Conformational Analysis with Carbon−Carbon Coupling Constants. A Density Functional and Molecular Mechanics Study

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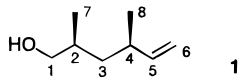
For a 1,3-dimethylated model compound (**1**), $^3J_{CC}$ coupling constants were calculated by a density functional (SOS-DFPT/IGLO) method using molecular mechanics as well as *ab initio* optimized geometries. Boltzmann averaging of the calculated coupling constants for individual conformers resulted in good agreement with the experimental data. The comparison to calculated values allows a more quantitative interpretation of the experimental coupling constants for the conformational analysis of open chain compounds.

Introduction

Control of the conformation of flexible hydrocarbon chains is important in the design of functional molecules.[1] A prominent method to analyze conformer populations is based on the measurement of vicinal NMR coupling constants. The individual conformers present in an equilibrium differ in the vicinal coupling constants and, hence, the measured coupling constant is the weighted average over the total conformer population. Interpretation of these measured coupling constants requires knowledge of the coupling constants for the individual conformers, values that are not available from experiment. Conformational analysis then rests on estimates of these individual coupling constants based on the Karplus equation.[2,3] For $^3J_{HH}$ coupling constants, a large body of experimental data from rigid compounds allows a reliable estimate of such coupling constants.[2]

With the advent of new techniques[4,5] to measure $^3J_{CC}$ coupling constants in natural abundance of ^{13}C, these become of interest for the analysis of conformer populations. Due to the small range of 1−5 Hz for synclinal versus antiperiplanar dihedral angles, estimated values for the individual conformers are not accurate enough to be really useful for conformational analysis.[3] This is a situation in which calculations of such coupling constants based on first principles could be useful. Up to now, first principles calculations of $^{13}C-^{13}C$ coupling constants have only been performed on small model systems with no conformational freedom.[6] These studies focussed on $^1J_{CC}$ data.[7] Recently, $^3J_{HH}$ and $^3J_{CH}$ Karplus curves for a dipeptide model have been calculated based on density functional theory.[8] We have recently used an SOS-DFTP/IGLO approach to calculate ^{13}C NMR chemical shifts on MM3 geometries and to generate average chemical shifts by Boltzmann weighting according to MM3 energies[9,10] of the most important low-energy conformations. 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. We have now extended this computational protocol to calculate $^3J_{CC}$ coupling constants and to generate Boltzmann-averaged values. For a model compound (**1**, Scheme 1) we show that the experimental data can be well-reproduced and that conclusive insight into conformational behavior thus can be gained. To the best of our knowledge, this is the first study that employs theoretically predicted carbon-carbon coupling constants for conformational analysis.

Scheme 1



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Computational and Experimental Methods

The conformational space of **1** was exhaustively searched by means of the MCMM method[12] as implemented in MACROMODEL.[13] All local minima were further minimized by the full matrix Newton Raphson minimizer of MM3(94).[14] To test the quality of the MM3 force field, the nine energetically lowest conformers, whose population constituted 82% of the total Boltzmann distribution according to the MM3 energies, were further optimized at the HF/TZ+2P level of theory.[15] The

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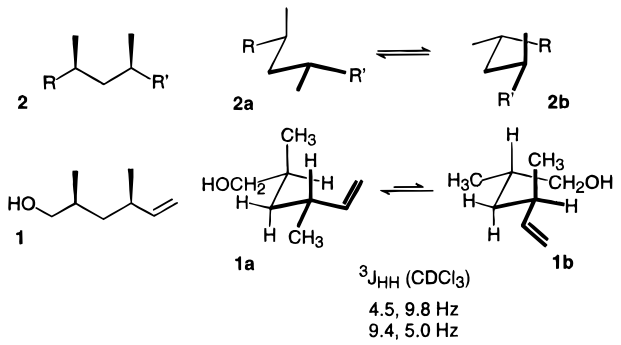
Scheme 2



energetic order of the conformers calculated by MM3 matched very well the energies obtained at MP2/TZ+2P using the HF/TZ+2P-optimized geometries. Carbon−carbon coupling constants were calculated for the nine lowest-lying energy minima obtained at MM3 as well as the HF/TZ+2P level. The calculations of the coupling constants were carried out with the Malkin code[16] in conjunction with the deMon Kohn-Sham program.[17] The Loc.1 approximation,[17] the Perdew exchange and correlation functional,[18] the IGLO-II basis set,[19] and the ii3-iglo auxiliary basis set were employed. A fine grid with 64 radial points was used in all calculations. The carbon atoms C2 and C4 were used as centers of perturbation, yielding all coupling constants of the other carbon atoms with these centers. The NMR experiments (GRECCO[4]) were carried out at 300 K on a Bruker AMX-500 spectrometer equipped with a multinuclear inverse probe with self-shielded gradient coils and a Bruker *z*-gradient accessory, which delivered sinusoidal gradients up to 8 G cm^{-1}. For GRECCO measurements of **1**, a nondegassed 70% solution in $CDCl_3$ was used.

Results and Discussion

The *syn*-dimethylated backbone segment **2** is a typical element of propiogenic natural products. This segment populates only two low-energy conformers, **2a** and **2b**, because any other diamond lattice type conformation leads to destabilizing *syn*-pentane interactions (Scheme 2).

Except when R = R′ in **2**, the conformers **2a** and **2b** will have different energies and will be populated to a different extent. For instance, the R′ group is in the sterically more encumbered "bent" position in **2a**, whereas it is in the sterically less hindered end of chain position in conformer **2b**. The reverse situation holds for the group R. Therefore, the differences in effective size between R and R′ will affect the position of the conformer equilibrium. If R′ is smaller than R, conformer **2a** will be favored. This is the case in compound **1** (scheme 2). From the measured vicinal $^3J_{HH}$ coupling constants, a 70% preference for one of the two conformers **1a** or **1b** can be deduced. However, lacking assignment of the two diastereotopic protons at C3, a conclusion as to which conformer is preferred could not be drawn from the proton−proton coupling constants. We adressed this question by measuring carbon−carbon coupling constants in a GRECCO[4] experiment for all pairs of carbon atoms involving C2 and C4 (Table 1). Figure 1 shows the antiphase doublet of the C4-selective GRECCO measurement that yields the coupling constant between C1 and C4 of 3.8 Hz.

Table 1. Contributions of the Individual Conformers to the Calculated $^3J_{CC}$ Coupling Constants (Hz) and Values for MM3 Geometries[a]

	relative energy (kJ/mol)	%	$^3J_{CC}$ C2−C5	C2−C8	C4−C1	C4−C7
1	0.0	24.0	1.1	4.2	3.9	1.3
2	0.3	21.2	1.1	4.0	5.8	1.2
3	0.7	18.6	1.0	4.2	4.1	1.2
4	3.9	5.0	3.8	1.5	1.7	4.5
5	4.8	3.5	4.1	0.8	1.1	4.4
6	5.5	2.7	4.1	0.9	0.4	5.3
7	5.7	2.4	1.2	3.7	3.8	1.5
8	5.8	2.3	1.4	4.2	5.7	1.4
9	6.1	2.1	0.1	5.1	0.0	5.3
Σ		81.8	1.4	3.7	4.1	1.8

[a]The MM3 energy and percentage of the total conformation population are given for each conformer.

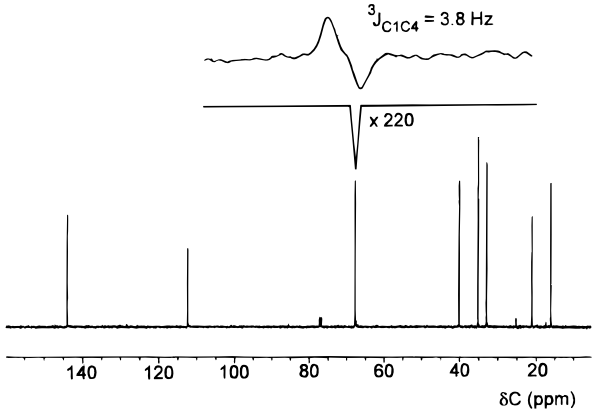


Figure 1. ^{13}C NMR spectrum of compound **1** and a section of the extended GRECCO spectrum showing the antiphase doublet that yields $^3J_{C1C4}$ = 3.8 Hz.

The four $^3J_{CC}$ coupling constants (C2−C5, C2−C8, C4−C1, C4−C7) contain information about the preferred conformation. From the small coupling constants, it can be deduced that C2 and C5 as well as C4 and C7 are predominantly in a synclinal arrangement, whereas the large coupling constants for the pairs C2−C8 and C1−C4 indicate a predominant antiperiplanar arrangement. Therefore, the 70% conformational preference deduced from the vicinal proton coupling constants is ascribed to conformer **1a**. This conclusion is strengthened by force field calculations (MM3) as well as by *ab initio* calculations on the MP2/TZ+2P//HF/TZ+2P level of theory.

Next, we were interested in a more quantitative interpretation of the measured carbon−carbon coupling constants. A huge body of knowledge on substituent effects[11] allows reliable prediction of $^3J_{HH}$ coupling constants for the individual conformers. In contrast, prediction of $^3J_{CC}$ values for individual conformers based on model compounds is less accurate, even more so as an experimental error of ±0.3 Hz has to be allowed for the reported values of the model compounds.

We therefore set out to calculate $^3J_{CC}$ coupling constants for the individual conformers of **1** on MM3 as well as *ab initio* optimized geometries. The coupling constants were then Boltzmann-weighted according to the MM3 energies of the individual conformers. Table 1 lists all individual contributions of the various conformers to the Boltzmann-averaged $^3J_{CC}$ constants. The individual

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Table 2. Experimental and Calculated ^{13}C NMR Coupling Constants (Hz) of Compound 1[a]

carbon coupled to	C2			C4		
	expl	MM3	TZ+2P	expl	MM3	TZ+2P
C1	37.6	37.5	36.2	3.8	4.1	4.0
C2		–		–	0.1	0.0
C3	35.4	32.1	32.2	34.4	31.1	31.1
C4	–	0.2	0.0		–	
C5	1.4	1.4	1.3	42.4	38.4	38.0
C6	–	0.0	0.0	–	1.5	1.6
C7	35.6	32.4	31.6	2.2	1.8	1.5
C8	3.3	3.7	3.7	33.9	31.6	30.7

[a] Calculations were performed for the 10 lowest energy conformers and Boltzmann-weighted at 298 K. Results obtained with MM3 as well as with HF/TZ+2P optimized geometries are compared.

coupling constants of conformers 1−3 and 4−6 are within the same range. These two sets of conformers represent the three rotamers of the CH_2−OH group of **1a** and **1b**, respectively. It should be noted that the position of the CH_2−OH group exerts quite a large influence on the coupling constants. In Table 2, the Boltzmann-averaged values are compared to the experimental data. The agreement of calculated and experimental $^3J_{CC}$ coupling constants is very good. As can be seen from table 2, the calculated $^3J_{CC}$ constants depend only marginally on the level of geometry optimization. This is an important result, since high level *ab initio* optimizations are computationally expensive. Apart from the four $^3J_{CC}$ values, Table 2 contains $^1J_{CC}$ coupling constants that are also well-represented by the calculations, although the absolute error is larger and the geometry dependence is more pronounced than for the $^3J_{CC}$ coupling constants.

Conclusion

$^3J_{CC}$ coupling constants can be reliably calculated on the basis of molecular mechanics (MM3) geometries by a density functional (SOS-DFPT/IGLO) method. Boltzmann-averaging of the calculated coupling constants for individual conformers of compound **1** resulted in good agreement with the experimental data. This sets the stage for conformational analysis of open chain compounds by comparison of calculated and experimental data.

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