

Conformational analysis of the chemical shifts for molecules containing diastereotopic methylene protons

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ARTICLE INFO

Article history:

Received 17 July 2011

Revised 30 August 2011

Available online 7 September 2011

Keywords:

Diastereotopic protons

Chemical shifts

Vibrational correction

Rotational average

Boltzmann average

Conformational analysis

ABSTRACT

Quantum chemistry SCF/GIAO calculations were carried out on a set of compounds containing diastereotopic protons. Five molecules, including recently synthesized 1,3-di(2,3-epoxypropoxy)benzene, containing the chiral or pro-chiral center and the neighboring methylene group, were chosen. The rotational averages (i.e. normalized averages with respect to the rotation about the torsional angle τ with the exponential energy weight at temperature T) calculated individually for each of the methylene protons in 1,3-di(2,3-epoxypropoxy)benzene differ by ca. 0.6 ppm, which is significantly less than the value calculated for the lowest energy conformer. This value turned out to be low enough to guarantee the proper ordering of theoretical chemical shifts, supporting the interpretation of the ^1H NMR spectrum of this important compound. The rotational averages of chemical shifts for methylene protons for a given type of conformer are shown to be essentially equal to the Boltzmann averages (here, the population-weighted averages for the individual conformers representing minima on the $E(\tau)$ cross-section). The calculated Boltzmann averages in the representative conformational space may exhibit completely different ordering as compared to the chemical shifts calculated for the lowest-energy conformer. This is especially true in the case of molecules, for which no significant steric effects are present. In this case, only Boltzmann averages account for the experimental pattern of proton signals. In addition, better overall agreement with experiment (lower value of the root-mean-square deviation between calculated and measured chemical shifts) is typically obtained when Boltzmann averages are used.

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1. Introduction

The problem of the chemical shift inequivalence of diastereotopic protons or groups of protons is nowadays widely undertaken in most of the textbooks devoted to NMR spectroscopy. The presence of the (pro)chiral center in the vicinity of the methylene group makes the free rotation about a single bond unable to average the electron density around protons, and for this reason they may be responsible for the presence of two rather than one signal on the ^1H NMR spectrum. The same applies to the groups of protons, like the methyl protons of the isopropyl group. However, the difference between their chemical shifts, although typically small, is difficult to predict intuitively. In addition, signals often exhibit complex multiplet structures due to strong spin–spin coupling within the second-order spin systems. Note that even in the case as simple as $\text{CH}_3\text{--CH}_2\text{--C}^*\text{H}(\text{OH})\text{--CH}_3$ (the $A_3\text{MNX}$ case on typical, say 600 MHz spectrometers) the methylene protons are responsible for quite complex group of signals at δ 1.45 ppm (this value refers to the CDCl_3 solution). Thus, the proper interpretation of the NMR spectra of compounds containing diastereotopic protons frequently

requires additional endeavors, like two-dimensional spectroscopy, which shows the direct correlation between nuclei. Alternatively, one could use quantum chemistry calculations for which the relation chemical shift – nucleus is known *a priori*. Calculations for diastereoisomers and molecules containing diastereotopic protons were already carried out a number of times [1–7].

One of the compounds containing diastereotopic protons is 1,3-di(2,3-epoxypropoxy)benzene (**1**, cf. Fig. 1). It was recently obtained [8] for the subsequent use in the synthesis of porous microspheres. Its ^1H NMR spectrum is relatively simple. However, the presence of two pairs of the diastereotopic protons on each of its sides in the direct vicinity of the oxygen atoms, in conjunction with a narrow range of chemical shifts for all aliphatic protons (<1.5 ppm) make the assignment based on only 1D spectra somewhat ambiguous. This prompted us to investigate the proposed assignment via quantum chemistry calculations and, in addition, to develop a systematic approach when dealing with calculations on diastereotopic protons. Thus, a few other compounds containing diastereotopic protons (also shown in Fig. 1) were investigated. They are: 2,3-epoxypropoxybenzene (**2**), 2,3-epoxypropyl methyl ether (**3**), 2-phenyl-1-butanol (**4**), and acetaldehyde diethyl acetal (**5**).

The results of quantum chemistry calculations are meaningful only if they correspond to the observables measured for the real

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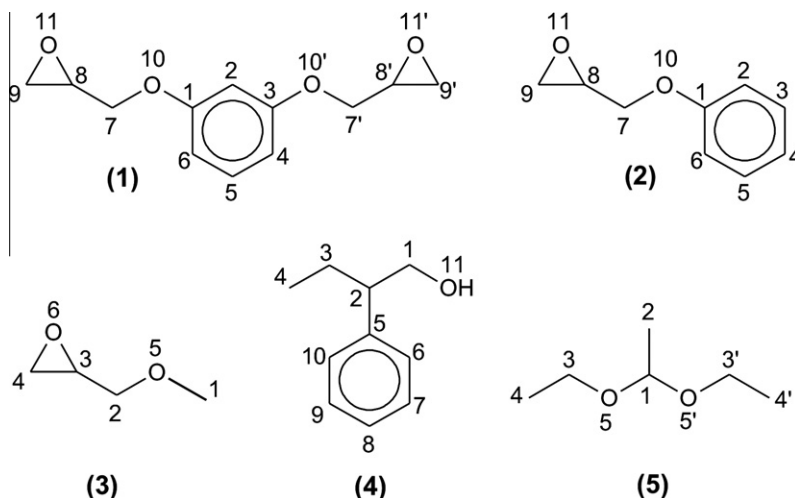


Fig. 1. Molecules considered in the present work: 1,3-di(2,3-epoxypropoxy)benzene (**1**), 2,3-epoxypropoxybenzene (**2**), 2,3-epoxypropyl methyl ether (**3**), 2-phenyl-1-butanol (**4**), and acetaldehyde diethyl acetal (**5**).

system. Thus, the choice of the relevant model prior to calculations is an essential issue. Typical spectroscopic calculations for rigid systems, like benzene, can be carried out for a single molecule. In the case of vibrational spectrum the molecular force field should be (by definition) calculated at a molecular geometry optimized at the same level of theory. To refine the calculated spectra the perturbational (see e.g. [9–11]) or scaling (see e.g. [12–14] and references therein) procedures can then be applied. On the other hand the choice of the relevant molecular geometry is essential in the prediction of various NMR spectra [15]. For example, good results can be obtained using B3LYP-optimized geometries followed by SCF/GIAO calculations. When dealing with the vibrational corrections to nuclear shielding the so-called effective geometries [16,17] are recommended, though equilibrium geometries can be also used [18–20]. Procedures that take into account the effect of the molecular surrounding (e.g. the solvent effect) are also known (e.g. the COSMO model [21,22]). However, flexible systems, like systems containing aliphatic chains, are more problematic. Such calculations are sometimes carried out using fixed molecular geometries (especially for systems of appreciable size; see e.g. [4]), but the formal procedure should account for the presence of various close-lying conformers in the bulk phase. In such a case some of the properties, like chemical shifts δ , are likely to be Boltzmann averages

$$\delta^B = \frac{\sum_i^{\text{all conf.}} \delta_i \exp(-\Delta E_i/kT)}{\sum_i^{\text{all conf.}} \exp(-\Delta E_i/kT)}, \quad (1)$$

where δ_i and ΔE_i denote the chemical shift and relative energy (with respect to the lowest-energy conformer) of the i th conformer, for which the rotational averages

$$\delta^{\text{rot}} = \frac{\int_{-\pi}^{\pi} \delta(\tau) \exp(-E(\tau)/kT) d\tau}{\int_{-\pi}^{\pi} \exp(-E(\tau)/kT) d\tau}, \quad (2)$$

are observed. In Eq. (2) $\delta(\tau)$ and $E(\tau)$ denote the functional dependences of the chemical shift and energy, respectively, on the torsional angle. Apparently in the case of compounds presented in Fig. 1 calculations based on one conformer are not adequate. One would expect that the average chemical shift for a given nucleus calculated according to Eq. (1) differs significantly from the value calculated for the lowest-energy conformer if (i) there are conformers, for which its chemical shift differs significantly from that of the lowest-energy conformer and (ii) the relative energies ΔE_i are low enough to guarantee the significant population of these conformers.

The presented calculations clearly show that in order to account for the proper ordering of theoretical ^1H NMR signals for systems **1–3** the important, carefully chosen conformers have to be considered. However, there are systems (like **4** and **5**) for which reasonable results can be obtained using only the lowest-energy conformers.

2. Computational details

The equilibrium geometries of all conformers of all molecules were obtained at the DFT/B3LYP level of theory [23,24] with 6–311G** basis set [25]. The choice of conformers will be described in the following sections. The subsequent frequency calculations proved that the obtained structures correspond to local minima. The calculations of the isotropic magnetic shielding constants (σ) were carried out within the SCF/GIAO framework [26–29] with the same basis set, and at the B3LYP-optimized geometries (the so-called B3LYP//SCF/GIAO calculations). The chemical shifts δ ($\delta = \sigma_{\text{reference}} - \sigma_{\text{sample}}$) were calculated relative to TMS, for which similar calculations were performed at the corresponding theoretical levels. These calculations were carried out using the PQS quantum chemistry software [30,31].

Rotational averages of chemical shifts of diastereotopic protons H7(7')_a and H7(7')_b of **1** (cf. Fig. 1) with respect to the rotation about a C7–C8 single bond were obtained according to Eq. (2). The O10–C7–C8–O11 torsional angle (cf. Fig. 1) was chosen as τ . The constrained geometry optimization (DFT/B3LYP) for τ ranging from -180° to 180° at 10° intervals, followed by calculations of isotropic magnetic shielding constants (SCF/GIAO) was carried out. Numerical integration of Eq. (2) using 32-points Gaussian quadrature was then performed. The results were tested against the trapezoidal integration scheme, and accepted, since the agreement between the calculated averages was of the order of $10^{-3}\%$. These calculations, as well as calculations of Boltzmann averages according to Eq. (1), were carried out assuming room temperature ($kT = 0.58 \text{ kcal mol}^{-1}$).

To fully rely on the calculated values the vibrational correction to the shielding of one of the diastereotopic protons was also obtained. We used the following formula [20,32,33]

$$\Delta\sigma = \frac{1}{4} \sum_K^{3N-6} \frac{1}{\omega_K} \left[\left(\frac{d^2\sigma}{dQ_K^2} \right)_e - \frac{1}{\omega_K} \left(\frac{d\sigma}{dQ_K} \right)_e \sum_L^{3N-6} \frac{F_{e,KLL}}{\omega_L} \right], \quad (3)$$

where ω denotes the harmonic frequency, Q – the normal coordinate, F – the cubic force constant. Indexes K and L refer to normal

modes of vibrations, and subscript e indicates that the value is to be computed at equilibrium geometry. The shielding constant derivatives and the cubic force constants were first obtained in the basis of internal coordinates, and then transformed to normal coordinate representation after solving the vibrational problem. These calculations were carried out for proton H_{2a} of the smallest system (i.e. **3**). In addition, we made the following simplifications. First, the derivatives of the shielding constant were computed in the subspace of the selected internal coordinates: $r_1 = C2-H_{2a}$, $r_2 = C2-O5$ and $r_3 = C2-C3$ bonds, as well as $\theta_1 = O5-C2-H_{2a}$, $\theta_2 = C3-C2-H_{2a}$, and $\theta_3 = H_{2b}-C2-H_{2a}$ valence angles (cf. Fig. 1; changes in the internal coordinates that are more distant from H_{2a} are not expected to bring about significant changes in its shielding). The derivatives were computed by numerical differentiation with the steps being 0.005 Å and 1° for bond lengths and valence angles, respectively. Second, only the diagonal second derivatives of the shielding constants were computed. It was checked that inclusion of the off-diagonal derivatives which might be important, e.g. $\partial^2\sigma/\partial r_1\partial r_2$, has only minor effect on the overall value of the vibrational correction. Third, only the diagonal cubic force constants were calculated. The vibrational problem itself was solved in the full space of linearly independent internal coordinates, providing us with the transformation matrix to the normal coordinate representation. The described procedure was successfully applied in the determination of the vibrational correction to the nitrogen shielding [34]. The determination of the vibrational effect on the chemical shift required similar calculations for one of the protons of TMS, for which the internal coordinate space was chosen as: $r_1 = C-H$, $r_2 = Si-C$, $\theta_1 = H-C-H$, and $\theta_2 = Si-C-H$.

3. Results and discussion

3.1. Rotational averages

Fig. 2 shows the dependence of the total energy of **1**, as well as the corresponding σ curves of H_{7a} and H_{7b} vs. the torsional angle

$\tau = O10-C7-C8-O11$. We have chosen the lowest-energy conformer, denoted **1a** ($\tau = -162.4^\circ$, *vide infra*). Variation of the τ angle leads to two additional minima: **1a₂** ($\tau = -55.1^\circ$, $\Delta E = 1.36 \text{ kcal mol}^{-1}$), and **1a₃** ($\tau = 87.0^\circ$, $\Delta E = 0.48 \text{ kcal mol}^{-1}$). The highest-energy barrier is of the order of 10 kcal mol^{-1} , which is low enough for all the conformers to be present in the bulk phase. Actually any reaction, for which the energy barrier expressed as ΔG (which roughly corresponds to the calculated ΔE in this case) is lower than 20 kcal mol^{-1} is known to be spontaneous at room temperature. Apparently the $\sigma(\tau)$ curves for protons H_{7a} and H_{7b} are not the same (or symmetry related to each other), which is obvious in a view of the presence of the chiral carbon atom next to the methylene group. Magnetic shielding constants for both diastereotopic protons H_7 differ significantly when going from one conformer to the other; $\Delta\sigma$ reaches the value close to 1.2 ppm at about $\tau = -150^\circ$. The calculated values are reported in Table 1, which includes also the full rotational averages (σ^{rot} , cf. Eq. (2)), and Boltzmann averages (σ^B , cf. Eq. (1)) for protons H_{7a} and H_{7b} , respectively (the orientation of “a” and “b” protons relative to the chiral center will be reported later). The rotational averages for both protons differ by as much as 0.6 ppm. This is to be contrasted with the analogous case of the enantiotopic methylene protons, an example of which (for glycine, which was studied before [2]) is shown in Fig. 3 (B3LYP//SCF/GIAO with 6–311G** basis set results). In this case one of the $\sigma(\tau)$ curves can be obtained from the other by reflection in the $\tau = 0^\circ$ plane; when integrated with the symmetric $E(\tau)$ weight according to Eq. (2) they have to give identical rotational averages. Note that enantiotopic methylene protons of glycine are incorrectly called diastereotopic in the original paper. The results clearly show that the rotational average is very close to the Boltzmann average – the observed difference is not larger than 0.05 ppm. Thus, in the following the Boltzmann averages will be reported. The second point is that the average shielding constants of diastereotopic methylene protons differ from the shielding constants of the lowest-energy conformer by as much as 0.3 ppm – as will be shown this difference is essential in the prediction of the correct order of proton signals.

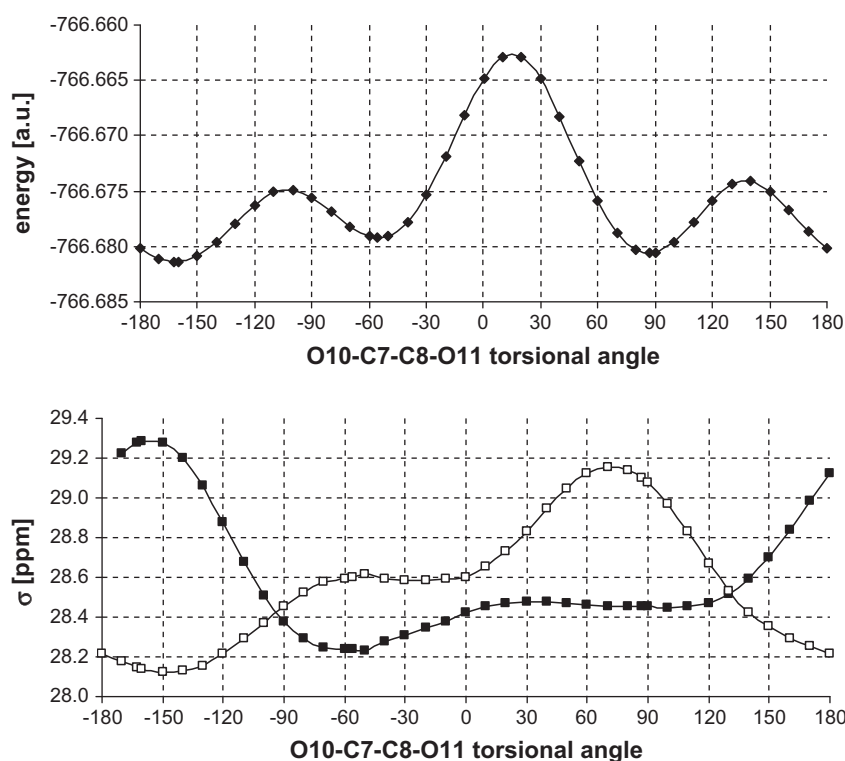


Fig. 2. Energy and magnetic shielding constants of methylene protons H_{7a} (filled squares) and H_{7b} (empty squares) of **1** as a function of torsional angle $O10-C7-C8-O11$.

Table 1

Relative energies (with respect to the lowest conformer **1a**), Boltzmann factors, isotropic magnetic shielding constants for protons $H7(7')_a$ and $H7(7')_b$ for all conformers of **1a**-type, as well as their rotational and Boltzmann averages.

	1a	1a₂	1a₃	σ^B	σ^{rot}
ΔE [kcal mol ⁻¹]	0.00	1.36	0.48		
$\exp(-\Delta E/kT)$	1.00	0.10	0.44		
$\sigma(H7_a/H7'_a)$	28.15	28.60	29.10	28.45	28.40
$\sigma(H7_b/H7'_b)$	29.27	28.24	28.45	28.97	28.99

3.2. The vibrational correction

The overall correction to the shielding constant amounts to -0.43 ppm, which is a typical value for protons. The first-order term (with respect to shielding, i.e. the second term in Eq. (3)) is -0.37 ppm; it mostly follows from the stretching of the C2–H_{2a} bond (-0.35 ppm). All the remaining terms are insignificant. Note that the dominant, first-order effect can be almost fully accounted for using one internal coordinate. The second-order term that follows from this vibration amounts to $+0.13$ ppm. It is canceled out by the negative terms that follow from the remaining vibrations. Thus, the extension of the internal coordinate space by adding C2–O5 and C2–C3 bonds, as well as O5–C2–H_{2a}, C3–C2–H_{2a}, and H_{2b}–C2–H_{2a} valence angles is important from the point of view of obtaining the accurate value of the vibrational correction. Further extension by adding C1–O5 bond, and C1–O5–C2 and C1–O5–C2–H_{2a} angles did not change its overall value.

Similar calculations were carried out for TMS. The overall correction to the shielding constant of one of protons is -0.38 ppm, which gives the correction to chemical shift of 0.05 ppm. Thus, we conclude that the molecular vibrations do not significantly affect the chemical shifts of the diastereotopic protons. In the following we will report the uncorrected values.

3.3. ¹H NMR spectra of the epoxy compounds **1**, **2**, and **3**

Molecule **1** is the most complex one of all considered. It has a number of close-lying conformers with different $\tau_1 = \text{C2–C1–O10–C7}$, $\tau_2 = \text{C1–O10–C7–C8}$, $\tau_3 = \text{O10–C7–C8–O11}$ torsional angles (and their primed analogs, cf. Fig. 1). Only the major points related to the conformational analysis will be reported here. The lowest-energy structure **1a** (cf. Fig. 4) has C₂ symmetry and S/S configuration on both chiral centers 8/8' (or R/R for its enantiomer). τ_1 and τ_2 are close to 180° , and $\tau_3 = -162.4^\circ$. The second conformer, denoted **1b** (cf. Fig. 4), for which $\tau_1 \approx 0^\circ$ and $\tau_2 \approx 180^\circ$, is by 0.21 kcal mol⁻¹ higher in energy. Additional conformers can be formed by rotating the epoxy-ring around the C7–C8 bond, what leads to structures **1a₂**, **1a₃**, **1b₂**, and **1b₃**. Their spectroscopic and structural data are given in Table 2. It is, in fact, the cross-section of the potential energy surface of **1a** with respect to this rotation that is shown in Fig. 2. The conformers having C_s symmetry are obtained by changing the configuration on one of the chiral centers (S/R configuration or its enantiomer R/S; both are diastereoisomers of the C₂ structures). They are very close in energy as compared to the C₂ analogs (their energies are only up to 0.05 kcal mol⁻¹ higher), and have essentially the same shielding constants of all aliphatic protons (which is obvious, since both substituents are very distant; thus, they behave either like identical species, or like enantiomers, which have the same NMR spectra). Therefore, they do not have to be considered in obtaining the Boltzmann averages. Additional conformers, for which τ_2 significantly deviates from 180° (e.g. $\tau_2 = -83.6^\circ$) are more than 2.5 kcal mol⁻¹ higher in energy as compared to **1a**, which corresponds to the contribution of about 1% (and less) in thermal equilibrium at room temperature. They are also not important from the point of view of averaging of the chemical shifts. Asymmetric conformers can be formed by combining torsional angles on the left-hand side of **1a** and **1b**, with these on their right-hand side. They are also not expected to cause any change in averaging of the chemical shifts – changing of the

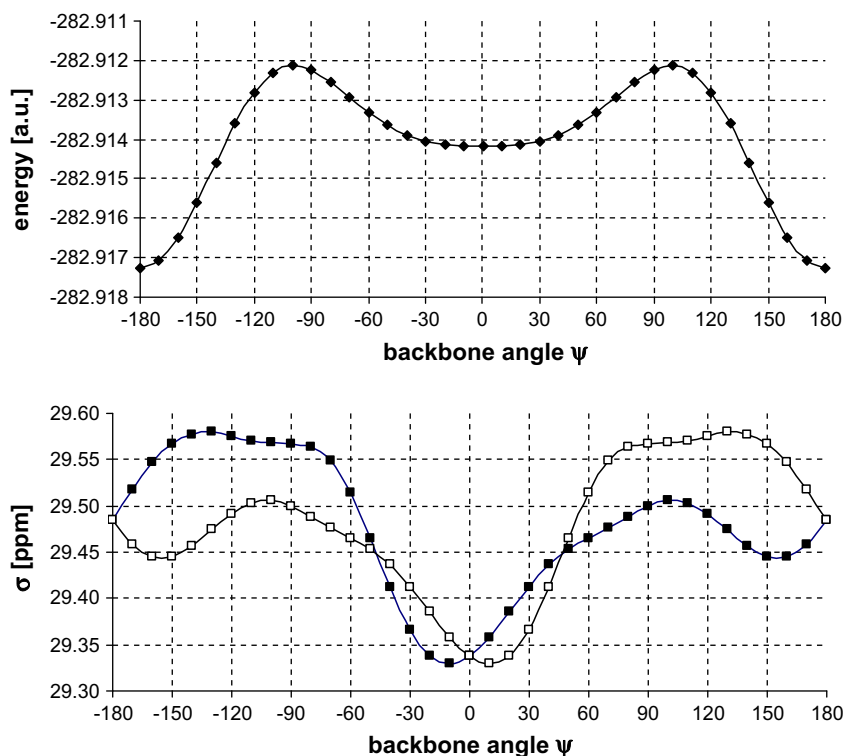


Fig. 3. Energy and magnetic shielding constants of methylene protons of glycine as a function of backbone angle [2].

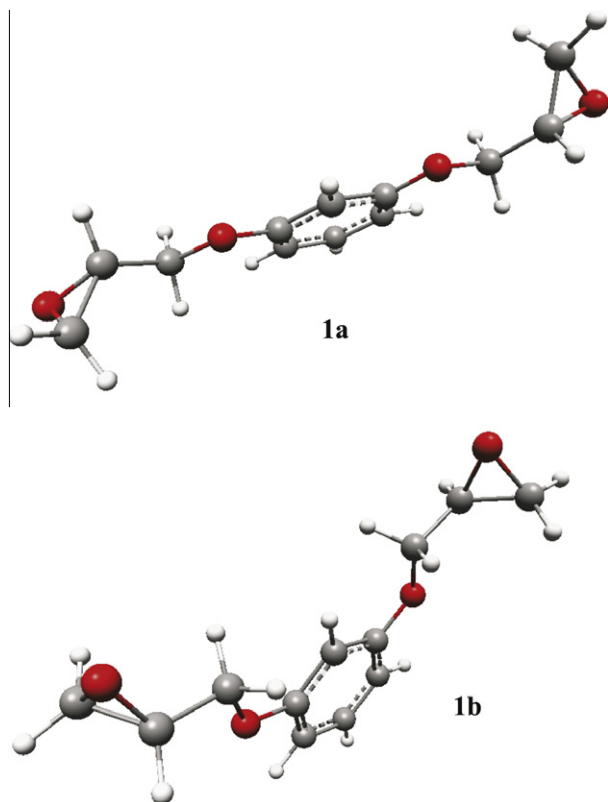


Fig. 4. The lowest-energy C_2 symmetry conformers of **1**. The C_s symmetry conformers can be obtained by changing the configuration of one of the chiral centers to R.

orientation of one substituent does not alter the chemical shifts associated with the other one in a noticeable way. Thus, we believe that six conformers we have already introduced fully represent the real system on which the measurements were carried out.

The calculated chemical shifts relative to TMS ($\sigma = 32.25$ ppm at B3LYP//SCF/GIAO//6–311G** level) for each of the conformers, as well as Boltzmann averages are compared to experimental values [8] in Table 2. The orientation of diastereotopic protons “a” and “b” for **1** relative to the chiral center of the S configuration is shown in Fig. 5. Indexes “a” and “b” have to be interchanged in the case of R-type chiral center. Note that the assignment of the diastereotopic protons “a” and “b” to signals is based in this work on matching the sequence of calculated average and measured chemical

shifts. As can be seen the theoretical chemical shifts obtained for the lowest-energy structure **1a** (and **1b**) do not predict the correct order of signals. One of the diastereotopic protons H7(H7') is strongly deshielded ($\delta > 4$ ppm), the other one – strongly shielded ($\delta < 3$ ppm). The signal attributed to H8(H8') protons is predicted to lie between these two. However, the substantial contribution from the remaining conformers, for which shielding of protons H7(H7') is swapped (see also Fig. 2), changes this picture – the Boltzmann averages for H7_{a,b} and H8 are now in the right order. The agreement between calculated average and experimental chemical shifts of aliphatic protons is within the error limits of the SCF/GIAO approach. Only for one proton the deviation close to 0.7 ppm was found. Chemical shifts of the aromatic protons were also calculated. Significant changes in the shielding between **1a**- and **1b**-type conformers are observed for *ortho* protons relative to the substituents due to the steric (van der Waals) effect; the more distant, *meta* proton (H5) is hardly affected by the change of the τ_2 angle. Boltzmann averaged chemical shifts for aromatic protons also exhibit good agreement with experimental values.

An analysis of the data reported in Table 2 reveals that all aliphatic protons have underestimated, while aromatic protons – overestimated chemical shifts. This is also the case of most chemical shifts of the remaining systems discussed in the following paragraphs. Systematic errors frequently account for some shortcomings of the applied methodology that follow from the adopted approximations. Our earlier investigations [35] inclined us to use SCF/GIAO rather than DFT/GIAO chemical shift calculations that follow DFT geometry optimization. In this work we also calculated the DFT-B3LYP/GIAO chemical shifts for **1**. This time Boltzmann averages δ^B turned out to be somewhat superior to the SCF/GIAO values (on average by 0.1–0.2 ppm), and both aliphatic and aromatic protons had underestimated chemical shifts. However, the observation regarding swaps between δ^B s and chemical shifts calculated for single conformer remains the same. Thus we conclude that the reported methodology related to the necessity of using Boltzmann averages is general in the case of compounds similar to the ones considered here.

The above discussion in relation to only diastereotopic protons of **1** could have been based on results obtained for only **1a**-type conformers, since chemical shifts for **1b**-type conformers are nearly identical. However, taking into account the latter ones in Boltzmann averaging, better agreement for the aromatic protons was obtained. It is also worth while to note that the root-mean-square (RMS) deviation between the calculated and experimental chemical shifts for all eight proton signals is reduced from 0.46 ppm, when only the lowest-energy conformer is considered, down to 0.37 ppm for Boltzmann averages.

Table 2

1,3-di(2,3-epoxypropoxy)benzene (**1**). Energies, relative energies (with respect to the lowest conformer **1a**), Boltzmann factors, torsional angles (see text for details), and calculated proton chemical shifts (relative to TMS) for each conformer are given. The last two columns refer to the Boltzmann average and the experimental chemical shift.

	1a	1a₂	1a₃	1b	1b₂	1b₃	δ^B	δ^{expt}
$E + 766$ [a.u.]	–0.68139	–0.67923	–0.68062	–0.68105	–0.67876	–0.68015		
ΔE [kcal mol ^{–1}]	0.00	1.36	0.48	0.21	1.65	0.78		
$\exp(-\Delta E/kT)$	1.00	0.10	0.44	0.70	0.06	0.27		
τ_1 [deg]	178.1	–178.0	–178.8	–2.2	1.8	2.0		
τ_2 [deg]	–177.7	176.4	179.9	–177.9	176.5	179.5		
τ_3 [deg]	–162.4	–55.1	87.0	–162.4	–55.6	87.4		
$\sigma(\text{H7}_a/\text{H7}'_a)$	4.10	3.65	3.15	4.10	3.66	3.11	3.80	4.20
$\sigma(\text{H7}_b/\text{H7}'_b)$	2.98	4.01	3.80	2.96	4.02	3.76	3.26	3.93
$\delta(\text{H8}/\text{H8}')$	3.06	2.70	3.17	3.07	2.72	3.17	3.07	3.34
$\sigma(\text{H9}_a/\text{H9}'_a)$	2.70	2.58	2.57	2.71	2.59	2.57	2.66	2.90
$\sigma(\text{H9}_b/\text{H9}'_b)$	2.43	3.20	2.24	2.43	3.20	2.22	2.42	2.75
$\delta(\text{H2})$	7.04	6.95	7.24	6.00	6.01	5.84	6.64	6.52
$\delta(\text{H4}/\text{H6})$	6.39	6.37	6.29	6.87	6.82	6.97	6.57	6.52
$\delta(\text{H5})$	7.69	7.66	7.64	7.68	7.66	7.73	7.68	7.20

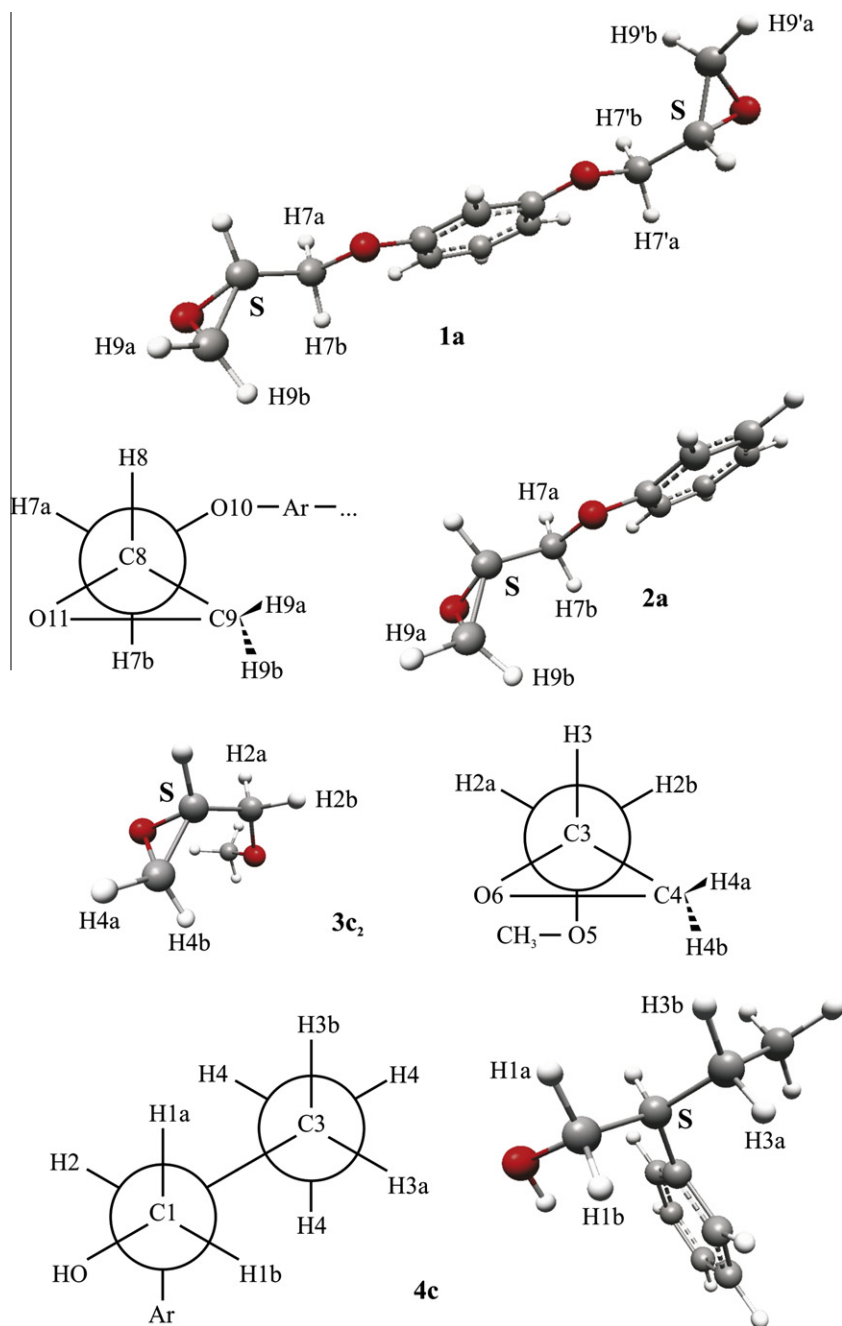


Fig. 5. Orientation of the diastereotopic methylene protons relative to the chiral center in **1–4**. Snapshots and Newman projections are shown.

Similar calculations were carried out on simpler system **2** (which can be obtained from **1** by removing one of the substituents). Atomic labels, the definition of torsional angles, and the orientation of diastereotopic protons relative to S-type chiral center are the same as in **1** (cf. Figs. 1 and 5). This time only three conformers: **2a**, **2a₂**, and **2a₃** were considered. All the data are collected in Table 3. First it should be noted that the chemical shifts of the aliphatic protons in **2** are very close to these of **1**. This is not a surprise since the presence of the second substituent in *meta* position relative to the first one hardly affects chemical shifts of the associated nuclei. This observation strengthens our conclusion concerning the choice of conformers for molecule **1** – due to very similar chemical shifts for symmetric (C_2 or C_s) and asymmetric conformers, the inclusion of the latter ones will not affect Boltzmann averages. The results for **2** are fully consistent with these

for **1** – only Boltzmann averages account for the observed experimental pattern.

All nine conformers of (**3**) obtained by combining three orientations of methoxy-group ($\tau_1 = C1-O5-C2-C3$ torsional angle) with three orientations of the epoxy-ring ($\tau_2 = O5-C2-C3-O6$, cf. Fig. 1) were considered. They are named **3a**, **3a₂**, **3a₃**, ..., **3c₃**, respectively. The orientation of diastereotopic protons relative to S-type chiral center is reported in Fig. 5. The results are given in Table 4. The lowest-energy structure is **3c₂**. All conformers have totally different proton chemical shifts; the differences between the lowest and the highest values for protons $2H_a$ and $2H_b$ are even above 1.6 ppm, and for the remaining protons they are also significant. Four conformers were found to have Boltzmann factor not lower than 0.3. Thus, Boltzmann averages exhibit totally different order as compared to the chemical shifts predicted by the calculations

Table 3

2,3-epoxypropoxybenzene (**2**). Energies, relative energies (with respect to the lowest conformer **2a**), Boltzmann factors, torsional angles (see text for details), and calculated proton chemical shifts (relative to TMS) for each conformer are given. The last two columns refer to the Boltzmann average and the experimental chemical shift.

	2a	2a₂	2a₃	δ^B	δ^{expt}
$E + 499$ [a.u.]	-0.49501	-0.49399	-0.49473		
ΔE [kcal mol ⁻¹]	0.00	0.64	0.18		
$\exp(-\Delta E/kT)$	1.00	0.34	0.74		
τ_1 [deg]	177.6	-177.1	-179.2		
τ_2 [deg]	-177.3	175.8	179.7		
τ_3 [deg]	-162.4	-55.1	86.7		
$\delta(\text{H7}_a)$	4.10	3.67	3.14	3.69	4.17
$\delta(\text{H7}_b)$	2.99	4.01	3.80	3.44	3.94
$\delta(\text{H8})$	3.06	2.73	3.16	3.04	3.32
$\delta(\text{H9}_a)$	2.70	2.58	2.57	2.63	2.85
$\delta(\text{H9}_b)$	2.44	3.20	2.25	2.49	2.72
$\delta(\text{H2/H4/H6})$	7.11	7.09	7.11	7.11	6.94
$\delta(\text{H3/H5})$	7.70	7.68	7.69	7.69	7.25

on the lowest-energy conformer. Only the former ones account for the observed experimentally order of signals. The largest observed difference between the average theoretical and experimental value was found for H3; still it is lower than 0.5 ppm. In addition, the RMS values between the calculated and experimental chemical shifts for all six signals are 0.37 and 0.32 ppm for the **3c₂** conformer and the Boltzmann average, respectively.

3.4. ¹H NMR spectra of **4** and **5**

It is clear that in the theoretical prediction of the ¹H NMR spectrum of molecular fragments containing diastereotopic protons it is necessary to incorporate the low-energy conformers that differ in the torsional angles on bonds next to the chiral center. In such a case calculations carried out on only one, say the lowest-energy conformer, may lead to too large difference in theoretical chemical shifts corresponding to inequivalent methylene protons, and, in addition, predict wrong sequence of signals on the spectrum. Incorporating various close-lying conformers in the calculations changes this picture. On the other hand conformers, for which ΔE is significantly greater than kT at the temperature of experiment, do not contribute significantly to the Boltzmann average. One of the effects responsible for increasing of the ΔE value is a steric effect: the direct vicinity of two molecular fragments aligned in an unfavorable way increases the electron–electron repulsion and, as a consequence, increases the energy of a given conformer. Systems **1–3** considered so far contain oxygen atom separating two molecular fragments: 1,2-epoxypropyl group and aromatic ring (or methyl group), preventing the overlapping of

the associated electronic clouds. It is thus not surprising that there are some conformers for which ΔE is well below 1 kcal mol⁻¹. Different shielding of the diastereotopic methylene protons in these conformers follows from their different orientation relative to the epoxy oxygen atom lone electron pairs. This is not the case of the next system, 2-phenyl-1-butanol (**4**). In fact, this molecule contains two pairs of diastereotopic protons which are not chemically equivalent in spite of free rotation about single bonds C1–C2 and C2–C3. Note, that methylene protons of the epoxy-ring in **1–3** are also diastereotopic, but there is no free rotation that could potentially average their shielding.

As in the case of **3**, nine conformers of **4** differing in angles $\tau_1 = \text{O11–C1–C2–C3}$ and $\tau_2 = \text{C1–C2–C3–C4}$, cf. Fig. 1, were considered. They are denoted **4a**, **4a₂**, **4a₃**, ..., **4c₃**, respectively. The orientation of diastereotopic protons relative to S-type chiral center is reported in Fig. 5. The structural and spectroscopic data are given in Table 5 (the data for the hydroxyl proton are not included). The lowest-energy structure is **4c**. In contrast to **3** only two conformers of **4** have the Boltzmann factor greater than 0.3, and as many as four conformers are 2 kcal mol⁻¹ higher than **4c** due to steric effects of the methylene protons with the aromatic ring. In addition, the chemical shifts found for different conformers are differentiated to lesser extent as compared to **3** – only in the case of one proton (H3_b) the difference between the lowest and the highest value is somewhat greater than 1 ppm (in contrast to 1.6 found for **3**). For this reason no significant differences between chemical shifts of **4c** and Boltzmann averages are expected. Indeed, the value greater than 0.2 ppm was found for only H3_b proton, and for the remaining protons they are not larger than 0.15 ppm. This is to be compared with 0.3–0.4 ppm (three protons), >0.4 ppm (two protons), and ca. 0.4 ppm (two protons) found for **1**, **2**, and **3**, respectively. Though we also observe a swap of one pair of theoretical chemical shifts, still, in contrast to molecules **1–3**, it refers to diastereotopic H3 protons themselves. It is due to significant contribution from structure **4a**, for which proton 3H_b exhibits higher chemical shift. However, slight reduction of RMS between the calculated and experimental chemical shifts for all nine signals, from 0.34 ppm for **4c**, down to 0.30 ppm for Boltzmann averages, is also observed.

Molecule **5** contains two pro-chiral centers; thus, its methylene protons are also diastereotopic. A number of conformers differing in $\tau_1 = \text{O5'–C1–O5–C3}$, $\theta_1 = \text{C1–O5–C3–C4}$, $\tau_2 = \text{O5–C1–O5'–C3'}$, $\theta_2 = \text{C1–O5'–C3'–C4'}$ torsional angles can be formed. The choice of the lowest-energy conformers is not as obvious as in the case of the previous systems. The symmetric (C_s) conformer ($\tau_{1,2} \approx \pm 150^\circ$, $\theta_{1,2} \approx 180^\circ$) turned out to be more than 5 kcal mol⁻¹ higher compared to the lowest one we found. Instead of performing the usual conformational search at MM or semiempirical levels (frequently providing inadequate energetic order of conformers), we

Table 4

2,3-epoxypropyl methyl ether (**3**). Energies, relative energies (with respect to the lowest conformer **3c₂**), Boltzmann factors, torsional angles (see text for details), and calculated proton chemical shifts (relative to TMS) for each conformer are given. Chemical shifts for the methyl group were calculated as an average for three protons. The last two columns refer to the Boltzmann average and the experimental chemical shift.

	3a	3a₂	3a₃	3b	3b₂	3b₃	3c	3c₂	3c₃	δ^B	δ^{expt}
$E + 307$ [a.u.]	-0.70570	-0.70440	-0.70344	-0.70551	-0.70626	-0.70306	-0.70535	-0.70647	-0.70292		
ΔE [kcal mol ⁻¹]	0.49	1.30	1.90	0.60	2.14	0.13	0.70	0.00	2.23		
$\exp(-\Delta E/kT)$	0.44	0.11	0.04	0.36	0.03	0.80	0.30	1.00	0.02		
τ_1 [deg]	-176.4	74.9	-83.1	-179.7	-73.3	80.6	173.2	89.0	-87.3		
τ_2 [deg]	-162.3	-171.6	-160.0	87.6	86.7	82.3	-57.6	-47.3	-69.4		
$\delta(\text{H2}_a)$	2.44	2.37	2.87	3.25	3.10	3.77	3.39	3.28	4.00	3.26	3.68
$\delta(\text{H2}_b)$	3.53	4.09	3.40	2.56	3.10	2.48	3.17	3.54	2.91	3.13	3.34
$\delta(\text{H3})$	2.78	2.64	2.75	2.89	2.84	2.78	2.51	2.51	2.38	2.67	3.14
$\delta(\text{H4}_a)$	2.54	2.60	2.52	2.41	2.43	2.43	2.40	2.45	2.53	2.46	2.79
$\delta(\text{H4}_b)$	2.29	2.25	2.32	2.07	2.09	2.05	2.90	2.82	2.69	2.43	2.61
$\delta(\text{H1})$	3.17	3.13	2.23	3.17	3.24	3.29	3.10	3.18	2.99	3.20	3.41

Table 5
2-phenyl-1-butanol (**4**). Energies, relative energies (with respect to the lowest conformer **4c**), Boltzmann factors, torsional angles (see text for details), and calculated proton chemical shifts (relative to TMS) for each conformer are given. Chemical shifts for the methyl group were calculated as an average for three protons. The last two columns refer to the Boltzmann average and the experimental chemical shift.

	4a	4a₂	4a₃	4b	4b₂	4b₃	4c	4c₂	4c₃	δ^B	δ^{expt}
$E + 464$ [a.u.]	-0.84057	-0.83779	-0.83822	-0.83960	-0.83585	-0.83896	-0.84145	-0.83816	-0.84041		
ΔE [kcal mol ⁻¹]	0.55	2.30	2.03	1.16	3.51	1.56	0.00	2.06	0.65		
$\exp(-\Delta E/kT)$	0.39	0.02	0.03	0.14	0.00	0.07	1.00	0.03	0.33		
τ_1 [deg]	58.0	56.1	61.4	-56.0	-59.9	-53.5	173.3	170.7	173.7		
τ_2 [deg]	-169.5	65.5	-73.8	-168.8	80.8	-59.8	-172.7	64.3	-69.4		
$\delta(\text{H3}_a)$	1.34	2.14	1.51	1.54	1.62	1.40	1.43	1.55	1.41	1.43	1.54
$\delta(\text{H3}_b)$	2.27	1.21	1.86	1.33	1.66	1.53	1.34	1.35	1.54	1.56	1.73
$\delta(\text{H2})$	2.00	2.43	2.15	1.90	2.33	1.95	2.44	2.87	2.39	2.29	2.64
$\delta(\text{H1}_a)$	3.32	3.86	3.52	3.59	3.90	3.62	3.42	3.41	3.65	3.47	3.68
$\delta(\text{H1}_b)$	3.33	3.42	3.42	3.61	3.79	3.77	3.11	3.88	2.91	3.20	3.66
$\delta(\text{H4})$	0.78	0.86	1.38	0.81	0.78	1.06	0.82	0.74	1.13	0.88	0.81
$\delta(\text{H6}/\text{H10})$	7.42	7.34	7.40	7.80	7.96	7.90	7.56	7.59	7.52	7.55	7.17
$\delta(\text{H7}/\text{H9})$	7.62	7.61	7.59	7.60	7.62	7.58	7.70	7.71	7.67	7.66	7.30
$\delta(\text{H8})$	7.52	7.51	7.49	7.54	7.52	7.49	7.59	7.57	7.56	7.56	7.21

Table 6
Acetaldehyde diethyl acetal (**5**). Energies, relative energies (with respect to the lowest conformer **5a**), Boltzmann factors, torsional angles (see text for details), and calculated proton chemical shifts (relative to TMS) for each conformer are given. Chemical shifts for the methyl group were calculated as an average for three protons. The last two columns refer to the Boltzmann average and the experimental chemical shift.

	5a	5b	δ^B	δ^{expt}
$E + 387$ [a.u.]	-0.62035	-0.61923		
ΔE [kcal mol ⁻¹]	0.00	0.70		
$\exp(-\Delta E/kT)$	1.00	0.30		
τ_1 [deg]	-64.9	65.7		
θ_1 [deg]	167.6	177.1		
τ_2 [deg]	-68.2	-153.3		
θ_2 [deg]	179.4	176.8		
$\sigma(\text{H3}_a/\text{H3}'_a)$	3.34	3.34	3.34	3.63
$\sigma(\text{H3}_b/\text{H3}'_b)$	3.17	2.97	3.12	3.48
$\delta(\text{H4}/\text{H4}'')$	1.24	1.28	1.25	1.21
$\delta(\text{H2})$	1.26	1.27	1.26	1.30
$\delta(\text{H1})$	4.27	3.81	4.16	4.69

carried out the energy scans with respect to τ_1 and θ_1 torsions adopting 15° increments and optimizing the remaining geometrical parameters, starting from the symmetric structure. The (asymmetric) structures corresponding to the lowest-energy minima on these energy cross-sections were then subjected to full geometry optimization. Only one conformer, named **5b**, turned out to be less than 1 kcal mol⁻¹ higher in energy as compared to the lowest-energy structure **5a**. The remaining ones were at least 2 kcal mol⁻¹ above **5a**. Note that identical molecules can be formed by changing the sign of the torsional angles accordingly (e.g. in the case of **5b** the set of torsional angles $\tau_1 = -65.7^\circ$, $\theta_1 = -177.1^\circ$, $\tau_2 = 153.3^\circ$, and $\theta_2 = -176.8^\circ$ represents the same molecule). Therefore, conformers **5a** and **5b** are representative in the calculations of the spectroscopic parameters of **5**. Their structural and spectroscopic data are given in Table 6. As can be seen the inclusion of the higher energy conformer **5b** in the calculations does not bring about significant changes in the calculated chemical shifts. This time, however, the deviations between Boltzmann averaged and experimental values are somewhat higher as compared to these calculated for **5a** alone.

4. Conclusions

This work reports the calculations of chemical shifts of diastereotopic methylene protons in various compounds. These protons always have different chemical shifts regardless the nature of the solvent (chiral or non-chiral) used in the experiment. It is shown

that free rotation about a single bond next to the chiral center provides different values of shielding constants (and chemical shifts) of diastereotopic methylene protons. Enantiotopic methylene protons exhibit the same rotational averages for symmetry reason. The observed, rotational averages of diastereotopic protons are nearly the same as Boltzmann averages based on the properly selected conformers.

Proper selection of conformers differing in torsional angles in the vicinity of the chiral center is especially important in the case of molecules with no significant steric effects. In this case a number of conformers, for which ΔE relative to lowest one is, say, below 1 kcal mol⁻¹, i.e. it is close to kT at the temperature of experiment, can be found. This is frequently the case of compounds containing relatively rigid fragments well separated from each other. These conformers may exhibit very different shielding of diastereotopic protons ($\Delta\sigma$ can be larger than 1.5 ppm) and, consequently, significantly affect final, average chemical shifts. In this case the proper ordering of the calculated chemical shifts can be achieved only when Boltzmann averages are used. The important conformers can be often selected intuitively, e.g. by considering the molecular symmetry. However, there are systems for which steric effects increase the ΔE value of various conformers above 2 kcal mol⁻¹. Such conformers hardly affect the Boltzmann average – reasonable results can be obtained by performing calculations only on one, the lowest-energy conformer. However, some improvement of the results can be obtained when relying on Boltzmann averages. In addition, the vibrational effects are not essential in the theoretical prediction of the chemical shifts of the diastereotopic protons. Although they contribute in the noticeable way to the magnetic shielding constants, the relative values calculated with respect to the TMS reference remain unaffected. Finally, we would like to point out that similar effects can be observed in the case of other magnetic properties, like spin–spin coupling constants.

Finally, it should be noted that the presented procedure may not be of general applicability to all known systems. The molecules considered in the present work are fairly simple, in that there are no unusual conjugation effects, significant steric strain effects, etc. that could, for example, hinder, or even stop the rotation about some bonds. Different approaches, specific to each system would be required in such cases. However, the presented results refer to a broad range of organic compounds; thus, may be of interest to quite wide community of organic chemists using NMR technique as a structural tool. In addition, the overall discussion would remain valid in the case of calculations carried out at higher theoretical levels than these considered here, which provide more reliable results. This refers to not only calculations of the chemical shifts, but also to the determination of improved relative energies, which

in some cases may not be well accounted for by DFT approach with typical density functionals (like dispersive-type interactions between molecular fragments connected by a single bond), leading to poor cluster populations.

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