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Computational determination of the enthalpic and entropic contributions to the conformational preference of monosubstituted cyclohexanes. Molecular mechanics, semiempirical and density functional theory methods and *ab initio* calculations[†]

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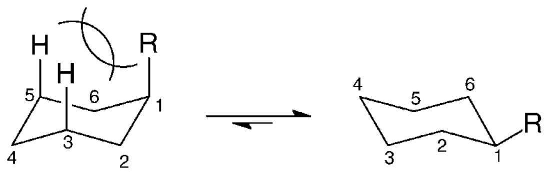
ABSTRACT: Several computational methods [MM2, MM3, PM3, AM1, MNDO, HF/3-21G(d), HF/6-31G(d), B3LYP/3-21G(d), B3LYP/6-31G(d), MP2/6-31G(d), etc.] were examined in their efficiency to reproduce the experimentally obtained thermodynamic data for axial ⇌ equatorial equilibria in benzylcyclohexane (**7**) and sulfur-containing derivatives methylthio (**8**), methylsulfinyl (**9**), and methylsulfonylcyclohexane (**10**). While in general, best agreement between the theoretical results and the experimental data was found when electronic correlation was included in fairly robust MP2/6-31G(d) calculations, for the estimation of conformational parameters in larger systems the use of lower level HF and B3LYP methods is anticipated to afford reliable data at reasonable computing times. In most cases, proper estimation of ΔS° parameters requires consideration of $\Delta S^\circ_{\text{mixing}}$, which appears as dominant term for $\Delta S^\circ_{\text{total}}$ parameters. It is appreciated that a proper comprehension of the conformational behavior of monosubstituted cyclohexanes requires of satisfactory understanding of the enthalpic and entropic contributions to the conformational free energy difference, ΔG°. Copyright © 2002 John Wiley & Sons, Ltd.

KEYWORDS: conformational analysis; theoretical chemistry; monosubstituted cyclohexanes; enthalpic and entropic parameters; molecular mechanics; semiempirical; *ab initio* calculations

INTRODUCTION

A proper understanding of the conformational behavior of monosubstituted cyclohexanes is of fundamental importance in organic chemistry since it effectively models larger and more complex molecules.[1] Alkyl groups prefer equatorial over axial positions in order to elude the repulsive steric interactions with the C(3,5) methylenes [Eqn. (1)],[2] and in order to minimize torsional strain arising form two *gauche* arrangements present in the axial R—C(1)—C(2)—C(3) and R—C(1)—C(6)—C(5) segments.[3,4] Furthermore, $\sigma \rightarrow \sigma^*$ stereoelectronic interactions involving C(2)—C(3), C(6)—C(5) and antiperiplanar C(1)—R orbitals may stabilize the equatorial isomer.[5] It is usually observed that the bulkier the alkyl group the larger the preference for the equatorial form.[2]



(1)

In this context, force field calculations[6] and experimental variable-temperature NMR data[7] showed that while the conformational free energy differences (ΔG° values) increase along the series methyl → ethyl → isopropyl, the *enthalpic* contributions to the equatorial preference decrease along this series (entries 1–3 in Table 1), so that it is the $T\Delta S^\circ$ term that accounts for the observed trend in ΔG° values.

It is apparent form Table 1 that the benzyl group exhibits a thermodynamic behavior that resembles ethyl (entries 4 and 2, respectively),[8] and an interpretation of this result will be advanced below. In contrast, the axial isomer of *tert*-butylcyclohexane has greater entropy in the axial relative to the equatorial isomer (entry 5 in Table 1), and this most interesting observation has been

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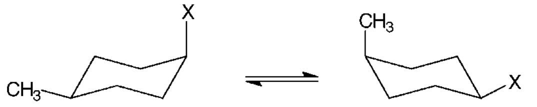
Table 1. Experimental enthalpic and entropic contributions to the conformational free energy differences ($\Delta G^{\circ}_{298\,\mathrm{K}}$) of relevant alkyl groups 3[a,7–9]

Entry	R	$\Delta H^{\circ a}$	$\Delta S^{\circ b}$	$\Delta G^{\circ}_{298\,\mathrm{K}}{}^{a}$
1	CH_3	−1.75	−0.03	−1.74
2	CH_3CH_2	−1.60	+0.64	−1.79
3	$(CH_3)_2CH$	−1.52	+2.31	−2.21
4	$PhCH_2$	−1.52	+0.81	−1.76
5	$(CH_3)_3C^{c}$	−5.00	−0.44	−4.87

[a] In kcal mol^{-1}.

[b] In cal $deg^{-1}mol^{-1}$.

[c] Calculated, see Ref. 9; for other calculations in the literature on the conformational preference of the *tert*-butyl group, see Refs 3a, 4, 6 and 10.



1, X = SCH_3 **4**, X = SC_6H_5

2, X = $S(O)CH_3$ **5**, X = $S(O)C_6H_5$

3, X = SO_2CH_3 **6**, X = $SO_2C_6H_5$

Scheme 1

ascribed to increased confinement in the latter conformer.[9]

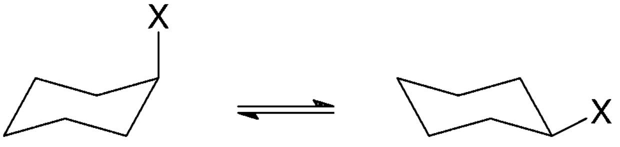
Therefore, a proper comprehension of the conformational behavior requires of a satisfactory knowledge of the enthalpic and entropic contributions to ΔG°. Indeed, such dissection of conformational energies into ΔH° and ΔS° components has been essential for interpretation of the conformational preference exhibited be various substituted heterocycles.[11–14]

More recently, a variable-temperature NMR study of (*cis*-4-methylcyclohexyl) methyl sulfide (**1**), sulfoxide (**2**) and sulfone (**3**) and (*cis*-4-methylcyclohexyl) phenyl sulfide (**4**), sulfoxide (**5**) and sulfone (**6**) (Scheme 1) allowed the determination of the thermodynamic parameters, ΔH° and ΔS°, for the sulfur-containing groups present in these molecules.[15] (Table 2).

Reproduction of the experimental results with Allinger's MM3 program[16] was successfully accomplished in the case of the sulfoxide and sulfide groups; nevertheless, the original force field parameters did not adequately reproduce the experimentally observed behavior of the sulfonyl derivatives. Thus, reparametrization of the torsion parameters in C_{sp^3}—C_{sp^3}—C_{sp^3}—SO_2 segments was carried out, and inclusion of the new parameters reproduced the conformational behavior of model sulfones.[15]

In view of several reports describing the successful application of *ab initio* theoretical methods in the determination of structure and relative energies of the conformers in monosubstituted cyclohexanes derivatives,[3a,4,17] we decided to evaluate the accuracy of force field, semiempirical and *ab initio* methods in the estimation of the ΔH° and ΔS° values available for benzylcyclohexane (entry 4 in Table 1) and for sulfur-containing cyclohexane derivatives (Table 2). It may be argued that with the present-day computational capability of desktop computers, there is no need to publish molecular mechanics (force field), semiempirical and low-level *ab initio* calculations on small molecules. Nevertheless, cyclohexane derivatives **1**–**6** (Scheme 1) and benzylcyclohexane (**7**) serve as models for larger molecules where, when justified by a correct performance, the use of lower level calculations can lead to substantial saving of computer time. For instance, we find that computations at the semiempirical (AM1, PM3, MNDO) level are usually 30–40 times faster than those carried out at the *ab initio* level. In this regard, molecular mechanics (force field) parameters are well optimized for

Table 2. Thermodynamic parameters for the methylthio, methylsulfinyl, methylsulfonyl, phenylthio, phenylsulfinyl and phenylsulfonyl Groups in Cyclohexane.[15]



Entry	X	$\Delta H^{\circ a}$ (kcal mol^{-1})	$\Delta S^{\circ b}$ (cal $deg^{-1}mol^{-1}$)	$\Delta G^{\circ}_{298\,\mathrm{K}}{}^{c}$ (kcal mol^{-1})
1	CH_3S	-1.05 ± 0.09	$+0.48 \pm 0.31$	−1.19
2	$CH_3S(O)$	-1.08 ± 0.06	$+1.55 \pm 0.30$	−1.54
3	CH_3SO_2	-2.66 ± 0.09	-0.26 ± 0.30	−2.58
4	C_6H_5S	-1.04 ± 0.11	$+0.32 \pm 0.38$	−1.12
5	$C_6H_5S(O)$	-1.22 ± 0.06	$+1.82 \pm 0.15$	−1.76
6	$C_6H_5SO_2$	-2.44 ± 0.10	$+1.66 \pm 0.26$	−2.94

[a] Negative values indicate that the equatorial conformer is favored enthalpically.

[b] Positive values indicate that the equatorial conformer is favored entropically.

[c] Negative values indicate that the equilibrium is shifted to the equatorial isomer.

hydrocarbons, so that calculated conformational data are generally in good agreement with experimental[8] or *ab initio*[18] results.

RESULTS AND DISCUSSION

Computational methods

Molecular mechanics calculations. The MM2[19] and MM3(94)[16] force fields were used to evaluate the intramolecular energetics. While the former program has proven fairly successful for modeling a large variety of hydrocarbons,[20] MM3 takes into account entropy components to free energy (MM2 refers exclusively to potential energy). Indeed, the type of parameterization used in the MM3 program[16] allows for reproduction of vibrational data, and also parameters that depend on vibrational levels such as entropy.

Geometry optimizations (with no symmetry constraints) of all conformers were performed using semiempirical (PM3, AM1 and MNDO)[21] and *ab initio* [HF/ and B3LYP/3–21G(d) or /6–31G(d)] levels of theory, using the Gaussian 98 series of programs.[22] Thermodynamics corrections of energy in *ab initio* calculations were carried out by zero-point-energy (ZPE) correction, scaled by the corresponding factor for HF/3–21G and B3LYP/3–21G, a correction factor equal to 0.8095 was used; the correction factor for HF/6–31G(d) was 0.9135, whereas for B3LYP/6–31G(d) calculations the correction factor was 0.9804.[23] The consideration of electronic correlation is very important in conformational studies;[24] thus, hybrid functionals B3LYP at the 6–31G(d,p)//6–31G(d) and also *ab initio* MP2/6–31G(d) levels were also examined.

The estimation of the total entropy content for axial and equatorial conformers involved consideration of the sum of vibrational, rotational, translational and electronic entropies as computed, and also calculation of the entropies of mixing. To this effect, uniform scanning at 10° increments was carried out for rotation of the substituent (Chart 1), allowing for complete relaxation of the rest of the atomic coordinates. The conformational energy maps originating from each minimum energy conformation were drawn by means of the Surfer program.[25]

The free-space intramolecular entropy[26] was calculated according to Eqn. (2), where R is the gas constant, n is the number of conformational states sampled (1296 in this study) and P_i is the Boltzmann probability of the ith conformational state:

$$S^\circ = -R\sum_{i=1}^{n} P_i \ln P_i \qquad (2)$$

The P_i data, in turn, were computed from the relationship in Eqn. (3), where E_i is the intramolecular conformational energy of the ith state:

$$P_i = \frac{\mathrm{e}^{-E_i/RT}}{\sum_{i=1}^{n} \mathrm{e}^{-E_i/RT}}$$

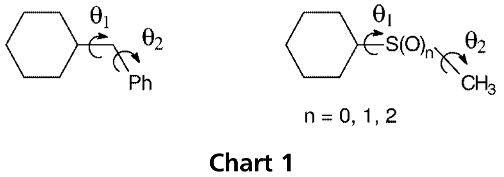


Chart 1

Benzylcyclohexane (7)

Figure 1 presents the energy profiles for rotation around the C(1)—CH$_2$ bond in both the axial and equatorial conformations of benzylcyclohexane (**7**), calculated with hybrid functional B3LYP/6–31G(d).

As anticipated from the analysis of *gauche* interactions present in the axial and equatorial conformers of benzylcyclohexane (Scheme 2), three populated rotamers in the equatorial isomer versus two in the axial form (the phenyl-inside rotamer of **7**-axial (ax) is over 4 kcal mol^{-1} higher in energy and can be disregarded) imply that the entropy of mixing should make a substantial contribution to the free energy difference, in favor of **7**-equatorial (eq). This entropic behavior, the increased entropy content in **7**-eq relative to **7**-ax, is also reproduced by molecular mechanics, semiempirical and *ab initio* methods (Table 3).

Table 3 collects the calculated thermodynamic parameters at various levels of theory, and compares them with the experimentally obtained values in entry 1.

The determination of the entropy of mixing was accomplished by evaluation of the fractional populations in axial and equatorial benzyl, as outlined in Chart 1 and according to Eqns (2) and (3). It is instructive to note the difference in ΔS° with and without $\Delta S^\circ_{\mathrm{mixing}}$. This correction is, of course, essential in MM2 calculations (since this force field is not parameterized to reproduce entropic parameters, see above), as well as in PM3 and AM1 modeling (entries 4 and 5 in Table 3), where the sum of computed $\Delta S^\circ_{\mathrm{rotational}} + \Delta S^\circ_{\mathrm{vibrational}} + \Delta S^\circ_{\mathrm{translational}} + \Delta S^\circ_{\mathrm{electronic}}$ is too small, relative to the experimental ΔS° value. Finally, consideration of $\Delta S^\circ_{\mathrm{mixing}}$ seems to be relevant in DFT and *ab initio* calculations (entries 7–12 in Table 3) since this correction affords $\Delta S^\circ_{\mathrm{total}}$ values that are closer to the experimental result.

Interestingly, all computational methods reproduce the *tendencies* of both the enthalpic (**7**-ax → **7**-eq exothermic process) and entropic (positive ΔS° in going from **7**-ax to **7**-eq) experimental thermodynamic par-

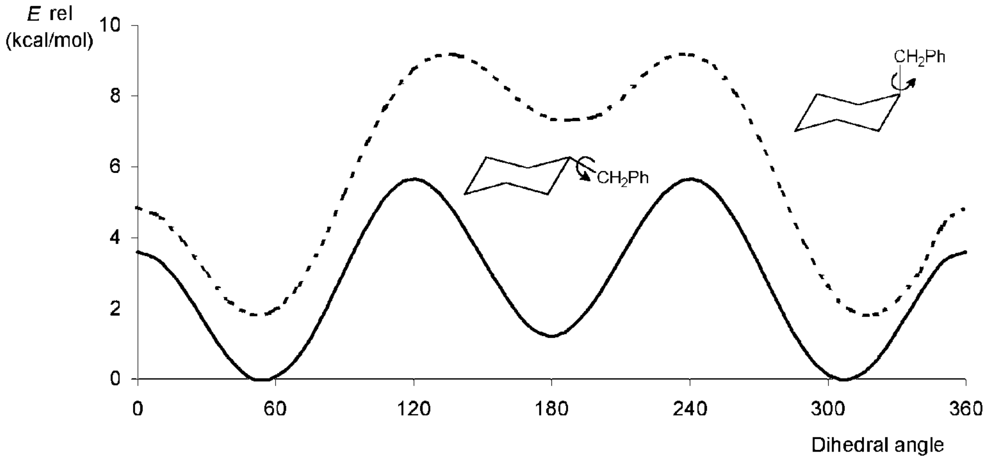
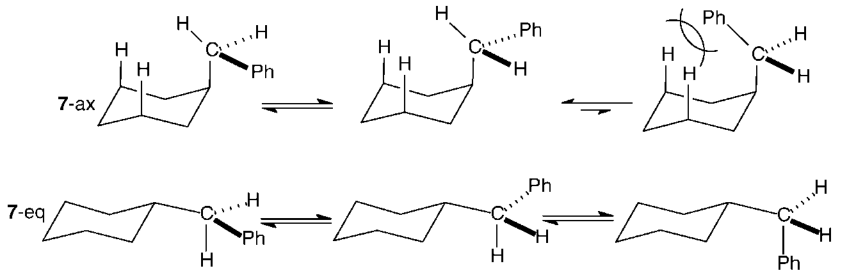
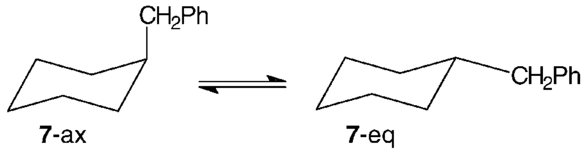


Figure 1. Rotation around the C(1)—CH_2Ph bond in axial benzylcyclohexane (dashed line) and equatorial benzylcyclohexane (solid line), according to B3LYP/6–31G(d) calculations (fully optimized geometries)



Scheme 2

Table 3. Gas-phase thermodynamic parameters ($\Delta H°$, $\Delta S°$, $\Delta G°_{298\ K}$) calculated[a] for the axial ⇌ equatorial equilibrium of benzylcyclohexane (**7**)



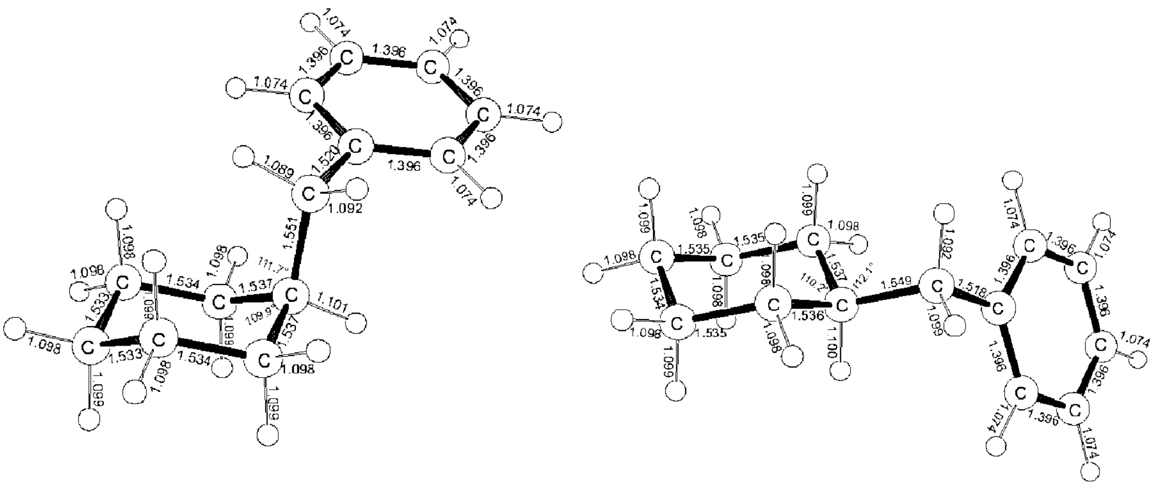
			$\Delta S°$ (cal deg^{-1} mol^{-1})			
Entry	Method of determination	$\Delta H°$ (kcal mol^{-1})	$\Delta S°_{total}$	$\Delta S^{\circ d}$	$\Delta S°_{mixing}$	$\Delta G°_{298\ K}$ (kcal mol^{-1})
1	Experimental[b]	-1.52 ± 0.1	$+0.81 \pm 0.3$	—	—	-1.76 ± 0.2
2	MM2[b]	−1.26	+0.63	—	+0.63	−1.45
3	MM3[c]	−1.76	+1.62	+0.95	+0.67	−2.25
4	PM3	−0.78	+1.46	+0.23	+1.23	−1.22
5	AM1	−0.44	+0.62	+0.05	+0.57	−0.62
6	MNDO	−1.19	+0.72	+0.64	+0.08	−1.40
7	HF/3–21G(d)	−1.63	+0.78	+0.60	+0.18	−1.86
8	HF/6–31G(d)	−1.79	+0.70	+0.55	+0.15	−1.99
9	B3LYP/3–21G(d)	−1.46	+1.02	+0.92	+0.10	−1.76
10	B3LYP/6–31G(d)	−1.68	+0.78	+0.72	+0.06	−1.91
11	MP2/6–31G(d)//HF/6–31G(d)	−1.49	+0.70	+0.55	+0.15	−1.70
12	MP2/6–31G(d)//B3LYP/6–31G(d)	−1.43	+0.78	+0.72	+0.06	−1.66

[a] The entropy of mixing was calculated using the same basis sets that were employed for energy determination.

[b] Ref 8.

[c] Ref 27.

[d] Sum of $\Delta S°_{rotational} + \Delta S°_{vibrational} + \Delta S°_{translational} + \Delta S°_{electronic}$.



7-ax 7-eq

Figure 2. Structural parameters calculated for axial and equatorial benzylcyclohexane, at the B3LYP/6–31G(d) level of theory

ameters. The best agreement between the theoretical results and the experimental data was found when electronic correlation, and also fairly robust basis sets, were included in *ab initio* [MP2/6–31G(d)] calculation, (see entries 11 and 12 in Table 3); nevertheless, for the estimation of conformational parameters in larger systems, the use of lower level HF and B3LYP methods in expected to afford reliable data at reasonable computing times.

No significant differences in key geometric parameters were calculated by the methods used. Figure 2 presents the calculated structural parameters for the lowest energy axial and equatorial isomers of benzylcyclohexane at the B3LYP/6–31G(d) level of theory. It can be noted that lengths and angles involving the C—CH_2Ph bond are essentially the same in **7**-ax and **7**-eq (Fig. 2).

Methylthio-, methylsulfinyl- and methylsulfonylcyclohexane (8–10)

Figures 3, 4 and 5 present the energy profiles for rotation around the C(1)—S bond in both the axial and equatorial conformers of methylthiocyclohexane (**8**), methylsulfinylcyclohexane (**9**) and methylsulfonylcyclohexane (**10**), respectively, calculated at the B3LYP/6–31G(d) level of theory. Although the use of DFT methods to estimate barrier heights has proven to be inadequate in some cases,[3a] the curves presented in Figs 3–5 were reproduced by HF methods, so the potential energy curves appear to be correct.

The energy profiles presented in Figs 3–5 support Eliel and Kandasamy's arguments,[28] in the sense that three populated rotamers in the equatorial isomers of **8–10** versus one in axial sulfoxide **9**-ax or two in **8**-ax and **10**-

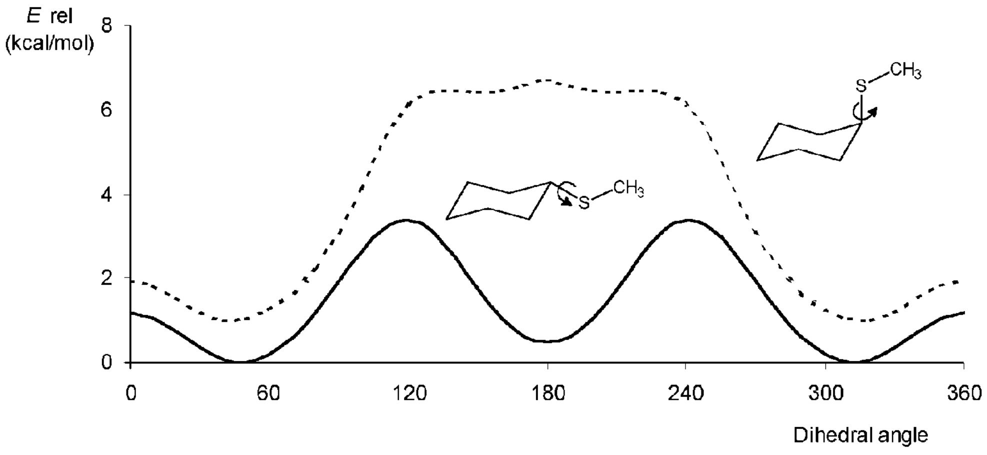


Figure 3. Rotation around the C(1)—S bond in axial methylthiocyclohexane **8**-ax (dashed line) and equatorial methylthiocyclohexane **8**-eq (solid line), according to B3LYP/6–31G(d) calculations (fully optimized geometries)

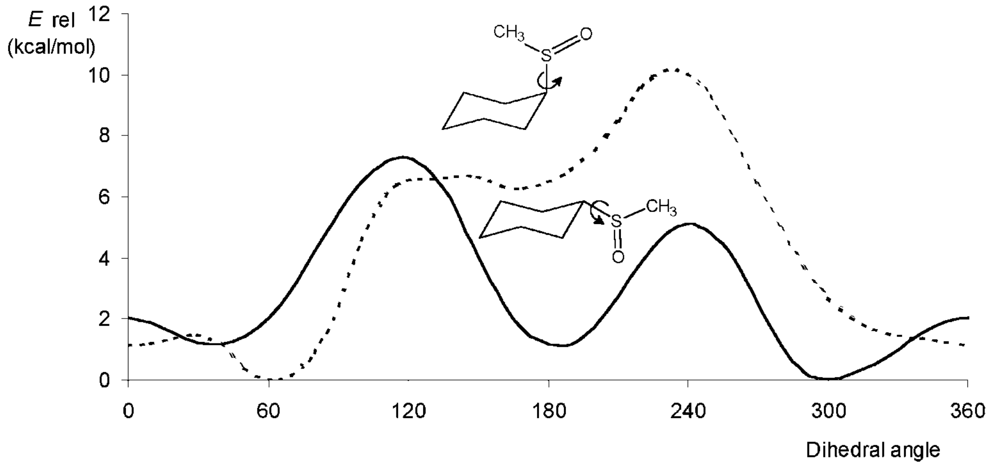


Figure 4. Rotation around the C(1)—S bond in axial methylsulfinylcyclohexane **9**-ax (dashed line) and equatorial methylsulfinylclohexane **9**-eq (solid line), according to B3LYP/6–31G(d) calculations (fully optimized geometries)

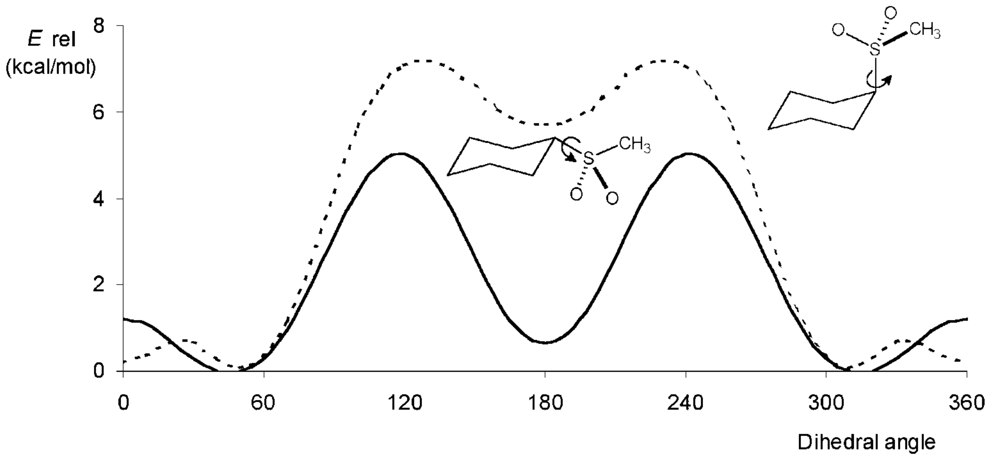
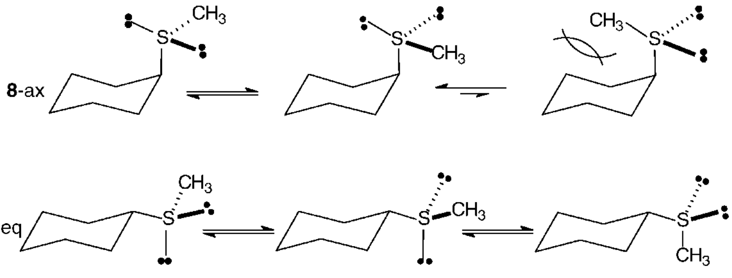


Figure 5. Rotation around the C(1)—S bond in axial methylsulfonylcyclohexane **10**-ax (dashed line) and equatorial methylsulfonylclohexane **10**-eq (solid line), according to B3LYP/6–31G(d) calculations (fully optimized geometries)

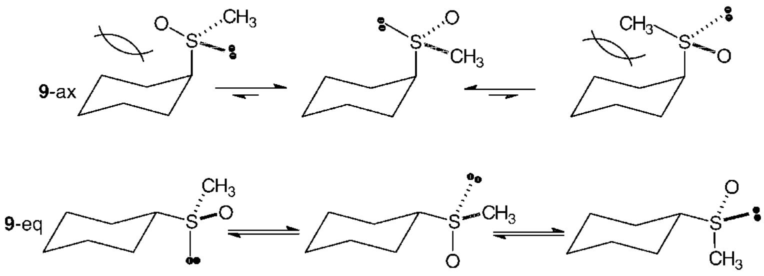
ax make a substantial contribution to $\Delta G^\circ_{\mathrm{ax/eq}}$. In particular, two populated rotamers of axial methylthio group versus three in the equatorial isomer (Scheme 3) suggests an entropy of mixing approaching $R\ln3 - R\ln2 = 0.80$ cal deg^{-1} mol^{-1} (experimental, $\Delta S^\circ_{\mathrm{ax}\rightarrow\mathrm{eq}} = +0.48 \pm 0.31$ cal deg^{-1} mol^{-1}).[15]

In the case of the methylsulfinyl group, essentially only one axial rotamer is anticipated, leading to maximum theoretical value for $\Delta S^\circ_{\mathrm{mixing}} = R\ln3 - R\ln1 = 2.18$ cal deg^{-1} mol^{-1} (experimental, $\Delta S^\circ_{\mathrm{ax}\rightarrow\mathrm{eq}} = +1.55 \pm 0.30$ cal deg^{-1} mol^{-1}).[15] This prediction (Scheme 4) is thus supported by the relative energies presented in Fig. 4.

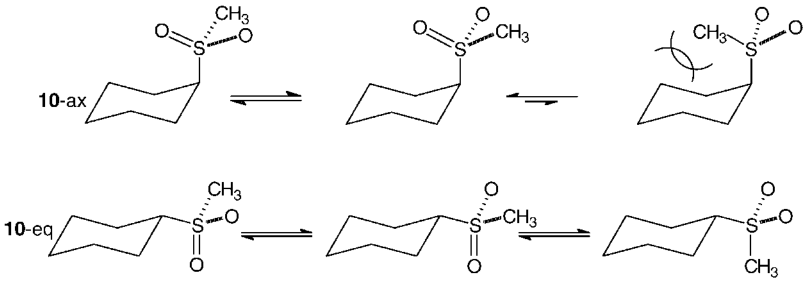
Finally, with regard to the sulfonyl group, three populated rotamers for equatorial **10** versus two for **10**-



Scheme 3



Scheme 4



Scheme 5

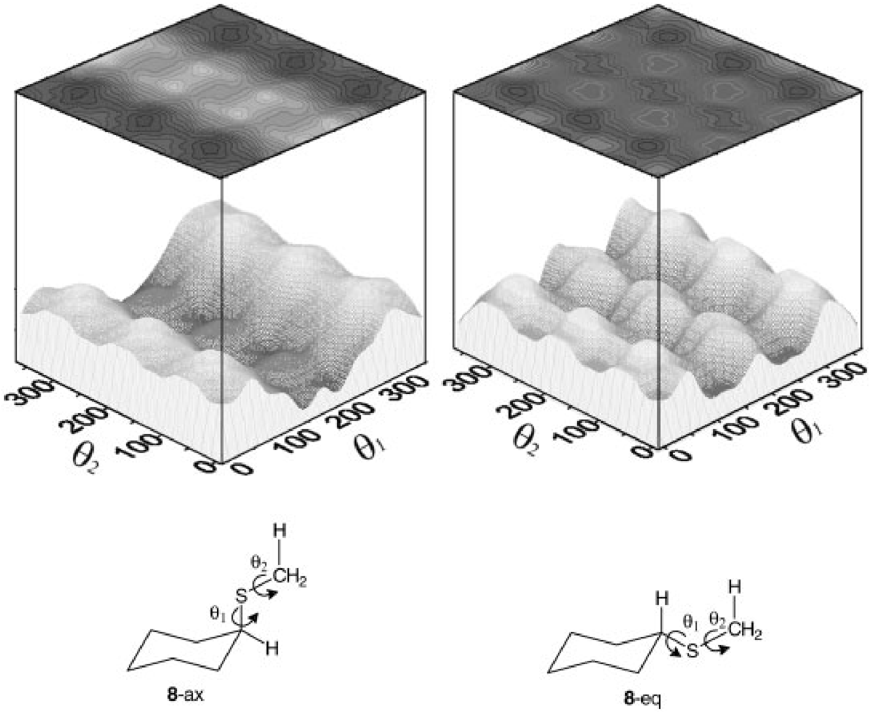


Figure 6. Population surfaces for axial (left) and equatorial (right) *S*-methyl group rotation in cyclohexane, estimated at the B3LYP/6–31G(d) level of theory

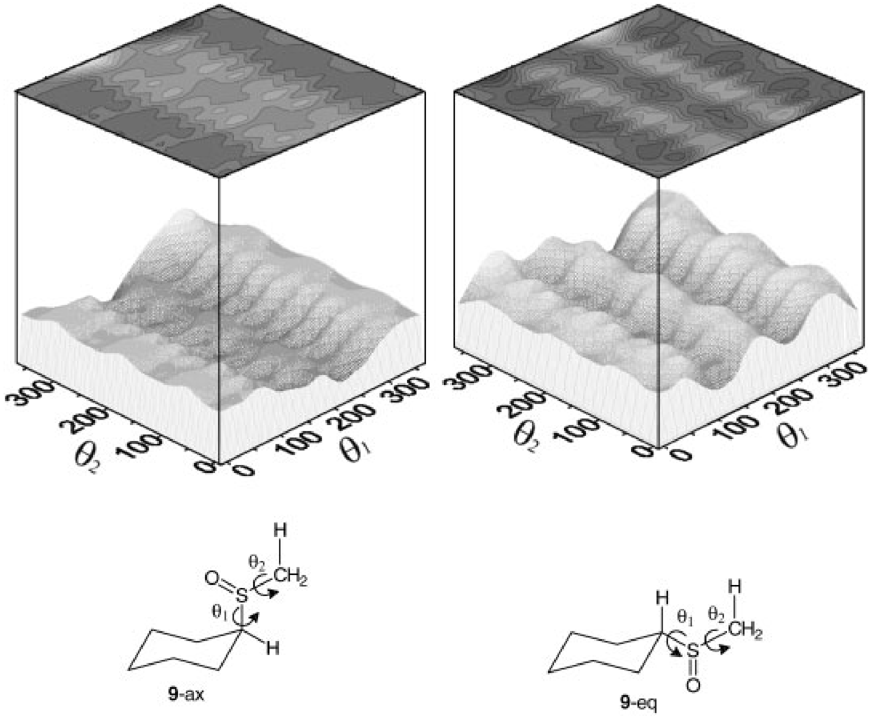


Figure 7. Population surfaces for axial (left) and equatorial (right) methylsulfinyl group rotation in cyclohexane, estimated at the B3LYP/6–31G(d) level of theory

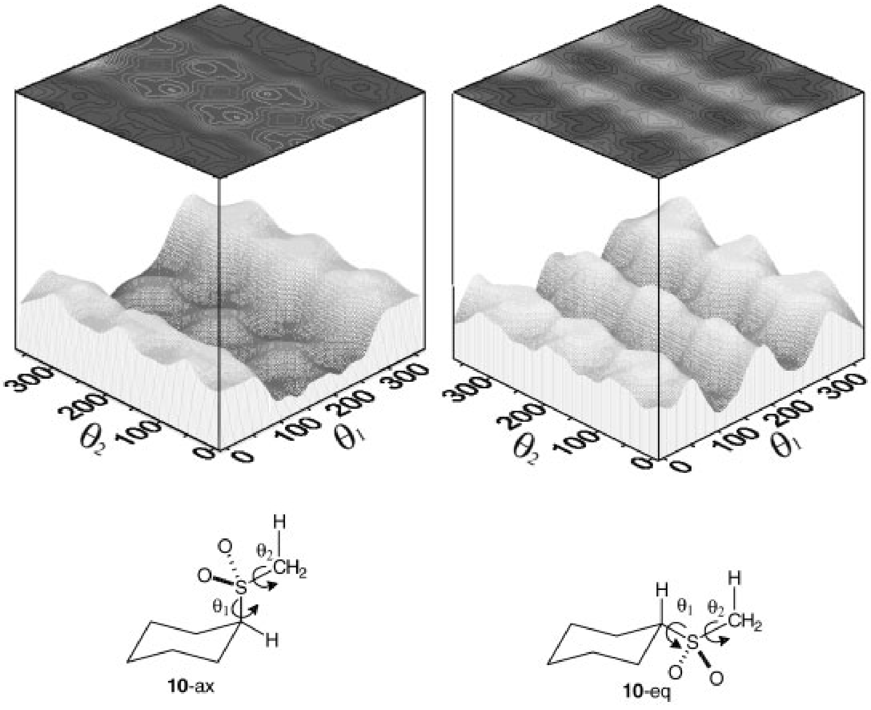
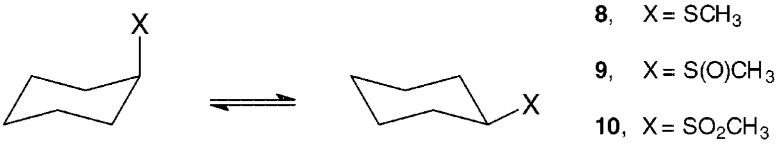


Figure 8. Population surfaces for axial (left) and equatorial (right) methylsulfonyl group rotation in cyclohexane, estimated at the B3LYP/6–31G(d) level of theory

Table 4. Gas-phase enthalpy difference ($\Delta H°$, kcal mol^{-1}) calculated for the axial ⇌ equatorial conformational equilibria of cyclohexane derivatives **8–10**



Entry	Method of Determination	X: SCH_3	X: $S(O)CH_3$	X: SO_2CH_3
1	Experimental[a]	-1.05 ± 0.09	-1.08 ± 0.06	-2.66 ± 0.09
2	MM3[a, b]	−1.51	−1.05	−0.66
3	MM3[c]	−1.06	−1.08	−2.37
4	MNDO	−0.85	−1.18	−1.44
5	PM3	−1.74	−1.69	−2.04
6	HF/3–21G(d)	−0.95	−0.89	−1.97
7	HF/6–31G(d)	−1.49	−1.31	−2.78
8	B3LYP/3–21G(d)	−0.77	−0.53	−1.39
9	B3LYP/6–31G(d)	−1.39	−1.01	−2.09
10	MP2/6–31G(d)//HF/6-31G(d,p)	−0.94	−0.99	−1.51

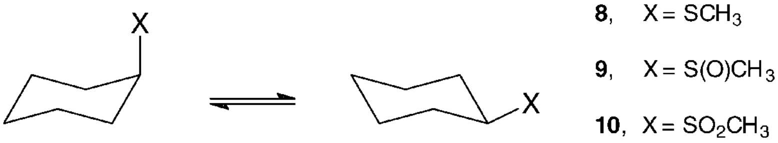
[a] Ref 15.
[b] $\varepsilon = 8.9$, original parameters.
[c] New parameters, see Ref. 15.

ax (Fig. 5 and Scheme 5) implies a positive entropy change in going from the axial to equatorial isomer, approaching $\Delta S°_{ax \rightarrow eq} = R\ln3 - R\ln2 = +0.80$ cal deg^{-1} mol^{-1}. The experimentally observed negative $\Delta S°$ value, -0.29 ± 0.30 cal deg^{-1} mol^{-1},[15] although small, is contrary to anticipation.

Figures 6–8 present the Boltzmann populations in axial and equatorial **8–10**, derived at the B3LYP/6–31G(d) level of theory, based on Eqns (2) and (3) and Chart 1. It is appreciated that all three axial isomers are confined to rotamers with the *S*-methyl group outside the ring, with concomitant entropy loss.

Tables 4–6 collect the thermodynamic parameters for axial ⇌ equatorial equilibria of sulfur-containing cyclo-

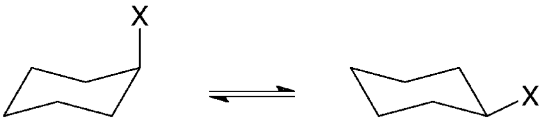
Table 5. Gas-phase entropy difference ($\Delta S°$, eu) calculated for the axial ⇌ equatorial conformational equilibria of cyclohexane derivatives **8–10**



		X								
		SCH_3			$S(O)CH_3$			SO_2CH_3		
Entry	Method of determination	$\Delta S°_{total}$	ΔS^{oc}	$\Delta S°_{mixing}$	$\Delta S°_{total}$	ΔS^{oc}	$\Delta S°_{mixing}$	$\Delta S°_{total}$	ΔS^{oc}	$\Delta S°_{mixing}$
1	Experimental[a]	$+0.46 \pm 0.31$	—	—	$+1.53 \pm 0.30$	—	—	-0.28 ± 0.30	—	—
2	MM3[a, b]	+1.20	+0.59	+0.61	+1.66	+0.76	+0.90	+1.30	+0.90	+0.40
3	MM3[c]	+1.31	+0.76	+0.55	+2.05	+1.22	+0.83	+1.06	+0.63	+0.43
4	MNDO	+0.70	+0.37	+0.33	+0.18	+0.83	−0.65	+0.45	+0.35	+0.10
5	PM3	+0.80	+0.89	−0.09	+2.07	+0.27	+1.80	+2.76	+0.43	+2.33
6	HF/3–21G(d)	+0.68	+0.29	+0.39	+0.75	+0.40	+0.35	+0.52	+0.20	+0.32
7	HF/6–31G(d)	+0.75	+0.41	+0.34	+1.01	+0.83	+0.18	+0.44	+0.26	+0.18
8	B3LYP/3–21G(d)	+0.99	+0.27	+0.72	+1.05	+0.37	+0.68	+0.55	+0.18	+0.37
9	B3LYP/6–31G(d)	+1.10	+0.43	+0.67	+1.39	+0.95	+0.44	+0.42	+0.25	+0.17
10	MP2/6–31G(d)	+0.97	+0.97	—[d]	+1.59	+1.59	—[d]	+0.59	+0.59	—[d]

[a] Ref 15.
[b] $\varepsilon = 8.9$. Revised torsional parameters, see Ref. 15.
[c] Sum of $\Delta S°_{rotational} + \Delta S°_{vibrational} + \Delta S°_{traslational} + \Delta S°_{electronic}$.
[d] Not estimated, owing to the excessive amount of computing time that is required at this level.

Table 6. Gas-phase conformational free energy difference ($\Delta G^\circ_{298\ \mathrm{K}}$, kcal mol^{-1}) calculated for the axial $\rightleftharpoons$ equatorial conformational equilibria of cyclohexane derivatives **8–10**



8, X = SCH_3

9, X = $S(O)CH_3$

10, X = SO_2CH_3

		X		
Entry	Method of determination	SCH_3	$S(O)CH_3$	SO_2CH_3
1	Experimental[a]	−1.19 ± 0.18	−1.54 ± 0.15	−2.58 ± 0.18
2	MM3[a,b]	−1.69	−1.32	−0.80
3	MM3[c]	−1.22	−1.33	−2.50
4	MNDO	−1.05	−1.23	−1.57
5	PM3	−1.98	−2.46	−2.87
6	HF/3–21G(d)	−1.15	−1.11	−2.12
7	HF/6–31G(d)	−1.71	−1.61	−2.86
8	B3LYP/3–21G(d)	−1.07	−0.84	−1.56
9	B3LYP/6–31G(d)	−1.72	−1.42	−2.15
10	MP2/6–31G(d)	−1.23	−1.46	−1.68

[a] Ref 15.

[b] $\varepsilon = 8.9$, original parameters.

[c] New parameters, see Ref. 15.

hexane derivatives **8**–**10**, calculated at various levels of theory. The data are compared with the experimental values (entry 1 in Tables 4–6).

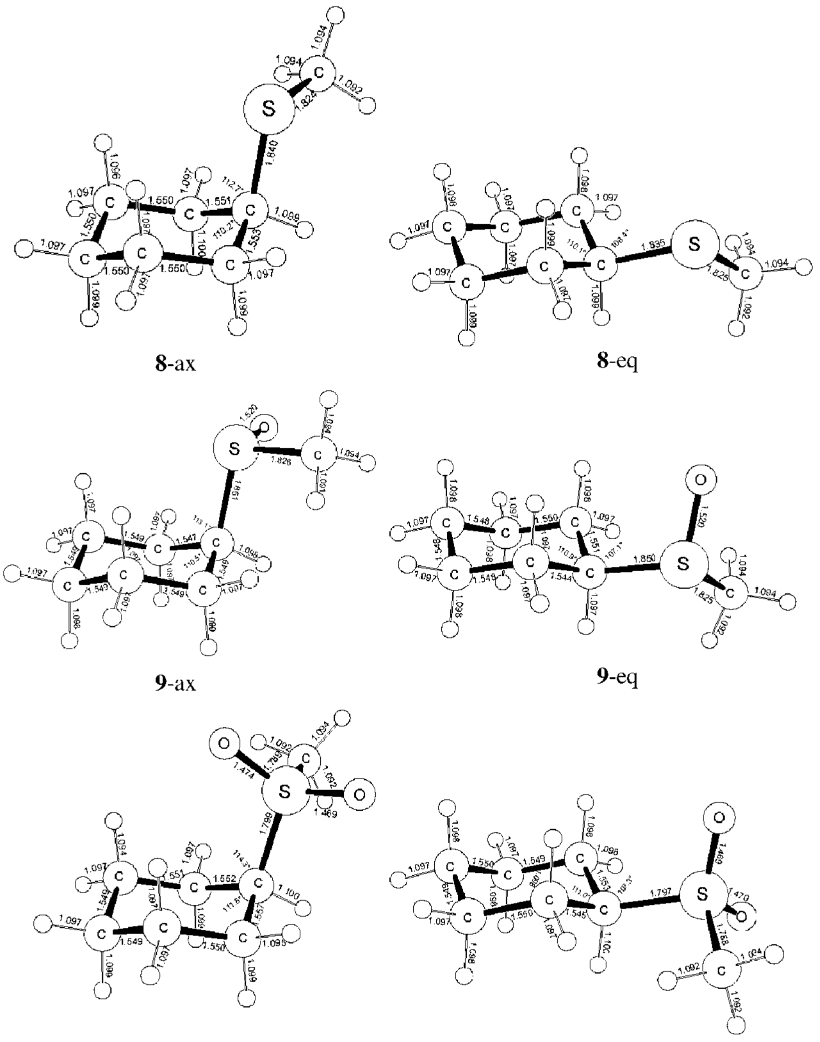
Examination of Table 4 shows that, as pointed out in the Introduction, MM3 (original parameters, entry 2) fails to reproduce the experimentally observed enthalpic behavior of sulfone **10**. The calculated conformational preferences with the parameters developed in Ref. 15 are, as expected from the parameterization procedure, much closer to the experimental values. Likewise, MNDO and PM3 semiempirical modeling of **8**–**10** (entries 4 and 5 in Table 4) is not successful. In contrast, HF, B3LYP/6–31G(d), and MP2/6–31G(d)//HF/6–31G(d,p) calculations (entries 6, 7, 9 and 10 in Table 4) afforded ΔH° (ax→eq) values that are in agreement with experimental results for sulfide **8** and sulfoxide **9**. The computed data for sulfone **10** (entries 6–10) are more scattered.

It was of interest to examine the calculated values for ΔS°, with and without consideration of the $\Delta S^\circ_{\mathrm{mixing}}$ term. In the case of sulfide **8**, all computational methods predicted $\Delta S^\circ_{\mathrm{total}}$ values that are actually larger than the experimental result. With the exception of PM3 (entries 5 in Table 5), all methods provided $\Delta S^\circ_{\mathrm{mixing}}$ values that are fairly close to the experimentally determined ΔS°. It could be argued that the entropy parameter is dominated by entropy of mixing in the **8**-ax $\rightleftharpoons$ **8**-eq equilibrium, so that consideration of $\Delta S^\circ_{\mathrm{mixing}}$ [according to Chart 1 and Eqns (2) and (3)] may suffice for analysis of the entropy change.

In contrast, a correct estimation of ΔS° for the conformational equilibrium in sulfoxide **9** appears to require consideration of both $\Delta S^\circ_{\mathrm{mixing}}$ and computed ($\Delta S^\circ_{\mathrm{rotational}} + \Delta S^\circ_{\mathrm{vibrational}} + \Delta S^\circ_{\mathrm{traslational}} + \Delta S^\circ_{\mathrm{electronic}}$) terms, as provided by HF, B3LYP and MP2 calculations (entries 6–10 in Table 5).

Finally, for the conformational equilibrium of methylsulfone **10**-ax $\rightleftharpoons$ **10**-eq, with the exception of the semiempirical PM3 method that provides a too large positive value for $\Delta S^\circ_{\mathrm{mixing}} = +2.33$ eu, all computational methods afford $\Delta S^\circ_{\mathrm{total}}$ that are positive and in the range +0.40 to +0.59 cal deg^{-1} mol^{-1}. The experimental value, $\Delta S^\circ = -0.28 \pm 0.3$,[15] although small, is contrary to expectation. In the absence of a suitable explanation for the experimental value, suggesting entropy loss in going from axial to equatorial methylsulfone **10** (compare with positive ΔS° anticipated in Scheme 5 and Fig. 8), we have undertaken the experimental reevaluation of the **3**-ax $\rightleftharpoons$ **3**-eq equilibrium (Scheme 1). That work is in progress.

Figure 9 presents the calculated structural parameters for the lowest energy axial and equatorial isomers of sulfide **8**, sulfoxide **9** and sulfone **10** at the B3LYP/6–31G(d) level of theory. Salient observations are (1) the increase in C(2)—C(1)—S bond angle in going from the axial thioether to the axial sulfoxide, and then to the axial sulfone: 112.7°, 113.1° and 114.3°, respectively. This increased tilting of the substituent away from the cyclohexane ring is ascribed to increasing steric repulsion in the series. (2) The similarity of C—S bonds in axial and equatorial **8**, **9** and **10** seems to be contrary to expectation in terms of $\sigma_{\mathrm{C—C}} \rightarrow \sigma^*_{\mathrm{C—S}}$ stereoelectronic stabilization of the equatorial isomers.[5] (3) The similarity of the S—O sulfinyl bonds in axial and equatorial **9** and **10** is also relevant, since $\sigma_{\mathrm{C—C}} \rightarrow \sigma^*_{\mathrm{S—O}}$ stabilizing stereoelectronic interactions could also be anticipated for antiperiplanar arrangements of such bonds.[29]



8-ax **8**-eq

9-ax **9**-eq

10-ax **10**-eq

Figure 9. Structural parameters calculated for axial and equatorial **8–10**, at the B3LYP/6–31G(d) level of theory

From examination of Tables 4–6, it can be appreciated that MM3 (new parameters[15]) affords $\Delta G°$ values that are in good agreement with the experimental data. Semiempirical (MNDO, PM3) computational methods generally fail to model the thermodynamic parameters for the conformational behavior exhibited by the sulfur-containing groups in cyclohexane. DFT methods (entries 8 and 9 in Table 6) gave results that were closer to the experimental data, but HF and MP2 *ab initio* calculations with 3–21G(d) and 6–31G(d) basis sets proved most reliable (entries 6, 7 and 10 in Table 6). Thus, in spite of the fact that these *ab initio* methods are the most expensive, they are to be recommended for modeling of sulfur-containing groups.

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