Research Article

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Observed and calculated ^{1}H and ^{13}C chemical shifts induced by the *in situ* oxidation of model sulfides to sulfoxides and sulfones

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A series of model sulfides was oxidized in the NMR sample tube to sulfoxides and sulfones by the stepwise addition of *meta*-chloroperbenzoic acid in deuterochloroform. Various methods of quantum chemical calculations have been tested to reproduce the observed ^{1}H and ^{13}C chemical shifts of the starting sulfides and their oxidation products. It has been shown that the determination of the energy-minimized conformation is a very important condition for obtaining realistic data in the subsequent calculation of the NMR chemical shifts. The correlation between calculated and observed chemical shifts is very good for carbon atoms (even for the 'cheap' DFT B3LYP/6-31G* method) and somewhat less satisfactory for hydrogen atoms. The calculated chemical shifts induced by oxidation (the $\Delta\delta$ values) agree even better with the experimental values and can also be used to determine the oxidation state of the sulfur atom (–S–, –SO–, –SO_2–).

Supporting information may be found in the online version of this article.

Keywords: NMR; ^{1}H; ^{13}C; *in situ* oxidation of sulfides to sulfoxides and sulfones; chemical shifts induced by oxidation; DFT calculations

Introduction

Compounds containing the sulfoxide and sulfone groups have been used as versatile intermediates in organic synthesis for carbon–carbon bond-forming reactions,[1–5] rearrangements[6–8] and eliminations.[9] They have also been used as catalysts for asymmetric synthesis.[10] These functional groups are also present in many biologically and medically important products (e.g. antibiotics[11,12] or potassium channel activators[13]).

When two different alkyl substituents are attached to the sulfur atom, the sulfoxide becomes chiral. The NMR parameters that are most often used to determine the configuration at asymmetric centers are the NOE contacts between spatially closed hydrogen atoms or certain spin–spin coupling constants which are known to be related to the stereochemistry (the most often used are the Karplus-type relations of vicinal coupling constants to the dihedral angle of coupled nuclei). In the NMR spectra of sulfoxides, it is impossible to observe coupling constants with oxygen, which would be necessary to deduce the torsion angles O–S–C–H or O–S–C–C and thus determine the configuration of the sulfoxide group. The NOE contacts of the sulfoxide oxygen are also inaccessible. The configuration of the sulfoxide functional groups can be elucidated by NMR spectroscopy only indirectly (e.g. by aromatic solvent-induced shift (ASIS) or by the interaction with shift reagents[14]). In the past, various attempts to determine the configuration of the sulfoxide group by NMR spectroscopy were made.

Some relations between the chemical shifts of neighboring hydrogen atoms and the configuration of the sulfoxide group have been observed[15–17] but are not generally applicable. These chemical shift relations can only be used for the particular type of compounds where they were observed. An acetylene-like anisotropy of the sulfoxide group was proposed[17–22] (protons situated near a plane perpendicular to the S=O bond and passing through its center are deshielded, whereas protons situated near the sulfur atom and more or less in line with the direction of the S=O bond suffer from a shielding effect, unlike the same protons in the parent sulfide). However, the concept of acetylene-like anisotropy was later criticized as being oversimplified and inadvisable.[23] Other procedures for the determination of the sulfoxide group configuration have used solvent-induced shifts,[12,23,24] shift reagents[24–26] and chiral NMR reagents.[27–31]

Quantum chemical calculations can be used for the estimation of the energy-optimized geometry of medium-size molecules as well as for the theoretical prediction of NMR parameters (shielding constants and coupling constants). High-level *ab initio* calculations with gauge-independent atomic orbitals (GIAO) have been shown to provide good agreement with the experimental NMR data.[32,33] The combination of theoretical calculations and experimental NMR spectra has already been used for the solution of various stereochemical problems.[34–36]

We have decided to use this approach for determining the configuration at the sulfur atom in chiral sulfoxides. The prerequisite for the successful use of such a method is a proper methodology for a theoretical calculation of realistic values of the chemical shifts. For this purpose, we have chosen a series of simple acyclic and cyclic sulfoxides, sulfones and their parent sulfides **1**–**12** (Fig. 1). In this article, we present the results of the theoretical calculations of the ^{1}H and ^{13}C chemical shifts of

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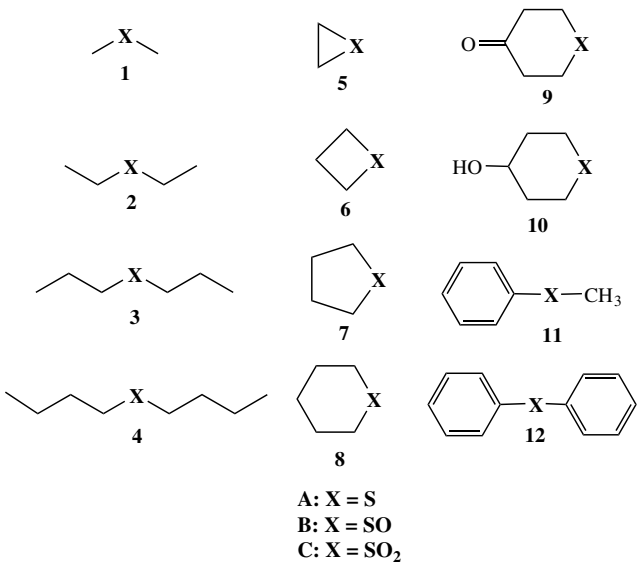

Figure 1. The model sulfides, sulfoxides and sulfones investigated.

these compounds in comparison with the experimental data. The application of this method for the structure determination of chiral sulfoxides will be presented in our next article.

Experimental

All of the sulfides **1A–12A**, the sulfoxides **1B** and **8B**, the dimethylsulfone (**1C**), the deuterated solvents ($CDCl_3$, CD_2Cl_2) and *meta*-chloroperbenzoic acid (MCPBA) used in this work were obtained commercially from Sigma–Aldrich Co. The sulfoxides **1B–12B** and sulfones (**1C–12C**) were prepared by an *in situ* stepwise oxidation of corresponding sulfides (**1A–12A**) with MCPBA in an NMR tube in a $CDCl_3$ solution. The oxidation reactions were monitored by the ^{1}H and ^{13}C NMR spectra as shown for the *in situ* oxidation of dipropylsulfide (**3A**) in Fig. 2. The addition of MCPBA was finished when sulfide was completely oxidized to corresponding sulfone and small amount of unreacted MCPBA appeared in the spectrum (final molar ratio of added MCPBA to sulfone was about 2.1 : 1).

The structures of the products were determined from the NMR spectra, and the presence of the corresponding sulfoxides and sulfones was confirmed by mass spectrometry directly in the $CDCl_3$ solutions. The preparation of sulfone **5C** is not possible by simple oxidation of sulfide **5A**.[9]

The NMR spectra were measured on a Bruker Avance 600 (with ^{1}H at 600.13 MHz and ^{13}C at 150.9 MHz frequency) using a 5 mm TXI cryo-probe and about 5–10 mg of sample in 0.6 ml of $CDCl_3$. The chemical shifts are given in δ-scale (with the ^{1}H shifts referenced to TMS and the ^{13}C referenced to $CDCl_3$ using $\delta(CDCl_3)$ 77.00 ppm). The typical experimental conditions for the ^{1}H NMR spectra were 16 scans, a spectral width of 6 kHz, and an acquisition time of 5 s, yielding 60 K data points. The FIDs were zero-filled to 128 K data points. The 2D-homonuclear (H,H-COSY and H,H-ROESY) and 2D-heteronuclear (H,C-HSQC and H,C-HMBC) experiments were performed when needed for the structural assignments of signals (with standard 2D-NMR pulse sequences of Bruker software being used). For selected compounds with a six-membered ring (**8A–8C, 9A–9C** and **10A**), the low- temperature ^{1}H and ^{13}C NMR spectra (at 0°, −25°, −50°, −75°) in dichloromethane were also measured.

The geometry optimizations and chemical shift calculations were conducted using the Gaussian 03 software package.[37] Six different combinations of geometry optimization and chemical shift calculations were used for all of the compounds [B3LYP/6-31G*//B3LYP/6-31G*, B3LYP/6-311++G**//B3LYP/6-31G*, B3LYP/6-311++G(3df,3pd)//B3LYP/6-31G*, B3LYP/6-311++G**//B3LYP/6-311++G**, B3LYP/6-311++G(3df,3pd)//B3LYP/6-311++G**, B3LYP/6-311++G(3df,3pd)//B3LYP/6-311++G(3df,3pd)].

Results

Detailed analysis of compounds 1A, 1B and 1C

Being the simplest compounds in our series, dimethylsulfide (**1A**), dimethylsulfoxide (**1B**) and dimethylsulfone (**1C**) were used for testing the methods of the theoretical calculations. The geometry optimization and chemical shift calculations were performed at various levels of theory. Several methods [the Hartree–Fock (HF) method, density functional theory (DFT) and Moeller–Plesset perturbation theory (MP2) as well as various basis sets (6-31G*, 6-311++G**, 6-311++G(3df,3pd), IGLO-II[38] and IGLO-III[38])] were used in calculations. As the ultimate proof of the method's efficiency, we used the comparison of the calculated chemical shift differences between dimethylsulfoxide and dimethylsulfide and between dimethylsulfone and dimethysulfide with the corresponding differences obtained experimentally. We observed that the HF method did not provide satisfactory results in the calculations of the ^{13}C chemical shift differences (Table 1), whereas the DFT and MP2 methods worked quite well. The B3LYP functional provided slightly better results than the BPW functional. The effect of the basis set used was found to be very important (with differences of up to 2.5 ppm going from the 6-31G* to the 6-311++G(3df,3pd) basis set). We tested also the IGLO-II and IGLO-III basis sets designed for chemical shift calculations[38] and the results were also very close to the experimental ones (with a calculated chemical shift difference of 22.7 ppm for **1B**–**1A** and of 25.0 ppm for **1C**–**1A**; the experimental values were 22.85 and 24.57 ppm). The method of geometry optimization was not crucial – the chemical shifts calculated on molecules previously optimized with the B3LYP/6-31G*, with the B3LYP/6-311++G** and with the MP2/6-311++G** methods were similar and close to the experimental values (for a detailed comparison, see Table 1).

On the other hand, the calculated hydrogen chemical shift differences (Table 1) were much less encouraging. All of the methods, even those with a large basis set, underestimated the ^{1}H chemical shift differences. The calculated differences were at least about 0.3 ppm lower than the experimental ones. This inaccuracy in the ^{1}H chemical shift calculations could be attributed to neglecting the solvent and vibrational averaging[39] in the calculations. We tried to simulate the chloroform solvent with a continuum polarizable model (PCM), but this implicit solvation model did not improve the results. The 'best' calculated hydrogen chemical shift differences were 0.25 ppm for **1B–1A** and 0.68 ppm for **1C–1A**, and hence significantly lower than the experimental values of 0.50 and 0.88 ppm. This finding is in agreement with the previously published observation that PCM models are not suitable for the calculations of NMR parameters.[40,41] The IGLO-II and IGLO-III basis sets yielded similar results as the default Gaussian basis sets.

To acquire deeper insight into the sulfoxide group anisotropy[42] pattern, we performed a series of calculations of the individual

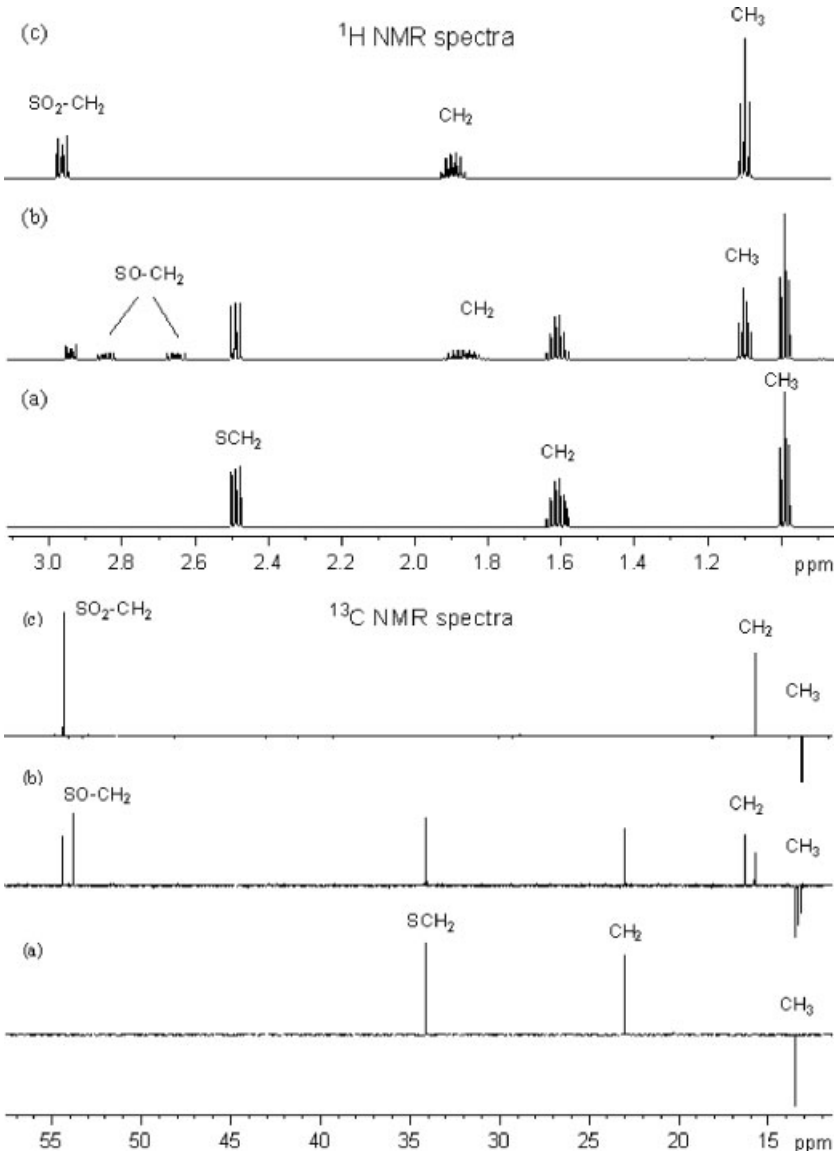

Figure 2. The *in situ* stepwise oxidation of dipropylsulfide (**3A**) monitored by the ^{1}H and ^{13}C (APT-pulse sequence) NMR spectra: (a) **3A** in $CDCl_3$; (b) after the first addition of MCPBA – the initial **3A** together with **3B** and **3C** are observed; (c) after the second addition of MCPBA – only the final product sulfone **3C** is present.

hydrogen chemical shifts in dimethylsulfoxide (**1B**), where the torsion angle C–S–C–H was adjusted to cover the entire range of the free rotation of the methyl group (360°) with a step of 10° (Fig. 3). We also calculated the dependence of the hydrogen chemical shift in dimethylsulfide (**1A**) on the rotation of the methyl group. The differences between the hydrogen chemical shift in **1B** and **1A** are also shown in Fig. 3. It is clearly shown in the figure that the chemical shift differences observed upon sulfide-to-sulfoxide oxidation are mainly governed by the orientation of the studied hydrogen and the oxygen atom. The influence of the sulfur-free electron pair is much lower; this can be explained by the fact that in the parent dimethylsulfide (**1A**) one of the electron pairs is in approximately the same position as in dimethylsulfoxide (**1B**).

Other sulfides, sulfoxides and sulfones

For the geometry optimization and chemical shift calculation of all the other compounds **2A–12C**, we used the DFT method with the B3LYP functional. There were two reasons for the selection of the B3LYP functional: (i) it yielded satisfactory results in the **1A–1C** calculations and (ii) is the most widely used for NMR parameter calculations within the chemical community.

For each compound, we studied six different methods of geometry optimization and chemical shift calculations. The methods differed in the size of the basis sets used. As the simplest model, we used geometries optimized at the B3LYP/6-31G* level and chemical shifts calculated at the same level. The most expensive model used the B3LYP/6-311++G(3df,3pd) method for both geometry optimization and chemical shift calculations.

Conformation

Chemical shifts are sensitive to the conformation of molecules. The rotamers of dimethylsulfide (**1A**) and dimethylsulfoxide (**1B**) have already been discussed above. The calculated lowest energy

Table 1. The experimental and calculated ^{13}C and ^{1}H chemical shift differences using the geometry optimization of B3LYP/6-311++G**

Method	Functional/basis set	$\Delta\delta(^{13}C)$	$\Delta\delta(^{13}C)$	$\Delta\delta(^{1}H)$	$\Delta\delta(^{1}H)$
		1B–1A	**1C–1A**	**1B–1A**	**1C–1A**
Exp.		22.85	24.57	0.50	0.88
HF	6-31G*	18.93	21.50	0.36	0.55
	6-311++G**	19.44	22.22	0.23	0.53
DFT	BPW/6-31G*	20.08	21.50	0.21	0.46
	BPW/6-311++G**	21.64	24.59	0.12	0.61
	B3LYP/6-31G*	20.55	21.66	0.22	0.44
	B3LYP/6-311++G**	22.29	24.68	0.11	0.55
	B3LYP/6-311++G(3df,3pd)	23.00	23.84	0.19	0.63
	MP2/6-31G*	22.13	23.68	0.25	0.39
	MP2/6-311++G**	23.42	25.65	0.11	0.45
	MP2/6-311++G(3df,3pd)	23.24	25.54	0.22	0.58
	B3LYP/6-31G*[a]	22.74	23.52	0.18	0.63
	B3LYP/6-311++G**[b]	21.73	21.46	0.15	0.59

[a] Geometry optimization with B3LYP/6-31G*.
[b] Geometry optimization with MP2/6-311++G**.

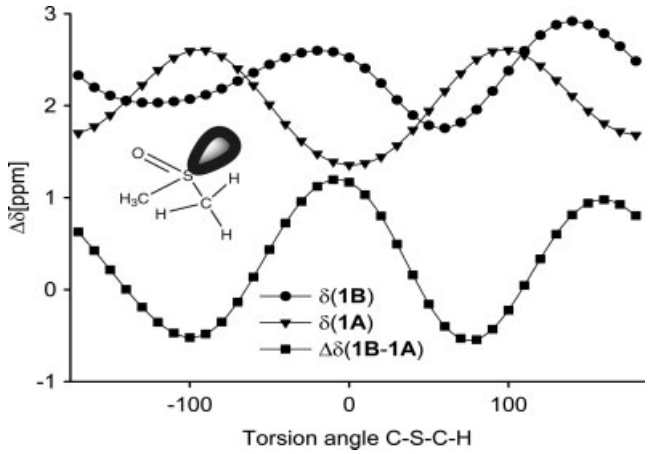

Figure 3. The dependence of the calculated [B3LYP/6-311++G(3df,3pd)] hydrogen chemical shift on the C–S–C–H torsion angle in dimethylsulfoxide **1B** (circles) and in dimethylsulfide **1A** (triangles) and the difference of the chemical shifts **1B–1A** (squares).

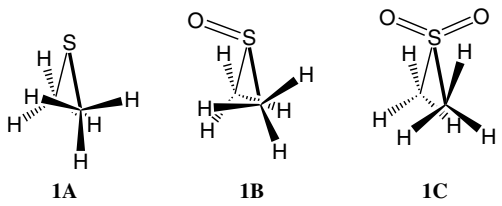

Figure 4. The calculated lowest energy conformers of compounds **1A, 1B** and **1C**.

conformation of dimethylsulfone (**1C**) is shown in Fig. 4 (along with those of **1A** and **1B**).

The conformations of diethylsulfide (**2A**), the sulfoxide **2B** and the sulfone **2C** were studied in detail. Various conformers can be constructed depending on the dihedral angle C–S–C–C. Some of the conformers could be excluded because of the overlap of the hydrogen atoms in them. Three conformers of the sulfide **2A**, four of the sulfoxide **2B** and three of the sulfone **2C** were optimized at the B3LYP/6-31G* level, and the chemical shifts were calculated at the 6-311++G(3df,3pd) level. In all three cases, the zig-zag conformer had the lowest energy, but the other conformers were only slightly less stable (0.1–1.2 kcal/mol) and should be considered in the conformational equilibrium. The chemical shifts were therefore calculated as a population-weighted average of the chemical shifts of all the conformers. The relative energies of the conformers, their chemical shifts and the average chemical shifts are summarized in Table S1 in supporting information. However, the differences between the chemical shifts of the most stable zig-zag conformer and the weighted average chemical shifts are rather small (up to 3 ppm in the ^{13}C chemical shifts and up to 0.3 ppm in the ^{1}H chemical shifts), and therefore we used only the zig-zag conformation in the chemical shift calculations of dipropyl **3A**–**3C** and dibutyl derivatives **4A**– **4C**.

The four-membered ring in the sulfide **6A**, the sulfoxide **6B** and the sulfone **6C** was found to be almost planar after geometry optimization. The calculated torsion angles S–C–C–C were 0° for **6A**, 26° for **6B** and 12° for **6C**.

The geometry-optimized structures of the sulfide **7A** and the sulfone **7C** are represented by two twist conformations with atoms C2, S and C5 in the plane and atoms C3 and C4 out of the plane. Both conformations have identical energy and the NMR spectra indicate their fast interconversion in solution (only one signal was observed for the hydrogens in positions 2 and 5). For the sulfoxide **7B**, three conformers were found – the first two energetically equivalent twist forms with C2–S–C5 in the plane and C3 and C4 out of the plane that are analogical to those found for **7A** and **7C,** while the third is an envelope form with a sulfur atom out of the plane and an oxygen in the flagpole position. This third envelope conformation is 0.7 kcal/mol less stable (B3LYP/6-311++G(3df,3pd)//B3LYP/6-31G*). In solution, all the conformations are probably present in a fast equilibrium (Fig. 5).

The NMR spectra indicate a fast equilibrium of the two energetically equivalent chair forms of **8A** and **8C** in solution (discussion concerning conformation of thiacyclohexanes was recently reviewed[43]). It was found previously that sulfoxide **8B** appears in solution as a mixture of two conformers with an oxygen atom in the axial or equatorial position[42] (Fig. 6). By

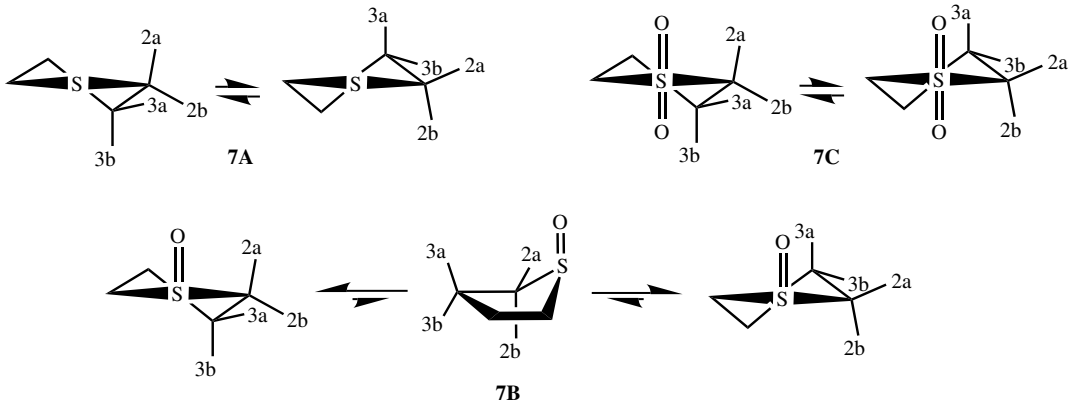

Figure 5. The conformational equilibria of sulfide **7A**, sulfoxide **7B** and sulfone **7C**.

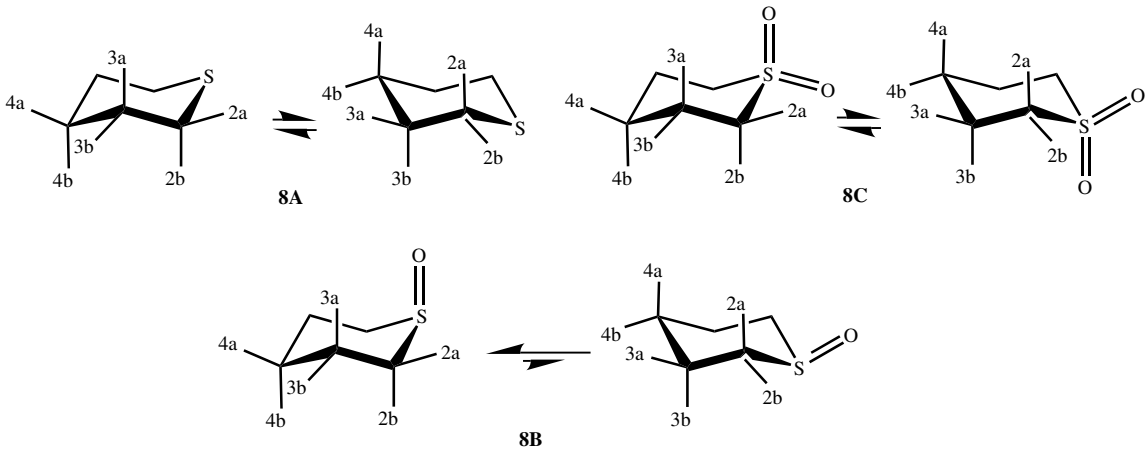

Figure 6. The conformational equilibria of sulfide **8A**, sulfoxide **8B** and sulfone **8C**.

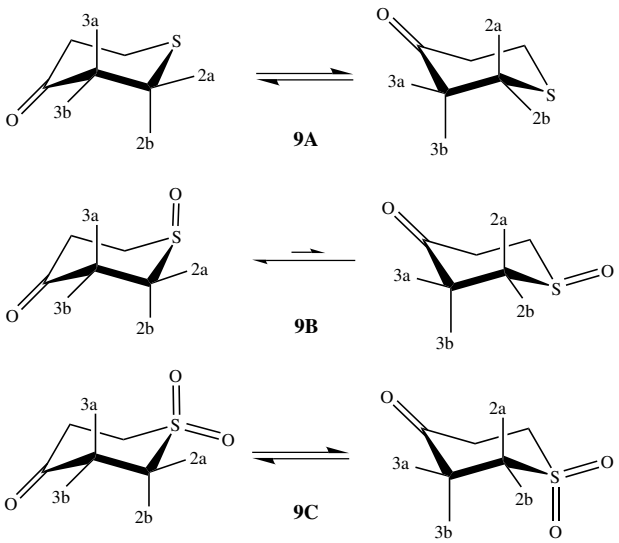

Figure 7. The expected conformation equilibria of compounds **9A,9B** and **9C**.

cooling the solution to −75 °C, the individual hydrogen and carbon resonances of the two conformers can be observed. Our calculations also indicated that the O-axial conformer is more stable than the O-equatorial one (by 0.3 kcal/mol).

Two energetically equivalent chair forms are possible for the sulfide **9A** and the sulfone **9C,** which, according to their ^{1}H NMR spectra, are in a fast equilibrium in solution. For sulfoxide **9B**, the two chair forms differ by the orientation of the sulfoxide oxygen (Fig. 7). The conformation with an axial oxygen is more stable (by 1.79 kcal/mol, B3LYP/6-311++G(3df,3pd)//B3LYP/6-31G*), and also the calculated differences of carbon chemical shifts between the sulfoxide **9B** and the sulfide **9A** are much closer to the experimental values for the conformer with axial oxygen. We did not observe any splitting of signals into two sets after the cooling of the sulfoxide **9B** solution to −75 °C. This indicates that the population of the equatorial conformer is very low or the conformational equilibrium is still fast at −75 °C.

In the geometry-optimized lower energy conformation of the parent sulfide **10A**, the hydroxy group is equatorial and the conformer with an axial hydroxy group is less stable by0.56 kcal/mol. In the sulfoxide **10B**, the sulfoxide oxygen atom was found to be axial (based on the experimental and calculated dipole moments).[44] In the lower energy conformer of the *cis*-sulfoxide **10B**, the hydroxy group is equatorial and the sulfoxide oxygen is axial (the other axial–equatorial conformer is less stable by 1.00 kcal/mol). In the *trans*-sulfoxide derivative with lower energy, both the hydroxy group and the sulfoxide oxygen are axial, and the diequatorial conformer is less stable by 1.60 kcal/mol). In the sulfone derivative **10C** with lower energy, the hydroxy group is axial (the equatorial conformer is less stable by 0.74 kcal/mol).

Magnetic Resonance in Chemistry

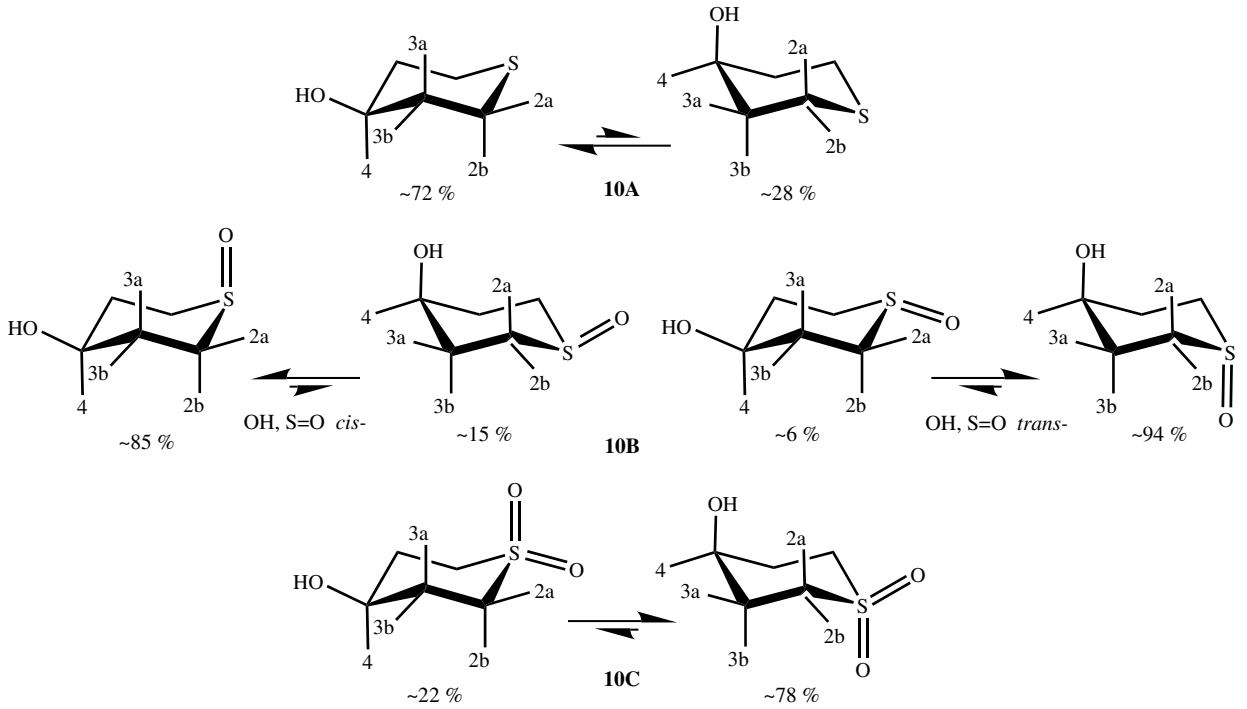

Figure 8. The conformation equilibria of compounds **10A,10B** and **10C**.

This is in good agreement with the experimental ^{1}H NMR data. All of the forms were found to be in the chair conformation. In the sulfide **10A**, hydrogen H-4 gives a triplet of triplets with vicinal J(H,H) = 9.3 and 3.6 Hz indicating a preferred conformation with equatorial OH group. When using coupling constants J(ax,ax) = 11.07 Hz and J(eq,eq) = 2.72 described for *trans*- and *cis*-4-tert-butylcyclohexanol[45] as model values equilibrium population of **10A-OHeq : 10A-OHax** = 79: 21 can be calculated. This is in a good agreement with the ratio 72 : 28 estimated from the calculated 0.56 kcal/mol lower energy for **10A-OHeq**. Two sulfoxides appeared upon oxidation of the sulfide; in one of them, the conformation with axial OH group is strongly preferred and in the other it was equatorial OH preferred (from the observed vicinal couplings). The calculated conformation equilibria of the compounds **10A, 10B** and **10C** in solution are shown in Fig. 8.

The geometry-optimized conformation of methylphenylsulfide (**11A**) was planar (with all of the carbons and the sulfur atom in one plane). In methylphenylsulfoxide (**11B**), the phenyl carbons, sulfur and oxygen were in one plane (probably due to the conjugation of the π electrons), whereas the methyl group was out of the plane. In methylphenylsulfone (**11C**), the methyl group was perpendicular to the phenyl ring while both oxygen atoms were symmetrically located close to the plane of phenyl ring (torsion angle C2–C1–S–O1 = C2–C1–S–O2 = 23°).

The conformation in the compounds **12A, 12B** and **12C** is defined by a torsion angle around the C_{ipso}–S bonds. A symmetrical 'roof-like' conformation was found by an energy minimization for these compounds.

Carbon chemical shifts

The correlation of all the calculated and the experimental ^{13}C NMR chemical shifts is depicted in Fig. 9. The computational models are compared in Table 2, where the average absolute and relative errors are shown. The average absolute error is defined as an average distance from the linear correlation between the experimental and calculated chemical shifts. The average relative error is defined as the average difference between the experimental and calculated sulfoxide–sulfide and sulfone–sulfide chemical shift differences, and the calculated values are in better agreement with the experimental data. The complete experimental and calculated ^{13}C chemical shifts are summarized in Table S2 in supporting information with the

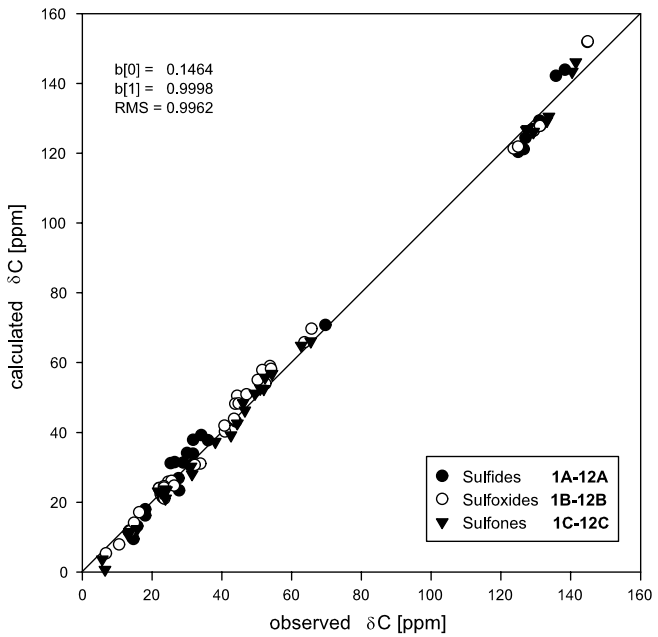

Figure 9. The correlation between the calculated [B3LYP/6-311++G(3df,3pd)] and observed ^{13}C chemical shifts in the sulfides **1A–12A**, the sulfoxides **1B–12B** and the sulfones **1C–12C**.

Table 2. The methods of the geometry and chemical shift calculations

Geometry optimization	Chemical shift calculation	Average absolute error $^{13}C^a$	Average relative error $^{13}C^b$	Average absolute error $^{1}H^a$	Average relative error $^{1}H^b$
6-31G*	6-31G*	2.8	1.27	0.21	0.20
6-31G*	6-311++G**	3.2	1.33	0.20	0.21
6-31G*	6-311++G(3df,3pd)	3.2	1.33	0.16	0.20
6-311++G**	6-311++G**	3.4	1.35	0.20	0.21
6-311++G**	6-311++G(3df,3pd)	3.3	1.38	0.17	0.20
6-311++G(3df,3pd)	6-311++G(3df,3pd)	2.9	1.51	0.19	0.22

The average absolute errors of the calculated ^{1}H and ^{13}C chemical shifts in the whole series of the compounds **1A–12C.**
[a] Average distance from the linear correlation between the experimental and calculated data.
[b] Average difference between the calculated and experimental chemical shift differences (sulfoxide–sulfide and sulfone–sulfide).

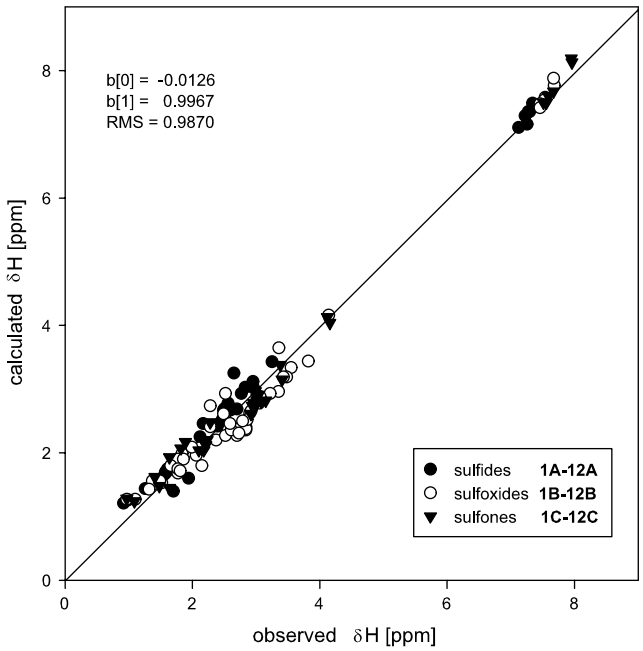

Figure 10. The correlation between the calculated [B3LYP/6-311++G(3df,3pd)]and observed ^{1}H chemical shifts in the sulfides **1A–12A**, the sulfoxides **1B–12B** and the sulfones **1C–12C**.

correlation between calculated shielding values and the observed chemical shifts depicted in Figure S2. The calculated chemical shifts were referenced to fit the experimental values best.

As shown in Table 2, all of the methods yielded results with almost the same precision. The most expensive method provided the correlation of experimental and calculated chemical shifts with a slope closer to −1. When a larger basis set was used, the calculated shieldings were lower. This is in agreement with the previously observed basis set dependence of the chemical shift calculations.[46]

Hydrogen chemical shifts

The correlation between the experimental and calculated shifts is similar to those for the carbon atoms (Fig. 10). The absolute errors of about 0.2 ppm are about 10× lower than for the carbon atoms, but when the approximately 20× smaller spectral width of the ^{1}H NMR spectra is taken into account, the relative errors for the hydrogens are somewhat larger than those for the carbon atoms. Although in most cases the calculated and experimental chemical shifts yield the same order of protons, in some cases the calculated proton shifts are not sufficient for an unequivocal structural assignment. When a larger basis set was used, the calculated shieldings were, like with the carbon shieldings, lower. The complete experimental and calculated ^{1}H chemical shifts are summarized in Table S3 in supporting information, and correlation between calculated shielding values and the observed chemical shifts is shown in Figure S2.

Chemical shifts induced by the oxidation of sulfides

The comparison of the NMR data inside the series of compounds **1–12** reveals some characteristic changes of the chemical shifts induced by oxidation (sulfide to sulfoxide or sulfide to sulfone). In general, larger induced shifts are observed for carbon atoms. The magnitude and sign of the induced shifts ($\Delta\delta$ values) depend mainly on the distance of the given nuclei from the sulfur atom and on its orientation to the oxygen atom(s) bonded to sulfur. The ranges of the oxidation-induced shifts observed for the carbon atoms and hydrogens are provided in Table 3. The induced shifts show much larger variations in cyclic molecules. The extreme values are observed for the smallest molecules like **1** between acyclic compounds and the compounds **5** and **6** with a three- and four-membered ring.

Conclusions

The correlation between the calculated and experimental ^{13}C chemical shifts in the series of model sulfides, sulfoxides and sulfones is very good even for the cheapest B3LYP/6-31G* method and somewhat less satisfactory for the ^{1}H chemical shifts. The agreement between experimental and calculated chemical shifts proved the structures, which were calculated and discussed above in detail.

The conformational analysis is very important for the calculation of realistic chemical shifts. In the case of flexible molecules where more conformers are present in conformation equilibrium (fast on the NMR timescale) the NMR parameters of populated conformers have to be weighted according to their Boltzmann distribution.

The calculated chemical shifts induced by oxidation ($\Delta\delta$ values) provide somewhat better agreement with experimental data than chemical shifts calculated for individual compounds. For sulfoxides, they also show some characteristic relations to the orientation of sulfoxide group. This is illustrated on calculated induced ^{1}H and ^{13}C chemical shifts for cyclic sulfoxides **8B, 9B** and **10B** with a six-membered ring in Fig. 11. While both geminal hydrogens in the

Table 3. The ranges of the chemical shift differences induced by oxidation ($\Delta\delta$) observed for the atoms at the α-, β- and γ-position in the series of compounds **1–10**

	$\Delta\delta$ (sulfoxide–sulfide)			$\Delta\delta$ (sulfone–sulfide)		
	Cα	Cβ	Cγ	Cα	Cβ	Cγ
Acyclic	+19.79 to +22.85	−6.68 to −7.88	−0.04 to −0.16	+20.28 to +24.57	−7.25 to −8.17	−0.29 to −0.35
Cyclic	+14.30 to +26.60	−5.14 to −17.15	−3.43 to −5.99	+13.45 to +39.64	−3.47 to −21.98	−2.55 to −6.90
	Hα	Hβ	Hγ	Hα	Hβ	Hγ
Acyclic	+0.19 to +0.50	+0.11 to +0.23	+0.11	+0.45 to +0.88	+0.15 to +0.28	+0.07 to +0.10
Cyclic	−0.04 to +0.88	−0.91 to +0.58	−0.26 to +0.28	+0.21 to +0.91	−0.77 to +0.58	+0.06

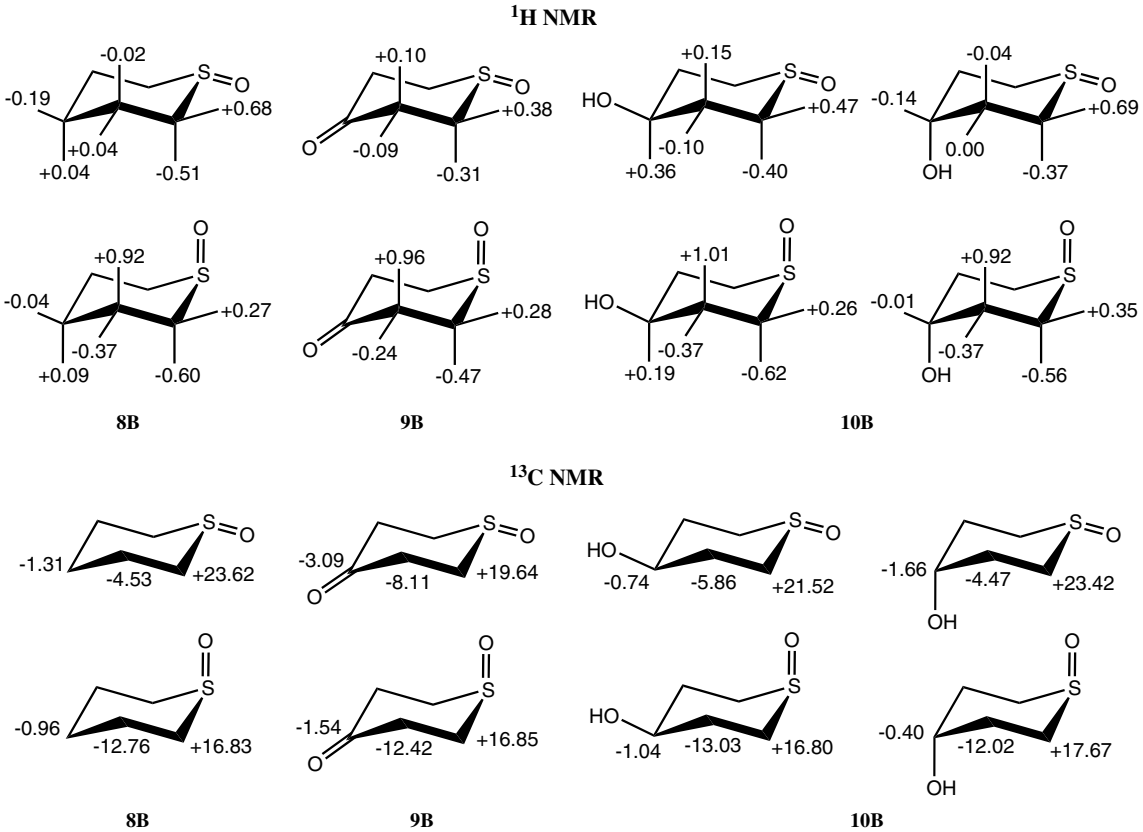

Figure 11. The calculated proton and carbon-13 chemical shifts induced by the oxidation of sulfides to sulfoxides **8B, 9B** and **10B**.

α-position to S═O group show similar induced shift for axial and equatorial orientation of the S═O group (about −0.3 to −0.6 ppm) for axial-H and about +0.3 to +0.7 ppm for equatorial-H, a characteristic difference appears for protons in β-position, where axial sulfoxide group induces a strong downfield shift (about +1.0 ppm) on axial-H and smaller upfield shift on equatorial-H (about −0.35 ppm), while in the case of equatorial S═O group the effect on both β-hydrogen atoms is small (−0.1 to +0.1 ppm).

The orientation of the S═O group can be distinguished also by the induced shifts in ^{13}C NMR spectra. The equatorial S═O group induces significantly larger downfield shifts on the α-carbon (about +20 to +24 ppm against +16 to +18 ppm) and smaller upfield shifts on the β-carbon than axial S═O group (about −4 to −8 ppm against −12 to −13 ppm). The detailed comparison with corresponding experimental data is hindered by the absence of experimental data for conformationally frozen sulfides **8A, 9A** and **10A** and will be tested on proper rigid models. Nevertheless, comparison of the calculated and experimental proton and carbon chemical shifts induced by the oxidation of sulfides seems to be a promising method for determining the chiral sulfoxide configuration. The application on chiral sulfoxides is in progress, and the results will be published in our future paper.

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Supporting information

Supporting information may be found in the online version of this article.

References

[1] D. K. Bates, M. D. Xia, *J. Org. Chem.* **1998**, *63*, 9190.
[2] J. S. Brunck, B. Deicke, J. Voss, *Tetrahedron* **1997**, *53*, 5641.
[3] B. Schuler, G. Adiwidjaja, J. Voss, *Eur. J. Org. Chem.* **1999**, 1481.
[4] B. Schuler, J. Voss, *Eur. J. Org. Chem.* **1999**, 943.
[5] Y. Tamura, J. Uenishi, H. Ishibashi, *Chem. Pharm. Bull.* **1984**, *32*, 891.
[6] K. Burgess, J. Cassidy, I. Henderson, *J. Org. Chem.* **1991**, *56*, 2050.
[7] S. Goldmann, R. W. Hoffmann, N. Maak, K. J. Geueke, *Chem. Berichte-Recueil* **1980**, *113*, 831.
[8] S. Braverman, *The chemistry of sulphones and sulphoxides* (Eds: Patai, Rappoport, Strirling), Wiley: New York, **1988**, 717.
[9] T. Harel, E. Arnir, S. Rozen, *Org. Lett.* **2006**, *8*, 1213.
[10] P. Kielbasinski, M. Albrycht, M. Mikolajczyk, M. W. Wieczorek, W. R. Majzner, A. Filipczak, P. Ciolkiewicz, *Heteroatom. Chem.* **2005**, *16*, 93.
[11] R. D. G. Cooper, P. V. Demarco, J. C. Cheng, N. D. Jones, *J. Am. Chem. Soc.* **1969**, *91*, 1408.
[12] K. E. Kover, Z. Gyorgydeak, *Mag. Res. Chem.* **1992**, *30*, 137.
[13] R. Bastin, H. Albadri, A. C. Gaumont, M. Gulea, *Org. Lett.* **2006**, *8*, 1033.
[14] T. J. Wenzel, *Discrimination of Chiral Compounds Using NMR Spectroscopy*, Wiley-Interscience: New York, **2007**.
[15] J. Kitchin, R. J. Stoodley, *Tetrahedron* **1973**, *29*, 3023.
[16] M. J. Cook, A. P. Tonge, *J. Chem. Soc. Perkin 2* **1974**, 767.
[17] A. B. Foster, J. M. Duxbury, T. D. Inch, J. M. Webber, *Chem. Commun.* **1967**, 881.
[18] K. W. Buck, A. B. Foster, W. D. Pardoe, M. H. Qadir, J. M. Webber, *Chem. Commun.* **1966**, 759.
[19] A. B. Foster, T. D. Inch, M. H. Qadir, J. M. Webber, *Chem. Commun.* **1968**, 1086.
[20] C. R. Johnson, W. O. Siegl, *Tetrahedron Lett* **1969**, 1879.
[21] R. M. Dodson, E. H. Jancis, G. Klose, *J. Org. Chem.* **1970**, *35*, 2520.
[22] P. S. Portoghese, V. G. Telang, *Tetrahedron* **1971**, *27*, 1823.
[23] I. Sataty, *Org. Magn. Res.* **1974**, *6*, 8.
[24] U. Folli, D. Iarossi, F. Taddei, *J. Chem. Soc. Perkin 2* **1974**, 933.
[25] P. Geneste, J. L. Olive, S. N. Ung, M. Elamoudielfaghi, J. W. Easton, H. Bierbeck, J. K. Saunders, *J. Org. Chem.* **1979**, *44*, 2887.
[26] R. R. Fraser, Y. Y. Wigfield, *J. Chem. Soc. D Chem. Commun.* **1970**, 1471.
[27] T. Yabuuchi, T. Kusumi, *J. Am. Chem. Soc.* **1999**, *121*, 10646.
[28] N. Gautier, N. Noiret, C. NugierChauvin, H. Patin, *Tetrahedron – Asymmetry* **1997**, *8*, 501.
[29] W. H. Pirkle, D. L. Sikkenga, *J. Chromat.* **1976**, *123*, 400.
[30] M. Deshmukh, E. Dunach, S. Juge, H. B. Kagan, *Tetrahedron Lett.* **1984**, *25*, 3467.
[31] J. A. Dale, H. S. Mosher, *J. Am. Chem. Soc.* **1973**, *95*, 512.
[32] M. Kaupp, M. Bühl, V. G. Malkin, *Calculation of NMR and EPR Parametres*, Wiley-VCH: Weinheim, **2004**.
[33] W. Koch, M. C. Holthausen, *A Chemist's Guide to Density Functional Theory* (2 edn), Wiley-VCH: Weinheim, **2000**.
[34] P. Bour, M. Budesinsky, V. Spirko, J. Kapitan, J. Sebestik, V. Sychrovsky, *J. Am. Chem. Soc.* **2005**, *127*, 17079.
[35] V. Sychrovsky, Z. Vokacova, J. Sponer, N. Spackova, B. Schneider, *J. Phys. Chem. B* **2006**, *110*, 22894.
[36] V. Sychrovsky, J. Sponer, L. Trantirek, B. Schneider, *J. Am. Chem. Soc.* **2006**, *128*, 6823.
[37] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. Montgomery, J. A., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, Gaussian, Inc., Wallingford CT, **2004**.
[38] W. Kutzelnigg, U. Fleischer, M. Schindler, *Al-Cl: The IGLO-Method: Ab Initio Calculation and Interpretation of NMR Chemical Shifts and Magnetic Susceptibilities*, vol. 23 Springer-Verlag: Heidelberg, **1990**.
[39] M. Dracinsky, J. Kaminsky, P. Bour, *J. Chem. Phys.* **2009**, *130*, 094106.
[40] M. Dracinsky, J. Kaminsky, P. Bour, *J. Phys. Chem. B* **2009**, *113*, 14698.
[41] M. Dracinsky, P. Bour, *J. Chem. Theory Comput.* **2010**, *6*, 288.
[42] R. J. Abraham, J. J. Byrne, L. Griffiths, *Magn. Res. Chem.* **2008**, *46*, 667.
[43] E. Kleinpeter, *Adv. Heterocycl. Chem.* **2004**, *86*, 41.
[44] J. C. Martin, J. J. Uebel, *J. Am. Chem. Soc.* **1964**, *86*, 2936.
[45] F. C. L. Anet, *J. Am. Chem. Soc.* **1962**, *84*, 1053.
[46] T. Zuschneid, H. Fischer, T. Handel, K. Albert, G. Häfelinger, *Z. Naturforsch. B* **2004**, *59*, 1153.

