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Enthalpic and Entropic Contributions to the Conformational Free Energies of Methylthio, Methylsulfinyl, Methylsulfonyl, Phenylthio, Phenylsulfinyl, and Phenylsulfonyl [$S(O)_nR$, $n = 0, 1, 2$; $R = CH_3$, Ph] Groups in Cyclohexane

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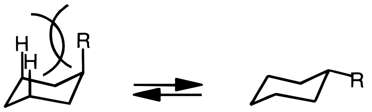
A variable-temperature NMR study of (*cis*-4-methylcyclohexyl)methyl sulfide (**1**), sulfoxide (**2**), and sulfone (**3**), as well as (*cis*-4-methylcyclohexyl)phenyl sulfide (**4**), sulfoxide (**5**), and sulfone (**6**) allowed determination of the thermodynamic parameters, $\Delta H°$ and $\Delta S°$, for the title groups. Reproduction of the experimental results with Allinger's MM3 program was successfully accomplished in the case of the sulfoxide and sulfide groups. Nevertheless, modification of the original force field torsional parameters was required in order to adequately reproduce the experimentally observed behavior of the sulfonyl derivatives. Rationalization of the enthalpic and entropic contributions to $\Delta G°$ [$S(O)_nR$, $n = 0, 1, 2$; $R = CH_3$, Ph] is advanced in terms of the steric characteristics of these sulfur-containing groups and the resulting rotameric populations in the axial and equatorial monosubstituted cyclohexanes.

Introduction

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 prevent the repulsive steric interactions with the C(3,5) methylenes (eq 1), and 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[3] and experimental NMR data[4] showed that while the conformational free energy differences ($\Delta G°$ values) increase along the series methyl → ethyl → isopropyl, the *enthalpic* contributions to the equatorial preference actually decrease along this series (entries 1−3 in Table 1), so that it is the $T\Delta S°$ term that accounts for the observed trend.

Table 1. Enthalpic and Entropic Contributions to the Conformational Free Energy Differences ($\Delta G°_{298K}$) of Relevant Alkyl Groups (eq 1)[4−6]

entry	R	$\Delta H°$	$\Delta S°$	$\Delta G°_{298K}$
1	Me	−1.75	−0.03	−1.74
2	Et	−1.60	+0.64	−1.79
3	*i*-Pr	−1.52	+2.31	−2.21
4	Bn	−1.52	+0.81	−1.76
5	*t*-Bu	−5.00	−0.44	−4.87

Furthermore, the benzyl group exhibits similar thermodynamic behavior (entry 4 in Table 1),[5] whereas by contrast, the axial isomer of *tert*-butylcyclohexane has greater entropy in the axial relative to the equatorial isomer (entry 5 in Table 1).[6]

The interesting observations described in the previous paragraph have been well discussed in the literature[3−6] and provide convincing evidence that a proper understanding of conformational behavior is viable only with adequate knowledge of the enthalpic and entropic contributions to $\Delta G°$. Indeed, such dissection of conformational energies into $\Delta H°$ and $\Delta S°$ components has been essential for interpretation of the conformational behavior of various substituted heterocycles.[7−10]

Two decades ago, Eliel and Kandasamy determined the conformational energies of the methylthio, methylsulfinyl, and methylsulfonyl groups by low-temperature ^{13}C

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[10] (a) Juaristi, E.; Cuevas, G. *Tetrahedron Lett.* **1992**, *33*, 2271. (b) Juaristi, E.; Cuevas, G. *J. Am. Chem. Soc.* **1993**, *115*, 1313.

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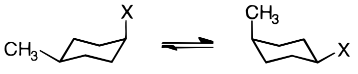
Scheme 1



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 = $SO_2C_6H_5$

NMR signal area measurements.[11] The single-temperature $-\Delta G°_{178K}$ values obtained in this work were anticipated to become more negative at higher temperature owing to entropy effects. In particular, three populated rotamers in the equatorial isomers versus one [$CH_3S(O)$] or two [CH_3S, CH_3SO_2] populated rotamers in the axial form[12] imply that the entropy of mixing should make a substantial contribution to the free energy difference.

The present paper reports the results of variable-temperature ^{13}C NMR measurements in (*cis*-4-methylcyclohexyl)methyl sulfide, sulfoxide, and sulfone (**1**−**3**), as well as in the SC_6H_5 analogues **4**−**6**, which permitted the determination of $\Delta H°$ and $\Delta S°$ in axial to equatorial equilibria (Scheme 1). The *cis*-methyl at C(4) serves as a counterpoise substituent,[11,13] so that equilibrium constants, K, are closer to unity.

Results

A. **Synthetic and Spectroscopic Part.** *trans*-4-Methylcyclohexyl mesylate (**7**) was prepared from *trans*-4-methylcyclohexanol[14] according to the usual procedure[15] and reacted with sodium thiomethoxide ($CH_3S^-Na^+$) to give *cis*-**1**, or with sodium thiophenoxide ($C_6H_5S^-Na^+$) to give *cis*-**4**. Oxidation of *cis*-**1** and *cis*-**4** with 1 equiv of sodium periodate afforded sulfoxides *cis*-**2** and *cis*-**5**, respectively, whereas treatment of *cis*-**1** with excess hydrogen peroxide gave sulfones *cis*-**3** and *cis*-**6**, respectively (Scheme 2).

Application of Eliel's equation[16] [$K = (\delta_{eq} - \delta_{mobile})/(\delta_{mobile} - \delta_{ax})$] to the variable temperature ^{13}C NMR data[17] (Table 2, Supporting Information) affords the equilibrium constants listed in Table 3. Plots of ln K versus $1/T$ (Figure 1) show good correlations, and the thermodynamic parameters derived from linear regression are listed in Table 4. Consideration of the thermodynamic parameters of the counterpoise substituent, $\Delta H°(CH_3) = -1.75$ kcal/mol and $\Delta S°(CH_3) = -0.03$ cal/K·mol,[4a] gives the data collected in Table 5.

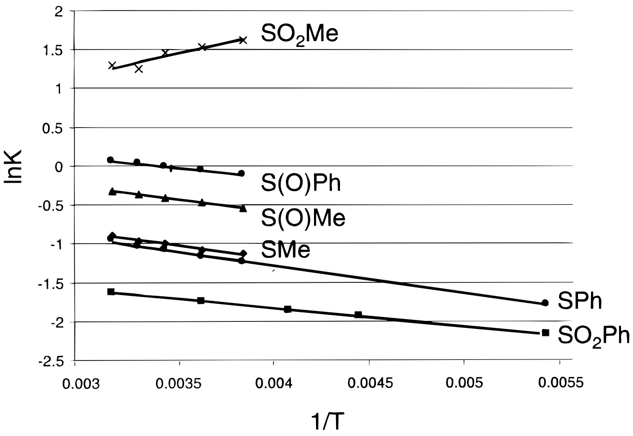
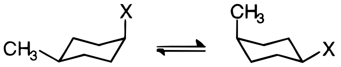


Figure 1. ln K as a function of $1/T$ for **1**−**6**.

Table 3. Variable-Temperature Conformational Equilibrium Constants of Compounds 1−6 (Scheme 1) in $CDCl_3$

compd	temp, K	K	$\Delta G°$, kcal/mol	compd	temp, K	K	$\Delta G°$, kcal/mol
1	313	0.409	0.556	**4**	300	0.352	0.622
1	300	0.383	0.572	**4**	288	0.337	0.622
1	288	0.372	0.566	**4**	273	0.312	0.631
1	273	0.341	0.583	**4**	258	0.289	0.636
1	258	0.322	0.581	**4**	183	0.166	0.653
2	313	0.728	0.197	**5**	313	1.06	−0.036
2	300	0.696	0.216	**5**	300	1.03	−0.018
2	288	0.665	0.233	**5**	288	0.98	−0.012
2	273	0.621	0.258	**5**	273	0.94	−0.034
2	258	0.579	0.280	**5**	258	0.89	−0.060
3	313	3.677	−0.810	**6**	313	0.195	−1.017
3	300	3.491	−0.825	**6**	303	0.192	−0.944
3	288	4.280	−0.832	**6**	273	0.174	−0.949
3	273	4.604	−0.828	**6**	243	0.154	−0.903
3	258	5.067	−0.832	**6**	223	0.143	−0.862
4	313	0.384	0.605	**6**	183	0.113	−0.793

Table 4. Thermodynamic Parameters for 1−6



X	$\Delta H°$ (kcal/mol)	$\Delta S°$ (cal/°K·mol)
CH_3S	+0.70 ± 0.09	+0.45 ± 0.31
$CH_3S(O)$	+0.67 ± 0.06	+1.52 ± 0.30
CH_3SO_2	−0.91 ± 0.09	−0.28 ± 0.30
PhS	+0.71 ± 0.11	+0.31± 0.38
PhS(O)	+0.53 ± 0.06	+1.76± 0.15
$PhSO_2$	−0.49 ± 0.10	+1.66 ± 0.26

Discussion

Table 5 includes the conformational free energy differences at 298 K and 178 K, estimated by incorporation of the experimentally derived enthalpy and entropy terms into equation $\Delta G° = \Delta H° - T\Delta S°$. Comparison of these values with those reported by Eliel[11] for **1**−**3** shows excellent agreement. Indeed, for the series CH_3S, $CH_3S(O)$, and CH_3SO_2, we obtain $\Delta G°_{178K} = -1.14, -1.36, -2.61$ kcal/mol, respectively, to be compared with Eliel and Kandasamy's −1.00, −1.20, and −2.50 kcal/mol, respectively.[11]

With respect to enthalpy terms, the similarity among those obtained for the methylthio and methylsulfinyl groups ($\Delta H° = -1.05$ and -1.08 kcal/mol, respectively) is in line with expectation (see above) that a sulfur lone pair confronts the ring in both these systems. On the other hand, the more than double $\Delta H°$ term for CH_3SO_2, −2.66 kcal/mol, reflects the additional steric repulsion caused by the oxygen-inside interaction in the axial sulfone, worth ca. 1.6 kcal/mol. A similar trend is found

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(11) Eliel, E. L.; Kandasamy, D. *J. Org. Chem.* **1976**, *41*, 3899.

(12) The methyl-inside rotamer of axial methylthio- and methylsulfonylcyclohexane is nearly 3 kcal/mol higher in energy and can be disregarded. The oxygen-inside rotamer of axial methylsulfinylcyclohexane is nearly 1.5 kcal/mol higher in energy,[11] thus the axial sulfoxide exists largely (over 90%) with the sulfur lone pair pointing inside the ring.

(13) Eliel, E. L.; Della, E. W.; Williams, T. H. *Tetrahedron Lett.* **1963**, 831.

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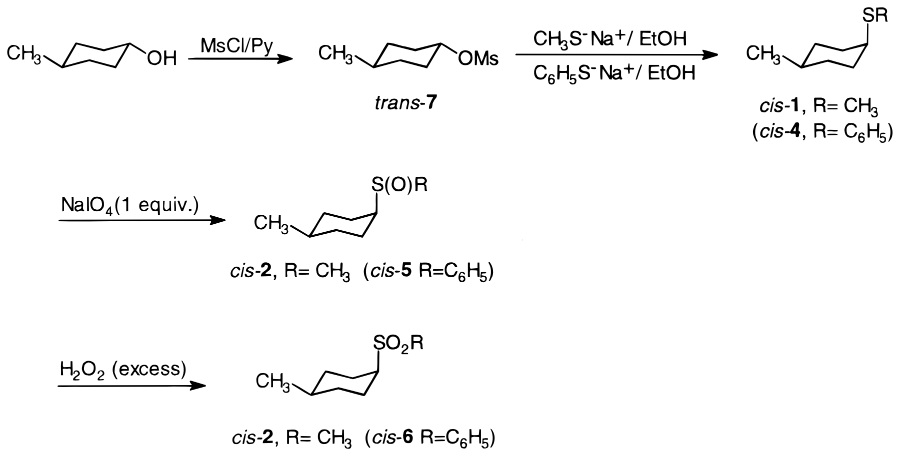
(16) Eliel, E. L. *Chem. Ind. (London)* **1959**, 568.

(17) $CH_3-C(4)$ provides the most adequate spread ($\delta_{eq} - \delta_{ax}$) of chemical shifts to make such a calculation reliable. The shifts δ_{eq} and δ_{ax} were determined by measurement below coalescence temperature (assuming linear temperature dependence).

Scheme 2



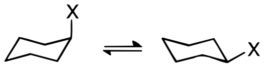
trans-**7**

cis-**1**, R= CH_3
(*cis*-**4**, R= C_6H_5)

cis-**2**, R= CH_3 (*cis*-**5** R=C_6H_5)

cis-**2**, R= CH_3 (*cis*-**6** R=C_6H_5)

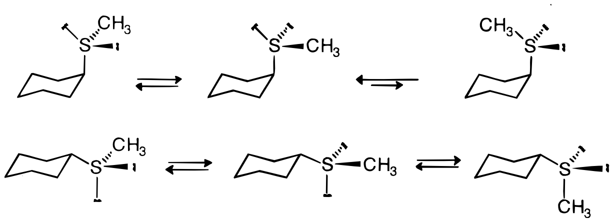
Table 5. Thermodynamic Parameters for the Methylthio, Methylsulfinyl, Methylsulfonyl, Phenylthio, Phenylsulfinyl, and Phenylsulfonyl Groups in Cyclohexane



entry	X	$\Delta H°$,[a] kcal/mol	$\Delta S°$,[b] cal/K·mol	$\Delta G°_{298K}$,[c] kcal/mol	$\Delta G°_{178K}$,[c] kcal/mol
1	CH_3S	−1.05 ± 0.09	+0.48 ± 0.31	−1.19	−1.14
2	$CH_3S(O)$	−1.08 ± 0.06	+1.55 ± 0.30	−1.54	−1.36
3	CH_3SO_2	−2.66 ± 0.09	−0.26 ± 0.30	−2.58	−2.61
4	C_6H_5S	−1.04 ± 0.11	+0.32 ± 0.38	−1.12	−1.10
5	$C_6H_5S(O)$	−1.22 ± 0.06	+1.82 ± 0.15	−1.76	−1.54
6	$C_6H_5SO_2$	−2.44 ± 0.10	+1.66 ± 0.26	−2.94	−2.74

[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.

Scheme 3

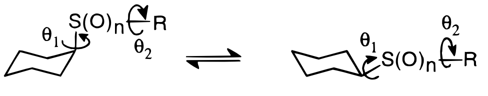


in the phenyl analogues, with $\Delta H° = -1.04$ and -1.22 kcal/mol for the sulfide and sulfoxide, respectively, and then a substantial $\Delta H° = -2.24$ kcal/mol for the sulfone derivative (Table 5, entries 4, 5, and 6).

The entropy data obtained in the present work is also congruent with expectation in the cases of the sulfide and sulfoxide groups. As discussed in the Introduction, two populated rotamers of axial methylthio group versus three in the equatorial isomer (Scheme 3) suggests an entropy of mixing approaching $R \ln 3 - R \ln 2 = 0.80$ cal/K·mol (experimental, $\Delta S° = +0.48$ cal/K·mol). In the case of the methylsulfinyl group, only one axial rotamer indicates a maximum value for $\Delta S°$ mixing $= R \ln 3 - R \ln 1 = 2.18$ cal/K·mol (experimental, $\Delta S° = +\ 1.55$ cal/K·mol). Again, this trend is reproduced in the C_6H_5S/$C_6H_5S(O)$ series, with $\Delta S°$ values of +0.32 and +1.82 cal/K·mol, respectively.

With regard to the sulfonyl groups, the experimentally observed negative $\Delta S°$ value for the axial to equatorial conversion of the methylsulfonyl group, $\Delta S° = -0.29$ cal/K·mol (Table 5, entry 3), although small, is contrary to that anticipated based on steric terms.[11] Nevertheless, the corresponding value for the $C_6H_5SO_2$ group, $\Delta S° = +1.66$ cal/K·mol (Table 5, entry 6) seems congruent with expectation.

B. **Molecular Mechanics Calculations.** The MM3-(94)[18] force field was used to evaluate the intramolecular energetics for equilibria **8**−**13**-ax ⇌ **8**−**13**-eq. Uniform scanning at 5° increments was carried out for the θ_1 and θ_2 dihedral angles (eq 2), allowing for complete relaxation of the rest of the atomic coordinates. The conformational energy plots originating from each minimum energy conformation were drawn by means of the Surfer program.[19]



8-**13**-ax **8**-**13**-eq (2)

The free-space intramolecular entropy[20] was calculated according to eq 3 where R is the gas constant, n is the number of conformational states sampled, and P_i is the Boltzmann probability in the ith conformational state.

$$S^{\gamma} = -\,R\sum_{i=1}^{n} P_i \ln P_i \tag{3}$$

The P_i, in turn, were computed from the relationship

$$P_i = \frac{e^{-E_i/RT}}{\sum_{i=1}^{n} e^{-E_i/RT}} \tag{4}$$

where E_i is the intramolecular conformational energy of the ith state.

Table 6 presents the calculated thermodynamic data for equilibria **1**−**6**-ax ⇌ **1**−**6**-eq and includes the corresponding experimental values for comparison purposes. The agreement between experiment and MM3 is good for

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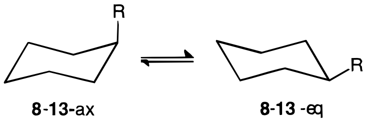
[18] Allinger, N. L.; Yuh, Y. H.; Lii, J. H. *J. Am. Chem. Soc.* **1989**, *111*, 8551.

[19] *Surfer* version 4.0, Golden Software, Inc., 809 14th St., P.O. Box 281, Golden, CO 80402-0281.

[20] Flory, P. J. *Statistical Mechanics of Chain Molecules*; Wiley: New York, 1969. See also: López de Compadre, R. L.; Pearlstein, R. A.; Hopfinger, A. J.; Seydel, J. K. *J. Med. Chem.* **1987**, *30*, 900.

Table 6. Comparison of Experimental (this work) and Calculated [MM3(94) Force Field, $\epsilon = 8.9$]. Thermodynamic Data for 8−13-ax ⇌ 8−13-eq



R	$\Delta H°_{\text{exptl}}$	$\Delta S°_{\text{exptl}}$	$\Delta H°_{\text{MM3}}$	$\Delta S°_{\text{MM3}}$
SCH_3	−1.05	+0.46	−1.51	+0.61
$S(O)CH_3$	−1.08	+1.53	−1.05	+0.90
SO_2CH_3	−2.66	−0.28	−0.66	+0.40
SC_6H_5	−1.04	+0.32	−1.45	+0.16
$S(O)C_6H_5$	−1.22	+1.82	−0.99	+0.90
$SO_2C_6H_5$	−2.24	+1.66	−0.70	+0.16

Table 7. Revised Torsional Parameters for the $C_{sp^3}-C_{sp^3}-C_{sp^3}-SO_2$ Segment, in kcal/mol

segment	V_1	V_2	V_3
C−C−C−SO_2	−0.394	0.0	−0.368

sulfides and sulfoxides, but for sulfones the agreement is poor. The possibility was considered that solvation by hydrogen bonding solvents such as chloroform or methylene chloride could be responsible for the discrepancy in the case of the sulfonyl derivatives, but then it seems odd that sulfoxides should not be affected too by solvation effects not taken into account in the force field. Furthermore, MM3 calculations did not reproduce the energy barriers calculated for rotation around the $CH_3CH_2-CH_2SO_2CH_3$ bond by means of ab initio methods.[21]

As it turns out,[22] sulfide and sulfoxide force field parameters were determined with the aid of Hartree−Fock calculations which contained polarization functions, but the sulfone parameters were obtained from ab initio calculations which did not include polarization functions, rendering the results highly suspect. Indeed, examination of the various parameters contributing to the steric energy calculated in the force field revealed anomalous values for the estimated torsional energies in $C_{sp^3}-C_{sp^3}-C_{sp^3}-S(O)_n$ segments. Thus, reparametrization was carried out by systematic modification of the V_1 and V_3 torsion parameters, maintaining $V_2 = 0$ and $V_1{:}V_3 = 1.5{:}1.4$, until the calculation matched the experimentally observed $\Delta H°$ values. Table 7 presents the revised torsional parameters for the $C_{sp^3}-C_{sp^3}-C_{sp^3}-SO_2$ segment.

Inclusion of the new parameters collected in Table 7 did reproduce the energy barriers for rotation in the model, $CH_3CH_2-CH_2SO_2CH_3$, as estimated by ab initio methods.

Figures 2−7 present the Boltzmann populations in axial and equatorial **8**−**13**.

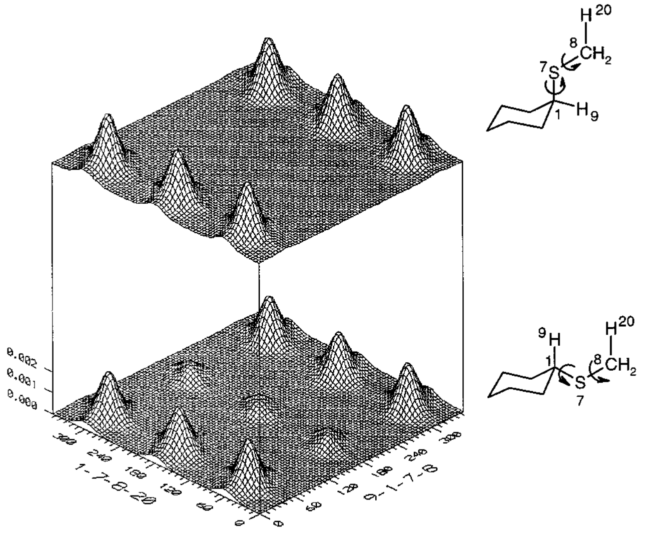


Figure 2. Population surfaces for axial (top) and equatorial (bottom) *S*-methyl group rotation in cyclohexane.

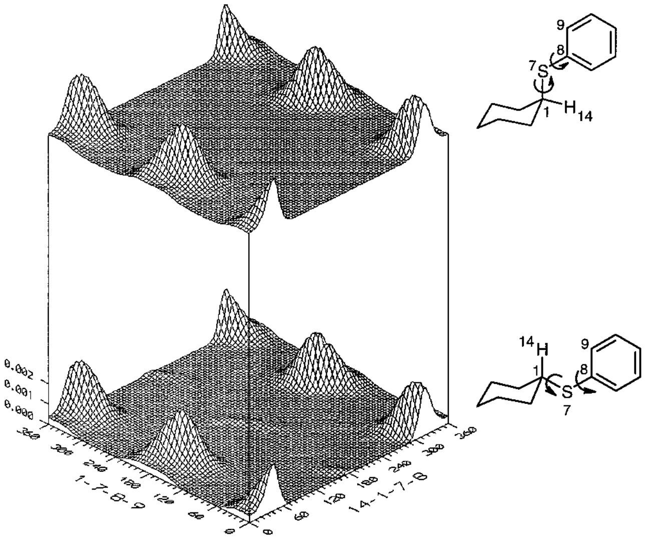


Figure 3. Population surfaces for axial (top) and equatorial (bottom) *S*-phenyl group rotation in cyclohexane.

Experimental Section

General Information. ^{13}C NMR (67.5 MHz) spectra were recorded on a 270 MHz spectrometer. Chemical shifts are given in parts per million downfield from TMS (δ). The probe thermocouple was used for temperature measurement, after calibration. Temperatures are believed to be accurate to within ±2 K.

(*cis*-4-Methylcyclohexyl)methyl Sulfide (*cis*-1). Sodium thiomethoxide (0.18 g, 2.60 mmol) in 10 mL of ethanol was treated with 0.5 g (2.60 mmol) of *trans*-4-methylcyclohexyl methanesulfonate (**7**, prepared from *trans*-4-methylcyclohexanol[14] according to the usual procedure[15]) in 4 mL of ethanol, and the reaction mixture was heated to reflux for 4 h and stirred at ambient temperature for 55 h. Extraction with CH_2Cl_2 and the usual workup procedure afforded 0.09 g (24.0% yield) of *cis*-**1** as a yellowish oil. ^1H and ^{13}C NMR spectra were essentially identical to those reported in the literature.[11]

(*cis*-4-Methylcyclohexyl)methyl Sulfoxide (*cis*-2). *cis*-**1** (0.22 g, 1.52 mmol) was oxidized with sodium periodate (0.34 g, 1.58 mmol) following the literature procedure, to give 0.18 g (74.4% yield) of *cis*-**2** as a hygroscopic solid, mp 60−61 °C (lit.[11] 58−59 °C). ^1H and ^{13}C NMR spectra were essentially identical to those reported.[11]

(*cis*-4-Methylcyclohexyl)methyl Sulfone (*cis*-3). The procedure used was similar to that of Eliel and Kandasamy,[11] with 0.24 g (1.66 mmol) of *cis*-**1**, to obtain 0.25 g (85.2% yield) of the desired product, whose ^1H and ^{13}C NMR data were similar to those reported.[11]

(*cis*-4-Methylcyclohexyl)phenyl Sulfide (*cis*-4). In a 50-mL round-bottom flask was placed an ethanolic solution of sodium ethoxide (0.1 g, 4.34 mmol of sodium in 10 mL of ethanol), and to this was added dropwise a solution of 0.3 mL (2.92 mmol) of thiophenol in 1.0 mL of ethanol. The resulting thiophenoxide solution was treated with 0.5 g (2.60 mmol) of mesylate **7** dissolved in 4.0 mL of ethanol, and the reaction mixture was heated to reflux for 60 h. Extraction with CH_2-

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(21) The ab initio calculations were done with Gamess(US) 6-31G**, with inclusion of electron correlation.

(22) Allinger, N. L., personal communication.

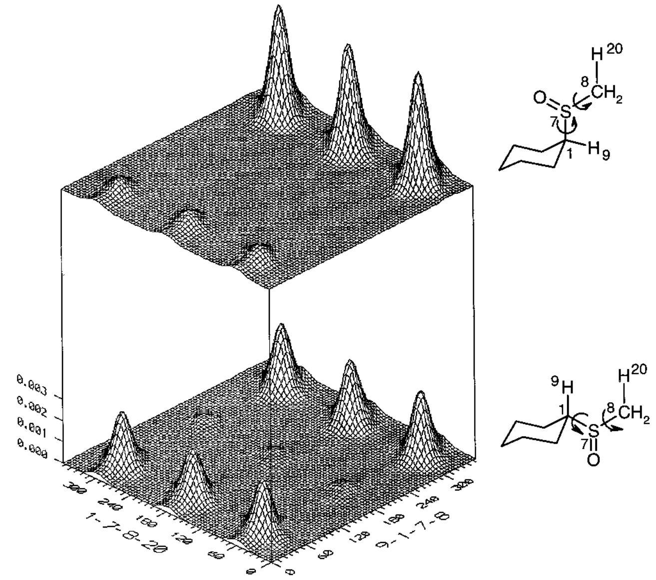

Figure 4. Population surfaces for axial (top) and equatorial (bottom) methylsulfinyl group rotation in cyclohexane.

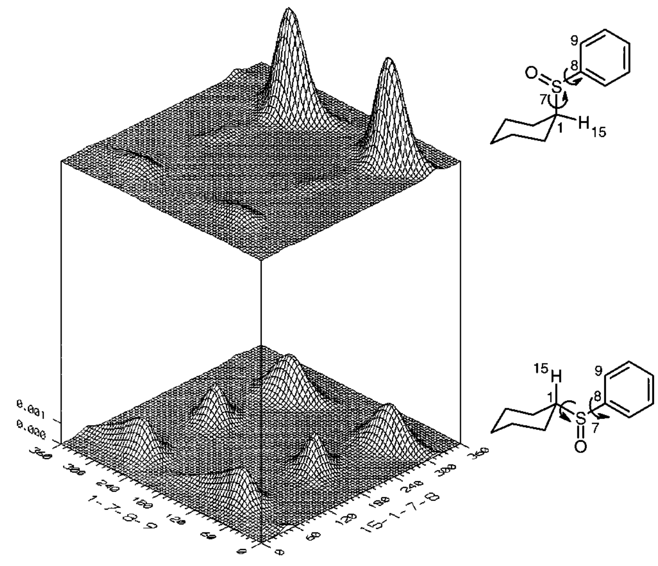

Figure 5. Population surfaces for axial (top) and equatorial (bottom) phenylsulfinyl group rotation in cyclohexane.

Cl_2 was followed by neutralization with aqueous 10% KOH. The usual workup procedure afforded 0.52 g (97% yield) of *cis*-**4**. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.93 (d, $J = 5.9$ Hz, 3 H), 1.42−1.86 (m, 9 H), 3.47 (m, 1 H), 7.14−7.4 (m, 5 H). ^{13}C NMR (CD_2Cl_2, 67.5 MHz) δ 21.6, 30.3, 31.6, 45.6, 126.5, 129.0, 131.4, 136.6. Anal. Calcd for $C_{13}H_{18}S$: C, 75.67; H, 8.79. Found: C, 75.87; H, 8.72.

(*cis*-4-Methylcyclohexyl)phenyl Sulfoxide (*cis*-5). In a 25-mL round-bottom flask was placed 0.2 g (0.97 mmol) of sulfide *cis*-**4**, 3.0 mL of CH_2Cl_2, and 10 mL of CH_3OH. This solution was cooled to 0 °C before the slow addition of 0.23 g (1.07 mmol) of $NaIO_4$ dissolved in 2.5 mL of water. The resulting reaction mixture was stirred for 8 h at 0 °C and then left standing in the refrigerator for 24 h. The usual workup procedure afforded 0.17 g (79% yield) of the desired product, *cis*-**5**, as a colorless oil. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.96 (d, $J = 6.6$ Hz, 3 H), 1.39−1.81 (m, 9 H), 2.20 (m, 1 H), 7.50.-7.67 (m, 5 H). ^{13}C NMR (CD_2Cl_2, 67.5 MHz) δ 20.2, 22.1, 24.0, 30.8, 30.8, 31.4, 64.0, 125.5, 129.3, 131.4, 143.9.

(*cis*-4-Methylcyclohexyl)phenyl Sulfone (*cis*-6). A solution containing 0.2 g (9.7 mmol) of sulfide *cis*-**4**, 4.0 mL of a 1:1 mixture of acetic anhydride and acetic acid, and 1.4 mL of 30% aqueous H_2O_2 was stirred at ambient temperature for 3 h. The reaction mixture was diluted with 14.0 mL of water and extracted with CH_2Cl_2. The organic phase was washed with saturated aqueous $NaHCO_3$ and water, dried with Na_2SO_4, and concentrated in the rotary evaporator to give 0.19 g (81.1% yield) of *cis*-**6** as a white solid that was recrystallized from hexane, mp 63−64 °C. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.91 (d, $J = 7.2$ Hz, 3 H), 1.41−1.93 (m, 9 H), 2.91 (m, 1 H), 7.5−7.88 (m, 5 H). ^{13}C NMR (CD_2Cl_2, 270 MHz) δ 18.2, 21.1, 27.7, 30.6, 63.0, 129.2, 129.5, 133.9, 138.3. Anal. Calcd for $C_{13}H_{18}O_2S$: C, 65.51; H, 7.61. Found: C, 65.36; H, 7.63.

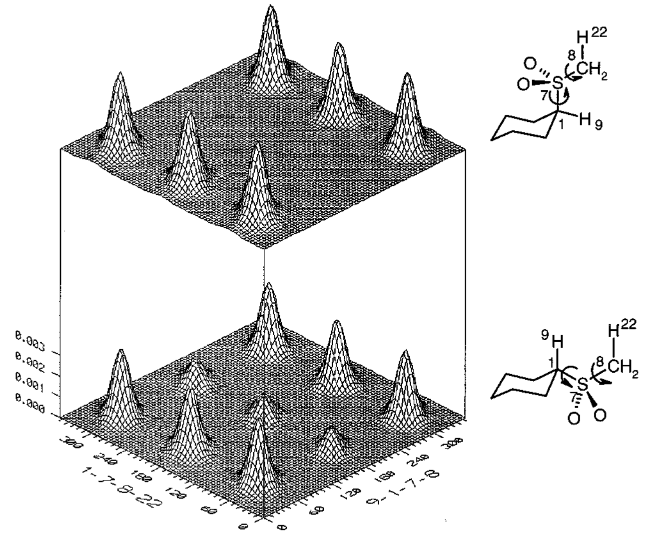

Figure 6. Population surfaces for axial (top) and equatorial (bottom) methylsulfonyl group rotation in cyclohexane.

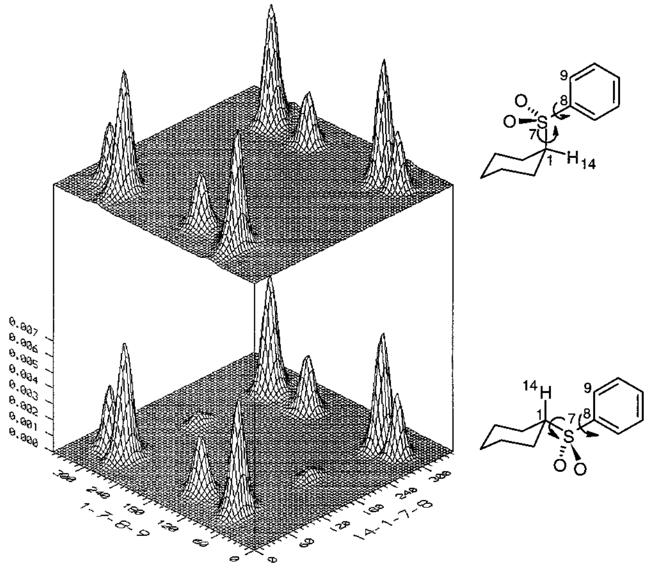

Figure 7. Population surfaces for axial (top) and equatorial (bottom) phenylsulfonyl group rotation in cyclohexane.

Supporting Information Available: Variable-temperature ^{13}C NMR chemical shifts of *cis*-**1**−**3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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