/5), 168.7 (s; CO ₂ CH ₃), 193.6 (d; ² <i>J</i> (P,C) = 8.1 Hz; <i>cis</i> -CO), 197.4 (s; <i>trans</i> -CO); ¹ H NMR: δ = 0.58 (d, ³ <i>J</i> (P,H) = 19.0 Hz, 3H; C8-CH ₃), 1.52 (s, 6H; C3/6-CH ₃), 1.71 (s, 6H; C4/5-CH ₃), 3.62 (s, 6H; CO ₂ CH ₃)

[a] CDCl₃, 20 °C; ¹³C NMR: 50.3 MHz; ³¹P NMR: 81.0 MHz. The deuterated solvent was used as internal standard, 85 % H₃PO₄ as external standard.

Complex **5** shows a ³¹P NMR resonance (δ = 63.0) that is considerably low-field shifted compared to that of 3,4-dimethyl-2,5,6-triphenyl-1-phosphabicyclo[2.2.1]heptadiene^[7] (**9**) (δ = −8.4). The magnitude of the coupling constant $|J(^{183}\text{W}, ^{31}\text{P})|$, 294.8 Hz, indicates not only the direct bond to the phosphorus atom, but also that the latter is bonded to nitrogen (further NMR data in Table 1). The highly symmetrical structure of the heterocyclic ligand in complex **8** is demonstrated by the symmetry-related reduction in the number of cage carbon signals and those of the directly bonded methyl groups. As expected,^[16] the ³¹P NMR resonance of complex **8** is observed at high field (δ = −67.2), although this is low-field shifted in comparison to that for [(2,3-bis-(methyloxycarbonyl)-1-bis(trimethylsilyl)methyl-1*H*-phosphirene]pentacarbonyltungsten(**0**)]^[17] (δ = −74.6, ¹*J*(¹⁸³W, ³¹P) = 281.1 Hz^[17]) and also has a lower coupling constant $|J(^{183}\text{W}, ^{31}\text{P})|$ of 242.0 Hz.

The molecular structure of complex **5** in the crystal (Figure 2) shows the characteristic norbornadiene-type ring system; two molecules are linked by hydrogen bonds (Figure 2 bottom). The P–C bonds in the six-membered ring are markedly lengthened at about 187 pm, and the C–P–C and P–N–C angles are widened (ca. 96 and 100.7(3)°, respectively); this is similar to the situation in the uncoordinated 1-phosphanorborna-2,5-diene derivative **9** (P–C 186.9(4) and 186.9(3) pm; C–P–C 96.1(2) and P–C–C 97.6(2)°^[7]). The structure of complex **8** (Figure 3) displays notably narrow endocyclic angles in the phosphirane ring system, a considerably lengthened P–C8 bond (192.4(3) pm), and a P–W bond considerably shorter than expected at 245.69(8) pm.^[16]

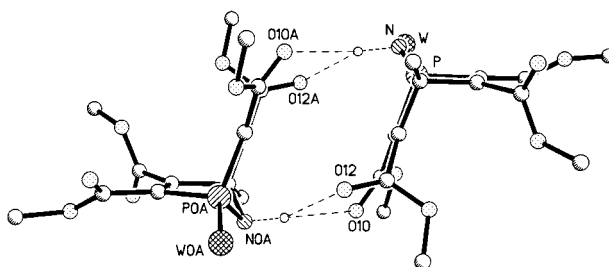
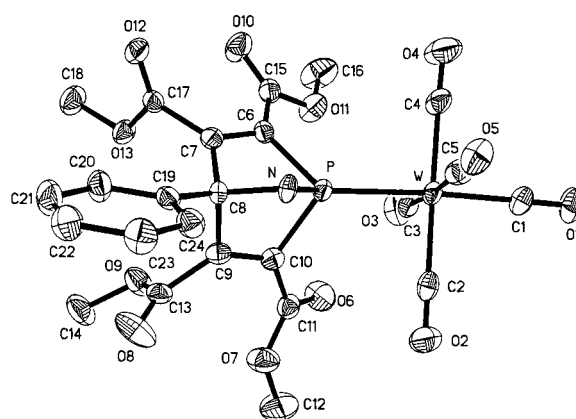
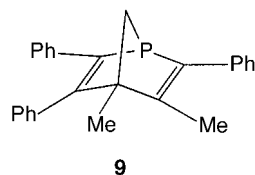


Figure 2. a) Molecular structure of complex **5** in the crystal. View direction from 'above' onto the nitrogen atom. Ellipsoids represent 50 % probability levels; H atoms are omitted for clarity. Selected bond lengths [pm] and angles [°]: P–N 172.2(4), P–C6 187.3(5), P–C10 185.7(5), N–C8 148.1(6), C6–C7 133.4(7), C7–C8 156.1(7), C8–C9 155.2(7), C9–C10 133.3(7), W–P 245.25(13), C6–P–C10 95.6(2), N–P–W 124.8(2), C10–P–W 120.3(2), C6–P–W 128.6(2), C8–N–P 100.7(3). b) The hydrogen-bonded dimer of complex **5** in the crystal.

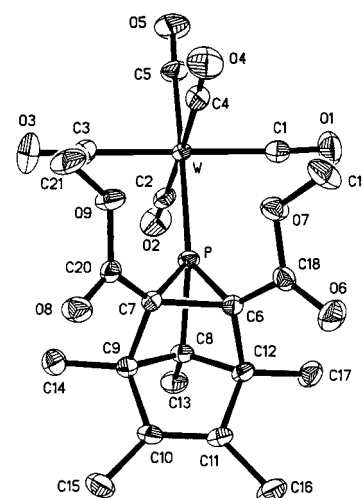


Figure 3. Molecular structure of complex **8** in the crystal. View direction from 'below' onto the six-membered ring. Ellipsoids represent 50 % probability levels; H atoms are omitted for clarity. Selected bond lengths [pm] and angles [°]: P–C6 183.6(3), P–C7 183.0(3), C6–C7 155.9(3), P–C8 192.4(3), C10–C11 133.6(4), P–W 245.69(8); C7–P–C6 50.34(11), C6–C7–P 65.04(13), C6–C7–P 64.63(13), C6–P–C8 72.21(12).

Experimental Section

Preparation of complexes **5** and **8**: 2*H*-azaphosphirene tungsten complex **1** (0.3 g, 0.5 mmol) and DMAD (0.5 mL, 0.6 mmol) were stirred for 25 min in benzonitrile (3 mL; **5**) or toluene (3 mL; **8**) at 75 °C. The solution was concentrated to dryness in vacuo (ca. 0.01 mbar), and the residue subjected

to low-temperature column chromatography on silica (-20°C , hexane/diethyl ether 99/1). The eluents were concentrated to dryness in vacuo, and the residues crystallized from pentane at -20°C . **5**: Pale yellow crystals, yield 0.18 g (51%), m.p. 128°C (decomp). **8**: Pale yellow crystals, yield 0.25 g (81%), m.p. 89°C (decomp).

Received: July 27, 1998 [Z12209IE]
German version: *Angew. Chem.* **1999**, *111*, 158–160

Keywords: 1,3-dipoles • norbornadienes • P ligands • tungsten

- [1] G. Kaupp, H. Prinzbach, *Justus Liebigs Ann. Chem.* **1969**, 725, 52.
- [2] Reviews: a) K. C. Bishop III, *Chem. Rev.* **1976**, 76, 461; b) K. Hirao, A. Yamashita, O. Yonemitsu in *Carbocyclic Cage Compounds: Chemistry and Applications* (Eds.: E. Osawa, O. Yonemitsu), VCH, New York, **1992**, p. 383ff.
- [3] a) Derivatives: R. Kitzing, R. Fuchs, M. Joyeux, H. Prinzbach, *Helv. Chim. Acta* **1968**, 51, 888; b) parent system: H.-J. Altenbach, B. Blech, J. A. Marco, E. Vogel, *Angew. Chem.* **1982**, 94, 789; *Angew. Chem. Int. Ed. Engl.* **1982**, 21, 772.
- [4] a) E. Fluck, *Chem.-Ztg.* **1981**, 105, 323; b) L. D. Quin, K. A. Mesch, K. C. Caster, *Proc. 1981 Int. Conf. Phosphorus Chem. (ACS Symp. Ser. 1981, 171, 623)*.
- [5] A. Marinetti, F. Mathey, J. Fischer, A. Mitschler, *J. Am. Chem. Soc.* **1982**, 104, 4484.
- [6] a) D. Neibecker, R. Reau, *New J. Chem.* **1991**, 15, 279; b) S. Levlievre, F. Mercier, F. Mathey, *J. Org. Chem.* **1996**, 61, 3531.
- [7] F. Mathey, F. Mercier, C. Charrier, *J. Am. Chem. Soc.* **1981**, 103, 4595.
- [8] The synthesis of a 7-aza-1-phosphanorbornadiene was recently reported: M. Regitz, XIVth International Conference on Phosphorus Chemistry, Cincinnati/Ohio, USA, July **1998**, lecture LT5-3.
- [9] Reviews: a) M. Regitz, A. Hoffmann, U. Bergsträßer in *Modern Acetylene Chemistry* (Eds.: P. J. Stang, F. Diederich), VCH, New York, **1995**, p. 173ff; b) R. Streubel, *Angew. Chem.* **1995**, 107, 478; *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 436.
- [10] R. Streubel, H. Wilkens, A. Ostrowski, C. Neumann, F. Ruthe, P. G. Jones, *Angew. Chem.* **1997**, 109, 1549; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 1492.
- [11] R. Streubel, A. Rohde, F. Ruthe, J. Jeske, P. G. Jones, *Eur. J. Inorg. Chem.* in press.
- [12] K. Maitra, J. H. Nelson, *Bull. Soc. Chim. Fr.* **1997**, 134, 859.
- [13] A. Schmidpeter in *Comprehensive Heterocyclic Chemistry II Vol. 3* (Eds. A. R. Katritzky, C. W. Rees, E. F. V. Scriven), Pergamon, Oxford, **1996**, p. 709ff.
- [14] Selected MS data (pos. CI, NH_3 , 70 eV, ^{184}W): **5**: m/z (%): 761 (100) [$(M + \text{NH}_4)^+$]; **8**: m/z (%): 632 (42) [M^+]; correct C,H elemental analyses for **5** and **8**.
- [15] Crystal structure analyses: The crystals (**5**: $0.70 \times 0.50 \times 0.30$ mm; **8**: $0.58 \times 0.48 \times 0.40$ mm) were mounted in inert oil at -100°C on a Siemens P4 diffractometer. Intensities were registered by using ω scans in the 2θ region $6-50^{\circ}$. Absorption corrections were based on Ψ scans. The structures were solved by direct methods (SHELXS-86) and refined against F^2 using SHELXL-93 (G. M. Sheldrick, Universität Göttingen). Hydrogen atoms were refined by using a riding model, with the exception of methyl H (rigid groups) and the nitrogen-bonded H0 in **5** (freely refined). **5**: $\text{C}_{24}\text{H}_{18}\text{NO}_{13}\text{PW}$, $M_r = 743.21$, monoclinic, space group $\text{C}2/c$, $a = 2513.1(3)$, $b = 1455.1(2)$, $c = 1552.6(2)$ pm, $\beta = 108.941(10)^{\circ}$, $V = 5.3699(10)$ nm ^{3} , $Z = 8$, $\rho_{\text{calcd}} = 1.839$ Mg m $^{-3}$, $\lambda = 0.71073$ pm, $T = 173$ K. Of a total of 9431 reflections, 4720 were independent ($R_{\text{int}} = 0.0497$). Final $wR2 = 0.0620$ for all data, conventional $R(F)$ ($R1$) = 0.0307, for 369 parameters and 265 restraints; max. $\Delta\rho = 798$ and 913 e nm $^{-3}$. **8**: $\text{C}_{21}\text{H}_{21}\text{O}_9\text{PW}$, $M_r = 632.20$, triclinic, space group $P\bar{1}$, $a = 966.5(2)$, $b = 985.2(2)$, $c = 1322.9(3)$ pm, $\alpha = 111.29(2)$, $\beta = 91.12(2)$, $\gamma = 92.00(2)^{\circ}$, $V = 1.1722(4)$ nm ^{3} ; $Z = 2$, $\rho_{\text{calcd}} = 1.791$ Mg m $^{-3}$, $\lambda = 0.71073$ pm, $T = 173$ K. Of a total of 6336 reflections, 3989 were independent ($R_{\text{int}} = 0.0101$). Final $wR2 = 0.0428$ for all data, conventional $R1 = 0.0165$, for 296 parameters and 217 restraints; max. $\Delta\rho = 890$ and 660 e nm $^{-3}$. Crystallographic data (excluding structure factors) for the structures reported in this paper

have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-102463 and CCDC-102464. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

- [16] Review: F. Mathey, *Chem. Rev.* **1990**, 90, 997.
- [17] a) A. Ostrowski, J. Jeske, P. G. Jones, R. Streubel, *J. Chem. Soc. Chem. Commun.* **1995**, 2507; b) A. Ostrowski, J. Jeske, F. Ruthe, P. G. Jones, R. Streubel, *Z. Anorg. Allg. Chem.* **1997**, 623, 1897.

Synthesis and Crystal Structure of the Bis(allyl)calcium Complex $[\text{Ca}\{\text{C}_3(\text{SiMe}_3)_2\text{H}_3\}_2 \cdot (\text{thf})_2]^{**}$

Melanie J. Harvey, Timothy P. Hanusa,* and Victor G. Young, Jr.

The cyclopentadienyl ring and its substituted derivatives are the most frequently encountered ligands in organocalcium, -strontium, and -barium chemistry.^[1, 2] Alkaline-earth metal complexes containing other carbanionic groups (e.g., alkyls,^[3, 4] indenyl,^[5] pentadienyl,^[6] or fluorenyl^[7]) are described, but as a class have received far less attention. The allyl anion represents the simplest π -delocalized ligand, and although some allylbarium compounds are known,^[8, 9] the allyl-(Ca,Sr,Ba) bond has never been structurally authenticated. By applying the methods of steric stabilization that allowed the isolation of a bis(pentadienyl)calcium compound,^[6] we now describe the synthesis of the first crystallographically characterized bis(allyl)calcium complex.

In order to improve the solubility and crystallinity of the final compound, we selected 1,3-bis(trimethylsilyl)propene as the ligand precursor. This was converted into its lithium salt,^[10] and then transmetalated with KOtBu in hexane at room temperature to yield $\text{K}[\text{C}_3(\text{SiMe}_3)_2\text{H}_3]$ in quantitative yield. Reaction of slightly more than two equivalents of $\text{K}[\text{C}_3(\text{SiMe}_3)_2\text{H}_3]$ with CaI_2 in THF at -78°C produces the colorless complex $[\text{Ca}\{\text{C}_3(\text{SiMe}_3)_2\text{H}_3\}_2(\text{thf})_2]$ in high yield. It has good solubility in THF and aromatic hydrocarbons. The ^1H NMR spectrum of the complex in $[\text{D}_8]\text{THF}$ contains a singlet for the trimethylsilyl protons, a doublet at $\delta = 2.98$ ($^3J = 16$ Hz) corresponding to the protons on the carbon atoms adjacent to the SiMe_3 groups, and a triplet at $\delta = 6.87$ from the unique hydrogen atom on the center carbon atom. The spectrum is invariant from room temperature to

[*] Prof. T. P. Hanusa, M. J. Harvey
Department of Chemistry
Vanderbilt University
Nashville, TN 37235 (USA)
Fax: (+1)615-322-4936
E-mail: t.hanusa@vanderbilt.edu
Dr. V. G. Young, Jr.
Department of Chemistry
University of Minnesota
Minneapolis, MN 55455 (USA)

[**] This work was supported by the National Science Foundation.

172(2) K, which suggests that the molecule is either non-fluxional or the rearrangements are of extremely low energy. Note that the C1 and C3 carbon atoms of [1,3-bis(trimethylsilyl)allyl]lithium are also magnetically equivalent to 170 K.^[10] Below this temperature, some inequivalence appears in their ¹³C NMR shifts, but isotopic perturbation experiments suggest this is the result of unsymmetrical solvation of the lithium cation, rather than asymmetric Li–C₃ bridging.

The solid-state structure of the bis(allyl)calcium compound was obtained on a colorless crystal slowly grown from a saturated THF/toluene solution.^[11] The complex crystallizes as the disolvate [Ca{C₃(SiMe₃)₂H₃}(thf)₂], with a crystallographically imposed C₂ axis through the calcium atom; only half the molecule is unique (Figure 1). Disorder that was found in one thf molecule was successfully resolved with a two-site model. The two allyl ligands are in an *anti* configuration, and the angle between the C₃ planes is 115.5°. The C–C bonds in the allyl ligand are essentially the same length at 1.402(4) Å (C1–C2) and 1.387(4) Å (C1–C3).

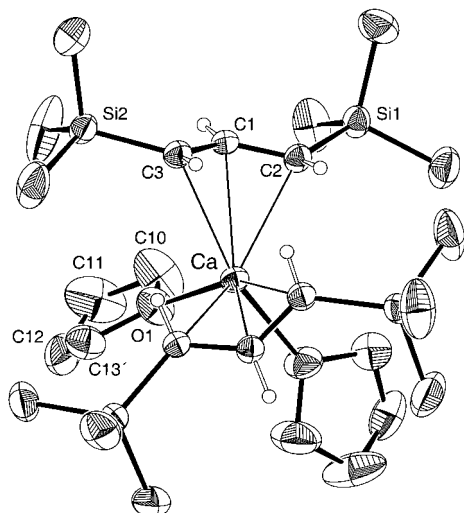


Figure 1. ORTEP plot of [Ca{C₃(SiMe₃)₂H₃}(thf)₂]. For clarity, the hydrogen atoms not directly bonded to the C₃ allyl fragment are not shown, and only one of the conformations of the thf ligands is depicted. Selected bond lengths [Å] and angles [°]: Ca–C2 2.648(3), Ca–C1 2.652(3), Ca–C3 2.662(3), Ca–O1 2.353(2), C1–C3 1.387(4), C1–C2 1.402(4); O1–Ca–O1' 80.44(13), C3–C1–C2 129.8(3).

The allyl ligands are bound in a symmetrical η^3 manner to the metal, with an average Ca–C distance of 2.654(5) Å and a spread of only 0.014 Å. Such symmetrical bridging is not observed in allylmagnesium compounds,^[12] but is similar to that found for Group 1 allyl complexes.^[13] The allyl–Ca distance is indistinguishable from that for cyclopentadienyl rings in formally six-coordinate Ca^{II} centers (e.g., 2.64(2) Å in [Ca(C₅Me₅)₂]^[14] and 2.67(2) Å in [[Ca{C₅(C₃H₇)₄H}I(thf)₂]₂]^[15] it is remarkable that a three-carbon ligand maintains the same separation. It should be noted that in transition metal [(C₃R_nH_{5–n})MCp] complexes, the allyl ligand binds more closely to the metal than does the Cp ring.^[16, 17]

The extent of interaction of the allyl group with the Ca^{II} center can be evaluated by several structural criteria. The C–C–C angle of 129.8(3)° is equivalent to the 130.3° angle predicted for free [C₃(SiMe₃)₂H₃][–] from ab initio SCF

calculations.^[18] In contrast, the hydrogen atoms, which were successfully refined, clearly lie out of the plane of the allyl-carbon atoms: the C3–C1–C2–H2 torsion angle is 16.9°, that for C2–C1–C3–H3 is 16.2°, and the central C1–H1 bond is tipped toward the calcium atom, and forms an angle of 12.8° with the C₃ plane (Figure 2).

Such hydrogen atom displacements are reminiscent of those calculated or found in other main group and transition metal allyl structures. In the almost completely ionic [Cs(C₃H₅)], for example, the terminal hydrogen atoms are rotated by 24.1° out of the allyl plane, and the central hydrogen atom is tipped toward the cesium atom by 8.0°.^[13] The same pattern is observed in the transition metal complex bis(η^3 -allyl)nickel.^[19] This atomic arrangement has been attributed to the relief of steric interaction between the metal and the allylic hydrogen atoms and to rehybridization of the allyl carbon atoms to improve metal–ligand bonding. Interestingly, the Si1 atom lies 0.38 Å out of the C₃ plane away from the calcium atom; the C3–C1–C2–Si1 torsion angle is 166.4°. The significance of this feature is difficult to interpret, as the Si2 atom is only 0.07 Å from the C₃ plane (C2–C1–C3–Si2 178.1°).

In summary, we have found that the allyl ligand in [Ca{C₃(SiMe₃)₂H₃}(thf)₂] displays an intriguing mix of structural features, including a metal–allyl distance that is the same as that found for calcium cyclopentadienyl complexes, but hydrogen atom displacements that are typical of those in other main group and transition metal π -allyl compounds. The presence of the trimethylsilyl groups, although clearly beneficial in stabilizing the compound, limit the reactivity of the allyl anion. The synthesis of other, less sterically hindered, derivatives will be required to study the reactions of heavy Group 2 allyl complexes more fully.

Experimental Section

[Ca{C₃(SiMe₃)₂H₃}(thf)₂]: CaI₂ (0.450 g, 1.53 mmol) was suspended in THF (100 mL) under nitrogen at –78 °C. A solution of K[C₃(SiMe₃)₂H₃] (0.772 g, 3.44 mmol) in THF (50 mL) was added dropwise with stirring over 30 min. After being allowed to warm to room temperature overnight, the reaction mixture was stripped to dryness, and the residue extracted with toluene. The extract was filtered, evaporated to dryness, and the crude product recrystallized from toluene/THF. [Ca{C₃(SiMe₃)₂H₃}(thf)₂] was obtained as air-sensitive colorless needles (0.78 g, 93 %, m.p. 130–131 °C. Elemental analysis calcd for C₂₆H₃₈CaO₂Si₄ (%): C 56.25, H 10.53; found C 54.59, H 10.26. The low value for carbon probably reflects the high air-sensitivity of the compound and/or partial loss of coordinated THF. For comparison the elemental analysis of [Ca{C₃(SiMe₃)₂H₃}(thf)] (%): C 54.70, H, 10.43; ¹H NMR (300 MHz, [D₈]THF, 20 °C): δ = –0.05 (s, 36H, Si(CH₃)₃), 2.98 (d, 4H, C2,C3-allyl-H; ³J = 16 Hz), 6.87 (t, 2H, C1-allyl-H; ³J = 16 Hz); ¹³C NMR (75.5 MHz, [D₈]THF, 20 °C): δ = 161 (C2,C3-allyl), 76.8 (C1-allyl), 1.87 (Si(CH₃)₃); IR (KBr): $\tilde{\nu}$ = 2956 (s, sh), 1595 (w), 1452 (w, br), 1249 (s, sh), 1009 (m, br), 984 (m), 863 (s), 839 (s) cm^{–1}.

Received: August 4, 1998 [Z12248IE]
German version: *Angew. Chem.* **1999**, *111*, 241–242

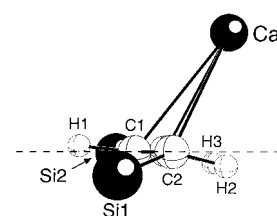


Figure 2. Hydrogen atom displacements in the allyl ligand of [Ca{C₃(SiMe₃)₂H₃}(thf)₂]. For clarity, the methyl groups have been removed from the silicon atoms, and a dotted line added in the plane of the allyl ligand.

Keywords: allyl complexes • calcium • main group elements • structure elucidation

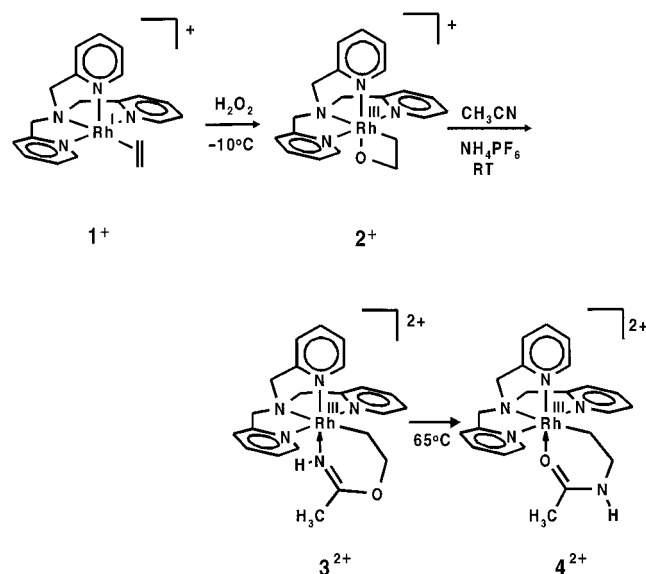
- [1] T. P. Hanusa, *Polyhedron* **1990**, *9*, 1345–1362.
- [2] T. P. Hanusa, *Chem. Rev.* **1993**, *93*, 1023–1036.
- [3] F. G. N. Cloke, P. B. Hitchcock, M. F. Lappert, G. A. Lawless, B. Royo, *J. Chem. Soc. Chem. Commun.* **1991**, 724–726.
- [4] C. Eaborn, S. A. Hawkes, P. B. Hitchcock, J. D. Smith, *Chem. Commun.* **1997**, 1961–1962.
- [5] J. S. Overby, T. P. Hanusa, *Organometallics* **1996**, *15*, 2205–2212.
- [6] J. S. Overby, T. P. Hanusa, *Angew. Chem.* **1994**, *106*, 2300–2302; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2191–2193.
- [7] G. Mösges, F. Hampel, P. v. R. Schleyer, *Organometallics* **1992**, *11*, 1769–1770.
- [8] A. Yanagisawa, S. Habaue, H. Yamamoto, *J. Am. Chem. Soc.* **1991**, *113*, 8955–8956.
- [9] A. Yanagisawa, S. Habaue, K. Yasue, H. Yamamoto, *J. Am. Chem. Soc.* **1994**, *116*, 6130–6141.
- [10] G. Fraenkel, A. Chow, W. R. Winchester, *J. Am. Chem. Soc.* **1990**, *112*, 1382–1386.
- [11] Crystal structure data of $[\text{Ca}\{\text{C}_3(\text{SiMe}_3)_2\text{H}_3\}_2(\text{thf})_2]$: tetragonal, space group $P4_2/n$, $a = 14.7796(1)$, $c = 16.5390(1)$ Å, $V = 3612.72(7)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 1.021$ g cm⁻³, $M_r = 555.17$. Refinement of 3212 reflections collected at the University of Minnesota at 173 ± 2 K with $I > 2.0\sigma(I)$ led to residuals of $R(F^2) = 0.0605$ and $R_w(F^2) = 0.1204$. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-102493. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [12] M. Marsch, K. Harms, W. Massa, G. Boche, *Angew. Chem.* **1987**, *99*, 706–707; *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 696–697.
- [13] N. van E. Hommes, M. Bühl, P. von R. Schleyer, Y.-D. Wu, *J. Organomet. Chem.* **1991**, *409*, 307–320.
- [14] R. A. Williams, T. P. Hanusa, J. C. Huffman, *Organometallics* **1990**, *9*, 1128–1134.
- [15] D. J. Burke, E. K. Alexander, T. P. Hanusa, *Organometallics* **1994**, *13*, 2773–2786.
- [16] A. E. Smith, *Inorg. Chem.* **1972**, *11*, 165–170.
- [17] N. W. Murrall, A. J. Welch, *J. Organomet. Chem.* **1986**, *301*, 109–130.
- [18] Full geometry optimization (HF/6-31G*) was performed assuming C_s symmetry; the SCF implementation provided in the MacSpartan Plus package (Wavefunction, Inc., Irvine, CA, USA) was used. Other geometric features of note: C–C 1.391 Å, C_{allyl}–Si 1.811 Å, C–C–Si 125.8°.
- [19] R. Goddard, C. Krüger, F. Mark, R. Stansfield, X. Zhang, *Organometallics* **1985**, *4*, 285–290.

Amidation of $[\text{Rh}^{\text{I}}(\text{ethene})]^+$ via a 2-Rhodaioxetane

Bas de Bruin, Mark J. Boerakker, René de Gelder, Jan M. M. Smits, and Anton W. Gal*

The formation of a C–N bond from an olefin and an amine or amide is a very desirable transformation.^[1] A catalytic version of this reaction could be a valuable alternative to classical industrial preparations of amines or amides. However, the few catalytic examples reported so far for this reaction are either slow or limited in scope (specific substrate or intramolecular reaction).^[2] Therefore, any new approach to formation of C–N bonds from olefins is of great interest. In this context we wish to report the two-step formation of a C–N bond from an olefin, with hydrogen peroxide and a nitrile (as an amide equivalent), via a 2-rhodaioxetane (1-oxa-2-rhodacyclobutane) complex.

Recently, we described the oxidation of $[(\text{tpa})\text{Rh}^{\text{I}}(\text{ethene})]^+$, 1^+ , (tpa = *N,N,N*-tri(2-pyridylmethyl)amine) with H_2O_2 to the 2-rhodaioxetane 2^+ (Scheme 1).^[3] The isolation of 2^+ gave us the unique opportunity to study the reactivity of an



Scheme 1. Step-wise amidation of the $\text{Rh}^{\text{I}}(\text{ethene})$ complex 1^+ ; oxidation with H_2O_2 to 2-rhodaioxetane 2^+ , formation of imino ester 3^{2+} by reaction with $\text{NH}_4^+/\text{MeCN}$, and thermal rearrangement to amide 4^{2+} .

unsubstituted 2-metallaioxetane.^[4, 5] The 2-rhodaioxetane 2^+ is stable in neat CH_3CN . However, addition of one mole of NH_4PF_6 per mole of 2^+ to a solution of $2 \cdot \text{BPh}_4$ in CH_3CN at room temperature results in quantitative conversion into the dicationic imino ester 3^{2+} within four hours (Scheme 1). We

[*] Prof. Dr. A. W. Gal, Dipl.-Chem. B. de Bruin, M. J. Boerakker, Dr. R. de Gelder, J. M. M. Smits
 Department of Inorganic Chemistry
 University of Nijmegen
 Toernooiveld 1, 6525 ED Nijmegen (Netherlands)
 Fax: (+31) 24-35534540
 E-mail: gal@sci.kun.nl

Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.

precipitated pure **3**·(BPh₄)₂·1.5 H₂O by addition of NaBPh₄ and MeOH. Crystals of **3**·(BPh₄)₂·MeOH that were suitable for X-ray diffraction were obtained by crystallization from a saturated solution of DMSO layered with MeOH. The crystal structure of **3**²⁺[6] shows that the O,C-coordinated 2-oxyethyl fragment in **2**⁺ has been converted into a N,C-coordinated 2-(acetimidoyloxy)ethyl fragment, which is in accordance with the NMR data (see Table 1). The acetimidoyl-NH fragment of **3**²⁺ shows a clear NOE contact with the nearby axial NCH₂-Py protons in the ¹H NOESY spectrum.

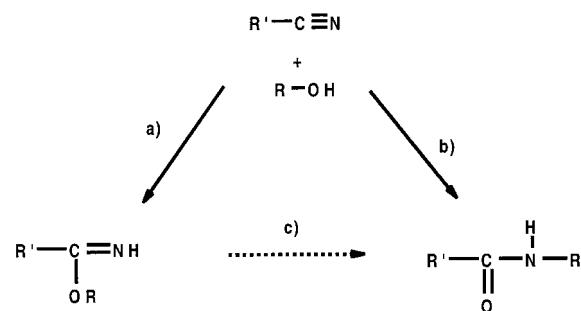
Table 1. Selected NMR data for **2**⁺, **3**²⁺, and **4**²⁺.^[a]

	2 ⁺ Y = O	3 ²⁺ Y = O	4 ²⁺ Y = N
¹ H NMR:			
(δ)RhCH ₂ CH ₂ Y	2.37	3.38	3.47
(³ J(Rh,H))	(2.4)	(2.7)	(2.4)
RhCH ₂ CH ₂ Y	4.92	4.26	3.23
(³ J(H,H))	(7.5)	(5.6)	(5.9)
¹³ C NMR:			
(δ)RhCH ₂ CH ₂ Y	1.3	28.5	33.3
(¹ J(Rh,C))	(18.4)	(26.6)	(27.7)
RhCH ₂ CH ₂ Y	78.7	71.8	41.5
(² J(Rh,C))	(4.0)	(0)	(0)

[a] ¹H NMR: in CD₃CN; ¹³C NMR: in [D₆]acetone (**2**⁺) or in [D₆]DMSO (**3**²⁺, **4**²⁺).

The ¹H NMR spectrum recorded immediately after the addition of NH₄PF₆ to a solution of **2**·BPh₄ in CD₃CN shows (besides signals of **2**⁺ and **3**²⁺) signals indicative of the presence of a C-coordinated 2-hydroxyethyl group.^[7] It seems, therefore, that the reaction proceeds via the intermediate 2-hydroxyethyl complex [(tpa)Rh^{III}(CH₂CH₂OH)(MeCN)]²⁺ **2a**²⁺, which results from protonation of the 2-rhodaioxetane oxygen atom and solvation by MeCN. This complex rearranges to imino ester **3**²⁺ by addition of the 2-hydroxyethyl group to the activated C≡N bond of the coordinated CH₃CN molecule.^[8] This rearrangement is analogous to a Pinner reaction^[9] (Scheme 2, path a).

Heating a solution of **2**·BPh₄ in CD₃CN to 65 °C for four hours in the presence of approximately one equivalent of NH₄PF₆ results in the formation of the trideuterated amide [D₃]**4**²⁺ via the trideuterated imino ester [D₃]**3**²⁺, as evident by ¹H NMR spectroscopy (Scheme 1). We obtained undeuterated **4**²⁺ as pure **4**·(BPh₄)₂·MeCN through the analogous



Scheme 2. Reaction of alcohols with nitriles in acidic media. a) Formation of the imidate by Pinner addition; b) formation of amide by Ritter reaction; c) rearrangement of the imidate to an amide.

reaction in MeCN, followed by addition of one equivalent of NaBPh₄ and partial evaporation of the solvent.

Opaque, colorless crystals of **4**·(BPh₄)₂·CH₃CN that were suitable for X-ray diffraction were obtained by the slow cooling of a hot, saturated solution of **4**·(BPh₄)₂ in CH₃CN. The crystal structure of **4**²⁺ (Figure 1)^[10] confirms the rearrangement of the N,C-coordinated 2-(acetimidoyloxy)ethyl group in **3**²⁺ to the O,C-coordinated 2-(acetylaminio)ethyl group in **4**²⁺. Bond lengths observed for **4**²⁺ are comparable to those of other rhodium and iridium amide complexes.^[11]

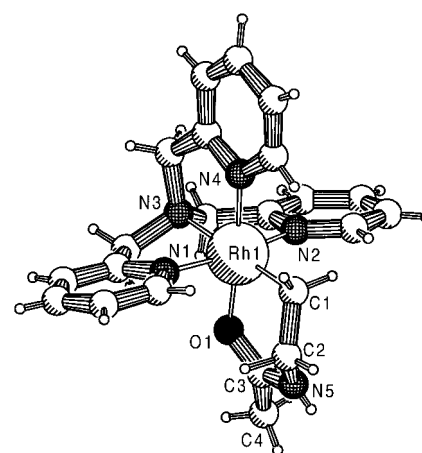


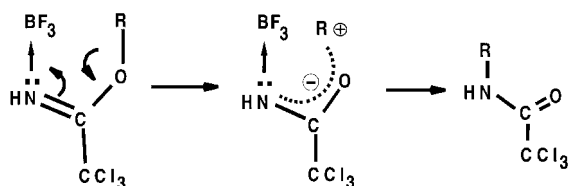
Figure 1. X-ray crystal structure of amide **4**²⁺. Selected bond lengths [Å] and angles [°]: Rh1–N1 2.034(4), Rh1–N2, 2.048(4), Rh1–N3 2.142(3), Rh1–N4 2.007(4), Rh1–O1 2.051(3), Rh1–C1 2.063(5), C1–C2 1.496(9), C2–N5 1.443(7), N5–C3 1.319(6), O1–C3 1.261(5), C3–C4 1.487(6); O1–Rh1–C1 91.1(2), Rh1–C1–C2 111.7(4), C1–C2–N5 114.5(5), C2–N5–C3 124.9(5), N5–C3–O1 121.4(5), C3–O1–Rh1 126.8(3), C4–C3–O1 118.9(4), C4–C3–N5 119.7(5).

Heating a CD₃CN or [D₆]DMSO solution of a sample of pure **3**·(BPh₄)₂·MeOH to 65 °C resulted in quantitative rearrangement to **4**²⁺ within 3.5 hours. The lack of incorporation of CD₃CN upon rearrangement of **3**²⁺ to **4**²⁺ in CD₃CN demonstrates that the transformation is truly intramolecular. The rearrangement was found to be unaffected by the presence of up to ten mol H₂O per mol **3**²⁺ in both CD₃CN and [D₆]DMSO, which showed that imino ester **3**²⁺ and amide **4**²⁺ are both relatively stable towards hydrolysis.

The observed bands $\tilde{\nu}_{\text{C=N}}$ (1634 cm^{−1}) for **3**²⁺ and $\tilde{\nu}_{\text{C=O}}$ (1600 cm^{−1}) for **4**²⁺ are in accordance with their crystal structure. Selected NMR data for the RhCH₂CH₂O fragment of **2**⁺, the RhCH₂CH₂OC(Me)=NH fragment of **3**²⁺, and the RhCH₂CH₂NHC(Me)=O fragment of **4**²⁺ are summarized in Table 1. The significant up-field shifts in the ¹H and ¹³C NMR spectra of the CH₂N fragment in **4**²⁺ relative to the CH₂O fragment in **2**⁺ and **3**²⁺ are diagnostic of the conversion of **3**²⁺ to **4**²⁺.

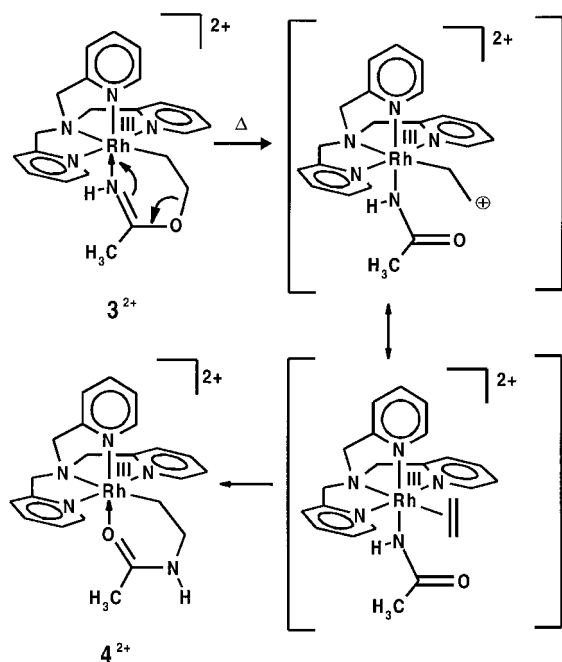
The overall rearrangement of intermediate **2a**²⁺ to **4**²⁺ is analogous to the Ritter reaction^[9] (Scheme 2, path b). To the best of our knowledge, the conversion of Pinner-type product **3**²⁺ into Ritter-type product **4**²⁺ is an unprecedented example of the rearrangement of an alkylalkanimidate to an *N*-alkylalkanamide (Scheme 2, path c: R,R' = alkyl). The heating of alkylalkanimidates generally results in elimination of

alcohols.^[12] However, the BF_3 -catalyzed rearrangement of alkyltrichloroacetimidates (Scheme 2, path c: $\text{R} = \text{alkyl}$, $\text{R}' = \text{CCl}_3$) to *N*-alkyltrichloroacetamides has been reported.^[13] The mechanism proposed for this reaction involves the formation of an alkyl cation–trichloroacetimidate ion pair (Scheme 3).



Scheme 3. Proposed mechanism for the BF_3 -catalyzed rearrangement of alkyltrichloroacetimidates to *N*-alkyltrichloroacetamides.^[13]

We propose that the mechanism for the transformation of 3^{2+} to 4^{2+} proceeds via the route shown in Scheme 4. β -elimination of the acetimidato group gives an acetamidato–ethene complex, which then reacts through the migratory insertion of the ethene into the $\text{Rh}–\text{N}$ bond.



Scheme 4. Proposed mechanism for the thermal rearrangement of 3^{2+} to 4^{2+} .

The overall conversion of ethene complex 1^+ into a $\kappa^2\text{-N,C}$ -2-(acetilamino)ethyl complex 4^{2+} (Scheme 1) is the first example of a two-step amidation of a coordinated olefin by H_2O_2 and H^+/MeCN . The synthetic applicability of this reaction is currently under investigation.

Experimental Section

$3 \cdot (\text{BPh}_4)_2 \cdot \text{NH}_4\text{PF}_6$ (25 mg, 0.15 mmol) was added to a solution of $2 \cdot \text{BPh}_4$ (100 mg, 0.13 mmol) in CH_3CN (10 mL), and the solution stirred at room temperature for 4 hours. Subsequently, a solution of NaBPh_4 (45 mg, 0.13 mmol) in CH_3CN (5 mL) was added, and the solvent was partially

evaporated under vacuum to about 5 mL. Compound $3 \cdot (\text{BPh}_4)_2 \cdot 1.5 \text{H}_2\text{O}$ was precipitated as a white powder by adding MeOH (ca. 10 mL). Opaque colorless crystals of $3 \cdot (\text{BPh}_4)_2 \cdot \text{MeOH}$ were obtained by slow crystallization of the above powder from DMSO/MeOH at -10°C . Yield: 131 mg (88%). The presence of approximately 1.5 mol water and 1 mol MeOH per mol 3^{2+} in the powder and the crystals, respectively, was confirmed by ^1H NMR spectroscopy. ^1H NMR (200.13 MHz, CD_3CN , 298 K): $\delta = 8.70$ (d, 1H, $^3J(\text{H,H}) = 5.6$ Hz; $\text{Py}_a\text{-H6}$), 8.32 (d, 2H, $^3J(\text{H,H}) = 5.9$ Hz; $\text{Py}_b\text{-H6}$), 8.0–6.8 (m, 9H; py-H4 , -H5 , and -H3), 7.31 (m, 8H; BAr-H2), 7.03 (t, 8H, $^3J(\text{H,H}) = 7.3$ Hz; BAr-H3), 6.87 (t, 4H, $^3J(\text{H,H}) = 7.3$ Hz; BAr-H4), 5.48 (d[AB], 2H, $^3J(\text{H,H}) = 16.8$ Hz; $\text{NCH}_2\text{-Py}_b$), 5.08 (d[AB], 2H, $^3J(\text{H,H}) = 16.8$ Hz; $\text{NCH}_2\text{-Py}_b$), 4.84 (s, 2H; $\text{NCH}_2\text{-Py}_a$), 4.26 (t, 2H, $^3J(\text{H,H}) = 5.6$ Hz; $\text{RhCH}_2\text{CH}_2\text{O}$), 3.38 (dt, 2H, $^3J(\text{H,H}) = 5.6$ Hz, $^2J(\text{H,Rh}) = 2.7$ Hz; $\text{RhCH}_2\text{CH}_2\text{O}$), 2.11 (s, 3H; $\text{OC}(\text{CH}_3)=\text{N}$); the ^1H NMR spectrum in $[\text{D}_6]\text{DMSO}$ shows an additional signal at $\delta = 8.35$ (brs, 1H, NH); $^{13}\text{C}\{^1\text{H}\}$ NMR (50.33 MHz, $[\text{D}_6]\text{DMSO}$, 298 K): $\delta = 179.5$ ($\text{OC}(\text{CH}_3)=\text{N}$), 164.3 ($\text{Py}_b\text{-C2}$), 163.2 ($\text{Py}_a\text{-C2}$), 163.4 (q, $^1J(\text{C,B}) = 48.6$ Hz; BAr-C1), 150.2 ($\text{Py}_b\text{-C6}$), 148.8 ($\text{Py}_a\text{-C6}$), 140.1 ($\text{Py}_b\text{-C4}$), 139.5 ($\text{Py}_a\text{-C4}$), 135.6 (BAr-C2), 126.0 ($\text{Py}_b\text{-C3}$), 125.3 (q, $^3J(\text{C,B}) = 2.8$ Hz; BAr-C3 , $\text{Py}_a\text{-C3}$), 124.9 ($\text{Py}_b\text{-C5}$), 122.3 ($\text{Py}_a\text{-C5}$), 121.6 (BAr-C4), 71.8 ($\text{RhCH}_2\text{CH}_2\text{O}$), 65.6 ($\text{N-CH}_2\text{-Py}_a$), 64.9 ($\text{NCH}_2\text{-Py}_b$), 28.4 (d, $^1J(\text{C,Rh}) = 26.4$ Hz, $\text{RhCH}_2\text{CH}_2\text{O}$), 21.6 ($\text{OC}(\text{CH}_3)=\text{N}$); FT-IR (KBr): $\tilde{\nu} = 3605$ (m), 3509 (m), 3275 (m), 1634 cm^{-1} (s, $\text{C}=\text{N}$); FAB-MS (*m*-nitrobenzylalcohol (Noba)/ CH_3CN): m/z : 798 [$M - \text{BPh}_4$] $^+$, 478 [$M - \text{H} - (\text{BPh}_4)_2$] $^+$, 393 [$M - (\text{CH}_2\text{CH}_2\text{OC}(\text{CH}_3)=\text{N}) - (\text{BPh}_4)_2 + \text{H}$] $^+$; FAB-MS (*m*-Noba/ CH_3CN) from a sample prepared from a CD_3CN solution: m/z : 801 [$M - \text{BPh}_4$] $^+$, 481 [$M - \text{H} - (\text{BPh}_4)_2$] $^+$, 393 [$M - (\text{CH}_2\text{CH}_2\text{OC}(\text{CD}_3)=\text{N}) - (\text{BPh}_4)_2 + \text{H}$] $^+$; elemental analysis calculated for $3 \cdot (\text{BPh}_4)_2 \cdot 1.5 \text{H}_2\text{O}$ ($\text{C}_{70}\text{H}_{69}\text{N}_5\text{O}_2\text{B}_2\text{Rh}$): C 73.44, H 6.07, N 6.12; found: C 73.50, H 6.32, N 6.02; calculated for $3 \cdot (\text{BPh}_4)_2 \cdot \text{MeOH}$ ($\text{C}_{71}\text{H}_{70}\text{N}_5\text{O}_2\text{B}_2\text{Rh}$): C 74.16, H 6.14, N 6.09; found: C 74.30, H 6.09, N 6.41.

$4 \cdot (\text{BPh}_4)_2 \cdot \text{NH}_4\text{PF}_6$ (45 mg, 0.28 mmol) was added to a solution of $2 \cdot \text{BPh}_4$ (100 mg, 0.13 mmol) in CH_3CN (10 mL), and the solution heated to 65°C for 4 h. Subsequently a solution of NaBPh_4 (90 mg, 0.26 mmol) in CH_3CN (5 mL) was added, and the solvent was partially evaporated under vacuum to about 3 mL. The solution was again heated to 65°C and allowed to cool slowly to room temperature, which resulted in the slow crystallization of $4 \cdot (\text{BPh}_4)_2 \cdot \text{CH}_3\text{CN}$ as opaque colorless crystals that were suitable for X-ray diffraction studies. Yield: 107 mg (71%). ^1H NMR (200.13 MHz, CD_3CN , 298 K): $\delta = 8.59$ (d, 1H, $^3J(\text{H,H}) = 6.2$ Hz; $\text{Py}_a\text{-H6}$), 8.43 (d, 2H, $^3J(\text{H,H}) = 5.9$ Hz; $\text{Py}_b\text{-H6}$), 8.0–6.8 (m, 9H; py-H4 , -H5 , and -H3), 7.31 (m, 8H; BAr-H2), 7.03 (t, 8H, $^3J(\text{H,H}) = 7.3$ Hz; BAr-H3), 6.87 (t, 4H, $^3J(\text{H,H}) = 7.3$ Hz; BAr-H4), 5.45 (d[AB], 2H, $^3J(\text{H,H}) = 15.9$ Hz; $\text{NCH}_2\text{-Py}_b$), 5.07 (d[AB], 2H, $^3J(\text{H,H}) = 15.9$ Hz; $\text{NCH}_2\text{-Py}_b$), 4.94 (s, 2H; $\text{NCH}_2\text{-Py}_a$), 3.47 (dt, 2H, $^3J(\text{H,H}) = 5.9$ Hz, $^3J(\text{Rh,H}) = 2.4$ Hz; $\text{RhCH}_2\text{CH}_2\text{NH}$), 3.23 (t, 2H, $^3J(\text{H,H}) = 5.9$ Hz; $\text{RhCH}_2\text{CH}_2\text{NH}$), 1.80 (s, 3H, $\text{NHC}(\text{CH}_3)=\text{O}$); the ^1H NMR spectrum in $[\text{D}_6]\text{DMSO}$ shows an additional signal at $\delta = 9.81$ (brs, 1H, NH); $^{13}\text{C}\{^1\text{H}\}$ NMR (50.33 MHz, $[\text{D}_6]\text{DMSO}$, 298 K): $\delta = 178.8$ ($\text{NHC}(\text{CH}_3)=\text{O}$), 164.9 ($\text{Py}_b\text{-C2}$), 164.3 ($\text{Py}_a\text{-C2}$), 163.4 (q, $^1J(\text{C,B}) = 48.6$ Hz; BAr-C1), 150.7 ($\text{Py}_a\text{-C6}$), 150.4 ($\text{Py}_b\text{-C6}$), 140.3 ($\text{Py}_b\text{-C4}$), 139.4 ($\text{Py}_a\text{-C4}$), 135.6 (BAr-C2), 125.9 ($\text{Py}_b\text{-C3}$), 125.3 (q, $^3J(\text{C,B}) = 2.8$ Hz; BAr-C3 , $\text{Py}_a\text{-C3}$), 124.8 ($\text{Py}_b\text{-C5}$), 122.5 ($\text{Py}_a\text{-C5}$), 121.6 (BAr-C4), 65.4 ($\text{NCH}_2\text{-Py}_b$), 63.9 ($\text{NCH}_2\text{-Py}_a$), 41.5 ($\text{RhCH}_2\text{CH}_2\text{NH}$), 33.3 (d, $^1J(\text{C,Rh}) = 27.7$ Hz, $\text{RhCH}_2\text{CH}_2\text{NH}$), 21.5 ($\text{NHC}(\text{CH}_3)=\text{O}$); FT-IR (KBr): $\tilde{\nu} = 3307$ (s, NH), 1600 cm^{-1} (s, $\text{C}=\text{O}$); FAB-MS (*m*-Noba/ CH_3CN): m/z : 798 [$M - \text{BPh}_4$] $^+$, 478 [$M - \text{H} - (\text{BPh}_4)_2$] $^+$, 393 [$M - (\text{CH}_2\text{CH}_2\text{NHC}(\text{CH}_3)=\text{O}) - (\text{BPh}_4)_2 + \text{H}$] $^+$; elemental analysis calculated for $4 \cdot (\text{BPh}_4)_2 \cdot \text{CH}_3\text{CN}$, ($\text{C}_{72}\text{H}_{69}\text{N}_6\text{ORhB}_2$): C 74.62, H 6.00, N 7.25; found: C 74.68, H 6.50, N 7.21.

Received: June 17, 1998 [Z12005IE]

German version: *Angew. Chem.* **1999**, *111*, 118–121

Keywords: alkene complexes • amidations • C–N coupling • oxidations • rhodium

- [1] a) D. M. Roundhill, *Chem. Rev.* **1992**, *29*, 1; b) D. M. Roundhill, *Catal. Today* **1997**, *37*, 155; c) J. J. Brunet, *Gazz. Chim. Ital.* **1997**, *127*, 111.
- [2] a) M. Beller, M. Eichberger, H. Trauthwein, *Angew. Chem.* **1997**, *109*, 2306; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2225; b) J. J. Brunet, G. Commenges, D. Neibecker, K. Philippot, *J. Organomet. Chem.* **1994**,

- 469, 221; c) A. L. Casalnuovo, J. C. Calabrese, D. Milstein, *J. Am. Chem. Soc.* **1988**, *110*, 6738; d) R. Dorta, P. Egli, F. Zürcher, A. Togni, *J. Am. Chem. Soc.* **1997**, *119*, 10857; e) M. A. Giardello, V. P. Conticello, L. Bard, M. R. Gagné, T. J. Marks, *J. Am. Chem. Soc.* **1994**, *116*, 10241; f) Y. Li, T. J. Marks, *J. Am. Chem. Soc.* **1996**, *118*, 9295; g) Y. Li, T. J. Marks, *Organometallics* **1996**, *15*, 3770; h) A. L. Seligson, W. C. Troglér, *Organometallics* **1993**, *12*, 744, and references therein.
- [3] B. de Bruin, M. J. Boerakker, J. J. M. Donners, B. E. C. Christiaans, P. P. J. Schlebos, R. de Gelder, J. J. M. Smits, A. L. Spek, A. W. Gal, *Angew. Chem.* **1997**, *109*, 2153; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2064.
- [4] The few isolated 2-metallaioxetanes known are all stabilized by various substituents. Consequently, it is difficult to deduce the intrinsic reactivity of the unsubstituted 2-metallaioxetane moiety from these substituted examples: a) V. W. Day, W. G. Klempner, S. P. Lockledge, D. J. Main, *J. Am. Chem. Soc.* **1990**, *112*, 2031; b) A. A. Zlota, F. Frolow, D. Milstein, *J. Am. Chem. Soc.* **1990**, *112*, 6411; c) M. J. Calhorda, A. M. Galvão, C. Ünaleroglu, A. A. Zlota, F. Frolow, D. Milstein, *Organometallics* **1993**, *12*, 3316; d) D. P. Klein, J. C. Hayes, R. G. Bergman, *J. Am. Chem. Soc.* **1988**, *110*, 3704; e) J. C. Hartwig, R. G. Bergman, R. A. Andersen, *Organometallics* **1991**, *10*, 3344; f) J. C. Hartwig, R. G. Bergman, R. A. Andersen, *J. Am. Chem. Soc.* **1990**, *112*, 3234; g) S. Baba, T. Ogura, S. Kawaguchi, H. Tokunan, Y. Kai, N. Kashi, *J. Chem. Soc. Chem. Commun.* **1972**, 910; h) L. Pandolfo, G. Paiaro, G. Valle, P. Ganis, *Gazz. Chim. Ital.* **1985**, *115*, 65; i) W. A. Herrmann, U. Küsthardt, A. Schäfer, E. Herdtweck, *Angew. Chem.* **1986**, *98*, 818; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 817; j) R. Schlödder, J. A. Ibers, M. Lenarda, M. Graziani, *J. Am. Chem. Soc.* **1974**, *96*, 6893; k) M. Lenarda, N. B. Pahor, M. Calligaris, M. Graziani, L. Randaccio, *J. Chem. Soc. Dalton Trans.* **1978**, 279.
- [5] For an overview of 2-metallaioxetane reactivity, see K. A. Jørgensen, B. Schiøtt, *Chem. Rev.* **1990**, *90*, 1483.
- [6] Details of the crystal structure determination are available as supporting information on the WWW.
- [7] $\delta(\text{CD}_3\text{CN}) = 4.02$ (t, $^3J(\text{H,H}) = 7.4$ Hz; $\text{RhCH}_2\text{CH}_2\text{O}$), 3.27 (dt, $^3J(\text{H,H}) = 7.4$ Hz, $^2J(\text{Rh,H}) = 2.7$ Hz; $\text{RhCH}_2\text{CH}_2\text{O}$). These signals are similar to those recorded for separately prepared $[(\text{tpa})\text{Rh}^{\text{III}}(2\text{-hydroxyethyl})(\text{Cl})]\text{BPh}_4$: $\delta(\text{CD}_3\text{CN}) = 3.98$ (t, $^3J(\text{H,H}) = 7.9$ Hz; $\text{RhCH}_2\text{CH}_2\text{O}$), 3.16 (dt, $^3J(\text{H,H}) = 7.9$ Hz, $^2J(\text{Rh,H}) = 2.6$ Hz; $\text{RhCH}_2\text{CH}_2\text{O}$).
- [8] For the intramolecular Pinner reaction from $[(\text{PMe}_3)_4\text{Ir}^{\text{III}}(\text{CH}_2\text{OH})(\text{N}=\text{CMe})]^{2+}$ to $\kappa^2\text{-N,C-2-(acetimidoyloxy)-methyl complex } [(\text{PMe}_3)_4\text{Ir}^{\text{III}}(\text{CH}_2\text{OC}(\text{Me})=\text{NH})]^{2+}$, see D. L. Thorn, J. C. Calabrese, *J. Organomet. Chem.* **1984**, *272*, 283. For other examples of nitrile $\text{C}\equiv\text{N}$ -bond activation by metal coordination (including Pinner type reactions with alcohols), see B. N. Storhoff, H. C. Lewis Jr., *Coord. Chem. Rev.* **1977**, *23*, 1.
- [9] For the Pinner syntheses, see J. March, *Advanced Organic Chemistry*, 4th ed, Wiley, **1992**, p. 892, and references therein. For the Ritter reaction, see J. March, *Advanced Organic Chemistry*, 4th ed, Wiley, **1992**, p. 970, and references therein.
- [10] Single crystals of $4 \cdot (\text{BPh}_4)_2 \cdot \text{CH}_3\text{CN}$ were mounted in air on a glass fibre. Intensity data were collected on an Enraf–Nonius CAD4 diffractometer with graphite monochromatized $\text{Cu}_{\text{K}\alpha}$ radiation ($\lambda = 1.541838$ Å). Data were collected at room temperature (θ – 2θ scan mode). Unit cell dimensions were determined from the angular setting of 15 reflections. Intensity data were corrected for Lorentz and polarization effects. A semi-empirical absorption correction (ψ scan)^[10a] was applied. The structures were solved by the program system DIRDIF^[10b] by using the program PATTY^[10c] to locate the heavy atom and were refined with standard methods (refinement against F^2 of all reflections with SHELXL97^[10d] with anisotropic parameters for the non-hydrogen atoms. The hydrogen atoms of the methyl groups were refined as rigid rotors with idealized sp^3 hybridization and a C–H bond length of 0.97 Å to match the maximum electron density in a difference Fourier map. The hydrogen atom attached to the nitrogen atom was taken from a difference Fourier map. All other hydrogen atoms were initially placed at calculated positions and were freely refined subsequently. Crystal data ($\text{C}_{72}\text{H}_{60}\text{B}_2\text{N}_6\text{ORh}$, $M_r = 1158.86$): monoclinic, space group $C2/c$, $a = 28.270(2)$, $b = 23.0952(14)$, $c = 21.520(2)$ Å, $\beta = 119.793(6)^\circ$, $V = 12192.9(16)$ Å³, $Z = 8$, $\rho_{\text{calcd}} = 1.263$ g cm^{−3}; final R indices: $R_1 = 0.0552$ (for 6778 reflections considered observed ($I > 2\sigma(I)$)), $wR_2 = 0.1255$ (all data) for the 993 total variables.^[10e] a) A. C. T North, D. C. Philips, F. S. Mathews; *Acta Crystallogr.* **1968**, *A24*, 351; b) P. T. Beurskens, G. Beurskens, W. P. Bosman, R. de Gelder, S. Garcia-Granda, R. O. Gould, R. Israel, J. M. M. Smits, DIRDIF-96, computer program system for crystal structure determination by Patterson and direct methods applied to difference-structure factors, Crystallography Laboratory, University of Nijmegen (Netherlands), **1996**; c) P. T. Beurskens, G. Beurskens, M. Strumpel, C. E. Nordman in *Patterson and Pattersons* (Eds.: J. P. Glusker, B. K. Patterson, M. Rossi), Clarendon, Oxford, **1987**, p. 356; d) G. M. Sheldrick, SHELXL-97, program for the refinement of crystal structures, Universität Göttingen (Germany), **1997**; e) Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-101855 and CCDC-101856 for $4 \cdot (\text{BPh}_4)_2 \cdot \text{MeCN}$ and $3 \cdot (\text{BPh}_4)_2 \cdot \text{MeOH}$, respectively. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [11] a) O. Heilmann, H. D. Hausen, W. Kaim, *Z. Naturforsch. Teil B* **1994**, *49*, 1554; b) B. McCulloch, J. Halpern, M. R. Thompson, C. R. Landis, *Organometallics* **1990**, *9*, 1392; c) M. Costa, G. P. Chiusoli, F. Salvadori, G. Bocelli, *Gazz. Chim. Ital.* **1995**, *125*, 589; d) B. E. Villarroya, L. A. Oro, F. J. Lahoz, A. J. Edwards, M. A. Ciriano, P. A. Alonso, A. Tiripicchio, M. Tiripicchio Camellini, *Inorg. Chim. Acta* **1996**, *250*, 241; e) M. I. Arriortua, J. L. Pizarro, J. Ruiz, J. M. Morena, E. Colacio, *Inorg. Chim. Acta* **1995**, *231*, 103; f) G. Bocelli, G. P. Chiusoli, M. Costa, M. Michelotti, *J. Chem. Soc. Perkin Trans. 1* **1994**, 1347; g) N. W. Alcock, J. M. Brown, P. J. Maddox, *J. Chem. Soc. Chem. Comm.* **1986**, 1532; h) N. W. Alcock, J. M. Brown, A. E. Derome, A. R. Lucy, *J. Chem. Soc. Chem. Comm.* **1985**, 575.
- [12] The thermal decomposition of alkylalkanimidates yields, among others, nitriles and alcohols or trisubstituted 1,3,5-triazines and alcohols: a) F. Cramer, K. Pawelzik, J. Kupper, *Angew. Chem.* **1956**, *20*, 649; b) P. Reynaud, R. C. Moreau, *Bull. Soc. Chim. Fr.* **1964**, 2997. See also ref. [13].
- [13] F. Cramer, N. Hennrich, *Chem. Ber.* **1961**, 976, and references therein.

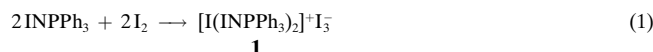
Domino Effect in the Buildup of N-I-N-I Chains of the N-Iodine(triphenylphosphane)imine

Jutta Grebe, Gertraud Geiseler, Klaus Harms, Bernhard Neumüller, and Kurt Dehnicke*

Nitrogen–iodine compounds are often associated through N-I-N-I chains of the donor–acceptor type. Examples are the iodine–nitrogen derivatives $\text{NI}_3 \cdot \text{NH}_3$ ^[1] and $\text{NI}_3 \cdot \text{pyridine}$,^[2] which form polymers, and the iodine azide which is monomeric in the gas phase^[3, 4] but forms zigzag chains with the iodine atoms in the solid state through the α -N atoms of the azide groups.^[3] The hypervalent character of the iodine atoms in these compounds, which causes the association, reveals itself above all in the ionic derivatives $[\text{I}_2\text{N}_3]^+[\text{SbF}_6]^-$,^[5] $[\text{PPh}_4]^+[\text{I}(\text{N}_3)_2]^-$,^[6] and in the halide complexes of *N*-iodosuc-

[*] Prof. Dr. K. Dehnicke, Dr. J. Grebe, G. Geiseler, Dr. K. Harms, Priv.-Doz. Dr. B. Neumüller
Fachbereich Chemie der Universität
Hans-Meerwein-Strasse, D-35032 Marburg (Germany)
Fax: (+49) 6421-28-8917

cinimide $[\text{PPh}_4]^+[\text{X}(\text{INC}_4\text{O}_2\text{H}_4)_2]^-$ ($\text{X} = \text{Cl}, \text{Br}, \text{I}$).^[7] On the other hand, *N*-iodine(triphenylphosphane)imine shows no tendency at all towards intermolecular $\text{N}-\text{I}\cdots\text{N}$ association in the solid state, although—according to the crystal structure analysis—the nitrogen atom is sp^3 -hybridized and shows Lewis basicity, while the iodine atom should be Lewis acidic because of its hypervalent character.^[8] We have now found that such an association is initiated, however, if INPPH_3 is allowed to react with elemental iodine. This leads to the formation of the binuclear complex **1** [Eq. (1)] when equimolar quantities of the reactants are applied.



According to the crystal structure analysis,^[9] in complex **1** the iodine cation I1 , which is formed by redox disproportionation, links the nitrogen atoms of both the INPPH_3 molecules with each other through $\text{N}-\text{I}-\text{N}$ bonds that differ only slightly in length (224.8 and 231.1 pm) (Figure 1). The bond angle at I1 is almost linear (176.1°), which is in agreement with the

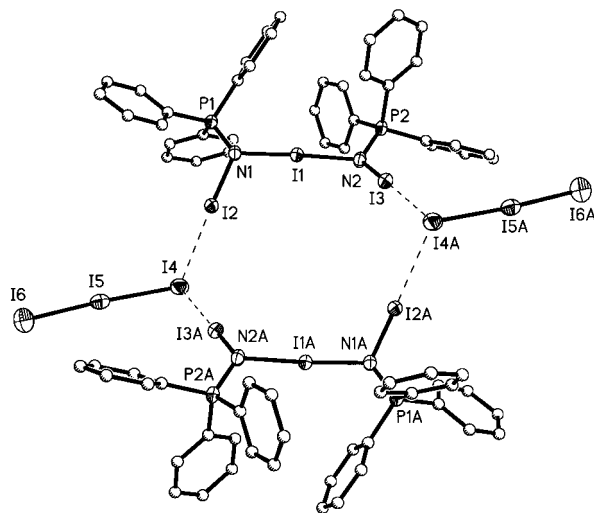
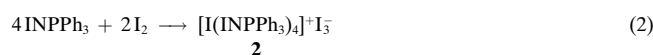


Figure 1. Structure of the dimeric ion pair in **1** in the crystal. Selected bond lengths [pm] and angles $^\circ$: $\text{I1}-\text{N1}$ 224.8(4), $\text{I1}-\text{N2}$ 231.1(4), $\text{I2}-\text{N1}$ 210.4(4), $\text{I3}-\text{N2}$ 209.1(4), $\text{I2}-\text{I4}$ 333.3(1), $\text{I3}-\text{I4A}$ 329.20(6), $\text{I4}-\text{I5}$ 303.2(1), $\text{I5}-\text{I6}$ 282.1(1), $\text{P}-\text{N}$ (av) 162.2; $\text{I1}-\text{N1}-\text{I2}$ 111.2(2), $\text{I1}-\text{N2}-\text{I3}$ 110.9(2), $\text{N1}-\text{I1}-\text{N2}$ 176.1(1), $\text{I2}-\text{I4}-\text{I5}$ 112.52(2), $\text{I2}-\text{I4}-\text{I3A}$ 92.26(2), $\text{I3A}-\text{I4}-\text{I5}$ 91.93(2).

VSEPR theory^[10] (three equatorially arranged lone pairs of electrons at I1). Two of the cations in **1** are connected with the triiodide ions through both the terminal iodine atoms to form a centrosymmetric nonplanar twelve-membered ring (Figure 1). These interionic $\text{I}^{\delta+}\cdots\text{I}_3^-$ distances of 333.3 pm correspond quite well to the $\text{I}\cdots\text{I}$ bond lengths of between 331.5 and 338.5 pm in diorganodiiodonium iodides such as $t\text{Bu}(i\text{Pr})\text{-PI}_2\cdots\text{I}$ and are described as soft–soft interactions.^[11]

If the amount of iodine applied in Equation (1) is halved, four INPPH_3 molecules can associate to form the tetranuclear complex **2** [Eq. (2)]. According to the crystal structure analysis,^[9] in the cation of **2** the iodine atoms located at the



beginning and at the end are linked by the triiodide ion to form a twelve-membered ring again with C_2 symmetry (Figure 2); the twofold axis runs through the atoms I1 and I5 . The support span of the terminal iodine atoms I3 and I3A

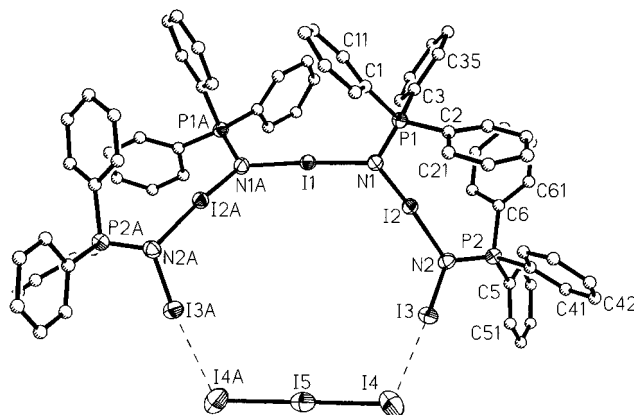
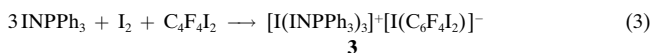


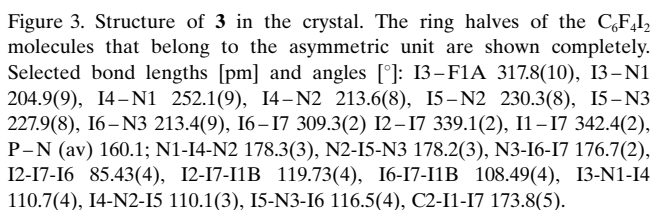
Figure 2. Structure of **2** in the crystal. Selected bond lengths [pm] and angles $^\circ$: $\text{I1}-\text{N1}$ 226.5(5), $\text{I2}-\text{N1}$ 212.5(4), $\text{I2}-\text{N2}$ 256.1(5), $\text{I3}-\text{N2}$ 207.4(5), $\text{I3}-\text{I4}$ 369.86(7), $\text{I4}-\text{I5}$ 289.84(6), $\text{P}-\text{N}$ (av) 161.1; $\text{N1}-\text{I1}-\text{N1A}$ 176.8(2), $\text{N1}-\text{I2}-\text{N2}$ 175.4(2), $\text{I1}-\text{N1}-\text{I2}$ 115.2(2), $\text{I2}-\text{N2}-\text{I3}$ 105.4(2), $\text{N2}-\text{I3}-\text{I4}$ 166.2(1), $\text{I3}-\text{I4}-\text{I5}$ 102.33(1).

of the cation allows only a weak interaction with the I_3^- ion as shown by the distances $\text{I3}\cdots\text{I4}$ of 369.9 pm. However, these distances are still significantly shorter than the van der Waals sum of radii (440 pm). In the cation of **2**, now, the three bridging iodine atoms I1 , I2 , and I2A have iodonium character with linear functionality. But in the $\text{N}-\text{I}-\text{N}$ chain of **2** the distances alternate more strongly than in **1**; the shortest bond of 207.4 pm starts from the quasi-terminal iodine atom I3 and is thus only a little longer than in INPPH_3 (205.6 pm).^[8] The short $\text{N2}-\text{I3}$ bond in **2** is followed by the long $\text{N2}-\text{I2}$ bond (256.1 pm) in the chain, while the two following $\text{N}-\text{I}$ bonds (212.5 and 226.5 pm) suffer an attenuation in the alternation of distances.

The building block missing between **1** and **2**, that is the linkage of three INPPH_3 molecules, could only be prepared by avoiding formation of triiodide. We achieved this by the complexation of the iodine ion formed according to Equation (3) with the relatively strong electrophile 1,4-diiodotetrafluorobenzene. According to the crystal structure analysis^[9]



this electrophile serves as a bridging ligand between symmetry-equivalent iodide ions (Figure 3). Along with the short intermolecular contacts $\text{I3}\cdots\text{F1C}$ (317.8 pm) and $\text{I3}\cdots\text{F2D}$ (323.3 pm), which are shorter than the van der Waals sum of radii by 42 pm and 37 pm, respectively, this leads to a three-dimensional network. It is in the nature of the $\text{I}\cdots\text{I}$ distances between the iodide ion I7 and the iodine atoms of the 1,4-diiodotetrafluorobenzene molecules (339.1 and 342.4 pm) that they are longer than the interionic distance $\text{I7}\cdots\text{I6}$ to the cation of **3** (309.3 pm). $\text{I}\cdots\text{I}$ distances of 339.8 pm are also found between the iodide ion and diiodoacetylene [$\text{cyclo-C}_3(\text{NMe}_2)_3]^+[\text{I}-\text{C}\equiv\text{C}-\text{I}\cdots\text{I}]^-$ with a zigzag chain structure in



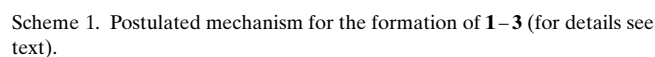
The stepwise buildup of the N-I-N chains in **1–3** can be understood as a domino mechanism^[14] (Scheme 1). For the initiating step one can presume the addition of an iodine molecule to the nitrogen atom of the *N*-iodine(triphenyl-

Experimental Section

3: A solution of INPPH_3 (0.95 g, 2.36 mmol) in dichloromethane (10 mL) was added to 1,4-diiodotetrafluorobenzene (0.95 g, 2.36 mmol) in dichloromethane (6 mL) and a few mg only of iodine to avoid formation of triiodide. After adding a few drops of *n*-hexane to the reaction mixture, it was allowed to stand for several days at -18°C . A few orange single crystals were grown and characterized by X-ray diffraction only.

Received: July 31, 1998 [Z12229 IE]
German version: *Angew. Chem.* **1999**, *111*, 183–186

Keywords: iodine • oligomers • phosphaneimines



- [1] H. Hartl, H. Bärnighausen, J. Jander, *Z. Anorg. Allg. Chem.* **1968**, 375, 225.
- [2] H. Hartl, D. Ullrich, *Z. Anorg. Allg. Chem.* **1974**, 409, 228.
- [3] P. Buzek, T. M. Klapötke, P. von R. Schleyer, I. C. Tornieporth-Oetting, P. S. White, *Angew. Chem.* **1993**, 105, 289; *Angew. Chem. Int. Ed. Engl.* **1993**, 32, 275.
- [4] M. Otto, S. D. Lotz, G. Frenking, *Inorg. Chem.* **1992**, 31, 3647.
- [5] I. C. Tornieporth-Oetting, P. Buzek, P. von R. Schleyer, T. M. Klapötke, *Angew. Chem.* **1992**, 104, 1391; *Angew. Chem. Int. Ed. Engl.* **1992**, 31, 1338.
- [6] U. Müller, R. Dübgen, K. Dehnicke, *Z. Anorg. Allg. Chem.* **1980**, 468, 7.
- [7] M. Ghassemzadeh, H. Goesmann, D. Fenske, K. Dehnicke, *Z. Naturforsch. B* **1994**, 49, 602.
- [8] J. Grebe, F. Weller, K. Dehnicke, *Z. Naturforsch. B* **1996**, 51, 1739.
- [9] Crystal structure analysis: Enraf-Nonius CAD4 four-circle diffractometer, Mo K_{α} radiation, graphite monochromator, ω scans, temperature 203(2) K, cell determination with 25 reflections, Lorentzian and polarization corrections, direct methods, refinement against F^2 , H atoms in calculated positions; calculations performed with: SHELXS-97, SHELXL-97, SHELXTL, PLATON-94, ORTEP 1·CH₂Cl₂: C₃₇H₃₃Cl₂I₆N₂P₂, space group $P\bar{1}$, $a = 985.6(1)$, $b = 1346.1(1)$, $c = 1669.8(1)$ pm, $\alpha = 95.99(1)$, $\beta = 94.87(1)$, $\gamma = 97.53(1)^\circ$, $Z = 2$, $V =$

2173.3(3) Å³, $\rho_{\text{calcd}} = 2.139 \text{ g cm}^{-3}$, $\theta = 2.3\text{--}26.0^\circ$. Of 8907 reflections collected, 8523 were independent ($R_{\text{int}} = 0.0117$), and 7879 with $I > 2\sigma(I)$, 443 parameters, $R_1 = 0.0326$, wR_2 (all data) = 0.0866. **2**: C₇₂H₆₀I₈N₄P₄, space group C2/c, $a = 1616.0(1)$, $b = 2493.1(2)$, $c = 1792.1(1) \text{ pm}$, $\beta = 96.54(1)^\circ$, $Z = 4$, $V = 7173.1(8) \text{ Å}^3$, $\rho_{\text{calcd}} = 1.963 \text{ g cm}^{-3}$, $2\theta = 4.6\text{--}50.0^\circ$. Of 6674 reflections collected, 6292 were independent ($R_{\text{int}} = 0.0202$), and 5231 with $I > 2\sigma(I)$, 399 parameters, $R_1 = 0.0381$, wR_2 (all data) = 0.0963. **3**: C₆₀H₄₅F₄I₇N₃P₃, space group P1, $a = 933.2(2)$, $b = 1406.6(1)$, $c = 2376.7(2) \text{ pm}$, $\alpha = 94.19(1)$, $\beta = 101.15(1)$, $\gamma = 96.89(1)^\circ$, $Z = 2$, $V = 3023.9(7) \text{ Å}^3$, $\rho_{\text{calcd}} = 2.049 \text{ g cm}^{-3}$, $\theta = 2.4\text{--}25.0^\circ$. Of 11262 reflections collected, 10551 were independent ($R_{\text{int}} = 0.0162$), and 8827 with $I > 2\sigma(I)$, 695 parameters, $R_1 = 0.0622$, wR_2 (all data) = 0.1721. Further details of the crystal structure investigations can be obtained from the Fachinformationszentrum Karlsruhe, D-76344 Eggenstein-Leopoldshafen, Germany (fax: (+49) 7247-808-666; e-mail: crysdata@fiz-karlsruhe.de), on quoting the depository numbers CSD-410019 (**1**), CSD-410020 (**2**), and CSD-410018 (**3**).

- [10] R. J. Gillespie, *Angew. Chem.* **1967**, 79, 885; *Angew. Chem. Int. Ed. Engl.* **1967**, 6, 819; R. J. Gillespie, E. A. Robinson, *Angew. Chem.* **1996**, 108, 539; *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 477.
- [11] V. Stenzel, J. Jeske, W. W. du Mont, P. G. Jones, *Inorg. Chem.* **1997**, 36, 443, and references therein.
- [12] R. Weiß, M. Rechinger, F. Hampel, A. Wolski, *Angew. Chem.* **1995**, 107, 483; *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 441.
- [13] K.-F. Tebbe, in *Rings, Chains and Macromolecules of Main Group Elements* (Ed.: A. L. Rheingold), Elsevier, Amsterdam, **1977**, pp. 551–606.
- [14] In recent years domino processes became increasingly important for stereo- and regiocontrolled C–C coupling reactions,^[15] in the biosynthesis,^[16] for metal-catalyzed syntheses,^[17] and in cyclization cascade reactions;^[18] cf. also ref. [19].
- [15] T.-L. Ho, *Tandem Organic Reactions*, Wiley-Interscience, New York, **1992**; *Frontiers in Organic Synthesis, Chem. Rev.* **1996**, 96, 1–600; L. F. Tietze, U. Beifuss, *Angew. Chem.* **1993**, 105, 137; *Angew. Chem. Int. Ed. Engl.* **1993**, 32, 131.
- [16] J. K. Sutherland in *Comprehensive Organic Synthesis*, Vol. 3 (Eds.: B. M. Trost, I. Fleming, G. Pattenden), Pergamon, Oxford, **1991**, p. 341.
- [17] P. Canonne, R. Boulanger, M. Bernatchez, *Tetrahedron Lett.* **1987**, 28, 4997; D. P. Curran in *Comprehensive Organic Synthesis*, Vol. 4 (Eds.: B. M. Trost, I. Fleming, M. F. Semmelhack), Pergamon, Oxford, **1991**, chapter 4.2; H. M. L. Davies, T. J. Clark, H. D. Smith, *J. Org. Chem.* **1991**, 56, 3817; R. Grigg, P. Kennewell, A. J. Teasdale, *Tetrahedron Lett.* **1992**, 33, 7789.
- [18] A. Padwa, *Chem. Commun.* **1998**, 1417.
- [19] E. J. Corey, X. M. Cheng, *The Logic of Chemical Synthesis*, Wiley-Interscience, New York, **1989**, p. 31.
- [20] N. Bricklebank, S. M. Godfrey, A. G. Mackie, C. A. McAuliffe, R. G. Pritchard, P. J. Kobryn, *J. Chem. Soc. Dalton Trans.* **1993**, 101; S. M. Godfrey, D. G. Kelly, C. A. McAuliffe, A. G. Mackie, R. G. Pritchard, S. M. Watson, *J. Chem. Soc. Chem. Commun.* **1991**, 1163.

Oxidations of C–H and O–H Bonds by Isolated Copper(III) Complexes**

Mark A. Lockwood, Teresa J. Blubaugh, Andrea M. Collier, Scott Lovell, and James M. Mayer*

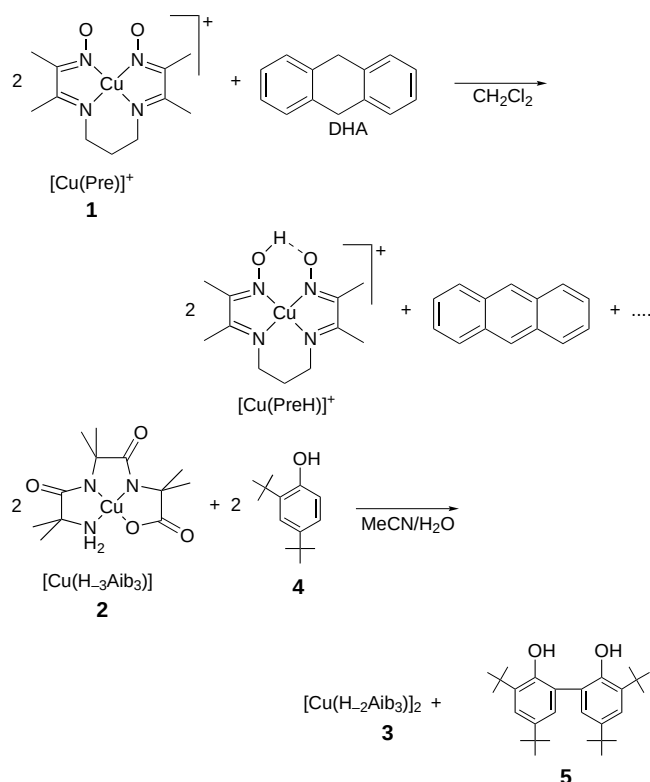
Metal-mediated abstractions of hydrogen atoms from C–H and O–H bonds are of interest due to their involvement in metalloenzyme and industrial oxidations. We have shown that metal–oxo complexes oxidize hydrocarbons by a hydrogen-atom abstraction mechanism, which is attributed to their thermodynamic affinity for a hydrogen atom ($\equiv \text{H}^\cdot + \text{e}^-$) rather than any radical character within the oxidant.^[1] We propose that any metal complex with sufficient affinity for an electron and a proton should exhibit such reactivity. Copper(III) complexes are attracting attention as models for intermediates in copper enzymes such as cytochrome c oxidase and dopamine β -hydroxylase.^[2] Proposed catalytic cycles for these and other enzymes involve H-atom abstraction from C–H and/or O–H bonds. Here we report apparent examples of such reactions for two known copper(III) complexes, [Cu(Pre)](ClO₄) (**1**-ClO₄)^[3] and [Cu(H₃Aib₃)] (**2**).^[4] Both complexes are reported to undergo aqueous electrochemical reductions with uptake of one proton [Eq. (1)].



[Cu(Pre)]⁺ (**1**) oxidizes dihydroanthracene (DHA) to anthracene in 60 % yield in CH₂Cl₂. To our knowledge, this is the first report of intermolecular hydrocarbon oxidation by an isolable copper(III) complex (Scheme 1). Other workers have reported intramolecular ligand C–H bond oxidation in copper(III) compounds,^[5] and Karlin et al. have very recently observed intermolecular C–H bond oxidations in a copper complex + O₂ system.^[6] The disappearance of **1** in the presence of excess DHA at 20 °C, as monitored by optical spectroscopy in the absence of air or light, followed simple second-order kinetics over several half lives with no apparent induction period [$k_2 = 2.0(\pm 0.1) \times 10^{-3} \text{ M}^{-1} \text{ s}^{-1}$]. At higher temperatures, the kinetics are increasingly complicated by decomposition of **1** and possibly other reactions. A preliminary Eyring plot (based on k_2 values from 287–328 K) gives $\Delta H^\ddagger \approx 15 \text{ kcal mol}^{-1}$ and $\Delta S^\ddagger \approx -23 \text{ cal K}^{-1} \text{ mol}^{-1}$, consistent with a bimolecular rate-determining step (1 cal = 4.184 J). A competition experiment at 55 °C using 9,9',10,10'-[D₄]dihydroanthracene showed a primary kinetic isotope effect of 3.3 ± 0.3 . The oxidation of xanthene to bixanthenyl by **1** (detected by GC/MS) is about 10 times faster than DHA oxidation, while reaction with fluorene under similar conditions failed to produce any detectable amounts of 9,9'-bifluorenyl. The relative rates are consistent with the C–H bond strengths (in kcal mol⁻¹) of the substrates: k_2 (xanthene (75.5)) > k_2 (DHA (78)) > k_2 (fluorene (80)).^[7]

[*] Prof. J. M. Mayer, M. A. Lockwood, T. J. Blubaugh, A. M. Collier, S. Lovell
Department of Chemistry, University of Washington
Box 351700; Seattle, WA 98195 (USA)
Fax: (+1) 206-685-8665
E-mail: mayer@chem.washington.edu

[**] We are grateful to the U.S. National Institutes of Health for financial support, and Professor K. Karlin for helpful comments.



Scheme 1. Oxidations by Cu^{III} complexes. Pre = 3,9-dimethyl-4,8-diazaundecane-2,10-dionedioximate; Aib₃ = tri- α -aminoisobutyric acid.

The protonated ligand of **2**, tri- α -aminoisobutyric acid, was synthesized in about 40% overall yield by using the recently developed peptide-coupling reagent, HATU.^[8] The copper(II) complex was oxidized to $[\text{Cu}^{\text{III}}(\text{H}_3\text{Aib}_3)]$ (**2**) by using IrCl_6^{2-} .^[9] Complex **2** showed no reactivity with DHA or fluorene over several days at room temperature in aqueous acetonitrile. However, **2** readily oxidizes 2,4,6-tri-*tert*-butylphenol under similar conditions to the corresponding phenoxyl radical, which was detected by EPR and UV/Vis spectroscopies.^[10] 2,4-Di-*tert*-butylphenol (**4**) reacts with **2** to give an 85% yield (HPLC, GC) of 2,2'-dihydroxy-3,3',5,5'-tetra-*tert*-butylbiphenyl (**5**), the coupling product from the 2,4-di-*tert*-butylphenoxyl radical (Scheme 1). This reaction also follows a second-order rate law; at 30 °C, $k_2 = 7.4 \times 10^{-3} \text{ M}^{-1} \text{ s}^{-1}$, $\Delta H^\ddagger = 8.3 \pm 1.1 \text{ kcal mol}^{-1}$ and $\Delta S^\ddagger = -27 \pm 3 \text{ cal K}^{-1} \text{ mol}^{-1}$ (283–313 K). Compound **4** is similarly oxidized by **1** (rapidly forming >90% yield of **5**) as well as by copper μ -oxo dimers^[2e, 5a] and copper peroxo complexes.^[11] Phenol **4** (O–H bond strength: 81 kcal mol⁻¹^[12]) is oxidized much faster than DHA (C–H bond strength: 78 kcal mol⁻¹).

Reaction mixtures of **2** and 2,4-di-*tert*-butylphenol slowly deposit dark blue crystals of dimeric $[\text{Cu}^{\text{II}}(\text{H}_2\text{Aib}_3)]_2$ (**3**, Figure 1). Whereas the peptide functions as a tetradentate chelate ligand in **2**,^[4] in **3** it functions as a tridentate chelate ligand for one copper center, with coordination through the terminal amine group (N(4) and N(3), respectively), the carbonyl oxygen atom of a protonated amide (N(1) and N(6), respectively), and the N atom of the deprotonated amide (N(5) and N(2), respectively), and as a monodentate ligand (through the carboxylate group) for the other copper center.

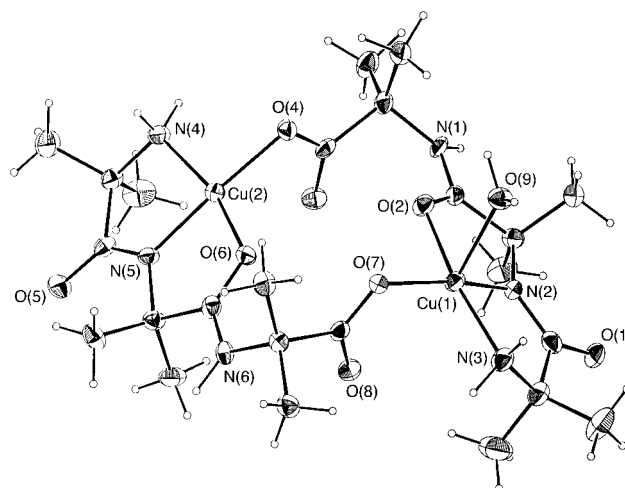


Figure 1. Molecular structure of **3**; solvent molecules have been omitted for clarity. Selected bond lengths [Å]: Cu(1)–O(2) 2.007(4), Cu(1)–N(2) 1.902(4), Cu(1)–N(3) 1.992(4), Cu(1)–O(7) 1.981(4), Cu(1)–O(9) 2.323(4), Cu(2)–N(4) 1.987(4), Cu(2)–N(5) 1.881(4), Cu(2)–O(4) 1.955(4), Cu(2)–O(6) 1.964(4).

Cu(1) also has an axially bound water molecule (2.323(4) Å), and Cu(2) has a weak interaction (3.47 Å) with a carboxylate oxygen atom [O(5)] of an adjacent molecule. Formation of **3** from **2** involves addition of an electron to copper and protonation of an amide nitrogen atom. However, it is possible that hydrogen is initially transferred from the phenol **4** to an amide oxygen atom of **2**. Protonation at this site has been observed in a macrocyclic copper(II) complex.^[13]

In summary, the isolated Cu^{III} complex **1** oxidizes hydrocarbon substrates. The reactions are faster for substrates with weaker C–H bonds. Complexes **1** and **2** oxidize substituted phenols to radicals or radical coupling products. The reactivity of **1** and **2** are therefore consistent with their acting as hydrogen-atom abstracting reagents, as predicted based on the ground state thermodynamics. As found for oxyl radicals,^[14] H-atom abstraction is much faster from O–H bonds than from C–H bonds of the same strength. Correlation of the rate constants for C–H bond oxidation with enthalpic driving force, as we have done in other systems,^[1] is complicated by the coordination of axial ligands on reduction of square-planar d⁸ Cu^{III} complexes. The driving force is affected by the nature of the axial ligands and ligand coordination leads to a significant entropic contribution.^[15] Addition of $\text{H}^\cdot$ to **1** gives $[\text{Cu}(\text{PreH})]^+$, in which the hydrogen atom bridges the two oxime-oxygen atoms,^[16] further complicating the transition state.

Experimental Section

All reactions were performed under an inert atmosphere using dry solvents. Complex **1** was prepared according to the literature method.^[3] HATU^[8] was used as the coupling reagent in the preparation of tri- α -aminoisobutyric acid (Aib₃) because the reported procedure using carbodiimide coupling^[17] did not work in our hands.

2: Instead of the reported flow electrochemical preparation,^[4] **2** was prepared as follows: Copper acetate (0.06 g, 0.29 mmol) was added to a solution of the tripeptide (0.10 g, 0.32 mmol) in 0.1 M NaOH (5 mL). Acetate buffer (7 mL, pH 3.5) and Na_2IrCl_6 (0.16 g, 0.29 mmol) were added and the solution was stirred for several hours at room temperature. The resulting brown solution was lyophilized, redissolved in water, eluted through an ion-exchange column (Bio-Rad AG 11A8), and lyophilized a

second time. Recrystallization from CH₃CN yielded **2** (62 mg, 50%) as a brown powder.

Complexes **1** and **2** were identified by comparison to the reported spectroscopic data (UV/Vis for both, ¹H NMR for **2**)^[3,4] and by redox titration.

3: Isolated in 50% yield based on **2**. UV/Vis (CH₃OH): λ_{max}(ε) = 618 (140). FAB-MS (calcd. for C₂₄H₂₄N₆O₅Cu₂): 671 ([M⁺ – H]). Crystals: 0.33 × 0.16 × 0.05 mm, triclinic *P* $\bar{1}$, *a* = 11.659(1), *b* = 11.854(1), *c* = 15.695(1) Å, α = 97.48(1), β = 101.75(1), γ = 101.87(1)°, *V* = 2044.5(5) Å³, *Z* = 2, ρ_{calcd} = 1.389 g cm⁻³. Nonius KappaCCD diffractometer, MoKα (λ = 0.7107 Å), 161 K, ω scans, 33764 measured, 7769 independent, 5258 observed reflections [*F* > 3σ(*F*)]. Solved by direct methods (SIR92)^[18] and refined using maXus (MacScience, Japan, 1997). *R* = 0.057 [*F* > 3σ(*F*)], *wR* = 0.068 for 460 parameters, Δρ_{max/min} = 1.49, –0.97 e Å⁻³. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-102174. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Received: July 2, 1998 [Z 12086IE]

German version: *Angew. Chem.* **1999**, *111*, 178–180

Keywords: copper • hydrocarbons • oxidations • phenols • radical reactions

- [1] a) K. A. Gardner, L. L. Kuehnert, J. M. Mayer, *Inorg. Chem.* **1997**, *36*, 2069; b) K. Wang, J. M. Mayer, *J. Am. Chem. Soc.* **1997**, *117*, 1470; c) J. M. Mayer, *Acc. Chem. Res.* **1998**, *31*, 341.
- [2] a) G. P. Panigrahi, *Top. Chem. Ser. I*, **1991**, 189–210; b) *Bioinorganic Chemistry of Copper* (Eds.: K. D. Karlin, Z. Tyeklar), Chapman and Hall, New York, **1993**; c) J. P. Klinman, *Chem. Rev.* **1996**, *96*, 2541–2561; d) W. B. Tolman, *Acc. Chem. Res.* **1997**, *30*, 227–237; e) V. Mahadevan, Z. Hou, A. P. Cole, D. E. Root, T. K. Lal, E. I. Solomon, T. D. P. Stack, *J. Am. Chem. Soc.* **1997**, *119*, 11996.
- [3] Y. Sulfab, N. J. Al-Shatti, *Inorg. Chim. Acta* **1984**, *87*, L23.
- [4] a) D. W. Margerum, *Pure Appl. Chem.* **1983**, *55*, 23–34; b) L. L. Diaddario, W. R. Robinson, D. W. Margerum, *Inorg. Chem.* **1983**, *22*, 1021; c) D. W. Margerum, W. M. Scheper, M. R. McDonald, F. C. Fredericks, L. Wang, H. D. Lee in ref. [2b], pp. 213–221.
- [5] a) S. Mahapatra, J. A. Halfen, W. B. Tolman, *J. Am. Chem. Soc.* **1996**, *118*, 11575–11586; b) K. V. Reddy, S.-J. Jin, P. K. Arora, D. S. Sfeir, S. C. F. Maloney, F. L. Urbach, L. M. Sayre, *J. Am. Chem. Soc.* **1990**, *112*, 2332; c) references [1,2,4].
- [6] H. V. Obias, Y. Lin, N. N. Murthy, E. Pidcock, E. I. Solomon, M. Ralle, N. J. Blackburn, Y.-M. Neuhold, A. D. Zuberbühler, K. D. Karlin, *J. Am. Chem. Soc.* **1998**, in press.
- [7] See reference [1a] for references to C–H bond strengths.
- [8] HATU = *O*-(7-azabenzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; available from PerSeptive Biosystems, Framingham, MA; A. L. A. Carpino, A. El-Faham, F. Albericio, *Tetrahedron Lett.* **1994**, *35*, 2279–2282.
- [9] D. W. Margerum, K. L. Chellappa, F. P. Bossu, G. L. Burce, *J. Am. Chem. Soc.* **1975**, *97*, 6894.
- [10] A. R. Forrester, J. M. Hay, R. H. Thomson, *Organic Chemistry of Stable Free Radicals*, Academic Press, London, **1968**, p. 282.
- [11] a) P. P. Paul, Z. Tyeklar, R. R. Jacobson, K. D. Karlin *J. Am. Chem. Soc.* **1991**, *113*, 5322–5332; b) J. A. Halfen, V. G. Young, Jr., W. B. Tolman *Inorg. Chem.* **1998**, *37*, 2102–2103.
- [12] M. Lucarini, P. Pedrielli, G. F. Pedulli, S. Cabiddu, C. Farruoni *J. Org. Chem.* **1996**, *61*, 9259.
- [13] F. Kou, S. Zhu, H. Lin, Y. Chen, H. Wang, X. Yao, *Chem. Commun.* **1996**, 59.
- [14] M. Folti, K. U. Ingold, J. Luszyk, *J. Am. Chem. Soc.* **1994**, *116*, 9440.
- [15] M. P. Youngblood, D. W. Margerum, *Inorg. Chem.* **1980**, *19*, 3068.
- [16] A. W. Addison, M. Carpenter, L. K.-M. Lau, M. Wicholas, *Inorg. Chem.* **1978**, *17*, 1545.
- [17] S. T. Kirksey, Jr., T. A. Neubecker, D. W. Margerum, *J. Am. Chem. Soc.* **1979**, *101*, 1631.
- [18] A. Altomare, G. Cascarano, C. Giacovazzo, M. C. Burla, G. Polidori, M. Camalli, *J. Appl. Crystallogr.* **1994**, *27*, 435–442.

Half-Sandwich Alkyl and Hydrido Complexes of Yttrium: Convenient Synthesis and Polymerization Catalysis of Polar Monomers**

Kai C. Hultzs, Thomas P. Spaniol, and Jun Okuda*

Structurally well characterized organometallic complexes of rare earth metals^[1] such as lanthanocene hydrides and alkyls of the type [(η⁵-C₅R₅)₂LnX₂] (X = H, alkyl) have recently attracted considerable interest as cocatalyst-free homogeneous polymerization catalysts for both nonpolar and polar monomers.^[2] Catalyst systems based on complexes with only one cyclopentadienyl ligand are anticipated to show greater activity towards sterically more demanding monomers.^[3] However, conventional synthesis of mono(cyclopentadienyl) rare earth complexes [(η⁵-C₅R₅)LnX₂(L)_n], where at least one ligand X is a hydride or alkyl, is often hampered by ate-complex formation with concomitant alkali metal salt incorporation.^[3,4] Consequently, only a limited number of this type of half-sandwich complexes has been synthesized, and their catalytic performance still remains unexplored.^[5] We report here a remarkably facile alkane elimination as a route^[6] to yttrium complexes of the type [(η⁵-C₅Me₄SiMe₂X')-YX₂(thf)], as well as preliminary results on the polymerization of *tert*-butyl acrylate and acrylonitrile with these complexes.

Reaction of [Y(CH₂SiMe₃)₃(thf)₂] (**1**)^[7] with (C₅Me₄H)SiMe₂X' (X' = NHCMe₃, Me, Ph, C₆F₅) in pentane at 0 °C for 2 h resulted in the quantitative formation (according to ¹H NMR spectroscopy) of the half-sandwich yttrium complexes [(η⁵:η¹-C₅Me₄SiMe₂NCMe₃)Y(CH₂SiMe₃)(thf)] (**2**) or [(η⁵-C₅Me₄SiMe₂X')Y(CH₂SiMe₃)₂(thf)] (**3**) along with tetramethylsilane (Scheme 1, Table 1). The linked amido-cyclopentadienyl complex **2** was isolated as colorless crystals. Complexes **3a–c** are colorless to slightly yellow crystals which melt below room temperature. All complexes are readily soluble in aliphatic and aromatic hydrocarbons. Remarkably, no formation of the metallocene complex could be observed by ¹H NMR spectroscopy: The excess cyclopentadiene was left unchanged even in the presence of two equivalents of (C₅Me₄H)SiMe₃. The presence of the silicon substituent on cyclopentadiene is crucial for this complexation reaction to be successful. Mixtures of mono- and bis(cyclopentadienyl) complexes were obtained when silicon-free cyclopentadienes such as C₅Me₅H or C₅Me₄H₂ were employed.

When complexes **2** and **3** are in solution at room temperature, the coordinated thf groups are labile on both the chemical and NMR time scale. This is shown by the instantaneous exchange of all coordinated thf molecules upon addition of excess [D₈]THF and the substantial high-field

[*] Prof. Dr. J. Okuda, Dipl.-Chem. K. C. Hultzs, Dr. T. P. Spaniol
Institut für Anorganische Chemie und
Analytische Chemie der Universität
J.-J.-Becher-Weg 24, D-55099 Mainz (Germany)
Fax: (+49) 6131-39-5605

[**] This work was supported by the Fonds der Chemischen Industrie, BASF AG (Kunststofflaboratorium), and the Bundesministerium für Bildung, Wissenschaft, Forschung und Technologie. K.C.H. thanks the Fonds der Chemischen Industrie for a doctoral scholarship.

Table 1. Selected spectroscopic data of **2**, **3a–c**, and **4**. NMR spectra in [D₆]benzene at 400 MHz (¹H), 100.6 MHz (¹³C), 79.5 MHz (²⁹Si), and 376.4 MHz (¹⁹F) and at 25 °C (unless stated otherwise).

2: ¹H NMR: δ = –0.93 (d, ²*J*(Y,H) = 3.1 Hz, 2H, Y–CH₂), 0.28 (s, 9H, CH₂SiMe₃), 0.74 (s, 6H, SiCH₃), 1.02 (m, 4H, β -CH₂, thf), 1.38 (s, 9H, C(CH₃)₃), 2.04, 2.19 (s, 6H, ring CH₃), 3.30 (m, 4H, α -CH₂, thf); ¹³C NMR: δ = 4.7 (CH₂SiCH₃), 8.4 (NSiCH₃), 11.5, 14.0 (ring CH₃), 24.7 (β -CH₂, thf), 26.2 (d, ¹*J*(Y,C) = 44.9 Hz, YCH₂), 36.0 (C(CH₃)₃), 54.0 (C(CH₃)₃), 70.7 (α -CH₂, thf), 106.6 (ring C at Si), 122.3, 126.4 (ring C); ²⁹Si NMR: δ = –25.0 (NSiMe₂), –2.7 (d, ²*J*(Y,Si) = 1.9 Hz, CH₂SiMe₃)

3a: ¹H NMR: δ = –0.61 (d, ²*J*(Y,H) = 3.1 Hz, 4H, YCH₂), 0.30 (s, 18H, CH₂SiCH₃), 0.41 (s, 9H, SiCH₃), 1.15 (m, 4H, β -CH₂, thf), 1.96, 2.24 (s, 6H, ring CH₃), 3.52 (m, 4H, α -CH₂, thf); ¹³C NMR: δ = 2.6 (SiCH₃), 4.6 (CH₂SiCH₃), 11.5, 14.6 (ring CH₃), 24.8 (β -CH₂, thf), 34.7 (d, ¹*J*(Y,C) = 43.7 Hz, YCH₂), 70.4 (α -CH₂, thf), 115.0 (ring C at Si), 123.3, 126.4 (ring C); ²⁹Si NMR: δ = –10.3 (SiMe₃), –3.2 (d, ²*J*(Y,Si) = 2.1 Hz, CH₂SiMe₃)

3b: ¹H NMR: δ = –0.58 (d, ²*J*(Y,H) = 3.1 Hz, 4H, YCH₂), 0.30 (s, 18H, CH₂SiCH₃), 0.69 (s, 6H, Si(CH₃)Ph), 1.20 (m, 4H, β -CH₂, thf), 1.97, 2.15 (s, 6H, ring CH₃), 3.47 (m, 4H, α -CH₂, thf), 7.17 (m, 3H, C₆H₅), 7.53 (m, 2H, C₆H₅); ¹³C NMR: δ = 1.8 (Si(CH₃)Ph), 4.6 (CH₂SiCH₃), 11.6, 14.8 (ring CH₃), 24.9 (β -CH₂, thf), 34.9 (d, ¹*J*(Y,C) = 43.7 Hz, YCH₂), 70.0 (α -CH₂, thf), 112.6 (ring C at Si), 123.6, 127.1 (ring C), 128.0, 128.8, 134.3 (C₆H₅), 141.6 (*ipso*-C₆H₅); ²⁹Si NMR: δ = –13.8 (SiMe₂Ph), –3.2 (d, ²*J*(Y,Si) = 2 Hz, CH₂SiMe₃)

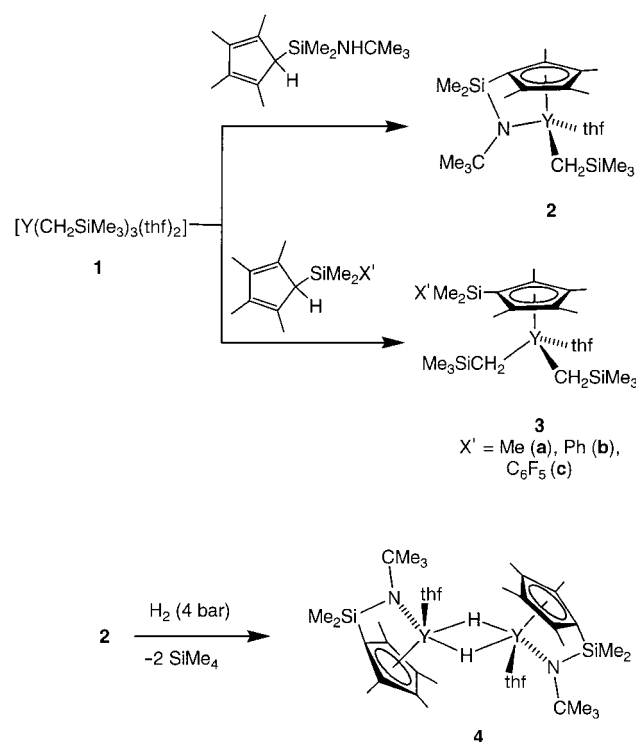
3c: ¹H NMR: δ = –0.65 (d, ²*J*(Y,H) = 3.1 Hz, 4H, YCH₂), 0.28 (s, 18H, CH₂SiCH₃), 0.78 (t, 6H, ³*J*(F,H) = 1.6 Hz, Si(CH₃)C₆F₅), 1.25 (m, 4H, β -CH₂, thf), 1.85, 2.19 (s, 6H, ring CH₃), 3.50 (m, 4H, α -CH₂, thf); ¹³C NMR: δ = 2.6 (Si(CH₃)C₆F₅), 4.5 (CH₂SiCH₃), 11.4, 14.3 (ring CH₃), 25.0 (β -CH₂, thf), 35.0 (d, ¹*J*(Y,C) = 43.7 Hz, YCH₂), 69.9 (α -CH₂, thf), 110.0 (ring C at Si), 112.3 (*ipso*-C₆F₅), 123.9, 126.9 (ring C), 136.2, 147.8, 150.2 (m, C₆F₅); ²⁹Si NMR: δ = –13.8 (SiMe₂C₆F₅), –3.2 (d, ²*J*(Y,Si) = 1.8 Hz, CH₂SiMe₃); ¹⁹F NMR: δ = –105.6 (m, *m*-C₆F₅), –130.7 (t, ³*J*(F,F) = 21 Hz, *p*-C₆F₅), –139.0 (m, *m*-C₆F₅)

4: ¹H NMR ([D₈]toluene, 50 °C): δ = 0.69 (s, 6H, SiCH₃), 1.36 (s, 9H, C(CH₃)₃), 1.46 (brm, 4H, β -CH₂, thf), 2.09, 2.22 (s, 6H, ring CH₃), 3.82 (brm, 4H, α -CH₂, thf), 5.50 (t, 1H, ¹*J*(Y,H) = 28.8 Hz, Y₂H₂); ¹³C NMR ([D₈]toluene, 50 °C): δ = 8.6 (SiCH₃), 12.2, 14.3 (ring CH₃), 25.2 (β -CH₂, thf), 36.8 (C(CH₃)₃), 55.0 (C(CH₃)₃), 72.1 (α -CH₂, thf), 108.5 (ring C at Si), 125.8 (ring C); ²⁹Si NMR ([D₈]toluene, 50 °C): δ = –25.5

4 (major isomer): ¹H NMR ([D₈]toluene, –40 °C): δ = 0.81, 0.95 (s, 3H, SiCH₃), 1.17 (m, 4H, β -CH₂, thf), 1.52 (s, 9H, C(CH₃)₃), 2.02 (s, 6H, ring CH₃), 2.11, 2.54 (s, 3H, ring CH₃), 3.47, 3.85 (brm, 2H, α -CH₂, thf), 5.27 (t, 1H, ¹*J*(Y,H) = 29.0 Hz, Y₂H₂); ¹³C NMR ([D₈]toluene, –40 °C): δ = 8.2, 9.3 (SiCH₃), 12.1, 12.3, 13.9, 14.7 (ring CH₃), 25.0 (β -CH₂, thf), 36.3 (C(CH₃)₃), 54.7 (C(CH₃)₃), 72.7 (α -CH₂, thf), 107.1 (ring C at Si), 119.6, 122.8, 126.0, 126.2 (ring C); ²⁹Si NMR ([D₈]toluene, –40 °C): δ = –25.6

4 (minor isomer): ¹H NMR ([D₈]toluene, –40 °C): δ = 1.20 (m, 4H, β -CH₂, thf), 1.44 (s, 9H, C(CH₃)₃), 2.05, 2.14, 2.20, 2.51 (s, 3H, ring CH₃), 3.78 (brm, 4H, α -CH₂, thf), 5.45 (t, 1H, ¹*J*(Y,H) = 28.6 Hz, Y₂H₂); ¹³C NMR ([D₈]toluene, –40 °C): δ = 8.5, 9.0 (SiCH₃), 11.6, 13.3, 14.1, 15.2 (ring CH₃), 24.9 (β -CH₂, thf), 36.4 (C(CH₃)₃), 55.0 (C(CH₃)₃), 72.4 (α -CH₂, thf), 107.7 (ring C at Si), 119.9, 123.3, 125.8 (ring C); ²⁹Si NMR ([D₈]toluene, –40 °C): δ = –25.7

shift of the signals for the α - and β -protons in the ¹H NMR spectrum at low temperatures. (Decoalescence of the signals into those for free and coordinated thf was observed at –80 °C for **2**.) The temperature dependence of the equilibrium constants was obtained from the chemical shifts of α - and β -CH₂.^[8, 9] The plot of ln *K* versus 1/*T* gave the thermodynamic parameters $\Delta_r H^\circ$ = (24 ± 3) kJ mol^{–1} and $\Delta_r S^\circ$ = (61 ± 12) J K^{–1} mol^{–1} for **2**. The positive reaction entropy and enthalpy is in accordance with a dissociative process. Complex **2** is relatively thermally robust, decomposing by a first-order rate law with a half-life of $t_{1/2}$ = (600 ± 10) min (k_1 = (1.92 ±



Scheme 1.

4) × 10^{–5} s^{–1}) at 50 °C in [D₆]benzene (determined by NMR spectroscopy) to give SiMe₄ and other yet unidentified products of C–H activation. The activation parameters $\Delta H^\ddagger$ = (145 ± 16) kJ mol^{–1} and $\Delta S^\ddagger$ = (110 ± 50) J K^{–1} mol^{–1} were calculated from the temperature dependence of the rate constant of the decomposition of **2**. The bis(alkyl) complexes **3a–c** slowly decompose at room temperature.

Hydrogenolysis of **2** in pentane at room temperature led to the dimeric hydrido complex **4** as a colorless powder in reproducibly good yield (Scheme 1).^[10] The ¹H NMR spectrum of **4** at 50 °C in [D₈]toluene (Figure 1), with only one hydride signal at δ = 5.50 (¹*J*(Y,H) = 28.8 Hz), agrees with a molecule with an internal mirror plane. However, this spectrum is the result of fast interconversion of two asymmetric diastereomers. Their interconversion is slowed down sufficiently at –40 °C, so that a ¹H NMR spectrum containing two triplets for the bridging hydrides (δ = 5.27, 5.45; ¹*J*(Y,H) = 29.0 and 28.6 Hz, respectively) as well as a doublet of all other signals could be obtained. The signal ratio shows that **4** exists as a 4:1 mixture of two asymmetric diastereomers in [D₈]toluene.

An ORTEP diagram of the structure of **4** in the solid state is shown in Figure 2.^[11] The crystal contains racemic pairs of C₂-symmetric homochiral dimers. Thus, the two linked amido-cyclopentadienyl yttrium units are connected by two hydrogen atoms in a *transoid* fashion. The Y₂H₂ core is significantly distorted (considering the well-known problem in the refinement of hydrogen atoms), possibly due to steric repulsion between the two (η^5 : η^1 -C₅Me₄SiMe₂NCMe₃) ligands and due to the strong *trans* influence of the amido ligand (Y1–H1 2.48(4), Y1–H2 1.98(6), Y2–H1 2.39(4), Y2–H2 2.31(6) Å;

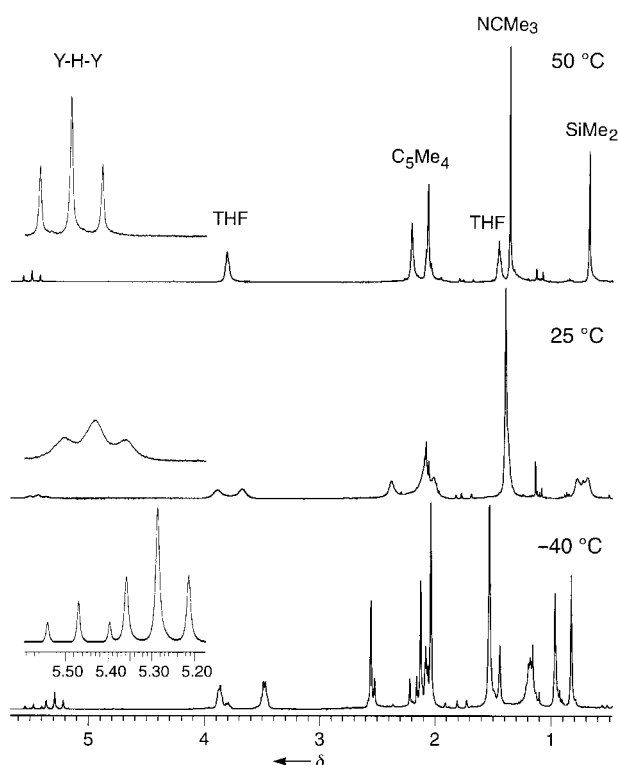


Figure 1. Temperature dependence of the ^1H NMR spectrum of **4** in $[\text{D}_8]\text{toluene}$.

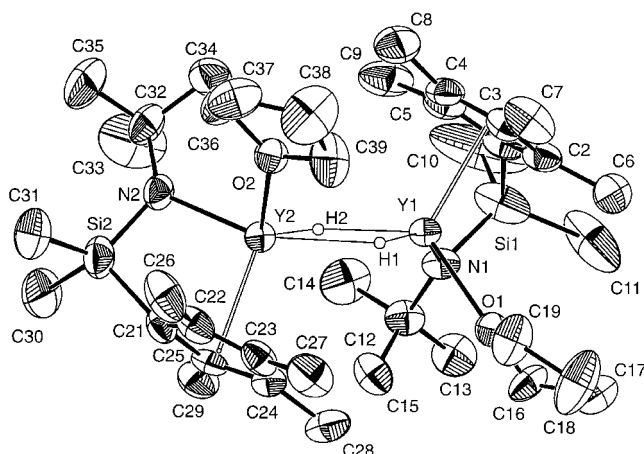


Figure 2. ORTEP diagram of the molecular structure of **4**. Thermal ellipsoids are drawn at the 30% probability level. Hydrogen atoms, except for the two bridging hydrides, are omitted for the sake of clarity. Selected bond lengths [$\text{\AA}$] and angles [$^\circ$]: Y1–H1 2.48(4), Y1–H2 1.98(6), Y2–H1 2.39(4), Y2–H2 2.31(6), $\text{Cp}_{\text{cent}}1\text{--Y1}$ 2.351(8), $\text{Cp}_{\text{cent}}2\text{--Y2}$ 2.342(8), Y1–N1 2.250(6), Y2–N2 2.237(6), Y1–O1 2.361(5), Y2–O2 2.378(5), Y1...Y2 3.672(1); Y1–H1–Y2 98(2), Y1–H2–Y2 117(2), H1–Y1–H2 74(2), H1–Y2–H2 71(2), $\text{Cp}_{\text{cent}}1\text{--Y1--N1}$ 97.8(2), $\text{Cp}_{\text{cent}}1\text{--Y1--O1}$ 112.6(2), $\text{Cp}_{\text{cent}}1\text{--Y1--H1}$ 105(2), $\text{Cp}_{\text{cent}}1\text{--Y1--H2}$ 119(2), N1–Y1–O1 93.1(2), N1–Y1–H1 156.8(9), N1–Y1–H2 95(2), $\text{Cp}_{\text{cent}}2\text{--Y2--N2}$ 97.4(2), $\text{Cp}_{\text{cent}}2\text{--Y2--O2}$ 113.5(2), $\text{Cp}_{\text{cent}}2\text{--Y2--H1}$ 103(1), $\text{Cp}_{\text{cent}}2\text{--Y2--H2}$ 118(2), N2–Y2–O2 94.8(2), N2–Y2–H1 160(1), N2–Y2–H2 99(1).

Y1–H2–Y2 117(2), Y1–H1–Y2 98(2) $^\circ$). The Y...Y distance (3.672(1) $\text{\AA}$) is comparable to that of other dimeric yttrium hydrido complexes.^[12] The Y–N bond lengths (2.250(6) and 2.237(6) $\text{\AA}$) are significantly shorter than those observed

in the heterobimetallic ytrocenes $\text{Li}[\text{Y}(\eta^5\text{--}\eta^1\text{--C}_5\text{R}_4\text{SiMe}_2\text{NCH}_2\text{CH}_2\text{X})_2]$ ($\text{C}_5\text{R}_4 = \text{C}_5\text{Me}_4$, $\text{C}_5\text{H}_3\text{tBu}$; $\text{X} = \text{OMe}$, NMe_2)^[13a] and the half-sandwich complex $[\text{Li}(\text{thf})][\text{Y}(\eta^5\text{--}\eta^1\text{--C}_5\text{Me}_4\text{SiMe}_2\text{NCH}_2\text{CH}_2\text{OMe})(o\text{--C}_6\text{H}_4\text{CH}_2\text{NMe}_2)\text{Cl}]$,^[13b] but slightly longer than in $(\eta^5\text{--}\eta^1\text{--C}_5\text{Me}_4\text{SiMe}_2\text{NCMe}_3)\text{YN}(\text{SiMe}_3)_2$.^[13c] In contrast to lanthanocene hydrides, **4** does not undergo H/D scrambling in deuterated solvents and is thermally stable in $[\text{D}_6]\text{benzene}$ at 50 $^\circ\text{C}$ for more than 24 hours.^[14]

α -Olefins such as 1-hexene or styrene react sluggishly with alkyl complexes **2** and **3a** (25 $^\circ\text{C}$, $[\text{D}_6]\text{benzene}$, several days), whereas the hydrido complex **4** forms well-defined mono-insertion products. Ethene is readily polymerized by all complexes. Moreover, complexes **2**, **3a**, and **4** catalyze the polymerization of polar monomers, such as *tert*-butyl acrylate, and, in contrast to the lanthanocene hydrido and alkyl

Table 2. Polymerization of *tert*-butyl acrylate and acrylonitrile by **2**, **3a**, and **4** in toluene.

Cat.	<i>T</i> [$^\circ\text{C}$]	<i>t</i> [h]	$[\text{M}_0]/[\text{cat.}]$	Yield [%]	$M_n \times 10^{-3}$ [g mol^{-1}]	M_w/M_n	mm ^[c] [%]	mr ^[c] [%]	rr ^[c] [%]
<i>tert</i> -butyl acrylate									
2	25	2	95	85	25 ^[a]	1.56	21	50	29
2	–30	18	79	98	30 ^[a]	1.97	19	50	31
2	–30	18	201	90	38 ^[a]	1.61	25	49	26
2	–30	18	309	38	38 ^[a]	1.50	29	48	23
3a	–30	17	77	99	68 ^[a]	1.62	25	45	30
4	25	3	181	11	13 ^[a]	1.69	30	46	24
acrylonitrile									
2	25	16	328	24	3.3 ^[b]		27	41	32
2	–30	48	198	48	5.0 ^[b]		30	44	26
3a	–30	14	256	66	3.4 ^[b]		26	43	31
4	25	24	185	24	–		30	41	29

[a] By gel permeation chromatography in THF, universal calibration relative to polystyrene standard. [b] By ^1H NMR spectroscopic end-group analysis. [c] mm, mr, and rr are iso-, hetero-, and syndiotactic triads, respectively.

complexes, they catalyze the polymerization of acrylonitrile as well (Table 2).^[15] *tert*-Butyl acrylate is polymerized in the presence of either of the complexes **2**, **3**, or **4** at temperatures as low as –30 $^\circ\text{C}$ (i.e., well below the decomposition temperatures) to give poly(*tert*-butyl acrylate) in high yields and with molecular weights M_n greater than 20000. Initiation is somewhat slower when the hydrido complex **4** is used. The molecular-weight distributions of the resulting polymers are in the range of 1.5–2.0,^[16] and the polymer microstructure as judged by ^{13}C NMR spectroscopy is predominantly atactic. An intense orange-red solution forms as soon as acrylonitrile is added to a solution of **2**, **3a**, or **4** in toluene ($\lambda_{\text{max}}(\epsilon) = 353 \text{ nm}$ (22000) for **2** in the presence of one equivalent of acrylonitrile), followed by the precipitation of yellow, atactic poly(acrylonitrile). This unusual color is ascribed to an intermolecular charge transfer band between an f^0d^0 complex and an electron acceptor.^[17] Rapid chain propagation appears to be preceded by a slow initiation step in which the coordinated thf ligand at the yttrium center is substituted by the monomer to generate the active species, the keteneimino complex $[(\eta^5\text{--C}_5\text{Me}_4\text{SiMe}_2\text{X})\text{Y}(\text{N}=\text{C}=\text{CHCH}_2\text{R})]$, by 1,4-insertion.^[18]

Experimental Section

2: To a solution of **1** (250 mg, 0.51 mmol), prepared from the reaction of $\text{YCl}_3(\text{thf})_{3.5}$ and $\text{LiCH}_2\text{SiMe}_3$, in pentane (10 mL) was added a solution of $(\text{C}_5\text{Me}_4\text{H})\text{SiMe}_2\text{NHCMc}_3^{[3b]}$ (128 mg, 0.51 mmol) in pentane (3 mL) at 0 °C. After the mixture was stirred at this temperature for 2 h, the solution was decanted and concentrated in vacuo. The crude product was recrystallized from pentane at –30 °C to give 233 mg (92 %) of **2** as colorless microcrystals. Complexes **3a–c** were prepared in a similar manner.

4: A solution of **2** (630 mg, 1.27 mmol) in pentane (10 mL) was loaded in a thick-walled 100-mL glass vessel. H_2 (4 atm) was charged at room temperature, and the reaction mixture was stirred vigorously. After 7 h of stirring, the solution above the white precipitate was decanted to provide 335 mg (64 %) of the colorless powder **4**.

Correct elemental analyses (C, H, N) were obtained for all compounds.

Received: August 13, 1998 [Z12286IE]

German version: *Angew. Chem.* **1999**, *111*, 163–165

Keywords: alkyl complexes • cyclopentadienides • hydrido complexes • polymerizations • yttrium

- [1] H. Schumann, J. A. Meese-Marktscheffel, L. Esser, *Chem. Rev.* **1995**, *95*, 865.
- [2] a) P. L. Watson, G. W. Parshall, *Acc. Chem. Res.* **1985**, *18*, 51; b) H. Yasuda, H. Yamamoto, Y. Takemoto, M. Yamashita, K. Yokota, S. Miyake, A. Nakamura, *Makromol. Chem. Macromol. Symp.* **1993**, *67*, 187; c) H. Yasuda, E. Ihara, *Bull. Chem. Soc. Jpn.* **1997**, *70*, 1745; d) D. G. H. Ballard, A. Courtis, J. Holton, J. McMeeking, R. Pearce, *J. Chem. Soc. Chem. Commun.* **1978**, 994; e) G. Jeske, H. Lauke, H. Mauermann, P. N. Swepston, H. Schumann, T. J. Marks, *J. Am. Chem. Soc.* **1985**, *107*, 8091; f) E. B. Coughlin, J. E. Bercaw, *J. Am. Chem. Soc.* **1992**, *114*, 7606; g) H. Yasuda, H. Yamamoto, K. Yokota, S. Miyake, A. Nakamura, *J. Am. Chem. Soc.* **1992**, *114*, 4908; h) M. Yamashita, Y. Takemoto, E. Ihara, H. Yasuda, *Macromolecules* **1996**, *29*, 1798; i) L. S. Boffa, B. M. Novak, *Macromolecules* **1997**, *30*, 3494.
- [3] a) P. J. Shapiro, E. Bunel, W. P. Schaefer, J. E. Bercaw, *Organometallics* **1990**, *9*, 867; b) P. J. Shapiro, W. D. Cotter, W. P. Schaefer, J. A. Labinger, J. E. Bercaw, *J. Am. Chem. Soc.* **1994**, *116*, 4623; c) C. J. Schaverien, *Organometallics* **1994**, *13*, 69.
- [4] a) I. Albrecht, H. Schumann, *J. Organomet. Chem.* **1986**, *310*, C29; b) H. Schumann, I. Albrecht, J. Pickardt, E. Hahn, *J. Organomet. Chem.* **1984**, *276*, C5.
- [5] a) H. van der Heijden, C. J. Schaverien, A. G. Orpen, *Organometallics* **1989**, *8*, 255; b) H. van der Heijden, P. Pasman, E. J. M. de Boer, C. J. Schaverien, A. G. Orpen, *Organometallics* **1989**, *8*, 1459; c) H. J. Heeres, A. Meetsma, J. H. Teuben, R. D. Rogers, *Organometallics* **1989**, *8*, 2637; d) H. Schumann, J. A. Meese-Marktscheffel, A. Dietrich, *J. Organomet. Chem.* **1989**, *377*, C5; e) A. Mandel, J. Magull, *Z. Anorg. Allg. Chem.* **1996**, *622*, 1913.
- [6] a) M. Booi, N. H. Kiers, H. J. Heeres, J. H. Teuben, *J. Organomet. Chem.* **1989**, *364*, 79; b) Y. Mu, W. E. Piers, D. C. MacQuarrie, M. J. Zaworotko, V. G. Young, Jr., *Organometallics* **1996**, *15*, 2720.
- [7] M. F. Lappert, R. Pearce, *J. Chem. Soc. Chem. Commun.* **1973**, 126.
- [8] a) F. L. Slejko, R. S. Drago, D. G. Brown, *J. Am. Chem. Soc.* **1972**, *94*, 9210; b) M. L. H. Green, L.-L. Wong, A. Sella, *Organometallics* **1992**, *11*, 2660.
- [9] J. Okuda, F. J. Schattenmann, S. Wocadlo, W. Massa, *Organometallics* **1995**, *14*, 789.
- [10] Complexes **3a** and **3b** can be hydrogenated in a similar fashion to yield a pentane-soluble complex with the probable formula $[(\eta^5\text{-C}_5\text{Me}_4\text{SiMe}_2\text{X}')\text{YH}_2]_4 \cdot 2\text{thf}$ ($\text{X}' = \text{Me}, \text{Ph}$). A highly fluxional tetrameric structure is implied by the ^1H NMR spectrum, in which each hydride ligand couples to four yttrium atoms: K. C. Hultsch, J. Okuda, unpublished results.
- [11] a) Crystal size $0.70 \times 0.28 \times 0.15$ mm, monoclinic, space group $P2_1/n$ (no. 14), $Z = 4$; $a = 14.522(4)$, $b = 16.575(4)$, $c = 20.118(9)$ Å, $\beta = 110.65(3)^\circ$, $V = 4531(3)$ Å³, $\rho_{\text{calcd}} = 1.206$ g cm^{–3}, $T = 293(2)$ K, $3 < \theta < 23^\circ$, ($\lambda(\text{MoK}\alpha) = 0.71070$ Å, $\mu = 2.631$ mm^{–1}); of 12 823 reflections measured, 6266 were independent ($R_{\text{int}} = 0.1073$) and 3012 observed ($I > 2\sigma(I)$), Lorentz polarization and empirical absorption corrections (ψ scans), Patterson and Fourier syntheses (SHELXS-86 and SHELXL-93), 431 parameters, $R = 0.0509$, $wR_2 = 0.0933$, max./min. residual electron density $0.409/-0.384$ e Å^{–3}. b) Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-410087. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [12] a) W. J. Evans, J. H. Meadows, A. L. Wayda, W. E. Hunter, J. L. Atwood, *J. Am. Chem. Soc.* **1982**, *104*, 2008; b) W. J. Evans, D. K. Drummond, T. P. Hanusa, R. J. Doedens, *Organometallics* **1987**, *6*, 2279; c) J. P. Mitchell, S. Hajela, S. K. Brookhart, K. I. Hardcastle, L. M. Henling, J. E. Bercaw, *J. Am. Chem. Soc.* **1996**, *118*, 1045; d) R. Duchateau, C. T. van Wee, A. Meetsma, P. T. van Duijnen, J. H. Teuben, *Organometallics* **1996**, *15*, 2279; e) W. P. Kretschmer, S. I. Troyanov, A. Meetsma, B. Hessen, J. H. Teuben, *Organometallics* **1998**, *17*, 284.
- [13] a) K. C. Hultsch, T. P. Spaniol, J. Okuda, *Organometallics* **1997**, *16*, 4845; b) K. C. Hultsch, T. P. Spaniol, J. Okuda, *Organometallics* **1998**, *17*, 485; c) Y. Mu, W. E. Piers, M.-A. MacDonald, M. J. Zaworotko, *Can. J. Chem.* **1995**, *73*, 2233.
- [14] a) K. H. den Haan, Y. Wielstra, J. H. Teuben, *Organometallics* **1987**, *6*, 2053; b) M. Booi, B.-J. Deelman, R. Duchateau, D. S. Postma, A. Meetsma, J. H. Teuben, *Organometallics* **1993**, *12*, 3531.
- [15] Coordinative polymerization of acrylonitrile was first observed with complexes of iron and nickel: a) A. Yamamoto, S. Ikeda, *J. Am. Chem. Soc.* **1967**, *89*, 5989; b) A. Yamamoto, K. Morifuji, S. Ikeda, T. Saito, Y. Uchida, A. Misono, *J. Am. Chem. Soc.* **1968**, *90*, 1878.
- [16] The slightly broad polydispersity values may be caused by slow initiation but fast propagation.
- [17] Oxidation of another d⁰ complex, $[\text{Cp}_2\text{ZrHCl}]$, by tetracyanoethylene (TCNE) was recently reported: H. Kunkely, A. Vogler, *Transition Met. Chem.*, in press; d² complexes of the type $[\text{Cp}_2\text{MH}_2]$ ($\text{M} = \text{Mo}, \text{W}$) are known to form intensely colored charge-transfer adducts with electron acceptors: A. Nakamura, S. Otsuka, *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3641.
- [18] Preliminary NMR experiments showed that the reaction between equimolar amounts of **4** and acrylonitrile gives a tautomer of the keteneiminato complex $\{[(\eta^5\text{-}\eta^1\text{-C}_5\text{Me}_4\text{SiMe}_2\text{NCMe}_3)\text{Y}(\text{N}=\text{CHCH}=\text{CH}_2)_2]\}$: ^1H NMR ($[\text{D}_6]\text{benzene}$, 25 °C): $\delta = 0.79$ (s, 6H, SiCH_3), 1.28 (s, 9H, $\text{C}(\text{CH}_3)_3$), 1.86, 2.21 (s, 6H, ring CH_3), 5.35 (d, $^3J(\text{H,H})_{\text{trans}} = 16.8$ Hz, 1H, $\text{N}=\text{CHCH}=\text{CH}_2$), 5.51 (d, $^3J(\text{H,H})_{\text{cis}} = 9.8$ Hz, 1H, $\text{N}=\text{CHCH}=\text{CH}_2$), 5.85 (m, $\text{N}=\text{CHCH}=\text{CH}_2$), 8.72 (dt, $^3J(\text{H,H}) = 8.2$ Hz, $^3J(\text{Y,H}) = 2.7$ Hz, $\text{N}=\text{CHCH}=\text{CH}_2$); ^{13}C NMR ($[\text{D}_6]\text{benzene}$, 25 °C): $\delta = 8.3$ (NSiCH₃), 11.2, 14.2 (ring CH_3), 36.6 ($\text{C}(\text{CH}_3)_3$), 53.9 ($\text{C}(\text{CH}_3)_3$), 108.2 (ring C at Si), 123.2, 127.2 (ring C), 130.0 ($\text{N}=\text{CHCH}=\text{CH}_2$), 141.8 ($\text{N}=\text{CHCH}=\text{CH}_2$), 174.7 ($\text{N}=\text{CHCH}=\text{CH}_2$). For a similar dimeric alkylidenamido yttrocene, see W. J. Evans, J. H. Meadows, W. E. Hunter, J. L. Atwood, *J. Am. Chem. Soc.* **1984**, *106*, 1291.

Formation of a Curved Silver Nitrate Network That Conforms to the Shape of C₆₀ and Encapsulates the Fullerene—Structural Characterization of C₆₀{Ag(NO₃)₃}₅**

Marilyn M. Olmstead, Kalyani Maitra,
and Alan L. Balch*

*Dedicated to Professor Raymond M. Keefer
on the occasion of his 85th birthday*

The nearly spherical architecture of C₆₀ makes it an attractive candidate for the construction of larger, supra-molecular structures. Containing its curved external surface presents an interesting challenge, since many of the building blocks that are available to the chemist present flat surfaces which need to be manipulated in some fashion in order to effectively surround the fullerene, either in part or entirely. Weak complexes are formed between C₆₀ and a number of bowl-shaped molecules including calixarenes,^[1] cyclodextrins,^[2] and cyclotrimeratrylene,^[3] and several of these assemblies have been structurally characterized. Metal complexes have been prepared with specific ligands designed to wrap flat benzene rings into curved arms that can encircle C₆₀.^[4] Fullerenes are also known to cocrystallize with a variety of molecules that include organic, organometallic, and inorganic species.^[5]

Here we report on the creation of a complex network from very simple components, silver(I) nitrate and C₆₀. Although silver ions are known to interact with olefins and arenes, there have been only limited reports of Ag⁺–C₆₀ interactions. Mass spectrometric studies have presented evidence for the existence of [Ag_xC₆₀]⁺ (*x* = 1–5) and [Ag(C₆₀)₂]⁺ in the gas phase.^[6] In solution the electronic spectrum of C₆₀ itself is unaffected by the presence of silver ions.^[7] However, fullerenes that are chemically modified by the addition of potentially coordinating amino ether groups do show spectroscopic changes that were attributed to Ag⁺–C₆₀ π interactions.^[8]

Dark red, nearly black blocks of C₆₀{Ag(NO₃)₃}₅ were obtained in 63 % yield by the diffusion of a solution of silver nitrate in ethanol into a solution of C₆₀ in benzene. The structure of the new solid has been determined through a single-crystal X-ray diffraction study. As seen in Figure 1, the solid has a complex structure in which the silver nitrate portion forms a zeolite-like network.^[9] Within this network, rounded cavities are formed, and these are occupied by the fullerene molecules. Figure 1a shows a view of the entire structure with van der Waals surfaces; Figure 1b shows the same portion but with the fullerene molecules removed. The cavities that the fullerenes occupy are clearly visible and form apparent channels within the silver nitrate network. However,

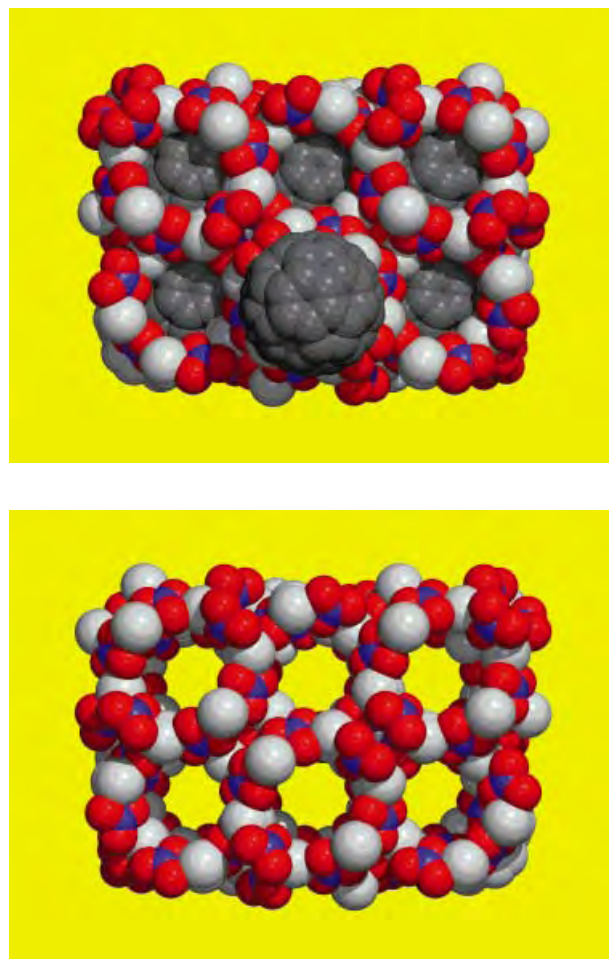


Figure 1. Structure of C₆₀{Ag(NO₃)₃}₅ with van der Waals contours for the various atoms. a) A portion of the complete structure with only one fullerene shown in the upper most layer. b) Part of the silver nitrate network with the fullerenes removed. Silver is shown as light gray, oxygen red, nitrogen dark blue, and carbon dark gray.

the silver nitrate network encapsulates each fullerene in a fashion that precludes movement of the fullerene molecules from one cavity to another.

The nature of the network of silver nitrate ions is shown in Figure 2. There are four “straps” which surround the fullerene in two perpendicular planes. Figure 3 presents some details of the arrangement of one of the straps, the one that comes closest to the fullerene. The nitrate ions have the expected trigonal-planar geometry and are fully ordered. Each silver ion is surrounded by six oxygen atoms with Ag–O distances that range from 2.34(12) to 2.814(12) Å. One of the silver ions, Ag1, resides on a mirror plane perpendicular to *a* (position *m*). A second silver ion, Ag2, also resides on this plane, but is disordered with respect to the mirror plane that is perpendicular to *b* (position *d*). The Ag2⋯Ag2' distance is 1.137(9) Å. The third silver ion, Ag3, is disordered with respect to a center of inversion (position *e*) and is separated from its centrosymmetric counterpart by 0.633(13) Å. The molecule of C₆₀ falls on a site (position *d*) with *mm* symmetry. In the asymmetric unit there is a total of 1.25 Ag⁺, 1.25 (NO₃)[–], and 0.25 C₆₀.

[*] Prof. Dr. A. L. Balch, Dr. M. M. Olmstead, Dr. K. Maitra
Department of Chemistry
University of California, Davis
Davis, California 95616 (USA)
Fax: (+1) 530-752-8995
E-mail: albalch@ucdavis.edu

[**] This work was supported by the U.S. National Science Foundation (grant CHE 9610507). We thank Dr. B. Bolskar for useful discussions.

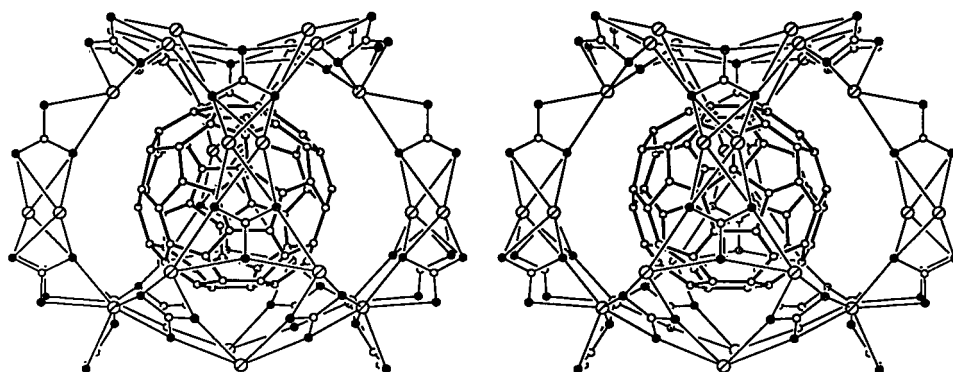


Figure 2. A stereoscopic drawing that shows how the silver nitrate network encapsulates the fullerene. Within the silver nitrate network, the silver ions are indicated by circles with a slash, the nitrogen atoms by circles with a dot in the center, and the oxygen atoms by simple circles.

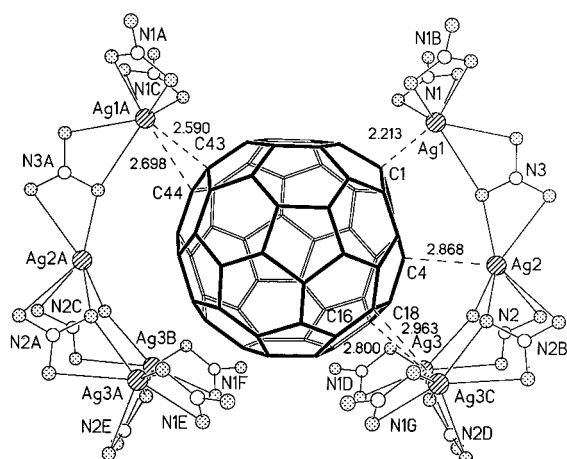


Figure 3. A drawing of a fragment of the structure of $C_{60}[Ag(NO_3)_5]$ that shows the interaction of the two closest straps with one orientation of the fullerene. The other orientations of the fullerene involve identical distances.

The fullerene cavity resides at the intersection of two perpendicular mirror planes, but the fullerene molecules themselves are not centered within this site. Rather, the center of the fullerene molecule is shifted by 0.185 Å from the special position of mm symmetry, and one of the fullerene mirror planes is rotated by 5.2° from the crystallographic mirror plane. Thus, there are four possible locations for the fullerene within the cavity. Figure 3 shows one of those orientations and the nature of the fullerene–silver contacts along the straps that interact most closely with the fullerene. The other two straps are positioned further away from the fullerene in the cavity shown. The contacts between Ag2 and Ag3 and the fullerene carbon atoms are quite long and do not correspond to normal bonding distances. However, Ag1 does interact with the fullerene in two ways. On one side it engages in η^2 coordination, with Ag–C distances (2.590(10) and 2.698(10) Å) that are within the range found for such bonding.^[10] On the opposite side, the Ag1–C1 distance (2.213(6) Å) is quite short, and the location of the silver ion is directly over a single carbon atom so that η^1 coordination is involved. This is the first case of η^1 coordination of a transition metal to a fullerene that is crystallographically determined.^[11] It is well established that a silver ion can interact with olefins

and aromatic hydrocarbons in both η^1 and η^2 fashion, and that for η^2 bonding the silver ion is not necessarily symmetrically disposed with respect to the olefin.^[12]

Despite the good solubility of silver nitrate in water, crystalline $C_{60}[Ag(NO_3)_5]$ is stable in the presence of air and moisture. A crystal that was immersed in water for one hour retained its ability to diffract X-rays, but after immersion for 20 hours the crystal, which retained its external shape, no longer gave clear spots on rotation photographs.

Crystals of $C_{60}[Ag(NO_3)_5]$ are more stable toward exposure to an aqueous solution of sodium chloride. After 28 hours of immersion in a sodium chloride solution, a crystal retained its ability to diffract X-rays, although after five days of immersion it no longer diffracted. The greater stability toward a sodium chloride solution is attributed to precipitation of silver chloride on the crystal surface and the resultant inhibition of diffusion.

Considerable attention has also been given to the intercalation of metal atoms into the C_{60} lattice, where the cubic close packing of the C_{60} molecules creates tetrahedral and octahedral holes.^[13] In part work in this area has been prompted by the observation of superconductivity of materials with the composition (alkali metal)₃ C_{60} .^[14] The present study demonstrates that it is possible to use solution-phase techniques to construct new fullerene phases that incorporate inorganic components. It is noteworthy that in $C_{60}[Ag(NO_3)_5]$, the cubic close packing of C_{60} molecules is not present. Moreover, $C_{60}[Ag(NO_3)_5]$ is the first case in which a fullerene and an ionic component, rather than a second molecular component, cocrystallize. The complex structure found for $C_{60}[Ag(NO_3)_5]$ is also related to those of a variety of new solids that have been created from inorganic and organic components.^[15] For example, at the opposite end of the size scale, acetylenediide has been fully encapsulated by nine silver ions in $Ag_2C_2 \cdot 8AgF$.^[16] Additionally, a hydrothermal synthesis of a dense, crystalline inorganic/organic layered compound has been devised to form the fumaric acid complex $[Cu_2(O_2CCH=CHCO_2)]$.^[17]

Experimental Section

A saturated solution of silver(I) nitrate in absolute ethanol was carefully placed over a solution of C_{60} (2.1 mg, 2.9×10^{-3} mmol) in benzene. The mixture was allowed to stand undisturbed and protected from light for one week. During that time dark red, nearly black cubic crystals formed in 63 % yield (based on C_{60}). The IR spectrum of $C_{60}[Ag(NO_3)_5]$ in a Nujol mull showed a strong broad shoulder in the region between 1339 and 1311 cm^{-1} for the nitrate group and another peak at 1180 cm^{-1} that is characteristic of C_{60} .

Crystal data for $C_{60}[Ag(NO_3)_5]$: black block, $0.04 \times 0.10 \times 0.12$ mm, tetragonal, space group $P4_2/nmc$, $a = b = 13.934(3)$, $c = 18.504(3)$ Å, $V = 3835.2(15)$ Å³, $\lambda = 0.71073$ Å, $Z = 4$, $\rho_{calcd} = 2.719$ Mg m⁻³, $\mu(MoK\alpha) = 2.615$ mm⁻¹; ω scans, $2\theta_{max} = 50^\circ$; $T = 140$ K; of 2049 reflections collected,

1852 were independent ($R_{\text{int}}=0.033$) and included in the refinement; Lorentzian polarization and absorption corrections (psi scans) performed; min./max. transmission = 0.74/0.90; solution by direct methods (SHELXS-97); refinement by full-matrix least squares based on F^2 (SHELXL-97); 141 parameters, $R = 0.1486$, $wR = 0.2301$ for all data; $R1 = 0.0843$ computed for 1004 observed data ($>2\sigma(I)$). The fullerene molecule was refined as a rigid group with the use of parameters from a well-determined structure.^[18] Twinning is an unlikely explanation for the disorder because there was no evidence of abnormal peak shapes or spurious reflections between layer lines. The space group determination was completely unambiguous; therefore, there was only one minor violation (0, 0, 11) of the conditions for systematic absences. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-102135. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Received: July 14, 1998 [Z121451E]
German version: *Angew. Chem.* **1999**, *111*, 243–245

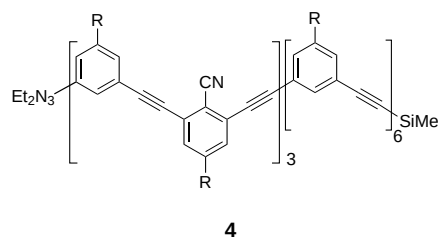
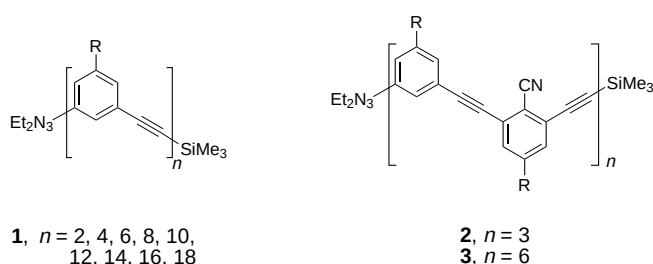
Keywords: fullerenes • network structures • nitrates • silver

- [1] J. L. Atwood, L. J. Barbour, C. L. Raston, I. B. N. Sudria, *Angew. Chem.* **1998**, *110*, 1029–1031; *Angew. Chem. Int. Ed.* **1998**, *37*, 981–983; J. L. Atwood, G. A. Koutsantonis, C. L. Raston, *Nature* **1994**, *368*, 229–231.
- [2] Z. Yoshida, H. Takekuma, S. Takuma, Y. Matsubara, *Angew. Chem.* **1994**, *106*, 1658–1660; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1597–1599.
- [3] J. W. Steed, P. C. Junk, J. L. Atwood, M. J. Barnes, C. L. Raston, R. S. Burkhart, *J. Am. Chem. Soc.* **1994**, *116*, 10346–10347.
- [4] A. L. Balch, V. J. Catalano, J. W. Lee, M. M. Olmstead, *J. Am. Chem. Soc.* **1992**, *114*, 5455–5457; V. J. Catalano, N. Parodi, *Inorg. Chem.* **1997**, *36*, 537–541.
- [5] M. M. Olmstead, A. S. Ginwalla, B. C. Noll, D. S. Tinti, A. L. Balch, *J. Am. Chem. Soc.* **1996**, *118*, 7737–7745; A. L. Balch, J. W. Lee, B. C. Noll, M. M. Olmstead, *J. Chem. Soc. Chem. Commun.* **1993**, 56–58; J. D. Crane, P. B. Hitchcock, H. W. Kroto, R. Taylor, D. M. R. Walton, *J. Chem. Soc. Chem. Commun.* **1992**, 1764–1765; R. E. Douthwaite, M. L. H. Green, S. J. Heyes, M. J. Rosseinsky, J. F. C. Turner, *J. Chem. Soc. Chem. Commun.* **1994**, 1367–1368.
- [6] J. E. Reddic, J. C. Robinson, M. A. Duncan, *Chem. Phys. Lett.* **1997**, *279*, 203–208.
- [7] A. Ikeda, C. Fukuhara, S. Shinkai, *Tetrahedron Lett.* **1996**, *37*, 7091–7094.
- [8] A. Ikeda, C. Fukuhara, S. Shinkai, *Chem. Lett.* **1997**, 407–408.
- [9] C_{60} has been introduced into a preformed, large-pore aluminophosphate: A. Gügel, K. Müllen, H. Reichert, W. Schmidt, G. Schön, F. Schüth, J. Spickermann, J. Titman, K. Unger, *Angew. Chem.* **1993**, *105*, 618–619; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 556–557.
- [10] Since the fullerene was modeled as a rigid group, any distortion of the fullerene by coordination is masked, and the Ag–C distances are subject to additional uncertainty.
- [11] For a review on exohedral metal–fullerenes, see A. L. Balch, M. M. Olmstead, *Chem. Rev.* **1998**, *98*, 2123–2165.
- [12] H. C. Kang, A. W. Hanson, B. Eaton, V. Boekelheide, *J. Am. Chem. Soc.* **1985**, *107*, 1979–1985.
- [13] Review: M. J. Rosseinsky, *J. Mater. Chem.* **1995**, *5*, 1497–1513.
- [14] O. Gunnardson, *Rev. Mod. Phys.* **1997**, *69*, 575–606; R. C. Haddon, *Acc. Chem. Res.* **1992**, *25*, 127–133.
- [15] A. Müller, H. Reuter, S. Dillinger, *Angew. Chem.* **1995**, *107*, 2505–2539; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2328–2361.
- [16] G.-C. Guo, G.-D. Zhou, Q.-G. Wang, T. C. W. Mak, *Angew. Chem.* **1998**, *110*, 652–654; *Angew. Chem. Int. Ed.* **1998**, *37*, 630–632.
- [17] D. M. Young, U. Geiser, A. J. Schultz, H. H. Wang, *J. Am. Chem. Soc.* **1998**, *120*, 1331–1332.
- [18] M. Fedurco, M. M. Olmstead, W. R. Fawcett, *Inorg. Chem.* **1995**, *34*, 390–392.

Controlling the Secondary Structure of Nonbiological Oligomers with Solvophobic and Coordination Interactions**

Ryan B. Prince, Takashi Okada, and Jeffrey S. Moore*

The study of conformationally ordered structures in solution from synthetic chain molecules is an important problem whose ultimate aim is to mimic the properties and functions of natural biopolymers. Well-defined conformations of nonbiological oligomers have been achieved by a variety of strategies including intramolecular hydrogen bonding,^[1–3] donor–acceptor complexation,^[4] control of monomer torsion through local steric and electrostatic interactions,^[1, 5] and metal–ligand interactions.^[6–9] Ordered structure in proteins and nucleic acids depends upon a combination of specific and nonspecific noncovalent forces. In general, most evidence supports a picture in which nonspecific hydrophobic interactions provide the energetic driving force for folding, while directional interactions play a structure-defining role. In search of a system that depends on nondirectional forces to drive conformational ordering, we recently reported the solution behavior of a homologous series of *meta*-connected phenylacetylene oligomers **1**.^[10] The helical conformation results in a tubular cavity, which upon modification could allow for the creation of novel receptor or catalytic systems.



$R = -CO_2(CH_2CH_2O)_3CH_3$

We now report one such modification of the tubular cavity that leads to a highly ordered secondary structure controlled

[*] Prof. J. S. Moore, R. B. Prince, T. Okada
Departments of Chemistry, Materials Science & Engineering
and
The Beckman Institute for Advanced Science and Technology
University of Illinois at Urbana-Champaign
Urbana, IL 61801 (USA)
Fax: (+1) 217-244-8068
E-mail: moore@aries.scs.uiuc.edu

[**] This work was supported by the National Science Foundation (grant CHE 97-27172).

by a combination of solvophobic and metal-coordination interactions. To the best of our knowledge, this is the first example of a nonbiological oligomer whose solution structure has been designed to involve both nonspecific (solvophobic^[11]) and specific (metal-coordination) interactions.^[12] These features are present in dodecamer **3**,^[13] whose backbone consists of twelve nonpolar phenylacetylene units, each attached to a polar triethyleneglycol monomethyl ether side chain. Six cyano groups that are available for coordination to a metal are located on every other aromatic ring. In the helical conformation, this sequence places the six cyano groups into the interior of the tubular cavity, creating two approximately trigonal planar coordination sites.^[14] Molecular models reveal that each nitrogen atom lies about 2.1 Å from the helical axis, a distance consistent with that needed for metal–nitrile ligation (Figure 1).^[15, 16]

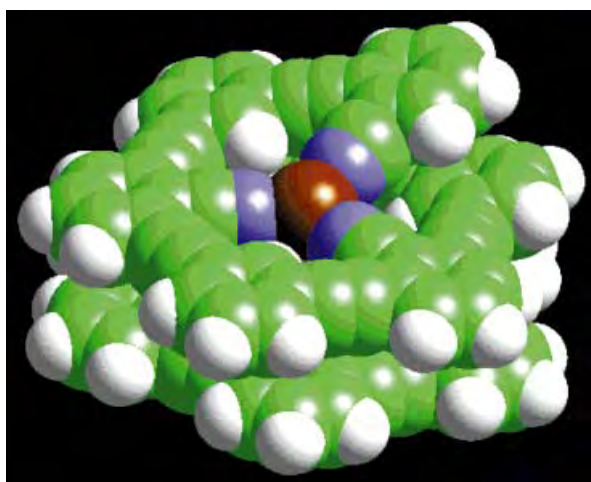


Figure 1. Space-filling model of **3** coordinating to two Ag⁺ ions. The triethyleneglycol side chains have been omitted for clarity.

To demonstrate metal-induced formation of the helical structure, there are two important issues that must be addressed. First, a solvent must be used which, on its own, is not capable of causing a solvophobically driven helical structure. Tetrahydrofuran was selected for this reason since **3** displays all of the spectroscopic signatures of the random coil conformation in this solvent.^[10] Second, the metal used must prefer to bind in a trigonal-planar coordination environment. Silver triflate (AgO₃SCF₃) was selected since it can adopt such a geometry.^[17, 18]

The only difference between the chemical structures of **3** and **1** ($n = 12$) is the presence of six additional cyano groups. This makes **1** ($n = 12$) an ideal control compound since any spectroscopic changes observed for **3** but not for **1** upon addition of metal will indicate interactions between the metal and the cyano groups. Addition of 40 molar equivalents of AgO₃SCF₃ to the oligomers of series **1** resulted in no change in the ¹H NMR or UV/Vis spectra. This shows that silver cations do not interact with the backbone, side chains, or end groups. It also indicates that a solvophobically driven helical conformation is not induced due to the slight increase in the polarity of the solvent upon addition of AgO₃SCF₃.

The structure and stoichiometry of the self-assembled helicate of **3** in solution can be deduced from UV/Vis spectroscopy. Addition of AgO₃SCF₃ to solutions of **3** results in a decrease in the absorption of the band at 306 nm, while the intensity of the band at 288 nm remains relatively constant (Figure 2). These changes are indicative of a cisoid conformation of the diphenylacetylene units, consistent with the

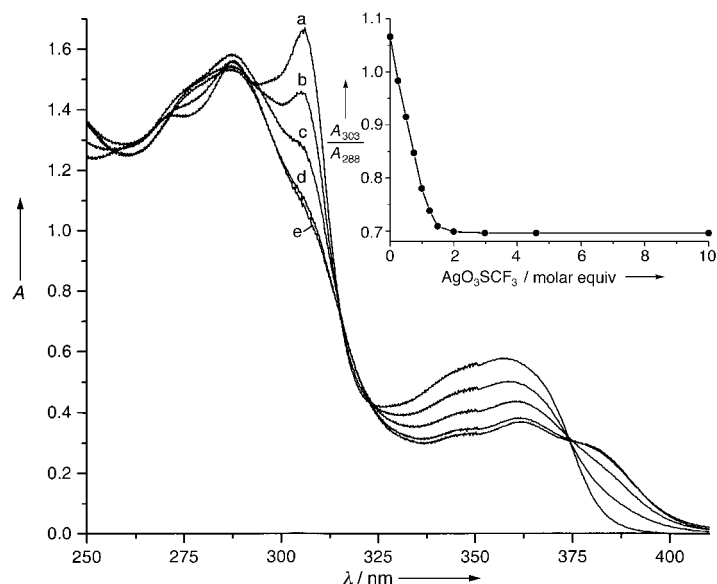
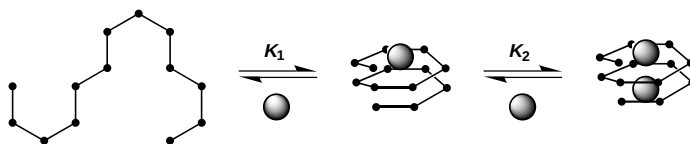


Figure 2. UV absorbance spectra of **3** in THF with increasing amounts of AgO₃SCF₃: a) 0, b) 0.5, c) 1.0, d) 1.5, and e) 2.0 equiv. Inset: Plot of A_{306}/A_{288} versus the number of molar equivalents of AgO₃SCF₃. A = absorbance ($c(\mathbf{3}) = 6.7 \times 10^{-6}$ M).

putative helical conformation.^[10] In addition, the presence of a clear isobestic point at 375 nm exhibits that only a single species is formed during the complexation. The inset of Figure 2 shows a Ag⁺ titration curve for **3**. It can be seen that the ratio of the two $\pi - \pi^*$ absorbances continues to decrease until two equivalents of AgCF₃SO₃ are added. These results as well as those of electrospray ionization mass spectrometry^[19] (ESI-MS) are consistent with a single-stranded helicate of **3**. From the titration curve we estimate the product of the two association constants, $K_1 K_2$ (Scheme 1), to be greater than 10^{12} M^{-2} .



Scheme 1. Schematic representation of the metal-induced formation of helical structures. The metal ions (Ag⁺) are shown as spheres.

Further evidence for the helical conformation is provided by ¹H NMR spectroscopy (Figure 3). For these studies we synthesized the symmetrical sequence **5** to simplify the spectra.^[20] The addition of two molar equivalents of AgO₃SCF₃ to solutions of **5** results in dramatic upfield shifts of all aromatic resonances as well as a significant dispersion of chemical shifts. High dispersion of ¹H NMR signals is typical

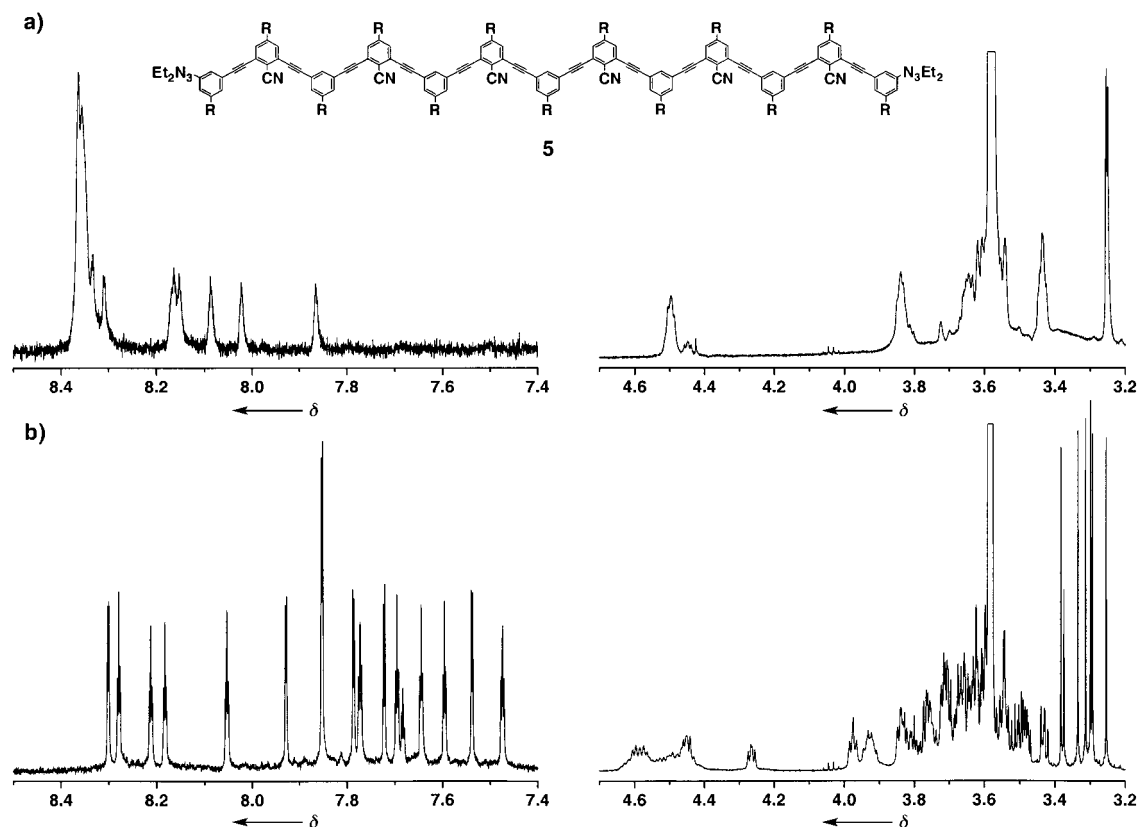


Figure 3. ^1H NMR spectra of **5** in $[\text{D}_8]\text{THF}$ upon the addition of AgO_3SCF_3 : a) 0 and b) 2.0 equiv (500 MHz, 25°C , $c = 0.7\text{ mm}$); $\text{R} = \text{CO}_2(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_3$.

of proteins in a well-ordered solution conformation, and probably indicates the same for $[\mathbf{5} \cdot \text{Ag}_2]^{2+}$.^[21] The upfield shifts suggest that **5** adopts a π -stacked structure upon the addition of AgO_3SCF_3 . These observations are all consistent with the putative helical conformation. Addition of more than two molar equivalents of AgO_3SCF_3 resulted in no change to the ^1H NMR spectrum, again showing that **5** binds to only two equivalents of metal.^[22]

It was possible to probe the symmetry and dynamics of the metal complex from its ^1H NMR spectrum. The NMR resonances from the side-chain methylene protons are split into overlapping AA'BB' patterns. Thus, the CH_2 protons become diastereotopic, as expected for a slowly exchanging helical conformation. Moreover, signals for only seven aromatic rings and terminal side-chain methyl groups ($\delta = 3.2\text{--}3.4$) are observed upon complexation (Figure 3b). This indicates that on the NMR time scale there is a C_2 axis through the central aromatic ring. This is consistent with **5** coordinating to two molecules of AgO_3SCF_3 in a 6_1 helical conformation.

Not only can solvophobic interactions be used to induce a helical structure,^[10] but in the case of **3** they appear to be important to the stability and formation of the metal-induced helicate. Oligomers **2** and **4** differ only by the presence of six additional phenylacetylene units that are not able to coordinate to a metal center. Both oligomers contain three cyano groups on alternating aromatic rings, which should bind one equivalent of AgO_3SCF_3 . The addition of up to 40 molar equivalents of AgO_3SCF_3 to solutions of **2** in THF resulted in

no change to the UV/Vis, ^1H NMR, or ESI-MS spectra, indicating no metal–ligand interactions. However, the addition of AgO_3SCF_3 to solutions of **4** in THF provided a helical conformation, as shown by UV/Vis and ^1H NMR spectroscopy. From the UV titration curve the association constant was determined to be $2 \times 10^4\text{ M}^{-1}$.^[23, 24] This result suggests that $K_2 \gg K_1$ and that the binding of two equivalents of AgO_3SCF_3 to **3** is a cooperative process.

To quantify these effects, the binding was studied by isothermal titration microcalorimetry. As shown in Figure 4, the addition of AgO_3SCF_3 to solutions of **2** resulted in no

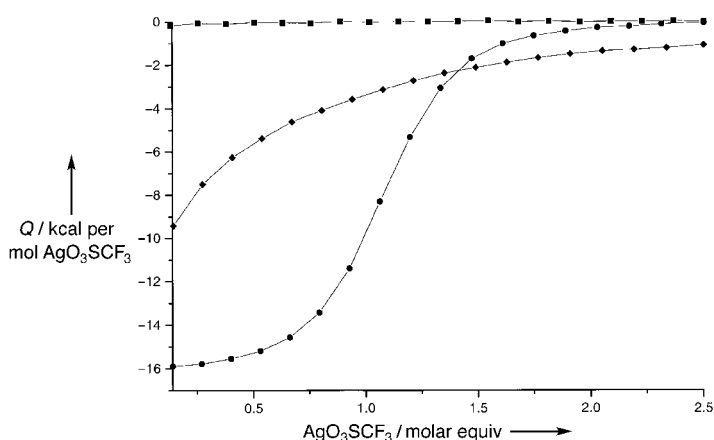


Figure 4. Heat generated Q as a function of the amount of AgO_3SCF_3 added to solutions of **2** ($\blacksquare$), **3** ($\bullet$), and **4** ($\blacklozenge$) in THF, as determined by isothermal titration microcalorimetry ($T = 28^\circ\text{C}$, $c = 0.2\text{ mm}$).

generation of heat and no formation of a complex, consistent with the observations noted above. Upon addition of AgO_3SCF_3 to solutions of **3**, heat was evolved (ca. 16 kcal mol^{-1}) until two equivalents of metal were added. This is consistent with the formation of complex $[\mathbf{3} \cdot \text{Ag}]^{2+}$. The addition of AgO_3SCF_3 to dodecamer **4** also resulted in the generation of heat, but no defined end point was reached due to the lower association constant. These results indicate that the addition of phenylacetylene segments that cannot bind metals to **2** allows for metal–ligand coordination to occur and shows that solvophobic interactions play a role in the metal-induced formation of the helical structure.

In conclusion, our results demonstrate that the oligomer sequence **1** can be modified to tightly and selectively bind metal ions in the internal cavity of a helical structure. The strength of metal ion binding appears to be derived from a combination of solvophobic interactions that favor the helical structure along with the more usual metal–ligand interactions.

Received: August 7, 1998 [Z 12267 IE]
German version: *Angew. Chem.* **1999**, *111*, 245–249

Keywords: conformation analysis • coordination chemistry • helical structures • oligomers • supramolecular chemistry

- [1] S. H. Gellman, *Acc. Chem. Res.* **1998**, *31*, 173–180.
- [2] J. L. Matthews, D. Seebach, *Chem. Commun.* **1997**, 2015–2022.
- [3] Y. Hamuro, S. J. Geib, A. D. Hamilton, *J. Am. Chem. Soc.* **1997**, *119*, 10587–10593.
- [4] R. S. Lokey, B. L. Iverson, *Nature* **1995**, *375*, 303–305.
- [5] D. Bassani, J.-M. Lehn, G. Baum, D. Fenske, *Angew. Chem.* **1997**, *109*, 1931–1933; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1845–1847.
- [6] A. Rigault, J. Siegel, J. Harrowfield, B. Chevrier, D. Moras, J.-M. Lehn, *Proc. Natl. Acad. Sci. USA* **1987**, *84*, 2566–2569.
- [7] T. M. Garrett, U. Koert, J.-M. Lehn, A. Rigault, D. Meyer, J. Fischer, *J. Chem. Soc. Chem. Commun.* **1990**, 557–558.
- [8] A. Williams, *Chem. Eur. J.* **1997**, *3*, 15–19.
- [9] C. Piquet, G. Bernardinelli, G. Hopfgartner, *Chem. Rev.* **1997**, *97*, 2005–2062.
- [10] J. C. Nelson, J. G. Saven, J. S. Moore, P. G. Wolynes, *Science* **1997**, *277*, 1793–1796.
- [11] A. Ben-Naim, *J. Phys. Chem.* **1971**, *54*, 1387–1404.
- [12] The solvophobically induced helical structure of **3** was characterized by the same methods as oligomers **1**. Solutions of **3** in acetonitrile provided helical structures, as indicated by ^1H NMR and UV/Vis spectroscopy. Thus, the secondary structure of **3** can be controlled using a solvophobic driving force, and the cyano groups on the interior of the tubular cavity do not appear to inhibit the formation of helical structures.
- [13] Oligomers **2**–**5** were shown to be pure by ^1H NMR spectroscopy, size-exclusion chromatography, high-performance liquid chromatography, and matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS). Compounds **2** and **3** gave acceptable elemental analyses. Further details of the preparation and characterization of all compounds will be reported elsewhere.
- [14] For examples of preorganized, ion-binding systems substituted with cyano groups, see a) K. Paek, C. B. Knobler, E. F. Maverick, D. J. Cram, *J. Am. Chem. Soc.* **1989**, *111*, 8662–8671; b) Y. Tobe, N. Utsumi, A. Nagano, K. Naemura, *Angew. Chem.* **1998**, *110*, 1347–1349; *Angew. Chem. Int. Ed.* **1998**, *37*, 1285–1287.
- [15] R. H. P. Francisco, Y. P. Mascareñas, J. R. Lechat, *Acta Crystallogr. Sect. B* **1979**, *35*, 177–178.
- [16] L. Carlucci, G. Ciani, D. Prosperpio, A. Sironi, *J. Am. Chem. Soc.* **1995**, *117*, 4562–4569.

- [17] D. Venkataraman, Y. Du, S. Wilson, K. Hirsch, P. Zhang, J. Moore, *J. Chem. Ed.* **1997**, *74*, 915.
- [18] Similar behavior is observed for solutions of **3** with Cu^+ salts, but not with Cu^{2+} salts. This is explained by the ability of Cu^+ ions to adopt trigonal-planar coordination environments, while Cu^{2+} ions prefer a square-planar or octahedral bonding geometry.
- [19] Additional evidence for the stoichiometry of metal binding is provided by ESI-MS. The major peak is assigned to a doubly charged species corresponding to $[\mathbf{3} \cdot \text{Ag}]^{2+}$.
- [20] The NMR spectra of **3** are similar to those of **5**, but there are twice as many resonances.
- [21] K. Wuthrich, *NMR of Proteins and Nucleic Acids*, Wiley, New York, **1986**.
- [22] The addition of less than two equivalents of AgO_3SCF_3 to a solution in THF results in broad, undefined signals in the aromatic region, characteristic of a system that is fluxional on the NMR time scale.
- [23] K. A. Connors, *Binding Constants: The Measurement of Molecular Complex Stability*, Wiley, New York, **1987**.
- [24] The UV/Vis spectra showed a clear isobestic point at 375 nm, indicative of only one species being formed upon complexation.

Peptide Folding: When Simulation Meets Experiment

Xavier Daura, Karl Gademann, Bernhard Jaun, Dieter Seebach, Wilfred F. van Gunsteren,* and Alan E. Mark

The last two decades have seen the horizons of science and engineering being expanded greatly by the use of computer simulation techniques. In particular, computer simulation is the method of choice to study processes that are dangerous, costly, or even impossible to carry out experimentally, or that are of microscopic nature and thereby partially inaccessible to detailed observation. Molecular dynamics (MD) simulations, in which Newton's equations of motion are integrated to reproduce the time evolution (trajectory) of the atoms in a system, are widely used to study dynamic processes in biomolecular systems at atomic resolution.^[1]

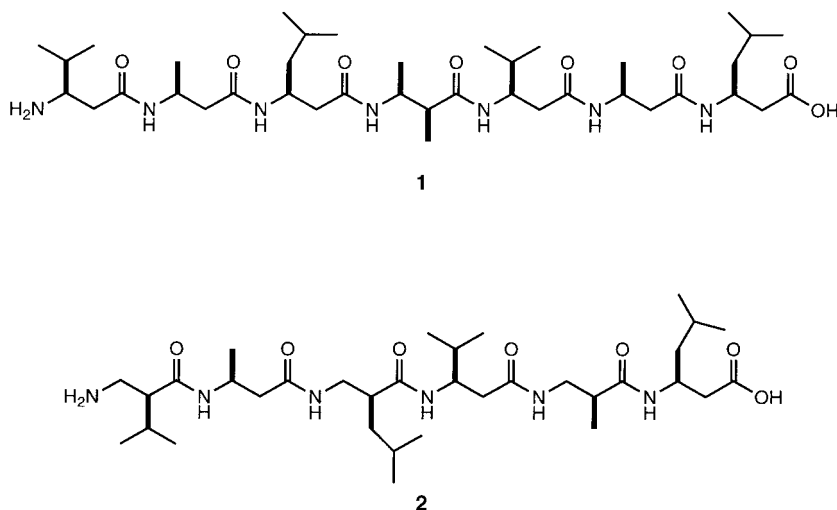
The ultimate goal of any simulation is to characterize and predict the behavior of real systems. Whether this goal is achieved depends on the quality of the model used and the computational power available. No model is an exact representation of the real system. All models must be verified, normally by comparison to experimental data. In the case of simulations aimed at understanding the mechanism of peptide or protein folding, verification represents a significant challenge. First, the dynamics of individual atoms during the process of folding cannot yet be directly observed experimentally. Experimental data at atomic resolution is only available for equilibrium distributions of conformations under

[*] Prof. Dr. W. F. van Gunsteren, Dr. X. Daura, Dr. A. E. Mark
Laboratorium für Physikalische Chemie, ETH Zürich
ETH-Zentrum, CH-8092 Zürich (Switzerland)
Fax: (+41) 1-632-1039
E-mail: wfvgn@igc.phys.chem.ethz.ch
K. Gademann, Prof. Dr. B. Jaun, Prof. Dr. D. Seebach
Laboratorium für Organische Chemie, ETH Zürich
ETH-Zentrum, CH-8092 Zürich (Switzerland)

specific conditions. Second, the time scale on which the relevant biomolecular systems can be simulated in atomic detail is currently on the order of picoseconds to nanoseconds, while the lower limit for proteins as well as most peptides to fold is believed to be microseconds. Third, the process of peptide folding involves many (peptide and solvent) degrees of freedom and is governed by small (free) energy differences, on the order of a few multiples of $k_B T$ (k_B = Boltzmann's constant), which puts very high demands on the accuracy of the atomic interaction function and model that is used.

Here we show that reversible folding of peptides in solution in atomic detail has come within the reach of computer simulation. This is especially useful since peptides are highly flexible molecules for which little structural information can be obtained by experiment. Yet, their structures are highly relevant to their interactions in living organisms.

We present MD simulation studies on the folding of two β -peptides. β -Peptides are nonnatural peptides composed of β -amino acids (R^4 -NH-C β HR ^{3} -C α HR ^{2} -CO-R ^{1}).^[2] They have recently attracted much attention due to their potential use as peptide mimetics which are stable to peptidases and whose conformation can be tuned by altering the position of the side chain.^[2-6] The β -peptides studied were the β -heptapeptide **1** and the β -hexapeptide **2**.



H- β^3 -HVal- β^3 -HAla- β^3 -HLeu-(*S,S*)- β^3 -HAla(α Me)- β^3 -HVal- β^3 -HAla- β^3 -HLeu-OH **1**

H- β^2 -HVal- β^3 -HAla- β^2 -HLeu- β^3 -HVal- β^2 -HAla- β^3 -HLeu-OH **2**

In **1** all side chains are in position R^3 (except for residue number four, which is methylated at both R^3 and R^2 positions), while in **2** the side chains alternate between positions R^2 and R^3 . In methanol and pyridine, **1** adopts a left-handed helix (hydrogen bonds between residues i and $i+2$) consisting of three residues per turn (3_1 -helix), in which the amide C=O bonds point in the direction of the N terminus (Figure 1 a).^[3] In the same solvents, **2** predominantly forms a right-handed helix (hydrogen bonds between residues i and $i+1$, and between i and $i-3$) in which the amide C=O bonds point alternately up and down the helix axis (Figure 1 b, c).^[4, 5]

The folds of the β -hepta- and β -hexapeptides were modeled based on NMR data.^[3-5] Slightly different structures for **2** in methanol (Figure 1 b) and in pyridine (Figure 1 c) were inferred. The NMR data obtained in pyridine could be fitted by a model in which the β -hexapeptide forms a regular helix with hydrogen bonds NH(3)-O(4), NH(4)-O(1), and NH(6)-O(3). A hydrogen bond is here considered to exist if the proton-acceptor distance is less than 0.25 nm and the donor-proton-acceptor angle is greater than 135°. To simultaneously satisfy all the distance constraints derived from the 34 NOEs detected in methanol, the β -hexapeptide is forced to adopt a distorted helix containing just one hydrogen bond, NH(4)-O(1) (Figure 1 b). Three of the 34 NOEs are responsible for this distortion. The root mean square difference (RMSD) in atom position between the two model structures (Figures 1 b, c) is 0.07 nm (backbone, residues 2-5).

For several reasons, these systems are well suited for the study of peptide folding by MD simulation. First, although the time scale on which they fold in methanol is not known experimentally, in simulations these peptides fold on a time scale of nanoseconds. This is fast when compared with small helix-forming α -peptides in aqueous solution.^[7] Second, methanol has a lower density than water, making it a computationally less expensive solvent (by a factor of about three) in which to simulate folding. Third, β -peptides can adopt a range of secondary-structure elements depending on the side-chain composition and position. The small differences in the sequences of the two peptides lead to two profoundly different folds (Figure 1), although Seebach and co-workers^[4] had designed the β -hexapeptide to form the left-handed helix of the β -heptapeptide. Because the conformation is sensitive to the precise nature of the atomic interactions, the system is a very sensitive test case for the force field used in the simulations. It should be noted that the GROMOS96 force field^[8] used in this work has not been developed for β -amino acids or β -peptides. Therefore, there can be no suspicion that the force field has been artificially

adjusted to favor the experimentally observed folds. Finally, there is no fundamental difference between the study by MD simulation of the folding of these two β -peptides in methanol and the folding of a peptide composed of α -amino acids in water, other than the time scale on which folding occurs and the time scale that can be simulated.

Figure 2 shows, as a function of time, the RMSD between the structures given in Figure 1, which represent the predominant conformation in solution at 298 K modeled based on experimental NMR data, and conformations sampled during the simulations at 340 K. For the β -heptapeptide **1** a particular conformation was considered to be folded if the RMSD was 0.1 nm or less (backbone, residues 2-6).^[9] For the β -hexapeptide **2** a lower boundary of 0.08 nm (backbone, residues 2-5) was used in proportion with the number of residues in the two peptides. As can be seen from Figure 2, both **1** and **2** fold and

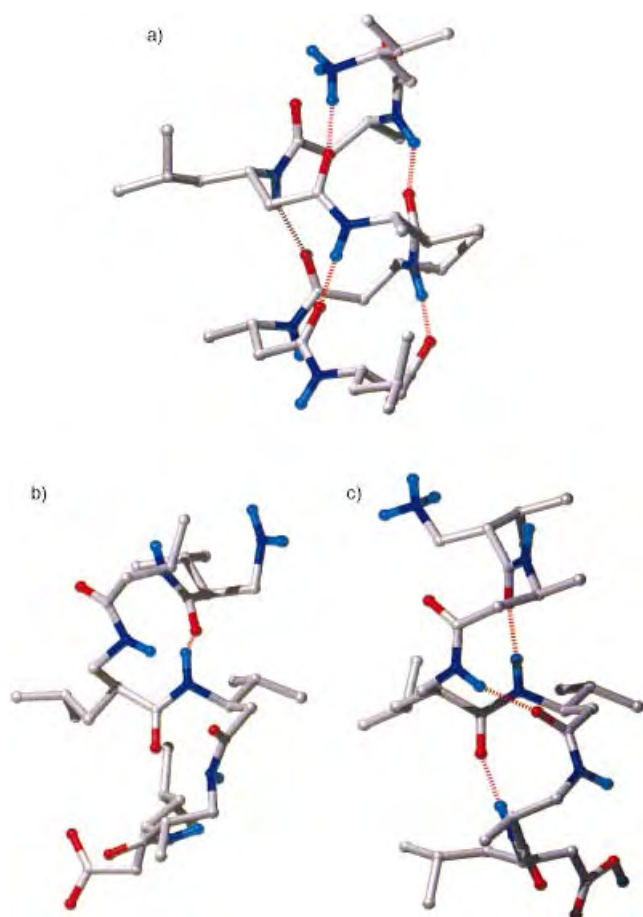


Figure 1. a) Molecular model for the β -heptapeptide **1** derived from NMR data obtained in methanol at 298 K.^[3] b) Molecular model for the β -hexapeptide **2** derived from NMR data obtained in methanol at 298 K.^[5] c) Molecular model for the β -hexapeptide **2** derived from NMR data obtained in pyridine at 298 K.^[4] Hydrogen bonds (with a maximum proton–acceptor distance of 0.25 nm and a minimum donor–proton–acceptor angle of 135°) are shown with red dashed lines.

unfold several times during the 50 ns of simulation. In Figure 3 examples of folded and unfolded conformations from the simulations are shown. Although the simulation of **1** was initiated from the 3_1 -helical model structure, this peptide readily folds from a totally extended structure at 340 K.^[9] The right-handed helical β -hexapeptide is clearly less stable than the left-handed helical β -heptapeptide at 340 K. The maximum lifetime observed for the left-handed helical β -heptapeptide conformation was on the order of 10 ns, while for the right-handed helical β -hexapeptide conformation it was on the order of 3 ns. Cluster analysis (see the Experimental Section) was performed using 5000 structures extracted from the trajectories at time intervals of 0.01 ns. For **1** the conformer represented by Figure 1a was the predominant conformer in the simulation, being populated approximately 50% of the time. In the case of **2** a single conformation did not so clearly dominate. Three clusters, including the most populated one, which together cover approximately 30% of the total ensemble would incorporate the conformation represented by Figure 1c. Interestingly, the left-handed 3_1 -helix was (approximately 1.3% of the time) among the

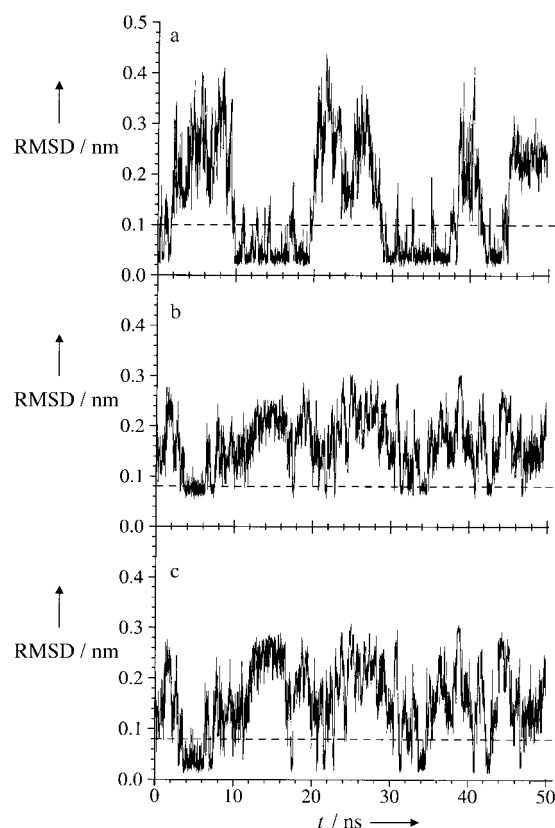


Figure 2. Backbone root-mean-square deviation (RMSD) of atom positions of the simulated structures from the model structures as a function of time at 340 K: a) RMSD from the model structure in Figure 1a for residues 2–6 of the β -heptapeptide **1**. b) RMSD from the model structure in Figure 1b for residues 2–5 of the β -hexapeptide **2** (0.33 nm for the initial (extended) structure). c) RMSD from the model structure in Figure 1c for residues 2–5 of the β -hexapeptide **2** (0.36 nm for the initial (extended) structure). Structures with an RMSD below the dashed lines have unequivocally the same fold as the model structures to which they are compared.

alternate conformations sampled by the β -hexapeptide during the simulation. By classification of all conformations with a backbone RMSD from the respective model structures of 0.10 nm (residues 2–6, **1**, Figure 2a) or 0.08 nm (residues 2–5, **2**, Figure 2c) as being folded and all conformations with an RMSD greater than 0.15 nm (**1**) or 0.12 nm (**2**) as being unfolded, the free energy of folding $\Delta G_{\text{folding}}$ was estimated to be 0 and 4 kJ mol^{−1} at 340 K for **1** and **2**, respectively.

The question of whether Figure 1b is an appropriate model for the most populated conformation of the β -hexapeptide **2** in methanol at room temperature can now be addressed. The simulation (Figure 2b, c) clearly suggests that Figure 1c represents a better model structure for **2** in methanol than Figure 1b. The conformation in Figure 1b is, in fact, high in energy in the force field due to both unfavorable bonded (bond angles, torsional angles) and nonbonded interactions, suggesting that such a conformation, even if it fulfils all the NOEs obtained in methanol, is improbable. More likely, the observed NOEs result from a mixture of two or more conformations in rapid equilibrium at 298 K. The three NOEs that are violated by the molecular model in Figure 1c are characteristic of a left-handed 3_1 -helix, and were not observed

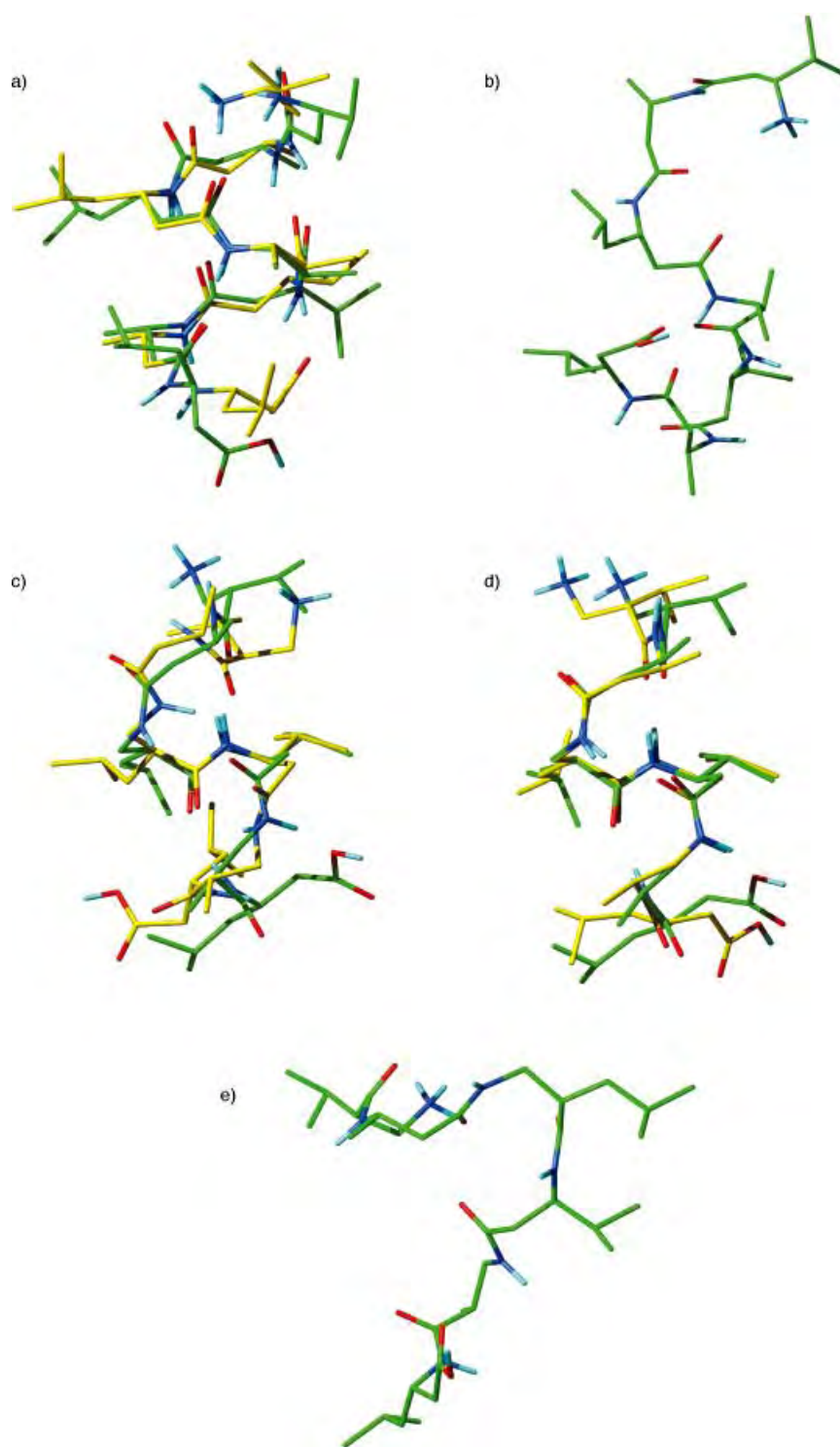


Figure 3. Selected conformations from the simulations: a) Superposition of the model structure in Figure 1a and the conformation of the β -heptapeptide **1** at time point 18 ns in the simulation [backbone RMSD of 0.03 nm (residues 2–6)]. b) Conformation of the β -heptapeptide **1** at time point 24 ns in the simulation [backbone RMSD of 0.25 nm (residues 2–6)]. c) Superposition of the model structure in Figure 1b and the conformation of the β -hexapeptide **2** at time point 5 ns in the simulation [backbone RMSD of 0.07 nm (residues 2–5)]. d) Superposition of the model structure in Figure 1c and the conformation of the β -hexapeptide **2** at time point 5 ns in the simulation [backbone RMSD of 0.02 nm (residues 2–5)]. e) Conformation of the β -hexapeptide **2** at time point 26 ns in the simulation [backbone RMSD from the model structures in Figure 1b, c of 0.21 nm (residues 2–5)].

in pyridine. The right-handed helical conformation of the β -hexapeptide was the predominant conformation in the simulation at 340 K. Nevertheless, several alternate conformations were also populated significantly, including a left-handed 3_1 -helix (1.3 %). When averaged over the ensemble of conformations generated at 340 K using $\text{NOE} \propto \langle 1/r^6 \rangle^{-1/6}$, only one NOE observed in methanol is violated by more than 0.1 nm. Despite the fact that the results at 340 K cannot be directly related to the experimental results obtained at room temperature, it is clear that the right-handed helical conformation of the β -hexapeptide **2** is not as stable in methanol at 298 K as the left-handed helical conformation of the β -heptapeptide **1**, and alternate conformations, including perhaps the 3_1 -helix, account for some of the observed NOEs.

With this work we believe we have clearly demonstrated the ability to simulate in atomic detail the reversible folding of peptides in solution, albeit of non-natural β -peptides. Despite the small differences in sequence between the two peptides studied, the simulations correctly predict a left-handed 3_1 -helical fold for the β -heptapeptide and a right-handed helical fold for the β -hexapeptide. These results open a wide range of possibilities for the use of MD simulations in understanding the process of peptide folding and predicting possible folds of peptides in solution.

Experimental Section

Two 50-ns MD simulations at 340 K and 1 atm were performed for **1** and **2**. Periodic boundary conditions were applied. The initial structures were 3_1 -helical for **1** (Figure 1a) and extended (all backbone dihedral angles set to 180°) for **2**. The β -heptapeptide **1** was solvated with 962 methanol molecules in a rectangular box, and the β -hexapeptide **2** was solvated with 1435 methanol molecules in a truncated octahedron. In both cases the initial minimum distance between peptide and wall was chosen equal to the cut-off for the nonbonded interactions (1.4 nm). The temperature used for the simulations corresponds to the melting temperature of **1** in the force field, as estimated previously.^[9] No restraints were applied. Parameter settings not commented here were as in reference [9]. The GROMOS96 package of programs and force field were used.^[8]

To find clusters of structures in a trajectory the RMSD of atom positions between all pairs of structures was determined. For each structure the number of other structures for which the RMSD was 0.1 nm or less (backbone, residues 2–6) for **1** or 0.08 nm or less (backbone, residues 2–5) for **2**

(neighbor conformations) was calculated. The structure with the highest number of neighbors was taken as the center of a cluster, and formed together with all its neighbors a (first) cluster. The structures of this cluster were thereafter eliminated from the pool of structures. The process was repeated until the pool of structures was empty. In this way, a series of nonoverlapping clusters of structures was obtained.

Free energies of folding were calculated as $\Delta G_{\text{folding}} = -k_B T \ln(p_{\text{folded}}/p_{\text{unfolded}})$, where k_B is the Boltzmann constant, T is the temperature, and p_{folded} and p_{unfolded} are the relative probabilities of the folded and unfolded conformations; p_{folded} and p_{unfolded} are approximated by the number of folded and unfolded conformations sampled in the simulations.

Received: September 1, 1998 [Z12359IE]
German version: *Angew. Chem.* **1999**, *111*, 249–253

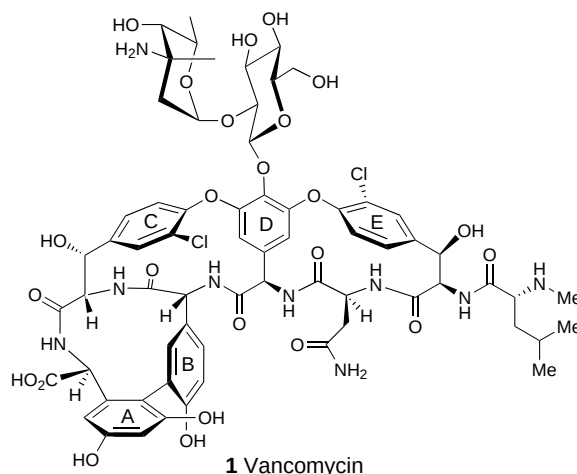
Keywords: computer chemistry • conformation analysis • molecular dynamics • peptide folding • peptides

- [1] *Computer simulation of biomolecular systems, theoretical and experimental applications*, Vols. 1–3 (Eds.: W. F. van Gunsteren, P. K. Weiner, A. J. Wilkinson), Kluwer, Dordrecht, **1989–1997**.
- [2] D. Seebach, M. Overhand, F. N. M. Kühnle, B. Martinoni, L. Oberer, U. Hommel, H. Widmer, *Helv. Chim. Acta* **1996**, *79*, 913–941.
- [3] D. Seebach, P. E. Ciceri, M. Overhand, B. Jaun, D. Rigo, L. Oberer, U. Hommel, R. Amstutz, H. Widmer, *Helv. Chim. Acta* **1996**, *79*, 2043–2066.
- [4] D. Seebach, K. Gademann, J. V. Schreiber, J. L. Matthews, T. Hintermann, B. Jaun, L. Oberer, U. Hommel, H. Widmer, *Helv. Chim. Acta* **1997**, *80*, 2033–2038.
- [5] D. Seebach, S. Abele, K. Gademann, G. Guichard, T. Hintermann, B. Jaun, J. L. Matthews, J. V. Schreiber, L. Oberer, U. Hommel, H. Widmer, *Helv. Chim. Acta* **1998**, *81*, 932–982.
- [6] a) T. Hintermann, D. Seebach, *Chimia* **1997**, *50*, 244–247; b) X. Daura, W. F. van Gunsteren, D. Rigo, B. Jaun, D. Seebach, *Chem. Eur. J.* **1997**, *3*, 1410–1417; c) D. H. Appella, L. A. Christianson, I. L. Karle, D. R. Powell, S. H. Gellman, *J. Am. Chem. Soc.* **1996**, *118*, 13071–13072; d) D. H. Appella, L. A. Christianson, D. A. Klein, D. R. Powell, X. Huang, J. J. Jr. Barchi, S. H. Gellman, *Nature* **1997**, *387*, 381–384; e) S. Krauthäuser, L. A. Christianson, D. R. Powell, S. H. Gellman, *J. Am. Chem. Soc.* **1997**, *119*, 11719–11720; f) S. H. Gellman, *Acc. Chem. Res.* **1998**, *31*, 173–180; g) S. Borman, *Chem. Eng. News* **1997**, *75*(24), 32–35; h) U. Koert, *Angew. Chem.* **1997**, *109*, 1922–1923; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1836–1837; i) B. L. Iverson, *Nature* **1997**, *385*, 113–115.
- [7] a) S. Williams, T. P. Causgrove, R. Gilmanshin, K. S. Fang, R. H. Callender, W. H. Woodruff, R. B. Dyer, *Biochemistry* **1996**, *35*, 691–697; b) P. A. Thompson, W. A. Eaton, J. Hofrichter, *Biochemistry* **1997**, *36*, 9200–9210.
- [8] W. F. van Gunsteren, S. R. Billeter, A. A. Eising, P. H. Hünenberger, P. Krüger, A. E. Mark, W. R. P. Scott, I. G. Tironi, *Biomolecular Simulation: The GROMOS96 manual and user Guide*, Vdf Hochschulverlag AG an der ETH Zürich, Zürich, **1996**, pp. 1–1042.
- [9] X. Daura, B. Jaun, D. Seebach, W. F. van Gunsteren, A. E. Mark, *J. Mol. Biol.* **1998**, *280*, 925–932.

Total Synthesis of Vancomycin**

K. C. Nicolaou,* Helen J. Mitchell,
Nareshkumar F. Jain, Nicolas Winssinger,
Robert Hughes, and Toshikazu Bando

Within the class of the glycopeptide antibiotics^[1] vancomycin (**1**)^[2] occupies a commanding position as a highly effective and widely used clinical agent for combating severe bacterial infections caused by drug resistant pathogens.^[1–3] This novel



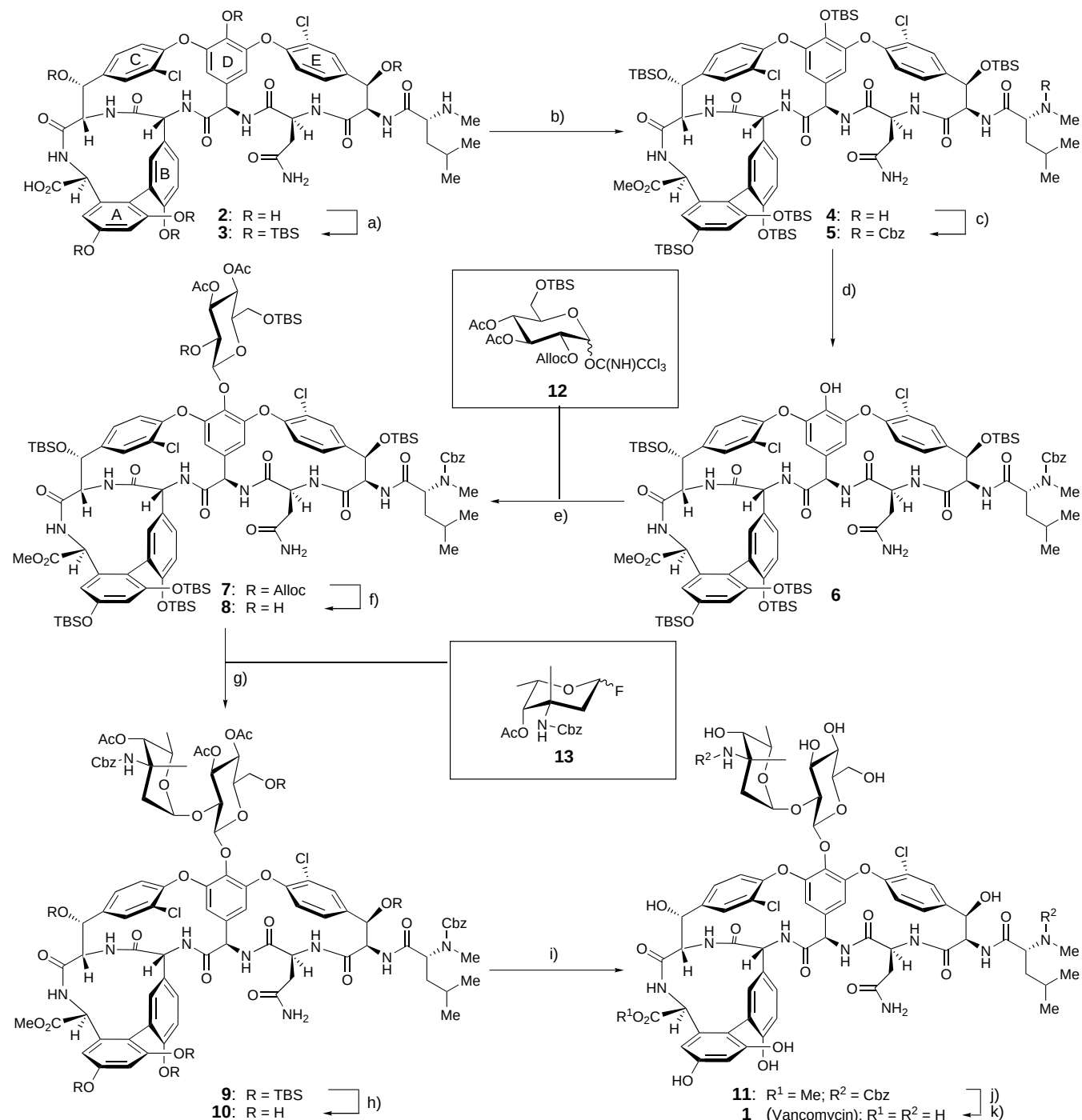
antibiotic, isolated from actinomycetes *Streptomyces orientalis* (later renamed *Nocardia orientalis* and finally reclassified as *Amycolatopsis orientalis*^[2c]), has recently^[3] moved to center stage by virtue of its increasing importance in chemistry, biology, and medicine. The total synthesis of this antibiotic has long been considered as a formidable challenge to synthetic organic chemistry.^[4] Intense research efforts in recent times have culminated in the total synthesis of the vancomycin aglycon **2** (see Scheme 1), recently accomplished by the research group of Evans^[5] and our own.^[6] Herein we wish to report the total synthesis of vancomycin (**1**) itself. This synthesis involves sequential glycosidations of a suitably protected derivative of the previously synthesized vancomycin aglycon **2**^[6] and delivers the target molecule in a highly efficient and stereoselective manner.

[*] Prof. Dr. K. C. Nicolaou, H. J. Mitchell, Dr. N. F. Jain, N. Winssinger, R. Hughes, Dr. T. Bando
Department of Chemistry and
The Skaggs Institute for Chemical Biology
The Scripps Research Institute
10550 North Torrey Pines Road, La Jolla, CA 92037 (USA)
Fax: (+1) 619-784-2469
E-mail: kcn@scripps.edu
and
Department of Chemistry and Biochemistry
University of California, San Diego
9500 Gilman Drive, La Jolla, CA 92093 (USA)

[**] We thank Dr. D. H. Huang and Dr. G. Siuzdak for NMR and mass spectrometric assistance, respectively. This work was financially supported by the National Institutes of Health (USA), The Skaggs Institute for Chemical Biology, and grants from Pfizer, Schering Plough, Hoffmann La Roche, and Merck.

Before the challenging task of attaching the carbohydrate moieties onto the aglycon of vancomycin at the phenolic group of ring D could be attempted a suitably protected derivative had to be constructed. To this end, **2** was persilylated with TBSOTf in the presence of 2,6-lutidine to afford, after aqueous workup, the hexa(TBS) derivative **3** in 72% yield. Exposure of **3** to excess CH_2N_2 in diethyl ether

gave methylester **4** (91% yield), which led to the Cbz-protected derivative **5** (92% yield) upon treatment with CbzCl and an aqueous solution of NaHCO_3 . The key removal of the TBS group on ring D of **5** was effected selectively by exposure to $\text{KF} \cdot \text{Al}_2\text{O}_3$,^[7] which furnished the desired vancomycin glycoside acceptor **6** in 60% yield (Scheme 1; Table 1).

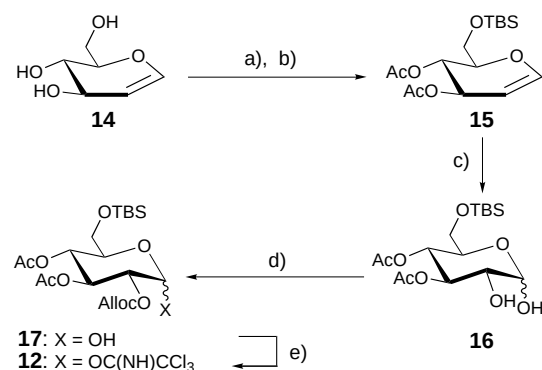


Scheme 1. Total synthesis of vancomycin (**1**). a) TBSOTf (20 equiv); 2,6-lutidine (60 equiv), $\text{CH}_2\text{Cl}_2/\text{DMF}$ (10/1), $0 \rightarrow 23^\circ\text{C}$, 7 h, 72%; b) CH_2N_2 (excess), Et_2O , 0°C , 30 min, 91%; c) Cbz-Cl (5.0 equiv), NaHCO_3 (10.0 equiv), 1,4-dioxane/ H_2O (10/1), 0°C , 30 min, 92%; d) $\text{KF} \cdot \text{Al}_2\text{O}_3$ (ca. 1 equiv), CH_3CN , 0°C , 2 h, 60%; e) **12** (5.0 equiv), $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (10.0 equiv), CH_2Cl_2 , -78°C , 6 h, 82%; f) $n\text{Bu}_3\text{SnH}$ (4.0 equiv), $[\text{Pd}(\text{PPh}_3)_4]$ (0.1 equiv), CH_2Cl_2 , 23°C , 30 min, 85%; g) **13** (4.0 equiv), $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (3.0 equiv), CH_2Cl_2 , -30°C , 2 h, 84%; h) $\text{HF} \cdot \text{pyr.}/\text{pyr.}$ (1:1, excess), THF, $0 \rightarrow 23^\circ\text{C}$, 12 h, 80%; i) K_2CO_3 (5.0 equiv), MeOH, 23°C , 4 h, 95%; j) Raney nickel, $n\text{PrOH}/\text{H}_2\text{O}$ (2/1), 23°C , 45 min; k) LiOH (solid, 5.0 equiv), THF/ H_2O (1/1), 0°C , 20 min, 85% (from **11**). Alloc = allyloxycarbonyl, Cbz = benzyloxycarbonyl, DMF = dimethylformamide, TBS = *tert*-butyldimethylsilyl, TBSOTf = *tert*-butyldimethylsilyltrifluoromethanesulfonate.

Table 1. Selected physical and spectroscopic data for **6**, **7**, and **9**.

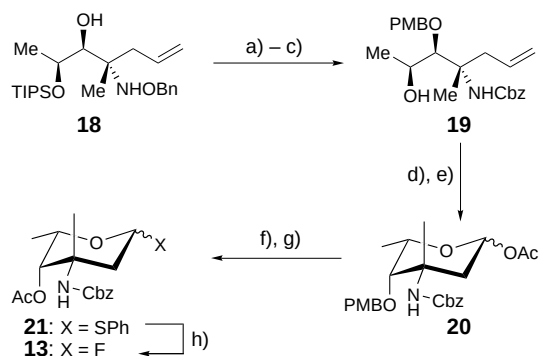
6: $R_f = 0.31$ (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]_D^{25} = -14.0$ ($c = 1.12$ in CHCl_3); IR (film): $\tilde{\nu} = 3403, 2995, 2857, 1751, 1676, 1670, 1658, 1508, 1472, 781 \text{ cm}^{-1}$; $^1\text{H NMR}$ (600 MHz, CD_3OD, 330 K): $\delta = 7.71$ (s, 1H), 7.47 (dd, $J = 1.0, 8.5 \text{ Hz}$, 1H), 7.37–7.22 (m, 8H), 7.04 (d, $J = 8.0 \text{ Hz}$, 1H), 7.01 (dd, $J = 2.0, 8.5 \text{ Hz}$, 1H), 6.75 (d, $J = 8.5, 1 \text{ Hz}$), 6.40 (d, $J = 2.0 \text{ Hz}$, 1H), 6.32 (d, $J = 2.0 \text{ Hz}$, 1H), 5.86 (brs, 2H), 5.69 (s, 1H), 5.46 (d, $J = 10.0 \text{ Hz}$, 1H), 5.34 (s, 1H), 5.33 (s, 1H), 5.14 (m, 2H), 4.96 (m, 1H), 4.91 (s, 1H), 4.85 (m, 1H), 4.70 (m, 1H), 4.08 (s, 1H), 3.74 (s, 3H), 2.95 (s, 3H), 2.38 (m, 2H), 1.80 (m, 1H), 1.48 (m, 2H), 1.00 (s, 9H), 0.93 (m, 6H), 0.90 (s, 9H), 0.84 (s, 9H), 0.63 (s, 9H), 0.21 (s, 6H), 0.16 (s, 3H), 0.10 (s, 3H), 0.08 (s, 6H), 0.06 (s, 3H), 0.06 (s, 3H), 0.02 (s, 3H), -0.8 (s, 3H); $^{13}\text{C NMR}$ (150 MHz, $[\text{D}_6]\text{acetone}$, 315 K): <math>\delta = 175.6, 173.4, 172.8, 171.1, 168.0, 156.3, 155.8, 155.8, 153.9, 152.1, 150.1, 149.1, 148.3, 148.2, 137.2, 136.4, 133.5, 133.4, 133.0, 129.5, 129.1, 128.2, 127.6, 127.4, 126.9, 126.4, 124.7, 120.4, 113.4, 113.1, 111.6, 105.0, 99.1, 74.6, 74.5, 70.3, 66.9, 64.1, 64.1, 64.0, 58.1, 55.3, 55.3, 49.1, 42.5, 41.3, 37.5, 36.4, 36.3, 35.1, 26.3, 26.2, 26.1, 25.7, 25.6, 25.5, 25.3, 25.2, 25.1, 23.6, 22.6, 22.3, 19.4, 19.3, 19.1, 19.0, 18.9, 18.7, 18.6, 18.6, 18.4, 18.3, $-3.7, -3.7, -3.8, -3.9, -4.1, -4.1, -4.2, -4.3, -4.5, -4.6$; HR-MS (FAB): calcd for $\text{C}_{92}\text{H}_{130}\text{Cl}_2\text{N}_8\text{O}_{19}\text{Si}_5\text{Cs}$ [$M + \text{Cs}^+$]: 1993.6730; found: 1993.6606.</math> 7: $R_f = 0.33$ (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]_D^{25} = +7.9$ ($c = 0.3$ in CHCl_3); IR (film): $\tilde{\nu} = 3550, 2956, 2929, 2874, 2857, 1760, 1691, 1667, 1644, 1599, 1504, 1471, 1416, 1362, 1307, 1234, 1172, 1111, 1062, 948, 923, 837, 781 \text{ cm}^{-1}$; $^1\text{H NMR}$ (600 MHz, CD_3OD, 330 K): $\delta = 7.52$ (s, 1H), 7.51 (s, 1H), 7.45 (m, 2H), 7.42–7.30 (m, 10H), 7.27 (s, 1H), 7.07 (d, $J = 2.0 \text{ Hz}$, 1H), 7.01 (dd, $J = 2.0, 8.5 \text{ Hz}$, 1H), 6.77 (d, $J = 8.5 \text{ Hz}$, 1H), 6.42 (d, $J = 2.0 \text{ Hz}$, 1H), 6.35 (d, $J = 2.0 \text{ Hz}$, 1H), 5.80–5.75 (m, 3H), 5.56–5.15 (m, 6H), 5.05–4.85 (m, 6H), 4.64 (m, 2H), 4.30 (dd, $J = 4.5, 11.0 \text{ Hz}$, 1H), 4.11 (s, 1H), 3.85–3.80 (m, 1H), 3.82 (dd, $J = 3.0, 9.0 \text{ Hz}$, 1H), 3.75 (s, 3H), 2.94 (s, 3H), 2.50–2.39 (m, 2H), 2.03 (s, 3H), 2.00 (s, 3H), 1.84 (m, 1H), 1.60–1.45 (m, 2H), 1.02 (s, 9H), 0.95 (s, 9H), 0.92–0.91 (m, 6H), 0.87 (s, 9H), 0.78 (s, 9H), 0.75 (s, 9H), 0.65 (s, 9H), 0.23 (s, 6H), 0.21 (s, 3H), 0.12 (s, 6H), 0.11 (s, 3H), 0.09 (s, 6H), 0.02 (s, 3H), -0.07 (s, 3H), -0.08 (s, 3H), -0.11 (s, 3H); $^{13}\text{C NMR}$ (150 MHz, $[\text{D}_6]\text{acetone}$, 315 K): <math>\delta = 181.5, 171.8, 171.1, 170.5, 170.1, 170.1, 169.8, 169.0, 167.9, 167.9, 156.4, 155.8, 154.7, 154.0, 152.9, 151.8, 151.7, 141.4, 139.6, 138.0, 137.3, 137.2, 136.1, 132.7, 131.9, 130.5, 129.5, 129.5, 129.4, 129.3, 129.3, 129.0, 128.9, 128.8, 128.5, 128.0, 127.6, 127.3, 126.9, 126.4, 126.0, 124.9, 120.6, 120.5, 1118.2, 113.2, 111.6, 106.9, 104.5, 76.9, 76.8, 74.7, 74.2, 74.1, 74.0, 70.3, 69.0, 68.0, 64.2, 63.6, 60.1, 60.1, 57.7, 57.6, 55.6, 55.3, 54.8, 54.0, 52.8, 52.7, 52.2, 49.2, 39.7, 38.7, 38.7, 37.3, 36.6, 30.0, 26.4, 26.2, 26.2, 26.0, 25.7, 25.6, 25.5, 23.6, 23.5, 23.4, 22.8, 22.8, 20.9, 20.6, 19.0, 18.8, 18.3, 18.3, 14.2, 11.7, $-3.9, -3.9, -4.2, -4.2, -4.3, -4.5, -4.6, -4.7, -4.8, -4.9, -5.3, -5.4$; HR-MS (FAB): calcd for $\text{C}_{112}\text{H}_{162}\text{Cl}_2\text{N}_8\text{O}_{28}\text{Si}_6\text{Cs}$ [$M + \text{Cs}^+$]: 2440.8874; found: 2440.8738.</math> 9: $R_f = 0.36$ (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]_D^{25} = -9.0$ ($c = 0.3$ in CHCl_3); IR (film): $\tilde{\nu} = 3550, 2928, 2876, 2856, 1755, 1718, 1682, 1654, 1504, 1470, 1458, 1416, 1298, 1252, 1062, 837 \text{ cm}^{-1}$; $^1\text{H NMR}$ (600 MHz, CD_3OD, 333 K): $\delta = 7.60$–7.41 (m, 3H), 7.40–7.18 (m, 10H), 7.09 (s, 2H), 7.03 (m, 2H), 6.79 (s, 1H), 6.78 (s, 1H), 6.44 (d, $J = 2 \text{ Hz}$, 1H), 6.32 (s, 1H), 5.80 (s, 2H), 5.66–5.30 (m, 6H), 5.29–4.80 (m, 8H), 5.01 and 4.88 (AB, $J = 12.5 \text{ Hz}$, 2H), 4.66 (m, 2H), 4.18–4.07 (m, 2H), 3.85–3.80 (m, 2H), 3.77 (s, 3H), 3.64 (m, 1H), 2.94 (s, 3H), 2.50 (m, 2H), 2.05 (s, 3H), 2.05–2.00 (m, 2H), 2.03 (s, 3H), 1.96 (s, 3H), 1.55 (m, 3H), 1.29 (s, 3H), 1.09 (d, $J = 5.5 \text{ Hz}$, 3H), 1.03 (s, 9H), 0.96 (s, 9H), 0.93 (m, 6H), 0.88 (s, 9H), 0.82 (s, 9H), 0.76 (s, 9H), 0.66 (s, 9H), 0.24 (s, 6H), 0.19 (s, 3H), 0.14 (s, 3H), 0.12 (s, 3H), 0.10 (s, 12H), 0.04 (s, 3H), -0.06 (s, 6H); $^{13}\text{C NMR}$ (150 MHz, $[\text{D}_6]\text{acetone}$, 315 K): <math>\delta = 175.6, 173.4, 172.8, 171.2, 169.0, 169.0, 168.8, 168.1, 168.1, 168.0, 167.9, 167.9, 167.9, 157.5, 157.5, 156.4, 156.4, 156.4, 155.8, 155.3, 155.3, 155.0, 138.6, 138.5, 138.4, 138.4, 138.4, 137.3, 137.3, 137.3, 130.0, 130.0, 129.4, 129.4, 129.4, 129.0, 128.9, 128.9, 128.7, 128.7, 128.5, 128.5, 128.5, 120.8, 120.6, 120.6, 113.4, 112.0, 111.6, 98.6, 98.4, 95.2, 64.0, 60.2, 60.2, 60.1, 60.1, 60.1, 59.8, 59.8, 59.8, 59.8, 55.4, 55.4, 55.4, 55.4, 55.3, 55.3, 55.3, 55.2, 54.6, 53.4, 52.7, 52.1, 39.4, 39.3, 37.4, 37.3, 37.3, 36.4, 36.4, 36.4, 26.5, 26.4, 26.4, 26.2, 26.2, 26.2, 26.1, 25.7, 25.7, 24.2, 23.7, 23.7, 20.7, 20.7, 20.7, 20.6, 20.6, 20.6, 19.1, 19.1, 19.1, 18.8, 18.3, 18.3, 17.9, 17.8, 17.6, $-3.8, -3.8, -4.2, -4.2, -4.2, -4.2, -4.4, -4.4, -4.6, -4.7, -4.8, -4.8$; HR-MS (FAB): calcd for $\text{C}_{125}\text{H}_{179}\text{Cl}_2\text{N}_9\text{O}_{31}\text{Si}_6\text{Cs}$ [$M + \text{Cs}^+$]: 2676.1712; found: 2676.1552.</math>

The final reaction scheme for the successful attachment of the disaccharide unit onto substrate **6** required considerable experimentation and fine-tuning of the protecting groups and glycosidation reaction. For example, initial successes of glycosidation with fully O-benzylated and N-Cbz protected carbohydrate donors^[8] were countered by failure to remove the benzyl groups without reductive cleavage of the chloride on ring E. Similarly, attempts at glycosidation with persilylated or peracetylated carbohydrate donors were thwarted by steric hindrance, lability under the glycosidation conditions used, and/or low reactivity. A rewarding compromise was obtained when the glucose-derived donor was loaded with a trichloroacetimidate^[9] at C1, an allyloxycarbonyl group at C2, acetate groups at C3 and C4, and a TBS group at C6 ($\rightarrow$ **12**, Schemes 1 and 2) and the vancosamine-derived donor included a fluoride^[10] activating group at C1, a Cbz group on the nitrogen atom and an acetate group at C4 ($\rightarrow$ **13**, Schemes 1 and 3). The two carbohydrate donors **12** and **13** were prepared from readily available starting materials as summarized in Schemes 2 and 3, respectively.



Scheme 2. Synthesis of glucose donor **12**. a) TBS-Cl (1.0 equiv); imidazole (1.5 equiv), DMF, 0 $\rightarrow$ 23 $^{\circ}\text{C}$, 1 h, 82%; b) Ac_2O (3.0 equiv), Et_3N (5.0 equiv), 4-DMAP (0.1 equiv), CH_2Cl_2 , 23 $^{\circ}\text{C}$, 2 h, 97%; c) OsO_4 (0.05 equiv), NMO (1.2 equiv), acetone/ H_2O (9/1), 23 $^{\circ}\text{C}$, 12 h, 84%; d) Alloc-Cl (1.0 equiv), Et_3N (1.5 equiv), 4-DMAP (0.1 equiv), CH_2Cl_2 , 23 $^{\circ}\text{C}$, 10 min, 35%; e) Cl_3CCN (10.0 equiv), DBU (0.05 equiv), CH_2Cl_2 , 0 $^{\circ}\text{C}$, 89%. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, 4-DMAP = 4-dimethylaminopyridine, NMO = 4-methylmorpholine *N*-oxide

Glycosidation of **6** with excess trichloroacetimidate **12** proceeded smoothly at -78°C in dichloromethane and in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ to afford monosaccharide **7** in 82% yield.^[11] The desired β stereochemistry was assumed at this stage, based on model studies, and was later confirmed by the successful conversion of this intermediate into vancomycin (**1**). The C2 hydroxyl group of the glucose ring was then liberated selectively and in high yield (85%) by treatment with $n\text{Bu}_3\text{SnH}/\text{Pd}$ ^[12] to afford the new glycoside acceptor **8** onto which vancosamine had to be installed. The latter goal was achieved by reaction of **8** with excess vancosamine donor **13** in dichloromethane and in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ at -30°C , to furnish the vancomycin derivative **9** in a yield of 84%. The required α stereochemistry of the newly formed glycoside bond, presumably enhanced by participation of the C4 acetoxy group as observed from model studies, was finally confirmed by the completion of the total synthesis of



Scheme 3. Synthesis of vancosamine donor **13**. a) NaH (1.1 equiv), PMB-Cl (1.3 equiv), THF, 0 → 23 °C, 3 h, 93%; b) LiAlH₄ (4.0 equiv), Et₂O, reflux, 18 h; c) Cbz-Cl (1.5 equiv), NaHCO₃ (2.0 equiv), 1,4-dioxane/H₂O (4/1), 23 °C, 2 h, 81% (over two steps); d) O₃ (excess), CH₂Cl₂, -78 °C, 10 min; Me₂S -78 → 23 °C, 6 h, 92%; e) Ac₂O (2.0 equiv), Et₃N (3.0 equiv), 4-DMAP (0.1 equiv), CH₂Cl₂, 23 °C, 2 h, 96%; f) PhSH (4.0 equiv); BF₃·Et₂O (4.0 equiv), CH₂Cl₂, -20 °C, 1 h, 91%; g) Ac₂O (2.0 equiv), Et₃N (3.0 equiv), 4-DMAP (0.1 equiv), CH₂Cl₂, 23 °C, 2 h, 97%; h) 1. NBS (1.5 equiv), acetone/H₂O (9/1), 0 °C, 30 min, 94%; 2. DAST (1.2 equiv), CH₂Cl₂, 0 °C, 30 min, 100%. DAST = diethylaminosulfur trifluoride, NBS = *N*-bromosuccinimide, PMB = *para*-methoxybenzyl, TIPS = triisopropylsilyl.

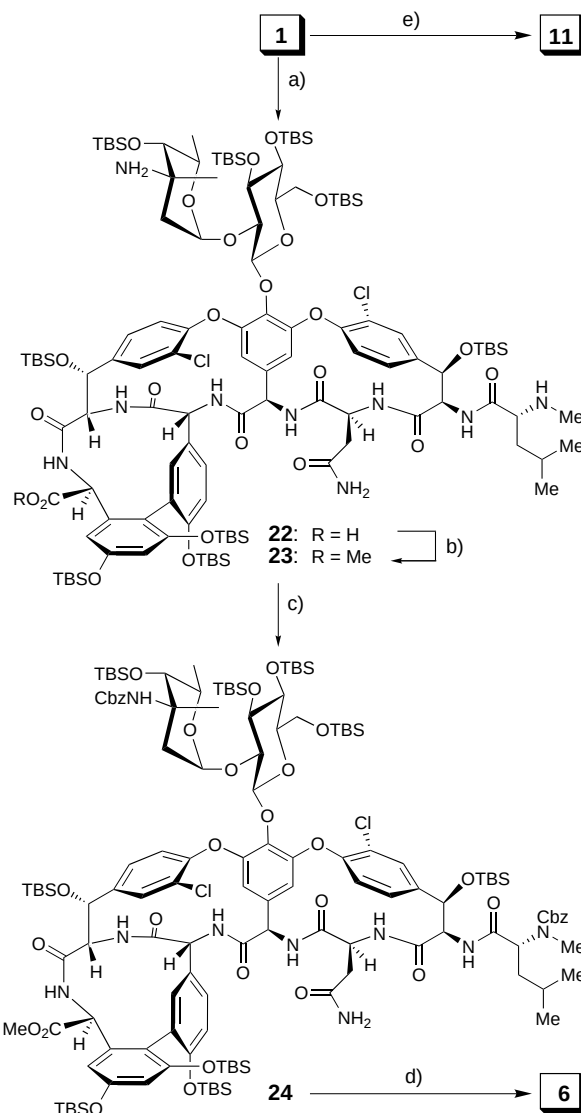
vancomycin (**1**) by sequential removal of the protecting groups from **9** (→ **10** → **11** → **1**; see Scheme 1). Synthetic **11** was found to be spectroscopically (NMR) and chromatographically^[13] identical with a sample prepared from natural vancomycin (**1**)^[14] as indicated in Scheme 4. Synthetic vancomycin (**1**) was identical with an authentic sample (mixed NMR, HPLC^[13]).

We also developed a synthesis of the acceptor **6** from vancomycin (**1**, Scheme 4) to facilitate semisynthetic studies and in order to pave the way for the practical construction of vancomycin libraries. Thus, vancomycin (**1**) was persilylated by exposure to excess TBSOTf and 2,6-lutidine in solution (dichloromethane/DMF) to give, after aqueous work-up, the nona(TBS) derivative **22** in 65% yield. Treatment of **22** with excess CH₂N₂ in diethyl ether furnished methylester **23**, which was converted into the bis(Cbz) derivative **24** by exposure to excess Cbz-Cl and NaHCO₃ (80% over two steps). Finally, reaction of the latter compound (**24**) with TFA/Me₂S/CH₂Cl₂ (1/1/1) at ambient temperature and under carefully controlled conditions furnished the desired vancomycin acceptor **6** in a yield of 60%.

The work described here completes the total synthesis of vancomycin (**1**) from simple chemical building blocks and opens the way for the design and synthesis of vancomycin libraries for biological studies. Ahead lies the particularly attractive semisynthesis of analogues^[15] with molecular diversity around the carbohydrate region of the molecule in which solid-phase and/or combinatorial chemistry may play an important role. Furthermore, with the conquest of vancomycin (**1**) the fall of other members of the group of the glycopeptide antibiotics should be considered as a matter of time.

Received: November 24, 1998 [Z 127071E]
German version: *Angew. Chem.* **1999**, *111*, 253–255

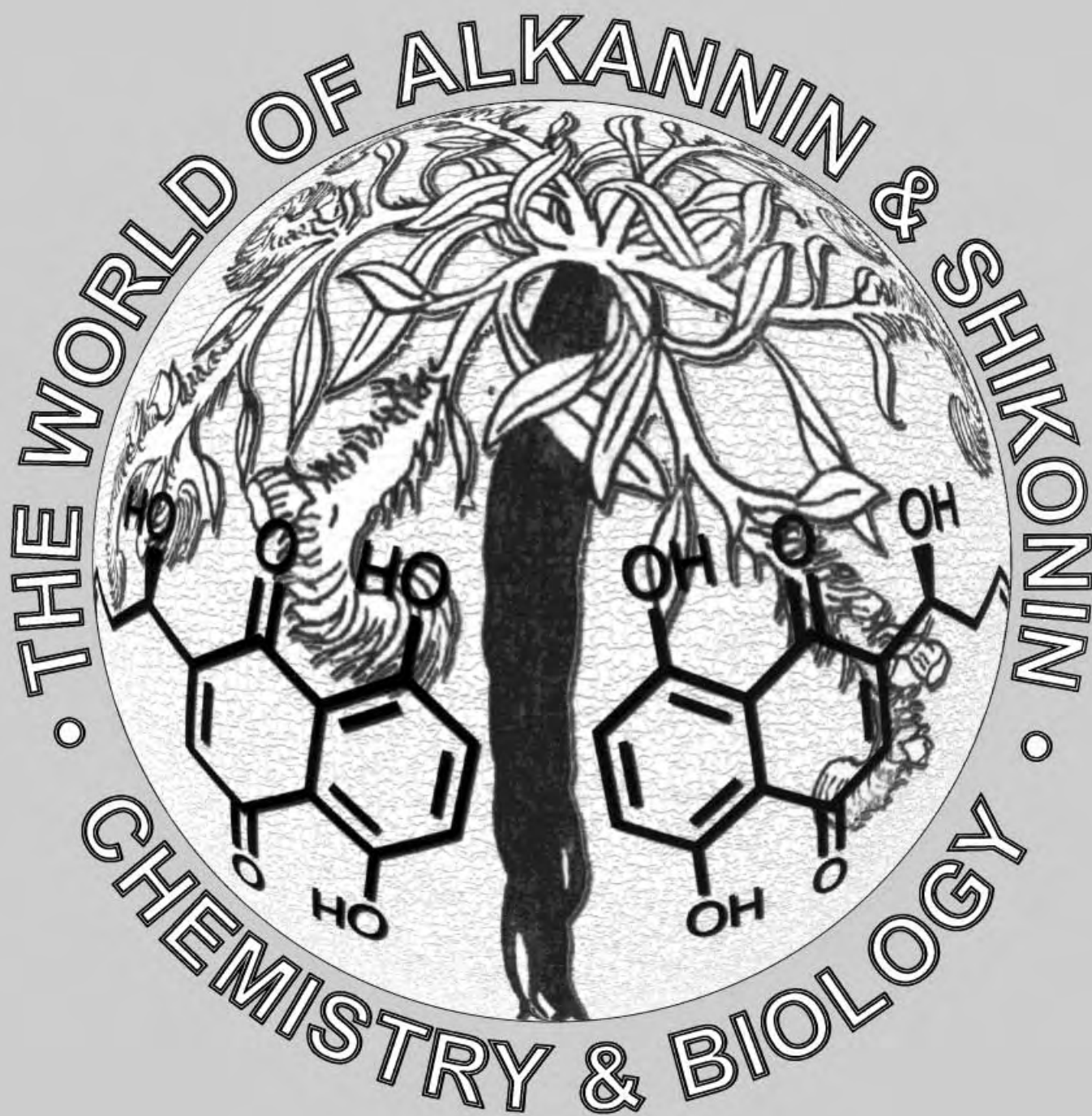
Keywords: amino acids • antibiotics • glycosidations • total synthesis • vancomycin



Scheme 4. Degradation of vancomycin (**1**). a) TBSOTf (excess); 2,6-lutidine (excess), CH₂Cl₂/DMF (10/1), 0 → 23 °C, 18 h; aq. NaHCO₃, 23 °C, 60 h, 65%; b) CH₂N₂ (excess), Et₂O, 0 °C, 30 min; c) Cbz-Cl (5.0 equiv), NaHCO₃ (excess), 1,4-dioxane/H₂O (10/1), 0 °C, 30 min, 80% (over two steps); d) TFA/Me₂S/CH₂Cl₂ (1/1/1; 0.01 M), 23 °C, 3 h, 60%; e) 1. Cbz-Cl (3.0 equiv), NaHCO₃ (7.0 equiv), 1,4-dioxane/H₂O (5/1), 0 °C, 30 min; 2. MeI (20 equiv), NaHCO₃ (10.0 equiv), DMF, 0 °C, 30 min. TFA = trifluoroacetic acid.

- [1] *Glycopeptide Antibiotics*, (Ed.: R. Nagarajan), Marcel Dekker, New York, **1994**.
- [2] a) G. M. Sheldrick, P. G. Jones, O. Kennard, D. H. Williams, G. A. Smith, *Nature* **1978**, *271*, 223; b) P. J. Loll, A. E. Bevivino, B. D. Korty, P. H. Axelson, *J. Am. Chem. Soc.* **1997**, *119*, 1516; c) M. H. McCormick, W. M. Stark, R. C. Pittenger, G. M. McGuire, *Antibiot. Ann.* **1955–1956**, 606; d) C. M. Harris, T. M. Harris, *J. Am. Chem. Soc.* **1982**, *104*, 4293; e) C. M. Harris, H. Kopecka, T. M. Harris, *J. Am. Chem. Soc.* **1983**, *105*, 6915.
- [3] For reviews in the area, see a) A. V. R. Rao, M. K. Gurjar, K. L. Reddy, A. S. Rao, *Chem. Rev.* **1995**, *95*, 2135; b) K. Burgess, D. Lim, C. I. Martinez, *Angew. Chem.* **1996**, *108*, 1162; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1077; c) J. P. Zhu, *Synlett* **1997**, 133, and references therein.
- [4] a) D. A. Evans, J. A. Ellman, K. M. DeVries, *J. Am. Chem. Soc.* **1989**, *111*, 8912; D. A. Evans, C. J. Dinsmore, *Tetrahedron Lett.* **1993**, 34,

- 6029; D. A. Evans, C. J. Dinsmore, D. A. Evrard, K. M. DeVries, *J. Am. Chem. Soc.* **1993**, *115*, 6426; D. A. Evans, P. S. Watson, *Tetrahedron Lett.* **1996**, *37*, 3251; D. A. Evans, C. J. Dinsmore, A. M. Ratz, *Tetrahedron Lett.* **1997**, *38*, 3189; D. A. Evans, C. J. Dinsmore, A. M. Ratz, D. A. Evrard, J. C. Barrow, *J. Am. Chem. Soc.* **1997**, *119*, 3417; D. A. Evans, J. C. Barrow, P. S. Watson, A. M. Ratz, C. J. Dinsmore, D. A. Evrard, K. M. DeVries, J. A. Ellman, S. D. Rychnovsky, J. J. Lacour, *J. Am. Chem. Soc.* **1997**, *119*, 3419; b) K. C. Nicolaou, C. N. C. Boddy, S. Natarajan, T. Y. Yue, H. Li, S. Bräse, J. M. Ramanjulu, *J. Am. Chem. Soc.* **1997**, *119*, 3421; K. C. Nicolaou, X.-J. Chu, J. M. Ramanjulu, S. Natarajan, S. Bräse, F. Rübsam, C. N. C. Boddy, *Angew. Chem.* **1997**, *109*, 1518; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1539; K. C. Nicolaou, J. M. Ramanjulu, S. Natarajan, S. Bräse, H. Li, C. N. C. Boddy, F. Rübsam, *Chem. Commun.* **1997**, 1899; c) D. L. Boger, Y. Nomoto, B. R. Teegarden, *J. Org. Chem.* **1993**, *58*, 1425, and references therein; D. L. Boger, R. M. Borzilleri, S. Nukui, *Bioorg. Med. Chem. Lett.* **1995**, *5*, 3091; D. L. Boger, R. M. Borzilleri, S. Nukui, *J. Org. Chem.* **1996**, *61*, 3561; D. L. Boger, R. M. Borzilleri, S. Nukui, R. T. Beresis, *J. Org. Chem.* **1997**, *62*, 4721; D. L. Boger, O. Loiseleur, S. L. Castle, R. T. Beresis, J. H. Wu, *Bioorg. Med. Chem. Lett.* **1997**, *7*, 3199; D. L. Boger, R. T. Beresis, O. Loiseleur, J. H. Wu, S. L. Castle, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 721; D. L. Boger, S. Miyazaki, O. Loiseleur, R. T. Beresis, S. L. Castle, J. H. Wu, Q. Jing, *J. Am. Chem. Soc.* **1998**, *120*, 8920; d) R. Beugelmans, G. P. Singh, M. Bois-Choussy, J. Chastanet, J. Zhu, *J. Org. Chem.* **1994**, *59*, 5535; R. Beugelmans, J. Zhu, N. Hussion, M. Bois-Choussy, G. P. Singh, *J. Chem. Soc. Chem. Commun.* **1994**, 439; R. Beugelmans, S. Bourdet, J. Zhu, *Tetrahedron Lett.* **1995**, *36*, 1279; J. Zhu, R. Beugelmans, S. Bourdet, J. Chastanet, G. Roussi, *J. Org. Chem.* **1995**, *60*, 6389; M. Bois-Choussy, R. Beugelmans, J.-P. Bouillon, J. Zhu, *Tetrahedron Lett.* **1995**, *36*, 4781; J. Zhu, J.-P. Bouillon, G. P. Singh, J. Chastanet, R. Beugelmans, *Tetrahedron Lett.* **1995**, *36*, 7081; R. Beugelmans, L. Neuville, M. Bois-Choussy, J. Zhu, *Tetrahedron Lett.* **1995**, *36*, 8787; R. Beugelmans, M. Bois-Choussy, C. Vergne, J.-P. Bouillon, J. Zhu, *Chem. Commun.* **1996**, 1029; M. Bois-Choussy, L. Neuville, R. Beugelmans, J. Zhu, *J. Org. Chem.* **1996**, *61*, 9309; C. Vergne, M. Bois-Choussy, R. Beugelmans, J. Zhu, *Tetrahedron Lett.* **1997**, *38*, 1403; C. Vergne, M. Bois-Choussy, J. Zhu, *Synlett* **1998**, 1159; e) A. J. Pearson, J. G. Park, *J. Org. Chem.* **1992**, *57*, 1744; A. J. Pearson, J. G. Park, P. Y. Zhu, *J. Org. Chem.* **1992**, *57*, 3583; A. J. Pearson, H. Shin, *Tetrahedron* **1992**, *48*, 7527; A. J. Pearson, K. Lee, *J. Org. Chem.* **1994**, *59*, 2304; A. J. Pearson, H. Shin, *J. Org. Chem.* **1994**, *59*, 2314; A. J. Pearson, K. Lee, *J. Org. Chem.* **1995**, *60*, 7153; A. J. Pearson, G. Bignan, *Tetrahedron Lett.* **1996**, *37*, 735; A. J. Pearson, G. Bignan, P. Zhang, M. Chelliah, *J. Org. Chem.* **1996**, *61*, 3940; A. J. Pearson, P. Zhang, G. Bignan, *J. Org. Chem.* **1997**, *62*, 4536; f) A. V. R. Rao, T. K. Chakraborty, S. P. Joshi, *Tetrahedron Lett.* **1992**, *33*, 4045; A. V. R. Rao, T. K. Chakraborty, K. L. Reddy, A. S. Rao, *Tetrahedron Lett.* **1992**, *33*, 4799; A. V. R. Rao, M. K. Gurjar, V. Kaiwar, V. B. Khare, *Tetrahedron Lett.* **1993**, *34*, 1661; A. V. R. Rao, K. L. Reddy, M. M. Reddy, *Tetrahedron Lett.* **1994**, *35*, 5039; A. V. R. Rao, T. K. Chakraborty, K. L. Reddy, A. S. Rao, *Tetrahedron Lett.* **1994**, *35*, 5043; A. V. R. Rao, K. L. Reddy, A. S. Rao, *Tetrahedron Lett.* **1994**, *35*, 5047; A. V. R. Rao, K. L. Reddy, A. S. Rao, *Tetrahedron Lett.* **1994**, *35*, 8465; A. V. R. Rao, K. L. Reddy, A. S. Rao, T. V. S. K. Vittal, M. M. Reddy, P. L. Pathi, *Tetrahedron Lett.* **1996**, *37*, 3023; A. V. R. Rao, M. K. Gurjar, P. Lakshmipathi, M. M. Reddy, M. Nagarajan, S. Shashwati, B. V. N. B. S. Sarma, N. K. Tripathy, *Tetrahedron Lett.* **1997**, *38*, 7433; A. V. R. Rao, *Pure Appl. Chem.* **1998**, *70*, 391; g) D. W. Hobbs, W. C. Still, *Tetrahedron Lett.* **1987**, *28*, 2805; N. Pant, A. D. Hamilton, *J. Am. Chem. Soc.* **1988**, *110*, 2002; M. J. Stone, M. S. Van Dyk, P. M. Booth, D. H. Williams, *J. Chem. Soc. Perkin Trans. I* **1991**, 1629; A. G. Brown, M. J. Crimmin, P. D. Edwards, *J. Chem. Soc. Perkin Trans. I* **1992**, 123; R. B. Lamont, D. G. Allen, I. R. Clemens, C. E. Newall, M. V. J. Ramsay, M. Rose, S. Fortt, T. Gallagher, *J. Chem. Soc. Chem. Commun.* **1992**, 1693; R. G. Dushin, S. J. Danishefsky, *J. Am. Chem. Soc.* **1992**, *114*, 3471; K. Nakamura, S. Nishiyama, S. Yamamura, *Tetrahedron Lett.* **1996**, *37*, 191; H. Konishi, T. Okuno, S. Nishiyama, S. Yamamura, K. Koyasu, Y. Terada, *Tetrahedron Lett.* **1996**, *37*, 8791.
- [5] D. A. Evans, M. R. Wood, B. W. Trotter, T. I. Richardson, J. C. Barrow, J. L. Katz, *Angew. Chem.* **1998**, *110*, 2864; *Angew. Chem. Int. Ed.* **1998**, *37*, 2700; D. A. Evans, C. J. Dinsmore, P. S. Watson, M. R. Wood, T. I. Richardson, B. W. Trotter, J. L. Katz, *Angew. Chem.* **1998**, *110*, 2868; *Angew. Chem. Int. Ed.* **1998**, *37*, 2704.
- [6] K. C. Nicolaou, S. Natarajan, H. Li, N. F. Jain, R. Hughes, M. E. Solomon, J. M. Ramanjulu, C. N. C. Boddy, M. Takayanagi, *Angew. Chem.* **1998**, *110*, 2872; *Angew. Chem. Int. Ed.* **1998**, *37*, 2708; K. C. Nicolaou, N. F. Jain, S. Natarajan, R. Hughes, M. E. Solomon, H. Li, J. M. Ramanjulu, M. Takayanagi, A. E. Koumbis, T. Bando, *Angew. Chem.* **1998**, *110*, 2879; *Angew. Chem. Int. Ed.* **1998**, *37*, 2714; K. C. Nicolaou, M. Takayanagi, N. F. Jain, S. Natarajan, A. E. Koumbis, T. Bando, J. M. Ramanjulu, *Angew. Chem.* **1998**, *110*, 2881; *Angew. Chem. Int. Ed.* **1998**, *37*, 2717.
- [7] E. A. Schmittling, J. S. Sawyer, *Tetrahedron Lett.* **1991**, *32*, 7207.
- [8] K. C. Nicolaou, H. J. Mitchell, F. L. van Delft, F. Rübsam, R. M. Rodriguez, *Angew. Chem.* **1998**, *110*, 1972; *Angew. Chem. Int. Ed.* **1998**, *37*, 1871.
- [9] R. R. Schmidt, J. Michel, *Angew. Chem.* **1980**, *92*, 763; *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 731.
- [10] T. Mukaiyama, Y. Murai, S. Shoda, *Chem. Lett.* **1981**, 431; K. C. Nicolaou, A. Chucholowski, R. E. Dolle, J. L. Randall, *J. Chem. Soc. Chem. Commun.* **1984**, 1155.
- [11] The structure of a minor product (ca. 8 %) isolated from this reaction is still under investigation and the possibility of it being the α -anomer of **7** has not been excluded.
- [12] F. Guibe, Y. Saint M'Leux, *Tetrahedron Lett.* **1981**, *22*, 3591.
- [13] HPLC conditions for compound **11**: C18 reverse-phase column (HP-LiChroCART 4 $\times$ 250 mm), gradient solvent system 5 $\rightarrow$ 100% CH₃CN (in H₂O with 1 % trifluoroacetic acid) over 15 min, flow rate 1.5 mL min⁻¹, 23 °C, retention time: 8 min 29 s for **11**, 5 min 38 s for **1**.
- [14] We thank Dr. Homer Pearce of Lilly Research Laboratories for a generous gift of natural vancomycin (**1**).
- [15] To the best of our knowledge the chemical glycosidation of vancomycin aglycon has not been reported. For the chemical glycosidation of vancomycin pseudoaglycon, see a) M. Ge, C. Thompson, D. Kahne, *J. Am. Chem. Soc.* **1998**, *120*, 11014. For enzymatic glycosidation of vancomycin aglycon, see P. J. Solenberg, P. Matsushima, D. R. Stack, S. C. Wilkie, R. C. Thompson, R. H. Baltz, *Chem. Biol.* **1997**, *4*, 195.



ANGEWANDTE
CHEMIE — © WILEY-VCH

The Chemistry and Biology of Alkannin, Shikonin, and Related Naphthazarin Natural Products**

Vassilios P. Papageorgiou,* Andreana N. Assimopoulou, Elias A. Couladouros, David Hepworth, and K. C. Nicolaou*

There can be few natural products with histories as rich as those of the enantiomeric naphthoquinones alkannin (**1**) and shikonin (**2**). Extracts from the roots of *Alkanna tinctoria* in Europe and *Lithospermum erythrorhizon* in the Orient have been used independently for many centuries as natural red dyes and as crude drugs with the magic property of accelerating wound healing. It was only in 1935 that the major constituents of these extracts, **1** and **2**, were correctly identified as

enantiomers, and in 1976 that the wound healing properties of alkannin (**1**) were clinically demonstrated. Today shikonin (**2**) has a high value both for its medicinal and coloring properties, especially in Japan. With synthetic chemists unable, until recently, to devise an efficient synthetic route, and sources from the plants unable to meet demands, it was left to biotechnologists to develop the first commercial plant-cell culture manufacturing process. In Europe, alkannin derivatives are the

active principles of a pharmaceutical ointment used for the treatment of ulcers and burns. This review is an attempt to tell the “whole story” of **1** and **2**, from the 5th century BC and presents up to date aspects of plant biology, pharmacology, and bioorganic, synthetic, and medicinal chemistry.

Keywords: bioorganic chemistry • natural products • phytochemistry • quinones • wound healing

1. Historical Introduction

The story of the enantiomeric naphthoquinone natural products alkannin (**1**) and shikonin (**2**; Figure 1) can be traced back many centuries. In fact, the story comprises two sub-

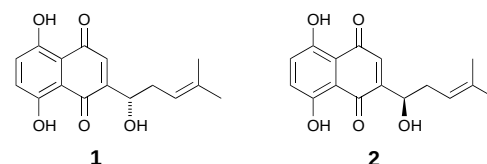


Figure 1. Structures of alkannin (**1**) and shikonin (**2**).

plots that have run remarkably parallel courses in Europe and the Orient, being united only in the 20th century.

In Europe, the *S* enantiomer, alkannin (**1**, Figures 1 and 2), is found in the roots of the plant *Alkanna tinctoria* TAUSCH (*AT*) (Figure 3a), also known as *Anchusa tinctoria*, and in common English as alkanet.^[1] The compound is a major component of the deep red pigments that are easily extracted from the roots of the plant.^[2] It was probably the highly colored nature of alkannin that first captured the attention of botanists. Its use as a dyestuff for fabrics almost certainly dates back centuries BC.^[3] Perhaps the first recorded use of *AT* roots is found in the works of the Greek doctor and philosopher Hippocrates (4th and 5th centuries BC) who described their use for the treatment of ulcers.^[4] The botanist and scholar Theophrastus (3rd and 4th centuries BC) also alluded to their application as dyes and medicines.^[5] Alexander the Great was known to have employed doctors trained in herbal medicine,^[6] and it thus seems likely that the medicinal

[*] Prof. V. P. Papageorgiou, A. N. Assimopoulou
Organic Chemistry Laboratory, Chemical Engineering Department
Aristotle University of Thessaloniki, 54006 Thessaloniki (Greece)
Fax: (+30)31-996252
E-mail: vaspap@eng.anth.gr

Prof. K. C. Nicolaou, Dr. D. Hepworth
Department of Chemistry and
The Skaggs Institute for Chemical Biology
The Scripps Research Institute
10550 North Torrey Pines Road, La Jolla, California 92037 (USA)
Fax: (+1)619-784-2469
E-mail: kcn@scripps.edu

and

Department of Chemistry and Biochemistry
University of California, San Diego
9500 Gilman Drive, La Jolla, California 92093 (USA)

Prof. E. A. Couladouros
Chemical Laboratories
Agricultural University of Athens, Iera Odos 75, 118.55 (Greece)
and
Organic and Bio-organic Laboratories, NCSR “DEMOKRITOS”
153.10 Ag. Paraskevi Attikis, POB 60228 (Greece)

[**] A list of abbreviations not defined in the main text can be found at the end of the article.

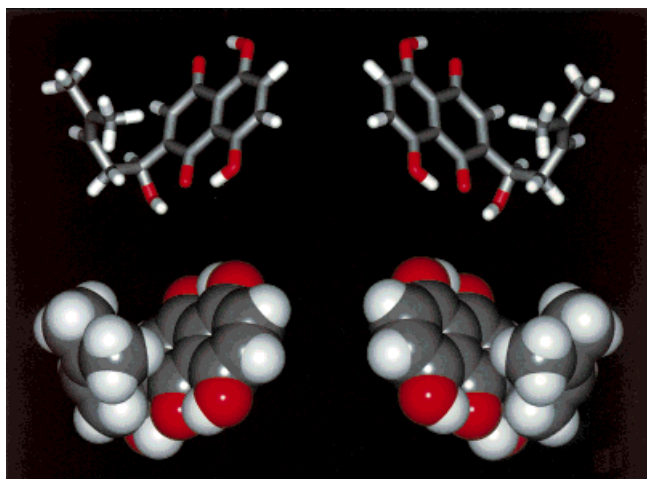


Figure 2. Computer-generated molecular models of alkannin (1) (left) and shikonin (2) (right). Color code: gray: carbon; white: hydrogen; red: oxygen.

properties of *AT* root were used to treat the sick and injured during his campaigns. Dioscorides (Figure 4), who many consider to be the founder of pharmacognosy, described the properties in more detail in his *De Materia Medica* around 77 AD (Figure 5).^[7]

While discussing the properties of the related species *Anchusa eteria*, Dioscorides goes on to describe rather more bizarre effects:^[8] “.ye roots red,.having something like blood in them. But ye faculty of it, and ye leaves is to help ye venemous-beast-bitten, especially ye viper-bitten, being eaten or drank or hanged about one. And if one having chewed it, do spitt it out into ye mouth of ye venemous beast, it will kill him.”

Despite this blatant detour into fiction, the wound healing properties of *AT* have been reported by others. Pliny, a Roman herbalist contemporary with Dioscorides, independently made very similar claims for the medicinal properties of *AT*:^[9] “.It stains the hands the colour of blood; it is used for imparting rich colours to wool. Applied with cerate it heals



V. P. Papageorgiou



A. N. Assimopoulou



E. A. Couladouros



D. Hepworth



K. C. Nicolaou

Vassilios P. Papageorgiou was born in 1942 in Greece and received his Ph.D. and D.Sc. degree from the Aristotle University of Thessaloniki working on the isolation and structure elucidation of wound-healing agents of plant origin. After postdoctoral work at the Pharmacy School, University of Kentucky, he was elected Professor of Organic Chemistry and then Head of the Department of Chemical Engineering at the University of Thessaloniki. He is currently Dean at the School of Engineering. His research interests include the isolation and study of biologically active molecules of plant origin and the development of novel wound-healing agents.

Andreana N. Assimopoulou was born in Greece in 1974. She received her B.Sc. in Chemical Engineering in 1997 from the Aristotle University of Thessaloniki. She is currently a postgraduate student in the Papageorgiou group.

Elias A. Couladouros, born in 1956 in Greece, received his B.Sc. from the University of Athens and his Ph. D. from the Agricultural University of Athens under the direction of Professor M. P. Georgiadis. After a postdoctoral stint in the Nicolaou group at the University of Pennsylvania (1988–89), he joined the faculty of the Agricultural University of Athens, where he is currently Associate Professor of Chemistry. He is also a Visiting Professor at the research center “Demokritos” in Athens. His research interests focus on new synthetic methods and the total synthesis of natural products.

David Hepworth, born in 1970 in England, studied Chemistry at the University of Oxford. He completed his D.Phil. under the supervision of Prof. S. G. Davies in 1996, working on asymmetric synthesis with organochromium chemistry and chiral hydroxylamines. Since joining the Nicolaou group in 1997, he has completed a synthesis of alkannin and shikonin, and worked in the epothilone team.

K. C. Nicolaou is the Chairman of the Department of Chemistry at The Scripps Research Institute, La Jolla, California where he holds the Darlene Shiley Chair in Chemistry and the Skaggs Professorship of Chemical Biology. He is also Professor of Chemistry at the University of California, San Diego.

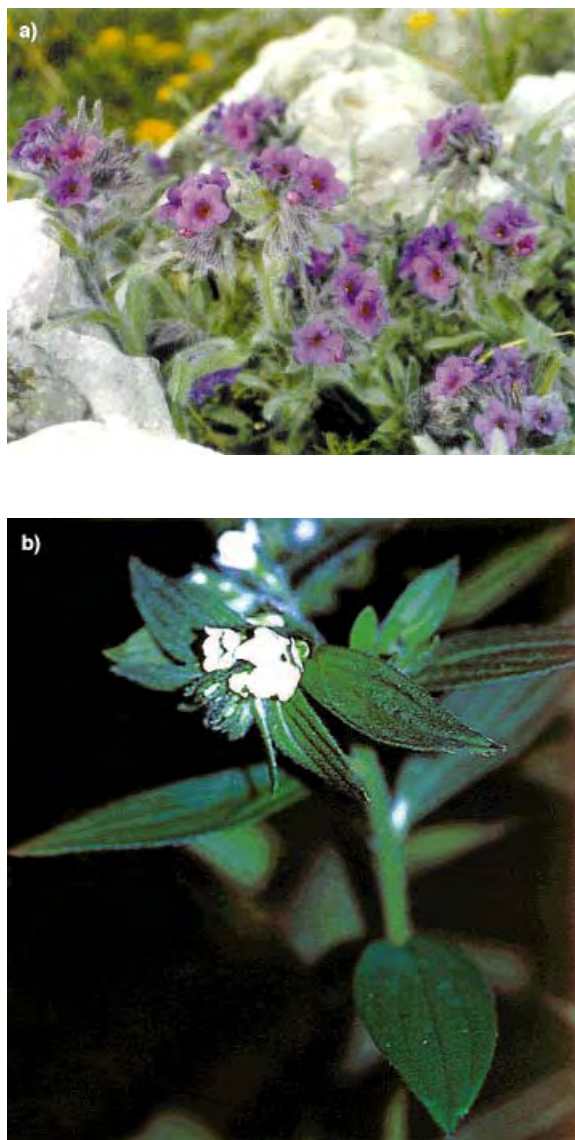


Figure 3. The plants a) *Alkanna tinctoria* TAUSCH, a source of alkannin (1), and b) *Lithospermum erythrorhizon* SIEB. ET ZUCC., a common source of shikonin (2) (courtesy of Medpharm Scientific Publications (a) and Kyoto Pharmaceutical University (b)).

ulcerous sores, those of the aged in particular: it is employed also for the cure of burns.”

For centuries Dioscorides *De Materia Medica* remained one of the standard botanical texts in Europe, with many other herbals being developed from it. Thus, the properties of alkanet became known across Europe, and possibly even further afield.^[10] The English “gentleman student of Physick and astrology” Nicolas Culpeper, from the 17th century AD, stated that alkanet helps to cure “old ulcers, hot inflammations, and burning by common fire”.^[11] Furthermore, the medical doctor William Salmon described in *English Herbs* (ca. 1710),^[12] a formula for: “..deep wounds and punctures of the nerves made with thrusts, stabs or pricking with any pointed weapon..” The recipe is as follows: “Olive oil 2lbs., Alkanet Root 3 or 4 ounces, Earthworms cleaned and purged number 40. Boil them together, then strain out whilst hot and keep it close for use.”



Figure 4. The founder of pharmacognosy Dioscorides collecting botanical samples (courtesy of Parke Davis).

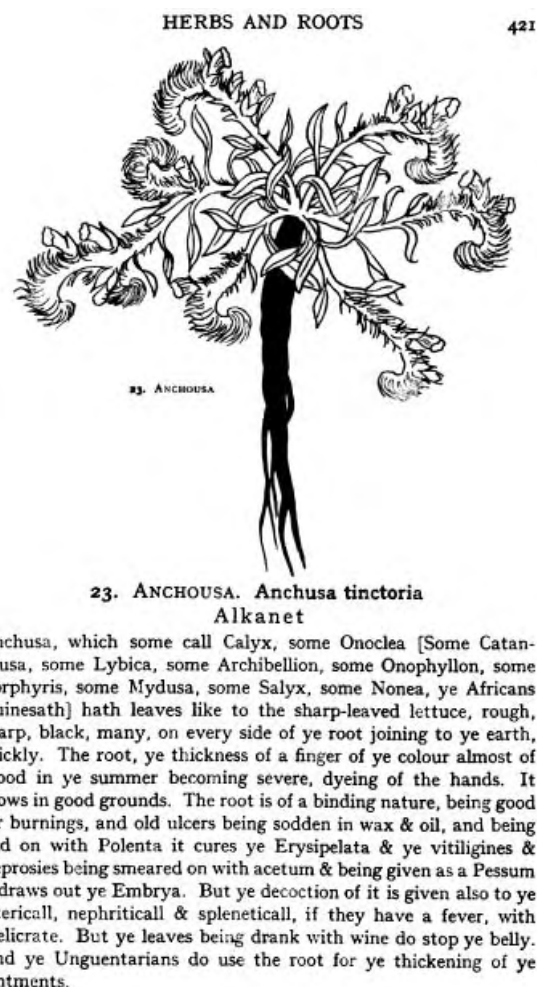


Figure 5. English translation of a passage from Dioscorides' *De Materia Medica*.

Since then, however, the medicinal properties of the plant seem either to have drifted into folklore, or been forgotten. In fact, many modern accounts of herbal medicine describe the roots as being; “rarely used for medicinal purposes”,^[12] “not widely available”,^[13] and as having “no medicinal importance”.^[14] However, alkannin (**1**) is still listed in the *Merck Index* as an astringent.^[15]

Nevertheless, in 1976 Papageorgiou described the results of experiments, which confirmed the wound healing properties and antimicrobial properties of *AT* root extracts (Sections 5.1 and 5.3, respectively) and was the first to identify alkannin derivatives as the active components. More recently, such compounds have also been shown to exhibit significant antitumor, antibacterial, and anti-inflammatory activities. These aspects will be dealt with in Section 5.

The tale of shikonin (**2**), the *R* enantiomer, is set in the Orient, originally in China. This molecule is the major constituent of the red pigment extracts from the roots of the plant *Lithospermum erythrorhizon* SIEB. ET ZUCC. (*LE*) (Figure 6), known in Chinese by various names including *tzu ts'ao*, *tzu-ken* (purple root), and *hung-tzu ken* (reddish-purple root). The use of **2** for dyeing silk probably dates back as far as



Figure 6. Roots of the plant *Lithospermum erythrorhizon* SIEB. ET ZUCC. (courtesy of Kyoto Pharmaceutical University).

the use of **1** in Europe. Its application to traditional Chinese medicine may have originated with the great surgeon Hua To (born ca. 136–141 AD), who is considered to be among the first to have used crude drugs such as antiseptics and anti-inflammatory ointments.^[16] Its use can be traced back with certainty to the latter days of the Ming dynasty, as it is included in the classic compilation of traditional Chinese medicine *Pen Ts'ao Kang Mu*, which was written in 1596 AD.^[17]

The development of Chinese medicine is considered to be a process of constant distillation and selection of all that has gone before, rather than the linear path taken by Western medicine, whereby recent developments are built upon by others, and what has gone before becomes assumed or forgotten. It is thus testimony to the medicinal properties of *LE* roots that they are still included in compilations of ingredients for traditional Chinese and other oriental medi-

cines.^[18] The treatable indications claimed for *LE* roots include: burns, anal ulcers, hemorrhoids, infected crusts, bedsores, external wounds, and oozing dermatitis. These are notably similar to the medicinal properties claimed independently for *AT* in many of the ancient herbal texts. Various preparations that contain **2** and its derivatives are still used today for medicinal purposes in China, Japan, and Korea. In addition, they are also used in Japan as cosmetics^[19] and dyestuffs.^[20] As with alkannin (**1**), the medicinal properties claimed for shikonin (**2**) have more recently been tested scientifically. The interesting findings of these experiments will also be described in Section 5.

In Europe and North America, **1** is mainly used today as a pigment for food coloring^[13, 21] and cosmetics.^[13, 22] Worldwide, however, there has been extensive scientific research concerning these natural products in many areas throughout the disciplines of chemistry and biology. This review is an attempt to bring together material from over 400 articles and patents that have been written in this field, most of which have appeared since the first review in 1980.^[23]

2. Isolation and Identification of Alkannin and Shikonin

Shikonin (**2**) was first isolated as its acetate (**15**) from the roots of *LE* by the Japanese chemists Majima and Kuroda in 1922.^[24] These workers determined many of the chemical properties of **2**, and noting its physical and chemical similarities to the known compound naphthazarin (Section 4.1), proposed structure **3** (Figure 7). Unfortunately, they failed to

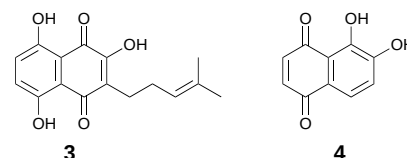


Figure 7. Wrongly assigned structures for shikonin (**3**) and naphthazarin (**4**).^[24]

realize that **2** was optically active, and were probably further confused by the widely accepted, but incorrect, structural assignment for naphthazarin (**64**) as 5,6-dihydroxy-1,4-naphthoquinone (**4**). Brockmann reinvestigated **2** after the structure of naphthazarin (**64**) was correctly revised to 5,8-dihydroxy-1,4-naphthoquinone.^[1] He was the first to identify alkannin (**1**) and shikonin (**2**) as enantiomers, to correctly assign their structures, and to finally unite the stories of these natural products, which had for so long run in parallel. The absolute configurations of **1** and **2** were later determined by degradation to malic acid.^[25]

Brockmann found that the specific rotations of **1** and **2** were not of identical magnitude, but that the values for **1** were generally greater than those for **2**. He suggested that this was a consequence of the presence of a quantity of the racemate, which he termed shikalkin (**1/2**), in the extracts of *LE*. More recently, the ratio of enantiomers in various sources of alkannin (**1**) and shikonin (**2**) have been examined by circular

dichroism^[26] and chiral stationary-phase HPLC.^[27] Interestingly, it was found that the ratio of **1**:**2** varies with the species of plant from which it was extracted.^[26] In this respect, **1** and **2** may be unique among natural products.

In addition to being found in the plants *Alkanna tinctoria* and *Lithospermum erythrorhizon*, **1**, **2**, and related compounds have been isolated from many other *Boraginaceae*. Table 1 gives an up-to-date compilation of selected natural products in the alkannin and shikonin class, together with their occurrence and the biological activities investigated for each.

3. Production of Alkannin and Shikonin

For organic chemists uninitiated in the chemistry of quinones, the structures of alkannin (**1**) and shikonin (**2**) may look misleadingly simple. However, in spite of great efforts over many years by several research groups worldwide, a much needed viable synthetic route to these enantiomers has remained elusive until very recently (Section 4.3.4).

At present we have to rely upon nature, the master organic chemist, for commercial sources of shikonin (**2**). The attempted cultivation of *LE* plants in Japan failed to meet the demand for this valuable natural product. Plants must grow for five to seven years before the shikonin concentration in their roots reaches one to two percent. Formerly, the entire supply of **2** in Japan had to be imported from China and Korea. These difficulties of supply motivated research into producing **2** from plant cell cultures. The fruits of these studies are a highly effective commercial production method for **2**, together with a wealth of information concerning the biosynthesis of **2** and related molecules.

3.1. Production of Alkannin and Shikonin from Cell Tissue Cultures

The first successful production of shikonin (**2**) and a range of ester derivatives from callus cultures was achieved by Tabata and co-workers in 1974.^[91] Since the natural product accumulates only in cork layers in the roots of the plant, they reasoned that the biosynthesis may be triggered by certain environmental factors associated with the production of cork cells.

The culturing of callus tissues, originally derived from germinating *LE* seeds, could be initiated on a Linsmaier–Skoog (LS) medium^[92] that contained kinetin (10^{-6} M) and 2,4-dichlorophenoxyacetic acid (10^{-6} M), but these cultures failed to produce any naphthoquinone pigments. However, transfer of these callus tissues after three months to a culture medium that contained the auxin 3-indoleacetic acid (IAA) stimulated pigment production. It was necessary to conduct the whole tissue culture in the dark for successful naphthoquinone pigment formation, which is consistent with the location of the natural products in the plant roots, and in line with the authors original hypothesis. The possibility that failure of **2** to accumulate in cells illuminated with white light was a result of decomposition of the photosensitive product was ruled out.

When the cells were illuminated only in the period prior to the triggering of pigment formation with IAA, complete inhibition of shikonin production was still observed. In fact, it was found that light disrupts one of the key enzymes in the biosynthetic route (Section 3.2).

Further experimentation identified additional controlling factors in the biosynthesis of **1** and **2**. While pigment formation occurred when callus cultures were grown in LS agar medium, the process failed completely when conducted in a LS liquid medium in the absence of agar. It was suggested that this effect arose from a triggering of the secondary metabolism by a polysaccharide present in the agar. This hypothesis has been supported by experimentation.^[93] More significantly, upon transfer of cells initially cultured in LS liquid medium to the specially developed production medium M9, which contains nitrate ions as the source of nitrogen in place of ammonium ions (which have been shown to inhibit shikonin biosynthesis), the cultures started to produce large quantities of shikonin.^[94] This medium also contains Cu^{2+} ions, which activate the biosynthesis.^[94] Polysaccharides, similar to those identified in agar that activate secondary metabolism, have been isolated from these shikonin-producing cells cultured in the M9 medium.^[95] Gibberelin A_3 deactivates shikonin biosynthesis even at concentrations as low as 10^{-7} M without affecting cell growth. It was suggested that this may be one of the important endogenous regulators of the biosynthesis.^[96] Furthermore, glutamine has been shown to inhibit pigment formation,^[97] while activated charcoal promotes it.^[98]

Further improvements in shikonin production have been made by selection of the most active variant cell lines with improved stability, a process assisted by the brightly colored nature of the natural product,^[99] and by modification of the culture medium.^[100]

These advances have enabled the efficient commercial production of **1** and **2** by the Mitsui Petrochemical Company.^[101, 102] Remarkably, **2** can be produced in upwards of 4 g L^{-1} of liquid culture by this method. This process was the world's first commercial application of plant tissue culture for the production of a secondary metabolite, and remains as one of the few that have been operated on a commercial scale. It has, consequently, been covered in many reviews,^[99c, 103] hence its rather brief coverage here.

The great success of this method has prompted investigations into shikonin (**2**) and alkannin (**1**) production by culturing cells of many other *Boraginaceae* species, which were met with varying degrees of success.^[26, 104–107] Improvement of the culture process with *LE* cells is still the subject of intense research and many publications appear each year in this area.^[108]

3.2. Biosynthesis of Alkannin and Shikonin

The extensive research into the production of **1** and **2** from cell cultures has facilitated the elucidation of several stages in the biosynthesis of these and related natural products.^[109] The generally accepted biosynthetic route is shown in Scheme 1. The two key precursors are 4-hydroxybenzoic acid (PHB, **45**)

Table 1. Selected members of the alkannin/shikonin family of natural products.^[a]

Compound	R	Name	Occurrence and biological properties
1		alkannin (also arnebin-4)	roots: <i>Alkanna tinctoria</i> , ^[1, 2, 28–31, 159] <i>Arnebia hispidissima</i> , ^[2, 32, 33] <i>A. nobilis</i> , ^[171] <i>A. tinctoria</i> , ^[34] <i>Macrotomia cephalotes</i> , ^[35] <i>M. euchroma</i> , ^[36] <i>Onosma echioides</i> , ^[37] <i>O. paniculata</i> , ^[105g] <i>Plagiobotrys arizonicus</i> . ^[26] cell cultures: <i>Alkanna tinctoria</i> , ^[104b] <i>Echium lycopsis</i> . ^[26] biological activity: wound healing (Section 5.1), antiinflammatory (Section 5.1), antibacterial (Section 5.3), inhibition of topoisomerase-I (Section 5.2), antithrombotic (Section 5.4).
5		acetylalkannin or arnebin-3	roots: <i>Alkanna tinctoria</i> , ^[38, 241a] <i>Arnebia euchroma</i> , ^[44] <i>A. hispidissima</i> , ^[33] <i>A. nobilis</i> , ^[171] <i>Macrotomia cephalotes</i> . ^[35, 39] cell cultures: <i>Alkanna tinctoria</i> , ^[104a] <i>Echium lycopsis</i> , ^[26] <i>Onosma paniculatum</i> . ^[105g] biological activity: antimicrobial (Section 5.3), inhibition of topoisomerase-I (Section 5.2), antithrombotic (Section 5.4), antitumor (Section 5.2).
6		isobutyrylalkannin	roots: <i>Alkanna tinctoria</i> , ^[40] cell cultures: <i>Echium lycopsis</i> . ^[26]
7		isovalerylalkannin	roots: <i>Alkanna tinctoria</i> , ^[38, 47, 202] <i>Arnebia hispidissima</i> , ^[33] <i>A. tinctoria</i> , ^[34] <i>Macrotomia cephalotes</i> , ^[35, 39] <i>Onosma heterophylla</i> . ^[41] cell cultures: <i>Echium lycopsis</i> . ^[26] biological activity: inhibition of topoisomerase-I (Section 5.2).
8		α -methylbutyrylalkannin	roots: <i>Alkanna tinctoria</i> , ^[38] <i>Macrotomia cephalotes</i> . ^[35, 39] biological activity: antimicrobial (Section 5.3).
9		β,β -dimethylacrylalkannin or arnebin-1	roots: <i>Alkanna tinctoria</i> , ^[159] <i>Arnebia euchroma</i> , ^[42–45] <i>A. gutatta</i> , ^[42] <i>A. nobilis</i> , ^[171] <i>Lithospermum erythrorhizon</i> , ^[42] <i>Macrotomia cephalotes</i> , ^[39] <i>Onosma heterophylla</i> , ^[41] <i>O. hookeri</i> , ^[42] <i>O. paniculata</i> . ^[42] cell cultures: <i>Alkanna tinctoria</i> , ^[104a] <i>Echium lycopsis</i> , ^[26] <i>Onosma paniculatum</i> . ^[105g] biological activity: inhibition of topoisomerase-I and anticancer (Section 5.2), antimicrobial (Section 5.3), antithrombotic (Section 5.4), antiinflammatory (Section 5.1).
10		teracrylalkannin	roots: <i>Arnebia densiflora</i> . ^[46] biological activity: antimicrobial (Section 5.3).
11		angelylalkannin	roots: <i>Alkanna tinctoria</i> . ^[30, 38, 47, 202]
12		β -hydroxyisovalerylalkannin	roots: <i>Arnebia euchroma</i> , ^[42, 44] <i>A. hispidissima</i> , ^[33] <i>Macrotomia cephalotes</i> . ^[35] cell cultures: <i>Echium lycopsis</i> . ^[26] biological activity: antimicrobial (Section 5.3).
13		β -acetoxyisovalerylalkannin	roots: <i>Alkanna tinctoria</i> , ^[203] <i>Arnebia euchroma</i> , ^[42–44] <i>Moltkiopsis ciliata</i> , ^[85] <i>Onosma heterophylla</i> . ^[41] cell cultures: <i>Onosma paniculatum</i> . ^[105g] biological activity: antimicrobial (Section 5.3).
14		unnamed	roots: <i>Cynoglossum officinale</i> , ^[36] <i>Eritrichium incanum</i> , ^[36] <i>E. sichotense</i> , ^[36] <i>Lappula con-sanguinea</i> , ^[36] <i>Lappula echinata</i> , ^[36] <i>Mertensia maritima</i> . ^[36]

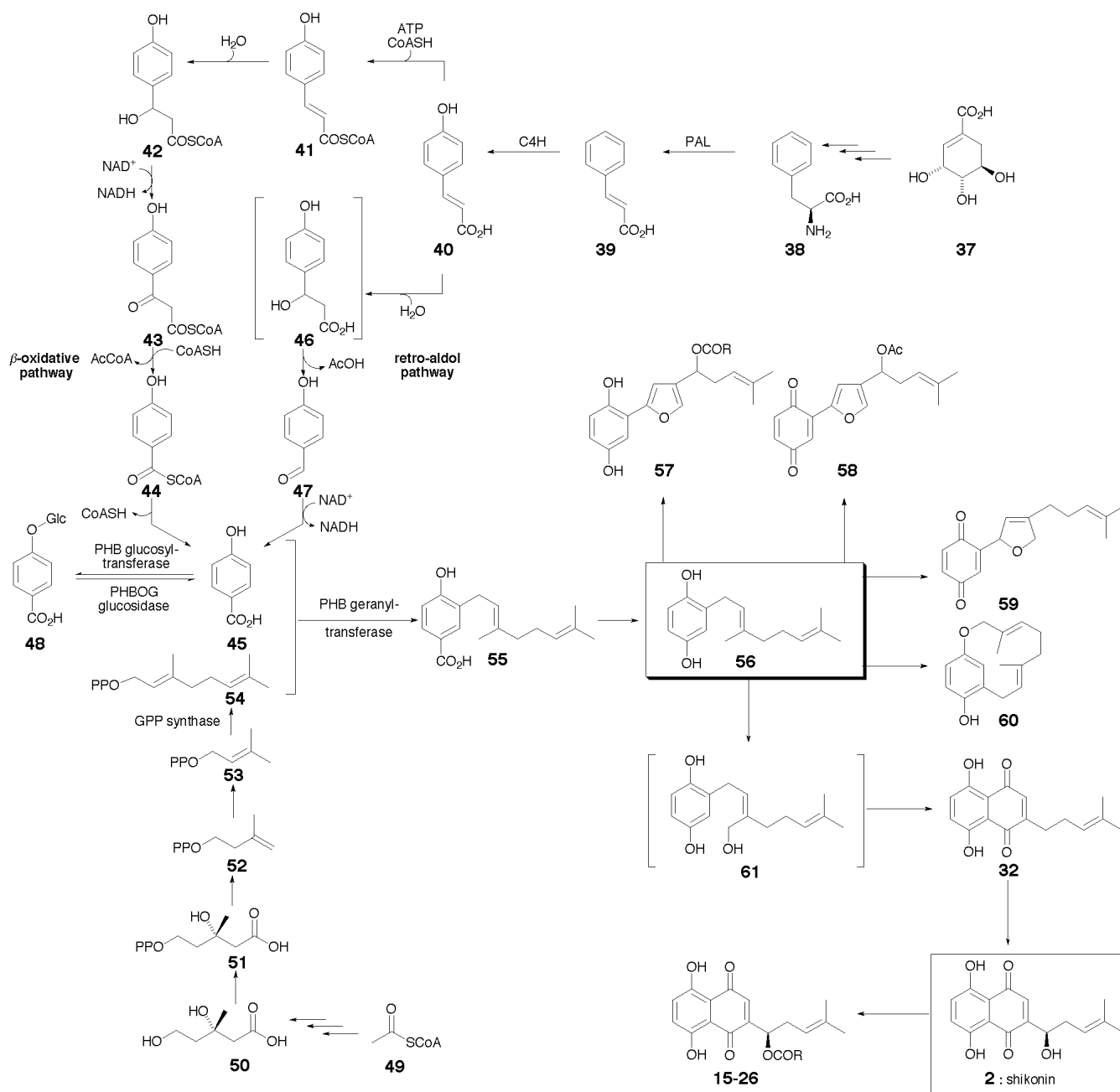
Table 1. (Continued)

Com- pound	R	Name	Occurrence and biological properties
2		shikonin	roots: <i>Arnebia euchroma</i>,^[42–44, 48, 49] <i>A. hispidissima</i>,^[32] <i>A. guttata</i>,^[49, 50] <i>A. tibetiana</i>,^[51–53] <i>Cynoglossum officinale</i>,^[36] <i>Echium lycopsis</i>,^[54] <i>E. rubrum</i>,^[55, 69] <i>E. vulgare</i>,^[36] <i>Eritrichium incanum</i>,^[36] <i>E. sichotenze</i>,^[36] <i>Jatropha glandulifera</i>,^[56] <i>Lappula consanguinea</i>,^[36] <i>L. echinata</i>,^[36] <i>Lithospermum erythrorhizon</i>,^[48, 57–61, 77] <i>L. officinale</i>,^[58–62] <i>Macrotomia echinoides</i>,^[63] <i>M. ugamensis</i>,^[52, 53, 64] <i>M. euchroma</i>,^[36, 65, 66] <i>Mertensia maritima</i>,^[36] <i>Onosma caucasicum</i>,^[52, 55] <i>O. confertum</i>,^[78] <i>O. hookeri</i>,^[42] <i>O. livanovii</i>,^[63] <i>O. polyphyllum</i>,^[67] <i>O. tauricum</i>,^[68] <i>O. sericum</i>,^[63] <i>O. setosum</i>,^[63] <i>O. visianii</i>,^[69] <i>O. zerizaminium</i>.^[52–53, 70] cell cultures: <i>Arnebia euchroma</i>,^[107e,f] <i>Echium lycopsis</i>,^[26] <i>Lithospermum erythrorhizon</i>,^[91, 99a] <i>Onosma paniculatum</i>.^[105] biological effects: antitumor (Section 5.2), antiamebic (Section 5.3), antipyretic and analgesic (Section 5.1), antifungal and antibacterial (Section 5.3), wound healing (Section 5.1), chemopreventive (Section 5.2), antiinflammatory (Section 5.1), inhibition of topoisomerase-II (Section 5.2), inhibition of microsomal monooxygenase,^[71] stimulation of peroxidase,^[72] protection from uv-radiation,^[73] inhibition of testosterone-α-reductase,^[19f] induction and secretion of nerve growth factor.^[74]
15		acetylshikonin	roots: <i>Arnebia decumbens</i>,^[75] <i>A. euchroma</i>,^[36, 42–44, 49] <i>A. guttata</i>,^[42, 49, 50] <i>Cynoglossum officinale</i>,^[36] <i>Echium vulgare</i>,^[36] <i>Eritrichium incanum</i>,^[36] <i>E. sichotenze</i>,^[36] <i>Jatropha glandulifera</i>,^[56] <i>Lappula consanguinea</i>,^[36] <i>L. echinata</i>,^[36] <i>Lithospermum arvense</i>,^[76] <i>L. erythrorhizon</i>,^[42, 57, 77] <i>Mertensia maritima</i>,^[36] <i>Onosma confertum</i>,^[78] <i>O. hookeri</i>,^[42] <i>O. paniculatum</i>,^[42] cell cultures: <i>Arnebia euchroma</i>,^[107e,f] <i>Echium lycopsis</i>,^[26] <i>L. erythrorhizon</i>,^[91, 99a] <i>O. echinoides</i>.^[106]
16		1-methoxyacetylshikonin	roots: <i>Arnebia euchroma</i> . ^[44]
17		propionylshikonin	cell cultures: <i>Lithospermum erythrorhizon</i> . ^[79]
18		isobutyrylshikonin	roots: <i>Cynoglossum officinale</i>,^[36] <i>Echium vulgare</i>,^[36] <i>Eritrichium sichotenze</i>,^[36] <i>Lappula consanguinea</i>,^[36] <i>L. echinata</i>,^[36] <i>Lithospermum arvense</i>,^[76] <i>L. erythrorhizon</i>,^[57, 80] <i>Macrotomia euchroma</i>,^[36] <i>Mertensia maritima</i>.^[36] cell cultures: <i>Arnebia euchroma</i>,^[107f] <i>Echium lycopsis</i>,^[26] <i>Lithospermum erythrorhizon</i>.^[91, 99a]
19		isovalerylshikonin	roots: <i>Arnebia decumbens</i>,^[81] <i>Cynoglossum officinale</i>,^[36] <i>Echium vulgare</i>,^[36] <i>Lappula consanguinea</i>,^[36] <i>L. echinata</i>,^[36] <i>Lithospermum arvense</i>,^[76] <i>L. erythrorhizon</i>,^[36, 57, 82] <i>Macrotomia euchroma</i>.^[36] cell cultures: <i>Echium lycopsis</i>,^[26] <i>L. erythrorhizon</i>.^[91, 99a] biological effects: inhibition of topoisomerase-I (Section 5.2).
20		α -methylbutyrylshikonin	roots: <i>Cynoglossum officinale</i>,^[36] <i>Echium vulgare</i>,^[36] <i>Eritrichium incanum</i>,^[36] <i>E. sichotenze</i>,^[36] <i>Lappula consanguinea</i>,^[36] <i>L. echinata</i>,^[36] <i>L. erythrorhizon</i>,^[77, 82] <i>Mertensia maritima</i>.^[36] cell cultures: <i>L. erythrorhizon</i>.^[99a] biological activity: antimicrobial (Section 5.3).
21		β,β -dimethylacrylshikonin	roots: <i>Alkanna hirsutissima</i>,^[83] <i>Arnebia euchroma</i>,^[36, 49, 84] <i>A. guttata</i>,^[49, 84] <i>A. tibetiana</i>,^[53] <i>Cynoglossum officinale</i>,^[36] <i>Echium vulgare</i>,^[36] <i>Eritrichium incanum</i>,^[36] <i>E. sichotenze</i>,^[36] <i>Jatropha glandulifera</i>,^[56] <i>Lappula consanguinea</i>,^[36] <i>L. echinata</i>,^[36] Other <i>Echium</i> species,^[53] <i>L. erythrorhizon</i>,^[36, 80, 82, 84] <i>Macrotomia ugamensis</i>,^[53] <i>Mertensia maritima</i>,^[36] <i>Moltkiopsis ciliata</i>,^[85] <i>Onosma confertum</i>,^[78] <i>O. paniculatum</i>,^[84] <i>O. hookeri</i>,^[84] <i>O. zerizaminium</i>.^[53] cell cultures: <i>Arnebia euchroma</i>,^[107e] <i>Echium lycopsis</i>,^[26] <i>L. erythrorhizon</i>.^[91, 99a]
22		teracrylshikonin	roots: <i>Arnebia euchroma</i>,^[49] <i>A. guttata</i>,^[49] <i>Lithospermum erythrorhizon</i>,^[86] <i>L. euchromum</i>.^[86] cell cultures: <i>Arnebia euchroma</i>.^[107e] biological activity: antimicrobial (Section 5.3).
23		angelylshikonin	roots: <i>Alkanna hirsutissima</i> . ^[87, 88]
24		β -hydroxyisovalerylshikonin	roots: <i>Arnebia euchroma</i>,^[49] <i>A. guttata</i>,^[49, 50] <i>Lithospermum arvense</i>,^[76] <i>L. erythrorhizon</i>,^[57, 61, 77, 86] <i>L. euchromum</i>.^[86] cell cultures: <i>Arnebia euchroma</i>,^[107e] <i>Echium lycopsis</i>,^[26] <i>L. erythrorhizon</i>.^[91, 99a] biological activity: antimicrobial (Section 5.3).

Table 1. (Continued)

Compound	R	Name	Occurrence and biological properties
25		β -acetoxy-isovalerylshikonin	roots: <i>Macrotomia euchroma</i> . ^[89]
26		benzoylshikonin	roots: <i>Moltkiopsis ciliata</i> . ^[85]
27		unnamed	roots: <i>Lithospermum erythrorhizon</i> . ^[61]
28		arnebin-2	roots: <i>Arnebia nobilis</i> . ^[171b]
29		acetylarnebin-2	roots: <i>Onosma heterophylla</i> . ^[41]
30		arnebin-5	roots: <i>Arnebia nobilis</i> . ^[171b]
31		arnebin-6	roots: <i>Arnebia nobilis</i> . ^[171b]
32		deoxyalkannin, deoxyshikonin, or arnebin-7	roots: <i>Alkanna tinctoria</i> , ^[241a] <i>A. hirsutissima</i> , ^[88] <i>Arnebia decumbens</i> , ^[75] <i>A. euchroma</i> , ^[42–44, 49] <i>A. hispidissima</i> , ^[33] <i>A. guttata</i> , ^[42, 49, 50] <i>A. nobilis</i> , ^[90] <i>Cynoglossum officinale</i> , ^[36] <i>E. vulgare</i> , ^[36] <i>Eritrichium incanum</i> , ^[36] <i>E. sichotense</i> , ^[36] <i>Lappula consanguinea</i> , ^[36] <i>L. echinata</i> , ^[36] <i>Lithospermum erythrorhizon</i> , ^[36, 42, 77, 82] <i>Macrotomia cephalotes</i> , ^[35, 39] <i>M. euchroma</i> , ^[82] <i>Mertensia maritima</i> , ^[36] <i>Onosma confertum</i> , ^[78] <i>O. heterophylla</i> . ^[41] cell cultures: <i>Arnebia euchroma</i> , ^[107e,f] <i>Echium lycopsis</i> , ^[26] <i>L. erythrorhizon</i> , ^[91, 99a] <i>O. paniculatum</i> . ^[105g] biological effects: antidermatophytic and antibacterial (Section 5.3), antitumor (Section 5.2).
33		alkannan	roots: <i>Alkanna tinctoria</i> , ^[1] <i>Cynoglossum officinale</i> , ^[36] <i>Echium vulgare</i> , ^[36] <i>Eritrichium incanum</i> , ^[36] <i>E. sichotense</i> , ^[36] <i>Lappula consanguinea</i> , ^[36] <i>L. echinata</i> , ^[36] <i>Lithospermum erythrorhizon</i> , ^[36] <i>M. euchroma</i> , ^[36] <i>Mertensia maritima</i> . ^[36]
34		anhydroalkannin	roots: <i>Lithospermum erythrorhizon</i> , ^[61] <i>Macrotomia euchroma</i> . ^[82]
35		lithospermidin-A	roots: <i>Lithospermum erythrorhizon</i> . ^[77]
36		lithospermidin-B	roots: <i>Lithospermum erythrorhizon</i> . ^[77]

[a] 1) ester hydrolysis may occur during some extraction procedures, which leads to the isolation of alkannin (**1**) and shikonin (**2**) in addition to, or rather than, their ester derivatives; 2) in many cases, no attempt was made to assign the absolute stereochemistry of each derivative, so alleged alkannin derivatives may be shikonin derivatives, or vice versa, or even racemates. Recent circular dichroism (CD)^[26, 166f, 172] and chiral HPLC^[27] experiments have shown that *Arnebia euchroma* contains mainly alkannin derivatives, while *Onosma confertum* contains mainly shikonin derivatives. However, the stereochemistry may vary between ester derivatives from the same plant, and even between plants from different locations.^[26] Differences may be noted between extracts from plants and those from cell cultures.^[26]

Scheme 1. Biosynthesis of shikonin (**2**).

and geranyl pyrophosphate (GPP, **54**). These components are unified in a reaction mediated by the enzyme PHB geranyl-transferase to yield *m*-geranylPHB (**55**). In general, far more is known about the early stages of the biosynthetic route to **2** than the later ones.

GPP (**54**) is derived from the well-defined isoprenoid pathway^[110] that starts from acetyl-CoA (**49**), and proceeds via mevalonic acid (**50**), while PHB (**45**) is formed from phenylpropanoid metabolites. L-Phenylalanine (**38**), originally derived from shikimic acid (**37**), is converted into cinnamic acid (**39**) by the enzyme phenylalanine ammonia lyase (PAL), with the transformation to coumaric acid (**40**) then being mediated by cinnamate 4-hydroxylase (C4H). There is some dispute as to whether the biosynthetic conversion of coumaric acid (**40**)

into **45** occurs by the β -oxidative pathway^[111] or the retro-aldol pathway.^[112] This question has implications beyond the biosynthesis of shikonin since PHB (**45**) is a biosynthetic intermediate for many metabolites, such as the ubiquinones (**62**)^[113] and vitamin E (**63**)^[114] (Figure 8).

A large volume of evidence has been gathered in favor of this biosynthetic route. Feeding experiments have been used to show that shikimic acid (**37**), L-phenylalanine (**38**), cinnamic acid (**39**), PHB (**45**), *m*-geranylPHB (**55**), *m*-geranyllhydroquinone (**56**), and mevalonic acid (**50**) are all intermediates in the biosynthetic route.^[115] Furthermore, PHB (**45**), *m*-geranylPHB (**55**), and *m*-geranyllhydroquinone (**56**) have been isolated from shikonin-free cell cultures of *LE* grown in LS liquid medium (in which shikonin biosynthesis is

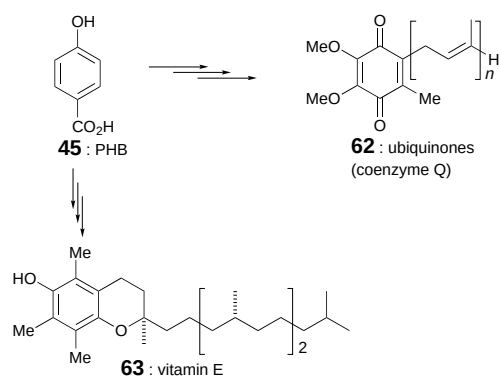


Figure 8. 4-Hydroxybenzoic acid (PHB, **45**) as a versatile biosynthetic intermediate.

inhibited).^[115b] PHB (**45**) actually accumulates in the vacuoles of shikonin-free cells as its β -D-glucoside PHBOG (**48**),^[116] which is speculated to be a defense mechanism since **45** is known to be toxic to the cells.^[117] Intermediates up to *m*-geranylPHB (**55**) have been detected from these shikonin-free cells, from which it was suggested that its conversion into *m*-geranylhydroquinone (**56**) is repressed by ammonium ions.^[118] Once transferred to the production medium M9, which induces shikonin biosynthesis, the amount of PHBOG (**48**) decreased rapidly, which thus implicated PHB (**45**) or PHBOG (**48**) as intermediates.^[116] It has been shown more recently that deoxyshikonin (**32**) is in fact a biosynthetic precursor to shikonin (**2**).^[115c] This provides the only direct evidence for any of the steps that follow the production of *m*-geranylhydroquinone (**56**). The other steps from **56** to shikonin (**2**) are speculative only.

Indirect evidence in favor of the biosynthetic route has been gained by the isolation of structurally related secondary metabolites from various species of *Boraginaceae*, both from plants and cell cultures. Evidence in favor of intermediate **61** comes from the isolation of the furan and dihydrofuran products, shikonofurans (**57**),^[119] echinofuran (**58**),^[120] and dihydroechinofuran (**59**).^[121] Presumably, the cyclic arylether arnebinol (**60**) is derived from an allylic hydroxylation at the *trans* terminal methyl group of **59** prior to macroetherification.^[122]

Several of the enzymes involved in shikonin biosynthesis have been identified and their location within the cell defined. PHB geranyltransferase is the enzyme that is repressed upon exposure of *LE* cell cultures to white light,^[94c] which thus halts shikonin production. It has been isolated from cell-free extracts of *LE* and its properties were investigated.^[123] Similar enzymes have been identified and characterized in ubiquinone biosynthesis,^[114] and the utility of a prenyltransferase, formed by *E. coli* overproduction, in organic synthesis has been demonstrated.^[124] It has also been suggested that the biosynthesis may be inhibited by light through the photo-degradation of flavin mononucleotide (FMN), a cofactor that may be required for one or more of the oxidation processes that lead to shikonin. In support of this, the FMN photo-degradation product lumiflavin was shown to inhibit shikonin biosynthesis, most likely through disruption of PHB geranyltransferase.^[125]

PHB geranyltransferase has been localized to a microsomal fraction of *LE* cells that contain specific vesicle membranes derived from the endoplasmic reticulum.^[126] PHB glucosyltransferase, which catalyses the conversion of PHB (**45**) into PHBOG (**48**), has also been partially purified and its characteristics assessed.^[127] It has been localized to the cytosol,^[128] as has the glucosidase responsible for the reverse transformation, and the enzyme responsible for GPP (**54**) production, GPP synthase.^[129] Thus, it appears that PHBOG (**48**) is stored in the vacuoles prior to triggering shikonin biosynthesis, possibly to protect it from the glucosidase.^[128] Upon transfer of the cells to the production medium, this store of PHBOG (**48**) may be utilized for shikonin biosynthesis. It has been suggested that all steps subsequent to, and including the coupling of PHB (**45**) and GPP (**54**), take place in a special vesicle or biosynthetic site, which facilitates not only the orderly biosynthetic reactions, but also the transport and secretion of the secondary metabolite.^[126]

Publications concerning shikonin biosynthesis continue to appear at a steady rate, most notably from the laboratories of Mamoru Tabata at Kyoto University, Japan. Studies in this area are presumably on-going and we wait with anticipation for more detailed information on the later stages of the biosynthetic route.

4. Chemistry of Alkannin and Shikonin

Before discussing the chemistry of alkannin and shikonin, it will be instructive to consider first the chemical properties of the parent naphthoquinone, naphthazarin (**64**).

4.1. Chemistry of Naphthazarin

Naphthazarin (commonly considered as 5,8-dihydroxy-1,4-naphthoquinone, **64a**; Figure 9) has been used historically as a rather expensive purple dye. It occurs naturally in the wood bark of *Lomatia obliqua*^[130] and in walnut husks of *Juglans mandschurica maxim* var. *Sieboldianna* Makino.^[131] It can be prepared directly either by heating 1,5-dinitronaphthalene with sulfur and fuming sulfuric acid,^[132] or by double Friedel–Crafts acylation of either hydroquinone,^[133] or 1,4-dimethoxybenzene (**65**),^[134] with maleic anhydride in fused AlCl_3 – NaCl . Yields for both processes are generally low. An indirect, three-step procedure with dichloromaleic anhydride is usually employed today to produce larger quantities of naphthazarin for laboratory use (Scheme 2, Table 2).^[135]

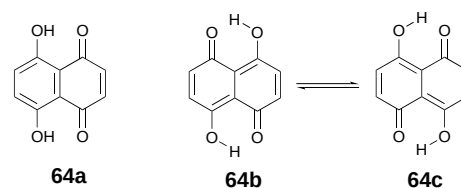


Figure 9. Structures of naphthazarin (**64**).

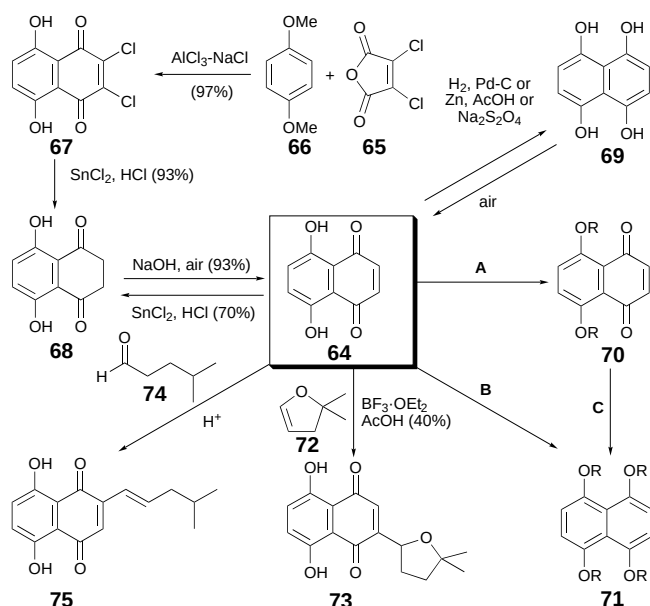
Scheme 2. Chemistry of naphthazarin (**64**).

Table 2. Reaction conditions for pathways A–C in Scheme 2.

R	A	B	C
Me	MeOTs, K ₂ CO ₃ (44 %) ^[147–148]	Na ₂ S ₂ O ₄ , NaOH MeI (44 %) ^[149] or 1) H ₂ Pd-C, DMF 2) NaH, Me ₂ SO ₄ , DMF (72 %) ^[150]	Na ₂ S ₂ O ₄ , NaOH MeI (48 %) ^[149]
Ac	Ac ₂ O, NaOAc ^[133]	Ac ₂ O, NaOAc, Zn ^[133]	Ac ₂ O, NaOAc Zn ^[133]
TMS	MTMSTFA (100 %) ^[151a]	MTMSTFA, NH ₄ I (100 %) ^[151b]	–
TBS	MTBSTFA (94 %) ^[152]	MTBSTFA, NH ₄ I (89 %) ^[152]	–

The symmetry of naphthazarin (**64**) has been a matter of some debate.^[136] The most important aspect from the synthetic viewpoint is that rapid “tautomerization” occurs, which leads to a structure that is essentially centrosymmetric as evidenced from its ¹H NMR spectrum, which exhibits only a single signal at $\delta_{\text{H}} = 7.13$, midway between the signals expected for the aromatic (ca. $\delta_{\text{H}} = 7.25$) and quinoid protons (ca. $\delta_{\text{H}} = 6.95$).^[137] In fact, the interconversion of naphthazarin structures may be more accurately described as a tunneling process, since it has not been possible to split the aromatic and quinonid signals below a coalescence temperature. Furthermore, the spectroscopic properties of naphthazarin (**64**), including its intense color in solution, appear to be more consistent with a 1,5-quinoid structures (**64b, c**; Figure 9) than the more commonly depicted 1,4-quinoid structure (**64a**).^[138]

Naphthazarin (**64**) has been described in the crystalline state as deep brown–red crystals with a green–golden luster and as deep green crystals with a metallic reflex.^[139] It is readily soluble in organic solvents such as benzene and dichloromethane to form blood-red solutions. Upon treatment of these solutions with strong alkali, the quinone is extracted into the aqueous phase as its deep “cornflower

blue” dianion. In fact, this property has allowed the use of naphthazarin (**64**) as a pH indicator.^[139] Upon immediate acidification of the blue solution, naphthazarin can be recovered, while prolonged exposure to atmospheric oxygen prior to acidification causes oxidation of the aromatic nucleus to give naphthopurpurin (2,5,8-trihydroxy-1,4-naphthoquinone).^[132]

Naphthazarin (**64**) may be oxidized to the naphthodiquinone (**124**) (see Scheme 12) upon treatment with Pb(OAc)₄,^[133] or more effectively, phenyliodonium bis(trifluoroacetate).^[140] Highly reactive diquinone (**124**) has been used for the synthesis of cage compounds,^[140] and in a synthesis of cycloshikonin (Section 4.3.3, Scheme 12).^[141]

Reduction of naphthazarin (**64**) may be effected with a number of reagents. Use of catalytic hydrogenation, sodium dithionite, or zinc, all give rise to the highly air-sensitive 1,4,5,8-tetrahydroxynaphthalene (**69**).^[139] In particular, alkaline solutions of **69** are rapidly oxidized to the naphthazarin dianion upon exposure to atmospheric oxygen.^[135] Reduction of **64** with tin(II) chloride in hydrochloric acid affords the more air-stable crystalline diketo tautomer of leuconaphthazarin (**68**).^[142–143] Reduction of halogenated naphthazarins by this method occurs with concomitant dehalogenation and formation of **68**. This feature has allowed the more efficient large-scale preparation of naphthazarin (**64**) by a three-step sequence. Friedel–Crafts acylation of 1,4-dimethoxybenzene (**66**) and dichloromaleic anhydride (**65**) proceeds, in contrast to the reaction with maleic anhydride, in very high yield.^[144] Tin(II) chloride reduction of 2,3-dichloronaphthazarin (**67**),^[142] followed by air oxidation of an alkaline solution of leuconaphthazarin (**68**), affords naphthazarin (**64**) in very good overall yield.^[135]

Methods for the bis-protection, and reductive tetra-protection of naphthazarin (**64**) are summarized in Scheme 2. Etherification of the phenolic groups is rather difficult, presumably due to the stability of the naphthazarin dianion.

Naphthazarin (**64**) reacts with only a limited range of electrophiles. The scope of these reactions is probably limited by the tendency of **64** to bind Lewis acids. Satisfactory yields of alkylated products are obtained upon reaction with oxonium ions derived from cyclic enolethers, as exemplified by the synthesis of cycloshikonin (**73**) (Scheme 2).^[145] During unsuccessful attempts to synthesize shikonin (**2**), Brockmann demonstrated that condensation reactions of aldehydes with **64** under acidic conditions provided complex mixtures of products, which included alkene derivatives such as **75** (Scheme 2).^[1]

The adjacent keto and phenolic oxygen atoms make naphthazarins ideal substrates for the formation of metal chelates.^[136, 146] These have been studied in some detail with regards to a number of specific properties such as magnetic exchange interactions between paramagnetic ions.^[136, 146] See also Section 5.2.

Controlled nucleophilic addition reactions with naphthazarin (**64**) have not yet been achieved. Complex mixtures generally result, including both 1,2- and 1,4-addition products.^[153] One of the only useful compounds in this respect is the bisulfite addition compound Alizarin Black S, which was formerly used in printing.^[142] Recently, an efficient procedure

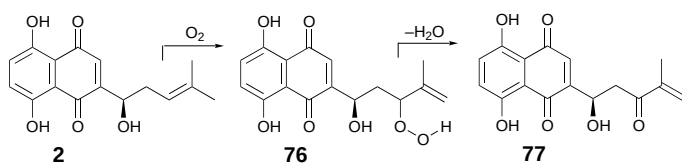
for formal 1,4-addition has been reported via the leuco form of the respective bromo derivative.^[153]

Cycloaddition reactions are generally the most useful and successful reactions of naphthazarin (**64**). In particular, Diels–Alder reactions with **64** have found extensive use in the construction of anthracycline antibiotics. This aspect has been dealt with extensively elsewhere^[154] and will not be discussed here.

4.2. Reactivity of Alkannin and Shikonin

In general, the chemistry of alkannin (**1**) and shikonin (**2**) has many similarities to the chemistry of naphthazarin (**64**). The major tautomeric form of the quinone nucleus substituted by an electron-donating group is that depicted in **1** and **2**.^[137] The hydroxyl-containing side-chain introduces some interesting properties that render **1**, **2**, and their derivatives far more sensitive than **64**.

In acidic conditions (either Brønsted or Lewis), cyclization of the side chain to the tetrahydrofuran isomer **73** (cycloshikonin) occurs readily.^[1, 2, 155, 156] Quinones **1** and **2** are also susceptible to photooxidation by exposure to air and light.^[157] The major photolytic product **77** is thought to arise through the mechanism indicated in Scheme 3. Polymerization of **1** and **2** occurs readily by the action of acids, bases, heat, and light.^[158, 159] Compounds **1** and **2** have also been shown to undergo racemization under strongly acidic conditions.^[1]

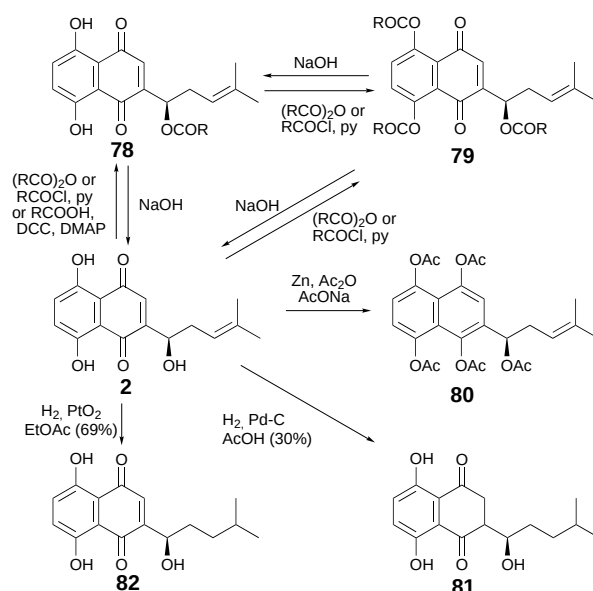


Scheme 3. Photooxidation of shikonin (**2**).^[157]

The aliphatic hydroxyl group in shikonin may be selectively acylated in the presence of the phenolic hydroxyl groups by standard esterification methods.^[160] Conversely, acylshikonin derivatives **78** can be produced through the selective hydrolysis of triacylated shikonin derivatives **79** (Scheme 4).^[161] All other protection-deprotection chemistry resembles that of naphthazarin (**64**). Hydrogenation of **2** with Pd catalysis causes reduction of both the quinone and the alkene groups to afford **81**, while use of catalytic PtO₂ allows for selective alkene reduction to dihydroshikonin **82** (Scheme 4).^[156a] The quinone may be selectively reduced with Zn or Na₂S₂O₄^[139] to provide a highly air-sensitive tetrahydroxynaphthalene derivative, which has been trapped as the pentaacetyl derivative **80** (Scheme 4).^[162]

The acid/base color chemistry of **1** and **2** (Figure 10) resembles that of naphthazarin (**64**).

The only examples of ring functionalization of **1**, **2**, and its derivatives were undertaken by Shukla and co-workers, who performed a double Mannich-type addition to afford **83**, and a reaction with diazomethane, which proceeds by a sequence of cycloaddition followed by N-methylation, to provide **85**



Scheme 4. Selected reactions of shikonin (**2**).

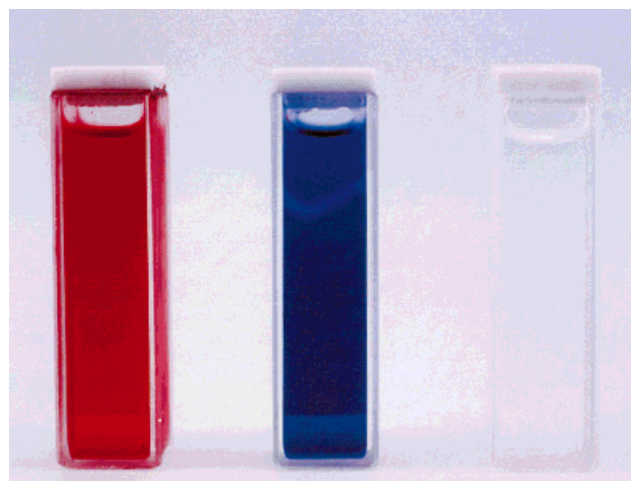
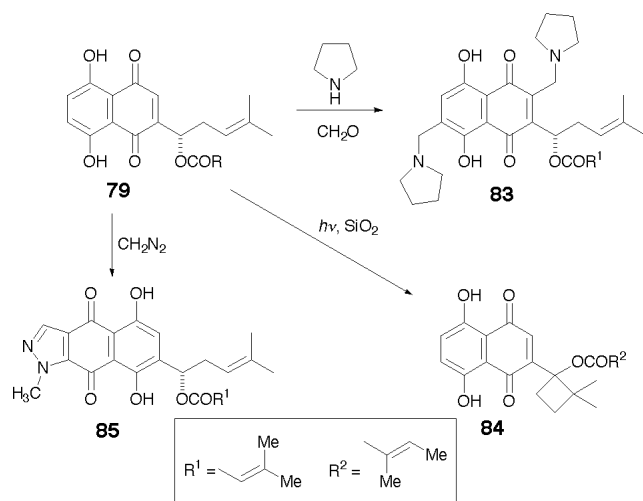


Figure 10. Solutions of alkannin (**1**) in CH₂Cl₂ (red) and in 1N aqueous NaOH (cornflower blue) as contrasted with a solution of pentaacetyl derivative **80** in CH₂Cl₂ (colorless, barely visible).

(Scheme 5).^[163] An interesting rearrangement to the cyclobutane derivative **84** has been observed during the isolation of certain alkannin esters.^[87]

A large number of physical techniques have been applied for the analysis and study of **1**, **2**, and their derivatives. Chromatographic techniques used include TLC,^[87, 164] densitometry,^[165] gel permeation,^[159] and HPLC.^[27, 42, 43, 49, 50, 166] The properties studied include UV/Vis,^[33, 52, 53, 77, 166c, 167, 168] IR,^[44, 50, 52, 53, 77, 167] ¹H NMR,^[33, 44, 50, 77, 167] ¹³C NMR,^[169a, 170] mass spectrometry,^[38, 40, 44, 89, 166c,h, 171a] circular dichroism,^[26a, 166f, 170, 172, 173] and indirect atomic absorption.^[174] Polarography,^[175] voltammetry,^[176] differential pulse voltammetry,^[177] and even a photoacoustic technique for transdermal adsorption measurements,^[178] have been utilized for qualitative and quantitative determinations of **1**, **2**, and their derivatives.

Scheme 5. Chemistry of alkannin ester **79**.^[87, 163]

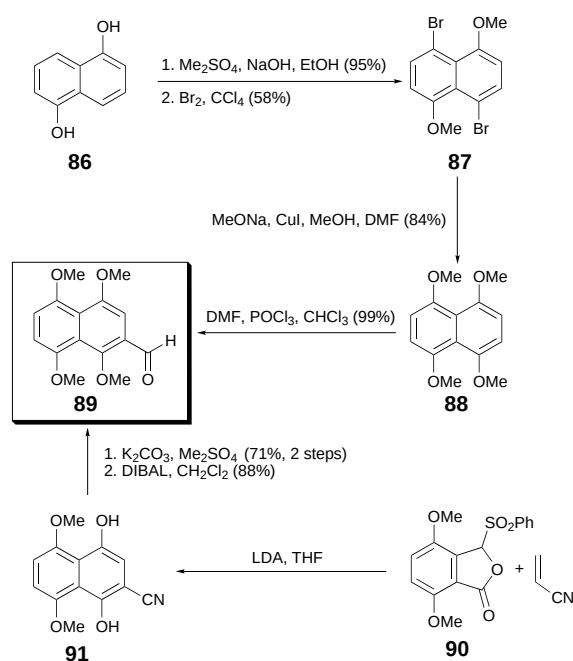
4.3. Total Syntheses of Alkannin and Shikonin

4.3.1. Introduction

There are several problems that must be overcome in order to accomplish an efficient synthesis of alkannin (**1**) and/or shikonin (**2**). As mentioned above, the natural product is sensitive to Brønsted and Lewis acids, light, and oxygen. There are further practical difficulties, such as the strong affinity of naphthazarins for both silica and alumina, which makes chromatographic purification difficult. Clearly, the most general approach to substituted naphthazarins, the Friedel–Crafts acylation of hydroquinones with maleic anhydride derivatives (Section 4.1) is not applicable here. Naturally, an ideal synthesis of **1** and **2** would be one in which protection of the naphthazarin system was not required. So far, this has not been realized. Perhaps the most challenging aspect of this synthetic problem, however, is the development of an effective protecting system for the naphthoquinone core. The sensitivity of the natural product to a variety of reagents and conditions besides acids, light, and oxygen (for example, with reducing agents and nucleophiles) severely limits the options available for the final deprotection steps of the synthesis.

Most of the successful syntheses of **1** and **2** have been achieved through the use of 1,4,5,8-tetramethoxynaphthalene (**88**, Scheme 6) and its derivatives, as a protected form of the naphthazarin core. While **88** can be prepared directly from naphthazarin (**64**) by reductive methylation (Scheme 2), a more economical approach, which avoids the use of this costly material, has been devised by Terada and co-workers.^[149] Thus, the cheap starting material 1,5-dihydroxynaphthalene (**86**, Scheme 6) was O-methylated before bromination, and subsequent copper(I)-assisted methoxylation afforded **88**.^[149]

Formylation of 1,4,5,8-Tetramethoxynaphthalene (**88**) by the Vilsmeier method produces **89** (Scheme 6) in almost quantitative yield.^[149] This intermediate is common to most of the syntheses of **1** and **2** reported thus far. An alternative approach to **89** has recently been described by the Coula-douros group (Scheme 6).^[179] This method employs an annu-

Scheme 6. Two syntheses of key intermediate **89**.^[149, 179]

lation reaction of the phthalide anion derived from **90** with acrylonitrile to afford **91**.^[180] Subsequent O-methylation and DIBAL reduction provided **89**. This method is notable for the high overall yield obtained and the possibility that hydroquinone **91** may be used to produce a naphthalene intermediate with orthogonal protection of the two aromatic rings. This may be of assistance for improving the efficiency of its subsequent demasking to a naphthazarin (see below).

Methods for the release of naphthazarins from tetramethoxynaphthalene derivatives have been thoroughly investigated by Tanoue and Terada.^[181] They found that boron tribromide, one of the standard reagents for aromatic ether cleavage, successfully converts tetramethoxynaphthalene (**88**) into naphthazarin (**64**) in 68 % yield after air oxidation of the originally produced tetrahydroxynaphthalene.^[149] This method is, however, unsuitable for the preparation of 2-substituted derivatives of **64**, since polymeric materials are formed. Instead, a two-step procedure was developed (Scheme 7, Table 3). Initial oxidation with ceric ammonium nitrate (CAN) affords two regioisomeric products, the selectivity being dependent upon the nature of the substituent R. For

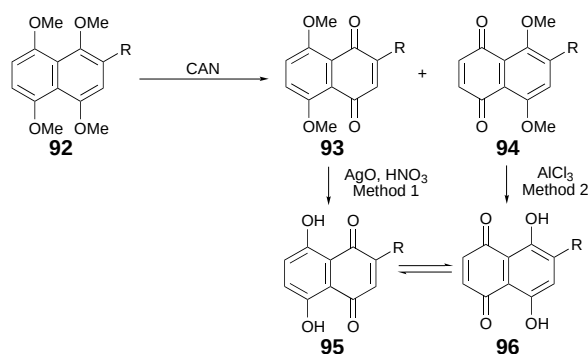
Scheme 7. Deprotection of tetramethoxynaphthalene derivatives.^[181]

Table 3. Yields for the reactions shown in Scheme 7.

R	CAN oxidation		Demethylation method yield [%]	
	93 [%]	94 [%]		
a H	70	–	–	–
b CH ₂ OH	75	13	1	53
c CH(OH)CH ₃	61	13	1	52
d CH(OH)(CH ₂) ₃ CH ₃	42	16	1	22
e CH(OH)(CH ₂) ₃ CH(CH ₃) ₂	52	17	1	22
f CH(OH)(CH ₂) ₃ C(CH ₃) ₂ OH	70	15	1	28
g CH(OH)(CH ₂) ₃ COCH ₃	33	33	1	27
h COCH ₃	3	77	2	71
i CHO	0	85	2	43

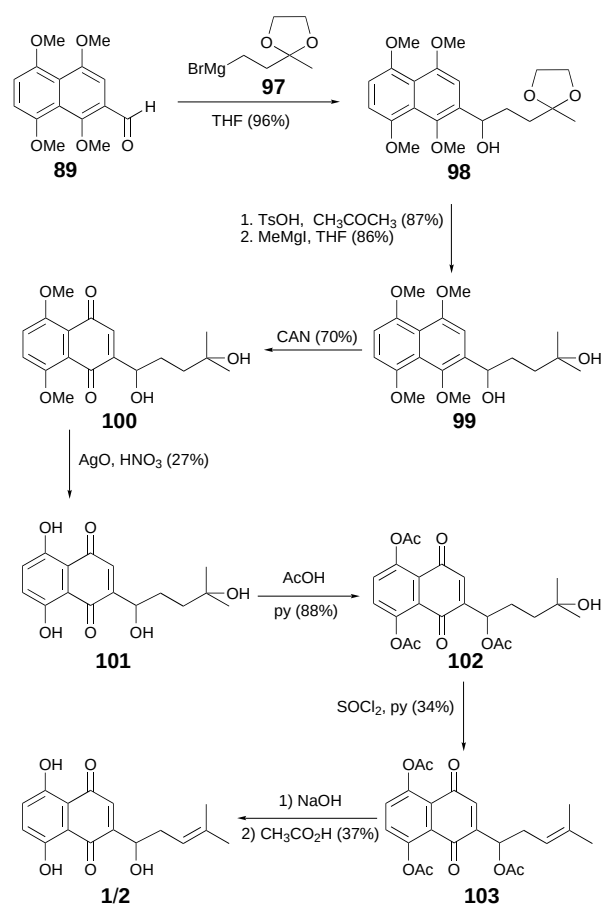
electron-donating groups such as hydroxyalkyl (Table 3, entries **b–g**), the substituted ring is preferentially oxidized, while electron-withdrawing groups such as acetyl and formyl, favor isomer **94** as the major product. In the former case, regioselectivity is usually modest. Methoxyquinones of form **93** can be further demethylated by treatment with AgO/HNO₃, although generally in low yield. The regioisomeric quinones **94** failed to react under these conditions, and required the action of AlCl₃. These latter conditions would be unsuitable in a synthesis of **1** and **2**. Tautomerization between **95** and **96** occurs readily, with **95** being favored when R is electron donating, and **96** the major isomer when R is electron withdrawing.^[137]

Despite being far from ideal, tetramethoxynaphthalene derivatives were, until recently, the only protected form of naphthazarins suitable for the synthesis of **1** and **2**.

4.3.2. Syntheses of Shikalkin (1/2)

After Terada and co-workers had developed a method for the conversion of tetramethoxynaphthalenes into naphthazarins they were able to complete the first synthesis of shikalkin **1/2** in 1983 (Scheme 8).^[182] Addition of the Grignard reagent **97** to the formyl derivative **89** produced intermediate **98** in good yield. Ketal hydrolysis and subsequent addition of methylmagnesium iodide afforded diol **99**. At this stage, these researchers opted to release the naphthoquinone from its protected form by the two-step CAN/AgO/HNO₃ sequence, as described previously. In this case, the initial CAN oxidation proceeded with reasonably high selectivity in favor of the desired isomer **100**, and in moderate yield, although the AgO/HNO₃ demethylation, as ever, gave only a poor yield of the naphthoquinone **101**. Treatment of **101** with acetic anhydride in pyridine selectively produced triacetate **102**. This allowed subsequent elimination with thionyl chloride and pyridine to afford **103**, the low yield being a consequence, in part, of the production of significant amounts of the terminal alkene regioisomer. The synthesis was completed by alkaline hydrolysis of the acetate groups to yield shikalkin (**1/2**). This research group also used this method for the preparation of isomers of **1**.^[183]

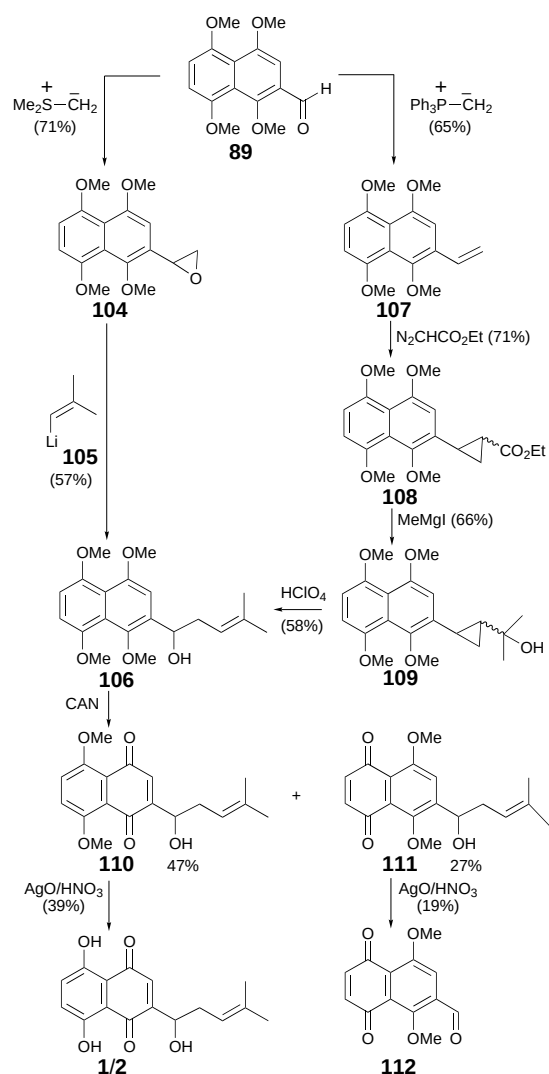
Researchers from Russia have reported two approaches to **1/2** from the formyl derivative **89** (Scheme 9). Conversion of aldehyde **89** into epoxide **104** was achieved in good yield with standard sulfur ylid methodology.^[184] The epoxide was



Scheme 8. The first synthesis of shikalkin (**1/2**) by Terada and co-workers.^[149, 182]

opened by treatment with the organolithium reagent **105** to afford **106**. This intermediate was common to their alternative approach, which utilized a Wittig olefination, a cyclopropanation, and a double Grignard addition to form the key intermediates **109**.^[185] The transformation into **106** was accomplished by an intriguing acid-catalyzed rearrangement. Conversion of **106**, obtained from both routes, into **1/2** was effected by the usual two-step sequence. In this case, the regioselectivity of the initial CAN oxidation was negligible, and once again the second demethylation reaction was low-yielding. Attempts to convert the undesired regioisomer **111** into **1/2** by AgO/HNO₃ treatment led, rather curiously, to the aldehyde product **112**, and not to **1/2**.

More recently, Torii and co-workers have reported a synthesis of **1/2** also starting from formyl derivative **89** (Scheme 10).^[186] The initial step is a McMurry-type coupling between **89** and the unsaturated aldehyde **113** mediated by a low-valent vanadium species.^[187] Closure of diols **114** to the cyclic carbonates **115** (presumably a mixture of diastereoisomers) set the stage for a palladium-catalyzed allylic reduction. Unfortunately, this reaction afforded a significant amount of a regioisomeric alkene (ca. 28%), and a rather elaborate reaction sequence was required before acetate **116** could be obtained in a pure form. These workers developed an alternative method for the deprotection of the tetramethoxynaphthalene core, which employed an anodic oxidation.

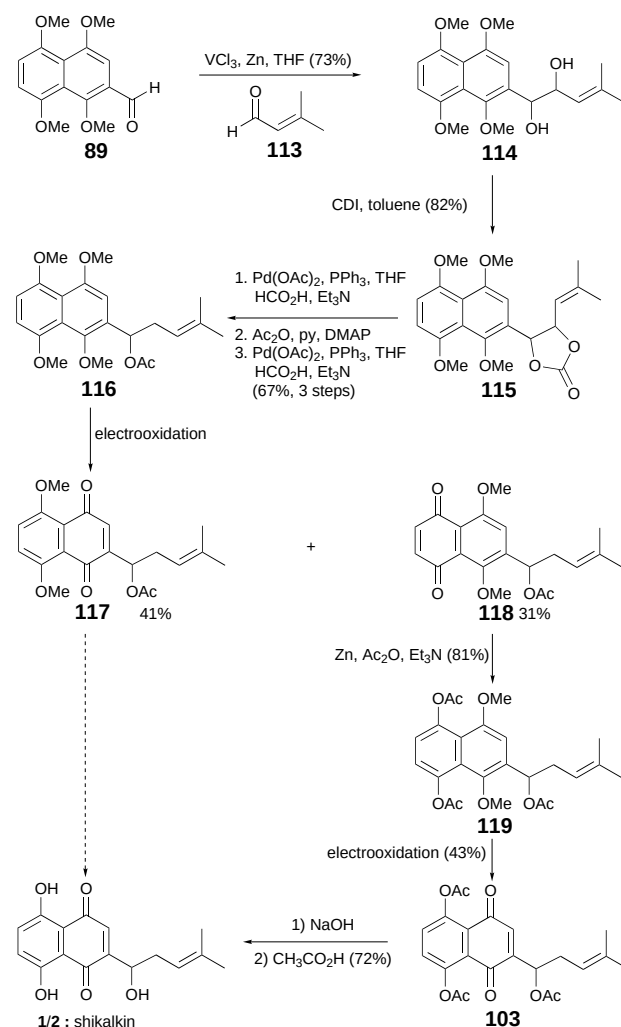


Scheme 9. Further syntheses of shikalkin (**1/2**) from the formyl derivative **89**.^[184, 185]

Despite significant experimentation, however, they were unable to improve the regioselectivity of the initial oxidative demethylation. In fact, the desired isomer **118** (which would be the unwanted one for a AgO/HNO₃ demethylation) was the minor product of this reaction. In order to achieve the second demethylation, a reductive acetylation to provide **119** was required, whereupon selective oxidation of the methoxylated ring could be achieved by a second anodic oxidation. Alkaline hydrolysis of **103** completed the synthesis. These researchers apparently made no attempt to demethylate their unwanted regioisomer **117**, although its transformation into acetylshikonin (**15**), and then to **1/2**, should be possible by AgO/HNO₃ treatment. Thus, the anodic oxidation method is complementary to the previously described two-step demethylation procedure.^[181]

4.3.3. Approaches via Cycloshikonin

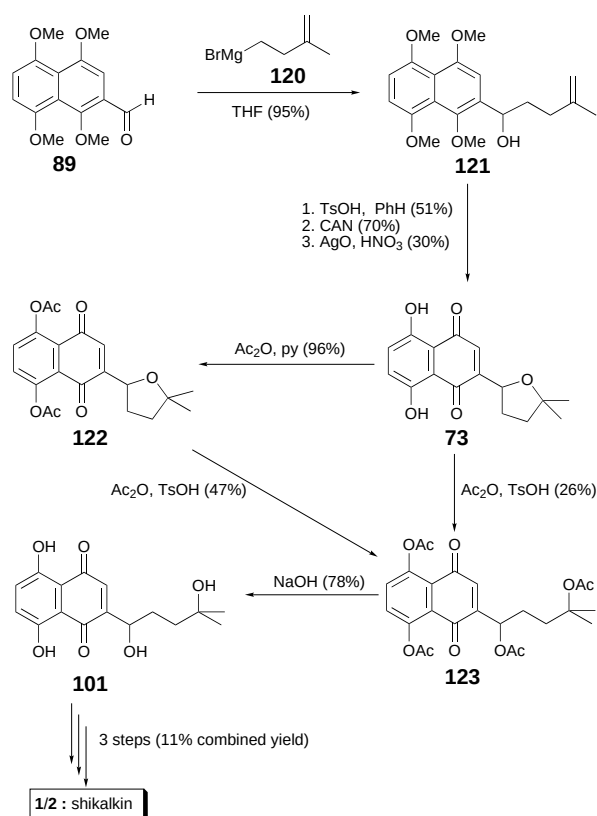
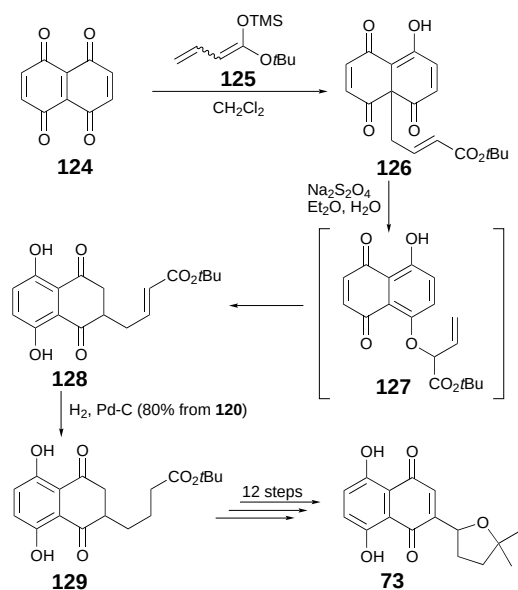
Terada and co-workers have also shown that cycloshikonin (**73**) may be converted into shikalkin (**1/2**) itself (Scheme 11).^[188] Thus, a synthesis of **73** constitutes a formal



Scheme 10. The approach of Torii and co-workers for a total synthesis of shikalkin (**1/2**).^[186]

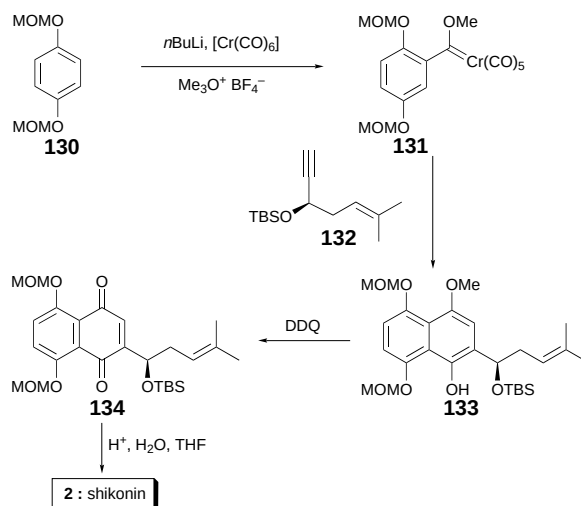
synthesis of **1/2**. The key step is the opening of the tetrahydrofuran ring to **123** with *p*-toluenesulfonic acid in the presence of acetic anhydride, starting either from **73** itself or more efficiently from the diacetate **122**. Alkaline hydrolysis of **123** provided **101**, which was an intermediate in their earlier synthesis of shikalkin.^[149, 182] The initial approach to cycloshikonin (**73**) developed by this group (Scheme 11), in which the key steps are addition of the Grignard reagent **120**, followed by acid-catalyzed ring closure,^[188] has been superseded by the report of the direct synthesis of **73** from naphthazarin (**64**) (Scheme 2).^[145]

An interesting, although rather long, route to cycloshikonin (**73**) has recently been reported by Aso and Kanematsu (Scheme 12).^[141] The γ -addition of silyl keteneacetal **125** to the highly reactive naphthodiquinone **124** afforded **126**, which underwent two consecutive reductive [3,3] sigmatropic rearrangements to produce, after hydrogenolysis, leuconaphthazarin (**129**) in 80% overall yield. Conversion into cycloshikonin (**73**) was then achieved in a rather inefficient 12-step linear sequence. Although impractical for the synthesis of shikonin (**1**) and cycloshikonin (**73**), this route may be of some utility for the synthesis of analogues.


 Scheme 11. Terada's approach to shikalkin (**1/2**) via cycloshikonin (**73**).^[188]

 Scheme 12. Kanematsu's synthesis of cycloshikonin (**73**).^[141]

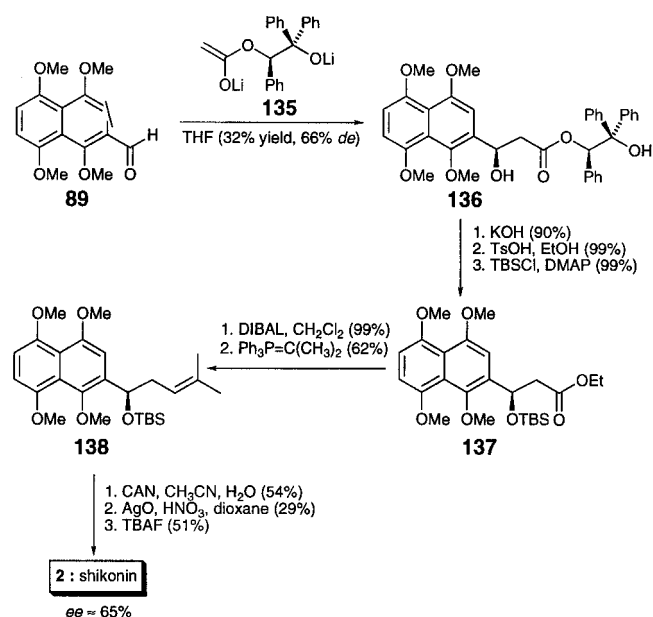
4.3.4. Asymmetric Approaches

The first asymmetric synthesis of **2** was disclosed in a patent,^[189] and involves an elegant application of the Dötz annulation reaction (Scheme 13).^[190] Thus, MOM-protected hydroquinone **130** was converted into the chromium carbene intermediate **131**, by the standard method, after *ortho* lithiation of **130**. Thermolysis with enantiomerically pure alkyne **132** provided the protected naphthazarin **133**. The


 Scheme 13. A stereoselective synthesis of shikonin (**2**) by the Dötz annulation reaction.^[189]

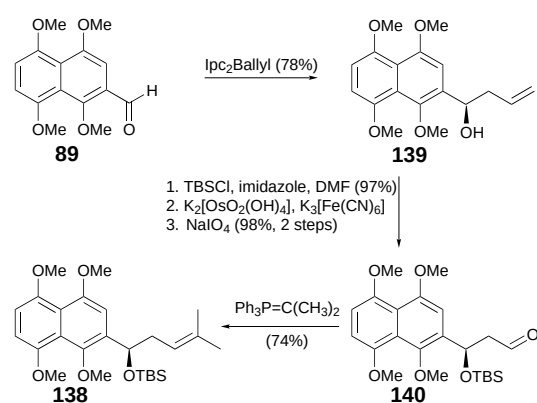
phenolic group in **133** allowed selective oxidation of the more functionalized ring of the naphthalene to produce quinone **134**, which was then converted into shikonin (**2**) by acid hydrolysis. Unfortunately, the authors failed to quote yields for the synthesis, so it is not possible to comment on the efficiency of their route. It should be noted, however, that the published synthesis of alkyne **132** involves a five-step linear sequence from commercially available starting materials and uses a Sharpless asymmetric epoxidation to secure the required stereochemistry.^[191]

The asymmetric approach to **1** and **2** taken by Braun and Bauer was to perform an asymmetric aldol addition onto the formyl derivative **89**,^[192] by using their asymmetric acetate enolate equivalents derived from (*R*)- and (*S*)-(2-hydroxy-1,2,2-triphenylethyl) acetate (Scheme 14).^[193] While these reagents generally give very high stereocontrol, the selectivity


 Scheme 14. Braun's synthesis of shikonin (**2**) by an asymmetric aldol reaction.^[192]

in this case was rather modest (ca. 5:1 after purification). An early transition state is usually invoked to explain the asymmetric induction obtained with these reagents, but the electron-rich nature of aldehyde **89** may disfavor this scenario, and lead to the poor selectivity. Conversion of the initial aldol adduct **136** into **138** was achieved by standard methods. These workers considered it prudent to protect the aliphatic hydroxyl group in an attempt to improve the efficiency of the final deprotection steps. However, no improvement in yield for the demethylation sequence was observed. The enantiomeric excess (ee) of shikonin (**2**) produced by this route was determined to be approximately 65% by CD measurements.

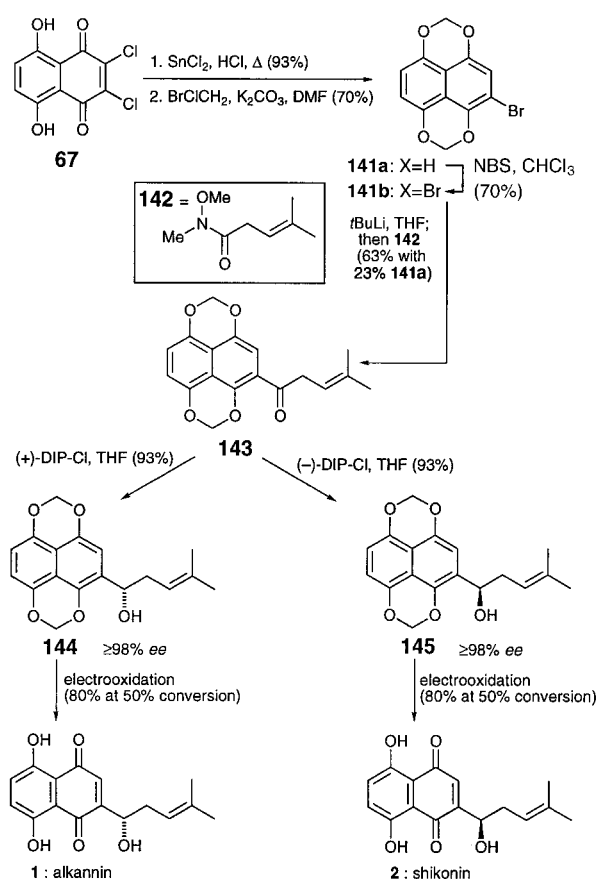
The Coulaudouros group has recently achieved a synthesis of alkannin intermediate **138**,^[179] by an asymmetric allylation reaction with allyldiisopinocampheylborane (Scheme 15).^[194] Thus, alcohol **139** was produced in 82% ee (based on an 80% ee of the chiral reagent). Construction of the side-chain was completed after hydroxyl protection by a high-yielding three-step sequence.



Scheme 15. Improved approach to **138** by asymmetric allylation (Coulaudouros and co-workers).^[179]

Recently, the Nicolaou group reported highly efficient total syntheses of both alkannin (**1**) and shikonin (**2**) (Scheme 16).^[195] This strategy was designed with three considerations in mind: 1) to use a commercially viable source of the naphthazarin core; 2) to produce a late-stage intermediate from which it would be possible to form both alkannin (**1**) and shikonin (**2**) in high ee; and 3) to devise a novel protecting system for the naphthazarin core, which could be cleaved at the end in one step, and under mild conditions.

The first aim was achieved by using 2,3-dichloronaphthazarin (**67**) as the readily available starting material (Section 4.1).^[144] It was reasoned that ketone **143** should be an ideal intermediate to access both enantiomeric series, since arylalkyl ketones of this type are generally considered to be excellent substrates for many asymmetric reducing agents.^[196] Furthermore, it was anticipated that bis(methyleneacetal) derivatives such as **A** (Figure 11) would provide a solution to the deprotection problem. In this case, oxidative treatment may still produce two regioisomeric intermediates **B** and **C**, but spontaneous elimination of formaldehyde should afford



Scheme 16. Nicolaou's stereocontrolled total synthesis of alkannin (**1**) and shikonin (**2**).^[195]

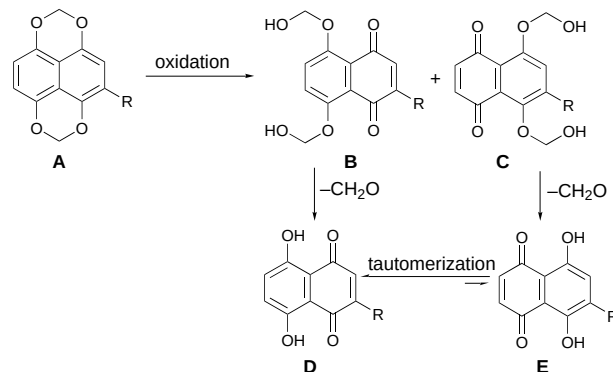


Figure 11. Projected deprotection of bis(methyleneacetal) derivatives, and preferential formation of naphthazarin isomer **D** (Nicolaou and Hepworth).^[195]

the two naphthazarin isomers **D** and **E**. These isomers should rapidly tautomerize in favor of the desired form **D** by virtue of the stabilizing effect of the electron-donating alkyl group.^[137]

The plans came to fruition in a concise and highly efficient synthesis. Thus, bromine-substituted methyleneacetal **141b** (Scheme 16) was prepared from 2,3-dichloronaphthazarin (**67**) by tin(II) chloride reduction,^[142] O-alkylation with bromochloromethane,^[197] and subsequent bromination with NBS. Halogen–metal exchange with *tert*-butyllithium followed by the addition of Weinreb amide **142** afforded ketone **143**. Separate reduction of **143** with each enantiomer of DIP-Cl^[198]

afforded the enantiomeric alcohols **144** and **145** in high yield and excellent ee. Cleavage of the methyleneacetal protecting groups was achieved by anodic oxidation. The yields of shikonin and alkannin were high (about 80%, based on recovered starting alcohol) provided the reaction was taken no further than 50% conversion. Furthermore, the oxidation did not require any elaborate electrochemical equipment. A power supply that forced a constant potential difference across the cell of 3 V, and low-cost graphite-rod electrodes were used.^[199] This sequence may provide a commercially viable synthetic route to **1** and **2**.

5. Biological Activity of Alkannin, Shikonin, and Their Derivatives

Biological investigations over the last 25 years have shown that many of the medicinal properties claimed for *AT* and *LE* in the historical texts do indeed have a sound scientific basis, and that the active components are **1**, **2**, and their derivatives. Each of the major biological effects, namely: wound healing, antitumor, antimicrobial, and antithrombotic properties will be considered in turn. References for other biological properties not discussed are given in Table 1.

5.1. Wound Healing and Anti-Inflammatory Effects

As described in the introduction, *AT* and *LE* roots have been used for the treatment of wounds since ancient times. Not until 1976, however, was this medicinal property confirmed experimentally, and the active components identified by Papageorgiou.^[200]

Many samples of *AT* taken from different locations were obtained, and the roots extracted.^[159] After further extraction and chromatographic separation, the initial hexane extract was divided into: waxes,^[201] fluorescent compounds, natural polymers,^[159] and pigments.^[2] These extracts were tested by topical application on skin ulcers induced in laboratory animals (for example, rats, cats, dogs). The pigment-containing fraction showed excellent healing effects, with the other fractions being completely inactive. Chemical analysis of the pigments identified the following esters of alkannin: β , β -dimethylacrylate (**9**),^[159] angelate (**11**),^[202] isovalerate (**7**),^[202] and the novel β -acetoxyisovalerate (**13**).^[203] Interestingly, free alkannin (**1**) was not detected during the isolation.^[204]

An ointment containing the alkannin esters extracted from *AT* root (HISTOPLASTIN RED and afterwards HELI-DERM) was formulated and patented following these successful animal trials.^[47, 205] This preparation was then tested clinically on patients suffering from indolent ulcers of the lower leg, which had resisted all previous attempts at treatment, being applied topically each day around the edge of the ulcer.^[206] The results were dramatic (Figure 12). After three to four weeks of treatment, there was proliferous growth of granulation tissue, and within five to six weeks, complete healing, or at least considerable reduction in ulcer size, was observed. The success rate was 80%, with no skin inflammation being observed at any stage of the treatment.



Figure 12. An indolent ulcer before (right) and after (left) four weeks of treatment with HISTOPLASTIN RED. The patient was a 62 year old woman and the ulcer on her right leg was previously unresponsive to treatment for ten years.

The efficacy of this ointment has been further tested for the treatment of burns, in which it was shown to be significantly superior to the drugs Betadin and Fucidin.^[207] It has also been applied successfully to the treatment of leprosy ulcers, decubitus, traumatic ulcers,^[208] and acute anal fissures.^[209]

Several in vivo animal studies have been undertaken in Japan to assess the efficacy of shikonin (**2**) and its derivatives on various aspects of wound healing. In 1977 Hayashi reported the results of extensive tests on rats with **2**, acetylshikonin (**15**), the Japanese preparation Shiunko, and crude ether extracts of “shikon” (*LE* root).^[210] Each increased proliferation of granuloma tissue induced by a subcutaneous cotton pellet implant. These preparations, when applied topically, also showed anti-inflammatory effects against acute edema induced by several methods, including histamine, serotonin, heat, and uv radiation, and promoted wound healing. Mild antipyretic and analgesic effects were also observed. He concluded that these drugs were effective for the treatment of cutaneous injuries.

Ozaki and co-workers compared Japanese “Shikon”, “Koushikon” (both of which are *LE* roots that contain mainly shikonin (**2**), and its esters), and “Nanshikon” (the root of *Macrotomia euchroma* PAULS which contains mainly alkannin esters). They found that the proliferation of granulation tissue induced by the ether extracts from these roots correlated well with the total naphthoquinone pigment content, and seemed to be independent of both the side-chain stereochemistry and the aliphatic ester group.^[211] A separate comparison of the anti-inflammatory activities of alkannin (**1**) and shikonin (**2**) also led to the conclusion that the absolute configuration has little influence on biological activity.^[212]

Seto and co-workers studied the effects of shikonin and several derivatives as pure compounds on various aspects of wound healing, including anti-inflammatory effects.^[162] Shikonin (**2**) was shown to be more active than acetylshikonin (**15**) with respect to acceleration of granuloma formation, but equally active to the pentaacetyl derivative MDS-004 (**80**; Figure 13). Furthermore, in contrast to **2** and **15**, MDS-004

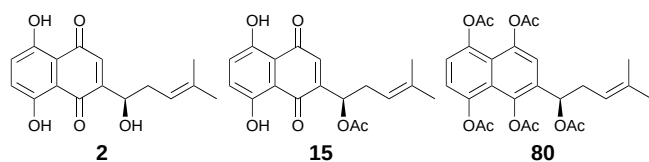


Figure 13. Structures of shikonin (**2**), acetylshikonin (**15**), and MDS-004 (**80**).

(**80**) showed strong inhibition when applied topically against delayed-type allergies (ear edema) induced by oxazolone and dinitrofluorobenzene. MDS-004 (**80**) has the significant marketing advantage of being a colorless compound, rather than a brightly colored pigment. Again, in contrast to **2** and **15**, MDS-004 was also orally active against carrageenan-induced hind paw edema, and exhibited a tendency to heal gastric ulcers induced by acetic acid. Thus, in these model studies, MDS-004 (**80**) was shown to have improved pharmacological properties relative to shikonin (**2**). Interestingly, and in contrast to the study by Hayashi,^[210] none of the derivatives tested showed any healing ability for incised and open wounds. No reports of clinical trials for either **80** or **2** have yet been published.

The anti-inflammatory effects of extracts from *Arnebia euchroma* (alkannin esters),^[213] and β,β -dimethylacrylalkannin (**9**) in particular,^[214] have been studied and have shown similar results to those previously described.^[162, 210, 212] More recently, shikonin (**2**) has been shown to inhibit the biosynthesis of leukotriene B_4 and 5-hydroxyeicosatetraenoic acid, which the authors suggested may play a major role in the mechanism of its anti-inflammatory effects.^[215]

In recent years, significant advances have been made in understanding the biochemistry of wound healing and tissue repair, which is a highly complex and delicate balance of degradative and regenerative processes.^[216] Although the efficacy of alkannin and shikonin derivatives have been demonstrated in vivo, their precise mode of action remains undetermined.

5.2. Antitumor Activity

In addition to the wound healing properties described above, *LE* root extracts have been used in Chinese traditional medicine for many years as a cancer treatment.^[217] Its use for this purpose, however, is missing from several current pharmacopoeias of Chinese medicine,^[18] and may be less common than the applications already described. While various types of *Anchusa* have been used for cancer treatment, dating back as far as the 12th century AD,^[218] *AT* appears not to have been used in this regard. Nevertheless, **1**, **2**, and their derivatives have been investigated as potential drug candidates for various aspects of cancer treatment within the last 25 years.

The increasing problem of cancer in the developed world, it now being second only to cardiovascular disease as a cause of death, has motivated the extensive growth of cancer research in recent years. Mass screening programs of natural products and synthetic compounds by the National Cancer Institute of

the USA have identified the quinone moiety as a pharmacophore that commonly affords cytotoxic activity.^[219] Of over 1500 quinones screened in one campaign in 1974, more than 10% exhibited significant in vivo (mice or rats) activity against at least one of the following cancer cells: L1210 leukemia, Walker carcinosarcoma 256 (W256), Adenocarcinoma 755, Sarcoma 180, Lewis lung carcinoma, and in vitro cytotoxicity against KB cells in culture. Among the active quinones tested, alkannin (**1**), its acetate (**5**), its isobutyrate (**6**), and its β,β -dimethylacrylate (**9**), all exhibited in vitro cytotoxicity against KB cells.^[219]

Alkannin derivatives **1**, **5**, **9**, and **28** (Table 1) isolated from the roots of *Arnebia nobilis* were previously shown to be active against W256 in rats and P388 lymphoid leukemia in mice.^[163, 220] The synthetic derivatives **83** and **85** (Scheme 5) were shown to have comparable activities.

Similar results were obtained by Sankawa et al.^[156] in Japan. Shikonin (**2**) and a range of simple derivatives completely inhibited tumor growth in mice at a dose of 5–10 mg kg⁻¹ day⁻¹. They found that **2** caused acute toxicity at higher doses (see Section 5.5), but was inactive at lower doses. More recently, however, it has been shown that while alkannin (**1**) and shikonin (**2**) both exhibit cytotoxic activity at high concentrations (100 μ g mL⁻¹–10 ng mL⁻¹), they displayed immunostimulating activities at extremely low concentrations (10 ng mL⁻¹–10 fg mL⁻¹) in vitro on human granulocytes and lymphocytes.^[221]

The chemopreventive properties of alkannin (**1**) and shikonin (**2**) derivatives have been examined by several other groups. Chemoprevention is based on the idea that non-carcinogenic, synthetic or natural products can inhibit the process of carcinogenesis. The mutagenic effects of picrolonic acid, benzo[a]pyrene,^[222] and 4-nitroquinoline-1-oxide^[223] on the bacterium *Salmonella typhimurium* TA98 was inhibited in vitro by extracts from *LE* root. Shikonin (**2**) has been shown to inhibit the early antigen activation by 12-*O*-tetradecanoylphorbol-13-acetate (TPA) of the Epstein–Barr virus in Raji cells,^[224] although significant cytotoxicity was also noted at the concentrations tested. Chemopreventive effects have also been demonstrated in vivo, with shikonin (**2**) reducing the incidence of azoxymethane-induced intestinal tumors in rats.^[225]

Platinum complexes of naphthazarins, including **1**, **2**, and their derivatives, exhibit similar antitumor activities to cisplatin, but with lower nephrotoxicity.^[226] Copper complexes of shikonin (**2**) have been patented as DNA cleaving agents.^[227]

Several research groups have investigated the biological mechanism through which **1**, **2**, and their derivatives produce their cytotoxic activity. There are a number of ways in which quinones can disrupt cellular processes.^[228] One of the most commonly proposed mechanisms of quinone cytotoxicity is through “oxidative stress”, which arises from the capacity of these compounds to enter redox cycles. For example, quinones can undergo a one-electron reduction, catalyzed by enzymes such as NADPH-cytochrome P-450 reductase, to form a semiquinone radical.^[228] This radical is thought to initiate a redox cycle since it can readily autooxidize in the presence of dioxygen to regenerate the quinone and form the

superoxide radical anion. The generation of free radicals from this, or the semiquinone, by a chain mechanism may also cause cellular damage, which could contribute to their cytotoxicity.

It has been proposed that the reaction of quinones as electrophiles with cellular nucleophiles may be, at least partly, responsible for their cytotoxic behavior.^[228] Perhaps the most appealing of the cytotoxicity mechanisms for quinones, at least from a chemists viewpoint, is that of bioreductive alkylation.^[229] In this mechanism reduction of the molecule in vivo promotes the elimination of a suitably positioned leaving group to produce a highly potent alkylating agent. This electrophile may serve to capture cellular nucleophiles, such as glutathione or DNA, which may eventually lead to cell death. The process, shown in Figure 14 for **1**, **2**, and their derivatives, is well established, perhaps most famously for the antitumor natural product mitomycin C.^[230] Moore was the first to suggest that **1**, **2**, and their derivatives could function in this manner, although no evidence was presented to support this hypothesis.^[229]

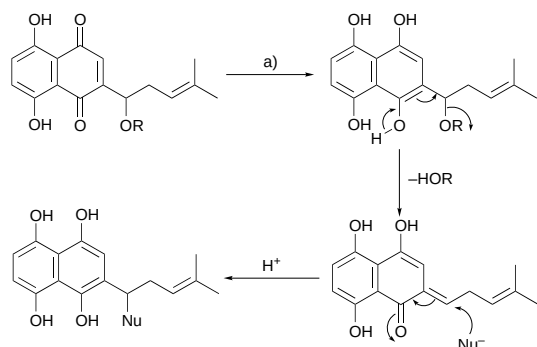


Figure 14. A plausible bioreductive alkylation mechanism of alkannin (**1**) and shikonin (**2**) (Moore).^[229] a) Reduction, Nu = nucleophile.

Inhibition of enzymes vital for cell metabolism or replication may also be a process through which quinones are toxic to cells. In this regard it has been demonstrated in vitro that shikonin (**2**) and its derivatives can interact strongly with DNA topoisomerases.^[160, 231] These enzymes control the topological state of DNA by concerted breaking and rejoining of DNA strands.^[232] Topoisomerases have been identified as targets for chemotherapy since they are involved in many important processes such as DNA replication, transcription, and recombination. A range of shikonin esters have been tested for their inhibitory effects on topoisomerase-I.^[160] The mechanism of action of the well-known anticancer agent camptothecin involves inhibition of this enzyme. A selection of typical examples is given in Table 4, which also shows that several of these derivatives are more potent in vitro inhibitors than camptothecin. In general, the shorter chain esters (C_2 – C_6) were more potent than longer chain derivatives. The selective inhibition of topoisomerase-I with no activity against topoisomerase-II (from Hella cells) was reported in this study.^[233] However, a separate study showed shikonin (**2**) can induce DNA cleavage mediated by topoisomerase-II (from calf thymus), through the formation of a cleaveable complex.^[231] Through the application of a DNA unwinding assay, these authors were also able to establish that **2** did not

Table 4. Inhibition of topoisomerase-I by shikonin esters.^[161]

Compound	R	IC ₅₀ [μM]
15	CH ₃	45 ± 3
146	CH ₂ =CHCH ₂	40 ± 3
147	CH ₃ (CH ₂) ₂	144 ± 10
148	CH ₃ (CH ₂) ₄	207 ± 15
149	CH ₃ (CH ₂) ₆	> 625
shikonin (2)	–	208 ± 10
camptothecin	–	127 ± 9

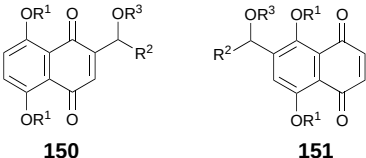
intercalate with the DNA. These studies suggest that the cytotoxic activity of **1**, **2**, and their derivatives may be due, at least in part, to their interactions with these important enzymes.

Recently, Ahn and co-workers have undertaken more in-depth investigations to elucidate the mechanism of cytotoxicity for **1**, **2**, and their derivatives.^[234] Furthermore, these researchers have prepared a series of analogues in an attempt to identify structure–activity relationships and subsequently to produce more active derivatives. These racemic analogues were synthesized by a “modified Terada method”.^[149, 153]

To test whether electrophilic arylation was an important mechanism for these compounds, Ahn and coworkers prepared 5,8-dimethoxy-1,4-naphthoquinone (DMNQ) derivatives and compared the biological data with those of the corresponding naphthazarin derivatives. They reasoned that this structural modification should increase the electrophilicity of the quinone moiety (as it prevents the rapid “tautomerization” present in the naphthazarins),^[137] but decrease the susceptibility of the naphthoquinone to one-electron reduction (since the semiquinone produced on reduction of the latter should achieve greater delocalization than the corresponding radical from a DMNQ derivative). Their ability to capture cellular nucleophiles was assessed by incubation of the quinones with glutathione. As predicted, the general order was: 6-substituted DMNQs > 2-substituted DMNQs > naphthazarins. When the cytotoxicity of 2-substituted naphthazarins **150a–c**, and DMNQ derivatives **150d–f** against L1210 cells were compared, however, the latter were found to be three- to tenfold less active (Table 5). From these experiments the authors deduced that redox cycling plays a prominent role in the cytotoxicity of 2-substituted naphthazarins.

In a protection study, tocopherol, an antioxidant which has been used to scavenge radicals derived from redox cycling, reduced the cytotoxicity of shikonin (**2**) by 25%, while aurintricarboxylic acid (ATA), a general inhibitor of endonucleases, gave a protective effect of 50% at 1 μM (Table 6).^[235] A combination of ATA and tocopherol produced a protective effect of 80%. These results suggest that at least two different mechanisms of cytotoxic action may be operating with these agents.

Further trends in cytotoxicity can be deduced from Table 5. Acetylation of the 2-substituted DMNQ derivatives **150d–f**

Table 5. Cytotoxicity and in vivo activity of shikonin analogues.^[234–238]


Compound	R ¹	R ²	R ³	ED ₅₀ [μg mL ⁻¹] ^[a]	T/C (%) ^[b]
2	H	3-methyl but-2-enyl	H	0.02	92.5
150 a	H	Bu	H	0.03	–
150 b	H	pentyl	H	0.04	–
150 c	H	<i>i</i> -pentyl	H	0.05	–
150 d	Me	Bu	H	0.41	–
150 e	Me	pentyl	H	0.37	–
150 f	Me	<i>i</i> -pentyl	H	0.15	–
150 g	Me	Bu	Ac	0.07	–
150 h	Me	pentyl	Ac	0.06	–
150 i	Me	<i>i</i> -pentyl	Ac	0.05	–
150 j	H	pentyl	Ac	–	255
150 k	H	nonyl	Ac	–	197
151 a	Me	Bu	H	0.05	141
151 b	Me	pentyl	H	0.06	110
151 c	Me	<i>i</i> -pentyl	H	1.10	–
151 d	Me	Me	Ac	0.09	–
151 e	Me	Bu	Ac	0.03	–
151 f	Me	<i>i</i> -pentyl	COPr	0.03	–
151 g	Me	<i>i</i> -pentyl	Ac	0.02	148
151 h	Me	<i>i</i> -pentyl	COPr	0.03	198
151 i	Me	<i>i</i> -pentyl	COpentyl	0.03	217
151 j	Me	<i>i</i> -pentyl	COheptyl	0.10	205

[a] Cytotoxicity was measured in vitro against L1210 cancer cells. [b] Life-span increase, relative to a control, for mice bearing S-180 cells (dose 10 mg kg⁻¹ day⁻¹).

Table 6. Protection from shikonin cytotoxicity.^[235]

Protective agent	Concentration ^[a]	Protection [%]
tocopherol	0.3 mM	25 ± 0.23
ATA	1 μM	50 ± 0.81
tocopherol and ATA	not given	80

[a] Concentration of protective agent. Shikonin concentration was 60 nM throughout.

leads to compounds **150 g–i**, which showed an approximately threefold increase in activity. The 6-substituted derivatives of DMNQ **151 a–c** showed cytotoxicities similar to those of the corresponding naphthazarin derivatives (**150 a–c**) (Table 5). By variation of R¹ and R³ a range of 6-substituted DMNQ analogues (**151 d–j**) were investigated. None of these were significantly more potent in vitro than **2** or any of the other analogues examined.

In vivo tests for many of the analogues were undertaken on mice with S-180 cells. A dose of 10 mg kg⁻¹ day⁻¹ was administered and the increase in life-span relative to a control was recorded. The results (Table 5) can be compared with the cytotoxicity values from in vitro screens, and those for shikonin (**2**) obtained from a previous study^[156a] with an identical dosage. There was no correlation between in vitro cytotoxicity and life-span increase. Nevertheless, the analogues tested, which have recently been patented,^[236] showed

improved antitumor properties over shikonin (**2**). The investigators concluded that binding to endonucleases, such as topoisomerase-I, may be the most plausible mode of in vivo antitumor action of these compounds. They suggest that making structural modifications that increase selective binding to endonucleases while decreasing the nonselective binding to cellular nucleophiles and participation in redox cycling may be the best approach for future developments. In order to achieve this, the question of stereochemistry should no longer be ignored.

Recent reports from the same group have concentrated along these lines in the study of the antitumor activity of arylacetyl esters of shikonin.^[237, 238] Cytotoxicities for 17 analogues were determined in vitro against A549, L1210, and K562 cancer cells. The analogues were found to be much less active against the solid tumor cell line A549 than the leukemic cells L1210 and K562. The cytotoxicity of these analogues against A549 cells was, however, correlated to their anti-cell adhesive properties,^[238] which they suggest may be their mode of action. The 4-(*N,N*-dimethylamino)phenylacetyl derivative of shikonin (**2**), which was synthesized with the aim of improving the water solubility, was one of the most active, showing a T/C value of 192 %.

While further research in the field is certain to continue, the emergence of a clinically useful anticancer agent remains to be seen.

5.3. Antimicrobial Activity

Over the past 30 years the antimicrobial activity of **1**, **2**, and their derivatives has been investigated by a number of groups. Crude preparations derived from plant roots containing these substances were initially shown to exhibit antibacterial and antifungal properties.^[239] This was not sufficient, however, to implicate **1**, **2**, and their derivatives as the active components of the plant roots, and systematic studies for each of the common sources of **1** and **2**, namely *LE*,^[82, 240] *AT*,^[164, 241] and *Arnebia nobilis*,^[171] were therefore undertaken to show that this is, indeed the case. Extracts from pigment-producing callus cultures of *LE* showed antibacterial activity similar to the plant roots.^[242]

In general, **1**, **2**, and their derivatives were found to be active against Gram-positive bacteria such as *Staphylococcus aureus*, *Enterococcus faecium*, and *Bacillus subtilis* with minimum inhibitory concentrations (MIC) of between 0.3 and 6.25 μg mL⁻¹.^[231, 240a,b, 241a,b, 243] They were inactive against Gram-negative bacteria, such as *Escherichia coli* and *Pseudomonas aeruginosa*.^[231, 240a,b, 241b] Plant extracts containing **1**, **2**, and their derivatives have also been shown to act against various species of lactic acid bacteria.^[244]

Although initial reports indicated that **1**, **2**, and their derivatives exhibit a bacteriostatic effect,^[245] a recent kinetic study has demonstrated that the action is, in fact, bactericidal.^[246] This same study showed that such derivatives are selectively toxic to methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* (MRSA and MSSA, respectively). Because of its low toxicity, it was suggested that shikonin (**2**) may be a useful therapeutic agent against MRSA.

There is generally less agreement in the literature concerning the antifungal properties of **1**, **2**, and their derivatives. Honda and co-workers have shown that shikonin (**2**) and deoxyshikonin (**32**), extracted from the cell cultures of *LE*, exhibited significant antidermatophytic properties against five fungi tested: *Saccharomyces sake*, *Trichophyton rubrum*, *T. mentagrophytes*, *T. tonsulans* var. *sulfureum*, *Microsporum gypseum*, and *Epidermophyton floccosum* (MIC < 25 $\mu\text{g mL}^{-1}$).^[247] The action was shown to be fungistatic rather than fungicidal. Deoxyshikonin (**32**) was generally more active. An ointment for the control of athlete's foot with this as the active component has been patented.^[248] Other antimicrobial preparations containing shikonin as the active principle have also been patented.^[249] Shikonin (**2**) and deoxyshikonin (**32**) were shown to be inactive (MIC > 200 $\mu\text{g mL}^{-1}$) against several other fungi, including *Candida albicans*.^[247] Several groups have also shown that **1**, **2**, and their derivatives were inactive against *Candida albicans*,^[231, 243, 247] while other researchers have shown them to be active.^[171a, 239, 241a] The crude ethanol extract from *Arnebia nobilis* has been tested in vivo on guinea pigs against experimentally induced *Candida albicans* infection.^[250] By topical application twice daily of 0.1 mL of a 5 % solution of the arnebins in polyethylene glycol, the infection was cleared within six days.

Shikonin (**2**) has been shown to exhibit a significant antiamebic effect in vitro on *Entamoeba histolytica*, but the therapeutic effect was weak when administered orally to rats with experimental intestinal amebiasis.^[251] Its activity against *Aedes aegypti* larvae has also been demonstrated.^[252]

Papageorgiou and co-workers studied structure–activity relationships for the antimicrobial properties of the constituents of *AT*,^[241b] and reached the following conclusions: 1) the antibacterial effect of the hexane extract arises from the naphthoquinone pigment, with the naphthazarin system being necessary for activity; 2) alkylation of the phenolic groups leads to complete loss of activity; 3) polymerization results in complete loss of activity; and 4) since **1**, **2**, and their esters are all active, the aliphatic side chain may act as a delivery system for the naphthazarin. It was thus suggested that screening a variety of ester derivatives may lead to products with greater potency, which is a goal that remains to be reached.

5.4. Antithrombotic Activity

Thrombus formation in humans can restrict blood flow to vital tissues or organs and cause peripheral, cerebral, or coronary ischemia. Embolism of the thrombosis can be catastrophic, and is a common cause of death. Platelet aggregation is considered to be a major pathogenic mechanism that leads to arterial thrombosis.

Arnebia euchroma is one of the so-called “vasoactive-antithrombotic” herbs of Chinese medicine. Recently, four compounds were isolated from crude extracts and shown to inhibit platelet aggregation induced by collagen. Although their structures were assigned as shikonin (**2**), acetylshikonin (**15**), β,β -dimethylacrylshikonin (**21**), and teracrylshikonin (**22**),^[253] they remain under suspicion, since alkannin deriva-

Table 7. Inhibition of collagen-induced platelet aggregation by alkannin (**1**) and esters.^[253]

Compound	Platelet aggregation [%] ^[a]	IC ₅₀ [$\mu\text{g mL}^{-1}$]
Control	89.0 $\pm$ 0.3	–
β,β -dimethylacrylshikonin (21)	21.0 $\pm$ 18.1	4.2
teracrylshikonin (22)	0	2.8
acetylshikonin (15)	0	2.1
shikonin (2)	67.5 $\pm$ 4.9	10.7

[a] Measured with a substrate concentration of 20 $\mu\text{g mL}^{-1}$.

tives (**1**, **5**, **9**, **10**) were isolated from this source (see Table 1, note 2).^[42, 44] Results of in vitro tests are presented in Table 7.

Acetylshikonin **15** also inhibits arachidonic acid induced platelet aggregation. It was suggested that **15** acts through suppression of phosphoinositide breakdown.^[253b]

5.5. Toxicity, Pharmacokinetics, and Other Pharmacological Aspects

In vitro and in vivo potencies are not the only factors to be considered if **1**, **2**, and/or their derivatives are to become therapeutically useful drugs. Aspects such as toxicity, metabolism, and formulation are also vitally important.

Alkannin (**1**) was shown to have low toxicity when administered orally in a feeding study.^[254] The LD₅₀ was 3 g kg^{−1} in mice and less than 1 g kg^{−1} in rats. No evidence of toxicity was observed when **1** was fed to mice for 15 weeks at 1 % of their diet (average total intake 3.38 g). Autopsies showed the animals had no Heinz bodies and their vital organs were of unchanged morphology. Alkannin was excreted in the urine and not deposited in abdominal fat. Similar results were demonstrated for shikonin (**2**) and acetylshikonin (**15**).^[210] Shikonin **2** and its derivatives are rather more toxic to mice by intraperitoneal administration. Results are summarized in Table 8.

Table 8. Toxicity of shikonin and esters to mice by intraperitoneal administration.

Compound	LD ₅₀ [mg kg ^{−1}]
shikonin (2)	20 $\pm$ 5 ^[210b]
acetylshikonin (15)	41 $\pm$ 10 ^[210b] ; 22.75 ^[213]
β,β -dimethylacrylshikonin (21)	48 $\pm$ 5 ^[214]

In addition, during in vivo testing of **1**, **2**, and their derivatives for antitumor effects, toxicity has been observed. Table 9 indicates the derivatives for which this was the case (dose administered intraperitoneally). Alkannin (**1**)^[255] and

Table 9. Toxic doses of **1**, **2** and their derivatives in mice and rats.

Compound	Toxic dose
shikonin (2)	10 $\times$ 5 mg kg ^{−1} day ^{−1} ^[156a]
shikonin (2)	30 mg kg ^{−1} day ^{−1} ^[156a]
alkannin (33)	30 mg kg ^{−1} day ^{−1} ^[156b]
alkannin leucoacetate	30 mg kg ^{−1} day ^{−1} ^[156b]
cycloalkannin diacetate	30 mg kg ^{−1} day ^{−1} ^[156b]
β,β -dimethylacrylalkannin (9)	10 mg kg ^{−1} day ^{−1} ^[220]
α -methoxyphenylacetyl shikonin	7.75 mg kg ^{−1} day ^{−1} ^[257]

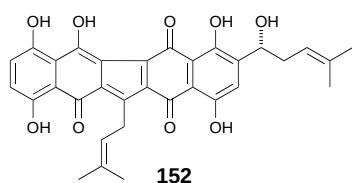
alkannin esters (**5–13**)^[200] are nonmutagenic according to the Ames test.^[256]

A pharmacokinetic study has been described using [³H]shikonin in mice.^[257] The absorption was rapid after both oral and intramuscular administration, with radioactivity detectable in plasma after about one minute. Other results are presented in Table 10. Within 96 hours of intravenous injection, the total radioactivity excreted was 40.5 % in the urine and 40.3 % in feces, with 3.6 and 7.7 %, respectively, being as the unchanged drug.

Table 10. Pharmacokinetic data for shikonin (**2**) in mice.^[257]

Administration	Peak level in plasma [min]	Bioavailability [%]
oral	5.78	34.3
intramuscular	7.62	64.7

As a predictive model to mimic the transformation of shikonin (**2**) in the human gastrointestinal tract, Kadota and co-workers have incubated **2** with *Bacteroides fragilis* subsp. *thetaotus* from human feces.^[258] Ten metabolites were detected: five monomers, including anhydroalkannin (**34**), deoxyshikonin (**32**), cycloshikonin (**73**), and five dimeric structures such as shikometabolin A (**152**).



Cheng and co-workers were able to dramatically improve the pharmaceutical properties of **1** and **2** through the formation of a 1:1 inclusion complex with hydroxypropyl- β -cyclodextrin.^[259] Water solubility was improved 200-fold and photochemical decomposition rate constants decreased from 0.329 to 0.156 h⁻¹. Furthermore, the release rate of **1** and **2** was enhanced dramatically at one tenth of the control preparation Shiunko ointment.

6. Summary and Outlook

The ancient medicinal properties claimed for *AT* and *LE* have, at least in part, been confirmed by scientific experimentation within the last 25 years. These investigations resulted in the identification of alkannin (**1**), shikonin (**2**), and related derivatives as the active components. The clinical application of preparations that contain ester derivatives of **1** extracted from *AT* for the treatment of burns and ulcers is, perhaps, the most dramatic development. The use of **1**, **2**, and related derivatives in other therapeutic areas, particularly in cancer chemotherapy, is still in development. Significant developments are to be expected in this area in the future.

The value of **2** in Japan motivated biotechnologists to develop the world's first manufacturing process utilizing plant cell cultures. The research in this area has provided a wealth of knowledge to the field of biotechnology. In addition, great

insights into the biosynthesis of these natural products and to our understanding of plant secondary metabolism in general, has been gained from this work.

The challenge of synthesizing these deceptively simple-looking compounds has kept a number of synthetic chemists occupied worldwide for many man-years. The pioneering work of Terada, and others in the field, laid the foundations upon which recent advances in the chemical synthesis of these substances relied. These developments should allow for many future adventures in the chemistry, biology and medicine of alkannin (**1**), shikonin (**2**), and related naphthazarins.

Addendum

Since the initial submission of this review a number of papers concerning various aspects of the chemistry and biology of alkannin and shikonin have appeared in the literature. To provide literature coverage up to November 30, 1998 these are included here under the following categories: medicinal properties,^[260] physical properties and analysis,^[261] cell cultures and biosynthesis,^[262] dyeing,^[263] and miscellaneous biological properties.^[264]

Recently, the wound-healing ability of HELIXDERM has been evaluated in further clinical trials. This study was undertaken at the Freie Universität of Berlin under the supervision of Prof. C. E. Orfanos, and showed that HELIXDERM gave very good results in terms of granulation and epithelization.

In addition, it has come to our attention that further research concerning the anticancer properties of "shikonin mixture" has been conducted in China. In vitro experiments were conducted which indicated that the pigment mixture was active against stomach and esophagus cancer cell lines.^[265] Perhaps more significantly, clinical trials have been conducted using shikonin mixture for 19 patients with later stage lung cancer. From this study the authors concluded that "Shikonin mixture is safe and effective for later-stage cancer".^[266] Further studies to test these claims are certainly necessary.

Appendix: List of Abbreviations Used

CDI	<i>N,N'</i> -carbonyldiimidazole
DCC	dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL	diisobutylaluminum hydride
DIP-Cl	<i>B</i> -chlorodiisopinocampheylborane
DMAP	4-dimethylaminopyridine
DMF	<i>N,N</i> -dimethylformamide
<i>hν</i>	light
Ipc	isopinocampheyl
LDA	lithium diisopropylamide
MOM	methoxymethyl
MTBSTFA	<i>N</i> -methyl- <i>N</i> - <i>tert</i> -butyldimethylsilylacetamide
MTMSTFA	<i>N</i> -methyl- <i>N</i> -trimethylsilylacetamide
NBS	<i>N</i> -bromosuccinimide
py	pyridine
TBAF	tetrabutylammonium fluoride

TBS	<i>tert</i> -butyldimethylsilyl
THF	tetrahydrofuran
TMS	trimethylsilyl
Ts	<i>p</i> -toluenesulfonyl

V.P.P. greatly appreciates the help of Professor A. Sagredos and Assistant Professor A. Mellidis for their contribution during this project. Additionally, much credit is due to Dr. Christos Verelis, Under-Secretary of the Environment, Physical Planning, and Public Works of Greece, for his continuing interest and valuable assistance for the development of the pharmaceutical preparations HISTOPLASTIN RED and HELIXDERM. K.C.N and D.H. would like to thank Dr. Paul King, Mr. Christopher Boddy, and Mr. Nicolas Winssinger for assistance in the preparation of this manuscript. We thank Mr. K. Goto and Dr. T. Konoshima of Kyoto Pharmaceutical University, Parke-Davis, and Medpharm Scientific Publications for the use of illustrations. This work was financially supported by the National Institutes of Health (USA) and The Skaggs Institute for Chemical Biology.

Received: November 27, 1997

Revised version: February 26, 1998 [A261 IE]

German version: *Angew. Chem.* **1999**, *111*, 280–311

- [1] H. Brockmann, *Justus Liebigs Ann. Chem.* **1936**, 521, 1–47.
- [2] a) R. H. Thomson, *Naturally Occurring Quinones*, 2nd ed., Academic Press, New York, **1971**, pp. 248–251; b) R. H. Thomson, *Naturally Occurring Quinones III, Recent Advances*, Chapman & Hall, **1987**, pp. 219–223.
- [3] P. Weigle, *Ancient Dyes for Modern Weavers*, Watson-Guptil, New York, **1974**, pp. 50–52.
- [4] Translations of the works of Hippocrates by Francis Adams can be found in the *Internet Classics Archive*. For the use of alkanet, see <http://webatoms.com/Classics/Hippocrates/ulcers.10.10.html>.
- [5] Theophrastus, *Enquiry into Plants and Minor works on Odours and Weather Signs*, Vol. 2 (Translation by A. Hort), Harvard University Press, Cambridge, Massachusetts, **1949**, chap. 7.9.3, p. 113.
- [6] M. Wood, *In the Footsteps of Alexander the Great*, University of California Press, Los Angeles, **1997**, pp. 143–144.
- [7] P. Dioscorides in *De Materia Medica*, Vol. IV.23 (Ed.: Max Wellman), Berloni Apud Weidmannos, Berlin, **1958**, pp. 187–188; b) R. T. Gunther, *The Greek Herbal of Dioscorides*, Vol. IV, Hafner, New York, **1968**, p. 421.
- [8] The effect has also been written about for alkanet.^[11a]
- [9] Pliny, *The Natural History*, Vol. 4, Book XXII, chap. 23 (Translation by J. Bostock), H. T. Riley, George Bell, London, **1890**, p. 409.
- [10] Its use for wound healing is apparently recorded in an ancient Arabic treatise.^[220] Also see L. Boulous, *Medicinal Plants of North Africa*, Reference Publications, Algonac, Michigan, **1983**, pp. 35–37.
- [11] a) N. Culpeper, *The English Physitian Enlarged*, Churchill, London, **1695**, pp. 3–4; b) N. Culpeper, *Pharmacopoeia Londinensis*, Streeter, London, **1672**, *Roots*, p. 1.
- [12] R. C. Wren in *Potters New Cyclopaedia of Botanical Drugs and Preparations* (Ed.: R. W. Wren), Health, Devon, **1975**, pp. 11–12.
- [13] A. Y. Leung, S. Foster, *Encyclopedia of Common Natural Ingredients*, Wiley, New York, **1996**, pp. 19–20.
- [14] a) M. Wichtl, *Herbal Drugs and Phytopharmaceuticals: A Handbook for Practice on a Scientific Basis* (Ed.: N. G. Bisset), Medpharm, Stuttgart, **1994**, pp. 55–56; b) *Teedrogen und Phytopharmaka 3* (Ed.: M. Wichtl), Medpharm, Stuttgart, **1997**.
- [15] *The Merck Index*, 11th ed. (Ed.: S. Budavari), Merck, Rahway, NJ, **1989**, p. 43.
- [16] R. Hyatt, R. Feldman, *Chinese Herbal Medicine: Ancient Art and Modern Science*, Schocken Books, New York, **1978**, pp. 17–28.
- [17] B. E. Read, *Chinese Medicinal Plants from the Pen Ts'ao Kang Mu (AD 1596)*, 3rd ed., Peking Natural History Bulletin, Peking, **1936**, p. 38.
- [18] *A Barefoot Doctor's Manual* (Translation of a Chinese Instruction to Certain Chinese Health Personnel), US Government Printing Office, Washington, **1974**, p. 908; b) H.-Y. Hsu, W. G. Preacher, *Chinese Herb Medicine and Therapy*, Oriental Healing Arts Institute of USA, Los Angeles, **1982**, p. 147; c) *Handbook of Commonly Used Chinese Herbal Prescriptions*, (Translation by W. Yu-Ching), Oriental Healing Arts Institute, **1983**, p. 59; d) *The Pharmacopoeia of Japan*, Yakuji Nippo, Tokyo, **1982**, p. 1115.
- [19] For recent patents and publications related to this aspect, see a) S. Ootani, I. Takagishi (Pentel K. K.) JP-B 06336411, **1994** [*Chem. Abstr.* **1994**, 122, 142067p]; b) A. Hashimoto, A. Kusumi, K. Yamaguchi (Sunstar) JP-B 04029915, **1992** [*Chem. Abstr.* **1992**, 116, 241988x]; c) S. Shimoyama, T. Shimoyama, (Ihara Chemical Industry) WO-B 9201022, **1992** [*Chem. Abstr.* **1992**, 116, 196225h]; d) T. Okuda, (Amato Pharmaceutical Products) JP-B 01215861, **1989** [*Chem. Abstr.* **1990**, 112, 185548g]; e) S. Mori, H. Otsuke, S. Kida, H. Bando (Sunstar; Sanwa Chemical Industry) JP-B 01275520, **1989** [*Chem. Abstr.* **1990**, 112, 164775p]; f) M. Tsuboi, K. Matsui, Y. Ando, (Ichimura) JP-B 63083017, **1988** [*Chem. Abstr.* **1989**, 111, 45072b]; g) K. Hara, S. Murata, (Kao) JP-B 62270545, **1987** [*Chem. Abstr.* **1988**, 109, 197176k]; h) M. Tsuboi, Y. Ando, K. Matsui, (Ichimura) JP-B 62116520, **1987** [*Chem. Abstr.* **1988**, 108, 26820r]; i) K. Matsui, M. Tsuboi, Y. Ando, (Ichimura Co) JP-B 62089772, **1987** [*Chem. Abstr.* **1987**, 107, 204937y]; j) T. Morimoto, H. Ikeda, E. Inui, M. Hara, Y. Omura (Mitsui Petrochemical Industries) JP-B 62070305, **1987** [*Chem. Abstr.* **1987**, 107, 64658f]; k) T. Morimoto, H. Ikeda, E. Inui, M. Hara, (Mitsui Petrochemical Industries) JP-B 62070315, **1987** [*Chem. Abstr.* **1987**, 107, 46072f]; l) T. Morimoto, H. Ikeda, E. Inui, M. Hara, (Mitsui Petrochemical Industries; Sanwa Kagaku Kogyo K. K.) JP-B 61252299, **1986** [*Chem. Abstr.* **1987**, 106, 143807m]; m) T. Morimoto, H. Ikeda, E. Inui, M. Hara, (Mitsui Petrochemical Industries; Sanwa Kagaku Kogyo K. K.) JP-B 61252298, **1986** [*Chem. Abstr.* **1987**, 106, 143806k]; n) T. Morimoto, H. Ikeda, E. Inui, M. Hara, (Mitsui Petrochemical Industries; Sanwa Kagaku Kogyo K. K.) JP-B 61252297, **1986** [*Chem. Abstr.* **1987**, 106, 143805j]; o) T. Suzuki, S. Abe, (Shiesido) JP-B 61130233, **1986** [*Chem. Abstr.* **1986**, 105, 139645u]; p) T. Suzuki, S. Abe, (Shiesido) JP-B 61130232, **1986** [*Chem. Abstr.* **1986**, 105, 139644j]; q) A. Yamagata, H. Tezuka, (Guerlain Kaihatsu Kenkyusho K. K.) JP-B 61118306, **1986**, 105, 120746f]; r) T. Morimoto, H. Ikeda, (Mitsui Petrochemical Industries) JP-B 60169413, **1985** [*Chem. Abstr.* **1985**, 104, 24086z]; s) Mitsui Petrochemical Industries, JP 60094499, **1985** [*Chem. Abstr.* **1985**, 103, 106631s]; t) S. Kubo, E. Kawada (Shiesido) DE-B 3433648, **1985** [*Chem. Abstr.* **1985**, 103, 92640e]; u) Shiesido, JP-B 60058911, **1985** [*Chem. Abstr.* **1985**, 103, 76074t]; v) Ichimaru Farukosu K. K., JP 59010507, **1984** [*Chem. Abstr.* **1984**, 100, 144835g]; w) K. Matsui, H. Ando, T. Endo, JP-B 52094432, **1977** [*Chem. Abstr.* **1978**, 88, 27680a]; x) S. Kishimoto, K. Aota (Kanebo) JP-B 52027692, **1977** [*Chem. Abstr.* **1977**, 87, 189309i].
- [20] For some patents and publications, see a) C. Suga (Ichimaru Co.), JP-B 07216249, **1995** [*Chem. Abstr.* **1995**, 123, 259672]; b) C. Suga (Mitsui Petrochemical Industries) JP-B 06248581, **1994** [*Chem. Abstr.* **1994**, 122, 33501]; c) I. Fumoto, C. Suga (Mitsui Petrochemical Industries) JP-B 03012458, **1991** [*Chem. Abstr.* **1991**, 114, 249246]; d) M. Schallies, *Prax. Naturwiss. Chem.* **1989**, 38, 31–36; e) C. Suga (Mitsui Petrochemical Industries) JP-B 63156741, **1988** [*Chem. Abstr.* **1988**, 110, 40446]; f) E. Benk, *Riechst. Aromen Körperpflege*, **1967**, 17, 3–4.
- [21] R. Winter, *A Consumer's Dictionary of Food Additives*, Crown, New York, **1984**, p. 25.
- [22] a) R. Winter, *A Consumer's Dictionary of Cosmetic Ingredients*, Crown, New York, **1984**, p. 23; b) For a recent patent, see H. Lorenz (Goldwell) DE-B 4201749 [*Chem. Abstr.* **1993**, 119, 146341].
- [23] V. P. Papageorgiou, *Planta Med.* **1980**, 38, 193–203.
- [24] R. Majima, C. Kuroda, *Acta Phytochim. (Tokyo)* **1922**, 1, 43–65.
- [25] H. Arakawa, M. Nakazaki, *Chem. Ind. (London)* **1961**, 947.
- [26] H. Fukui, M. Tsukada, H. Mizukami, M. Tabata, *Phytochemistry* **1983**, 22, 453–456.
- [27] Y. Ikeda, N. Ishida, C. Fukaya, K. Yokoyama, M. Tabata, H. Fukui, G. Honda, *Chem. Pharm. Bull.* **1991**, 39, 2351–2352.

- [28] a) J. Pelletier, *Ann. Chim. Phys.* **1832**, 51, 191–192; b) J. Pelletier, *Ann.* **1833**, 6, 27.
- [29] P. Bolley, R. Wydler, *Justus Liebigs Ann. Chem.* **1847**, 62, 141.
- [30] K. Brand, A. Lohmann, *Ber. Dtsch. Chem. Ges. B* **1935**, 68, 1487–1494.
- [31] H. Raudnitz, W. Stein, *Ber. Dtsch. Chem. Ges. B* **1935**, 68, 1479–1484.
- [32] A. C. Jain, S. K. Mathur, *Bull. Nat. Inst. Sci. India* **1965**, 28, 52–56 [*Chem. Abstr.* **1967**, 66, 26143m].
- [33] H. A. Khan, I. Chandrasekharan, A. Ghanim, *Phytochemistry* **1983**, 22, 614–615.
- [34] T. S. El-Afly, N. D. El-Tanbouly, N. M. Sokkar, *Egypt. J. Pharm. Sci.* **1996**, 37, 65–70 [*Chem. Abstr.* **1997**, 126, 328044s].
- [35] R. Chaisuksant, I. Niopas, A. Voulgaropoulos, A. S. Mellidis, V. P. Papageorgiou, *Pharmazie* **1995**, 50, 363–364.
- [36] S. A. Fedoreev, O. E. Krivoshekova, V. A. Denisenko, P. G. Gorovoi, O. B. Maksimov, *Khim. Prir. Soedin* **1979**, 625–630 [*Chem. Abstr.* **1981**, 94, 80213a].
- [37] a) N. N. Boldyrev, *Farmatsiya* **1939**, 10, 24–25; *Khim. Ref. Zh.* **1940**, 5, 108 [*Chem. Abstr.* **1942**, 36, 39103].
- [38] P. De Leo, A. Miceli, L. Ronzini, L. Sanasi, R. Sgarra, *Agro Food Ind. Hi-Tech* **1996**, 7, 23–25.
- [39] V. P. Papageorgiou, *Planta Med.* **1979**, 37, 259–263.
- [40] V. P. Papageorgiou, A. S. Mellidis, A. N. Assimopoulou, A. Tsarbo-poulos, *J. Mass Spectrom.* **1998**, 33, 89–91.
- [41] A. S. Mellidis, V. P. Papageorgiou, *J. Nat. Prod.* **1987**, 50, 618–619.
- [42] S. Fu, T. Shang, P. Xiao, *Yaoxue Xuebao* **1984**, 19, 921–925 [*Chem. Abstr.* **1985**, 103, 11307b].
- [43] L. Shurong, M. Lu, *Yaowu Fenxi Zazhi* **1986**, 6, 280–282 [*Chem. Abstr.* **1986**, 106, 50609h].
- [44] S. Fu, P. Xiao, *Zhongcaoyao* **1986**, 17, 434–437 [*Chem. Abstr.* **1987**, 106, 55728f].
- [45] G.-S. Liu, *Yao Hsueh T'ung Pao* **1981**, 16, 14–15 [*Chem. Abstr.* **1981**, 95, 156425q].
- [46] N. Kirimer, B. Boazan, K. H. C. Baser, *Fitoterapia* **1995**, 66, 499–500 [*Chem. Abstr.* **1996**, 124, 284323j].
- [47] V. P. Papageorgiou, DE-B 2829744, **1979** [*Chem. Abstr.* **1979**, 91, 181441s].
- [48] M. Zhang, Y. Jin, L. Guo, Y. Cai, *Zhongcaoyao* **1989**, 20, 449–450 [*Chem. Abstr.* **1990**, 112, 33368k].
- [49] F. Zhu, F. Lu, G. Xiang, *Sepu* **1984**, 1, 131–133 [*Chem. Abstr.* **1985**, 103, 59142w].
- [50] F. Lu, Q. Xiang, F. Zhu, *Zhiwu Xuebao* **1983**, 25, 455–459 [*Chem. Abstr.* **1984**, 100, 99960f].
- [51] A. S. Romanova, A. I. Ban'kovskii, K. I. Boryaev, SU-B 200737, **1967** [*Chem. Abstr.* **1968**, 68, 62695t].
- [52] A. S. Romanova, A. I. Ban'kovskii, N. V. Tareeva, L. D. Marenova, K. I. Boryaev, *Lek. Rast.* **1969**, 15, 529–537 [*Chem. Abstr.* **1971**, 75, 85209w].
- [53] N. V. Tareeva, A. S. Romanova, A. I. Ban'kovskii, *Sb. Nauch. Rab., Vses. Nauchno-Issled. Inst. Lek. Rast.* **1970**, 1, 175–181 [*Chem. Abstr.* **1972**, 76, 70042h].
- [54] L. R. Shcherbanovskii, Yu. A. Luks, *Khim. Prir. Soedin.* **1974**, 513–514 [*Chem. Abstr.* **1975**, 82, 28587p].
- [55] A. S. Romanova, N. V. Tareeva, A. I. Ban'kovskii, *Khim. Prir. Soedin.* **1967**, 3, 71 [*Chem. Abstr.* **1967**, 67, 18548c].
- [56] J. A. Ballantine, *Phytochemistry* **1969**, 8, 1587–1590.
- [57] O. E. Krivoshekova, S. A. Fedoreev, V. A. Denisenko, O. B. Maksimov, P. G. Gorovoi, *Khim. Prir. Soedin* **1976**, 726–730 [*Chem. Abstr.* **1977**, 86, 86122b].
- [58] N. V. Tareeva, A. S. Romanova, A. I. Ban'kovskii, P. N. Kibal'chich, *Khim. Prir. Soedin.* **1966**, 2, 359–360 [*Chem. Abstr.* **1967**, 66, 79524t].
- [59] a) M. Kuhara, *J. Chem. Soc.* **1879**, 35, 22–25; b) M. Kuhara, *Ber. Dtsch. Chem. Ges.* **1878**, 11, 2143–2147.
- [60] C. Kuroda, *J. Tokyo Chem. Soc.* **1918**, 39, 1051–1115.
- [61] G. Bai, X.-J. Jin, *Chem. Res. Chin. Univ.* **1994**, 10, 263–265 [*Chem. Abstr.* **1995**, 122, 183154h].
- [62] S. Miura, *Shoyakugaku Zasshi* **1963**, 17, 45–49 [*Chem. Abstr.* **1965**, 61, 3065c].
- [63] A. S. Romanova, N. V. Tareeva, L. N. Pervykh, G. K. Kalashnikova, K. I. Boryaev, D. Pakalns, A. V. Patudin, *Khim. Prir. Soedin.* **1981**, 96 [*Chem. Abstr.* **1981**, 95, 3375y].
- [64] A. S. Romanova, A. I. Ban'kovskii, *Khim. Prir. Soedin.* **1965**, 226–227 [*Chem. Abstr.* **1965**, 63, 16773e].
- [65] A. S. Romanova, A. I. Ban'kovskii, N. V. Tareeva, K. I. Boryaev, I. A. Gubanov, SU-B 240933, **1969**, [*Chem. Abstr.* **1969**, 71, 53591r].
- [66] M. E. Pimenova, N. V. Tareeva, *Rastit. Resur.* **1980**, 16, 82–86 [*Chem. Abstr.* **1980**, 92, 143310m].
- [67] L. R. Shcherbanovskii, *Khim. Prir. Soedin.* **1972**, 8, 666 [*Biol. Abstr.* **1974**, 57, 4830].
- [68] L. R. Shcherbanovskii, *Khim. Prir. Soedin.* **1972**, 8, 238 [*Biol. Abstr.* **1973**, 55, 16427].
- [69] L. R. Shcherbanovskii, *Khim. Prir. Soedin.* **1971**, 4, 517–518 [*Chem. Abstr.* **1972**, 54, 51321].
- [70] A. S. Romanova, A. I. Ban'kovskii, K. I. Boryaev, N. V. Tareeva, SU-B 200735, **1967** [*Chem. Abstr.* **1969**, 68, 62694s].
- [71] M. Tsuboi, Y. Ando, K. Matsui, JP-B 62116520, **1985** [*Chem. Abstr.* **1988**, 108, 26820r].
- [72] L. N. Blagonravova, L. R. Shcherbanovskii, *Prikl. Biokhim. Mikrobiol.* **1974**, 10, 666–669 [*Chem. Abstr.* **1975**, 82, 27824b].
- [73] A. Crespa Ayuso, L. Crespa Ayuso, ES-B 356371, **1970** [*Chem. Abstr.* **1970**, 73, 44118f].
- [74] Y. Hashimoto, Y. Myama, A. Mizuchi, N. Fukazawa (Mitsui Toatsu Chemicals) JP-B 06340526 [*Chem. Abstr.* **1995**, 122, 178412m].
- [75] M. Afzal, G. Al-Oriquat, *Agric. Biol. Chem.* **1986**, 50, 1651–1652.
- [76] W. Cisowski, W. Dembska-Migas, J. Dzikowska, *Acta Pol. Pharm.* **1993**, 50, 443–446 [*Chem. Abstr.* **1994**, 121, 200860j].
- [77] S. Hisamichi, F. Yoshizaki, *Shoyakugaku Zasshi* **1982**, 36, 154–159 [*Chem. Abstr.* **1982**, 97, 178739p].
- [78] K.-H. Ai, F.-Y. Li, W. Wang, Y. Y. Wu, *Zhiwu Xuebao* **1989**, 31, 549–553 [*Chem. Abstr.* **1990**, 112, 115753w].
- [79] S. A. Fedoreyev, V. A. Denisenko, N. I. Kulesh, N. P. Krasovskaya, M. M. Kozynenko, V. P. Bulgakov, Yu. N. Zhuravlev, *Khim. Farm. Zh.* **1993**, 27, 33–37 [*Chem. Abstr.* **1994**, 120, 240061k].
- [80] I. Morimoto, T. Kishi, S. Ikegami, Y. Hirata, *Tetrahedron Lett.* **1965**, 4737–4739.
- [81] M. Afzal, G. Al Oriquat, *Agric. Biol. Chem.* **1986**, 50, 759–760.
- [82] K. Kyogoku, H. Terayama, Y. Tachi, T. Suzuki, M. Komatsu, *Shoyakugaku Zasshi* **1973**, 27, 24–30 [*Chem. Abstr.* **1974**, 80, 112549u].
- [83] M. Afzal, N. Muhammad, *Agric. Biol. Chem.* **1983**, 47, 411–412.
- [84] C. W. Sung, K. S. Liu, N. W. Li, *Yao Hsueh T'ung Pao* **1980**, 15, 3–5 [*Chem. Abstr.* **1981**, 94, 71295b].
- [85] These workers actually found the quinone pigments in aerial parts of the plant. N. A. Salam, T. Sarg, Y. Ibrahim, S. Khafagy, *Acta Pharm. Jugosl.* **1981**, 31, 237–241 [*Chem. Abstr.* **1982**, 96, 118993m].
- [86] I. Morimoto, Y. Hirata, *Tetrahedron Lett.* **1966**, 3677–3680.
- [87] M. Afzal, M. Tofeeq, *J. Chem. Soc. Perkin Trans 1* **1976**, 15, 1579–1582.
- [88] M. Afzal, M. Tofeeq, *J. Chem. Soc. Perkin Trans 1* **1975**, 14, 1334–1335.
- [89] P. Cong, *Yaoxue Xuebao* **1984**, 19, 450–454 [*Chem. Abstr.* **1985**, 103, 104350a].
- [90] Y. N. Shukla, J. S. Tandon, M. M. Dhar, *Indian J. Chem.* **1973**, 11, 528–529.
- [91] a) M. Tabata, H. Mizukami, N. Hiraoka, M. Konoshima, *Phytochemistry* **1974**, 13, 927–932; b) M. Konoshima, H. Mizukami, M. Tabata, *Shoyakugaku Zasshi* **1974**, 28, 74 [*Biol. Abstr.* **1976**, 61, 51525].
- [92] E. M. Linsmaier, F. Skoog, *Physiol. Plant* **1965**, 18, 100–127.
- [93] M. Tabata, H. Mizukami, N. Hiraoka, M. Konoshima, *Phytochemistry* **1983**, 22, 2451–2453.
- [94] a) Y. Fujita, Y. Hara, C. Suga, T. Morimoto, *Plant Cell Rep.* **1981**, 1, 59–60; b) Y. Fujita, Y. Hara, T. Ogino, C. Suga, *Plant Cell Rep.* **1981**, 1, 61–63; c) L. Heide, N. Nishioka, H. Fukui, M. Tabata, *Phytochemistry* **1989**, 28, 1873–1877; d) H. Mizukami, M. Konoshima, M. Tabata, *Phytochemistry* **1977**, 16, 1183–1186.
- [95] M. Tani, H. Fukui, M. Shimomura, M. Tabata, *Phytochemistry* **1992**, 31, 2719–2723.
- [96] N. Yoshikawa, H. Fukui, M. Tabata, *Phytochemistry* **1986**, 25, 621–622.
- [97] K. Yazaki, H. Fukui, M. Kikuma, M. Tabata, *Plant Cell Rep.* **1987**, 6, 131–134.
- [98] Y. Fujita, N. Yoshikawa, M. Tabata, *Phytochemistry* **1984**, 23, 301–305.

- [99] a) H. Mizukami, M. Konoshima, M. Tabata, *Phytochemistry* **1978**, *17*, 95–97; b) Y. Fujita, S. Takahashi, Y. Yamada, *Agric. Biol. Chem.* **1985**, *49*, 1755–1759; c) Y. Fujita, M. Tabata, *Plant Biol.* **1987**, *3*, 169–185 (Plant Tissue Cult.); d) Y. Fujita, S. Takahashi, Y. Yamada, *Eur. Congr. Biotechnol.*, 3rd, Vol. 1, VCH, Weinheim, **1984**, pp. 161–166.
- [100] Y. Fujita, Y. Hara, *Agric. Biol. Chem.* **1985**, *49*, 2071–2075.
- [101] M. E. Curtin, *Biotechnology* **1983**, *1*, 649–657.
- [102] For patents relating to this process, see a) Y. Motoyama (Mitsui Petrochemical Industries) JP-B 03176454, **1991** [*Chem. Abstr.* **1991**, *115*, 231894d]; b) Mitsui Petrochemical Industries, JP-B 58101687, **1983** [*Chem. Abstr.* **1983**, *99*, 156862n]; c) Mitsui Petrochemical Industries, JP-B 57063082, **1982** [*Chem. Abstr.* **1982**, *97*, 108555b]; d) Mitsui Petrochemical Industries, JP-B 57063081, **1982** [*Chem. Abstr.* **1982**, *97*, 90440y]; e) Mitsui Petrochemical Industries, EP-B 71999, **1983** [*Chem. Abstr.* **1983**, *98*, 196387]; f) Mitsui Petrochemical Industries, JP-B 57039779 **1982** [*Chem. Abstr.* **1982**, *97*, 4700d]; g) Mitsui Petrochemical Industries, JP-B 57039778, **1982** [*Chem. Abstr.* **1982**, *97*, 4699k].
- [103] a) H. N. Chang, S. J. Sim, *Biotechnol. Agric. For.* **1996**, *38*, 233–242 (Plant Protoplasts and Genetic Engineering VII); b) W. W. Su, *Appl. Biochem. Biotechnol.* **1995**, *50*, 189–230; c) H. J. Chi, *Hwahak Sekye* **1994**, *34*, 1063–1064 [*Chem. Abstr.* **1995**, *123*, 54169p]; d) O. Sahai, *Bioprocess Prod. Flavor Fragrance Color Ingredients* **1994**, 239–275; d) D. Fang, S. Hou, X. Li, *Zhongcaoyao* **1992**, *23*, 209–212 [*Chem. Abstr.* **1992**, *117*, 76285b]; f) Y. L. Chan, L. F. Liu, *Kexue Nongye (Taipei)* **1991**, *39*, 181–185; g) Y. Fujita, C. Suga, *Fragrance J.* **1991**, *19*, 33–36; h) Y. Fujita, *Kagaku to Kagyo (Tokyo)* **1990**, *43*, 1102–1104 [*Chem. Abstr.* **1990**, *113*, 170344j]; i) T. Vanek, *Chem. Listy* **1989**, *83*, 287–300 [*Chem. Abstr.* **1989**, *110*, 189343t]; j) H. X. Fan, W. H. Zhu, *Xiaoxue Xuebao* **1988**, *23*, 716–720 [*Chem. Abstr.* **1989**, *110*, 91988g]; k) Y. Fujita, *Ciba Found. Symp.* **1988**, *137*, 228–238 (Appl. Plant Cell Tissue Cult.); l) V. Petiard, P. Steck, *NATO ASI Ser. Ser. A* **128** **1987**, 139–153 (Perspect. Biotechnol.); m) Y. Fujita, *Kagaku Kogyo* **1987**, *38*, 405–409 [*Chem. Abstr.* **1987**, *107*, 57303m]; n) Y. Fujita, C. Suga, K. Matsubara, Y. Hara, *Nippon Nogei Kagaku Kaishi* **1986**, *60*, 849–854 [*Chem. Abstr.* **1987**, *106*, 16951d]; o) M. Tabata, Y. Fujita in *Biotechnology in Plant Science* (Eds.: P. R. Day, M. Zaitlin, A. Hollaender), Academic Press, Florida, **1985**, p. 207; p) M. Tabata, *Yaoxue Tongbao* **1985**, *20*, 519–521 [*Chem. Abstr.* **1986**, *104*, 166825p]; q) P. Brodelius, *Hereditas (Lund Swed.)* **1985**, (Suppl. 3), 73–81; r) Y. Fujita, T. Morimoto, *Saibo Kogaku* **1985**, *4*, 405–411 [*Chem. Abstr.* **1985**, *103*, 140168f]; s) Y. Fujita, *Yuki Gosei Kagaku Kyokashii* **1985**, *43*, 1003–1012 [*Chem. Abstr.* **1986**, *104*, 49737a]; t) P. F. Heinsteins, *J. Nat. Prod.* **1985**, *48*, 1–9.
- [104] From *Alkanna tinctoria*, see a) H. Urbanek, K. Bergier, S. Katarzynna, M. Saniewski, J. Patkowski, *Plant Cell Rep.* **1996**, *15*, 637–641; b) G. Mita, C. Gerardi, A. Miceli, R. Bollini, P. De Leo, *Plant Cell Rep.* **1994**, *13*, 406–410.
- [105] From *Onosma paniculatum*, see a) W. Ning, T. Yu, R. Cao, *Zhiwu Shengli Xuebao* **1996**, *22*, 74–80 [*Chem. Abstr.* **1996**, *125*, 190281n]; b) W. Wen, R. Cao, *Nanjing Daxue Xuebao, Ziran Kexue* **1995**, *31*, 334–337 [*Chem. Abstr.* **1996**, *124*, 82234v]; c) W. Ning, R. Q. Cao, *3rd Met. Ions Biol. Med. Proc. Int. Symp.* (Libbey, Montrouge, France) **1994**, 473–476 [*Chem. Abstr.* **1995**, *122*, 286710r]; d) R. Cao, Q. Zhao, *Biochem. Eng. 2001, Proc. Asia-Pac. Biochem. Eng. Conf.* (Eds.: S. Furusaki, I. Endo, R. Matsuno), Springer, Tokyo, **1992**, pp. 286–288 [*Chem. Abstr.* **1993**, *119*, 137416k]; e) L. Zhou, G. Zheng, S. Wang, *Yunnan Zhiwu Yanjiu* **1991**, *13*, 315–320 [*Chem. Abstr.* **1992**, *117*, 44645c]; f) L. Zhou, G. Zheng, S. Wang, F. Gan, *Tianran Chanwu Yanjiu Yu Kaifa* **1991**, *3*, 34–38 [*Chem. Abstr.* **1991**, *115*, 252160b]; g) R. Zhu, R. Cao, M. Wang, D. Pan, Z. Du, *Zhiwu Xuebao* **1990**, *32*, 749–752 [*Chem. Abstr.* **1991**, *114*, 225685z].
- [106] From *Onosma echinodes*, see S. Koul, M. Sambyal, R. K. Khajuria, S. M. Jain, *Fitoterapia* **1993**, *64*, 552–553 [*Chem. Abstr.* **1994**, *121*, 78272b].
- [107] From *Arnebia euchroma*, see a) S. Chen, S. Huo, *Tianran Chanwu Yanjiu Yu Kaifa* **1994**, *6*, 97–100 [*Chem. Abstr.* **1995**, *122*, 185416u]; b) L. V. Kozlovitseva, G. V. Zaitseva, S. E. Strogov, *Biotechnologia* **1994**, *3*, 24–26 [*Chem. Abstr.* **1994**, *121*, 228870m]; c) O. V. Zakhlenjuk, *Biopolim. Kletka* **1994**, *10*, 32–37 [*Chem. Abstr.* **1995**, *122*, 235505v]; d) J.-W. Dong, H.-C. Ye, X. Wu, G.-F. Li, Z.-R. Wu, L.-M. Gu, J.-L. Chen, *Zhiwu Xuebao*, **1993**, *35*, 57–61 [*Biol. Abstr.* **1993**, *96*, 60965]; e) G. Xiang, F. Lu, F. Zhu, G. Li, H. Ye, J. Dong, X. Wu, J. Chen, *Zhiwu Xuebao* **1992**, *34*, 470–474 [*Chem. Abstr.* **1993**, *118*, 98068f]; f) V. N. Davydenkov, A. V. Patudin, Yu. G. Popov, S. A. Rabinovich, A. I. Miroshnikov, *Khim. Farm. Zh.* **1991**, *25*, 53–55 [*Chem. Abstr.* **1991**, *115*, 47729c]; g) H. Ye, Z. Yin, G. Li, X. Wu, J. Dong, Z. Wu, *Zhiwu Xuebao* **1991**, *33*, 927–931 [*Chem. Abstr.* **1992**, *117*, 23461z].
- [108] For advances since 1990, see a) P. Lui, Z. Wei, Z. Xu, X. Chu, R. Cao, *Zhiwu Shengli Xuebao* **1996**, *22*, 243–250 [*Chem. Abstr.* **1997**, *127*, 92755s]; b) W. Ning, R. Cao, *Zhiwu Xuebao* **1996**, *38*, 367–374 [*Chem. Abstr.* **1997**, *126*, 211065h]; c) S. Liang, J. Gao, K. Gao, S. Qi, L. Lin, *Yaowu Shengwu Jishu* **1996**, *34*, 229–234 [*Chem. Abstr.* **1997**, *126*, 143342u]; d) X.-M. Luo, L. Yuan, M. Zhou, P. Quyang, *Nanjing Huangong Daxue Xuebao* **1996**, *18*, 12–16 [*Chem. Abstr.* **1997**, *126*, 88324n]; e) V. P. Bulgakov, M. V. Khodakovskaya, M. M. Kozryenko, N. V. Labetskaya, Yu. N. Zhuravlev, *Prikl. Biokhim. Mikrobiol.* **1996**, *32*, 453–457 [*Chem. Abstr.* **1997**, *126*, 6523q]; f) X. Luo, L. Yuan, M. Zhou, P. Ouyang, *Huaxue Gongye Yu Gongcheng (Tianjin)* **1996**, *13*, 1–6 [*Chem. Abstr.* **1996**, *125*, 56298v]; g) X. Luo, L. Yuan, M. Zhou, P. Ouyang, *Nanjing Huangong Xueyuan Xuebao* **1995**, *17*, 60–64 [*Chem. Abstr.* **1996**, *124*, 53782s]; h) L. Yuan, X. Luo, M. Zhou, P. Ouyang, *Nanjing Huangong Xueyuan Xuebao* **1995**, *17*, 78–82 [*Chem. Abstr.* **1996**, *124*, 53780q]; i) H. Lu, Q. Zhao, R. Cao, Z. Xia, *Zhiwu Shengli Xuebao* **1995**, *21*, 111–116 [*Chem. Abstr.* **1995**, *123*, 254619x]; j) X. Luo, L. Yuan, P. Ouyang, *Huaxue Fanying Gongcheng Yu Gongyi* **1995**, *11*, 192–197 [*Chem. Abstr.* **1995**, *123*, 196682z]; k) G. V. Zaitseva, S. E. Strogov, D. B. Travnikov, N. V. Dudnik, E. M. Fetisova, *Biotechnologia* **1994**, 24–27 [*Chem. Abstr.* **1995**, *122*, 131066m]; l) L. Yuan, M. Zhou, P. Ouyang, *Nanjing Huangong Xueyuan Xuebao* **1994**, *16*, 16–19 [*Chem. Abstr.* **1994**, *121*, 253761j]; m) W. Ning, R. Cao, *Shengwu Gongcheng Xuebao* **1994**, *10*, 76–80 [*Chem. Abstr.* **1994**, *121*, 155797f]; n) L. Yuan, P. Ouyang, *Nanjing Huangong Xueyuan Xuebao*, **1992**, *14*, 44–47 [*Chem. Abstr.* **1994**, *120*, 75536j]; o) L. Yuan, P. Ouyang, *Huaxue Fanying Gongcheng Yu Gongyi* **1992**, *8*, 379–384 [*Chem. Abstr.* **1994**, *120*, 52716d]; p) V. Srinivasan, D. D. Y. Ryu, *Biotechnol. Bioeng.* **1993**, *42*, 793–799; q) L. Yuan, P. Ouyang, *Biochem. Eng. 2001, Proc. Asia-Pac. Biochem. Eng. Conf.* (Eds.: S. Furusaki, I. Endo, R. Matsuno), Springer, Tokyo, **1992**, pp. 258–261 [*Chem. Abstr.* **1993**, *119*, 137409k]; r) H. N. Chang, S. J. Sim, *Biochem. Eng. 2001, Proc. Asia-Pac. Biochem. Eng. Conf.* (Eds.: S. Furusaki, I. Endo, R. Matsuno), Springer, Tokyo, **1992**, pp. 237–241 [*Chem. Abstr.* **1993**, *119*, 137405f]; s) W. T. Seo, Y. H. Park, T. B. Choe, *J. Microbiol. Biotechnol.* **1992**, *2*, 41–45; t) S. J. Sim, H. N. Chang, *Biotechnol. Lett.* **1993**, *15*, 145–150; u) D. J. Kim, H. N. Chang, *5th Proc. Eur. Congr. Biotechnol.* (Munksgaard, Copenhagen) **1990**, *1*, 124–127; v) V. Srinivasan, D. D. Y. Ryu, *Biotechnol. Bioeng.* **1992**, *40*, 69–74; w) K. Shimomura, H. Sudo, H. Saga, H. Kamada, *Plant Cell Rep.* **1991**, *10*, 282–285; x) Y. H. Park, T. Woen, J. R. Liu, *J. Ferment. Bioeng.* **1990**, *70*, 317–321; y) D. J. Kim, H. N. Chang, *Biotechnol. Bioeng.* **1990**, *36*, 460–466; z) D. J. Kim, H. N. Chang, *Biotechnol. Lett.* **1990**, *12*, 443–446; aa) D. J. Kim, H. N. Chang, *Biotechnol. Lett.* **1990**, *12*, 289–294.
- [109] For a recent and more detailed review, see M. Tabata, *Shokubutsu Soshiki Baiyo* **1996**, *13*, 117–125 [*Chem. Abstr.* **1996**, *125*, 243054z].
- [110] J. Mann, *Chemical Aspects of Biosynthesis*, Oxford Chemistry Primers, No. 20 (Ed.: S. G. Davies), Oxford University Press, Oxford, **1994**, pp. 31–52.
- [111] R. Löschler, L. Heide, *Plant Physiol.* **1994**, *106*, 271–279.
- [112] a) K. Yazaki, L. Heide, M. Tabata, *Phytochemistry* **1991**, *30*, 2233–2236; b) J.-P. Schnitzler, J. Madlung, A. Rose, H. U. Seitz, *Planta* **1992**, *188*, 594–600; c) C. J. French, C. P. Vance, G. H. N. Towers, *Phytochemistry* **1976**, *15*, 564–566.
- [113] R. E. Olsen, H. Rudney, *Vitam. Horm. (NY)* **1983**, *40*, 1–43.
- [114] a) R. E. Beyer, K. Nordenbrand, L. Ernster, *Chem. Scr.* **1987**, *27*, 145–153; b) G. W. Burton, K. U. Ingold, *Acc. Chem. Res.* **1986**, *19*, 194–201; c) S. Kasperek in *Vitamin E: A Comprehensive Treatise, Vol. 1* (Ed.: L. J. Machlin), Marcel Dekker, New York, **1980**, pp. 7–65.
- [115] a) H. V. Schmidt, M. H. Zenk, *Tetrahedron Lett.* **1971**, 4151–4155; b) H. Inouye, S. Ueda, K. Inoue, H. Matsumura, *Phytochemistry*

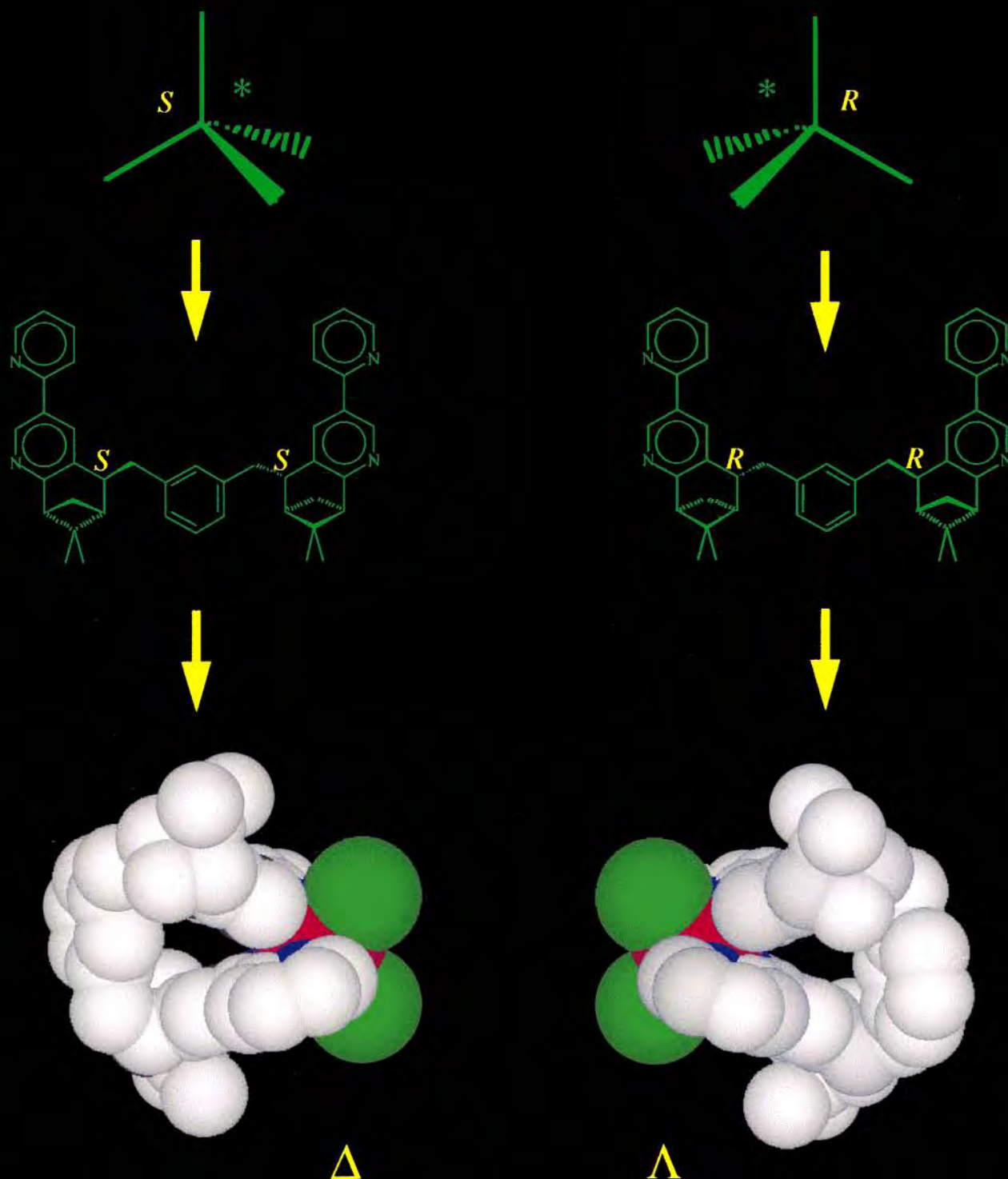
- 1979**, 18, 1301–1308; c) T. Okamoto, K. Yazaki, M. Tabata, *Phytochemistry* **1995**, 38, 83–88.
- [116] K. Yazaki, H. Fukui, M. Tabata, *Phytochemistry* **1986**, 25, 1629–1632.
- [117] S. Gaisser, L. Heide, *Phytochemistry* **1996**, 41, 1065–1072.
- [118] K. Yazaki, H. Fukui, M. Tabata, *Chem. Pharm. Bull.* **1986**, 34, 2290–2293.
- [119] a) F. Yoshizaki, S. Hisamichi, Y. Kondo, Y. Sato, S. Nozoe, *Chem. Pharm. Bull.* **1982**, 30, 4407–4411; b) X.-S. Yao, Y. Ebizuka, H. Noguchi, F. Kiuchi, H. Seto, U. Sankawa, *Tetrahedron Lett.* **1983**, 24, 2407–2410.
- [120] H. Inouye, H. Matsumura, M. Kawasaki, K. Inoue, M. Tsukada, M. Tabata, *Phytochemistry* **1981**, 20, 1701–1705.
- [121] H. Fukui, M. Tani, M. Tabata, *Phytochemistry* **1992**, 31, 519–521.
- [122] X.-S. Yao, Y. Ebizuka, H. Noguchi, F. Kiuchi, M. Shibuya, Y. Itaka, H. Seto, U. Sankawa, *Chem. Pharm. Bull.* **1991**, 39, 2956–2961.
- [123] a) L. Heide, M. Tabata, *Phytochemistry* **1987**, 6, 1645–1650; b) L. Heide, M. Tabata, *Phytochemistry* **1987**, 6, 1651–1655; c) R. Boehm, S.-M. Li, M. Melzer, L. Heide, *Phytochemistry* **1997**, 44, 419–424.
- [124] L. Wessjohann, B. Sonntag, *Angew. Chem.* **1996**, 108, 1821–1823; *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 1697–1699.
- [125] M. Tabata, K. Yazaki, Y. Nishikawa, F. Yoneda, *Phytochemistry* **1993**, 32, 1439–1442.
- [126] Y. Yamaga, K. Nakanishi, H. Fukui, M. Tabata, *Phytochemistry* **1993**, 32, 633–636.
- [127] A. Bechthold, U. Berger, L. Heide, *Arch. Biochem. Biophys.* **1991**, 288, 39–47.
- [128] K. Yazaki, K. Inushima, M. Kataoka, M. Tabata, *Phytochemistry* **1995**, 38, 1127–1130.
- [129] S. Sommer, K. Severin, B. Camara, L. Heide, *Phytochemistry* **1995**, 38, 623–627.
- [130] M. Moir, R. H. Thomson, *Phytochemistry* **1973**, 12, 1351.
- [131] A. Ohta, P. M. Sivalingham, S. Lin, N. Ikekawa, N. Yaginuma, Y. Inada, *Toxicon* **1973**, 11, 235–241.
- [132] L. F. Fieser, *J. Am. Chem. Soc.* **1928**, 50, 439–465.
- [133] K. Zahn, P. Ochwat, *Justus Liebigs Ann. Chem.* **1928**, 462, 72–97.
- [134] H. Brockmann, K. Müller, *Justus Liebigs Ann. Chem.* **1939**, 540, 51–72.
- [135] J. R. Lewis, J. G. Paul, *Z. Naturforsch. B* **1977**, 32, 1473–1475.
- [136] C. A. Tsipis, M. P. Sigalas, V. P. Papageorgiou, M. N. Bakola-Christianopoulou, *Can. J. Chem.* **1983**, 61, 1500–1504, and references therein.
- [137] R. E. Moore, P. J. Scheuer, *J. Org. Chem.* **1966**, 31, 3272–3283.
- [138] S. Bratan, F. Strobusch, *J. Mol. Struct.* **1980**, 61, 409–414.
- [139] *Elsevier's Encyclopaedia of Organic Chemistry, Series III, Vol. 12B*, (Ed.: F. Radt), pp. 3184–3188, and references therein.
- [140] S. Yoshino, K. Hayakawa, K. Kanematsu, *J. Org. Chem.* **1981**, 46, 3841–3846.
- [141] M. Aso, K. Kanematsu, *Chem. Pharm. Bull.* **1993**, 41, 1549–1556.
- [142] D. B. Bruce, R. H. Thomson, *J. Chem. Soc.* **1952**, 2759–2766.
- [143] M. S. Pearson, B. J. Jenschky, F. X. Greer, J. P. Hagstrom, N. M. Wells, *J. Org. Chem.* **1978**, 43, 4617–4622.
- [144] R. Huot, P. Brassard, *Can. J. Chem.* **1974**, 52, 838–842.
- [145] Y. Tanoue, A. Terada, H. Taniguchi, T. Okuma, H. Kaai, M. Anan, Y. Kakara, M. Doi, S.-I. Morishita, *Bull. Chem. Soc. Jpn.* **1993**, 66, 3712–3715.
- [146] C. G. Pierpont, L. C. Francesconi, D. N. Hendrickson, *Inorg. Chem.* **1978**, 17, 3470–3477.
- [147] D. B. Bruce, R. H. Thomson, *J. Chem. Soc.* **1955**, 1089–1096.
- [148] T. H. Smith, H. Y. Wu, *J. Org. Chem.* **1982**, 47, 1974–1976, and references therein.
- [149] A. Terada, Y. Tanoue, A. Hatada, H. Sakamoto, *Bull. Soc. Chem. Jpn.* **1987**, 60, 205–213.
- [150] M. Kawasaki, F. Matsuda, S. Terashima, *Tetrahedron Lett.* **1986**, 27, 2145–2148.
- [151] a) M. N. Bakola-Christianopoulou, V. P. Papageorgiou, K. K. Apazidou, *Phosphorous Sulfur Silicon Relat. Elem.* **1994**, 88, 53–65; b) M. N. Bakola-Christianopoulou, V. P. Papageorgiou, K. K. Apazidou, *J. Chromatogr.* **1993**, 645, 293–301.
- [152] M. N. Bakola-Christianopoulou, K. K. Apazidou, *J. Org. Chem.* **1996**, 61, 1850–1853.
- [153] E. A. Couladouros, Z. F. Plyta, V. P. Papageorgiou, *J. Org. Chem.* **1996**, 61, 3031–3033.
- [154] a) J. F. M. de Bie, R. M. Peperzak, M. J. Daenen, H. W. Scheeren, *Tetrahedron* **1993**, 49, 6463–6472, and references therein; b) Y. Naruta, K. Maruyama in *The Chemistry of the Quinonoid Compounds, Vol. II* (Ed.: S. Patai, Z. Rapaport), Wiley, New York, **1988**, pp. 277–303.
- [155] C. Coffey in *Rodd's Chemistry of Carbon Compounds, IIIG*, Elsevier, Amsterdam, **1978**, p. 238.
- [156] a) U. Sankawa, Y. Ebizuka, T. Miyazaki, Y. Isomura, H. Otsuka, S. Shibata, M. Inomata, F. Fukuoka, *Chem. Pharm. Bull.* **1977**, 25, 2392–2395; b) U. Sankawa, H. Otsuka, Y. Kataoka, Y. Iitaka, A. Hoshi, K. Kureitani, *Chem. Pharm. Bull.* **1981**, 29, 116–122.
- [157] a) H.-W. Cheng, F.-A. Chen, H.-C. Hsu, C.-Y. Chen, *Int. J. Pharm.* **1995**, 120, 137–144; b) F.-A. Chen, H.-W. Cheng, A.-B. Wu, H.-C. Hsu, C.-Y. Chen, *Chem. Pharm. Bull.* **1996**, 44, 249–251.
- [158] L. M. Van Der Vijver, K. W. Gerritsma, *J. Chromatogr.* **1975**, 114, 443–450.
- [159] V. P. Papageorgiou, *Chem. Chron.* **1978**, 7, 45–54.
- [160] B.-Z. Ahn, K.-U. Baik, G.-R. Kweon, K. Lim, B.-D. Hwang, *J. Med. Chem.* **1995**, 38, 1044–1047.
- [161] J. Otsuki, K. Otsuki, JP-B 7240788, **1972** [*Chem. Abstr.* **1973**, 78, 15906j].
- [162] Y. Seto, S. Motoyoshi, H. Nakamura, J. Imuta, T. Ishitoku, S. Isayama, *Yakugaku Zasshi* **1992**, 112, 259–271 [*Chem. Abstr.* **1992**, 117, 124158].
- [163] S. B. Katti, Y. N. Shukla, J. S. Tandon, *Indian J. Chem. Sect. B* **1979**, 18, 440–442.
- [164] V. P. Papageorgiou, DSc thesis, Polytechnic School Thessaloniki (Greece), **1976**.
- [165] V. P. Papageorgiou, M. Liakopoulou-Kyriakides, C. Papadakis, *Flavour Fragrance J.* **1985**, 1, 21–24.
- [166] a) E. Yesilada, E. Sezik, M. Aslan, A. Yesilada, *J. Liq. Chromatogr. Relat. Technol.* **1996**, 19, 3369–3381; b) R. Chaisuksant, PhD thesis, Aristotle University of Thessaloniki (Greece), **1994**; c) Y. Arai, T. Hanai, A. Nosaka, K. Yamaguchi, *J. Liq. Chromatogr.* **1990**, 13, 2449–2464; d) L. Snyder, J. Gajch, J. Kirkland, *Practical HPLC Method Development*, Wiley, Toronto, **1988**; e) S. Nickel, T. Carrol, *J. Chromatogr.* **1984**, 295, 521; f) M. Tsukada, H. Fukui, C. Habara, M. Tabata, *Shoyakugaku Zasshi* **1983**, 37, 299–306 [*Chem. Abstr.* **1984**, 101, 97723c]; g) L. X. Lin, J. W. Lan, Y. Han, M. F. Han, K. D. Lin, *Yaoxue Xuebao* **1995**, 30, 123–126 [*Chem. Abstr.* **1995**, 122, 248473h]; h) N. Shibayama, R. Yamaoka, M. Sato, J. Iida, *Shitsuryo Bunseki*, **1991**, 39, 123–131 [*Chem. Abstr.* **1992**, 116, 131028b].
- [167] V. P. Papageorgiou, DE-B 2829744, **1979** [*Chem. Abstr.* **1979**, 181441s].
- [168] T. Tani, Y. Sakakibara, K. Yamamoto, *Jpn. J. Appl. Phys. Suppl.* **1989**, 28–3, 239–245.
- [169] a) K. Inoue, M. Akaji, H. Inouye, *Chem. Pharm. Bull.* **1985**, 33, 3993–3997; b) V. P. Papageorgiou, *Planta Med.* **1979**, 37, 185–187.
- [170] V. P. Papageorgiou, *Planta Med.* **1980**, 40, 305–307.
- [171] a) Y. N. Shukla, J. S. Tandon, D. S. Bhakuni, M. M. Dhar, *Experientia* **1969**, 25, 357–358; b) Y. N. Shukla, J. S. Tandon, D. S. Bhakuni, M. M. Dhar, *Phytochemistry* **1971**, 10, 1909–1915.
- [172] K. H. Ai, J. Jin, H. Liu, *Yaoxue Xuebao* **1993**, 28, 282–285 [*Chem. Abstr.* **1993**, 119, 82263a].
- [173] A. A. Nabiullin, S. A. Fedoreev, T. N. Deshko, *Khim. Prir. Soedin.* **1983**, 568–573 [*Chem. Abstr.* **1984**, 100, 117799s].
- [174] A. V. Kovatsis, V. P. Papageorgiou, M. Christianopoulou, *Toxicol. Aspects (9th Int. Congr. Eur. Assoc. Poison Control Cent.)* **1980**, 43–54.
- [175] W. Otake, N. Sugiyama, K. Saito, H. Sato, *Nihon Daigaku Nojuigakubu Gijutsu Kenkyu Hokoku* **1990**, 218–223 [*Chem. Abstr.* **1991**, 114, 198810c].
- [176] R. Chaisuksant, A. Voulgaropoulos, A. S. Mellidis, V. P. Papageorgiou, *Analyst* **1993**, 118, 1346.
- [177] R. Chaisuksant, A. Voulgaropoulos, A. S. Mellidis, V. P. Papageorgiou, *Analysis* **1994**, 22, 400–403.
- [178] a) R. Takamoto, R. Namba, S. Yamamoto, T. Takamatsu, M. Matsuoka, T. Sawada, *Bunseki Kagaku* **1996**, 45, 225–238 [*Chem. Abstr.* **1996**, 124, 211615w]; b) R. Takamoto, R. Namba, M. Matsuoka, T. Sawada, *Anal. Chem.* **1992**, 64, 2661–2663; c) R. Takamoto, R. Namba, O. Nakata, T. Sawada, *Anal. Chem.* **1990**, 62, 674–677.

- [179] E. A. Couladouros, Z. F. Plyta, A. T. Strongilos, V. P. Papageorgiou, *Tetrahedron Lett.* **1997**, 38, 7263–7266.
- [180] a) F. M. Hauser, D. J. Mal, *J. Am. Chem. Soc.* **1983**, 105, 5688–5690; b) M. D. Shair, T. Y. Yoon, K. K. Mosny, T. C. Chou, S. J. Danishefsky, *J. Am. Chem. Soc.* **1996**, 118, 9509–9525; c) B. L. Chenard, M. G. Dolson, A. D. Sercel, J. S. Swenton, *J. Org. Chem.* **1984**, 49, 318–325.
- [181] Y. Tanoue, A. Terada, *Bull. Chem. Soc. Jpn.* **1988**, 61, 2039–2045.
- [182] A. Terada, Y. Tanoue, A. Hatada, H. Sakamoto, *J. Chem. Soc. Chem. Commun.* **1983**, 987–988.
- [183] Y. Tanoue, A. Terada, H. Taniguchi, S.-I. Morishita, *Suisan Daigakko Kenkyu Hokoku* **1994**, 42, 157–162.
- [184] A. M. Moiseenkova, N. N. Balaneva, V. L. Novikov, G. B. Elyakov, *Dokl. Akad. Nauk. SSSR* **1987**, 295, 614–617.
- [185] V. L. Novikov, N. N. Balaneva, A. M. Moiseenkova, G. B. Elyakov, *Izv. Akad. Nauk SSSR Ser. Khim.* **1992**, 1901–1910.
- [186] S. Torii, K. Akiyama, H. Yamashita, T. Inokuchi, *Bull. Chem. Soc. Jpn.* **1995**, 68, 2917–2922.
- [187] a) J. H. Freudenberger, A. W. Konradi, S. F. Pedersen, *J. Am. Chem. Soc.* **1989**, 111, 8014–8016; b) A. W. Konradi, S. F. Pedersen, *J. Am. Chem. Soc.* **1994**, 116, 1316–1323.
- [188] Y. Tanoue, A. Terada, Y. Sugyo, *J. Org. Chem.* **1987**, 52, 1437–1439.
- [189] Y. Shimai, T. Koga (Pias) JP-B 63156741, **1988** [*Chem. Abstr.* **1989**, 110, 23567u].
- [190] a) K. H. Dötz, *Angew. Chem.* **1984**, 96, 573; *Angew. Chem. Int. Ed. Engl.* **1984**, 23, 587–608; b) K. H. Dötz in *Organometallics in Organic Synthesis* (Eds.: A. de Meijere, H. Tom Dieck) Springer, Berlin, **1988**, pp. 85–104; c) P. J. Harrington, *Transition Metal in Total Synthesis*, Wiley, New York, **1990**, pp. 346–399; d) W. D. Wulff in *Comprehensive Organic Synthesis*, Vol. 5 (Eds.: B. M. Trost, I. Fleming, L. A. Paquette), Pergamon, New York, **1991**, pp. 1065–1113.
- [191] J. S. Yadav, P. K. Deshpande, G. V. M. Sharma, *Tetrahedron* **1990**, 46, 7033–7046.
- [192] M. Braun, C. Bauer, *Liebigs Ann. Chem.* **1991**, 1157–1164.
- [193] a) M. Braun, R. Devant, *Tetrahedron Lett.* **1984**, 25, 5031–5034; b) R. Devant, U. Mahler, M. Braun, *Chem. Ber.* **1988**, 121, 397–406.
- [194] a) P. K. Jadhav, K. S. Bhat, P. T. Perumal, H. C. Brown, *J. Org. Chem.* **1986**, 51, 432–439; b) Y. Yamamoto, N. Asao, *Chem. Rev.* **1993**, 93, 2207–2293.
- [195] K. C. Nicolaou, D. Hepworth, *Angew. Chem.* **1998**, 110, 864–866; *Angew. Chem. Int. Ed.* **1998**, 37, 839–841.
- [196] “Stereoselective Synthesis”: M. M. Midland, L. A. Morrel, *Methoden Org. Chem. (Houbden-Weyl)* 4th ed. 1952–, VI. E21, D, chap. 2.3.3.2, pp. 4049–4066.
- [197] F. Dallacker, J. Jacobs, W. Coerver, *Z. Naturforsch. B* **1983**, 38, 1000–1007.
- [198] a) H. C. Brown, J. Chandrasekharan, P. V. Ramachandran, *J. Am. Chem. Soc.* **1988**, 110, 1539–1546; b) P. V. Ramachandran, A. V. Teodorovic, M. V. Rangaishenvi, H. C. Brown, *J. Org. Chem.* **1992**, 57, 2379–2386; c) R. K. Dar, *Aldrichimica Acta* **1994**, 27, 43–51.
- [199] D. A. Frey, N. Wu, K. D. Moeller, *Tetrahedron Lett.* **1996**, 37, 8317–8320.
- [200] V. P. Papageorgiou, *Experientia* **1978**, 34, 1499–1501.
- [201] V. P. Papageorgiou, *Chem. Chron.* **1977**, 6, 365–374.
- [202] V. P. Papageorgiou, G. A. Digenis, *Planta Med.* **1980**, 39, 81–84.
- [203] V. P. Papageorgiou, *Planta Med.* **1977**, 31, 390–394.
- [204] It is thought that the isolation procedure adopted by Brockmann^[1] may have caused ester hydrolysis. See Table 1, note 1.
- [205] V. P. Papageorgiou, DE-B 2700448, **1978**, US-A 4282250, **1981**, [*Chem. Abstr.* **1978**, 89, 152707m].
- [206] The clinical trials were undertaken at Heidberg Dermatological Clinic, Hamburg by Prof. A. Winkler.
- [207] C. Michaelides, C. Striglis, P. Panayotou, I. Ioannovich, *Ann. Medit. Burns Club* **1993**, VI, 24–25.
- [208] M. Owili, Clinical Report to the Pharmaceutical Company CHROPI S.A., Kenyatta National Hospital, Nairobi, Kenya, October 17, **1986**.
- [209] G. Karkanas, N. Alexandropoulos, N. Haritopoulos, *Abstr. Pap. 45th Hellenic Natl. Conf. (Athens)* **1991**, p. 61.
- [210] a) M. Hayashi, *Nippon Yakurigaku Zasshi* **1977**, 73, 177–191 [*Chem. Abstr.* **1977**, 88, 44862d]; b) M. Hayashi, *Nippon Yakurigaku Zasshi* **1977**, 73, 193–203 [*Chem. Abstr.* **1977**, 88, 44863e]; c) M. Hayashi, *Nippon Yakurigaku Zasshi* **1977**, 73, 205–214 [*Chem. Abstr.* **1977**, 88, 44864f].
- [211] a) Y. Ozaki, A. Ohno, K.-I. Abe, Y. Saito, M. Satake, *Biol. Pharm. Bull.* **1993**, 16, 683–685; b) Y. Ozaki, A. Ohno, Y. Saito, M. Satake, *Biol. Pharm. Bull.* **1994**, 17, 1075–1077; c) Y. Ozaki, L. Xing, M. Satake, *Biol. Pharm. Bull.* **1996**, 19, 233–236.
- [212] S. Tanaka, M. Tajima, M. Tsukada, M. Tabata, *J. Nat. Prod.* **1986**, 49, 466–469.
- [213] Z.-B. Lin, B.-L. Chai, P. Wang, Q.-X. Guo, F.-S. Lu, G.-Q. Xiang, *Peiching I Hsueh Yuan Hsueh Pao* **1980**, 12, 101–106 [*Chem. Abstr.* **1980**, 93, 143008q].
- [214] Z.-B. Lin, P. Wang, Y. Ruan, Q.-X. Guo, *Acta Pharmacol. Sin.* **1980**, 1, 60–63 [*Biol. Abstr.* **1981**, 73, 34163].
- [215] W. J. Wang, J. Y. Bai, D. P. Lui, L. M. Xue, X. Y. Zhu, *Yaoxue Xuebao* **1994**, 29, 161–165 [*Chem. Abstr.* **1994**, 121, 148550s].
- [216] P. Martin, *Science* **1997**, 276, 75–81.
- [217] F. Hübötter, *Beiträge zur Kenntnis der chinesischen sowie der tibetisch-mongolischen Pharmakologie*, Urban und Schwarzenberg, Berlin, **1913**, p. 324.
- [218] J. L. Hartwell, *Plants Used Against Cancer: A Survey*, Quarterman, Lawrence, MA, **1982**, pp. 68–72.
- [219] J. S. Driscoll, G. F. Hazard, Jr., H. B. Wood, Jr., A. Goldin, *Cancer Chemother. Rep. Part 2*, **1974**, 4(2), 1–362.
- [220] S. K. Gupta, I. S. Mathur, *Indian J. Cancer* **1972**, 9, 50–55.
- [221] H. Wagner, B. Kreher, K. Jurcic, *Arzneim. Forsch.* **1988**, 38, 273–275.
- [222] a) H. Lee, J.-Y. Lin, *Mutation Res.* **1988**, 204, 229–234; b) T. Hamano, I. Yasuda, Y. Watanabe, T. Konoshima, T. Harukuni, *Kenkyu Nenpo Tokyo-toristu Eisei Kenkyusho* **1992**, 43, 46–50 [*Chem. Abstr.* **1993**, 118, 204762q].
- [223] A. Ohtsuka, T. Nunoshiba, K. Nakayama, R. Namiuchi, S. Saigusa, T. Sotani, H. Nishioka, *Sci. Eng. Rev. Doshisha Univ.* **1986**, 27, 65–73.
- [224] a) T. Konoshima, M. Kozuka, J. Koyama, T. Okatani, K. Tagahara, H. Tokuda, *J. Nat. Prod.* **1989**, 52, 987–995; b) G. J. Kapadia, V. Balasubramanian, H. Tokuda, T. Konoshima, M. Takasaki, J. Koyama, K. Tagahara, H. Nishino, *Cancer Lett.* **1997**, 113, 47–53.
- [225] N. Yoshimi, A. Wang, Y. Morishita, T. Tanaka, S. Sugie, K. Kawai, Y. Yamahara, H. Mori, *Jpn. J. Cancer Res.* **1992**, 83, 1273–1278.
- [226] a) V. P. Papageorgiou, M. N. Christianopoulou, L. L. Boutis, A. Papageorgiou, C. A. Tsipis, *Inorg. Chem. Acta* **1986**, 124, 203–206; b) A. N. Sagredos, V. P. Papageorgiou, A. S. Mellidis, EP-B 144809, **1985** [*Chem. Abstr.* **1985**, 103, 196266d].
- [227] H. Sakurai, N. Hashimoto, JP-B 06100569, **1992** [*Chem. Abstr.* **1994**, 121, 244290c].
- [228] M. G. Miller, A. Rodgers, G. M. Cohen, *Biochem. Pharmacol.* **1986**, 35, 1177–1184.
- [229] H. W. Moore, *Science* **1977**, 197, 527–531.
- [230] M. Tomasz, C. M. Mercado, J. Olson, N. Chatterjee, *Biochemistry* **1974**, 13, 4878–4887.
- [231] N. Fujii, Y. Yamashita, Y. Arima, M. Nagashima, H. Nakano, *Antimicrob. Agents Chemother.* **1992**, 36, 2589–2594.
- [232] For a review, see S. J. Froelich-Ammon, N. Osheroff, *J. Biol. Chem.* **1995**, 270, 21429–21432.
- [233] Earlier, these authors had reported activity of acetylshikonin (**15**) against both topoisomerase-I and -II: K. R. Kweon, K. U. Baik, K. Lim, B. D. Hwang, B. Z. Ahn, *Proc. Am. Assoc. Cancer Res. Annu. Meet.* **1993**, 34, 328.
- [234] B.-Z. Ahn, D.-E. Sok, *Curr. Pharm. Des.* **1996**, 2, 247–262, and references therein.
- [235] B.-Z. Ahn, G.-Y. Song, K. U. Baik, D. E. Sok, *Korean J. Med. Chem.* **1996**, 6, 98–109.
- [236] a) B. Z. Ahn, Y. Kim, K. U. Baik, WO-B 9703940, [*Chem. Abstr.* **1997**, 126, 199354s]; b) B. Z. Ahn, K. U. Baik, WO-B 9502572 [*Chem. Abstr.* **1995**, 123, 227829j].
- [237] S.-H. Kim, G.-Y. Song, G.-Z. Jin, B.-Y. Ahn, *Arch. Pharm. Res.* **1996**, 19, 416–422.
- [238] S.-H. Kim, G.-Y. Song, D.-E. Sok, B.-Y. Ahn, *Arch. Pharm. Res.* **1997**, 20, 155–157.
- [239] D. S. Bhakuni, M. L. Dhar, M. M. Dhar, B. N. Dhawan, B. N. Mehrotra, *Indian J. Exp. Biol.* **1969**, 7, 250–262 [*Biol. Abstr.* **1970**, 53, 43416].
- [240] a) Y. Tanaka, T. Odani, *Yakugaku Zasshi* **1972**, 92, 525–530 [*Chem. Abstr.* **1972**, 92, 97680t]; b) K. Kyogoku, H. Terayama, Y. Tachi, T.

- Suzuki, M. Komatsu, *Shoyakugaku Zasshi* **1973**, 27, 31–36 [*Chem. Abstr.* **1974**, 80, 52315c]; c) Y. Tanaka, T. Odani, T. Kanaya, *Shoyakugaku Zasshi* **1974**, 28, 173–178 [*Chem. Abstr.* **1975**, 83, 152418u].
- [241] a) V. P. Papageorgiou, A. S. Mellidis, A. N. Sagredos, *Chem. Chron.* **1980**, 9, 57–63; b) V. P. Papageorgiou, A. Winkler, A. N. Sagredos, G. A. Digenis, *Planta Med.* **1979**, 35, 56–60.
- [242] M. Tabata, H. Mizukami, S. Naoye, K. Masao, *Yakugaku Zasshi* **1975**, 95, 1376–1379 [*Biol. Abstr.* **1976**, 62, 18482].
- [243] M. Tabata, M. Tsukada, H. Fukui, *Planta Med.* **1982**, 44, 234–236.
- [244] a) L. R. Shcherbanovskii, G. I. Nilov, Z. D. Rabinovich, V. A. Gorina, *Rast. Resur.* **1972**, 8, 112–115 [*Chem. Abstr.* **1972**, 76, 136281u]; b) L. P. Shcherbanovskii, *Ukr. Bot. Zh.* **1971**, 28, 504–508 [*Chem. Abstr.* **1971**, 76, 68687d]; c) L. R. Shcherbanovskii, A. Yu. Luks, I. G. Kapelev, *Mikrobiol. Zh. (Kiev)* **1975**, 37, 629–634 [*Chem. Abstr.* **1976**, 84, 728c]; d) L. R. Shcherbanovskii, *Abstr. Pap. 8th Fitonitsidy: Rol Biogeotsenozakh, Znach. Med. Mater. Soveshch. (Kiev, USSR)* **1979**, pp. 121–126 [*Chem. Abstr.* **1982**, 97, 89062v].
- [245] I. Inagaki, M. Yamazaki, A. Takahashi, K. Ooye, S. Shibata, S. Takada, *Nagoya Shiritsu Daigaku Yakugakubu Kenkyu Nempo* **1967**, (15), 27–32 [*Chem. Abstr.* **1968**, 69, 41955h].
- [246] M. Liu, T. Ohuchi, T. Ieiri, M. Ohe, S. Matsuzaki, *Dokkyo J. Med. Sci.* **1996**, 23, 63–69.
- [247] G. Honda, F. Sakakibara, K. Yazaki, M. Tabata, *J. Nat. Prod.* **1988**, 51, 152–154.
- [248] M. Tabata, Y. Honda, (Mitsubishi Petrochemical) JP-B 62289516, **1987**, [*Chem. Abstr.* **1988**, 109, 806m].
- [249] a) V. V. Gusev, A. A. Alekseev, E. V. Makarov, A. V. Barinov, SU-B 1829942, **1993** [*Chem. Abstr.* **1995**, 123, 179515e]; b) V. V. Gusev, A. A. Alekseev, E. V. Makarov, A. V. Barinov, SU-B 1829944, **1993** [*Chem. Abstr.* **1995**, 123, 179516f].
- [250] S. Wahab, R. N. Tandon, Z. Jacob, B. Chandra, O. P. Srivastava, *Indian J. Med. Res. Suppl.* **1979**, 76, 77–82.
- [251] M. A. Rubinchik, *Abstr. Pap. Mater. Vses. Konf. Issled. Lek. Rast. Perspekt. Ikh Isol'z Proivod. Lek. Prep. (Bittsa, USSR)* **1970**, pp. 236–237 [*Chem. Abstr.* **1975**, 83, 671h].
- [252] a) H. M. S. Sulaiman, S. N. H. Naqvi, A. M. S. Mohammad, *Curr. Sci.* **1978**, 47, 743–744 [*Chem. Abstr.* **1979**, 90, 1653k]; b) S. N. H. Naqvi, H. M. S. Sulaiman, M. Afzal, A. M. S. Mohammad, *Pak. J. Zool.* **1984**, 16, 175–180 [*Chem. Abstr.* **1986**, 104, 2173y]; c) N. S. Gorgefs, S. N. H. Naqvi, L. J. Rashan, S. J. Zakaria, *Folia Histochem. Cytochem.* **1978**, 16, 51–55 [*Chem. Abstr.* **1978**, 89, 18317f].
- [253] a) Y.-S. Chang, S.-C. Kuo, S.-H. Weng, S.-C. Jan, F.-N. Ko, C.-M. Teng, *Planta Med.* **1993**, 59, 401–404; b) F.-N. Ko, Y.-S. Lee, S.-C. Kuo, Y.-S. Chang, C.-M. Teng, *Biochem. Biophys. Acta.* **1995**, 1268, 329–334.
- [254] L. Majlathova, *Nahrung* **1971**, 15, 505–508 [*Chem. Abstr.* **1971**, 76, 12251j].
- [255] L. Tikkanen, T. Matsushima, S. Natori, K. Yoshihira, *Mutation Res.* **1983**, 124, 25–34.
- [256] B. N. Ames, J. McCann, E. Yamasaki, *Mutation Res.* **1975**, 31, 347–363.
- [257] W. J. Wang, M. G. Yi, X. Y. Zhu, *Yaoxue Xuebao* **1988**, 23, 246–251 [*Chem. Abstr.* **1988**, 109, 47792u].
- [258] a) M. R. Meselhy, S. Kadota, K. Tsubono, A. Kusai, M. Hattori, T. Namba, *Tetrahedron Lett.* **1994**, 35, 583–586; b) M. R. Meselhy, S. Kadota, K. Tsubono, M. Hattori, T. Namba, *Tetrahedron* **1994**, 50, 3081–3098.
- [259] C. Y. Chen, F.-A. Chen, A.-B. Wu, H.-C. Hsu, J.-J. Kang, H. W. Cheng, *Int. J. Pharm.* **1996**, 141, 171–178.
- [260] a) “Inhibition of Topoisomerase I by Naphthoquinone Derivatives”: Z. F. Plyta, T. Li, V. P. Papageorgiou, A. S. Mellidis, A. N. Assimopoulou, E. N. Pitsinos, E. A. Couladouros, *Bioorg. Med. Chem. Lett.* **1998**, 8, 3385–3390; b) “Evaluation of antibacterial effect of shikonin ointment against methicillin-resistant *Staphylococcus aureus*”: T. Sekine, K. Kojima, S. Sasaki, T. Matsumoto, T. Yamamoto, Y. Maitani, T. Nagai, *S.T.P. Pharma Sci.* **1998**, 8, 255–259 [*Chem. Abstr.* **1998**:770483];^[267] c) “Preparation and evaluation of shikonin ointment for wound healing: effectiveness in an experimental wound healing model in rats”: T. Sekine, K. Kojima, S. Ota, T. Matsumoto, T. Yamamoto, Y. Maitani, T. Nagai, *S.T.P. Pharma Sci.* **1998**, 8, 249–253 [*Chem. Abstr.* **1998**:770482];^[267] d) “Evaluation of Shikonin on granulation tissue formation compared with carrageenan”: T. Sekine, K. Kojima, T. Matsumoto, T. Yamamoto, Y. Maitani, T. Nagai, *Biol. Pharm. Bull.* **1998**, 21, 950–952; e) “Heat-shock protein formation inhibitors containing dihydroxynaphthoquinones”: Y. Kiyosuke, S. Tsuzuki, T. Shirakami, M. Morino, C. Yoshikumi, (Kureha Chemical Industry Co.) JP 10212230, **1998** [*Chem. Abstr.* **1998**, 129, 144853]; f) “Some phytochemicals and related compounds in vegetables as potent inhibitors of human DNA topoisomerase II”: M. Miyahara, M. Kawasaki, H. Akiyama, T. Narui, M. Toyoda, T. Okuyama, Y. Saito, *Food Factors Cancer Prev. [Int. Conf.]* **1997**, 182–187 [*Chem. Abstr.* **1998**, 129, 197664]; g) “Apoptosis inducer”: M. Nakayama, N. Ikeda, Y. Kato, *Frangrance J.* **1998**, 26, 72–80; h) “Shikonin, an ingredient of *Lithospermum erythrorhizon*, inhibits angiogenesis in vivo and in vitro”: T. Yuki Hisa, Y. Kimura, K. Takada, F. Suzuki, M. Takigawa, *Anticancer Res.* **1998**, 18(2A), 783–790; i) “Haloacetylshikonin derivatives: synthesis and evaluation of antitumor activity”: X.-G. Zheng, G.-Z. Jin, G.-Y. Song, C. Hoon, B.-Z. Ahn, *Yakuhak Hoechi* **1998**, 42, 159–164 [*Chem. Abstr.* **1998**, 129, 16007]; j) “Study of the accelerating effect of shikonin and alkannin on the proliferation of granulation tissue in rats”: Y. Ozaki, I. Sakaguchi, M. Tujimura, N. Ikeda, M. Nakayama, Y. Kato, H. Suzuki, M. Satake, *Biol. Pharm. Bull.* **1998**, 21, 366–370; k) “Antiviral and antifungal activities of some naphthoquinones isolated from the roots of *Lithospermum erythrorhizon*”: C. Li, Y. Fukushi, J. Kawabata, S. Tahara, J. Mizutani, I. Uyeda, *Nippon Noyaku Gakkaishi* **1998**, 23, 54–57 [*Chem. Abstr.* **1998**, 128, 241823]; l) “Heat-shock protein 47 (HSP 47) formation inhibitors containing shikonin”: Y. Kiyosuke, S. Tsuzuki, T. Shirakami, M. Morino, C. Yoshikumi, (Kureha Chemical Industry Co.) JP 10045575, **1998** [*Chem. Abstr.* **1998**, 128, 158908]; m) “Heat-shock protein 27 (HSP 27) formation inhibitors containing shikonin”: M. Morino, S. Tsuzuki, T. Shirakami, Y. Seiho, C. Yoshikumi, (Kureha Chemical Industry Co.) JP 10045574, **1998** [*Chem. Abstr.* **1998**, 128, 158907]; n) “Shikonin for wound treatment”: A. A. Adamyan, S. V. Dobysh, G. V. Polikakhina, I. A. Argunovskij, P. M. Golovanova, L. R. Makarova, N. N. Tuzova, (Aktzionernoe Obshchestvo Zakrytogo Tipa Mnogoprofilnyj Kompleks “universal”, Russia; Obshchestvo S Ogranichennoj Otvetstvennostyu Nauchno-Tekhnicheskij Tsentr “riza”): RU 2071788, **1997** [*Chem. Abstr.* **1997**, 127, 351235]; o) “Inhibition of xanthine oxidase by hydroxylated anthraquinones and related compounds”: S.-Y. Sheu, H.-C. Chiang, *Anticancer Res.* **1997**, 17, 3293–3297; p) “Study on baths with crude drug. III. The effect of *Ligustici chuanxiong rhizoma* extract on the percutaneous absorption of some natural compounds”: K. Sekiya, S. Kadota, K. Katayama, T. Koizumi, T. Namba, *Biol. Pharm. Bull.* **1997**, 20, 983–987.
- [261] a) “Determination of shikonin content with thin layer chromatography-chemiluminescence”: H. Li, B. Wang, Z. Pang, *Fenxi Huaxue* **1998**, 26, 1282 [*Chem. Abstr.* **1998**, 129, 347370]; b) “Enantiomeric ratio of shikonin derivatives as a possible key for the determination of the origin of *Lithospermum Radix*”: J. S. Kang, B. Z. Ahn, G. Blaschke, *Arch. Pharmacol. Res.* **1998**, 21, 565–569; c) “In vitro biotransformation of shikonin by LC-MS”: H. Li, S. Luo, T. Zhou, S. Yang, *Zhongguo Yaoxue Zazhi (Beijing)* **1997**, 32(Suppl.), 37–39 [*Chem. Abstr.* **1998**:660197];^[267] d) “Evaluation of superoxide anion radical scavenging activity of shikonin by electron spin resonance”: T. Sekine, T. Masumizu, Y. Maitani, T. Nagai, *Int. J. Pharm.* **1998**, 174, 133–139 [*Chem. Abstr.* **1998**:655481];^[267] e) “Quantitative determination of naphthoquinones of *Arnebia densiflora* (Nordm.) Ledeb. by an improved high-performance liquid chromatographic method”: B. Bozan, K. H. C. Baser, S. Kara, *J. Chromatogr. A* **1997**, 782(1), 133–136 [*Chem. Abstr.* **1997**, 127, 298820].
- [262] a) “Shikonin production by hairy roots of *Lithospermum erythrorhizon* in bioreactors with in situ separation”: S. J. Sim, H. N. Chang, *Hairy Roots* (Ed.: P. M. Doran), Harwood, Amsterdam, **1997**, pp. 219–225; b) “Changes of intracellular Ca^{2+} and cAMP during the formation of shikonin derivatives promoted by *Aspergillus oryzae* elicitor”: W. Ning, R. Cao, J. Wang, Y. Liu, X. Lu, *Zhiwu Shenglixue Tongxun* **1998**, 34, 194–196 [*Chem. Abstr.* **1998**, 129, 328285]; c) “The effects of Ca^{2+} during the elicitation of shikonin derivatives in *Onosma paniculatum* cells”: W. Ning, J.-X. Wang, Y.-M. Liu, N. Li, R.-Q. Cao, *In Vitro Cell. Dev. Biol.* **1998**, 34, 261–265 [*Chem. Abstr.* **1998**, 129, 313453]; d) “Effects of fungal

- elicitors on the cell growth and the shikonin biosynthesis in *Arnebia euchroma* cells in suspension culture" C.-J. Liu, S.-S. Hou, *Zhiwu Shengli Xuebao* **1998**, *24*, 6–10 [*Chem. Abstr.* **1998**, *129*, 148102]; e) "4-Hydroxybenzoate 3-geranyltransferase from *Lithospermum erythrorhizon*. Purification of a plant membrane-bound prenyltransferase": A. Muehlenweg, M. Melzer, S.-M. Li, L. Heide, *Planta* **1998**, *205*, 407–413; f) "Shikonin: a geranyl diphosphate-derived plant hemiterpenoid formed via the mevalonate pathway": S.-M. Li, S. Hennig, L. Heide, *Tetrahedron Lett.* **1998**, *39*, 2721–2724; f) "Formation and secretion of a new brown benzoquinone by hairy root cultures of *Lithospermum erythrorhizon*": H. Fukui, A. F. M. F. Hasan, T. Ueoka, M. Kyo, *Phytochemistry* **1998**, *47*, 1037–1039; g) "Enhancement of shikonin production in cell suspension cultures of *Arnebia euchroma* employing two-liquid-phase systems": X. Fu, D. Lu, *Chin. J. Chem. Eng.* **1998**, *6*, 86–90 [*Chem. Abstr.* **1998**, *128*, 307562]; h) "Isolation of shikonin derivatives from organic solvent by macroporous adsorption resin": Q. Men, D. Lu, G. Zhang, *Gaoxiao Huaxue Gongcheng Xuebao* **1998**, *12*, 23–27 [*Chem. Abstr.* **1998**, *128*, 307561]; i) "Shikonin production by cell suspension culture of *Onosma paniculatum* in turbine stirred bioreactor": H. Zhang, W. Ning, Q. Zhao, R. Cao, Y. Che, *Nanjing Daxue Xuebao, Ziran Kexue* **1997**, *33*, 455–458 [*Chem. Abstr.* **1998**, *128*, 229385]; j) "Plant cell and tissue culture. Industrial applications": C. Ponzzone, *Chim. Ind. (Milan)* **1997**, *79*, 1217–1221; k) "Manufacture of plant secondary metabolites using coronatines": T. Gyoso, Y. Hara, (Mitsui Petrochemical Industries, Ltd., Japan) JP 10033190, **1998** [*Chem. Abstr.* **1998**, *128*, 139817]; l) "Regulatory role of microsomal 3-hydroxy-3-methylglutaryl-coenzyme A reductase for shikonin biosynthesis in *Lithospermum erythrorhizon* cell suspension cultures": B. M. Lange, K. Severin, A. Bechthold, L. Heide, *Planta* **1998**, *204*, 234–241; m) "Relationship between active oxygen burst and shikonin derivatives formation in cultured *Onosma paniculatum* cells induced by *Aspergillus* elicitor": W. Ning, H. Xu, R. Cao, *Nanjing Daxue Xuebao, Ziran Kexue* **1997**, *33*, 259–264 [*Chem. Abstr.* **1998**, *128*, 137643]; n) "cDNA cloning and gene expression of phenylalanine ammonia-lyase in *Lithospermum erythrorhizon*": K. Yazaki, M. Kataoka, G. Honda, K. Severin, L. Heide, *Biotechnol. Biochem.* **1997**, *61*, 1995–2003; o) "*Arnebia euchroma*: in vitro culture and the production of shikonin and other secondary metabolites": O. V. Zakhlenjuk, V. A. Kunakh, *Biotechnol. Agric. For.* **1998**, *41* (*Medicinal and Aromatic Plants X*), 28–44 [*Chem. Abstr.* **1998**, *128*, 101107]; p) "*Alkanna tinctoria* T. (alkanets): in vitro culture and the production of alkannin and other secondary metabolites": C. Gerardi, G. Mita, E. Grillo, G. Giovinazzo, A. Miceli, P. De Leo, *Biotechnol. Agric. For.* **1998**, *41* (*Medicinal and Aromatic Plants X*), 14–27 [*Chem. Abstr.* **1998**, *128*, 74326]; q) "Measurement of phenolic compounds and their effect on shikonin production in *Lithospermum* cultured cells": K. Yazaki, H. Fukui, Y. Nishikawa, M. Tabata, *Biosci. Biotechnol. Biochem.* **1997**, *61*, 1674–1678 [*Chem. Abstr.* **1998**, *128*, 1945]; r) "Induction of phytoalexin by uptake of naphthoquinones in cell cultures of petunia": M.-J. Kim, S.-S. Kwak, *Han'guk Nonghwa Hakhoechi* **1997**, *40*, 352–356 [*Chem. Abstr.* **1997**, *127*, 245602]; s) "Biotechnology in detergents and cosmetics": S. Ito, *Baioisaiensu to Indasutori* **1997**, *55*, 541–545 [*Chem. Abstr.* **1998**, *127*, 189671]; t) "Effects of methyl jasmonate on shikonin and dihydroechinofuran production in *Lithospermum* cell cultures" K. Yazaki, K. Takeda, M. Tabata, *Plant Cell Physiol.* **1997**, *38*, 776–782; u) "Plant regeneration from callus cultures of *Lithospermum erythrorhizon*": H. J. Yu, S. K. Oh, M. H. Oh, D. W. Choi, Y. M. Kwon, S. G. Kim, *Plant Cell Rep.* **1997**, *16*, 261–266; v) "4-Hydroxybenzoate prenyltransferases in cell-free extracts of *Lithospermum erythrorhizon* cell cultures": R. Boehm, S.-M. Li, M. Melzer, L. Heide, *Phytochemistry* **1997**, *44*, 419–424.
- [263] a) "Chemical properties of shikonin from the view point of dyeing": N. Nagashima, K. Sakata, A. Katayama, *Nippon Sanshigaku Zasshi* **1998**, *67*, 123–127 [*Chem. Abstr.* **1997**, *129*, 150067]; b) "Red colorants, their production and cosmetics containing the colorants": M. Oinuma, S. Shimoyama, Y. Noda, (Den Material K. K.) JP 09296125 **1998** [*Chem. Abstr.* **1998**, *128*, 26758].
- [264] a) "The ability of the naphthoquinone shikonin to influence microorganisms in the rhizosphere of *Lithospermum erythrorhizon*": L. A. Brigham, P. J. Michaels, H. E. Flores, *Curr. Top. Plant Physiol.* **1998**, *18* (*Radical Biology: Advances and Perspectives on the Function of Plant Roots*), 451–453 [*Chem. Abstr.* **1998**, *129*, 300083]; b) "Effect of substituent and ring changes in naturally occurring naphthoquinones on the feeding response of larvae of the Mexican bean beetle, *Epilachna varivestis*": M. Weissenberg, J. Meisner, M. Klein, I. Schaeffler, M. Eliyahu, H. Schmutterer, K. R. S. Ascher, *J. Chem. Ecol.* **1997**, *23*, 3–18 [*Chem. Abstr.* **1997**, *126*, 167886].
- [265] G. Lu, J. Liao, *Chung Hsi I Chieh Ho Tsa Chih (Chinese Journal of Modern Developments in Traditional Medicine)* **1990**, *10*, 422–5, 390.
- [266] X. P. Guo, X. Y. Zhang, S. D. Zhang, *Chung Hsi I Chieh Ho Tsa Chih (Chinese Journal of Modern Developments in Traditional Medicine)* **1991**, *11*, 598–9, 580.
- [267] Accession number for CAPLUS database. Not yet published in *Chemical Abstracts*.

Transfer of Chirality to Metal Centers



Predetermined Chirality at Metal Centers

Ulrich Knof and Alex von Zelewsky*

Enantiopure compounds are of central importance in many domains of chemistry. A classical method for the preparation of an enantiopure substance is the resolution of a racemate. Much more effective is, however, the selective synthesis of the desired stereoisomer. Stereoselective methods of synthesis have belonged for a long time to the standard repertoire of organic chemistry. The method of "asymmetric synthesis" has been known since the 19th century^[1] and asymmetric catalysis has seen an enormous development in recent decades. A similar development has just about started in inorganic chemistry. One

hundred years after the formulation of the theory of coordination compounds by Alfred Werner, stereochemical considerations are again of central interest in the development of the chemistry of coordination compounds. We describe here the state of the art of stereoselective synthesis in coordination chemistry. The enormous variability of the stereochemistry of metal complexes as a consequence of the many possible central atoms and a variable coordination geometry, makes a reasonably comprehensive coverage of the field an endeavor of considerable dimensions. The use of organic ligands, where the configuration can be

controlled by known methods, is the main feature by which chiral information can be transferred to the metal center. In this way, a predetermination of the absolute configuration at the metal center can be reached. The multidisciplinary and fascinating field of stereoselective synthesis and of stereoselective self-association of coordination compounds is in this way closely linked to classic organic stereochemistry.

Keywords: chirality • coordination chemistry • helical structures • supramolecular chemistry • transition metals

1. Introduction

1.1. Scope and Limits

A comprehensive description of the predetermination of chirality at carbon centers would require a multivolume publication. Predetermination of chirality at tetrahedral carbon centers has for a long time been the central interest in synthetic organic chemistry. The first big challenge was the stereoselective generation of carbon centers in the classical synthesis of natural compounds. Organic chemists have developed efficient methods for the creation of stereogenic centers with predetermined chirality. Today such methods form the highly sophisticated science and art of organic synthesis. Originally chemists were not able to synthesize synthetic analogues of natural compounds in an enantioselective way. This even gave rise to a criminal story in which the murderer was identified because the toxin (muscarin) was

used in the racemic form to poison the victim.^[2] Contrary to the highly developed asymmetric synthesis in organic chemistry, predetermination of chirality at metal centers has become only recently a subject of systematic investigation. This is of course a consequence of the fact that the chirality of coordination compounds is a much more complex phenomenon than that of organic compounds, because of the higher coordination numbers and the multitude of possible central atoms.^[3, 4]

Chiral coordination compounds that are synthesized from racemic or achiral species are, of course, formed as racemates. There are exceptions, as for instance in the spontaneous enrichment of one enantiomer upon crystallization. We do not treat these rare cases here. Such processes are only observable when a chiral induction occurs upon nucleation, and a rapid racemization takes place in solution at the same time. Such very special conditions are only realized in rare cases and a general applicability or a predetermination of chirality is therefore not possible in this way. We describe here how stereoselective synthesis of coordination compounds can be achieved through enantiopure chiral ligands. This predetermination of the chirality of the metal center yields, just as in organic chemistry, preferentially products of *one* absolute configuration.

[*] Prof. Dr. A. von Zelewsky, Dr. U. Knof
Institut für Anorganische Chemie
Universität Fribourg, CH-1700 Fribourg (Switzerland)
Fax: (+41) 26-300-97-38
E-mail: alexander.vonzewelsky@unifr.ch

1.2. Chirality in Coordination Chemistry

Predetermination of chirality in coordination compounds has up to now received relatively little attention. This is mirrored in the relatively small number of papers published in this field over the years. In recent times, however, interest in inorganic stereochemistry seems to have risen rapidly. In particular, stereochemically well-defined building blocks are needed for the assembly of supramolecular structures, a field that has found great interest in coordination chemistry. It is evident that upon formation of supramolecular structures from a large number of racemic components a large number of stereoisomers can be formed. The functionality of these aggregates is therefore not exactly defined. The preparation of species with predetermined chirality is therefore a strong challenge for the contemporary coordination chemist.

The coordination geometry of central importance in inorganic stereochemistry is the octahedron. We designate, from IUPAC nomenclature,^[5] this geometry as *OC-6*. A total of 144 “edge configurations” can be formed in *OC-6* through the use of chelates, cage ligands, or macrocycles, or a combination thereof.^[3, 6] Half of these edge configurations, that means 72, are inherently chiral. Δ and Λ are today the generally accepted descriptors for the chirality of these helical structures.^[5] Figure 1 shows as an example the complex $[\text{Ru}(\text{bpy})_3]^{2+}$ where the three bipyridine (bpy) ligands form

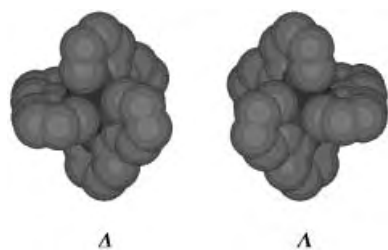


Figure 1. The pair of enantiomers Δ/Λ - $[\text{Ru}(\text{bpy})_3]^{2+}$. For a stereo representation see also ref. [3] and table of contents text.

either a right or a left helix. Typical octahedral complexes are $[\text{M}(\text{aa})_3]$ and $[\text{M}(\text{aa})_2\text{X}_2]$. In the first case, a homoleptic tris complex with a didentate ligand, D_3 symmetry results (Figure 1). In the second case with only two didentate ligands, the symmetry is C_2 . The complex $[\text{Co}(\text{en})_2(\text{Cl})(\text{NH}_3)]^{2+}$ with two didentate and two monodentate ligands belongs to this second group. In 1911 A. Werner^[7] achieved for the first time the resolution of an octahedral complex into the enantiomers with this complex.

As an example we consider a typical case where chiral didentate ligands with carbon centers of the absolute configuration *R* are coordinated to an octahedral metal center. Two possible species can be formed: Δ -(*aaR*)₃ and Λ -(*aaR*)₃. The complexes with Δ and Λ configuration are no longer enantiomers but are instead diastereomers because of the chiral ligands. We speak of predetermination of chirality at a metal center if one of the two species is preferentially formed in a diastereoselective synthesis of a metal complex. In some cases it is possible that chirality can be predetermined through other mechanisms, for example, through the diastereoselective formation of ion pairs with consecutive electron transfer.

Tetrahedral configuration of four different ligands (*T-4* from IUPAC) is the source of chirality in innumerable cases of organic compounds. The fact that stereoisomers, which are only distinguished in the configuration at such a center, can often be prepared without racemization is in the first-line a consequence of the generally high substitution stability of carbon centers. In contrast *T-4* metal centers are very often highly labile. It is even difficult to prepare species with four different monodentate ligands in most cases, and the aimed synthesis of one enantiomer is therefore in most cases excluded. The first *T-4* complexes where racemates could be resolved were species where one ligand was an aromatic π acceptor of the cyclopentadienyl anion type.^[8–10] Even though enantiopure substances have been obtained in some cases, a comparable manifoldness of methods and compounds such as in organic chemistry is excluded.

Alexander von Zelewsky, was born on July 17 1936 in Zürich. He studied chemistry at the ETH Zürich where he received his doctoral degree with a thesis on single crystal EPR spectroscopy. From 1965–1967 he worked at the University of California at Berkeley as a Miller Fellow in the field of NMR spectroscopy. In 1968 he returned to the ETH and was appointed as full professor at the University of Fribourg (Switzerland) in 1969 where he initially investigated spectroscopic problems in coordination chemistry. His main research topic is now stereoselective synthesis in coordination chemistry and especially predetermination of chirality at metal centers. In the present review this subject is discussed starting with early developments up to the newest results from the laboratory of Fribourg.

Ulrich Knof was born in 1968 in Essen and studied chemistry from 1987 to 1992 at the Ruhr-Universität Bochum (Germany). He obtained his PhD degree with Karl Wieghardt in 1995, whom he followed afterwards to the Max-Planck-Institut für Strahlenchemie in Mülheim. Since 1996 he has worked as a Postdoc in the group of A. von Zelewsky in the field of stereoselective synthesis of coordination compounds.

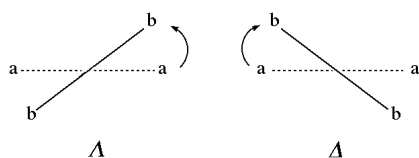


A. von Zelewsky



U. Knof

The other well known coordination geometry with coordination number four is square planar ($SP-4$). This geometry, however, is inherently achiral. An $SP-4$ center with four different ligands (Mabcd) does not yield one pair of enantiomers such as in $T-4$, but it results in three achiral stereoisomers. However, $SP-4$ complexes that deviate significantly from planarity can be chiral, and it was recently shown that this chirality can be predetermined.^[11, 12] The helicity in these non-octahedral compounds is indicated by the general “skew-line system”, which projects the ligand onto lines.^[3] If the line in the back has to be turned clockwise (through an acute angle) to be congruent with the front line the arrangement is designated as Δ , while the opposite case is termed Λ (Scheme 1).



Scheme 1. Definition of the configurations Δ and Λ in non-octahedral complexes.

What has been said for $T-4$ complexes in respect to lability is even more true for coordination number five. The well known stereochemical lability of complexes with coordination number five leads in most cases to an extremely rapid racemization.

The strongest motivation for a systematic investigation of the predetermined of chirality in the sense discussed above was, and still is, the assembly of complex structures, notably of polynuclear metal complexes with well defined configuration. This field is presently expanding rapidly and it will require methods for the stereoselective assembly of supramolecular structures in the future.

2. Predetermined Chirality in Octahedral Complexes

2.1. Complexes with Didentate Ligands

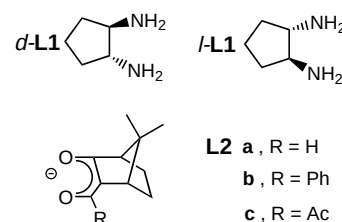
2.1.1. Complexes with Three Chiral Didentate Ligands

Octahedral complexes have represented since the beginning of coordination chemistry one of the most investigated types of complexes. Octahedral metal complexes with non-racemic chiral ligands were already reported in the beginning of the century.^[13–15] The understanding for this form of isomerism was, however, still quite limited in the first publications. A report published by Smirnoff, shortly after Werner's death, can be considered to be a breakthrough in the field.^[16] Smirnoff investigated platinum(IV) complexes with nonracemic *l* and *d* forms of propylenediamine (pn) (following the modern nomenclature (*S*)- and (*R*)-1,2-diaminopropane). The absolutely correct analysis of the stereochemical conditions was based exclusively on polarimetric measurements. Smirnoff prepared a series of complexes where one, two, or

three optically active propylenediamine ligands were coordinated to one platinum center. The other coordination sites were occupied with nonchiral ligands. Smirnoff expected that the molar rotations of the investigated compounds would be proportional to the number of the optically active substituents, that is in a ratio of 1:2:3. The measurements showed, however, a significantly higher value for the tris-substituted $[\text{Pt}(\text{pn})_3]^{4+}$ complex. In the 1920 publication Smirnoff analyzed this observation as follows: “The excess of rotation must be due to the asymmetry of the complex itself”.^[16] His conclusions were: “..., that optically active diamine molecules of a given configuration will be bound to the Pt atom in only one of two possible forms of mirror isomers”. This is a very clear description of the concept of predetermined of chirality at a metal center.

The pioneering work of Smirnoff and Werner was continued during several decades by the groups of Gillard and Bailar.^[17–23] These authors reproduced the synthesis of the platinum complexes and made similar investigations with coordination compounds of cobalt, chromium, and rhodium as the central atoms. In all these cases, the Λ configuration was preferred for *l*-pn and the Δ configuration for *d*-pn. Dwyer et al. determined in 1959 the equilibrium constant between the Δ and the Λ form of $[\text{Co}(l\text{-pn})_3]^{3+}$ to be 5.75.^[24]

A classical series of investigations of the stereochemistry of octahedral coordination compounds was described in a paper of Jaeger and Blumendal in 1928.^[25] Cobalt(III) complexes with the chiral ligand 1,2-diaminocyclopentane (**L1**) were investigated. It was observed through oxidation of solutions



that contained the racemic ligand and cobalt(II) ions that in a first step either $\text{trans-}[\text{Co}(d\text{-L1})_2\text{Cl}_2]^+$ or $\text{trans-}[\text{Co}(l\text{-L1})_2\text{Cl}_2]^+$ were formed. Complexes where both ligand forms were mixed were not observed. Both *trans* complexes form the inherently chiral *cis* form upon heating. The *d*-L1 ligand forms thereby exclusively the Λ -configured complex $\Lambda\text{-cis-}[\text{Co}(d\text{-L1})_2\text{Cl}_2]^+$. With another *d*-L1 molecule a species $\Lambda\text{-}[\text{Co}(d\text{-L1})_3]^{3+}$ was obtained. If the *cis* complex was treated with *l*-L1, no mixed complex was formed but the two species $\Lambda[\text{Co}(d\text{-L1})_3]^{3+}$ and $\Delta\text{-}[\text{Co}(l\text{-L1})_3]^{3+}$ were formed in a ratio of 2:1. The stereoselectivity seems to be high in this case. Microscopic investigations of the crystals formed did not show the formation of other isomers. In these investigations mainly racemic ligands were used. Therefore one cannot really speak of predetermined chirality at the metal center.

Other ligands, which were important for the development of asymmetric synthesis in coordination chemistry, are the β -ketoenolates of camphene. Camphene is a natural product and is easily available in enantiopure form, and the simple transformation of the hydroxymethylene form (**L2a**) was

already described in 1894.^[26] The spectra and the mutarotation of a series of complexes of the benzoyl derivative (**L2b**) were investigated by Lowry et al. in the 1920s.^[27–32] A systematic investigation of this group of sterically demanding ligands was started by Lifschitz.^[33, 34] This author observed only one isomer of cobalt(III) and chromium(III) complexes of the ligand (+)-**L2a**. A definitive assignment of the absolute configuration was not possible at this time. Mason et al. proved 40 years later with more developed analytical methods that the complexes described formed diastereoselectively were Δ -configured species.^[35–37]

Gillard et al. investigated also chromium, cobalt, and rhodium as central atoms with these ligands. $[\text{Rh}((+)\text{-L2a})_3]^{3+}$ was the first complex of the ligand (+)-**L2a** that seemed to be formed preferentially in the Δ configuration,^[38] despite the higher thermodynamic stability of the Λ configuration. The Δ isomer is formed in a kinetically controlled way.

Everett et al. investigated the cobalt(III) and vanadium(III) complex with (+)- and (–)-**L2a** and the acyl derivative (+)-**L2c**.^[39] The results observed with (+)-**L2a** are in agreement with those of Gillard et al.^[38] In 1968 it was proved that the enantiomers (+)- and (–)-**L2a** form complexes of opposite helicity (Λ/Δ). The vanadium(III) complexes of (+)-**L2a** are highly labile.^[39] It was shown that all four possible isomeric forms (Δ -mer, Λ -mer, Δ -fac, Λ -fac) are in thermodynamic equilibrium. *mer* signifies an arrangement of three groups on a meridian, whereas *fac* designates a facial arrangement where the ligands mount a face of an octahedron (Figure 2).

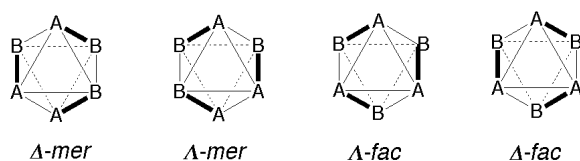
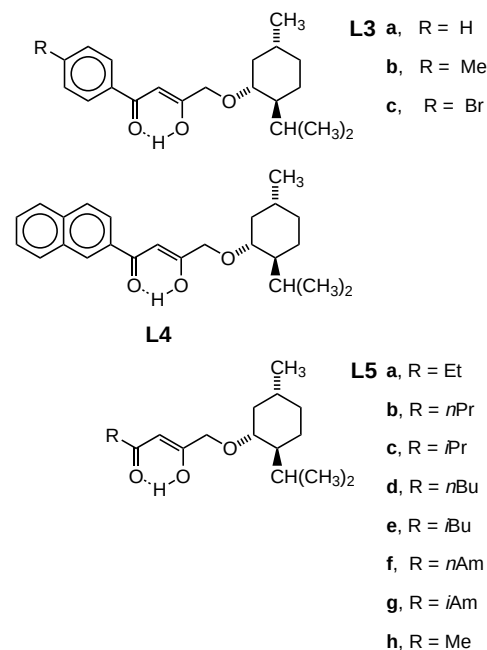


Figure 2. Schematic representation of isomers $[\text{M}(\text{AB})_3]$ where AB is a didentate ligand.

A series of detailed investigations of trisdidentate complexes with chiral ligands were carried out by Okawa et al. with the *l*-menthyl-substituted acetylacetonate ligands **L3–5**.^[40–42] In all these ligands a *l*-menthyl group was bound to an acetylacetonate unit and was substituted additionally by a phenyl (**L3**), a naphthyl (**L4**), or an alkyl group (**L5**). The metal centers Sc^{III} , Y^{III} , La^{III} , Al^{III} , Ga^{III} , and In^{III} form preferentially facially Δ -configured complexes with the phenyl substituted ligands **L3a** and **L3b** in solution.^[40] The stereoselectivity increases with increasing size of the metal ion; the lanthanum complexes ($r(\text{La}^{3+}) = 1.02 \text{ \AA}$) were formed with a very high stereoselectivity, whereas for Al^{III} , which has a radius of about 50 % of that for lanthanum ($0.51 \text{ \AA}$), a lower selectivity was observed. It seems that the stereochemically active groups are oriented in such a way that the mutual interaction is stronger in the case of the larger central atoms, which leads therefore to higher selectivity. The authors discussed three noncovalent $\text{CH} \cdots \pi$ interactions between the methyl groups of the menthyl units and the aromatic π systems of the aryl rings as a cause for this behavior. As shown



with the example of $[\text{Al}(\text{L3b})]^{3+}$, it is possible that in the solid state another configuration is preferred compared to the solution state. In the solid state this complex is present preferentially in the Δ configuration (Figure 3), whereas in solution an excess of Λ configuration is formed.^[40]

The Δ form is preferred apparently also in solution for the complexes with Co^{III} , Cr^{III} , Mn^{III} , Pr^{III} , Nd^{III} , Eu^{III} , Gd^{III} , Dy^{III} , Ho^{III} , Er^{III} , and Tm^{III} .^[41, 43, 44] The observation that larger ions showed high stereoselectivities is only valid for Δ -configured complexes. Cobalt forms almost exclusively complexes of the Δ form with these ligands, despite the smaller ionic radius. It seems that there is no unambiguous correlation between the radius of the metal ion and the preferred configuration. Complexes with Ga^{III} ($0.62 \text{ \AA}$) formed preferentially the Δ configuration, whereas Co^{III} with almost the same radius ($0.63 \text{ \AA}$) preferred the Δ configuration.

The aromatic ring in ligand **L3a** can be substituted with one methyl group (**L3b**) and one bromo (**L3c**) in the *para* position.^[45, 46] The stereoselectivity in the Co^{III} complexes with these substituted ligands increases in the series (**L3c** < **L3a** < **L3b**). It seems that the selectivity is in the first-line a consequence of electronic factors and not steric influences. The $\text{CH} \cdots \pi$ interaction and therewith also the selectivity is increased parallel to the increase of π electron density in the ring. The preference of the Δ configuration is not influenced by this substitution.

Another possible way to increase the $\text{CH} \cdots \pi$ interaction is to enlarge the aromatic π system. Ligand **L4** is obtained if the

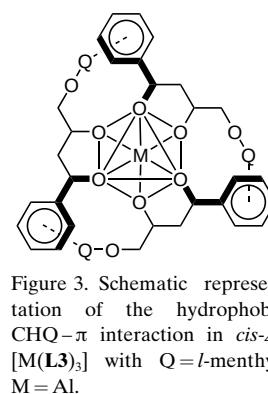
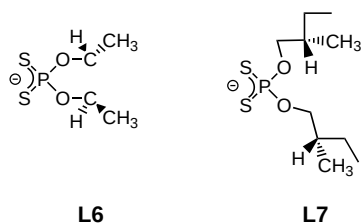


Figure 3. Schematic representation of the hydrophobic $\text{CH} \cdots \pi$ interaction in *cis*- Δ - $[\text{M}(\text{L3})_3]$ with $\text{Q} = l$ -menthyl, $\text{M} = \text{Al}$.

phenyl group is replaced by a naphthyl group.^[47] The selectivity increases as predicted for the complexes of Co^{III}, Cr^{III}, and Mn^{III} with this ligand relative to ligand **L3a**. The preference for the Δ configuration is preserved also in this case.

Finally, it is possible to replace the aromatic groups of the ligand **L3** and **L4** by various alkyl groups (**L5a–f**).^[42] The CH– π interactions are no longer possible. They are replaced by menthyl–methyl interactions, which are, however, much less pronounced. Consequently, the equilibrium shows only weak preference for a given configuration. Already small variations suffice for inversion of the preferred helicity at the metal center. Whereas the facial Δ configuration is preferred in the Co^{II} and Co^{III} complexes with the ethyl (**L5a**) and the iso-butyl (**L5e**) substituted ligands, the iso-propyl (**L5c**) and iso-amyl (**L5f**) substituted forms give preferentially the *fac*- Δ configuration. However, *n*-propyl (**L5c**), *n*-butyl (**L5d**) and *n*-amyl (**L5f**) groups yield no preference at all. There are obviously two possibilities for the relative orientation of the menthyl and alkyl groups: One of them prefers the formation of the *fac*- Δ -isomer (**L5a,e**) whereas the other leads to *fac*- Λ -isomer (**L5c,g**). For **L5b,d,f** the difference in energy is too small to lead to any stereoselectivity. This behavior shows the relative strength of the CH– π relative to the menthyl–methyl interactions. The Cr^{III} and Co^{III} complexes in a methyl substituted form of the ligand (**L5h**) show interesting aspects.^[48] This ligand forms complexes, as with those ligands with odd numbers of substituted alkyl groups (**L5c**, **L5f**), preferentially in the Δ configuration. Ligands with the even numbered alkyl chains (**L5a** and **L5e**) form, on the other hand, preferentially complexes of the Λ form.

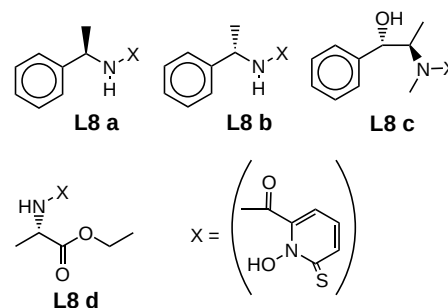
The equilibria between the isomers and the analysis of the factors that influence this equilibria were studied in a series of publications by Biscarini and Kuroda.^[49–53] When the (*R,R*) form of ligand **L6**^[49] is treated with Cr^{III} in a synthesis under kinetically controlled conditions the Δ isomer is formed in a first step. After equilibration an excess of the Λ form (*K* = 0.86) is present.^[52] In a publication of 1988 the influence of the



solvent on the preferred configuration was investigated.^[49] The Λ -*R,R* form of [Cr((–)-**L6**)₃] is preferred in the solid state and in THF, acetonitrile, and acetone, whereas the Δ -*R,R* form is present in higher concentrations in all solvents that form hydrogen bridges such as chloroform, dichloromethane, and ethanol. Cr^{III} forms complexes preferentially of the Δ configuration with ligand **L7** in the *S,S* form, independent of the solvent.^[53] In the solid state [Cr((*S,S*)-**L7**)₃] crystallizes in a molecular packing that contains the Δ and Λ complexes in a 1:1 ratio. No selectivity would have been found if only the crystalline product had been analyzed. This example shows

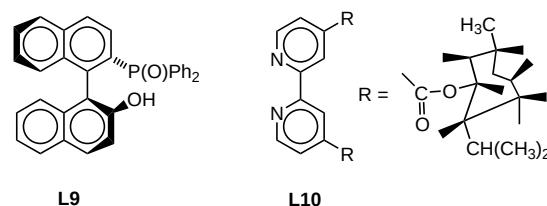
clearly that the analysis of molecular structures in single crystals does not always give clues to the compositions in solution.

The unsymmetrical ligand groups of the hydroxypyridine-thione **L8a–d**^[54] coordinates with oxygen and sulfur donor atoms and forms C₃-symmetric complexes with Fe^{III}, Cr^{III}, and Co^{III}. The two enantiomeric forms of the ligands (**L8a** and **L8b**) form, as expected, complexes of opposite helicity.



Whereas **L8a** yields Δ -configured Fe^{III} and Co^{III} complexes, ligand **L8b** forms Λ complexes of these metals. It is quite unexpected, however, that Cr^{III} shows an opposite preference. In this case the *R* form yields Δ and the *S* form Λ complexes. The same behavior is observed in complexes of ligands **L8c** and **L8d**. **L8c** forms Δ -configured complexes with Fe^{III} and Co^{III} whereas Cr^{III} prefers the Λ form. Correspondingly, **L8d** yields Δ -configured iron complexes but Λ -configured chromium complexes.

Complexes of chiral binaphthol ligands have been used frequently for asymmetric catalysis. In general, the stereochemistry of the catalytically active complexes has not been investigated in detail. Exceptions are the thoroughly investigated complexes of iron(III) and vanadium(III) complexes of ligand **L9**.^[55] The *S* form of the ligand yields the Δ -configured complex, while the *R* form yields a Λ -configured complex. The synthesis seems to be completely stereoselective; the other isomer cannot be found.

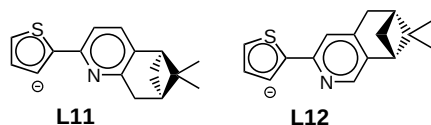


Ruthenium complexes of chiral enantiopure ligands have been used as catalysts for photocatalytic synthesis. Whereas Δ - and Λ -[Ru(bpy)₃]²⁺ complexes racemize, chiral bipyridine ligands such as **L10** are preferred because their configurations are relatively stable and they can be used therefore during a much longer time.^[56–59]

2.1.2. Complexes with Two Chiral Didentate Ligands

One of the rare modern examples for a chiral predetermined by two didentate ligands has been described for platinum(IV) compounds.^[11] Thienylpyridine ligands that are

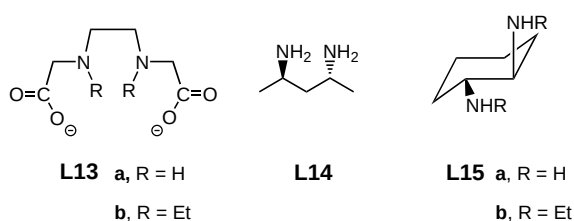
substituted with terpene groups in the *R,R* form (**L11**) give distorted square-planar platinum complexes with predetermined chirality (see Section 3.1). Oxidative addition of alkyl



halides yields, in a completely stereoselective reaction, exclusively the Δ product of edge configuration. The chiral predetermination has therefore been completely preserved upon the transition from four to six coordination. If the steric constraint through the chelate ligand is diminished through a different orientation of the pinene group, as in **L12**, a mixture of isomers is found upon oxidative addition.

2.1.3. Complexes with One Chiral Didentate Ligand

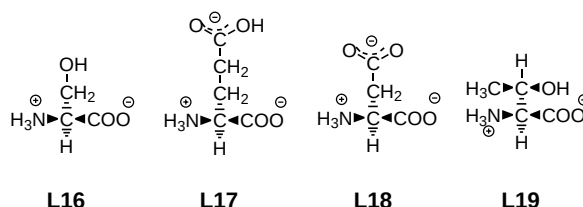
Investigations on this type of complexes have been carried out by Yashiro and Yeno with the achiral tetradentate ligand **L13a** and the enantiopure diamine ligand (*R,R*)-**L14** and (*R,R*)-**L15a**.^[60, 61] The stereoselectivity $\Delta/\Lambda = 3:97$ is surprisingly high in the $[\text{Co}^{\text{III}}(\text{L13a})]$ complex with the chiral ligand (*R,R*)-**L14**— $[\text{Co}^{\text{III}}(\text{L13a})(\text{L14})]^+$ —as compared with a Δ/Λ ratio of only 60:40 for the corresponding (*R,R*)-**L15a** complex. X-ray analyses show that the chelate rings of the didentate ligands have a chair form in the Δ -configured complex whereas the Λ configuration makes a “skew-boat” form necessary, which explains the high stereoselectivity in the former case. This type of steric interaction is much more pronounced in chelates that form six-membered rings (**L14**) with the metal, relative to five-membered rings (**L15a**). Therefore a stronger stereochemical preference is to be expected for the six-membered rings.



To increase the diastereoselectivity also in the case of the five-membered chelates, ligands **L13a** and **L15a** were N-ethylated. As a consequence, ligands **L13b** and **L15b** show much more pronounced stereoselectivities. With **L13b** and (*R,R*)-**L15a** a stereoselectivity Δ/Λ of 96:4 is reached. The steric interaction between the *N*-alkyl substituent in **L13b** and the NH groups in (*R,R*)-**L15a** are responsible for the strongly preferred formation of the Δ diastereomer. Two effects result from the use of the bisethylated **L15b** and the unsubstituted (**L13a**) ligands: The ratio Δ/Λ of 2:98 shows an increased stereoselectivity and, more surprisingly, the preferred configuration changes from Δ to Λ . The reason for this behavior is the interaction between the *N*-alkyl substituent of the didentate ligand and the acetate-chelate ring that forms the tetradentate ligand.

Ligand **L3a**, which has already been discussed, was also used to predetermine the configuration in complexes with tetradentate Schiff-base ligands of the salen type.^[62] The ligand forms cobalt(III) complexes with Schiff bases of the type *N,N'*-disalicylideneethylenediamine in the Λ configuration of the edge configuration **II** (see Figure 6). The selectivity can be traced back to the CH– π interaction that has already been discussed in detail between the *l*-menthyl group and the aromatic ring of the Schiff-bases.

A limiting case of stereoselectivity is the coordination of one amino acid and two achiral didentate ligands on one metal center. Only sterically demanding ligands lead to measurable effects in the chiral induction upon complex formation. The structures of Δ and Λ -[M(polypyridine)₂-(amino acid)] can be studied by equilibria, because small influences in the side chains of the amino acid can have a strong influence on the position of the equilibrium. The coordination of an (*S*)-amino acid with an apolar side chain leads in general to a preference of the Δ form of the complex. The chiral induction can be traced back in this case to the repulsive intramolecular ligand–ligand interaction in the less preferred Λ isomer.^[63–67] The interpretation of the results for the (*S*)-amino acids with polar side chains are less straightforward. In this case the metal ion and the diimine ligand determine the helicity of the final product. As an example, (*S*)-serin (**L16**) as the chiral ligand, gives a stronger preference of the Δ isomer in the case of Ru^{II} complexes relative to Co^{III} as the central metal.^[68, 69] In addition it was observed that in Ru^{II} complexes with (*S*)-glutamate (**L17**), (*S*)-aspartate (**L18**), and (*S*)-serine (**L16**) a stronger discrimination is obtained with 2,2'-bipyridine (**L16**) relative to 1,10-phenanthroline (**L17**).^[68, 70, 71] This effect is explained by a higher flexibility of



the bipyridine ligand,^[70] which leads to a decrease of the intramolecular ligand–ligand interaction and therewith to an amplification of other noncovalent interactions. Therefore hydrogen bridges, hydrophobic interactions, or solvation effects^[72, 73] can play a more important role. The sensitivity of the equilibrium situation in this series is documented by the fact that the chiral induction that leads to the preferred formation of the Δ form is observed only for (*S*)-glutamate (**L17**) and (*S*)-threonine (**L19**), whereas (*S*)-aspartate (**L18**) and (*S*)-serine (**L16**) show no selection at all.^[68, 70, 71, 74]

2.2. Complexes with Terdentate Ligands

Predetermination of chirality in octahedral complexes has been studied only in a few cases with terdentate ligands. Such ligands can have edge configuration **3** or **4**, where **4** is

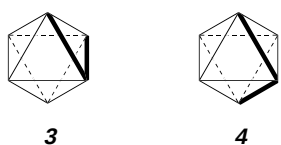
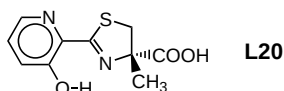


Figure 4. Edge configurations in octahedral complexes with tridentate ligands.

inherently achiral for ligands of the symmetry ABA (Figure 4). Raymond et al.^[75] used the demetallated form of ferri-thiocine (**L20**) as a ligand. This siderophore is neither a catecholate nor a hydroxamate and it is therefore basically different from the siderophores described in Section 2.5.

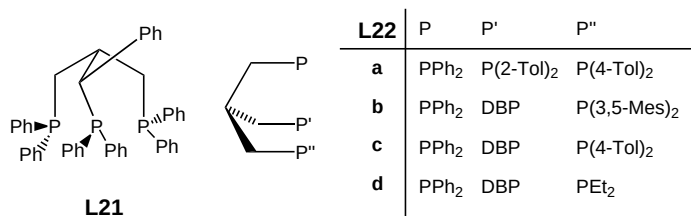


L20

The ligand coordinates through a central nitrogen atom, a phenolate, and a carboxylate oxygen atom. The natural enzyme (**L20**) forms a 2:1 complex with iron. In order to study the stereochemistry the kinetically more stable Cr^{III} and Co^{III} complexes were investigated. The meridional edge configuration **4** was obtained. The mirror plane of this configuration is, however, no longer present in this ligand of the ABC type (Scheme 2). The enantiopure ligand, for instance in the *S* configuration, forms exclusively meridional Δ and Λ diastereomers (see Figure 2). The Cr^{III} complex is formed in a Λ : Δ diastereomeric ratio of 62.5:37.5, that is the selectivity is relatively weak.

Scheme 2. Arrangement of **L20** in the Cr^{III} complex.

The tripod ligand **L21**^[76a] has three phosphorus donor atoms. The Λ configuration is obtained through coordination of the *R* form of the ligand in a rhodium(i) center. This result was evident from an X-ray analysis of the solid (Figure 5), but NMR spectra



showed that the same form is also strongly favored in solution. The free coordination sites are occupied with a norbornadiene group.

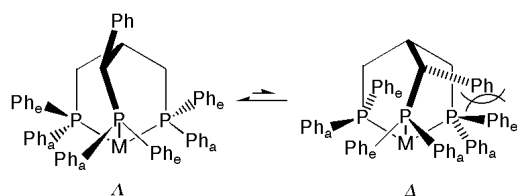
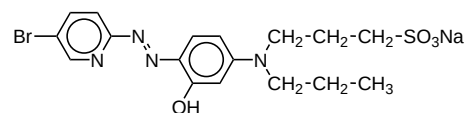


Figure 5. Schematic representations of Δ and Λ diastereomers of a Rh complex with (*R*)-**L21**.

A group of tripod ligands (**L22**) described by Huttner shows another type of chirality (DBP = dibenzophospholyl).^[76b] It is not the edge configuration that is chiral, but the tripod ligand

coordinates with three different phosphane groups and generates therewith a chiral environment. The other coordination sites of the Ir^{III} complex are occupied with acetonitrile molecules.

Another limiting case of chiral predetermination of metal centers is their synthesis at chiral ammonium interfaces as templates. Publications from Kunitake^[77] show that a glutamine-functionalized surface can induce chirality in complexes with tridentate N₂O ligands (**L23**).



L23

2.3. Complexes with Tetradentate Ligands

Octahedral complexes with tetradentate ligands have two "free" coordination sites where substitution reactions can occur. Such complexes can be used as enantiopure building blocks, for example for the synthesis of polynuclear metal complexes if they can be prepared stereoselectively. Tetradentate ligands, which are not branched, can wrap around an octahedron according to the edge configurations **8**, **11**, or **14** (Figure 6), where **14** is inherently achiral through the mirror plane. Besides the classification of the complexes according to edge configurations, the designations *cis-α* for **8** and *cis-β* for **11** has been frequently used. The achiral form **14** can be called a *trans* configuration.

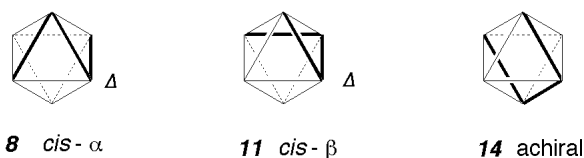


Figure 6. Edge configurations for linear tetradentate ligands.

The possibility of predetermination of chirality in octahedral complexes with tetradentate ligands was already reported in 1990 by Bosnich.^[78] Ligand (*S,S*)-**L24** coordinates through four nitrogen donor atoms and yields Δ -configured complexes of edge configuration **11**. In this case chirality is not only induced at the metal center but also at the coordinating nitrogen atoms (Figure 7)

The group of Vagg and Williams synthesized a series of cobalt(III) complexes with linear tetradentate N₄ ligands with

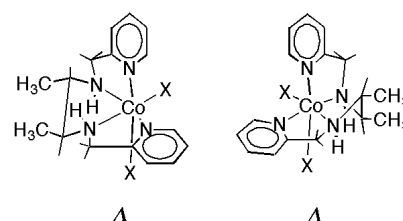
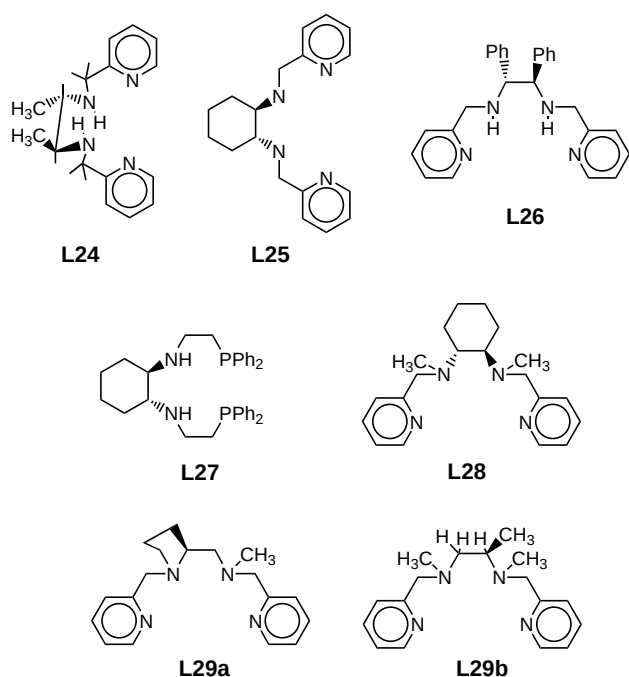


Figure 7. Δ and Λ diastereomers of [Co(**L24**)X₂].

terminal pyridyl groups. Of special interest are the influences of C and N substitution on the stereoselectivity. In this respect one can generally distinguish two sorts of stereoselectivity: the arrangement of the ligand in a given edge configuration and the helicity of the metal center. A series of ligands (**L24–30**) was obtained through substitution of a given molecular skeleton. Contrary to (*S,S*)-**L24**, Δ -configured complexes of edge configuration **11** were obtained with the ligands (*R,R*)-**L25**^[74] and (*R,R*)-**L26**.^[79] It was also proved for **L26** that rhodium(III) shows the same stereochemical preference. The substitution of the pyridine groups in ligand **L25** by diphenylphosphane groups (**L27**) showed no influence on the stereochemistry of the complex formation. Again, the Δ -configured edge configuration **11** was obtained for the cobalt complex.^[80]



The stereochemistry of coordination compounds often changes drastically even if only small changes occur in a ligand. The methylation of the secondary amine of ligand (*R,R*)-**L25** gives ligand (*R,R*)-**L28**.^[81] This variation is sufficient to change from a **11- Δ** to a **8- Δ** preference. This effect is also observed with complexes of the unsymmetrical ligand (*S*)-**L29a** (Figure 8). Analogous results are obtained for the easily accessible dimethyl derivative (*R*)-**L29b**. The latter

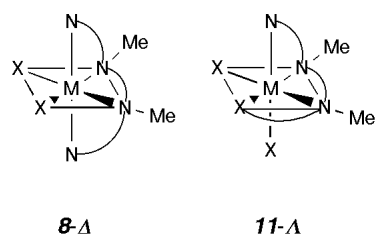
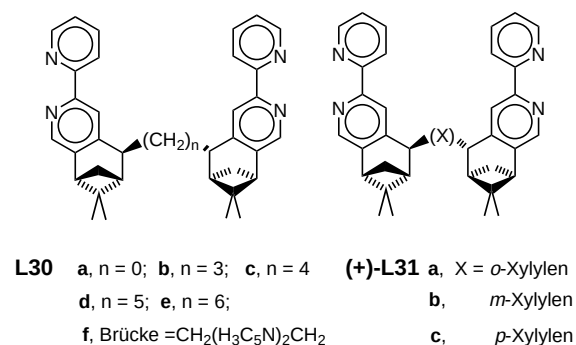


Figure 8. Comparison of a Δ -configured complex of edge configuration **8** as shown for **L28** and a Δ -configured complex with edge configuration **11**.

forms stereoselective Δ -configured cobalt complexes of edge configuration **8**.^[82] The two coordination sites that are occupied with chloride ligands can be substituted in stereospecific substitution reactions.

Besides the cobalt complexes with aliphatic *N*₄-donor ligands, ruthenium(II) complexes with chiral bipyridine derivatives have found a wide interest. The so called CHIRAGENS (from CHIRality GENerator) **L30** and **L31**^[83, 84] can coordinate only in edge configuration **8**. Therewith one source of isomerism is already eliminated. The other, the chirality at the metal center, is controlled through the use of enantiopure chiral ligands. The formation of several isomers is excluded in the case of these ligands. The method of synthesis of the chiral



bipyridine derivatives is extremely variable and allows for the preparation of a large number of tetradentate ligands. The structure of these molecules can be engineered in various ways: The bridging group that links the two bipyridine rings can be any of a large number of aliphatic, aromatic, or even functionalized synthons, and the pinene group can be attached to one of the pyridine rings in either the 4,5-, or the 5,6-position (see Section 4.1).

The first molecules of the series of the CHIRAGEN ligands were described 1993.^[83] The bipyridine units are connected through aliphatic C₄, C₅, or C₆ bridges (**L30c–e**) and they yield exclusively the Δ -configured Ru complexes. An X-ray analysis of a complex of the C₆-bridged derivative (**L30e**) proves this assignment. Substitution of the monodentate ligands is possible in all these complexes under retention of the configuration of the metal center. Osmium(II) also forms mononuclear complexes of Δ configuration with **L30e**.^[85]

Xylene bridged ligands were prepared to amplify the tendency for preorganisation by making the molecule more rigid. All three isomers, the *ortho*, *meta*, and *para* forms, have been used (**L31a–c**).^[86] Ru complexes were also obtained stereoselectively in the Δ form with these ligands. Δ -configured complexes could not be detected. The assignment of the configuration can be again based on an X-ray structure analysis of the complex Δ -[Ru(**L31a**)(dmbpy)](PF₆)₂ where dmbpy = 4,4'-dimethyl-2,2'-bipyridine. The application of CHIRAGEN ligands is not restricted to mononuclear complexes. If two “free” coordination sites are replaced by a potentially bridging ligand, dinuclear complexes can be prepared stereoselectively (see Section 4).

As already described in the introduction to this section, octahedral complexes of tetradentate ligands are promising

for use in stereoselective catalysis because two coordination sites are available for substitution reactions. The catalytic decarboxylation and epimerization of amino acids at cobalt(III) complexes with enantiopure, chiral aliphatic N_4 ligands was investigated. The dichlorocobalt(III) complexes used had the inherently achiral edge configuration **14** (see Figure 6). The coordination of the amino acid changes the edge configuration to **11**, which is formed in the Δ form. Chirality is in this case clearly not induced through the incoming ligand, because both forms of the amino acids (R and S) lead to complexes with the same helicity at the metal center. It is the tetradentate ligand that predetermines the chirality. The didentate ligand transforms the complexes into the inherently chiral edge configuration where the chiral predetermination becomes observable (Figure 9).

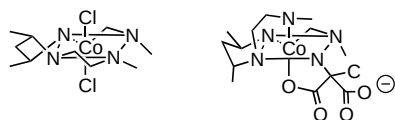


Figure 9. Stereoselective transformation of an achiral edge configuration (**14**, left) into a chiral (**11**, right) configuration through substitution of two monodentate ligands for a didentate ligand.

The ligands **L32**,^[87–94] which were used for these investigations, are in all cases based on the same molecular skeleton in which the length of the bridge ($n = 0, 1$) and the substituents (R^1 – R^8) can be varied. Only complexes with Δ stereochemistry were obtained, either with the tetradentate ligands (S)-**L32** or with (R)-**L32**. It is noteworthy that the ligands that are isolated in the S form are substituted at the outer bridges (R^2 – R^3 and R^6 – R^7), respectively, and the R -configured ligands are substituted at the middle bridge (R^4 – R^5). It can be concluded that an R configuration of the middle bridge leads to a Δ complex in the same way as an S configuration of the outer bridge does.

2.4. Complexes with Pentadentate Ligands

Octahedral complexes with pentadentate ligands have often been used for investigations of inner sphere electron transfer reactions, because only one site of the octahedron is available for substitution. Linear, pentadentate ligands can, in principle, coordinate as edge configurations **22**, **23**, **28**, **30**, of which number **23** is inherently achiral through a mirror plane (Figure 10).

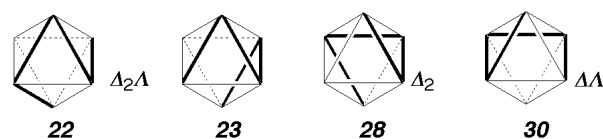
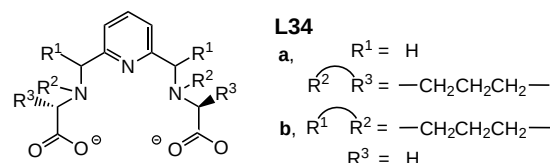
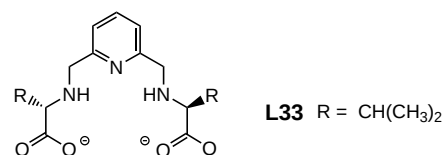


Figure 10. Edge configurations for linear pentadentate ligands. The descriptors with indices designate the relative number of edges that have Δ and Λ orientations.

Bernauer synthesized the ligand **L33** in 1984.^[95] This ligand can coordinate for steric reasons only in the chiral configuration of highest symmetry **28**. It was shown for the



cobalt(III) complex that the S,S form of the ligand yields exclusively the Δ configuration of the complex (Figure 11). Through variation of the number and of the nature of the substituents it was possible to investigate for **L34** the influence of steric factors on the helicity of the metal center as well as the influence of the chirality.^[96] The X-ray analysis of Δ -[Co((S,S)-**L34a**) H_2O](ClO_4) is the basis for the spectroscopic investigation and characterization of further complexes. It was concluded that the Δ form of the cobalt(III) complex is also obtained from the Δ form of the ligand **L34b**, whereas (S)-**L34b** yields a Δ -configured complex. This example demonstrates, as has already been discussed, that purely geometrical aspects, as well as the chirality of the ligand, have to be considered in order to predict the preferred configuration correctly.

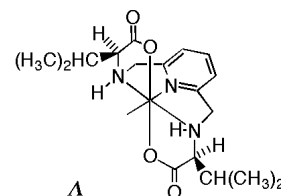
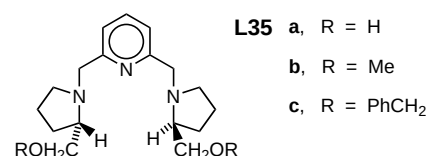


Figure 11. One diastereomer of the edge configuration **28** for chiral pentadentate ligands.

Not only can inert metal ions such as cobalt(III) be investigated with these pentadentate ligands, but the methodology of stereochemical predetermination is also applicable for labile metal ions. Copper(II) complexes have been synthesized and discussed in detail. For this purpose **L34** was modified. The terminal carboxylic acid groups were replaced by alcohol (**L35a**) or ether groups (**L35b,c**). The S,S -configured ligands **L35a–c** yield, in the same way as the



structurally similar **L34** ligands, the Δ form of the complexes, in analogy to the cobalt(III) complexes described above. The chirality of the nitrogen atom of the pyrrolidine rings is fixed through complexation in the R configuration.

2.5. Complexes with Hexadentate Ligands

Out of the numerous possibilities of geometrical configurations of hexadentate chelate ligands in octahedral complexes, the following edge configurations have been observed: **41**, **52**, **53**, **54**, **57**, **83**, **87** (Figure 12). A classic paper, in which

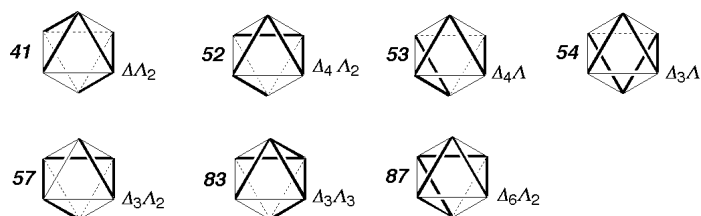


Figure 12. Edge configurations for hexadentate ligands.

the predetermination of chirality at the metal center is the subject of investigation, describes the cobalt(III) complexes with nonracemic 1,2-propylenediaminetetracetate (**L36**) as the ligand. Only the inherently chiral edge configuration **41** is possible for this ligand. Dwyer and Garvan^[97] showed that only one diastereomeric form can be isolated, that is, the configuration at the metal center is determined through the configuration at the chiral carbon center in the ligand. The isomeric purity of the complex was demonstrated by fractional crystallization, whereas its absolute configuration could not be determined, and therefore no reliable predictions were possible.

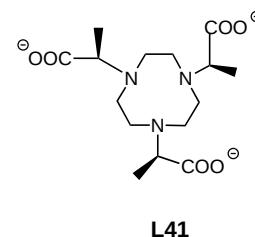
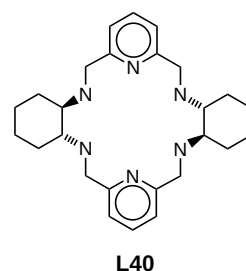
Gollogly and Hawkins^[98] calculated in 1967, by methods of conformational analysis, differences in energy for the diastereomeric forms of analogous complexes with **L37** as the ligands. These authors predicted a relatively large difference in energy based on van der Waals interactions for both configurations at the metal center for a given chirality of the ligand. This prediction was confirmed in 1974 through the X-ray analysis of the complex.^[99] The predetermined absolute configuration is [Δ -Co(*(R)*-**L37**)]³⁺.

Another relatively early publication comes again from the group of Dwyer.^[23] This investigation concerns the non-branched hexadentate ligand **L38**. Stereoselectivity is again demonstrated, but the results are less clear because the possibility of the formation of four different edge configurations **52**, **53**, **54**, and **57** is not discussed in more detail. All these edge configurations are inherently chiral and it is not known which edge configuration is formed by this ligand.

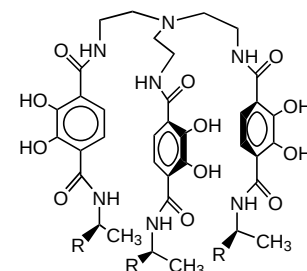
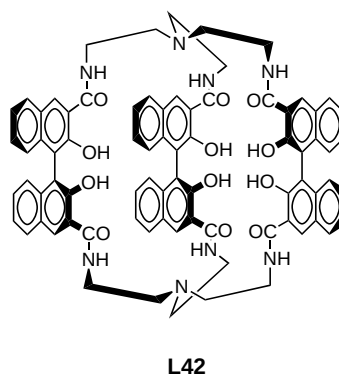
A series of mono- and dinuclear species were synthesized in 1994 by the group of Bosnich.^[100] The ligand (*S,S*)-**L39** is

octadentate, and it can coordinate up to two metal centers. One coordination site is an octahedron, whereas the second represents a square where two oxygen donor atoms function as μ_2 bridges. The octahedral binding site can be considered as an open, twice branched ligand. This corresponds therefore to the edge configuration **41**, that was already discussed for 1,2-propylene diamine-tetracetate (**L36**). The zinc and cobalt complexes, which were prepared with **L39** were obtained as single diastereoisomers. X-ray analysis shows Δ -configured Zn^{II} and Co^{III} centers for the octahedral coordination sites, whereas the Mn^{II} complex has an Λ configuration. The authors explain this "inversion" of the configuration by the larger ionic radius of Mn^{II}.

Macrocyclic ligands have also been used for the stereoselective synthesis of metal complexes.^[101] Replacement of the ethylene bridges in the hexadentate ligand pyan through enantiomerically pure 1,2-diaminocyclohexane yields the chiral ligand *trans*-**L40**. Metal complexes of the edge configuration **87** are obtained in defined stereochemistry with this ligand. Another edge configuration is **83**. An example is the chiral ligand **L41**^[102] where triazacyclononane has been functionalized with three propionate groups. The (*R,R,R*)-ligand forms Λ -configured cobalt and indium complexes.^[103]



Triscatecholates that have been built into completely closed sepulchrates or into open systems have also been applied in many cases in coordination chemistry. The sepulchrate of the bicapped tris(binaphthol) ligand **L42** comprises nine edges. The derived edge configuration can be described as an inverse



L43, R = Et, Ph

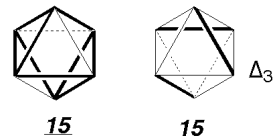
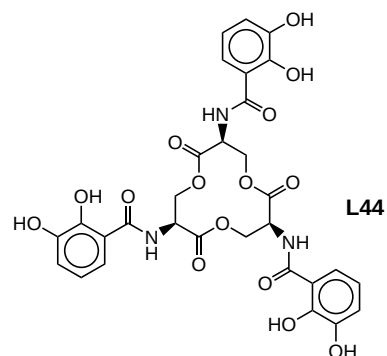
“three-edge-case”. In an octahedron, a maximum of twelve edges can be occupied. If the occupied edges are replaced by nonoccupied ones, an x -edge configuration is transformed into the symmetry equivalent $(12 - x)$ case. **L42** occupies therefore the edge configuration that is inverted to **15**. It will be designated as **15** (Figure 13). (*R*)-**L42** forms Δ -configured complexes with Ga^{III} , Cr^{III} , and Fe^{III} .^[104] As opposed to the se-


Figure 13. Complementary edge configurations **15** and **15**.

pulchrate, the tripodal triscatecholate ligand (*S*)-**L43**^[105] corresponds to an open chain and assumes edge configuration **83**, just like the tripodal ligand **L41**. The Fe^{III} and Ga^{III} complexes also show a stereo-selectivity, which can be attributed to nonbonding interactions between weakly polar groups.

2.5.1. Biological Systems

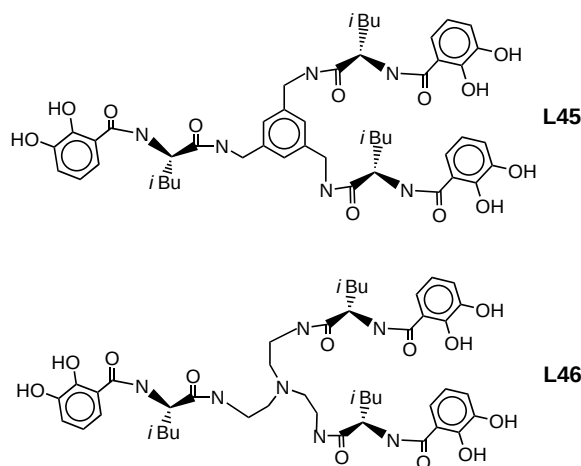
Chiral predetermination has also been observed in biological systems. In such cases, chiral information can be transferred from the apoproteins to the coordinating metal center. Particularly investigated examples for such cases are the siderophores. The siderophores are biomolecules that bind Fe^{III} sufficiently strongly to make it available to the cell under physiological conditions. A well investigated and documented case is enterobactin [$\text{Fe}(\text{L44})$]³⁻, which is responsible for the transport of iron in bacteria. It is one of



the strongest natural Fe^{III} binders known. Natural enterobactin is optically active and its Δ configuration can be deduced from the CD spectrum.^[106] An X-ray analysis of the analogous vanadium(IV) complex confirms this assumption.^[107] The stereochemistry of the metal center is in this case of importance, because bacteria can make use only of the Δ form of the complex.

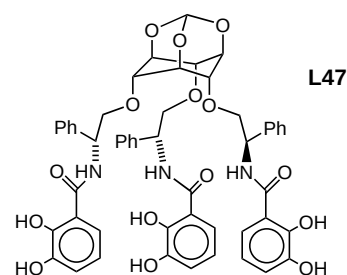
Shanzer et al.^[108] presented a concept for the synthesis of model compounds in 1986. The predetermination of the chirality of the metal center is attributed to the favorable steric interactions and the formation of hydrogen bridges. This principle seems to be generally applicable in this family of compounds. In order to understand the structures and the mechanisms of the action of the siderophores several low molecular iron complexes with triscatecholate ligands have been synthesized as model compounds in the past 15 years.

The first chiral model complex that is formed selectively in the natural Δ configuration was prepared in 1987 by Shanzer et al.^[109] The tripodal triscatecholate ligand **L45** is based on 1,3,5-tris(aminomethyl)benzene, and it occupies the edge configuration **83**. Later, the tris(2-aminoethyl)amine building



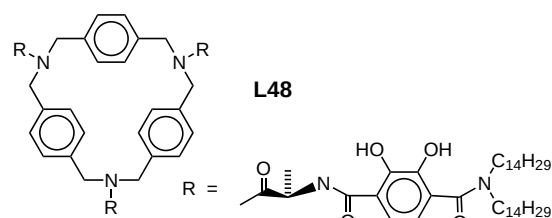
block was also used for the synthesis of a triscatecholate ligand **L46**.^[110] The stability constant for the Fe^{III} complex of this ligand reaches almost the value of the natural enterobactin ligand. One reason for the increased stability is the preorganization through formation of hydrogen bridges in ligand **L46**. In contrast to that, ligand **L45** is accidentally orientated in protic solvents.

Ferrichrom is also a growth factor for bacteria. The catecholate groups in enterobactin (**L44**) are replaced by hydroxamate groups and it shows no C_3 molecular symmetry. Model investigations for this biomolecule have been carried out with a trishydroxamate ligand (**L47**) with a sterically less-demanding quaternary carbon atom as the basic structure.



The chirality is controlled through Δ -amino acids, and it corresponds again to edge configuration **83** (see Figure 12).^[111] The hydrogen bridging system of this molecule leads, through a propeller-like structure, to a Δ -*cis* configuration.^[112] The effectiveness of this model compound was shown in cultures of bacteria.

The group of Murakami^[113] combined a hexapus cyclophane as a C_3 -symmetric ground structure through an alanine group with the coordinating catecholate segments (**L48**). The Δ form of the amino acid leads to Fe^{III} complexes with Δ configuration. This example shows that the amino acid determines the stereochemical preference in a given ground structure. The group of Kishi et al. synthesized models for



enterobactin from the C_3 -symmetric ligand **L47**.^[114] The *S* form yields preferentially the Δ -configured complex. The stereochemical preferences were determined with isostructural diamagnetic Ga^{III} complexes.

Raymond et al.^[107, 115] looked at the stereochemistry of enterobactin analogues through a new perspective, by variation of the metal and not the biomolecule. In 1978^[106] a rhodium(III) complex of the enterobactin ligand (**L44**) was prepared. A comparison of the CD spectra with that of enantiopure rhodium(III)-triscatecholate complexes with known configuration led to the determination of the chirality of the metal center in the siderophore. Thereby it was assumed that a ligand of a given configuration yields complexes of the same metal helicity with different metals. There are, however, cases where this assumption is not valid.^[54, 100] Only some time later was the first X-ray structural characterization of a metal enterobactin complex successful, and yielded the absolute configuration of the vanadium complex of apoferritin.^[107, 115] This was the first definitive proof of the configuration of the metal center in the biomolecule almost 20 years after it had been derived from other information. The siderophores show clearly that in biological systems nonracemic ligands are used for the predetermination of chirality at metal centers.

3. Predetermined Chirality in Mononuclear, Nonoctahedral Complexes

3.1. "Square-Planar" Complexes

Square-planar coordination geometry is particularly prominent in coordination compounds of d^8 metals. This coordination geometry is inherently achiral. It can be, however, distorted into a chiral structure by sterically demanding ligands. Achiral ligands of this kind yield in such cases racemates.^[116] Nonracemic chiral ligands can also predetermine the chirality in square-planar complexes. Pt^{II} for example forms Δ -*cis*-configured complexes of the form $[PtL_2]$ stereoselectively with the didentate ligands (*R,R*)-**L11**, (*R,R*)-**L12**, and (*6R,7S*)-**L49** (Figure 14).^[11, 12]

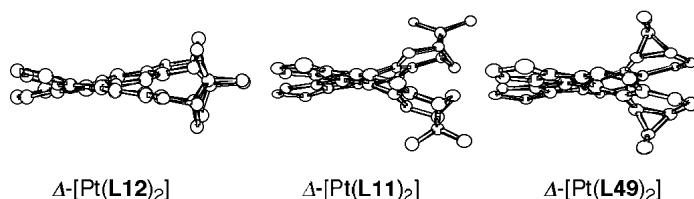
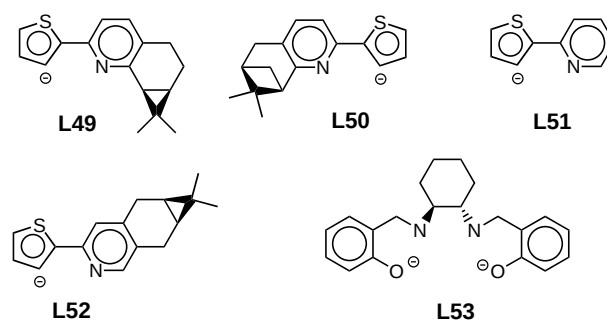


Figure 14. Helical distortion in "quadratic-planar" coordination geometry in $[PtL_2]$ complexes.

The steric requirements of these ligands are decisive for the predetermination of chirality in square-planar complexes. The orientation of the pinene group in ligand **L50**, which is derived from (–)- β -pinene, determines the chirality of the complex $[Pt(\mathbf{L50})(\mathbf{L51})]$ at the metal center. The configuration is

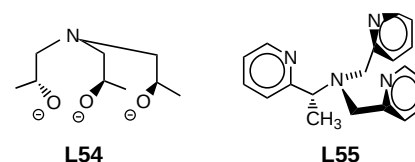


predetermined, even though **L51** is an achiral ligand. In the complex $[Pt(\mathbf{L52})_2]$, on the other hand, no unambiguous predetermination of the configuration is observed. The chiral groups point outwards in this case and do not interact sufficiently strongly.

Ligand **L53**, which is obtained through condensation of (*R,R*)-cyclohexanediamine with salicylaldehyde, predetermines the chirality in its *SP-4* complex with Pt^{II} .^[117] The X-ray structure analysis confirms a small but significant chiral distortion, and the CD spectrum shows the preference for one configuration in solution. An analysis of the published data shows that this complex has a Δ configuration.

3.2. Trigonal-Bipyramidal Complexes

Trigonal-bipyramidal coordination geometry occurs preferentially with tripodal ligands. There are several factors that can cause chirality at the metal center in this case. One possibility is the tripod ligand has three different ligand arms.^[118] Another case is represented by a C_3 -symmetric ligand where each of the arms carries a chiral center. An example is ligand **L54**, where the chirality of the complex is predetermined through the chirality of the ligands.^[119]



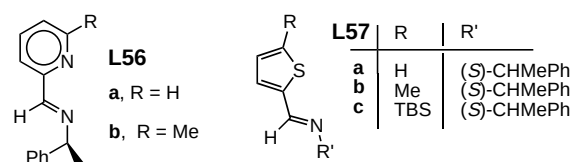
Canary et al. report the propeller-like orientation of a tripod ligand coordinated to a metal center.^[120] The ligand (**L55**) was prepared in enantiopure form and it already shows a helical orientation in its free form. The *R* form of the ligand forms a chiral Δ -configured metal center upon coordination with Zn^{II} and Cu^{II} .

3.3. Tetrahedral Complexes

The most common source of chirality in organic chemistry, a tetrahedrally coordinated *Mabcd* center with four monodentate ligands, is rare in coordination chemistry.^[8–10, 121, 122] Moreover, chiral predetermination of tetrahedral centers in coordination chemistry is very unlikely because the “coordination properties” of metal and carbon centers are very different.

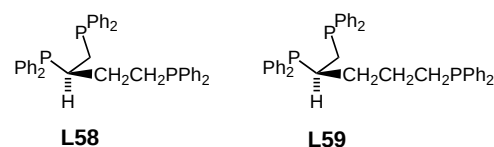
T-4 complexes with two symmetric didentate ligands AA show the symmetry D_{2d} and are therefore inherently achiral. Two unsymmetrical ligands AB lead in *T*-4 to C_2 -symmetric complexes, which are in principle chiral. This chirality can be predetermined through the use of nonracemic chiral AB ligands.

Pioneering work in this field was carried out by van Koten et al.^[123, 124] Chiral pyridinecarbaldehydeimine derivatives **L56** in the *S* form strongly prefer the *A* configuration in silver(i) and copper(i) complexes. The ligand with an unsubstituted



pyridine ring (**L56a**) yields a higher diastereoselectivity relative to the one with a methyl group (**L56b**). The silver complexes show a diastereomeric ratio of *A*-(*S*)-**L56a**:*A*-(*S*)-**L56a** = 99:1 and *A*-(*S*)-**L56b**:*A*-(*S*)-**L56b** = 95:5. The copper complexes show generally smaller selectivities of *A*-(*S*)-**L56a**:*A*-(*S*)-**L56a** = 85:15 and *A*-(*S*)-**L56b**:*A*-(*S*)-**L56b** = 75:25. A similar behavior was observed in the case of copper(i) and silver(i) complexes with thiophene-2-carbaldehydeimine ligands (**L57**).^[125] The stereoselectivity is higher for the silver complexes relative to the copper species.

Diastereoselectivity can also be observed in a *T*-4 complex with two monodentate ligands and an asymmetric didentate ligand of the form [Co(CO)(NO)(triphos)], as shown by Brunner et al.^[126] **L58** forms 83 % of the *S*-configured cobalt



complex. The longer alkyl chain (by one CH_2 group) in **L59** decreases the diastereoselectivity significantly to 63 % (Figure 15).

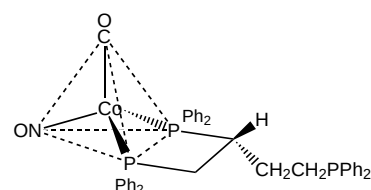
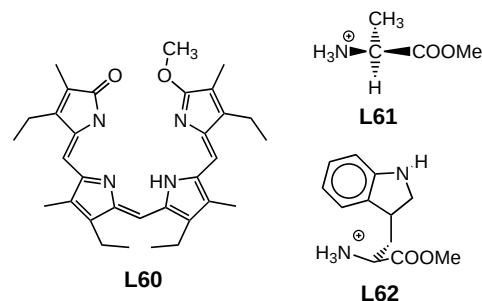


Figure 15. Example of a tetrahedral cobalt complex with **L58**.

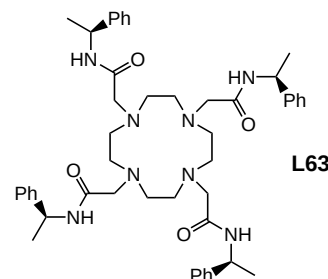
A limiting case for the predetermination of metal centers is presented in the work of Mizutani, Ogoshi et al.^[127] These authors do not investigate primarily predetermination of chirality at the metal center, but the transfer of chirality. The chirality of esters of amino acids is in this case used to induce one preferred helicity in racemic zinc–biliverdine (**L60**) complexes. The interaction between the chelate ligand and



the esters of the amino acid is in this case a consequence of the zinc atom, which forms a fivefold coordinated complex. The observed enantiomeric excesses are dependent on the host molecule and they lie between 42 % for the *S*-alanine methyl ester (**L61**) and 73 % for the *S*-tryptophan methyl ester (**L62**).

3.4. Square-Antiprismatic Complexes

Coordination number eight often leads to a square-antiprismatic coordination geometry. This coordination number is rarely encountered in transition metal coordination chemistry, but it is frequent in complexes of the lanthanides. Parker et al. investigated the Pr, Eu, Tb, Dy, and Yb complexes of the chiral C_4 -symmetric ligand **L63**.^[128] Both forms of the ligand (*R,R,R,R* and *S,S,S,S*) were prepared and it was shown that the chirality of the stereocenters of the amide groups determines the chirality of the N-substituents and therewith the configuration of the macrocyclic 12-membered ring. The chirality of the terbium complex was investigated in view of its photophysical properties.



4. Predetermined Chirality in Polynuclear Complexes

The methods for the control of chirality in mononuclear coordination compounds, discussed in the preceding chapters can be, in principle, transferred to polynuclear complexes. Predetermination of chirality in polynuclear complexes is especially important from a practical point of view, since the number of possible isomers increases exponentially with the

number of metal centers. Separation of the isomers becomes more and more difficult. Polynuclear coordination species can be used potentially in molecular devices. The functions that can be carried out by molecular devices can, however, be only well defined if the compounds are stereochemically pure. Polynuclear ruthenium(II) complexes have often been investigated in this connection. The CHIRAGENs **L30** and **L31**^[83, 84, 86] (described in Section 2.3) have been used successfully for the synthesis of oligonuclear ruthenium complexes in stereochemically well-defined form. An example is the synthesis of Δ, Δ -[Ru₂((-)-**L31b**)₂(bpym)](PF₆)₄ from **L31**.^[84] Two Δ -[Ru((-)-**L31b**)]²⁺-fragments are connected in this

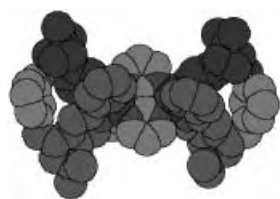
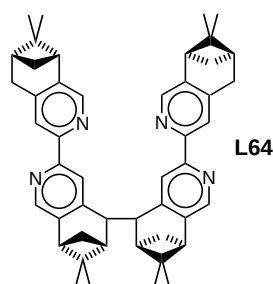


Figure 16. Structure of a dinuclear meso complex Δ, Δ -[Ru₂((+)-**L31b**)(bpym)((-)-**L31b**)](PF₆)₄ with chiral metal centers.

complex through a 2,2'-bipyrimidine (bpym) bridge. Both complexes, the homochiral and the heterochiral meso form Δ, Δ -[Ru((-)-**L31b**)(bpym)Ru((+)-**L31b**)](PF₆)₄ can be prepared from the enantiomerically pure building blocks (Figure 16).

Similar ligands where the two pinenobipyridine groups are not connected through an aryl group but through a propyl chain (**L30b**) or even if they are directly connected (**L30a**)

cannot coordinate in a tetradentate manner at one metal center for steric reasons. Instead, these ligands can coordinate as bridging units in a bisdidentate way. The Δ, Δ - and the Λ, Λ -configured complexes can be formed stereoselectively from nonracemic [Ru(bpy)₂]²⁺ fragments with **L30b** and **L30a**. A CHIRAGEN ligand with 5,5'-dimethylene-2,2'-bipyridine as a bridge^[129] represents a trisdidentate ligand (**L30f**). This ligand can bind three [Ru(bpy)₂]²⁺ fragments, to yield Δ, Δ, Δ - and $\Lambda, \Lambda, \Lambda$ -configured complexes if enantiomerically pure building blocks are used. These nonracemic building blocks can be obtained either through classical resolution of a racemate with tartrates^[130, 131] or through stereoselective synthesis. An example for the latter case are the mononuclear ruthenium



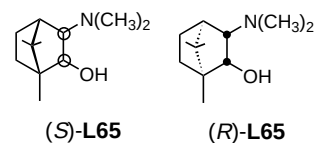
complexes with the *m*-xylene-bridged ligand **L31b**, which were already discussed in Section 2.3. The predetermined fragment Δ -[Ru(**L31b**)] has also been treated with the ligands **L30a, b**, and **f**.

Another interesting ligand of the CHIRAGEN series is the Super CHIRAGEN **L64**. Both pyridine rings of this ligand are condensed in the 4,5-position

to pinene groups. The resulting ligands are C₂ symmetric and sterically demanding. The chiral information is amplified through this multiplication of pinene groups. The coordination chemistry of these ligands is similarly varied as that of the directly bridged ligands (**L30a**).

Polynuclear metal complexes can be built not only from ruthenium centers, but also tetrahedral zinc atoms can be formed in dimeric complexes in a chirally predetermined

manner.^[132] Noyori et al. have prepared the dimeric zinc complex [Zn₂(**L65**)₂(CH₃)₂] from a trigonal methylzinc complex of the ligand (2*S*)- or (2*R*)-**L65**. The enantiomerically



pure *S* form of the ligand forms *S*-configured metal centers. The heterochiral dimer, which is formed from the racemic ligand is more stable in solution as well as in the solid (Figure 17).

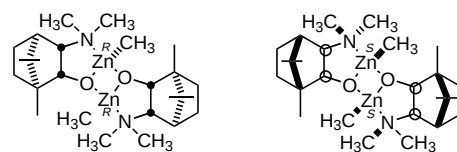


Figure 17. Dimers with *R,R*- and *S,S*-configured zinc coordination centers.

4.1. Helicates

In helical, polynuclear metal complexes two forms of chirality must be distinguished. The first is the chirality at the metal center, which has already been discussed in detail, and the second is the orientation of the bridging ligands in the complex, which determines the sense of rotation of the resulting helix. The latter is designated with the descriptors *P* for right-handed and *M* for left-handed orientations (Figure 18). Achiral ligands yield racemates of *P*- and *M*-configured helicates. The chirality of the metal center and therewith the helicity of the whole molecule can be, however, again predetermined through the use of chiral ligands.^[133]

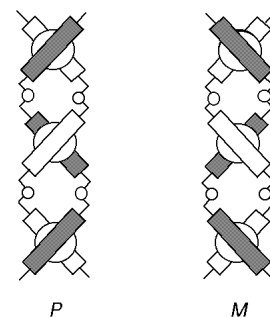
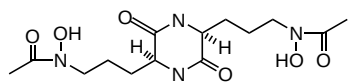
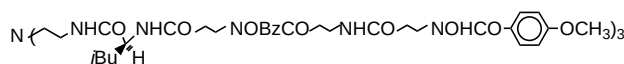
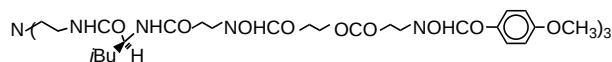


Figure 18. *P*- and *M*-configured helices.

The first example of a helix with predetermined chirality was published by Raymond et al.^[134] Dinuclear iron complexes with rhodothorulic acid (**L66**), a dihydroxamate siderophore, were synthesized to investigate mechanisms of microbial transport of iron (see Section 2.5.1). The dinuclear complex [Fe₂(**L66**)₃] with clearly Δ -*cis*-configured iron centers is formed as a triple helix between pH 4 and 11. Even though the chirality of the helix is not explicitly discussed in this publication, it is evident from the given data that it has a *P* configuration.

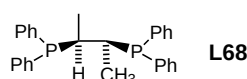
Shanzer et al.^[135] described in 1987 the predetermination of the chirality of a dinuclear triple helix that is stabilized through hydrogen bridges between the single strands. The ligand **L67a** is constructed on the basis of tris(2-aminoethyl)-amine. The chirality is introduced through the L-leucine

**L66****L67 a****L67 b**

groups and the three arms of the ligands are built up as an alternating sequence of hydroxamate and amide groups. This ligand forms stable, dinuclear complexes of *P*-helicity with iron(III). The configuration is stabilized through hydrogen bridges between the peripheral amide proton of one strand and the central amide carbonyl group of the neighboring strand. In order to test the hydrogen bridge hypothesis a ligand was synthesized where the peripheral amides are replaced by ester groups (**L67b**). Hydrogen bridges cannot be formed anymore in the same way. The result is an inversion of the helix and, indeed, the *M* form is preferred.

A series of investigations where helical chirality is predetermined were carried out around 1985.^[136–138] It is interesting to note that the concept of a “helix” is not used. The complexes were discussed in terms of configuration chirality. Stereoselective synthesis of helical systems of this sort have

been developed for molybdenum dimers. Cotton, Peacock et al. described in 1984 the synthesis of a bis(*S,S*)-2,3-(diphenylphosphanyl)butane (**L68**) bridged di-

**L68**

nuclear molybdenum complex where the “free” coordination sites are occupied with four chloride or bromide ions (Figure 19).^[139, 140] These complexes can be designated as *M*-

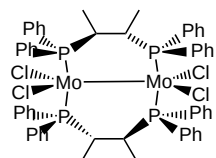
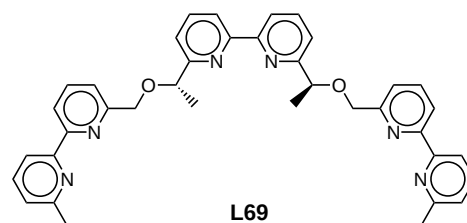


Figure 19. The orientation of chiral bridging ligands that determine the configuration in $[\text{Mo}_2(\text{L68})\text{Cl}_4]$.

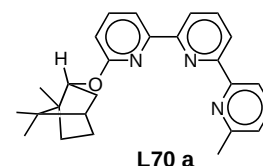
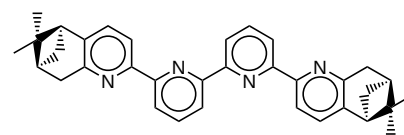
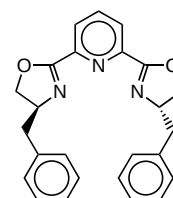
configured double helices from the current nomenclature. It should be noted that in these cases the metal itself cannot be considered to be a center of chirality. The helicity is defined only through the orientation of the ligands relative to each other. If the bridging diphosphane ligands are substituted by (*R,R*)-*trans*-1,2-diaminocyclohexane (dach), a complex $[\text{Mo}_2\text{Cl}_4((R,R)\text{-dach})_2]$, is obtained in a *P* configuration.^[141]

Helical silver(I) and copper(I) systems have been the subject of many investigations. The group of Lehn^[142] have described the coordination chemistry of these metals with a ligand where three bipyridine units are connected through chiral bridges. This hexadentate ligand **L69** forms only one diastereomeric form of the trinuclear complex with copper(I) and silver(I) ions. Other diastereomers were not observed in the NMR spectra, which indicates an abundance of less than 5%. The Δ configuration can be derived from the sign of the CD spectra in the case of the copper(I) complex. A strong

**L69**

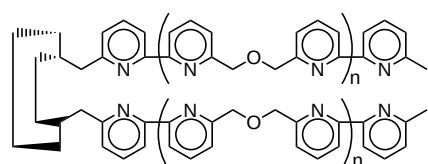
indication for the formation of oligonuclear helical metal complexes is the amplification of the Cotton effect relative to the monomers.^[4]

Constable et al. have described an example where the helicity could be predetermined through the use of an unsymmetrical chiral terpyridine ligand.^[143] Beside the helicity of the metal center, the described complexes can, in principle, also form other isomers, namely head–head (HH) and head–tail (HT) coordination. Both kinds of isomerism are predetermined in the case of the dinuclear copper(I) complex of the nonracemic ligand (**L70a**). The *M*-configured

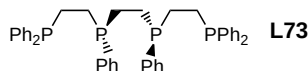
**L70 a****L70 b****L71**

complex of the HT form is obtained in a diastereomeric ratio of 6.5:1. An increased stereoselectivity is obtained through the synthesis of a C_2 -symmetric ligand (**L70b**) from four pyridine and two pinene units.^[144] In this case there are no head–tail isomers and the introduction of a second chiral group increases the diastereoselectivity to 95.3%. The *S*-configured ligand forms a *P* helix and the *R*-configured ligand as expected an *M* helix. Williams et al. obtained a high selectivity in the formation of a dinuclear double helix with the C_2 -symmetric ligand **L71**.^[145]

Siegel et al. showed that the chirality of a helix can also be defined by a terminal chiral element.^[146, 147] An example is the formation of a trinuclear helix with copper(I) as the coordination center. The ligands **L72a–c** consist of up to three achiral bipyridine units, which are connected through ether bridges. Two such strands are anchored at a chiral backbone, which transforms the stereochemical information onto the

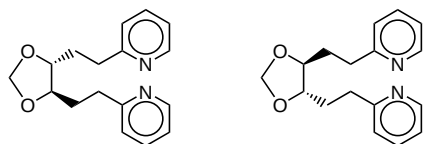


L72 a, $n = 0$; b, $n = 1$; c, $n = 2$



helix. This transfer of chiral information can take place at a distance of up to 2 nm. The *P* form of the helix is obtained from the *R* enantiomer of the ligand. The formation of dinuclear silver helices is not restricted to nitrogen donor ligands. Tetradentate phosphor ligands such as **L73** form a D_2 -symmetric *M*-double helix through spontaneous self association if the *S,S* form is used.^[148]

Another example for the predetermination of the chirality of helices formed by silver ions with coordination number two has been described by Kotsuki et al.^[149] These authors use an enantiomerically pure bispyridyl ligand based on an oxolane scaffold (**L74**). The *R,R* form of ligand **L74a** forms polymeric

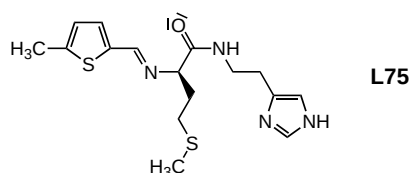


L74 a

L74 b

chains with *M* helicity, while the *S,S* form of **L74b** gives the enantiomeric complex with *P* helicity. It is interesting to note that the racemic ligand does not form mixtures of both polymers but discrete dinuclear species, which are formed through one *R*- and one *S*-configured ligand. This is a special type of molecular recognition of enantiomeric ligands, whereby two identical ligands in the homochiral complex are strongly disfavored. All three species are labile in solution and show identical NMR spectra. The stabilization of the heterochiral form is evident through its spontaneous formation from a mixture of both polymeric enantiomers.

Van Koten et al. have synthesized polymeric silver(i) and copper(i) helices that are also stable in solution.^[150, 151] A 1:1 mixture of the polydentate ligand **L75** with Cu^{I} and Ag^{I} salts



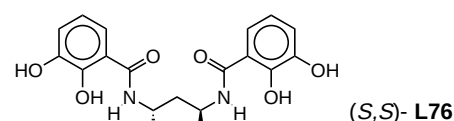
L75

yields stable complexes, which form polymeric chains in the solid state. Each ligand forms a bridge between three metal centers. The structural analysis of the silver complex shows a trigonal coordination of each silver center by one imidazole N,

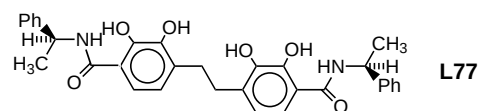
one imine N, and one methionine S atom. Weaker interactions can be attributed to an amide O and a thiophene S atom. If the ligand (*R*)-**L75** is used, the helix is Δ configured.

Helically predisposed polymers that show helicity by themselves, can lead to helical complexes too. Stable helical metal complexes have, for example, been obtained by complex formation of nickel(ii) ions with such a ligand.^[152]

Catecholates are also suitable for the synthesis of helices with predetermined chirality. Gallium(iii) complexes were obtained with ligand **L76** in the *S,S* as well as in the *R,R* form. The structure of the ligand prevents a tetradentate coordination to one central metal, instead two metal centers are bridged by the bisdidentate ligand. It is shown by X-ray analysis that the *R,R* form yields a Δ,Δ -configured complex. The reaction of the racemic ligand with gallium(iii) ions shows that in this case helices formed from ligands with the same chirality are also less stable than the heterochiral analogues.^[153] The heterochiral form is preferred over the



(*S,S*)- **L76**

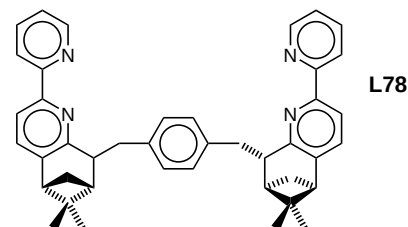


L77

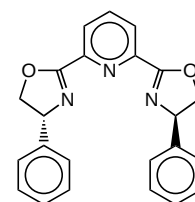
homochiral one in a ratio of 6:1 under equilibrium conditions. The *S,S* form of the chiral biscatecholate ligand **L77** forms diastereoselectively only a homochiral isomer with Ti^{IV} ions.^[154] The metal and the helical chirality cannot be assigned with certainty from the published data.

4.1.1. Cyclic Helices

Cyclic helices have been obtained and characterized only in a few cases until now. A stereochemically completely predetermined cyclic molecular helicate is obtained from silver(i) ions with the tetradentate nonracemic ligand **L78** from the CHIRAGEN family.^[155] Self assembly leads in this



L78



L79

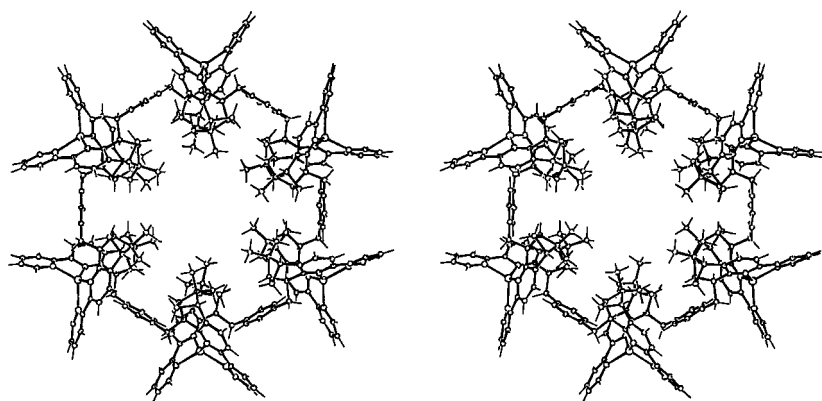
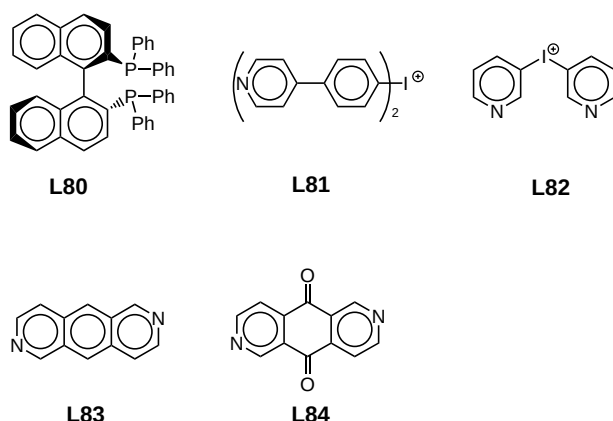


Figure 20. Chiral, predetermined hexanuclear cyclic helix with ligand **L78**.

case to diastereoselective formation of a hexanuclear complex in almost quantitative yield. The nonracemic ligand (*8R,10R*)-**L78** is formed out of two (*8R,10R*)-5,6-pineno-2,2'-bipyridine units and it predetermines the *P* form of the single stranded helix. Isomers have not been observed (Figure 20). Another single stranded cyclic helix^[*] with three silver centers is described by Williams et al.^[145] The ligand (*R,R*)-oxazoline-pyridine (**L79**) is tridentate and it forms a trinuclear cyclic helix with *M* helicity.

4.1.2. Molecular Squares

An aesthetically fascinating group of molecules are the molecular squares.^[156–165] Only a few of them have been prepared in predetermined nonracemic form. Some examples have been described by the group of Stang.^[166, 167] Two groups of squares can be distinguished: In the first group the molecular species are formed by four transition metal ions, whereas the second group consists of two transition metals and two iodonium ions. The *R*- or *S*-didentate ligands **L80**, which determine the chirality, are used as terminal ligands (Figure 21).



these fragments through the choice of the **L80** enantiomer. Both metal centers are chiral. The ligands **L81**, however, do not lead to helical chirality because of their high symmetry. Six diastereomeric structures are in principle possible with a ligand of lower symmetry such as bis(3-pyridyl)iodonium (**L82**). One of these diastereomers is clearly preferred in the case of palladium complexes, whereas the preference is less pronounced in the case of the platinum complex. A definitive assignment of the most abundant diastereomer is not possible from the published data.

In the squares with four metal centers, chiral Pt- and Pd-**L80** fragments are connected through the C_2 -symmetric ligand 2,6-diazaanthracene (**L83**) and 2,6-diazaanthracene-9,10-dione (**L84**). **L83** yields only one diastereomer for Pt and Pd, whereas in the case of **L84** the diastereomeric excess is 81 % (Pd) and 72 % (Pt).

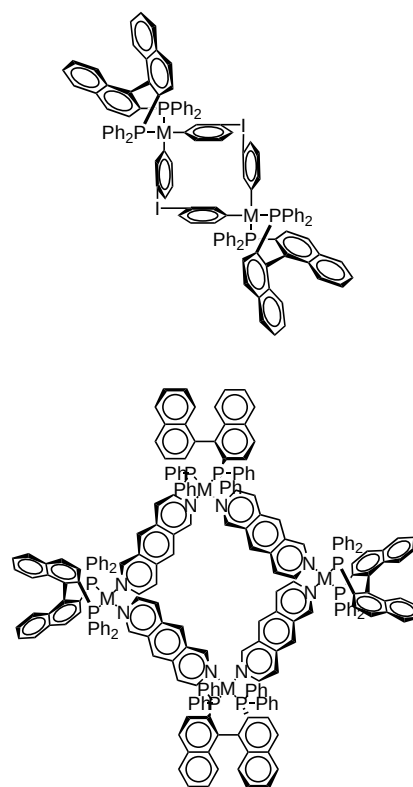


Figure 21. Two examples of chirally predetermined molecular squares. M = Pd, Pt.

The hybrid molecules consisting of iodonium and transition metal ions are obtained from palladium(II)- or platinum(II)-**L80** triflates. The chirality of the metal center is determined in

[*] The authors designate the structure as a triple stranded helix.

5. Summary and Outlook

Predetermination of chirality in molecules can be reached, in general, only through diastereoselective processes. Chirality is therewith not generated in an absolute sense but it is induced. This induction takes place in coordination chemistry in general from a given chirality in the ligand sphere to a

preferred chirality at the metal center. Chiral predetermination has been observed most often in octahedral coordination geometry. It is, however, also possible in tetrahedral, distorted planar, and fivefold coordinated species. It is useful to classify the complexes of octahedral coordination geometry by the denticity of the chiral ligands that predetermine the configuration at the metal center. Chiral induction is, as a general rule, not very efficient for didentate ligands, whereas for ligands of higher denticity, especially those with four, five, and six donor atoms, a complete chiral induction can often be observed.

The possibility of an asymmetric synthesis of coordination compounds had already been formulated in a clear way by Smirnov in 1920^[16]: "The examples of asymmetric synthesis described in this work prove that this concept is not restricted to the C-atom with its tetrahedral bonding scheme, but that it can be observed in a much stronger way also at atoms of heavy metals with completely different spatial conditions". In the decades following Smirnov's publication, only sporadic contributions have been published for the asymmetric synthesis of coordination compounds. A systematic investigation has started only recently.

It is highly probable that this development will continue in an accelerated rhythm. Predetermined chirality at metal centers is of central interest from different points of view. In the first place it opens new possibilities and new viewpoints with respect to enantioselective catalysis, since catalytic processes at metal centers are enantioselective if the metal center itself determines the chirality of the product. A second very important field of application is supramolecular chemistry, where chiral structures with metal centers are formed in self-assembling systems. Geometrically and functionally defined aggregates can only be obtained when the chirality at the individual centers can be predetermined through a judicious choice of chiral building blocks. Finally, a third field where metal complexes with predetermined chirality are of special interest is bioinorganic chemistry. Moreover, the possibility to predetermine the chirality at metal centers is a relatively new field of basic research where new and unexpected results can be obtained.

Received: April 1, 1998 [A 2751E]

German version: *Angew. Chem.* **1999**, *111*, 312–333

- [1] E. Fischer, *Ber. Dtsch. Chem. Ges.* **1894**, *27*, 3189–3232.
- [2] D. L. Sayers, R. Eustace, *The Documents in the Case*, Victor Gollancz, London, **1930**.
- [3] A. von Zelewsky, *Stereochemistry of Coordination Compounds*, Wiley, Chichester, **1996**.
- [4] M. Ziegler, A. von Zelewsky, *Coord. Chem. Rev.* **1998**, submitted.
- [5] International Union of Pure and Applied Chemistry, *Nomenclature of Inorganic Chemistry, Recommendations 1990*, Blackwell Scientific Publications, Oxford, **1990**.
- [6] M. Brorson, T. Damhus, C. E. Schäffer, *Inorg. Chem.* **1983**, *22*, 1569–1573.
- [7] A. Werner, *Chem. Ber.* **1911**, *44*, 1887–1898.
- [8] H. Brunner, *Angew. Chem.* **1969**, *81*, 395–396; *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 382–383.
- [9] H. Brunner, E. Schmidt, *J. Organomet. Chem.* **1970**, *21*, P53–P54.
- [10] H. Brunner, *Angew. Chem.* **1971**, *83*, 274–285; *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 249–260.
- [11] M. Gianini, A. Forster, P. Haag, A. von Zelewsky, H. Stoeckli-Evans, *Inorg. Chem.* **1996**, *35*, 4889–4895.
- [12] M. Gianini, A. von Zelewsky, H. Stoeckli-Evans, *Inorg. Chem.* **1997**, *36*, 6094–6098.
- [13] L. Tschugaeff, W. Sokoloff, *Ber. Dtsch. Chem. Ges.* **1909**, *42*, 55–68.
- [14] H. Volk, *Ber. Dtsch. Chem. Ges.* **1912**, *45*, 3744–3748.
- [15] A. Werner, *Helv. Chim. Acta* **1918**, *1*, 5–32.
- [16] A. P. Smirnov, *Helv. Chim. Acta* **1920**, *3*, 177–195.
- [17] J. C. Bailar, J. P. McReynolds, *J. Am. Chem. Soc.* **1939**, *61*, 3199–3203.
- [18] M. Martinette, J. C. Bailar, *J. Am. Chem. Soc.* **1952**, *74*, 1054–1056.
- [19] E. J. Corey, J. C. Bailar, *J. Am. Chem. Soc.* **1959**, *81*, 2620–2629.
- [20] J. H. Dunlop, R. D. Gillard, *J. Inorg. Nucl. Chem.* **1965**, *27*, 361–363.
- [21] J. H. Dunlop, R. D. Gillard, G. Wilkinson, *J. Chem. Soc.* **1964**, 3160–3163.
- [22] R. D. Gillard, G. Wilkinson, *J. Chem. Soc.* **1964**, 1368–1372.
- [23] F. P. Dwyer, T. E. MacDermott, A. M. Sargeson, *J. Am. Chem. Soc.* **1963**, *85*, 661–663.
- [24] F. P. Dwyer, F. L. Garvan, A. Shulman, *J. Am. Chem. Soc.* **1959**, *81*, 290–294.
- [25] F. M. Jaeger, H. B. Blumendal, *Z. Anorg. Allg. Chem.* **1928**, *175*, 161–230.
- [26] A. W. Bishop, L. Claisen, W. Sinclair, *Justus Liebigs Ann. Chem.* **1894**, *281*, 314–398.
- [27] S. H. French, T. M. Lowry, *Proc. R. Soc. London A* **1924**, *106*, 489–512.
- [28] H. Burgess, T. M. Lowry, *J. Chem. Soc. Trans.* **1924**, *125*, 2081–2096.
- [29] I. J. Faulkner, T. M. Lowry, *J. Chem. Soc. Trans.* **1925**, *127*, 1080–1085.
- [30] T. M. Lowry, H. Burgess, I. J. Faulkner, R. C. Traill, *Proc. R. Soc. London A* **1931**, *132*, 387–397.
- [31] T. M. Lowry, R. C. Traill, *Proc. R. Soc. London A* **1931**, *132*, 398–415.
- [32] T. M. Lowry, R. C. Traill, *Proc. R. Soc. London A* **1931**, *132*, 416–427.
- [33] J. Lifschitz, *Recl. Trav. Chim. Pays-Bas* **1922**, *41*, 627–636.
- [34] J. Lifschitz, *Z. Phys. Chem.* **1923**, *105*, 27–54.
- [35] R. E. Ballard, A. J. McCaffery, S. F. Mason, *Proc. Chem. Soc.* **1962**, 331–332.
- [36] S. F. Mason, *Q. Rev. Chem. Soc.* **1963**, *17*, 20–66.
- [37] A. J. McCaffery, S. F. Mason, R. E. Ballard, *J. Chem. Soc.* **1965**, 2883–2892.
- [38] J. H. Dunlop, R. D. Gillard, R. Ugo, *J. Chem. Soc. A* **1966**, 1540–1547.
- [39] Y. T. Chen, G. W. Everett, *J. Am. Chem. Soc.* **1968**, 6660–6665.
- [40] H. Okawa, H. Tokunaga, T. Katsuki, M. Koikawa, S. Kida, *Inorg. Chem.* **1988**, *27*, 4373–4377.
- [41] M. Nakamura, H. Okawa, S. Kida, S. Misumi, *Bull. Chem. Soc. Jpn.* **1984**, *57*, 3147–3151.
- [42] S. Maeda, M. Nakamura, H. Okawa, S. Kida, *Polyhedron* **1987**, *6*, 583–586.
- [43] H. Okawa, K. Ueda, S. Kida, *Inorg. Chem.* **1982**, *21*, 1594–1598.
- [44] H. Okawa, M. Nakamura, Y. Shuin, S. Kida, *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3657–3658.
- [45] M. Nakamura, H. Okawa, S. Kida, *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3377–3378.
- [46] M. Nakamura, H. Okawa, T. Ito, M. Kato, S. Kida, *Bull. Chem. Soc. Jpn.* **1987**, *60*, 539–543.
- [47] M. Nakamura, H. Okawa, S. Kida, *Inorg. Chim. Acta* **1984**, *96*, 111–114.
- [48] M. Nakamura, H. Okawa, S. Kida, *Chem. Lett.* **1981**, 547–550.
- [49] P. Biscarini, R. Kuroda, *Inorg. Chim. Acta* **1988**, *154*, 209–214.
- [50] P. Biscarini, *Inorg. Chim. Acta* **1985**, *99*, 183–188.
- [51] P. Biscarini, *Inorg. Chim. Acta* **1985**, *99*, 189–194.
- [52] R. Kuroda, P. Biscarini, *J. Chem. Soc. Dalton Trans.* **1990**, 3393–3397.
- [53] P. Biscarini, R. Franca, R. Kuroda, *Inorg. Chem.* **1995**, *34*, 4618–4626.
- [54] K. Abu-Dari, K. N. Raymond, *J. Coord. Chem.* **1992**, *26*, 1–14.
- [55] R. J. Cross, L. J. Farrugia, P. D. Newman, R. D. Peacock, D. Stirling, *J. Chem. Soc. Dalton Trans.* **1996**, 4449–4458.
- [56] K. Ohkubo, M. Fukushima, H. Ohta, S. Usui, *J. Photochem. Photobiol. A* **1996**, *98*, 137–140.

- [57] K. Ohkubo, T. Hamada, M. Watanabe, M. Fukushima, *Chem. Lett.* **1993**, 1651–1654.
- [58] K. Ohkubo, M. Watanabe, H. Ohta, S. Usui, *J. Photochem. Photobiol. A* **1996**, 95, 231–233.
- [59] K. Ohkubo, T. Hamada, T. Inaoka, H. Ishida, *Inorg. Chem.* **1989**, 28, 2021–2022.
- [60] M. Yashiro, T. Murata, M. Sato, M. Kosaka, K. Kobayashi, T. Sakurai, S. Yoshikawa, M. Komiyama, S. Yano, *J. Chem. Soc. Dalton Trans.* **1994**, 1511–1516.
- [61] M. Yashiro, T. Murata, S. Yoshikawa, S. Yano, *J. Chem. Soc. Dalton Trans.* **1994**, 1073–1077.
- [62] M. Nakamura, H. Okawa, T. Inazu, S. Kida, *Bull. Chem. Soc. Jpn.* **1982**, 55, 2400–2403.
- [63] R. S. Vagg, P. A. Williams, *Inorg. Chim. Acta* **1981**, 51, 61–65.
- [64] S. Bunel, G. Larrazabal, A. Decinti, *J. Inorg. Nucl. Chem.* **1981**, 43, 2781–2783.
- [65] A. Decinti, M. Contreras, E. Moraga, G. Larrazabal, *Polyhedron* **1992**, 11, 1235–1250.
- [66] A. Tatehata, *Inorg. Chem.* **1982**, 21, 2496–2499.
- [67] F. S. Stephens, R. S. Vagg, P. A. Williams, *Inorg. Chim. Acta* **1983**, 72, 253–261.
- [68] R. S. Vagg, P. A. Williams, *Inorg. Chim. Acta* **1981**, 52, 69–72.
- [69] A. Pasini, *Gazz. Chim. Ital.* **1983**, 113, 793–797.
- [70] T. J. Goodwin, P. A. Williams, R. S. Vagg, *Inorg. Chim. Acta* **1982**, 63, 133–140.
- [71] R. S. Vagg, P. A. Williams, *Inorg. Chim. Acta* **1982**, 58, 101–105.
- [72] D. A. Buckingham, L. G. Marzilli, A. M. Sargeson, *J. Am. Chem. Soc.* **1967**, 5133–5138.
- [73] D. P. Craig, D. P. Mellor, *Top. Curr. Chem.* **1976**, 63, 1–48.
- [74] T. J. Goodwin, P. A. Williams, F. S. Stephens, R. S. Vagg, *Inorg. Chim. Acta* **1984**, 88, 165–181.
- [75] E. F. Hahn, T. J. McMurry, A. Hugi, K. N. Raymond, *J. Am. Chem. Soc.* **1990**, 112, 1854–1860.
- [76] a) Y. Yao, C. J. A. Daley, R. McDonald, S. H. Bergens, *Organometallics* **1997**, 16, 1890–1896; b) H. Heide, J. Scherer, A. Asam, G. Huttner, O. Walter, L. Zsolnai, *Chem. Ber.* **1995**, 128, 293–301.
- [77] K. Toyohara, T. Yamami, T. Nishimi, T. Kunitake, *Chem. Lett.* **1994**, 673–676.
- [78] B. Bosnich, W. R. Kneen, *Inorg. Chem.* **1970**, 9, 2191–2194.
- [79] R. R. Fenton, R. S. Vagg, P. A. Williams, *Inorg. Chim. Acta* **1988**, 148, 37–44.
- [80] M. Atoh, H. O. Soerensen, P. Andersen, *Acta Chem. Scand.* **1997**, 51, 1169–1177.
- [81] R. R. Fenton, F. S. Stephens, R. S. Vagg, P. A. Williams, *Inorg. Chim. Acta* **1991**, 182, 67–75.
- [82] R. R. Fenton, F. S. Stephens, R. S. Vagg, P. A. Williams, *Inorg. Chim. Acta* **1992**, 201, 157–164.
- [83] P. Hayoz, A. von Zelewsky, H. Stoeckli-Evans, *J. Am. Chem. Soc.* **1993**, 115, 5111–5114.
- [84] H. Muerner, P. Belser, A. von Zelewsky, *J. Am. Chem. Soc.* **1996**, 118, 7989–7994.
- [85] K. E. Gunde, A. Credi, E. Jandrasics, A. von Zelewsky, F. S. Richardson, *Inorg. Chem.* **1997**, 36, 426–434.
- [86] H. Muerner, A. von Zelewsky, H. Stoeckli-Evans, *Inorg. Chem.* **1996**, 35, 3931–3935.
- [87] R. C. Job, T. Bruice, *J. Am. Chem. Soc.* **1974**, 96, 809–819.
- [88] M. Ajioka, S. Yano, K. Matsuda, S. Yoshikawa, *J. Am. Chem. Soc.* **1981**, 103, 2459–2460.
- [89] M. Yashiro, M. Ajioka, S. Yano, K. Toriumi, T. Ito, S. Yoshikawa, *Inorg. Chem.* **1986**, 25, 1709–1715.
- [90] M. Yamaguchi, S. Yamamatsu, T. Furusawa, S. Yano, M. Saburi, S. Yoshikawa, *Inorg. Chem.* **1980**, 19, 2010–2016.
- [91] M. Yamaguchi, S. Yano, M. Saburi, S. Yoshikawa, *Bull. Chem. Soc. Jpn.* **1980**, 53, 691–698.
- [92] M. Yamaguchi, S. Yano, M. Saburi, S. Yoshikawa, *Inorg. Chem.* **1980**, 19, 2016–2021.
- [93] M. Yamaguchi, S. Yamamatsu, H. Oikawa, M. Saburi, S. Yoshikawa, *Inorg. Chem.* **1981**, 20, 3179–3186.
- [94] M. Yamaguchi, Y. Masui, M. Saburi, S. Yoshikawa, *Inorg. Chem.* **1982**, 21, 4138–4143.
- [95] K. Bernauer, P. Pousaz, *Helv. Chim. Acta* **1984**, 67, 796–803.
- [96] K. Bernauer, H. Stoeckli-Evans, D. Hugi-Cleary, H. J. Hilgers, H. Abd-el-Khalek, J. Porret, J. J. Sauvain, *Helv. Chim. Acta* **1992**, 75, 2327–2329.
- [97] F. P. Dwyer, F. L. Garvan, *J. Am. Chem. Soc.* **1961**, 83, 2610–2615.
- [98] J. R. Gologly, C. J. Hawkins, *Aust. J. Chem.* **1967**, 20, 2395–2402.
- [99] A. Kobayashi, F. Marumo, Y. Saito, *Acta Crystallogr. Sect. B* **1974**, 30, 1495–1498.
- [100] C. Fraser, R. Ostrander, A. L. Rheingold, C. White, B. Bosnich, *Inorg. Chem.* **1994**, 33, 324–337.
- [101] P. M. Fitzsimmons, S. C. Jackels, *Inorg. Chim. Acta* **1996**, 246, 301–310.
- [102] G. Saenz, R. M. L. Warren, M. Shang, G. Lappin, *J. Coord. Chem.* **1995**, 34, 129–137.
- [103] R. C. Matthews, D. Parker, G. Ferguson, B. Kaitner, A. Harrison, L. Royle, *Polyhedron* **1991**, 10, 1951–1953.
- [104] P. Baret, V. Beaujolais, D. Gaude, C. Coulombeau, J.-L. Pierre, *Chem. Eur. J.* **1997**, 6, 969–973.
- [105] T. B. Karpishin, T. D. P. Stack, K. N. Raymond, *J. Am. Chem. Soc.* **1993**, 115, 6115–6125.
- [106] J. V. McArdle, S. R. Sofen, S. R. Cooper, K. N. Raymond, *Inorg. Chem.* **1978**, 17, 3075–3078.
- [107] T. B. Karpishin, K. N. Raymond, *Angew. Chem.* **1992**, 104, 486–488; *Angew. Chem. Int. Ed. Engl.* **1992**, 31, 466–468.
- [108] A. Shanzer, J. Libman, S. Lifson, C. E. Felder, *J. Am. Chem. Soc.* **1986**, 108, 7609–7619.
- [109] Y. Tor, J. Libman, A. Shanzer, S. Lifson, *J. Am. Chem. Soc.* **1987**, 109, 6517–6518.
- [110] Y. Tor, J. Libman, A. Shanzer, C. E. Felder, S. Lifson, *J. Am. Chem. Soc.* **1992**, 114, 6661–6671.
- [111] Y. Tor, J. Libman, A. Shanzer, *J. Am. Chem. Soc.* **1987**, 109, 6518–6519.
- [112] I. Dayan, J. Libman, Y. Agi, A. Shanzer, *Inorg. Chem.* **1993**, 32, 1467–1475.
- [113] Y. Hisaeda, T. Ihara, T. Ohno, Y. Murakami, *Chem. Lett.* **1991**, 2139–2142.
- [114] B. Tse, Y. Kishi, *J. Am. Chem. Soc.* **1993**, 115, 7892–7893.
- [115] T. B. Karpishin, T. M. Dewey, K. N. Raymond, *J. Am. Chem. Soc.* **1993**, 115, 1842–1851.
- [116] C. Deuschel-Cornioley, H. Stoeckli-Evans, A. von Zelewsky, *J. Chem. Soc. Chem. Commun.* **1990**, 121–122.
- [117] A. Wojtczak, E. Szlyk, M. Jaskolski, E. Larsen, *Acta Chem. Scand.* **1997**, 51, 274–278.
- [118] A. Abufarag, H. Vahrenkamp, *Inorg. Chem.* **1995**, 34, 3279–3284.
- [119] W. A. Nugent, R. L. Harlow, *J. Am. Chem. Soc.* **1994**, 116, 6142–6148.
- [120] J. W. Canary, C. S. Allen, J. M. Castagnetto, Y. Wang, *J. Am. Chem. Soc.* **1995**, 117, 8484–8485.
- [121] H. Brunner, W. Miehl, *Angew. Chem.* **1983**, 95, 162; *Angew. Chem. Int. Ed. Engl.* **1983**, 22, 164–165.
- [122] “Transition Metal Chemistry and Optical Activity—Werner-Type Complexes, Organometallic Compounds, Enantioselective Catalysis”: H. Brunner, E. Schmidt in *Chirality—from weak Bosons to the α -Helix* (Ed.: R. Janoschek), Springer, Berlin, **1991**, p. 166–179.
- [123] G. C. Van Stein, G. Van Koten, C. Brevard, *J. Organomet. Chem.* **1982**, 226, C27–C30.
- [124] G. C. Van Stein, G. Van Koten, B. De Bok, L. C. Taylor, K. Vrieze, C. Brevard, *Inorg. Chim. Acta* **1984**, 89, 29–39.
- [125] J. F. Modder, J.-M. Ernstling, K. Vrieze, M. de Wit, C. H. Stam, G. van Koten, *Inorg. Chem.* **1991**, 30, 1208–1214.
- [126] H. Brunner, P. Faustmann, A. Dietl, B. Nuber, *J. Organomet. Chem.* **1997**, 542, 255–263.
- [127] T. Mizutani, S. Yagi, A. Honmaru, H. Ogoshi, *J. Am. Chem. Soc.* **1996**, 118, 5318–5319.
- [128] R. Dickins, J. Howard, C. Lehmann, J. Moloney, D. Parker, R. Peacock, *Angew. Chem.* **1997**, 109, 541–543; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 521–523.
- [129] N. C. Fletcher, F. R. Keene, H. Viebrock, A. von Zelewsky, *Inorg. Chem.* **1997**, 36, 1113–1121.
- [130] X. Hua, A. von Zelewsky, *Inorg. Chem.* **1991**, 30, 3796–3798.
- [131] X. Hua, A. von Zelewsky, *Inorg. Chem.* **1995**, 34, 5791–5797.
- [132] M. Kitamura, M. Yamakawa, H. Oka, S. Suga, R. Noyori, *Chem. Eur. J.* **1996**, 2, 1173–1181.

- [133] C. Piguet, G. Bernadinelli, G. Hopfgartner, *Chem. Rev.* **1997**, 97, 2005–2062.
- [134] C. J. Carrano, K. N. Raymond, *J. Am. Chem. Soc.* **1978**, 100, 5371–5374.
- [135] J. Libman, Y. Tor, A. Shanzer, *J. Am. Chem. Soc.* **1987**, 109, 5880–5881.
- [136] R. D. Peacock, I. F. Fraser, *Inorg. Chem.* **1985**, 24, 988–989.
- [137] I. F. Fraser, A. McVitie, R. D. Peacock, *Polyhedron* **1986**, 5, 39–45.
- [138] S. Christie, I. F. Fraser, A. McVitie, R. D. Peacock, *Polyhedron* **1986**, 5, 35–37.
- [139] P. Agaskar, F. A. Cotton, I. F. Fraser, R. D. Peacock, *J. Am. Chem. Soc.* **1984**, 106, 1851–1853.
- [140] P. A. Agaskar, F. A. Cotton, I. F. Fraser, L. Manojlovic-Muir, K. W. Muir, R. D. Peacock, *Inorg. Chem.* **1986**, 25, 2511–2519.
- [141] M. Gerards, *Inorg. Chim. Acta* **1995**, 229, 101–103.
- [142] W. Zarges, J. Hall, J. M. Lehn, C. Bolm, *Helv. Chim. Acta* **1991**, 74, 1843–1852.
- [143] E. C. Constable, T. Kulke, M. Neuburger, M. Zehnder, *Chem. Commun.* **1997**, 489–490.
- [144] G. Baum, E. C. Constable, D. Fenske, T. Kulke, *Chem. Commun.* **1997**, 2043–2044.
- [145] C. Provent, S. Hewage, G. Brand, G. Bernardinelli, L. J. Charbonniere, A. F. Williams, *Angew. Chem.* **1997**, 109, 1346–1348; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 1287–1289.
- [146] C. R. Woods, M. Benaglia, F. Cozzi, J. S. Siegel, *Angew. Chem.* **1996**, 108, 1977–1980; *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 1830–1833.
- [147] C. R. Woods, M. Benaglia, P. Blom, A. Fuchicello, F. Cozzi, J. S. Siegel, *Polym. Prepr.* **1996**, 37, 480–481.
- [148] A. L. Airey, G. F. Swiegers, A. C. Willis, S. B. Wild, *J. Chem. Soc. Chem. Commun.* **1995**, 695–696.
- [149] T. Suzuki, H. Kotsuki, K. Isobe, N. Moriya, Y. Nakagawa, M. Ochi, *Inorg. Chem.* **1995**, 34, 530–531.
- [150] J. F. Modder, G. Van Koten, K. Vrieze, A. L. Spek, *Angew. Chem.* **1989**, 101, 1723–1725; *Angew. Chem. Int. Ed. Engl.* **1989**, 28, 1698–1700.
- [151] J. F. Modder, K. Vrieze, A. L. Spek, G. Challa, G. van Koten, *Inorg. Chem.* **1992**, 31, 1238–1247.
- [152] Y. Dai, T. J. Katz, D. A. Nichols, *Angew. Chem.* **1996**, 108, 2230–2232; *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 2109–2111.
- [153] E. J. Enemark, T. D. P. Stack, *Angew. Chem.* **1995**, 107, 1082–1084; *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 996–998.
- [154] M. Albrecht, *Synlett* **1996**, 565–567.
- [155] O. Mamula, A. von Zelewsky, G. Bernadinelli, *Angew. Chem.* **1998**, 110, 302–305; *Angew. Chem. Int. Ed. Engl.* **1998**, 37, 289–293.
- [156] P. J. Stang, B. Olenyuk, J. Fan, A. M. Arif, *Organometallics* **1996**, 15, 904–908.
- [157] P. J. Stang, K. Chen, A. M. Arif, *J. Am. Chem. Soc.* **1995**, 117, 8793–8797.
- [158] P. J. Stang, D. H. Cao, S. Saito, A. M. Arif, *J. Am. Chem. Soc.* **1995**, 117, 6273–6283.
- [159] P. J. Stang, K. Chen, *J. Am. Chem. Soc.* **1995**, 117, 1667–1668.
- [160] C. M. Drain, J.-M. Lehn, *J. Chem. Soc. Chem. Commun.* **1994**, 117, 2313–2315.
- [161] P. J. Stang, J. A. Whiteford, *Organometallics* **1994**, 13, 3776–3777.
- [162] P. J. Stang, D. H. Cao, *J. Am. Chem. Soc.* **1994**, 116, 4981–4982.
- [163] M. Fujita, Y. J. Kwon, S. Washizu, K. Ogura, *J. Am. Chem. Soc.* **1994**, 116, 1151–1152.
- [164] J. Rauter, E. C. Hillgeris, A. Erxleben, B. Lippert, *J. Am. Chem. Soc.* **1994**, 116, 616–624.
- [165] M. Fujita, S. Nagao, M. Iida, K. Ogura, *J. Am. Chem. Soc.* **1993**, 115, 1574–1576.
- [166] P. J. Stang, B. Olenyuk, *Angew. Chem.* **1996**, 108, 798–802; *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 732–736.
- [167] B. Olenyuk, J. A. Whiteford, P. J. Stang, *J. Am. Chem. Soc.* **1996**, 118, 8221–8230.

Efficient Assays for Combinatorial Methods for the Discovery of Catalysts

Thomas Bein*

The activities associated with chemical research and development often involve a significant manual component and specialized skills. Thus, the typical organic synthesis in the laboratory requires many operations such as weighing, setup of equipment, filtration, and distillation. Similarly, assessing the properties of interest, such as the pharmacological activity of organic compounds or the superconductivity of metal oxides, is a complex endeavor. This high level of manual human involvement has been maintained even in the computer age, at a time when many mental processes such as complex calculations as well as control of equipment are highly automated. The discovery of new compounds with useful properties has therefore been fairly slow and expensive.

The desire to change all this has led, first in the area of pharmaceutical research, to the development of combinatorial methods in chemistry.^[1] These methods target two interdependent aspects of the discovery process: synthesis and characterization. By learning from the powerful paradigm of the immune system chemists initially targeted the automated synthetic combination of appropriate organic building blocks such as amino acids. Even random combinations of just 20 amino acids can produce large numbers of different oligopeptides; for example, one can prepare 64 million different hexapeptides. One can distinguish the generation of building-block combinations on mixtures of beads as well as in rapid parallel synthesis in miniature reactors such as on 96-well plates. The former allow the formation of vast numbers of different compounds, but active beads must be identified by some tracking method. Parallel synthesis in discrete reactors usually limits the number of possible products, but the products are identified by position. The characterization of the resulting thousands or millions of new products poses enormous challenges for creative assays. Some of the earliest assays involve binding studies; for example, beads bearing the products of solid-phase organic synthesis can be exposed to receptors attached to fluorescent or colored chromophores. Strong binding is detected by the optical change of the active beads. The promise and excitement associated with the combinatorial approach has led to explosive growth in this field; nearly every major drug

company now has an active effort in combinatorial organic chemistry.

In comparison to the developments in molecular organic chemistry, other fields of chemistry and materials science have not yet experienced such a broad effort to accelerate the scientific discovery process.^[2] There is, however, one notable exception: the American company Symyx, which has recently become a combinatorial pioneer in many areas of materials synthesis and catalysis. There are interesting differences between the synthesis of organic compounds by the permutation of molecular building blocks (in linear, cyclic, starlike, or other arrangements) and the preparation of materials such as oxide superconductors or X-ray phosphors. The latter are made by mixing different quantities of starting materials; diversity can be generated by gradual changes in composition as well as processing conditions. Symyx's now famous "library" of thousands of luminescent spots on a single wafer demonstrates the power of parallel synthesis and array-based assays; the optical properties of all spots can be assessed simultaneously, even with the human eye.^[3] Two major synthetic methods have been developed so far: 1) gas-phase deposition on wafers with control of deposition time and masking to build the array (see above), and 2) liquid dosing into miniature wells,^[4] followed by some thermal and/or reactive processing.

Will it be possible to create new catalysts with combinatorial approaches? Nature teaches us that the answer is clearly "yes": The powerful natural catalysts, enzymes, are basically combinations of the natural amino acids in different sequences and sizes. Recent work has been focused on the design of combinatorial enzyme libraries that aim to improve features such as temperature or chemical stability.^[5] In a very creative use of natural systems, Schultz and Lerner have recently demonstrated that antibodies can be made catalytically active when they are raised against molecular models of the presumed shape of the transition state of a chemical reaction.^[6] Catalytic antibodies can have chemoselectivity and enantioselectivity, with high activity. In an extension of this approach, powerful chemical selection tools can be applied to antibody catalysis to find active systems.^[7]

In homogeneous molecular chemistry, where discrete building blocks can be assembled, several recent examples of automated or semiautomated catalyst discovery have been reported.^[8, 9] Different core structures have been assembled on beads, and diversity was introduced by the attachment of

[*] Prof. T. Bein
Department of Chemistry, Purdue University
West Lafayette, IN 47907-1393 (USA)
Fax: (+1) 765-494-0239
E-mail: tbein@chem.purdue.edu

combinations of building blocks to the cores. Several of these systems were then metalated and resulted in a set of catalyst candidates. In an early example, Ellman reported the solid-phase synthesis of 2-pyrrolidinemethanol ligands that were examined in enantioselective addition reactions after cleavage from the support.^[10] The high-throughput screening of metal catalysts for an asymmetric C–H insertion that involved diazo compounds was achieved by Burgess and co-workers,^[11] and disulfonamide-based chelating ligands were prepared in a parallel synthesis and screened in solution for the enantioselective addition of diethylzinc to aldehydes.^[12]

Hoveyda and co-workers showed that ligand diversity can be developed without the need to synthesize all possible permutations of building blocks, which thus reduces dramatically the synthetic efforts for catalyst development.^[13] In this example of the titanium-catalyzed enantioselective addition of trimethylsilylcyanide to epoxides, various dipeptide Schiff base ligands were synthesized. It was possible to vary the building blocks at just one position at a time on the core structure in order to improve catalytic activity and selectivity. The final catalyst was the combination of all the optimized ligands at the various positions. This counterintuitive result suggests that there may be other examples where cooperativity in metal coordination spheres may be less important for catalytic behavior. It was also shown that this ligand discovery process can also be performed in a very efficient way on a solid support.^[14] Sigman and Jacobsen found synergistic effects between components of Schiff base catalysts for the highly enantioselective asymmetric Strecker reaction.^[15]

In another peptide-based assembly method a library of phosphane-containing peptides was used to complex rhodium and was shown to give moderate enantiomeric excess in the asymmetric hydrogenation of enamide.^[16] Alternative approaches include the one-pot screening of a library of prochiral substrates with a chiral catalyst.^[17] The first examples of combinatorially prepared inorganic catalysts have also been reported. Hill and Gall synthesized various polyoxometalates for the aerobic oxidation of the mustard analogue tetrahydrothiophene from stock solutions that contained precursors such as Na_2WO_4 , Na_2MoO_4 , and Na_2HPO_4 .^[18]

As demonstrated in the above example,^[13] the creative design of the catalytic assay is a key element in the development of effective “algorithms” for the discovery of new homogeneous catalysts. It would be intriguing to create truly parallel means to detect catalytic activity in arrays. The enthalpy changes associated with many chemical reactions have been observed with infrared cameras to achieve this feat. The advent of sensitive thermal imagers (infrared cameras) with array detectors also allows the arrays of reactive solutions to be monitored. Reetz and co-workers^[19] applied this concept in the study of the homogeneous enantioselective acylation of a chiral alcohol (1-phenylethanol) that was catalyzed by immobilized lipase (from *Candida antarctica*), as well as in the enantioselective ring opening of chiral epoxides with transition metal salen catalysts (salen = *N,N'*-bis(salicylidene)ethylenediamine dianion). The reactants were placed in arrays of small vials, and the PtSi-based thermal imager (staring into the vials from above) could clearly distinguish active from nonactive vials. An extra twist

was provided for the detection of enantioselectivity of the catalysts: The array of reactants included the two different enantiomers of substrate, for which the catalysts showed drastically different activities. Crabtree and co-workers recognized the attractive features of color changes for parallel assay purposes and developed reactive dyes that contain an electron donor and acceptor linked by a reactive functionality such as C=C.^[20] When this functionality is changed during the catalytic reaction, for example, by hydrosilation, the electronic connection between the donor and acceptor groups is interrupted, and the color of the dye fades (Figure 1). This elegant approach promises to be amenable to many other catalytic reactions.^[27]

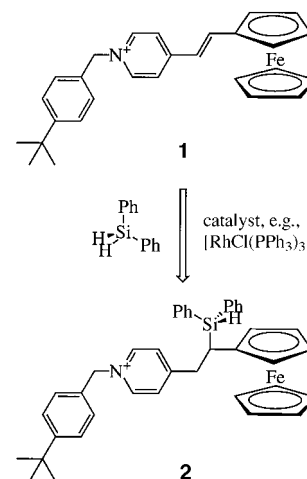


Figure 1. The use of a reactive dye **1** for the detection of hydrosilation activity. The dye changes its color from deep purple to light yellow following hydrosilation with a homogeneous catalyst within a few minutes.^[20]

Very different types of challenges await the practitioner of heterogeneous catalysis. While arrays of heterogeneous catalysts such as metal alloys or mixed oxides could be automatically constructed along the lines developed by Symyx and others (gas-phase deposition or liquid dosing), the assay of catalytic activity is nontrivial. Even if one accepts the presence of different surface areas and dispersions of active material, which can lead to significant errors in the determination of “intrinsic” activity such as turnover frequency, an efficient determination of activity and selectivity under realistic conditions might require different solutions for every different catalytic system under study.^[21] Several promising developments in this area have recently been reported. Recent work by Morken and co-workers has extended the earlier work of Willson^[22] with heated catalyst pellets (metals on alumina were used to oxidize hydrogen), and focused on the heat evolved from several thousand encoded beads that were partially immersed in a reactive solution for an acylation reaction.^[23]

In a recent interesting development Maier and co-workers showed that thermal imaging can be a very sensitive means of detecting activity in positional catalytic libraries that contain only about 200 μg of catalyst on each position.^[24] Tiny wells in slate (chosen for its low thermal reflectivity to avoid

interference) were filled with sol–gel precursor solutions for amorphous microporous mixed-metal oxides of different compositions, which were processed to yield an array of catalyst candidates (Figure 2). A thermal image of the whole

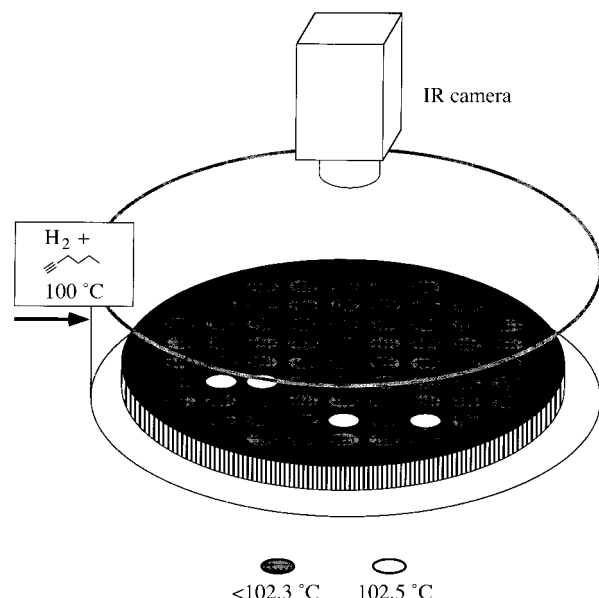


Figure 2. The arrangement used for thermal imaging of the hydrogenation activity of catalyst spots (ca. 200 µg per spot) on a slate substrate. The catalysts were prepared by the combination of titania or silica sols with solutions of metal salts in the slate wells, followed by heating to 250 °C. The IR camera detects temperature differences as small as 0.1 °C.^[24]

array without substrate was stored and subsequently subtracted from the images of the array under operation. This technique allowed Maier et al. to minimize the effect of different thermal emissivities of the catalyst wells, such that they could detect very small temperature differences associated with catalytic activity. Thermal imaging was shown to offer convenient and fast parallel assays of whole catalyst libraries, in this case for the hydrogenation of 1-hexyne at 100 °C and the oxidation of isooctane and toluene at 350 °C. An obvious limitation of thermal imaging is the absence of chemical information about the products generated by the catalysts. However, it might be possible to use the emission or absorption of IR radiation by the reaction products to achieve this goal.

Other strategies have been shown to provide information on chemical selectivity together with information on catalytic activity. Mallouk and co-workers demonstrated that metal alloy electrocatalysts could be optimized by using the production of protons during the electrochemical oxidation of methanol in a fuel cell.^[25] An elegant technique based on a fluorescent pH indicator allowed the researchers to identify active catalyst spots (Figure 3). These spots were generated by deposition of different metal salt solutions at various ratios with a commercial ink jet printer, followed by reduction with NaBH₄. Another important recent development is the detection of catalytic reaction products that evolve from an array of solid catalysts on a porous support in a pseudo-parallel fashion by using laser ionization techniques (Figure 4).^[26] This approach addresses in an effective way the

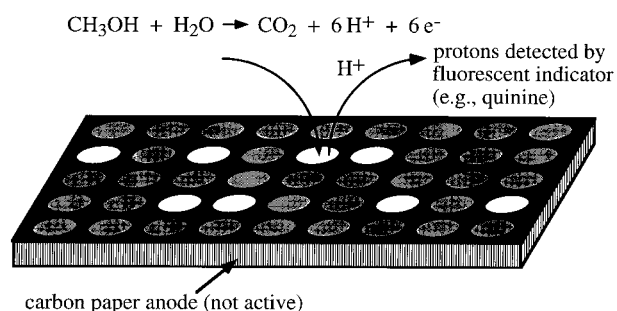


Figure 3. Ternary and quaternary arrays are used for the anodic oxidation of methanol in an aqueous indicator solution. A fluorescence indicator such as quinine shows the evolution of protons near the anode over the most active catalysts spots.^[25]

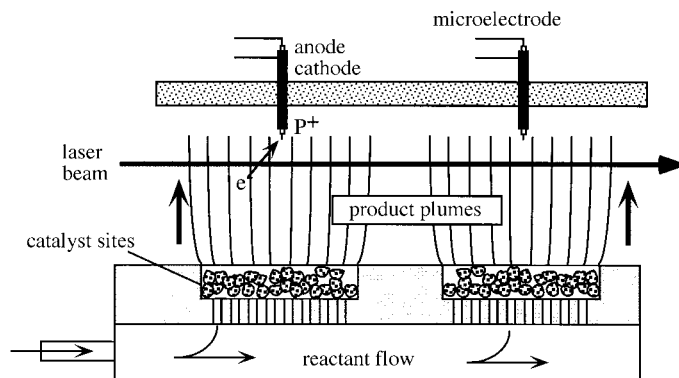


Figure 4. High-throughput screening of catalyst libraries with laser-induced resonance-enhanced multiphoton ionization for selective detection of reaction products. In this case, dehydrogenation of cyclohexane to benzene was detected. The latter was selectively photoionized by pulsed, tunable ultraviolet light in the vicinity of the catalytic sites (5 × 5 mm) of the array. The laser generates photoions P⁺ and photoelectrons depending on the bias voltage.^[26]

great need for the identification of reaction products that emanate from positional catalyst libraries.

In summary, following the revolutionary developments in pharmaceutical science, combinatorial approaches are now being explored in such diverse areas as materials design and homogeneous and heterogeneous catalysis. The issues associated with the parallel synthesis of many materials, as well as their structural and physical characterization in an efficient manner will continue to challenge the creativity of scientists and engineers involved in this exciting field.

German version: *Angew. Chem.* **1999**, *111*, 335–338

Keywords: analytical methods • combinatorial chemistry • heterogeneous catalysis • homogeneous catalysis

- [1] Reviews and special issues: a) *Chem. Rev.* **1997**, *97*, 347–510; b) H. Fenniri, *Curr. Med. Chem.* **1996**, *3*, 343–378; c) W. H. Weinberg, B. Jandeleit, K. Self, H. Turner, *Curr. Opin. Solid State Mater. Sci.* **1998**, *3*, 104–110; d) F. Balkenhohl, C. von dem Bussche-Hünnefeld, A. Lansky, C. Zechel, *Angew. Chem.* **1996**, *108*, 2436–2487; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2288–2337.
- [2] a) X.-D. Xiang, X. Sun, G. Briceno, Y. Lou, K.-A. Wang, H. Chang, W. G. Wallace-Freedman, S.-W. Chen, P. G. Schultz, *Science* **1995**, *268*, 1738–1740; b) G. Briceno, H. Chang, X. Sun, P. G. Schultz, X.-D.

- Xiang, *Science* **1995**, 270, 273–275; c) P. G. Schultz, X.-D. Xiang, *Curr. Opin. Solid State Mater. Sci.* **1998**, 3, 153–158.
- [3] E. Danielson, J. H. Golden, E. W. McFarland, C. M. Reaves, W. H. Weinberg, X. Di Wu, *Nature* **1997**, 389, 944–948.
- [4] X.-D. Sun, K.-A. Wang, Y. Yoo, W. G. Wallace-Freedman, C. Gao, X.-D. Xiang, P. G. Schultz, *Adv. Mater.* **1997**, 9, 1046–1049.
- [5] O. Kuchner, F. H. Arnold, *Trends Biotechnol.* **1997**, 15, 523–530.
- [6] a) P. G. Schultz and R. A. Lerner, *Science* **1995**, 269, 1835–1842; b) J. R. Jacobsen, P. G. Schultz, *Curr. Opin. Struct. Biol.* **1995**, 5, 818–824.
- [7] K. D. Janda, L.-C. Lo, C.-H. L. Lo, M.-M. Sim, R. Wang, C.-H. Wong, R. A. Lerner, *Science* **1997**, 275, 945–948.
- [8] For a recent review, see K. D. Shimizu, M. L. Snapper, A. H. Hoveyda, *Chem. Eur. J.* **1998**, 4, 1885–1889.
- [9] C. Gennari, H. P. Nestler, U. Piarulli, B. Salom, *Liebigs Ann.* **1997**, 637–647.
- [10] G. C. Liu, J. A. Ellman, *J. Org. Chem.* **1995**, 60, 7712–7713.
- [11] K. Burgess, H.-J. Lim, A. M. Porte, G. A. Sulikowski, *Angew. Chem.* **1996**, 108, 192–194; *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 220–222.
- [12] C. Gennari, S. Ceccarelli, U. Piarulli, C. A. G. N. Montalbetti, R. F. W. Jackson, *J. Org. Chem.* **1998**, 63, 5312–5313.
- [13] B. M. Cole, K. D. Shimizu, C. A. Krueger, J. P. A. Harrity, M. L. Snapper, A. H. Hoveyda, *Angew. Chem.* **1996**, 108, 1776–1779; *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 1668–1671.
- [14] K. D. Shimizu, B. M. Cole, C. A. Krueger, K. W. Kuntz, M. L. Snapper, A. Hoveyda, *Angew. Chem.* **1997**, 109, 1782–1785; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 1704–1707.
- [15] M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, 120, 4901–4902.
- [16] S. R. Gilbertson, X. Wang, *Tetrahedron Lett.* **1996**, 37, 6475–6478.
- [17] X. Gao, H. B. Kagan, *Chirality* **1998**, 10, 120–124.
- [18] C. L. Hill, R. D. Gall, *J. Mol. Catal. A* **1996**, 114, 103–111.
- [19] M. T. Reetz, M. H. Becker, K. M. Kühling, A. Holzwarth, *Angew. Chem.* **1998**, 110, 2792–2795; *Angew. Chem. Int. Ed.* **1998**, 37, 2647–2650.
- [20] A. C. Cooper, L. H. McAlexander, D.-H. Lee, M. T. Torres, R. H. Crabtree, *J. Am. Chem. Soc.* **1998**, 120, 9971–9972.
- [21] Additional critical issues have been discussed; see R. Schlögl, *Angew. Chem.* **1998**, 110, 2467–2470; *Angew. Chem. Int. Ed.* **1998**, 37, 2333–2336.
- [22] F. C. Moates, M. Somani, J. Annamalai, J. T. Richardson, D. Luss, R. C. Willson, *Ind. Eng. Chem. Res.* **1996**, 35, 4801–4803.
- [23] S. J. Taylor, J. P. Morken, *Science* **1998**, 280, 267–270.
- [24] A. Holzwarth, H.-W. Schmidt, W. F. Maier, *Angew. Chem.* **1998**, 110, 2788–2792; *Angew. Chem. Int. Ed.* **1998**, 37, 2644–2647.
- [25] E. Reddington, A. Sapienza, B. Gurau, R. Viswanathan, S. Saranganpani, E. S. Smotkin, T. E. Mallouk, *Science* **1998**, 280, 1735–1737.
- [26] S. M. Senkan, *Nature* **1998**, 394, 350–353.
- [27] R. Dagani, *Chem. Eng. News* **1998**, 76(38), 13.

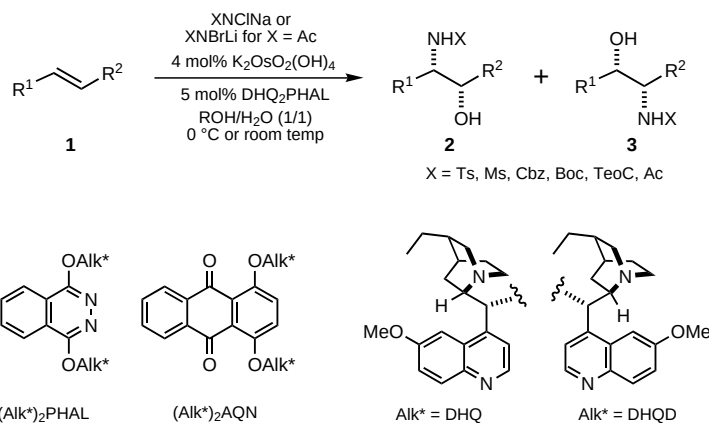
Sharpless Asymmetric Aminohydroxylation: Scope, Limitations, and Use in Synthesis

Peter O'Brien*

Since Sharpless' seminal contribution in 1996,^[1] the catalytic and asymmetric conversion of alkenes into enantiomerically enriched N-protected amino alcohols [asymmetric aminohydroxylation (AA)] has rapidly become an extremely useful process. Using a reaction that is a close cousin of asymmetric dihydroxylation,^[2] it is now possible to prepare amino alcohols (with different N-protecting groups) in good yields and high enantiomeric excesses from a range of alkene types. This is important since the β -amino alcohol functionality is found in many biologically active compounds and is therefore considered an important pharmacophore. Indeed, a large proportion of the recent papers on asymmetric aminohydroxylation have focussed on its application for the synthesis of biologically active compounds; these are summarized at the end of this article. The main purpose of this highlight is however to compare the yields, regioselectivities, and enantioselectivities obtained by using the different types of AA reactions. In addition, it is hoped that the present discussion

will provide useful guidelines for those using Sharpless AA in synthesis.

Currently, there are six different methods available for carrying out asymmetric aminohydroxylations. All of the methods have originated from the Sharpless group and they differ only in the N-protecting group (*p*-toluenesulfonyl (Ts),^[1] methanesulfonyl (Ms),^[3] benzyloxycarbonyl (Cbz),^[4] *tert*-butoxycarbonyl (Boc),^[5, 6] 2-trimethylsilylethoxycarbonyl (TeoC),^[7] or Ac^[8]) that is introduced (Scheme 1). Each



Scheme 1. Overview of Sharpless asymmetric aminohydroxylation (AA).

[*] Dr. P. O'Brien
Department of Chemistry
University of York
Heslington, York YO10 5DD (UK)
Fax: (+44) 1904-432516
E-mail: paob1@york.ac.uk

method uses a combination of osmium tetroxide (obtained from $\text{K}_2\text{OsO}_2(\text{OH})_4$), alkaloid-derived ligands (e.g. 1,4-bis(dihydroquininyl)phthalazine ((DHQ)₂PHAL) or 1,4-bis(dihydroquininyl)anthraquinone ((DHQ)₂AQN)), and the Li or Na salt of an N-halogenated sulfonamide, alkyl carbamate, or amide in an alcohol/water solvent mixture; two regioisomers **2** and **3** can be produced from an unsymmetrical alkene such as **1**. As with asymmetric dihydroxylation, dihydroquinine (DHQ)- and dihydroquinidine (DHQD)-derived ligands produce enantiocomplementary results.

Table 1 contains a direct comparison of the reaction conditions of all six variants. They are very similar and only subtle differences between the conditions are noticeable.

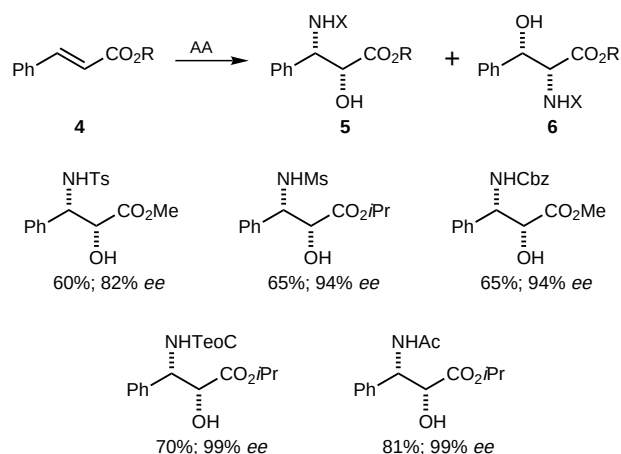
Table 1. Summary of the six different methods used for amino-hydroxylation.

Meth-	N Source (equiv)	Solvent	Temp [°C]	(DHQ) ₂ PHAL [mol %]
A	TsNCINa (3.5)	<i>t</i> BuOH/water (1:1) ^[b]	RT	5
B	MsNCINa (3)	<i>n</i> PrOH/water (1:1)	RT	5
C	CbzNCINa (3)	<i>n</i> PrOH/water (1:1) ^[c]	RT	5
D	BocNCINa (3)	<i>n</i> PrOH/water (2:1)	0	6
E	TeoCNCINa (3)	<i>n</i> PrOH/water (1:1)	RT	5
F	AcNBrLi (1)	<i>n</i> PrOH/water (1:1.5)	4	5

[a] 4 mol % $\text{K}_2\text{OsO}_2(\text{OH})_4$ used in each of methods A–F. [b] MeCN/water (1:1) also used as solvent. [c] *i*PrOH/water (1.5:1) and MeCN/water (1:1) also used as solvent.

Thus, for efficient introduction of a Boc-protecting group, the reaction is carried out at 0 °C in the presence of less water and more ligand (to minimize competing dihydroxylation).^[5] With the sulfonamide and acetamide reactions (Methods A, B, and F), the *N*-haloamine salt is prepared from the corresponding *N*-haloamides, whereas for the carbamate reactions (Methods C, D, and E), the *N*-haloamine salt is prepared in situ from the carbamate and *tert*-butylhypochlorite/NaOH. As we shall see, the general trend is that higher yields and better enantioselectivities are obtained with sterically less demanding substituents [e.g. X = Ms (Method B), TeoC (Method E), or Ac (Method F)] on the nitrogen atom. In addition, the TeoC carbamate reaction has the highest rate of all of the processes and this means that lower catalyst loadings (e.g. 2 mol % osmium) are possible. From a synthetic viewpoint, the Boc, Cbz, and TeoC protecting groups are the most readily removed.

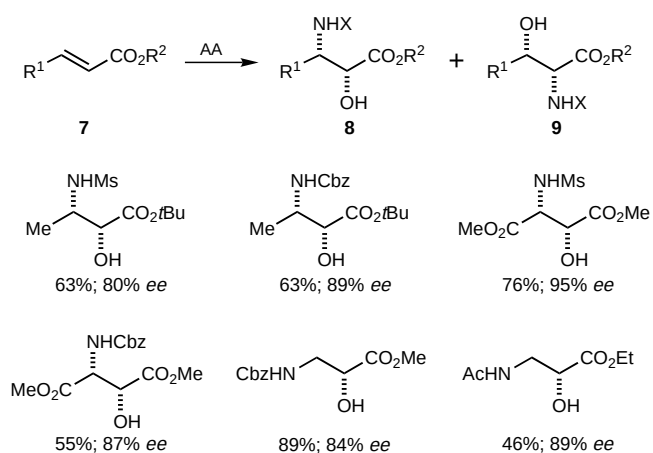
Cinnamates **4** have proved to be one of the most successful (and therefore popular) types of alkene substrates for AA reactions. Regioisomer **5** is produced preferentially when (DHQ)₂PHAL is used, and a selection of results is presented in Scheme 2. The highest yields and enantiomeric excesses are obtained for the TeoC-carbamate (Method E) and the acetamide (Method F) processes; the higher yields probably reflect a better level of regioselectivity in these cases. It has recently been noted^[9] that the preferred regioselectivity observed with (DHQ)₂PHAL as a ligand can be overturned by changing to the related (DHQ)₂AQN ligand (see Scheme 1 for ligand structure). Thus, Cbz-carbamate AA of methyl cinnamate **4** (R = Me) using (DHQ)₂PHAL gave a 65 % yield (ca. 7:1 regioselection) of pure regioisomer **5** (R = Me) of 94 % *ee*, whereas the same reaction using (DHQ)₂AQN



Scheme 2. Asymmetric aminohydroxylation of cinnamates using (DHQ)₂PHAL.

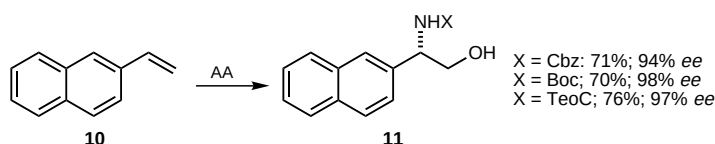
generated a 58 % yield (ca. 4:1 regioselection) of pure regioisomer **6** (R = Me) of 95 % *ee*. This is an amazing observation: the ligand affects the regioselectivity of the reaction but does not affect the *sense* and *degree* of asymmetric induction.

The results of aminohydroxylating some α,β -unsaturated compounds (similar in structure to the cinnamates) are presented in Scheme 3. From these results, it appears that Cbz-carbamate-based AA (Method C) is best for crotonates and acrylates, whereas the chloramine-M approach (Method B) is optimal for AA of *trans*-dimethylfumarate. The effect of ligand structure on the regioselectivity observed with crotonates and acrylates has not been reported to date.



Scheme 3. Asymmetric aminohydroxylation of crotonates, acrylates, and dimethylfumarate.

In contrast to α,β -unsaturated esters, styrenes and vinyl arenes were initially absent from the list of compounds which had been successfully aminohydroxylated. It was only with the advent of the carbamate- and acetamide-based processes that such compounds became viable substrates for AA reactions. A very detailed paper^[5] has recently appeared on these transformations and a representative example is depicted in Scheme 4. AA of 2-vinylnaphthalene **10** using any of the



Scheme 4. Asymmetric aminohydroxylation of 2-vinylnaphthalene.

carbamate-based processes generated amino alcohol **11** of $\geq 94\%$ ee in $\geq 70\%$ yield.^[5, 10] The reaction tolerates equally well electron-donating and -withdrawing substituents on the aromatic ring in substituted styrenes. However, these results do hide to some extent the fact that *careful* column chromatography is generally required to separate the major product from around 15 % of the regioisomeric amino alcohol and from the excess carbamate.

The regioselectivity observed in AA reactions of styrenes is found to be dependent on the nature of the ligand, the solvent, and the N-protecting group introduced (Table 2).^[5, 8] Thus, in

Table 2. Aminohydroxylation of styrenes—dependence of regioselectivity on ligand type and solvent.

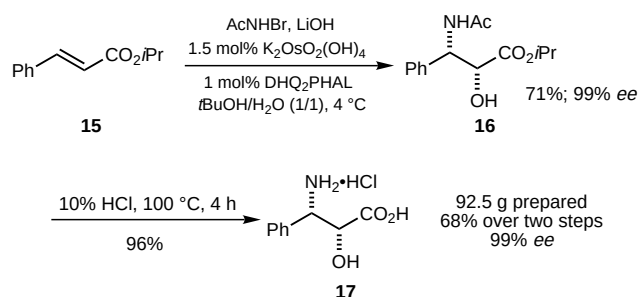
X	Conditions	13:14
Ac	(DHQD) ₂ PHAL (<i>n</i> PrOH/water)	2.5:1 ^[a]
Ac	(DHQD) ₂ PHAL (MeCN/water)	1:2.4 ^[a]
Ac	(DHQD) ₂ AQN (MeCN/water)	1:9 ^[a]
Cbz	(DHQ) ₂ PHAL (<i>n</i> PrOH/water)	7.3:1
Cbz	(DHQ) ₂ PHAL (MeCN/water)	3:1
Cbz	(DHQ) ₂ AQN (MeCN/water)	1:3

[a] Not separable by chromatography.

the AA of styrene **12**, amino alcohols **13** are the major products using (DHQ)₂PHAL or (DHQD)₂PHAL in an alcohol/water solvent mixture but increasing amounts of amino alcohols **14** are produced when the solvent is changed to acetonitrile/water and the ligand is changed to (DHQ)₂AQN or (DHQD)₂AQN. The remarkable ligand-dependence is very similar to that observed with AA reactions of cinnamates (*vide infra*) but none of these regioselectivity issues are easily explained. Interestingly, the enantiomeric excesses of amino alcohols **13** and **14** are similar and high with the acetamide-based process (F), whereas with the Cbz-carbamate process (C), amino alcohol **13** is obtained with considerably higher enantiomeric excess than its regioisomer **14**. Unfortunately, although better regioselectivity (and higher enantioselectivity) was obtained for amino alcohol **14** over **13** using the acetamide-based AA process, the two products were inseparable by chromatography. A recent report^[6] on AA reactions of other styrenes has revealed the surprising fact that the regioselectivity observed with (DHQ)₂PHAL is different to that obtained with (DHQD)₂PHAL even though the enantiomeric excesses of the products (opposite absolute configuration) were essentially the same. In these examples, lower levels of regioselectivity manifest themselves in lower

isolated yields. Clearly, the nature of the ligand ((DHQ)₂-PHAL versus (DHQD)₂PHAL versus (DHQ)₂AQN) can have a dramatic and unexpected effect on the regioselectivity of the AA reactions of styrenes (and almost certainly other alkenes, but the results have not been published).

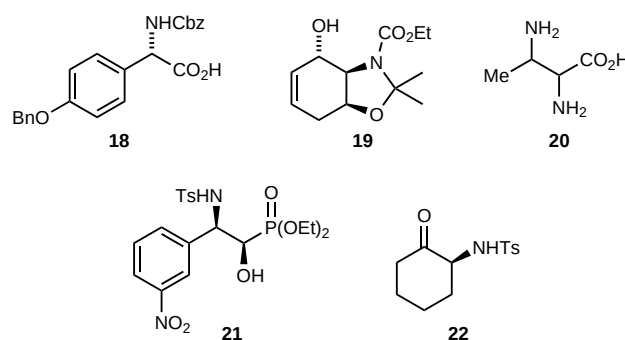
The previously described developments of the AA reaction have meant that its application to synthesis has now become appropriate. A useful example is Sharpless' efficient, large-scale, concise, and eminently attractive preparation of the precursor to the Taxol side chain **17** (Scheme 5).^[8] Thus, an



Scheme 5. Large-scale two-step synthesis of precursor to the Taxol side chain.

AA reaction on isopropyl cinnamate (120 g) that employed just 1.5 mol% K₂OsO₂(OH)₄ (3.5 g) and *N*-bromoacetamide generated amino alcohol **16** of 99% ee in 71% yield after recrystallization. This was readily hydrolyzed to give enantiomerically pure hydrochloride salt **17** (92.5 g; 68% yield over the two steps).

A number of other significant results in the use of AA in synthesis have now appeared. For example: aminohydroxylation of styrenes has been used in a two-step synthesis of *N*-protected amino acids such as **18**,^[5] a diastereo- and enantioselective aminohydroxylation reaction of a dienylsilane was used to prepare enantiomerically pure allylic alcohol **19** (Scheme 6);^[11] all four isomers of 2,3-diaminobutanoic acid



Scheme 6. Examples of use of asymmetric aminohydroxylation in synthesis.

20 have been prepared by using carbamate-based AA of *tert*-butyl crotonate as the pivotal point in the synthetic approach;^[12] chloramine-T-based AA reactions on vinyl phosphonates^[13] and silyl enol ethers^[14] have been used to synthesize enantiomerically enriched sulfonamides **21** and **22** respectively. More recent synthetic developments include

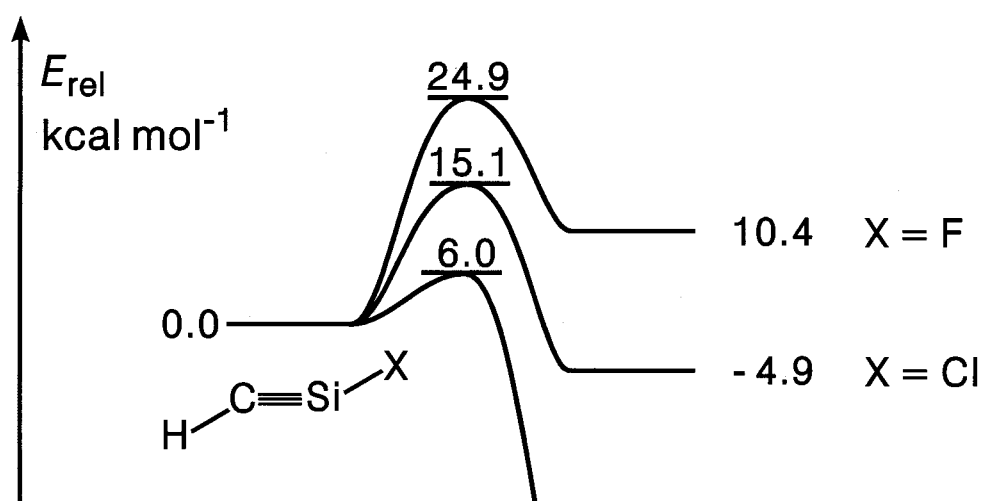
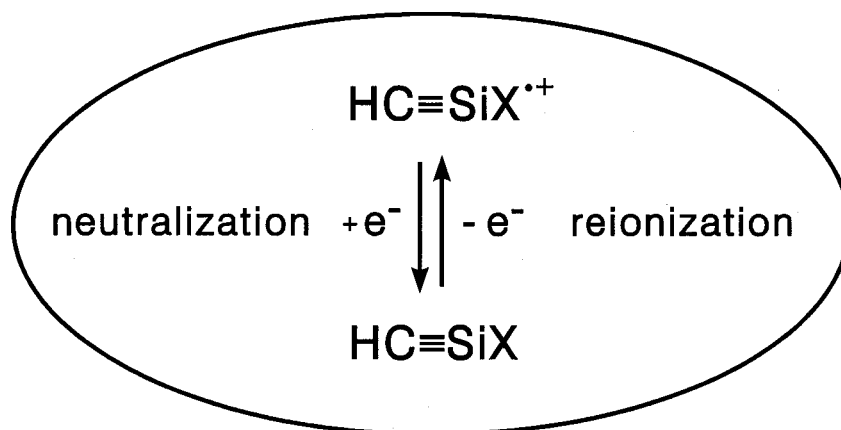
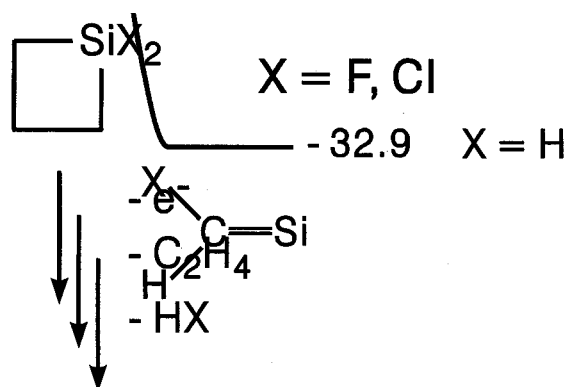
the direct introduction of heterocycles in AA reactions,^[15,16] the application of AA methodology in the preparation of a fragment for the total synthesis of the vancomycin aglycon,^[17] and a silica-gel-supported variant of AA.^[18] All of these examples, some of which have been carried out on a reasonably large scale, serve to illustrate that AA has a promising synthetic future. A few issues, such as lack of regioselectivity and poor substrate scope in certain cases, need to be resolved but it is instructive to see what impressive achievements have been reached in such a short space of time. With six different methods currently at our disposal, we are surely not too far from being able to convert any alkene into an amino alcohol in a catalytic and asymmetric fashion.

German version: *Angew. Chem.* **1999**, *111*, 339–342

Keywords: amino alcohols • aminohydroxylations • asymmetric catalysis • asymmetric synthesis • osmium

- [1] G. Li, K. B. Sharpless, *Angew. Chem.* **1996**, *108*, 449–452; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 451–454.
- [2] H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483–2547.
- [3] J. Rudolph, P. C. Sennhenn, C. P. Vlaar, K. B. Sharpless, *Angew. Chem.* **1996**, *108*, 2991–2995; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2810–2813.
- [4] G. Li, H. H. Angert, K. B. Sharpless, *Angew. Chem.* **1996**, *108*, 2995–2999; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2813–2817.
- [5] K. L. Reddy, K. B. Sharpless, *J. Am. Chem. Soc.* **1998**, *120*, 1207–1217.
- [6] a) P. O'Brien, S. A. Osborne, D. D. Parker, *Tetrahedron Lett.* **1998**, *39*, 4099–4102, b) P. O'Brien, S. A. Osborne, D. D. Parker, *J. Chem. Soc. Perkin Trans. 1* **1998**, 2519–2526.
- [7] K. L. Reddy, K. R. Dress, K. B. Sharpless, *Tetrahedron Lett.* **1998**, *39*, 3667–3670.
- [8] M. Bruncko, G. Schlingloff, K. B. Sharpless, *Angew. Chem.* **1997**, *109*, 1580–1583; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1483–1486.
- [9] B. Tao, G. Schlingloff, K. B. Sharpless, *Tetrahedron Lett.* **1998**, *39*, 2507–2510.
- [10] G. Li, R. Lenington, S. Willis, S. H. Kim, *J. Chem. Soc. Perkin Trans. 1* **1998**, 1753–1754.
- [11] R. Angelaud, Y. Landais, K. Schenk, *Tetrahedron Lett.* **1997**, *38*, 1407–1410.
- [12] H. Han, J. Yoon, K. D. Janda, *J. Org. Chem.* **1998**, *63*, 2045–2048.
- [13] G. Cravotto, G. B. Giovenzana, R. Pagliarin, G. Palmisano, M. Sisti, *Tetrahedron: Asymmetry* **1998**, *9*, 745–748.
- [14] P. Phukan, A. Sudalai, *Tetrahedron: Asymmetry* **1998**, *9*, 1001–1005.
- [15] A. S. Pilcher, H. Yagi, D. M. Jerina, *J. Am. Chem. Soc.* **1998**, *120*, 3520–3521.
- [16] a) L. J. Goosen, H. Liu, K. R. Dress, K. B. Sharpless, *Angew. Chem.* **1999**, *111* in press; *Angew. Chem. Int. Ed. Engl.* **1999**, *38*, in press, b) L. J. Goosen, H. Liu, K. R. Dress, D. M. Jerina, K. B. Sharpless, *Tetrahedron Lett.* **1998**, *39*, 7669–7672.
- [17] K. C. Nicolau, S. Natarajan, H. Li, N. F. Jain, R. Hughes, M. E. Solomon, J. M. Ramanjulu, C. N. C. Boddy, M. Takayanagi, *Angew. Chem.* **1998**, *110*, 2872–2878; *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 2708–2714.
- [18] C. E. Song, C. R. Oh, S. W. Lee, S.-g. Lee, L. Canali, D. C. Sherrington, *Chem. Commun.* **1998**, 2435–2436.

Neutralization of cation radicals affords the neutral silynes $\text{H-C}\equiv\text{Si-F}$ and $\text{H-C}\equiv\text{Si-Cl}$.



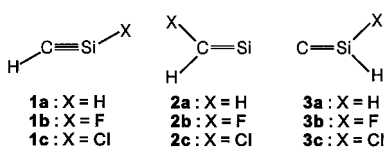
HCSiF and HCSiCl: The First Detection of Molecules with Formal C≡Si Triple Bonds**

Miriam Karni, Yitzhak Apeloig, Detlef Schröder, Waltraud Zummack, Roberto Rabezzana, and Helmut Schwarz*

Dedicated to Professor Jack D. Dunitz on the occasion of his 75th birthday

The synthesis and isolation of compounds having multiple bonds to silicon has been one of the major challenges in main group chemistry.^[1] The first stable compounds with double bonds to silicon were synthesized in 1981,^[2] and since then this group of compounds has been studied extensively, both experimentally^[3] and theoretically.^[4] In contrast, compounds with triply bonded silicon are still largely unknown except for HSi≡N which has been characterized by matrix isolation spectroscopy.^[5] The formation of transient HC≡SiCH₃,^[6] HC≡SiCl,^[7] and H₃CSi≡SiCH₃^[8] has been suggested but conclusive evidence for the existence of silynes (RC≡SiR) or disilynes (RSi≡SiR) has not yet been presented, and their synthesis remains one of the “holy grails” of silicon chemistry.

One of the major obstacles in the preparation of triply bonded silicon compounds, even as transients, is the existence of more stable isomers.^[9, 10] For the [C,Si,H₂] parent system, the silyne **1a** is calculated^[11] to be less stable than the silylidene **2a** by 32.9 kcal mol⁻¹, and the barrier for the **1a**→**2a** rearrangement is only 6 kcal mol⁻¹.^[9a, 14] The isomeric vinylidene **3a** is 85.8 kcal mol⁻¹ less stable than **2a**. Accordingly, only **2a** has been detected and characterized spectroscopically in the gas phase,^[15] while the shallow wells of the high-energy isomers **1a** and **3a** are beyond the means of the conventional variant of neutralization-reionization (NR)^[16] mass spectrometry used in this study.^[17]



Theoretical studies by two of us^[9] have revealed that substitution affects strongly and even reverses the stability order between formally triply bonded silicon species^[18] and their other isomers (Figure 1 a). Thus, the fluorosilyne **1b** is predicted to be more stable than its isomers **2b** and **3b** by 10.4 and 48.0 kcal mol⁻¹, respectively. Furthermore, the barrier of 24.9 kcal mol⁻¹ associated with the interconversion **1b**→**2b** is significantly larger than for the parent silyne (**1a**→**2a**), suggesting that **1b** is amenable for experimental detection. The situation is similar for X = Cl (Figure 1 a) and X = OH.^[9a] The dramatic effect of X can be attributed mostly to the high *D*(Si–F) and *D*(Si–Cl) bond energies which exceed *D*(C–F)

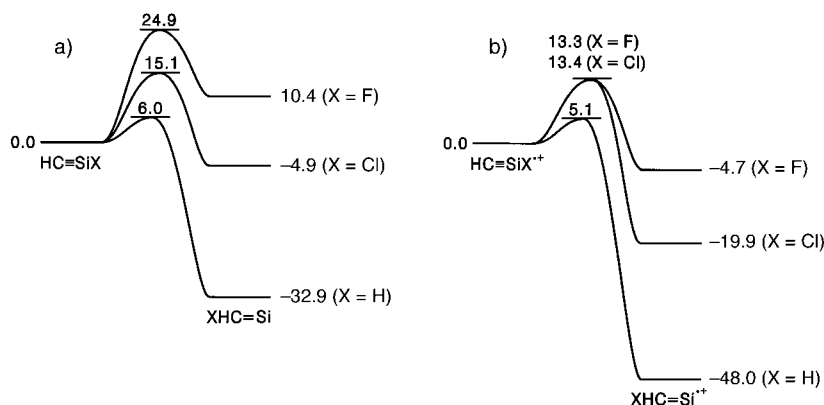


Figure 1. Schematic potential-energy profiles [kcal mol⁻¹] for a) the neutral and b) the cationic [C,H,Si,X] isomers **1** and **2** (X = H, F, Cl) calculated at the QCISD(T)/6-31G** level of theory.

and *D*(C–Cl), respectively, while *D*(Si–H) is smaller than *D*(C–H).^[19]

Herein, we examine these theoretical predictions by means of neutralization-reionization (NR) mass spectrometry and provide the first firm evidence for the existence of compounds with formal C≡Si triple bonds. Our experimental approach for generating neutral HC≡SiX is based upon the neutralization of the corresponding radical cations. A prerequisite for such experiments is that the geometry changes occurring upon neutralization of the radical cations **1b**^{•+} and **1c**^{•+} are associated with minor excitations of the neutral species. This condition is fortunately fulfilled, as the calculated energy differences of the vertical versus adiabatic neutralizations of **1b**^{•+} and **1c**^{•+}, respectively, are less than 4 kcal mol⁻¹. In conjunction with the significant height of the calculated activation barriers for migration of either X = F or Cl, respectively, the silyne structures may thus be preserved upon neutralization.

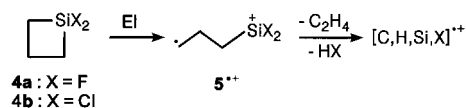
Experimentally^[20] it is not trivial, however, to generate the desired radical cations **1b**^{•+} and **1c**^{•+} in a straightforward manner and in sufficient yields. Many potential organosilicon precursors do not yield abundant molecular ions but undergo instead facile α cleavages. For example, upon ionization the precursors (CH₃)_(4-n)SiX_n (*n* = 1–3; X = F, Cl) show predominant losses of open-shell fragments, producing closed-shell silylium ions which would require an additional homolytic bond cleavage in order to afford the desired radical cations. Consequently, for most halosilanes, the yields of [C,H,Si,X]^{•+} ions are generally low—at most moderate. An efficient

[*] Prof. Dr. H. Schwarz, Dr. D. Schröder, W. Zummack, Dr. R. Rabezzana
Institut für Organische Chemie der Technischen Universität
Strasse des 17. Juni 135, D-10623 Berlin (Germany)
Fax: (+49) 30-314-21102

Dr. M. Karni, Prof. Dr. Y. Apeloig
Department of Chemistry and the Lise Meitner-Minerva Center
for Computational Quantum Chemistry
Technion – Israel Institute of Technology
Haifa, 32000 (Israel)

[**] This work was supported by the German-Israeli Foundation for Scientific Research and Development (GIF), the Minerva Foundation, the Technion Fund for the Promotion of Research, the Deutsche Forschungsgemeinschaft, the Volkswagen-Stiftung, and the Fonds der Chemischen Industrie.

generation of silicon-containing $[C,H,Si,X]^{++}$ radical cations would require compounds which form abundant molecular ions upon ionization. These open-shell species may then undergo consecutive losses of closed-shell neutral particles leading to the desired $[C,H,Si,X]^{++}$ ions. The 1,1-dihalosilacyclobutanes **4** ($X = F, Cl$) fulfill these requirements:^[23] ionization of **4** leads to an intense molecular ion, presumably the distonic^[24] ion 5^{++} , which subsequently eliminates C_2H_4 and HX to give abundant amounts of $[C,H,Si,X]^{++}$ ions (Scheme 1).



Scheme 1. Formation and fragmentation of 5^{++} .

The collisional activation (CA) mass spectra of the $[C,H,Si,X]^{++}$ ions are in full accord with the anticipated connectivities of $1b^{++}$ and $1c^{++}$ (Figures 2a and 3a, respectively). Thus, the intense SiX^+ fragments are in keeping with

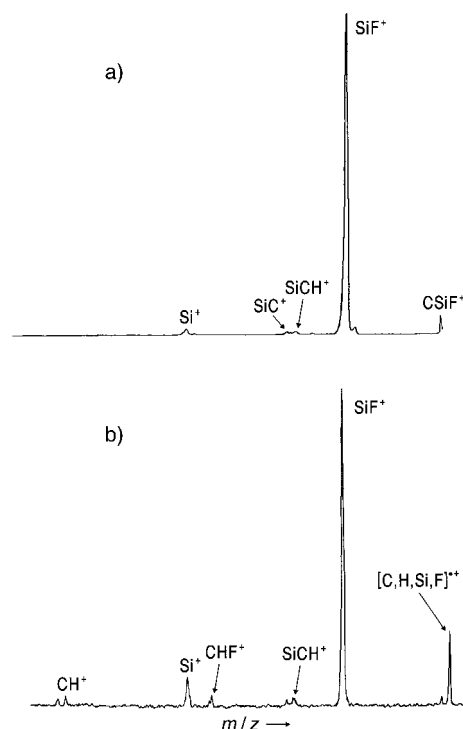


Figure 2. a) Collisional activation (He, 80 % transmission) and b) neutralization-reionization (Xe, 80 % transmission/ O_2 , 80 % transmission) mass spectra of $[C,H,Si,F]^{++}$ ions; the precursor ion was generated by electron ionization of 1,1-difluorosilacyclobutane (**4a**) and mass-selected with sectors B(1) and E(1).

the silyne structures as are the other, minor fragments. In particular, the $SiCH_n^+$ ($n = 0, 1$) signals are much more intense than the CH_nX^+ signals, the latter pointing towards the silylidene ions $2b^{++}$ and $2c^{++}$. We conclude that the majority of the precursor $[C,H,Si,X]^{++}$ ($X = F, Cl$) ions have the silyne structures, even though the corresponding silylenes $2b^{++}$ and $2c^{++}$ are thermochemically more stable (Figure 2b). This conclusion is also in accordance with the generation of

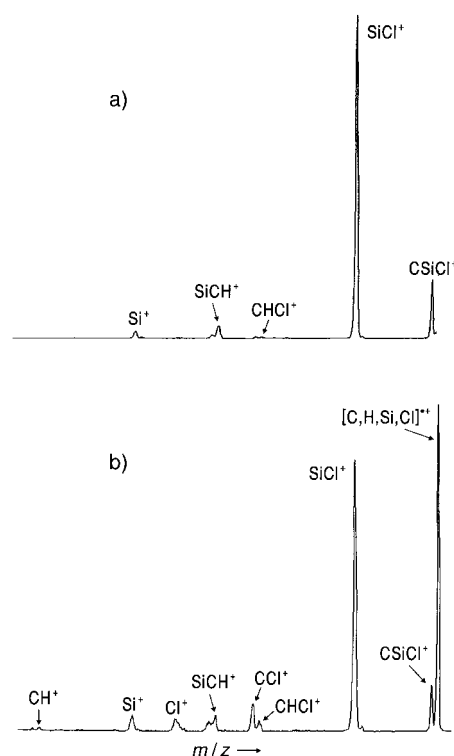


Figure 3. a) Collisional activation (He, 80 % transmission) and b) neutralization-reionization (Xe, 80 % transmission/ O_2 , 80 % transmission) mass spectra of $[C,H,Si,Cl]^{++}$ ions; the precursor ion was generated by electron ionization of 1,1-dichlorosilacyclobutane (**4b**) and mass-selected with sectors B(1)

$[C,H,Si,X]^{++}$ ions by consecutive fragmentation of 5^{++} (Scheme 1).

The NR spectra of the $[C,H,Si,X]^{++}$ ($X = F, Cl$) ions (Figures 2b and 3b) show pronounced recovery signals due to reionized $[C,H,Si,X]$ molecules, along with the characteristic SiX^+ fragments. The observation of the recovery signals implies that the neutral $[C,H,Si,X]$ species have lifetimes of at least a microsecond. While in a preparative sense, this lifetime may appear to be rather short, it is sufficient to allow for a complete dissipation of internal energy in the internal rovibrational modes for small species such as $[C,H,Si,X]$, which hence can be considered to be stable species as isolated molecules. In analogy to the above interpretation of the CA mass spectra, we therefore conclude that the NR experiments demonstrate the existence in the gas phase of the neutral silynes $HC\equiv SiF$ (**1b**) and $HC\equiv SiCl$ (**1c**). For $X = Cl$, however, the CH_nCl^+ fragments ($n = 0, 1$) observed in Figure 3b imply the occurrence of partial rearrangement to the silylidene isomer **2c** (see below).

While the above reasoning is self-consistent, one objection remains. Thus, the observed CA and NR spectra may also be consistent with the interpretation that the precursor ions are $2b^{++}$ or $2c^{++}$, rather than $1b^{++}$ and $1c^{++}$, respectively, because the predominance of the SiX^+ ions may simply reflect an energetically favored dissociation channel as suggested by our calculations. Thus, for $X = F$ and Cl , respectively, the fragments $[SiX^+ + CH^+]$ stemming from $HC\equiv SiX^{++}$ are calculated to be 26.9 and 20 kcal mol⁻¹, respectively, more stable^[25] than $[HXC + Si^{++}]$, the lowest energy fragmentation channel of

$\text{HXC}=\text{Si}^{++}$. For $\text{X}=\text{Cl}$ this option can be excluded by a further experiment. As shown in Figure 3a, a significant fraction of $[\text{C}_2\text{H}_2\text{Si}_2\text{Cl}]^{++}$ undergoes collision-induced loss of a hydrogen atom to yield the ion $[\text{C}_2\text{Si}_2\text{Cl}]^{++}$. If the precursor ions were 2c^{++} , the connectivity of this fragment should be $\text{Cl}-\text{C}-\text{Si}$, while $\text{C}-\text{Si}-\text{Cl}$ is expected from 1c^{++} . An experimental distinction of the two connectivities should hence be possible based on the observation of either CCl^+ (characteristic of $\text{Cl}-\text{C}-\text{Si}$) or SiCl^+ (characteristic of $\text{C}-\text{Si}-\text{Cl}$). To test this point, mass-selected $[\text{C}_2\text{H}_2\text{Si}_2\text{Cl}]^{++}$ ions were collisionally activated, yielding $[\text{C}_2\text{Si}_2\text{Cl}]^{++}$ fragments which were again mass-selected and subjected to yet another collision event. The corresponding CA/CA spectrum of the $[\text{C}_2\text{Si}_2\text{Cl}]^{++}$ ions shows an intense SiCl^+ fragment (100%) along with less intense signals due to SiC^+ (10%) and Si^+ (10%), while CCl^+ is not observed above the noise level of 4%. Thus, the hydrogen atom loss from $[\text{C}_2\text{H}_2\text{Si}_2\text{Cl}]^{++}$ yields ClSiC^+ and not SiCCl^+ , indicating that the precursor beam consists of genuine $\text{HC}\equiv\text{SiCl}^{++}$ (1c^{++}) ions.^[26] By analogy, we assume that the recovery signal in the NR spectrum of $[\text{C}_2\text{H}_2\text{Si}_2\text{F}]^{++}$ is due to the formation of the silyne 1b . Finally, this analysis supports the conclusion that the CH_nCl^+ fragments ($n=0, 1$) observed in the NR spectrum of $[\text{C}_2\text{H}_2\text{Si}_2\text{Cl}]^{++}$ are due to a collision-induced rearrangement of neutral 1c to 2c . This interpretation is also in accord with the lower intensities of CH_nF^+ in the NR spectrum of $[\text{C}_2\text{H}_2\text{Si}_2\text{F}]^{++}$, because for $\text{X}=\text{F}$ the neutral silyne is more stable than the silylidene, and the $1\text{b} \rightarrow 2\text{b}$ isomerization barrier is higher than for $\text{X}=\text{Cl}$ (Figure 1a).

In summary, the present results provide the first experimental evidence for the existence of neutral $\text{HC}\equiv\text{SiX}$ ($\text{X}=\text{F}, \text{Cl}$) molecules with $\text{C}\equiv\text{Si}$ triple bonds. This success calls for experimental studies of related systems by more direct techniques, for example, matrix isolation spectroscopy. Silynes of the type $\text{RC}\equiv\text{SiX}$, where substituents $\text{X}=\text{F}, \text{Cl}$, or an alkoxy group^[9a] maximize thermochemical stability, and where R is a bulky group which increases kinetic stability, for example 2,4,6-tris[bis(trimethylsilyl)methyl]phenyl,^[3d] are promising candidates for isolation as long-lived compounds.

Received: September 3, 1998 [Z 12375 IE]
German version: *Angew. Chem.* **1999**, *111*, 344–347

Keywords: ab initio calculations • mass spectrometry • silicon • silynes

- [1] For comprehensive reviews, see: a) *The Chemistry of Organic Silicon Compounds* (Eds.: S. Patai, Z. Rappoport), Wiley, New York, **1989**; b) *The Chemistry of Organic Silicon Compounds*, Vol. 2 (Eds.: Z. Rappoport, Y. Apeloig), Wiley, New York, **1998**.
- [2] a) A. G. Brook, F. Abdesaken, B. Gutekunst, G. Gutekunst, R. K. Kallury, *J. Chem. Soc. Chem. Commun.* **1981**, 191; b) R. West, M. J. Fink, J. Michl, *Science* **1981**, *214*, 1343.
- [3] a) G. Raabe, J. Michl in *The Chemistry of Organic Silicon Compounds* (Eds.: S. Patai, Z. Rappoport), Wiley, New York, **1989**, p. 1015; b) H. Sakurai in *The Chemistry of Organic Silicon Compounds*, Vol. 2 (Eds.: Z. Rappoport, Y. Apeloig), Wiley, New York, **1998**, p. 827; c) T. Müller, W. Ziche, N. Auner in *The Chemistry of Organic Silicon Compounds*, Vol. 2 (Eds.: Z. Rappoport, Y. Apeloig), Wiley, New York, **1998**, p. 857; d) N. Tokitoh, R. Okazaki in *The Chemistry of Organic Silicon Compounds*, Vol. 2 (Eds.: Z. Rappoport, Y. Apeloig),

- Wiley, New York, **1998**, p. 1063; e) M. Driess, *Adv. Organomet. Chem.* **1996**, *39*, 193; f) R. Okazaki, R. West, *Adv. Organomet. Chem.* **1996**, *39*, 232.
- [4] a) Y. Apeloig in *The Chemistry of Organic Silicon Compounds* (Eds.: S. Patai, Z. Rappoport), Wiley, New York, **1989**, p. 103; b) Y. Apeloig, M. Karni, T. Müller in *Organosilicon Chemistry II. From Molecules to Materials* (Eds.: N. Auner, J. Weis), VCH, Weinheim, **1996**, p. 263.
- [5] G. Maier, J. Glatthaar, *Angew. Chem.* **1994**, *106*, 486; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 473.
- [6] M. Urbanová, E. A. Volnina, L. E. Gusel'nikov, Z. Bastl, J. Pola, *J. Organomet. Chem.* **1996**, *509*, 73.
- [7] M. Jakoubková, R. Fajgar, J. Tláškal, J. Pola, *J. Organomet. Chem.* **1994**, *466*, 29.
- [8] A. Sekiguchi, S. S. Zigler, R. West, J. Michl, *J. Am. Chem. Soc.* **1986**, *108*, 4241.
- [9] a) Y. Apeloig, M. Karni, *Organometallics* **1997**, *16*, 310; b) Y. Apeloig, K. Albrecht, *J. Am. Chem. Soc.* **1995**, *117*, 7263.
- [10] a) S. Koseki, M. S. Gordon, *J. Phys. Chem.* **1988**, *92*, 364; b) S. Koseki, M. S. Gordon, *J. Phys. Chem.* **1989**, *93*, 118; c) B. T. Colgrove, H. F. Schaefer III, *J. Phys. Chem.* **1990**, *94*, 5593; d) R. Grev, H. F. Schaefer III, *J. Chem. Phys.* **1992**, *97*, 7990.
- [11] All calculations were performed using standard routines of Gaussian 94.^[12] The energies reported throughout the paper refer to the QCISD(T)/6-31G** level of theory and include corrections for zero point energy (ZPE) scaled by a factor of 0.98.^[13]
- [12] Gaussian 94, Revision E.2, M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. Keith, G. A. Petersson, J. A. Montgomery, K. Raghavachari, M. A. Al-Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, G. Cioslowski, B. B. Stefanov, A. Nanayakkara, M. Challacombe, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. Defrees, J. Baker, J. P. Stewart, M. Head-Gordon, C. Gonzalez, J. A. Pople, Gaussian, Inc., Pittsburgh, PA, **1995**.
- [13] A. P. Scott, L. Radom, *J. Phys. Chem.* **1996**, *100*, 16502.
- [14] For recent calculations of $[\text{C}_2\text{H}_2\text{Si}]$ at other levels of theory, see: a) M. T. Nguyen, D. Sengupta, L. G. Vanquickenborne, *Chem. Phys. Lett.* **1995**, *244*, 83; b) R. Stegmann, G. Frenking, *J. Comput. Chem.* **1996**, *17*, 78.
- [15] a) K. P. Lim, F. W. Lampe, *Int. J. Mass Spectrom. Ion. Processes* **1990**, *101*, 245; b) R. Srinivas, D. Sülzle, H. Schwarz, *J. Am. Chem. Soc.* **1991**, *113*, 52; c) C. D. Sherrill, H. F. Schaefer III, *J. Phys. Chem.* **1995**, *99*, 1949; d) M. Izuha, S. Yamamoto, S. Saito, *J. Chem. Phys.* **1996**, *105*, 4923.
- [16] a) N. Goldberg, H. Schwarz, *Acc. Chem. Res.* **1994**, *27*, 347; b) C. A. Schalley, G. Hornung, D. Schröder, H. Schwarz, *J. Chem. Soc. Rev.* **1998**, *27*, 91.
- [17] For an example of the application of more sophisticated variants of this method, see: D. Schröder, C. A. Schalley, N. Goldberg, J. Hrušák, H. Schwarz, *Chem. Eur. J.* **1996**, *2*, 1235.
- [18] The term "formal" pays tribute to the fact that the silynes have bent structures, unlike the linear arrangements expected for triple bonds; for a more detailed discussion see ref. [9].
- [19] Dissociation energies D in H_3MX ($\text{M}=\text{C}, \text{Si}$; $\text{X}=\text{H}, \text{F}, \text{Cl}$) [kcal mol^{-1}]: $D(\text{C}-\text{H})=105$, $D(\text{C}-\text{F})=113$, $D(\text{C}-\text{Cl})=83$, $D(\text{Si}-\text{H})=92$, $D(\text{Si}-\text{F})=152$, $D(\text{Si}-\text{Cl})=110$. Data from: a) S. G. Lias, J. E. Bartmess, J. F. Liebman, J. L. Holmes, R. D. Levin, W. G. Mallard, *J. Phys. Chem. Ref. Data Suppl.* **1988**, *17*; b) R. Becerra, R. Walsh in *The Chemistry of Organic Silicon Compounds*, Vol. 2 (Eds.: Z. Rappoport, Y. Apeloig), Wiley, New York, **1998**, p. 153.
- [20] The experiments were performed with a modified VG ZAB/HF/AMD 604 four-sector mass spectrometer^[21] of BEBE configuration (B stands for magnetic and E for electric sectors). $[\text{C}_2\text{H}_2\text{Si}_2\text{X}]^{++}$ ions ($\text{X}=\text{F}, \text{Cl}$) were generated by electron ionization (electron energy 70 eV) of the 1,1-dihalosilacyclobutanes **4**; similar results were obtained with other precursors such as $(\text{CH}_3)_{(4-n)}\text{SiX}_n$ ($n=1-3$, $\text{X}=\text{F}, \text{Cl}$). All chlorosilanes were commercially available (ABCR, Karlsruhe), and the fluorides were prepared^[22] by treating the neat chlorides with anhydrous ZnF_2 . The ions having a kinetic energy of 8 keV were mass-selected using B(1) and E(1), and the respective mass spectra were recorded by scanning B(2). For collisional activation helium was used as collision gas. In the NR experiments,^[16,21d] neutralization was

afforded by xenon, and oxygen was used for reionization. The CA/CA mass spectrum of $[C, Si, Cl]^+$ was obtained by daughter ion selection with B2, and recording the subsequent fragmentations by scanning E(2).^[21c] All spectra were accumulated and on-line processed with the AMD/Intectra data system; in general 5 to 50 spectra were averaged to improve the signal-to-noise ratio.

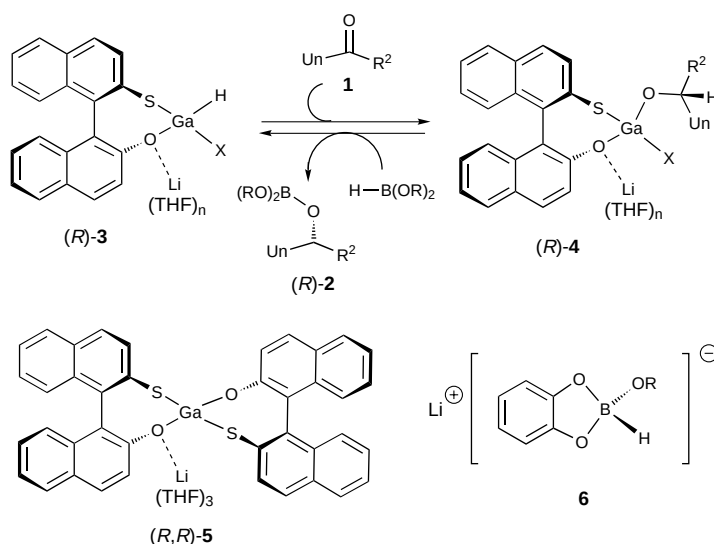
- [21] a) R. Srinivas, D. Sülzle, T. Weiske, H. Schwarz, *Int. J. Mass Spectrom. Ion Processes* **1991**, 107, 368; b) R. Srinivas, D. Sülzle, W. Koch, C. H. DePuy, H. Schwarz, *J. Am. Chem. Soc.* **1991**, 113, 5970; c) D. Schröder, H. Schwarz, *Int. J. Mass Spectrom. Ion Processes* **1995**, 146/147, 183; d) C. A. Schalley, D. Schröder, H. Schwarz, *Int. J. Mass Spectrom. Ion Processes* **1996**, 153, 173.
- [22] A. E. Newkirk, *J. Am. Chem. Soc.* **1946**, 68, 2736.
- [23] In analogy, photolysis of **4** (X = Cl) has been speculated to yield neutral **1c**, see ref. [7].
- [24] For a definition and examples for distonic ions: R. L. Smith, P. K. Chou, H. I. Kenttämää in *The Structure and Dynamics of Organic Ions* (Eds.: T. Baer, C. Y. Ng), Wiley, London, **1996**, p. 197.
- [25] According to the experimental data in ref. [19a], the preference for SiF^+ formation is only 16 kcal mol⁻¹. However, we trust our calculated value of 26.9 kcal mol⁻¹. A similar discrepancy between calculated and experimental energetics of SiF^+ was reported earlier, see: E. W. Ignacio, H. B. Schlegel, *J. Phys. Chem.* **1990**, 94, 7439.
- [26] While the fragmentations of $[Si, C, Cl]^+$ leading to $[SiCl^+ + C]$ and to $[Si^+ + CCl]$ may also be attributed to the mere energetic preference of these exit channels ($\Sigma\Delta H_i^0 = 386$ and 388 kcal mol⁻¹, respectively), compared to those for the formation of $[SiC^+ + Cl]$ ($\Sigma\Delta H_i^0 = 416$ kcal mol⁻¹) or $[Si + CCl^+]$ ($\Sigma\Delta H_i^0 = 405$ kcal mol⁻¹), of the higher energy channels only SiC^+ is observed experimentally, but not the lower energy fragment CCl^+ ; data taken from refs. [19a,b,27].
- [27] A. E. Ketvirtis, D. K. Bohme, A. C. Hopkinson, *J. Phys. Chem.* **1995**, 99, 16121.

Catalytic Enantioselective Reduction of Ketones by a Chiral Gallium Complex and Catecholborane**

Alan Ford and Simon Woodward*

Practical catalytic reduction of prochiral ketones to secondary alcohols of high enantiopurity is indispensable to many organic preparations. Oxazaborolidine-catalyzed BH_3 reduction^[1] and ruthenium-catalyzed transfer hydrogenation^[2] are effective for the reduction of $R^1C(O)R^2$ **1** provided an appropriate difference, steric or electronic, exists between the groups. As steric differences cannot always be realized, alternative catalysts that sense electronic differences between the groups in addition to steric requirements are highly desirable. In a seminal paper Noyori described the use of

$[LiAlH(OEt)(BINOL \text{ dianion})]$ (BINOL = 2,2'-dihydroxy-1,1'-binaphthyl) in stoichiometric amounts to effect an electronically controlled hydride addition to **1** (R^1 = unsaturated unit, R^2 = alkyl).^[3] We have used the principles of "hard" and "soft"^[4] Lewis acids and bases to attempt a catalytic analogue of this reagent. Monothiolbinaphthol (MTB)^[5] and $LiGaH_4$ ^[6] were selected as the "soft" ligand/catalyst combination and catecholborane as a "hard" terminal hydride source to promote only the removal of alkoxide products and not the chiral ligand from **4** (Scheme 1). While a



Scheme 1. Reduction of ketone **1** with a complex of MTB and $LiGaH_4$ (Un = unsaturated unit) as well as with the complex **5** and the borate **6**.

range of spectator ligands gave moderate selectivities (X = OMe (72% ee), 2-S-C₁₀H₇ (72% ee), 1,2-HOCH₂CH₂SH (24% ee)), a mixture of $LiGaH_4$ and two MTB ligands proved particularly effective for a range of ketones (Table 1); the mixture was characterized in the solid state as **5**, which is isostructural with the gallium–BINOL catalysts of Shibasaki.^[7]

These reactions are technically simple, stirring the reaction is not essential and any cryostat or even a domestic freezer suffices for cooling. At catalyst loadings below 2.5 mol % the enantioselectivity falls: At 1 mol % (–25 °C) **1a** is reduced in 86% ee and with 0.5 mol % (0 °C) in 72% ee. Pre-storage of solutions of $LiGaH_4$ /2MTB at ambient temperature for two

Table 1. Enantioselective reduction of ketones **1** by **5** (2.5 mol %) and catecholborane (1.1 equiv) by method B (see experimental section, unless otherwise stated).

Ketone	R ¹	R ²	Yield [%]	ee [%]
a	Ph	Me	89–95 ^[a]	89–91 ^[a]
b	Ph	Et	96	93
c	Ph	<i>n</i> Bu	80	92
d	Ph	<i>i</i> Bu	65	92
e	4-BrPh	Me	80	87
f	4-MePh	Me	95	87
g	2-furyl	<i>n</i> -C ₆ H ₁₃	76	81
h	PhCH=CH	Me	70	75
i	EtC≡C	Me	60	63

[a] Using methods A–C.

[*] Dr. S. Woodward, A. Ford
Department of Chemistry, University of Hull
Kingston-upon-Hull HU6 7RX (UK)
Fax: (+44) 1482-466410
E-mail: s.woodward@chem.hull.ac.uk

[**] This work was supported by the EPSRC (ROPA GR/K91682). We also thank Profs. Serafino Gladiali and Davide Fabbri for a generous gift of 1,1'-bi(2-thionaphthol) and Dr. Simon J. Teat (Daresbury Laboratory) for solving the structure of compound **5**.

Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.

weeks did not affect the *ee* value for the reduction of **1a**, neither did deliberate addition of water to the reaction (one equivalent per Ga, to simulate impure “wet” ketones).

The enantioselectivity in the reduction of **1a** shows an unusual temperature dependence: a maximum *ee* value is attained at -20 to -15°C , both the chemical yield and *ee* value decrease steadily at temperatures below this range. At -78°C an 18% yield of racemic alcohol is realized. One explanation of this behavior is that transmetalation of **4** to **3** ($\text{X} = \text{MTB dianion}$) is slow below -20°C and that an achiral catalytic process begins to compete. Support for this hypothesis comes from the observation that added lithium alkoxides do catalyze catecholborane reduction of **1a** via the borate **6**.^[8] The use of the MTB ligand is vital to the reaction; LiGaH_4 with either 1,1'-bi(2-naphthol) or 1,1'-bi(2-thionaphthol) leads to low selectivities (3–34% *ee*). The probable causes are decomplexation of the chiral ligand by catecholborane and poor lithium coordination. Both the presence of **6** and removal of the chiral ligand may account, in part, for the lower enantioselectivities encountered in some recent titanium work.^[9]

The solid-state structure of the pre-catalyst **5**^[7] is not retained in solution during the catalysis. The new species formed are currently still under investigation. However, the absence of a nonlinear effect^[10] in the reduction of **1a** by **5** suggests that a mononuclear catalyst with a single active MTB ligand is responsible for the enantioselection. In Noyori's BINAL reagent^[3] the (*R_a*)-ligand gives the (*R*)-alcohol because of repulsion between the n electrons of the reagent and the π electrons of the substrate. The similarity in the *ee* value for the reduction of **1a–d** suggests a related electronic control with **5**, but steric factors cannot be ruled out.

Experimental Section

All operations were performed under argon. A solution of MTB (15 mg, 0.05 mmol) in THF (5 mL) was treated with LiGaH_4 (100 μL of a 0.25 M solution in Et_2O) and the mixture stirred (20°C , 25 min). The reaction was cooled to -20°C and catecholborane (1.1 mL of a 1 M THF solution, 1.1 mmol) and ketone (1.0 mmol) were added. The solution was stirred at -20°C for 18 h (method A), or sealed and stored at -20°C (method B; -15°C and 4 mol % catalyst for **1d**). Alternatively, the catecholborane and ketone were added at -78°C and the reaction mixture stirred as it warmed to room temperature overnight (method C). Normal workup procedures afforded the alcohols **2** as essentially single products (the *ee* values were determined by gas chromatography on a chiral column (LIPODEX A or CYCLODEX B) or the α -methoxy- α -(trifluoromethyl)phenyl acetate analyzed for the alcohol of **1h**).

Received: July 28, 1998 [Z12216IE]

German version: *Angew. Chem.* **1999**, *111*, 347–349

Keywords: asymmetric reductions • gallium • hydrides • ketones

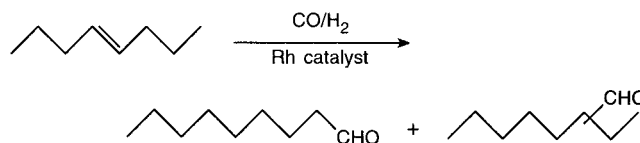
- [1] a) Review: E. J. Corey, C. J. Helal, *Angew. Chem.* **1998**, *110*, 2092–2118; *Angew. Chem. Int. Ed.* **1998**, *37*, 1987–2012; b) E. J. Corey, R. K. Bakshi, S. Shibata, C.-P. Chen, V. K. Singh, *J. Am. Chem. Soc.* **1987**, *109*, 7925–7926.
[2] Review: R. Noyori, S. Hashiguchi, *Acc. Chem. Res.* **1997**, *30*, 97–102.
[3] R. Noyori, I. Tomino, Y. Tanimoto, M. Nishizawa, *J. Am. Chem. Soc.* **1984**, *106*, 6709–6716.

- [4] R. G. Pearson, *Coord. Chem. Rev.* **1990**, *100*, 403–425.
[5] S. M. Azad, S. M. W. Bennett, S. M. Brown, J. Green, E. Sinn, C. M. Topping, S. Woodward, *J. Chem. Soc. Perkin Trans 1* **1997**, 687–694.
[6] A. E. Shirk, D. F. Shriver, *Inorg. Synth.* **1977**, *17*, 45–47.
[7] Data for structure **5** are given in the supporting information. BINOL analogues are known, see a) M. Shibasaki, H. Sasai, T. Arai, *Angew. Chem.* **1997**, *109*, 1290–1310; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1237–1256; b) T. Iida, N. Yamamoto, H. Sasai, M. Shibasaki, *J. Am. Chem. Soc.* **1997**, *119*, 4783–84; c) T. Iida, N. Yamamoto, S. Matsunaga, H.-G. Woo, M. Shibasaki, *Angew. Chem.* **1998**, *110*, 2383–2386; *Angew. Chem. Int. Ed.* **1998**, *37*, 2223–2226.
[8] For related chemistry, see a) C. W. Lindsley, M. DiMare, *Tetrahedron Lett.* **1994**, *35*, 5141–5144; b) A. Arase, M. Hoshi, T. Yamaki, H. Nakanishi, *J. Chem. Soc. Chem. Commun.* **1994**, 855–856.
[9] a) G. Giffels, C. Dreisbach, U. Kragl, M. Weigerding, H. Waldmann, C. Wandrey, *Angew. Chem.* **1995**, *107*, 2165–2166; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2005–2006; b) F. Almqvist, L. Torstensson, A. Gudmundsson, T. Frejd, *Angew. Chem.* **1997**, *109*, 388–389; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 376–377.
[10] a) Review: C. Girard, H. B. Kagan, *Angew. Chem.* **1998**, *110*, 3088–3127; *Angew. Chem. Int. Ed.* **1998**, *37*, 2922–2959; b) D. G. Blackmond, *J. Am. Chem. Soc.* **1997**, *119*, 12934–12937; c) D. Guillaenex, S. H. Zhao, O. Samuel, D. Rainford, H. B. Kagan, *J. Am. Chem. Soc.* **1994**, *116*, 9430–9439.

Hydroformylation of Internal Olefins to Linear Aldehydes with Novel Rhodium Catalysts**

Lars A. van der Veen, Paul C. J. Kamer, and
Piet W. N. M. van Leeuwen*

Hydroformylation is one of the world's largest homogeneously catalyzed processes in industry, which produces more than six million tons of aldehydes and alcohols annually.^[1] Since linear aldehydes are the most desired products a key issue in this process is the control of regiochemistry. High selectivities in the hydroformylation of terminal alkenes have been reported for both diphosphites and diphosphanes.^[2] Selective hydroformylation of internal alkenes, which is of great interest in industry and in synthetic organic chemistry, on the other hand is still a relatively unexplored terrain (Scheme 1).



Scheme 1. The hydroformylation of *trans*-4-octene to linear and branched aldehydes.

[*] Prof. Dr. P. W. N. M. van Leeuwen, L. A. van der Veen,
Dr. P. C. J. Kamer
Institute of Molecular Chemistry
University of Amsterdam
Nieuwe Achtergracht 166, 1018 WV Amsterdam (The Netherlands)
Fax: (+31)20-525-6456
E-mail: pwnm@anorg.chem.uva.nl

[**] This work was supported by SON/STW.

Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.

weeks did not affect the *ee* value for the reduction of **1a**, neither did deliberate addition of water to the reaction (one equivalent per Ga, to simulate impure “wet” ketones).

The enantioselectivity in the reduction of **1a** shows an unusual temperature dependence: a maximum *ee* value is attained at -20 to -15°C , both the chemical yield and *ee* value decrease steadily at temperatures below this range. At -78°C an 18% yield of racemic alcohol is realized. One explanation of this behavior is that transmetalation of **4** to **3** ($\text{X} = \text{MTB dianion}$) is slow below -20°C and that an achiral catalytic process begins to compete. Support for this hypothesis comes from the observation that added lithium alkoxides do catalyze catecholborane reduction of **1a** via the borate **6**.^[8] The use of the MTB ligand is vital to the reaction; LiGaH_4 with either 1,1'-bi(2-naphthol) or 1,1'-bi(2-thionaphthol) leads to low selectivities (3–34% *ee*). The probable causes are decomplexation of the chiral ligand by catecholborane and poor lithium coordination. Both the presence of **6** and removal of the chiral ligand may account, in part, for the lower enantioselectivities encountered in some recent titanium work.^[9]

The solid-state structure of the pre-catalyst **5**^[7] is not retained in solution during the catalysis. The new species formed are currently still under investigation. However, the absence of a nonlinear effect^[10] in the reduction of **1a** by **5** suggests that a mononuclear catalyst with a single active MTB ligand is responsible for the enantioselection. In Noyori's BINAL reagent^[3] the (*R_a*)-ligand gives the (*R*)-alcohol because of repulsion between the n electrons of the reagent and the π electrons of the substrate. The similarity in the *ee* value for the reduction of **1a–d** suggests a related electronic control with **5**, but steric factors cannot be ruled out.

Experimental Section

All operations were performed under argon. A solution of MTB (15 mg, 0.05 mmol) in THF (5 mL) was treated with LiGaH_4 (100 μL of a 0.25 M solution in Et_2O) and the mixture stirred (20°C , 25 min). The reaction was cooled to -20°C and catecholborane (1.1 mL of a 1 M THF solution, 1.1 mmol) and ketone (1.0 mmol) were added. The solution was stirred at -20°C for 18 h (method A), or sealed and stored at -20°C (method B; -15°C and 4 mol % catalyst for **1d**). Alternatively, the catecholborane and ketone were added at -78°C and the reaction mixture stirred as it warmed to room temperature overnight (method C). Normal workup procedures afforded the alcohols **2** as essentially single products (the *ee* values were determined by gas chromatography on a chiral column (LIPODEX A or CYCLODEX B) or the α -methoxy- α -(trifluoromethyl)phenyl acetate analyzed for the alcohol of **1h**).

Received: July 28, 1998 [Z12216IE]

German version: *Angew. Chem.* **1999**, *111*, 347–349

Keywords: asymmetric reductions • gallium • hydrides • ketones

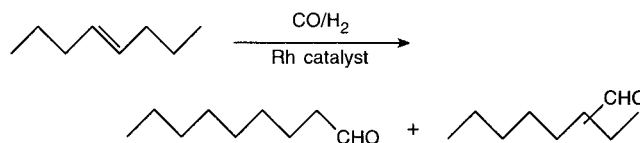
- [1] a) Review: E. J. Corey, C. J. Helal, *Angew. Chem.* **1998**, *110*, 2092–2118; *Angew. Chem. Int. Ed.* **1998**, *37*, 1987–2012; b) E. J. Corey, R. K. Bakshi, S. Shibata, C.-P. Chen, V. K. Singh, *J. Am. Chem. Soc.* **1987**, *109*, 7925–7926.
[2] Review: R. Noyori, S. Hashiguchi, *Acc. Chem. Res.* **1997**, *30*, 97–102.
[3] R. Noyori, I. Tomino, Y. Tanimoto, M. Nishizawa, *J. Am. Chem. Soc.* **1984**, *106*, 6709–6716.

- [4] R. G. Pearson, *Coord. Chem. Rev.* **1990**, *100*, 403–425.
[5] S. M. Azad, S. M. W. Bennett, S. M. Brown, J. Green, E. Sinn, C. M. Topping, S. Woodward, *J. Chem. Soc. Perkin Trans 1* **1997**, 687–694.
[6] A. E. Shirk, D. F. Shriver, *Inorg. Synth.* **1977**, *17*, 45–47.
[7] Data for structure **5** are given in the supporting information. BINOL analogues are known, see a) M. Shibasaki, H. Sasai, T. Arai, *Angew. Chem.* **1997**, *109*, 1290–1310; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1237–1256; b) T. Iida, N. Yamamoto, H. Sasai, M. Shibasaki, *J. Am. Chem. Soc.* **1997**, *119*, 4783–84; c) T. Iida, N. Yamamoto, S. Matsunaga, H.-G. Woo, M. Shibasaki, *Angew. Chem.* **1998**, *110*, 2383–2386; *Angew. Chem. Int. Ed.* **1998**, *37*, 2223–2226.
[8] For related chemistry, see a) C. W. Lindsley, M. DiMare, *Tetrahedron Lett.* **1994**, *35*, 5141–5144; b) A. Arase, M. Hoshi, T. Yamaki, H. Nakanishi, *J. Chem. Soc. Chem. Commun.* **1994**, 855–856.
[9] a) G. Giffels, C. Dreisbach, U. Kragl, M. Weigerding, H. Waldmann, C. Wandrey, *Angew. Chem.* **1995**, *107*, 2165–2166; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2005–2006; b) F. Almqvist, L. Torstensson, A. Gudmundsson, T. Frejd, *Angew. Chem.* **1997**, *109*, 388–389; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 376–377.
[10] a) Review: C. Girard, H. B. Kagan, *Angew. Chem.* **1998**, *110*, 3088–3127; *Angew. Chem. Int. Ed.* **1998**, *37*, 2922–2959; b) D. G. Blackmond, *J. Am. Chem. Soc.* **1997**, *119*, 12934–12937; c) D. Guillaenex, S. H. Zhao, O. Samuel, D. Rainford, H. B. Kagan, *J. Am. Chem. Soc.* **1994**, *116*, 9430–9439.

Hydroformylation of Internal Olefins to Linear Aldehydes with Novel Rhodium Catalysts**

Lars A. van der Veen, Paul C. J. Kamer, and
Piet W. N. M. van Leeuwen*

Hydroformylation is one of the world's largest homogeneously catalyzed processes in industry, which produces more than six million tons of aldehydes and alcohols annually.^[1] Since linear aldehydes are the most desired products a key issue in this process is the control of regiochemistry. High selectivities in the hydroformylation of terminal alkenes have been reported for both diphosphites and diphosphanes.^[2] Selective hydroformylation of internal alkenes, which is of great interest in industry and in synthetic organic chemistry, on the other hand is still a relatively unexplored terrain (Scheme 1).



Scheme 1. The hydroformylation of *trans*-4-octene to linear and branched aldehydes.

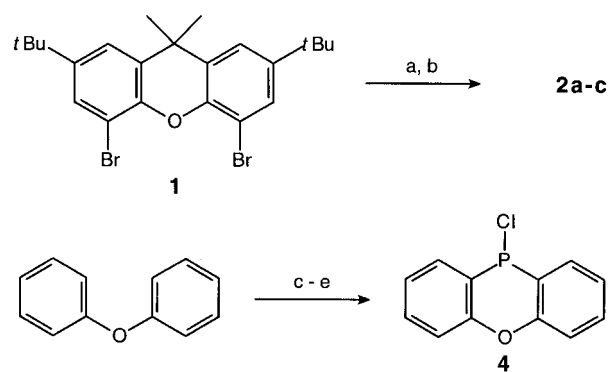
[*] Prof. Dr. P. W. N. M. van Leeuwen, L. A. van der Veen,
Dr. P. C. J. Kamer
Institute of Molecular Chemistry
University of Amsterdam
Nieuwe Achtergracht 166, 1018 WV Amsterdam (The Netherlands)
Fax: (+31)20-525-6456
E-mail: pwnm@anorg.chem.uva.nl

[**] This work was supported by SON/STW.

Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.

Very few rhodium catalysts have been reported that will hydroformylate internal alkenes at acceptable rates, and even fewer that will produce linear aldehydes preferentially.^[3] Considerable progress in this field has been made by using bulky diphosphites as modifying ligands.^[4] However, because of the intrinsically low long-term stability of phosphites the development of new efficient catalysts for the hydroformylation of internal alkenes continues to be an important goal.

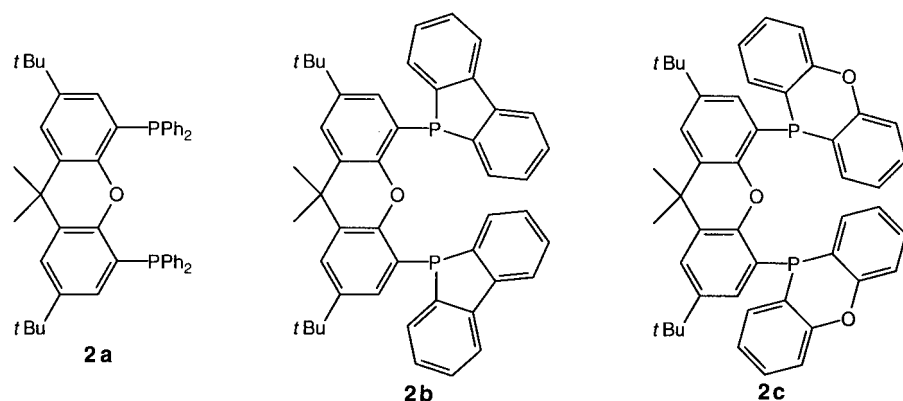
In our effort to develop ligands that induce high regioselectivity in the rhodium-catalyzed hydroformylation, we have reported on new diphosphanes with large bite angles.^[2f] This work and studies done by Casey and co-workers^[2c, 5] showed that high selectivities towards linear aldehydes can be obtained with rigid diphosphanes with chelate bite angles close to 120°. Herein we describe the synthesis of new dibenzophospholyl- and phenoxaphosphanyl-substituted xanthene ligands **2b** and **2c**, and their high activity and selectivity in the rhodium-catalyzed hydroformylation of 1-octene. More importantly, **2b** and **2c** exhibit an unprecedented high activity and selectivity in the hydroformylation of *trans*-2- and -4-octene



Scheme 2. Synthesis of diphosphanes **2a–c** and the monophosphane **4**. a) *n*BuLi, THF, 1 h at -60°C ; b) Ph_2PCl , **3** or **4**, THF, 1 h at -60°C then 16 h at 20°C , 81 % (**2a**), 67 % (**2b**), or 75 % (**2c**); c) *n*BuLi, TMEDA, Et_2O /hexanes (1/2), 1 h at 0°C then 16 h at 20°C ; d) $i\text{Pr}_2\text{NPCl}_2$, hexanes, 1 h at -60°C then 16 h at 20°C ; e) PCl_3 , 16 h at reflux, 54 %.

phanes known. Since large steric differences in the catalyst complexes of the ligands **2b** and **2c** are not anticipated, the higher activity of **2c** relative to **2b** might be ascribed to very subtle effects in the bite angle or electronic characteristics of the phosphorus heterocycles.

Although the high 1:b ratios of ligands **2b** and **2c** are in good agreement with our earlier observations that diphosphanes with natural bite angles close to 120° give very selective catalysts,^[2f] the selectivity for the formation of the linear aldehyde of both **2b** and **2c** is considerably lower than that of **2a**. This is a consequence of a dramatic increase in the rate of isomerization of 1-octene to form internal alkenes, which are not hydro-



to linear nonanal. To the best of our knowledge diphosphanes **2b** and **2c** constitute the first rhodium catalysts with modified phosphane groups for the selective linear hydroformylation of internal olefins.

The diphosphanes **2a–c** were synthesized by dilithiation of 4,5-dibromo-2,7-di-*tert*-butyl-9,9-dimethylxanthene **1** with *n*-butyllithium in THF at -60°C , followed by reaction with the corresponding chlorophosphane (Scheme 2).^[6] The natural bite angles of **2a–c** are 110, 120, and 119° , respectively.^[7] 9-Chlorodibenzo[*b*,*d*]phosphole (**3**) was prepared from a literature procedure.^[8] 10-Chlorophenoxaphosphane (**4**) was obtained in 54 % yield by dilithiation of diphenyl ether with *n*-butyllithium and *N,N,N',N'*-tetramethylethylenediamine (TMEDA) in diethyl ether/hexanes (1/1) at room temperature, followed by reaction with diisopropylphosphoramidous dichloride at -60°C , and refluxing the resulting 10-(diisopropylamino)phenoxaphosphane in phosphorus trichloride.

The activity and selectivity of ligands **2a–c** were first tested in the hydroformylation of 1-octene (Table 1). Under mild reaction conditions the diphosphanes **2b** and **2c** both showed a higher activity and a higher linear:branched (1:b) ratio compared to the parent diphosphane **2a**. The extraordinary high activity of **2c** places it among the most active diphos-

Table 1. Hydroformylation of 1-octene.^[a]

Ligand	Isomerization [%] ^[b]	1:b ^[b,c]	Selectivity [%] ^[b,d]	TOF ^[e]
PPh_3	1.2	3.1	74	1880
2a	3.9	49	94	250
2b	16	65	83	360
2c	13	68	86	1100

[a] Reactions were carried in a 180 mL stainless steel autoclave in toluene at 80°C under an atmosphere of CO/H_2 (1:1) with an initial pressure of 20 bar, catalyst precursor: $[\text{Rh}(\text{CO})_2(\text{dipivaloyl}(\text{methano})\text{ate})]$, $[\text{Rh}] = 1.0\text{ mM}$, $\text{Rh}:\text{P}:\text{1-octene} = 1:10:673$. [b] Determined by GC with decane as the internal standard. [c] 1:b ratio includes all branched aldehydes. [d] Selectivity for the linear aldehyde. [e] Turnover frequencies (TOF) were calculated as $(\text{mol aldehyde})/(\text{mol catalyst})^{-1}\text{h}^{-1}$ at 20–30 % conversion.

formylated as long as 1-octene is present. The reason why **2b** and **2c** display such a high isomerization activity relative to **2a** is not completely clear yet, but we speculate that it could be caused by the higher rigidity and the larger bite angles of the former ligands.

The high activity of diphosphanes **2b** and **2c**, combined with the very high 1:b ratio and rate of isomerization that leads to the internal olefins, prompted us also to test the ligands in

the hydroformylation of simple internal alkenes of low reactivity. A relatively high temperature and low pressure were used to enhance the rate of isomerization and to prevent hydroformylation of the internal alkenes. In the hydroformylation of *trans*-2-octene both ligands **2b** and **2c** showed a high activity and selectivity towards the formation of linear nonanal (Table 2). The hydroformylation of 1-octene formed

Table 2. Hydroformylation of *trans*-2- and -4-octene.^[a]

Ligand	Substrate	<i>t</i> [h]	Conversion [%] ^[b]	1:b ^[d]	1-Nonanal [%] ^[c]	TOF ^[d]
PPh ₃	2-octene	1.0	8.5	0.9	46	39
2b	2-octene	1.0	10	9.5	90	65
2c	2-octene	1.0	22	9.2	90	112
PPh ₃	4-octene	17	9.0	0.3	23	2.4
2b	4-octene	17	54	6.1	86	15
2c	4-octene	17	67	4.4	81	20

[a] As Table 1, but at 120 °C and with an initial pressure of CO/H₂ (1/1) of 2 bar. [b] Determined by GC with decane as an internal standard. [c] Percentage of linear nonanal in all products other than octenes. [d] See Table 1.

in situ by isomerization was highly favored over the hydroformylation of the large excess of 2-octene, and no hydrogenation was observed. The high selectivity of ligands **2b** and **2c** was even more pronounced in the hydroformylation of *trans*-4-octene; selectivities in the formation of linear nonanal still exceeded 80 % although three consecutive double bond isomerizations had to precede hydroformylation. From these remarkable results it can be concluded that diphosphane rhodium complexes can be very efficient for the selective linear hydroformylation of internal alkenes, an area that seemed hardly accessible. The high activity and selectivity of diphosphanes **2b** and **2c** may open up a new range of applications for hydroformylation catalyzed by diphosphane rhodium complexes. One of the possible interesting industrial applications could be the linear hydroformylation of "Raffinate 2", a mixture of butenes that originates from steam crackers.^[1d]

Received: August 17, 1998 [Z 12298 IE]
German version: *Angew. Chem.* **1999**, *111*, 349–351

Keywords: homogeneous catalysis • hydroformylations • phosphorus heterocycles • rhodium

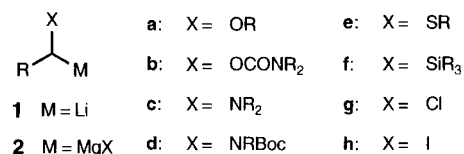
- [1] a) G. W. Parshall, *Homogeneous Catalysis: The Applications and Chemistry of Catalysis by Soluble Transition Metal Complexes*, Wiley, New York, **1980**; b) C. A. Tolman, J. W. Faller in *Homogeneous Catalysis with Metal Phosphine Complexes* (Ed.: L. H. Pignolet), Plenum, New York, **1983**, pp. 81–109; c) M. Beller, B. Cornils, C. D. Frohning, C. W. Kohlpaintner, *J. Mol. Catal. A* **1995**, *104*, 17–85; d) C. D. Frohning, C. W. Kohlpaintner in *Applied Homogeneous Catalysis with Organometallic Compounds: a comprehensive handbook in two volumes, Vol. 1* (Eds.: B. Cornils, W. A. Herrmann), VCH, Weinheim, New York, **1996**, pp. 27–104.
- [2] a) G. J. H. Buisman, E. J. Vos, P. C. J. Kamer, P. W. N. M. van Leeuwen, *Tetrahedron: Asymmetry* **1995**, *6*, 719–738; b) A. van Rooy, P. C. J. Kamer, P. W. N. M. van Leeuwen, K. Goubitz, J. Fraanje, N. Veldman, A. L. Spek, *Organometallics* **1996**, *15*, 835–847; c) C. P. Casey, G. T. Whiteker, M. G. Melville, L. M. Petrovich, J. A. Gavney Jr., D. R. Powell, *J. Am. Chem. Soc.* **1992**, *114*, 5535–5543; d) C. P. Casey, E. L.

- Paulsen, E. W. Beuttenmueller, B. R. Proft, L. M. Petrovich, B. A. Matter, D. R. Powell, *J. Am. Chem. Soc.* **1997**, *119*, 11 817–11 825; e) G. D. Cuny, S. L. Buchwald, *J. Am. Chem. Soc.* **1993**, *115*, 2066–2068; f) M. Kranenburg, Y. E. M. van der Burgt, P. C. J. Kamer, P. W. N. M. van Leeuwen, *Organometallics* **1995**, *14*, 3081–3089.
- [3] a) P. W. N. M. van Leeuwen, C. F. Roobeek, *J. Organomet. Chem.* **1983**, *258*, 343–350; b) A. van Rooy, E. N. Orij, P. C. J. Kamer, P. W. N. M. van Leeuwen, *Organometallics* **1995**, *14*, 34–43; c) B. Breit, R. Winde, K. Harms, *J. Chem. Soc. Perkin Trans. 1* **1997**, 2681–2682.
- [4] a) E. Billig, A. G. Abatjoglou, D. R. Bryant (Union Carbide), EP 213639, **1987** [*Chem. Abstr.* **1987**, *107*, 7392r]; b) P. M. Burke, J. M. Garner, W. Tam, K. A. Kreutzer, A. J. J. M. Teunissen, C. S. Snijder, C. B. Hansen (DSM, Du Pont), WO 97/33854, **1997** [*Chem. Abstr.* **1997**, *127*, 294939r].
- [5] C. P. Casey, L. M. Petrovich, *J. Am. Chem. Soc.* **1995**, *117*, 6007–6014.
- [6] All new compounds were fully characterized. See the supporting information for the experimental details.
- [7] C. P. Casey, G. T. Whiteker, *Isr. J. Chem.* **1990**, *30*, 299–304.
- [8] H. T. Teunissen, F. Bickelhaupt, *Phosphor Sulphur Silicon* **1996**, *118*, 309–312.

α -Chloroalkylmagnesium Reagents of > 90 % ee by Sulfoxide/Magnesium Exchange**

Reinhard W. Hoffmann* and Peter G. Nell

α -Heterosubstituted organometallic reagents such as **1** are attractive chiral d¹-synthons^[1] provided that they have sufficient configurational stability and that they can be generated in high stereochemical purity (Scheme 1). The (α -alkoxy)-



Scheme 1. The organolithium compounds **1a–h** and the Grignard reagents **2a–h**. Boc = *tert*-butoxycarbonyl.

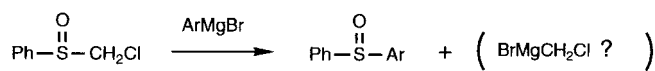
alkyllithium reagents **1a,b**^[2] and (α -amino)alkyllithium reagents **1c,d**^[3] are prominent examples. Reagents **1**, in which X is a heteroatom of the second row of the periodic table (see **1e,f**) have much lower barriers to racemization.^[4] Their diminished configurational stability limits their use in stereoselective synthesis. Higher configurational stability may be expected for the corresponding magnesium reagents **2**, since previous studies^[5,6] indicated compounds of the type **2h** to be configurationally stable on a macroscopic time scale at or above –78 °C. We have therefore explored diastereoselective and enantioselective routes to reagents of the type **2**. We

[*] Prof. Dr. R. W. Hoffmann, Dipl.-Chem. P. G. Nell
Fachbereich Chemie der Universität
Hans-Meerwein-Strasse, D-35032 Marburg (Germany)
Fax: (+49) 6421/28-8917
E-mail: RWHO@ps1515.chemie.uni-marburg.de

[**] This study was supported by the Deutsche Forschungsgemeinschaft (SFB 260) and the Fonds der Chemischen Industrie. We thank Dr. K. Harms for the crystal structure analysis.

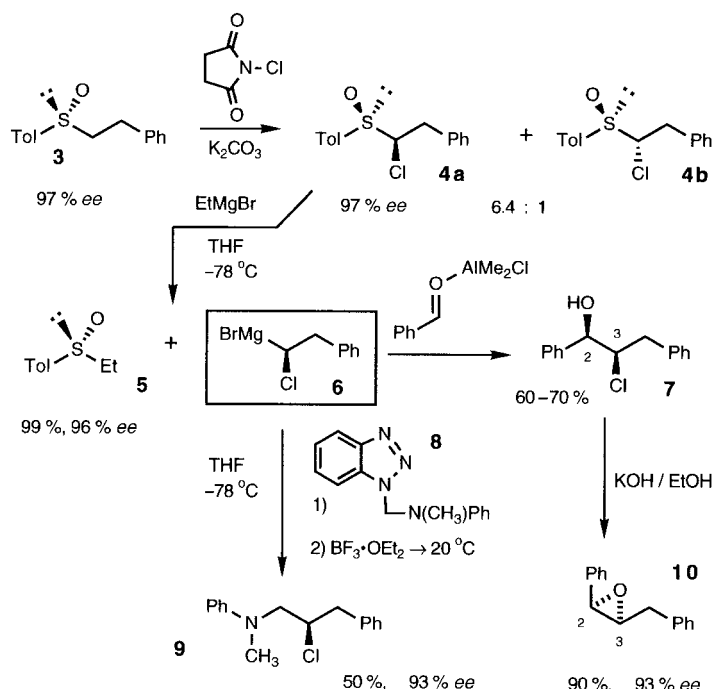
report here on a facile generation of the α -chloroalkylmagnesium reagents **2g** with an enantiomeric excess of larger than 90 %.

Our approach is based on the sulfoxide/magnesium exchange reaction,^[7] a reaction that has mainly been applied to modify sulfoxides or to generate vinylic^[8–10] or cyclopropyl-^[11, 12] Grignard reagents. But exchange reactions were also reported for α -chloroalkyl sulfoxides (Scheme 2).^[13] We



Scheme 2. Exchange reactions with α -chloroalkyl sulfoxides.

adapted this reaction to furnish enantiomerically enriched α -chloroalkylmagnesium compounds **6**: starting point is the (*R*)-(2-phenylethyl)tolyl sulfoxide (**3**) of 99 % *ee* ($[\alpha]_{\text{D}}^{20} = +125$ ($c = 2.24$, acetone)); Scheme 3). Chlorination of **3**^[11] with *N*-chlorosuccinimide/ K_2CO_3 furnished a 6.4:1 mixture of the



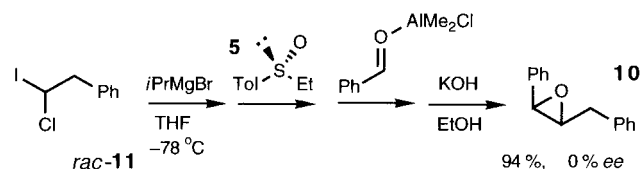
Scheme 3. Synthesis of and reactions with the Grignard reagent **6**.

diastereomeric α -chlorosulfoxides **4**, which could be separated by simple crystallization from acetone. The enantiomeric purity of **4a** (m.p. = 77–78 °C, $[\alpha]_{\text{D}}^{20} = -92$ ($c = 2.00$, acetone)) was 97 % according to chiral HPLC. The relative configuration of **4b** (and by inference of **4a**) has been secured by X-ray crystal structure analysis. Reaction of **4a** with 1.3 equivalents of ethylmagnesium bromide in THF at –78 °C generated the sulfoxide **5** (99 %, $[\alpha]_{\text{D}}^{22} = +198$ ($c = 1.00$, acetone); $[\alpha]_{\text{D}}^{25} = +202.6$ ^[11]) with > 96 % *ee* (HPLC) with inversion of configuration at sulfur.^[8] Our interest was focused on the Grignard reagent **6** which is generated as a coproduct in this reaction. The Grignard reagent **6** can be trapped at –78 °C by benzaldehyde activated by dimethylaluminum chloride to furnish the chlorohydrin **7** (60–70 % yield) in a *syn/anti* ratio

of 90:10 (only the major diastereomer is shown). The crude chlorohydrins were cyclized to the epoxides **10**, which were obtained in a 88:12 ratio (only the major diastereomer of **10** is shown). ¹H NMR spectroscopic analyses in the presence of [Eu(hfc)₃] (hfc = 3-(heptafluoropropylhydroxymethylene)-D-camphorate) revealed an enantiomeric purity of **10** of 93 % *ee* and showed, with reference to material of known absolute configuration^[6, 14] that the major enantiomer of **10** has the configuration (2*R*, 3*S*). The chlorohydrin **7** should therefore have the indicated configuration (2*R*, 3*R*).

The reaction sequence has also been carried out with the *p*-chlorophenyl analogue of **4a** (*p*-ClC₆H₄ instead of *p*-Tol) to provide the chlorohydrin **7** and the epoxide **10** with similar yields and enantiomeric purities. The α -chloroalkyl-Grignard reagent **6** generated in this fashion has been trapped with the α -aminomethylbenzotriazole **8**.^[15] The product **9** obtained in 50 % yield showed on HPLC analysis with a chiral stationary phase an *ee* value of 93 %. The absolute configuration of **9** is assigned in analogy to that of the chlorohydrin **7**.

We postulated that the enantiomeric composition of **6** is derived directly from the diastereomeric purity of the sulfoxide **4a**. To establish that the enantiomeric purity of **6** is not induced in any way by the presence of the chiral coproduct **5**, racemic **6** was generated by reaction of the racemic chloriodoalkane **11** with isopropylmagnesium bromide at –78 °C. Enantiomerically pure sulfoxide **5**^[11] was added after 10 min, followed again after 10 min by benzaldehyde/dimethylaluminum chloride. This reaction resulted in the formation of 94 % of the chlorohydrin **7**, which was found to be racemic after conversion to the epoxide **10** (Scheme 4).



Scheme 4. Formation of and reaction with *rac*-**6**.

This study shows that the sulfoxide/magnesium exchange reaction can be applied to generate chiral Grignard reagents **6**. The reaction occurs with retention of configuration at the chlorine-bearing carbon center. Preliminary experiments indicate that the Grignard reagent **6** is subject to a slow racemization under the reaction conditions. Experiments are in progress to delineate to which extent this is a purely thermal racemization or a halide-induced racemization process.^[10, 16]

Received: July 6, 1998 [Z12094IE]
German version: *Angew. Chem.* **1999**, *111*, 354–355

Keywords: chirality • configurational stability • Grignard reagents • sulfoxides

[1] D. Seebach, *Angew. Chem.* **1979**, *91*, 259–278; *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 239–258.

[2] For leading references see: a) W. C. Still, C. Sreekumar, *J. Am. Chem. Soc.* **1980**, *102*, 1201–1202; b) S. D. Rychnovsky, D. J. Skaltitzky, *J. Org.*

- Chem.* **1992**, *57*, 4336–4339; c) D. Hoppe, T. Hense, *Angew. Chem.* **1997**, *109*, 2376–3410; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2282–2316.
- [3] For leading references see: a) P. Beak, A. Basu, D. J. Gallagher, Y. S. Park, S. Thayumanavan, *Acc. Chem. Res.* **1996**, *29*, 552–560; b) A. R. Katritzky, M. Qi, *Tetrahedron* **1998**, *54*, 2647–2668.
- [4] For leading references see: R. W. Hoffmann, R. K. Dress, T. Ruhland, A. Wenzel, *Chem. Ber.* **1995**, *128*, 861–870.
- [5] a) R. W. Hoffmann, A. Kusche, *Chem. Ber.* **1994**, *127*, 1311–1316; b) R. W. Hoffmann, M. Julius, F. Chemla, T. Ruhland, G. Frenzen, *Tetrahedron* **1994**, *50*, 6049–6060; c) W. Klute, M. Krüger, R. W. Hoffmann, *Chem. Ber.* **1996**, *129*, 633–638.
- [6] V. Schulze, R. W. Hoffmann, *Chem. Eur. J.* **1999**, *5*, 337–344.
- [7] B. J. Wakefield, *Organomagnesium Methods in Organic Synthesis*, Academic Press, London, **1995**, p. 58.
- [8] C. Cardellicchio, V. Fiandanese, F. Naso, A. Scilimati, *Tetrahedron Lett.* **1992**, *33*, 5121–5124.
- [9] a) C. Cardellicchio, V. Fiandanese, F. Naso, *J. Org. Chem.* **1992**, *57*, 1718–1722; b) T. Satoh, K. Takano, H. Someya, K. Matsuda, *Tetrahedron Lett.* **1995**, *36*, 7097–7100; c) C. Cardellicchio, A. Iacuone, F. Naso, P. Tortorella, *Tetrahedron Lett.* **1996**, *37*, 6017–6020.
- [10] T. Satoh, K. Takano, H. Ota, H. Someya, K. Matsuda, K. Yamakawa, *Tetrahedron* **1998**, *54*, 5557–5574.
- [11] T. Satoh, T. Sato, T. Oohara, K. Yamakawa, *J. Org. Chem.* **1989**, *54*, 3130–3136.
- [12] T. Satoh, K. Horiguchi, *Tetrahedron Lett.* **1995**, *36*, 8235–8238.
- [13] a) M. Hojo, R. Masuda, T. Saeki, K. Fujimori, S. Tsutsumi, *Synthesis* **1977**, 789–791; b) T. Satoh, Y. Mizu, T. Kawashima, K. Yamakawa, *Tetrahedron* **1995**, *51*, 703–710; c) T. Satoh, K. Takano, *Tetrahedron* **1996**, *52*, 2349–2358.
- [14] The *cis* arrangement of the substituents in the epoxide **10** is deduced from the characteristic^[17] ¹H NMR signal at $\delta = 4.18$ for H-2. The absolute configuration of **10** was secured in the context of a related study into the enantioselective iodine/magnesium exchange:^[6] a sample of enantio-enriched iodohydrin **12** was converted once to the epoxide *ent*-**10** of 29% *ee* and once by reduction with triphenyltin hydride to the dextrorotatory alcohol **13** ($[\alpha]_D^{25} = +3.9$ (*c* = 3.60, ethanol)) of known absolute configuration^[18] in 95% yield (Scheme 5).

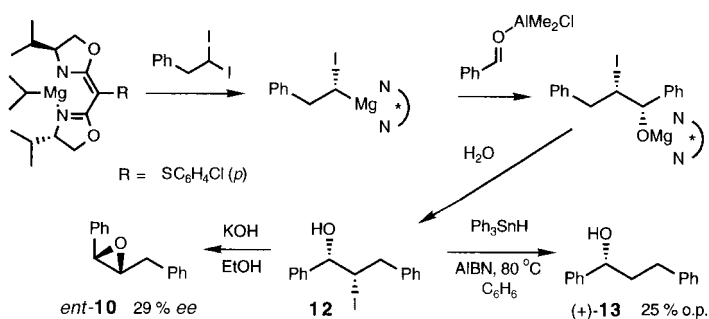
Synthesis, Structure, and Radical Anion of the First Stable *p*-Phosphaquinone**

Shigeru Sasaki, Fumiki Murakami, and Masaaki Yoshifuji*

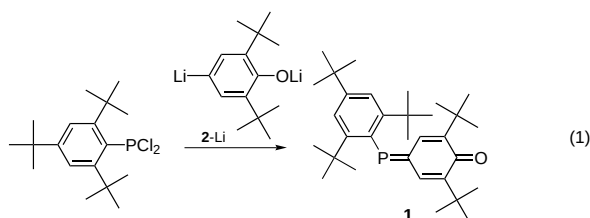
Dedicated to Professor Edgar Niecke on the occasion of his 60th birthday

Quinoid compounds have attracted considerable interest for a long time owing to their unique structure, properties, and large potential for application.^[1] Thus, a variety of quinoid compounds such as quinones, quinodimethanes, and quino-diimines has played an important role in a wide range of research areas. On the other hand, stable quinoid compounds which contain heavier main group elements had not been known until recently, in spite of progress in the chemistry of heavier main group elements, where double bonds between the most of the typical elements and carbon become available. There have been several reports of matrix isolation^[2] of the reactive quinoid molecules and isomeric structures such as tetrathiotetracene,^[3] but *p*-diphosphaquinone, characterized and reported by Märkl et al.,^[4] is the only example of a stable quinoid molecule containing heavier main group elements. However, it has not been obtained in pure form, since not only the quinoid structure but also the double bond between carbon and a heavier element make the species inherently unstable. Here we report the synthesis, structure, redox properties, and generation of the radical anion of the first stable *p*-phosphaquinone **1**. Employment of the 3,5-di-*tert*-butyl-4-oxocyclohexa-2,5-dien-1-ylidene moiety, which has been one of the most frequently utilized structures in the chemistry of the quinoid molecules, was essential for the synthesis as well as the effective kinetic protection of **1**.

To construct the quinoid skeleton of **1**, we used the 2,6-di-*tert*-butyl-4-lithiophenoxide ion **2** as a key synthetic intermediate [Eq. (1)], since we expected the extremely high



Scheme 5. AIBN = 2,2'-azobisisobutyronitrile; o.p. = optical purity.



- [15] For leading references see: A. R. Katritzky, X. Lan, J. Z. Yang, O. V. Denisko, *Chem. Rev.* **1998**, *98*, 409–548.
- [16] a) W. T. Miller, D. M. Whalen, *J. Am. Chem. Soc.* **1964**, *86*, 2089–2090; b) J. Villiéras, *Bull. Soc. Chim. Fr.* **1967**, 1511–1520; c) G. Köbrich, F. Ansari, *Chem. Ber.* **1967**, *100*, 2011–2020.
- [17] Y. Tamura, S. M. Bayomi, K. Sumoto, M. Ikeda, *Synthesis* **1977**, 693–695.
- [18] J. L. von dem Bussche-Hünnefeld, D. Seebach, *Tetrahedron* **1992**, *48*, 5719–5730.

[*] Prof. Dr. M. Yoshifuji, Dr. S. Sasaki, F. Murakami
Department of Chemistry, Graduate School of Science
Tohoku University
Aoba, Sendai 980-8578 (Japan)
Fax: (+81)22-217-6562
E-mail: yoshifj@mail.cc.tohoku.ac.jp

[**] This work was supported by The Japan Securities Scholarship Foundation and a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture, Japan (nos. 08454193 and 09239101). Shin-Etsu Chemical Company is gratefully acknowledged for the donation of silicon chemicals. We also thank the Instrumental Analysis Center for Chemistry, Graduate School of Science, Tohoku University for obtaining 600-MHz NMR spectra, mass spectra, and elemental analysis. This work was partially carried out in the Advanced Instrumental Laboratory for Graduate Research of the Department of Chemistry, Graduate School of Science, Tohoku University.

nucleophilicity^[5] to be sufficient for the attack at the phosphorus atom of the starting phosphane, assistance of the oxide ion in the elimination of chloride ion to afford the quinoid system **1**, and effective steric protection of the resultant *p*-phosphaquinone structure by the two *tert*-butyl groups. Thus, 2,6-di-*tert*-butyl-4-iodophenol^[6] was lithiated with two equivalents of *n*-butyllithium and added to a solution of dichloro(2,4,6-tri-*tert*-butylphenyl)phosphane in THF.^[7] Although the mechanism is not clear, the reaction proceeded as expected and formation of a 10:3 mixture of **1** and bis(2,4,6-tri-*tert*-butylphenyl)diphosphene^[7] was confirmed by ³¹P NMR spectroscopy. Repeated extraction with *n*-pentane, chromatographic separation on silica gel, and purification by gel permeation chromatography (GPC) afforded almost pure phosphoquinone **1**. Further recrystallization from benzene gave analytically pure **1** in 30% yield as air-stable orange plates suitable for an X-ray crystallographic analysis.

The proton-coupled ³¹P NMR spectrum of **1** (81 MHz) shows a doublet at $\delta = 327.4$ with $J(\text{P,H}) = 12.0$ Hz. The significant deshielding suggests a low-lying excited state due to the quinoid structure of **1**, and the large coupling of the phosphorus atom with the proton in the position *cis* to the lone pair is consistent with the structure and an empirical rule that the ³¹P nucleus of phosphalkenes has a larger coupling with nuclei *cis* to its lone pair than those *trans* to it.^[8] In the ¹H NMR spectrum of **1**, the signals at $\delta = 7.41$ ($J(\text{H,H}) = 2.3$, $J(\text{P,H}) = 12.5$ Hz) and 5.74 ($J(\text{H,H}) = 2.3$, $J(\text{P,H}) = 4.1$ Hz) were easily assigned based on the coupling pattern to the vinyl protons *cis* and *trans* to the phosphorus lone pair, respectively. The vinyl and *tert*-butyl protons *cis* to the 2,4,6-tri-*tert*-butylphenyl group are strongly shielded, probably due to the ring current of the aromatic ring. The ¹³C NMR signal of the P=C carbon atom appears as a doublet; its chemical shift ($\delta = 167.61$) and coupling constant ($J(\text{P,C}) = 40.0$ Hz) are within the range of typical phosphalkenes.^[9] The signal at $\delta = 185.90$ ($J(\text{P,C}) = 6.7$ Hz) as well as the IR band ($\tilde{\nu}_{\text{CO}} = 1598 \text{ cm}^{-1}$) of the carbonyl group are typical for the 3,5-di-*tert*-butyl-4-oxocyclohexa-2,5-dien-1-ylidene system.^[10] The UV/Vis spectrum of **1** in hexanes shows one broad peak at $\lambda_{\text{max}} = 372$ ($\epsilon = 22100$, $\pi \rightarrow \pi^*$), which is responsible for the orange color of **1**.

The structure of **1** was unambiguously confirmed by an X-ray crystallographic analysis (Figure 1). The P=C bond length of 1.705(2) Å is within the range of known phosphalkenes, though slightly longer than the average.^[9] The bond lengths and angles within the 3,5-di-*tert*-butyl-4-oxocyclohexa-2,5-dien-1-ylidene moiety show values similar to those for the known 3,5-di-*tert*-butyl-4-oxocyclohexa-2,5-dien-1-ylidene structures.^[11] Thus, the six-membered ring is composed of two double bonds (C2=C3 1.347(2), C5=C6 1.350(2) Å) and four single bonds (C1-C2 1.446(2), C3-C4 1.497(2), C4-C5 1.482(2), C6-C1 1.444(2) Å). Interestingly, the C=P bond points slightly in the less crowded direction with bond angles of 126.5(1)° and 115.9(1)° for P1-C1-C2 and P1-C1-C6, respectively, probably due to the bulkiness of the 2,4,6-tri-*tert*-butylphenyl moiety. All the spectroscopic as well as crystallographic data are consistent with the quinoid structure of **1**.

Since benzoquinones are known to undergo a two-step reversible reduction,^[1, 12] and some sterically protected phos-

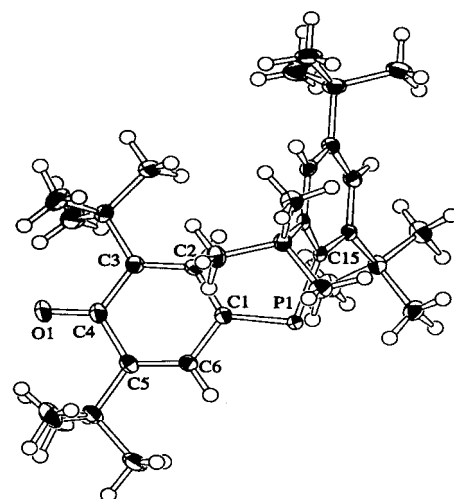


Figure 1. ORTEP drawing of the molecular structure of **1** with 50% probability ellipsoids. Selected bond lengths [Å] and angles [°]: P1–C1 1.705(2), P1–C15 1.847(2), C1–C2 1.446(2), C2–C3 1.347(2), C3–C4 1.497(2), C4–C5 1.482(2), C5–C6 1.350(2), C1–C6 1.444(2), O1–C4 1.238(2); C1–P1–C15 101.58(7), P1–C1–C2 126.5(1), P1–C1–C6 115.9(1), C2–C1–C6 117.5(1), C1–C2–C3 122.8(1), C2–C3–C4 118.7(1), O1–C4–C3 120.5(2), O1–C4–C5 120.7(1), C3–C4–C5 118.8(1), C4–C5–C6 118.4(1), C1–C6–C5 123.4(2).

phalkenes are also reported to give redox systems stable enough to allow observation of the corresponding radical anion,^[13] we became interested in the redox properties of **1** and measured its cyclic voltammogram (Figure 2). The first

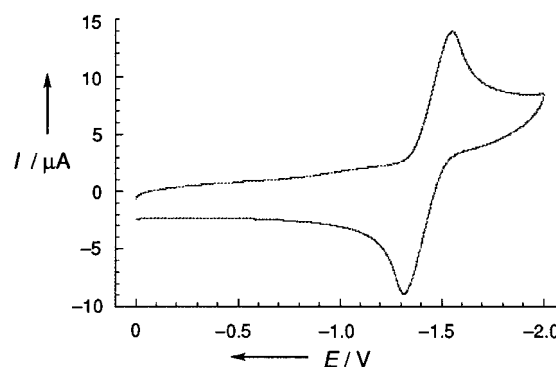
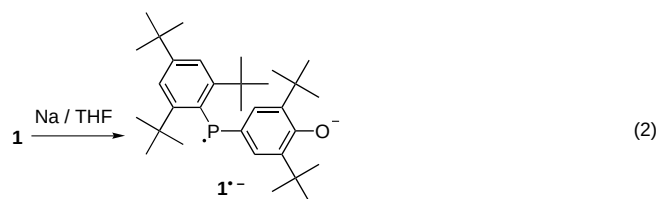


Figure 2. Cyclic voltammogram of **1** (10^{-4} M in THF; supporting electrolyte: 0.1 M *n*Bu₄NClO₄; working electrode: glassy carbon; counter electrode: Pt wire; reference electrode: Ag/0.01 M AgNO₃ in acetonitrile with 0.1 M *n*Bu₄NClO₄ ($E_{1/2}(\text{ferrocene/ferrocenium}) = 0.180$ V); scan rate: 100 mV s⁻¹; 22 °C). *I* = current, *E* = potential.

redox wave appearing at -1.43 V vs. Ag/Ag⁺ is reversible. However, the second reduction at -2.45 V is irreversible, and scanning to this second reduction makes the first one also irreversible. The first reduction potential is intermediate in value of those of quinones^[12] and phosphalkenes.^[13] The difference of the first and second reduction peak potentials ($\Delta E = 0.90$ V) is larger than that of *p*-benzoquinones and quinone methides ($\Delta E = 0.6–0.8$ V).^[12]

Although **1** did not afford a two-step reversible redox system like the *p*-benzoquinones, the first reversible wave suggested considerable stability of the phosphasemiquinone

radical anion $1^{\cdot-}$. Thus, the reduction of **1** with sodium metal was carried out [Eq. (2)] and monitored by EPR spectroscopy. The orange color of a solution of **1** in THF became green upon



contact with the sodium mirror, and an EPR signal consisting of a doublet due to hyperfine coupling with one ^{31}P nucleus ($a(\text{P}) = 9.3 \text{ mT}$ at $g = 2.0069$) was observed at room temperature (Figure 3a). The appearance of the spectrum, where the

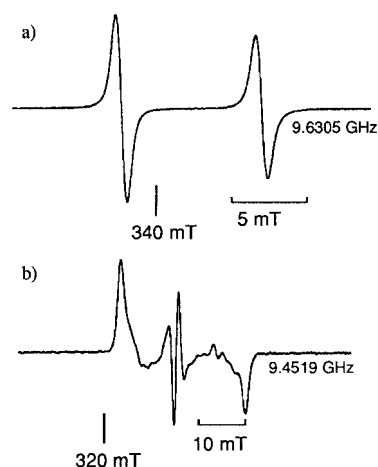


Figure 3. EPR spectra of $1^{\cdot-}$ generated by the reduction of **1** with sodium metal in THF a) at 295 K and b) at 77 K.

upfield peak is broader due to large anisotropy of the hyperfine coupling, is typical of radical anions of low-coordinated phosphorus compounds. The EPR spectrum of the frozen solution of $1^{\cdot-}$ at 77 K (Figure 3b) was also characterized by large anisotropy of hyperfine coupling with the ^{31}P nucleus. The spectrum was approximately reproduced by assigning $g_{xx} = 2.0094$, $g_{yy} = 2.0094$, $g_{zz} = 2.0022$, $a_{xx}(\text{P}) = 0.25$, $a_{yy}(\text{P}) = 1.7$, and $a_{zz}(\text{P}) = 26.1 \text{ mT}$. From these principal values of the hyperfine coupling tensor, isotropic (contact) and anisotropic (dipolar) coupling constants of 9.35 and 8.38 mT were obtained. Comparison of the isotropic and anisotropic coupling constants of $1^{\cdot-}$ with those of the phosphorus atom^[14] suggests that about 2 and 64% of the unpaired electron is localized on the 3s and 3p orbitals of phosphorus, respectively. The appearance of the spectra of both solution and frozen solution originating from large anisotropy of hyperfine coupling is similar to those for the known radical anions of low-coordinated phosphorus compounds such as phosphalkenes^[13] and diphosphenes.^[15] However, both $a_{zz}(\text{P})$ and $a_{iso}(\text{P})$ are considerably larger than those for the radical anions of other low-coordinate phosphorus compounds, but very similar to those of diarylphosphanyl radicals $\text{Ar}_2\text{P}^{\cdot}$.^[16] This indicates significant contribution of the canonical structure shown in Equation (2).

Experimental Section

1: 2,6-Di-*tert*-butyl-4-iodophenol (1.06 g, 3.18 mmol) dissolved in THF (10 mL) was treated with *n*-butyllithium (6.44 mmol, 1.61 mol L^{-1} in *n*-hexane) at -78°C and allowed to warm to room temperature. The resultant colorless solution was added to dichloro(2,4,6-tri-*tert*-butylphenyl)phosphane (1.09 g, 3.13 mmol) in THF (10 mL) at -78°C . After being stirred for 15 min at -78°C , the dark yellow-green solution was warmed to room temperature and stirred for 2 h to afford a dark purple solution. Disappearance of the starting material and formation of **1** and bis(2,4,6-tri-*tert*-butylphenyl)diphosphene (10:3 ratio) were monitored by ^{31}P NMR spectroscopy. The solution was diluted with *n*-pentane (20 mL), and insoluble salts were removed by filtration. The filtrate was concentrated and purified by repeated extraction with *n*-pentane, column chromatography (SiO_2 , *n*-hexane/ $\text{CH}_2\text{Cl}_2/\text{Et}_3\text{N}$), and GPC (Jaigel 1H+2H, chloroform). Recrystallization from benzene afforded orange plates of **1** (30%). M.p. 172.0°C (decomp); ^1H NMR (200 MHz, CDCl_3 , 22°C , TMS): $\delta = 7.48$ (d, $J(\text{P,H}) = 1.1 \text{ Hz}$, 2H; $\text{H}_{\text{arom.}}$), 7.41 (dd, $J(\text{H,H}) = 2.3 \text{ Hz}$, $J(\text{P,H}) = 12.5 \text{ Hz}$, 1H; vinyl H *trans* to Ar), 5.74 (dd, $J(\text{H,H}) = 2.3 \text{ Hz}$, $J(\text{P,H}) = 4.1 \text{ Hz}$, 1H; vinyl H *cis* to Ar), 1.41 (s, 18H; *o*- $\text{C}(\text{CH}_3)_3$), 1.36 (s, 9H; *p*- $\text{C}(\text{CH}_3)_3$), 1.33 (s, 9H; $\text{C}(\text{CH}_3)_3$ *trans* to Ar), 0.96 (s, 9H; $\text{C}(\text{CH}_3)_3$ *cis* to Ar); $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3 , 22°C , TMS): $\delta = 185.90$ (d, $J(\text{P,C}) = 6.7 \text{ Hz}$; C=O), 167.61 (d, $J(\text{P,C}) = 40.0 \text{ Hz}$; C=P), 155.13 (s; *o*- $\text{C}_{\text{arom.}}$), 151.46 (s; *p*- $\text{C}_{\text{arom.}}$), 145.02 (d, $J(\text{P,C}) = 33.3 \text{ Hz}$; $=\text{CC}(\text{CH}_3)_3$ *trans* to Ar), 143.86 (d, $J(\text{P,C}) = 23.2 \text{ Hz}$; $=\text{CC}(\text{CH}_3)_3$ *cis* to Ar), 134.46 (d, $J(\text{P,C}) = 57.3 \text{ Hz}$; *ipso*- $\text{C}_{\text{arom.}}$), 133.93 (d, $J(\text{P,C}) = 41.1 \text{ Hz}$; $=\text{CH}$ *trans* to Ar), 128.00 (d, $J(\text{P,C}) = 13.1 \text{ Hz}$; $=\text{CH}$ *cis* to Ar), 121.71 (s; *m*- $\text{C}_{\text{arom.}}$), 38.03 (s; *o*- $\text{C}(\text{CH}_3)_3$), 35.14 (s; $\text{C}(\text{CH}_3)_3$ *trans* to Ar), 35.05 (s; *p*- $\text{C}(\text{CH}_3)_3$), 34.84 (s; $\text{C}(\text{CH}_3)_3$ *cis* to Ar), 33.58 (d, $J(\text{P,C}) = 6.0 \text{ Hz}$; *o*- $\text{C}(\text{CH}_3)_3$), 31.26 (s; *p*- $\text{C}(\text{CH}_3)_3$), 29.67 (s; $\text{C}(\text{CH}_3)_3$ *trans* to Ar), 29.32 (s; $\text{C}(\text{CH}_3)_3$ *cis* to Ar); ^{31}P NMR (81 MHz, CDCl_3 , 22°C , ext. 85% H_3PO_4): $\delta = 327.4$ (d, $J(\text{P,H}) = 12.0 \text{ Hz}$); IR (KBr): $\tilde{\nu} = 2954, 2908, 2868, 1631, 1598, 1556, 1475, 1456, 1394, 1365, 1250, 1207, 1128, 1018, 930, 885, 820, 752, 648, 600, 490 \text{ cm}^{-1}$; UV/Vis (hexanes): λ_{max} (ϵ) = 372 nm (22 100); MS (low resolution, 70 eV, EI): m/z (%): 480 (100) $[\text{M}]^+$, 465 (61) $[\text{M} - \text{Me}]^+$, 423 (20) $[\text{M} - \text{tBu}]^+$, 57 (25) $[\text{tBu}]^+$; C,H analysis calcd for $\text{C}_{32}\text{H}_{49}\text{OP}$: C 79.95, H 10.27; found: C 79.89, H 10.27.

Crystal data for **1** ($\text{C}_{32}\text{H}_{49}\text{OP}$): $M_r = 480.71$, orange plates grown from benzene, crystal dimensions $0.50 \times 0.50 \times 0.30 \text{ mm}^3$, monoclinic, space group $P2_1/c$ (no. 14), $a = 13.887(2)$, $b = 11.094(2)$, $c = 20.087(9) \text{ \AA}$, $\beta = 102.620(3)^\circ$, $V = 3019(1) \text{ \AA}^3$, $Z = 4$, $\rho_{\text{calcd}} = 1.057 \text{ g cm}^{-3}$, $\mu = 0.111 \text{ mm}^{-1}$, $T = 100(1) \text{ K}$, $F(000) = 1056.00$. A Rigaku RAXIS-IV imaging plate area detector with graphite-monochromated $\text{MoK}\alpha$ radiation ($\lambda = 0.71070 \text{ \AA}$) was used. Of 4860 reflections measured ($2\theta_{\text{max}} = 50.1^\circ$), 4213 were observed [$I > 3.00\sigma(I)$]. The structure was solved by direct methods (SIR92),^[17] expanded using Fourier techniques (DIRDIF94),^[18] and refined by full-matrix least squares on F for 504 variable parameters. The non-hydrogen atoms were refined anisotropically, and hydrogen atoms isotropically. $R = 0.038$, $R_w = 0.056$, Goodness of fit $S = 1.10$ for observed reflections, and $R = 0.046$, $R_w = 0.064$ for all reflections. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.26 and $-0.23 \text{ e \AA}^{-3}$, respectively. Structure solution, refinement, and graphical representation were carried out using the *teXsan* package.^[19] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-102095. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Received: July 7, 1998 [Z12108IE]
German version: *Angew. Chem.* **1999**, *111*, 351–354

Keywords: EPR spectroscopy • phosphalkenes • quinones • radical ions • redox chemistry

[1] *The Chemistry of the Quinoid Compounds, Parts 1 and 2* (Ed.: S. Patai), Wiley, London, **1974**; *The Chemistry of the Quinoid Compounds, Vol. 2, Parts 1 and 2* (Eds.: S. Patai, Z. Rappoport), Wiley, Chichester, **1988**.

- [2] H. Bock, S. Mohmand, T. Hirabayashi, G. Maier, H. P. Reisenauer, *Chem. Ber.* **1983**, *116*, 273–281.
- [3] J. M. Williams, J. R. Ferraro, R. J. Thorn, K. D. Carlson, U. Geiser, H. H. Wang, A. M. Kini, M.-H. Whangbo in *Organic Superconductors (Including Fullerenes): Synthesis, Structure, Properties, and Theory*, Prentice-Hall, New Jersey, **1992**, pp. 11–64.
- [4] G. Märkl, R. Hennig, K. M. Raab, *Chem. Commun.* **1996**, 2057–2058.
- [5] H. Kurata, T. Tanaka, T. Sauchi, T. Kawase, M. Oda, *Chem. Lett.* **1997**, 947–948.
- [6] K. Ley, E. Müller, R. Mayer, K. Scheffler, *Chem. Ber.* **1958**, *91*, 2670–2681.
- [7] M. Yoshifuji, I. Shima, N. Inamoto, K. Hirotsu, T. Higuchi, *J. Am. Chem. Soc.* **1981**, *103*, 4587–4589; M. Yoshifuji, I. Shima, N. Inamoto, K. Hirotsu, T. Higuchi, *J. Am. Chem. Soc.* **1982**, *104*, 6167.
- [8] E. Fluck, G. Heckmann in *Phosphorus-31 NMR Spectroscopy in Stereochemical Analysis* (Eds.: J. G. Verkade, L. D. Quin), VCH, New York, **1987**, pp. 61–113.
- [9] R. Appel in *Multiple Bonds and Low Coordination in Phosphorus Chemistry* (Eds.: M. Regitz, O. Scherer), Thieme, Stuttgart, **1990**, pp. 157–219.
- [10] J. Zhou, A. Rieker, *J. Chem. Soc. Perkin Trans. 2* **1997**, 931–938.
- [11] G. G. Aleksandrov, Y. T. Struchkov, D. I. Kalinin, M. G. Neigant, *Zh. Strukt. Khim.* **1973**, *14*, 852–858; R. West, J. A. Jorgenson, K. L. Stearley, J. C. Calabrese, *J. Chem. Soc. Chem. Commun.* **1991**, 1234–1235.
- [12] J. Q. Chambers in *The Chemistry of the Quinoid Compounds, Part 2* (Ed.: S. Patai), Wiley, London, **1974**, pp. 737–791; J. Q. Chambers in *The Chemistry of the Quinoid Compounds, Vol. 2, Part 2* (Eds.: S. Patai, Z. Rappoport), Wiley, Chichester, **1988**, pp. 719–758.
- [13] M. Geoffroy, A. Jouaiti, G. Terron, M. Cattani-Lorente, Y. Ellinger, *J. Phys. Chem.* **1992**, *96*, 8241–8245.
- [14] J. R. Morton, K. F. Preston, *J. Magn. Reson.* **1978**, *30*, 577–582.
- [15] M. Culcasi, G. Gronchi, J. Escudié, C. Couret, L. Pujol, P. Tordo, *J. Am. Chem. Soc.* **1986**, *108*, 3130–3132; A. J. Bard, A. H. Cowley, J. E. Kilduff, J. K. Leland, N. C. Norman, M. Pakulski, G. A. Heath, *J. Chem. Soc. Dalton Trans.* **1987**, 249–251; S. Shah, S. C. Burdette, S. Swavey, F. L. Urbach, J. D. Protasiewicz, *Organometallics* **1997**, *16*, 3395–3400.
- [16] M. Geoffroy, E. A. C. Lucken, C. Mazeline, *Mol. Phys.* **1974**, *28*, 839–845; B. Çetinkaya, A. Hudson, M. F. Lappert, H. Goldwhite, *J. Chem. Soc. Chem. Commun.* **1982**, 609–610.
- [17] A. Altomare, M. C. Burla, M. Camalli, M. Cascarano, C. Giacovazzo, A. Guagliardi, G. Polidori, *J. Appl. Crystallogr.* **1994**, *27*, 435.
- [18] P. T. Beusken, G. Admiraal, G. Beusken, W. P. Bosman, R. de Gelder, R. Israel, J. M. M. Smits, The DIRDIF-94 program system, Technical Report of the Crystallography Laboratory, University of Nijmegen, The Netherlands, **1994**.
- [19] Crystal Structure Analysis Package, Molecular Structure Corporation, **1985** and **1992**.

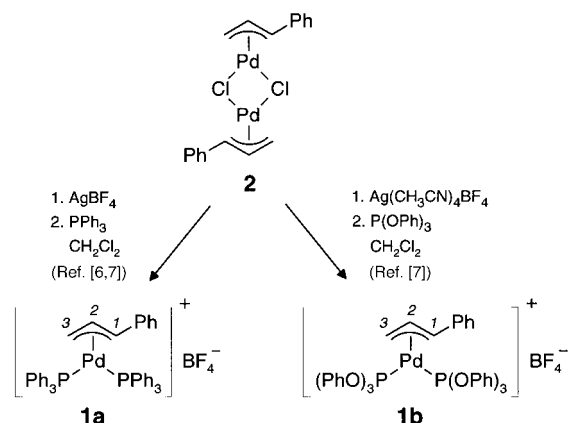
Kinetics and Mechanisms of the Reactions of π -Allylpalladium Complexes with Nucleophiles**

Oliver Kuhn and Herbert Mayr*

Dedicated to Professor Wolfgang Steglich on the occasion of his 65th birthday

Palladium(0)-catalyzed allylations of nucleophiles proceed under mild conditions, often with high regio- and stereo-selectivity.^[1] Detailed mechanistic investigations revealed that these reactions generally involve the intermediacy of cationic allylpalladium complexes which have been isolated and characterized by X-ray crystallography.^[2] In the course of our program to quantify the reactivities of cationic electrophiles^[3] we have now turned to palladium-stabilized allyl cations. Herein we report on the kinetics of the reactions of the allylpalladium complexes **1a** and **1b** with noncharged nucleophiles, and we demonstrate how to employ the electrophilicity parameters derived therefrom for analyzing the reactivities of these cationic complexes.

The allylpalladium complexes **1a**, **b**^[4] were synthesized from **2**^[5] using known procedures^[6, 7] (Scheme 1). The reaction products **4a–f** were obtained from the nucleophiles **3a–f** and



Scheme 1. Synthesis of the complexes **1a**-BF₄ and **1b**-BF₄ from **2**.

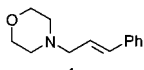
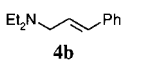
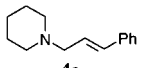
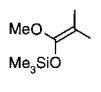
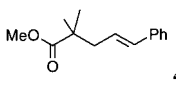
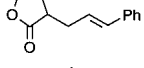
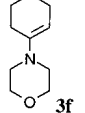
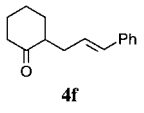
the allyl complexes **1a** and **1b**, either by employing stoichiometric quantities of the allylpalladium tetrafluoroborates **1a**-BF₄ or **1b**-BF₄ or by generating **1a** and **1b** in situ in the presence of the nucleophiles **3** from [Pd(PPh₃)₄] or [Pd₂(dba)₃·CHCl₃]/P(OPh)₃ (10 mol %) and 3-phenylallyl acetate, as specified in Table 1 (Scheme 2; dba = dibenzylideneacetone).

To determine the reaction kinetics, the allyl complexes **1a**-BF₄ and **1b**-BF₄ were prepared and combined with 10–50 equivalents of the nucleophiles **3a–f**, and the decay of the

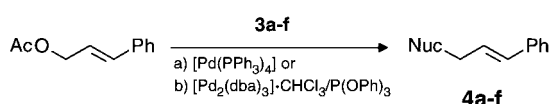
[*] Prof. Dr. H. Mayr, Dr. O. Kuhn
Institut für Organische Chemie der Universität
Karlstrasse 23, D-80333 München (Germany)
Fax: (+49)89-5902-254
E-mail: hmyr@cup.uni-muenchen.de

[**] We thank C. Schlierf for experimental contributions as well as the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for financial support.

Table 1. Products and rate constants (20 °C, CH₂Cl₂) of the reactions of **1a** and **1b** with the nucleophiles **3a–f**.

Nucleophile	Product	Yield [%]	Pd complex	<i>k</i> [L mol ⁻¹ s ⁻¹] (number of experiments)
		61 ^[a]	1a -BF ₄	4.49 ± 0.30 (3)
		67 ^[a]	1a -BF ₄ 1a -PF ₆ 1a -BF ₄ ^[h] 1a -BF ₄ ^[i] average value	7.53 ± 0.18 (4) 7.03 ± 0.40 (2) 7.30 6.49 7.25 ± 0.42 (8)
		61 ^[a]	1a -BF ₄ 1a -PF ₆ average value	29.9 ± 1.2 (6) 36.8 30.9 ± 2.8 (7)
		70 ^[e] 69 ^[b]	1a -BF ₄ 1b -BF ₄	0.35 ± 0.03 ^[f] (4)
		52 ^[b]	1b -BF ₄	4.49 ± 0.23 (3)
		55 ^[g]	1b -BF ₄	17.5 ± 2.1 (4)

[a] Reaction of 3-phenylallyl acetate with **3** in the presence of [Pd(PPh₃)₄] (10 mol %). [b] Dropwise addition of 3-phenylallyl acetate and **3** to a solution of [Pd₂(dba)₃·CHCl₃] (10 mol %) and P(OPh)₃. [c] Calculated from Δ*H*[‡] = (32.74 ± 2.05) kJ mol⁻¹ and Δ*S*[‡] = (–68.35 ± 9.49) J mol⁻¹ K⁻¹ (six experiments in the range between –72 and –31 °C). [d] Calculated from Δ*H*[‡] = (26.18 ± 1.53) kJ mol⁻¹ and Δ*S*[‡] = (–84.29 ± 6.99) J mol⁻¹ K⁻¹ (six experiments in the range between –72 and –30 °C). [e] Reaction of **3d** with stoichiometric amounts of **1a**-BF₄. [f] The ¹H NMR spectroscopic investigation in CDCl₃ yielded *k* = 0.2 L mol⁻¹ s⁻¹. [g] Reaction of **3f** with stoichiometric amounts of **1b**-BF₄. [h] Under addition of 3 equivalents of toluene. [i] Under addition of 5 equivalents of fumaronitrile.



Scheme 2. Palladium-catalyzed synthesis of **4a–f**.

absorbance at 350 nm (**1a**) or 330 nm (**1b**) was determined by using an immersion probe and fiber optics.^[8] The pseudo first-order rate constants were found to depend linearly on the concentrations of the nucleophiles, indicating a second-order rate law. The observation of isosbestic points (Figure 1) rules out the appearance of long-lived intermediates.

Neither the replacement of BF₄[–] by PF₆[–] nor the addition of toluene or fumaronitrile (additives for trapping PdL₂ fragments^[9]) affected the reaction rates noticeably (Table 1).

In accord with these findings we suggest the mechanism outlined in Scheme 3.^[10] While the initial attack of the nucleophiles at the metal centers of **1a** and **1b** cannot be excluded by the kinetic data, the direct nucleophilic attack at the allyl ligand, as depicted in Scheme 3, is highly probable in

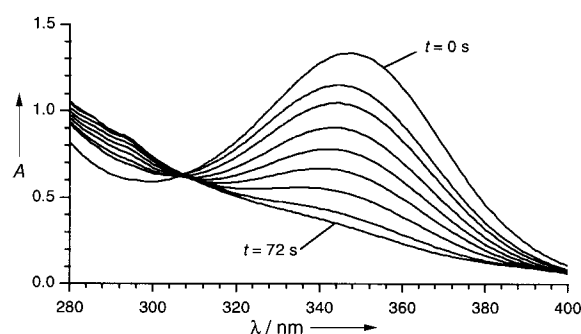
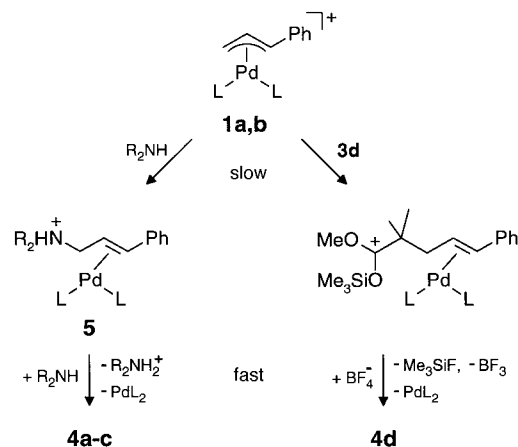


Figure 1. UV spectra during the reaction of the complex **1a**-BF₄ with diethylamine **3b** (CH₂Cl₂, 20 °C).



Scheme 3. Proposed mechanism of the synthesis of **4a–d**, which proceeds via **1a, b**.

view of the stereoselectivities of the reactions of related allylpalladium complexes with amines^[11] and silylated ketene acetals.^[12] Identical rates for the disappearance of the reactants and the appearance of **4d** were found when the reaction of **1b**-BF₄ with **3d** was monitored by ¹H NMR spectroscopy, in accord with the mechanism in Scheme 3. The rate constant determined from NMR spectra in CDCl₃ is 35 % smaller than that determined from UV spectra in CH₂Cl₂,^[13] corroborating the internal consistency of these kinetic data.

In previous work we have shown that the reactions of cationic metal π complexes^[14] with noncharged nucleophiles follow the same linear free enthalpy relationship [Eq. (1);

$$\lg k = s(E + N) \quad (1)$$

E = electrophilicity parameter, *N* = nucleophilicity parameter, *s* = nucleophile-specific slope parameter] as the corresponding reactions of ordinary carbocations.^[3] It seemed probable, therefore, that the rate constants summarized in Table 1 could be reproduced by Equation (1). However, since reliable reactivity parameters for the amines **3a–c** are not available at present, only the *E* parameter of **1b** can be determined by substituting the lg *k* value and the *N* and *s* parameters of **3d–f** into Equation (1).

In spite of its relatively large error limit, the electrophilicity parameter *E*(**1b**) = –10.1 ± 0.8 (Table 2) provides a semi-quantitative characterization of the electrophilic reactivity of **1b**, since the *E* value is based on reactions with nucleophiles

Table 2. Determination of the electrophilicity parameter E for the allylpalladium complex **1b**.

Nucleophile	N	s	$\lg k^{[a]}$	E
3d	9.49 ^[b]	0.93 ^[b]	-0.45	-10.0
3e	11.7 ^[b]	0.93 ^[b]	0.65	-11.0
3f	10.5 ^[c]	1	1.24	-9.3

[a] From Table 1 of this work. [b] Ref. 15. [c] H. Mayr, A. R. Ofial, K.-H. Müller, N. Hering, unpublished results.

of large structural variety (Table 2). The relative reactivities of the complexes **1a** and **1b** towards diethylamine and piperidine (Table 1) yield $E(\mathbf{1a}) \approx -12.5$. Because of the higher electron-donating ability of $\text{P}(\text{Ph})_3$ compared to $\text{P}(\text{OPh})_3$, **1a** is two orders of magnitude less electrophilic than **1b**.

The E parameters thus derived now allow one to compare the reactivities of **1a** and **1b** with those of other electrophiles. As shown in Figure 2, the palladium complexes **1a** and **1b** are

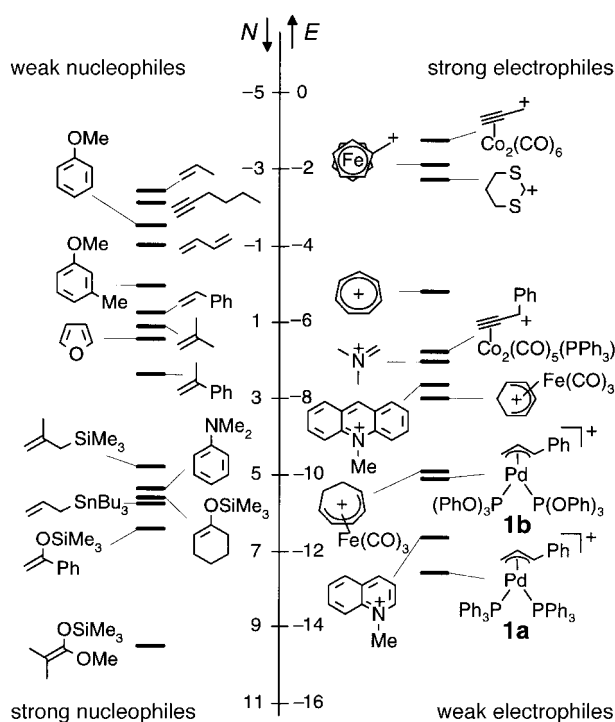
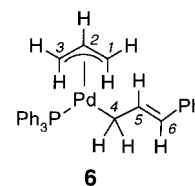


Figure 2. Combination of the electrophilicity and the nucleophilicity scale.

considerably weaker electrophiles than dicobalt-coordinated propargyl cations,^[14c] the tropylium ion,^[3a] or iminium ions.^[16] By using the respective electrophilicities as criteria, **1b** corresponds to the tricarbonylironcycloheptadienyl ion,^[14a] while **1a** corresponds to the N -methylquinolinium ion.

The approximation $s \approx 1$, which holds for most nucleophiles, implies the rule of thumb that electrophiles and nucleophiles which are located on an equal level in Figure 2 ($N + E = -5$) will combine slowly at room temperature, whereas electrophiles will not react with nucleophiles which are located above them.^[3] The applicability of this rule to reactions of allylpalladium complexes is limited, however: Because of the ambident electrophilic character of **1**, reactions with nucleophiles may either occur at the allyl ligand or at the metal center. The latter reaction is not covered by Equation (1).

This is exemplified by the fact that the reaction of **1a** with allyltributylstannane, which does not follow clear-cut second-order kinetics, is approximately 10^4 times faster than predicted by Equation (1). The NMR spectroscopic monitoring of this reaction showed the formation of the bisallyl complex **6**,^[17] indicating the attack of allylstannane at the palladium center, in accord with literature reports.^[18]



Equation (1) and Figure 2, therefore, allow one to predict that only nucleophiles with $N > 6-7$ may attack directly at the allylic ligand of **1a** and **1b**. If reactions with weaker nucleophiles take place, they must proceed by initial attack at the metal center, which has consequences for the regio- and stereoselectivities.

Received: August 7, 1998 [Z12264IE]
German version: *Angew. Chem.* **1999**, *111*, 356–358

Keywords: allyl complexes • carbocations • kinetics • palladium • reaction mechanisms

- [1] a) B. M. Trost, T. R. Verhoeven in *Comprehensive Organometallic Chemistry*, Vol. 8 (Eds.: G. Wilkinson, F. G. A. Stone, E. W. Abel), Pergamon, Oxford, **1982**, pp. 799–938; b) S. Godleski in *Comprehensive Organic Synthesis*, Vol. 4 (Eds.: B. M. Trost, I. Fleming, M. F. Semmelhack), Pergamon, Oxford, **1991**, pp. 585–659; c) B. M. Trost, D. L. Van Vranken, *Chem. Rev.* **1996**, *96*, 395–422; d) P. von Matt, G. C. Lloyd-Jones, A. B. E. Minidis, A. Pfaltz, L. Macko, M. Neuburger, M. Zehnder, H. Rüegger, P. S. Pregosin, *Helv. Chim. Acta* **1995**, *78*, 265–284; e) J. Sprinz, M. Kiefer, G. Helmchen, M. Reggelin, G. Huttner, O. Walter, L. Zsolnai, *Tetrahedron Lett.* **1994**, *35*, 1523–1526; f) A. Stolle, J. Ollivier, P. P. Piras, J. Salaün, A. de Meijere, *J. Am. Chem. Soc.* **1992**, *114*, 4051–4067.
- [2] a) P. S. Manchand, H. S. Wong, J. F. Blount, *J. Org. Chem.* **1978**, *43*, 4769–4774; b) N. W. Murall, A. J. Welch, *J. Organomet. Chem.* **1986**, *301*, 109–130; c) D. P. Grant, N. W. Murall, A. J. Welch, *J. Organomet. Chem.* **1987**, *333*, 403–414.
- [3] a) H. Mayr, M. Patz, *Angew. Chem.* **1994**, *106*, 990–1010; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 938–957; b) H. Mayr, O. Kuhn, M. F. Gotta, M. Patz, *J. Phys. Org. Chem.* **1998**, *11*, 642–654.
- [4] Physical properties: O. Kuhn, Dissertation, Universität München, **1998**.
- [5] P. R. Auburn, P. B. Mackenzie, B. Bosnich, *J. Am. Chem. Soc.* **1985**, *107*, 2033–2046.
- [6] R. R. Schrock, J. A. Osborn, *J. Am. Chem. Soc.* **1971**, *93*, 3089–3091.
- [7] B. Åkermark, B. Krakenberger, S. Hansson, A. Vitagliano, *Organometallics* **1987**, *6*, 620–628.
- [8] H. Mayr, R. Schneider, C. Schade, J. Bartl, R. Bederke, *J. Am. Chem. Soc.* **1990**, *112*, 4446–4454.
- [9] a) B. Crociani, S. Antonaroli, F. Di Bianca, L. Canovese, F. Visentin, P. Uguagliati, *J. Chem. Soc. Dalton Trans.* **1994**, 1145–1151; b) P. B. Mackenzie, J. Whelan, B. Bosnich, *J. Am. Chem. Soc.* **1985**, *107*, 2046–2054.
- [10] In contrast, the first step of the aminations of allylpalladium complexes containing stronger donor ligands (chloride, amines) is reversible, and the deprotonation of the allylammonium ions (e.g. **5**) becomes rate-determining, resulting in a second-order dependence of the rates on amine concentration: A. Vitagliano, B. Åkermark, *J. Organomet. Chem.* **1988**, *349*, C22–C26.
- [11] A ratio of 93:7 to 86:14 for *trans*:*cis* attack was observed for the additions of secondary amines to (4-methoxy-1,2,3- η^3 -cyclohexenyl)-palladium tetrafluoroborates: J.-E. Bäckvall, R. E. Nordberg, K. Zetterberg, B. Åkermark, *Organometallics* **1983**, *2*, 1625–1629.
- [12] C. Carfagna, L. Mariani, A. Musco, G. Sallase, R. Santi, *J. Org. Chem.* **1991**, *56*, 3924–3927.

- [13] The solvent dependence of the reactions of cationic electrophiles with neutral nucleophiles was shown in Table 1 of ref. [3a].
- [14] a) Tricarbonyldienyliron cations: H. Mayr, K.-H. Müller, D. Rau, *Angew. Chem.* **1993**, *105*, 1732–1734; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1630–1632; b) ferrocenylmethyl cations: H. Mayr, D. Rau, *Chem. Ber.* **1994**, *127*, 2493–2498; c) hexacarbonylpropargyldicobalt cations: O. Kuhn, D. Rau, H. Mayr, *J. Am. Chem. Soc.* **1998**, *120*, 900–907.
- [15] J. Burfeindt, M. Patz, M. Müller, H. Mayr, *J. Am. Chem. Soc.* **1998**, *120*, 3629–3634.
- [16] H. Mayr, A. R. Ofial, *Tetrahedron Lett.* **1997**, *38*, 3503–3506.
- [17] ¹H NMR (400 MHz, CD₂Cl₂): δ = 1.98 (d, *J* = 7.3 Hz, 2H, 4-H), 3.14–3.47 (m, 2H, 1-H-*anti*, 3-H-*anti*), 4.02 (d, *J* = 6.8 Hz, 2H, 1-H-*syn*, 3-H-*syn*), 5.33–5.46 (m, 1H, 2-H), 6.21 (d, *J* = 15.7 Hz, 1H, 6-H), 6.41–6.52 (m, 1H, 5-H), 7.11–7.45 (m, Ph).
- [18] a) A. Goliaszewski, J. Schwartz, *Organometallics* **1985**, *4*, 417–419; b) A. Goliaszewski, J. Schwartz, *Tetrahedron* **1985**, *24*, 5779–5789; see also: B. Henc, P. W. Jolly, R. Salz, S. Stobbe, G. Wilke, R. Benn, R. Mynott, K. Seevogel, R. Goddard, C. Krüger, *J. Organomet. Chem.* **1980**, *191*, 449–475.

The 2-*N,N*-Dibenzylamino Group as a Participating Group in the Synthesis of β-Glycosides**

Hailong Jiao and Ole Hindsgaul*

2-Amino-2-deoxyglycopyranosides are important constituents of proteoglycans, glycoproteins, peptidoglycans, and glycolipids, which are widely distributed in living organisms or plants.^[1,2] Most are N-acetylated and are present in 1,2-*trans*-glycosidic linkages. Numerous synthetic approaches to this class of glycosidic linkage have been developed. Because of its nucleophilicity, the amino functionality is always protected during the glycosylation reaction to avoid N-glycosylation, and the choice of protecting group can provide control of stereoselectivity. The most commonly used method for the construction of 1,2-*trans*-glycosidic linkages employs 2-amino sugar donors that contain a participating group as the amino-protecting functionality. The ideal amino protecting group should be stable and impart sufficient reactivity, stereoselectivity, and high yield in glycosylation reactions. Moreover, the protecting group should be readily removed under mild conditions and in high yield.

Many amino protecting groups have been developed for the 1,2-*trans*-glycosylation of 2-amino sugars. The *N*-phthalimido (NPhth)^[3] group is most widely used for this purpose. The *N*-acetamido (NHAc) group has also been used,^[2] but the oxazolinium intermediate **1** (Figure 1), which is presumed to

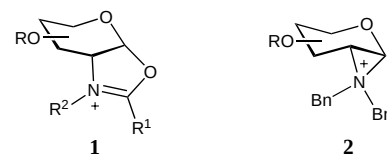


Figure 1. Postulated intermediates in glycosylation reactions. R = Bn, R¹ = Me, R² = Ph; Bn = benzyl.

be formed in the glycosylation reaction, is rather stable and makes this donor unreactive. Generation of a free amine from either NPhth or NHAc requires strongly basic conditions that often cause partial decomposition of the product.^[4] A number of alternative amino protecting groups have therefore been developed. These include *N*-4,5-dichlorophthaloyl (NDCPhth),^[5a] *N*-tetrachlorophthaloyl (NTCPhth),^[5b, c] *N*-2,2,2-trichloroethoxycarbonyl (NTroc),^[5d] *N*-trichloroacetyl (NCOCl₃),^[5e] *N*-dichloroacetyl (NCOCHCl₂),^[5f] *N*-monochloroacetyl (NCOCH₂Cl),^[5g] *N*-trifluoroacetyl (NCOCF₃),^[5h] *N*-sulfonyl (NSO₂Ph),^[5i] *N,N*-diacetyl (NAC₂),^[5j] *N*-acetyl-*N*-2,2,2-trichloroethoxycarbonyl (NACTroC),^[5k] and *N*-*p*-nitrobenzyloxycarbonyl (PNZ).^[5l] These protecting groups have proven very useful.

In the course of a program on the preparation of N-linked oligosaccharide analogues, we found that attempted synthesis of the β-GalNPhth(1→2)α-Man linkage resulted in an unusually high proportion of α-linked disaccharide, despite the expected participation of the NPhth group. A similar situation had been previously encountered.^[6] A β:α mixture (3:1, 75% yield) was formed on glycosylation of acceptor **7** with the tri-*O*-benzyl-NPhth-thioglycoside donor **8** (see Scheme 1). This was presumably due to a “mismatch”^[7] in the donor–acceptor pair, and we therefore sought out an alternative donor that would not result in an intermediate similar to the oxazolinium ion **1**. In the search for such a donor, we also recognized that the final deprotection step in almost all synthetic schemes for oligosaccharides involves the removal of persistent *O*-benzyl ether groups by hydrogenolysis. We therefore elected to examine the *N,N*-dibenzylthioglycoside donor **6** as a potential glycosylation agent. 2-Amino sugars bearing *N*-alkyl groups have not previously been used as glycosylation donors, presumably because of the expected problematic N-glycosylation.

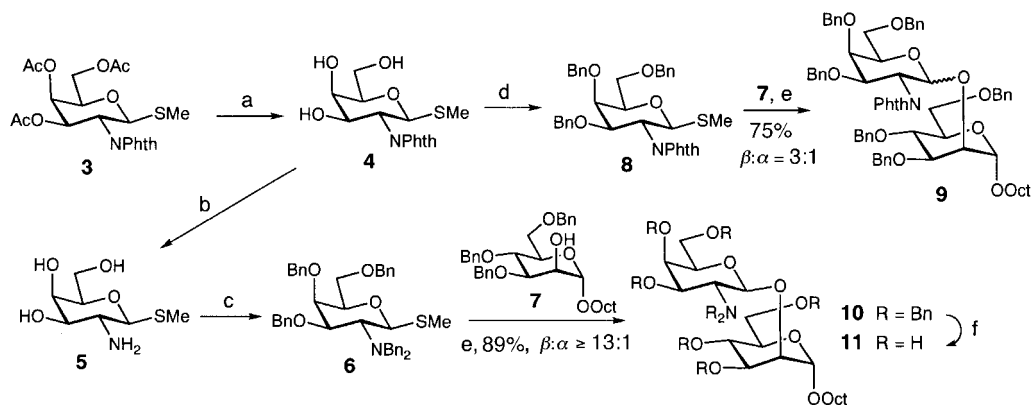
The donors **6** and **8** were prepared as shown in Scheme 1. Removal of the phthalimido group in **4** followed by *O*- and *N*-benzylation with BnBr and NaH in DMF provided **6** in 85% overall yield. Treatment of **4**, which is obtained from **3**,^[8] with BnBr and NaH in the presence of Bu₄NI in DMF gave **8** in high yield (88%).

To evaluate **6** as a glycosyl donor for the synthesis of the 2-amino-2-deoxy-β-D-galactopyranosyl-(1→2)-α-D-mannopyranoside sequence, we condensed it with octyl 3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (**7**)^[9] in the presence of the neutral promoter dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSBF₄)^[10] (Scheme 1). The glycosylation with **6** resulted in excellent β-selectivity (β:α ≥ 13:1) and high yield (86%). One-step deprotection of **10** by hydrogenolysis gave the free amine **11** in 94% yield.

We then investigated the behavior of **6** with the partially protected galactopyranosides **12–15**,^[9] which represent a

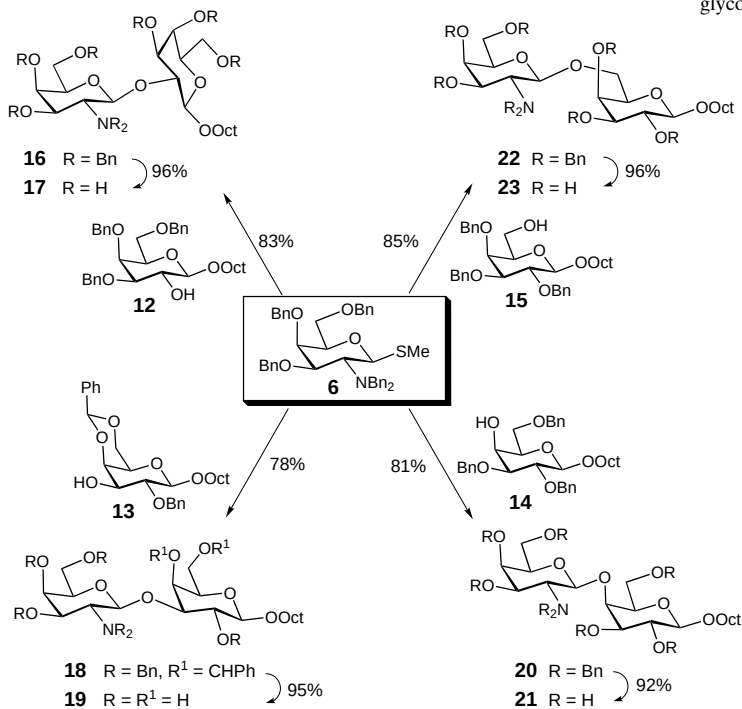
[*] Prof. O. Hindsgaul, H. Jiao
Department of Chemistry
University of Alberta
Edmonton, Alberta, T6G 2G2 (Canada)
Fax: (+1) 403-492-7705
E-mail: ole.hindsgaul@ualberta.ca

[**] We thank Dr. A. Morales-Isquierdo for measuring the high-resolution mass spectra (ES) on a Macromass ZabSpec Hybrid Sector-TOF, and Dr. A. Otter for recording the NMR spectra on a Varian-INOVA 600 spectrometer. This work was supported by PENCE and NSERC of Canada.



Scheme 1. Synthesis of donors **6** and **8**. a) NaOMe (0.02 M), MeOH, room temperature (RT), 1 h; b) $\text{NH}_2\text{NH}_2/\text{EtOH}$ (1/10), reflux; c) BnBr (7.5 equiv), NaH (10 equiv), DMF, $0^\circ\text{C} \rightarrow \text{RT}$, overnight, 85% (over three steps a–c); d) BnBr (4.5 equiv), NaH (9 equiv), Bu_4NI (9 equiv), DMF, $0^\circ\text{C} \rightarrow \text{RT}$, 4 h, 88%; e) **6** or **8** (2 equiv), DMTBSF_4 (4 equiv), 4-Å molecular sieves, CH_2Cl_2 , $-30 \rightarrow 0^\circ\text{C}$, 2 h; f) $\text{Pd}(\text{OH})_2/\text{C}$, H_2 , HCl (0.2%), EtOH, 3 h, 94%.

spectrum of acceptor reactivities (Scheme 2). The glycosylation was carried out in a range of solvents, and dichloromethane emerged as the preferred solvent (Table 1). Reaction of **6** with the **12**–**15** in the presence of DMTBSF_4 and 4-Å molecular sieves in dichloromethane gave the protected disaccharides **16**, **18**, **20**, and **22** in good yields (>78%) and high β -selectivities ($\beta:\alpha > 11:1$; Table 1). The glycosylation rates and yields were similar for both primary and secondary sugar alcohols. Hydrogenolysis of disaccharides **16**, **18**, **20**, and **22** over Pearlman's catalyst in ethanol with 0.2% HCl smoothly removed O- and N-benzyl groups. Subsequent purification by C-18 Sep-Pak adsorption^[11] gave the deprotected disaccharides **17**, **19**, **21**, and **23** in yields of over 92% (Scheme 2).



Scheme 2. Reaction of **6** with various partially protected galactopyranosides. Synthesis of **16**, **18**, **20**, and **22**: a) **6** (2 equiv), DMTBSF_4 (4 equiv), 4-Å molecular sieves, CH_2Cl_2 , $-30 \rightarrow 0^\circ\text{C}$, 2 h. Deprotection to **17**, **19**, **21**, and **23**: b) $\text{Pd}(\text{OH})_2/\text{C}$, H_2 , HCl (0.2%), EtOH, 3 h.

Table 1. Reaction of glycosyl donors **6** and **8** with glycosyl acceptors **7** and **12**–**15**.

Glycosyl donor	Glycosyl acceptor	Solvent	Reaction time [h]	Yield ^[a] [%]	$\beta:\alpha$ ^[b]
6	15	$\text{CCl}_4/\text{CH}_2\text{Cl}_2$ (10:1)	10	67	2:1
6	14	$\text{CCl}_4/\text{CH}_2\text{Cl}_2$ (10:1)	10	54	10:1
6	13	$\text{CCl}_4/\text{CH}_2\text{Cl}_2$ (10:1)	10	59	3:1
6	15	$\text{MeCN}/\text{CH}_2\text{Cl}_2$ (3:1)	8	85	5:1
6	14	$\text{MeCN}/\text{CH}_2\text{Cl}_2$ (3:1)	8	62	11:1
6	13	$\text{MeCN}/\text{CH}_2\text{Cl}_2$ (3:1)	8	70	10:1
6	15	CH_2Cl_2	2	85	18:1
6	14	CH_2Cl_2	2	81	50:1
6	13	CH_2Cl_2	2	78	11:1
6	12	CH_2Cl_2	2	83	>50:1
6	7	CH_2Cl_2	2	86	13:1
8	7	CH_2Cl_2	2	75	3:1

[a] Yield of products purified by column chromatography and based on glycosyl acceptor. [b] Ratio determined by ^1H NMR spectroscopic analysis.

In summary, thioglycoside **6** is a new and mechanistically different glycosyl donor. The glycosidic linkage is formed with high β/α -stereoselectivity and in excellent yield for a range of challenging acceptors. Although we have no direct evidence, the intermediacy of **2** (Figure 1) likely accounts for the net retention of configuration at C1. The N-benzyl groups can be removed very efficiently by hydrogenolysis, which obviates the need for harsh basic or alternative chemical reactions for N-deprotection. We propose that, because of the unique sp^3 hybridization of the nitrogen atom in donor **6**, such donors represent very useful alternatives when the use of N-acylated donors results in low yields or poor stereoselectivities. The behavior of N,N-dibenzyl-protected acceptors in glycosylation reaction is under investigation.

Experimental Section

6: To a solution of **5** (300 mg, 1.4 mmol) in DMF (25 mL) at 0°C was added NaH (430 mg, 80%, 14.4 mmol). The mixture was stirred for 30 min at room temperature, and then BnBr (1.3 mL, 10.8 mmol) was added. After 10 h the mixture was worked up and subjected to column chromatography to give **6** (850 mg,

90%). ¹H NMR (CDCl₃): δ = 4.85 (d, 2H, *J* = 11.5 Hz, 2 × OCHPh), 4.61 (d, 1H, *J* = 11.5 Hz, OCHPh), 4.55 (d, 1H, *J* = 11.5 Hz, OCHPh), 4.48, 4.43 (2d, 2H, *J* = 11.5 Hz, OCH₂Ph), 4.32 (d, 1H, *J* = 10.0 Hz, H1), 4.15 (d, 1H, *J* = 2.5 Hz, H4), 3.86 (dd, 1H, *J* = 10.5, 2.5 Hz, H3), 3.79 (br, 4H, N(CH₂Ph)₂), 3.65–3.58 (m, 2H, 2 × H6), 3.47 (m, 1H, H5), 3.45 (t, 1H, *J* = 10.0 Hz, H2), 1.90 (s, 3H, SMe); selected ¹³C NMR data (CDCl₃): δ = 85.39, 82.22, 76.64, 74.27, 73.68, 72.21, 70.58, 68.87, 58.15, 12.15; HR-MS (ES): *m/z*: 660.3146 [M+H]⁺.

8: Compound **4** (190 mg, 0.56 mmol), NaH (85 mg, 95%, 3.36 mmol), and Bu₄NI (1.24 g, 3.36 mmol) in DMF (20 mL) were stirred for 30 min at room temperature, and then BnBr (0.4 mL, 3.36 mmol) was added. After 4 h the mixture was worked up and purified by column chromatography to give **8** (300 mg, 88%). ¹H NMR (CDCl₃): δ = 5.14 (d, 1H, *J* = 10.5 Hz, H1), 4.98 (d, 1H, *J* = 11.5 Hz, OCHPh), 4.85 (t, 1H, *J* = 10.5 Hz, H2), 4.60 (d, 2H, *J* = 12.0 Hz, 2 × OCHPh), 4.51, 4.46 (2d, 2H, *J* = 11.5 Hz, OCH₂Ph), 4.39 (dd, 1H, *J* = 11.0, 2.8 Hz, H3), 4.32 (d, 1H, *J* = 12.0 Hz, OCHPh), 4.10 (d, 1H, *J* = 2.8 Hz, H4), 3.83 (t, 1H, *J* = 6.5 Hz, H5), 3.66 (m, 2H, 2 × H6), 2.15 (s, 3H, SMe); selected ¹³C NMR data (CDCl₃): δ = 80.76, 77.53, 77.39, 74.53, 73.55, 72.37, 71.51, 68.50, 51.04, 11.05; HR-MS (ES): *m/z*: 610.2188 [M+H]⁺.

General procedure for glycosylation and deprotection: A mixture of glycosyl donor (2 equiv), alcohol acceptor (1 equiv), and 4-Å molecular sieves in dichloromethane was stirred for 1 h at room temperature, cooled to –30 °C, and treated with DMTSBF₄ (4 equiv). The temperature was increased to 0 °C over 2 h. Thin-layer chromatography (TLC) showed complete disappearance of starting alcohol. After workup and chromatographic purification, disaccharides **9**, **10**, **16**, **18**, **20**, and **22** were obtained. The yields and β:α ratios are shown in Table 1. Protected disaccharides **10**, **16**, **18**, **20**, and **22** were subjected to hydrogenolysis over Pd(OH)₂/C (10%) in EtOH with HCl (0.2%) for 3 h. The mixture was then filtered through a Millex-GV filter unit. The residue was purified with a C-18 Sep-Pak cartridge to give **11**, **17**, **19**, **21**, and **23**, respectively. The yields are shown in Scheme 2. Selected physical data are given in the following:

9: ¹H NMR (CDCl₃): δ = 5.14 (d, 1H, *J* = 3.5 Hz, H1), 5.23 (d, 1H, *J* = 8.5 Hz, H1').

10: ¹H NMR (CDCl₃): δ = 5.03 (d, 1H, *J* = 2.0 Hz, H1), 4.36 (d, 1H, *J* = 7.8 Hz, H1'); ¹³C NMR (CDCl₃): δ = 101.40 (C1'), 97.13 (C1), 59.05 (C2').

11: ¹H NMR (D₂O): δ = 4.98 (d, 1H, *J* = 1.7 Hz, H1), 4.38 (d, 1H, *J* = 8.3 Hz, H1'), 2.90 (dd, 1H, H2'); ¹³C NMR (D₂O): δ = 102.80 (*J*(C1',H1') = 160.6 Hz, C1'), 98.20 (*J*(C1',H1') = 170.7 Hz, C1'); HR-MS (ES): *m/z*: 454.6257 [M+H]⁺.

16: ¹H NMR (CDCl₃): δ = 5.01 (d, 1H, *J* = 8.0 Hz, H1'), 4.51 (d, 1H, *J* = 7.8 Hz, H1); ¹³C NMR (CDCl₃): δ = 102.60, 97.95 (C-1', C1).

17: ¹H NMR (D₂O): δ = 4.51 (d, 1H, *J* = 7.9 Hz, H1'), 3.0 (dd, 1H, H2'); HR-MS (ES): *m/z*: 454.2695 [M+H]⁺.

18: ¹H NMR (CDCl₃): δ = 5.06 (d, 1H, *J* = 8.0 Hz, H1'), 4.58 (d, 1H, *J* = 8.0 Hz, H1); ¹³C NMR (CDCl₃): δ = 103.00, 101.00 (C1', C1).

19: ¹H NMR (D₂O): δ = 4.53 (d, 1H, *J* = 8.1 Hz, H1'), 4.43 (d, 1H, *J* = 8.1 Hz, H1), 2.93 (dd, 1H, H2'); ¹³C NMR (D₂O): δ = 103.10 (*J*(C1',H1') = 160.2 Hz, C1), 105.90 (*J*(C1',H1') = 160.3 Hz, C1'); HR-MS (ES): *m/z*: 454.2652 [M+H]⁺.

20: ¹H NMR (CDCl₃): δ = 5.08 (d, 1H, *J* = 7.8 Hz, H1'), 4.36 (d, 1H, *J* = 8.0 Hz, H1); ¹³C NMR (CDCl₃): δ = 103.86, 100.88 (C1', C1).

21: ¹H NMR (D₂O): δ = 4.52 (d, 1H, *J* = 8.2 Hz, H1'), 4.41 (d, 1H, *J* = 7.9 Hz, H1), 2.90 (dd, 1H, H2'); ¹³C NMR (D₂O): δ = 103.50 (*J*(C1',H1') = 160.4 Hz, C1), 105.50 (*J*(C1',H1') = 161.7 Hz, C1'); HR-MS (ES): *m/z*: 454.2654 [M+H]⁺. **22:** ¹H NMR (CDCl₃): δ = 4.76 (d, 1H, *J* = 8.0 Hz, H1'), 4.42 (d, 1H, *J* = 7.7 Hz, H1); ¹³C NMR (CDCl₃): δ = 104.10, 102.49 (C1', C1).

23: ¹H NMR (D₂O): δ = 4.72 (d, 1H, *J* = 8.6 Hz, H1'), 4.42 (d, 1H, *J* = 8.1 Hz, H1), 3.22 (dd, 1H, H2'); HR-MS (ES): *m/z*: 454.2652 [M+H]⁺.

Received: July 14, 1998

Revised version: August 31, 1998 [Z12149IE]

German version: *Angew. Chem.* **1999**, *111*, 421–424

Keywords: glycosylations • oligosaccharides • protecting groups • thioglycosides

- [1] a) H. G. Garg, K. von dem Bruch, H. Kunz, *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 277–310; b) R. R. Schmidt, *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21–123; c) S. Umezawa, *Adv. Carbohydr. Chem. Biochem.* **1974**, *30*, 111–182.
- [2] J. Banoub, P. Boullanger, D. Lafont, *Chem. Rev.* **1992**, *92*, 1167–1195.
- [3] R. U. Lemieux, T. Takeda, B. Y. Chung, *A.C.S. Symp. Ser.* **1976**, *39*, 90–115.
- [4] J.-C. Michalski, J. Peter-Katalinic, H. Egge, J. Paz-parente, J. Montreuil, G. Strecker, *Carbohydr. Res.* **1984**, *134*, 177–189.
- [5] a) M. Lergenmuller, Y. Ito, T. Ogawa, *Tetrahedron* **1998**, *54*, 1381–1394; b) J. S. Debenham, R. Madsen, C. Robert, B. Fraser-Reid, *J. Am. Chem. Soc.* **1995**, *117*, 3302–3303; c) J. C. Castro-Palomino, R. R. Schmidt, *Tetrahedron Lett.* **1995**, *30*, 5343–5346; d) U. Ellervik, G. Magnusson, *Carbohydr. Res.* **1996**, *280*, 251–260; e) G. Blatter, J.-M. Beau, J.-C. Jacquinet, *Carbohydr. Res.* **1994**, *260*, 189–202; f) A. J. Acher, D. Shapiro, *J. Org. Chem.* **1969**, *34*, 2652–2654; g) T. Ziegler, *Carbohydr. Res.* **1994**, *262*, 195–212; h) W. Meyer zu Reckendorf, N. Wassiliadou-Micheli, *Chem. Ber.* **1970**, *103*, 1792–1796; i) D. A. Griffith, S. J. Danishefsky, *J. Am. Chem. Soc.* **1990**, *112*, 5811–5819; j) J. C. Castro-Palomino, R. R. Schmidt, *Tetrahedron Lett.* **1995**, *36*, 6871–6874; k) W. Dullenkopf, J. C. Castro-Palomino, L. Manzoni, R. R. Schmidt, *Carbohydr. Res.* **1996**, *296*, 135–147; l) X. Qian, O. Hindsgaul, *Chem. Commun.* **1997**, 1059–1060.
- [6] a) O. Kanie, S. C. Crawley, M. M. Palcic, O. Hindsgaul, *Carbohydr. Res.* **1993**, *243*, 139–164; b) M. Kobayashi, F. Yamazaki, Y. Ito, T. Ogawa, *Carbohydr. Res.* **1990**, *201*, 51–67.
- [7] N. M. Spijker, C. A. A. van Boeckel, *Angew. Chem.* **1991**, *103*, 179–182; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 180–183.
- [8] A. Hasegawa, T. Nagahama, H. Ohki, M. Kiso, *J. Carbohydr. Chem.* **1992**, *11*, 699–714.
- [9] H. Jiao, O. Hindsgaul, unpublished results.
- [10] Y. Ito, S. Nunomura, S. Shibayama, T. Ogawa, *J. Org. Chem.* **1992**, *57*, 1821–1831, and references therein.
- [11] M. M. Palcic, L. D. Heerze, M. Pierce, O. Hindsgaul, *Glycoconjugate J.* **1988**, *5*, 49–63.

Supramolecular Catalysis of Ester and Amide Cleavage by a Dinuclear Barium(II) Complex**

Roberta Cacciapaglia,* Stefano Di Stefano, Erik Kelderman, and Luigi Mandolini*

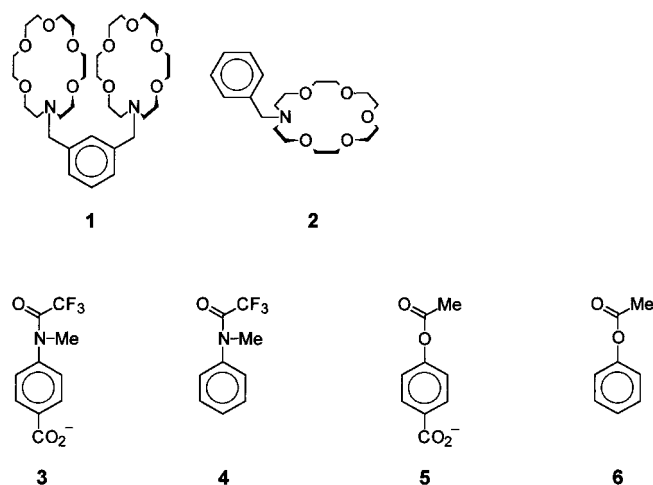
A most exciting development in supramolecular chemistry has been the design, synthesis, and evaluation of abiotic catalysts that share with natural enzymes a number of features related to efficient catalysis.^[1] Our research efforts are aimed at the development of prototype supramolecular catalysts by means of a modular approach in which an efficient catalytic unit for a given reaction and a receptor unit that is complementary to a nonreacting part of the substrate are covalently connected by means of a suitable spacer.

We have now considered the bis-barium(II) complex **1** · (Ba²⁺)₂ of the homoditopic ligand **1**, in which two aza[18]-

[*] Dr. R. Cacciapaglia, Prof. Dr. L. Mandolini, Dr. S. Di Stefano, Dr. E. Kelderman
Dipartimento di Chimica and Centro CNR
di Studio sui Meccanismi di Reazione
Università La Sapienza
Box 34–ROMA 62, I-00185 Roma (Italy)
Fax: (+390) 6-490421
E-mail: cacciapaglia@uniroma1.it
lmandolini@uniroma1.it

[**] The authors greatly acknowledge financial contributions from MURST, and from the HCM programme of the European Union.

crown-6 units are connected by an *m*-xylylene spacer, as a possible catalyst for the ethoxide-induced cleavage reactions of amide **3** and ester **5**. The two metal ions in the homobimetallic complex are expected to perform different functions, as



depicted in Figure 1. One of the metal ions would bind and activate the ethoxide ion nucleophile,^[2] while the other would serve as an anchoring group for the distal carboxylate of the substrate. The synergistic action of two metal centers has been used by several research groups in successful attempts to construct bifunctional enzyme models.^[3]

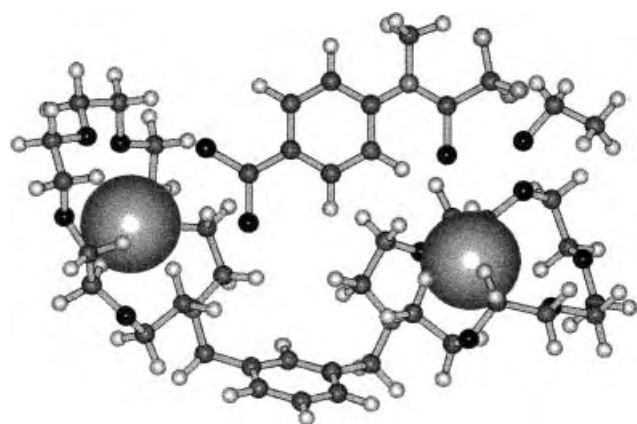


Figure 1. Computer-generated model of the complex between catalyst **1**·(Ba²⁺)₂, the ethoxide ion nucleophile, and the amide substrate **3** (structure **II** in Scheme 1).

A novel and distinctive feature of our catalyst is that substrate recognition takes place by means of a distal group, rather than the group(s) that undergo reaction.^[3] The rationale behind the design of our catalyst is well illustrated by the inhibition experiment plotted in Figure 2. The ethoxide ion of a ternary complex [(18C6)Ba(OEt)]⁺ (18C6 = [18]crown-6) cleaves trifluoroacetanilide^[4] (and phenyl acetate)^[5] much more rapidly than free ethoxide ion. Addition of increasing amounts of tetramethylammonium acetate causes a gradual drop of the rate of amide cleavage, until the reactivity of free ethoxide ion is eventually reached. This is consistent with the

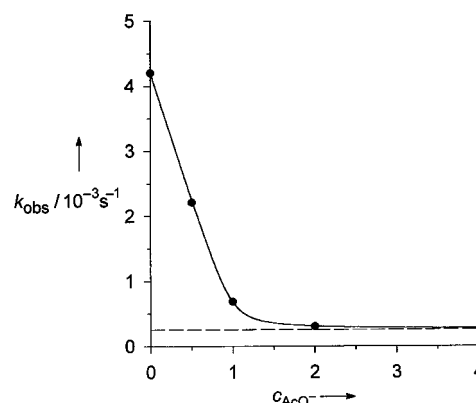
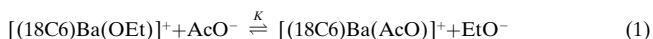


Figure 2. Influence of the amount of tetramethylammonium acetate (c_{AcO^-} , given in molar equivalents) on the rate of ethanolysis k_{obs} of **4** (0.054 mM) at 25°C and in the presence of a 5.0 mM 1:1:1 mixture of Me₄NOEt, Ba(SCN)₂, and 18C6. The solid line is calculated on the basis of the equilibrium of Eq. (1), with $K = 69$. The horizontal dashed line represents the reactivity of free ethoxide ion.

counterion exchange equilibrium [Eq. (1)], in which AcO[−] ion favorably competes with EtO[−] ion for the crown-complexed metal ion ($K = 69$).



Since the equilibrium constant for binding of EtO[−] ion to [(18C6)Ba]²⁺ is large ($K > 10^4 \text{ M}^{-1}$),^[5] it is concluded that anchorage of carboxylate ion to the metal ion is virtually quantitative ($K > 10^5 \text{ M}^{-1}$) under the conditions of the experiments listed in Table 1. Indeed we find that **1**·(Ba²⁺)₂ shows efficient catalysis in the ethoxide-induced cleavage reactions of anilide **3** and ester **5**, but not for the corresponding reactions of the parent compounds **4** and **6**. Furthermore, the bimetallic catalyst is superior to the barium complex of the monotopic ligand **2** for **3** and **5**, but for **4** and **6** the two catalysts show very nearly the same activity.^[6] Clearly, bifunctional catalysis is observed when the ditopic character of the

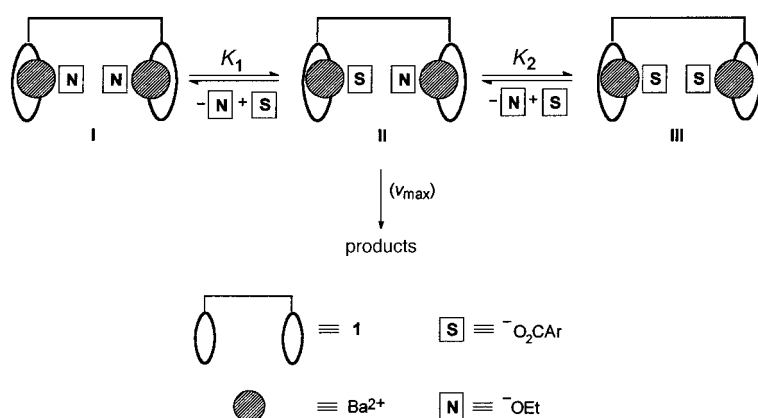
Table 1. Effect of additives on the basic ethanolysis of substrates **3–6**.^[a]

Substrate	Ba(SCN) ₂ [mM]	2 [mM]	1 [mM]	$k_{\text{obs}}^{[b]}$ [s ^{−1}]	k_{rel}
3	–	–	–	3.54×10^{-5}	1.0
	1.00	–	–	8.28×10^{-4}	23
	2.00	2.00	–	8.04×10^{-4}	23
	2.00	–	1.00	3.06×10^{-2}	865
4	–	–	–	5.10×10^{-5}	1.0
	1.00	–	–	2.16×10^{-4}	4.2
	2.00	2.00	–	2.47×10^{-4}	4.8
	2.00	–	1.00	3.64×10^{-4}	7.1
5	–	–	–	9.12×10^{-4}	1.0
	1.00	–	–	5.17×10^{-2}	57
	2.00	2.00	–	5.53×10^{-2}	61
	2.00	–	1.00	1.14	1250
6	–	–	–	1.44×10^{-3}	1.0
	1.00	–	–	4.80×10^{-2}	33
	2.00	2.00	–	5.86×10^{-2}	41
	2.00	–	1.00	5.07×10^{-2}	35

[a] Reaction conditions: 0.050 mM substrate, 1.00 mM Me₄NOEt, EtOH, 25°C. [b] First-order rate constants were determined from time-course kinetic studies. Error limits are in the order of $\pm 3–5\%$.

catalyst is combined with the presence of a carboxylate anchoring group.

Further analysis of the catalytic activity of **1**·(Ba²⁺)₂ was carried out in the presence of a large excess of EtO[−] ion, which causes the catalyst to be fully saturated with EtO[−] as shown by structure **I** in Scheme 1. According to the mecha-



Scheme 1. Equilibria leading to the productive and unproductive catalyst-substrate complexes **II** and **III**.

nism outlined in Scheme 1, addition of the amide substrate **3** would cause the gradual conversion of **I** into the 1:1 productive complex **II**, but further addition of **3** would yield the unproductive 1:2 complex **III**. As expected from this mechanism, a bell-shaped profile is observed in a plot of initial rate v_0 versus substrate concentration (Figure 3). A standard

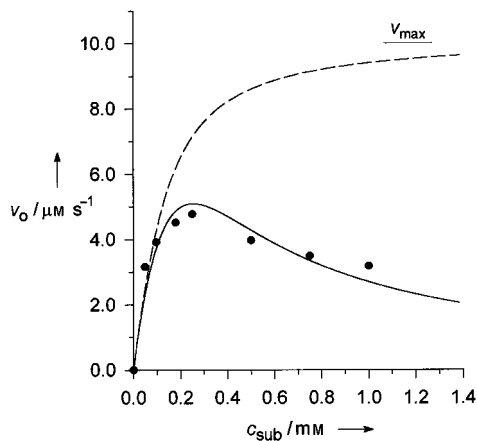


Figure 3. Plot of initial rate versus substrate concentration c_{sub} for the catalyzed ethanolsysis of **3**. Reaction conditions: 0.10 mM **1**, 0.20 mM Ba(SCN)₂, 5.00 mM Me₄NOEt. Calculation of the solid line is based on Scheme 1, with $v_{\max} = 1.0 \times 10^5 \text{ M s}^{-1}$, $K_1 = 65$, and $K_2 = K_1/4$ (see text). The dashed line is a Michaelis-Menten plot calculated without the K_2 equilibrium step shown in Scheme 1.

curve-fitting procedure based on Scheme 1 was used to obtain best fit for $v_{\max}$ and K_1 values, whereas K_2 was assigned the statistically corrected value of $K_1/4$ to avoid the use of too many variables. The fairly good quality of the fit supports the validity of Scheme 1. Highly significant is the finding that the K_1 value compares very well with the K value determined from the experiment plotted in Figure 2.^[7]

Also consistent with the proposed mechanism is the finding that catalytic ethanolsysis of **3** is inhibited by benzoate anion derivatives (Table 2). Anion **8** is a stronger inhibitor than **7**, on account of the presumably higher basicity of the former. Furthermore it is apparent that the affinity of **8** for the catalyst is twice as great as that of **3**. Since **8** is the reaction product, severe product inhibition is expected. Indeed we found that only four to five turnovers are seen in the ethanolsysis of **3** before product inhibition shuts down the reaction. The first two turnovers are shown graphically in Figure 4.

In conclusion, the bis-barium complex of **1** catalyzes the cleavage of amide and ester substrates endowed with a carboxylate anchoring group. The catalyst shows high structural recognition of the substrate, induces fairly high reaction rates with catalytic turnover, and is subjected to competitive inhibition by an inert substrate, as well as by the reaction product. Given the extreme structural

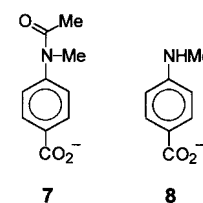


Table 2. Competitive inhibition of the catalyzed ethanolsysis of **3**.^[a, b]

Inhibitor ^[c]	v_0 [M s ^{−1}]	v_{rel}
none	3.9×10^{-6}	1.0
7	2.3×10^{-6}	0.59
8	1.3×10^{-6}	0.33

[a] Reaction conditions: 0.10 mM **1**, 0.20 mM Ba²⁺, 0.10 mM substrate, 5.00 mM Me₄NOEt, EtOH, 25 °C. [b] Determined from measurements of initial rates. Error limits are in the order of ± 5 –10%. [c] Inhibitor concentration is 0.10 mM.

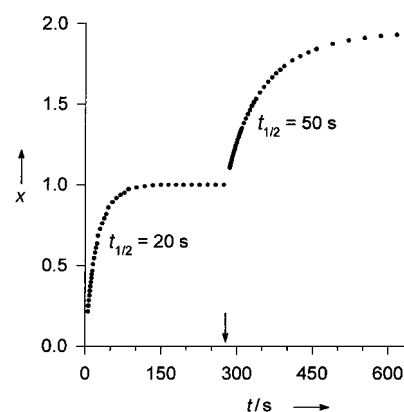


Figure 4. Turnover catalysis with product inhibition in the ethanolsysis of **3** under the conditions outlined in Figure 3. One molar equivalent of **3** is added at time zero. A second molar equivalent is added at the time indicated by the arrow. Further portions of **3** (1 mol equiv) solvolyze with increasingly lower rates (not shown in the plot). x = turnover number.

simplicity of precursor **1**, and the fact that the active form of the catalyst is spontaneously self-assembled when the separate components are mixed, our catalyst represents an extremely parsimonious realization of an artificial amidase/esterase. The function of the binding step is manifold. It selects the substrate, provides electronic activation to the

amide/ester group undergoing reaction,^[6] and converts reacting groups into neighboring groups. Based on the assumption that, under the conditions of the experiments listed in Table 1, only half of the catalyst is in the active form of a 1:1 ethoxide complex, rate enhancements for reactions catalyzed by the bimetallic vs. monometallic catalyst translate into an effective molarity (EM)^[8] value of 0.08 M for the reaction of **3** and one of 0.04 M for the reaction of **5**. We believe that the loss of entropy associated with torsional motions around two C–C and two C–N bonds is largely responsible for these relatively low EM values.^[8] Current work is aimed at the construction of more preorganized, and hopefully more efficient, catalysts.

Experimental Section

Ligands **1**^[9] and **2**^[10] and compounds **3**·H⁺,^[11] **4**,^[12] **5**·H⁺,^[13] and **7**·H⁺^[13] were prepared according to published procedures (melting points and/or spectral data in agreement with literature data). The compound **8**·H⁺ was a commercial sample. Acids **3**·H⁺, **5**·H⁺, **7**·H⁺, and **8**·H⁺ were converted in situ into the Me₄N⁺ salts by neutralization with Me₄NOEt. Spectrophotometric rate measurements were carried out in the thermostatted cell compartment of a Hewlett Packard HP 8452A diode array spectrometer. For initial rate measurements, a fast mixing accessory, HI-TECH SCIEN-TIFIC SFA-12, was connected to the spectrometer and the process was monitored at the isosbestic point for the free and the Ba²⁺-paired reaction product ($\lambda = 276$ nm). Other materials, apparatus and techniques were as reported previously.^[4, 5]

Received: July 31, 1998 [Z 122351E]
German version: *Angew. Chem.* **1999**, *111*, 359–362

Keywords: alkaline earth metals • enzyme mimetics • macrocyclic ligands • supramolecular chemistry

barium ion transforms an electron-donating (rate-retarding) carboxylate into an electron-withdrawing (rate-enhancing) carboxylate–metal ion pair.

- [7] The close similarity of the two values would indicate that the higher affinity for the monometallic complex of the more basic AcO[−] ion is substantially counterbalanced by the statistical factor 2 which operates in the binding of the less basic **3** to the bimetallic complex. The fact that the ligand is not exactly the same in the two cases is presumably unimportant.
- [8] The effective molarity (EM) for an intramolecular reaction is defined by the ratio $k_{\text{intra}}/k_{\text{inter}}$, where k_{inter} refers to the intermolecular model reaction. For a discussion of structure effects on the EM value see: a) A. J. Kirby, *Adv. Phys. Org. Chem.* **1980**, *17*, 183–278; b) L. Mandolini, *Adv. Phys. Org. Chem.* **1986**, *22*, 1–111.
- [9] M. R. Johnson, I. O. Sutherland, R. F. Newton, *J. Chem. Soc. Perkin Trans. 1* **1980**, 586–600.
- [10] M. R. Johnson, I. O. Sutherland, R. F. Newton, *J. Chem. Soc. Perkin Trans. 1* **1979**, 357–371.
- [11] A. Rosowsky, J. H. Freisheim, H. Bader, R. A. Forsch, S. A. Susten, C. A. Cucchi, E. Frei, *J. Med. Chem.* **1985**, *28*, 660–667.
- [12] E. J. Bourne, S. H. Henry, C. E. M. Tatlow, J. C. Tatlow, *J. Chem. Soc.* **1952**, 4014–4019.
- [13] F. D. Chattaway, *J. Am. Chem. Soc.* **1931**, 2495–2496.

Continuous Amination of Propanediols in Supercritical Ammonia**

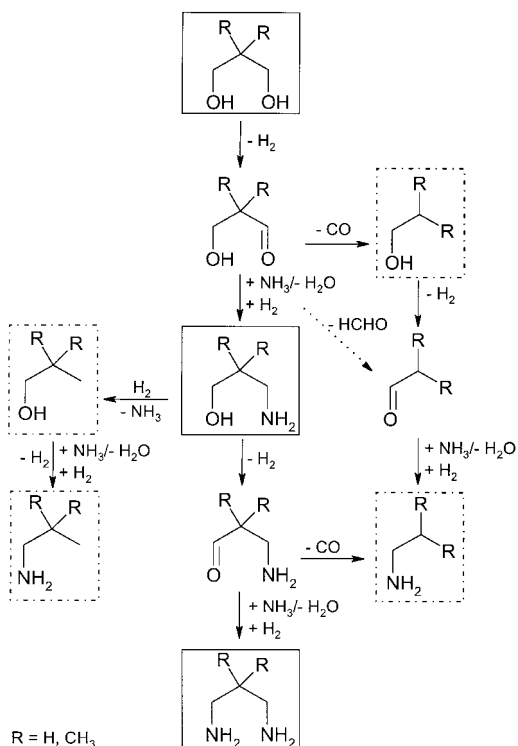
Achim Fischer, Tamas Mallat, and Alfons Baiker*

The heterogeneously catalyzed amination of alcohols has been established as the most important industrial process for the manufacture of a variety of aliphatic and aromatic amines.^[1–6] However, the yields and selectivities are usually rather low in the synthesis of primary aliphatic diamines from the corresponding diols and ammonia. The transformation of a simple aliphatic alcohol to the corresponding amine on a metal catalyst includes three major reaction steps (Scheme 1): 1) dehydrogenation to a carbonyl compound; 2) condensation with ammonia or an amine to form an imine or an enamine; and 3) hydrogenation to the corresponding amine.^[7, 8] Each intermediate and the product amine can undergo various side reactions such as condensation, decarbonylation, disproportionation, and hydrogenolysis.^[4, 9–11] The direct transformation of an aliphatic diol to the corresponding diamine requires the repetition of steps 1–3, which favors the formation of the by-product. In addition, the bifunctional intermediates extend the scope of possible side reactions (for example, oligomerization and cyclization).^[12, 13] However, reasonable yields have still been reported for the amination of alkanediols with secondary amines, as the tertiary amine product is moderately reactive.^[7, 14] Unfortunately, the situation is the reverse in aminations with ammonia, as the reactivities of the inter-

- [1] a) R. Breslow, *Acc. Chem. Res.* **1995**, *28*, 146–153; b) Y. Murakami, J. Kikuchi, Y. Hisaeda, O. Hayashida, *Chem. Rev.* **1996**, *96*, 721–758; c) A. J. Kirby, *Angew. Chem.* **1996**, *108*, 770–790; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 707–724; d) D. J. Cram, J. M. Cram, *Container Molecules and Their Guests*, The Royal Society of Chemistry, Cambridge, **1994**, pp. 65–84.
- [2] R. Cacciapaglia, L. Mandolini, *Chem. Soc. Rev.* **1993**, *22*, 221–231.
- [3] a) K. D. Karlin, *Science* **1993**, *261*, 701–708; b) N. N. Murthy, M. Mahroof-Tahir, K. D. Karlin, *J. Am. Chem. Soc.* **1993**, *115*, 10404–10405; c) D. H. Vance, A. W. Czarnik, *J. Am. Chem. Soc.* **1993**, *115*, 12165–12166; d) M. Yashiro, A. Ishikubo, M. Komiyama, *J. Chem. Soc. Chem. Commun.* **1995**, 1793–1794; e) M. W. Göbel, *Angew. Chem.* **1994**, *106*, 1201–1203; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1141–1143; f) H. Steinhagen, G. Helmchen, *Angew. Chem.* **1996**, *108*, 2489–2492; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2339–2342; g) M. Wall, R. C. Hynes, J. Chin, *Angew. Chem.* **1993**, *105*, 1696; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1633–1635; h) N. H. Williams, J. Chin, *Chem. Commun.* **1996**, 131–132; i) P. Hurst, B. K. Takasaki, J. Chin, *J. Am. Chem. Soc.* **1996**, *118*, 9982–9983; j) W. H. Chapman, Jr., R. Breslow, *J. Am. Chem. Soc.* **1995**, *117*, 5462–5469; k) T. Koike, M. Inoue, E. Kimura, M. Shiro, *J. Am. Chem. Soc.* **1996**, *118*, 3091–3099; l) K. G. Ragunathan, H.-J. Schneider, *Angew. Chem.* **1996**, *108*, 1314–1316; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1219–1221; m) P. Molenveld, S. Kapsabelis, J. F. J. Engbersen, D. N. Reinhoudt, *J. Am. Chem. Soc.* **1997**, *119*, 2948–2949; n) S. Liu, Z. Luo, A. D. Hamilton, *Angew. Chem.* **1997**, *109*, 2794–2796; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2678–2680.
- [4] R. Cacciapaglia, S. Di Stefano, E. Kelderman, L. Mandolini, F. Spadola, *J. Org. Chem.*, **1998**, *63*, 6476–6479.
- [5] R. Cacciapaglia, L. Mandolini, V. Van Axel Castelli, *J. Org. Chem.* **1997**, *62*, 3089–3092.
- [6] Reactions of **3** and **5** are more sensitive to the presence of the metal ion than the corresponding reactions of **4** and **6** because binding to the

[*] Prof. Dr. A. Baiker, Dipl.-Chem. A. Fischer, Dr. T. Mallat
Laboratory of Technical Chemistry
Swiss Federal Institute of Technology, ETH-Zentrum
Universitätsstrasse 6, CH-8092 Zurich (Switzerland)
Fax.: (+41) 1-632-11-63
E-mail: baiker@tech.chem.ethz.ch

[**] Financial support from Lonza Ltd, Visp (Switzerland) is kindly acknowledged.



Scheme 1. Important reactions that occur in the amination of alkanediols with ammonia. The continuous and dashed line frames indicate the detected main and by-products, respectively.

mediate and product primary amines are significantly higher than that of ammonia. The above considerations account for the difficulties in the selective synthesis of primary diamines from diols. A practical solution is the separate preparation of the aminoalcohol intermediate and its further amination with ammonia. This method provides good selectivities to diamines.^[15–19]

Intrigued by the obvious advantages of the one-step process, we reinvestigated the amination of alkanediols with ammonia in a continuous fixed-bed reactor at pressures where the ammonia forms a supercritical fluid (critical data of ammonia: $T_c = 132.4^\circ\text{C}$, $P_c = 114.8\text{ bar}$ ^[20]). The amination of 1,3-propanediol and 2,2-dimethyl-1,3-propanediol were chosen as test reactions. Two types of catalysts were used: an unsupported Co catalyst stabilized by 5 wt % Fe and a commercial silica-supported Ni catalyst. Preliminary experiments indicated that—in agreement with the literature data^[21]—a rather high ammonia/alcohol molar ratio in the range of 10/1 to 100/1 was necessary to suppress the dimerization and oligomerization of the intermediate and product amines. A small ratio of hydrogen in the feed (1–5 mol % of the reaction mixture) was sufficient to prevent the undesired dehydrogenation reactions and the formation of nitriles and carbonaceous deposit.

Figure 1 illustrates the role of the total pressure in the amination of 1,3-propanediol over the unsupported Co–Fe catalyst. The conversion varied only from 85 to 99 % over the whole pressure range studied. However, a pressure increase from 50 to over 100 bar had a striking effect on the amination selectivity. The technically important cumulative selectivity to 3-amino-1-propanol and 1,3-diaminopropane increased from about 1 % to 43–48 %.

On the basis of literature data^[22–25] it is expected that at 135 bar or above, where the selectivity to the diamine is constant (Figure 1), the reaction mixture is in the supercritical

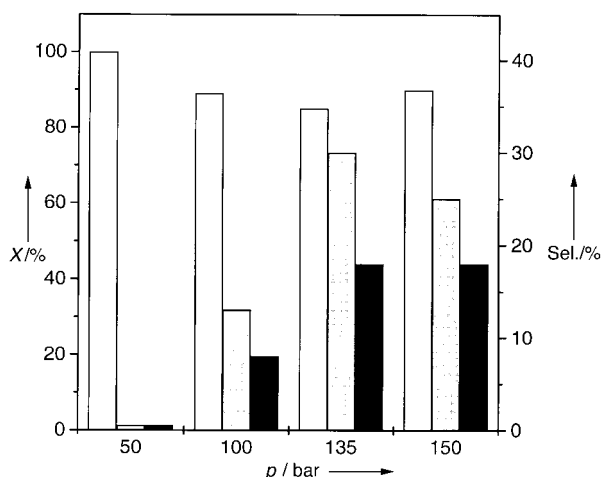


Figure 1. Influence of pressure on the conversion X ($\square$) of propanediol, and the selectivity to 3-amino-1-propanol ($\blacksquare$) and 1,3-diaminopropane ($\bullet$). Conditions: catalyst: 95 wt % Co and 5 wt % Fe, 195°C , space time 11 g h mol^{-1} , molar ratio of alcohol/ H_2 /ammonia: 1/2/60.

(sc) region. To confirm this assumption the phase composition of the reaction mixture was investigated in a 50 mL quartz autoclave. The presence of a homogeneous fluid at 130 bar and 200°C was confirmed by visual inspection. Accordingly, we propose that the remarkable improvement in amination selectivity with increasing pressure is connected with the change of the medium in the near critical region of ammonia (110–120 bar) and at the reaction temperature of 60°C above the critical temperature.

It seems from Figure 1 that the amination selectivity increased in both consecutive steps, namely in the formation and in the further amination of the aminoalcohol intermediate. In a control experiment the intermediate 3-amino-1-propanol was fed into the reactor under similar conditions. Figure 2 shows the effect of increasing pressure: likewise a

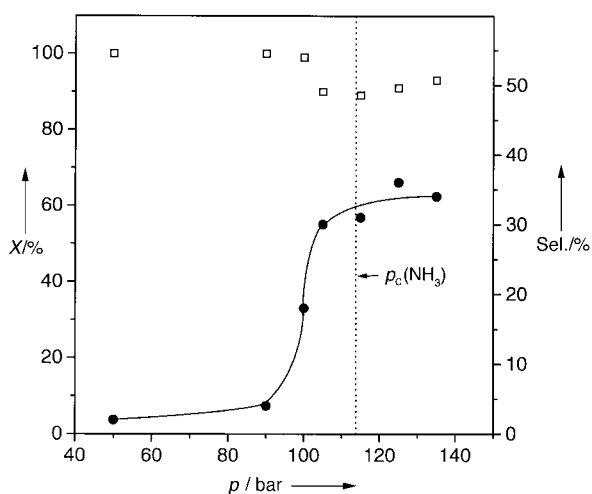


Figure 2. Effect of pressure on the conversion X ($\square$) of 3-amino-1-propanol and the selectivity to 1,3-diaminopropane ($\bullet$). Conditions: catalyst: 95 wt % Co and 5 wt % Fe, 195°C , space time 11 g h mol^{-1} , molar ratio of alcohol/ H_2 /ammonia: 1/2/40.

small drop in conversion and a significant improvement in diamine selectivity was observed in the near critical region. Below and above this region the variations in conversion and selectivity were minor.

The striking effect of supercritical conditions in the amination of alkanediols was not limited to the use of the Co–Fe catalyst or 1,3-propanediol as reactant. Figure 3

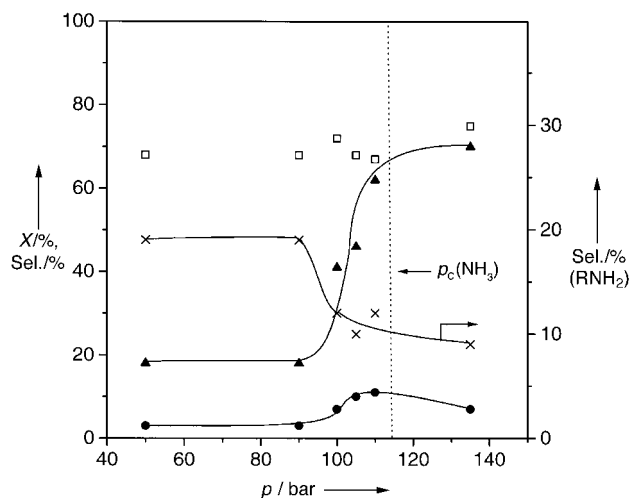


Figure 3. Influence of pressure on the conversion X (□) of 2,2-dimethyl-1,3-propanediol, and the selectivity to 2,2-dimethyl-3-amino-1-propanol (●) and 2,2-dimethyl-1,3-diaminopropane (▲) and alkylamine (×). Conditions: catalyst: 56 wt % Ni on a support (Engelhard Ni-6458), 210 °C, space time 11 g mol⁻¹, molar ratio of alcohol/H₂/ammonia: 1/2/60.

presents another example: the amination of 2,2-dimethyl-1,3-propanediol. In this case the reaction was carried out with the supported Ni catalyst. Again, the increasing pressure had only minor influence on the diol conversion, but favored the formation of the aminoalcohol intermediate and especially the desired diamine product. The changes in selectivity were negligible below 90 bar, and only minor above the critical pressure of ammonia.

Before the possible reasons for the observed selectivity enhancement could be discussed we had to ascertain that in the amination of various alkanediols and aminoalcohols the conversion above 60 % had only a small influence on the selectivity to the corresponding diamines. For example, the selectivity in the amination of 2,2-dimethyl-1,3-propanediol at 227 °C to 2,2-dimethyl-1,3-diaminopropane decreased from 58 to 53 % when the conversion increased (by increasing the contact time) from 61 to 89 %. A minor variation in selectivity of about ± 2 % was observed in the amination of 1,3-propanediol in a similar conversion range. The likely interpretation for the small effect of increasing conversion is that not only is more diamine formed from the aminoalcohol intermediate at higher contact time, but also more is consumed by consecutive side reactions such as disproportionation or hydrogenolysis (degradation). Accordingly, the changes in selectivity with increasing pressure (Figures 1–3) cannot be traced to the small variations in conversion.

At medium pressures (<90 bar) the reaction mixture consists of two phases: a liquid phase that is rich in the non-volatile alkanediol and amines (depending on the conversion

along the catalyst bed), and a gas phase that contains dominantly ammonia. In this pressure range the influence of total pressure on conversion and product composition was minor as illustrated in Figures 1–3. In the near critical region the transformation of the two-phase system to a homogeneous sc fluid generally results in a significant improvement of mass transport because of the elimination of the phase transfer resistance, and the higher diffusion coefficients and lower viscosity, relative to the situation in the liquid phase. Besides, the effect of pressure on the chemical equilibria and reaction rates can also be crucial.^[26–28] Unfortunately, for a network of consecutive and parallel reactions the effect of pressure is rather complex because of the different reaction volumes (ΔV_r) and activation volumes ($\Delta V^\ddagger$). We assume that in the supercritical region the surface ammonia concentration is significantly higher than under two phase conditions, which govern in the subcritical region. Although this change is mainly a consequence of the enhanced mass transfer in the sc fluid, a change in adsorption equilibrium (solvent effect) can also contribute. There are some recent examples in the literature on the enhancement of stereoselectivity (*cis/trans* ratio) in the hydrogenation of vegetable oils in sc CO₂.^[29] The improvement was attributed to the significantly better hydrogen availability on the metal surface that arises from the elimination of mass transport limitations in the sc fluid phase.

A clearer picture is obtained by analysis of the influence of the subcritical–supercritical transition on the main reaction steps and the side reactions. The major side reactions that produce monofunctional alcohols and amines are illustrated in Scheme 1. Decarbonylation of the intermediate aldehydes on the metal surface results in primary alcohols and amines. Amination of the alkanol by-product via the aldehyde intermediate leads to alkylamines. This aldehyde intermediate can also form by the (acid-base catalyzed) retro-aldol reaction.^[13] The variation of the total amount of alkylamines detected in the liquid product is illustrated in Figure 3 for the amination of 2,2-dimethyl-1,3-propanediol. The main by-product was isobutylamine. A significant drop in the amount of this by-product in the near critical and supercritical region corroborates the picture discussed above. In the supercritical region of ammonia, the dimerization and oligomerization side reactions were not important.

We suggest that the changes in amination selectivity and alkanediol conversion in the near critical region arise from the increased ammonia concentration at the surface. This change favors the amination and suppresses the degradation-type (hydrogenolysis) side reactions. The situation is rather similar to the well-known, and widely applied, selective poisoning of metal catalysts.^[30–32] For example, the presence of strongly adsorbing amines in the hydrogenation of carbonyl compounds hinders the C–O bond hydrogenolysis, and the corresponding alcohols can be prepared in very high yields.

In the amination of alkanediols and alkanolamine (Figures 1 and 2), the small drop in conversion and the strong decrease in the amount of alkylamines by-products in the liquid phase (Figure 3) are clear indications of selective poisoning: the degradation-type reactions are effectively slowed down but also the first step, the dehydrogenation of the alcohol to the carbonyl compound, is affected. On the

other hand, the higher ammonia concentration at the surface favors the fast addition of ammonia to the aldehyde-type intermediates, and suppresses the reaction of the alcoholic OH group with the intermediate or product amines that leads to dimerization products. That is, the weaker basicity of ammonia, relative to the product amines, is partly compensated by its higher concentration at the surface. All these effects can contribute to the remarkable enhancements in the overall amination selectivities (Figures 1–3).

In conclusion we can state that the application of scNH_3 as a solvent and reactant in the amination of simple alkanediols and aminoalcohol affords significant improvement in selectivities to primary diamines, relative to the procedure at subcritical pressure. Most of the changes in selectivities occur in a narrow pressure range in the near critical region of the medium. The selectivity improvement is attributed to the higher concentration of ammonia at the surface, which favors the amination with ammonia and suppresses the hydrogenolysis-type (degradation) side reactions. It seems that the phenomenon is not limited to a specific catalyst or reactant, though the final selectivity is a function of the structure of the reactant aminoalcohol or diol. We are presently working on the extension to other amination reactions where the low reactivity of ammonia relative to the product amine prevents the efficient synthesis of primary amines.

Experimental Section

The Co–Fe catalyst was prepared by co-precipitation. Aqueous solutions of cobalt nitrate, iron nitrate, and ammonium carbonate were mixed at room temperature and the pH adjusted to 7. The precipitate was filtered off, dried at 120 °C in a vacuum, and calcined at 400 °C for 4 h. The BET surface area was 8 m² g^{−1} and the pore volume 0.1 cm³ g^{−1}.

The commercial Ni catalyst (Engelhard No. 6458) contained 56 wt % of pre-reduced Ni. The BET surface area was 180 m² g^{−1} and the pore volume 0.3 cm³ g^{−1}.

The amination experiments were carried out isothermally in a continuous tubular reactor with an inner diameter of 13 mm. The reactor was loaded with crushed and sieved catalyst particles of 140 to 400 μm. The liquid ammonia and 1,3-propanediol or the solution of 2,2-dimethyl-1,3-propanediol in ammonia were dosed into the reactor by ISCO D500 syringe pumps. The total pressure in the reaction system was set by a TESCOM back-pressure regulator. Details of the reaction conditions are indicated in the figure captions. The liquid product was separated from the gas and analyzed on an HP 5890 gas chromatograph (HP 1701 column). The products were identified by GC-MS analysis.

Received: June 26, 1998 [Z120571E]

German version: *Angew. Chem.* **1999**, *111*, 362–365

Keywords: aminations • ammonia • diols • heterogeneous catalysis • supercritical fluids

- [1] M. G. Turcotte, T. A. Johnson, *Kirk-Othmer, Encycl. Chem. Technol.*, Vol. 2, Wiley, New York, **1992**, p. 369.
- [2] G. C. Carter, A. R. Doumaux, S. W. Kaiser, P. R. Umberger, *Kirk-Othmer, Encycl. Chem. Technol.*, Vol. 8, Wiley, New York, **1992**, p. 74.
- [3] D. M. Roundhill, *Chem. Rev.* **1992**, *92*, 1.
- [4] A. Baiker in *Catalysis of Organic Reactions* (Eds.: J. R. Kosak, T. A. Johnson), Marcel Dekker, New York, **1994**, p. 91.
- [5] A. Fischer, T. Mallat, A. Baiker, *Catal. Today* **1997**, *37*, 167.
- [6] T. Mallat, A. Baiker in *Handbook of Heterogeneous Catalysis*, Vol. 5 (Eds.: G. Ertl, H. Knözinger, J. Weitkamp), WILEY-VCH, Weinheim, **1997**, p. 2334.

- [7] R. E. Vultier, A. Baiker, A. Wokaun, *Appl. Catal.* **1987**, *30*, 167.
- [8] J. Kijenski, P. J. Niedezielski, A. Baiker, *Appl. Catal.* **1989**, *53*, 107.
- [9] A. Baiker, J. Kijenski, *Catal. Rev. Sci. Eng.* **1985**, *27*, 653.
- [10] J. Kijenski, J. Burger, A. Baiker, *Appl. Catal.* **1984**, *11*, 295.
- [11] R. J. Card, J. L. Schmitt, *J. Org. Chem.* **1981**, *46*, 754.
- [12] G. Sirokmán, A. Molnár, M. Bartok, *J. Mol. Catal.* **1983**, *19*, 35.
- [13] Á. Molnár, G. Sirokman, M. Bartok, *J. Mol. Catal.* **1983**, *19*, 25.
- [14] J. Runeberg, A. Baiker, J. Kijenski, *Appl. Catal.* **1985**, *17*, 309.
- [15] R. Becker, V. Menger, W. Reif, A. Henne (BASF AG), US-A 5608113, **1997**, [*Chem. Abstr.* **1996**, *124*, 316502].
- [16] C. A. Gibson, J. R. Winters (Union Carbide), US-A 4400539, **1983**, [*Chem. Abstr.* **1983**, *99*, 21938w].
- [17] A. Moriya (Nippon Shokubai Co.), EP-B 0652207, **1994**, [*Chem. Abstr.* **1995**, *123*, 9064].
- [18] T. Hironaka, N. Nagasaka, Y. Hara (Tosoh Corp.), EP-B 0526851, **1992**, [*Chem. Abstr.* **1993**, *118*, 212475].
- [19] F. Merger, A. Segnitz (BASF AG), US-A 4158017, **1979**.
- [20] *Encyclopedie de Gaz*, Elsevier, **1976**, p. 951.
- [21] H. Feichtinger, H. Aschmann, H. Birnkraut (Ruhchemie AG), US-A 4078003, **1978**, [*Chem. Abstr.* **1975**, *83*, 78566x].
- [22] E. Brunner, *J. Chem. Thermodynamics* **1988**, *20*, 1397.
- [23] E. Brunner, *J. Chem. Thermodynamics* **1988**, *20*, 273.
- [24] J. C. Giddings, M. N. Myers, L. McLaren, R. A. Keller, *Science* **1968**, *162*, 67.
- [25] S. Borman, *Sci. Technol.* **1995**, *33*.
- [26] A. Baiker, *Chem. Rev.* **1999**, in press.
- [27] C. Eckert, B. L. Knutson, P. G. Debenedetti, *Nature* **1996**, *383*, 313.
- [28] P. E. Savage, S. Gopalan, T. I. Mizan, C. J. Martino, E. E. Brock, *AIChE J.* **1995**, *41*, 1723.
- [29] T. Tacke, S. Wielander, P. Panster in *High Pressure Chemical Engineering*, Vol. 12 (Eds.: R. von Rohr, C. Trepp), Elsevier, Zurich, Switzerland, **1996**, p. 17.
- [30] P. N. Rylander, *Catalytic Hydrogenation over Platinum Metals*, Academic Press, New York, **1967**.
- [31] P. Rylander, *Catalytic Hydrogenation in Organic Synthesis*, Academic Press, New York, **1979**.
- [32] M. Freifelder, *Practical Catalytic Hydrogenation—Techniques and Applications*, Wiley-Interscience, New York, **1971**.

Calcium, Strontium, and Barium Acetylides—New Evidence for Bending in the Structures of Heavy Alkaline Earth Metal Derivatives**

David C. Green, Ulrich Englich, and Karin Ruhlandt-Senge*

Since their development in the early 1900s, Grignard reagents have proven to be immensely useful in synthetic chemistry and are among the most common organometallic reagents.^[1, 2] In contrast, information about beryllium, calcium, strontium, and barium analogues is scarce.^[1c, 2, 3] Organo-

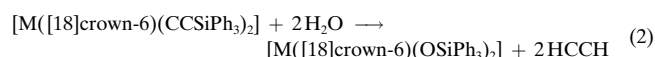
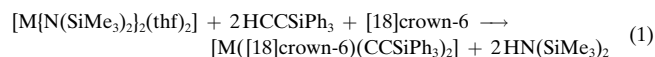
[*] Prof. Dr. K. Ruhlandt-Senge, D. C. Green, Dr. U. Englich
Department of Chemistry
1-014 Center for Science and Technology
Syracuse University
Syracuse NY 13244-4100 (USA)
Fax: (+1) 315-443-4070
E-mail: kruhland@syr.edu

[**] This work was supported by the National Science Foundation (CHE-9702246) and the Deutsche Forschungsgemeinschaft (Postdoctoral stipend for U. E.). Purchase of the X-Ray diffractometer was made possible with grants from NSF (CHE-95–27898), the W. M. Keck Foundation, and Syracuse University.

metallic compounds of the heavy alkaline earth metals are more difficult to access due to enhanced reactivity and decreased kinetic stability.^[1c, 2a,b, 3a,b] The high electropositive character and large ionic radii of the heavy alkaline earth metals result in a chemistry that is mostly governed by electrostatic and steric requirements. Consequently, the formation of polymeric, insoluble solids is frequently observed.^[1c, 2, 3]

Well characterized organometallic calcium, strontium, and barium derivatives are mainly limited to compounds exhibiting metal– π interactions, such as cyclopentadienyl compounds,^[3a,b] fluorenyl and indenyl complexes,^[4] and a few others.^[5] In contrast, there are still very few σ -bound organometallic compounds and these are often only characterized by the products of their reactions with electrophiles.^[1c] Structurally characterized σ -bound alkaline earth metal compounds include $[\text{Ca}\{\text{CH}(\text{SiMe}_3)_2\}_2(1,4\text{-dioxane})_2]$,^[6] $[\text{Ca}\{\text{C}(\text{SiMe}_3)_3\}_2]$,^[7] and $[[[(\text{C}_3\text{H}_7)_4\text{C}_5\text{H}]\text{Ca}(\mu\text{-C}\equiv\text{CPh})(\text{thf})_2]]_2]$,^[8] no well characterized compounds displaying σ -bound Sr–C or Ba–C moieties have been reported. This lack of data^[9] is contradicted by the recent use of, for example, allylbarium reagents in the α -selective and stereospecific allylation of carbonyls or imines,^[10] the utilization of organobarium derivatives as effective polymerization initiators,^[11] and the employment of organocalcium reagents in the synthesis of functionalized polymers.^[12]

We present here a family of calcium, strontium, and barium triphenylsilylethynyl derivatives $[\text{M}(\text{[18]crown-6})(\text{CCSiPh}_3)_2]$ ($\text{M} = \text{Ca}$ (**1a**), Sr (**1b**), and Ba (**1c**)), which were synthesized by treatment of alkaline earth metal amides with triphenylsilylethyne in the presence of [18]crown-6 [Eq. (1); $\text{M} = \text{Ca}$, Sr, Ba]. The compounds crystallize as colorless solids that can be stored indefinitely under inert gas. They are extremely sensitive to oxygen and moisture; contact with water results in immediate decomposition under formation of $[\text{M}(\text{[18]crown-6})(\text{OSiPh}_3)_2]$ and acetylene [Eq. (2)].^[13]



Compounds **1a–c** were characterized by NMR and IR spectroscopy, and their structures elucidated by X-ray crystallography. The IR frequencies at 1980 (**1a**), 1969 (**1b**), and 1955 cm^{-1} (**1c**) for the $\text{C}\equiv\text{C}$ bond as compared to those for the neutral precursor HCCSiPh_3 (2036 cm^{-1}) clearly indicate the presence of the ethynyl derivative, and are also in accord with those observed in $[[[(\text{C}_3\text{H}_7)_4\text{C}_5\text{H}]\text{Ca}(\mu\text{-CCR})(\text{thf})_2]]_2]$ ^[8] and a series of polymeric derivatives $[[\text{M}(\text{CCPh})_2]_n]$ ($\text{M} = \text{Ca}$, Sr, Ba).^[14] A decrease in ethynyl stretching frequency was also observed upon descending Group 1.^[15]

Compounds **1a–c** crystallize as monomeric molecules in which the metal atom lies in the center of the crown and the ethynyl ligands are arranged *trans* to each other (C–M–C 168.7(2)° (**1a**), 166.0(1)° (**1b**; Figure 1), and 162.7(1)° (**1c**; Figure 2)). The M–C distances are 2.523(7) and 2.558(7) Å (**1a**), 2.692(4) and 2.723(4) Å (**1b**), and 2.852(3) and 2.853(3) Å (**1c**). The $\text{C}\equiv\text{C}$ distances are 1.229(8) and

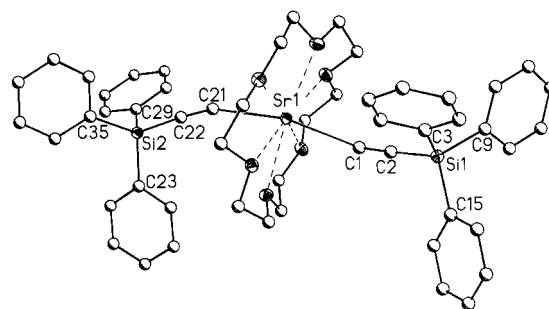


Figure 1. Structure of **1b** in the crystal (anisotropic displacement parameters depicting 30% probability). All hydrogen atoms have been omitted for clarity.

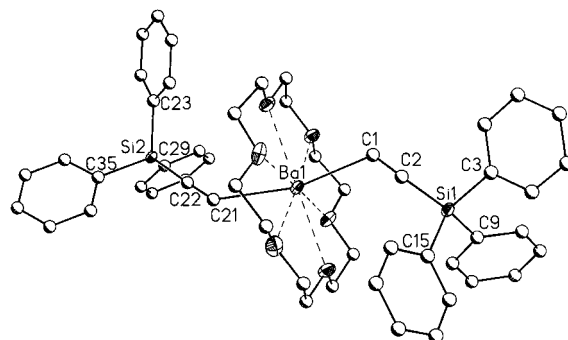


Figure 2. Structure of **1c** in the crystal (anisotropic displacement parameters depicting 30% probability). All hydrogen atoms have been omitted for clarity.

1.234(8) Å (**1a**), 1.201(5) and 1.222(5) Å (**1b**), and 1.223(4) and 1.236(5) Å (**1c**). Interestingly, the ethynyl ligand is not bound linearly to the metal center, and the M–C–C angles are 162.4(5) and 164.0(5)° (**1a**), 158.9(3) and 159.7(3)° (**1b**), and 126.6(3) and 141.3(3)° (**1c**).

The Ca–C distances in **1a**, in which the Ca atom is eight-coordinate, compare well with those in $[\text{Ca}\{\text{CH}(\text{SiMe}_3)_2\}_2(1,4\text{-dioxane})_2]$ (2.483(5) Å)^[6] and $[\text{Ca}(\text{C}(\text{SiMe}_3)_3)_2]$ (2.459(9) Å),^[7] in which the Ca atom is four-coordinate and two-coordinate, respectively. The good agreement of the bond lengths despite the increased coordination number at the metal in **1a** can be explained by the *sp* hybridization of the ligand carbon atom, resulting in a decreased effective ionic radius. No σ -bonded organostrontium or -barium compounds are available for structural comparison with **1b** and **1c** which display a smooth increase in metal–carbon distance as compared to **1a** (effective ionic radii for a coordination number 8: 1.12 (Ca), 1.26 (Sr), and 1.42 Å (Ba)).^[16]

Two main structural trends are observed in **1a–c** upon descending Group 2: a decrease in the C–M–C and the M–C–C angles. The decrease in C–M–C angle is in agreement with results of calculations which indicated low energy barriers between linear and bent structures.^[17] The small degree of bending observed in **1a–c** might be explained by steric repulsion between the crown ether and the ligand.

More unusual are the M–C–C angles in **1a–c**. Angles close to 160° are observed for **1a** and **1b**, those for **1c** are considerably narrower with 126.6(3) and 141.3(3)°. This finding does not correlate well with literature values; terminal acetylide groups generally display angles close to 180° as

observed in $[\text{Mg}(\text{tmeda})_2(\text{CCR})_2]$ ($\text{R} = \text{Ph}$,^[18] $t\text{Bu}$ ^[19]) or $[\text{U}(\text{C}_5\text{H}_5)_3(\text{CCPh})]$.^[20] The unusual geometry in **1c** can be explained by the high s-character of the sp-hybridized carbon atom of the ethynyl group causing a low directionality of the ligand orbitals. The resulting very low energy barrier is responsible for the bending at the C atom.^[21] Moreover, the large ionic radius of barium and the small size of the ligand allow for extensive structural flexibility in the ligand orientation, accounting for the large variation observed in the ethynyl ligation. The smaller degree of bending for **1a** and **1b** might be due to space limitations resulting in reduced structural flexibility. The low energy barrier for the bending might also allow for packing effects. If one considers the unusual Ba-C-C angles on the basis of metal–ligand π interactions, as discussed in various alkali metal acetylide derivatives,^[22] or in $[\text{Be}(\text{NMe}_3)(\text{CCMe})_2]_2$,^[23] the bending in **1c** can also be explained by a partial side-on orientation of the ligand resulting in a π interaction.

Experimental Section

All reactions were performed under vigorous exclusion of water and oxygen. The compounds $[\text{M}(\text{N}(\text{SiMe}_3)_2)_2(\text{thf})_2]$ ($\text{M} = \text{Ca}, \text{Sr}, \text{Ba}$) were prepared by treating the alkaline earth metal iodides with potassium amide.^[24] All reagents and solvents were purified by standard procedures.

1a–c: To a 100 mL Schlenk flask was added $[\text{Ca}(\text{N}(\text{SiMe}_3)_2)_2(\text{thf})_2]$ (0.25 g, 0.5 mmol), $[\text{Sr}(\text{N}(\text{SiMe}_3)_2)_2(\text{thf})_2]$ (0.28 g, 0.5 mmol), or $[\text{Ba}(\text{N}(\text{SiMe}_3)_2)_2(\text{thf})_2]$, [18]crown-6 (0.13 g, 0.5 mmol), and THF (15 mL). In a second flask HCCSiPh_3 (0.28 g, 1.0 mmol) was dissolved in THF (10 mL). Both flasks were cooled to -80°C and the contents combined at -80°C and stirred. The colorless solutions were filtered, and the resulting clear solutions were stored at -20°C . Colorless crystals formed overnight.

1a: M.p. 261°C ; yield: 0.15 g (34.4 %); ^1H NMR (300 MHz, 25°C , C_6D_6): $\delta = 3.31$ (s, 24H, [18]crown-6), 7.21 (m, 18H, Ph_3Si), 8.10 (m, 12H, Ph_3Si); IR (Nujol): $\tilde{\nu} = 3854\text{s}, 3822\text{s}, 3752\text{s}, 3736\text{s}, 3712\text{s}, 3691\text{s}, 3676\text{s}, 3650\text{s}, 3630\text{s}, 3620\text{s}, 3568\text{s}, 3062\text{s}, 3042\text{s}, 2922\text{s}, 1980\text{s}, 1831\text{w/m}, 1564\text{w/m}, 1481\text{s}, 1427\text{s}, 1351\text{s}, 1284\text{m}, 1261\text{m}, 1249\text{s}, 1185\text{m}, 1107\text{s}, 1029\text{m}, 997\text{m}, 972\text{s}, 846\text{m}, 744\text{s}, 705\text{s}, 656\text{s}, 617\text{m}, 544\text{cm}^{-1}\text{w/m}$.

1b: M.p. 269°C ; yield: 0.14 g (30.0 %); ^1H NMR (300 MHz, 25°C , C_6D_6): $\delta = 3.22$ (s, 24H, [18]crown-6), 7.21 (m, 18H, Ph_3Si), 8.12 (m, 12H, Ph_3Si); IR (Nujol): $\tilde{\nu} = 3853\text{m}, 3750\text{m}, 3675\text{m}, 3648\text{m}, 2284\text{w}, 1969\text{m}, 1829\text{w}, 1772\text{w}, 1733\text{w}, 1716\text{w}, 1698\text{w}, 1684\text{w}, 1670\text{w}, 1636\text{w}, 1616\text{w}, 1558\text{w}, 1540\text{w}, 1521\text{w}, 1506\text{w}, 1427\text{m}, 1350\text{m}, 1285\text{w}, 1248\text{w}, 1186\text{w}, 1101\text{s}, 1039\text{w}, 1020\text{w}, 997\text{w}, 969\text{m}, 843\text{w}, 746\text{w}, 703\text{s}, 654\text{w}, 618\text{cm}^{-1}\text{w}$.

1c·2THF: M.p. 232°C ; yield: 0.26 g (54.7 %); ^1H NMR (300 MHz, 25°C , C_6D_6): $\delta = 1.43$ (m, 8H, THF), 3.09 (s, 24H, [18]crown-6), 3.58 (m, 8H, THF), 7.19 (m, 18H, Ph_3Si), 8.11 (m, 12H, Ph_3Si); IR (Nujol): $\tilde{\nu} = 2930\text{s}, 1955\text{s}, 1830\text{s}, 1773\text{s}, 1566\text{s}, 1426\text{s}, 1346\text{s}, 1305\text{m/s}, 1283\text{s}, 1261\text{s}, 1245\text{s}, 1185\text{s}, 1092\text{s}, 1063\text{s}, 1028\text{s}, 997\text{m/s}, 961\text{s}, 911\text{s}, 859\text{m}, 828\text{s}, 745\text{s}, 703\text{s}, 652\text{s}, 617\text{cm}^{-1}\text{m}$.

Crystal data for **1a**: $\text{C}_{52}\text{H}_{54}\text{CaO}_6\text{Si}_2$, $M_r = 871.21$, monoclinic, space group $P2_1/n$, $a = 15.9096(5)$, $b = 17.0207(6)$, $c = 18.6612(7)$ Å, $\beta = 114.924(1)^\circ$, $V = 4582.7(3)$ Å³, T (K) = 120, $Z = 4$, $\mu = 0.239\text{ mm}^{-1}(\text{MoK}\alpha)$; colorless rods $0.15 \times 0.15 \times 0.40\text{ mm}^3$; 4865 independent reflections ($3.4 \leq 2\theta \leq 42.00^\circ$); $R_1 = 0.0713$ for 3013 data $I > 2\sigma(I)$ and $wR_2 = 0.1426$ for all data. **1b**: $\text{C}_{52}\text{H}_{54}\text{O}_6\text{Si}_2\text{Sr}$, $M_r = 918.75$, monoclinic, space group $P2_1/n$, $a = 15.9659(1)$, $b = 17.1540(2)$, $c = 18.5590(1)$ Å, $\beta = 115.13(1)^\circ$, $V = 4601.81(6)$ Å³, T (K) = 90, $Z = 4$, $\mu = 1.273\text{ mm}^{-1}(\text{MoK}\alpha)$. Colorless plates of dimensions $0.30 \times 0.18 \times 0.12\text{ mm}^3$, 10456 independent reflections ($3.4 \leq 2\theta \leq 57.00^\circ$); $R_1 = 0.0723$ for 7537 data $I > 2\sigma(I)$ and $wR_2 = 0.1157$ for all data. **1c**·2THF: $\text{C}_{60}\text{H}_{70}\text{BaO}_6\text{Si}_2$, $M_r = 1112.68$, triclinic, space group $P\bar{1}$, $a = 11.5909(1)$, $b = 15.9312(2)$, $c = 16.8368(2)$ Å, $\alpha = 70.912(1)$, $\beta = 89.602(1)$, $\gamma = 74.824(1)^\circ$, $V = 2825.06(5)$ Å³, T (K) = 90, $Z = 2$, $\mu = 0.797\text{ mm}^{-1}(\text{MoK}\alpha)$. Colorless rods of dimensions $0.64 \times 0.10 \times 0.10\text{ mm}^3$, 12906 independent reflections ($3.1 \leq 2\theta \leq 57.00^\circ$); $R_1 = 0.0471$ for 11048 data $I > 2\sigma(I)$ and $wR_2 = 0.1185$ for all data. The crystals were mounted on the diffractometer as described

previously.^[25] The data were collected utilizing a Siemens SMART system, complete with 3-circle goniometer and CCD detector as described earlier.^[26] The crystal structures of **1a** and **1b** were solved with direct methods, **1c** by Patterson synthesis. All structures were refined by full-matrix least-squares refinement on F^2 .^[27] All non-hydrogen atoms were refined anisotropically. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-102521–CCDC-102523. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Received: August 25, 1998 [Z12327IE]

German version: *Angew. Chem.* **1999**, *111*, 365–367

Keywords: acetylides • alkaline earth metals • structure elucidation

- a) P. R. Markies, O. S. Ackerman, F. Bickelhaupt, W. J. J. Smeets, A. L. Spek, *Adv. Organomet. Chem.* **1991**, *32*, 147; b) F. Bickelhaupt, *J. Organomet. Chem.* **1994**, *475*; c) W. E. Lindsell in *Comprehensive Organometallic Chemistry* (Eds.: G. Wilkinson, F. G. A. Stone, E. W. Abel), Pergamon, Oxford, **1982**.
- a) G. E. Coates, M. L. H. Green, K. Wade, *Organometallic Compounds, Vol. 1*, Methuen, London, **1969**; b) S. T. Ioffe, A. N. Nesmeyanov, *The Organo Compounds of Magnesium, Beryllium, Calcium, Strontium, and Barium*, North Holland, Amsterdam, **1967**.
- a) T. P. Hanusa, *Acc. Chem. Res.* **1993**, *93*, 1023; b) T. P. Hanusa, *Polyhedron* **1990**, *9*, 1345; c) N. A. Bell in *Comprehensive Organometallic Chemistry* (Eds.: G. Wilkinson, F. G. A. Stone, E. W. Abel), Pergamon, Oxford, **1982**.
- See for example: a) K. A. Allen, B. G. Gowenlock, W. E. Lindsell, *J. Organomet. Chem.* **1974**, *65*, 1; b) J. S. Overby, T. P. Hanusa, *Organometallics* **1996**, *15*, 2205; c) G. Mösges, F. Hampel, P. von R. Schleyer, *Organometallics* **1992**, *11*, 1769.
- a) K. Mashima, H. Sugiyama, N. Kamehisa, Y. Kai, H. Yasuda, N. Nakamura, *J. Am. Chem. Soc.* **1994**, *116*, 6977; b) A. Nakamura, K. Mashima, *J. Organomet. Chem.* **1995**, *500*, 261; c) J. S. Overby, T. P. Hanusa, *Angew. Chem.* **1994**, *106*, 2300; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2191; d) S. Harder, M. Lutz, *Organometallics* **1997**, *16*, 225.
- F. G. Cloke, P. B. Hitchcock, M. F. Lappert, G. A. Lawless, B. Royo, *J. Chem. Soc. Chem. Commun.* **1991**, 724.
- C. Eaborn, S. A. Hawkes, P. B. Hitchcock, J. D. Smith, *Chem. Commun.* **1997**, 1961.
- D. Burkey, T. P. Hanusa, *Organometallics* **1996**, *15*, 4971.
- C. Elschenbroich, A. Salzer, *Organometallics*, 2nd ed., VCH, New York, **1992**.
- a) A. Yanagisawa, S. Habaue, K. Ysaue, H. Yamamoto, *J. Am. Chem. Soc.* **1994**, *116*, 6130; b) A. Yanagisawa, K. Ogasawara, K. Yasue, H. Yamamoto, *Chem. Commun.* **1996**, 367, and references therein.
- a) L. C. Tang, C. Mathis, B. Francois, *J. Organomet. Chem.* **1983**, *243*, 359; b) B. De Groof, M. Van Beulen, M. Szwarc, *Macromolecules* **1975**, *8*, 396; c) B. De Groof, W. Morteier, M. Van Beulen, M. Szwarc, *Macromolecules* **1977**, *10*, 598.
- R. A. O'Brien, T. Chen, R. D. Rieke, *J. Org. Chem.* **1992**, *57*, 2667.
- The compounds $\text{M}([\text{18}]\text{crown-6})(\text{OSiPh}_3)_2$ ($\text{M} = \text{Ca}, \text{Sr}, \text{Ba}$) have been identified by X-ray crystallography and IR spectroscopy.
- M. A. Coles, F. A. Hart, *J. Organomet. Chem.* **1971**, *32*, 279.
- R. Nast, J. Gremm, *Z. Anorg. Allg. Chem.* **1963**, *325*, 62.
- R. D. Shannon, *Acta Crystallogr. A* **1976**, *32*, 751.
- a) M. Kaupp, P. von R. Schleyer, H. Stoll, H. Preuss, *J. Chem. Phys.* **1991**, *94*, 1360; b) M. Kaupp, P. von R. Schleyer, H. Stoll, H. Preuss, *J. Am. Chem. Soc.* **1991**, *113*, 6012; c) L. Seijo, Z. Brandiarán, S. Huzinaga, *J. Chem. Phys.* **1991**, *94*, 3762; d) M. Hargittai, M. Kolonits, D. Knausz, I. Hargittai, *J. Chem. Phys.* **1992**, *96*, 8990; e) M. Kaupp, P. von R. Schleyer, *J. Am. Chem. Soc.* **1992**, *114*, 491.
- B. Schubert, U. Behrens, E. Weiss, *Chem. Ber.* **1981**, *114*, 2640.
- M. Geissler, J. Kopf, E. Weiss, *Chem. Ber.* **1989**, *122*, 1395.
- J. L. Atwood, C. F. Hains, *J. Chem. Soc. Chem. Commun.* **1973**, 452.
- D. M. Root, C. R. Landis, T. Cleveland, *J. Am. Chem. Soc.* **1993**, *115*, 4201.

- [22] B. Goldfus, P. von R. Schleyer, F. Hampel, *J. Am. Chem. Soc.* **1997**, *119*, 1072, and references therein.
 [23] N. A. Bell, I. W. Nowell, H. M. M. Shearer, *J. Chem. Soc. Chem. Commun.* **1982**, 147.
 [24] D. C. Green, K. Ruhlandt-Senge, unpublished results.
 [25] H. Hope, *Progr. Inorg. Chem.* **1994**, *41*, 1.
 [26] S. Chadwick, K. Ruhlandt-Senge, *Chem. Eur. J.* **1998**, *4*, 1768.
 [27] G. M. Sheldrick, SHELXTL Version 5, Siemens Analytical X-ray Instruments, Madison, WI, **1994**.

Ce₁₆Si₁₅O₆N₃₂—An Oxonitridosilicate with Silicon Octahedrally Coordinated by Nitrogen**

Klaus Köllisch and Wolfgang Schnick*

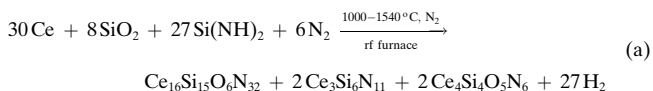
Octahedrally coordinated silicon is a peculiarity in silicate chemistry because the vast majority of natural and synthetic oxosilicates contain SiO₄ tetrahedra as typical structural building units.^[1] However, there are only a small number of silicates, in which the coordination number of silicon is larger than four.^[1–3] Most of the known examples are high-pressure phases like the rutile-type SiO₂ modification stishovite, the perovskite-analogous (Mg,Fe)SiO₃, which is found in the deeper crust of the earth, or hollandite-analogous CaAl₂-Si₂O₈.^[2] At lower pressure several silicates are accessible that contain SiO₆ octahedra and SiO₄ tetrahedra (e.g. K₂Si₄O₉,^[4] BaSi₄O₉,^[5] and Na_{1.8}Ca_{1.1}Si₆O₁₄).^[6] Furthermore there are a small number of silicon phosphates that have been obtained at ambient pressure and these contain polymeric network structures of SiO₆ octahedra and PO₄ tetrahedra (e.g. SiP₂O₇ (form I),^[7] Rb₂SiP₄O₁₃,^[8] (NH₄)₂SiP₄O₁₃).^[9] Owing to its enhanced basicity Si rather than P prefers the octahedral coordination in these compounds.^[8]

A formal exchange of oxygen by nitrogen leads from the oxosilicates to the nitridosilicates. Yet all known representatives are constructed from SiN₄ tetrahedra. Unlike their oxidic analogues, more varied possibilities for the linkage of the SiX₄ building units (X = N, O) occur in the nitridosilicates.^[10]

The compounds in the Si–Al–O–N and Si–O–N systems (“sialons” and “sions”, respectively) have gained significant importance in materials science because of their outstanding thermal, chemical, and mechanical stability.^[11] These compounds may be viewed as a link between oxidic silicates and

aluminosilicates on one hand and the nitridosilicates and nitridoaluminosilicates on the other.^[12, 13] Among the hitherto known crystalline nitridosilicates,^[10] oxonitridosilicates, and oxonitridoaluminosilicates^[11–13] as well as all the glassy phases that have been investigated in the systems Si–O–N and Si–Al–O–N^[11, 14] no experimental evidence for the occurrence of octahedrally coordinated silicon has yet been found.

With Ce₁₆Si₁₅O₆N₃₂ we have now synthesized the first oxonitridosilicate containing SiN₆ octahedra.^[15] This new sion has been obtained by the reaction of stoichiometric amounts of cerium metal with silicon diimide and silicon dioxide in a radio frequency (rf) furnace under nitrogen atmosphere (ambient pressure) [Eq. (a)].



Despite varying all experimental parameters (stoichiometry, reaction temperature, reaction time) we have not yet succeeded in synthesizing single-phase Ce₁₆Si₁₅O₆N₃₂. Under optimized conditions (see Experimental Section) coarsely crystalline Ce₁₆Si₁₅O₆N₃₂ was obtained as ruby-red single crystals in a yield of approximately 20% among yellow Ce₃Si₆N₁₁^[16] and yellow-orange Ce₄Si₄O₅N₆.^[17] All three phases are easily distinguishable in the reaction product due to their crystal habitus and their color, and they are obtained in the ratio given in Equation (a). Similar to all other highly condensed nitridosilicates, Ce₁₆Si₁₅O₆N₃₂ is stable up to 1600 °C and insensitive to hot acids and alkalis.

The X-ray structural analysis using diffraction data obtained on a four-circle diffractometer initially yielded a simple perovskite-type structure with a cubic lattice constant *a* = 385.1 pm. However neither a plausible composition of the compound nor a sufficient anisotropic refinement of the crystal structure could be performed based on this unit cell. A complete set of precession photographs revealed a 4 × 4 × 4 superstructure with a cubic lattice constant *a*' = 1540.36(9) pm. Accordingly the volume of the unit cell is 64 times as large as that of the simple perovskite structure type. In order to record even the weak superstructure reflections the data collection was performed by using the Stoe-IPDS image plate diffraction system.

According to the single-crystal X-ray structure determination,^[18] the solid contains a three-dimensional network of corner-sharing SiN₆ octahedra and Si(O,N)₄ tetrahedra^[15] (Figure 1). The structure may be viewed as a distorted defect variant Ce₁₆(Si₁₅□₁)O₆N₃₂□₁₀ of a 4 × 4 × 4 superstructure derived from the perovskite type (ABX₃). From a total of 64 octahedra per unit cell only four remain unchanged, four have been eliminated, and 56 have been replaced by tetrahedra (Figure 2).

A partial replacement of octahedra by tetrahedra in the perovskite structure type under formation of a superstructure has been reported, for example, for Sr₃Al₂O₆,^[19] in which every fourth octahedron remains unchanged. A nearly complete substitution of 15 from 16 octahedra, as occurs in Ce₁₆Si₁₅O₆N₃₂, is to our knowledge unprecedented. However the few remaining SiN₆ octahedra in Ce₁₆Si₁₅O₆N₃₂ are nearly regular and they are only slightly tilted from their ideal

[*] Prof. Dr. W. Schnick, Dipl.-Chem. K. Köllisch
 Institut für Anorganische Chemie der Universität
 D-80333 München (Germany)
 Fax: (+49) 89-5902-577
 E-mail: wsc@anorg.chemie.uni-muenchen.de

[**] Financial support by the Deutsche Forschungsgemeinschaft (“Schwerpunktprogramm Nitridobrücken”, Projekt SCHN 377/7 and Gottfried-Wilhelm-Leibniz-Programm), the Fonds der Chemischen Industrie, and the BMBF is gratefully acknowledged. The authors also would like to thank the Universität Bayreuth, Germany, where the experimental investigations were performed at the Laboratorium für Anorganische Chemie. Data collection using the Stoe-IPDS system by Prof. Dr. J. Beck, Institut für Anorganische Chemie, Universität Giessen, is also acknowledged.

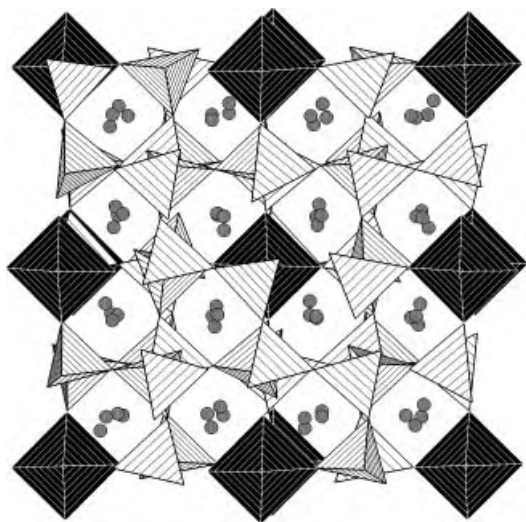


Figure 1. Crystal structure of $\text{Ce}_{16}\text{Si}_{15}\text{O}_6\text{N}_{32}$ (view along $[100]$), which is a defect variant of a $4 \times 4 \times 4$ superstructure of the perovskite type.

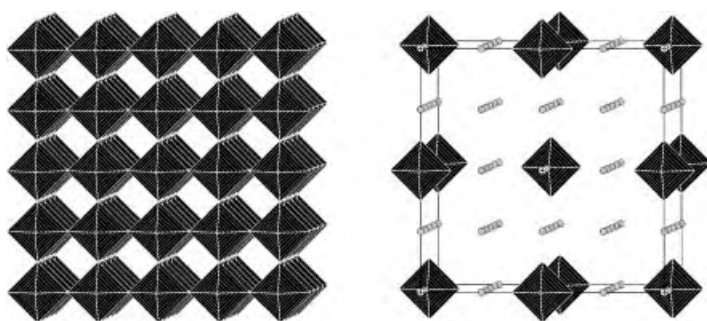


Figure 2. Idealized representation of the Si-O-N network in $\text{Ce}_{16}\text{Si}_{15}\text{O}_6\text{N}_{32}$ (right) and the relation to a $4 \times 4 \times 4$ superstructure of the cubic perovskite type (left). The octahedra (four per unit cell) are depicted as closed polyhedra, the tetrahedral centers (56 per unit cell) as grey spheres, and the omitted octahedra (four per unit cell) as spheres marked with a cross.

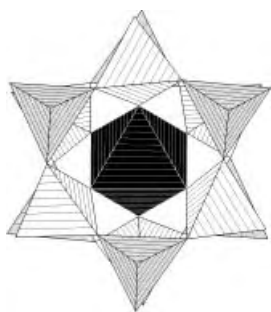


Figure 3. Environment of the SiN_6 octahedra in $\text{Ce}_{16}\text{Si}_{15}\text{O}_6\text{N}_{32}$ (view along $[111]$). Each SiN_6 octahedron is connected to two parallel rings formed from six $\text{Si}(\text{O},\text{N})_4$ tetrahedra.

to the same^[29] or a higher number^[12, 13, 29] of neighboring Si atoms. Therefore the $\text{Si}(\text{O},\text{N})_4$ tetrahedra of the network presumably are Q^3 units, and each of them contains one $\text{O}^{[1]}$ atom terminally bound to Si.^[*]

[*] The superscripted numbers in square brackets following the element symbols define their coordination numbers.

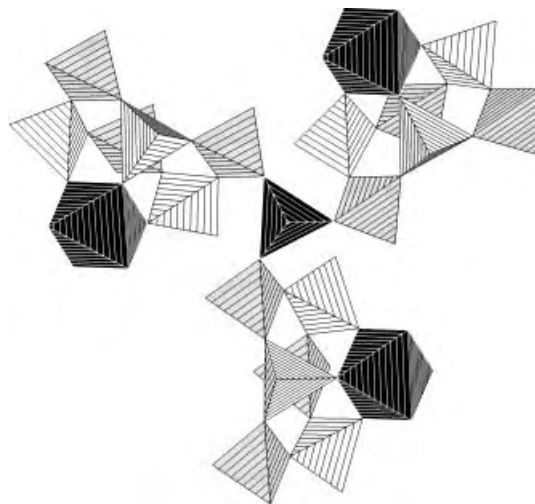


Figure 4. Connection of octahedra and tetrahedra in $\text{Ce}_{16}\text{Si}_{15}\text{O}_6\text{N}_{32}$ (view along $[111]$). The octahedron ring units are further connected by $\text{Si}(\text{O},\text{N})_4$ tetrahedra (black). Here only one ring per octahedron is depicted.

The bond lengths to the bridging atoms ($\text{Si}-(\text{O},\text{N})^{[2]}$ 170.1(8)–176.8(9) pm) are in a typical range.^[1, 2, 10, 12, 13] As expected^[21] the respective distances to the terminal atoms in the $\text{Si}(\text{O},\text{N})_4$ tetrahedra are shorter (165.2(8)–171.1(9) pm). Due to the higher coordination number of silicon in the SiN_6 octahedra ($\text{Si}^{[6]}-\text{N}$: 210.5(8) pm) the Si–N bond lengths are longer than those in SiN_4 tetrahedra ($\text{Si}^{[4]}-\text{N}$ 164–197 pm).^[10] Because of the larger ionic radius^[22] of N^{3-} these distances are longer than those in SiO_6 octahedra (typical values for $\text{Si}^{[6]}-\text{O}$ 170–184 pm).^[1]

In this defect variant the Ce^{3+} ions occupy positions that are comparable to the respective sites in the regular perovskite structure type (Figure 1). The Ce^{3+} ions are octahedrally, eightfold, or tenfold coordinated ($\text{Ce} \cdots (\text{N},\text{O})$ 232.0(8)–300.7(8) pm).

Most oxosilicates are constructed from SiO_4 tetrahedra.^[1, 23] Accordingly oxygen may be terminally bound to Si ($\text{O}^{[1]}$) or it may function as a simple bridge between two Si ($\text{O}^{[2]}$, e.g. in quartz SiO_2).^[24] In nitridosilicates nitrogen can either be bound to one ($\text{N}^{[1]}$), two ($\text{N}^{[2]}$), three ($\text{N}^{[3]}$), or even four ($\text{N}^{[4]}$) neighboring Si.^[10] As in oxosilicates, the SiX_4 tetrahedra ($\text{X} = \text{O}, \text{N}$) in nitridosilicates may be linked through corners but additionally they may also be connected through edges.^[10] $\text{Ce}_{16}\text{Si}_{15}\text{O}_6\text{N}_{32}$ is the first nitridosilicate with silicon in an octahedral coordination. In analogy to oxosilicates, SiX_6 octahedra ($\text{X} = \text{O}, \text{N}$) are predominantly expected in high-pressure phases.^[1–3] However investigations (e.g. high-pressure sintering, hot-pressing) on Si_3N_4 , which is currently the most important nitridic material, gave no indication of a possible increase of the coordination number of silicon from four to six.^[11]

On the basis of the results of this work, the occurrence of silicon in an octahedral coordination is anticipated in nitridosilicates, oxonitridosilicates, and oxonitridoaluminosilicates as well as in the glassy phases of the systems Si–O–N and Si–Al–O–N. Furthermore, high-pressure investigations in these systems might reveal several interesting and new compounds.

Experimental Section

In a typical batch $\text{Si}(\text{NH})_2$ (0.69 mmol), Ce (0.76 mmol), and SiO_2 (0.20 mmol) were thoroughly mixed in a glove box under a purified argon atmosphere. The reaction batch then was transferred into a tungsten crucible, and placed into the reactor of a radio frequency (rf) furnace which was inductively heated^[25] under a purified N_2 atmosphere (1 bar). During the reaction the crucible was heated to 850 °C within 5 min. After 10 min at this temperature, it was heated to 1540 °C over 3 h and held at this temperature for 1 h. Afterwards the crucible was allowed to cool down to 1200 °C over 53 h and to 900 °C over 15 h. Finally the reaction product was quenched to room temperature. In accordance with the X-ray structure determination, the analytical composition of $\text{Ce}_{16}\text{Si}_{15}\text{O}_6\text{N}_{32}$ was confirmed by energy-dispersive X-ray microanalysis (Ce, Si). The absence of hydrogen (N–H) was checked by IR spectroscopy.

Received: September 4, 1998 [Z 123781E]
German version: *Angew. Chem.* **1999**, *111*, 368–370

Keywords: materials science • nitridosilicates • silicon • solid-state chemistry • structure elucidation

- [1] F. Liebau, *Structural Chemistry of Silicates*, Springer, Berlin, **1985**, pp. 14–51.
- [2] L. W. Finger, R. M. Hazen, *Acta Crystallogr. Sect. B* **1991**, *47*, 561.
- [3] R. M. Hazen, R. T. Downs, L. W. Finger, *Science* **1996**, *272*, 1769.
- [4] D. K. Swanson, C. T. Prewitt, *Am. Mineral.* **1983**, *68*, 581.
- [5] L. W. Finger, R. M. Hazen, B. A. Fursenko, *J. Phys. Chem. Solid.* **1995**, *56*, 1389.
- [6] T. Gasparik, J. B. Parise, B. A. Eiben, J. A. Hriljac, *Am. Mineral.* **1995**, *80*, 1269.
- [7] D. M. Poojary, R. B. Borade, F. L. Campbell III, A. Clearfield, *J. Solid State Chem.* **1994**, *112*, 106.
- [8] K. Königstein, M. Jansen, *Chem. Ber.* **1994**, *127*, 1213.
- [9] A. Durif, M. T. Averbuch-Pouchot, J. C. Guitel, *Acta Crystallogr. Sect. B* **1976**, *32*, 2957.
- [10] W. Schnick, H. Huppertz, *Chem. Eur. J.* **1997**, *3*, 679.
- [11] S. Hampshire in *Materials Science and Technology*, Vol. 11 (Eds.: R. W. Cahn, P. Haasen, E. J. Kramer), VCH, Weinheim, **1994**, p. 119.
- [12] R. Lauterbach, W. Schnick, *Z. Anorg. Allg. Chem.* **1998**, *624*, 1154.
- [13] W. Schnick, H. Huppertz, R. Lauterbach, *J. Mater. Chem.*, in press.
- [14] S. Kohn, W. Hoffbauer, M. Jansen, R. Franke, S. Bender, *J. Non-Cryst. Solids* **1998**, *224*, 232.
- [15] A direct differentiation of O and N in the network $[\text{Si}_{15}\text{O}_6\text{N}_{32}]^{48-}$ by X-ray diffraction methods is not possible because of the very similar scattering factors of both elements. Under the assumption that only Ce^{3+} ions occur, lattice-energetic calculations using the MAPLE^[26] algorithm (Madelung part of lattice energy) and valence sum calculations with the bond-length/bond-strength concept^[27] yielded a high preference for SiN_6 octahedra. In contrast, in the $\text{Si}(\text{O},\text{N})_4$ tetrahedra no convincing differentiation between N and O was possible. Maybe both elements are even statistically disordered on the X sites of the SiX_4 tetrahedra. This situation frequently has been found in several Si–Al–O–N compounds (compare, for example, refs. [28,29] and the references therein). An unequivocal differentiation of O and N may be possible after neutron diffraction experiments. Significant experimental results for the identification and differentiation of the $\text{SiO}_{(4-x)}\text{N}_x$ tetrahedra ($0 \leq x \leq 4$) might also be available from ^{29}Si and ^{15}N MAS NMR investigations.^[14,29] With respect to the paramagnetic behavior of $\text{Ce}_{16}\text{Si}_{15}\text{O}_6\text{N}_{32}$, however, those investigations seem to be less promising.
- [16] T. Schlieper, W. Schnick, *Z. Anorg. Allg. Chem.* **1995**, *621*, 1535.
- [17] K. Köllisch, W. Schnick, unpublished results.
- [18] Crystal structure data: $\text{Ce}_{16}\text{Si}_{15}\text{O}_6\text{N}_{32}$: $P\bar{6}3$, $a = 1540.36(9)$ pm, $Z = 4$, Stoe-IPDS, $\text{MoK}\alpha$ radiation, graphite monochromator, $F(000) = 5640.0$, $\mu(\text{MoK}\alpha) = 20.04 \text{ mm}^{-1}$, 16170 measured reflections in the range $2^\circ \leq 2\theta \leq 56^\circ$, 1165 unique reflections with $F_o^2 \geq 2\sigma(F_o^2)$; numeric absorption correction (HABITUS), $R_{\text{int}} = 0.1073$. The crystal structure was solved by direct methods (SHELXTL, Vers. 5.03) and anisotropically refined by a least-squares procedure against F^2 with all data; 105

refined parameters, $R1 = 0.0353$ for $F_o^2 \geq 2\sigma(F_o^2)$, $wR2 = 0.0859$, $\text{GOF} = 1.085$. Further details on the crystal structure investigation may be obtained from the Fachinformationszentrum Karlsruhe, D-76344 Eggenstein-Leopoldshafen, Germany (fax: (+49) 7247-808-666; e-mail: crysdata@fiz-karlsruhe.de), on quoting the depositary number CSD-380184.

- [19] J. A. Alonso, I. Rasines, J. L. Soubeyrou, *Inorg. Chem.* **1990**, *29*, 4768.
- [20] L. Pauling, *The Nature of the Chemical Bond*, 3rd ed., Cornell University Press, Ithaca, New York, **1960**, p. 543.
- [21] H. Huppertz, W. Schnick, *Angew. Chem.* **1997**, *109*, 2765; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2651.
- [22] W. H. Baur, *Crystallogr. Rev.* **1987**, *1*, 59.
- [23] A rare example for a silicate with SiO_5 units is CaSi_2O_5 , which was obtained under high-pressure, see: R. J. Angel, N. L. Ross, F. Seifert, T. F. Fliervoet, *Nature* **1996**, *384*, 441.
- [24] However in stishovite $[\text{Si}^{(6)}\text{O}_2^{(3)}]$, which has a rutile type of structure, oxygen is coordinated by three silicon atoms.
- [25] The radio frequency (rf) furnace is described in ref. [13] and in T. Schlieper, W. Schnick, *Z. Anorg. Allg. Chem.* **1995**, *621*, 1037.
- [26] a) R. Hoppe, *Angew. Chem.* **1966**, *78*, 52; *Angew. Chem. Int. Ed. Engl.* **1966**, *5*, 95; b) R. Hoppe, *Angew. Chem.* **1970**, *82*, 7; *Angew. Chem. Int. Ed. Engl.* **1970**, *9*, 25.
- [27] N. E. Brese, M. O'Keeffe, *Acta Crystallogr. Sect. B*, **1991**, *47*, 192.
- [28] P. L. Wang, P.-E. Werner, *J. Mater. Sci.* **1997**, *32*, 1925.
- [29] A. Koroglu, D. C. Apperley, R. K. Harris, D. P. Thompson, *J. Mater. Chem.* **1996**, *6*, 1031.

A Paramagnetic Copper(III) Complex Containing an Octahedral $\text{Cu}^{\text{III}}\text{S}_6$ Coordination Polyhedron**

Carsten Krebs, Thorsten Glaser, Eckhard Bill, Thomas Weyhermüller, Wolfram Meyer-Klaucke, and Karl Wieghardt*

Most inorganic chemistry textbooks^[1] comment on the coordination chemistry of copper in the “unusual”, that is rare, oxidation state +III with d^8 electron configuration that there is only one *paramagnetic* ($S = 1$) species containing an octahedral coordination polyhedron known, namely $\text{K}_3[\text{Cu}^{\text{III}}\text{F}_6]$.^[2] On the other hand, a number of diamagnetic, square-planar Cu^{III} complexes have been described and have even been structurally characterized. We report here the synthesis, as well as the molecular and electronic structure of a new paramagnetic Cu^{III} species containing an octahedral $\text{Cu}^{\text{III}}\text{S}_6$ coordination polyhedron.

It is well established that thiolato ligands can lower the $\text{Cu}^{\text{III}}/\text{Cu}^{\text{II}}$ redox potential.^[3] In principle, they can stabilize high formal oxidation states of a given transition metal ion.

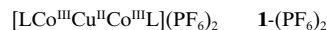
[*] Prof. Dr. K. Wieghardt, Dr. C. Krebs, Dr. T. Glaser, Dr. E. Bill, Dr. T. Weyhermüller
Max-Planck-Institut für Strahlenchemie
Stiftstrasse 34–36, D-45470 Mülheim an der Ruhr (Germany)
Fax: (+49) 208-3063951
E-mail: wieghardt@mpi-muelheim.mpg.de

Dr. W. Meyer-Klaucke
EMBL-Outstation Hamburg
Gebäude 25A, Notkestrasse 85, D-22603 Hamburg (Germany)

[**] This work has been financially supported by the Fonds der Chemischen Industrie

On the other hand, the conceivable generation of thiyl radical complexes during synthesis cannot be a priori rejected. Thus the electronic structures of a thiyl radical–Cu^{II} complex and that of a genuine thiolato–Cu^{III} species must be carefully—if possible experimentally—distinguished.

The reaction of mononuclear [Co^{III}L],^[4] in which L^{3−} is the hexadentate macrocyclic trianion 1,4,7-tris(4-*tert*-butyl-2-sulfidobenzyl)-1,4,7-triazacyclononane, with Cu^{II}(OAc)₂·H₂O (2:1) in methanol affords upon addition of NaPF₆ red crystals of the heterotrimeric complex **1**-(PF₆)₂. One-electron oxi-



dation of **1** in acetone using one equivalent of [Ni^{III}(tacn)₂](ClO₄)₃^[5] (tacn = 1,4,7-triazacyclononane) and addition of NaClO₄ yields blue-black microcrystals of **2**-(ClO₄)₃·2Me₂CO. Complex **2** is stable in the solid state for weeks but decomposes rapidly within minutes in solution (reduction).

Single crystals of **1**-(BPh₄)₂·6CH₃CN were found to be suitable for X-ray crystallography,^[6] and Figure 1 shows the

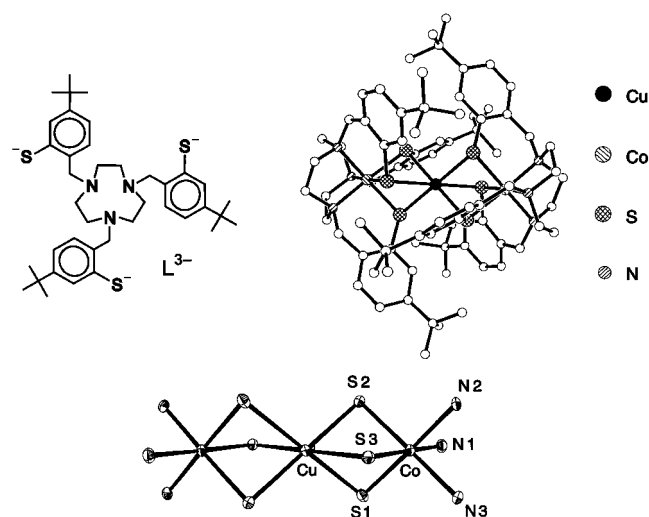


Figure 1. View of the 1,4,7-tris(4-*tert*-butyl-2-mercaptobenzyl)-1,4,7-triazacyclononane ligand (top left), structure of the dication in **1**-(BPh₄)₂·6CH₃CN (top right), and section of its structure (bottom). Selected bond lengths [Å] and angles [°]: Cu–S1 2.516(2), Cu–S2 2.388(1), Cu–S3 2.477(1), average Co–S 2.244(2), average Co–N 2.026(2), Cu···Co 3.153(1); Co–S1–Cu 82.64(4), Co–S2–Cu 85.79(4), Co–S3–Cu 83.61(5).

structure of the trinuclear dication. Both diamagnetic Co^{III} ions are in the terminal positions in an octahedral *cis*-N₃S₃ donor atom environment, whereas the central Cu^{II} ion is in a severely Jahn–Teller distorted, octahedral Cu^{II}S₆ polyhedron. The cation has crystallographically imposed C_i symmetry; the three independent Cu^{II}–S bond lengths differ significantly, whereas the Co^{III}–N and Co^{III}–S bond lengths are identical within experimental error, respectively. They are the same as observed in diamagnetic, mononuclear [Co^{III}L].^[4]

The cyclic voltammogram of **1** recorded in CH₃CN (0.10 M (*n*Bu₄N)PF₆) displays a reversible one-electron oxidation at E_{1/2} = +0.35 V versus ferrocenium/ferrocene (Fc⁺/Fc), which

is assigned to the Cu^{III}/Cu^{II} redox couple. In addition, a second quasi-reversible one-electron oxidation step at +0.90 V versus Fc⁺/Fc has been observed which might correspond to the Cu^{IV}/Cu^{III} couple. At E_p^{red} = −1.96 V versus Fc⁺/Fc complex **1** is irreversibly reduced (Cu^{II} → Cu^I). Note the analogous cadmium species [LCo^{III}Cd^{II}Co^{III}L](PF₆)₂ does not display any redox activity in the potential range +0.7 to −1.1 V versus Fc⁺/Fc.

Temperature-dependent magnetic susceptibility measurements (SQUID, 2–300 K; 1.0 T) on powdered samples revealed a temperature-independent magnetic moment of 1.74 μ_B (10–300 K) for **1**-(PF₆)₂ and slightly temperature-dependent moments between 2.4 and 2.6 μ_B (20–300 K) for **2**-(ClO₄)₃·2Me₂CO in reasonable agreement with the expected spin-only values for Cu^{II} (S = ½) and high-spin Cu^{III} ions (S = 1).

Metal K-edge X-ray absorption spectra (XAS)^[7] measured at the Co and Cu K-edges of **1**-(PF₆)₂ and **2**-(ClO₄)₃·2Me₂CO show unambiguously that oxidation of **1** to **2** affects only the central Cu ion. As displayed in Figure 2 the Co K-edge

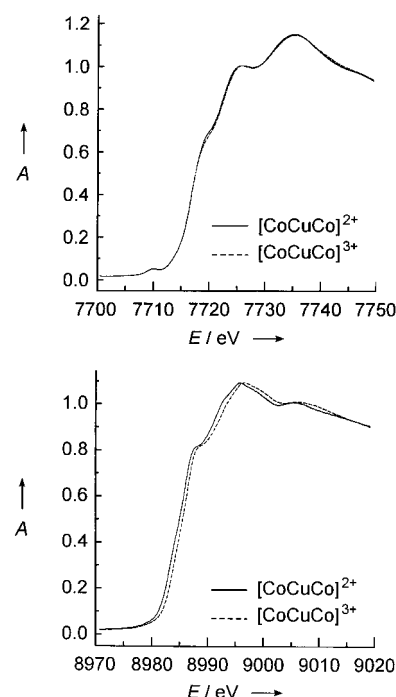


Figure 2. Metal K-edge X-ray absorption spectra (XAS spectra) of **1**-(PF₆)₂ and **2**-(ClO₄)₃·2Me₂CO. Top: Co K-edge, bottom: Cu K-edge. A = normalized absorption.

energies of **1** and **2** are identical, whereas the spectra measured at the Cu K-edge are significantly different. The Cu K-edge energy in **2** is about 0.7 eV higher than that in **1** in accord with a metal-centered one-electron oxidation of **1** to **2**.^[8] Furthermore, the analysis of the Co and Cu K-edge EXAFS spectra (extended X-ray absorption fine structure) of **1** and **2** shows that oxidation of **1** to **2** does not affect the Co–N and Co–S bond lengths (2.02(1) and 2.239(6) Å, respectively); they are in excellent agreement with the crystallographically determined values for **1**-(BPh₄)₂·6CH₃CN. Even the Cu–S distances in **1** and **2** appear to be identical (but see

the comment in ref. [9]). Clearly, the cations in **1** and **2** are isostructural and the Cu K-edge XAS and EXAFS spectra conclusively rule out a Cu^{II}–thiol formulation for **2**. Therefore, **2** is considered to be a genuine Cu^{III} species which is isoelectronic with the structurally characterized species [LCo^{III}Ni^{III}Co^{III}L]²⁺. We have shown previously^[10] that this compound can be oxidized by two successive one-electron steps to give a paramagnetic Ni^{III} and a diamagnetic Ni^{IV} complex.

Figure 3 shows the EPR spectra of **1** and **2** in CH₃CN solution and their simulations.^[11] The rhombic signal displaying Cu hyperfine splitting for **1** is characteristic for a Cu^{II} ion

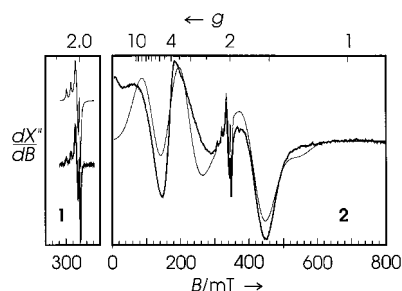


Figure 3. X-Band EPR spectra of **1**-(PF₆)₂ (left) at 10 K and of **2**-(ClO₄)₃·2Me₂CO (right) at 4 K in acetone and simulations (thin lines).^[11] Experimental conditions for **1**-(PF₆)₂ (in parentheses for **2**-(ClO₄)₃·2Me₂CO): frequency 9.46 GHz (9.65 GHz); energy 0.1 mW (1.0 mW), modulation amplitude 1.9 mT (1.3 mT); modulation frequency 100 kHz (100 kHz).

with $S = \frac{1}{2}$ ground state. In contrast, the spectrum of **2** is typical for a triplet ground state ($S = 1$) with small zero-field splitting. In summary, we have shown that six bridging thiolato ligands are capable of stabilizing a high-spin d⁸ electron configuration of a Cu^{III} ion.

Experimental Section

1-(PF₆)₂: To a suspension of [LCo^{III}]^[4] (0.35 g) in methanol (120 mL) was added Cu(OAc)₂·H₂O (0.05 g). After heating the mixture to reflux for 30 min, NaPF₆ (1.60 g) dissolved in methanol (20 mL) was added. Filtration and cooling to 4 °C initiated the precipitation of red crystals of **1**-(PF₆)₂ in 91% yield (0.39 g). Single crystals of **1**-(BPh₄)₂·6 CH₃CN were obtained by allowing an acetonitrile solution containing Na(BPh₄) to slowly diffuse into an acetonitrile solution of **1**-(PF₆)₂. ESI-MS (CH₃CN): 1641 [**1**-(PF₆)₂ – PF₆]⁺, 751 [**1**-(PF₆)₂ – 2 PF₆]²⁺; UV/Vis/NIR (CH₃CN): λ_{max} (ε) = 273 (52100), 455 (2870), 532 (3090), 797 nm (6380); elemental analysis calcd for C₇₈H₁₀₈N₆S₆Co₂CuP₂F₁₂ (%): C 52.2, H 6.1, N 4.7, S 10.7, Co 6.6, Cu 3.5; found: C 51.9, H 6.1, N 4.5, S 10.9, Co 6.5, Cu 3.5.

2-(ClO₄)₃·2Me₂CO: The synthesis was carried out under an argon blanketing atmosphere. To a solution of **1** (130 mg) in dry acetone (20 mL) was added [Ni^{III}(tacn)₂](ClO₄)₃ (53 mg).^[5] After stirring the mixture for 10 min at 40 °C, NaClO₄ (2.00 g) dissolved in acetone (20 mL) was added and the reaction volume was reduced by one half by rotary evaporation of the solvent. Storage of the resulting solution at –80 °C produced within 30 min blue-black crystals of **2** in 60% yield (0.08 g). ESI-MS (CH₃CN) 1602 [**2**-(ClO₄)₃·2Me₂CO – (2Me₂CO, ClO₄)⁺, 751 [**2**-(ClO₄)₃·2Me₂CO – (2Me₂CO, 3 ClO₄)²⁺; UV/Vis/NIR (CH₃CN): λ_{max} (ε) = 275 (63000), 560 (7000), 700 (5100), 1019 nm (1340); elemental analysis calcd for C₈₄H₁₂₀N₆S₆O₁₄Co₂CuCl₃ (%): C 52.6, H 6.3, N 4.4, S 10.0, Co 6.2, Cu 3.3, Cl 5.5; found: C 52.4, H 6.2, N 4.4, S 9.9, Co 6.2, Cu 3.3, Cl 5.5.

Received: August 5, 1998 [Z12250IE]

German version: *Angew. Chem.* **1999**, *111*, 370–372

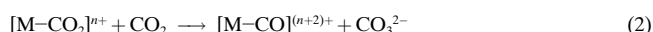
Keywords: cobalt • copper • EXAFS spectroscopy • S ligands

- a) F. A. Cotton, G. Wilkinson, *Advanced Inorganic Chemistry*, 5th ed., Wiley, New York **1988**, p. 774; b) N. N. Greenwood, A. Earnshaw, *Chemistry of the Elements*, Pergamon, Oxford, **1984**, p. 1379; c) A. F. Holleman, E. Wiberg, *Lehrbuch der Anorganischen Chemie* (Ed.: N. Wiberg), de Gruyter, Berlin, **1995**, p. 1337.
- a) W. Klemm, E. Huss, *Z. Anorg. Chem.* **1949**, *259*, 221; b) R. Hoppe, *Angew. Chem.* **1950**, *62*, 339.
- J. Hanss, H.-J. Krüger, *Angew. Chem.* **1996**, *108*, 2989; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2827.
- T. Beissel, T. Glaser, F. Kesting, K. Wiegardt, B. Nuber, *Inorg. Chem.* **1996**, *35*, 3936.
- K. Wiegardt, W. Walz, B. Nuber, J. Weiss, A. Ozarowski, H. Strateimer, D. Reinen, *Inorg. Chem.* **1986**, *25*, 1650.
- Crystal data for **1**-(BPh₄)₂·6 CH₃CN: Siemens P4 diffractometer, MoK_α radiation, graphite monochromator, intensity data collected at 163(2) K. Red crystal, 0.52 × 0.44 × 0.40 mm, triclinic, space group *P* $\bar{1}$ (No. 2); *a* = 13.592(3), *b* = 16.556(3), *c* = 17.268(3) Å, *α* = 99.64(3), *β* = 112.06(3), *γ* = 112.04(3)°, *V* = 3116(1) Å³, *Z* = 1, *ρ*_{calcd} = 1.273 g cm^{–3}, *μ*(MoK_α) = 0.59 mm^{–1}, *F*(000) = 1267, 9578 independent reflections; 730 parameters; *R* = 0.040; *wR*₂ = 0.0849. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-102164. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- XAS and EXAFS spectra measured at the Co and Cu K-edge of **1**-(PF₆)₂ and **2**-(ClO₄)₃·2Me₂CO were recorded at Messplatz D2 (EMBL-EXAFS) DORIS (DESY, Hamburg). Reduction of the data and normalization of the K-edge energies were performed with EXPROG, analysis of the fine structure with FEFF6 and FEFFIT: For more details see T. Glaser, T. Beissel, E. Bill, T. Weyhermüller, V. Schünemann, W. Meyer-Klaucke, A. X. Trautwein, K. Wiegardt, *J. Am. Chem. Soc.*, submitted.
- J. L. DuBois, P. Mukherjee, A. M. Collier, J. M. Mayer, E. I. Solomon, B. Hedman, T. D. P. Stack, K. O. Hodgson, *J. Am. Chem. Soc.* **1997**, *119*, 8578.
- Due to the Jahn–Teller effect the Cu–S bond lengths in **1** are not equidistant (X-ray structure analysis). This effect was not resolved in the analysis of the EXAFS spectra and, consequently, apparently large Debye–Waller factors (*σ*² = 0.014(7) Å²) for the sulfur atoms have been observed. In contrast, in **2** the Debye–Waller factors for the S atoms are normal (*σ*² = 0.010(4) Å²). The Cu–S bond length in **2** is therefore more reliably determined; it is shorter at 2.239(6) Å than the average Cu–S distance of 2.46 Å in **1**-(BPh₄)₂·6 CH₃CN.
- T. Beissel, F. Birkelbach, E. Bill, T. Glaser, F. Kesting, C. Krebs, T. Weyhermüller, K. Wiegardt, C. Butzlaff, A. X. Trautwein, *J. Am. Chem. Soc.* **1996**, *118*, 12376.
- The simulation of the spectrum of **1** for an $S = \frac{1}{2}$ system was achieved with a rhombic *g* tensor *g* = (2.022, 2.053, 2.118) and anisotropic Lorentzian line shapes *W* = (5.2, 7.9, 4.4) mT. The first-order hyperfine splitting was only included for *g*_z with *A*_z = 126 × 10^{–4} cm^{–1} (*I* = $\frac{3}{2}$). The spectrum of **2** was simulated by using a spin Hamiltonian operator for $S = 1$:^[12] $|D| = 0.20$ cm^{–1}; *E/D* = 0 (fixed), *g* = 2.051 with Gaussian line width *W* = 88 mT. (The weak signal at *g* = 2 is due to Cu^{II} impurity of **1** (< 1 %)). Cu hyperfine structure is not resolved. A similar zero-field parameter *D* = –0.188 cm^{–1} has been reported for Cu^{III} ions in an Al₂O₃ matrix.^[13] Within the ligand field model for **2** the observed values for *D* and *g* are consistent with an octahedrally coordinated Cu^{III} ion (high-spin d⁸) with large splitting of the ²A_{2g} ground and a ²T excited state (10 Dq > 20000 cm^{–1}).
- B. J. Gaffney, H. J. Silverstone, *EMR of Paramagnetic Molecules, Biological Magnetic Resonance, Vol. 13* (Eds.: L. J. Berliner, J. Reuben), Plenum, New York, **1993**, adapted and modified for an $S = 1$ spin Hamilton operator by E. Bill (Mülheim).
- W. E. Blumberg, J. Eisinger, S. Geschwind, *Phys. Rev.* **1963**, *130*, 900.

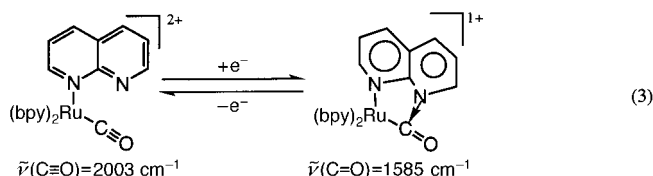
Selective Production of Acetone in the Electrochemical Reduction of CO₂ Catalyzed by a Ru–Naphthyridine Complex

Tetsunori Mizukawa, Kiyoshi Tsuge, Hiroshi Nakajima, and Koji Tanaka*

Electrochemical reduction of CO₂ with metal complexes is a feasible technique for the utilization of CO₂ as a C₁ source, though the reduction products usually have been limited to CO and/or HCOOH. Metal-catalyzed reductive disproportionation of CO₂ [Eq. (1)] proceeds through oxide transfer from a metal–CO₂ moiety to CO₂ [Eq. (2)] followed by reductive cleavage of the resultant metal–CO bond.



Acylation of the metal–CO bond would lead to a new methodology for carbon–carbon bond formation in the reduction of CO₂. Polypyridyl ruthenium carbonyl complexes such as [Ru(bpy)₂(quinoline)(CO)]²⁺ and [Ru(bpy)(terpyridine)(CO)]²⁺ (bpy = 2,2′-bipyridyl) work as catalysts for the reduction of CO₂ according to Equation (1),^[1] and one-electron reduction of these complexes causes a bathochromic shift of their ν(CO) bands by about 30–40 cm^{−1}.^[2] The mononaphthyridine complex [Ru(bpy)₂(napy)(CO)](PF₆)₂ (**1**; napy = 1,8-naphthyridine) undergoes a pronounced bathochromic shift of the ν(CO) band (Δν̄ = 418 cm^{−1}) upon one-electron reduction due to nucleophilic attack of the non-bonded nitrogen atom of the monodentate napy ligand on the carbonyl carbon atom [Eq. (3)].^[3]



Such a metallacyclization would suppress the reductive cleavage of the Ru–CO bond (CO evolution), and enable reduction of the CO group derived from CO₂. Here we report the first selective production of acetone in the electrochemical reduction of CO₂ catalyzed by [Ru(bpy)(napy)₂(CO)₂](PF₆)₂ (**2**) in the presence of (CH₃)₄NBF₄.

The two CO ligands of **2** are coordinated to Ru in *cis* positions, and the two napy moieties are linked to Ru in a monodentate manner, as depicted in the crystal structure (Figure 1).^[4]

[*] Prof. Dr. K. Tanaka, T. Mizukawa, Dr. K. Tsuge
Institute for Molecular Science
Myodaiji, Okazaki, Aichi, 444-8585 (Japan)
Fax: (+81) 564-5245
E-mail: ktanaka@ims.ac.jp
Dr. H. Nakajima
Japan Advanced Institute of Science and Technology
Tatsunokuchi, Ishikawa (Japan)

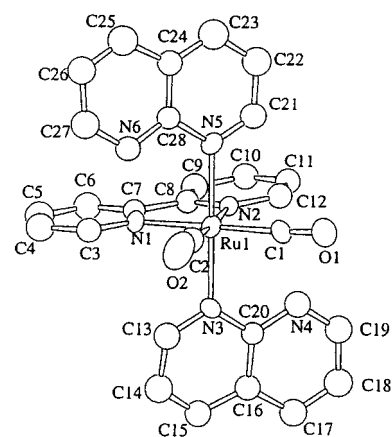


Figure 1. Molecular structure of the dication of **2** with atom labeling.

The cyclic voltammogram of **1** (0.1 mmol L^{−1}) in DMSO in the presence of (CH₃)₄NBF₄ (0.1 mol L^{−1}) under N₂ shows an irreversible cathodic wave at −1.40 V (all potentials are given versus that of Ag/Ag⁺) and three (quasi-)reversible redox couples at E_{pc} = −1.63, −1.80, and −2.02 V with peak separations (ΔE_{p-p}) of 60, 80 and 94 mV, respectively (Figure 2). The bis-napy complex **2** displays two irreversible

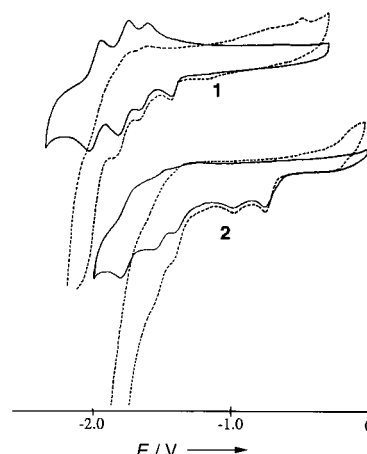


Figure 2. Cyclic voltammograms of **1** and **2** in the presence of (CH₃)₄NBF₄ under N₂ (—) and CO₂ (---) in DMSO. The potential E is given in V versus Ag/Ag⁺.

cathodic waves at E_{pc} = −0.76 and −0.98 V as well as three quasi-reversible couples at E_{pc} = −1.44, −1.58, and −1.94 V with ΔE_{p-p} = 80 mV under the same conditions. One irreversible cathodic wave of **1** (E_{pc} = −1.42 V) and two irreversible waves of **2** (E_{pc} = −0.76 and −0.98 V) result from reduction of the napy ligands followed by formation of the Ru–C(O)–N–N ring [Eq. (3)]. Introduction of CO₂ to the solutions of **1** and **2** in DMSO causes strong catalytic currents due to the reduction of CO₂ (Figure 2), since electrochemical reduction of CO₂ takes place at potentials more negative than −2.4 V in the absence of these complexes. It is noteworthy that the reduction of CO₂ by **2** occurs at potentials more negative than −1.4 V, while the threshold potential of the CO₂ reduction by **1** is close to −2.0 V.

In agreement with Equation (1), only CO and Li₂CO₃ were produced in the controlled potential electrolysis of **2**

(0.6 mmol L⁻¹) at -1.65 V with a glassy carbon (GC) electrode (4 cm²) in CO₂-saturated DMSO (30 mL)^[5] containing LiBF₄ (0.1 mol L⁻¹) as electrolyte. On the other hand, when (CH₃)₄NBF₄ was used as an electrolyte under otherwise similar conditions, acetone was selectively generated with a traces of CO. The amounts of these products increased with the electricity, as shown in Figure 3. Besides acetone and CO,

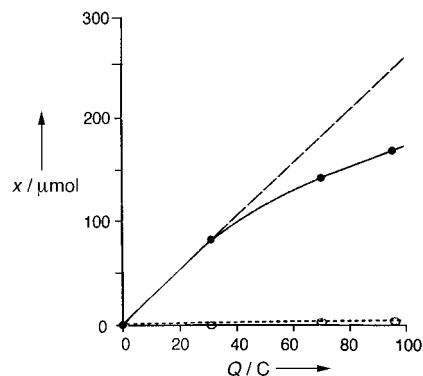
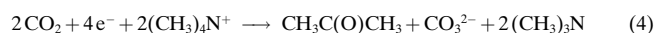


Figure 3. The amounts x of acetone (●) and CO (○) generated in the electrochemical reduction of CO₂ catalyzed by **2** in the presence of (CH₃)₄NBF₄ in DMSO at -1.60 V. The dashed line represents the theoretical amount of acetone expected based on Equation (4).

(CH₃)₃N and {(CH₃)₄N}₂CO₃ were the only other products detected in the solution. Thus, (CH₃)₄N⁺ works not only as an electrolyte, but also as a methylation reagent for the catalytic generation of acetone in the electrochemical reduction of CO₂ catalyzed by **2** [Eq. (4)].



Based on the stoichiometry of Equation (4), the current efficiency of acetone was 70 % at 100 °C (turnover number 8.5) and that of CO was less than 1 %. This first selective formation of acetone in the electrochemical reduction of CO₂ [Eq. (4)] is associated with the suppression of reductive cleavage of the Ru-CO bond [Eq. (1)] by the metallacyclization shown in Equation (3).^[6] Indeed, the current densities of the GC electrodes in the reduction of CO₂ catalyzed by **2** were 5 and 0.25 mA cm⁻² in the presence of (CH₃)₄NBF₄ [Eq. (4)]^[7] and LiBF₄ [Eq. (1)], respectively. Moreover, the electrolysis potential is of fundamental importance for the catalytic generation of acetone, since acetone undergoes irreversible reduction at potentials of -2.0 V on GC electrodes in DMSO. Therefore, from the viewpoints of the threshold potential for the reduction of CO₂ (Figure 2), **1** is not a suitable catalyst for the reduction shown in Equation (4) even though CO evolution is depressed by the metallacyclization reaction of Equation (3).^[8]

Experimental Section

To a solution of RuCl₃·3H₂O (1 mmol) in ethanol (50 mL) was added bpy (1 mmol), and the solution was heated under reflux for 2 h. Then Et₃N (0.5 mL) and napy (3 mmol) were added, and the solution was heated under reflux for 2 h. The reaction mixture was concentrated to about 5 mL. Addition of NaBF₄ (2 mmol) in H₂O resulted in precipitation of purple [Ru(bpy)(napy)₂Cl]BF₄ in 80 % yield. A suspension of [Ru(bpy)-

(napy)₂Cl]BF₄ in ethanol was heated at 60 °C under CO (40 atm) for 15 h. Concentration of the solution and treatment with an aqueous solution of NaBF₄ gave [Ru(bpy)(napy)₂(CO)₂](BF₄)₂ as a yellow powder in 70 % yield. Elemental analysis calcd for C₂₈H₂₀N₆B₂F₈Ru: C 44.98, H 2.68, N 11.24; found: C 44.83, H 2.39, N 11.24; IR: $\tilde{\nu}$ = 2077, 2027 cm⁻¹ (CO).

Received: June 8, 1998 [Z11960IE]
German version: *Angew. Chem.* **1999**, *111*, 373–374

Keywords: carbon dioxide • Ketones • N ligands • reductions • ruthenium

- [1] a) A. G. M. Mostafa Hossain, T. Nagaoka, K. Ogura, *Electrochim. Acta* **1997**, *42*(16), 2577; b) G. N. A. Nallas, K. J. Brewer, *Inorg. Chim. Acta* **1996**, *253*, 7; c) A. G. M. Mostafa Hossain, T. Nagaoka, K. Ogura, *Electrochim. Acta* **1996**, *41*(17), 2773; d) S. Matsuoka, T. Kohzaki, C. Pac, S. Yanagida, *Chem. Lett.* **1990**, *11*, 2047; e) S. Ikeda, Y. Saito, M. Yoshida, N. Noda, M. Maeda, K. Ito, *J. Electroanal. Chem. Interfacial Electrochem.* **1989**, *260*, 335; f) N. A. Maiorova, O. A. Khazova, Yu. B. Vasil'ev, *Elektrokhimiya* **1986**, *22*, 1196; g) Yu. B. Vasil'ev, V. S. Bagotskii, O. A. Khazova, N. A. Maiorova, *J. Electroanal. Chem. Interfacial Electrochem.* **1985**, *189*, 295.
- [2] a) H. Nakajima, Y. Kushi, H. Nagao, K. Tanaka, *Organometallics* **1995**, *14*; b) K. Toyohara, K. Tanaka, unpublished results.
- [3] H. Nakajima, K. Tanaka, *Chem. Lett.* **1995**, *10*, 891.
- [4] a) Crystal data for **1**: monoclinic, $P2_1/n$, $a = 10.696(2)$, $b = 14.989(3)$, $c = 18.395(2)$ Å, $\beta = 99.58(1)^\circ$, $V = 2907.7(8)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 1.707$ g cm⁻³, $20.2 < 2\theta < 23.6^\circ$, $\text{MoK}\alpha$ ($\lambda = 0.71069$ Å); of 7296 reflections observed, 6936 were independent. The structure was solved by direct methods (SAPI91) and refined against $|F|$ with 2230 reflections ($I > 3.0\sigma(I)$) and 234 parameters; $R = 0.071$ and $R_w = 0.060$. b) Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-101753. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [5] The concentration of residual water in the DMSO was 21 μmol L⁻¹.
- [6] The electrochemical reduction of CO₂ also took place in CH₃CN, though in this case CO₃²⁻ is likely to deposit on the electrode. An orange solution obtained upon concentration of the electrolyzed solution of **2** in CH₃CN became yellow after exposure to air. Appearance of the two $\nu(\text{CO})$ bands typical of **2** in the IR spectra of the resultant yellow solution strongly indicates that the reduced form of **2** is the stable catalyst in the formation of acetone.
- [7] An initial current density of 5 mA cm⁻² dropped to about one-third at 100 °C due to consumption of (CH₃)₄NBF₄. Renewed addition of electrolyte to the solution resulted in almost complete recovery of the initial current density.
- [8] Only a small amount of isopropyl alcohol was detected (current efficiency of about 10 %) in the electrochemical reduction of CO₂ catalyzed by **1** at -2.00 V in DMSO in the presence of (CH₃)₄NBF₄.

Homogeneous Hydrogenation Catalysis with Monodisperse, Dendrimer-Encapsulated Pd and Pt Nanoparticles**

Mingqi Zhao and Richard M. Crooks*

In this report we show that composite materials that consist of noble metal nanoparticles stabilized within dendrimer interiors are suitable for use as homogeneous hydrogenation catalysts. These interesting new materials are prepared by sorbing Pd^{II} or Pt^{II} ions into hydroxyl-terminated poly(amido-amine) (PAMAM) dendrimers (Gn-OH, where Gn represents the *n*th generation) where they complex with interior amine groups. Subsequent chemical reduction of the metal ions with BH₄⁻ yields dendrimer-encapsulated metal nanoparticles that contain the same number of atoms as were preloaded into the dendrimer initially. The resulting composites are soluble in water and stable, either dry or solvated, for at least several months. Thus, the dendrimer acts as both a template for the preparation of monodisperse nanoparticles and a porous stabilizer. Dendrimer-encapsulated Pd clusters exhibit high catalytic activity for the hydrogenation of alkenes in water. Importantly, the catalytic activity can be controlled by adjusting the size (generation) of the dendrimer; that is, the dendrimer acts as a “nanofilter” with a synthetically controllable mesh.

Stabilized noble metal nanoparticles have been used as catalysts and photocatalysts in solutions for many years.^[1–5] The activity of these materials is controlled by their size, crystal structure, and the nature of the stabilizer. Synthetic routes to soluble metal nanoparticles include chemical or electrochemical reduction of metal salts in the presence of stabilizers.^[2, 3, 6] The purpose of the stabilizer is to control the particle size and prevent agglomeration, but strong adsorption of the stabilizers on the active sites may result in a loss of catalytic activity. Ideally, a metal-particle catalyst should be surrounded by a nanofilter or weak adsorbents that permit passage of the substrate and product of the catalytic reaction, but which prevent agglomeration. The dendrimer plays just this role in the experiments described here.

Our approach for the preparation of dendrimer-encapsulated Pd and Pt metal particles is similar to that we,^[7] and later others,^[8] reported previously for Cu. As indicated above, the experiment is quite simple: first, a predetermined quantity of metal ions are extracted into the interior of a Gn-OH

dendrimer, and second the ions are chemically reduced with BH₄⁻ to yield zero-valent metal particles. Figure 1 shows absorption spectra of dendrimer-encapsulated Pd^{II} and Pt^{II}. For example, a 2.0 mM solution of PtCl₄²⁻ has a strong ligand–metal charge-transfer band at $\lambda_{\text{max}}(\epsilon) = 214 \text{ nm}$ (8000).^[9] After addition of 0.05 mM G4-OH to this solution, the band at 214 nm decreases and shifts to 221 nm and a new band at 249 nm appears.^[10] These changes are a consequence of the encapsulation of metal ions by the dendrimer. After reduction of the composite the spectrum changes significantly: there is now a much higher absorption intensity at low energy, which results from the interband transition of the encapsulated zero-valent metal particles.^[4, 11] Similar spectroscopic results are observed for the G4-OH/Pd^{II} composites. The bands at 217 and 276 nm that result from PdCl₄²⁻ disappear after the addition of G4-OH and new bands are evident at 225 and 300 nm.^[10] A new interband transition is observed after reduction.^[6]

Microscopy confirms that the chemical reduction of Pt^{II} or Pd^{II} encapsulated within G4-OH (G4-OH(Pt_n)_n and G4-OH(Pd_n)_n, respectively) yields intradendrimer metal nanoparticles (G4-OH(Pt_n) and G4-OH(Pd_n), respectively).^[12] High-resolution transmission electron microscopy (HRTEM) images (Figure 2) clearly show that dendrimer-encapsulated particles are quite monodisperse and that their shape is roughly spherical. The diameters of the metal particles for G4-OH(Pt₄₀), G4-OH(Pt₆₀), and G4-OH(Pd₄₀) particles are 1.4 ± 0.2 , 1.6 ± 0.2 , and $1.3 \pm 0.3 \text{ nm}$, respectively, which are slightly larger than the theoretical values of 1.1, 1.2, and 1.1, respectively, which are calculated using the as-

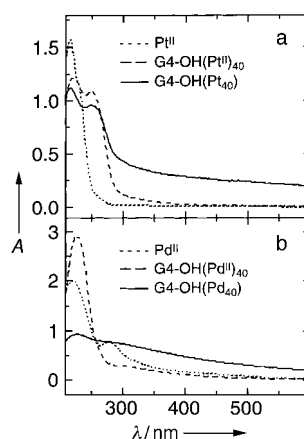


Figure 1. a) Absorption spectra of solutions containing 2.0 mM K₂PtCl₄ and 2.0 mM K₂PtCl₄ + 0.05 mM G4-OH before and after reduction with a fivefold molar excess of NaBH₄. Curves in b) were obtained under the same conditions as those in a) except 2.0 mM Na₂PdCl₄ was used in place of the K₂PtCl₄. The optical path length for all UV/Vis measurements was 0.1 cm.

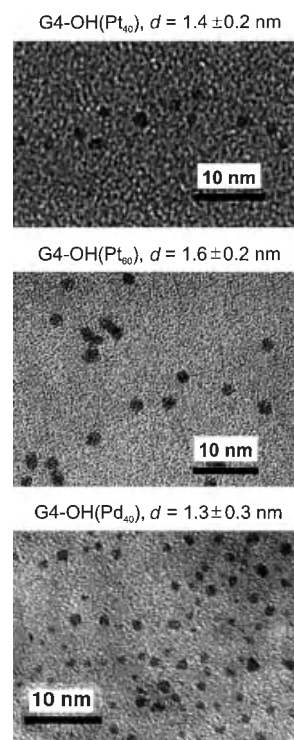


Figure 2. HRTEM images of G4-OH(Pt₄₀), G4-OH(Pt₆₀), and G4-OH(Pd₄₀), which show the monodisperse size and shape distribution.

[*] Prof. R. M. Crooks, M. Zhao
Department of Chemistry
P.O. Box 30012, Texas A&M University
College Station, TX 77842–3012 (USA)
Fax: (+1) 409-845-1399
E-mail: crooks@tamu.edu

[**] This work was supported by the National Science Foundation and the Robert A. Welch Foundation. M.Z. acknowledges fellowship support from the Electrochemical Society, The Eastman Chemical Company, and Phillips Petroleum. TEM results are based upon research conducted at the Transmission Electron Microscopy Laboratory in the Department of Earth and Planetary Science of the University of New Mexico, which is supported by NSF, NASA, and the State of New Mexico. We also acknowledge Professor David E. Bergbreiter and his research group for assistance with the hydrogenation catalysis measurements.

sumption that the particles are contained within the smallest sphere that circumscribes the Pt and Pd crystals with face-centered cubic packing. We confirmed the elemental composition of the nanoparticles with energy-dispersive spectroscopy (EDS). X-ray photoelectron spectroscopy (XPS) also provides elemental compositional information and oxidation states of $Gn-OH(M^{II})$ and $Gn-OH(M)$. The XPS data indicate the presence of carbon and nitrogen from the dendrimer and that the oxidation state of the metals changes after reduction of $Gn-OH(M^{II})$.^[13]

Ligand- or polymer-stabilized colloidal noble metals have been used for many years as catalysts for the hydrogenation of unsaturated organic molecules. Additionally, there is a special interest in the development of methodologies for catalyzing organic reactions in aqueous solutions.^[14] Accordingly, we investigated the catalytic hydrogenation of alkenes in aqueous solutions with these nanocomposite materials. The hydrogenation activities of dendrimer-encapsulated Pt and Pd nanoparticles for a simple alkene (allyl alcohol) and an electron-deficient alkene (*N*-isopropyl acrylamide) in water are given in Table 1. The product of these hydrogenation reactions was confirmed by GC and NMR spectroscopy. G4-OH(Pd₄₀) shows a high catalytic activity for the hydrogenation of both alkenes, while G4-OH(Pt₄₀) shows a reasonable rate for these reduction reactions. For example, the turnover frequencies (TOFs, mol of H₂ per mol of metal atoms per hour) of G4-OH(Pd₄₀) for the hydrogenation of *N*-isopropyl acrylamide and for allyl alcohol hydrogenation compare very favorably to water-soluble, polymer-bound Rh^I catalysts,^[15, 16] and are comparable to PVP-stabilized, colloidal Pd dispersions in water (colloid size: 4–60 nm, reaction temperature: 37 °C).^[17] The key result is that dendrimer-encapsulated Pt or Pd particles are accessible to substrates in solution and yield reasonable TOFs for hydrogenation reactions.

Importantly, the hydrogenation reaction rate can be controlled by using dendrimers of different generations. Dendrimer porosity is a function of generation: higher generation materials are less porous and thus less likely to admit substrates to interior metal nanoparticles.^[18] That is, the dendrimer acts as a selective nanoscopic filter that controls the catalytic activity of the composite (Figure 3). For example, the TOFs for G6-OH(Pd₄₀) and G8-OH(Pd₄₀) are only 10 %

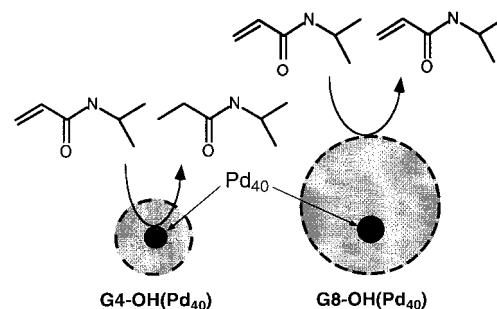


Figure 3. The hydrogenation rate can be controlled by using dendrimers of different generation: Pd or Pt clusters present within dendrimers of lower generation exhibit the highest catalytic activity. The sterically crowded terminal groups of higher generation dendrimers hinder substrate penetration.

and 5 %, respectively, of that for G4-OH(Pd₄₀) with *N*-isopropyl acrylamide. This result shows that it is possible to control reaction rates and do selective catalysis by adjusting the “mesh” of the dendrimer “nanofilter”.

Finally, dendrimer-encapsulated metal nanoparticles are stable before, during, and after hydrogenation reactions. For example, they do not aggregate for up to four months in water. Additionally they can be isolated as a black powder and redissolved in water to yield a stable, dark-brown solution that is identical to that present before drying. After hydrogenation reactions were run for up to three hours, solutions of G4-OH(Pt₄₀) and G4-OH(Pd₄₀) remained clear and there was no evidence for agglomeration, and also no changes were observed in the UV/Vis or IR spectra.

In summary, we have prepared nearly monodisperse metal particles for catalyst applications that employ dendrimers as both template and stabilizer. Dendrimer-encapsulated Pd nanoparticles show high catalytic activity for the hydrogenation of alkenes in aqueous solution. Dendrimer-encapsulated Pt or Pd particles are quite stable, yet the surface of the particles is accessible to substrates in solution. Importantly, the hydrogenation rate can be controlled by using dendrimers with different generations.

Received: September 7, 1998 [Z12382IE]

German version: *Angew. Chem.* **1999**, *111*, 375–377

Keywords: clusters • dendrimers • homogeneous catalysis • hydrogenations • nanostructures

Table 1. Hydrogenation activity of dendrimer-encapsulated Pt₄₀ and Pd₄₀ nanoparticles in water.^[a]

Catalyst	TOF ^[b]	
	<i>N</i> -isopropyl acrylamide	allyl alcohol
G4-OH(Pd)	372	218
G6-OH(Pd)	42	201
G8-OH(Pd)	17	134
G4-OH(Pt)	57	25
G6-OH(Pt)	30	–

[a] Hydrogenation reactions were carried out at 20 ± 2 °C with 2 × 10^{−4} M Pd⁰ or Pt⁰ composite catalysts. The turnover frequency (TOF) was calculated on the basis of H₂ uptake. The product of the hydrogenation reaction of allyl alcohol or *N*-isopropyl acrylamide was confirmed by GC or NMR spectroscopy. [b] Measured as mol of H₂ per mol of metal atoms per hour.

- [1] L. N. Lewis, *Chem. Rev.* **1993**, *93*, 2693–2730.
- [2] G. Schmid, *Chem. Rev.* **1992**, *92*, 1709–1727.
- [3] J. S. Bradley in *Clusters and Colloids* (Ed.: G. Schmid), VCH, Weinheim, **1994**, pp. 459–544.
- [4] D. N. Furlong, A. Launikonis, W. H. F. Sasse, *J. Chem. Soc. Faraday Trans. 1* **1984**, *80*, 571–588.
- [5] J. D. Aiken III, Y. Lin, R. G. Finke, *J. Mol. Catal. A* **1996**, *114*, 29–51.
- [6] M. T. Reetz, W. Helbig, S. A. Quaiser in *Active Metals: Preparation, Characterization, Applications* (Ed.: A. Fürstner), VCH, Weinheim, **1996**, pp. 279–297.
- [7] M. Zhao, L. Sun, R. M. Crooks, *J. Am. Chem. Soc.* **1998**, *120*, 4877–4878.
- [8] L. Balogh, D. A. Tomalia, *J. Am. Chem. Soc.* **1998**, *120*, 7355–7356.
- [9] M. Gerloch, E. C. Constable, *Transition Metal Chemistry: The Valence Shell in d-Block Chemistry*, VCH, Weinheim, **1994**, p. 1.

- [10] The intensity of the absorbance at 249 nm is proportional to the number of Pt^{II} ions in the dendrimer over the range 0–60. Titration results also show by plots of the absorbance at 225 or 300 nm against the number of Pd^{II} in the dendrimer that G4-OH can sorb at least 40 Pd^{II} ions.
- [11] U. Kreibitz, M. Vollmer, *Optical Properties of Metal Clusters*, Springer, Berlin, **1995**, p. 358.
- [12] Specimens for HRTEM observations were prepared by placing a drop of an aqueous solution of 0.05 mM G4-OH(Pt_n or Pd_n) on a holey-carbon-coated grid. We recorded the TEM images digitally with a charge-coupled-device (CCD) camera.
- [13] The shifts of the $\text{Pt}(4f_{7/2})$ peak from 72.8 to 71.3 eV and the $\text{Pt}(4f_{5/2})$ peak from 75.7 to 74.4 eV in the XPS spectra indicate the reduction of the Pt^{II} ion inside dendrimer. For the dendrimer-Pd composite G4-OH(Pd^{2+})₄₀ we observed the $\text{Pd}(3d_{5/2})$ peak shifted from 337.6 to 334.9 eV upon reduction. However, two oxidation states (II and 0) of Pd prior to reduction were observed. The zero state Pd may arise from the X-ray-induced reduction of Pd^{2+} centers.
- [14] W. A. Herrmann, C. W. Kohlpainter, *Angew. Chem.* **1993**, *105*, 1588–1608; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1524–1544.
- [15] D. E. Bergbreiter, Y.-S. Liu, *Tetrahedron Lett.* **1997**, *38*, 3703–3706.
- [16] F. Joó, L. Somsák, M. T. Beck, *J. Mol. Catal.* **1984**, *24*, 71–75.
- [17] L. Nádasdi, F. Joó, I. Horváth, L. Vígh, *Appl. Catal. A* **1997**, *162*, 57–69.
- [18] M. Wells, R. M. Crooks, *J. Am. Chem. Soc.* **1996**, *118*, 3988–3989.

Efficient, Reversible Redox-Switching of Molecular First Hyperpolarizabilities in Ruthenium(II) Complexes Possessing Large Quadratic Optical Nonlinearities**

Benjamin J. Coe,* Stephan Houbrechts, Inge Asselberghs, and André Persoons

Two research areas attracting great interest within the emerging field of “molecular electronics/photonics” are nonlinear optical (NLO) materials^[1] and molecular switches.^[2] It is anticipated that the former will be exploited in optoelectronic technologies, whilst the latter will provide the basis for a range of molecular-scale devices. The fusion of these two

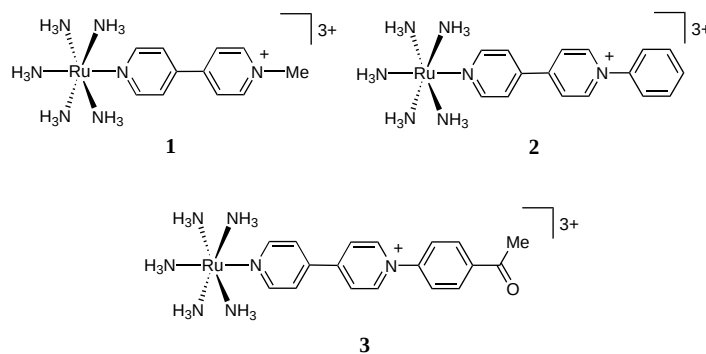
themes, that is the development of materials exhibiting switchable NLO properties, can hence be expected to lead to exciting and novel applications. However, this has been attempted in only a few instances to date, and with limited success.^[3–6]

At the molecular level, quadratic NLO effects are governed by first hyperpolarizabilities, β , which can lead to macroscopic phenomena such as second harmonic generation (SHG). Photoswitching of SHG has been observed recently in solutions of bacteriorhodopsin^[3] and in crystals of *N*-salicylidene-4-bromoaniline.^[4] In other studies focusing on molecular properties, a bis(thienyl)ethene was found to exhibit a change in β on photoisomerization,^[5] and it has been suggested that photoinduced proton-transfer may alter β in nitrobenzyl pyridines.^[7]

Transition metal organometallic and coordination complexes are an important class of NLO molecules,^[1d, 8] for which β data is becoming increasingly available,^[8, 9] largely due to the introduction of the versatile hyper-Rayleigh scattering (HRS) technique.^[10] The presence of redox-active metal centers provides extensive opportunities for modulation of NLO responses, but this has only been addressed previously in SHG photoswitching from $[\text{Ru}^{\text{II}}(\text{bpy})_3]^{2+}$ (bpy = 2,2'-bipyridine) derivatives in Langmuir–Blodgett (L–B) films.^[6] In the latter study, a 30 % decrease in SHG intensity was ascribed to the change in β upon metal-to-ligand charge-transfer (MLCT) excitation. However, although it has been reported that such octupolar complexes exhibit extremely large β values,^[9b] it now appears that these claims were exaggerated.^[11] Furthermore, only modest β changes occur upon oxidation of $[\text{Ru}^{\text{II}}(\text{bpy})_3]^{2+}$.^[12]

We have recently discovered that ruthenium(II) ammine complexes of 4,4'-bipyridinium ligands exhibit large, tunable β values which are associated with intense, low-energy MLCT excitations.^[13] The electron-rich, d^6 centers $[\text{Ru}^{\text{II}}(\text{NH}_3)_5]^{2+}$ or *trans*- $[\text{Ru}^{\text{II}}(\text{NH}_3)_4(\text{L})]^{2+}$ (L = 4-dimethylaminopyridine or 1-methylimidazole) behave as powerful π donors in conjunction with the ligands *N*-R-4,4'-bipyridinium (R = methyl (MeQ^+), phenyl (PhQ^+), or 4-acetylphenyl (4-AcPhQ⁺)). These complexes are ideally suited towards redox-switching of NLO responses because although air-stable, they feature completely reversible, one-electron $\text{Ru}^{\text{III/II}}$ couples at readily accessible potentials (0.46–0.48 V vs SCE for the PF_6^- salts in acetonitrile (MeCN)).^[13]

We have previously reported β data for $[\text{Ru}^{\text{II}}(\text{NH}_3)_5(\text{L})](\text{PF}_6)_3$ (L = MeQ^+ (1), PhQ^+ (2), 4-AcPhQ⁺ (3))



- [*] Dr. B. J. Coe
Department of Chemistry, University of Manchester
Oxford Road, Manchester M13 9PL (UK)
Fax: (+44) 161-275-4598
E-mail: b.coe@man.ac.uk
- Dr. S. Houbrechts,^[+] I. Asselberghs, Prof. A. Persoons
Laboratory of Chemical and Biological Dynamics
Center for Research on Molecular Electronics and Photonics
University of Leuven
Celestijnenlaan 200D, B-3001 Leuven (Belgium)
- [+] Present address:
Nano-Photonics Materials Laboratory,
The Institute of Physical And Chemical Research (RIKEN),
2-1 Hirosawa, Wako-shi, Saitama 351-01 (Japan)
- [**] Dr Houbrechts was a Research Assistant of the Fund for Scientific Research-Flanders. This work was supported by research grants from The Royal Society, from the Belgian National Fund for Scientific Research (G.0308.96), from the Belgian government (IUAP-P4/11), and from the University of Leuven (GOA/1/95). We thank Johnson Matthey plc for a generous loan of ruthenium trichloride.

obtained from 1064 nm HRS measurements in MeCN.^[13b,c] Due to absorption in the region of the second harmonic at 532 nm, the β_{1064} values are resonantly enhanced and the two-level model^[14] was used to derive static hyperpolarizabilities, β_0 . In order to confirm the validity of these data, we have carried out a limited solvent-dependence investigation with $[2](PF_6)_3$ (Table 1). As expected,^[13a] the MLCT absorption

Table 1. Solvent dependence of MLCT absorption and first hyperpolarizabilities of $[2](PF_6)_3$.

Solvent	DN ^[a] [kcal mol ⁻¹]	$\lambda_{\max}$ [MLCT] (ϵ) [nm] ([M ⁻¹ cm ⁻¹])	ϵ_{532} ^[b] [M ⁻¹ cm ⁻¹]	β_{1064} ^[c] [$\times 10^{30}$ esu]	β_0 ^[c] [$\times 10^{30}$ esu]
MeCN	14.1	628 (19 300) ^[d]	6200	858 ^[d]	220 ^[d]
acetone	17.0	654 (16 600)	3700	647	206
DMF	26.6	716 (22 600)	1500	524	233
DMSO	29.8	730 (24 500)	1100	414	193

[a] Gutmann donor number (Gutmann, V. *The Donor-acceptor Approach to Molecular Interactions*, Plenum, New York, 1978). [b] Extinction at the second harmonic wavelength (532 nm). [c] Solutions of about 10^{-5} M to ensure linear concentration dependences of $I_{2\omega}/I_{\omega}^2$. All samples were passed through a 0.45 μ m filter and were checked for fluorescence by using interference filters as described elsewhere.^[11, 15] One-dimensional hyperpolarizability is assumed, that is $\beta_{1064} = \beta_{333}$, and a relative error of $\pm 15\%$ is estimated. The quoted cgs units (esu) can be converted into SI units (C³m³J⁻²) by dividing by a factor of 2.693×10^{20} . [d] Ref. [13b].

maximum red shifts as the solvent Gutmann donor number increases. Decreasing absorption at 532 nm causes a reduction in β_{1064} , but β_0 remains constant within the experimental error. This proves that our β_0 values determined in MeCN are reliable and that the two-level model is valid for these complexes. Although one solvent study with *p*-nitroaniline (pNA) indicated a solvent dependence of β_0 ,^[16] it has been shown more recently that this may not be genuine.^[17] No other investigations into the solvent-dependence of β in metal complexes have been reported.

In order to facilitate chemical redox studies, $[1](PF_6)_3$ – $[3](PF_6)_3$ were metathesized to their chloride salts which show improved solubility in water. HRS and absorption spectral data for $[1]Cl_3$ – $[3]Cl_3$ are shown in Table 2. In each

Table 2. UV/Vis absorption and HRS data for $[1]Cl_3$ – $[3]Cl_3$ in water.

Compound	$\lambda_{\max}$ [$\pi \rightarrow \pi^*$] (ϵ) [nm] ([M ⁻¹ cm ⁻¹])	$\lambda_{\max}$ [MLCT] (ϵ) [nm] ([M ⁻¹ cm ⁻¹])	ϵ_{532} ^[a] [M ⁻¹ cm ⁻¹]	β_{1064} ^[b] [$\times 10^{30}$ esu]	β_0 ^[b] [$\times 10^{30}$ esu]
1	266 (15 000)	580 (13 000)	9400	510	67
2	280 (16 600)	616 (16 700)	7500	629	142
3	284 (21 700)	636 (16 700)	5800	656	180

[a, b] See Table 1 footnotes [b] and [c], respectively, for details. β_{1064} estimated by using the electric-field-induced-SHG β_{1064} value for pNA in methanol as an external reference.^[16]

case, the MLCT absorptions are blue-shifted and of reduced intensity with respect to those in MeCN [MLCT maxima: $[1](PF_6)_3$, 590 nm ($\epsilon = 15 800$ M⁻¹ cm⁻¹); $[3](PF_6)_3$, 654 nm ($\epsilon = 18 000$ M⁻¹ cm⁻¹).^[13c] In the absence of a suitable reference for aqueous solutions, these β_{1064} values were determined by using the electric-field-induced-SHG β_{1064} for pNA in methanol as an external reference.^[16] Their absolute magnitudes are hence of questionable accuracy and should not be compared with the data obtained in nonaqueous solvents (Table 1). However,

the relative ordering confirms that β_0 increases as the acceptor strength of L increases in the order MeQ⁺ < PhQ⁺ < 4-AcPhQ⁺.^[13c]

Solutions of $[1]Cl_3$ – $[3]Cl_3$ in water are deep blue due to their intense MLCT absorptions. Chemical oxidation using an excess of 1:1 30 % aqueous H₂O₂/2 M HCl results in complete bleaching, as shown in Figure 1 for $[2]Cl_3$. The oxidized

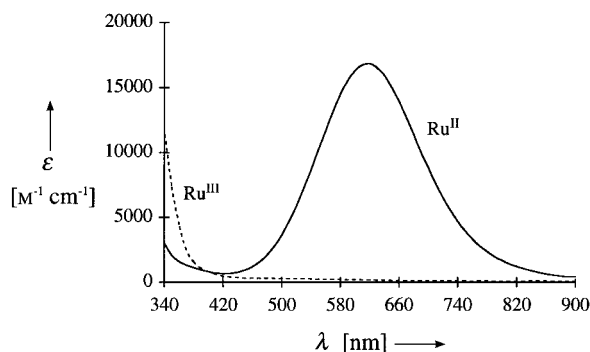
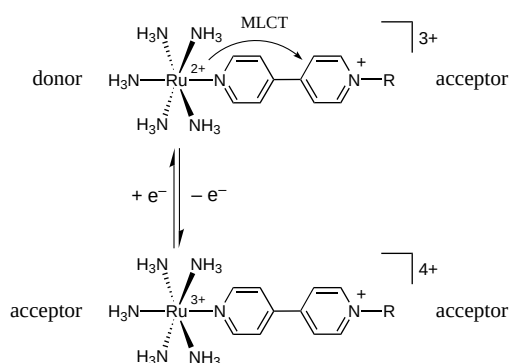


Figure 1. UV/Vis/NIR absorption spectrum of $[2]Cl_3$ (—) and of its Ru^{III} form (---) generated by H₂O₂/HCl oxidation in water (6.43×10^{-5} M).

complexes are indefinitely stable in solution and quantitative recovery of their Ru^{II} forms occurs upon reduction with 62 % hydrazine hydrate solution, as indicated by ϵ measurements. The Ru^{III} complexes exhibit no low-energy charge-transfer absorptions because they contain two opposing electron acceptors attached to a pyridyl ring (Scheme 1). In contrast



Scheme 1. Effects of Ru-based redox in the complex cations 1–3 (R = Me (1), Ph (2), 4-AcPh (3)).

to $[Ru^{II}(NH_3)_5]^{2+}$, the d⁵ $[Ru^{III}(NH_3)_5]^{3+}$ moiety is a powerful electron-withdrawing group which can engage in visible ligand-to-metal charge-transfer (LMCT) excitations when coordinated to donor-substituted ligands.^[18] Indeed, other workers have previously demonstrated the use of this acceptor function in mixed-valence complexes possessing relatively large β values.^[9a]

The solutions used for HRS study of $[1]Cl_3$ – $[3]Cl_3$ were oxidized in situ by addition of a 1:1 mixture of 30 % aqueous H₂O₂/2 M HCl. In each case, a dramatic decrease in the harmonic scattering intensity was observed, producing only very weak signals from which meaningful β values could not be derived. This is illustrated for $[3]Cl_3$ and its Ru^{III} form in Figure 2. As anticipated, the loss of the low-energy MLCT

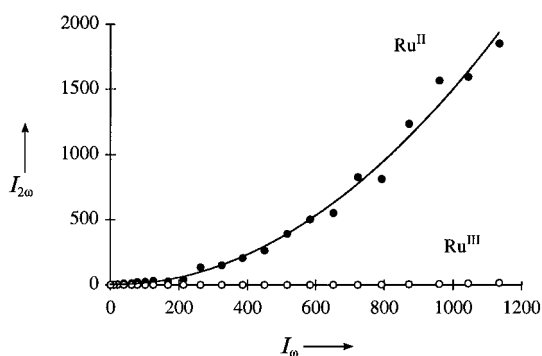


Figure 2. Plot of second harmonic intensity ($I_{2\omega}$) versus fundamental intensity (I_ω) for $[3]\text{Cl}_3$ (●) and for its Ru^{III} form (○) generated by $\text{H}_2\text{O}_2/\text{HCl}$ oxidation in water ($1.10 \times 10^{-5} \text{ M}$).

absorptions results in marked attenuation of the quadratic NLO responses, corresponding to a very effective switching of β . The complete reversibility of the $\text{Ru}^{\text{II/III}}$ redox couples of these complexes shown by cyclic voltammetric studies,^[13b,c] together with the reversibility of the MLCT bleaching suggests that the β switching should also be reversible. This is indeed found to be the case, as shown for **3** in Figure 3. Since

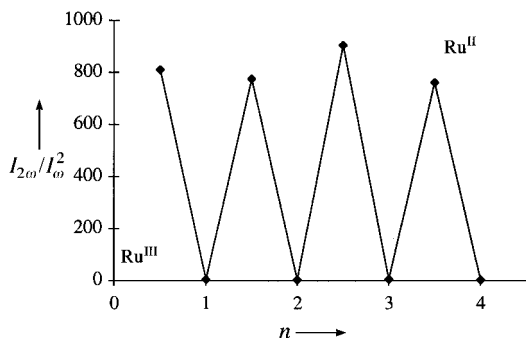


Figure 3. Redox-switching of HRS response between $[3]\text{Cl}_3$ and its Ru^{II} form with chemical oxidation by $\text{H}_2\text{O}_2/\text{HCl}$ and reduction by $\text{N}_2\text{H}_4 \cdot \text{H}_2\text{O}$. All data corrected for initial concentration of $5.80 \times 10^{-6} \text{ M}$; n = number of oxidations.

$I_{2\omega}/I_\omega^2$ is proportional to β^2 , the reduction in β on oxidation is estimated as being 10- to 20-fold, that is at least an order of magnitude.^[19]

To conclude, we have shown that completely reversible switching of large molecular quadratic NLO responses is possible in dipolar $\text{Ru}^{\text{II-4,4'-bipyridinium}}$ chromophores by exploitation of the redox properties of the $[\text{Ru}(\text{NH}_3)_5]^{x+}$ center ($x=2, 3$). This constitutes a novel approach to β modulation which is considerably more effective than any demonstrated previously. These highly stable complexes are easily synthesized and will be readily modified for incorporation into L-B or other thin film materials in which redox-switching of macroscopic NLO effects will be studied.

Experimental Section

The syntheses and full characterization of the salts $[\mathbf{1}](\text{PF}_6)_3$ – $[\mathbf{3}](\text{PF}_6)_3$ have been described previously.^[13c] Metathesis to the chloride salts is exemplified as follows: $[\mathbf{1}](\text{PF}_6)_3$ (88 mg, 0.11 mmol) was dissolved in acetone (5 mL) and a solution of $[\text{N}(\text{nBu})_4]\text{Cl}$ (0.5 g, 1.80 mmol) in acetone

(5 mL) was added dropwise. The deep blue precipitate was filtered off, washed thoroughly with acetone, and dried under vacuum (CaSO_4) at ambient temperature to afford $[\mathbf{1}]\text{Cl}_3 \cdot 2.5 \text{ H}_2\text{O}$ (55 mg, 98 %). C, H, N analysis: $[\mathbf{1}]\text{Cl}_3 \cdot 2.5 \text{ H}_2\text{O}$: Calcd for $\text{C}_{11}\text{H}_{26}\text{Cl}_3\text{N}_7\text{Ru} \cdot 2.5 \text{ H}_2\text{O}$ (%): C 25.97, H 6.14, N 19.27; found: C 26.18, H 6.24, N 19.03; $[\mathbf{2}]\text{Cl}_3 \cdot 3.5 \text{ H}_2\text{O}$: Calcd for $\text{C}_{16}\text{H}_{28}\text{Cl}_3\text{N}_7\text{Ru} \cdot 3.5 \text{ H}_2\text{O}$ (%): C 32.63, H 5.99, N 16.65; found: C 32.76, H 5.59, N 16.27; $[\mathbf{3}]\text{Cl}_3 \cdot 3 \text{ H}_2\text{O}$: Calcd for $\text{C}_{18}\text{H}_{30}\text{Cl}_3\text{N}_7\text{ORu} \cdot 3 \text{ H}_2\text{O}$ (%): C 34.76, H 5.83, N 15.76; found: C 34.81, H 5.76, N 15.32.

The experimental details of the HRS measurements have been described previously.^[7] The general procedure for the β switching experiments with $[\mathbf{1}]\text{Cl}_3$ – $[\mathbf{3}]\text{Cl}_3$ is exemplified as follows: To a solution of $[\mathbf{3}]\text{Cl}_3$ in water ($5.80 \times 10^{-6} \text{ M}$) was added 1:1 30 % aqueous $\text{H}_2\text{O}_2/2 \text{ M HCl}$ until the blue coloration was completely bleached. An excess of reagent was used in order to ensure complete oxidation and the solution was then made up to a known volume with water before HRS measurement. The complex was re-reduced by the dropwise addition of a slight excess of 62 % hydrazine hydrate solution until the blue coloration was fully restored, and the solution was again diluted to a known volume with water. The quadratic coefficients were adjusted to account for the progressive dilutions following each oxidation–reduction cycle.

Received: August 26, 1998 [Z12342IE]

German version: *Angew. Chem.* **1999**, *111*, 377–380

Keywords: donor–acceptor systems • molecular switches • nonlinear optics • ruthenium

- [1] a) *Nonlinear Optical Properties of Organic Molecules and Crystals*, Vols. 1, 2 (Eds.: D. S. Chemla, J. Zyss), Academic Press, Orlando, **1987**; b) “Materials for Nonlinear Optics: Chemical Perspectives”: *ACS Symp. Ser.* **1991**, 455; c) S. R. Marder, B. Kippelen, A. K.-Y. Jen, N. Peyghambarian, *Nature* **1997**, 388, 845; d) T. Verbiest, S. Houbrechts, M. Kauranen, K. Clays, A. Persoons, *J. Mater. Chem.* **1997**, 7, 2175.
- [2] a) J.-M. Lehn, *Supramolecular Chemistry—Concepts and Perspectives*, VCH, Weinheim, **1995**; b) M. D. Ward, *Chem. Soc. Rev.* **1995**, 24, 121.
- [3] Q. Song, C. Wan, C. K. Johnson, *J. Phys. Chem.* **1994**, 98, 1999.
- [4] K. Nakatani, J. A. Delaire, *Chem. Mater.* **1997**, 9, 2682.
- [5] S. L. Gilat, S. H. Kawai, J.-M. Lehn, *Chem. Eur. J.* **1995**, 1, 275.
- [6] H. Sakaguchi, L. A. Gomez-Jahn, M. Prichard, T. L. Penner, D. G. Whitten, T. Nagamura, *J. Phys. Chem.* **1993**, 97, 1474.
- [7] S. Houbrechts, K. Clays, A. Persoons, Z. Pikramenou, J.-M. Lehn, *Chem. Phys. Lett.* **1996**, 258, 485.
- [8] a) S. R. Marder in *Inorganic Materials* (Eds.: D. W. Bruce, D. O'Hare), Wiley, Chichester, **1992**; b) D. R. Kanis, M. A. Ratner, T. J. Marks, *Chem. Rev.* **1994**, 94, 195; c) N. J. Long, *Angew. Chem.* **1995**, 107, 37; *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 21; d) I. R. Whittall, A. M. McDonagh, M. G. Humphrey, M. Samoc, *Adv. Organomet. Chem.* **1998**, 42, 291.
- [9] Selected examples: a) W. M. Laidlaw, R. G. Denning, T. Verbiest, E. Chauchard, A. Persoons, *Proc. SPIE Int. Soc. Opt. Eng.* **1994**, 2143, 14; b) C. Dhenaut, I. Ledoux, I. D. W. Samuel, J. Zyss, M. Bourgault, H. Le Bozec, *Nature* **1995**, 374, 339; c) U. Behrens, H. Brussaard, U. Hagenau, J. Heck, E. Hendrickx, J. Körmich, J. G. M. van der Linden, A. Persoons, A. L. Spek, N. Veldman, B. Voss, H. Wong, *Chem. Eur. J.* **1996**, 2, 98; d) I. R. Whittall, M. G. Humphrey, A. Persoons, S. Houbrechts, *Organometallics* **1996**, 15, 1935; e) S. M. Lecours, H.-W. Guan, S. G. Dimagno, C. H. Wang, M. J. Therien, *J. Am. Chem. Soc.* **1996**, 118, 1497; f) S. Di Bella, I. Fragalà, I. Ledoux, M. A. Diaz-Garcia, T. J. Marks, *J. Am. Chem. Soc.* **1997**, 119, 9550; g) W. Wenseleers, A. W. Gerbrandt, E. Goovaerts, M. H. Garcia, M. P. Robalo, P. J. Mendes, J. C. Rodrigues, A. R. Dias, *J. Mater. Chem.* **1998**, 8, 925; h) G. Roth, H. Fischer, T. Meyer-Friedrichsen, J. Heck, S. Houbrechts, A. Persoons, *Organometallics* **1998**, 17, 1511.
- [10] a) K. Clays, A. Persoons, *Phys. Rev. Lett.* **1991**, 66, 2980; b) K. Clays, A. Persoons, *Rev. Sci. Instrum.* **1992**, 63, 3285.
- [11] I. D. Morrison, R. G. Denning, W. M. Laidlaw, M. A. Stammers, *Rev. Sci. Instrum.* **1996**, 67, 1445.
- [12] A. Persoons, K. Clays, M. Kauranen, E. Hendrickx, E. Put, W. Bijnen, *Synth. Met.* **1994**, 67, 31.

- [13] a) B. J. Coe, M. C. Chamberlain, J. P. Essex-Lopresti, S. Gaines, J. C. Jeffery, S. Houbrechts, A. Persoons, *Inorg. Chem.* **1997**, *36*, 3284; b) B. J. Coe, J. P. Essex-Lopresti, J. A. Harris, S. Houbrechts, A. Persoons, *Chem. Commun.* **1997**, 1645; c) B. J. Coe, J. A. Harris, L. J. Harrington, J. C. Jeffery, L. H. Rees, S. Houbrechts, A. Persoons, *Inorg. Chem.* **1998**, *37*, 3391.
- [14] a) J. L. Oudar, D. S. Chemla, *J. Chem. Phys.* **1977**, *66*, 2664; b) J. L. Oudar, *J. Chem. Phys.* **1977**, *67*, 446; c) J. Zyss, J. L. Oudar, *Phys. Rev. A* **1982**, *26*, 2016.
- [15] E. Hendrickx, C. Dehu, K. Clays, J. L. Brédas, A. Persoons, *ACS Symp. Ser.* **1995**, *601*, 82.
- [16] M. Stähelin, D. M. Burland, J. E. Rice, *Chem. Phys. Lett.* **1992**, *191*, 245.
- [17] J. N. Woodford, M. A. Pauley, C. H. Wang, *J. Phys. Chem. A* **1997**, *101*, 1989.
- [18] J. C. Curtis, B. P. Sullivan, T. J. Meyer, *Inorg. Chem.* **1983**, *22*, 224.
- [19] This was confirmed by the use of 100-fold concentrated solutions (ca. 10^{-3} M) which afforded larger HRS signals, allowing the derivation of β_{1064} values of 20, 35, and 62×10^{-30} esu for the oxidized forms of [1]Cl₃, [2]Cl₃, and [3]Cl₃, respectively (referenced to pNA in methanol). Excessive UV absorption by H₂O₂ prevents measurement of the spectra of the Ru^{III} forms, precluding the estimation of β_0 values.

Amphiphilic *p*-*tert*-Butylcalix[4]arene Scaffolds Containing Exposed Carbohydrate Dendrons**

René Roy* and Jin Mi Kim

Calixarenes are cyclic molecules containing a cavity useful in host–guest chemistry.^[1] Their intrinsic amphiphilic architecture also makes them ideal candidates for the study of water–monolayer surface interactions. In this respect, they surpass their cyclodextrin counterparts.^[2] In spite of these interesting features—and in addition possible variation of conformational organization, substitution of the upper and lower rims, and shape and size—only limited efforts have been made to construct biologically relevant calixarenes containing carbohydrate moieties.^[3, 4] In line with this concept, the synthesis of nondendritic galactose octamers attached to a calix[4]resorcinarene scaffold possessing lipophilic side chains has been described. However, as opposed to our work presented herein, the hydrophilic carbohydrate residues were used for polar attachment to a polar quartz surface.^[5]

We describe here the first synthesis of dendritic,^[6] water-soluble, carbohydrate-containing *p*-*tert*-butylcalix[4]arenes and their lectin-binding properties. These carbohydrate-containing calix[4]arenes can serve as models to further investigate factors influencing multivalent carbohydrate–protein interactions at the molecular level. The lipophilic *p*-*tert*-butyl

substituents provide the driving force for stable assembly and/or adhesion of a calixarene monolayer to a surface, while the hydrophilic carbohydrate ligands mimic the cell's saccharide-rich surface. This new type of hybrid molecules can serve as coating carbohydrate ligands in competitive solid-phase immunoassays (Figure 1).

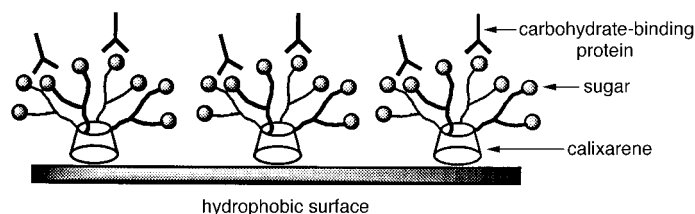


Figure 1. Glycocalix[4]arene hybrids used as coating antigens on a hydrophobic polystyrene surface.

Our model carbohydrate is the T_N antigen (GalNAc α 1 $\rightarrow$ O-Ser/Thr) corresponding to one of the immunodominant epitopes found in human adenocarcinomas mucins.^[7] This family of carbohydrate-associated tumor markers is usually cryptic in normal cells. We have also recently shown that the O-linked Ser/Thr residues in the analogous T antigen [Gal(β 1-3)-GalNAc(α 1 $\rightarrow$ O-Ser/Thr)] were not essential to generate mouse monoclonal antibodies that recognize cancer tissues.^[8] Consequently, the α -linked GalNAc moieties described herein were deprived of the O-Ser/Thr aglycon.

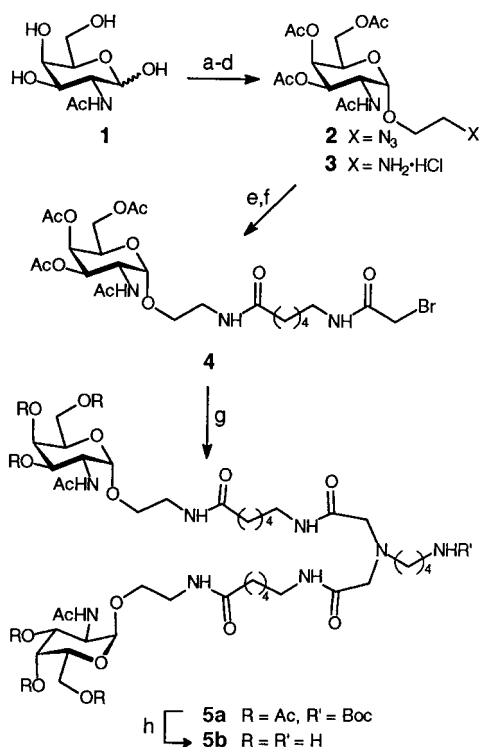
The synthetic strategy for the construction of glycocalix[4]arenes was to attach suitable spacer-substituted α -GalNAc residues to the calix[4]arene core; both convergent and divergent approaches were employed. The key α -D-GalNAc derivative **3** was prepared in four steps from *N*-acetyl-D-galactosamine (**1**) (Scheme 1). The required calix[4]arene core **7** was prepared by transforming commercial *p*-*tert*-butylcalix[4]arene (**6**) into the known tetraethyl ester^[9] followed by hydrolysis and treatment with thionyl chloride (Scheme 2). Direct amidation of **7** with amine **3** and subsequent de-O-acetylation provided tetravalent glycocalix[4]arene **8**.

Glycocalix[4]arenes of higher valencies were synthesized by a semiconvergent approach. Divalent α -D-GalNAc precursor **5a** and its deprotected form **5b** were first obtained by treatment of amine **3** with *N*-Boc-6-aminohexanoic acid followed by trifluoroacetylation and N-bromoacetylation to give **4** in 85 % yield (see Scheme 1). Double N-alkylation of mono-*N*-Boc-1,4-diaminobutane with **4** gave dimer **5a** in 73 % yield, which was deprotected to provide **5b**. Treatment of acid chloride **7** with mono-*N*-Boc-1,4-diaminobutane afforded **9** in 63 % yield. Trifluoroacetylation of **9** gave **10**, which was N,N-dialkylated with **4** to provide octavalent glycocalix[4]arene **11** in 64 % yield after deprotection (Scheme 3). Octameric tetraamine derivative **13** was also obtained by double N-alkylation of **10** using 4-bromoacetamido-1-Boc-butanedi-amine (51 %, Scheme 4). Finally, hexadecameric glyco-calix[4]arene **14** was prepared from octameric amine **13** and bromoacetamido-GalNAc derivative **4** after de-O-acetylation.

The ligands **5b**, **8**, **11**, and **14** were purified by size-exclusion chromatography (Sephadex LH20, MeOH). ¹H NMR spec-

[*] Prof. R. Roy, J. M. Kim
Department of Chemistry, University of Ottawa
10 Marie Curie, Ottawa, ON K1N 6N5 (Canada)
Fax: (+1) 613-562-5170
E-mail: rroy@science.uottawa.ca

[**] We thank the National Science and Engineering Research Council of Canada (NSERC) for financial support and Dr. P. Thibault, National Research Council of Ottawa (NRC), for MALDI-TOF mass spectrometry experiments.

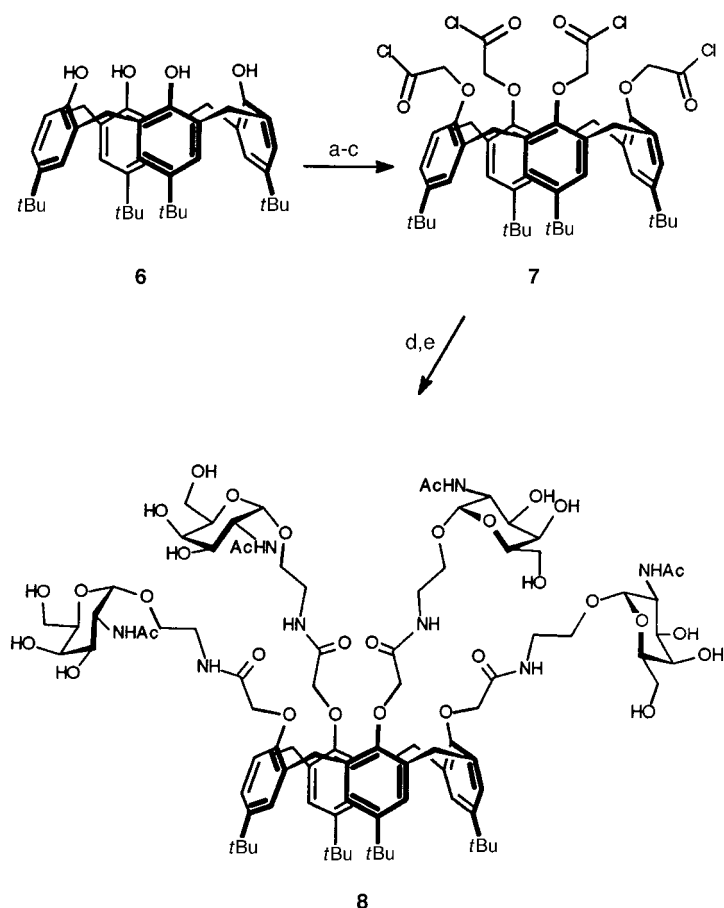


Scheme 1. Synthesis of key monomer **3** and dimer **5b**. a) $\text{HOCH}_2\text{CH}_2\text{Cl}$, $\text{BF}_3 \cdot \text{OEt}_2$, reflux for 4 h, 25°C for 48 h; b) NaN_3 (10 equiv), NaI (1 equiv), CH_3CN , reflux, 48 h, 85% (2 steps); c) Ac_2O , pyridine, 25°C , 16 h, 80%; d) 1. H_2 -Pd/C, AcOH , MeOH , 16 h; 2. Amberlite IRA-400(Cl) resin, MeOH , 16 h, quantitative; e) $\text{HO}_2\text{C}(\text{CH}_2)_5\text{NHBoc}$ (1.2 equiv), DIPEA (2.5 equiv), TBTU (1.2 equiv), CH_2Cl_2 , 0°C , 30 min, 76%; f) 1. 20% TFA , CH_2Cl_2 , 25°C , 2 h; 2. ClCOCH_2Br (1.2 equiv), DIPEA (2.5 equiv), CH_2Cl_2 , 0°C , 30 min, 85%; g) $\text{H}_2\text{N}(\text{CH}_2)_4\text{NHBoc}$ (0.9 equiv), DIPEA (1.2 equiv), CH_3CN , reflux, 48 h, 73%; h) 1. 1 M NaOMe , MeOH , pH 9, 25°C , 3 h; 2. 20% TFA , CH_2Cl_2 , 25°C , 2 h, 83% (2 steps). Boc = *tert*-butoxycarbonyl, DIPEA = diisopropylethylamine, TBTU = *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate, TFA = trifluoroacetic acid.

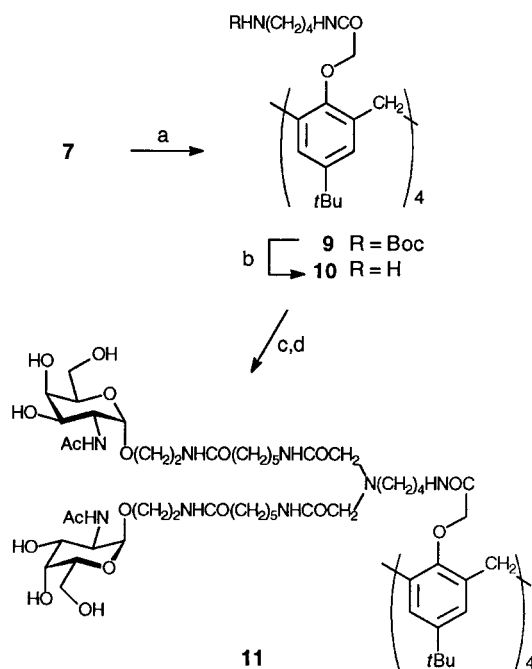
troscopy (D_2O) shows that water-soluble glycolix[4]arenes **8**, **11**, and **14** exist in the *cone* conformation as judged from the singlets in the aromatic region ($\delta = 6.8$) and the *tert*-butyl signals at $\delta = 1.1$ (Table 1). The ratios for the signals attributed to the anomeric ($\delta = 4.9$) and *tert*-butyl protons ($\delta = 1.1$) were used to confirm complete glycosylation.

These ligands were then evaluated for their relative lectin-binding properties against *Vicia villosa* agglutinin (VVA). This plant lectin has been used previously for binding studies against α -D-GalNAc derivatives.^[10] The direct binding abilities and cross-linking behavior of di- (**5b**), tetra- (**8**), octa- (**11**), and hexadeca- (**14**) toward VVA were initially determined by turbidimetric analysis. Hypervalent glycolix[4]arene dendrimers demonstrated direct binding to VVA by the rapid formation of insoluble precipitates (Figure 2). Allyl 2-acetamido-2-deoxy- α -D-galactopyranoside (allyl α -D-GalNAc) was used as an inhibitor for the cross-linking of octavalent **11** with VVA, thus demonstrating the sugar specificity of the binding. The interaction between **11** and VVA was so strong that a 250-fold molar excess of allyl α -D-GalNAc was necessary to disrupt the cross-linking interaction.

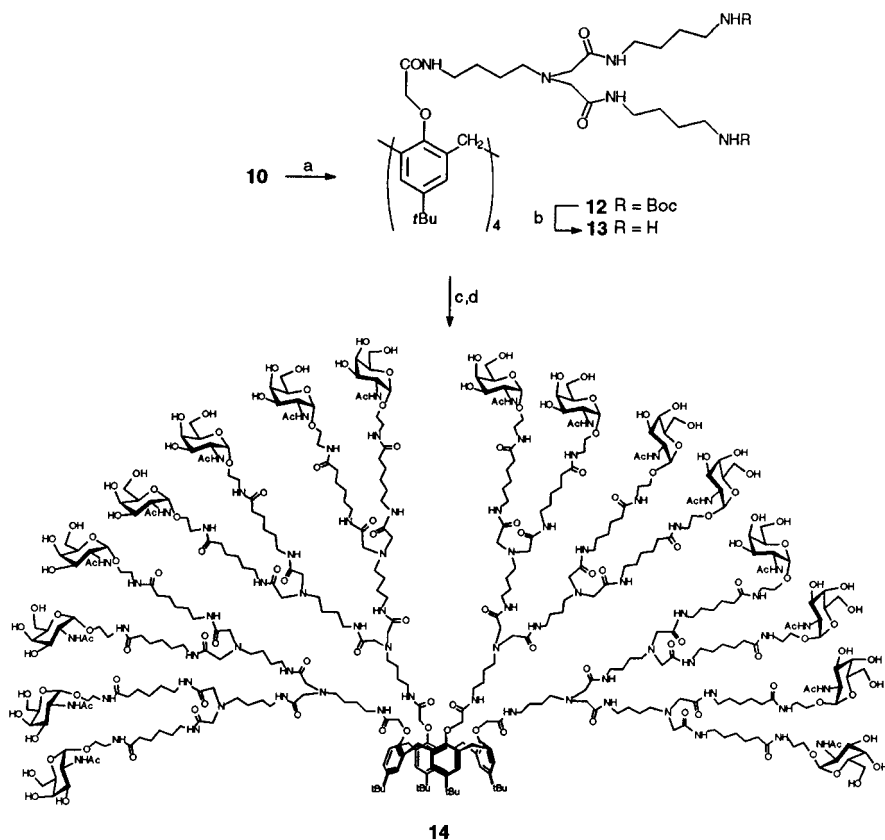
The efficiency of each glycolixarene to inhibit the binding of asialoglycophorin, a natural glycoprotein of human eryth-



Scheme 2. Synthesis of tetramer **8**. a) $\text{BrCH}_2\text{CO}_2\text{Et}$ (20 equiv), K_2CO_3 (20 equiv), acetone, 4-Å molecular sieves, reflux, 24 h, 84%; b) 1 M KOH , EtOH (1/1.1 v/v), reflux, 9 h, 90%; c) SOCl_2 , reflux, 2 h, quantitative; d) **3** (6 equiv), Et_3N (12 equiv), CH_2Cl_2 , $0-25^\circ\text{C}$, 2 h, 74%; e) NaOMe , MeOH , pH 9, 25°C , 2 h, 94%.



Scheme 3. Synthesis of octamer **11**. a) $\text{BocHN}(\text{CH}_2)_4\text{NH}_2$ (6 equiv), DIPEA (12 equiv), CH_2Cl_2 , 0°C , 3 h, 63%; b) 20% TFA , CH_2Cl_2 , 25°C , 2 h; c) **4** (10 equiv), DIPEA , CH_3CN , 60°C , 48 h; d) 1 M NaOMe , MeOH , 25°C , 16 h, 64% (2 steps).



Scheme 4. Syntheses of hexadecamer **14**. a) BocHN(CH₂)₄NHCOCH₂Br (10 equiv), DIPEA (14 equiv), CH₃CN, 60 °C, 48 h, 51 %; b) 20 % TFA, CH₂Cl₂, 25 °C, 2 h; c) **4** (20 equiv), DIPEA, CH₃CN, 60 °C, 48 h; d) 1M NaOMe, MeOH, 25 °C, 16 h, 69 % (2 steps).

rocytes, to VVA was measured by enzyme-linked lectin assay (ELLA). Asialoglycophorin (MN) was used as a coating antigen for the solid-phase competitive experiments (MN is a

Table 1. Selected physical data for representative compounds.

5a: [α]_D²⁰ = +59.1 (*c* = 1.0 in CHCl₃); ¹H NMR (500 MHz, CDCl₃): δ = 1.24–1.32 (q, *J* = 7.4 Hz, 4H; 2 × CH₂), 1.39 (s, 9H; *t*Bu), 1.47–1.53 (m, 8H; 4 × CH₂), 1.93, 1.96, 2.00, 2.11 (4 s, 24H; OAc), 2.13–2.17 (t, *J* = 7.4 Hz, 4H; CH₂CONH), 3.02–3.33 (m, 14H; CH₂ CHH), 3.45–3.52 (m, 2H; CHH), 3.55–3.66 (m, 2H; CH₂), 3.68–3.75 (m, 2H; CHH), 4.02–4.10 (m, 4H; CH₂), 3.70–3.76 (m, 2H; CHH), 4.02–4.10 (m, 4H; H-6), 4.12–4.16 (m, 2H; H-5), 4.54 (ddd, *J*_{2,3} = 11.4 Hz, *J*_{NH,2} = 9.5 Hz, 2H; H-2), 4.84 (d, *J*_{1,2} = 3.6 Hz, 2H; H-1), 4.93–4.99 (m, 1H; NHBoc), 5.10 (dd, *J*_{3,4} = 3.3 Hz, 2H; H-3), 5.32 (m, 2H; H-4), 6.90–7.05 (br, 4H; NH), 7.50–7.65 (br, 2H; NH); ¹³C NMR (125.8 MHz, CDCl₃): δ = 20.7 (CH₃CO₂), 23.0 (NHCOCH₃), 25.0, 26.1, 27.0 (3 × CH₂), 28.4 (*t*Bu), 29.0, 36.2, 38.6, 39.0, 39.7, 42.0 (6 × CH₂), 47.4 (C2), 58.8 (CH₂), 62.0 (C6), 66.7 (C5), 67.3 (C4), 68.1 (CH₂), 68.5 (C3), 98.4 (C1), 156.6 (Ar), 170.4, 170.5, 170.6, 170.7, 173.5 (C=O); positive-ion FAB-MS: *m/z* (%): 1275.6 (10.2) [*M*⁺+1].

8: positive-ion FAB-MS: *m/z* (%): 1865.8 (2.4) [*M*⁺+1].

11: [α]_D²⁰ = +53.6 (*c* = 0.5 in DMSO); MALDI-TOF MS calcd for C₂₁₂H₃₅₂N₃₂O₇₂: 4498; found: 4499 [*M*+1]. **12**: positive-ion FAB-MS calcd for C₁₅₆H₂₆₄N₂₄O₃₂: 2985; found: 2986 (0.2 %) [*M*+1].

12: positive-ion FAB-MS calcd for C₁₅₆H₂₆₄N₂₄O₃₂: 2985; found: 2986 (0.2 %) [*M*+1].

14: [α]_D²⁰ = +66.4 (*c* = 1.0 in MeOH); ¹H NMR (D₂O): δ = 1.11 (brs, 9H, *t*Bu), 1.32–1.43, 1.45–1.70 (m, 32H; internal CH₂), 2.11 (s, 48H; NAc), 2.25–2.37 (m, 32H; CH₂CONH), 2.50–2.66 (m, 24H; CH₂N), 3.14–3.44 (m, 124H; CONHCH₂, NCH₂CO, ArCHH, CHHO), 3.54–3.64 (m, 32H; NCHH, CHHO), 3.76–3.87 (m, 52H; H-6, 4 ArCHH, NCHH), 3.92–4.00 (m, 32H; H-2, H-5), 4.04 (dd, *J*_{3,4} = 2.8 Hz, 16H; H-4), 4.25 (dd, *J*_{2,3} = 11.0 Hz, 16H; H-3), 4.94 (d, *J*_{1,2} = 3.4 Hz, 16H; H-1), 6.92 (brs, 8H; Ar); ¹³C NMR (D₂O): δ = 21.7 (NAc), 23.4, 24.7, 25.4, 27.9, 30.8 (*t*Bu), 35.4, 38.5, 49.4 (C2), 54.8, 57.9, 60.7 (C6), 66.0, 67.4 (C3), 68.1 (C4), 70.6 (C5), 96.8 (C1), 128.4 (Ar), 172.4, 173.7, 174.0, 175.9, 176.3 (C=O).

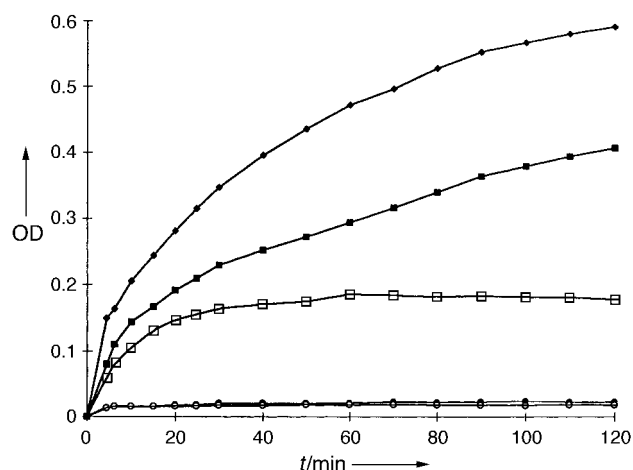


Figure 2. Turbidimetric analysis of the binding of glycolal[4]arenes with VVA. ●: **5b** (2-mer), ■: **8** (4-mer), ◆: **11** (8-mer), □: **14** (16-mer), ○: **11** with allyl α -D-GalNAc as an inhibitor. OD = optical density measured at 490 nm.

blood group serotype). Horseradish peroxidase labeled VVA (VVA-HRP) was used for the quantitative detection of inhibition by optical density. The results for the inhibition of asialoglycophorin–VVA binding are shown in Figure 3. The best result was obtained from the hexadecavalent conjugate **14** (IC₅₀ = 13.4 μ M), which represents a 12-fold increase in potency over that of the allyl α -D-GalNAc monomer (IC₅₀ = 158.3 μ M).

Our most important finding was the monolayer-forming ability of the GalNAc-containing calix[4]arenes. Tetra- and hexadecavalent glycolal[4]arenes **8** and **14**, respectively,

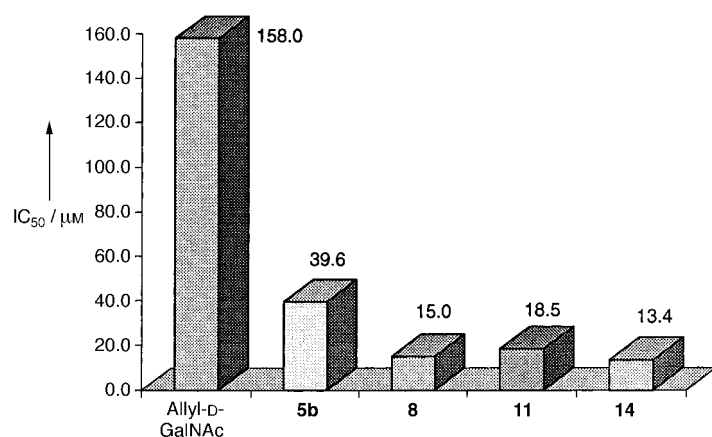


Figure 3. Enzyme-linked lectin assay of the inhibition of the binding of asialoglycophorin to horseradish peroxidase labeled VVA B₄ by allyl D-GalNAc and by ligands **5b**, **8**, **11**, and **14** (VVA B₄ is the isolectin made up of four B subunits).

were incubated at various concentrations (0.1–2.5 μg per well) on polystyrene microtiter plates in phosphate-buffered saline, and VVA-HRP was used to detect the direct binding properties. As shown in Figure 4, hexadeca-

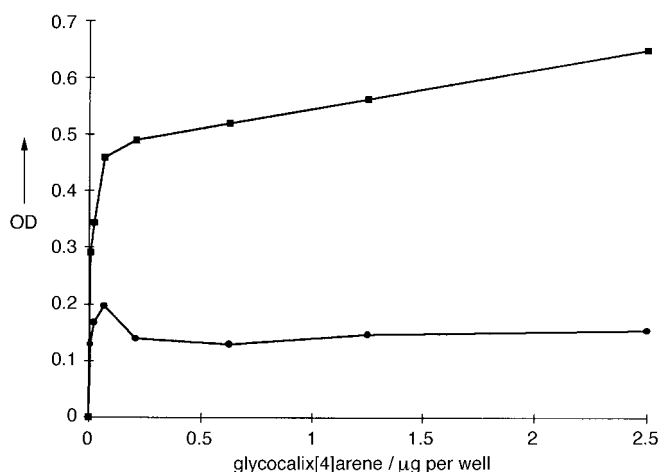


Figure 4. Enzyme-linked lectin assay (VVA-HRP) showing the hydrophobic adsorption of glycolal[4]arenes onto the surface of a polystyrene microtiter plate. ■: **14** (16-mer), ●: **8** (4-mer). OD = optical density measured at 410 nm.

calix[4]arene **14** was hydrophobically adsorbed onto the microtiter plate surface with as little as 0.2 μg of material per well. Moreover, the interaction could be again inhibited by adding excess allyl α-D-GalNAc monomer (data not shown).

Amphiphilic α-GalNAc-containing *p*-tert-butylcalix[4]arenes with up to 16 carbohydrate units were efficiently synthesized by a novel double N-alkylation strategy. In these novel biomaterials the carbohydrate residues are well exposed to aqueous environments as shown by their lectin-binding properties. Moreover, the materials can be directly adsorbed onto the lipophilic surface of polystyrene microtiter plates and thus should be useful in bioanalytical devices.

Keywords: calixarenes • dendrimers • glycosides • lectins

- [1] For recent reviews, see: a) A. Ikida, S. Shinkai, *Chem. Rev.* **1997**, *97*, 1713–1734; b) M. Takeshita, S. Shinkai, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1088–1097; c) C. D. Gutsche, *Aldrichimica Acta* **1995**, *28*, 3–9; c) V. Böhmer, *Angew. Chem.* **1995**, *107*, 785–818; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 713–745.
- [2] a) J. Szejtli, *J. Inclusion Phenom.* **1992**, *14*, 25–36; b) G. Wenz, *Angew. Chem.* **1994**, *106*, 851–870; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 803–822; c) S. Li, W. C. Purdy, *Chem. Rev.* **1992**, *92*, 1457–1470.
- [3] S. J. Meunier, R. Roy, *Tetrahedron Lett.* **1996**, *37*, 5469–5472.
- [4] a) A. Marra, A. Dondoni, F. Sansone, *J. Org. Chem.* **1996**, *61*, 5155–5158; b) A. Dondoni, M. Kleban, A. Marra, *Tetrahedron Lett.* **1997**, *38*, 7801–7804; c) A. Dondoni, A. Marra, M.-C. Scherrmann, A. Casnati, F. Sansone, R. Ungaro, *Chem. Eur. J.* **1997**, *3*, 1774–1782.
- [5] a) T. Fujimoto, C. Shimizu, O. Hayashida, Y. Aoyama, *J. Am. Chem. Soc.* **1997**, *119*, 6676–6677; b) O. Hayashida, C. Shimizu, T. Fujimoto, Y. Aoyama, *Chem. Lett.* **1998**, 13–14.
- [6] a) R. Roy, *Curr. Opin. Struct. Biol.* **1996**, *6*, 692–702; b) R. Roy, *Polym. News* **1996**, *21*, 226–232; c) R. Roy, *Top. Curr. Chem.* **1997**, *187*, 241–274; d) N. Jayaraman, S. A. Nepogodiev, J. F. Stoddart, *Chem. Eur. J.* **1997**, *3*, 1193–1199.
- [7] a) T. Toyokuni, A. Singhal, *Chem. Soc. Rev.* **1995**, *24*, 231–308; b) S. Hakomori, *Curr. Opin. Immunol.* **1991**, *3*, 646–653.
- [8] K. Rittenhouse-Diakun, Z. Xia, D. Pickhardt, M.-G. Baek, R. Roy, *Hybridoma* **1998**, *17*, 165–173.
- [9] K. Iwamoto, S. Shinkai, *J. Org. Chem.* **1992**, *57*, 7066–7073.
- [10] S. Sakai, T. Sasaki, *J. Am. Chem. Soc.* **1994**, *116*, 1587–1588.

Organically Templated Mixed-Valent Ti^{III}/Ti^{IV} Phosphate with an Octahedral–Tetrahedral Open Framework**

Sambandan Ekambaram and Slavi C. Sevov*

The zeolitic aluminum silicates and the more recently discovered microporous aluminum phosphates have attracted tremendous interest due to their application as catalysts, ion-exchangers, and molecular sieves in many technologically important processes. Nevertheless, due to the presence of main group elements only, these materials have no potential for redox reactions and redox catalysis. It is highly desirable, therefore, to build microporous compounds containing d-block metals as an integral part of the framework and in close proximity to the voids. Titanium has been of particular interest as a potential substitute for silicon owing to the available oxidation state of four and appropriate size. Substitutions of the tetrahedral silicon have been achieved at the doping level,^[1] and despite the small amounts of titanium, the resulting materials have shown highly improved

[*] Prof. S. C. Sevov, S. Ekambaram
Department of Chemistry and Biochemistry
University of Notre Dame
Notre Dame, IN 46556 (USA)
Fax: (+1) 219-631-6652
E-mail: ssevov@nd.edu

[**] We thank the National Science Foundation (DMR-9701550 and DMR-9703732) and the Bayer Corporation (Postdoctoral Fellowship) for the financial support.

were incubated at various concentrations (0.1–2.5 μg per well) on polystyrene microtiter plates in phosphate-buffered saline, and VVA-HRP was used to detect the direct binding properties. As shown in Figure 4, hexadecavalent glyco-

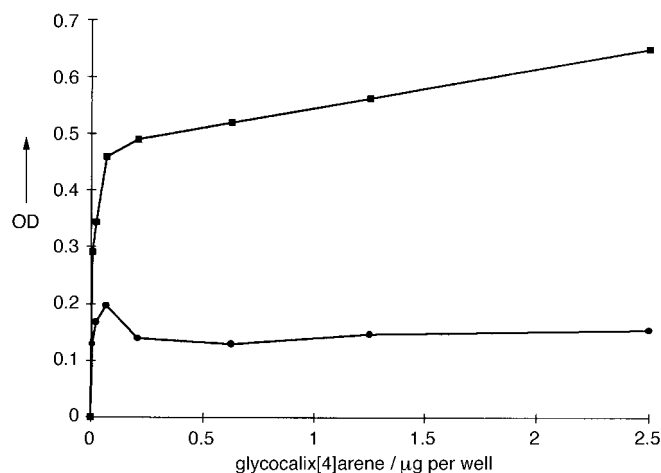


Figure 4. Enzyme-linked lectin assay (VVA-HRP) showing the hydrophobic adsorption of glycolix[4]arenes onto the surface of a polystyrene microtiter plate. ■: 14 (16-mer), ●: 8 (4-mer). OD = optical density measured at 410 nm.

calix[4]arene **14** was hydrophobically adsorbed onto the microtiter plate surface with as little as 0.2 μg of material

per well. Moreover, the interaction could be again inhibited by adding excess allyl α -D-GalNAc monomer (data not shown).

Amphiphilic α -GalNAc-containing *p*-tert-butylcalix[4]arenes with up to 16 carbohydrate units were efficiently synthesized by a novel double N-alkylation strategy. In these novel biomaterials the carbohydrate residues are well exposed to aqueous environments as shown by their lectin-binding properties. Moreover, the materials can be directly adsorbed onto the lipophilic surface of polystyrene microtiter plates and thus should be useful in bioanalytical devices.

Received: June 24, 1998

Revised version: October 13, 1998 [Z12049IE]

German version: *Angew. Chem.* **1999**, *111*, 380–384

Keywords: calixarenes • dendrimers • glycosides • lectins

- [1] For recent reviews, see: a) A. Ikida, S. Shinkai, *Chem. Rev.* **1997**, *97*, 1713–1734; b) M. Takeshita, S. Shinkai, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1088–1097; c) C. D. Gutsche, *Aldrichimica Acta* **1995**, *28*, 3–9; c) V. Böhmer, *Angew. Chem.* **1995**, *107*, 785–818; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 713–745.
- [2] a) J. Szejtli, *J. Inclusion Phenom.* **1992**, *14*, 25–36; b) G. Wenz, *Angew. Chem.* **1994**, *106*, 851–870; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 803–822; c) S. Li, W. C. Purdy, *Chem. Rev.* **1992**, *92*, 1457–1470.
- [3] S. J. Meunier, R. Roy, *Tetrahedron Lett.* **1996**, *37*, 5469–5472.
- [4] a) A. Marra, A. Dondoni, F. Sansone, *J. Org. Chem.* **1996**, *61*, 5155–5158; b) A. Dondoni, M. Kleban, A. Marra, *Tetrahedron Lett.* **1997**, *38*, 7801–7804; c) A. Dondoni, A. Marra, M.-C. Scherrmann, A. Casnati, F. Sansone, R. Ungaro, *Chem. Eur. J.* **1997**, *3*, 1774–1782.
- [5] a) T. Fujimoto, C. Shimizu, O. Hayashida, Y. Aoyama, *J. Am. Chem. Soc.* **1997**, *119*, 6676–6677; b) O. Hayashida, C. Shimizu, T. Fujimoto, Y. Aoyama, *Chem. Lett.* **1998**, 13–14.
- [6] a) R. Roy, *Curr. Opin. Struct. Biol.* **1996**, *6*, 692–702; b) R. Roy, *Polym. News* **1996**, *21*, 226–232; c) R. Roy, *Top. Curr. Chem.* **1997**, *187*, 241–274; d) N. Jayaraman, S. A. Nepogodiev, J. F. Stoddart, *Chem. Eur. J.* **1997**, *3*, 1193–1199.
- [7] a) T. Toyokuni, A. Singhal, *Chem. Soc. Rev.* **1995**, *24*, 231–308; b) S. Hakomori, *Curr. Opin. Immunol.* **1991**, *3*, 646–653.
- [8] K. Rittenhouse-Diakun, Z. Xia, D. Pickhardt, M.-G. Baek, R. Roy, *Hybridoma* **1998**, *17*, 165–173.
- [9] K. Iwamoto, S. Shinkai, *J. Org. Chem.* **1992**, *57*, 7066–7073.
- [10] S. Sakai, T. Sasaki, *J. Am. Chem. Soc.* **1994**, *116*, 1587–1588.

Organically Templated Mixed-Valent $\text{Ti}^{\text{III}}/\text{Ti}^{\text{IV}}$ Phosphate with an Octahedral–Tetrahedral Open Framework**

Sambandan Ekambaram and Slavi C. Sevov*

The zeolitic aluminum silicates and the more recently discovered microporous aluminum phosphates have attracted tremendous interest due to their application as catalysts, ion-exchangers, and molecular sieves in many technologically important processes. Nevertheless, due to the presence of main group elements only, these materials have no potential for redox reactions and redox catalysis. It is highly desirable, therefore, to build microporous compounds containing d-block metals as an integral part of the framework and in close proximity to the voids. Titanium has been of particular interest as a potential substitute for silicon owing to the available oxidation state of four and appropriate size. Substitutions of the tetrahedral silicon have been achieved at the doping level,^[1] and despite the small amounts of titanium, the resulting materials have shown highly improved

[*] Prof. S. C. Sevov, S. Ekambaram
Department of Chemistry and Biochemistry
University of Notre Dame
Notre Dame, IN 46556 (USA)
Fax: (+1) 219-631-6652
E-mail: ssevov@nd.edu

[**] We thank the National Science Foundation (DMR-9701550 and DMR-9703732) and the Bayer Corporation (Postdoctoral Fellowship) for the financial support.

catalytic properties.^[2] More recently, microporous titanium(IV) silicates such as ETS-4, ETS-10, and others with substantial fractions of titanium were discovered,^[3] and had shown good catalytic activity as well.^[4] These possess octahedral–tetrahedral frameworks comparable to those of some transition metal phosphates.^[5] Titanium-based microporous compounds with trivalent or mixed-valent titanium would be of even greater interest. Such reduced metal compounds with open frameworks are known for molybdenum, vanadium, and iron, for example, but none is known for titanium. Here we report the synthesis and structure of the first mixed-valent titanium(III)/titanium(IV) phosphate with open-framework structure, named TPO-1. The new compound, $\text{Ti}^{\text{III}}\text{Ti}^{\text{IV}}(\text{PO}_4)(\text{HPO}_4)_2(\text{H}_2\text{O})_2 \cdot 0.5\text{NH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_2$, is made hydrothermally by using a quite unconventional source for the titanium, the element itself.

The compound was initially obtained in an attempt to hydrothermally synthesize organically templated titanium borophosphate in an approach analogous to that employed for other transition metal borophosphates,^[6] and therefore the starting materials included boric acid. Later, the reaction conditions were optimized for high yield, and consisted of only titanium metal, phosphoric acid, and 1,3-diaminopropane. Interestingly, successful synthesis can be carried out only when elemental titanium is used. Our attempts to use TiF_3 or Ti_2O_3 as the source for titanium failed. TPO-1 crystallizes as square prisms and cubes with deep blue-purple color; the latter is the first indication of the presence of Ti^{III} centers.

The structure of TPO-1 was determined by single-crystal X-ray diffraction. It is built of octahedrally coordinated titanium and tetrahedrally coordinated phosphorus centers (Figures 1 and 2). Although the compound is phosphorus-rich

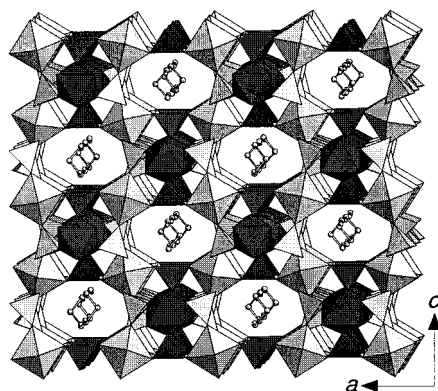


Figure 1. Polyhedral representation of the structure of TPO-1. The $\text{Ti}^{\text{IV}}\text{O}_6$ and PO_4 polyhedra are shown as darker polyhedra, and $\text{Ti}^{\text{III}}\text{O}_4(\text{H}_2\text{O})_2$ and $\text{PO}_3(\text{OH})$ as lighter polyhedra. The 1,3-diaminopropane molecules in the channels are shown as a ball-and-stick representation.

($\text{Ti}:\text{P}=2:3$) there is no P–O–P bonding. Also, unlike the titanosilicates that contain titanium in an octahedral environment,^[3] there is no Ti–O–Ti bonding either. The two types of titanium, Ti^{III} and Ti^{IV} , are in equimolar ratio. The Ti^{III} center is at an inversion center and has two water molecules (O7) in *trans* position. The distances around it are slightly longer than those around Ti^{IV} (Figure 3) as might be expected. The

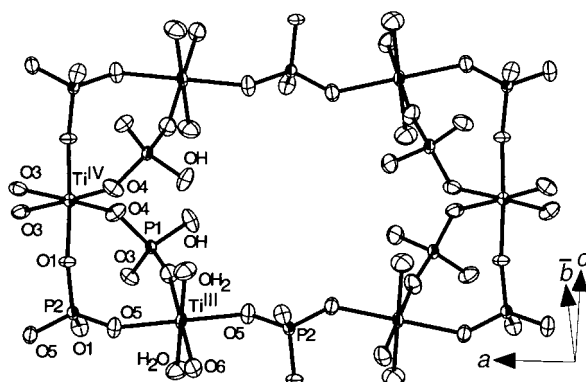


Figure 2. An ORTEP view (thermal ellipsoids at the 50% level) of the “real” cross-section of the channels (see text for more details). The view is approximately along the [011] direction of the orthorhombic cell. All hydroxyl groups and water molecules point towards the center of the channel.

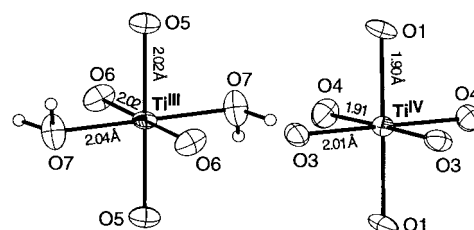


Figure 3. The coordination around Ti^{III} (left) and Ti^{IV} (right) with the distances to the nearest neighbors. All non-hydrogen atoms are drawn with thermal ellipsoids of 70% probability.

calculated valence sums for the two atoms are 3.17 and 4.32 for Ti^{III} and Ti^{IV} , respectively.^[7] The distance to the water molecules, 2.039(6) Å, is very similar to Ti–OH₂ distances in other Ti^{III} compounds; in the hexaaquatitanium(III) trication this distance lies between 2.018(5) and 2.046(6) Å,^[8] in a cesium titanium alum this distance is 2.028(5) Å.^[9] The structure has channels along the *b* axis, and the diaminopropane molecules are positioned inside them. The latter are disordered among two positions, and seem to be free of hydrogen bonding. The shortest N–O distance is 3.003 Å, and is to the OH group at P1 (Figure 2). The amount of the amine present, half of a molecule per formula unit, was additionally confirmed by elemental analysis. The channels are not exactly straight but rather zigzag within the *bc* plane (up and down in Figure 1). Thus, Figure 1 depicts only the “projection” of the opening. Figure 2, which is a view approximately along the [011] direction, shows the real size of the cross-section. The dimensions of that opening are 6.0–6.2 by 6.4–6.5 Å for the horizontal (OH–OH) and vertical (O5–O5) distances on Figure 2, respectively.

The IR spectrum of TPO-1 contains the characteristic bands of a free amine. Thus, broad bands observed at 3508, 3436, and 3152 cm^{-1} correspond to combination and overlapping of stretching vibrations of H_2O , NH_2 , and CH_2 groups. Sharp bands at 1635 and 1508 cm^{-1} (doublet) can be assigned to the bending vibrations of the NH_2 and CH_2 groups, respectively. At the same time the spectrum does not contain bands at around 3000–2800 and 2000 cm^{-1} that are characteristic for protonated amines (the stretching and combination bands of NH_3^+ , respectively). Multiple bands are observed in

the region 1100–900 cm⁻¹, and they correspond to vibrations of the phosphate group. The compound absorbs in the yellow–orange region with absorption bands at around 550 and 575 nm, and appears deep blue–purple.

The temperature dependence of the molar magnetic susceptibility of two samples showed Curie behavior. The measured points were fitted with $\chi_m = C_m/(T - \theta) + \text{TIP}$, where C_m and θ are the Curie and Weiss constants, respectively, and TIP is the temperature-independent paramagnetism resulting from mixing of low-lying empty states. The Weiss constant was approximately zero for both samples, –0.67 and –0.78 K, and indicates the lack of interactions between the Ti^{III} (d¹) atoms. The TIP values differed somewhat, 1.74 and 3.91×10^{-4} emu mol⁻¹, perhaps due to the quite different amounts of sample used for the two measurements. The Curie constant, however, was virtually identical for the two samples, and indicated magnetic moments of 1.24 and 1.21 μ_B , respectively. This is clearly consistent with one spin per mole of TPO-1, and unequivocally confirms the presence of Ti^{III} and Ti^{IV} in equimolar ratio. Further proof for this assignment is the g value of 2.026 derived from the EPR spectrum of the sample.

Thermogravimetric analysis of the sample showed two steps, one in the range 100–235 °C and another one in the 330–355 °C range, with weight losses of 7.22 and 5.30 %, respectively. These were attributed to dehydration (calcd 7.95 %) and removal of the 1,3-diaminopropane (calcd 8.8 %), respectively. Some coke formation that occurs during the latter step may explain the discrepancy between the observed and calculated weight losses. After the first step, that is above ~260 °C, the compound loses color and becomes white, the structure collapses, and the resulting X-ray powder diffraction pattern indicates amorphous state. This is attributed to the instability of square-planar titanium resulting from the removal of the two *trans* water molecules around the Ti^{III} center. This perhaps is followed by easy oxidation of the unsaturated titanium atoms and local geometrical rearrangement leading to the loss of crystallinity. According to the IR spectrum of the sample, the diaminopropane remains in the sample up to around 330 °C. Above 600 °C the compound recrystallizes into TiP₂O₇.^[10] Attempts to photodecompose the organic template by using a medium-pressure mercury lamp as source were unsuccessful.

Experimental Section

Synthesis: TPO-1 was initially synthesized from a mixture of elemental titanium, boric acid, phosphoric acid, 1,3-diaminopropane, HF, and water in a molar ratio of 1:6.54:13.65:2.21:3.36:600 in an attempt to make open-framework titanium borophosphate. Later it was found that boron and fluorine are not part of the structure, and the synthesis was optimized. The compound is synthesized hydrothermally as a single phase (according to the Guinier powder pattern) in 100 % yield with respect to Ti from a mixture of elemental titanium (Alfa-Aesar, powder, 325 mesh, 99 %), 1,3-diaminopropane (Acros, 99 %), H₃PO₄, and deionized water in molar ratio of 2:2.21:13.65:500 (pH 2). The mixture was heated in a teflon-lined stainless steel autoclave at 170 °C for one day under autogenous pressure. The product, aggregates of deep blue–purple square prisms, was consecutively washed with water, alcohol, and acetone. Elemental analysis performed by the Galbraith Laboratories: calcd: C 3.96, H 2.42, N 3.08; found: C 3.58, H 3.09, N 2.92.

Magnetic, thermal, and spectroscopic measurements: The magnetizations of two samples (38 and 94 mg) of two different reactions were measured at

a field of 3 T over the temperature range 10–270 K with a step of 10 °C on a Quantum Design MPMS SQUID magnetometer. An EPR spectrum of the compound was recorded at room temperature on a VARIAN spectrometer. Thermogravimetric analysis (TGA) was carried out in a flow of air (150 mL min⁻¹) on 36 mg of sample on a CAHN TG-131 unit up to 600 °C with a heating rate of 10 K min⁻¹. IR spectra (KBr disk) were taken before and after heat treatment on a Perkin-Elmer PARAGON-100. A spectrum in the visual region was recorded in reflection mode on a Varian Cary-3 from the sample contained in a thin-wall cuvet of fused silica.

Crystal structure determination: Data were collected from a single crystal with a cubic shape (0.20 × 0.20 × 0.20 mm) on a CAD4 single crystal diffractometer with monochromated MoK α radiation at 21 °C (ω -2 θ scans, $2\theta_{\text{max}} = 50^\circ$, one octant). After corrections for Lorentz and polarization effects the data set was consistent with one space group only, *Pnma* (no. 52). Direct methods revealed the two titanium and three phosphorus atoms. Subsequent least-squares refinement on F^2 followed by difference Fourier maps with the aid of the SHELXTL V5.0 package revealed the remaining oxygen atoms. The 1,3-diaminopropane molecule was found disordered on two sites, and therefore the corresponding carbon and nitrogen atoms were refined with fixed appropriate occupancies. All hydrogen atoms were located as required by geometry and refined as riding on the corresponding oxygen, nitrogen, and carbon atoms. The refinement of all nonhydrogen atoms with anisotropic thermal parameters converged with $R1/wR2$ ($I > 2\sigma I$) = 0.0667/0.1841 for 1104 reflections and 122 parameters. (crystal data: Ti₂(PO₄)(HPO₄)₂(H₂O)₂ · 0.5 NH₂CH₂CH₂CH₂NH₂, orthorhombic, *Pnma*, $a = 12.702(5)$, $b = 9.365(4)$, $c = 11.253(8)$ Å, $V = 1339(1)$ Å³ from Guinier data with Si as an internal standard and CuK α radiation, $Z = 4$, $\rho_{\text{calcd}} = 2.262$ g cm⁻³, $\mu = 16.28$ cm⁻¹, residual electron density = +1.38/–0.70 e Å⁻³ at 1.84/1.06 Å from O4/Ti^{IV}.) A data set collected on a different crystal showed the same disorder of the 1,3-diaminopropane in the channels. Both crystals were carefully checked for superstructure but none was found. Further details of the crystal structure investigation can be obtained from the Fachinformationszentrum Karlsruhe, D-76344 Eggenstein-Leopoldshafen, Germany (fax: (+49) 7247-808-666; e-mail: crysdata@fiz-karlsruhe.de), on quoting the depository number CSD-410058.

Received: August 12, 1998 [Z 12281 IE]

German version: *Angew. Chem.* **1999**, *111*, 384–386

Keywords: mixed-valent compounds • template synthesis • titanium • zeolite analogues

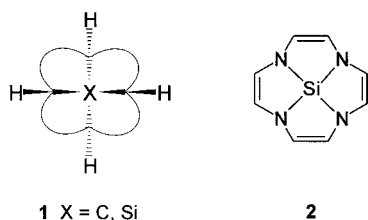
- [1] a) B. Notari, G. Perego, M. Tarramasso, (Snamprogetti S.p.A.), US-A 4410501, **1983**; b) T. Blasco, M. A. Camblore, A. Corma, J. Perez-Pariente, *J. Am. Chem. Soc.* **1993**, *115*, 11806.
- [2] a) M. Sasidharan, S. V. N. Raju, K. V. Srinivasan, V. Paul, R. Kumar, *Chem. Commun.* **1996**, 129; b) R. Kumar, G. C. G. Pais, B. Pandey, P. Kumar, *J. Chem. Soc. Chem. Commun.* **1995**, 1315; c) M. G. Clerici, P. Ingallina, *J. Catal.* **1993**, *140*, 71; d) P. Kumar, V. R. Hegde, B. Pandey, T. Ravindranathan, *J. Chem. Soc. Chem. Commun.* **1993**, 1553; e) J. S. Reddy, U. R. Khire, P. Ratnasamy, R. B. Mitra, *J. Chem. Soc. Chem. Commun.* **1992**, 1234; f) A. Thangaraj, R. Kumar, P. Ratnasamy, *J. Catal.* **1991**, *131*, 294; g) T. Tatsumi, M. Nakamura, S. Negishi, H. Tominaga, *J. Chem. Soc. Chem. Commun.* **1990**, 476.
- [3] a) S. M. Kuznicki (Engelhard Corporation), US-A 4853202, **1989**; b) S. M. Kuznicki (Engelhard Corporation), US-A 4938989, **1990**; c) D. M. Chapman, A. L. Roe, *Zeolites* **1990**, *10*, 730; d) D. M. Chapman (W. R. Grace & Co.-Conn.), US-A 5015453, **1991**; e) S. M. Kuznicki, K. A. Thrush, F. M. Allen, S. M. Levine, M. M. Hamil, D. T. Hayhurst, M. Mansour in *Molecular Sieves, Vol. 1* (Eds.: M. L. Occelli, H. Robson), Van Nostrand Reinhold, New York, **1992**, pp. 427–453; f) D. M. Poojari, R. A. Cahill, A. Clearfield, *Chem. Mater.* **1994**, *6*, 2364; g) M. W. Anderson, O. Terasaki, T. Ohsuna, A. Philippou, S. P. MacKay, A. Ferreira, J. Rocha, S. Lidin, *Nature* **1994**, *367*, 347; h) W. T. A. Harrison, T. E. Gier, G. D. Stucky, *Zeolites* **1995**, *15*, 408; i) G. Sankar, R. G. Bell, J. M. Thomas, M. W. Anderson, P. A. Wright, J. Rocha, *J. Phys. Chem.* **1996**, *100*, 449.
- [4] a) C. L. Bianchi, V. Ragaini, *J. Catal.* **1997**, *168*, 70; b) T. K. Das, A. J. Chandwadkar, S. Sivasanker, *Catal. Lett.* **1997**, *44*, 113; c) T. K. Das,

- A. J. Chandwadkar, S. Sivasanker, *J. Mol. Catal. A* **1996**, *107*, 199; d) R. Robert, P. R. Rajamohanam, P. Ratnasamy, *J. Catal.* **1995**, *155*, 345
- [5] a) R. Haushalter, L. Mundi, *Chem. Mater.* **1992**, *4*, 31, and references therein; b) V. Zima, K.-H. Lii, N. Nguyen, A. Ducouret, *Chem. Mater.* **1998**, *10*, 1914; c) K. H. Lii, Y. F. Huang, *J. Chem. Soc. Dalton Trans.* **1997**, 2221; d) K. H. Lii, Y. F. Huang, *Chem. Commun.* **1997**, 839; e) M. B. Korzenski, G. L. Schimek, J. W. Kolis, *Eur. J. Solid State Inorg. Chem.* **1998**, *35*, 143; f) Z. Bircsak, W. T. A. Harrison, *Inorg. Chem.*, **1998**, *37*, 3204.
- [6] S. C. Sevov, *Angew. Chem.* **1996**, *108*, 2814; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2630. The isostructural Ni^{II} , Fe^{II} , Mn^{II} , and Mg analogues were made later as well.
- [7] N. E. Brese, M. O'Keeffe, *Acta Crystallogr. Sect. B* **1991**, *47*, 192.
- [8] M. A. S. Aquino, W. Clegg, Q.-T. Liu, A. G. Sykes, *Acta Crystallogr. Sect. C* **1995**, *51*, 560.
- [9] J. Sygusch, *Acta Crystallogr. Sect. B* **1974**, *30*, 662.
- [10] H. F. McMurdie, M. C. Morris, E. H. Evans, B. Paretkin, W. Wong-Ng, Y. Zhang, C. R. Hubbard, *Powder Diffr.* **1987**, *2*, 41.

First Synthesis and Structure of a Tetraazasilafenestrane**

Bangwei Ding, Reinhart Keese,* and Helen Stoeckli-Evans

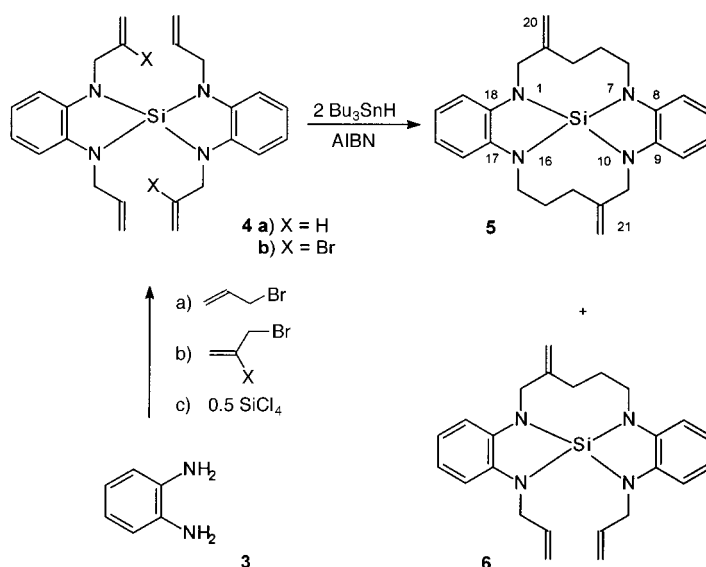
According to quantum-chemical calculations planar tetra-coordination should inherently be easier to achieve in silicon compounds than in the corresponding carbon compounds. These conclusions are based on results by Hoffmann, Alder, and Wilcox, who discussed the structural features of fenestranes of type **1** with $\text{X} = \text{C}$,^[1] as well as our computational



results for silafenestranes of type **1** with $\text{X} = \text{Si}$.^[2] Despite considerable computational efforts no structures with a planar-tetracoordinate $\text{C}(\text{C})_4$ substructure have been found.^[3] Schleyer et al. have computationally explored the prerequisites for enhanced planarization in compounds such as **1** ($\text{X} = \text{Si}$), and proposed that planar-tetrasubstituted silicon should

be favored by electronegative, π -donor substituents.^[4] In 1992 Boldyrev, Schleyer, and Keese reported computational results according to which **2** is planar and has a minimum energy at the ab initio HF/3-21G* level.^[5]

Whereas fenestranes have been prepared by a variety of methods,^[7] neither silafenestranes nor tetraazasilafenestranes have hitherto been reported. In the course of our investigations of these structurally unusual molecules, we examined ring-closure reactions of appropriately functionalized spiro-tetraazasilanes. Although Si–N bonds are kinetically labile and sensitive to moisture, spiro-tetraazasilanes such as **4a** and **4b** could readily be prepared from *o*-phenylenediamine (**3**). Since ring-closure metathesis reactions of **4a** with Grubbs' catalyst^[8] remained unsuccessful and radical-induced reactions with a dialkylborane led only to hydroboration of a double bond, we considered cyclization reactions of **4b**. Whereas Pd^0 - and Pd^{II} -induced cyclizations remained unsuccessful as well, ring-forming radical reactions were observed when **4b** was treated with Bu_3SnH and azobisisobutyronitrile (AIBN) under carefully controlled conditions (Scheme 1).^[9]



Scheme 1. Synthesis of **5** and **6**.

The tetraazasilafenestrane **5**, formed by a double 8-*endo* radical cyclization, was separated from the tricyclic compound **6** by chromatography and showed the expected number of NMR signals.^[10] In comparison with **4a**, **4b** and **6** the ^{29}Si NMR signal of **5** is shifted downfield, indicating a different environment for the silicon atom. Definite proof of the tetracyclic structure was established by an X-ray structure analysis (Figure 1).^[11] A salient feature of the SiN_4 core structure of **5** is the 84.7° angle between the planes of the diazasilacyclopentene rings. Since the planes of the two five-membered rings in tetraazasilaspiro[4.4]nonanes are almost perpendicular to each other, the distortion must be due to the alkylene chains bridging the spiro rings.^[12] Three of the four nitrogen atoms are in a pyramidal environment, leading to a pseudo-envelope conformation for both diazasilacyclopentene rings.^[13]

To realize planarization in the central SiN_4 core of tetraazasilafenestranes, smaller rings are required. Our efforts to

[*] Prof. Dr. R. Keese, Dipl.-Chem. B. Ding
Departement für Chemie und Biochemie der Universität
Freiestrasse 3, CH-3012 Bern (Switzerland)
Fax: (+41) 31-631-3423
E-mail: reinhart.keese@ioc.unibe.ch

Prof. H. Stoeckli-Evans
Institut de Chimie, Université de Neuchâtel
Avenue de Bellevaux 51, CH-2000 Neuchâtel (Switzerland)

[**] This work has been supported by the Swiss National Science Foundation (project no. 20-43565.95) B.D. is grateful for a scholarship of the Swiss Federal Scholarship Commission for Foreign Students (1996/1997).

Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.

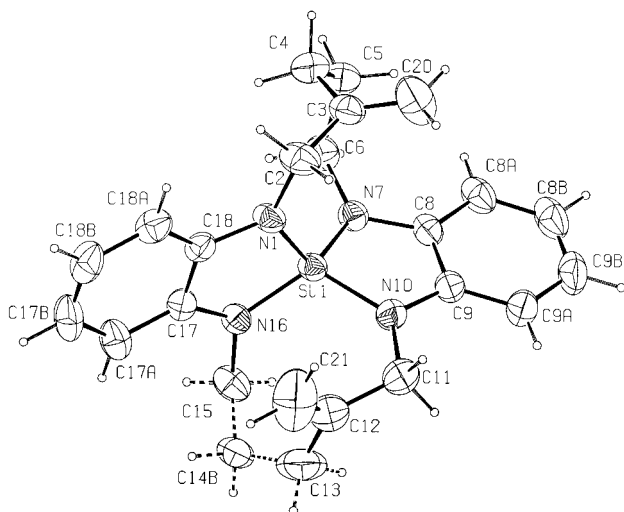


Figure 1. Structure of **5** in the crystalline state (thermal ellipsoids at the 50% probability level). Selected bond lengths [Å] and bond and torsional angles [°]: N–Si 1.7132(15)–1.7182(13); N1–Si–N16 91.81(7), N1–Si–N7 115.46(7), N1–Si–N10 121.96(7), N7–Si–N10 92.08(7); N16–Si–N1–C2 179.68(15), N16–Si–N1–C18 72.6(11), N1–Si–N16–C15 –171.47(13), N1–Si–N16–C17 –6.97, N10–Si–N7–C6 –173.26(14), N10–Si–N7–C8 –5.92(12), N7–Si–N10–C11 –175.09(15), N7–Si–N10–C9 5.92(12).

prepare such tetraazasilafenestranes by silylation of tetraazacycloalkanes have so far not led to pure compounds.^[14]

Experimental Section

A solution of Bu_3SnH (64 mg, 0.22 mmol) and AIBN (10 mg) in degassed benzene (10 mL) was added to **4b** (61 mg, 0.11 mmol) in degassed benzene (50 mL) under reflux. After 5 h another portion (10 mL) of the Bu_3SnH solution was added, and the reaction mixture heated under reflux overnight. After removal of the solvent and column chromatography, the mixture of **5** and **6** (34 mg) was separated by preparative thin-layer chromatography (TLC) to give 10 mg (22.7%) of **5** and 20 mg (45.4%) of **6**.

5: M.p. 180–182 °C; R_f (hexane/diethyl ether 40/1) = 0.60; ^1H NMR (300 MHz, CDCl_3 , TMS; see Scheme 1 for atom numbering): δ = 6.76–6.82 (m, 4H), 6.64–6.71 (m, 4H), 4.66 (s, C20–H_b + C21–H_b, 2H), 4.46 (s, C20–H_a + C21–H_a, 2H), 3.95 (d, J = 12.2 Hz, C2–H_a + C11–H_a, 2H), 3.71 (dt, J = 14.3, 3.7 Hz, C6–H_b + C15–H_b, 2H), 3.64 (d, J = 12.5 Hz, C2–H_b + C11–H_b, 2H), 3.31 (ddd, J = 14.5, 12.7, 2.6 Hz, C6–H_a + C15–H_a, 2H), 2.40 (dd, J = 14.34, 5.56 Hz, C4–H_b + C13–H_b, 2H), 2.16 (approx. dt, J = 13.97, 11.40, 2.57 Hz, C5–H_b + C14–H_b, 2H), 1.82 (m, C4–H_a + C13–H_a, 2H), 1.60 (m, C5–H_a + C14–H_a, 2H); ^{13}C NMR: δ = 145.29, 136.51, 135.64, 117.56, 117.49, 112.58, 108.03, 106.91, 50.19, 43.07, 32.47, 26.61; ^{29}Si NMR: δ = –21.39; MS (EI): m/z (%): 400 (100) [M^+], 385 (9), 371 (8), 200 (12), 149 (9), 137 (8), 109 (9), 97 (10), 81 (9), 69 (8), 56 (10); IR (CHCl_3): $\tilde{\nu}$ = 1480 (s), 1262 (s), 1228 (vs), 1100 cm^{-1} (vs); elemental analysis calcd for $\text{C}_{24}\text{H}_{28}\text{N}_4\text{Si}$: C 71.96, H 7.05, N 13.99; found: C 71.70, H 7.12, N 13.84.

Received: August 13, 1998 [Z122851E]
German version: *Angew. Chem.* **1999**, *111*, 387–388

Keywords: cyclizations • nitrogen • planar-tetracoordinate centers • silicon • spiro compounds

- R. Keese in *Advances in Strain in Organic Chemistry*, Vol. 3 (Ed.: B. Halton), JAI Press, Greenwich, CT, **1993**, pp. 229–267; D. Kuck, *Advances in Theoretically Interesting Molecules*, Vol. 4, JAI Press, Greenwich, CT, **1998**, pp. 81–155. Alkapanes, a family of strained polycyclic hydrocarbons, are the closest to showing planarity according to quantum-chemical approaches: J. E. Lyons, D. R. Rasmussen, M. P. McGrath, R. H. Nobes, L. Radom, *Angew. Chem.* **1994**, *106*, 1722–1724; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1667–1668.
- [4] a) J. Chandrasekhar, E.-U. Würthwein, P. von R. Schleyer, *Tetrahedron* **1981**, *37*, 921–927; b) E.-U. Würthwein, P. von R. Schleyer, *Angew. Chem.* **1979**, *91*, 588–589; *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 553; c) W. J. Hehre, L. Radom, P. von R. Schleyer, J. A. Pople, *Ab initio Molecular Orbital Theory*, Wiley, New York, **1986**, p. 84; d) J. B. Collins, J. D. Dill, E. D. Jemmis, Y. Apeloig, P. von R. Schleyer, R. Seeger, J. A. Pople, *J. Am. Chem. Soc.* **1976**, *98*, 5419–5427; e) M.-B. Krogh-Jespersen, J. Chandrasekhar, E.-U. Würthwein, J. B. Collins, P. von R. Schleyer, *J. Am. Chem. Soc.* **1980**, *102*, 2263–2268; f) J. Chandrasekhar, P. von R. Schleyer, *J. Chem. Soc. Chem. Commun.* **1981**, 260–261.
- [5] A. I. Boldyrev, P. von R. Schleyer, R. Keese, *Mendeleev Commun.* **1992**, 93–95. According to the X-ray structure analysis, the silaphthalocyanine reported in reference [6] contains a planar-tetracoordinate silicon. However, the Si–N distance of 1.93 Å is much larger than in **5** or calculated for **2**, and the formal valence of the silicon atom in this silaphthalocyanine is two instead of four.
- [6] M. Aldoshin, O. A. D'yachenko, L. O. Atomyan, A. N. Chekhlov, M. I. Alyanov, *Koord. Khim.* **1980**, *6*, 936–944.
- [7] M. Thommen, R. Keese, *Synlett* **1997**, *3*, 231–240.
- [8] G. C. Fu, S. T. Nguyen, R. H. Grubbs, *J. Am. Chem. Soc.* **1993**, *115*, 9856–9857.
- [9] K. J. Shea, R. O'Dell, D. Y. Sasaki, *Tetrahedron Lett.* **1992**, *33*, 4699–4702.
- [10] Z. Teng, R. Keese, H. Stoeckli-Evans, *Tetrahedron* **1998**, *54*, 10699–10702.
- [11] Crystal structure analysis of **5**: Single crystals of **5** were obtained from CH_2Cl_2 by slow evaporation at 500 mbar for 6–8 h at 19–21 °C. $\text{C}_{24}\text{H}_{28}\text{N}_4\text{Si}$, M_r = 400.59, colorless blocks, crystal dimensions 0.6 × 0.4 × 0.25 mm³, monoclinic, space group $P2_1/c$, a = 10.1412(9), b = 9.8408(6), c = 21.5219(19) Å, β = 97.513(11)°, V = 2129.4(3) × 10⁶ pm³, Z = 4, ρ_{calcd} = 1.250 g cm^{–3}, $F(000)$ = 856, μ = 0.128 mm^{–1}. Imaging plate diffraction system (STOE); of 16247 reflections measured, 4046 were independent. The structure was solved with SHELXS-97^[15] and refined for F^2 with SHELXL-97^[16] $R1$ [$= \sum(|F_o| - |F_c|)/\sum|F_o|$] = 0.0579 and $wR2$ [$= \sum(w(F_o^2 - F_c^2)^2)/\sum wF_o^2$] = 0.0931 for all data, GOF = 0.922, max./min. residual electron density 0.210/–0.276 e Å^{–3}. Atom C15 of one of the SiN_2C_3 rings is disordered (ratio A:B = 0.556:0.444). Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-102562. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [12] G. Rong, R. Keese, H. Stoeckli-Evans, *Eur. J. Inorg. Chem.* **1998**, 1967–1973.
- [13] The N atoms deviate from the best plane through the adjacent two carbon atoms and the silicon atom by –0.058 Å (N1), –0.096 Å (N7), 0.008 Å (N10) and –0.118 Å (N16).
- [14] Silylation of 1,4,8,11-tetraazacyclotetradecane gave a mixture of products with a strong peak at m/z 224 in the mass spectrum: M. Wollenweber, R. Keese, unpublished results.
- [15] G. M. Sheldrick, *Acta Crystallogr. Sect. A* **1990**, *46*, 467 (“SHELXS-90 Program for Crystal Structure Determination”).
- [16] G. M. Sheldrick, SHELXL-97, Universität Göttingen, Germany, **1997**.

- [1] a) R. Hoffmann, R. W. Alder, C. F. Wilcox, Jr., *J. Am. Chem. Soc.* **1970**, *92*, 4992–4993; b) R. Hoffmann, *Pure Appl. Chem.* **1971**, *28*, 181–194.
- [2] W. Luef, R. Keese, unpublished results.
- [3] M. J. M. Pepper, I. Shavitt, P. von R. Schleyer, M. N. Glukhovtsev, R. Janoscheck, M. Quack, *J. Comput. Chem.* **1995**, *16*, 207–225; W. Luef,

[Fe₂{SeC₆H₂-2,4,6-Ph₃]₂{N(SiMe₃)₂]₂] and [Fe₂{SeC₆H₂-2,4,6-Ph₃]₄], the First Three-Coordinate Selenolatoiron Complexes

Ralf Hauptmann, Rainer Kließ, and Gerald Henkel*

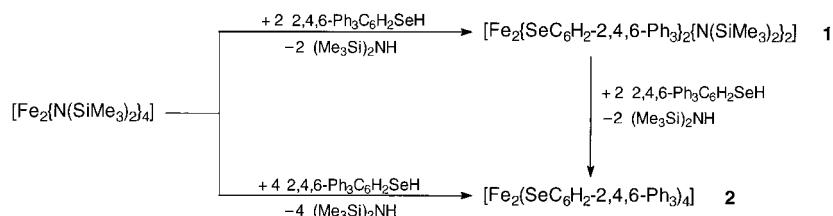
Dedicated to Professor Bernt Krebs on the occasion of his 60th birthday

Iron complexes with sterically nondemanding chalcogen ligands are characterized by a coordination number of 4 if the ligand donor functions are negatively charged. They comprise not only the mixed sulfidothiolato complexes of composition [Fe_nS_n(SR)₄]^{2−/3−} but also the homoleptic thiolato complexes of general formula [Fe(S-R)₄]^{−/2−}, which have attracted considerable interest as models for the active sites of 2Fe–2S (*n* = 2) and 4Fe–4S ferredoxins (*n* = 4) and of rubredoxins.^[1, 2] Within the ferredoxin-like complexes, FeS₄ tetrahedra are connected through common S⋯S edges. Similar connectivity patterns also occur in the dinuclear homoleptic alkane thiolato complexes of general formula [Fe₂(SR)₆]^{2−}, if the sulfur atoms are bound to primary or secondary C atoms. This pattern may change, however, if *tert*-butane thiolato ligands are used instead, as illustrated by the unexpected formation of the dinuclear iron complex [Fe₂(SC₄H₉)₅][−], in which the FeS₄ tetrahedra share a common face.^[3] In the meantime, related cobalt and nickel complexes are also known.^[4–6] In search of further parameters which may influence the coordination number and/or the degree of condensation within thiolatoiron complexes, sterically demanding thiolato ligands with bulky substituents have attracted increasing interest in the last few years. Following this concept, the first complexes of coordination number 2^[7] and 3^[8] were synthesized and structurally characterized.

Based on these considerations, we extended our approach to control the degree of condensation and/or the coordination number in transition metal chalcogenolate complexes by using selenolato ligands which combine high nucleophilicities with large spatial demands. Although we have obtained the first dinuclear cobalt complexes with face-sharing MSe₄ tetrahedra by using this concept,^[9] comparable results for iron complexes have so far remained elusive. More successful, however, were our efforts to stabilize unusually low coordination numbers. In this paper we report on the first selenolatoiron complexes of coordination number 3.

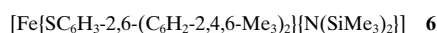
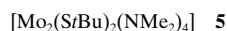
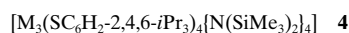
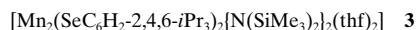
During our investigations of the reactivity of 2,4,6-triphenylselenophenol towards iron(II) bis(trimethylsilyl)amide,^[10]

we isolated the novel molecular complexes **1** and **2** in crystalline form (Scheme 1). Whereas **1** was obtained from the reaction of iron(II) bis(trimethylsilyl)amide with 2,4,6-triphenylselenophenol in the molar ratio of 1:1 in a mixture of toluene and hexane, the reaction in the 1:2 molar ratio led to the formation of **2**. Complex **1** can also be converted to **2** by treatment with two further equivalents of 2,4,6-triphenylselenophenol. These results demonstrate that the partial (formation of **1**) or complete (formation of **2**) replacement of amide ligands in the complex iron(II) bis(trimethylsilyl)amide can be controlled by varying the reaction conditions.



Scheme 1. Synthesis of **1** and **2** from [Fe₂{N(SiMe₃)₂]₄ and 2,4,6-Ph₃C₆H₂SeH.

Complex **1** with a mixed selenolatoamido ligand sphere is the first member of a new class of complexes. Closely related to **1** is the complex **3**, in which iron is replaced by manganese and which contains additional thf ligands.^[11] Interestingly, complexes with mixed thiolatoamido ligand spheres are also rare. The few examples known so far include the trinuclear complexes **4** (M = Zn^[12] and Fe^[8c]), the dinuclear complex **5**,^[13] and the mononuclear complex **6**.^[7] To date, complexes with mixed telluroolatoamido ligand spheres are completely unknown.



During the formation of **1**, the selenolato ligand evidently prefers the bridging position probably because it is a softer base than the leaving amide group. From a chemical point of view, the mixed selenolatoamido complex is of special interest because it should be possible to introduce ligands other than those described here by a controlled replacement of the terminally bonded bis(trimethylsilyl)amide groups by suitable acid–base reactions. Therefore, **1** might serve as a starting material for the synthesis of complexes with mixed chalcogen ligand spheres (e.g. sulfur/selenium) or complexes of higher nuclearities.

Crystals of **1** (Figure 1) and **2** (Figure 2) consist of isolated electroneutral [Fe₂{SeC₆H₂-2,4,6-Ph₃]₂{N(SiMe₃)₂]₂] and [Fe₂{SeC₆H₂-2,4,6-Ph₃]₄] molecules, respectively.^[14] In both cases, the iron atoms possess trigonal coordination geometries with pyramidally distorted FeSe₂N (**1**) and FeSe₃ (**2**) coordination sites. The mean bond angles of the iron atoms are 115.8° in **1** and 116.3° in **2**, respectively. The iron atoms are bridged by two selenolato ligands. In **2**, each of the iron atoms binds a further selenolato ligand, whereas in the case of **1**, the

[*] Prof. Dr. G. Henkel, Dr. R. Hauptmann, Dipl.-Chem. R. Kließ
Institut für Synthesechemie der Universität
Lotharstrasse 1, D-47048 Duisburg (Germany)
Fax: (+49) 203-3792110
E-mail: biohenkel@uni-duisburg.de

[**] Financial support by the Deutsche Forschungsgemeinschaft (DFG), the Bundesminister für Bildung, Wissenschaft, Forschung und Technologie (BMBF) and the Fonds der Chemischen Industrie is gratefully acknowledged.

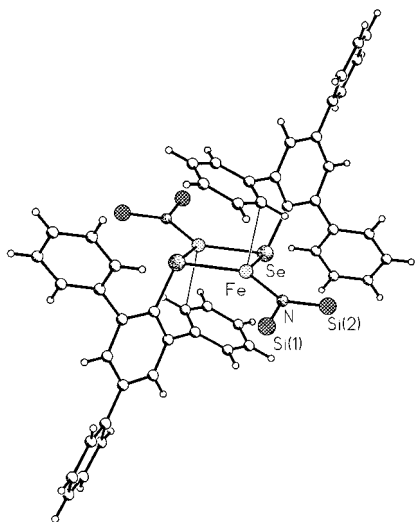


Figure 1. Structure of **1** in the crystal (methyl groups of the silyl substituents are omitted for clarity). Selected distances [Å] and angles [°]: Fe...Fe 3.170(1), Fe–Se 2.476(1) and 2.506(1), Fe–N 1.923(2), Fe...C 2.602(2); Se–Fe–N 116.6(1), Se–Fe–Se' 101.0(1), N–Fe–Se' 138.7(1), Se–Fe...C 88.3(1), Se'–Fe...C 95.6(1), N–Fe...C 101.7(1).

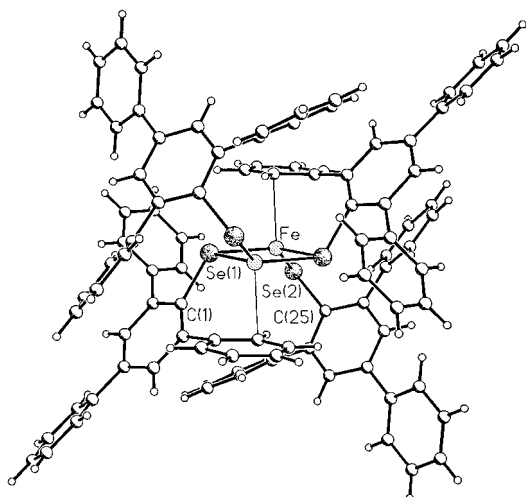


Figure 2. Structure of **2** in the crystal. Selected distances [Å] and angles [°]: Fe...Fe 3.207(1), Fe–Se(1) 2.491(1), Fe–Se(2) 2.383(1), Fe–Se(1') 2.449(1), Fe...C 2.530(2); Se(1)–Fe–Se(2) 129.2(1), Se(1)–Fe–Se(1') 99.0(1), Se(2)–Fe–Se(1') 120.7(1), Se(1)–Fe...C 87.2(3), Se(2)–Fe...C 119.9(3), Se(1')–Fe...C 90.5(3).

coordination is completed by a terminal bis(trimethylsilyl)-amide group.

In both complexes, the iron atoms deviate from the plane defined by the coordinating atoms by distances of 0.24 Å (**1**) and 0.46 Å (**2**), respectively. This is probably due to a specific orientation of the ligands which allows for a weak Fe...C interaction. One of the phenyl rings of each bridging selenolato ligand is oriented approximately parallel to the central Fe₂Se₂ unit, thus supporting this iron–carbon contact, which is roughly normal to the plane defined by the Se₂N or Se₃ donor set, respectively. As a consequence, the Fe atom is shifted from this plane in the direction of the phenyl ring. The corresponding Fe...C distances are 2.602(2) (**1**) and 2.530(3) Å (**2**), respectively. A similar weak Fe...C interac-

tion has been discussed in the complex [Fe(SC₆H₃-2,6-Me₂)₂] with formally two-coordinate iron centers (Fe...C 2.470 Å).^[7] In all these cases, however, the additional interactions have to be considered rather weak because Fe–C distances observed in other iron complexes containing η²-η⁶-coordinated carbon ligands range from 1.90 to 2.25 Å.^[15]

The similar geometries of the central Fe₂Se₂ units are reflected in the comparable Fe...Fe distances in **1** (3.170(1) Å) and **2** (3.207(1) Å). The corresponding (μ₂-Se)–Fe–(μ₂-Se) angles are as small as 101.0(1) and 99.0(1)°, and the Fe–(μ₂-Se)–Fe angles are 79.0(1) and 81.0(1)°, respectively. The mean Fe–(μ₂-Se) bond lengths in **1** (2.491 Å) and **2** (2.470 Å) differ only slightly. As expected, the terminal Fe–Se bonds in **2** are significantly shorter (2.383(1) Å). The Fe–N distance in **1** (1.923(2) Å) is in the same range as in the iron(II) bis(trimethylsilyl)amide used as starting material.^[16]

The results presented here clearly demonstrate that synthetically versatile and sterically demanding selenolato ligands can be used to prepare novel coordinatively unsaturated complexes that are stabilized by a weak binding interaction between the metal center and a carbon atom of a neighboring ligand. This type of interaction could be of interest to explain the stabilization and activation of the FeMo cofactor of nitrogenases (binding of small exogenic molecules such as H₂O or N₂), which contains coordinatively unsaturated trigonal FeE₃ units (E = S).^[17] Investigations of the reactivity of related sulfur complexes have already shown that small neutral molecules with suitable donor functions such as acetonitrile can be added very easily under expansion of the coordination sphere of the iron atom.^[18]

Experimental Section

All operations were performed in glove boxes under a pure dinitrogen atmosphere.

1: A solution of 2,4,6-triphenylselenophenol (1.93 g, 5 mmol) in toluene (20 mL) was added dropwise to a solution of iron(II) bis(trimethylsilyl)amide (1.88 g, 5 mmol) in toluene/hexane (1:1; 20 mL). The red-brown reaction mixture was stirred for 24 h at ambient temperature and then filtered. Within a period of three days at 2 °C, pale brown crystals were obtained. Yield: 0.63 g (21 %).

2: A solution of 2,4,6-triphenylselenophenol (1.31 g, 3.4 mmol) in toluene (20 mL) was added slowly to a solution of iron(II) bis(trimethylsilyl)amide (0.64 g, 1.7 mmol) in toluene (10 mL). After stirring for 48 h at ambient temperature, the red-brown reaction mixture was evaporated to dryness. The residue was recrystallized from hexane/toluene (1:2; 15 mL). Within two days at ambient temperature, red crystals were obtained. Yield: 0.84 g (30 %).

Received: May 4, 1998

Revised version: September 30, 1998 [Z 11809 IE]

German version: *Angew. Chem.* **1999**, *111*, 389–391

Keywords: iron • nitrogen • nitrogenase • selenium

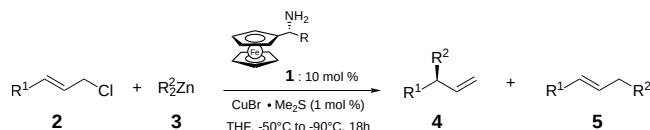
- [1] S. J. Lippard, J. M. Berg, *Bioanorganische Chemie*, Spektrum, Heidelberg, **1995**.
- [2] a) G. Henkel, B. Krebs, *Angew. Chem.* **1991**, *103*, 785; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 769; b) R. H. Holm, K. S. Hagen, *Inorg. Chem.* **1984**, *23*, 418.
- [3] C. Chen, G. Henkel, *Inorg. Chem.* **1993**, *32*, 1064.

- [4] S. Weißgräber, G. Henkel, *Angew. Chem.* **1992**, *104*, 1382; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1368.
- [5] K. Ruhlandt-Senge, P. P. Power, *J. Chem. Soc. Dalton Trans.* **1993**, 649.
- [6] A. Silver, M. Millar, *J. Chem. Soc. Chem. Commun.* **1992**, 948.
- [7] J. J. Ellison, K. Ruhlandt-Senge, P. P. Power, *Angew. Chem.* **1994**, *106*, 1248; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1178.
- [8] a) P. P. Power, S. C. Shoner, *Angew. Chem.* **1991**, *103*, 308; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 330; b) K. Ruhlandt-Senge, P. P. Power, *Bull. Soc. Chim. Fr.* **1992**, *129*, 594; c) F. M. MacDonnell, K. Ruhlandt-Senge, J. J. Ellison, R. H. Holm, P. P. Power, *Inorg. Chem.* **1995**, *34*, 1815.
- [9] G. Henkel, S. Weißgräber, unpublished results.
- [10] R. A. Andersen, K. Faegri, J. C. Green, A. Haaland, W.-P. Leung, K. Rypdal, *Inorg. Chem.* **1988**, *27*, 1782.
- [11] N. Bochmann, A. K. Powell, X. Song, *Inorg. Chem.* **1994**, *33*, 400.
- [12] H. Grützmacher, K. Steiner, H. Pritzkow, L. Zsolnai, G. Huttner, A. Sebal, *Chem. Ber.* **1992**, *125*, 2199.
- [13] M. H. Chisholm, J. F. Corning, J. C. Huffman, *Inorg. Chem.* **1983**, *22*, 38.
- [14] Crystal data: Siemens P4RA four circle diffractometer, Mo $\text{K}\alpha$ radiation ($\lambda = 0.71073 \text{ \AA}$), graphite monochromator, rotating-anode generator, scintillation counter, 150 K, empirical absorption corrections, SHELXTL-PLUS programs, direct methods, least-squares refinements, one scaling factor, one isotropic extinction parameter. **1**: $\text{C}_{60}\text{H}_{70}\text{N}_2\text{Si}_4\text{Fe}_2\text{Se}_2$, formula weight 1201.16, monoclinic, space group $P2_1/n$, $a = 10.822(1)$, $b = 17.705(3)$, $c = 15.720(2) \text{ \AA}$, $\beta = 106.34(1)^\circ$, $V = 2890.35 \text{ \AA}^3$, $Z = 2$, $\rho_{\text{calc}} = 1.380 \text{ g cm}^{-3}$, $\mu(\text{MoK}\alpha) = 1.88 \text{ mm}^{-1}$, transmission range 0.818–0.754, crystal dimensions ca. $0.77 \times 0.32 \times 0.28 \text{ mm}$, ω scan, $2\theta_{\text{max}} = 48^\circ$, 4729 unique reflections, $R(R_w) = 0.0266$ (0.0285) for 3833 observed reflections ($I > 2\sigma(I)$), 323 variables, non-hydrogen atoms anisotropic, H atoms at idealized positions. **2**: $\text{C}_{96}\text{H}_{68}\text{Fe}_2\text{Se}_4$, formula weight 1649.04, monoclinic, space group $P2_1/n$, $a = 12.073(4)$, $b = 18.531(7)$, $c = 16.563(6) \text{ \AA}$, $\beta = 98.39(3)^\circ$, $V = 3665.90 \text{ \AA}^3$, $Z = 2$, $\rho_{\text{calc}} = 1.494 \text{ g cm}^{-3}$, $\mu(\text{MoK}\alpha) = 2.43 \text{ mm}^{-1}$, transmission range 0.654–0.471, crystal dimensions ca. $0.62 \times 0.25 \times 0.19 \text{ mm}$, ω scan, $2\theta_{\text{max}} = 54^\circ$, 7953 unique reflections, $R(R_w) = 0.0461$ (0.0376) for 4749 observed reflections ($I > 2\sigma(I)$), 462 variables, non-hydrogen atoms anisotropic, H atoms at idealized positions. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-101550 (**1**) and CCDC-101551 (**2**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [15] A. J. Deeming in *Comprehensive Organometallic Chemistry* (Eds.: G. Wilkinson, F. G. A. Stone, E. W. Abel), Pergamon, Oxford, **1984**.
- [16] M. M. Olmstead, P. P. Power, S. C. Shoner, *Inorg. Chem.* **1991**, *30*, 2547.
- [17] a) J. Kim, D. C. Rees, *Nature* **1992**, *360*, 553; b) J. Kim, D. C. Rees, *Science* **1992**, *257*, 1667; c) M. K. Chan, J. Kim, D. C. Rees, *Science* **1993**, *260*, 792; d) J. T. Bolin, A. E. Ronco, T. V. Morgan, L. E. Mortenson, *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 1078; e) H. Schindelin, C. Kisker, J. L. Schlessman, J. B. Howard, D. C. Rees, *Nature* **1997**, *387*, 370.
- [18] R. Hauptmann, R. Klib, J. Schneider, G. Henkel, *Z. Anorg. Allg. Chem.* **1998**, *624*, 1927.

Copper(I)-Catalyzed Enantioselective Substitution of Allyl Chlorides with Diorganozinc Compounds**

Frank Dübner and Paul Knochel*

Catalytic asymmetric allylic substitutions are potentially useful methods for the preparation of a wide range of chiral molecules. Several highly enantioselective palladium(0)-catalyzed allylic substitutions have been described in recent years;^[1] however, these reactions are generally limited to symmetrical substrates. Only recently, several regioselective palladium(0)-catalyzed asymmetric allylation reactions have been reported.^[2] Alternatively, copper(I)-catalyzed asymmetric allylations can be performed. These reactions proceed with high S_N2' regioselectivity and therefore accommodate unsymmetrical allylic substrates as starting materials. A further advantage is that a broad range of organometallic compounds (organolithium, Grignard, and organozinc reagents) can be used in these allylic substitutions.^[3] Unfortunately, only moderate enantioselectivities are usually obtained in these copper(I)-catalyzed allylations.^[4] To develop such an asymmetric reaction, we have screened a broad range of ligands (amines, diamines, phosphanes, phosphites, sulfur derivatives) and have observed that primary amines show the highest catalytic activity. Further fine-tuning of chiral primary amines indicated that chiral ferrocenyl amines of type **1** are highly effective ligands. Thus, the substitution of various unsymmetrical allyl chlorides of type **2** with diorganozinc reagents **3** in the presence of $\text{CuBr} \cdot \text{Me}_2\text{S}$ (1 mol %) and **1** (10 mol %) as catalyst leads to the desired allylated products **4**. The reaction is highly regioselective (ratio **4:5** > 90:10) and affords products **4** with up to 87 % *ee* (Scheme 1 and Table 1).



Scheme 1. Copper(I)-catalyzed enantioselective allylation. The groups R^1 and R^2 are given in Table 1, and the group R is defined in Scheme 2.

The ligands **1** are readily prepared from the ferrocenyl ketones **6** by Corey–Bakshi–Shibata (CBS) reduction, leading to the ferrocenyl alcohols **8** with high enantioselectivity (> 99 % *ee*).^[5] Acylation of alcohols **8a–d** with acetic anhydride furnishes in quantitative yield the intermediate ferrocenyl acetates **9a–d**. Treatment with an aqueous NH_3 solution in CH_3CN provides the desired ferrocenyl amines **1a–d** in 44–66 % yield (Scheme 2).

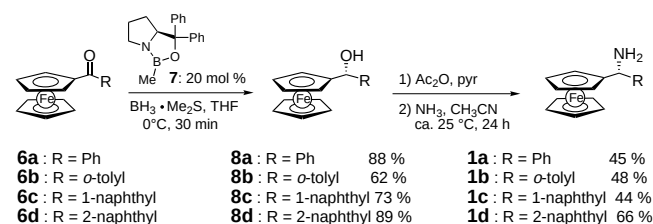
[*] Prof. Dr. P. Knochel, Dipl.-Chem. F. Dübner
Fachbereich Chemie der Universität
Hans-Meerwein-Strasse, D-35032 Marburg (Germany)
Fax: (+49) 6421-28-21-89
E-mail: knochel@ps1515.chemie.uni-marburg.de

[**] F.D. thanks Zeneca Ltd. for a fellowship and the Fonds der Chemischen Industrie for generous support. We thank the BASF AG, Degussa AG, Bayer AG, and Chemetall GmbH for generous gift of chemicals.

Table 1. Copper(I)-catalyzed substitutions of allyl chlorides **2** with diorganozinc compounds **3** in the presence of the ferrocenyl amine **1d** at -90°C .

Entry		R ¹		R ²	Product	S _N 2':S _N 2	ee [%] ^[a]	Yield [%] ^[b]
1	2a	Ph	3a	neopentyl	4a	95:5	82	68
2	2b	4-CF ₃ C ₆ H ₄	3a	neopentyl	4b	97:3	87	72
3	2c	1-naphthyl	3a	neopentyl	4c	94:6	71	65
4	2d	2-naphthyl	3a	neopentyl	4d	91:9	70	60
5	2e	c-C ₆ H ₁₁	3a	neopentyl	4e	98:2	76	67
6	2f	3-thienyl	3a	neopentyl	4f	94:6	63	70
7	2g	(Z)-TIPSOCH ₂ ^[c]	3a	neopentyl	4g	> 99:1	64	45
8	2a	Ph	3b	PhMe ₂ SiCH ₂	4h	90:10	42	50 ^[d]
9	2a	Ph	3c	Me ₃ SiCH ₂	4i	94:6	67	52 ^[d]
10	2a	Ph	3d	(+)-myrtanyl	4j	97:3	41	65 ^[d]
11	2a	Ph	3e	(-)-myrtanyl	4k	98:2	37	60 ^[d]

[a] Enantiomeric excess determined by gas chromatography (CP-Chirasil-Dex CB, $40 \rightarrow 80^{\circ}\text{C}$ at $2-4^{\circ}\text{C min}^{-1}$). [b] Yield of isolated products **4** + **5**. [c] TIPS = triisopropylsilyl. [d] The reaction was performed at -50°C .



Scheme 2. Synthesis of the ferrocenyl ligands **1a–d**.

The nature of the group R in the ligand is essential for obtaining a high level of enantioselectivity. Therefore, under standard reactions conditions (5 mol% of CuBr·Me₂S, 5 mol% of **1a–d**), the reaction of cinnamyl chloride (**2a**, 1.0 equiv) with dineopentylzinc (**3a**, 1.2 equiv) affords (+)-(S)-5,5-dimethyl-3-phenyl-1-hexene (**4a**) with 32% ee for **1a**, 16% ee for **1b**, 33% ee for **1c**, and 42% ee for **1d**. When the optimum ratio of 1:10 between CuBr·Me₂S and the amine is used, the enantioselectivity can be increased to 67% ee with the ligand **1d**. This ligand was used in all further experiments.

A short screening of the leaving group (Cl, Br, carbonate, xanthate, phosphate) showed that cinnamyl chloride was the best substrate. Likewise, investigations into the nature of the zinc reagent showed that no enantioselectivity was observed when RZnCl or RZnI was used instead of R₂Zn. Finally, there was an almost linear dependence of the enantioselectivity with the temperature. Thus, the reaction of **1a** with **3a** affords the product **4a** with 82% ee at -90°C (bath temperature), whereas an enantioselectivity of only 25% ee was observed at $+25^{\circ}\text{C}$ (Figure 1)!

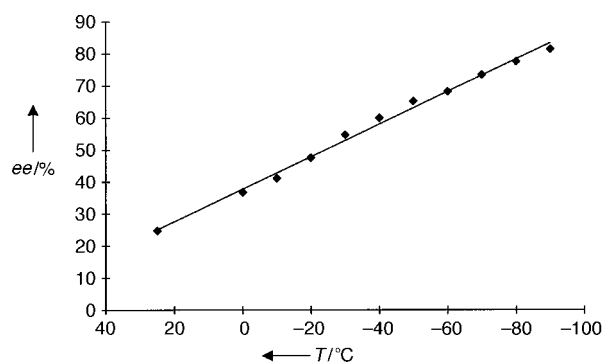


Figure 1. Dependence of the enantioselectivity on the temperature.

The asymmetric reaction was performed with various allylic chlorides **2** and various diorganozinc reagents **3** (Table 1). The reaction of **2b** (entry 2), which contains the electron-withdrawing 4-trifluoromethylphenyl substituent, with **3a** furnishes **4b** with the best enantioselectivity of 87% ee and in 72% yield. Naphthyl-substituted substrates give a lower stereoselectivity than those with a phenyl group, and provide the products **4c** and **4d** with 70–71% ee (entries 3 and 4). The allyl halide with a cyclohexyl substituent (**2e**) gives the substitution compound **4e** with a similar enantioselectivity as **2a** (entries 1 and 5). The presence of functional groups such as a 3-thienyl ring or a silyl ether at R¹ lowers the enantioselectivity somewhat to 63 and 64% ee (entries 6 and 7). Finally, it was observed that the use of sterically demanding diorganozinc compounds is important for obtaining good asymmetric inductions. Thus, the less reactive bis(trialkylsilylmethyl)-zinc compounds **3b** and **3c** give the desired substitution products of **2a** with 42–67% ee. A matched and mismatched stereoselectivity is observed for the reaction of bis(myrtanyl)zinc, which is prepared by hydroboration with Et₂BH^[6] of (+)- or (–)-β-pinene,^[7] leading to two diastereomeric products **4j** and **4k** with 41 and 37% ee, respectively.

We have reported a new copper(I)-catalyzed substitution of unsymmetrical allyl chlorides with diorganozinc compounds using the novel ferrocenyl amine **1d** as chiral ligand. The allylated products are obtained with moderate to good enantioselectivities (up to 87% ee) and excellent S_N2' regioselectivities. We are currently studying the scope of the reaction and further improving the activity of the catalyst.^[8]

Experimental Section

1d: A solution of **6d** (4.5 g, 13.2 mmol) in THF (30 mL) and BH₃·Me₂S (1.4 mL, 14 mmol) were added simultaneously over a period of 30 min to a solution of the CBS catalyst **7** (0.7 g, 2.5 mmol) in THF (80 mL) at 0°C under argon. After the mixture was stirred for an additional 30 min, it was quenched with aqueous ammonium chloride solution (70 mL). The organic layer was separated, dried over MgSO₄, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel with pentane/diethyl ether (1/1) as eluent to afford **8d** (4.0 g, 89%, 99.5% ee) as an orange solid (m.p. 117°C). The ferrocenyl alcohol **8d** (4.0 g, 11.6 mmol) was dissolved in dry pyridine (30 mL) and acetic anhydride (20 mL) at room temperature. After the mixture had been stirred for 18 h at room temperature, all volatile components were removed under high vacuum at 50°C to furnish the pure acetate **9a** (4.5 g, 100%) as a red "glue", which crystallized on standing to yield a red solid (m.p. 127°C). This acetate (3.0 g, 8 mmol) was dissolved in acetonitrile (200 mL) and 37%

aqueous ammonia solution (40 mL). After the mixture was stirred for 24 h at room temperature, it was poured into 10% aqueous hydrochloric acid (200 mL). The resulting precipitate was removed by filtration and washed with diethyl ether (4 × 20 mL). The residue was dissolved in 20% aqueous sodium hydroxide solution (200 mL), and the desired product was extracted with diethyl ether (3 × 50 mL). After the solution was dried over MgSO_4 , the solvent was removed under reduced pressure and pure **1d** (1.8 g, 66%) was obtained as an orange solid (m.p. 97 °C).

Enantioselective allylation of **2b** to **4b** (Table 1, entry 2): The ligand **1d** (70 mg, 0.2 mmol) and $\text{CuBr} \cdot \text{Me}_2\text{S}$ (3 mg, 0.02 mmol) were dissolved in THF (5 mL). After the clear solution was cooled to -90 °C, **3a** (0.3 mL, 2.4 mmol) and **2b** (440 mg, 2.0 mmol) were added successively. The reaction mixture was stirred for 18 h at -90 °C and then worked up as usual. The crude residue obtained after evaporation of the solvents was purified by flash chromatography (diethyl ether/pentane 1/50) to provide the desired product **4b** (370 mg, 72% yield; $S_N2:S_N2$ ratio = 97:3). The enantiomeric excess of the chiral product was determined by gas chromatography (Chiraldex capillary column) to be 87%.

Received: August 27, 1998 [Z 12344 IE]
German version: *Angew. Chem.* **1999**, *111*, 391–393

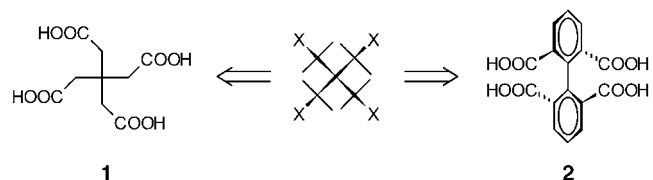
Keywords: asymmetric catalysis • copper • ferrocenes • substitutions

- [1] a) B. M. Trost, D. L. Van Vranken, *Chem. Rev.* **1996**, *96*, 395; b) O. Reiser, *Angew. Chem.* **1993**, *105*, 576; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 547.
- [2] a) T. Hayashi, M. Kawatsuma, Y. Kozumi, *Chem. Commun.* **1997**, 562; b) J. P. Janssen, G. Helmchen, *Tetrahedron Lett.* **1997**, *38*, 8025; c) R. Pretôt, A. Pfaltz, *Angew. Chem.* **1998**, *110*, 337; *Angew. Chem. Int. Ed.* **1998**, *37*, 323; d) B. M. Trost, I. Hachiya, *J. Am. Chem. Soc.* **1998**, *120*, 1104.
- [3] a) A. Commercon, M. Bourgain, M. Delaumeny, J. F. Normant, J. Villieras, *Tetrahedron Lett.* **1975**, 3837; b) P. Barsantai, V. Calo, L. Lopez, G. Marchese, F. Naso, G. Pesce, *J. Chem. Soc. Chem. Commun.* **1978**, 1085; c) C. C. Tseng, S. D. Paisley, H. L. Goering, *J. Org. Chem.* **1986**, *51*, 2884; d) J.-E. Bäckvall, M. Sellen, B. Grant, *J. Am. Chem. Soc.* **1990**, *112*, 6615; e) J.-E. Bäckvall, E. S. M. Persson, A. Bombrun, *J. Org. Chem.* **1994**, *59*, 4126; f) E. S. M. Persson, M. van Klaveren, D. M. Grove, J.-E. Bäckvall, G. van Koten, *Chem. Eur. J.* **1995**, *1*, 351.
- [4] The best enantioselectivity for a copper(I)-catalyzed allylation is 42% ee: M. van Klaveren, E. S. M. Persson, A. del Villar, D. M. Grove, J.-E. Bäckvall, G. van Koten, *Tetrahedron Lett.* **1995**, *36*, 3059.
- [5] L. Schwink, P. Knochel, *Chem. Eur. J.* **1998**, *4*, 950.
- [6] F. Langer, L. Schwink, A. Devasagayraj, P.-Y. Chavant, P. Knochel, *J. Org. Chem.* **1996**, *61*, 8229.
- [7] R. Köster, G. Griasnow, W. Larbig, P. Binger, *Justus Liebigs Ann. Chem.* **1964**, 672, 1.
- [8] A patent with Zeneca Ltd. has been filed.
- [9] The absolute configuration of the products **4** was determined by analogy with the literature: a) L. Lardicci, P. Salvadori, A. M. Caporusso, R. Menicagli, E. Belgodere, *Gazz. Chim. Ital.* **1972**, *102*, 64; b) L. Lardicci, R. Menicagli, P. Salvadori, *Gazz. Chim. Ital.* **1968**, *98*, 738.

Self-Assembly of 1,1'-Biphenyl-2,2',6,6'-tetracarboxylic Acid: Formation of an Achiral Grid with Chiral Compartments**

Petr Holý, Jiří Závada,* Ivana Císařová, and Jaroslav Podlaha

Supramolecular self-assembly is the spontaneous association of molecular subunits (tectons) into structurally well-defined aggregates, which are organized by noncovalent interactions (synthons).^[1,2] The most versatile synthons for the self-assembly of organic tectons are intermolecular hydrogen bonds. Tetrafunctional molecules with tetrahedrally arranged substituents have been investigated in this context and have shown to be endowed with the fascinating faculty of building diamond-like networks,^[3] with methanetetraacetic acid **1** being a prototypal example.^[4] We are interested in the hydrogen bond driven self-assembly of 2,2',6,6'-tetrasubstituted biaryls^[5,6] that are topologically related to the tetrasubstituted methanes. For example, if we stretch the D_{2d} symmetry conformer of the tecton **1** along its axis a framework of 1,1'-biphenyl-2,2',6,6'-tetracarboxylic acid (**2**) gradually (on further elaboration) emerges (Scheme 1).



Scheme 1. Stereochemical correlation of tectons **1** and **2**.

Consideration of models that use a double hydrogen bond as the synthon suggests that the self-assembling properties of the two topologically related tectons **1** and **2** should be entirely different. In contrast to the intrinsic propensity of the tetrahedral tecton **1** to form chairlike distorted cyclohexamers that underlie the three-dimensional diamondoid network,^[3,4] the biaryl tecton **2** should prefer to undergo cyclotetramerization and result ultimately in a unilayered "square" grid (Figure 1).

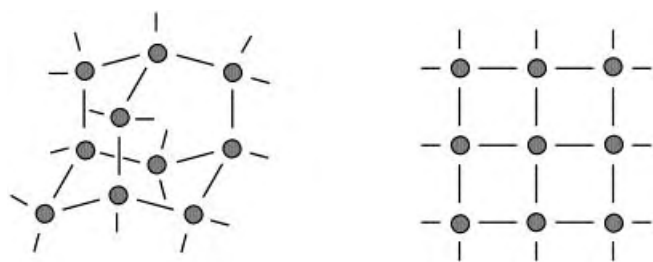


Figure 1. Schematic representation of diamondoid and square grids.

[*] Dr. J. Závada, P. Holý
Institute of Organic Chemistry and Biochemistry
Academy of Sciences of the Czech Republic
166 10 Prague 6 (Czech Republic)
Fax: (+420) 2-3111733
E-mail: zavada@uochb.cas.cz
I. Císařová, J. Podlaha
Charles-University, Department of Inorganic Chemistry
128 40 Prague 2 (Czech Republic)

[**] The financial support by the Grant Agency of the Czech Republic (grants no. 203/97/0025 and 203/96/0111) is gratefully acknowledged.

In accord with this *a priori* analysis a crystal structure determination^[7] of the tetraacid **2** confirmed an approximately perpendicular^[10] orientation of the aromatic rings in the individual tectons (Figure 2), and demonstrated their self-assembly by double hydrogen bonds.^[11] All four carboxyl

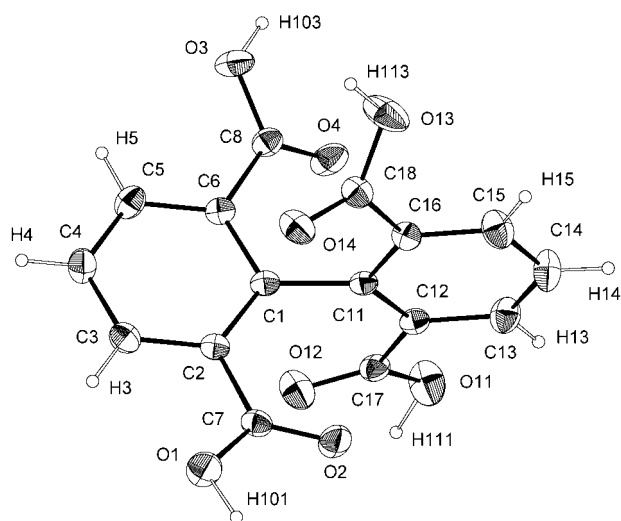


Figure 2. An ORTEP diagram of the molecular structure of **2** with the crystallographic numbering scheme.

groups participate in the intermolecular hydrogen bonding to give rise to a quasi-planar network set up from the hydrogen-bonded cyclotetramers (Figure 3). In contrast to the individual tectons **2**, which possess D_{2d} symmetry and are accordingly achiral, the self-assembled cyclotetramers possess (in an ideal arrangement) a unique^[12, 13] D_4 symmetry and are therefore, individually chiral. Homochiral cyclotetramers are arranged

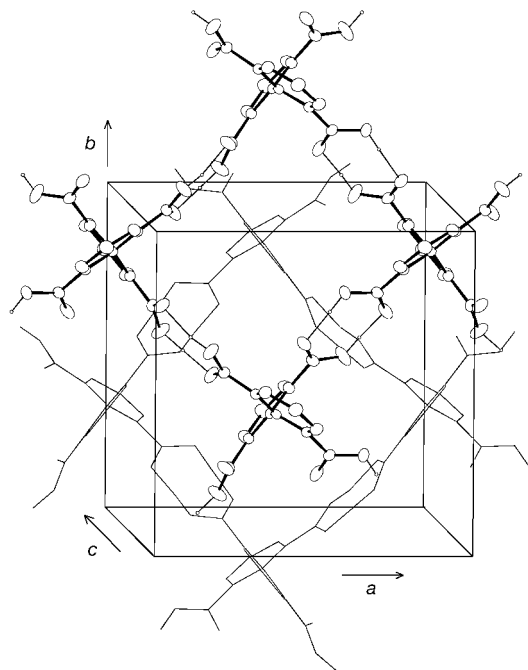


Figure 3. Self-assembly of **2** into unilayered hydrogen-bonded networks and stacking of neighboring layers in the crystal (the molecules in the second layer are distinguished by thinner lines).

diagonally, whereas alternation of chirality occurs in the horizontal and vertical rows of the network (Figure 4). In contrast to the chirality of the tetrameric compartments, the

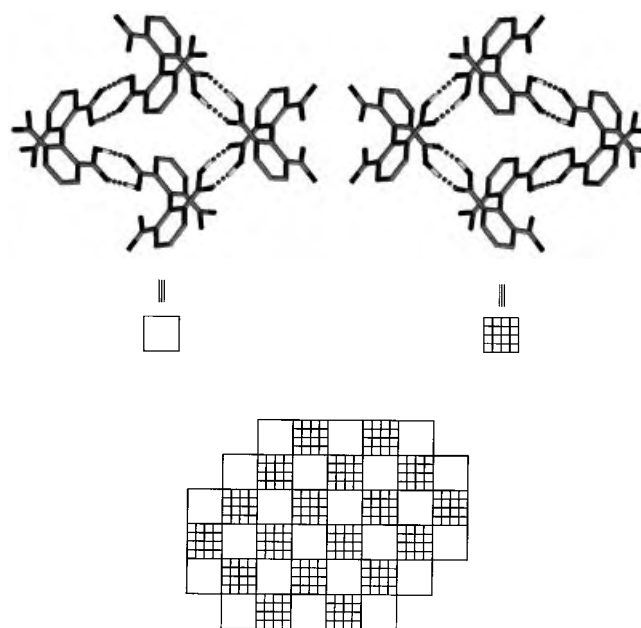


Figure 4. Schematic representation of the distribution of cyclotetramers of opposite chirality (indicated by empty and shaded squares) in the unilayered hydrogen-bonded network in the crystal of **2**.

infinite unilayered grid is achiral as a consequence of crystal symmetry. The neighboring grids are stacked in a staggered (non-concatenated) manner^[14] (Figure 3).

In this way, self-assembly of the biaryl tecton **2** represents a novel type of supramolecular architecture, which allows a further tuning in three important directions. Firstly, the effective size of the individual compartments may be varied extensively by using, for example, the principle^[15, 16] of vinylogy and phenylogy (namely the introduction of vinyl and phenyl spacers). Secondly, chirality of the individual macrocyclic compartments may be extended to the overall network^[17] by the use of chiral biaryl tectons. Thirdly, the stacking of the individual layers may be controlled^[18, 19] by introduction of appropriate substituents into the 4,4'-positions of the biaryl tecton. If successful, the proposed tuning of the structure might provide a novel access to the design of chiral porous solids.^[20]

Experimental Section

2: Potassium permanganate (8.69 g, 55 mmol) was gradually added (0.5 h) to a stirred suspension of 1,1'-biphenyl-2,2',6,6'-tetracarboxaldehyde^[21] (5.32 g, 20 mmol) in aqueous 0.3 M KOH solution (100 mL) at 80 °C. After additional (1 h) heating, the excess of the oxidant was destroyed by several drops of a 37% aqueous solution of formaldehyde. The precipitated manganese dioxide was filtered off and washed with hot water (100 mL). The combined aqueous solutions were reduced to 100 mL, acidified with concentrated hydrochloric acid to pH 1, and cooled in a refrigerator. The separated tetraacid **2** was collected, washed with water, and dried. Yield 5.41 g (82%), m.p. > 370 °C (> 350 °C^[22a] > 300 °C^[22b]). Single crystals were grown from hot water by slow cooling.

Received: August 11, 1998 [Z12276IE]

German version: *Angew. Chem.* **1999**, *111*, 393–395

Keywords: biaryls • carboxylic acids • chirality • crystal engineering • hydrogen bonds

- [1] a) G. R. Desiraju, *Angew. Chem.* **1995**, *107*, 2541–2558; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2311–2327; b) G. R. Desiraju, *Chem. Commun.* **1997**, 1475–1482; c) D. Su, X. Wang, M. Simard, J. D. Wust, *Supramol. Chem.* **1995**, *6*, 171–178.
- [2] a) J.-M. Lehn, *Supramolecular Chemistry: Concepts and Perspectives*, VCH, Weinheim, **1995**; b) C. B. Aakeroy, K. R. Seddon, *Chem. Soc. Rev.* **1993**, *22*, 397–408.
- [3] a) O. Ermer, *J. Am. Chem. Soc.* **1988**, *110*, 3747–3754; b) D. S. Reddy, D. C. Craig, G. R. Desiraju, *J. Am. Chem. Soc.* **1996**, *118*, 4090–4093; c) M. J. Zaworotko, *Chem. Soc. Rev.* **1994**, *23*, 283–288.
- [4] O. Ermer, *Angew. Chem.* **1988**, *100*, 856–860; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 829–833.
- [5] P. Vojtišek, I. Čisárová, J. Podlaha, Z. Žák, S. Böhm, M. Tichý, J. Závada, *Z. Kristallogr.* **1997**, *212*, 226–233.
- [6] M. Tichý, L. Ridvan, P. Holý, J. Závada, *Tetrahedron: Asymmetry* **1998**, *9*, 227–234.
- [7] Crystal data: $C_{16}H_{10}O_8$, $M_r = 330.24$, orthorhombic, space group $Pbca$ (no. 61), $a = 11.862(2)$, $b = 12.098(1)$, $c = 21.0333(2)$ Å, $V = 3018.4(6)$ Å³, $F(000) = 1360$, $\rho_{\text{calc}} = 1.453$ g cm⁻³ for $Z = 8$. A colorless plate with the dimensions $0.30 \times 0.19 \times 0.11$ mm was measured on a CAD4 diffractometer at 293(2) K (MoK_{α} radiation, $\lambda = 0.71073$ Å) by using θ - 2θ scan ($\theta_{\text{max}} = 25^\circ$). From a total of 2361 reflections measured in the range $h = 0$ –13, $k = 0$ –13, $l = 0$ –24, 1642 were regarded as observed from the criterion $I > 2\sigma(I)$. Data were corrected to Lorentzian polarization and absorption was neglected ($\mu = 0.119$ mm⁻¹). The structure was solved by direct methods (SHELXS86^[8]) and refined by full-matrix least squares based on F^2 (SHELXL93^[9]). The O-bonded hydrogen atoms were refined isotropically and the C-bonded hydrogen atoms were fixed ($U_{\text{eq}}(\text{H}) = 1.2 U_{\text{eq}}(\text{C})$). The refinement converged to $R = 0.0383$ and $R_w = 0.0874$, with GOF = 1.042 for 233 parameters. The final difference map displayed no peaks of chemical significance. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-102374. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [8] G. M. Sheldrick, *Acta Crystallogr. Sect. A* **1990**, *46*, 467–473.
- [9] G. M. Sheldrick, *SHELXL-93, Program for Crystal Structure Refinement from Diffraction Data*, University of Göttingen, **1993**.
- [10] The dihedral angle between the least squares planes of the aromatic rings is $86.26(6)^\circ$. However, the pivot atoms of the substituents are displaced from the aromatic planes by as much as $0.190(3)$ Å (C11). The carboxyl groups, the hydrogen atoms of which were located and refined, are also essentially planar but adopt various orientations relative to their parent aromatic rings, with the dihedral angles of the carboxyl planes relative to the adjacent aromatic rings being $8.1(4)^\circ$ for the C7-, $35.1(3)^\circ$ for C8-, $14.2(3)^\circ$ for C17-, and $44.5(2)^\circ$ for C18-carboxyl. Steric bulk imposed by the carboxyl groups together with the crystal packing is assumed to be the responsible factor.
- [11] There are two crystallographically independent double hydrogen bonds, both nearly planar and with asymmetrically disposed hydrogen atoms, one links O1 and O2 with O12' and O11' whereas the other links O3 and O4 with O14' and O13'.
- [12] According to Eliel,^[13] no organic molecules of D_4 symmetry have yet been synthesized. Also, to the best of our knowledge, no hydrogen bond organized substructure of D_4 symmetry has been found in any previously known crystal structure.
- [13] E. L. Eliel, S. H. Wilen, L. N. Mander, *Stereochemistry of Organic Compounds*, Wiley, **1994**, p. 79.
- [14] The roughly square cavities inside the cyclotetrameric compartments are approximately 5.6 Å and thus partly accommodate the nearly perpendicularly oriented phenyl rings of the neighboring layer. This may explain satisfactorily the staggered stacking of the individual layers as well as the observed absence of preferential cleavage of the crystal.
- [15] R. Leppkens, F. Voegtler, F. Luppen, *Chem. Ber.* **1982**, *115*, 926–933.
- [16] The vinyllog of the tetraacid **2**, 1,1'-biphenyl-2,2',6,6'-tetraacrylic acid, can be obtained from the easily accessible^[21] 1,1'-biphenyl-2,2',6,6'-tetracarboxaldehyde in a one-step reaction. P. Holý, J. Závada, I. Čisárová, J. Podlaha, unpublished results.
- [17] Viability of this concept has been already demonstrated in our recent crystallographic study^[5] of the chiral 2,2'-bipyridine-3,3'-dicarboxylic acid-1,1'-dioxide (C_2 symmetry), which revealed a self-assembly into a chiral “square” grid that was organized by the hydrogen bonding ($-N-O \cdots H-O-CO-$) synthon.
- [18] While generation of polar layers is relatively straightforward, their eclipsed stacking remains generally a great challenge for crystal engineering. The eclipsed stacking may be induced in the present case, for example, by introduction of the 4,4'-carboxyl groups into the tecton **2**, to allow the formation of an additional (orthogonal) network of intermolecular hydrogen bonds. A successful application of such a hydrogen-bond network in cross-linking supramolecular tapes has recently been reported.^[19]
- [19] G. T. R. Palmore, M. T. McBride, *Chem. Commun.* **1998**, 145–146.
- [20] M. J. Zaworotko, *Angew. Chem.* **1998**, *110*, 1269–1271; *Angew. Chem. Int. Ed.* **1998**, *37*, 1211–1213.
- [21] I. Agranat, M. Rabinovitz, W.-Ch. Shan, *J. Org. Chem.* **1979**, *44*, 1936–1940.
- [22] a) F. Mayer, *Chem. Ber.* **1911**, *44*, 2298–2305; b) K. E. Pryor, G. W. Shippy, D. A. Skyler, J. Rebek, *Tetrahedron* **1998**, 4107–4124.

High-Yielding Rotaxane Synthesis with an Anion Template**

Gosia M. Hübner, Jens Gläser, Christian Seel, and Fritz Vögtle*

Molecules such as rotaxanes and catenanes that are non-covalently interlocked by mechanical bonds between two or more molecular components are of current interest. Their synthesis is usually based on some kind of template assistance such as the preorganization of building blocks by metal coordination, hydrophobic and donor-acceptor interactions, or hydrogen bonding.^[1] Here we report on a new synthesis of rotaxanes based on the action of a supramolecular nucleophile, which is formed from the molecular recognition of an anionic stopper by a tetralactam wheel.

Some examples of recognition of anions by neutral organic ligands have been reported, and mostly feature several amide, sulfonamide, or urea groups as the hydrogen bond donors.^[2] Macrocyclic lactams such as **1**, which have often been used in rotaxane and catenane syntheses,^[1d] contain several aromatic

[*] Prof. Dr. F. Vögtle, G. M. Hübner, J. Gläser, Dr. C. Seel
Kekulé-Institut für Organische Chemie und Biochemie
der Universität
Gerhard-Domagk-Strasse 1, D-53121 Bonn (Germany)
Fax: (+49) 228-735662
E-mail: voegtle@uni-bonn.de

[**] We thank Prof. J. L. Sessler, University of Texas, Austin, for fruitful discussions and cooperation in regard to anion complexation and Prof. K. Gloe, Universität Dresden, and Dr. H. Stephan, Forschungszentrum Rossendorf, for investigating anion extraction from aqueous phases. We also thank our co-workers J. Flörke, C. Heim, and A. Mohry for providing some of the substances used. This work was supported by the Deutsche Forschungsgemeinschaft (Vo 145/47-1).

amide groups, the NH protons of which point toward the macrocycle center, as revealed by several X-ray structures.^[3]

Tetralactam **1a**^[4] (see Scheme 1) binds secondary amides in CD₂Cl₂ where it clearly serves as a hydrogen-bond donor.^[5] Semirotaxane complexes with in situ formed amide semi-axes^[6] are most likely the decisive precursors^[1d] in the corresponding rotaxane and catenane syntheses. We set out to elicit if anions that act as hydrogen-bond acceptors could also be bound in a similar way even if it can be ruled out on steric grounds that both isophthalic amide residues simultaneously contact one and the same anion.

Indeed, NMR experiments with tetrabutylammonium salts of halides and some oxoanions in CD₂Cl₂ show the strong downfield shifts of the NH protons typical for hydrogen bonding; the “inner” (H-2) protons of the isophthalic acid moieties of **1a** are likewise affected but to a somewhat lesser extent.^[7] Job plots confirm a 1:1 stoichiometry of the complexes.^[8] In some cases the binding is too tight for an accurate determination of the association constants (probably > 10⁵ M⁻¹) so that a 4:1 mixture of CD₂Cl₂ and CD₃OD had to

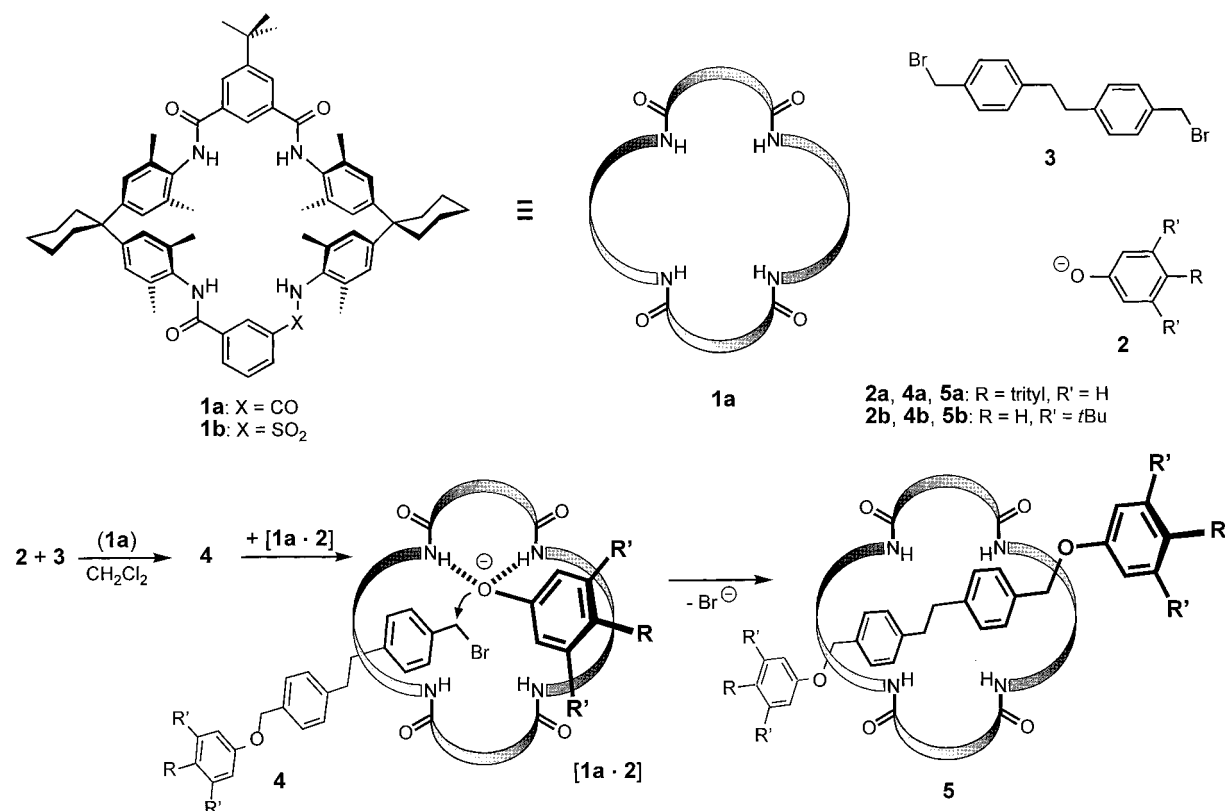
be used for the titrations to reduce the affinities.^[9] Mono-sulfonamide trilactam **1b** also serves as host, but the binding strength is considerably weaker, especially for halides. The anion binding properties are summarized in Table 1.

These results encouraged us to investigate the affinity of the macrocycles for organic anions that might serve as nucleophiles in S_N reactions, to evaluate their possible application in rotaxane syntheses. In fact, as revealed by NMR spectroscopy under typical synthetic conditions (5 mM tetralactam **1a**, CD₂Cl₂), phenolates, thiophenolates, and sulfonamide anions are bound close to quantitatively.^[10] Even if the association is remarkably strong, it was not clear, however, if a complex of a macrolactam such as **1a** with, for example, a phenolate stopper or a phenolate axle center piece would be a suitable template for a threading-type phenyl ether rotaxane synthesis, since these anions would probably be positioned “on top” of the wheel rather than thread through it under formation of a prerotaxane. The reaction of *p*-tritylphenolate **2a**, dibromide **3**,^[11] and wheel **1a**, nevertheless, produced the rotaxane **5a** in the surprisingly high yield of 95% (Scheme 1). This is

Table 1. Association constants K_a [M⁻¹] (error ± 15%) of the macrocycles **1a** and **1b** with anions^[a] determined by NMR titration at room temperature in CD₂Cl₂.

Ligand	Solvent	F ⁻	Cl ⁻	Br ⁻	I ⁻	AcO ⁻	NO ₃ ⁻	H ₂ PO ₄ ⁻
1a	CD ₂ Cl ₂	200	— ^[b]	— ^[b]	— ^[b]	1.8 × 10 ⁵	— ^[b]	— ^[b]
1a	CD ₂ Cl ₂ /CD ₃ OD (4/1)	— ^[c]	330	420	— ^[d]	120	250	— ^[d]
1b	CD ₂ Cl ₂	— ^[c]	290	290	50	1.5 × 10 ⁴	60	2.4 × 10 ³

[a] The anions were added as tetrabutylammonium salts. [b] K_a is too high to be determined by NMR spectroscopy. [c] No binding detected. [d] Same order of magnitude as Cl⁻ and Br⁻, but the shift values are small and the calculated values neither precise nor accurate.



Scheme 1. High-yielding anionic template synthesis of rotaxanes **5** with bis(phenyl ether) axes where phenolate–wheel complexes **[1a · 2]** act as supramolecular nucleophiles for the reaction with semiaxes **4**.

probably the highest yield reported so far for this kind of synthesis. We assume that in a first step the dibromide **3** reacts with the stopper-wheel complex [**1a**·**2a**] to form the semi-axle **4a** and probably causes subsequent dissociation of the resulting semirotaxane complex.^[12] Free **4a** then reacts with a second phenolate-lactam complex [**1a**·**2a**]—which acts as a supramolecular nucleophile—to furnish the rotaxane **5a**.^[13]

To the best of our knowledge this is the first case of a rotaxane synthesis based on the assistance of an anionic template. The yield of rotaxane **5b** with 3,5-di-*tert*-butylphenolate **2b** as the stopper component was 57%.^[14] With this smaller stopper the rotaxane is only metastable, that is, during the course of the synthesis at room temperature the axle slowly slips from the wheel and breaks the mechanical bond so that the free components remain. The process of decay can be monitored by NMR spectroscopy by the growth of signals of the free components. About 10% of dethreading is observed during 48 h at room temperature in CDCl₃.^[15]

To sum up, lactam macrocycles exhibit strong affinities for small inorganic anions as well as organic anions in nonpolar solvents. Based on the latter we were able to introduce a new anionic template synthesis of rotaxanes with high yield, which possibly also opens the way for the formation of other types of mechanically interlocked molecules such as catenanes and knots. We are currently investigating the scope of application for other organic anions such as thiophenolates, sulfonamides, and carboxylates as well as carbanions.^[16]

Experimental Section

5a: A mixture of **1a**^[4] (48.1 mg, 0.05 mmol), *p*-tritylphenol H-**2a** (33.6 mg, 0.1 mmol, Lancaster), and dibromide **3**^[11] (18.4 mg, 0.05 mmol) in CH₂Cl₂ (10 mL) was stirred with solid K₂CO₃ (25 mg) for 7 d at room temperature. The solid was removed by filtration, and the organic solution washed with water and dried over MgSO₄. Column chromatography on silica gel with CH₂Cl₂/ethyl acetate (30/1) yielded **5a** (89 mg, 0.048 mmol, 95%) as a white powder. M.p. 175–177 °C; ¹H NMR (250 MHz, CDCl₃): δ = 1.34 (s, 9H, *t*Bu-CH₃), 1.56, 1.68, and 2.34 (b, 4H, 8H, and 8H, respectively, cyclohexanediyl CH₂), 1.93 (s, 24H, aryl CH₃), 2.49 (s, 4H, C₂H₄), 4.52 (s, 4H, OCH₂), 6.49 and 6.90 (AA'BB', 8H, *J* = 8.7 Hz, phenoxy H-2/6 and H-3/5, respectively), 6.51 and 6.66 (AA'BB', 8H, *J* = 7.9 Hz, *p*-xylylene), 7.02 (s, 8H, amidophenyl), 7.1–7.25 (m, 30H, trityl), 7.43 (s, 1H, isophthaloyl H-2), 7.60 (t, 1H, *J* = 7.7 Hz, isophthaloyl H-5), 7.65 (s, 1H, isophthaloyl H-2), 8.12 (d, 2H, *J* = 7.7 Hz, isophthaloyl H-4/6), 8.16 (s, 2H, 5-*t*Bu-isophthaloyl H-4/6); ¹³C NMR (62.9 MHz, CDCl₃): δ = 18.83 (aryl CH₃), 23.00 (cyclohexanediyl CH₂), 26.34 (cyclohexanediyl CH₂), 31.16 (5-*t*Bu-isophthaloyl CH₃), 35.31 (5-*t*Bu-isophthaloyl C_q), 35.78 (cyclohexanediyl CH₂), 37.45 (C₂H₄), 45.41 (isophthaloyl-*t*Bu CH₃), 64.28 (Ph₃C), 69.86 (OCH₂), 113.27 (CH), 121.37 (CH), 125.97 (CH), 126.32 (C_q), 126.92 (CH), 127.48 (CH), 127.66 (CH), 128.10 (CH), 129.27 (CH), 130.36 (C_q), 130.91 (C_q), 131.01 (CH), 131.11 (C_q), 132.02 (CH), 132.36 (CH), 134.32 (C_q), 134.57 (C_q), 134.77 (C_q), 140.05 (C_q), 140.94 (C_q), 146.79 (C_q), 148.82 (C_q), 156.28 (C_q), 165.01 (CO), 165.45 (CO); MALDI-MS: *m/z*: 1863.2 [*M*⁺].

5b: As above but 3,5-di-*tert*-butylphenol H-**2b** (Aldrich) was used as the stopper, 0.1 equivalents dibenzo[18]crown-6 were added to the mixture, stirring was continued for 3 d, and the chromatography eluent was petroleum ether (40–60)/ethyl acetate (15/1). The yield was 57%. M.p. 206–208 °C; ¹H NMR (250 MHz, CDCl₃): δ = 1.23 (s, 36H, 3,5-di-*t*Bu-phenyl CH₃), 1.38 (s, 9H, isophthaloyl-*t*Bu CH₃), 1.56, 1.68, and 2.35 (b, 4H, 8H, and 8H, cyclohexanediyl CH₂), 1.94 and 1.95 (2 s, 12H each, aryl CH₃), 2.45 (s, 4H, C₂H₄), 4.58 (s, 4H, OCH₂), 6.45 and 6.60 (AA'BB', 8H, *J* = 7.9 Hz, *p*-xylylene H), 6.66 (s, 4H, phenoxy H-2/6), 7.04–7.08 (m, 10H, phenoxy H-4 and amidophenyl), 7.58 (s, 1H, isophthaloyl H-2), 7.62 (t, 1H, *J* = 7.7 Hz, isophthaloyl H-5), 7.74 (s, 1H, isophthaloyl H-2), 8.16 (d, 2H, *J* = 7.7 Hz, isophthaloyl H-4/6), 8.21 (s, 2H, 5-*t*Bu-isophthaloyl H-4/6);

¹³C NMR (62.9 MHz, CDCl₃): δ = 18.78 (aryl CH₃), 22.97 (cyclohexanediyl CH₂), 26.32 (cyclohexanediyl CH₂), 31.14 (*t*Bu-isophthaloyl CH₃), 31.33 (stopper-*t*Bu CH₃), 34.93 (stopper-*t*Bu C_q), 35.30 (*t*Bu-isophthaloyl C_q), 35.66 (cyclohexanediyl CH₂), 37.56 (C₂H₄), 45.29 (cyclohexanediyl C_q), 69.96 (OCH₂), 108.77 (stopper CH), 115.74 (stopper CH), 121.46 (CH), 124.17 (CH), 126.21 (CH), 126.78 (CH), 127.93 (CH), 128.62 (CH), 129.41 (CH), 130.34 (CH), 130.98 (C_q), 131.12 (C_q), 132.10 (CH), 134.38 (C_q), 134.48 (C_q), 134.66 (C_q), 134.78 (C_q), 140.80 (C_q), 148.62 (C_q), 148.74 (C_q), 152.60 (C_q), 154.16 (C_q), 157.92 (C_q), 164.96 (CO), 165.37 (CO); FAB-MS: *m/z*: 1580.1 [*MH*⁺].

Received: September 14, 1998 [Z12408IE]

German version: *Angew. Chem.* **1999**, *111*, 395–398

Keywords: host–guest chemistry • nucleophilic substitutions • rotaxanes • supramolecular chemistry • template synthesis

- Reviews: a) G. Schill, *Catenanes, Rotaxanes, and Knots*, Academic Press, New York, **1971**; b) D. B. Amabilino, J. F. Stoddart, *Chem. Rev.* **1995**, *95*, 2725–2825; c) H. W. Gibson in *Large Ring Molecules* (Ed.: J. A. Semlyen), Wiley, Chichester, **1996**, pp. 191–262; d) R. Jäger, F. Vögtle, *Angew. Chem.* **1997**, *109*, 966–980; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 930–944; e) *Catenanes, Rotaxanes, Knots* (Ed.: J. P. Sauvage), WILEY-VCH, in press. For recent reports, see M. Born, H. Ritter, *Adv. Mater.* **1996**, *8*, 149–151; D. G. Hamilton, J. K. M. Sanders, J. E. Davies, W. Clegg, S. J. Teat, *Chem. Commun.* **1997**, 897–898; A. Harada, J. Li, M. Kamachi, *Chem. Commun.* **1997**, 1413–1414; W. Herrmann, M. Schneider, G. Wenz, *Angew. Chem.* **1997**, *109*, 2618–2621; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2511–2514; C. Gong, H. W. Gibson, *Angew. Chem.* **1998**, *110*, 323–327; *Angew. Chem. Int. Ed.* **1998**, *37*, 310–314; A. G. Kolchinski, N. W. Alcock, R. A. Roesner, D. H. Busch, *Chem. Commun.* **1998**, 1437–1438; M. Fujita, M. Aoyagi, F. Ibukuro, K. Ogura, K. Yamaguchi, *J. Am. Chem. Soc.* **1998**, *120*, 611–612; D. A. Leigh, A. Murphy, J. P. Smart, M. S. Deleuze, F. Zerbetto, *J. Am. Chem. Soc.* **1998**, *120*, 6458–6467; N. Armaroli, F. Diederich, C. O. Dietrich-Buchecker, L. Flamigni, G. Marconi, J.-F. Nierengarten, J.-P. Sauvage, *Chem. Eur. J.* **1998**, *4*, 406–416; P. R. Ashton, M. C. T. Fyfe, M.-V. Martínez-Díaz, S. Menzer, C. Schiavo, J. F. Stoddart, A. J. P. White, D. J. Williams, *Chem. Eur. J.* **1998**, *4*, 1523–1534; T. Dönnwald, A. H. Parham, F. Vögtle, *Synthesis* **1998**, *3*, 339–348.
- W. B. Farnham, D. C. Roe, D. A. Dixon, J. C. Calbrese, R. L. Harlow, *J. Am. Chem. Soc.* **1990**, *112*, 7707–7718; P. J. Smith, M. V. Reddington, C. S. Wilcox, *Tetrahedron Lett.* **1992**, *33*, 6085–6088; B. C. Hamann, N. R. Branda, J. Rebek, Jr., *Tetrahedron Lett.* **1993**, *34*, 6837–6840; E. Fan, S. A. Van Arman, S. Kincaid, A. D. Hamilton, *J. Am. Chem. Soc.* **1993**, *115*, 369–370; P. B. Savage, S. K. Holmgren, S. H. Gellman, *J. Am. Chem. Soc.* **1994**, *116*, 4069–4070; T. R. Kelly, M. H. Kirn, *J. Am. Chem. Soc.* **1994**, *116*, 7072–7080; H. Ishida, M. Suga, K. Donowaki, K. Ohkubo, *J. Org. Chem.* **1995**, *60*, 5374–5375; J. Scheerder, J. E. J. Engberson, A. Casnati, R. Ungaro, D. N. Reinholdt, *J. Org. Chem.* **1995**, *60*, 6448–6454; C. Raposo, N. Pérez, M. Almaraz, L. Mussons, C. Caballero, J. R. Moran, *Tetrahedron Lett.* **1995**, *36*, 3255–3258; S. Nishizawa, P. Buhlmann, M. Iwao, Y. Umezawa, *Tetrahedron Lett.* **1995**, *36*, 6483–6486; A. P. Davis, J. F. Gilmer, J. J. Perry, *Angew. Chem.* **1996**, *108*, 1410–1413; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1312–1315; N. A. McDonald, E. M. Duffy, W. L. Jorgensen, *J. Am. Chem. Soc.* **1998**, *120*, 5104–5111. See also M. J. Deetz, B. D. Smith, *Tetrahedron Lett.* **1998**, 6841–6844. For other neutral receptors based on Lewis acids and recent general reviews, see B. Dietrich, *Pure Appl. Chem.* **1993**, *65*, 1457–1464; C. Seel, J. de Mendoza in *Comprehensive Supramolecular Chemistry*, Vol. 2 (Eds.: J. L. Atwood, J. E. D. Davies, D. D. MacNicol, F. Vögtle), Pergamon, Oxford, **1996**, pp. 519–552; K. T. Holman, J. L. Atwood, J. W. Steed in *Advances in Supramolecular Chemistry*, Vol. 4 (Ed.: G. W. Gokel), JAI, London, **1997**, pp. 287–330; F. P. Schmidtchen, M. Berger, *Chem. Rev.* **1997**, *97*, 1609–1646; *The Supramolecular Chemistry of Anions* (Eds.: A. Bianchi, K. Bowman-James, E. García-España), Wiley, Chichester, **1997**.
- S. Ottens-Hildebrandt, S. Meier, M. Nieger, F. Vögtle, E. Weber, *Supramol. Chem.* **1995**, *5*, 133–138; F. Vögtle, T. Dönnwald, T.

- Schmidt, *Acc. Chem. Res.* **1996**, 29, 451–460; S. Braschofs, *thesis*, University of Bonn, **1998**. In catenanes derived from these lactams, however, one amide group of each ring is inverted and the carbonyl points inwards to provide additional hydrogen bonds: S. Ottens-Hildebrandt, M. Nieger, K. Rissanen, J. Rouvinen, S. Meier, G. Harder, F. Vögtle, *J. Chem. Soc. Chem. Commun.* **1995**, 777–778; H. Adams, F. J. Carver, C. A. Hunter, *J. Chem. Soc. Chem. Commun.* **1995**, 809–810. A rotaxane was reported where one amide bond also seems to be inverted: D. A. Leigh, A. Murphy, J. P. Smart, A. M. Z. Slawin, *Angew. Chem.* **1997**, 109, 752–756; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 752–756.
- [4] F. Vögtle, M. Händel, S. Meier, S. Ottens-Hildebrandt, F. Ott, T. Schmidt, *Liebigs Ann.* **1995**, 739–743.
- [5] C. Seel, F. Vögtle, unpublished results. Quinone binding by a tetralactam of this type: C. A. Hunter, *J. Chem. Soc. Chem. Commun.* **1991**, 749–751; C. A. Hunter, R. J. Shannon, *J. Chem. Soc. Chem. Commun.* **1996**, 1361–1362.
- [6] Rotaxanes are molecular compounds that consist of one or more wheels and penetrating axles that are mechanically bound together and sterically prevented from dethreading by bulky stopper groups at both ends of the axles. Semirotaxanes and pseudorotaxanes are analogous “conventional” inclusion complexes that are not restrained mechanically from dissociation since the axles (here semi- and pseudoaxles, respectively) carry only one stopper or no stopper at all, respectively. We propose semi- and pseudorotaxanes that act as precursors in rotaxane syntheses to be called prerotaxanes. Compare with P. R. Ashton, D. Philp, N. Spencer, J. F. Stoddart, *J. Chem. Soc. Chem. Commun.* **1991**, 1677–1679.
- [7] The isophthaloylic H-2 proton signals of host **1a** in CD₂Cl₂ shift about 0.7 ppm downfield in the complex with bromide and 0.45 ppm with acetate anions relative to the free host. The complexation-induced shifts of the NH protons are 1.7 and 1.8 ppm, respectively (δ values for the complexes have been extrapolated from the titration curves). Preliminary studies also show that host **1a** can extract Cl[−] and Br[−] ions in the presence of tetrabutylammonium ions from an aqueous into an organic phase and maintain a clean 1:1 stoichiometry. The phase transfer of oxoanions is currently under investigation; H. Stephan, Forschungszentrum Rossendorf, personal communication.
- [8] M. T. Blanda, J. H. Horner, M. Newcomb, *J. Org. Chem.* **1989**, 54, 4626–4636.
- [9] Titrations were made by the stepwise addition of a solution of one of the salts to a solution of a macrocycle. Nonlinear curve-fitting of the shift values of all nonoverlapped signals with significant complexation-induced shifts gave the association constants K_a , the average of which is given for each anion. See C. S. Wilcox in *Frontiers in Supramolecular Organic Chemistry and Photochemistry* (Eds.: H.-J. Schneider, H. Dürr), VCH, Weinheim, **1991**, pp. 123–143, and references therein.
- [10] Addition of triethylammonium 3,5-di-*tert*-butylphenolate to **1a** in CD₂Cl₂ caused only weak chemical shifts. With protonated 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the counterion, the binding constant was about 30 M^{−1}. A very tight binding only occurred when the phosphazene base “P₄-*t*-Bu” (1-*tert*-butyl-4,4,4-tris(dimethylamino)-2,2-bis[tris(dimethylamino)phosphoranylideneamino]-2 λ^3 ,4 λ^3 -catenadiphosphazene; Fluka) was used to obtain the phenolate. The “free” anion is probably only formed in the nonpolar environment with this extremely strong, voluminous base. Line-broadening in the presence of less than one equivalent of phenolate **2** makes quantification difficult, but we estimate that at least 95% of the complex is formed at a concentration of 5 mM. The association constant in a mixture of CD₂Cl₂/CD₃OD (4/1) is 280 ± 10 M^{−1}, that is, similar to the inorganic anions. Thiophenol, toluene-4-sulfonamide, and *N*-(4-*tert*-butylphenyl)-4-*tert*-butylphenylsulfonamide behave in a similar way.
- [11] H. Steinberg, D. J. Cram, *J. Am. Chem. Soc.* **1952**, 74, 5388–5391.
- [12] Addition of dibromide **3** or a diphenyl ether derived from it without voluminous stopper groups did not cause any significant NMR shifts of the wheel protons in CD₂Cl₂, hence we assume that the semirotaxanes formed with monoether **4** are not stable and thus do not act as prerotaxanes.
- [13] In the syntheses of amide-based rotaxanes we often observed that highly reactive starting compounds such as aliphatic acid chlorides and aliphatic amines tended to produce considerably lower yields of rotaxanes relative to less active aromatic acid chlorides and anilines, respectively. We thus decided not to use preformed phenolate salts here, but rather to create them slowly in situ with a suspension of solid K₂CO₃ as the base.
- [14] The rotaxanes show the typical upfield shifts ($\Delta\delta$) of proton signals relative to the free components in the NMR spectra recorded in CDCl₃. Selected $\Delta\delta$ values of **5a** (**5b**): Axle: C₂H₄ 0.49 (0.46), OCH₂ 0.53 (0.48), *p*-xylylene 0.72 (the signal at lower field is overlapped in the free axle here) (0.79 and 0.80), oxophenyl H-2/6 0.37 (0.33); wheel: isophthaloyl H-2 0.46 and 0.48 (0.34 and 0.41).
- [15] Deslipping had earlier been observed with similar rotaxanes: M. Händel, M. Plevoets, S. Gestermann, F. Vögtle, *Angew. Chem.* **1997**, 109, 1248–1250; *Angew. Chem. Int. Ed. Engl.* **1996**, 36, 1199–1201. Newer results reveal the process being of first order; F. Vögtle, A. Affeld, C. Heim, unpublished results.
- [16] The new method has already been applied successfully to the synthesis of analogous rotaxanes with ester, thioester, sulfide, and acetal axles since the submission of this communication.

Replacement of C–O by P–O in Cyclic Acetals and Ketals**

Feng Wang, Shuguang Ma, W. Andy Tao, and R. Graham Cooks*

Organophosphorus compounds are used in plasticizers, pharmaceuticals, pesticides, and warfare agents. Owing to their wide application, a variety of mass spectrometric techniques have been suggested for their identification^[1] and used to study their gas-phase reactivity.^[2] Phosphanylium ions (phosphenium ions, R–P⁺–R), for example, participate in reactions that include insertion, proton transfer, hydride abstraction, electron transfer, cluster formation,^[2–4] and [4+2⁺] cycloaddition.^[5] However, most gas-phase ion chemical studies of organophosphorus esters have been limited to characterization of molecular ions and reactions of the ions with their neutral precursors.^[1, 4, 6] Methanol, formaldehyde, and alkene eliminations are commonly observed fragmentation processes. The generation and reaction of phosphorus-containing distonic ions has also received attention.^[6a, 7]

Aiming to explore the chemistry of phosphoryl-containing cations, and ultimately contribute to increased understanding of the mechanism of hydrolysis of oxyphosphoranes^[8] and related phosphoryl-transfer reactions in biomolecules,^[9] we report here on the reactions of the phosphonium ions CH₃P(O)OCH₃⁺ and CH₃OP(O)OCH₃⁺. Alkyl-substituted 1,3-dioxolanes are chosen as the neutral reactants because of their reactivity with the analogous acylium ions.^[10, 11]

In solution, acyl transfer is a well-documented method of converting aldehydes and ketones into acetals and ketals and so protecting or, in the case of transacetalization, transferring the carbonyl group. Eberlin et al. discovered and elucidated

[*] Prof. R. G. Cooks, F. Wang, S. Ma, W. A. Tao
Department of Chemistry
Purdue University
West Lafayette, IN 47907 (USA)
Fax: (+1) 765-494-0239
E-mail: cooks@purdue.edu

[**] This work was supported by the National Science Foundation and the U.S. Department of Energy, Office of Basic Energy Science.

the mechanism of gas-phase transacetalization involving acylium ions ($\text{RC}^+=\text{O}$) and cyclic acetals and ketals.^[10, 11] This reaction occurs by initial O-acylation followed by a ring-opening/ring-reclosing sequence in which a neutral carbonyl compound is eliminated and cyclic “ionic ketals”—in other words, 1,3-dioxo cations and their analogues—are formed. Just as hydrolysis regenerates neutral carbonyl compounds in the condensed phase, so collision-induced dissociation of the resonance-stabilized cyclic 1,3-dioxo cations reforms the acylium ions in high yields in the gas phase.

1,3,2-Dioxaphospholane and related oxyphosphoranes are routinely synthesized by condensation of phosphanes and phosphites with diols or diketones in solution,^[12] but net replacement of C–O by P–O in cyclic acetals and ketals through reaction with phosphoryl-containing compounds has not been reported. Mass spectrometry, which offers a unique solvent- and counterion-free environment, is a convenient way to investigate whether cyclic 1,3,2-diheterophospholanium ions can be generated by a transacetalization-like process from phosphoryl-containing ions. These ionic phosphorus-containing derivatives might be useful in protocols for on-line monitoring of phosphorus esters and related warfare agents. Because the polarity of the phosphoryl group is greater than that of the carbonyl group, the cyclic phosphonium ion is much more easily solvated, and ready solvation is the reason that transacetalization reactivity is masked in the condensed phase. Therefore, we explore a general but normally hidden aspect of the reactivity of phosphoryl-containing cations. More importantly, the demonstrated reactivity of the phosphoryl-containing cations provides information that might be useful in searching for deprotecting reagents in less acidic media.

The phosphonium ions $\text{CH}_3\text{P}(\text{O})\text{OCH}_3^+$ (m/z 93) and $\text{CH}_3\text{OP}(\text{O})\text{OCH}_3^+$ (m/z 109) were generated from dimethyl methylphosphonate by electron impact (70 eV). All ion–molecule reactions and triple-stage (MS^3) experiments were carried out with a home-built pentaquadrupole mass spectrometer. Ion–molecule reactions of $\text{CH}_3\text{P}(\text{O})\text{OCH}_3^+$ and $\text{CH}_3\text{OP}(\text{O})\text{OCH}_3^+$ with cyclic acetals and ketals occur readily and yield the corresponding 1,3,2-dioxaphospholanium ions. The typical product-ion spectrum for mass-selected $\text{CH}_3\text{OP}(\text{O})\text{OCH}_3^+$ (m/z 109) reacting with 2-methyl-1,3-dioxolane (m/z 88) is shown in Figure 1. Proton transfer, methyl cation transfer, and hydride abstraction are major competing reactions.

Scheme 1 outlines a general mechanism for formal replacement of C–O by P–O to yield 1,3,2-dioxaphospholanium ions, and Table 1 lists the collision-induced dissociation (CID)

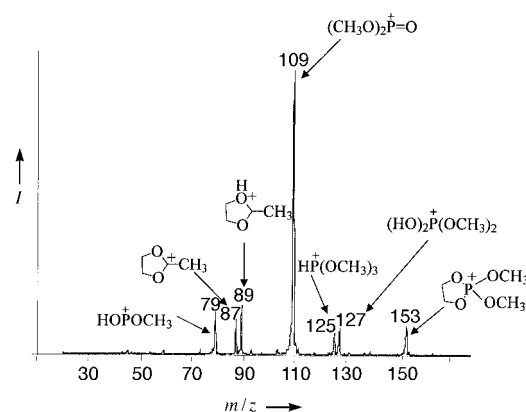
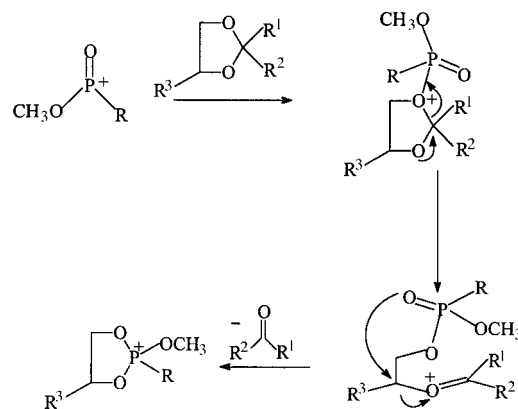


Figure 1. Product ion spectrum for ion–molecule reactions of $\text{CH}_3\text{OP}(\text{O})\text{OCH}_3^+$ (m/z 109) with 2-methyl-1,3-dioxolane (m/z 88) at nominally zero kinetic energy. I = relative abundance.



Scheme 1. Formal replacement of C–O by P–O to yield 1,3,2-dioxaphospholanium ions. $\text{R} = \text{OCH}_3, \text{CH}_3$; $\text{R}^1 = \text{H}, \text{CH}_3$; $\text{R}^2 = \text{CH}_3, \text{C}_6\text{H}_5$; $\text{R}^3 = \text{H}, \text{CH}_3$.

products of these ions. In most cases, the 1,3,2-dioxaphospholanium ions regenerate the reactant ions in high abundance upon CID. Correspondingly, in solution, 1,3,2-dioxaphosphoranes are often hydrolyzed or photolyzed back to the initial phosphonium ions.^[12, 13] Direct ketalization of phosphonium ions also occurs in the gas phase, as demonstrated with 2-methoxyethanol and 1,3-propanediol. The resulting product ions arising from loss of CH_3OH or H_2O were shown to have the same structures as those obtained by means of the corresponding transacetalization process.

The reactions displayed by $\text{CH}_3\text{P}(\text{O})\text{OCH}_3^+$ and $\text{CH}_3\text{OP}(\text{O})\text{OCH}_3^+$ can be used to differentiate isomeric acetals and ketals by revealing whether the alkyl substituent is located at

Table 1. Products of transacetalization in ion–molecule reactions with $\text{CH}_3\text{P}(\text{O})\text{OCH}_3^+$ and $\text{CH}_3\text{OP}(\text{O})\text{OCH}_3^+$, and CID fragments of the product 1,3,2-diheterophospholanium ions.

Compound	M_r	Substitution product ion		MS^3 products (I) ^[a]	
		$\text{CH}_3\text{P}(\text{O})\text{OCH}_3^+$	$\text{CH}_3\text{OP}(\text{O})\text{OCH}_3^+$	$\text{CH}_3\text{P}(\text{O})\text{OCH}_3^+$	$\text{CH}_3\text{OP}(\text{O})\text{OCH}_3^+$
2-methyl-1,3-dioxolane	88	137	153	93 (100)	109 (100), 127 (25)
2,2-dimethyl-1,3-dioxolane	102	137	153	93 (100)	109 (100), 127 (25)
4-methyl-1,3-dioxolane	88	151	167	93 (30), 111 (100)	109 (50), 127 (100)
2-phenyl-1,3-dioxolane	150	137	153	93 (100)	109 (100), 127 (30)
thiazolidine	89	136 (20)	152 (20)	— ^[b]	— ^[b]
		153 (100)	169 (100)	93 (100), 109 (25)	93 (<10), 109 (100), 125 (50)

[a] I = relative abundance. [b] MS^3 experiments could not be carried out due to the low ion abundance.

the 2-position. For instance, reaction of $\text{CH}_3\text{OP}(\text{O})\text{OCH}_3^+$ with 2-methyl-1,3-dioxolane gives an intact adduct of m/z 153, which dissociates on collision to reform the precursor ion $\text{CH}_3\text{OP}(\text{O})\text{OCH}_3^+$ (m/z 109) and protonated dimethyl phosphate ($(\text{CH}_3\text{O})_2\text{P}(\text{OH})_2^+$ (m/z 127) through a double hydrogen transfer rearrangement (Figure 2a).^[6b, 14] In contrast, $\text{CH}_3\text{OP}(\text{O})\text{OCH}_3^+$

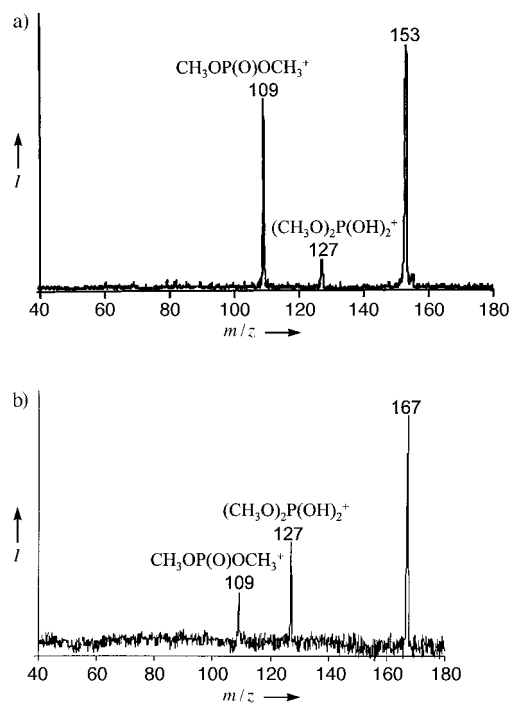


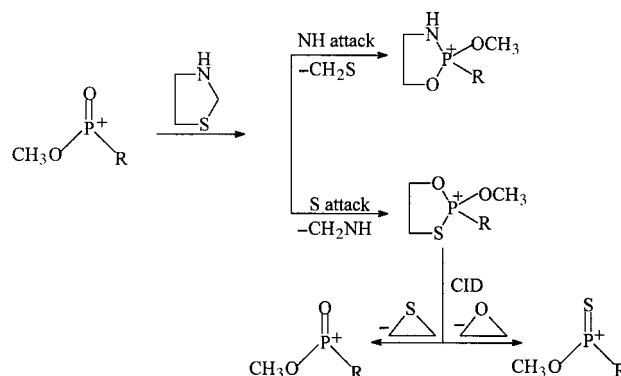
Figure 2. MS^3 sequential product ion spectra for the reaction of $\text{CH}_3\text{P}(\text{O})\text{OCH}_3^+$ (m/z 109) with 2-methyl-1,3-dioxolane (a) and 4-methyl-1,3-dioxolane (b). See text for details.

$(\text{O})\text{OCH}_3^+$ reacts with 4-methyl-1,3-dioxolane to form a product ion 14 Da higher in mass (m/z 167), which also dissociates to the initial phosphonium ion and protonated dimethyl phosphate (Figure 2b). These results show that substituents at the 4- and 5-positions remain in the resulting 1,3,2-dioxaphospholanium ions, whereas those at the 2-position are incorporated into the released neutral aldehyde or ketone. Furthermore, the above-mentioned double hydrogen-transfer process is confirmed to involve the ethylene portion of the product 1,3,2-dioxaphospholanium ion.

The Eberlin transacetalization is achieved by consecutive electrophilic ring opening and nucleophilic ring closing; hence, reaction rates are sensitive to electronic and steric effects, particularly those due to the 2-substituents.^[10, 11] Similar effects are noted in the reactions of $\text{CH}_3\text{P}(\text{O})\text{OCH}_3^+$ and $\text{CH}_3\text{OP}(\text{O})\text{OCH}_3^+$. Reactions with 2-methyl-1,3-dioxolane are faster than those of 4-methyl-1,3-dioxolane, as indicated by the high yield of 1,3,2-dioxaphospholanium ions. This suggests that recyclization induced by the intramolecular nucleophilic attack by the oxygen lone pair is rate limiting.

Thiazolidine has two nucleophilic sites (NH and S); hence it forms two cyclic phospholanium ions in reactions with $\text{CH}_3\text{P}(\text{O})\text{OCH}_3^+$ or $\text{CH}_3\text{OP}(\text{O})\text{OCH}_3^+$. Initial phosphorylation at S yields a 1-oxa-3-thia-2-phospholanium ion, at NH, a 1-aza-3-oxa-2-phospholanium ion. A 5:1 product ratio in

favor of reaction at sulfur has been observed for competitive phosphorylation. Furthermore, the 1,3,2-oxathiaphospholanium ions fragment to the initial reactant ions and their thio analogues (Scheme 2) in a ratio of 3:1 for $\text{CH}_3\text{P}(\text{O})\text{OCH}_3^+$



Scheme 2. Reaction of $\text{RP}(\text{O})\text{OCH}_3^+$ with thiazolidine. $\text{R} = \text{OCH}_3, \text{CH}_3$.

and 2:1 for $\text{CH}_3\text{OP}(\text{O})\text{OCH}_3^+$. This dissociation behavior confirms the cyclic structure of the diheterophospholanium ion, and it also provides a route for conversion of $\text{RRP}^+=\text{O}$ into $\text{RRP}^+=\text{S}$. A corresponding conversion of $\text{RC}^+=\text{S}$ into $\text{RC}^+=\text{O}$ has also been achieved.^[15]

We have found that in the gas phase representative phosphoryl-containing ions undergo structurally diagnostic transacetalization-like reactions with cyclic acetals and ketals to generate 1,3,2-dioxaphospholanium ions with characteristic dissociation behavior. The relatively high efficiency and structural specificity of the replacement of $\text{RRC}-\text{O}$ by RRP^+-O can be applied potentially to detect organophosphorus esters at trace levels. The methodology utilized here might also provide an alternative route to model phosphoryl migration in biosystems.^[9] Furthermore, owing to the importance of carbonyl group deprotection in organic synthesis, which is usually accomplished by aqueous acid hydrolysis, less acidic techniques are needed for acid-sensitive compounds. The use of transition metals and Lewis acids, oxidative methods, and phosphorus- and silicon-based reagents have been developed to meet this need. We describe here the first parallel gas-phase study to explore the nature of the deprotecting phosphorus-based reagents and provide experimental and theoretical thermochemical data on the deprotection process. Finally, the transacetalization reactivity described can be generalized to other ionic Lewis acids and leads to easy access to synthesis and characterization of a variety of transient heterocyclic cations, for example, tricoordinated cyclic boron cations.

Experimental Section

A pentaquadrupole mass spectrometer^[16] comprising three mass-analyzing quadrupoles (Q1, Q3, Q5) and two reaction quadrupoles (Q2, Q4) was used for the MS^2 and MS^3 experiments. $\text{CH}_3\text{P}(\text{O})\text{OCH}_3^+$ or $\text{CH}_3\text{OP}(\text{O})\text{OCH}_3^+$ ions were mass-selected by using Q1 and then allowed to undergo ion-molecule reactions with 1,3-dioxolanes or thiazolidine introduced into Q2. The products of the ion-molecule reactions were recorded by scanning Q5 with both Q3 and Q4 set in the broad-band rf-only mode. These products were characterized by MS^3 experiments, in which the 1,3,2-dioxaphospholanium ions formed in Q2 were mass-selected by using Q3 and allowed to

undergo energetic collisions with argon in Q4, while Q5 was scanned to record the sequential product ion spectrum. Typical reaction energy in Q2 and collision energy in Q4 are 0 eV and 10 eV (under multiple-collision conditions), respectively. All compounds are commercially available and were used without purification.

Received: August 11, 1998 [Z122721E]
German version: *Angew. Chem.* **1999**, *111*, 399–401

Keywords: acetals • ion–molecule reactions • mass spectrometry • phosphorus • transacetalizations

- [1] Selected references: a) P. A. D'Agostino, L. R. Provost, *J. Chromatogr. A* **1994**, *670*, 127; b) A. J. Bell, D. Despeyroux, J. Murrell, P. Watts, *Int. J. Mass Spectrom. Ion Processes* **1997**, *165*, 533, and references therein.
- [2] R. O'Hair in *The Chemistry of Organophosphorus Compounds*, Vol. 4 (Ed.: F. R. Hartley), Wiley, New York, **1996**.
- [3] K. K. Thoen, L. Gao, T. D. Ranatunga, P. Vainiotalo, H. I. Kenttämää, *J. Org. Chem.* **1997**, *62*, 8702.
- [4] R. Hodges, T. J. McDonnell, J. L. Beauchamp, *J. Am. Chem. Soc.* **1980**, *102*, 1327, and references therein.
- [5] S. Gevrey, M.-H. Taphanel, J.-P. Morizur, *J. Mass Spectrom.* **1998**, *33*, 399.
- [6] Selected references: a) L. Zeller, J. Farrell, Jr., P. Vainiotalo, H. I. Kenttämää, *J. Am. Chem. Soc.* **1992**, *114*, 1205; b) C. S. Harden, A. P. Snyder, G. A. Eiceman, *Org. Mass Spectrom.* **1993**, *28*, 585; c) T. Kuivalainen, R. Kostiainen, R. Uggla, M. R. Sundberg, H. Björk, *J. Am. Soc. Mass Spectrom.* **1996**, *7*, 189; d) J.-P. Morizur, S. Gevrey, A. Luna, M.-H. Taphanel, *J. Mass Spectrom.* **1997**, *32*, 550, and references therein.
- [7] R. Li, A. Schweighofer, H. Keck, W. Kuchen, H. I. Kenttämää, *Int. J. Mass Spectrom. Ion Processes* **1996**, *157/158*, 293.
- [8] F. H. Westheimer, *Acc. Chem. Res.* **1968**, *1*, 70.
- [9] a) C. Walsh, *Enzymatic Reaction Mechanisms*, W. H. Freeman, San Francisco, **1979**; b) R. Breslow, *Acc. Chem. Res.* **1991**, *24*, 317.
- [10] M. N. Eberlin, R. G. Cooks, *Org. Mass Spectrom.* **1993**, *28*, 679.
- [11] M. N. Eberlin, *Mass Spectrom. Rev.* **1997**, *16*, 113, and references therein.
- [12] a) R. R. Holmes, *Pentacoordinated Phosphorus*, Vol. 1/2 (ACS Monogr. **1980**, 175/176); b) D. E. C. Corbridge, *Phosphorus: An Outline of Its Chemistry, Biochemistry and Uses*, 5th ed., Elsevier Science, Amsterdam, **1995**.
- [13] G. H. McGall, R. A. McClelland, *Can. J. Chem.* **1991**, *69*, 2069, and references therein.
- [14] F. W. McLafferty, F. Tureček, *Interpretation of Mass Spectra*, 4th ed., University Science Books, Sausalito, CA, **1993**, p. 81.
- [15] L. A. B. Moraes, M. N. Eberlin, *J. Chem. Soc. Perkin Trans. 2* **1997**, 2105.
- [16] J. C. Schwartz, K. L. Schey, R. G. Cooks, *Int. J. Mass Spectrom. Ion Processes* **1990**, *101*, 1.

Ion-Channel Gating in Transmembrane Receptor Proteins: Functional Activity in Tethered Lipid Membranes**

Thierry Stora, Jeremy H. Lakey, and Horst Vogel*

In memory of Fritz Jähnig

The opening and closing (gating) of ion channels by ligand binding or by changes in the electrical transmembrane potential is the basis of many cellular signal-transduction processes.^[1] Furthermore it is of great pharmaceutical importance that the activity of membrane channels can be modulated by the binding of therapeutic agents and thus the understanding of these molecular interactions is a significant aspect in rational drug discovery and design. An increasing number of membrane channels are found to act as targets for medicines, and since combinatorial libraries of potential therapeutic compounds are growing rapidly, fast and highly sensitive methods for functional drug screening are required.^[2] Traditional methods such as patch clamp for the investigation of the function of channel proteins are poorly suited to high throughput screening. As an alternative, tethered lipid membranes^[3–6] offer attractive possibilities in this context as indicated by the detection and modulation of the channel activity of the small antibiotic peptide gramicidin.^[7]

Here we probe the function of a well-characterized pore-forming, transmembrane receptor protein by the measurement in situ of both the binding of ligands by surface plasmon resonance (SPR) and subsequent changes of the channel activity by impedance spectroscopy (IS).^[8,9]

The receptor protein OmpF was reconstituted into a fluid lipid bilayer coupled to a gold surface through the sulfur groups of so-called thiolipids^[4] present in the bilayer at a defined molar ratio (Figure 1). OmpF is a member of the porin family from the outer membrane of *Escherichia coli*. It functions as a trimer folded in the form of transmembrane β -barrels,^[10] which form distinct ion channels.^[11] This membrane protein is also the receptor for the antibacterial toxin colicin N.^[12] The colicins constitute a large family, which all exert their toxicity by initially binding to their receptor by a central region termed the receptor binding R domain.^[13] It has been shown recently that, whilst colicin N binds to detergent-solubilized OmpF with a dissociation constant K_d of 1 μ M, the

[*] Prof. H. Vogel, Dr. T. Stora
Laboratoire de Chimie Physique des Polymères et des Membranes
Département de Chimie
Ecole Polytechnique Fédérale de Lausanne
CH-1015 Lausanne (Switzerland)
Fax: (+41)21-6936190
E-mail: horst.vogel@epfl.ch
Dr. J. H. Lakey
School of Biochemistry and Genetics
The Medical School, Newcastle upon Tyne, NE2 4HH (UK)

[**] Financial support from the Swiss National Science Foundation, Priority Program on Biotechnology, grant 5002-35180 (H.V.), the BBSRC, and the Wellcome Trust (J.H.L.) is acknowledged. We thank M. Liley, S. Terrettaz for critical reading of the manuscript, Z. Dienes for the synthesis of the thiolipids, and T. Keller, L. Evans, and E. Raggett for their help in protein expression and purification.

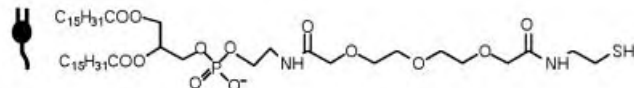


Figure 1. Schematic view of an OmpF-containing lipid bilayer tethered to a gold surface by the synthetic thiolipid *N*-[14'-sulfanyl-1',11'-dioxo-3',6',9'-trioxa-12'-azatetradecyl]-1,2-dipalmitoyl-*sn*-glycero-3-phosphoethanolamine shown at the bottom. The thiolipid is designed to form a suitable tethered lipid bilayer for the correct functioning of the reconstituted transmembrane protein.^[4] The bilayer can be tuned to an appropriate fluidity and composition, contacts an aqueous environment on both sides of the membrane to accommodate the extramembraneous parts of the protein; a self-assembled monolayer of sulfanylpropionic acid on the gold surface (not indicated) finally prevents all unfavorable interactions between the underlying gold support and the protein. (1) = tethered lipid bilayer, (2) = gold support, (3) = OmpF, (4) = R domain fragment of colicin N.

isolated R-domain protein fragment exhibited a dissociation constant of greater than $100\text{ }\mu\text{M}$.^[14] This result however did not correlate well with the observed affinity *in vivo*. In addition, preliminary experiments with black lipid membranes (BLM) revealed that the soluble R-domain fragment could cause closure of the porin channel in lipid bilayers. To obtain physiologically meaningful affinity data we used a tethered bilayer to enable both SPR and IS measurements of the interaction between the R fragment and OmpF.

The tethered lipid bilayers were formed in two steps: Firstly, thiolipids were self-assembled together with sulfanylpropionic acid to create gold surfaces coated with carboxylic acid that were decorated with a certain number of thiolipid anchors. The surface coat of sulfanylpropionic acid prevents the receptor protein from denaturation by direct contact to pure gold. This modified surface was then covered by a bilayer that comprised natural phospholipids and membrane receptors.^[15] The whole process was continuously monitored in situ by SPR, which measures the optical layer thickness and thus the amount of surface-immobilized lipid and protein.^[16] In addition, the electrical properties of the supported membranes were investigated by IS.^[17, 18] The calculated electrical capacitance and resistance of the tethered membranes are in agreement with published data.^[4–7] These results confirm that the proteolipid assembly on the gold surface adopts a bilayer membrane structure. Moreover, the conductivity of the membrane $1/R_{\text{lay}}$ was measured directly by monitoring the current at one single frequency ν_0 (Figure 2), which is important for the development of the on-line bioassay described below.

OmpF function was probed by independent measurement of its ability to both bind colicin N and form channels that can be modulated by the binding of the ligand. The specific binding of the TR domain of colicin N to the OmpF receptor was measured by SPR (Figure 3).^[19] An apparent dissociation

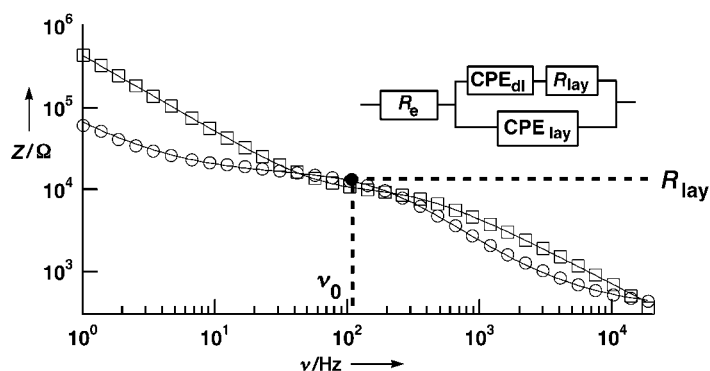


Figure 2. Real ($\circ$) and the imaginary ($\square$) part of the electrical impedance spectrum of a 3.14 mm² disk gold electrode covered with a supported bilayer: 166 data points equally spaced on the log scale between 1 Hz and 20 kHz were measured, with every fifth point shown. Solid lines represent the fit to the experimental points with the equivalent circuit shown in the top right corner: R_e accounts for the ohmic contributions of the buffer and the counter electrode; the tethered membrane is described by a constant phase element CPE_{lay} (used here as a generalized capacitance) in parallel with a resistance R_{lay} and another generalized capacitance CPE_{dl} in series.^[9, 18] The latter two describe the overall contribution of both the membrane-inserted porins and membrane defects. A constant phase element is defined as $1/(j\omega)^n S$, $j^2 = -1$, where ω is the radial frequency, S is the modulus and n the phase; $0 \leq n \leq 1$, where $n=0$ corresponds to an ideal resistance, while $n=1$ corresponds to an ideal capacitance. CPE_{lay} and CPE_{dl} behave approximately like capacitors, as can be seen from the fit values of n_{lay} and n_{dl} . By extraction of the capacitance of the layer from the capacitive, 90° out-of-phase current that arises from CPE_{lay} at the frequency where the phase shift of the whole electrochemical cell is maximum (that is, the current is the most capacitive), we obtained values of $0.9 \pm 0.1 \mu F cm^{-2}$. A specific layer resistance of $0.5 - 5 k\Omega cm^{-2}$ was directly deduced ($\bullet$) without fitting by measurement of the real part of the impedance at the frequency ν_0 where it is the most sensitive to this ohmic contribution (minimum in the phase shift); the relative difference between the value that we got from this procedure and the value obtained from the fit over the whole frequency range was less than 2%. Typical values for fit parameters are: $R_e = 300 - 500 \Omega$; $S_{lay} = 1.0 \times 10^{-7} \Omega^{-1} s^{n_{lay}}$; $n_{lay} = 0.90 \pm 0.05$; $S_{dl} = 3.0 \times 10^{-7} \Omega^{-1} s^{n_{dl}}$; $n_{dl} = 0.95 \pm 0.05$; $R_{lay} = 16 - 160 k\Omega$.

constant K_d of $0.6\mu\text{M}$ was obtained from the fit to the experimental data. OmpF channel activity was deduced from the membrane conductivity that was monitored by IS. Since ligand-gated ion-channel currents (10^8 ionss $^{-1}$) provide a considerable intrinsic amplification of the ligand binding,^[20] impedance measurements could be carried out with a much lower concentration of receptors in the membranes than for SPR measurements. The data in Figure 3 show that an increase in the R-domain concentration in the bulk solution changes the conductivity of the OmpF channels in the membrane, which reflects functional changes of the receptor upon ligand binding.^[21] From these measurements a K_d of $2\mu\text{M}$ was evaluated. The relative conductivity changes of 15% correspond to about 10^6 functional porins in the layer, as deduced from the values reported for the conductivity of a single OmpF porin channel.^[11] The data from IS clearly show for the first time that OmpF functions as a ligand-gated ion channel: the binding of the isolated R domain of the toxin on its receptor OmpF closes the ionic channel completely.

This new channel function of the porin, as detected by a novel measurement technique, was corroborated by further use of the well-established BLM technique. OmpF was reconstituted into free-standing bilayers by standard proto-

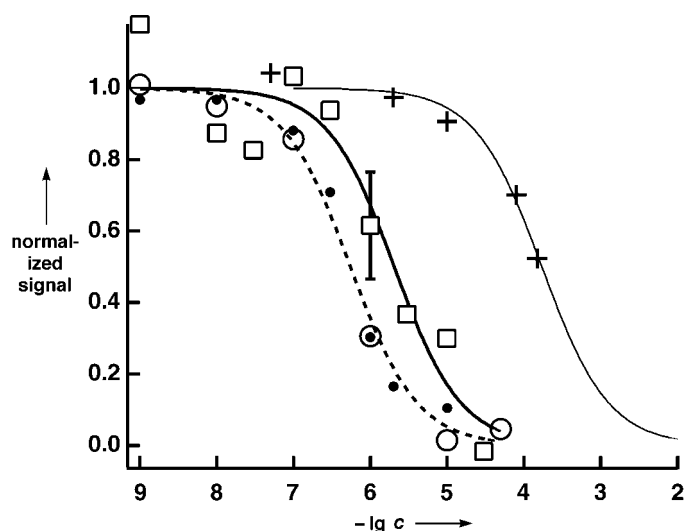


Figure 3. Interaction between colicin N and OmpF. (○): The binding of the colicin TR fragment to its receptor OmpF in a tethered bilayer as measured by SPR. $(\Gamma_{\max} - \Gamma)/\Gamma_{\max}$ is shown, where Γ and $\Gamma_{\max}$ are the mass of the bound TR fragments at the corresponding and at the highest bulk concentration (that is at saturation), respectively; $\Gamma_{\max} = 274 \text{ ng cm}^{-2}$. (□): OmpF channel gating in a tethered bilayer upon R-domain binding measured by IS. Initial value: 1.54 mS cm^{-2} ; final value: 1.35 mS cm^{-2} . A representative error bar is shown. (●): OmpF channel gating in a free standing bilayer (BLM) upon incubation of the colicin R domain. Initial BLM conductivity: 538 nS ; after titration: 0.1 nS . + : Binding of detergent-solubilized OmpF to the surface-immobilized colicin N fragments as monitored by SPR.^[9, 18] $(\Gamma_{\max} - \Gamma)/\Gamma_{\max}$ is shown, where Γ and $\Gamma_{\max}$ are the mass of the bound OmpF at the corresponding concentration and at saturation fitted to the experimental data, respectively. Saturation cannot be obtained experimentally because of the high bulk concentrations of porin required. The value of 808 ng cm^{-2} for $\Gamma_{\max}$, deduced from the fit, corresponds to one OmpF trimer per accessible R domain. Data are fitted by a Langmuir binding isotherm. K_d values of 0.6 and $2 \mu\text{M}$ are obtained from SPR (○) and IS (□) in the case of tethered bilayers, and $0.5 \mu\text{M}$ in the case of free-standing bilayers (●), (dashed lines for both SPR and BLM, thick solid line for IS). A K_d value of $170 \mu\text{M}$ is obtained in the case of OmpF solubilized in detergent. All data sets shown are normalized such that the initial fit values are equal to 1 and the final to 0; the values of the molar concentration c of the ligand in the bulk solution are given as negative decadic logarithms.

cols.^[22] The electrical conductivity across the BLM decreased with increasing concentrations of R domain in the surrounding buffer (Figure 3): the OmpF channels were completely blocked at ligand concentrations above $10 \mu\text{M}$. From this titration experiment a K_d value of $0.5 \mu\text{M}$ was obtained. This value confirms the data from IS and SPR of tethered bilayers. Finally, we have determined by SPR that the binding affinity of detergent-solubilized OmpF to surface-immobilized colicin TR domains is about two orders of magnitude lower than that of OmpF reconstituted in lipid bilayers (Figure 3).^[23] Again, this is in complete agreement with recently published results^[14] and, in the context of our BLM and combined SPR/IS measurements, demonstrates the importance of a lipid bilayer to retain proper native receptor binding activity.

In the context of screening for therapeutic agents, classical binding assays provide only limited information whereas by the combination of SPR and IS we have presented a rapid assay that independently probes both ligand binding and its functional consequences. With the help of nanotechnological fabrication and microfluidic devices,^[24] the miniaturization

and full automation of this technique opens the door to widespread application for functional screening of ligand–receptor interactions.

Received: July 21, 1998 [Z12190 IE]

German version: *Angew. Chem.* **1999**, *111*, 402–405

Keywords: analytical methods • ion channels • membranes • proteins • thin films

- [1] B. Hille, *Ionic channels of excitable membranes*, Sunderland, Sinauer, MA, **1992**.
- [2] J. Knowles, *Odyssey* **1997**, *3*(1), 18–24.
- [3] For a review, see E. Sackmann, *Science* **1996**, *271*, 43–48.
- [4] a) H. Lang, C. Duschl, H. Vogel, *Langmuir* **1994**, *10*, 197–210; b) S. Heyse, O. P. Ernst, Z. Dienes, K. P. Hofmann, H. Vogel, *Biochemistry* **1998**, *37*, 507–522.
- [5] a) M. Stelzle, G. Weismüller, E. Sackmann, *J. Phys. Chem.* **1993**, *97*, 2974–2981; b) E.-L. Florin, H. E. Gaub, *Biophys. J.* **1993**, *64*, 375–383; c) A. L. Plant, M. Gueguetckheri, W. Yap, *Biophys. J.* **1994**, *67*, 1126–1133; d) C. Steinem, A. Janshoff, W. P. Ulrich, M. Sieber, H. J. Galla, *Biochim. Biophys. Acta* **1996**, *1279*, 169–180.
- [6] a) Z. Salamon, J. T. Hazzard, G. Tollin, *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 6420–6423; b) R. Naumann, A. Jonczyk, R. Kopp, J. van Esch, H. Ringsdorf, W. Knoll, P. Graeber, *Angew. Chem.* **1995**, *107*, 2168–2171; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2056–2058.
- [7] B. A. Cornell, V. L. B. Braach-Maksyutis, L. G. King, P. D. J. Osman, B. Raguse, L. Wiczorek, R. J. Pace, *Nature* **1997**, *387*, 580–583.
- [8] W. Knoll *MRS Bull.* **1991**, *16*, 29–39.
- [9] S. Terrettaz, T. Stora, C. Duschl, H. Vogel, *Langmuir* **1993**, *9*, 1361–1369.
- [10] a) M. S. Weiss, U. Abele, J. Weckesser, W. Welte, E. Schiltz, G. E. Schulz, *Science* **1991**, *254*, 1627–1630; b) S. W. Cowan, T. Schirmer, G. Rummel, M. Steiert, R. Ghosh, R. A. Pauptit, J. N. Jansonius, J. P. Rosenbusch, *Nature* **1992**, *358*, 727–733.
- [11] a) H. Schindler, J. P. Rosenbusch, *Proc. Natl. Acad. Sci. USA* **1978**, *75*, 3751–3755; b) R. Benz, K. Janko, W. Boos, P. Läger, *Biochim. Biophys. Acta* **1978**, *511*, 305–319.
- [12] I. R. Vetter, M. W. Parker, A. D. Tucker, J. H. Lakey, F. Pattus, D. Tsernoglou, *Structure* **1998**, *6*, 863–874.
- [13] H. Nikaido, M. Vaara, *Microbiol. Rev.* **1985**, *49*, 1–32.
- [14] a) L. J. A. Evans, A. Cooper, J. H. Lakey, *J. Mol. Biol.* **1996**, *255*, 559–563; b) L. J. A. Evans, S. Labeit, A. Cooper, L. H. Bond, J. H. Lakey, *Biochemistry* **1996**, *35*, 15143–15148.
- [15] The freshly evaporated gold layer was cleaned by a discharge argon plasma in the vacuum chamber, and immediately incubated for 25 h in a solution of thiolipids and sulfanylpropionic acid (total concentration of 0.5 mg mL^{-1} in 48 mM octyl glucoside), at a molar ratio of 1:4 for SPR and 2:1 for IS. The self-assembled monolayer was then washed extensively with a 1 % octyl glucoside solution. It was transformed into a bilayer by stepwise dilution of a solution of 48 mM octyl glucoside, 0.5 mg mL^{-1} of dioleoyl lecithin, and OmpF ($230 \mu\text{g mL}^{-1}$ for SPR and $5 \mu\text{g mL}^{-1}$ for IS). Typical thiolipid surface coverage for SPR experiments was 10–25 %.
- [16] SPR was measured by directing a He-Ne laser light onto a 40 nm thick gold surface through a prism and detecting the dip in the reflected light as a function of the incident angle, as described in the literature.^[9] Protein surface coverage Γ is deduced from the SPR angle shift $\Delta\theta$ by using the equation, $\Delta\theta = \alpha \text{ dn/dc} \Gamma$ [Eq. (1)], with $\alpha = 1.3 \times 10^7 \text{ cm}^{-1}$ and a refractive index increment $\text{dn/dc} = 0.18 \text{ g}^{-1} \text{ cm}^3$ (*Handbook of Biochemistry*, CRC Press, Boca Raton, **1973**). From structural data of OmpF^[10] and Equation (1) we find that a full OmpF monolayer gives surface coverage of 714 ng cm^{-2} ($\Delta\theta_{\text{OmpF}} = 1.7^\circ$). This is significantly higher than for a bilayer composed of pure phosphatidylcholines ($\Delta\theta_{\text{lipid}} = 0.6^\circ$). Therefore, the amount of OmpF incorporated can be deduced directly from the layer angle shift $\Delta\theta_{\text{layer}}$ by using $\Gamma_{\text{OmpF}} = (\Delta\theta_{\text{layer}} - \Delta\theta_{\text{lipid}})/(\Delta\theta_{\text{OmpF}} - \Delta\theta_{\text{lipid}})$; this neglects the minor surface coverage occupied by the thiolipids. Typical values for $\Delta\theta_{\text{layer}}$ were 0.9° , which gives an estimated 30 % of the layer surface occupied by the incorporated OmpF.

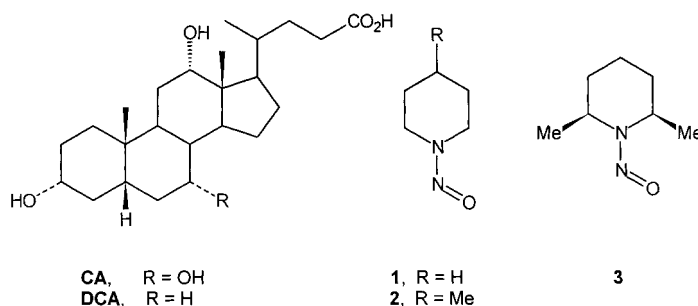
- [17] IS was done with the membrane-covered gold electrode as a working electrode against a counter/reference Ag/AgCl electrode in 0.3 M NaCl/20 mM sodium phosphate (pH 7.4). An alternating current voltage (10 mV root mean square amplitude) was applied and the current was recorded with a phase sensitive Lock-In amplifier to measure the complex impedance Z , as described elsewhere.^[9, 18]
- [18] T. Stora, R. Hovius, Z. Dienes, M. Pachoud, H. Vogel *Langmuir* **1997**, *13*, 5211–5214.
- [19] The T domain consists of the natural N terminus of colicin N (residues 1–67), and together with the R domain (68–190) forms half (= TR) of the entire colicin N molecule (1–387). TR served as a natural mass tag to amplify SPR signals, and did not affect the binding affinity of the isolated R domain to the OmpF receptors in the tethered membranes. The quantities of bound TR at saturation were higher than the expected amounts deduced from the estimation of the incorporated OmpF.^[11, 18] This could be a consequence of a favorable orientation of the membrane receptors, which arises from their asymmetric structure or to an underestimation of the receptor content in the layer that results from approximate values of the refractive index of the proteins. TR adsorption on a tethered membrane made of pure lipids was very limited, which leads to a mass adsorption of less than 12 ng cm⁻².
- [20] Since the OmpF single-channel conductivity was reported to be 0.8 nS^[11] when 10 mV are applied, a current of 8 pA that passes through a porin corresponds to 10⁸ ions s⁻¹.
- [21] The calculated capacitance of the layer remained constant within experimental errors. No changes in the conductivity were observed on a pure lipid-tethered membrane upon incubation of the R fragment.
- [22] OmpF reconstitution into BLMs were performed as described by R. Benz, *Crit. Rev. Biochem.* **1985**, *19*, 145–190. Black lipid membranes were formed by painting a hole of 0.6 mm diameter in a Teflon foil with a solution of 10 mg mL⁻¹ soya bean lecithin in decane. OmpF was incorporated afterwards by dilution of 1 µL of OmpF (0.125 mg mL⁻¹) in 1% octyl glucoside in the cell and by application of a constant voltage of 250 mV. The current was recorded at a transbilayer potential of 50 mV direct current. Titration was performed in a solution of 0.3 M NaCl/20 mM sodium phosphate (pH 7.4).
- [23] R and TR fragments contained hexahistidine sequences on their N termini which served as tags to immobilize the proteins on nitrilotriacetate-covered gold surfaces by following the procedure described in T. A. Keller, C. Duschl, D. Kröger, A.-F. Sévin-Landais, H. Vogel, S. E. Cervigni, P. Dumy, *Supramol. Sci.* **1995**, *2*, 155–160. SPR angle shifts of 0.72° and 1.00° (308 and 427 ng cm⁻²) were obtained. Only minor binding of the protein was observed at concentrations up to 100 µM upon addition of detergent-solubilized OmpF (as also used elsewhere^[14]) to the bulk phase. A further experiment was performed to reduce the packing of R at the interface in which 15% of the protein at the surface was the TR fragment immobilized through the histidine tag that was located at the random coil T domain.^[14] As a result, the R segments of the TR fragments protrude above the densely packed layer of T fragments. In this way we could measure an interaction between OmpF and R domain in detergent.
- [24] *Proceedings of the 2nd International Symposium on Miniaturized Total Analysis Systems* (Eds.: H. M. Widmer, E. Verpoorte, S. Barnard), AMI, Basel, **1996**.

Enantioselective Inclusion Complexation of *N*-Nitrosopiperidines by Steroidal Bile Acids**

Maria Gdaniec,* Maria J. Milewska, and
Tadeusz Połowski*

There is currently considerable interest in crystalline inclusion compounds formed by chiral host molecules on account of their application for chiral recognition and optical resolution of racemates.^[1] Owing to their ability to accommodate many types of organic guest molecules within their crystal lattices,^[2] naturally occurring cholic acid (CA) and deoxycholic acid (DCA) seem to be very promising hosts for this purpose. However, only very few successful examples of chiral resolution by enclathration with CA have been reported,^[3] and several attempts to use DCA as a resolving agent have failed.^[3, 4] On the other hand, we have found recently that the CA and DCA matrices force conformationally flexible molecules included in the crystals to assume chiral conformations, as indicated by the circular dichroism (CD) spectra.^[5]

Here we describe the efficiency of bile acids for chiral recognition of low molecular weight *N*-nitrosamines. The chirality of *N*-nitrosopiperidines **1**–**3** is solely due to hindered rotation of the nitroso group.^[6] Because of the partial double bond character of the bond between the two nitrogen atoms in the NNO group, the barrier to rotation about the N–N bond is relatively high (ca. 23–25 kcal mol⁻¹).^[7] Therefore the enantiomers of **2** and **3** are expected to be stable for a short period of time at ambient temperature even after liberation from the crystal host lattices. Obtaining **1**–**3** in the optically active form



is challenging from an experimental point of view and would afford very simple models for studying chiroptical spectra of the *N*-nitrosamino chromophore.^[8]

[*] Prof. Dr. M. Gdaniec
Faculty of Chemistry
A. Mickiewicz University
PL-60-780 Poznań (Poland)
Fax: (+48) 61-8658-008
E-mail: mg31@krystal.amu.edu.pl
Prof. Dr. T. Połowski, Dr. M. J. Milewska
Department of Chemistry
Technical University of Gdańsk
PL-80-952 Gdańsk (Poland)
Fax: (+48) 58-3472-694
E-mail: tadpol@chem.pg.gda.pl

[**] This work was partially supported by the Polish Committee for Scientific Research (grant no. 3 T09A 09014)

The colorless crystals of the 1:1 complexes of **1–3** with **CA** were obtained by crystallization of **CA** with the corresponding nitrosamine. The 2:1 **DCA** inclusion compounds were prepared by slow evaporation of a solution of **DCA** and the suitable *N*-nitrosopiperidine in methanol. The X-ray crystallographic analysis of the **CA** complexes^[9a–c, f] revealed that the host molecules are assembled through hydrogen bonds into typical corrugated **CA** bilayers. In the case of **1-CA** the guest molecules are accommodated in the α -type channels,^[2] while in **2-CA** and **3-CA** the channels are of β -type (Figure 1). The

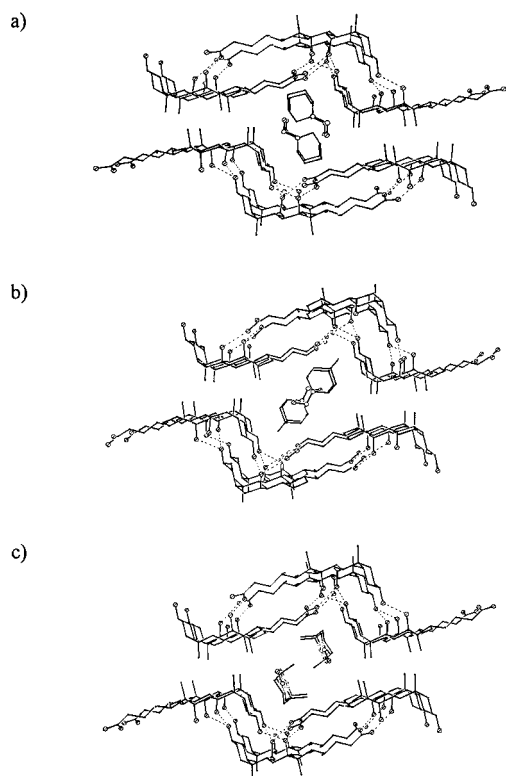


Figure 1. Crystal packing in a) **1-CA**, b) **2-CA**, and c) **3-CA**.

guest molecules are arranged in helicoidal columns propagating through the crystal (Figure 2). Inspection of the data showed that either only one enantiomer is selectively incorporated in the host–guest crystals (**1-CA** and **2-CA**) or a preferential complexation of one enantiomer occurs (**3-CA**, Figure 3). The absolute configuration of the nitrosamine guest molecules can be easily deduced from the X-ray crystal structures of the complexes. In the case of **1-CA** and **2-CA**, the *pR* (planar chirality) and *S* configurations were assigned to the guest molecules **1** and **2**, respectively, whereas for **3-CA** 72% of the nitrosamine molecules assume the *E* configuration (geometric enantiomerism)^[10] and the remaining 28% the *Z* configuration. The crystal structure of **3-CA** revealed that the guest nitrosamine **3** adopts a chair conformation with the methyl substituents occupying the axial positions. The diequatorial conformation is destabilized as a consequence of the strong pseudoallylic *A*^(1,3) strain caused by steric interactions between the nitroso group and nearly coplanar methyl substituents.^[11] The axial preference of methyl groups in **3** had been already deduced from ¹H and ¹³C NMR measurements

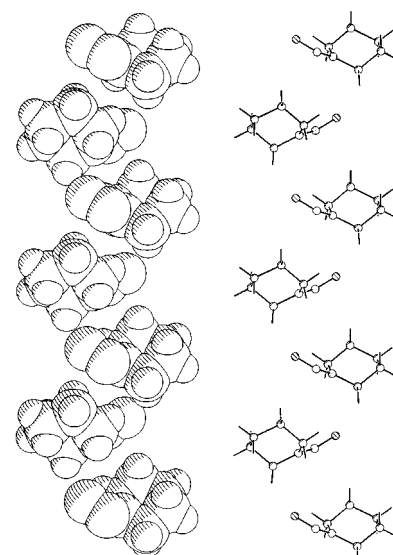


Figure 2. Helicoidal arrangement of the guest molecules in the crystal of **1-CA**.

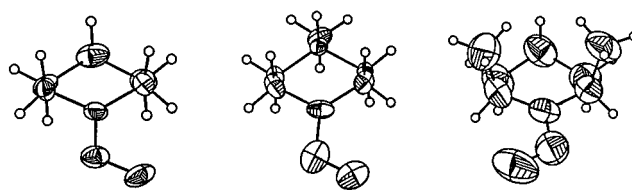


Figure 3. ORTEP drawings of the guest *N*-nitrosamines **1–3** (from left to right) in **1-CA**, **2-CA**, and **3-CA** showing the absolute configurations of the nitrosamines.

in solution.^[12] The X-ray data for **1-DCA** and **3-DCA** collected at 130 K showed disordered nitrosamine molecules with two enantiomeric molecules occupying the same site in the crystal.^[9d–f] Nevertheless, in the case of **3-DCA** the *E*:*Z* ratio of 2:1 indicates the ability of the **DCA** matrices to discriminate between the enantiomers. Unfortunately, no conclusive explanation for the preferably included stereoisomer of **1** in **DCA** could be obtained.

The chirality of the guest *N*-nitrosopiperidines can also be detected with CD spectroscopy (Table 1); the corresponding spectra can be taken for samples in the solid state (KBr disks;^[13] Figure 4) as well as in solution (Figure 5). Such

Table 1. Circular dichroism data of the **CA** and **DCA** inclusion compounds.

Compound	Medium	$\lambda_{\max}$ [nm] ([θ)] ^[a]
1-CA	KBr	357 (530) ^[b]
1-DCA	KBr	373 (406) ^[b]
2-CA	KBr	371 (320) ^[b]
2-CA	MeOH	350 (–770) ^[c]
2-DCA	KBr	358 (820) ^[b]
2-DCA	MeOH	351 (360) ^[c]
3-CA	KBr	377 (–770) ^[b]
3-CA	MeOH	350 (–) ^[c,d]
3-DCA	KBr	376 (–1200) ^[b]
3-DCA	MeOH	350 (–) ^[c,d]

[a] Molecular ellipticity in deg cm² dmol^{–1}. [b] Approximate values, determined by considering the weight concentration (KBr density 2.75 g cm^{–3}). [c] Measured immediately after dissolution. [d] Only the CE sign can be determined.

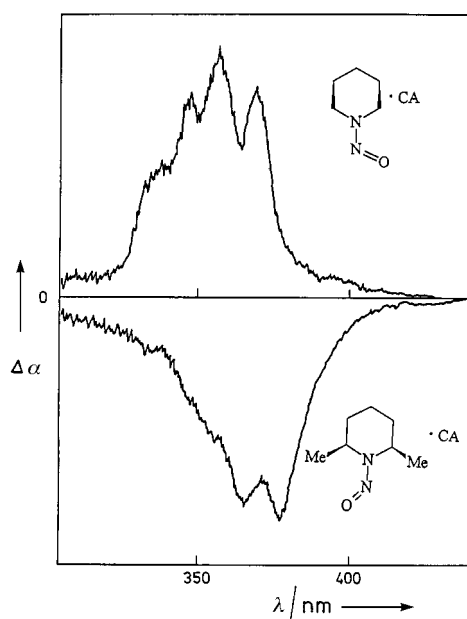


Figure 4. Solid-state CD spectra of **1-CA** and **3-CA** (KBr).

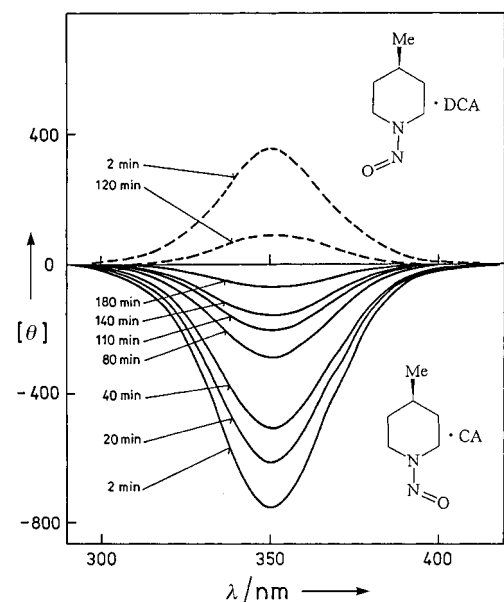


Figure 5. Decay of the CD signal of **2-DCA** (dashed lines) and **2-CA** (solid lines) in methanol at 22 °C.

measurements are possible since the nitrosamine $n-\pi^*$ band near 370 nm remains outside the absorption range of the bile acids. The carboxylic group absorbs at about 210 nm, and therefore the **CA** and **DCA** hosts are transparent at longer wavelengths. The CD spectra of **2-CA** and **2-DCA** in methanol exhibit a moderately strong Cotton effect (CE) near 350 nm, which gradually decreases at room temperature due to the slow N–N rotation and finally vanishes completely after about four hours (Figure 5). The nitrosamine **3** racemizes much faster than **2**, owing to a significantly lower energy barrier to rotation about the N–N bond (18.9 kcal mol^{−1}).^[7b] Therefore, the CD of **3-CA** and **3-DCA** in solution vanishes within a few minutes after dissolution. Nonetheless, the

negative CE sign can be unequivocally detected immediately after dissolution. In the case of **1** the racemization is caused not only by rotation of the nitroso group but also by inversion of the piperidine ring. The energy barrier of the second process is much lower (less than 6 kcal mol^{−1})^[14] than that of the first, and for this reason the CD of **1-CA** cannot be observed in solution at room temperature but only in the solid state. The CD spectra of the **CA** and **DCA** complexes with **1** and **2** in KBr exhibit positive CEs near 370 nm, whereas those of **3** (Figure 5) are characterized by negative CEs. At the first glance, it seems surprising that the CD spectra of **2-CA** in solution and in the solid state exhibit $n-\pi^*$ CEs of opposite signs, while **2-DCA**, **3-CA** and **3-DCA** show the same CD signs in the solid state as well as in solution. On the other hand, it is known that the nitrosamine CD is extremely sensitive to any deviations of the chromophore from planarity.^[15] An inherent chirality of the twisted NNO group may exert a strong contribution to the CE, which often overweighs the contribution of the dissymmetrically placed substituents and thus governs the sign of the CE.^[16] Indeed, the X-ray crystallographic data revealed small distortions of the nitrosamine group from planarity in **1-CA** and **2-CA**, as indicated by the corresponding torsional angles: C(2)–N–N–O 175.6(5)° (**1-CA**), 175.5(4)° (**2-CA**); C(6)–N–N–O −3.2(9)° (**1-CA**), 8.3(7)° (**2-CA**). These deviations are apparently due to the packing forces in the inclusion crystals and may be alleviated in solution. For these reasons configurational assignments based on solid-state CD measurements might be risky. However, the absolute configuration of the guest molecules can be easily predicted from the solution spectra. It is especially important for the **DCA** complexes; the data collected in Table 1 reveal that **DCA** preferentially enclathrates the *R* enantiomer of **2** and the *E* enantiomer of **3**.

Received: July 7, 1998 [Z 12109 IE]

German version: *Angew. Chem.* **1999**, *111*, 405–408

Keywords: chirality • circular dichroism • inclusion compounds • solid-state structures

- [1] a) F. Toda, *Top. Curr. Chem.* **1987**, *140*, 43–69; b) F. Toda in *Advances in Supramolecular Chemistry*, Vol. 2 (Ed.: G. W. Gokel), JAI Press, London, **1992**, pp. 141–191; c) F. Toda in *Inclusion Compounds*, Vol. 4 (Eds.: J. L. Atwood, J. E. D. Davies, D. D. MacNicol), Oxford University Press, Oxford, **1991**, pp. 126–187; d) G. Kaupp, *Angew. Chem.* **1994**, *106*, 768; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 728–729.
- [2] M. Miyata, K. Sada in *Comprehensive Supramolecular Chemistry*, Vol. 6 (Eds.: D. D. MacNicol, F. Toda, R. Bishop), Pergamon, Oxford, **1996**, pp. 147–176.
- [3] a) M. Miyata, M. Shibakami, K. Takemoto, *J. Chem. Soc. Chem. Commun.* **1988**, 655–656; b) K. Miki, N. Kasai, M. Shibakami, K. Takemoto, M. Miyata, *J. Chem. Soc. Chem. Commun.* **1991**, 1757–1759.
- [4] H. Sobotka, A. Goldberg, *Biochem. J.* **1932**, *26*, 905–909.
- [5] M. Gdaniec, T. Poloński, *J. Am. Chem. Soc.* **1998**, *120*, 7353–7354.
- [6] H. Völter, G. Helmchen, *Tetrahedron Lett.* **1978**, 1251–1254.
- [7] a) J. D. Cooney, S. K. Brownstein, J. W. ApSimon, *Can. J. Chem.* **1974**, *52*, 3028–3036; b) R. K. Harris, T. Pryce-Jones, F. J. Swinbourne, *J. Chem. Soc. Perkin Trans. 2* **1980**, 476–482.
- [8] T. Poloński, M. J. Milewska, A. Katrusiak, *J. Am. Chem. Soc.* **1993**, *115*, 11410–11417, and references therein.
- [9] X-ray crystal structures analyses: KUMA KM-4 diffractometer, Lorentz and polarization corrections, no absorption correction; the

structure was solved by direct methods with SHELXS-86 and refined by the full-matrix least-squares procedure against F^2 with SHELXL-93. a) Crystal structure data for **1-CA**: $C_{24}H_{40}O_5 \cdot C_5H_{10}N_2O$, crystal size $0.6 \times 0.3 \times 0.07$ mm, $T = 100$ K, monoclinic, $P2_1$, $a = 13.268(4)$, $b = 7.909(2)$, $c = 13.818(4)$ Å, $\beta = 106.03(2)^\circ$, $V = 1393.6(7)$ Å³, $Z = 2$, $\rho_{\text{calcd}} = 1.246$ g cm⁻³, $\mu = 0.086$ mm⁻¹, MoK α radiation ($\lambda = 0.71073$ Å). Data were collected up to $2\theta = 48^\circ$ (θ - 2θ scans). The structure was refined on 2058 reflections with positive F^2 values; 334 refined parameters; $R_1 = 0.044$, $wR_2 = 0.102$, GOF = 1.102 for 1691 reflections with $F > 4\sigma(F)$ ($R_1 = 0.106$, $wR_2 = 0.141$, GOF = 1.281 for all 2376 independent reflections). b) Crystal structure data for **2-CA**: $C_{24}H_{40}O_5 \cdot C_6H_{12}N_2O$, crystal size $0.6 \times 0.2 \times 0.07$ mm, $T = 100$ K, $P2_1$, $a = 12.353(2)$, $b = 7.675(1)$, $c = 16.359(4)$ Å, $\beta = 111.09(2)^\circ$, $V = 1447.1(5)$ Å³, $Z = 2$, $\rho_{\text{calcd}} = 1.232$ g cm⁻³, $\mu = 0.085$ mm⁻¹, MoK α radiation ($\lambda = 0.71073$ Å). Data were collected up to $2\theta = 52^\circ$ (θ - 2θ scans). The structure was refined on 2823 reflections with positive F^2 values; 343 refined parameters; $R_1 = 0.043$, $wR_2 = 0.110$, GOF = 1.051 for 2425 reflections with $F > 4\sigma(F)$ ($R_1 = 0.076$, $wR_2 = 0.125$, GOF = 1.084 for all 3066 independent reflections). c) Crystal structure data for **3-CA**: $C_{24}H_{40}O_5 \cdot C_7H_{14}N_2O$, crystal size $0.6 \times 0.2 \times 0.1$, $T = 293$ K, monoclinic, space group $P2_1$, $a = 12.754(3)$, $b = 7.881(2)$, $c = 16.355(3)$ Å, $\beta = 111.97(3)^\circ$, $V = 1524.5(6)$ Å³, $Z = 2$, $\rho_{\text{calcd}} = 1.200$ g cm⁻³, $\mu = 0.655$ mm⁻¹, CuK α radiation ($\lambda = 1.54178$ Å). Data were collected up to $2\theta = 140^\circ$ (θ - 2θ scans). The structure was refined on 2534 reflections with positive F^2 values; 343 refined parameters; $R_1 = 0.041$, $wR_2 = 0.111$, GOF = 1.077 for 2340 reflections with $F > 4\sigma(F)$ ($R_1 = 0.052$, $wR_2 = 0.122$, GOF = 1.084 for all 2639 independent reflections). The guest *N*-nitroso group is disordered over two positions. Restraints were imposed on 1–2 and 1–3 distances and planarity of the *N*-nitrosamino group during refinement. d) Crystal data for **1-DCA**: $2C_{24}H_{40}O_4 \cdot C_5H_{10}N_2O$, crystal size $0.6 \times 0.45 \times 0.2$ mm, $T = 130$ K, orthorhombic, $P2_12_12_1$, $a = 26.730(4)$, $b = 13.228(2)$, $c = 13.971(4)$ Å, $V = 4346(2)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 1.209$ g cm⁻³, $\mu = 0.081$ mm⁻¹, MoK α radiation ($\lambda = 0.71073$ Å). Data were collected up to $2\theta = 48^\circ$ (ω - θ scans). The structure was refined on 4345 reflections with the positive F^2 values; 530 refined parameters; $R_1 = 0.056$, $wR_2 = 0.132$, GOF = 1.070 for 3459 reflections with $F > 4\sigma(F)$ ($R_1 = 0.080$, $wR_2 = 0.148$, GOF = 1.073 for all 4347 independent reflections). The guest molecule is disordered over three positions. It was refined isotropically as a rigid body with molecular geometry fitted to that of **1** in **1-CA**. Sum of the occupancy factors was refined to 1.00 (0.55(1) for the *pR* isomer and 0.30(1) and 0.15(1) for the *pS* isomer). e) Crystal structure data for **3-DCA**: $2C_{24}H_{40}O_4 \cdot C_7H_{14}N_2O$, crystal size $0.4 \times 0.2 \times 0.2$ mm, $T = 130$ K, orthorhombic, $P2_12_12_1$, $a = 26.845(5)$, $b = 13.583(3)$, $c = 14.001(3)$ Å, $V = 5105(2)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 1.206$ g cm⁻³, $\mu = 0.080$ mm⁻¹, MoK α radiation ($\lambda = 0.71073$ Å). Data were collected up to $2\theta = 48^\circ$ (ω - θ scans). The structure was refined on 3661 reflections with the positive F^2 values; 539 refined parameters; $R_1 = 0.059$, $wR_2 = 0.147$, GOF = 1.013 for 2496 reflections with $F > 4\sigma(F)$ ($R_1 = 0.176$, $wR_2 = 0.200$, GOF = 1.094 for all 4485 independent reflections). The guest molecule was refined anisotropically, but disorder was suspected because of poor molecular geometry, the shape of the ellipsoids, and large residual peaks close to the *N*-nitroso atom. Therefore, the geometry of the guest was fitted to that found for **3** in the **3-CA** complex. Subsequently, the guest molecule was refined isotropically as a rigid body. Sum of the two occupancy factors of the guest molecules was kept fixed at 1.0. The occupancy of the higher populated *E* stereoisomer was refined at 0.67(1). f) Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-101943–CCDC-101947. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

- [10] E. L. Eliel, S. H. Wilen, *Stereochemistry of Organic Compounds*, Wiley, New York, **1994**, p. 1137–1138.
 [11] a) F. Johnson, S. K. Malhotra, *J. Am. Chem. Soc.* **1965**, *87*, 5492–5493; b) F. Johnson, *Chem. Rev.* **1968**, *68*, 375–413; c) M. Gdaniec, M. J. Milewska, T. Połoniński, *J. Org. Chem.* **1995**, *60*, 7411–7418.
 [12] a) Y. L. Chow, C. J. Colon, J. N. S. Tam, *Can. J. Chem.* **1968**, *46*, 2821–2825; b) R. R. Fraser, T. B. Grindley, *Tetrahedron Lett.* **1974**, 4169–

4172; c) R. R. Fraser, T. B. Grindley, S. Passannanti, *Can. J. Chem.* **1975**, *53*, 2473–2480.

- [13] A mixture of the complex (5 mg) and KBr (300 mg) was ground and formed into a disk with a radius of 10 mm. The disk was rotated around the optical axis, and the CD recordings were made for several positions in order to check the reproducibility of the spectra. For details of the experimental procedure, see also a) R. Kuroda, Y. Saito, *Bull. Chem. Soc. Jpn.* **1976**, *49*, 433–436; b) K. Rasmussen, N. Ch. P. Hald, *Acta Chem. Scand. Ser. A* **1982**, *36*, 549–554.
 [14] L. Lunazzi, D. Macciantelli, *J. Chem. Soc. Perkin Trans. 2* **1981**, 604–609.
 [15] a) G. V. Shustov, A. V. Kachanov, G. K. Kadorkina, R. G. Kostyanovsky, A. Rauk, *J. Am. Chem. Soc.* **1992**, *114*, 8257–8262; b) G. V. Shustov, A. Rauk, *J. Am. Chem. Soc.* **1995**, *117*, 928–934.
 [16] G. Snatzke, *Angew. Chem.* **1979**, *91*, 380; *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 363–377.

Total Synthesis of (–)-Strychnine via the Wieland–Gumlich Aldehyde**

Daniel Solé, Josep Bonjoch,* Silvinia García-Rubio, Emma Peidró, and Joan Bosch*

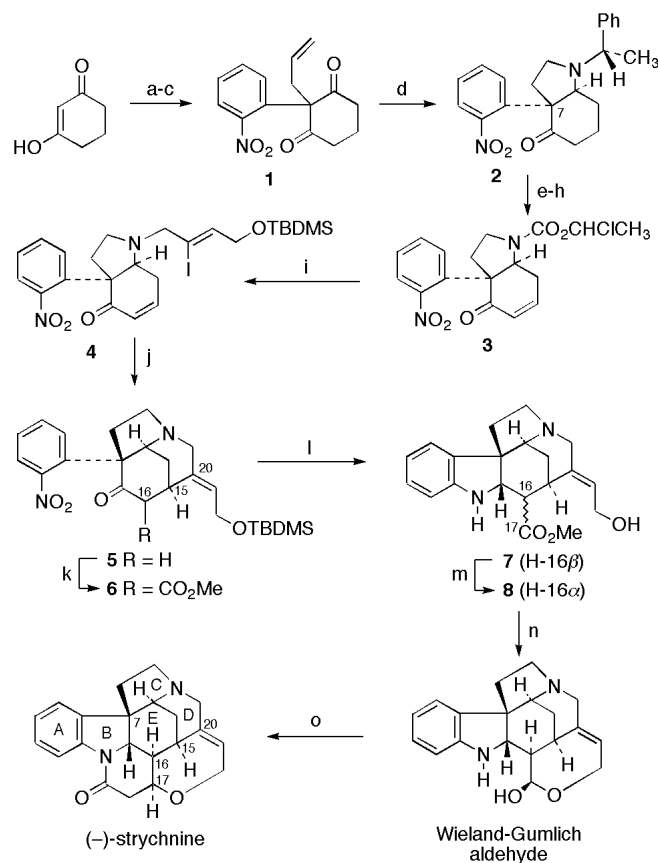
Strychnine, the most famous of the *Strychnos* alkaloids,^[1] is a natural product that has been known for a long time. Its complex heptacyclic structure, which is assembled from only 24 skeletal atoms and contains six contiguous asymmetric carbon atoms (five of which are in the core cyclohexane ring), represents a permanent challenge for synthetic organic chemists.^[2] The classical, pioneering total synthesis by Woodward et al.^[3] remained the only synthesis of strychnine for nearly 40 years, and five research groups have recently reported new total syntheses of this alkaloid, either via isostrychnine^[4] or via the Wieland–Gumlich aldehyde.^[5] However, only in one case has the enantioselective total synthesis of the natural enantiomer, (–)-strychnine, been achieved.^[5c] The elegant enantioselective synthesis of (–)-strychnine by Overman et al. takes advantage of the tandem cationic aza-Cope rearrangement/Mannich cyclization strategy for the construction of the basic skeleton of the alkaloid and—with almost the same number of reaction steps as the synthesis by Woodward et al.—upped the overall yield by a factor of 10⁵.

As the culmination of our studies on the synthesis of *Strychnos* alkaloids,^[6] we present here a new synthesis of (–)-strychnine which proceeds via the Wieland–Gumlich aldehyde and starts with 1,3-cyclohexanedione (the core ring E of strychnine),^[7] from which the pyrrolidine, piperidine, and indoline rings are successively built in three well-differenti-

[*] Prof. Dr. J. Bonjoch, Prof. Dr. J. Bosch, Dr. D. Solé, Dr. S. García-Rubio, E. Peidró
 Laboratory of Organic Chemistry, Faculty of Pharmacy
 University of Barcelona
 Av. Joan XXIII s/n, E-08028-Barcelona (Spain)
 Fax: (+34) 93-4021896
 E-mail: bonjoch@farmacia.far.ub.es

[**] This work was supported by DGICYT, Spain (Projects PB94-0214 and PB97-0877). Financial support from DGEU, Catalonia (1997SGR-0018 and 1997SGR-00166) is also acknowledged.

ated phases. This strategy has proved to be useful for the synthesis of pentacyclic *Strychnos* alkaloids of the curan type.^[6d] The most remarkable aspects of the synthesis are 1) easy generation (in only four steps from 1,3-cyclohexanedione) of the first enantiopure intermediate, the 4-(2-nitrophenyl)octahydroindol-4-one **2**, which contains the crucial quaternary C7 center (Scheme 1); 2) closure of the piperidine



Scheme 1. Synthesis of (–)-strychnine: a) 2-IC₆H₄NO₂, K₂CO₃, DMSO, 85–90 °C, 72 %; b) BrCH₂CH=CH₂, K₂CO₃, acetone, reflux, 85 %; c) toluene, sealed tube, 180–190 °C, 80 %; d) O₃, CH₂Cl₂, –78 °C, then (S)-PhCH(CH₃)NH₂·HCl, NaBH₃CN, *i*PrOH, 37 %; e) ClCO₂CHClMe, 135 °C, 72 %; f) HN(SiMe₃)₂, Me₃SiI, CH₂Cl₂/pentane 1/1, –20 °C; g) PhSeCl, (PhSe)₂, THF, 70 %; h) O₃, CH₂Cl₂, –78 °C, then *i*Pr₂NH, 72 %; i) MeOH, reflux, then (Z)-BrCH₂Cl=CHCH₂OTBDMS, K₂CO₃, LiI, CH₃CN, 50 °C, 74 %; j) Pd(OAc)₂, PPh₃, Et₃N, 90 °C, 53 %; k) LiN(SiMe₃)₂, HMPA, THF, –78 °C, then NCCO₂Me, 67 %; l) Zn dust, H₂SO₄, MeOH, reflux; m) NaH, MeOH, reflux, 26 %; n) DIBAL, toluene, –40 °C, 65 %; o) CH₂(CO₂H)₂, Ac₂O, NaOAc, AcOH, 110 °C, 49 %. DMSO = dimethyl sulfoxide, HMPA = hexamethyl phosphoramide, TBDMS = *tert*-butyldimethylsilyl.

ring by a Pd-catalyzed reaction (formation of the C15–C20 bond), which ensures the stereoselective incorporation of the C20 *E*-configured double bond; and 3) closure of the indoline ring in an advanced synthetic stage by reductive cyclization of the α -(2-nitrophenyl) ketone moiety.

The chiral nonracemic *cis*-octahydroindolone **2** was prepared as previously reported^[6d] from the prochiral dione **1** by a one-pot procedure consisting of an ozonolysis followed by a double reductive amination with (*S*)-1-phenylethylamine as the aminocyclization agent.^[8] Removal of the α -phenylethyl substituent via a carbamate followed by generation of the

enone moiety, deprotection of the pyrrolidine nitrogen atom, and finally alkylation of the resulting bicyclic secondary amine with (Z)-1-bromo-4-[(*tert*-butyldimethylsilyl)oxy]-2-iodobut-2-ene^[9] led to the key intermediate **4**.

It was our original hope that the closure of the piperidine ring containing the ethylidene group and the introduction of the functionalized one-carbon substituent at C16 could be achieved in a palladium-catalyzed tandem process.^[10] Disappointingly, however, numerous attempts to promote the tandem cyclization/carbonylation process (Pd catalyst, CO, MeOH)^[11] failed. Instead, the ester resulting from methoxycarbonylation of the initially formed vinyl palladium derivative was isolated.^[12] In light of these results, we turned our attention to a less direct strategy, in which cyclization and introduction of the functionalized C17 carbon atom would be achieved in two separate steps. After considerable experimentation with racemic compounds, the best results for the cyclization were obtained with Pd(OAc)₂ (0.3 equiv) and PPh₃ (0.6 equiv) as the catalyst in Et₃N at 90 °C for a short time (30 min). Under these conditions the tricyclic ketone **5** was isolated in 53 % yield. This key Heck-type cyclization takes place in a reductive form, and is a variant of the Heck reaction which has received comparatively little attention from a synthetic standpoint.^[13] Methoxycarbonylation of **5** with LiHMDS (HMDS = hexamethyldisilazane) and methyl cyanoformate provided β -keto ester **6** (55 % yield), a compound containing all but the two acetate-derived carbon atoms of the heptacyclic target molecule.

The synthesis of the Wieland–Gumlich aldehyde from **6** only required closure of the indoline ring and reduction of the ester functionality to an aldehyde. Treatment of **6** with zinc dust in 10 % sulfuric acid (in methanol) brought about both the removal of the TBDMS protecting group and the reductive cyclization of the α -(2-nitrophenyl) ketone moiety. Under the reaction conditions the initially formed anilinoacrylate intermediate undergoes further reduction to an epimeric mixture of esters **7** and **8** (ratio approximately 9:1). The mixture was equilibrated to pure **8**, which has the natural stereochemistry at C16, by treatment with NaH in refluxing MeOH. The pentacyclic ester **8**, which is also an intermediate in the synthesis by Overman et al.,^[5c] was isolated in 26 % overall yield from **6**. Finally, further adjustment of the oxidation level by partial reduction of ester **8** with DIBAH (DIBAH = diisobutylaluminum hydride) in toluene at –40 °C afforded the Wieland–Gumlich aldehyde.^[14, 15]

Although the conversion of the Wieland–Gumlich aldehyde into strychnine was reported many years ago,^[16] and there would therefore seem to be little need to perform such a conversion, for the sake of completion we followed the described protocol, thus fulfilling the total synthesis of the natural product. The resulting (–)-strychnine was identical to a natural specimen, as determined by thin-layer chromatography (TLC) as well as IR, ¹H NMR, and ¹³C NMR spectroscopy. The $[\alpha]_D^{25}$ value was –119.4 (*c* = 0.35, CHCl₃; reference [16]: $[\alpha]_D^{25}$ = –139 (*c* = 2.0, CHCl₃)), which represents 86 % *ee*,^[17] a value very similar to that obtained in our enantioselective synthesis of (–)-tubifolidine from azabicyclo **2**.^[6d]

We have accomplished a short enantioselective synthesis of (–)-strychnine (15 steps from commercially available 1,3-

cyclohexanedione), involving a transfer of chirality from (S)-1-phenylethylamine to generate an enantiopure 3a-(2-nitrophenyl)hexahydroindol-4-one, from which the additional rings of the target molecule are assembled with high stereocontrol. Taking into account our previous work,^[6d] the strategy developed here provides a general synthetic route for the enantioselective synthesis of *Strychnos* alkaloids.

Received: July 14, 1998 [Z12141 IE]
German version: *Angew. Chem.* **1999**, *111*, 408–410

Keywords: alkaloids • asymmetric synthesis • nitrogen heterocycles • palladium • total synthesis

- [1] a) U. Beifuss, *Angew. Chem.* **1994**, *106*, 1204–1209; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1144–1149; b) “Monoterpenoid Indole Alkaloids”: J. Sapi, G. Massiot in *The Chemistry of Heterocyclic Compounds, Suppl. to Vol. 25, Part 4* (Eds.: J. E. Saxton, E. C. Taylor), Wiley, New York, **1994**, pp. 279–355; c) J. Bosch, J. Bonjoch, M. Amat in *The Alkaloids, Vol. 48* (Ed.: G. A. Cordell), Academic Press, New York, **1996**, pp. 75–189; d) K. C. Nicolaou, E. J. Sorensen, *Classics in Total Synthesis*, VHC, Weinheim, **1996**, pp. 21–40, 641–653.
- [2] Moreover, it remains to be of interest from a pharmacological point of view; see, for example, P. Gharagozloo, M. Miyauchi, B. Birdsall, N. J. M. Birdsall, *J. Org. Chem.* **1998**, *63*, 1974–1980, and references therein.
- [3] R. B. Woodward, M. P. Cava, W. D. Ollis, A. Hunger, H. U. Daeniker, K. Schenker, *J. Am. Chem. Soc.* **1954**, *76*, 4749–4751; R. B. Woodward, M. P. Cava, W. D. Ollis, A. Hunger, H. U. Daeniker, K. Schenker, *Tetrahedron* **1963**, *19*, 247–288.
- [4] a) M. E. Kuehne, F. Xu, *J. Org. Chem.* **1993**, *58*, 7490–7497; b) V. H. Rawal, S. Iwasa, *J. Org. Chem.* **1994**, *59*, 2685–2686; see also reference [3].
- [5] a) P. Magnus, M. Giles, R. Bonnert, C. S. Kim, L. McQuire, A. Merritt, N. Vicker, *J. Am. Chem. Soc.* **1992**, *114*, 4403–4405; P. Magnus, M. Giles, R. Bonnert, G. Johnson, L. McQuire, M. Deluca, A. Merritt, C. S. Kim, N. Vicker, *J. Am. Chem. Soc.* **1993**, *115*, 8116–8129; b) G. Stork, reported at the Ischia Advanced School of Organic Chemistry, Ischia Porto, Italy, **1992**; c) S. D. Knight, L. E. Overman, G. Pairaudeau, *J. Am. Chem. Soc.* **1993**, *115*, 9293–9294; S. D. Knight, L. E. Overman, G. Pairaudeau, *J. Am. Chem. Soc.* **1995**, *117*, 5776–5788.
- [6] a) M. Amat, A. Linares, J. Bosch, *J. Org. Chem.* **1990**, *55*, 6299–6312; b) J. Gràcia, N. Casamitjana, J. Bonjoch, J. Bosch, *J. Org. Chem.* **1994**, *59*, 3939–3951; c) M. Amat, M.-D. Coll, J. Bosch, E. Espinosa, E. Molins, *Tetrahedron: Asymmetry* **1997**, *8*, 935–948; d) J. Bonjoch, D. Solé, S. García-Rubio, J. Bosch, *J. Am. Chem. Soc.* **1997**, *119*, 7230–7240.
- [7] The numbering system and ring labeling used throughout this paper is based on the biogenetic interrelationship of indole alkaloids: J. Le Men, W. I. Taylor, *Experientia* **1965**, *21*, 508–510.
- [8] In a preliminary study, this amine proved to be the most efficient chiral auxiliary for the enantioselective preparation of *cis*-3a-(2-nitrophenyl)octahydroindol-4-ones: D. Solé, J. Bosch, J. Bonjoch, *Tetrahedron* **1996**, *52*, 4013–4028.
- [9] This alkylating agent was prepared following the protocol by Rawal and Iwasa.^[4b]
- [10] It was expected that the transient alkylpalladium intermediate arising from the cyclization, which has no β -hydrogen atom available for β -elimination, was stable enough to allow intermolecular trapping with CO; for related processes, see R. Grigg, P. Kennewell, A. Teasdale, *Tetrahedron Lett.* **1992**, *33*, 7789–7792; E. Negishi, C. Coperet, S. Ma, T. Mita, T. Sugihara, J. M. Tour, *J. Am. Chem. Soc.* **1996**, *118*, 5904–5918.
- [11] $[\text{Pd}(\text{PPh}_3)_4]$, $\text{Pd}(\text{OAc})_2$, and $[\text{PdCl}_2(\text{PPh}_3)_2]$ were used as catalysts in several solvents (C_6H_6 , CH_3CN , DMF, DMF/ H_2O) under a variety of experimental conditions.
- [12] a) When the reaction was carried out in the presence of the trapping agent LiCN ,^[12b] the azatricyclic compound **5** was the only isolable

compound (<10%); b) R. Grigg, V. Santhakumar, V. Sridharan, *Tetrahedron Lett.* **1993**, *34*, 3163–3164.

- [13] a) In the Heck reaction with electron-deficient olefins, two competing reaction pathways can operate, namely, substitution (which involves β -H elimination) and 1,4-conjugate addition (which involves reduction of the σ -alkylpalladium intermediate); see, for example, G. K. Friestad, B. P. Branchaud, *Tetrahedron Lett.* **1997**, *38*, 5933–5936; H. Hagiwara, Y. Eda, K. Morohashi, T. Suzuki, M. Ando, N. Ito, *Tetrahedron Lett.* **1998**, *39*, 4055–4058, and references therein; b) the closure of the piperidine ring in the synthesis of strychnine by Rawal and Iwasa^[4b] involves a nonreductive intramolecular Heck reaction from a tetracyclic ABCE intermediate.
- [14] The chemical shifts of our synthetic sample were coincident with those reported for a natural sample of the Wieland–Gumlich aldehyde: G. Massiot, B. Massoussa, M.-J. Jacquier, P. Thépénier, L. Le Men-Olivier, C. Delaude, R. Verpoorte, *Phytochemistry* **1988**, *27*, 3293–3304.
- [15] Starting from *rac*-**4**, which is prepared from the N-methyl analogue of **2**,^[6d] we have also completed the synthesis of the racemic Wieland–Gumlich aldehyde.
- [16] F. A. L. Anet, R. Robinson, *Chem. Ind. (London)* **1953**, 245.
- [17] This *ee* value is in agreement with the optical purity of **2**, which was prepared from an (S)-1-phenylethylamine with about 96 % *ee* and used as a 97:3 mixture (according to HPLC analysis) of *cis* diastereomers.

Nickel-Catalyzed Homoallylation of Aldehydes and Ketones with 1,3-Dienes and Complementary Promotion by Diethylzinc or Triethylborane**

Masanari Kimura, Hidetaka Fujimatsu, Akihiro Ezoe, Kazufumi Shibata, Masamichi Shimizu, Satoru Matsumoto, and Yoshinao Tamaru*

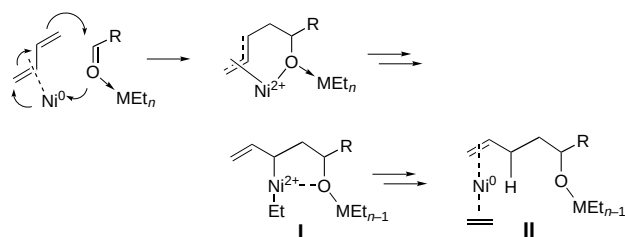
Allylation of carbonyl compounds is a fundamental process in organic syntheses, and many efficient methodologies have been developed.^[1] Besides the allyl derivatives of alkali and alkaline earth metals, those of transition metals^[2] and metal-oids (e.g., allylstannanes, -silanes, -boranes, etc.)^[1] have been utilized for the regio- and stereoselective allylation of carbonyl compounds. Homoallylation could have similar importance in organic transformations; however, this process has received little attention, probably owing to the limited variety of homoallylating agents $\text{CH}_2=\text{CHCH}_2\text{CH}_2\text{M}$, which are restricted to metals of high electropositivity such as Li and Mg, since the polarity of homoallylic C–M bonds is considerably lower than that of allylic C–M bonds.

By analogy with the stoichiometric homoallylation of carbonyl compounds with $[\text{ZrCp}_2(1,3\text{-diene})]$ (Cp = cyclo-

[*] Prof. Dr. Y. Tamaru, Dr. M. Kimura, H. Fujimatsu, A. Ezoe, K. Shibata, M. Shimizu, S. Matsumoto
Department of Applied Chemistry, Faculty of Engineering
Nagasaki University
1-14 Bunkyo-machi, Nagasaki 852–8521 (Japan)
Fax: (+81) 958-47-9008
E-mail: tamaru@net.nagasaki-u.ac.jp

[**] We thank Mr. Y. Ohhama, NMR Facility, for technical assistance. Financial support by the Ministry of Education, Science, Sports and Culture, Japanese Government, is gratefully acknowledged.

pentadienyl) complexes,^[3] we envisaged that a catalytic homoallylation of carbonyl compounds with 1,3-dienes^[4] might be realized by an appropriate combination of nickel(0) complexes of 1,3-dienes and ethylmetal compounds Et_nM (Scheme 1). These two might constitute an electron relay,^[5]



Scheme 1.

and through a sequence of reactions furnish the σ -allyl-ethylnickel(II) complex **I**, in which the σ -allyl structure is stabilized by coordination with the oxygen atom of the metal alkoxide. By virtue of this σ -allyl nature of complex **I**, the ethyl group would deliver hydrogen to the allylic position that is bound to nickel to produce the nickel(0) bishomoallyl alcohol complex **II**. The nickel(0) center of **II** can be used to repeat the reaction.

As we previously reported,^[6] triethylborane, in accordance with the scenario outlined above, acts as a Lewis acid to activate carbonyl compounds and as a reducing agent to promote the homoallylation (reductive coupling) of benzaldehyde with a variety of 1,3-dienes in the presence of a catalytic amount of [Ni(acac)₂] [1–10 mol %, acac = acetylacetonato, [Eq. (a)]]. The reaction proceeds at room temperature and provides bishomoallyl alcohols **1** in good yields and with high

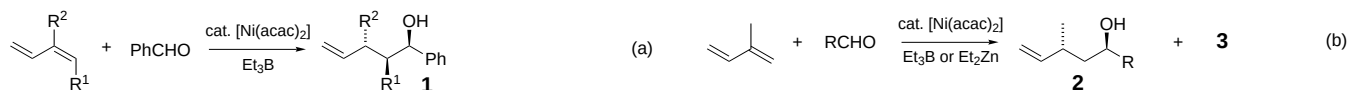
Here we disclose that diethylzinc also promotes the nickel-catalyzed homoallylation regio- and stereoselectively. This Et₂Zn/Ni combination is particularly effective for the homoallylation of saturated aldehydes and ketones, which is either reluctant or entirely unsuccessful with the previously reported Et₃B/Ni combination; hence, these two methods complement each other.

To clarify the scope of the Et₃B/Ni catalytic system, we examined the reaction of carbonyl compounds other than benzaldehyde with isoprene as the 1,3-diene (Table 1). The reaction was successful for aromatic and unsaturated aldehydes and provided 1,3-*anti*-**2** with excellent regio- and stereoselectivities [Table 1, entries 2 and 3; Eq. (b)]; however, it was only moderately successful for saturated aldehydes

Table 1. Nickel-catalyzed homoallylation of aldehydes and ketones with isoprene with promotion by diethylzinc or triethylborane.^[a]

Entry	Substrate	Product	Et ₂ Zn		Et ₃ B	
			time [h]	yield [%] (<i>syn:anti</i>) ^[b]	time [h]	yield [%] (<i>syn:anti</i>) ^[b]
1	PhCHO		4	2a : 63 (1:15); 3a : 16 ^[c]	35	2a : 90 (1:15); 3a : 0 ^[c]
2			1	2b : 66 (1:3); 3b : 3 ^[c]	22	2b : 77 (1: > 20); 3b : 0 ^[c]
3	Ph-CH=CH-CHO		0.5	2c : 0; 3c : 28 ^[c]	70	2c : 81 (1: > 20); 3c : 0 ^[c]
4	Ph-CH ₂ -CH ₂ -CHO		1 ^[d]	2d : 73 (1:15)	28	2d : 48
5			0.5	2e : 83 (1: > 20)	10	2e : 28
6	<i>t</i> BuCHO		1	2f : 66 (1:15)	48	2f : 16
7			1	4a , 5a : 69 (5.3:1)	25	4a , 5a : 0
8			1	4b : 61; 5b : 11	46	4b : 0; 5b : 0

[a] A mixture of [Ni(acac)₂] (0.1 mmol), isoprene (4 mmol), aldehyde or ketone (1 mmol), and Et₂Zn (2.4 mmol, 1M in hexane) or Et₃B (2.4 mmol, 1M in hexane) in dry THF (5 mL) was stirred at room temperature under N₂. [b] Yields refer to isolated, spectroscopically homogeneous materials. All products were characterized by ¹H (400 MHz), ¹³C NMR (100 MHz), and IR spectroscopy, high-resolution mass spectrometry, and/or elemental analyses. The *syn* and *anti* isomers were not separated; the ratios were determined by GLC and ¹H and/or ¹³C NMR spectroscopy. [c] **3a**: 1-Phenylpropan-1-ol; **3b**: 1-(2-furyl)propan-1-ol; **3c**: 3-phenylpentanal. [d] After addition of Et₂Zn to a mixture of [Ni(acac)₂], isoprene, and dihydrocinnamaldehyde at 0 °C, the mixture was stirred at room temperature for 1 h.

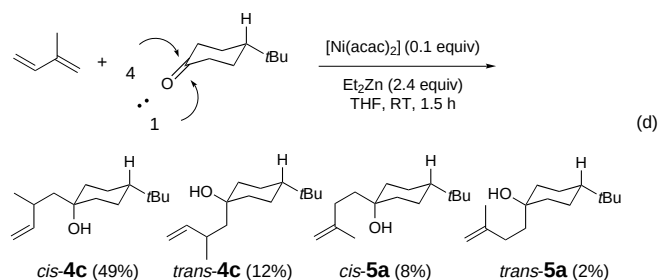
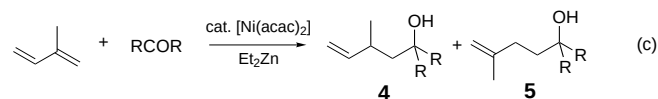


regio- and stereoselectivities. 2-Substituted 1,3-dienes react at the C1 position to provide 1,3-*anti*-**1**, and 1-substituted 1,3-dienes furnish either 1,2-*syn*-**1** (from *Z* dienes) or 1,2-*anti*-**1** (from *E* dienes) selectively.

(entries 4–6). The yields of isolated **2d–f** decreased with increasing steric hindrance at the carbonyl group. Ketones were entirely unreactive with the Et₃B/Ni catalyst system, and the expected products were not obtained (entries 7 and 8).

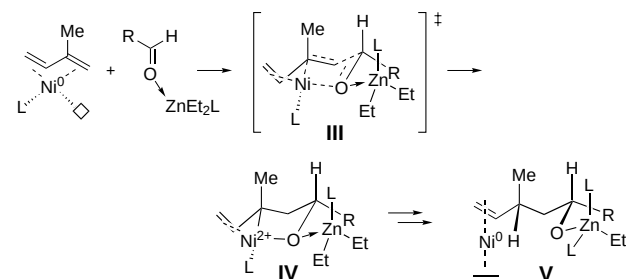
As shown in entries 1 and 2 of Table 1, the homoallylation of aromatic aldehydes with the $\text{Et}_2\text{Zn}/\text{Ni}$ system is plagued with the ethylation of the aldehydes, which leads to diminished yields of the desired products **2**. Apparently, the nickel catalyst takes part in the ethylation reaction; in the absence of the catalyst, neither ethylation nor homoallylation takes place. The reaction of cinnamaldehyde gave a complex mixture of products, of which only the conjugate addition product 3-phenylpentanal (**3c**) was identified (entry 3).

In contrast to these results, the $\text{Et}_2\text{Zn}/\text{Ni}$ system proved to be advantageous for reactions with saturated aldehydes and ketones. These reactions are completed within 1 h at room temperature and provide the homoallylation products in reasonable yields (entries 4–8). Interestingly, in these reactions no ethylation products are formed. For the reactions with alkyl-substituted aldehydes, 1,3-*anti* isomers **2d–f** were obtained with excellent selectivities (entries 4–6). In the reaction with ketones [entries 7 and 8; Eq. (c)], partial loss of regioselectivity is observed and mixtures of **4** (the C1 addition product) and **5** (the C4 addition product) were obtained in a



ratio of 5:1 to 6:1. Strong preference for equatorial attack over axial attack (ca. 4:1), as was observed for 4-*tert*-butylcyclohexanone [Eq. (d)], suggests that a bulky species participates in nucleophilic addition to the carbonyl group.^[7]

Scheme 2 presents our proposed mechanism for the homoallylation of aldehydes with the $\text{Et}_2\text{Zn}/\text{Ni}$ catalyst system. The *s-trans*-isoprenenickel(0) complex^[8] selectively reacts at the



Scheme 2.

C1 position, which bears the highest electron density, and the aldehyde carbonyl group is activated by coordination to Et_2Zn . In the cyclic transition state **III**, the aldehyde may be

arranged in such a way that the oxygen atom is placed in the vacant site of the nickel(0) complex (symbolized as $\diamond$) and the substituent R in a quasiequatorial position so as to avoid a quasi-1,3-diaxial repulsion that might result from an alternative orientation of the aldehyde. An ethyl group of the resulting 5-vinyl-2-oxa-1-nickelacyclopentane intermediate **IV** migrates from the zinc(II) to the nickel(II) center. β -Hydrogen elimination then delivers the hydrogen atom to the allylic position that is bound to the nickel center with retention of configuration. Reductive elimination of nickel(0) finally produces the Ni^0 complex of ethylene and 1,3-*anti*-**2** (**V**).^[9]

In the reactions with ketones, a 1,3-diaxial repulsion is inevitable in a transition state of type **III**. Accordingly, a sterically less demanding C4 addition of isoprene may compete with C1 addition and give a mixture of **4** and **5**.

In conclusion, we have demonstrated that both the $\text{Et}_2\text{Zn}/[\text{Ni}(\text{acac})_2]$ and $\text{Et}_3\text{B}/[\text{Ni}(\text{acac})_2]$ catalysts promote the homoallylation of carbonyl compounds. The former is particularly effective for reactions of saturated aldehydes and ketones, while the latter is advantageous for the homoallylation of aromatic and unsaturated aldehydes. Hence, these two systems complement each other and enable the successful homoallylation of a wide variety of aldehydes and ketones. With both catalytic systems, isoprene reacts with aldehydes to provide 1,3-*anti*-isomers **2** with excellent selectivity.

Experimental Section

2e: To a homogeneous solution of $[\text{Ni}(\text{acac})_2]$ (25.6 mg, 0.1 mmol) in dry THF (5 mL) were successively added isoprene (400 μL , 4 mmol), cyclohexanecarbaldehyde (112.2 mg, 1 mmol), and Et_2Zn (2.4 mL, 2.4 mmol in hexane). The mixture was stirred at room temperature for 30 min under N_2 and then quenched by addition of 2 M HCl (3 mL). The mixture was extracted with ethyl acetate (2×20 mL), and the organic extracts were combined, washed with saturated NaHCO_3 , dried over MgSO_4 , and concentrated in vacuo. The residue was purified by column chromatography on silica gel with hexane/ethyl acetate (16/1) to give **2e** (151 mg, 83 %). R_f = 0.58 (hexane/ethyl acetate 2/1); GLC retention time: 21.6 min (1,3-*syn*-**2e**: 22.1 min), Thermo-1000 (Shimadzu), initial T = 80 °C (8 min), heating rate 8 °C min⁻¹, final T = 240 °C, flow rate 1 mL s⁻¹, He); IR (neat): $\tilde{\nu}$ = 3340 (s), 1060 cm⁻¹ (m); ¹H NMR (400 MHz, CDCl_3): δ = 1.01 (d, J = 6.6 Hz, 3H), 1.03–1.36 (m, 7H), 1.42 (m, 1H, coalesces to dd, J = 7.7, 14.1 Hz on irradiation at δ = 3.47), 1.46 (m, 1H, coalesces to dd, J = 6.6, 14.1 Hz on irradiation at δ = 3.47), 1.57 (brs, 1H), 1.61–1.69 (m, 2H), 1.70–1.81 (m, 2H), 2.34 (m, 1H, coalesces to dt, J = 6.6, 7.7 Hz on irradiation at δ = 1.01), 3.47 (m, 1H), 4.94 (br d, J = 10.3 Hz, 1H), 5.04 (br d, J = 17.4 Hz, 1H), 5.81 (ddd, J = 7.7, 10.3, 17.4 Hz, 1H); ¹³C NMR (100 MHz, CDCl_3): δ = 19.9, 26.3, 26.4, 26.6, 27.6, 29.3, 35.4, 41.3, 44.0, 74.5, 112.6, 145.5 (1,3-*syn*-**2e**: δ = 21.5, 26.3, 26.4, 26.6, 27.9, 29.1, 34.9, 41.2, 44.2, 73.8, 113.5, 144.2). Satisfactory elemental analysis.

Received: July 20, 1998 [Z12176IE]

German version: *Angew. Chem.* **1999**, *111*, 410–413

Keywords: aldehydes • alkylations • ketones • nickel • zinc

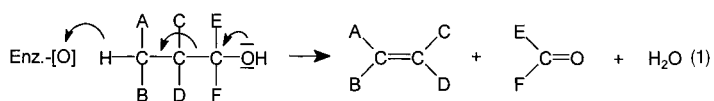
- [1] Y. Yamamoto, A. Asao, *Chem. Rev.* **1993**, *93*, 2207–2293.
- [2] a) J. Montgomery, E. Oblinger, A. V. Savchenko, *J. Am. Chem. Soc.* **1997**, *119*, 4911–4920; b) H. Nakamura, H. Iwami, Y. Yamamoto, *J. Am. Chem. Soc.* **1996**, *118*, 6641–6647, and references therein.
- [3] a) H. Yasuda, K. Tatsumi, A. Nakamura, *Acc. Chem. Res.* **1985**, *18*, 120–126; b) G. Erker, K. Engel, J. L. Atwood, W. E. Hunter, *Angew. Chem.* **1983**, *95*, 506–507; *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 494–

- 495; c) G. Erker, U. Dorf, *Angew. Chem.* **1983**, 95, 800; *Angew. Chem. Int. Ed. Engl.* **1983**, 22, 777–778.
- [4] For NiH-mediated stoichiometric homoallylation of carbonyl compounds with 1,3-dienes, see a) Y. Sato, M. Takimoto, M. Mori, *Synlett* **1998**, 734–736, and references therein; for transition metal catalyzed allylation with 1,3-dienes, see b) M. Takimoto, Y. Hiraga, Y. Sato, M. Mori, *Tetrahedron Lett.* **1998**, 39, 4543–4546, and references therein; c) K. Kitayama, H. Tsuji, Y. Uozumi, T. Hayashi, *Tetrahedron Lett.* **1996**, 37, 4169–4172; d) Y. Gao, H. Urabe, F. Sato, *J. Org. Chem.* **1994**, 59, 5521–5523.
- [5] A similar electron relay was suggested for the nickel(0)-catalyzed reductive coupling of aldehydes and alkynes to give allylic alcohols: E. Oblinger, J. Montgomery, *J. Am. Chem. Soc.* **1997**, 119, 9065–9066.
- [6] M. Kimura, A. Ezoe, K. Shibata, Y. Tamaru, *J. Am. Chem. Soc.* **1998**, 120, 4033–4034.
- [7] E. L. Eliel, S. H. Wilen, *Stereochemistry of Organic Compounds*, Wiley, New York, **1994**, p. 735.
- [8] Since the cyclic dienes 1,3-cyclohexadiene and 1,3-cyclooctadiene give intractable mixtures of products, the *s-trans*-dienenickel(0) complex is assumed to be a reactive species.
- [9] 5-Vinyl-2-oxa-1-palladacyclopentanes, the palladium analogues of **IV**, undergo ring opening to give mixtures of dienes and carbonyl compounds, the formal reverse of the present reaction: H. Harayama, T. Kuroki, M. Kimura, S. Tanaka, Y. Tamaru, *Angew. Chem.* **1997**, 109, 2449–2451; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 2352–2354.

Biosynthesis of Psoralen: Mechanism of a Cytochrome P450 Catalyzed Oxidative Bond Cleavage

Volker Stanjek, Martin Miksch, Patricia Lueer, Ulrich Matern, and Wilhelm Boland*

The oxidative cleavage of C–C bonds that leads to olefins and a carbonyl fragment is a common transformation in secondary metabolism and is generally catalyzed by enzymes requiring molecular oxygen as a cofactor. Typical examples are given by the formation of homo- and norterpene from isoprenoid precursors or by the biosynthesis of 1-alkenes from fatty acids. In general, the resulting unsaturated products are metabolites of precursors that already carry an oxygen atom [Eq. (1); Enz. = enzyme].^[1] Such transformations have been

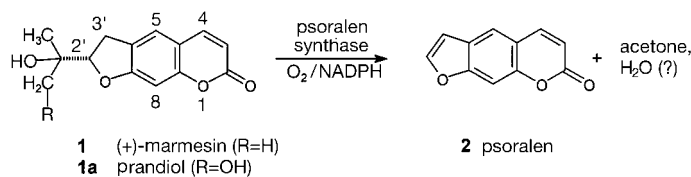


well studied for steroids, where angular methyl groups are oxidatively removed with concomitant introduction of a double bond into the carbon skeleton.^[2] The reactions are

[*] Prof. Dr. W. Boland, Dr. V. Stanjek, Dr. M. Miksch
Max-Planck-Institut für Chemische Ökologie
Tatzendpromenade 1a, D-07745 Jena (Germany)
Fax: (+49) 3641-643670
E-mail: boland@ice.mpg.de
P. Lueer, Prof. Dr. U. Matern
Institut für Pharmazeutische Biologie
Deutschhausstrasse 17A, D-35037 Marburg (Germany)

catalyzed by enzymes belonging to the large family of cytochrome P450. Specific enzymes endowed with multiple catalytic activities catalyze all required transformations, namely, 1) the functionalization of the unactivated methyl group to an alcohol, 2) the subsequent oxidation to an aldehyde, and 3) the actual oxidative bond cleavage generating the unsaturated nor-steroid and formic acid.^[3–6]

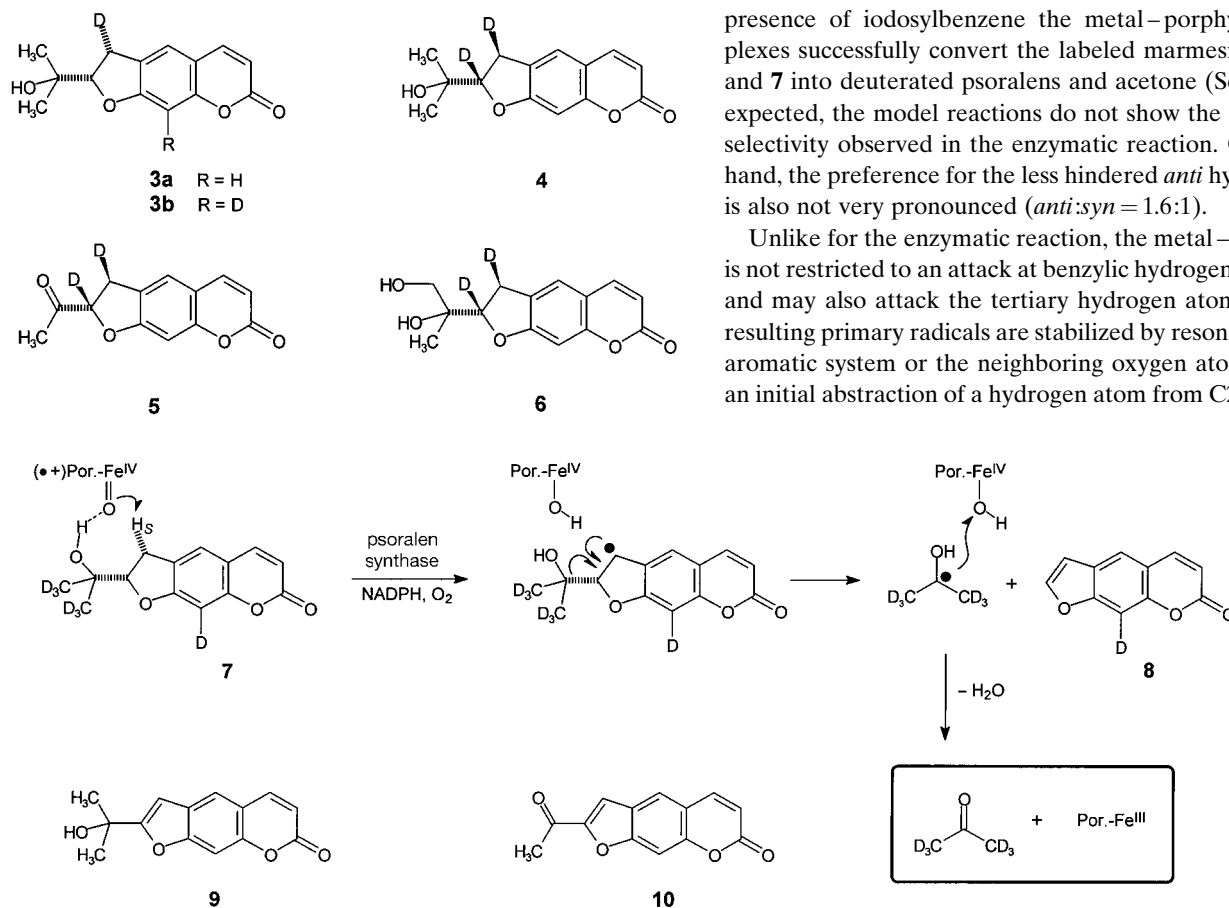
It is as yet unknown, whether or not this sequential degradation is representative for other oxidative bond cleavage reactions that lead to unsaturated natural products. For example, the dealkylation of (+)-marmesin (**1**) to the phototoxic furocoumarin psoralen (**2**) is achieved by the psoralen synthase (Scheme 1), an enzyme that also belongs to



Scheme 1. Cytochrome P450 catalyzed dealkylation of **1**.

the large family of cytochrome P450 catalysts.^[7] This dealkylation is of central importance for the biosynthesis of all other linear furocoumarins, since the resulting psoralen (**2**) serves as an intermediate en route to the other members of this family.^[8] Linear and angular furocoumarins are widespread in the plant kingdom, especially in the order of the Apiaceae, where they are produced in response to insect injury and infection.^[9] The existence of a natural product such as the diol **1a** (prandiol)^[10, 11] could indeed suggest a stepwise degradation of marmesin to psoralen that is analogous to the dealkylation of steroids. Here we disclose that the dealkylation of marmesin indeed does not involve a sequential oxidative degradation of the 2-hydroxy-2-propyl substituent, but proceeds in a single step to yield equimolar amounts of psoralen and acetone. The previously postulated, but now for the first time proven, one-step degradation^[12] may be representative for other oxidative transformations that lead to unsaturated nor- and seco-compounds in nature.

Unambiguous evidence for the one-step dealkylation and details of the stereochemical course of the reaction follow from transformations of the specifically deuterated precursors **3–7**^[13] by microsomes from elicited cell cultures of *Ammi majus* and subsequent analysis of the resulting products.^[14] Thus, if the microsomes are treated with [²H₇]marmesin (**7**) in the presence of NADPH and oxygen,^[7] equimolar amounts of [8-²H₁]psoralen (**8**) and [2H₆]acetone are formed (Scheme 2). Both products can be identified and quantified by GC-MS. Product **8** is readily distinguished from traces of natural [8-¹H]psoralen because of a remaining deuterium label at C8. About 20–40 % of the resulting psoralen are further oxidized to bergaptol (5-hydroxypsoralen).^[7] [2H₆]Acetone is unambiguously identified and quantified after derivatization to the corresponding imine with pentafluorobenzylhydroxylamine.^[15] With respect to the conservation of all six hydrogen isotopes in the C₃ fragment, an intermediate functionalization of the 2-hydroxy-2-propyl substituent is excluded (see **1a**).



Scheme 2. Psoralen synthase catalyzed dealkylation of **7**, mechanism, and products **9** and **10** from the model reactions with tetraphenylporphyrinato complexes of Fe^{III} or Mn^{III}. Por. = porphyrinato.

The stereochemical course of the oxidative bond cleavage was determined from the transformations of the metabolic probes **3a/3b** and **4**, which are labeled by deuterium atoms in *syn* or *anti* orientations relative to the 2-hydroxy-2-propyl substituent.^[13] In both cases an exclusive abstraction of the hydrogen isotope *syn* to the C₃ substituent is observed. While the transformation of **3a** proceeds with loss of the deuterium atom from C3' to yield unlabeled psoralen, **4** is analogously converted into a product with retention of the deuterium atoms at C3' and C8. Following administration of equimolar amounts of the precursor pairs **3a** and **4** or **3b** and **1**, the substrates **1** and **4** possessing a hydrogen atom in *syn* orientation relative to the C₃ substituent are preferably transformed. From the intensity distribution of the molecular ions of the isotopomeric psoralens, a kinetic isotope effect of $k_H/k_D \approx 4$ ($T = 20^\circ\text{C}$) can be calculated.^[16]

Concerning the substrate tolerance of the psoralen synthase, it is interesting to note that also the ketone **5** is deacylated by the microsomal enzyme to give [2',3'-²H₂]psoralen. In contrast, the diol **6** ([²H₂]prandiol)^[10] is not transformed. Since the stereochemistry of the deacylation of **5** is in line with the findings for the dealkylation of marmesin, both reactions are probably catalyzed by the same enzyme.

The enzymatic dealkylation of marmesin can be reproduced in a biomimetic fashion by tetraphenylporphyrinato complexes of Fe^{III}^[17] or Mn^{III},^[18] both of which can act as chemical models for cytochrome P450 enzymes. In the

presence of iodosylbenzene the metal–porphyrinato complexes successfully convert the labeled marmesins **3a**, **3b**, **4**, and **7** into deuterated psoralens and acetone (Scheme 2). As expected, the model reactions do not show the exclusive *syn* selectivity observed in the enzymatic reaction. On the other hand, the preference for the less hindered *anti* hydrogen atom is also not very pronounced (*anti:syn* = 1.6:1).

Unlike for the enzymatic reaction, the metal–oxo complex is not restricted to an attack at benzylic hydrogen atoms at C3' and may also attack the tertiary hydrogen atom at C2'. The resulting primary radicals are stabilized by resonance with the aromatic system or the neighboring oxygen atom. Following an initial abstraction of a hydrogen atom from C2', β-cleavage

will yield exclusively didehydromarmesin (**9**), while a primary radical formed on C3' can yield **2** and **9**. Accordingly, the oxidative degradation of marmesin by the active porphyrinato complexes furnishes the products **2** and **9** in approximately equal amounts. The oxidation of the ketone **5** yields acetylpsoralen (**10**) together with a very small amount of **2**, reflecting the pronounced resonance stabilization of the initial radical at C2' of **5**.^[19]

In agreement with the findings from the enzymatic reactions and the model reactions, the dealkylation of marmesin is assumed to proceed as outlined in Scheme 2. First, a reactive porphyrinyl-Fe^{IV}-O radical cation attacks C3'-H_s of the substrate **7**, leading to a benzylic radical that decays by β-cleavage into [8-²H]psoralen (**8**) and a 2-hydroxy-2-propyl radical. Following rapid "oxygen rebound"^[20] to the neighboring porphyrinyl-Fe^{IV}-OH center, formally the hydrate of [²H₆]acetone is produced. By analogy, the ketone **5** may be deacylated to yield psoralen and acetic acid via an intermediate acyl radical. The above results disprove mechanistic alternatives assuming hydroxylation and subsequent formation of a carbenium ion at C3', as proposed by Birch et al.^[21] Hydroxylated intermediates were observed neither during the enzymatic transformations nor in the course of the model reactions. Furthermore, the heterolytic fragmentation of a hypothetical 3'-hydroxymarmesin should proceed as an *anti* elimination. Instead, the almost exclusive *syn* elimination of an alkoxy or acyl residue together with a vicinal hydrogen

atom^[1, 4] is in good agreement with the radical abstraction and recombination process outlined in Scheme 2.^[20] In the course of the disproportionation of the benzylic radical (β -cleavage) into the olefin, the ensuing alkoxy or acyloxy radical will immediately recombine with the neighboring porphyrinyl-Fe^{IV}-OH center to avoid formation and escape of free radicals.

The oxidative bond cleavage reaction described here may also be representative for ring-cleavage reactions in the biosynthesis of seco compounds that are, as yet, not systematically addressed on mechanistic grounds. For example, the transformation of loganin into secologanin, a central step in the biosynthesis of indole and chinchona alkaloids, apparently proceeds without intermediates and is catalyzed by a cytochrome P450.^[22] Comparable reactions take place in the oxidative cleavage of ring A of the triterpenoid β -amyrin to provide nyctanthic acid^[23] or the oxidative degradation of acyclic geranylacetone to 4,8-dimethyl-1,3,7-nonatriene. The latter transformation is exceptionally widespread in higher plants in response to herbivory.^[24] The recent finding that the acyclic geranylacetone is degraded by *syn* elimination^[24, 25] strongly supports the significance of this unique stereochemical feature of cytochrome P450 catalyzed oxidative bond cleavage reactions.

Experimental Section

Enzymatic conversions were performed with microsomes from elicited cell cultures of *Ammi majus*.^[14] The labeled marmesin derivatives^[13] (40.0 nmol) were dissolved in Tris/HCl buffer (25.0 μ L, 50.0 mM, pH 7.5) containing EDTA (1.0 mM) and NADPH (10.0 μ L of a 10.0 mM solution in the same buffer), and a suspension of the microsomes (20.0 μ L) was added. After 30 min at 20 °C the reaction products were isolated by solid-phase microextraction (SPME, fiber coated with polymethylsiloxane).^[26] Equilibrium was reached after 30 min of extraction, and the products were then evaporated (250 °C) from the fiber in the injection port of the GC-MS instrument (GC-MS: Fisons MD 800, column: SE 30, 10 m $\times$ 0.31 mm, carrier gas: He, temperature program: 50 °C (2 min) to 280 °C at 20 °C min⁻¹, interface: 270 °C, mass range: 35–350 Da sec⁻¹). In each experiment about 5% of the substrates **3a**, **3b**, **4**, or **7** were transformed. To facilitate the analysis of acetone and [²H₆]acetone, the reaction mixture was treated prior to extraction with 5.0 μ L of a 0.1 mM solution of pentafluorobenzylhydroxylamine in Tris/HCl buffer.^[15] Formation of the amine was complete after 30 min. Following derivatization, acetone and psoralen could be quantified by GC-MS. Calibration was achieved with authentic references prepared from acetone and [²H₆]acetone.

In the model reactions solutions of the metalloporphyrinato complex (Fe³⁺ or Mn³⁺, 1.4 mmol) and the deuterated ($\pm$)-marmesins **3a**, **3b**, **4**, and **7** (8.1 mmol) in dichloromethane (3.0 mL) were stirred with iodosylbenzene (22.0 mmol) at 4 °C for 8 h. The products were analyzed by GC-MS without further workup. About 10% of the substrate was transformed. The carbonyl fragment was detected as described above as the pentafluorobenzylhydroxylamine.^[15]

Received: May 9, 1997

Revised version: October 7, 1998 [Z104261E]

German version: *Angew. Chem.* **1999**, *111*, 413–415

Keywords: biosynthesis • cytochrome • eliminations • furocoumarins • porphyrinoids

[1] W. Boland, *Pure Appl. Chem.* **1993**, *65*, 1133–1142.

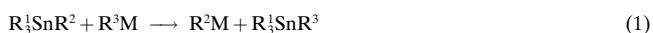
[2] a) M. Akhtar, J. N. Wright, *Nat. Prod. Rep.* **1991**, 527–551, and references therein.; b) “Bioorganic Chemistry, Models and Applications”: W.-D. Woggon in *Top. Curr. Chem.* **1996**, *184*, 39–96, and references therein.

- [3] A. Z. Shyadehi, D. C. Lamb, S. L. Kelly, D. E. Kelly, W.-H. Schunck, J. N. Wright, D. Corina, M. Akhtar, *J. Biol. Chem.* **1996**, *271*, 12445–12450, and references therein.
- [4] M. Akhtar, J. N. Wright, A. Z. Shyadehi, P. Robichaud, *Pure Appl. Chem.* **1994**, *66*, 2387–2390.
- [5] P. Lee-Robichaud, A. Z. Shyadehi, J. N. Wright, M. E. Akhtar, M. Akhtar, *Biochemistry* **1995**, *34*, 14104–14113.
- [6] M. Akhtar, D. Corina, S. Miller, A. Z. Shyadehi, J. N. Wright, *Biochemistry* **1994**, *33*, 4410–4418, and references therein.
- [7] H. Wendorff, U. Matern, *Eur. J. Biochem.* **1986**, *161*, 391–398.
- [8] K. D. Hauffe, K. Hahlbrock, D. Scheel, *Z. Naturforsch. C* **1986**, *41*, 228–239.
- [9] R. D. H. Murray, J. Méndez, S. A. Brown, *The Natural Coumarins*, Wiley, Chichester, **1982**.
- [10] A. Z. Abyshev, I. V. Brodskii, *Khim. Prir. Soedin* **1974**, *5*, 574–575.
- [11] S. K. Garg, N. D. Sharma, S. R. Gupta, *Planta Med.* **1981**, *43*, 306–308.
- [12] T. Hakamatsuka, M. F. Hashim, Y. Ebizuka, U. Sankawa, *Tetrahedron* **1991**, *47*, 5969–5978.
- [13] V. Stanjek, M. Miksch, W. Boland, *Tetrahedron* **1997**, *53*, 17699–17710.
- [14] D. Hamerski, R. C. Beier, R. E. Kneusel, U. Matern, K. Himmelsbach, *Phytochemistry* **1990**, *29*, 1137–1142.
- [15] D. Cancilla, S. S. Que Hee, *J. Chromatogr.* **1992**, *627*, 1–16.
- [16] A. Sorokin, A. Robert, B. Meunier, *J. Am. Chem. Soc.* **1993**, *115*, 7293–7299.
- [17] T. J. McMurry, J. T. Groves in *Cytochrome P-450, Structure, Mechanism, and Biochemistry* (Ed.: P. R. Ortiz de Montellano). Plenum, New York **1986**, 1–28.
- [18] P. W. White, *Bioorg. Chem.* **1990**, *18*, 440–456.
- [19] F. G. Bordwell, G.-Z. Ji, X. Zhang, *J. Org. Chem.* **1991**, *56*, 5254–5256.
- [20] J. T. Groves, G. A. McClusky, *J. Am. Chem. Soc.* **1976**, *98*, 859–861.
- [21] a) A. J. Birch, M. Maung, A. Pelter, *Aust. J. Chem.* **1969**, *22*, 1923–1932; b) C. F. Neville, M. F. Grundon, V. N. Ramachandran, G. Reisch, J. Reisch, *J. Chem. Soc. Perkin Trans. 1* **1991**, 2261–2268.
- [22] S. Damtoft, H. Franzyk, S. R. Jensen, *Phytochemistry* **1995**, *38*, 615–624.
- [23] G. H. Witham, *Proc. Chem. Soc.* **1960**, 2016–2020.
- [24] a) W. Boland, Z. Feng, J. Donath, A. Gäbler, *Naturwissenschaften*, **1992**, *79*, 368–371; b) W. Boland, A. Gäbler, M. Gilbert, Z. Feng, *Tetrahedron* **1998**, *54*, 14725–14736.
- [25] W. Boland, Z. Feng, J. Donath, in *Flavor Precursors* (Ed.: P. Schreier), Allured, Wheaton, IL, **1993**, pp. 123–136.
- [26] J. Pawliszyn, M. J. Yang, Z. Zhang, *Z. Anal. Chem.* **1994**, *66*, 844–853.

Transmetalation of Tetraalkynyltin Compounds with Grignard Reagents: Access to Mono- and Dialkyltin Products

Pascale Jaumier, Bernard Jousseume,* and Mohammed Lahcini

The transmetalation of organotin compounds with lithium reagents^[1] provides access to allyl-,^[2] vinyl-,^[2] and α -heteroalkyllithium reagents,^[3] especially for applications in organic synthesis.^[4] Recent examples of other such transmetalation reactions involved palladium,^[5] copper,^[6] and boron compounds.^[7] In these reactions [Eq. (1)], the organic group that

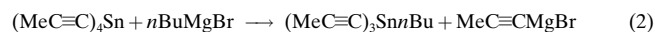


[*] Dr. B. Jousseume, Dr. P. Jaumier, Dr. M. Lahcini
Laboratoire de Chimie Organique et Organométallique
UMR 5802, Université Bordeaux I
351 Cours de la Libération, F-33405 Talence Cedex (France)
Fax: (+33) 5-56-84-6994
E-mail: b.jousseume@lcoo.u-bordeaux.fr

is transferred from tin to the other metal is the important part of the molecule, whereas the tetraorganotin compound (or the triorganotin halide in the case of the Stille reaction^[5]) is a secondary product.

On the other hand, there is no general route to monoorganotin compounds from an organometallic derivative and an inorganic tin compound such as tin tetrachloride. Alkylation or arylation leads to mixtures of mono-, di-, tri-, and tetraorganotin compounds, even when only one equivalent of alkylating (or arylating) agent is used.^[8] This is in contrast to silicon,^[9] for which monoalkylation (or arylation) is easy. Monoorganotin compounds are usually prepared from unsymmetrical or symmetrical tetraorganotin compounds by electrophilic cleavage of three reactive organic groups with halogens, protic acids, or tin tetrahalides. Some other methods are limited to specific substrates, mainly those with a β - or γ -carbonyl substituent.^[10] In our studies on trichloroorganotin compounds in which the organic moiety bears a polymerizable group,^[11] a direct route to monoorganotin compounds that avoids the use of hydrochloric acid or tin tetrachloride, which can react with the polymerizable group, was essential.

Monotransmetalation of tetraaryl-, tetraallyl-, or tetraalkynyltin with one equivalent of butyllithium in diethyl ether or THF at different temperatures did not give any selective reactions. Mixtures of mono-, di-, tri-, and tetrabutyltin were invariably obtained. The use of Grignard reagents was more successful. When tetrapropyn-1-yltin was treated with one equivalent of *n*-butylmagnesium bromide in diethyl ether, *n*-butyltripropyn-1-yltin was obtained [Eq. (2)] in 68 % yield with a purity of 95 % (Table 1). It was purified by chromatography on dry Florisil or by recrystallization.^[12, 13]



The reaction was extended to methyl-, isopropyl-, and *tert*-butylmagnesium halides with equal success (Table 1). Iodides reacted more slowly than the corresponding chlorides and bromides, and the highest selectivities and yields were obtained with tetrakis(phenylethynyl)tin. Selectivity was equally good in diethyl ether and THF, but THF induced slightly higher reaction rates, as is observed for lithium reagents.^[14] In THF, higher reaction temperatures allowed some more reluctant transmetalations, especially with secondary or tertiary organomagnesium compounds, to be performed.

Moreover, the reaction was successfully extended to two successive transmetalations to give dialkyltin dialkynides when two equivalents of Grignard reagent were used [Eq. (3), Table 1]. Thus, Grignard reagents are able to



discriminate between tetraalkynyltin, alkyltrialkynyltin, and dialkyldialkynyltin compounds; the electronic effects of the alkyl groups probably induce a sharp difference in the electrophilic properties of the tin atom with respect to the nucleophilic organomagnesium compounds. In contrast, phenyl and allyl groups, which have acceptor properties, do not lead to any selectivity: phenylmagnesium bromide and

Table 1. Alkyltrialkynyl- and dialkyldialkynyltin compounds obtained from tetraalkynyltin starting materials.

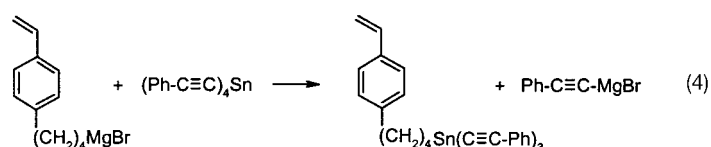
Starting material ^[a]	Product	Solvent	Purity [%] ^[b]	Yield [%]
(MeC≡C) ₄ Sn	(MeC≡C) ₃ SnMe ^[21]	Et ₂ O	85	41
(MeC≡C) ₄ Sn	(MeC≡C) ₃ Sn <i>n</i> Bu ^[21]	Et ₂ O	95	68
(MeC≡C) ₄ Sn	(MeC≡C) ₃ Sn <i>n</i> Pr	Et ₂ O	88	70
(BuC≡C) ₄ Sn	(BuC≡C) ₃ Sn <i>n</i> Bu ^[22]	Et ₂ O	92	43
(PhC≡C) ₄ Sn	(PhC≡C) ₃ SnMe ^[23]	Et ₂ O	100	87
(PhC≡C) ₄ Sn	(PhC≡C) ₃ Sn <i>n</i> Bu ^[24]	Et ₂ O	100	75
(PhC≡C) ₄ Sn	(PhC≡C) ₃ Sn <i>n</i> Pr	THF	95	89
(PhC≡C) ₄ Sn	(PhC≡C) ₃ Sn <i>n</i> Bu	THF	100	82
(MeC≡C) ₄ Sn	(MeC≡C) ₂ Sn <i>n</i> Bu ₂ ^[25]	Et ₂ O	93	70
(BuC≡C) ₄ Sn	(BuC≡C) ₂ Sn <i>n</i> Bu ₂ ^[22]	Et ₂ O	85	38
(PhC≡C) ₄ Sn	(PhC≡C) ₂ Sn <i>n</i> Pr ₂	THF	86	75

[a] Consumption of the starting material was in the range of 95–100 %.

[b] Percentage monoalkylation or dialkylation. By-products were dialkyltin compounds in monoalkylation reactions and monoalkylation compounds in dialkylation reactions.

tetrakis(phenylethynyl)tin gave mono- and diarylation products in equal amounts, and allylmagnesium bromide and tetrakis(phenylethynyl)tin furnished a mixture of mono-, di-, and triallyl derivatives.

From a practical point of view, this method is particularly interesting for the preparation of monoorganotin compounds when the corresponding trichlorides are unstable, as in the case, for instance, of *tert*-butyltrichlorotin,^[15] which decomposes to tin dichloride and *tert*-butyl chloride at room temperature, and (ω -styrylalkyl)trichlorotin compounds, which spontaneously oligomerize as soon as they are formed.^[16] Labile tin–alkynyl bonds allow the transformation of tetraorganotin compounds into stable but reactive monoorganotin compounds that can undergo further reactions (alkylation, reduction, halogenation, etc.) as trialkoxides or oxides after reaction with alcohols or water.^[17] Among these compounds, (ω -styrylalkyl)trialkynyltin compounds [Eq. (4)],



which are easily transformed into the corresponding oxides, are good candidates for the preparation of new tin-based^[18] organic–inorganic hybrid materials.

The secondary and tertiary alkyltrialkynyltin compounds are as reactive as the primary compounds. Isopropyltriphenylethynyltin gave the corresponding trichloride^[19] on treatment with HCl/MeOH, and hydrolysis of *tert*-butyltriphenylethynyltin led to the corresponding oxide.^[20]

Aryl groups are also displaced from tin by Grignard reagents. When one equivalent of tetraphenyltin was treated with four equivalents of methylmagnesium chloride in THF at reflux for 16 h, methyltriphenyltin (54 %) was formed together with dimethyldiphenyltin (6 %); 40 % of the tetraphenyltin remained unchanged. Transmetalation can thus occur with groups that are more strongly bonded to tin than alkynyl

moities. However the reaction is more difficult and less selective.

We have demonstrated that transmetalation of tetraorganotin compounds is not limited to organolithium, -boron, -copper, and palladium compounds, but that it is also possible with Grignard reagents and tetraalkynyltin compounds. In contrast to organolithium reagents, this transmetalation is highly selective and allows the preparation of alkyltrialkynyl and dialkyltrialkynyltin compounds and hence provides a new route to monoalkyltin alkoxides, oxides, and halides which avoids strong electrophilic reagents such as halogens, protic acids, or tin tetrahalides.

Experimental Section

The preparation of 4-(4-styryl)butyltris(phenylethynyl)tin is representative: A solution of tetrakis(phenylethynyl)tin (10 mmol, 5.23 g) in dry diethyl ether (20 mL) and toluene (40 mL) was treated with a ca. 1N solution of bromo(4-(4-styryl)butyl)magnesium in diethyl ether (10 mmol) at -20°C . After warming to room temperature, the solution was heated to reflux for 18 h. Then, water (0.5 mL) was added at -30°C , and the mixture treated with dry magnesium sulfate (5 g). After filtration and evaporation of the solvents under vacuum, rapid chromatography on dry Florisil gave 4-(4-styryl)butyltris(phenylethynyl)tin in 60% yield. M.p. 72°C ; ^1H NMR (250 MHz, CDCl_3): $\delta = 1.42$ (t, 2H, $^3J(\text{H,H}) = 7.2$, $^3J(\text{Sn,H}) = 61$ Hz), 1.62–1.80 (m, 4H), 2.54 (t, 2H, $^3J(\text{H,H}) = 7.2$ Hz), 5.06 (d, 1H, $^3J(\text{H,H}) = 10.9$ Hz), 5.54 (dd, 1H, $^3J(\text{H,H}) = 17.5$), 6.54 (dd, 1H, $^3J(\text{H,H}) = 17.5$, 10.9 Hz), 6.92–7.48 (m, 19H); ^{13}C NMR (62.9 MHz, CDCl_3): $\delta = 14.9$ ($^1J(\text{Sn,C}) = 640$ Hz), 24.5 ($^2J(\text{Sn,C}) = 35$ Hz), 33.9 ($^3J(\text{Sn,C}) = 81$ Hz), 34.7, 84.7 ($^1J(\text{Sn,C}) = 798$ Hz), 110.5 ($^2J(\text{Sn,C}) = 165$ Hz), 113.2, 123.1, 126.7, 129.1, 129.3, 129.4, 132.9, 135.8, 137.4, 142.7; ^{119}Sn NMR (74.6 MHz, CDCl_3): $\delta = -242$; elemental analysis calcd for $\text{C}_{36}\text{H}_{30}\text{Sn}$: C 74.38, H 5.20; found: C 73.6, H 5.1.

Received: July 20, 1998

Revised version: September 16, 1998 [Z12166IE]

German version: *Angew. Chem.* **1999**, *111*, 416–418

Keywords: alkylations • alkynes • Grignard reactions • tin • transmetalations

- [1] D. Seyferth, M. A. Weiner, *J. Org. Chem.* **1959**, *24*, 1395.
- [2] D. Seyferth, M. A. Weiner, *J. Am. Chem. Soc.* **1961**, *83*, 3583.
- [3] D. J. Peterson, *J. Am. Chem. Soc.* **1971**, *93*, 4027.
- [4] M. Pereyre, J. P. Quintard, A. Rahm, *Tin in Organic Synthesis*, Butterworths, London, **1987**; B. Jousseume, M. Pereyre in *Chemistry of Tin* (Ed.: P. J. Smith), 2nd ed., Blackie, Glasgow, **1998**, p. 290; T. Sato in *Comprehensive Organometallic Chemistry II, Vol. 11* (Eds.: G. Wilkinson, F. G. A. Stone, E. W. Abel), Pergamon Press, Oxford, **1995**, p. 355.
- [5] M. Kosugi, Y. Shimizu, T. Migita, *Chem. Lett.* **1977**, 1423; J. K. Stille, *Angew. Chem.* **1986**, *98*, 504. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508; T. N. Mitchell, *Synthesis* **1992**, 803; T. N. Mitchell in *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: F. Diederich, P. J. Stang), WILEY-VCH, Weinheim, **1998**, p. 167; V. Farina, *Pure Appl. Chem.* **1996**, *68*, 73; L. S. Hegedus, *Coord. Chem. Rev.* **1996**, *147*, 443.
- [6] J. R. Behling, K. A. Babiak, J. S. Ng, A. L. Campbell, R. Moretti, M. Koerner, B. H. Lipshutz, *J. Am. Chem. Soc.* **1988**, *110*, 2641.
- [7] M. Enders, A. Krämer, H. Pritzkow, W. Siebert, *Angew. Chem.* **1991**, *103*, 80; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 84; D. A. Singleton, J. P. Martinez, G. M. Ndiip, *J. Org. Chem.* **1992**, *57*, 5768, and references therein.
- [8] W. P. Neumann, *The Organic Chemistry of Tin*, Wiley, London, **1967**, p. 52; R. C. Poller, *The Chemistry of Organotin Compounds*, Logos, London, **1970**, p. 58; H. Schumann, I. Schumann in *Gmelin Handbook of Inorganic Chemistry, Organotin Compounds, Vol. 6* (Ed.: H. Bitterer), Springer, Berlin, **1979**, p. 210; J. L. Wardell in *Chemistry of Tin* (Ed.: P. G. Harrison), Blackie, Glasgow, **1989**, p. 149.
- [9] J. Y. Corey in *The Chemistry of Silicon Compounds* (Eds.: S. Patai, Z. Rappoport), Wiley, London, **1989**, p. 22.
- [10] E. J. Bulten, *J. Organomet. Chem.* **1975**, *97*, 167; E. J. Bulten, H. F. M. Gruter, H. F. Martens, *J. Organomet. Chem.* **1976**, *117*, 329; J. Murphy, R. C. Poller, *J. Organomet. Chem. Lib.* **1979**, *9*, 189; A. Meyer, *Ber. Dtsch. Chem. Ges.* **1885**, *16*, 1442; A. Tchakirian, M. Lesbre, M. Lewinsohn, *Bull. Soc. Chim. Fr.* **1936**, 138; J. G. F. Druce, *J. Chem. Soc.* **1922**, 1859; W. J. Pope, S. Peachy, *J. Chem. Soc.* **1903**, 7; E. J. Corey, T. M. Eckrich, *Tetrahedron Lett.* **1983**, *24*, 163; R. E. Hutton, J. W. Burley, *J. Organomet. Chem.* **1978**, *156*, 369; J. W. Burley, P. Hope, A. G. Mack, *J. Organomet. Chem.* **1984**, *277*, 737; P. G. Harrison, T. J. King, M. A. Healy, *J. Organomet. Chem.* **1979**, *182*, 17; E. J. Bulten, J. W. G. van den Hurk, *J. Organomet. Chem.* **1978**, *162*, 161; I. Ryu, H. Suzuki, S. Murai, N. Sonoda, *Organometallics* **1987**, *6*, 212; H. Nakahira, I. Ryu, M. Ikebe, Y. Oku, A. Ogawa, N. Kambe, N. Sonoda, S. Murai, *J. Org. Chem.* **1992**, *57*, 17; I. Ryu, S. Murai, N. Sonoda, *J. Org. Chem.* **1986**, *51*, 2389; H. Nakahira, I. Ryu, A. Ogawa, N. Kambe, N. Sonoda, *Organometallics* **1990**, *9*, 277; E. Nakamura, J. I. Shimada, I. Kuwajima, *Organometallics* **1985**, *4*, 641; E. Nakamura, I. Kuwajima, *Chem. Lett.* **1983**, 59; E. Fouquet, B. Jousseume, B. Maillard, M. Pereyre, *J. Organomet. Chem.* **1993**, 453, C1.
- [11] B. Jousseume, M. Lahcini, M. C. Rasclé, C. Sanchez, F. Ribot, *Organometallics* **1995**, *14*, 685; B. Jousseume, M. Lahcini, E. Fouquet, B. Barbe, *J. Org. Chem.* **1994**, *59*, 8292; M. Biesemans, R. Willem, S. Damoun, P. Geerlings, M. Lahcini, P. Jaumier, B. Jousseume, *Organometallics* **1996**, *15*, 2237; M. Biesemans, R. Willem, S. Damoun, P. Geerlings, P. Jaumier, B. Jousseume, E. R. T. Tiekink, M. Biesemans, R. Willem, *Organometallics* **1997**, *16*, 5124; M. Biesemans, R. Willem, S. Damoun, P. Geerlings, E. R. T. Tiekink, M. Lahcini, P. Jaumier, B. Jousseume, *Organometallics* **1998**, *17*, 90.
- [12] Ring opening of dimethylstannacyclobutane by methylmagnesium bromide to give 3-(trimethylstannyl)propylmagnesium bromide in low yield^[13] is, to the best of our knowledge, the only previous example of transmetalation of an organotin compound with a Grignard reagent.
- [13] J. W. F. L. Seetz, G. Schat, O. S. Akkerman, F. Bickelhaupt, *J. Am. Chem. Soc.* **1983**, *105*, 3336.
- [14] H. J. Reich, J. P. Borst, M. Coplien, N. H. Phillips, *J. Am. Chem. Soc.* **1992**, *114*, 6577, and references therein.
- [15] D. Haensslen, H. Puff, N. Beckermann, *J. Organomet. Chem.* **1985**, *293*, 191. We are indebted to Professor K. Jurkshat for bringing this publication to our attention.
- [16] M. Lahcini, T. Sessler, B. Jousseume, unpublished results. M. Lahcini, PhD thesis, University Bordeaux 1, **1994**.
- [17] P. Jaumier, B. Jousseume, M. Lahcini, F. Ribot, C. Sanchez, *Chem. Commun.* **1998**, 369.
- [18] F. Ribot, F. Banse, C. Sanchez, M. Lahcini, B. Jousseume, *J. Sol-Gel Sci. Technol.* **1997**, *8*, 529.
- [19] ^1H NMR (250 MHz, CDCl_3): $\delta = 1.53$ (d, 6H, $^3J(\text{Sn,H}) = 233$ Hz), 2.92 (m, 2H, $^2J(\text{Sn,H}) = 144$ Hz); ^{13}C NMR (62.9 MHz, CDCl_3): $\delta = 19.8$ ($^2J(\text{Sn,C}) = 48$ Hz), 41.9 ($^1J(\text{Sn,C}) = 682$ Hz); ^{119}Sn NMR (74.6 MHz, CDCl_3): $\delta = -177$.
- [20] ^1H NMR (250 MHz, CDCl_3): $\delta = 1.33$ (s, 4.5H, $^3J(\text{Sn,H}) = 137$ Hz), 1.52 (s, 4.5H, $^3J(\text{Sn,H}) = 151$ Hz); ^{13}C NMR (62.9 MHz, CDCl_3): $\delta = 30.3$ (1.5C, $^2J(\text{Sn,C}) = 20$ Hz), 31.3 (1.5C, $^2J(\text{Sn,C}) = 21$ Hz), 41.8 (0.5C, $^1J(\text{Sn,C}) = 900$ Hz), 42.7 (0.5C, $^1J(\text{Sn,C}) = 1250$ Hz); ^{119}Sn NMR (74.6 MHz, CDCl_3): $\delta = -336.7$ (0.5Sn), -495.2 (0.5Sn).
- [21] B. Wrackmeyer, G. Kehr, D. Wittinger, *Inorg. Chim. Acta* **1994**, *220*, 161.
- [22] S. D. Ibekwe, M. J. Newlands, *J. Chem. Soc.* **1965**, 4608.
- [23] J. Lorberth, *J. Organomet. Chem.* **1969**, *16*, 327.
- [24] H. Hartmann, H. Wagner, B. Karbstein, M. K. B. El A'ssar, W. Reiss, *Naturwiss. Rundsch.* **1964**, *51*, 216.
- [25] H. F. Reiff, B. R. Laliberte, W. E. Davidsohn, M. C. Henry, *J. Organomet. Chem.* **1968**, *15*, 247.

Synthesis of a Configurationally Stable Three-Legged Piano-Stool Complex**

Bruno Therrien and Thomas R. Ward*

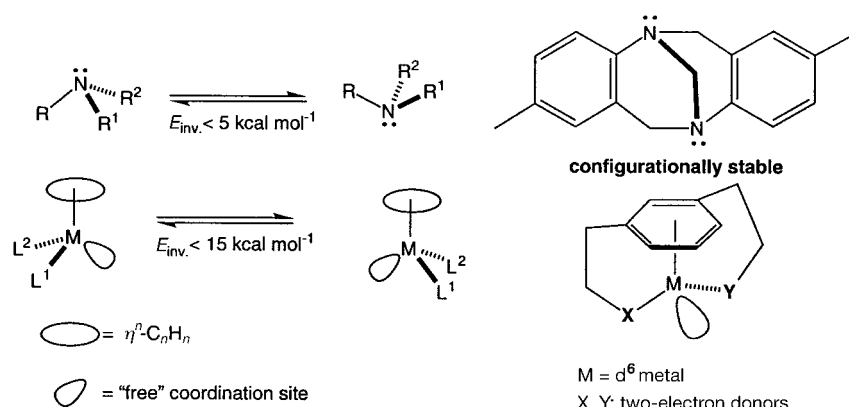
In memory of Vlado Prelog

Metal-based chirality is as old as coordination chemistry itself.^[1, 2] To a great extent, A. Werner derived his coordination theory from stereochemical arguments that eventually led to the proof of octahedral coordination of hexacoordinate metals. Seventy years later, H. Brunner revived the interest for metal-based chirality by initiating a systematic study of piano-stool complexes which are chiral at the metal center.^[3, 4] Compounds of the type $[(\eta^n\text{-C}_n\text{H}_n)\text{ML}^1\text{L}^2\text{L}^3]$ are chiral and have been resolved in many cases. Over the years, a number of groups has focused on applications of enantiopure piano-stool complexes in organic transformations. Several elegant examples of such complexes come from the groups of Brunner,^[4–6] Davies,^[7] Faller,^[8] and Gladysz.^[9] To the best of our knowledge, however, compounds that have metal-based and not ligand-based chirality have only found stoichiometric (and not catalytic) applications in organic chemistry.

Recently, piano-stool complexes with a d^6 electron count have been used as Lewis acid catalysts in C–C bond formations, for example, in Diels–Alder and Mukaiyama reactions.^[10–13] The prospect of using an asymmetric piano-stool complex devoid of ligand-based chirality as a catalyst for such enantioselective transformations is very appealing. This would allow one to address the role of chirality at the metal in enantioselective catalysis.^[14, 15] For this purpose, however, it is imperative to ensure configurational stability of the active catalyst (probably a two-legged piano-stool complex with a vacant site for substrate activation), as racemization at the metal center would have a dramatic effect on the enantiomeric excess of the resulting products. Theoretical^[16] as well as mechanistic studies^[9, 17–19] on the configurational stability of coordinatively unsaturated two-legged piano-stool complexes of the type $[(\eta^n\text{-C}_n\text{H}_n)\text{ML}^1\text{L}^2]$ ($n = 5–7$) suggest that, although some of these complexes indeed possess pyramidal ground-state geometries (and thus metal-centered chirality), the computed and experimentally determined inversion barriers are low, that is, less than 15 kcal mol^{-1} , thus hampering their use as enantioselective catalysts.

Inspired by Tröger's base, we set out to synthesize a configurationally stable piano-stool complex with chirality at the metal center by anchoring the metal in a rigid "bicyclic" framework (Scheme 1). Inspection of molecular models of such configurationally locked piano-stool complexes suggests that racemization can only occur by arene dissociation, an energetically costly process. Although tethered cyclopentadienyl ligands have received much attention,^[20–22] tethered benzene systems have attracted much less consideration.^[23–25] We report herein the synthesis of an enantiopure, configurationally stable, three-legged piano-stool ruthenium complex built from a prochiral ligand.

In recent years, "electronically asymmetric" ligands have received enormous attention in asymmetric catalysis. In



Scheme 1. Anchoring a configurationally labile chiral center in a bicyclic framework results in a configurationally stable complex.

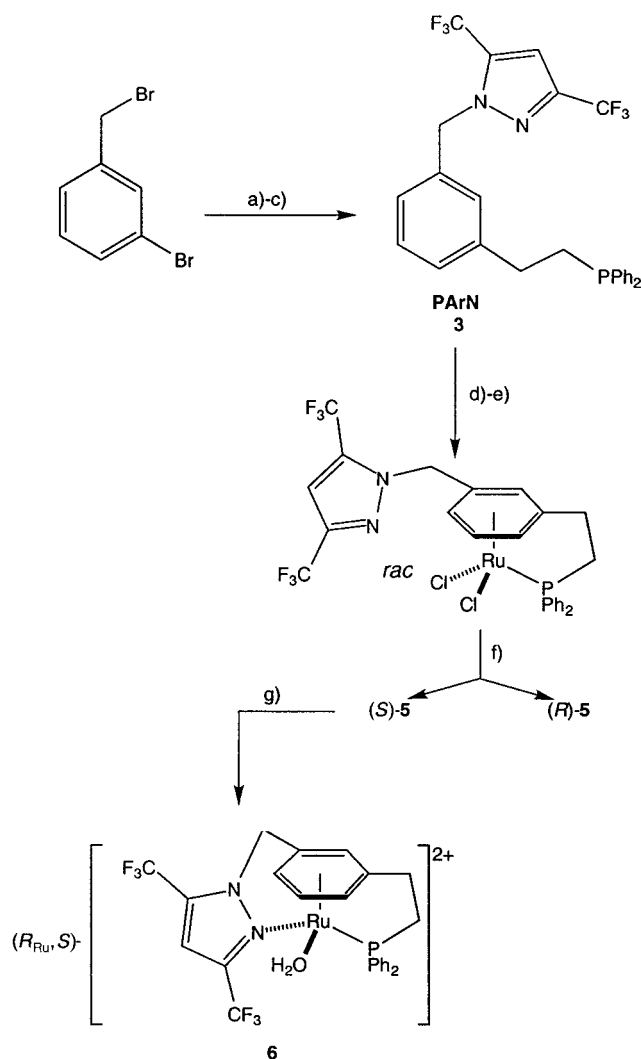
particular, phosphane-imine-based bidentate ligands have proven superior to C_2 -symmetric systems for a variety of enantioselective transformations.^[26–29] Tethering a phosphane and an electron-deficient pyrazole to an arene yields a potential ten-electron donor (PArN) with pronounced electronic asymmetry. Upon $\eta^6:\eta^1:\eta^1$ coordination to Ru^{II} , a three-legged piano-stool complex is formed: $[(\eta^6:\eta^1:\eta^1\text{-(PArN)})\text{-RuL}]^{2+}$ (L = weakly bound solvent molecule).

The synthesis of the ligand, outlined in Scheme 2, is straightforward. Nucleophilic substitution with 3,5-bis(trifluoromethyl)pyrazole on 3-bromobenzyl bromide followed by a Stille vinylation and a radical addition of HPPH_2 on the resulting double bond affords PArN (**3**) in 79% overall yield. Coordination of phosphane to $[(\eta^6\text{-C}_6\text{H}_5\text{CO}_2\text{Et})\text{RuCl}_2]_2$ ^[30] and subsequent thermal displacement of the arene ligand affords $[(\eta^6:\eta^1\text{-(PArN)})\text{RuCl}_2]$ (**5**). Upon η^6 coordination of the disubstituted arene to ruthenium, a planar chiral complex results. After many unsuccessful derivatization and crystallization experiments, we were pleased to find that the racemate could be resolved by preparative HPLC (800 mg of *rac*-**5** on a Chiralpak AD column with ethanol as eluent), affording a quasi-baseline separation of the enantiomers (*R*)-**5** (317 mg, 99.5% *ee*) and (*S*)-**5** (341 mg, 91% *ee*). Recrystallization from ethanol of the second enantiomer to be eluted affords enantiopure (HPLC) crystals suitable for anomalous X-ray diffraction, allowing unambiguous assignment of the absolute configuration. The molecular structure of (*S*)-**5** is depicted in Figure 1.^[31]

[*] Dr. T. R. Ward, B. Therrien
Department of Chemistry and Biochemistry
University of Berne
Freiestrasse 3, CH-3000 Berne 9 (Switzerland)
Fax: (+41) 31-631-3993
E-mail: ward@iac.unibe.ch

[**] This work was supported by the Swiss National Science Foundation and the Stiftung für Stipendien auf dem Gebiete der Chemie (award of an A. Werner Fellowship to T.R.W., 1994–1999).

Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.



Scheme 2. Preparation of enantiopure complex **6**. a) 3,5-bis(trifluoromethyl)pyrazole, NaH, DMF, 2 h at room temperature (RT) then 48 h at 60 °C (86 %); b) $[\text{Pd}(\text{PPh}_3)_4]$, $\text{Bu}_3\text{Sn}(\text{CH}=\text{CH}_2)$, toluene, 100 °C, 8 h (92 %); c) HPPH_2 , azobisisobutyronitrile (AIBN), CH_2Cl_2 , RT, $h\nu$, 24 h (quant.); d) $[(\eta^6\text{-C}_6\text{H}_5\text{CO}_2\text{Et})\text{RuCl}_2]$ (0.5 equiv), CH_2Cl_2 , RT, 0.5 h (82 %); e) CH_2Cl_2 , 110 °C, 24 h (quant.); f) HPLC (Chiralpak AD), EtOH; g) excess $\text{AgOSO}_2\text{CF}_3$, THF/ H_2O , RT, 24 h (quant.).

Treating (*R*)-**5** or (*S*)-**5** with an excess of $\text{AgOSO}_2\text{CF}_3$ (AgOTf) in THF affords, after aqueous workup, the piano-stool complexes $(R_{\text{Ru}}, S)\text{-}[(\eta^6\text{-C}_6\text{H}_5\text{CO}_2\text{Et})\text{Ru}(\text{OH}_2)](\text{OTf})_2$ ($(R_{\text{Ru}}, S)\text{-6}$) and $(S_{\text{Ru}}, R)\text{-6}$, respectively, which show chirality at the metal center. Upon $\eta^6\text{:}\eta^1\text{:}\eta^1$ coordination of PArN , the ^{31}P NMR signal is shifted from $\delta = +45.7$ for **5** to $\delta = +59.3$ for **6**. The presence of a unique signal suggests that a single diastereomer is formed upon coordination of the pyrazole nitrogen atom to ruthenium, locking its configuration. This was confirmed by an X-ray analysis of single crystals of **6** (Figure 2).^[31] Comparing the molecular structures of **5** and **6**, we note that, upon coor-

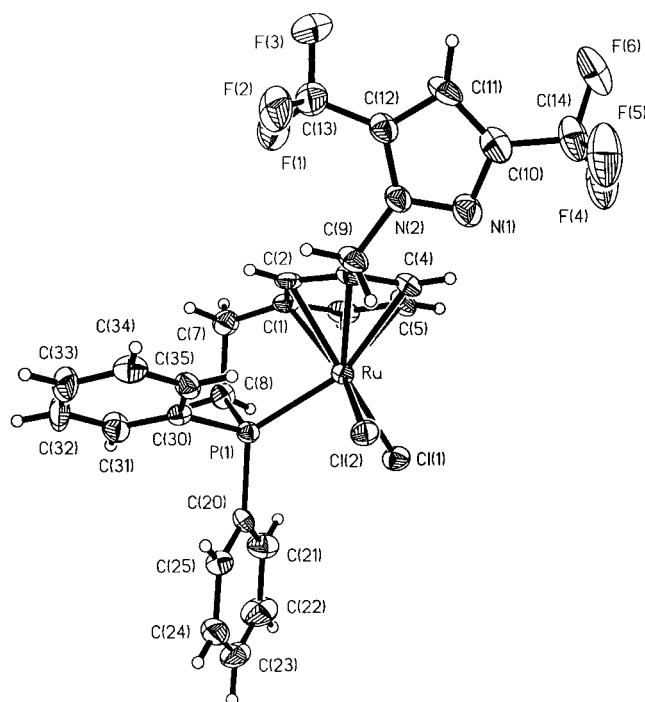


Figure 1. Molecular structure of (*S*)-**5**. Thermal ellipsoids are at the 50% probability level. Selected bond lengths [Å] and angles [°]: Ru– C_{Ar} 2.212 (mean), Ru– $\text{arene}_{\text{centroid}}$ 1.697(7), Ru–P 2.322(1), Ru–Cl(1) 2.408(1), Ru–Cl(2) 2.414(1); P(1)–Ru–Cl(2) 90.28(4), Cl(1)–Ru–Cl(2) 89.90(4), P(1)–Ru–Cl(1) 88.29(4).

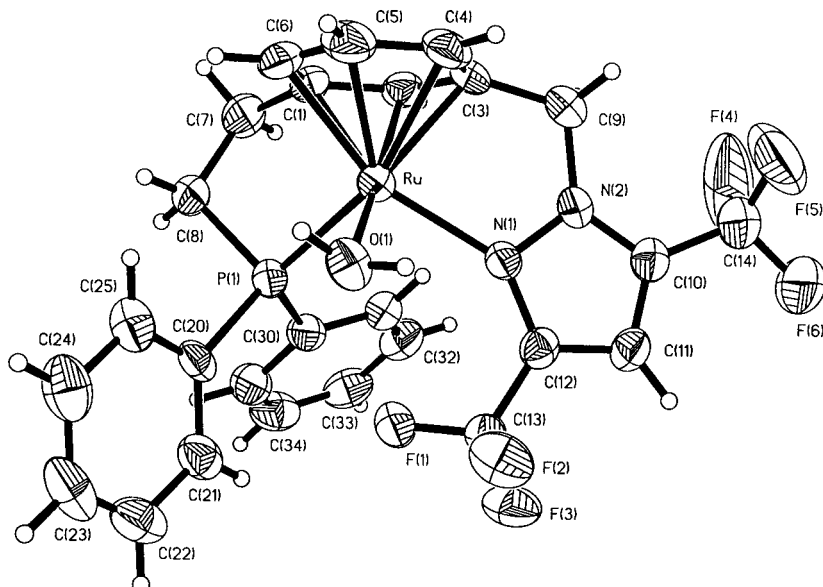


Figure 2. Molecular structure of **6**. Thermal ellipsoids are at the 50% probability level (triflate molecules omitted for clarity). Selected bond lengths [Å] and angles [°]: Ru– C_{Ar} 2.186 (mean), Ru– $\text{arene}_{\text{centroid}}$ 1.667(9), Ru–P 2.387(2), Ru–O(1) 2.134(4), Ru–N(1) 2.163(4); P(1)–Ru–O(1) 88.6(1), O(1)–Ru–N(1) 88.8(2), P(1)–Ru–N(1) 102.0(1).

dination of the pyrazole tether to yield a “bicyclic structure”, the Ru–P bond lengthens by 0.065 Å, while the Ru– $\text{arene}_{\text{centroid}}$ length shortens by 0.03 Å. The piano-stool geometry around ruthenium in **6** is slightly distorted (P–Ru–N 102.0(1)°), reflecting the large bite angle imposed by the 1,3-substitution pattern of the tethers on the arene. As

observed for related η^6 -arene–ruthenium complexes with tethered ligands, the coordinated arene deviates from planarity.^[25] (The greatest deviation from the least square plane of the arene is shown by C(2) for **5** (0.035(3) Å) and by C(3) for **6** (0.026(4) Å).)

The stereochemical stability of **5** and **6** is remarkable. All attempts to racemize enantiopure complexes **5** and **6** have failed, eventually yielding decomposition rather than racemization products. When **6** is dissolved in CH_2Cl_2 in the presence of an excess of a coordinating solvent (DMSO, benzaldehyde, methacrolein, water, ethanol, and acetonitrile), the CD trace is practically unaltered over a period of 48 h at room temperature. Upon heating, the slow appearance of decomposition products is observed by ^{31}P NMR and UV/Vis spectroscopy. The CD spectra of **5** and **6** are depicted in Figure 3. It appears that the configuration at the ruthenium

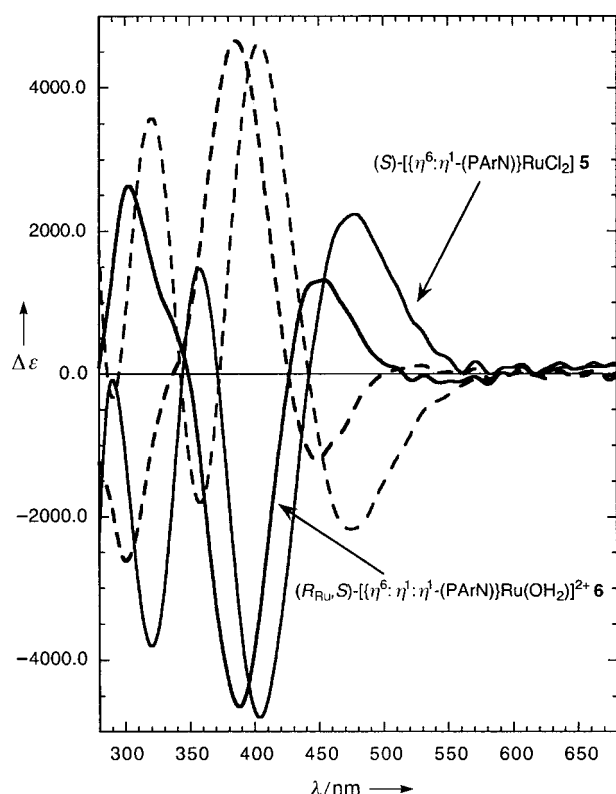


Figure 3. Circular dichroism spectra in CH_2Cl_2 of **5** ($[(S)\text{-}5] = 0.195 \text{ mm}$, thin solid line; $[(R)\text{-}5] = 0.227 \text{ mm}$, thin dashed line) and **6** ($[(R_{\text{Ru}},S)\text{-}6] = 0.339 \text{ mm}$, thick solid line; $[(S_{\text{Ru}},R)\text{-}6] = 0.435 \text{ mm}$, thick dashed line).

center is encoded by the planar chirality resulting from the η^6 coordination of the prochiral arene. Even in the event of phosphane and pyrazole decomplexation, the chirality at the metal can be reversibly recovered, thus allowing one to probe the role of chirality at the metal in enantioselective catalysis. We are currently investigating the catalytic properties of **6** in various C–C bond forming reactions.

Received: June 29, 1998 [Z 12064IE]

German version: *Angew. Chem.* **1999**, *111*, 418–421

Keywords: arene complexes • chirality • coordination modes

- [1] A. von Zelewsky, *Stereochemistry of Coordination Compounds*, Wiley, New York, **1996**.
- [2] G. B. Kauffman, *Coord. Chem. Rev.* **1974**, *12*, 105.
- [3] H. Brunner, *Angew. Chem.* **1969**, *81*, 395; *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 382.
- [4] H. Brunner, *Adv. Organomet. Chem.* **1980**, *18*, 151.
- [5] H. Brunner, J. Aclasis, M. Langer, W. Steger, *Angew. Chem.* **1974**, *86*, 864; *Angew. Chem. Int. Ed. Engl.* **1974**, *13*, 810.
- [6] H. Brunner, K. Fisch, P. G. Jones, J. Salbeck, *Angew. Chem.* **1989**, *101*, 1558; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1521.
- [7] S. G. Davies, *Aldrichim. Acta* **1990**, *23*, 31.
- [8] J. W. Faller, M. R. Mazzieri, J. T. Nguyen, J. Parr, M. Tokunaga, *Pure Appl. Chem.* **1994**, *66*, 1463.
- [9] Review: J. A. Gladysz, B. J. Boone, *Angew. Chem.* **1997**, *109*, 566; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 550.
- [10] T. Bach, D. N. A. Fox, M. T. Reetz, *J. Chem. Soc. Chem. Commun.* **1992**, 1634.
- [11] E. P. Kündig, B. Bourdin, G. Bernardinelli, *Angew. Chem.* **1994**, *106*, 1931; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1856.
- [12] D. Carmona, C. Cativiela, S. Elipse, F. J. Lahoz, M. P. Lamata, M. P. López-Ram de Viu, L. A. Oro, C. Vega, F. Viguri, *Chem. Commun.* **1997**, 2351.
- [13] D. L. Davies, J. Fawcett, S. A. Garratt, D. L. Russell, *Chem. Commun.* **1997**, 1351.
- [14] B. E. R. Schilling, R. Hoffmann, J. W. Faller, *J. Am. Chem. Soc.* **1979**, *101*, 592.
- [15] H. Brunner, H.-J. Lautenschlager, W. A. König, R. Krebber, *Chem. Ber.* **1990**, *123*, 847.
- [16] T. R. Ward, O. Schafer, C. Daul, P. Hofmann, *Organometallics* **1997**, *16*, 3207.
- [17] H. Brunner, R. Oeschey, B. Nuber, *Angew. Chem.* **1994**, *106*, 941; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 866.
- [18] H. Brunner, R. Oeschey, B. Nuber, *J. Organomet. Chem.* **1996**, *518*, 47.
- [19] H. Brunner, R. Oeschey, B. Nuber, *J. Chem. Soc. Dalton Trans.* **1996**, 1499.
- [20] Review: J. Okuda, *Comm. Inorg. Chem.* **1994**, *16*, 185.
- [21] M. D. Fryzuk, S. S. H. Mao, M. J. Zaworotko, L. R. MacGillivray, *J. Am. Chem. Soc.* **1993**, *115*, 5336.
- [22] B. Antelmann, U. Winterhalter, G. Huttner, B. C. Janssen, J. Vogelgesang, *J. Organomet. Chem.* **1997**, *545–546*, 407.
- [23] E. T. Singewald, C. A. Mirkin, A. D. Levy, C. L. Stern, *Angew. Chem.* **1994**, *106*, 2524; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2473.
- [24] A. N. Nesmeyanov, V. V. Krivykh, M. I. Rubinskaya, *J. Organomet. Chem.* **1979**, *164*, 159.
- [25] C. M. Hartshorn, P. J. Steel, *Angew. Chem.* **1996**, *108*, 2818; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2655.
- [26] P. von Matt, A. Pfaltz, *Angew. Chem.* **1993**, *105*, 614; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 566.
- [27] J. Sprinz, G. Helmchen, *Tetrahedron Lett.* **1993**, *34*, 1769.
- [28] A. Togni, U. Burckhardt, V. Gramlich, P. S. Pregosin, R. Salzmann, *J. Am. Chem. Soc.* **1996**, *118*, 1031.
- [29] J. M. Brown, D. I. Hulmes, P. J. Guiry, *Tetrahedron* **1994**, *50*, 4493.
- [30] B. Therrien, T. R. Ward, M. Pilkington, C. Hoffmann, F. Gilardoni, J. Weber, *Organometallics* **1998**, *17*, 330.
- [31] Crystal structure analysis of (S)-**5** and (rac)-**6**.^[32] Siemens SMART CCD diffractometer, $T = 200$ and 220 K , respectively, $\text{MoK}\alpha$ radiation (0.71073 Å). A complete hemisphere of data was scanned on ω (0.30° per frame) with a run time of 20 s for (S)-**5** and 60 s for (rac)-**6**, at the detector resolution of 512×512 pixels and a detector distance of 5.18 cm. A total of 1271 frames were collected for each data set; the collected frames were processed with the SAINT program,^[32] which automatically performs Lorentz and polarization corrections. The structure was solved by direct methods and refined by full-matrix least square of F^2 (SHELXL96,^[33] β test version). (S)-**5**: $\text{C}_{26}\text{H}_{21}\text{Cl}_2\text{F}_6\text{N}_2\text{PRu}$, $M_r = 678.39$; orthorhombic, space group $P2_12_12_1$; $a = 7.2072(1)$, $b = 13.5782(1)$, $c = 27.4530(3) \text{ Å}$, $V = 2686.57(5) \text{ Å}^3$, $Z = 4$, $\rho_{\text{calcd}} = 1.677 \text{ g cm}^{-3}$, $F(000) = 1352$, $\mu = 0.903 \text{ mm}^{-1}$, crystal size $0.04 \times 0.14 \times 0.32 \text{ mm}$; of 13697 reflections measured ($-6 \leq h \leq 8$, $-17 \leq k \leq 16$, $-34 \leq l \leq 29$), 5143 were unique; L_p and absorption corrections (psi scans); refinement of 346 variables with anisotropic displacement parameters for all non-hydrogen atoms gave $R = 0.0354$, $R_w = 0.0806$, and $S = 1.175$; modified statistical weight sug-

gested by SHELX; absolute structure parameter = -0.05 (4); max./min. residual electron density $0.524/-0.501$ e Å⁻³. Since all attempts to obtain X-ray quality crystals of enantiopure **6** failed, (*rac*)-**6** was analyzed: C₂₈H₂₃F₁₂N₂O₇PRuS₂, $M_r = 923.64$; orthorhombic, space group *Pbca*; $a = 19.4161(3)$, $b = 15.9196(2)$, $c = 22.0340(3)$ Å, $V = 6810.6(2)$ Å³, $Z = 8$, $\rho_{\text{calc}} = 1.802$ g cm⁻³, $F(000) = 3680$, $\mu = 0.744$ mm⁻¹, crystal size $0.09 \times 0.20 \times 0.32$ mm; of 34 713 reflections measured ($-19 \leq h \leq 24$, $-19 \leq k \leq 19$, $-27 \leq l \leq 25$), 6697 were unique; refinement of 485 variables with anisotropic thermal parameters for all non-hydrogen atoms gave $R = 0.0567$, $R_w = 0.1317$, and $S = 1.109$; max./min. residual electron density $0.731/-0.709$ e Å⁻³. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-102025 ((*S*)-**5**) and CCDC-102024 ((*rac*)-**6**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

[32] SAINT, version 4, Siemens Energy and Automation Inc. Madison, WI, 1995.

[33] SHELXTL, version 5.03 (for Silicon Graphics). Program Library for Structure Solution and Molecular Graphics, Siemens Analytical Instruments Division, Madison, WI, 1995; G. M. Sheldrick, SHELXL 1996; Program for the Refinement of Crystal Structures, Universität Göttingen, Germany, 1996.

[Co^{II}L(NCS)₂(SCN)₂]: The First Cobalt Complex to Exhibit Both Exchange Coupling and Spin Crossover Effects**

Sally Brooker,* Paul G. Plieger, Boujemaa Moubaraki, and Keith S. Murray*

The preparation of molecular materials with possible nanotechnological applications is an area of intense interest.^[1, 2] To produce molecules which can act as switches, detectors, or memory devices, the property of bistability is required. Classic examples of bistability are provided by spin-crossover compounds in which the transition from low to high spin is accompanied by a measurable change in magnetism and often also in color.^[1–5] Such a signal is vital as it indicates that a change has occurred. To be of use as components there are numerous requirements to be met. One requirement is that the spin crossover should be sharp and occur close to

room temperature, ideally with reproducible hysteresis loops (memory) arising from a polymeric structure.^[1] Most of the work done in this area has involved iron(II) compounds (d⁶), but other transition metals are also known to undergo spin transitions under appropriate conditions, and of interest to us here are cobalt(II) compounds (d⁷).

We are studying complexes of chelating ligands based on 3,6-diformylpyridazine.^[6–9] To date, very few pyridazine- or phthalazine-bridged dicobalt(II) complexes have been studied,^[10] and all of these have contained high-spin cobalt(II) ions throughout the temperature ranges studied. The structure and electrochemistry of the first macrocyclic pyridazine-bridged dicobalt complex was reported very recently.^[8] We report here on an air-stable dicobalt(II) complex of the Schiff-base macrocyclic ligand **L**, which exhibits unique magnetic properties for a cobalt complex and represents a first step towards the development of a “usable” spin-transition polymer.^[1]

The dicobalt(II) complex [Co₂L(NCS)₂(SCN)₂] (**1**) is readily crystallized in quantitative yield by diffusion of a solution of [Co₂L(MeCN)₄](ClO₄)₄ (**2**)^[8] in acetonitrile into a solution of sodium thiocyanate. The infrared spectrum of **1** shows that the macrocycle has remained intact during this reaction. The structure determination was carried out at 160 K on a crystal obtained from the reaction mixture (Figure 1). The asymmetric unit consists of half of a macrocyclic complex with the other half of the molecule generated by inversion. The

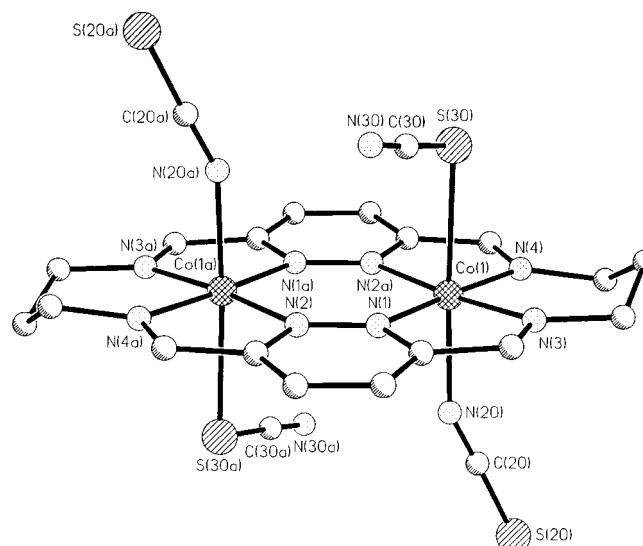
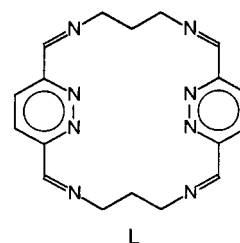


Figure 1. Perspective view of **1**. Selected interatomic distances [Å] and angles [°]: Co(1)–N(4) 1.922(3), Co(1)–N(3) 1.933(3), Co(1)–N(1) 1.966(3), Co(1)–N(2a) 1.983(3), Co(1)–N(20) 2.115(3), Co(1)–S(30) 2.5843(10), Co(1)···Co(1a) 3.813(1); N(4)–Co(1)–N(3) 93.80(12), N(4)–Co(1)–N(1) 175.87(11), N(3)–Co(1)–N(1) 82.07(11), N(4)–Co(1)–N(2a) 81.94(11), N(3)–Co(1)–N(2a) 174.70(11), N(1)–Co(1)–N(2a) 102.19(11), N(4)–Co(1)–N(20) 88.59(12), N(3)–Co(1)–N(20) 90.28(12), N(1)–Co(1)–N(20) 91.21(11), N(2a)–Co(1)–N(20) 92.76(11), N(4)–Co(1)–S(30) 87.49(9), N(3)–Co(1)–S(30) 89.87(9), N(1)–Co(1)–S(30) 92.69(8), N(2a)–Co(1)–S(30) 86.80(8), N(20)–Co(1)–S(30) 176.08(9), N(2)–N(1)–Co(1) 128.5(2), N(1)–N(2)–Co(1a) 129.3(2).

[*] Dr. S. Brooker, P. G. Plieger
Department of Chemistry
University of Otago
PO Box 56, Dunedin (New Zealand)
Fax: (+64) 3-479-7906
E-mail: sbrooker@alkali.otago.ac.nz

Prof. K. S. Murray, Dr. B. Moubaraki
Department of Chemistry
Monash University
Clayton, Victoria 3168 (Australia)
Fax: (+61) 3-990-545-97
E-mail: keith.s.murray@sci.monash.edu.au

[**] This work was supported by grants from the University of Otago, the Australian Research Council, and the Bilateral Research Activities Programme (International Science and Technology Linkages Fund). We thank Professor W. T. Robinson (University of Canterbury) for the X-ray data collection.

cobalt(II) ions have distorted octahedral geometries: in each case the basal plane consists of two bridging pyridazine nitrogen donors and two imine nitrogen donors. The axial sites are occupied by two thiocyanate anions, one bound through the N atom and the other through the S atom. The latter feature, S-bound thiocyanate, has not, to our knowledge, been observed before for cobalt(II) compounds.^[11] Interestingly, the Co–N_{macro} bond lengths are very similar (av Co–N_{macro} 1.951(4) Å) to those observed at 170 K for the perchlorate analogue **2** (av Co–N_{macro} 1.972(4) Å).^[8] In **1** the bond lengths to the thiocyanate axial donors are somewhat longer than the bond lengths to the macrocycle donors, as expected for Jahn-Teller distorted low-spin octahedral d⁷ systems (Co–N_{NCS} 2.115(3) Å, difference of 0.164(7) Å): a similar difference is observed in the case of **2** (av Co–N_{MeCN} 2.143(4) Å, difference of 0.171(8) Å). These bond lengths contrast with those recently observed in the high-spin compressed octahedral monocobalt(II) complex [Co(pyridazine)₄(NCS)₂] (Co–N_{pyrid} 2.199(2), 2.208(2); Co–N_{NCS} 2.057(2) Å).^[12] Like **2**, the macrocycle in **1** is very flat with only the central alkyl carbon atoms of the lateral groups displaced substantially from the macrocyclic plane. The pyridazine ring plane and the basal plane of the cobalt atoms are almost coplanar: they intersect at an angle of 3.3°.

The magnetic susceptibility of a sample of [Co₂L(NCS)₂·(SCN)₂] was determined over the temperature range 4.5–350 K in a field of 1 T. The plots of χ_m and μ_{eff} , per Co atom, as a function of temperature are shown in Figure 2. The

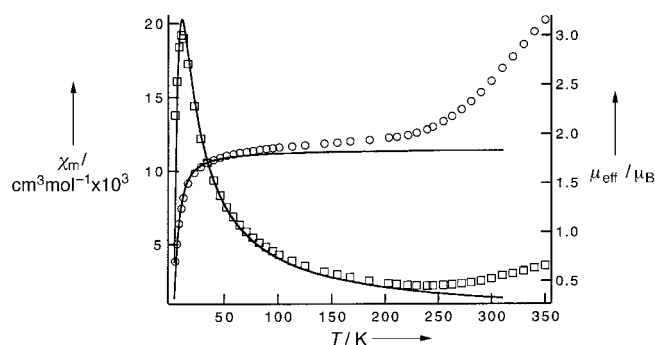


Figure 2. Experimental temperature dependence of χ_m ($\square$) and μ_{eff} ($\circ$) per Co atom for **1**. Estimated experimental errors in μ_{eff} are $\pm 0.02 \mu_B$ and in temperature ± 0.05 K. The solid lines are the calculated fits of the data to a $S = 1/2$ dimer model: $2J = -11.7 \text{ cm}^{-1}$, $g = 2.13$.

susceptibility data are identical in fields of 0.10 and 0.05 T, which indicates that saturation effects are absent. The molecular susceptibility drops slightly as the temperature is lowered from 350 K to 240 K and then increases to a maximum at 10 K before dropping rapidly at temperatures below this. The overall shape of this curve shows that the coupling is antiferromagnetic, and the χ_{max} value, which occurs at 10 K, indicates that the antiferromagnetic coupling is weak. The magnetic moment drops from $3.15 \mu_B$ per Co atom at 350 K to $0.70 \mu_B$ per Co atom at 4.5 K (Figure 2). There is a gently sloping “plateau” from approximately 40 K ($1.74 \mu_B$) to 221 K ($1.98 \mu_B$). But in the high-temperature region, beyond 221 K, the magnetic moment begins to increase noticeably, revealing that a gradual spin transition from $S = 1/2$ to $S = 3/2$ takes place. This transition occurs at an encouragingly high

temperature; however, the transition is not sharp, but rather occurs over a wide temperature range typical of many, but not all, cobalt(II) d⁷ mononuclear crossover systems.^[4, 13, 14] The shape of the curve in the plot of magnetic moment versus temperature in the crossover region is affected very little, if at all, by orbital contributions from the high-spin form as judged by comparison with a high-spin analogue of **1** (see above). No hysteresis was observed in the spin-transition region. This is indicative of a lack of intermolecular interactions between dimers.^[1] The $S = 3/2$ states of each Co^{II} ion are not fully populated at 350 K. There is no evidence for two separate crossover transitions per dicobalt(II) complex.

To estimate the degree of exchange coupling at low temperatures, it was assumed that the sample consists of coupled low-spin Co^{II} ions. When only the data from the 4.5 K to 200 K measurements is used, the fit obtained is as shown in Figure 2. The values obtained from the fit are $g = 2.13$ and $2J = -11.7 \text{ cm}^{-1}$. The g value has been confirmed by measurement of an EPR spectrum of a solid sample of **1** at 77 K, which showed a single broad line of $g = 2.14$. The fit of the low-temperature data is acceptable, with the deviations from calculated values above about 50 K indicative of the presence of the $S = 3/2$ state and of $3/2 - 3/2$ coupling. There are few low-spin Co^{II} dinuclear species known^[14, 15] for comparison to **1**, and these generally have different coordination numbers and hence geometries. For example, in the low-spin five-coordinate complex [Cosalen]₂ (salen²⁻ = *N,N'*-ethylenebis(salicylideneiminato) anion) $2J$ is equal to -42 cm^{-1} .^[15]

At 350 K the magnetic moment is $3.15 \mu_B$ per Co ion and continues to increase (Figure 2). Based on related monomeric $S = 3/2$ complexes, the moment could be expected to eventually “plateau” at about $4.2 \mu_B$.^[4, 5] However, the two cobalt ions are antiferromagnetically coupled by the double diazine bridge so the value is likely to be reduced somewhat by this interaction. Interestingly, comparison with related binuclear pyridazine/phthalazine-bridged complexes (all of which are high spin throughout the temperature range studied)^[10] also indicates that a value in the range $4.2 - 4.8 \mu_B$ might be expected.

There is a very real possibility that complexes related to **1**, suitably modified in design, may provide long-range magnetically coupled materials which exhibit spin crossover, and we are actively pursuing this line of research.^[9]

Experimental Section

1: A red solution of **2**^[8] (0.063 g, 0.073 mmol) in dry acetonitrile (30 mL) was placed in one side arm of an H-tube. Solid sodium thiocyanate (1.00 g, 12.3 mmol) was placed in the other side, and dry acetonitrile was gently layered over both sides until the H-tube was full (ca. 75 mL). After three days the colorless solution contained black crystals of **1** (0.050 g, 98%). Elemental analysis calcd for C₂₂H₂₀N₁₂S₄Co₂: C 37.8, H 2.9, N 24.1, S 18.4; found: C 37.6, H 2.8, N 23.8, S 18.1; IR (KBr): $\tilde{\nu} = 2074, 1624 \text{ cm}^{-1}$.

Crystal data for **1** (C₂₂H₂₀N₁₂S₄Co₂): black square plate, $0.30 \times 0.30 \times 0.25 \text{ mm}$, monoclinic, space group $P2_1/c$, $a = 9.0179(5)$, $b = 10.7406(5)$, $c = 13.7628(7) \text{ Å}$, $\beta = 91.872(1)^\circ$, $V = 1332.3(1) \text{ Å}^3$, $Z = 2$, $\mu = 1.60 \text{ mm}^{-1}$. Data were collected at 160 K on a Bruker SMART diffractometer with graphite-monochromated MoK α radiation. A total of 7790 reflections were collected in the range $4 < 2\theta < 53^\circ$, and the 2568 independent reflections were used in the structural analysis after a semiempirical absorption correction had been applied. The structure was solved by direct methods (SHELXS-97)^[16] and refined against all F^2 data (SHELXL-97)^[17] to $R1 = 0.047$ (for 2321 $F > 4\sigma(F)$); $wR2 = 0.131$ and GOF = 1.035 for all 2568 F^2 ;

191 parameters; all non-hydrogen atoms anisotropic). Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-102124. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Magnetic susceptibility studies were carried out with a Quantum Design MPMS SQUID magnetometer at an applied field of 1 T. The powdered sample was contained in a calibrated gelatine capsule which was held in the centre of a soda straw fixed to the end of the sample rod. The magnetization values of the instrument were calibrated against a standard palladium sample, supplied by Quantum Design, and also against chemical calibrants such as $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ and $[\text{Ni}(\text{en})_3](\text{S}_2\text{O}_3)$ (en = ethylenediamine).

Received: July 7, 1998 [Z12107IE]

German version: *Angew. Chem.* **1999**, *111*, 424–426

Keywords: cobalt • macrocyclic ligands • magnetic properties • Schiff bases • spin crossover

- [1] See, for example, O. Kahn, C. J. Martinez, *Science* **1998**, *279*, 44; and the recent structure of a Cu^{II} triazole analogue: Y. Garcia, P. J. van Koningsbruggen, G. Oravic, P. Guionneau, D. Chasseau, G. I. Cascarano, J. Moscovici, K. Lambert, A. Michalowicz, O. Kahn, *Inorg. Chem.* **1997**, *36*, 6357.
- [2] See, for example, H. Toftlund in *Magnetism: A Supramolecular Function* (Ed.: O. Kahn), Kluwer Academic, Amsterdam, **1996**, p. 323.

- [3] A. Real, J. Zarembowitch, O. Kahn, X. Solans, *Inorg. Chem.* **1987**, *26*, 2939.
- [4] B. J. Kennedy, G. D. Fallon, B. M. K. C. Gatehouse, K. S. Murray, *Inorg. Chem.* **1984**, *23*, 580.
- [5] G. De Munno, M. Julve, F. Lloret, J. Faus, A. Caneschi, *J. Chem. Soc. Dalton Trans.* **1994**, 1175.
- [6] S. Brooker, R. J. Kelly, G. M. Sheldrick, *J. Chem. Soc. Chem. Commun.* **1994**, 487; S. Brooker, R. J. Kelly, *J. Chem. Soc. Dalton Trans.* **1996**, 2117.
- [7] S. Brooker, R. J. Kelly, B. Moubaraki, K. S. Murray, *Chem. Commun.* **1996**, 2579.
- [8] S. Brooker, R. J. Kelly, P. G. Plieger, *Chem. Commun.* **1998**, 1079.
- [9] S. Brooker, R. J. Kelly, P. G. Plieger, B. Moubaraki, K. S. Murray, E. Bill, E. Bothe, unpublished results.
- [10] J. E. Andrew, P. W. Ball, A. B. Blake, *J. Chem. Soc. Chem. Commun.* **1969**, 143; P. W. Ball, A. B. Blake, *J. Chem. Soc. Dalton Trans.* **1974**, 852; T. Wen, L. K. Thompson, F. L. Lee, E. J. Gabe, *Inorg. Chem.* **1988**, *27*, 4190; A. Escuer, R. Vicente, B. Mernari, A. E. Gueddi, M. Pierrot, *Inorg. Chem.* **1997**, *36*, 2511.
- [11] In contrast, S-bound thiocyanate has been observed in Co^{III} complexes; see, for example, C. Hedtmann-Rein, M. Hanack, K. Peters, E.-M. Peters, H. G. von Schnering, *Inorg. Chem.* **1987**, *26*, 2647.
- [12] F. Lloret, G. De Munno, M. Julve, J. Cano, R. Ruiz, A. Caneschi, *Angew. Chem.* **1998**, *110*, 143; *Angew. Chem. Int. Ed.* **1998**, *37*, 135.
- [13] R. L. Martin, A. H. White, *Trans. Met. Chem.* **1968**, *4*, 113.
- [14] P. Thuery, J. Zarembowitch, *Inorg. Chem.* **1986**, *25*, 2001; D. Onggo, A. D. Rae, H. A. Goodwin, *Inorg. Chim. Acta* **1990**, *178*, 151, and references therein.
- [15] K. S. Murray, A. van den Bergen, B. J. Kennedy, B. O. West, *Austral. J. Chem.* **1986**, *39*, 1479; C. Daul, C. W. Schl pfer, A. von Zelewsky, *Struct. Bonding (Berlin)* **1979**, *36*, 129, and references therein.
- [16] G. M. Sheldrick, *Acta Crystallogr. Sect. A* **1990**, 467.
- [17] G. M. Sheldrick, SHELXL 97, Universit t G ttingen, Germany **1997**.