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Heptan-1,3,5,7-tetrol-diacetonides, Flexible Backbone Segments with a Marked Conformational Preference

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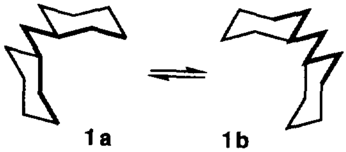
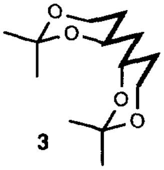
Abstract: Two (1,3-dioxan-4-yl)-methanes **3** and **10** have been synthesized by standard methods. Compound **3** has a marked (9:1) tendency to populate conformer **3b** as evidenced by the $^3J_{H,H}$-coupling constants in the inter-ring segment. The two additional methyl substituents in **10** increase this conformational preference to >95:5. Copyright © 1996 Elsevier Science Ltd

The properties of a compound depend among other factors on the kind of its molecular backbone and on the nature and location of the attached functional groups. For a given pattern of substituents the conformational flexibility of the backbone limits the distance between specific functional groups. It is therefore of interest to control the distance of functional groups on a flexible backbone by control of the conformer population. One aim is to develop flexible backbones with a single preferred conformation.[1] We have already outlined[2] considerations that led from a multi-conformational heptane chain (**2**) to dicyclohexyl-methane (**1**) a model backbone incorporating a heptane chain. Dicyclohexyl-methane (**1**) populates two isoenergetic conformers **1a** and **1b**, it is bi-conformational. In order to develop dicyclohexyl-methane further in the direction of a mono-conformational backbone one has to lift the degeneracy between **1a** and **1b**, for instance by replacing certain CH_2-groups by heteroatoms such as oxygens. A suitable target could therefore be the diacetonide **3**. We describe here the synthesis of the diacetonide **3** and congeners and report on the conformational behaviour of these molecular skeleta.

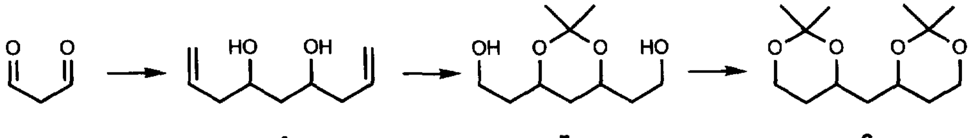

1a **1b**


2



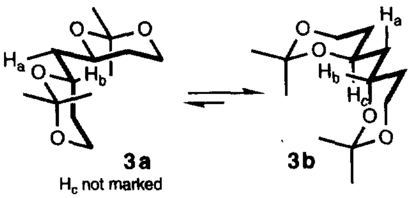
3

For the synthesis of **3**, malondialdehyde was allylated by the procedure of Imai[3] (2.5 equivalents of allyl chloride, 3 equivalents of sodium iodide, 3 equivalents of tin(II)-chloride-dihydrate in DMF 30°C) to give 32% of the nonadienediol **4** as a 1:1 anti/syn-mixture. Excess of 2,2-dimethoxypropane and catalytic amounts of camphorsulfonic acid in CH_2Cl_2 transformed **4** into an acetonide (92%) which was cleaved by ozonolysis (O_3 in methanol at -78°C) followed by reduction with an excess of $NaBH_4$ to give 89% of the diol **5**. Treatment of **5** with dimethoxypropane/camphorsulfonic acid led to 87% of a diastereomer mixture of **6**, from which the anti-diastereomer **3** could be obtained by crystallization from petroleum ether in 30% yield, m.p. 130°C.



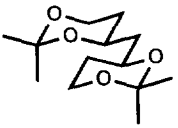
4 **5** **6**

MM3-calculations indicate that **3** should have a significant bias of the conformer equilibrium in the direction of a mono-conformational situation: According to these calculations the conformers **3a**, **3b**, and **3c** represent ca. 98% of the conformer population in 2:88:8 ratio. To simplify matters, we consider only the to conformer equilibrium between **3a** and **3b**, a situation which still comprises ca. 90% of the conformer population of **3**. An estimate of the position of this equilibrium can be arrived at based on $^3J_{H,H}$ coupling constants.[4] For instance, the coupling constants between H_a and H_b is large in conformer **3a** and small in conformer **3b**. The reverse holds for the coupling constants between H_a and H_c. It is these two coupling constants that are diagnostic for the conformation of the inter-ring segment in **3**. The apparent coupling constant between H_a and H_b (and H_a and H_c respectively) is the weighted average over the conformer population. A comparison of the apparent coupling constant for **3** with those of the individual conformers **3a** and **3b** would thus allow an estimate of the position of the conformer equilibrium. The coupling constants for the individual conformers **3a** and **3b** can be estimated, e.g. for H_a and H_b to be 10.9 Hz for **3a** and to be 2.3 Hz for **3b** based on a modified Karplus equation[5] which is implemented in the MACROMODEL[6] program.



3a
H_c not marked

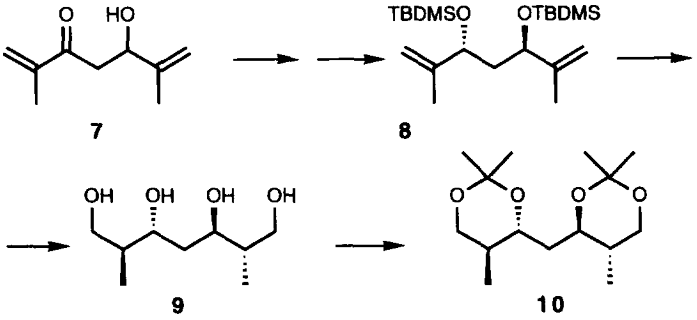
3b



3c

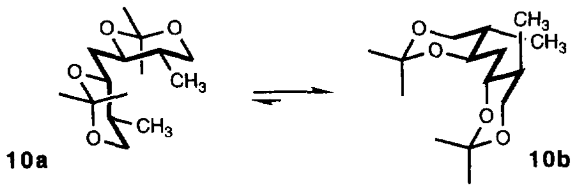
The experimental coupling constants for **3** cannot be directly taken from the spectra, because the coupling patterns are of higher order due to the c_2-symmetry of **3**. Nevertheless, approximate values of the coupling constants can be arrived at by simulation of the spectra.[7] The values of 9.5 Hz for H_a/H_b and 2.5 Hz obtained for H_a/H_c are in line with a ca. 9:1 preference of **3b** in the conformer equilibrium. Moreover, an X-ray structure analysis showed **3** to have the conformation **3b** in the crystal.

According to the MM3-calculations conformer **3c** is a minor contributor (8%) and **3a** an even less important contributor to the conformer equilibrium of **3**. Specific placement of two methyl groups as in **10** should selectively distabilize conformers of the **c** and **a** type and should lead to an even stronger preponderance of the **b** type conformer. For this reason the synthesis of **10** was undertaken by the following sequence of reactions:



Aldol addition between 2-methyl-1-butene-3-one and methacrolein led to the aldol **7**[8] in 70% yield. Reduction with tetramethylammonium triacetoxyborohydride in 1:1 acetonitrile/acetic acid at -40°C furnished 93% of a diol which was silylated with t-butyl-dimethyl-chlorosilane/imidazole in DMF to give 82% of **8**. Diastereoselective hydroboration[9] with 9-BBN led to a bis-silylated derivative of **9**. The situation was complicated by a partial migration of the silyl groups.[10] Removal of the silyl groups was effected with sodium fluoride in trifluoroacetic acid in ether. The resulting tetraol **9** was immediately converted into the crystalline diacetonide **10**, m.p. 97°C (46%) by treatment with 2,2-dimethoxypropane and trifluoroacetic acid.

MM3-calculations for **10** indicated that 99% of the conformer population is covered by **10a** and **10b** and that **10b** should represent 97% of the conformer population. The coupling constants arrived at by simulation of the spectra[7] amount to 10.4 and 2.2 Hz. The higher proportion of the **b** type conformer in **10** compared to **3** is reflected in the larger coupling constant being larger and the smaller coupling constant being smaller. The values approach those, which have been estimated for **10b** (11.6 and 2.1 Hz) by the MACRO-MODEL routine.



Thus, the bis-acetonide **10** is a further representative[11] of a fully flexible molecule with a defined shape: Both rings in **10** may invert, and, rotations about the inter-ring bonds are fully possible, yet a single conformer is populated to >95%. This demonstrates, how the bi-conformationl situation prevalent in **2** can be changed to a mono-conformational one by replacement of certain CH_2-groups by oxygen and by introduction of two methyl groups. When **10** is considered as a model backbone it incorporates e.g. a fully extended heptane chain as indicated in **10b**. But either or both of the methyl-groups in **10** could be considerd as being part of the main chain of the molecule. Looked at in this fashion **10b** serves also as a surrogate for a g^+ttt or a g^+ttg^+-conformation of a heptane chain.

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