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Z- and U-Shaped Open Chain Molecular Backbones by Conformation Design

Reinhard W. Hoffmann*, Ulrich Schopfer, and Martin Stahl
Philipps-Universität Marburg, Fachbereich Chemie
D - 35032 Marburg

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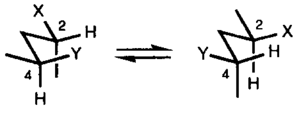
Abstract: *Derivatives 5 and 7 of 1,10-decanediol have been synthesized that exist in an intramolecularly hydrogen-bonded U-shaped conformation (5), or in a non-hydrogen-bonded Z-shaped conformation (7). Conformation design of these compounds rests on the introduction of four methyl groups, the relative configuration of the methyl bearing stereocenters and the presence of a configurationally defined double bond respectively.* © 1997 Elsevier Science Ltd.

It is an intellectual challenge to give a flexible hydrocarbon chain a particular folding pattern, simply by attaching substituents to it. If one places methyl substituents onto every second carbon atom of the chain, one generates hydrocarbon segments related to 2,4-dimethyl-pentane. The latter constitutes a good starting point for a more elaborate conformation design, because 2,4-dimethyl-pentane (**1**) populates two isoenergetic conformations comprising more than 90% of the total conformer population.[1] The energetic degeneracy of the two conformers **1a** and **1b** may be lifted, if other groups than methyl are chosen for the substituents X and Y.



a **b**

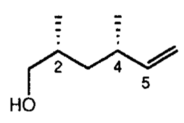
		a : b
1	X = Y = CH_3	1 : 1
2	X = CH_3; Y = $CH{=}CH_2$	1.5 : 1
3	X = CH_2OH; Y = CH_3	2 : 1
4	X = CH_2OH Y = $CH{=}CH_2$	3.5 : 1

For instance, when Y is a vinyl group, cf. **2**, the conformer equilibrium lies to the side of **2a**, in which the slimmer vinyl group occupies the position, in which it, rather than the methyl group, suffers a gauche interaction with C2.[2] On the other hand, when a substituent is chosen, which is effectively bigger than a methyl group, cf. the hydroxymethyl group X in **3**, the conformer **3a** is preferred, in which X is not exposed to a gauche interaction with C-4.[3] We have discussed before the whatever small effects by which the conformer equilibrium of **1** may be biased.[4] Here we would like to demonstrate, how a design of larger molecular skeleta with a preferred conformation is possible by a combination of such small effects.

Starting point and reference point for our study is compound **4**,[5] in which the conformational biases present in **2** and **3** cooperate. The stronger conformational bias for **4** of about 3.5 : 1 is deduced from comparison of the experimental $^3J_{H,H}$ coupling constants with those calculated for the individual conformers **4a** and **4b**. The experimental coupling constants are a weighted average over the total conformer population, to which the conformers **4a** and **4b** contribute to ca. 90 % according to MM3 calculations. The predominance of conformer **4a** in the conformer equilibrium was secured by determination [6] of characteristic $^3J_{C,C}$ coupling constants.

Conformation Design of a Flexible U-Shaped Backbone

When **4a** depicts the preferred conformation of **4**, homochiral combination of two molecules of **4** via the olefinic linkage leads to compound **5** [7] which should populate an U-shaped conformation, cf. **5a**.



4

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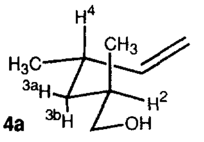
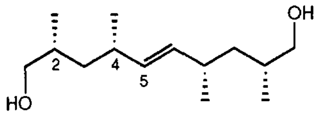


4a

$^3J_{H,H}$ Coupling Constants
(Hz, CDCl$_3$)

H^3-H^4	4.5/9.8	H^4-H^5	10.2
H^3-H^2	9.4/5.0		



5

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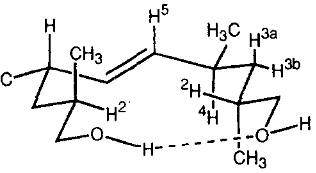


5a

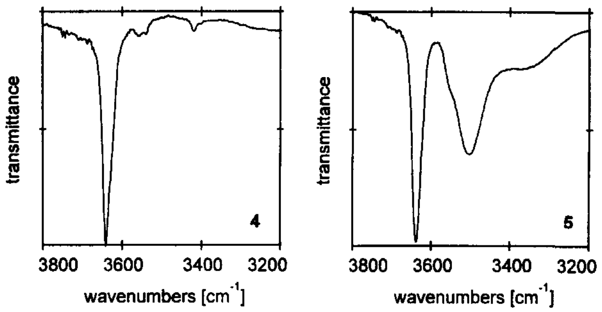
H^3-H^4	3.6/10.7	H^4-H^5	8.9

The coupling constants of H^3 in **5** show a higher conformational bias than that present in the parent molecule **4**. On the other hand the H^4/H^5-coupling was found to be smaller in **5** than in **4**. Apparently, the molecule has a tendency to swivel the double bond inbetween two arrangements. That **5a** is indeed the predominant conformer could be shown by measuring an NOE effect between H^2 and $H^{2'}$. This, however, is not straightforward, since H^2 and $H^{2'}$ are homotopic and the NOESY signal would be overlayed with the diagonal signals. We therefore used a new HSQC-NOESY pulse sequence [8] to demonstrate a strong NOE contact between H^2 and $H^{2'}$ in compound **5**. The predominance of the U-shaped conformation **5a** may, however, only in part be attributed to conformational preorganization by conformation design. Another factor could be the tendency to form an intramolecular hydrogen bond. Such an intramolecular hydrogen bond is indeed present in **5**: Recording of the OH-bands in the IR-spectra at a concentration (10^{-3} M in CCl_4) at which **4** shows only non-hydrogen bonded OH, reveals for **5** both a hydrogen bonded and a non-hydrogen bonded OH, cf. fig. 1, as would result from the presence of **5a**.

The bis-triisopropyl silyl derivative of **5** shows coupling constants at H^3 of 4.5/9.7 and 4.9/9.4 Hz, at H^5 of 8.1 Hz. The preference for a single conformation is therefore not as marked in the bis-silylether as in the diol **5**. Clearly, hydrogen bond formation augments the conformation design in the case of **5** to stabilize a U-shaped backbone conformation.

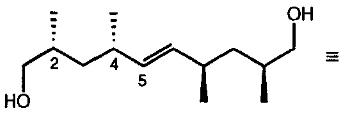
Figure 1

IR-spectra of **4** and **5** at 10^{-3}m in CCl_4

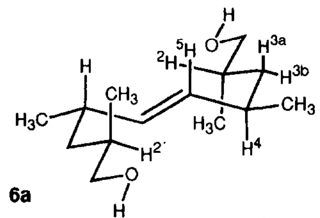


Conformation Design of a Flexible Z-Shaped Backbone

Combination of two molecules of **4** in a heterochiral fashion results in compound **6** [7] which should have a Z-shaped conformation. In **6** the effect of hydrogen bonding between the hydroxyl groups on the conformer population and that of conformation design are counteractive. There is therefore the chance to identify the stronger effect of the two.



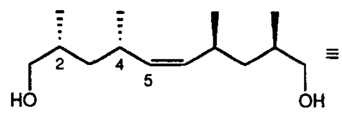
6



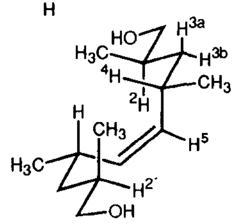
6a

$^3J_{H,H}$ Coupling Constants (Hz, $CDCl_3$)

H^3-H^4 4.3/10.1 H^4-H^5 8.1
H^3-H^2 9.4/4.8



7



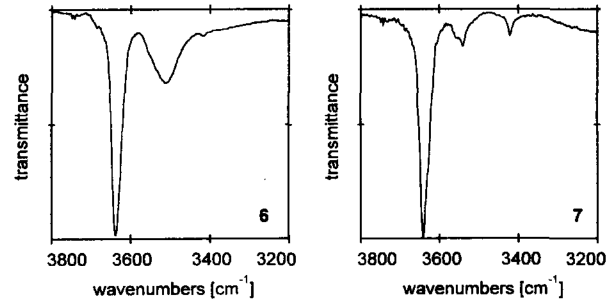
7a

H^3-H^4 3.9/10.2 H^4-H^5 10.0
H^3-H^2 4.2/9.8

The coupling constants of H^3 of **6** show a divergence and hence conformational bias very similar to that of the parent compound **4**. The absence of a NOE effect between H^2 and $H^{2'}$ is in line with a preponderance of a conformation, in which the two hydrogen atoms are remote from one another. Yet, the low coupling constant at H^5 signals considerable conformational disorder at both vinylic bonds C4-C5. The key information about the conformational behaviour of **6** comes again from the IR-spectra: **6** shows the presence

Figure 2

IR-spectra of **6** and **7** at 10^{-3} m in CCl_4



of an intramolecularly bridged OH to a significant extent. Apparently both Z- (non hydrogen bonded OH) and U-shaped (hydrogen bonded OH) conformers are populated. The energy gained by forming an intramolecular hydrogen bond therefore partially overrides the weak conformational control at the C4-C5-bonds. This, however, can be remedied by recourse to 1,3-allylic strain [9] to control the conformation at the vinylic bonds. Simply going to **7** [7] with a Z-double bond raises the energy required to rotate the C4-C5-bond out of the desired Z-shaped arrangement of the molecular backbone. The success of this design becomes evident both from the IR-spectrum of **7**, which shows only non-bonded OH, and the NMR-coupling constants, which demonstrate a large conformational bias both in the C2-C4-segments and around the C4-C5-bond. Clearly, in the case of **7**, the conformational control is powerful enough to prevent the formation of internally hydrogen bonded conformers *and* to stabilize the desired Z-shape of the molecular backbone.

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