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Open chain compounds with preferred conformations[1]

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The shape of a flexible molecule, *i.e.* the preferred conformation of a multi-substituted alkyl chain, may be controlled by the nature and location of the pendant substituents. Steric interactions between those substituents themselves as well as the main chain, or sterically demanding end-groups, can be used to realize conformation design of flexible molecules.

Introduction

Compounds may be described in terms of a molecular backbone and of the functional groups attached to it. The distance and spatial arrangement of the functional groups frequently defines the activity of biologically active compounds. In cases of flexible, open chain compounds, it is the conformational space of the molecular backbone that limits and defines the possible distance between the functional groups attached. Definite arrangements may prevail, if the backbone of the molecule shows a marked conformational preference.

For instance, extended hydrogen bonding networks lead in polypeptides and proteins to the secondary and tertiary structure. Oligosaccharides composed of pyranoses have more defined spatial structures than saccharides composed of furanoses due to the conformational preferences of six membered rings. In polypropionate natural products steric interactions between the pendant methyl groups may restrict the conformational space and lead to oligo-conformational systems.[2] At the present time, when the design of peptidomimetics, artificial receptors and synthetic hosts is of interest, the properties of molecular backbones, especially their conformational properties, merit more detailed consideration. It is important to recognize the principles that render segments of a flexible molecular backbone mono-conformational, and to identify typical substructures of backbones, which populate to more than 90% a single conformation.

Well known examples are the 'conversion' of a bi-conformational cyclohexane nucleus **1** into a monoconformational situation by 1,3-*cis* disubstitution (*cf.* **2**) or by attachment of a conformational anchor, *e.g.* a *tert*-butyl group, *cf.* **3** (Scheme 1). One should keep in mind that the molecules **2** and **3** are still conformationally fully flexible. It is only that a single conformation predominates substantially.

Commonly, this effect is ascribed to the destabilization of one conformer by 1,3-diaxial interactions, which are a special case of the (destabilizing) *syn*-pentane interaction, *cf.* **4**. *syn*-Pentane interactions between two CH_2 groups result in a destabilization of *ca.* 3 kcal mol^{-1} (1 cal = 4.184 J).[3,4,5] The avoidance of *syn*-pentane interactions is thus a powerful tool to reduce the number of low energy conformations of open chain compounds.[2,5] While pentane **5** is multiconformational, having five low energy conformations $E_r \leqslant 3.0$ kcal,[3] placement of substituents, *e.g.* methyl residues, in the 2,4 positions leads to 2,4-dimethylpentane **6**. The latter is 'bi-conformational' having only two low energy conformations **6a** and **6b** (Scheme 2). All other diamond lattice-type conformations are destabilized by *syn*-pentane interactions. Likewise, placement of substituents in the 2,4,6,8-positions of longer hydrocarbon chains will substantially reduce the number of low energy conformations available, creating bi-conformational situations in each dimethylpentane subsegment.

Placement of further substituents on the particular segment will not necessarily lead to a mono-conformational situation, since the additional *syn*-pentane interactions generated now affect all of the remaining low energy conformations. Different approaches towards reaching mono-conformational entities are the topic of this present account.

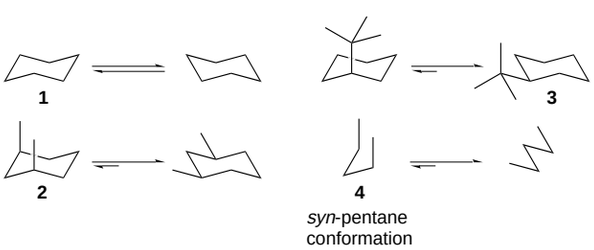
Heteroatoms as pending substituents

In 2,4-dimethylpentane **6** the two methyl groups within each pair of end groups are identical. Hence, the conformers **6a** and **6b** are enantiomorphous, *i.e.* isoenergetic. The two conformers of **6** are formally interconverted by a +120° rotation about one skeletal bond and a −120° rotation about the other one. Considering an individual methyl group, *e.g.* the squared one, it has no *gauche* interactions in conformer **6a** and one gauche interaction in **6b**. If the end groups (squared or circled) in **6** were different, the energetic degeneracy would be lifted. On replacement of the squared methyl group by a group of smaller size, as measured *e.g.* by the *A*-value, the conformer equilibrium should be shifted towards **6b**.

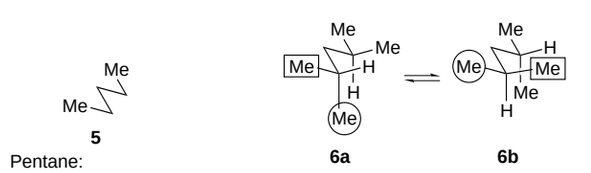
The ^{1}H–^{1}H vicinal coupling constants recorded for 2,4-dimethoxypentane[6] **7** or 2,4-dichloropentane[7] **8** document the expected shift in the conformer equilibrium; the conformer **b** (with the larger methyl group in the extended chain position) being preferred (Scheme 3).

The analysis of the conformer equilibria in such bi-conformational situations rests on the determination of vicinal coupling constants. The coupling constants between two individual hydrogens, *e.g.* H_a and H_b in **9** differ for the two conformers (Scheme 4).

The measured coupling constant is the weighted time average over the conformer population. If, for example, **9a** and **9b** are present in a 1 : 1 ratio, an average coupling constant of about 6–7 Hz should be observed. Any bias of the equilibrium towards one side leads to a divergence of the coupling constants. By



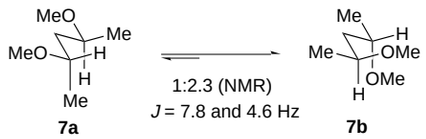
Scheme 1



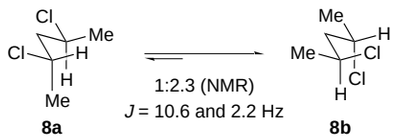
Scheme 2

comparison of the measured coupling constants with those calculated[8] for the individual conformers, the position of the equilibrium can be estimated.

At this point some general remarks are appropriate: We restrict our discussion to diamond lattice-type conformers. By this we imply backbone conformations with dihedral angles of 180 ± 15° or 60 ± 15°. If a conformation involving a *syn*-pentane interaction relaxes into the nearest energy minimum, this usually results in a skewed backbone conformation with dihedral angles of 90 ± 15°. These conformers are generally ⩾ 3 kcal higher in energy[9] than the lowest energy conformer. For this reason these skewed conformers contribute little to the overall conformer population and are not further considered here. Experimental information regarding the position of conformer equilibria derives from vicinal $^1H–^1H$ coupling constants between protons along the backbone of the molecule. The accuracy of these coupling constants obtained from first order multiplets in the ^1H NMR spectra is around ±0.1 Hz. If higher order multiplets have to be simulated, as is the case for all C_2-symmetrical structures such as **10** (Scheme 5), the coupling constants are accurate to about ±0.2 Hz. The experimental coupling constants are the weighted average of those of the populated conformers. In order to estimate the position of the conformer equilibrium for the bi-conformational backbone segments the coupling constants for the individual conformers have to be calculated. This is done by minimizing the individual conformer structures by the MM3* force field implemented in the MACROMODEL program.[8] This program also has a routine by which vicinal coupling constants are predicted for a given structure based on Karplus relationships. This routine makes provision for changes in the magnitude of coupling constants due to electronegative substituents on the backbone.[10] Clearly, coupling constants predicted this way will not be better than ±0.2 Hz. It is obvious that equating[11] experimental coupling constants with ±0.2 Hz accuracy with calculated coupling constants with ±0.2 Hz accuracy can give only a crude estimate of the conformer population. Nevertheless, the conformer population estimated this way agrees by and large with those calculated by MM3. Since it is not our aim to determine conformer populations accurately, but rather to identify substitution patterns that lead to a biased conformer equilibrium, the approach delineated above is sufficient for that purpose.



7a **7b**



8a **8b**

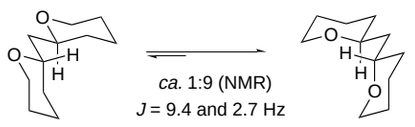
Scheme 3

9a **9b**

$J_{a,b}$ = large
$J_{a,c}$ = small

$J_{a,b}$ = small
$J_{a,c}$ = large

Scheme 4



10a **10b**

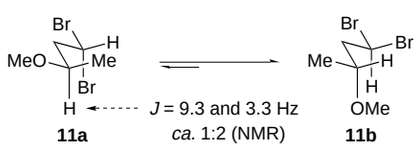
Scheme 5

The bias in the conformer equilibrium of the dimethoxy compound **7** can be attributed to a difference in effective size of a methoxy group *vs*. a methyl group—*cf* the *A*-values: Me = 1.74, MeO = 0.60. However, the conformer population depends not only on the differences in the van der Waals radii, but also on the restrictions in conformational space experienced by the methoxy group. This concerns both the energy and the number of the local C–C–O–CH_3 rotamers. The number of low energy rotamers for **7a** is 9 and for **7b** it is 4, giving more statistical weight to **7a**. The latter term affecting the conformer population of the backbone in **7** can be eliminated by tying the methoxy group into a ring. This is achieved by going from the dimethoxy compound **7** to the bis(tetrahydropyranyl)-methane **10**. In doing so, the methyl groups of **7** are also changed to CH_2R groups. But the latter should have no effect on the conformer equilibrium, since the R residue, being held in a ring, does not lead to any additional gauche interactions in either conformer **10a** or **10b**. When comparing the conformer equilibria of **7** and **10**, it becomes apparent that the equilibrium of **10** lies considerably more on the **b** side, as judged by the ^1H NMR coupling constants.[1] The situation in **10** probably reflects the true difference in effective size between an ether oxygen and a methylene group.

Our goal was to convert a bi-conformational situation as found in **6** into a mono-conformational one, as approximated by **10**. The key was to replace one of the 'methyl groups' in **6**, *e.g.* the squared one by a group of different size than the remaining circled group. For a broader study on how the effective sizes of two groups effect the conformer population, we wanted to avoid C_2-symmetric systems, such as **7** or **10**, and turned to derivatives of 1,1-dibromobutane such as **11** (Scheme 6). In doing so we use a dibromomethyl group as a conformational lock to secure a bi-conformational situation and we determine than, to what extent the differences in effective size, *e.g.* of a methoxy and a methyl group, shift the conformer population toward a mono-conformational situation. In fact, the coupling constant of the hydrogen α to the oxygen substituent in **11** revealed a noticeable shift of the conformer equilibrium towards **11b**.

Increasing the size of the methyl group in **11**—the latter prefers to go into the sterically less encumbered chain end position—to an isopropyl group results in only a negligeable change in the conformer equilibrium, as seen from the coupling constants of **12** (Scheme 7). The small difference between a methyl and isopropyl group in such a system is also evident from the coupling constants recorded for **13**.[12] A sizeable effect is, however, attained when going to a *tert*-butyl group, as seen for **14**.

When changes are made at the oxygen substituent, the effect of tying the methoxy group into a ring can also be picked up within the dibromomethyl series, *cf*. the differences in coupling constants between **11** and **15** (Scheme 8). A change of the methoxy group in **12** to a trimethylsilyloxy group in **16** has, on the other hand, only a small effect. Thus, a trimethylsilyloxy group is hardly larger than a methoxy group as viewed from the dibromomethyl reporter unit.



11a **11b**

Scheme 6

End-group control of conformation

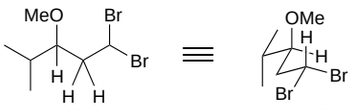
Coming back to the starting point **6**: when one replaces the squared methyl group in **6** by a really space-demanding substituent one should populate just the conformer **6a**. This is realized by going from **11** to **14**. The sizeable effect of the *tert*-butyl end group on the conformer population as seen for **14** has long been known as the *tert*-butyl effect,[13] according to which a *trans*-conformation is induced in structures such as **17** at the bond indicated (Scheme 9). Any other diamond lattice conformation around this bond would lead to *syn*-pentane interactions.

Hence, a combination of the structural elements **17** and **6**, as in compound **18**, should induce a t,g$^+$-conformation[14] as shown. In fact, a high tendency to adopt a single conformation has been reported for this compound by Luisi[15] based on measurements of the molecular rotation.

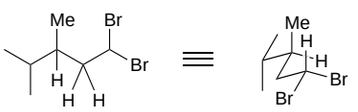
A more intricate situation of end-group control is seen in the examples **19** and **20** (Scheme 10). Obviously, steric bulk is not all that counts. In **19** and **20** an α-methoxyisobutyl residue is considered as the end group for the neighbouring bi-conformational segment. Since this segment is no longer symmetrically substituted, there are two sets of coupling constants, one large and one small in each. For the sake of simplicity we quote in Scheme 10 only the average value of the large coupling constants on the one side and of the small ones on the other side.

To evaluate the effect of the α-methoxyisobutyl group on the conformation of the C3–C4 bond (which in turn controls the conformation of the C4–C5 bond) in **19** and **20** we may consider just the number of low energy conformations which are free of *syn*-pentane interactions: For **19** there are three such conformations: (2,3g$^+$ 3,4t); (2,3t, 3,4t); and (2,3t 3,4g$^-$). Thus, in the bi-conformational segment C3 to C5, the 3,4t conformers are favoured by 2 : 1 over the 3,4g conformers according to this simplified analysis. The ^{1}H NMR coupling constants indicate a 1.5 : 1 preference for the t conformation in this segment.

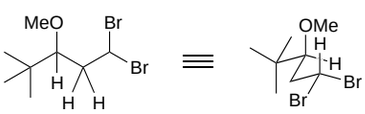
When going to **20** the situation is markedly different: there is only one conformer, the (2,3t 3,4t) conformer, which is free of *syn*-pentane interactions. Hence, compound **20** should have only one low energy conformation, the one shown, a fact that is reflected in the strong difference of the coupling constants recorded for **20**.[16] This effect can be used to selectively exert local conformation control in more extended molecular backbones such as **21** (Scheme 11).[17]



12 major conformer
J = 9.4 and 3.1 Hz by *ca.* 3:1 (NMR)

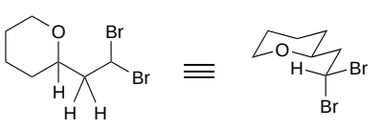


13 major conformer
J = 8.7 and 4.5 Hz by *ca.* 1.5:1 (NMR)

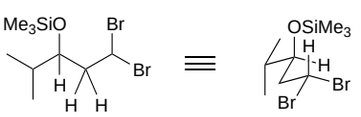


14 major conformer
J = 10.8 and 2.7 Hz by > 10:1 (NMR)

Scheme 7

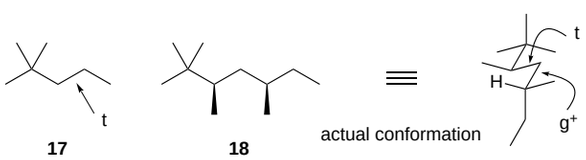


15 major conformer
J = 9.7 and 2.7 Hz by > 9:1 (NMR)



16 major conformer
J = 9.2 and 3.0 Hz by *ca.* 2:1 (NMR)

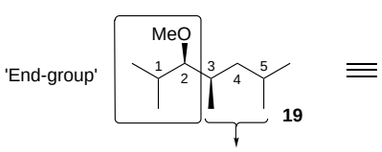
Scheme 8



17 **18** actual conformation

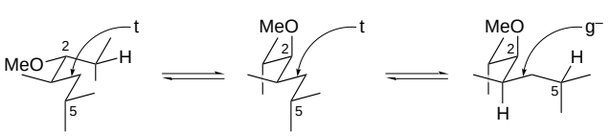
t = *trans*
g = *gauche*

Scheme 9

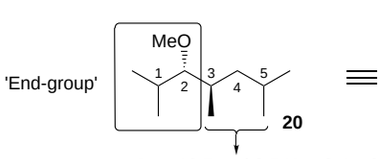


19

J_{av} = 8.6 and 5.7 Hz 3,4t : 3,4g = *ca.* 1.5 : 1 (NMR)

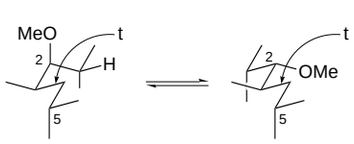


2,3g$^+$3,4t **19a** 2,3t 3,4t **19b** 2,3t 3,4g$^-$ **19c**



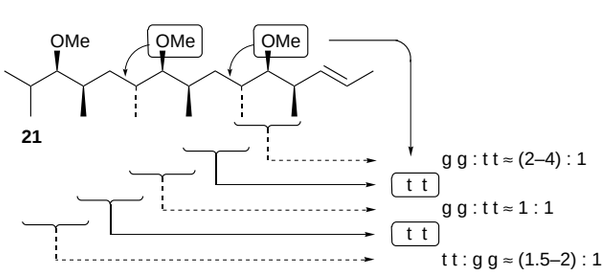
20

J_{av} = 10.7 and 3.5 Hz 3,4t : 3,4 others = *ca.* 15 : 1 (NMR)



2,3g$^+$3,4t **20a** 2,3t 3,4t **20b**

Scheme 10



Scheme 11

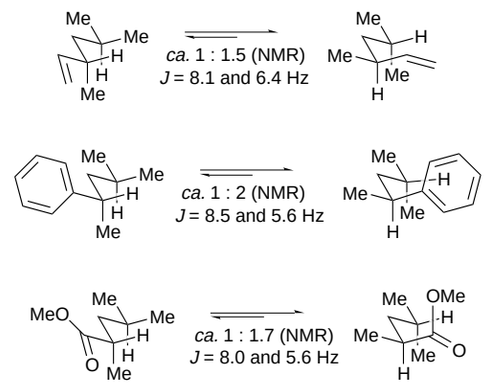
sp²-Hybridized substituents

sp²-Hybridized end groups, such as vinyl, phenyl and methoxycarbonyl are, on the other hand, slimmer than a CH_2R group. Therefore, in bi-conformational situations the former groups should be preferentially found in those positions, which are subject to the higher number of gauche interactions. This has been tested with a number of model compounds (Scheme 12).[16]

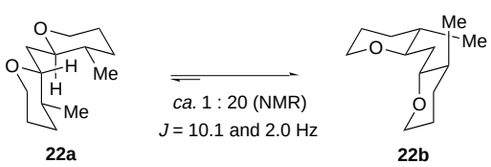
As can be seen from the coupling constants, the effects caused by a single sp²-hybridized substituent are rather small; ΔG values which affect the conformer equilibrium, do not exceed *ca*. 0.5 kcal mol^{-1}.

Conformation design

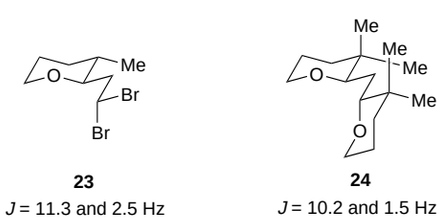
Many of the effects described above, which bias a bi-conformatonal towards a mono-conformational situation, are small or not far-reaching. For this reason effective conformation design to attain mono-conformational situations in larger molecular backbones would have to rely on the combination of several control elements. The introduction of polar repulsions, of hydrogen bonding networks, or of situations that profit from the attractive gauche effect,[18] would obviously offer additional strategies. At the present stage of the development of the field, we were interested to see how far one could go simply by using the effects discussed in the previous sections.



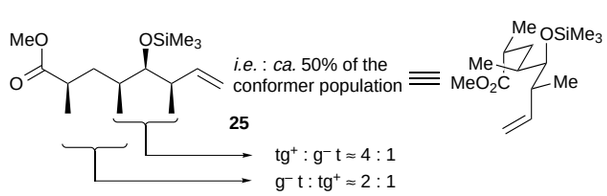
Scheme 12



Scheme 13



Scheme 14



Scheme 15

For example, in the case of **10**, introduction of two methyl groups to give **22** should reinforce the conformational preference. The two methyl groups in **22** have been strategically placed in the equatorial position to selectively destabilize the conformer **22a** by *syn*-pentane interactions between the methyl group and the backbone each relative to the conformer **22b** (Scheme 13).[1]

The same effect is seen[19] on comparison of the conformational preference of compound **23** with that of **15**. Since an essentially mono-conformational situation is already reached in compounds **22** and **23** by these tools, introduction of further methyl groups as in **24** has only a minor effect (Scheme 14).[1]

The effects that may be attained by multiple substitution of a chain with sp²-hybridized substituents are less striking. Nevertheless, the coupling constants recorded for **25**[16] indicate that about 50% of the total conformer population has a central g$^-$ttg$^+$ conformation (Scheme 15).

The various principles mentioned above are clearly manifest in nature's conformation design as illustrated by zincophorin **26**,[20] a natural ligand conformationally preorganized to complex Zn^{2+}. Inspection of part of its crystal structure lets one read nature's conformations design (Fig. 1).

The awareness of these and other factors, which render backbones of flexible molecules oligo- or mono-conforma-

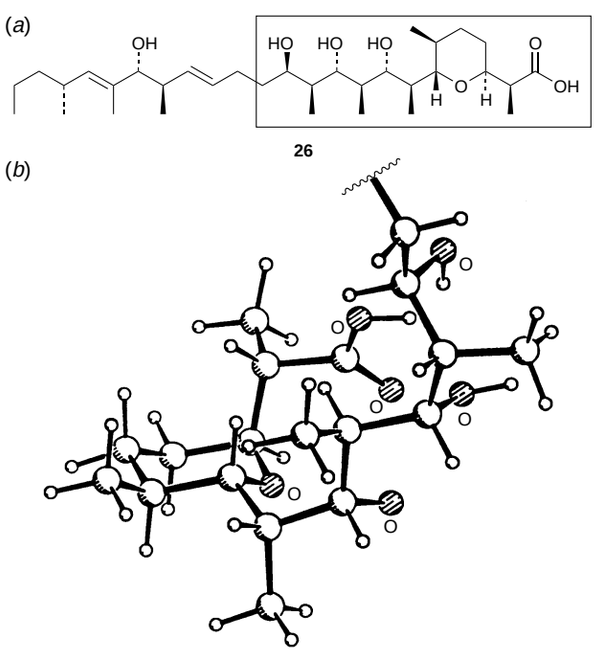
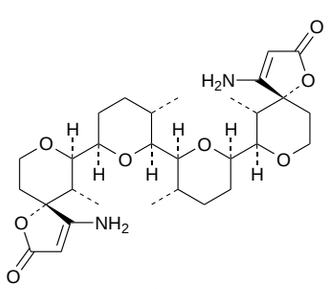


Fig. 1 (*a*) Structure of zincophorin with fragment highlighted, and (*b*) partial crystal structure of highlighted fragment



tional, is obviously important for contemporary drug design and the design of tailor-made host molecules. This has recently been demonstrated by W. C. Still[21] with the synthesis of artificial ligands such as **27**.

Acknowledgements

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