# Understanding conformer equilibria in solution with the aid of calculated $^{13}$C NMR spectra.[1] A density functional and molecular mechanics study

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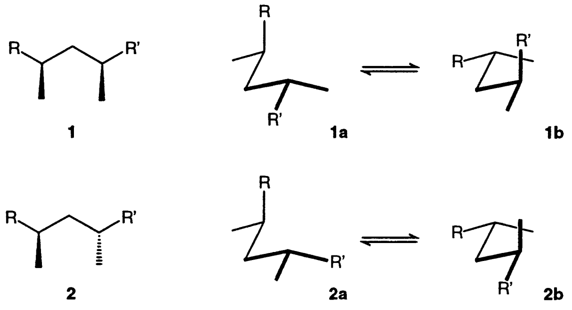
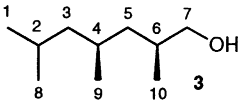
**MM3 conformational analyses were performed for a series of diastereomeric 2,4,6-trimethylated alcohols. Using MM3 geometries and energies, $^{13}$C NMR chemical shifts of 15–40 low energy conformers were calculated by means of an SOS–DFPT/IGLO approach and Boltzmann weighted. A comparison of calculated and experimental shifts allows us to analyse the conformational equilibria in solution and to estimate the importance of intramolecular hydrogen bonds in $CDCl_3$ solution.**

## Introduction

An understanding of the preferred conformations of flexible compounds is of great interest in organic chemistry. While *n*-alkanes have an enormous number of conformations of similar energy, the situation is different for alkane chains that carry a methyl group at every second carbon atom.[2–4] This leads to two possible diastereomeric segments **1** and **2**. For each of these segments, only the two conformers **a** and **b** are devoid of destabilizing *syn* pentane interactions (Scheme 1). In contrast to all other conformers, they can be referred to as 'diamond lattice' conformers because the dihedral angles along their carbon backbone are close to the ideal diamond state. These conformers constitute more than 90% of the local conformer distribution within a unit **1** or **2**. The 2,4-dimethylated segments **1** and **2** are recurring elements in polyketide natural products and polypropylene macromolecules. The unique combination of conformational bias and flexibility makes them ideal building blocks for a rational conformational design.[4] For this purpose, molecular mechanics calculations may be used to identify compounds with desired conformational preferences. In order to compare calculated conformer populations with reality, one needs experimental observables that are sensitive to changes in molecular geometry (configuration and conformation) and that can be reliably calculated from the predicted conformer distribution. $^{13}$C NMR chemical shifts provide such a link between experiment and theory,[5–7] as they depend strongly on molecular geometry. We have recently used an SOS-DFPT/IGLO approach to calculate $^{13}$C NMR chemical shifts on MM3(94) geometries and to generate average chemical shifts by Boltzmann weighting according to MM3(94) energies of the most important low energy conformers.[8] This method was successfully applied to distinguish diastereomers of small model compounds and to predict the relative configuration in the polyketide side chains of two natural products. In an extention of this work, we applied this computational protocol to larger flexible sequences **3**–**7**. We show that conformational equilibria in solution can be analysed even for long hydrocarbon chains and that, in particular, the population of hydrogen-bound conformers can be estimated.



**Scheme 1** Only two conformations **a** and **b** of 2,4-dimethylated pentanes are free of *syn* pentane interactions



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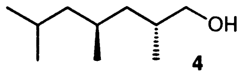

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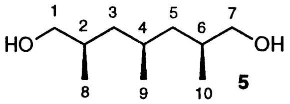

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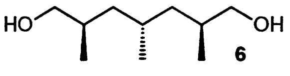

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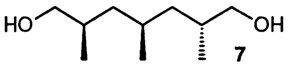

**7**

## Computational methods and experimental

The conformational space of compounds **3**–**7** was explored by the MCMM[9] method using the MM3* forcefield as implemented in MACROMODEL 4.5.[10] All dihedral angles along the carbon chain were subjected to the search. We used 6000 search steps for **3** and **4** and 10 000 steps for **5**–**7**. All local minima were further minimized by the full-matrix Newton Raphson Minimizer of MM3(94).[11] The complete conformational analysis of one diastereomer out of **5**–**7** accounted for 3 days of CPU time on an SGI R4400 workstation. The $^{13}$C NMR shielding constants were calculated for the lowest energy minima whose population constituted more than 80% of the total Boltzmann distribution of 298 K according to the MM3(94) energies. All calculations were carried out with the deMON NMR program, which uses the SOS–DFPT approach[12] in conjunction with the deMON Kohn–Sham program.[13] The Loc.1 approximation,[12] the Perdew–Wang exchange correlation potential,[14] the IGLO-II basis set[15] and the ii3-IGLO auxiliary basis set were employed. For a single conformer of **5**–**7**, the NMR calculation accounted for 5 h of CPU time on an IBM SP2. Chemical shifts ($\delta$) were obtained by subtracting the calculated shielding constants ($\sigma$) from the value calculated for $SiMe_4$ ($\sigma = 188.6$ ppm). NMR spectra were

**Table 1** Experimental and calculated (SOS-DFPT/IGLO) $^{13}C$ NMR chemical shifts of compounds **3**–**7**. deMON calculations were performed on the given number of *n* low energy conformers and Boltzmann weighted at 298 K. The offsets of 5.7, 7.8 and 7.6 ppm for methyl, methylene and methine carbon atoms were subtracted from the averaged chemical shifts. Numbers in parentheses give the total population that is covered by the *n* conformers, $\Delta E$ gives the energy shift that was applied to the non-H-bound conformers to account for solvation effects (see text)

| | | | | $\delta$ carbon atom | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *n*(%) | $\Delta E$/kJ mol$^{-1}$ | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| **3** | calc. | 18 (88) | 0 | 21.1 | 26.4 | 45.6 | 28.0 | 41.3 | 31.7 | 68.6 | 22.6 | 19.0 | 17.4 |
| | exp.[a] | | | 22.0 | 25.2 | 46.5 | 27.5 | 41.6 | 33.0 | 68.3 | 23.6 | 20.5 | 17.2 |
| **4** | calc. | 15 (89) | 0 | 21.3 | 26.4 | 46.3 | 28.0 | 40.6 | 32.0 | 69.8 | 22.3 | 18.2 | 16.2 |
| | exp.[a] | | | 22.4 | 25.0 | 47.6 | 27.3 | 40.8 | 33.0 | 68.8 | 23.1 | 19.4 | 16.2 |
| **5** | calc. | 40 (78) | 0 | 68.3 | 32.5 | 41.3 | 27.9 | 41.3 | 32.5 | 68.3 | 17.7 | 19.7 | 17.7 |
| | calc. | 40 (78) | 10 | 68.6 | 31.9 | 40.9 | 27.6 | 40.9 | 31.9 | 68.6 | 17.5 | 19.4 | 17.5 |
| | exp.[b] | | | 68.1 | 33.1 | 41.2 | 27.8 | 41.2 | 33.1 | 68.1 | 17.6 | 21.1 | 17.6 |
| **6** | calc. | 40 (86) | 0 | 69.4 | 32.3 | 41.0 | 27.3 | 41.0 | 32.3 | 69.4 | 16.6 | 18.9 | 16.6 |
| | calc. | 40 (86) | 10 | 69.5 | 32.1 | 40.9 | 27.4 | 40.9 | 32.1 | 69.5 | 16.4 | 18.3 | 16.4 |
| | exp.[b] | | | 69.0 | 33.2 | 41.5 | 27.1 | 41.5 | 33.2 | 69.0 | 16.4 | 19.1 | 16.4 |
| **7** | calc. | 40 (96) | 0 | 64.7 | 32.1 | 37.7 | 28.5 | 46.9 | 31.5 | 72.3 | 18.9 | 20.7 | 18.7 |
| | calc. | 40 (82) | 10 | 68.4 | 31.8 | 41.1 | 27.6 | 40.5 | 32.1 | 70.0 | 17.3 | 18.8 | 16.2 |
| | exp.[b] | | | 68.3 | 33.0 | 41.6 | 27.3 | 40.6 | 33.1 | 69.3 | 17.2 | 20.3 | 16.2 |

[a] Ref. 16. [b] This work, measured at a concentration of $6 \times 10^{-3}$ M.

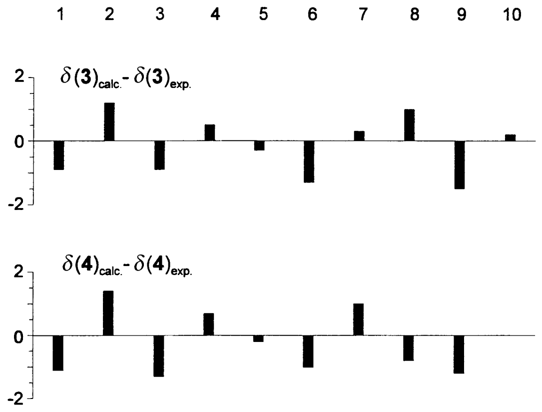

**Fig. 1** Bar graph of the differences between calculated and experimental $^{13}C$ NMR chemical shifts of **3** and **4**

obtained on a Bruker AMX-500 spectrometer at 300 K. The samples were $6 \times 10^{-1}$, $6 \times 10^{-2}$ and $6 \times 10^{-3}$ M solutions in $CDCl_3$. On the basis of the calculated values, the experimental shifts could be unequivocally assigned to the individual carbon atoms. IR spectra were recorded on a Bruker IFS 88 FTIR spectrometer of $10^{-3}$ M solutions in $CCl_4$ at 300 K.

## Results and discussion

For a number of tested compounds containing one 2,4-dimethylated chain segment, we had found[8] that the diastereomers **1** and **2** could be clearly distinguished and assigned by a comparison of experimental and calculated $^{13}C$ NMR chemical shifts. In order to extend this procedure to longer chains, we first carried out conformational analyses of the diastereomeric compounds **3** and **4**.[16] The conformational behaviour of methyl substituted hydrocarbon chains does not depend on solvation, as has been demonstrated by the analysis of $^{3}J_{CC}$ coupling constants for certain model compounds.[17] For the two alcohols **3** and **4** it can thus be expected that the energetic order of the conformers does not change significantly when going from the gas phase to $CDCl_3$ solution. The 2,4,6-trimethylated hydrocarbon backbone of **3** and **4** can be seen as a combination of two units of **1** or **2**. Three diamond lattice type conformations are possible for this system, the fourth combination is ruled out by a *syn* pentane interaction. Multiplied by the number of rotamers of the hydroxymethyl end group this results in a total of nine low energy conformers. According to the MM3(94) calculations these nine conformers lie in a very small energy window and contribute *ca.* 85% to the total Boltzmann distribution. All other conformers contain at least one *syn* pentane arrangement within the carbon skeleton. Therefore, there is a large energy gap of *ca.* 5 kJ mol$^{-1}$ after the first nine low energy conformers.

The $^{13}C$ NMR chemical shifts of the 15 lowest energy conformers of compounds **3** and **4** were calculated and averaged over the conformer population. The results are compiled in Table 1. We have previously shown[8] that chemical shifts are calculated too high by 5.7 ppm for $CH_3$, by 7.8 ppm for $CH_2$ and by 7.6 ppm for CH groups. These group specific constants have been subtracted from the calculated values in order to facilitate comparison between experimental and theoretical values (*cf.* data in Table 1). One can clearly distinguish the two compounds by means of our computational procedure. As in the case of our earlier calculations, the largest shift differences of corresponding carbon centres occur for methylene (C-3, C-5, C-7) and methyl groups (C-8, C-9, C-10). Fig. 1 shows bar graph representations of the shift differences ($\Delta\delta$) between the calculated and experimental shifts for each carbon atoms in **3** and **4**. All $\Delta\delta$ values are within the limits of 1.5 ppm, which is the expected range for this type of calculations. The RMS value for the agreement between experimental and calculated shifts for **5** and **6** is 2.91 and 3.08 ppm, respectively. One can conclude that the MM3(94) conformational energies model the situation in $CDCl_3$ solution quite well.

We then extended our investigations to the diastereomeric diols **5**–**7**, which served as intermediates in the synthesis of a marine natural product.[18] The presence of a second hydroxy group adds the possibility of forming intramolecular hydrogen bonds. In order to differentiate between intra- and intermolecular hydrogen bonds, we measured the $^{13}C$ NMR chemical shifts for a series of dilute concentrations in $CDCl_3$. From $6 \times 10^{-1}$ to $6 \times 10^{-3}$ M the carbon chemical shifts converged to the set of values listed in Table 1. The converging behaviour along the dilution series is a good indicator for the absence of intermolecular hydrogen bonds. In general, when performing spectroscopic studies on diols, intermolecular hydrogen bonds are negligible at concentrations of the order of $10^{-3}$ M.[19] The following discussion is therefore restricted to intramolecular hydrogen bonds and solute–solvent interactions.

Conformational analyses showed that for each of the diols **5**–**7** the rotamers of the two hydroxymethyl groups yields 27 different diamond lattice conformers. Only the chiral compound **7** has a chance to form an intramolecular hydrogen bond in such a diamond lattice conformation, whereas for the two *meso* compounds **5** and **6**, the geometries that allow intramolecular hydrogen bonds are subject to a *syn* pentane interaction. This is illustrated in the ball-and-stick plots of Fig. 2, where **5a**, **6a** and

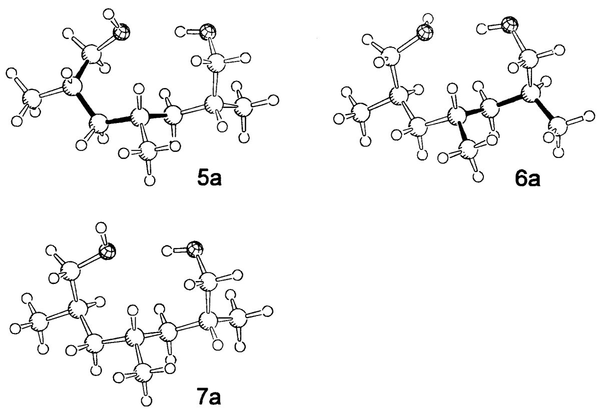

**Fig. 2** Structures of the hydrogen-bound conformers that are lowest in energy for each of the diols **5**–**7**; black bonds illustrate *syn* pentane interactions

**7a** are the energetically most favourable hydrogen-bound conformers of **5**–**7**, respectively. However, in a conformational analysis with MACROMODEL, which uses the MM3* forcefield, global minima with intramolecular hydrogen bonds were found for all three diastereomers. Thus in the MM3* forcefield a hydrogen bond overrides one *syn* pentane interaction. This is not true for the MM3(94) forcefield, which changed the energetic order of the conformers significantly for **5** and **6** upon re-minimization. Since the MM3(94) forcefield contains a somewhat improved routine for the calculation of hydrogen bonds that include a directional term,[20] we used the MM3(94) energies for further calculations.

According to the MM3(94) energetic order, conformers **5a** and **6a** as well as higher energy conformers of **5** and **6** that have an intramolecular hydrogen bond play only a minor role in the total distribution. In contrast, conformer **7a** with an intramolecular hydrogen bond dominates the conformer distribution of **7** completely (68% of the total population). We carried out calculations of $^{13}$C NMR chemical shifts for the 40 lowest energy conformers of **5**–**7**. For **5** and **6** this number could be reduced to *ca.* 20, because all conformers except the ones with $C_s$ symmetry exist as enantiomeric pairs. In order to test the validity of the MM3(94) conformer energies for describing the situation in $CDCl_3$ solution, we calculated the average $^{13}$C NMR shifts as described above.

The white bars in the diagrams of Fig. 3 show the differences ($\Delta\delta$) between calculated and experimental chemical shifts for all carbon centres in **5**–**7**. The agreement is fair when comparing the experimental and calculated chemical shifts **5** and **6**. There is no agreement for the diol **7**. It follows that the energetic order of the conformers changes upon solvation compared to the gas phase values of the calculation. To account for this, we assumed that conformers with free hydroxy groups will be stabilized more by solvation than those with an intramolecular hydrogen bond. It is clear that this will mainly affect the conformer population and hence the calculated chemical shifts of **7**, since in the gas phase its conformer population is completely dominated by one hydrogen-bound conformer.

A test of this assumption was performed by systematically lowering the MM3(94) energy of all conformers that do not have an intramolecular hydrogen bond by a constant $\Delta E$ and weighting the calculated chemical shifts again according to the resulting relative energies. This procedure implies the approximation that all conformers with free OH groups have the same solvation energy. It may be justified by the results of solvent accessible surface calculations within MACROMODEL[10] using probe radii between 200 and 250 pm for chloroform. The accessible surface of all unbridged conformers is very similar (2% deviation). The solvation energy of the hydrocarbon skeleton in the polarizable solvent chloroform should correlate with this value.

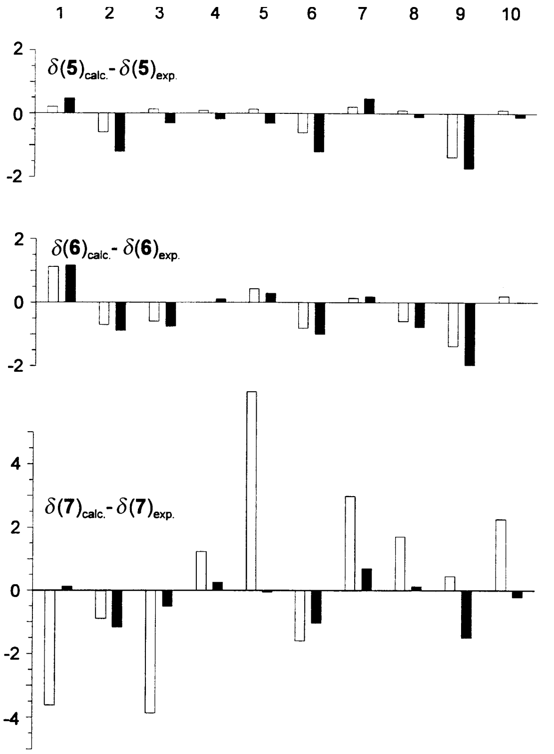

**Fig. 3** Bar graphs of the differences between calculated and experimental shifts of **5**–**7**; white bars: calculated values from Boltzmann averaging according to MM3(94) energies, black bars: calculated values from Boltzmann averaging according to an energy order of conformers, in which the energies of non-hydrogen bridged conformers have been lowered by 10 kJ mol$^{-1}$

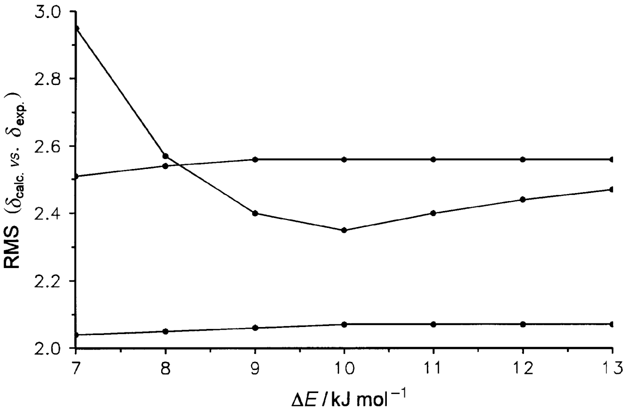

**Fig. 4** Plot of RMS values as a measure of the fit between Boltzmann-weighted and experimental chemical shifts of **5**–**7** as a function of the stabilization energy $\Delta E$ (kJ mol$^{-1}$) of conformers without an intramolecular hydrogen bond

Fig. 4 shows a plot of the RMS values of the experimental and calculated $\Delta\delta$ values as a function of the energetic lowering of the unbridged conformers $\Delta E$. Whereas for **6** and **7** the RMS values do not change significantly, there is a minimum in the RMS curve for the diol **7**, when the energy of the open chain conformers is lowered by 10 kJ mol$^{-1}$. The resulting, dramatic improvement in the calculated $^{13}$C NMR chemical shifts of **7** is illustrated in the third diagram in Fig. 3 (black bars). Experimental and calculated values now agree very well (RMS = 2.35 ppm). The RMS errors for the other two diols, **5** and **6**, are slightly higher than in the uncorrected case, but the agreement is still better than for **3** and **4** (2.56 and 2.07, respectively).

Another way to compare calculation and experiment is to regard the differences between the chemical shifts of corresponding carbon centres in pairs of the diols **5**–**7**. The RMS agreement between experimental and calculated shift differences is also a measure of the quality of the calculations, which cancels out all constitutional effects on chemical shifts and any systematic errors in the calculated values. In this case, one finds a minimum of the $\Delta\delta$ RMS values at 11 kJ mol$^{-1}$. The difference of 1 kJ mol$^{-1}$ between the results of the two evaluations may be regarded as an error margin. It should be noted that this is a very small error, since it corresponds to a difference of only 3% in the population of the lowest energy conformer of **7**. We can therefore assume that the energetic order of the conformers in $CDCl_3$ is closely approximated by the empirical inclusion of solvation effects.

The energy for one intramolecular hydrogen bond is calculated by MM3(94) to be *ca.* 9–9.5 kJ mol$^{-1}$ for the diols **5**–**7**. This means that one intramolecular hydrogen bond stabilizes the conformers of **5**–**7** somewhat less than does solvation of the two primary hydroxy groups in $CDCl_3$. This effect on the conformer distribution is most marked for the diastereomer **7**. Structure **7a** remains the global minimum, but now it accounts for only 4–7% of the total distribution.

At first sight it may seem surprising that the $CDCl_3$ solvent should stabilize two primary OH groups by 10 kJ mol$^{-1}$ relative to an intramolecular hydrogen bond. However, from a detailed quantum chemical investigation it is known that chloroform can act as a proton donor and break up the water dimer by forming a water–chloroform complex. At 298 K this equilibrium lies slightly on the side on the water dimer.[21] A detailed study of the OH stretching vibrations of a large number of alcohols in a set of solvents has also arrived at this conclusion, since solvation in chloroform always results in an unusually strong shift of the OH band towards higher frequencies.[22] The capability of chloroform to act as a proton donor is further demonstrated by its solvatochromic parameter $\alpha$.[23] The value of 0.2 places it in the vicinity of aniline (0.26). In addition, the difference in shape of bridged and unbridged conformers may contribute to the relative stabilization of unbridged conformers. Using the procedure described above, the solvent accessible surfaces of the hydrogen bridged conformers are calculated to be about 10% smaller than the surfaces of all other conformers. As chloroform is a very polarizable solvent, this should result in a lower solvation energy.

The results of this investigation are further corroborated by IR spectra that were measured for all three alcohols in a $10^{-3}$ M $CCl_4$ solution. All three samples showed an absorption at 3641 cm$^{-1}$ that can be attributed to the free, non-hydrogen-bound OH-stretching frequency and a small absorption at 3538 cm$^{-1}$ that may be due to a hydrogen bond to residual water impurities in the solvent. Only compound **7** showed a third peak at lower wavelength in the OH stretching region at 3516 cm$^{-1}$. This band contributes *ca.* 10% to the total OH stretching, which is an estimate of the population of the conformer with the intramolecular hydrogen bond.

## Conclusions

The validity of molecular mechanics calculations to model the conformational space of flexible chain molecules is greatly enhanced by methods that allow a direct comparison of calculated and experimental conformation-dependent quantities. With a study on the alcohols **3**–**7** it has been demonstrated that by combination of MM3(94) conformational analysis and SOS-DFPT/IGLO calculations of $^{13}$C NMR chemical shifts this aim can be reached. The principal conformational changes that result from solvation can thus be understood. In agreement with IR studies, it can be concluded for the diols **5** and **6** that conformers with intramolecular hydrogen bonds contribute very little to the total conformer distribution. Even for the diastereomer **7**, which can form an intramolecular hydrogen bond in a diamond-lattice backbone conformation, such an internally hydrogen-bridged conformer constitutes only 4–7% of the total conformer distribution in $CDCl_3$ solution in contrast to 68% calculated for the gas phase.

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