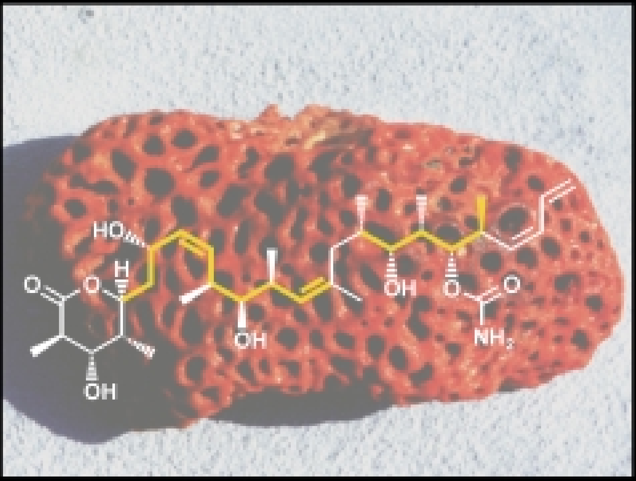
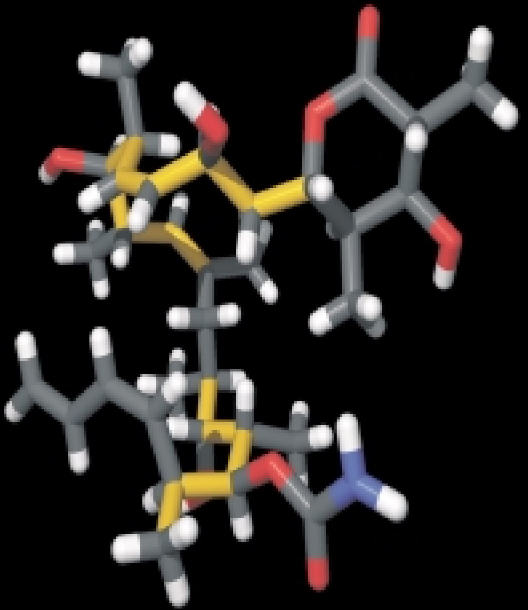
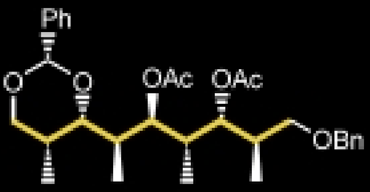
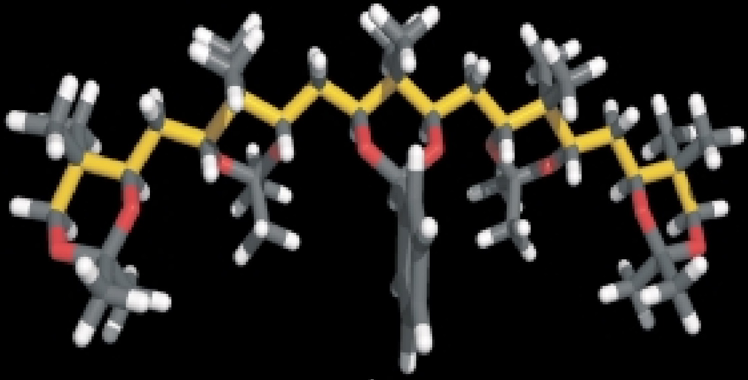
Conformation Design

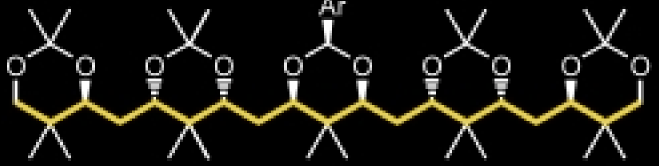


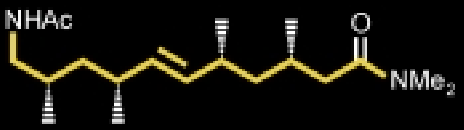


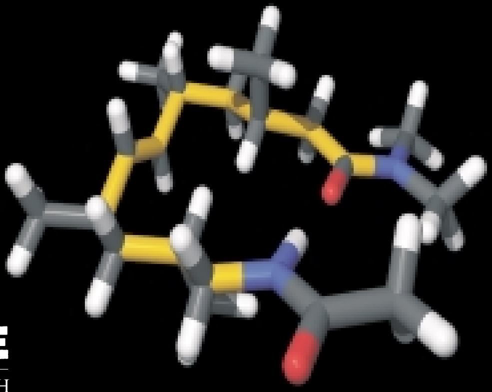
Nature does it - what about us ?











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Conformation Design of Open-Chain Compounds

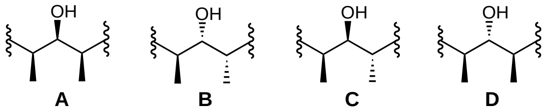
Reinhard W. Hoffmann*

At the brink of the 21st century, chemistry is increasingly concerned with the function that molecules fulfil as drugs, receptors, or—as ensemble of molecules—as materials. The capability of compounds to fulfil such functions cannot sufficiently be described by using only the terms composition and configuration. A decisive role is played in addition by the conformation of the molecules, which serves as the link between molecular composition and molecular function. Expressions such as "active conformation" or "competent conformation" allude to this aspect. Chemists have to develop an understanding how a flexible molecule adopts the conformation (a distinct shape) which is optimal for the function in question and how this process can be controlled. On the outset of such considerations, we may ask how nature succeeded in the process of evolution to endow flexible molecules with a preference to adopt the conformation which is optimal for the function it has to serve. In this review, I report on how we have reached a crude level of understanding of conformation design in nature with reference to the class of polyketide natural products, how we developed these insights into a conformation design of open-chain compounds, and which applications are already in sight.

Keywords: alkane · conformation analysis · polyketide · structure–activity relationships

1. Introduction

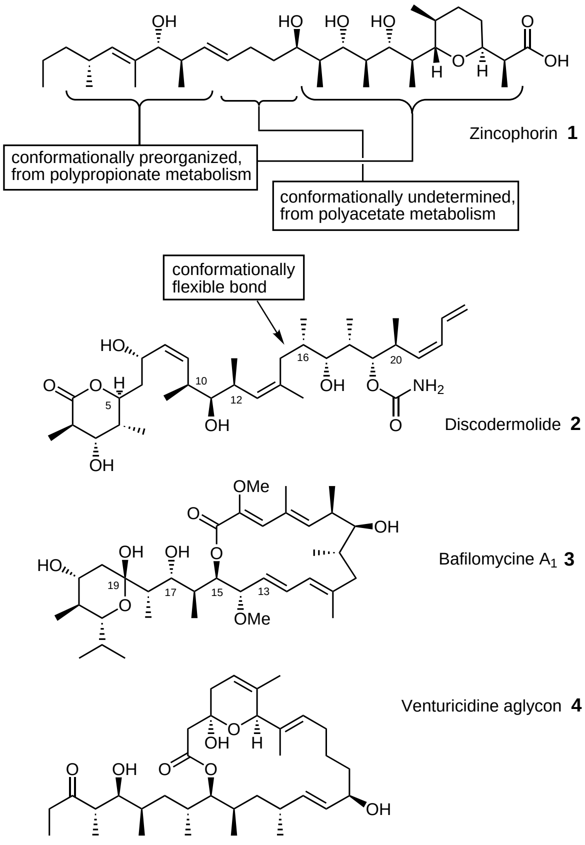
When working for more than two decades on the development of methods for the stereoselective synthesis of "stereotriads",[1] one obviously takes note of the large number of biologically active natural products, which contain such stereotriads as a characteristic structural element (Scheme 1).



Scheme 1. The four possible stereotriads **A**–**D** found in polypropionate natural products.

These are principally the polyketide natural products,[2] which are biogenetically derived from propionyl–coenzyme A through the fatty acid metabolism. Some examples may illustrate their structural diversity (Scheme 2).

An inspection of such structures certainly induced many to wonder what is the purpose of those numerous methyl side



Scheme 2. Some "polyketide" natural products.

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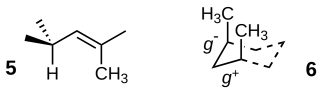
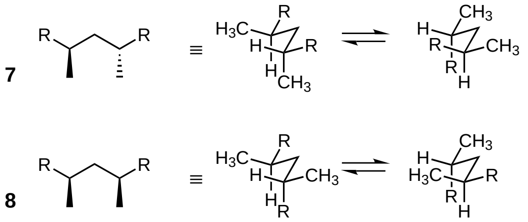
groups. In any case, nature could have made more extensive use of the polyacetate metabolism! What is the advantage gained in natural evolution to have individual stereotriads of a particular, rather than a different, configuration? There must have been a bonus for nature to develop the complex machinery[3] of the polypropionate metabolism. Such considerations strengthen the notion that the presence of the numerous methyl side groups is somehow connected with the backbone conformation of these molecules. The methyl groups do not affect the flexibility of the backbone, yet they reduce the number of low energy local conformers with the result that such molecules preferentially populate certain conformations. In short, we deal with "flexible molecules with a defined shape".[4]

Two principles became evident[5, 6] that nature uses to destabilize undesired conformations: one is to avoid 1,3-allylic strain;[7] the other is to avoid *syn*-pentane interactions. The significance[8] and the mode of operation[9] of 1,3-allylic strain became clear to us during the 1980s. In a substance such as **5**, a single conformation of the vinylic bond is almost completely (>90%) populated in which the H–C–C=C dihedral angle lies within 0 ± 30° (Scheme 3). The substructure **5** occurs, for instance, in zincophorin **1**[10] and in discodermolide **2**[11] (Scheme 2).



Scheme 3. Preferred conformation of a 1,1-disubstituted allylic system **5** and of a pentane **6** destabilized by a *syn*-pentane interaction.

A destabilizing *syn*-pentane interaction is created when a hydrocarbon chain is folded such that a g^+ dihedral angle is followed by one of g^- along the backbone[12] (see structure **6**). This places, in the case of **6**, two methyl (end)groups into a similar spatial proximity, as found in a 1,3-diaxial arrangement on a cyclohexane ring. The conformation shown in **6** is no minimum on the energy hypersurface; rather, the molecule relaxes by increasing the backbone dihedral angles to about 90°. The resulting conformers are still higher in energy (by about 14 kJ mol^{-1}) than other unstrained conformers.[13] For this reason, linear hydrocarbon chains in alkanes adopt conformations that are free of such *syn*-pentane interactions. The methyl side groups in the polyketide natural products cause the substructures of the style of **7** and **8** to have only two local conformations that are free of such destabilizing *syn*-pentane interactions[14] (Scheme 4).



Scheme 4. Biconformational segments of 2,4,6,... *n*-polymethylated alkane chains.

Perusal of numerous crystal structures of polyketide natural products showed that indeed the substructures **7** and **8** are present almost completely in one of the two low energy backbone conformations.[4] The fact that these expected conformations are present in the solid state does not, by itself, allow any conclusions regarding the nature of preferred conformations present in solution. Information on this aspect could be gained, for example, from vicinal ^3J coupling constants along the molecular backbone. Such data are hardly available, since the structural elucidation of polyketide natural products took place in a period in which high field NMR spectroscopy had not reached a level which would permit routine measurement of such coupling constants. If one wanted to learn more about the preferred conformations of polyketide natural products, the NMR spectra of representative examples would have to be reinvestigated with the more refined methods available today.

The limited data available do not give a uniform picture. For instance, a marked alteration of vicinal coupling constants[18] has been reported for the C-13 to C-19 chain of bafilomycine A_1 **3** as well as of the related compounds elaiomycine,[15] concanamycine,[15, 16] and hygrolidine.[17] This indicates the preferential population of a single local backbone conformation[19] at the four bonds of the skeleton between C-14 and C-18. It is unknown as to what extent this is supported by the formation of intramolecular hydrogen bonds.

The few vicinal coupling constants reported for discodermolide **2** do not allow any statement regarding a preferred

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backbone conformation. The data for discodermolide tetraacetate[20] reveal that the two local conformations are each populated about equally in both of the stereotriads C-10/C-12 and C-16/C-20. In contrast, the backbone segment C-4/C-10 appears to populate a single distinct conformation.

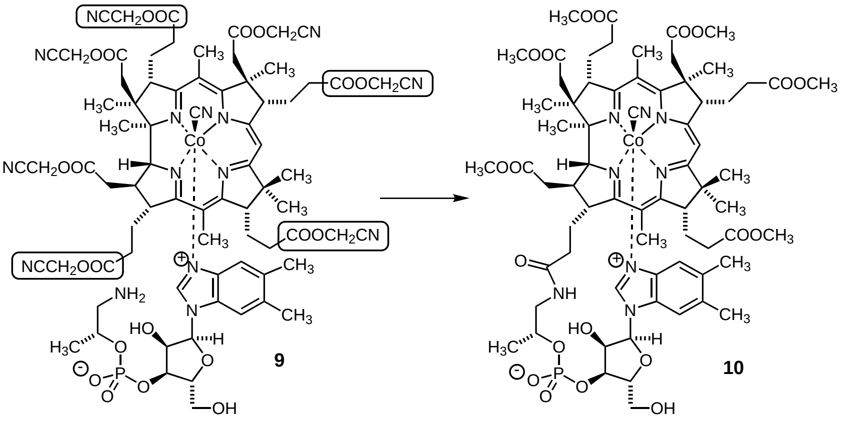
Such observations nurtured our speculation that nature used the methyl side groups in polyketide natural products to give these compounds a predisposition to adopt the conformation necessary for the biological function that they may have. Buoyed by such speculation, we attempt to "translate" the relative configuration of the numerous stereogenic centers in the polyketide natural products into the corresponding preferred backbone conformation.[4] Eventually, we had to overcome several conceptual barriers before we made the transgression from this curiosity-driven pastime to arrive at the statement:

Conformation design: nature does it—what about us?

From today's standpoint, not only does it matter if we understand nature's conformation design but whether we can reliably mimic it with model compounds and control the conformation and biological activity of designed molecules. The long term goal is to finely tune the conformational preorganization of a drug molecule in order to learn where the optimum between the extremes "rigid" and "unordered" lies. Only on the basis of such studies may we recognize why nature chose flexible backbones with a higher or lower preference to populate a preferred conformation. We should focus first on the local conformational preferences in small backbone segments. This might allow to address questions of whether it suffices for nature to reach optimal biological activity for drugs by maintaining a high conformational preference in individual local backbone segments or whether a lower global conformational preference of the backbone of a drug molecule is more important in order to optimize biological activity.

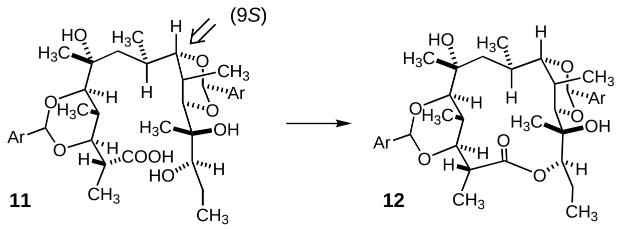
We are, with hindsight, ashamed of how long it took to realize that nature, in demonstrating a conformation design in polyketide natural products, provides us with a toolkit to effect a conformation design of other flexible molecules of interest. Already in the early 1980s, when investigating the allylboration of chiral α-substituted aldehydes, we recognized how the stereoselectivity of the reaction may be controlled by avoiding *syn*-pentane interactions across a newly forming bond.[21] On establishing the structure of the resulting complex, we realized that these molecules adopt conformations that avoid *syn*-pentane interactions, a result that manifested itself in conspicuous ^{13}C NMR chemical shifts.[22] We discussed these results at length with Professor J. K. Whitesell, who was, at that time, a visiting professor in Marburg. This led to insights into the interrelation of the relative configuration of adjacent stereogenic centers, the resulting conformational preferences, and ^{13}C NMR chemical shifts.[23] These insights were used later to predict one of these parameters based on the knowledge of the other two.[24] When persuing the synthesis of polyketide natural products in the 1980s, the NMR spectra of several synthetic intermediates made us conscious of the interrelation between the kind of preferred local backbone conformation and the relative configuration at stereogenic centers along the backbone. However, it did not occur to us at this stage to initiate a program on the conformation design of flexible molecules.

At the end of the 1980s, the significance of the proper conformational preorganization was generally recognized when it came to effect ring closure reactions to form macrocyclic compounds. A key example is given by the ring closure of the vitamin B_{12} precursor **9** to give, in a position-selective manner, the macrocycle **10**[25] (Scheme 5).



Scheme 5. The final ring-closing reaction in the synthesis of vitamin B_{12}.

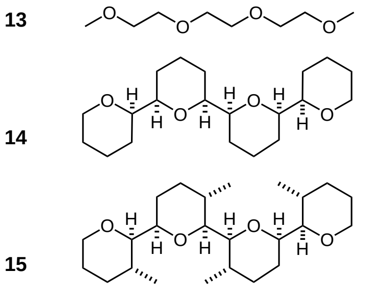
Another characteristic example was evident from the efforts to form the 14-membered lactone ring of erythronolide: Studies from the groups of Woodward,[26] Stork,[27] Yonemitsu,[28] and Paterson[29] underlined the importance of the (9*S*) configuration of the precursor **11** to populate that conformation,[30] which allows the ends to meet and thereby permits the closure of the lactone ring to form **12** (Scheme 6).



Scheme 6. Ring closure during the synthesis of the macrocycle of erythronolide.

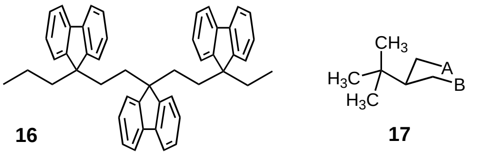
Despite all these insights, we did not envision the possibility to synthesize flexible molecules with a predetermined conformation. We happened, at the end of the 1980s, "to stand repeatedly at a door", to use the imagery of Hückel[31], "and had the door handle in our hands, but failed to open this door." Eventually in 1991, on inspecting crystal structures of numerous polyketide natural products did the pieces fall into place and we realized that conformation design should be feasible and rewarding. Through the "open door" we envisioned the possibilities similar to viewing a new fertile valley. Thus, we looked at who was tilling the land there.

Most conspicuous were the contributions guided by Still,[6, 32] who is to be recognized as the pioneer of intentional conformation design. He showed that the number of low energy conformations of the polyether chain **13** can be significantly reduced by ring annellation, that is, by the incorporation of two neighbouring chain bonds into a ring (Scheme 7). By judicious placement of methyl substituents, he reached molecule **15**, which has only a single low energy conformation. This preferred conformation made this compound a specific ligand for the enantioselective recognition of amino acids.[33, 34] By further optimization of the ligand **15**,[35–37] Still reached a leading position in conformation design of complexing ligands.[38]



Scheme 7. Conformational organization of a polyether chain by ring annellation and buttressing substituents.

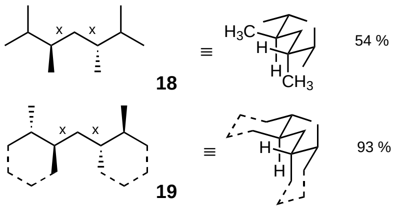
Also clearly directed at conformation design were the studies led by Alder,[39] who defined the conformation-controlling role of quaternary centers. He had entered this research area more or less by chance,[40] but then developed fascinating concepts for stabilizing the extended conformation of (linear) polymer chains like **16** and of macrocyclic two-dimensional networks[40] (Scheme 8).



Scheme 8. Effects of buttressing substituents on the folding of alkane chains.

There were signs of conformation design in the studies of DeClercq et al., who, by placing a *tert*-butyl group on a chain molecule **17**, made it energetically cheaper for the end groups A and B to find themselves in close proximity[41] (Scheme 8).

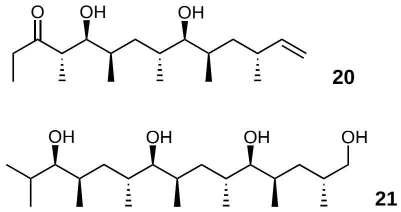
Over discussions with colleagues and with their kind advice we gradually became aware of earlier contributions to the field, which must now be considered as forerunners of a conformation design: This holds for the review of Anderson[42] and for the pioneering studies of Luisi,[43] in which the consequences of *syn*-pentane interactions are clearly delineated and have even been intentionally applied.[44] This holds also for the numerous single observations on preferred conformations of certain hydrocarbon backbones, which have been or could be ascribed to the avoidance of *syn*-pentane interactions, for instance, the studies by Firl,[45] Kishi,[46] Sih,[47] Allinger,[48] and Yamamoto.[49] The classical studies[50] on the conformation of polymer chains of polypropylene and other vinylic polymers should be mentioned in this context. In all these papers the conformational preferences and their causes have been clearly reported and discussed. The next step, however, to use this information to achieve an intentional conformation design, was still required. As a prelude, we started in 1991 with Thomas Sander and Martin Brumm to evaluate the conformational preferences of polysubstituted heptane chains by force field calculations.[51] On compound **18**, for example, the calculations showed that no single conformation exceeded a population of 10%, yet the calculations on the two central backbone bonds (marked on **18**) predicted a modest conformational preference of 54% for the conformation shown (Scheme 9). We realized that this conformational preference can be augmented significantly by ring annellation (see structure **19**), which reduces the number of freely rotating bonds. This led to our study of the bis(tetrahydropyranyl)methanes **28**.[52, 53] Our investigation at this stage were poorly focussed since we lacked information on problems for the solution of which conformation design would provide an essential element. In this situation, we resorted to writing a review before we had made any major contributions to the field. We hoped that this review[4] would be read by colleagues in bioorganic chemistry and drug research and that we would this way receive suggestions to interesting problems. The response did not meet our expectatons: A search in the Science Citation Index shows that this review was largely ignored by people in biomedical research. Thus, in the end, we had to go ahead by ourselves.



Scheme 9. Preferred conformation at the bonds marked with × and the percentage of these conformations in the total conformer population (calculated with the MM3* force field).

2. Tracing Nature: 2,4-Dimethylpentane Derivatives

The period started in which in our group Ulrike Rolle and then Richard Göttlich scouted out the possibilities of conformation design with great enthusiasm. Sobering results followed quickly. For instance, the crystal structure of venturicidine benzoate[54] and the conspicuous pattern of methyl substituents in the venturicinde aglycon **4** led us to believe that alkane chains with a substituent pattern similar to that in venturicidine, such as **20**, should preferentially populate a conformation with a fully extended backbone (Scheme 10).



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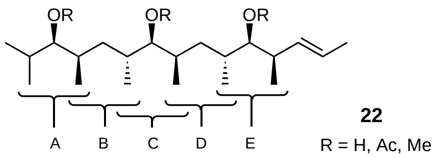
21

Scheme 10. Examples for polymethylated alkane chains with a substituent pattern corresponding to venturicidine.

For this reason, we developed an efficient method to synthesize compounds with structures similar to those found in venturicidine[55] and reached, for instance, the tetraol **21**.[55–57] With **21** in hand, we could not measure the vicinal $^3J_{H,H}$ coupling constants[58] which would allow a conformation analysis. The relevant ^1H NMR signals could not be resolved even using a 500 MHz instrument and—as we see it today—compound **21** has no tendency to populate a fully extended conformation!

We reacted to both failures aggresively: In a collaboration with Professor Berger—resulting in the dissertation of Thomas Fäcke—^{13}C NMR editing methods were developed through which $^3J_{H,H}$ coupling constants could be determined even when the ^1H signals overlayed.[59] Moreover, methods were developed which, for compounds with ^{13}C in its natural abundance, allow the determination of ^{13}C–^{13}C coupling constants,[60] which in turn give information on the conformation of a molecular backbone. Armed in this manner, we tackled the conformation analysis of the intermediate **22**,[57] which lies on the synthetic pathway of **21**, the largest such compound amenable to such an analysis (Scheme 11). The result[61] was a complete surprise for us: There was none or only a low, local conformational preference in the segments A and C. The high conformational preference hoped for in the *tt* conformation was, however, found in the segments B and D. In segment E, a preference for the *gg* conformation was found, a conformation in which the main chain bends to align the alkenyl residue sideways. This taught us how remote we were from a real understanding of the factors which determine the conformation in such compounds.



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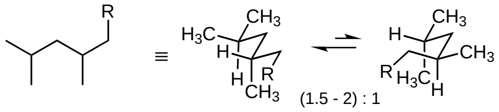
Scheme 11. Synthetic analogues to the polypropionate part of venturicidine.

In due course—initially more or less random, eventually quite focused–we synthesized and analyzed numerous model compounds. In this manner, we slowly recognized the factors which determine the local conformations in compound **22**, which allowed us to rationalize the initially surprising results. The results may be summarized as follows: Placing a residue *R* at the end of a 2,4-dimethylpentane segment (see structure **23**) favors the population of the extended conformation, yet the effects remain relatively small (<2:1)[61] (Scheme 12).

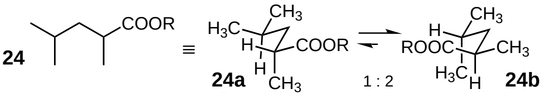


23

Scheme 12. Conformational preference of a 2,4-dimethylpentane skeleton (R = alkyl residue).

The connection of several 2,4-dimethylpentane units to give polymethylated alkane chains like **22** is synonymous with the extension of a 2,4-dimethylpentane unit. It is therefore no surprise that a connection of dimethylpentane segments by itself does not generate a high conformational preference. It should be mentioned that syndiotactic polypropylene has been found to crystallize as two polymorphs, one with an extended local conformation for all dimethylpentane segments,[62] and one with a doubly bent conformation for every second dimethylpentane segment.[63] In short, a 2,4,6,…*n*-polymethylated alkane chain has, for each dimethylpentane segment, only two low energy conformations. Compounds that populate a single backbone conformation cannot therefore be reached simply by placing methyl substituents at every other carbon atom at a chain, at least when they are arranged in a syndiotactic manner (compare also the situation in discodermolide tetraacetate discussed in the previous Section).

If one replaces one of the methyl groups in 2,4-dimethylpentane by a vinyl ester (**24**) or aldehyde residue, that is, residues bound via an sp^2-hybridized carbon atom, the conformer **24b** is preferentially populated (but only by a small margin; Table 1).[64] In **24b**, the less bulky sp^2-hybridized residue takes a position lateral to the main chain. These statements are based on a comparison of the $^3J_{H,H}$ coupling constants with those calculated for the individual low energy conformers (Scheme 13).



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24a

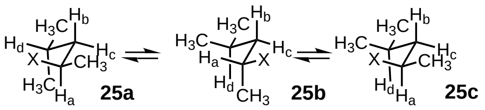
24b

Scheme 13. Conformational preference of a 2,4-dimethylpentanoate.

The position of the conformer equilibrium is determined by the fact that in **24a** the methyl group is oriented sideways to the main chain, where it experiences a *gauche* interaction with the main chain. In conformer **24b**, the ester group lies in this position. If a substituent is positioned at the end of the chain, it is free of such *gauche* interactions with the main chain. Consequently, the sterically less demanding substituent (compare the *A* values[65] describing the equatorial/axial equilibrium for monosubstituted cyclohexanes) will adopt the position lateral to the main chain. The effects, however, remain small. Even if they may be augumented or overcompensated by further substituents, local conformer preferences in excess of 80% are attained in this manner only with difficulty.[64]

A further variation in the 2,4-dimethylpentane system lies in the substitution of one or two of the methyl groups by halogen atoms or other heteroatom-bound groups (X in **25**;

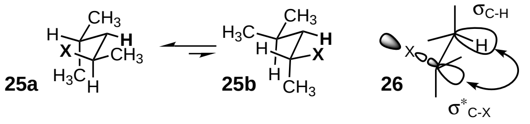
Table 1. Estimated conformer populations for 2-substited 4-methylpentanes from $^3J_{H,H}$ coupling constants and from force field calculations.



X =	Contribution (%) of the **a**, **b**, **c** conformers to the total conformer population[a]	NMR coupling constants [Hz]				Solvent	Estimated **a**:**b** from NMR data
		H_aH_b	H_aH_c	H_bH_d	H_cH_d		
COOMe	53 : 32 : 11	8.0	5.6	n.d.	n.d.[b]	$CDCl_3$	1.7 : 1
$CH=CH_2$	71 : 19 : 9	8.2	6.2	n.d.	n.d.	$CDCl_3$	1.5 : 1
C_6H_5	68 : 20 : 10	8.5	5.6	n.d.	n.d.	$CDCl_3$	2 : 1
$CH=O$	57 : 32 : 5	7.4	6.5	n.d.	n.d.	$CDCl_3$	1.2 : 1
OH	53 : 24 : 15	8.2	4.9	6.0	8.2[c,d]	$CDCl_3$	1.6 : 1
		8.2	4.9	6.0	8.2	DMSO	1.6 : 1
OMe	47 : 28 : 12	7.4	5.6	6.4	7.4[d]	$CDCl_3$	1.4 : 1
NH_2	50 : 34 : 7	7.8	5.9	6.4	7.8[c]	DMSO	1.4 : 1
NH_3^+ AcO^-	39 : 54 : –	5.9	8.6	8.2	6.2[c]	DMSO	1 : 1.7
NHMe	54 : 32 : 10	5.7	7.7	8.0	6.0	DMSO	1 : 1.6
		6.3	7.4	7.9	6.5	$CDCl_3$	1 : 1.3
NMe_2	58 : 31 : 8	7.1	7.1	7.1	7.1[c]	DMSO	1 : 1
		5.7	8.0	7.9	6.3	$CDCl_3$	1 : 1.5
NPhth[e]	78 : 7 : 10	9.9	4.8	4.8	10.3[c]	C_6D_6	3.7 : 1
Cl	63 : 29 : 4	9.3	4.8	5.4	8.6	$CDCl_3$	2.2 : 1

[a] The values, estimated with the MM3* force field, do not total 100 % on account of other conformation types. [b] n.d. = not determined. [c] Coupling constants were assigned by deuterium labeling. [d] The calculated (Macromodel) *gauche* coupling constants for the hydrogen atom positioned *α* to the oxygen atom depends on the spatial alignment of the OR group. These coupling constants were not used in the estimation of the **a**:**b** ratio. [e] NPhth = phthalimidyl.

Scheme 14). For 2-chloro- and 2-bromo-4-methylpentane **25** (X = Cl, Br), it had been shown earlier by IR studies[66] that conformer **25a** with the halogen atom lateral to the main chain predominates. An analysis of NMR coupling constants for a series of 2-heteroatom-substituted 4-methylpentanes **25**[67] showed that the conformational preferences are rather small (see Table 1). The largest effects were recorded for electronegative residues such as phthalimidyl-, chloro-, or bromo-substituents. This indicates that it is not only steric effects that dominate the conformer equilibrium. Perhaps there is an additional stabilization of **25a** by an $\sigma_{C-H}-\sigma^*_{C-X}$ hyperconjugation[68] (see structure **26**), which could not occur in **25b** on account of the absence of a C–H bond antiperiplanar to C–X.

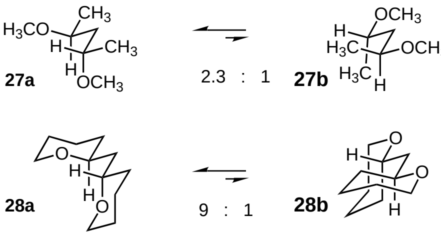


Scheme 14. Conformational preference of 2-X,4-methylpentanes.

However small the conformational preference were in the monosubstituted compounds **25**, higher preferences may be expected for 2,4-di-heterosubstituted pentanes. For a the *d*,*l*-stereoisomer, the conformational preferences found in the monosubstituted derivatives **25** should reinforce one another (they should counterbalance in the *meso*-isomers!). A starting point for further scrutiny was the dimethoxy compound **27**, on which previous investigations[69] indicated a 2.3:1 conformation preference towards positioning the methoxy groups lateral to the main chain. We surmised that the free rotation of the methoxy groups compromises the conformational preference to favor **27a**. This is a consequence of the methyl groups of the two methoxy units in **27b** may orient in three positions in space. In conformer **27a** only two arrangements are free of *syn*-pentane interactions. This increases statistically the population of the (undesired) conformer **27b** in the conformer equilibrium. By tying the methoxy groups into a ring, like in **28**, this effect can be avoided. Indeed, the bis(tetrahydropyranyl)methane **28** synthesized by B. Colin Kahrs showed clearly a more marked conformer preference of about 9:1[52] (Scheme 15).

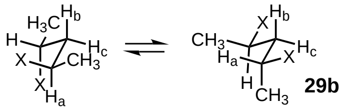
The tendency of electronegative heteroatoms to adopt a position lateral to the main hydrocarbon chain[70] has been exploited by Dirk Stenkamp in a systematic study[67, 71] of 2,4-disubstituted pentanes (**29**, Table 2).

The conformational preferences for the chloro- and bromo compounds, estimated from the vicinal $^3J_{H,H}$ coupling constants, agree with previous reports.[73] The dichloro compound **30** had been investigated before as a model compound for the local conformer preferences in polyvinylchloride.[74] This



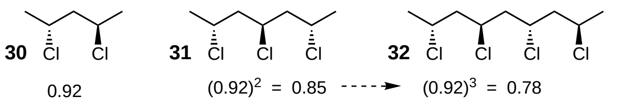
Scheme 15. Tying freely rotatable groups into rings increases the conformational preferences of a molecular skeleton.

Table 2. The $^3J_{H,H}$ coupling constants and the the derived conformer population for 2,4-disubstited pentanes.



X =	NMR coupling constants [Hz]		**a** : **b**
	H_aH_b	H_aH_c	
OMe	7.8	4.6	2.3 : 1[69]
OAc	9.0	3.8	3.5 : 1[72]
$C\equiv C\text{-}SiMe_3$	10.6	4.3	4.5 : 1
N_3	10.5	3.0	8 : 1
Cl	10.6	2.2	11.5 : 1
Br	10.8	4.4	11.5 : 1
NPhth	11.8	4.5	19 : 1

shifted our attention to syndiotactic 2,4,6,…*n*-polychlorinated alkanes, which might possess a marked preference for the fully extended conformation (Scheme 16). Compound **31** had already been evaluated by experiment and calculations.[75] We prepared **31** anew[76] and determined its $^3J_{H,H}$ coupling constants: These revealed in each of the segments of **31** the same conformational preference (0.92) as in the simple dichloropentane **30**. For the total molecule of **31**, the conformational preference amounts to only 0.85 (=(0.92)^2). On this basis, one would predict a total conformer preference of 0.78 for **32**, which thereby indicates the limitations of any conformation design along those lines. An acceptable total conformer preference for a larger molecule (arbitrarily set to >0.8) can only be reached if the local conformer preference in each of the segments is very high. In this respect, the diphthalimidyl compound **29** (Table 2) is promising.

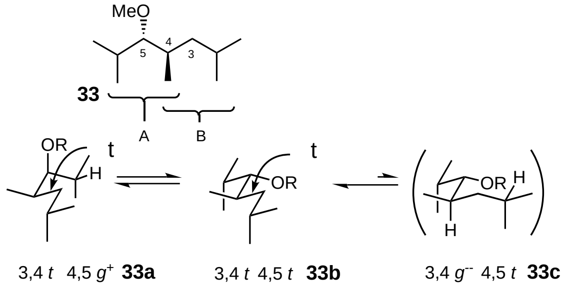


Scheme 16. Conformational preferences of fully extended alkane chains in compounds which model syndiotactic polyvinylchloride.

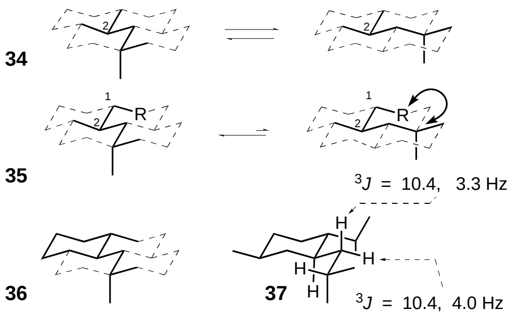
3. Conformation Control by Inductor Groups

In reconsidering the results obtained so far, we reexamined those cases in which we had (accidentally) encountered a high conformational preference. This held for the segments B and D in compound **22**. To account[61] for this high conformational preference, reference to the model compound **33** will be discussed: It is the "*anti*"-configuration of the methoxy and the methyl groups, in which the methoxy group at C-5 is placed in a position which allows only a single, low energy conformation in the neighbouring dimethylpentane segment B. The other local conformation in segment B (**33c**) is destabilized by a *syn*-pentane interaction with the methoxy group at C-5! The methoxy substitutent therefore induces a preferred *trans*-conformation of the C-3/C-4 bond (see **33a** and **33b** in Scheme 17).

We may conclude that the methoxy substituent serves as an inductor group as it selectively destabilizes one of the two backbone conformations in the neighbouring segment. Inductor groups—the groups that influence the population of a single conformation at a close by (but not necessarily adjacent) bond—were known. We refer to the effects of a *tert*-butyl group or, more generally, of quaternary centers.[39–41] With Martin Stahl and Ulrich Schopfer, we evaluated the requirements for inductor groups that would allow a conformation design in 2,4,6,…*n*-polysubstituted alkane chains.[77] The following principle became clear: Introduction of a substitutent at C-1 of a 2,4-dimethylpentane **34** destabilizes one of the two backbone conformations, provided the substituent is held antiperiplanar to the C-2 methyl group (see structure **35** in Scheme 18).

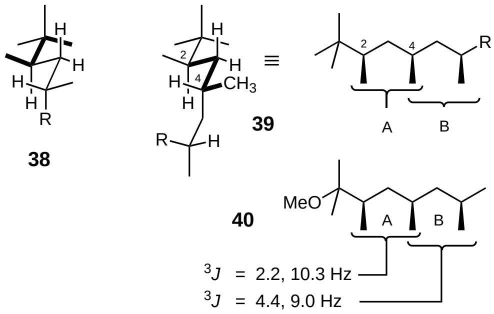


Scheme 17. Effect of an *anti*-positioned methoxy substituent in segment A on the conformational preference in segment B of compound **33**.



Scheme 18. Effect of a C-1-positioned inductor substituent on the conformer equilibrium in 2,4-dimethylpentane.

A simple means to hold a substituent at the position indicated in **35** is to annelate a six-membered ring in a chair conformation, as **36**. A compound of this type, **37**, was synthesized by Philipp Reiss.[78] The large difference in the $^3J_{H,H}$ coupling constants demonstrates the predominance of a single conformation, as predicted by calculations with the MM3* force field from the Macromodel program.[79] There is a foolproof possibility to hold a substituent antiperiplanar to the C-2 methyl group, as indicated in **35**, by chosing compound **38**, that is, by making use of the *tert*-butyl effect:[39–41] Due to the quaternary center at C-1, there is always one residue antiperiplanar to the C-2 methyl group (Scheme 19).

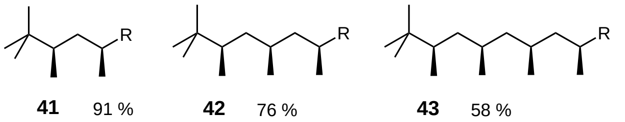


Scheme 19. Transmission of the conformation induction that originates from a *tert*-butyl residue from a dimethylpentane segment to a neighbouring one.

More fascinating was the insight that compound **38** may serve as such an inductor group to an attached second dimethylpentane segment **39**. The *tert*-butyl group induces a preferred conformation in segment A of compound **39**. This conformation places C-2 antiperiplanar to the C-4 methyl group, which should induce a preferred conformation in segment B of **39**.

This prediction was tested with compound **40**,[80] which contains a methoxy group, the presence of which would prevent overlay of the relevant ^{1}H NMR signals. The coupling constants recorded for **40** show that a local conformational preference prevails not only in segment A but also in segment B.

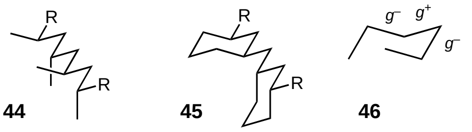
Such a transmission of the folding information from one to the next dimethylpentane segment requires that the methyl side groups are arranged in an isotactic manner, as in the structures **41** and **42**. Isotactic polypropylene crystallizes in a single modification, in which the chain adopts the expected helical conformation.[81] This is exactly the conformation which results from transmission of the folding information from adjacent segments. As soon as there is a single syndiotactic unit in a 2,4,6,…*n*-polysubstituted alkane chain, the transmission of the folding information is interrupted at this point. "Downstream" from such a syndiotactic unit, the chain can adopt a multitude of low energy conformations.[77] But, even in a homogenously isotactic substituted alkane, this transmission soon reaches its limitations. This was foreshadowed in the difference between the coupling constants for the segments A and B in compound **40**. Force field calculations indicate a rapid decrease in the overall conformational preference with an increase in the number n of adjacent dimethylpentane segments: By three segments, the total conformer preference falls below 60 % because of the number of individual, undesired conformers enduring a single *syn*-pentane interaction increases by $n(n+1)$ (Scheme 20).



41 91 % **42** 76 % **43** 58 %

Scheme 20. Calculated preference (percentage of the total conformer population) for attaining the fully extended conformation of derivatives of isotactic oligopropylene.

It is evident that the loss of entropy, which accompanies the population of a single conformation, will increase with the number of the freely rotating bonds and hence with the size of the molecule. Ring annellation reduces the entropy loss associated with the population of a single conformation (compare compounds **44** and **45**, which have the same number of bonds between the R groups; Scheme 21). In essence, ring annellation is no more than cheating. Yet nature is doing just the same by using the tetrahydropyrane ring frequently found in polyketide natural products and, in the end, we too did just the same in optimizing the conformational preference in going from 2,4-dimethoxypentane **27** to the bis(tetrahydropyranyl)methane **28**.



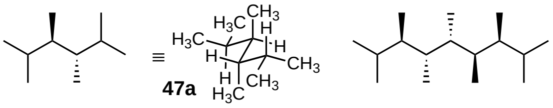
44 **45** **46**

Scheme 21. The number of freely rotating backbone bonds may be reduced by annelation.

4. Round Three: 2,3,4,5-Tetramethylhexane Derivatives

When trying to endow larger molecules with the preference for a single conformation, the main problem is the concomitant loss in entropy. The Gibbs–Helmholtz equation ($\Delta G = \Delta H - T\Delta S$), which has to be applied to conformer equilibria as well, suggests an escape route: The well behaved molecule, in the sense of enhancing the population of a single conformation, involves a loss in entropy. Nevertheless, enhanced population of the desired conformation may be attained if we penalize the undesired conformations with destabilizing enthalpy (a higher value of ΔH). We will simply increase the penalty for misbehaviour. In the molecules discussed in Section 3, each undesired backbone conformation was penalized by a simple *syn*-pentane interaction. We should address molecules in which any undesired conformation is penalized by two *syn*-pentane interactions or, similarly, by a *syn*-hexane interaction. A *syn*-hexane arrangement corresponds to a folding of a hexane backbone with a $g^-g^+g^-$ sequence of dihedral angles; see structure **46**. According to calculations on this compound,[13] this arrangement is not a minimum on the energy hypersurface[82] because of the presence of two *syn*-pentane interactions.

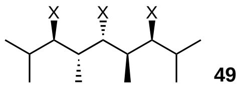
We considered *meso*-2,3,4,5-tetramethylhexane **47**, which has a backbone in which rotation from the conformation **47a** about the central C-3/C-4 bond creates two *syn*-pentane interactions simultaneously[77] (Scheme 22). Unfortunately, calculations on **47** predict merely a conformational preference of 44 %. This arises from the eight destabilizing *gauche* interactions present in the minimum energy conformation **47a**. These *gauche* interactions decrease the energy difference to the next higher undesired conformer. Any extension of such a system in the direction of larger compounds, such as **48**, appears to be unattractive at first sight. On the other hand, it is conceivable to make some compromises by selecting buttressing substituent groups, which, when positioned laterally to the main chain, cause only small (at least, smaller than methyl) *gauche* interactions. Such substituents, such as oxygen, chloro, vinyl, phenyl, or phthalimidyl residues, have been identified in Section 2. MM3* calculations indicate that high conformational preferences can indeed be reached with such substituents for extended molecules such as **49**[83] (Scheme 23).



47 *meso* MM3* : about 44 % **48**

Scheme 22. Preferred conformation of *meso*-2,3,4,5-tetramethylhexane.

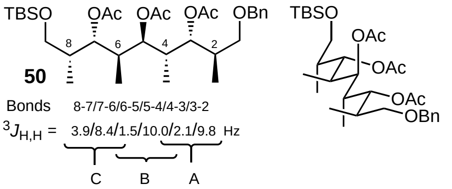
This encouraged Dirk Stenkamp to synthesize compound **50**,[83] which, according to the $^3J_{H,H}$ coupling constants, possesses a high conformational preference in the segments A and B (>90 %; Scheme 24). This can be traced back to the antiperiplanar placement of C-7-OAc/C-6-CH$_3$ (controls segment B) and C-5-OAc/C-4-CH$_3$ (controls segment A). The



49

	a	b	c	d	e	f	g	h
X =	OCH_3	OAc	Cl	Br	$HC{=}CH_2$	Ph	NPhth	CN
	13	49	89	91	77	96	98	53

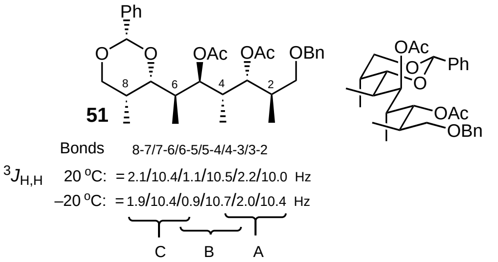
Scheme 23. Conformational preference (percentage of the total conformer population) for attaining a fully extended conformation of analogues of 2,3,4,5,6,7,8-heptamethylnonane.



Scheme 24. The $^3J_{H,H}$ coupling constants and preferred conformations of polyoxygenated, polymethylated alkanes **50**. TBS = *tert*-butyldimethylsilyl, Ac = acetyl, Bn = benzyl.

conformational preference in segment C is high but not as high as in the segments A and B. This can be attributed to the situation that the C-7/C-8 backbone bond in segment C no longer corresponds to a central bond in a tetramethylhexane **47**. Alternatively, since the C-9-OR and C-8-CH_3 groups are not necessarily antiperiplanar, the effect of C-9-OR as an inductor group on the conformation in segment C is only moderate. Such an antiperiplanar arrangement of C-9-OR and C-8-CH_3 may be enforced by combining the C-7 and C-9 oxygen-containing functional groups into an acetal ring.

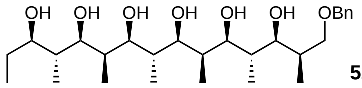
These considerations led to the synthesis of compound **51**, in which the conformational preference in each of the segments exceeds 90%. That the conformational preference does not yet exceed 95% can be recognized from the temperature dependence[83] of the vicinal coupling constants: Their difference is increased slightly upon lowering the temperature from +20 to −20°C (Scheme 25).



Scheme 25. The $^3J_{H,H}$ coupling constants and preferred conformation of compound **51**.

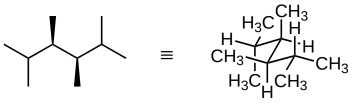
These results indicate how far a conformation design can be pushed based on highly substituted alkane chains. Another example, **52**, is provided from Paterson's group.[84] In compound **52**, the slightly curved conformation of the main chain is stabilized by a sequence of hydrogen bonded bridges (Scheme 26).

The *meso*-tetramethylhexane **47** is not the only starting point that can attain molecular backbones with a high conformational preference. The (R^*,R^*)-2,3,4,5-tetramethylhexane **53** likewise constitutes a system in which rotation about the central bond out of the conformation **53a** generates two simultaneous *syn*-pentane interactions (Scheme 27).



52

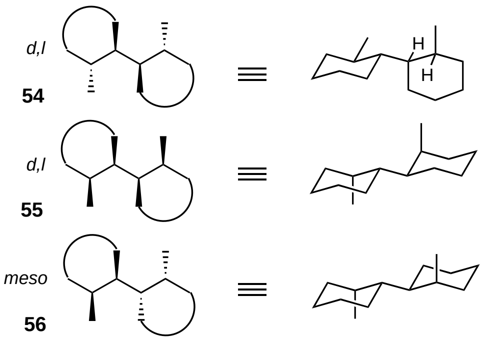
Scheme 26. Polyhydroxylated and polymethylated alkane chains having a high conformational preference for attaining a fully extended conformation.



53 *d,l* MM3* : about 40% **53a**

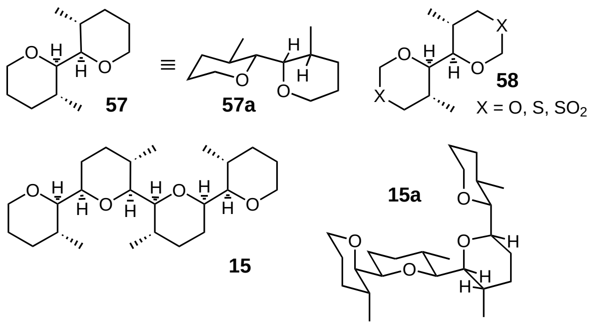
Scheme 27. Preferred conformation of *d,l*-2,3,4,5-tetramethylhexane.

Beginning with **53**, we would like to illustrate yet another way to avoid the dilemma of destabilizing the desired conformation **53a** by eight *gauche* interactions, which rendering the energy difference to the next higher conformation too small. Annellation of six-membered rings may help here too, since, for each inter-ring bond in a cyclohexane ring, one *gauche* arrangement is incorporated into the ring and is no longer destabilizing. Double annellation of six-membered rings of **53** generates either **54** or **55**. Likewise, ring annellation to the *meso*-compound **47** generates **56** (Scheme 28).



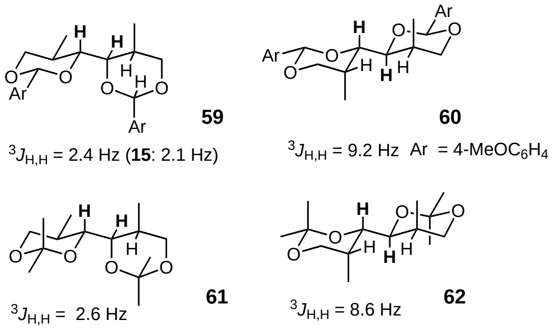
Scheme 28. Possible anellation of six-membered rings to 2,3,4,5-tetramethylhexane and preferred conformations of the resulting compounds.

Force field calculations indicate that all of these derivatives of dicyclohexyl should have a high conformational preference at the inter-ring bond. The largest energy difference between the most stable and the second-most stable conformation is calculated for compound **54**, in which the methyl groups are in an equatorial position. Still et al. had realized the high conformational preference of this system prior to our studies: They used the oxygenated derivatives **57**[33, 37] as well as the acetals **58**[34–36] to arrive at conformationally preorganized host molecules, such as **15**, to allow the enantioselective complexation of amino acids (Scheme 29).



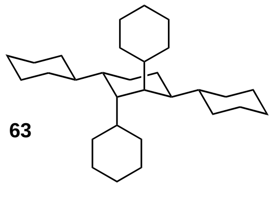
Scheme 29. Conformationally preorganized bis- and oligotetrahydropyrane derivatives investigated by Still et al.

Trixi Brandl, from our research group, synthesized and analyzed the benzylidene acetals **59** and **60** as well as the acetonides **61** and **62**. The $^3J_{H,H}$ coupling constants at the interring bond were taken from the ^{13}C side bands in the ^1H NMR spectrum. The values given in Scheme 30 attest to the high conformational preference.



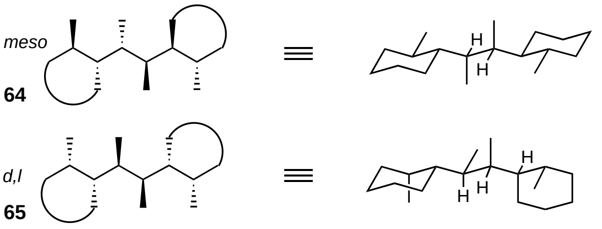
Scheme 30. Conformationally preorganized 4,4′-di-1,3-dioxane derivatives.

A further dicyclohexyl derivative with a high conformational preference at the inter-ring bonds is the *ctc*-tetracyclohexylcyclohexane **63** described by Biali et al (Scheme 31).[85]



Scheme 31. 1,2,3,4-Tetracyclohexylcyclohexane with a high conformational preference.

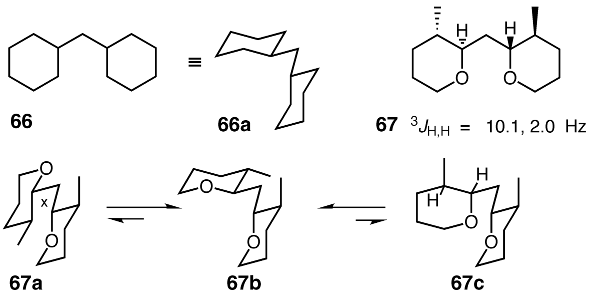
The effective six-ring annelation can also be applied to the homologues of the tetramethylhexanes **47** and **53**. The larger molecules **64** and **65** display, according to force field calculations, a high conformational preference at all the skeletal bonds linking the two cyclohexane rings. The high conformational preference can be ascribed to the fact that any 120° rotation about these skeletal bonds of the conformation shown generates simultaneously two *syn*-pentane interactions (Scheme 32).



Scheme 32. Possible anellation of six-membered rings to hexamethyloctane and preferred conformations of the resulting compounds.

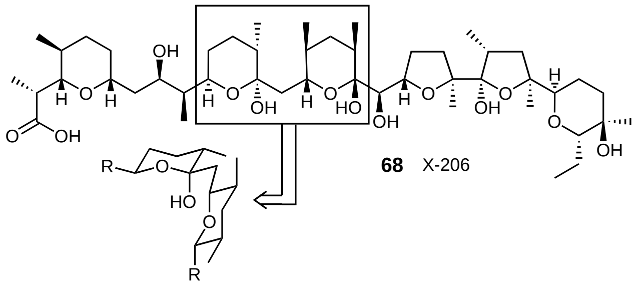
5. Dicyclohexylmethane Derivatives

The same situation can also be attained by suitable placement of methyl substituents at a dicyclohexylmethane skeleton **66**. By extension of the studies on the related bis(tetrahydropyranyl)methane **28**, two methyl groups were introduce to give **67** (Scheme 33). The preferred conformation is **67b**. A +120° rotation around the bond × leads to a *syn*-hexane destabilization (→**67a**). A −120° rotation generates conformer **67c**, which is destabilized by a lesser *syn*-pentan interaction between two oxygen atoms. Kahrs determined the relevant $^3J_{H,H}$ coupling constants which showed that **67** possesses a higher conformational preference than the parent compound **28**.[86]



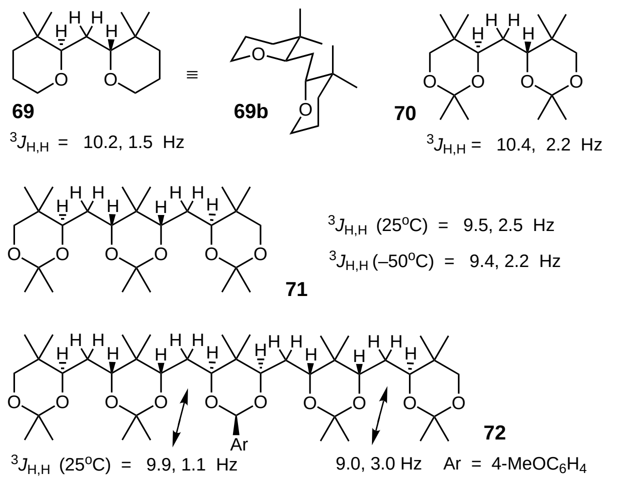
Scheme 33. Conformational preferences of dicyclohexylmethane and bis(tetrahydropyranyl)methane derivatives.

Structures related to **67** are found in natural products: Such a bis(tetrahydropyranyl)methane unit is central to the structure of the antibiotic X-206 (**68**; Scheme 34).[88] Here, the bis(tetrahydropyranyl)methane unit carries optimally positioned, butressing methyl substituents. The resulting high local conformational preference is critical to a distinct folding of the total molecule into a form optimal for binding and transporting cations. In this case, conformational control is ostensibly linked to the molecular function.



Scheme 34. A bis(tetrahydropyranyl)methane unit in the antibiotic X-206.

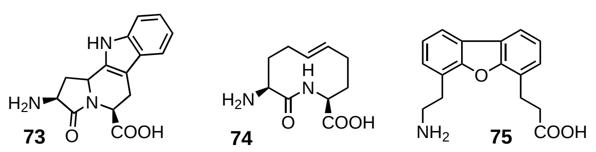
The conformational preference of the skeleton **67** may be further improved by placing two additional methyl groups to generate **69** (Scheme 35). In **69**, the conformer corresponding to **67c** is now stabilized as well by a *syn*-hexane situation. The coupling constants observed for **69**[52] document the outstanding preference of this system to adopt conformation **69b**. This holds likewise for the corresponding acetonide **70**.[53] When advancing to the corresponding trimer **71** and the pentamer **72**, which have been synthesized by Thomas Trieselmann, one recognizes a small decrease in the diffences of the coupling constants. This attests to the lowering of conformational preferences in larger molecules (the given coupling constants in **71** or **72** represent the average over two backbone segments!). Quite clearly, conformation control in larger molecules is a battle against the unavoidable loss of entropy. Nontheless, compounds **70**–**72** from our third round of conformation design demonstrate how far effective conformation control can be extended towards larger compounds.



Scheme 35. Bis(tetrahydropyranyl)methane derivatives carrying buttressing substituents to reach a high conformational preference.

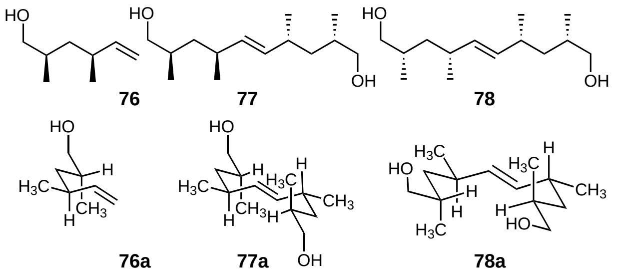
6. Applications of Conformation Design

All our investigations described in the previous Sections were motivated by the desire to delineate the scope of a conformation design and to demonstrate that we can understand, as well as reproduce, nature's conformation designs. In the area of peptides, nature demonstrates how closely tied any biological activity is to a distinct backbone conformation, the "active conformation".[89] For some of the biologically active peptides, one has well founded concepts as to the spatial disposition of the pharmacophoric groups. One tries to mimic these arrangements in rigid analogues as used in the development of peptidomimics.[90] This may be briefly illustrated for β-turn mimics:[91] A β-turn is a folding motif of a peptide chain, in which the chain direction is reversed in space to allow the formation of β-sheets. When designing β-turn mimics, one concentrates on rigid analogues, like **73**,[92] or ones of limited conformational mobility, such as **74**[93] or **75**[94] (Scheme 36).



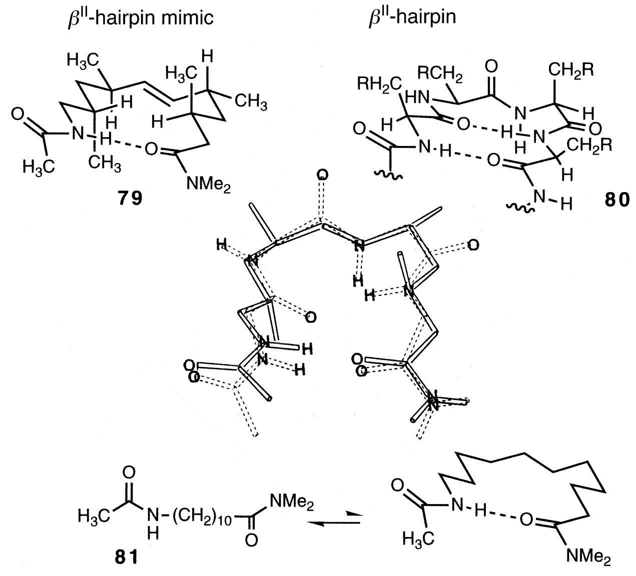
Scheme 36. Examples of β-turn mimics.

Conformationally mobile β-turn mimics would approximate the situation found in a natural β-turn more closely. It is therefore a challenge for conformation design to develop fully flexible but conformationally preorganized β-turn mimics. We considered the alcohol **76** as the starting point for such an endeavour. Ulrich Schopfer showed—in congruence with the principles delineated in Section 2—that **76** populates conformation **76a** by about 80% (Scheme 37). We then synthesized the diols **77** and **78**, in which two modules of the type **76** are joined in a heterochiral (**77**) and homochiral (**78**) manner. Compound **77** is expected to preferentially populate the Z-shaped conformation **77a**, while the stereoisomeric diol **78** populates, according to NOE experiments, the U-shaped conformation **78a**.[95]



Scheme 37. Conformationally preorganized derivatives of *trans*-5-decene-1,10-diol.

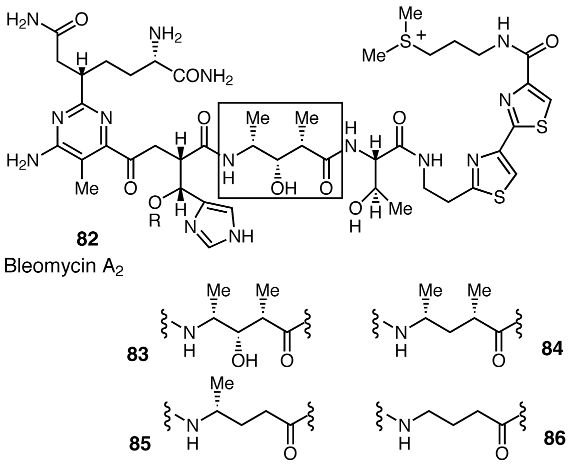
Conceptually, it is only a small step from **78** to **79**. An overlay of the most stable computed conformation of **79** with the structure of a prototypical β^{II}-hairpin[96] demonstrates the marked similarity of the three-dimensional structures (Scheme 38).



Scheme 38. Comparison of the structures of a β-hairpin mimic and of a β-hairpin, as well as a 10-acetamidodecanoic amide, which is not preorganized conformationally.

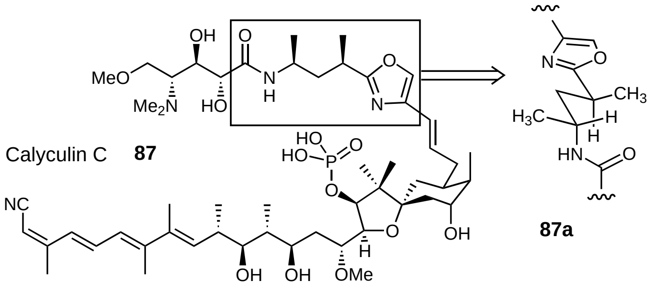
Compound **79**, synthesized by Ulrich Schopfer and Trixi Brandl showed a high preference for a conformation with an intramolecular amide hydrogen bridge in its ^{1}H NMR and IR spectra, which corresponds to that of a β-hairpin.[97] Compound **79** allows an easy identification of the elements of conformation design: the four methyl groups and the double bond. The analogous compound **81**, devoid of these elements, has the same distance between the amide moieties. Further, **81** is multiconformational as it possesses both intra- and intermolecularly NH-bridged conformations.

Other nonnatural amino acids, for example, β-[98, 99] and γ-[100]amino acids or certain THF–amino acids[101] may be substituted in such a manner, that peptides derived thereof may have distinct spatial structures.[99] Conformation design of such nonnatural amino acids is of particular interest because we have hitherto no information what advantage nature takes in using flexible backbones with preferred conformations instead of rigid modules in most biologically active compounds. Such information could be obtained by studying the consequences of changes in the disposition towards the active conformation of a given active compound while maintaining a constant distance between the pharmacophoric groups. Such a study has recently been reported for bleomycin A_2 **82**, in which a specific amino acid **83** serves as a conformationally preorganized linker unit between the two halves of the molecule containing the pharmacophoric groups[102] (Scheme 39). Replacement of the linker **83** by other γ-amino acids **84** to **86** leads to a diminishing tendency to populate a preferred conformation and a commensurate drop in biological activity by a factor of ten.[103] From these results, the group of Boger was able to clearly demonstrate a relationship between the tendency inherent in the backbone to populate a distinct active conformation with the biological activity.



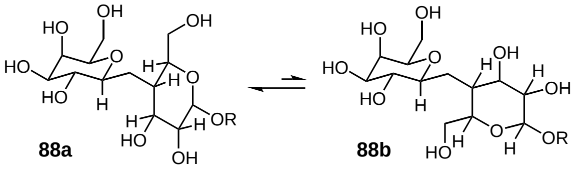
Scheme 39. Bleomycin A_2 and structural analogues.

A derivative of an amino acid enantiomeric to **84** is found in the molecular backbone of calyculin C **87**.[104] This unit has a high conformational preference and causes a distinct folding of the molecule (compare **87a**; Scheme 40) Surprisingly, the conformational preference of this linker unit is much higher in the natural product than in related model compounds like **84**.[105] The reason for this remains to be clarified.



Scheme 40. Calyculin C with a conformationally preorganized segment.

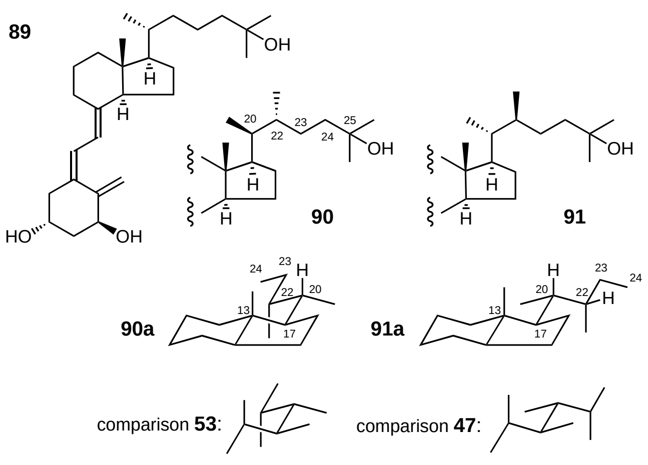
The interaction of a low molecular mass active compounds with a protein receptor leads to a bound molecule, the conformation of which is not necessarily identical with the most stable conformation in the unbound state. In these cases, the receptor selects one conformation from a pool of rapidly interconverting conformers of the guest. This one conformation corresponds to the active conformation. This has been reported for the binding of C-lactose **88** to bovine heart galectine.[106] The Curtin–Hammett principle therefore applies to the binding process; the statistical chance of each conformer to bind is the same averaged over the conformer population (Scheme 41).



Scheme 41. The lowest energy conformers of C-lactose.

Of more interest are those cases in which a biologically active compound is bound to two receptors in different conformations. C-Lactose was found to bind to ricine in the *anti*-conformation **88a**, whereas binding to bovine heart galectine occurred in the *syn*-conformation **88b**.[106, 107] This opened the possibility to synthesize rigid analogues of either **88a** or **88b** to achieve selective binding to the different receptors. Unfortunately, increasing the rigidity of biological active compounds, such as disaccharides, by adding bridging rings is not without further problems, as it does not guarantee a higher Gibbs free energy of binding to the corresponding receptor protein.[108] It is therefore of interest to establish whether selectivity in the binding to different receptors can be attained by using conformationally flexible, but conformationally preorganized, analogues of the natural guest molecule.

For this reason, the following example from vitamin D research should be highlighted: 1α,25-Dihydroxy vitamin D_3 (**89**; Scheme 42) has multifaceted biological activities affecting the calcium and phosphorus metabolisms, cell differentiation, and regulation of the immune system. For ther-



Scheme 42. Conformationally preorganized analogues of 1α,25-dihydroxy vitamin D_3.

apeutic applications, it is necessary to address these biological responses separately. Thus, vitamin D_3 analogues are desired which lead to only one of these responses. It has been found that the stereoid side chain of **89** is in a different conformation when bound to vitamin D receptor protein (VDR), which regulates calcium metabolism, or when bound to the vitamin D binding protein (DBP). This highlights that there are different and distinct active conformations of the C-17/C-25 side chain of vitamin D_3 and opens the opportunity to modify binding selectivity by conformation design.

By a change of the configuration of **89** at C-20, introduction of a further conformation-determining methyl group at C-22 produces **90** (its preferred conformation is indicated as **90a**), which binds more strongly to VDR than the parent **89**. Compound **90** is devoid of activity against DBP. The stereoisomeric compound **91** has only a low activity against VDR but binds strongly to DBP.[109] Force field calculations suggest[110] that in **90** the preferred conformation of C-13/C-17/C-20/C-22 is $>90\%$ *gauche* but in **91** $>90\%$ *trans*.[111] The next chain segment C-20/C-22/C-23/C-24 remains biconformational. In order to rationalize the conformational preferences of **90** and **91**, it is instructive to recognize the tetramethylhexane substructures **53** in compound **90** and **47** in compound **91**.

7. Retrospect and Outlook

There is an optimal time for every research project. The investigations towards a conformation design could not have been carried out twenty years earlier because neither computer hardware nor software was sufficient to calculate conformer populations routinely. Further, NMR spectroscopy had not reached a state that allowed conformation analyses of molecules of the size (up to about 90 skeleton atoms) considered here. To successfully tackle this project, the methods of stereoselective synthesis should have reached a state of reliability which permitted not only the synthesis and study of single molecules of interest but also of whole sets of stereoisomeric compounds. It was only at the beginning of the 1990s that developments permitted us to address all of the questions associated with conformation design.

Now at the beginning of this new century, biologists are increasingly thinking in chemical terms, that is, on a molecular level by considering single molecules and their individual function. Organic chemists are moving their frontiers, in the context of biochemical problems, towards ever larger molecules and defined molecular assemblies; these systems are synthesized and studied because of their biological properties. The structure and properties of such molecules are related through their folding, to which conformation is the key. Conformation analyses of large molecules is now within reach using advanced NMR techniques. As soon as one can investigate the interrelation between conformation and properties of larger molecules, conformation design of such entities will move into focus. This will require the cooperation of synthetic chemists, computational chemists, spectroscopists, and physical chemists. From the perspective of biology and chemistry moving closer together, the research topic covered here marks a development from the chemistry of the 1990s to that of the 21st century. Conformation is the mediator between structure and function (molecular properties, biological activity). Control of conformation by conformation design is what nature has been doing ever from the beginning. It is our task to learn to do it likewise.

I would like to thank my co-workers, the names of whom were mentioned in the text, for their courage to undertake pioneering studies in an uncharted area, for their creative contributions, and for their perseverance. These studies were initially supported by the VW Stiftung and later by the Deutsche Forschungsgemeinschaft. Constant support came from the Fonds der Chemischen Industrie. I would like to thank all of these organizations for putting us in a position to carry out this work.

Received: August 24, 1999 [A 359]

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[82] Such a conformation relaxes to another conformation. This second conformation is still quite strained and lies about 25 kJ mol^{-1} above the most stable all-*trans* conformation.[13]

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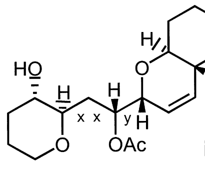
[86] Compound **i**, related to **67**, has a high conformational preference (about 85%) at the bonds marked × and adopts a conformation corresponding to **67b**. At the bond y, two conformers are populated in a *gauche* ordering of the oxygen functions.[87]



i

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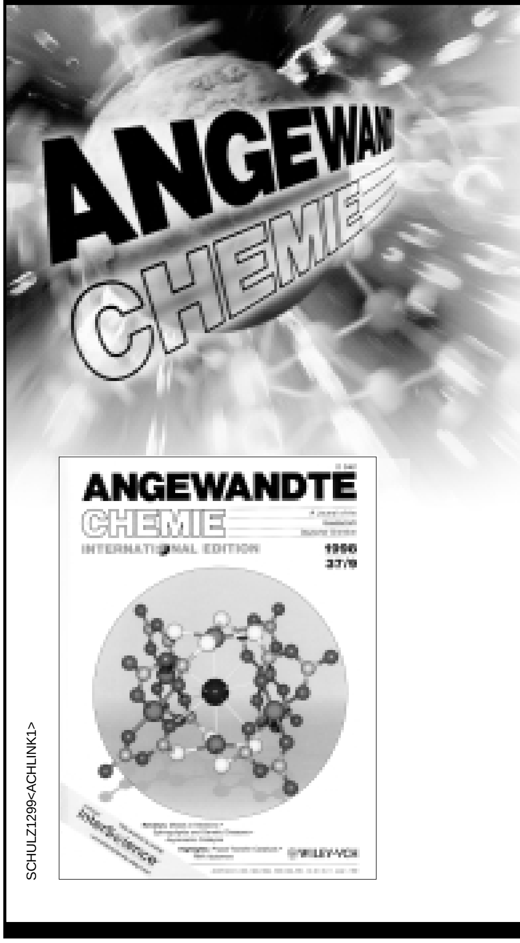

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