The alkyl/phenyl-folded conformation of alkyl 1-phenylethyl sulfides and sulfones as evidenced by *ab initio* MO calculations. Implication for the 1,2-asymmetric induction

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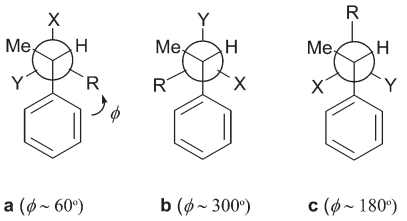
Ab initio MO calculations were carried out, at the MP2/6-311G(d,p)//MP2/6-31G(d) level, to investigate the conformational energy of alkyl 1-phenylethyl sulfides $C_6H_5CHCH_3SR$ and sulfones $C_6H_5CHCH_3SO_2R$ (R = CH_3, C_2H_5, *i*-C_3H_7, *t*-C_4H_9). In every case, a rotamer whereby the alkyl group (R) is synclinal to C_6H_5 (Ph) and antiperiplanar to the benzylic methyl group (Ph–C–S–R torsion angle $\phi \cong 60°$) has been found the most stable. Interatomic H/C_{ipso} distances at the stable geometries are found to be short. The results are interpreted in the context of the CH/π hydrogen bond occurring between CHs in R and the π-system of Ph. The implication of the above results to the stereochemical mechanism of the oxidation of sulfides to give diastereoisomeric sulfoxides was discussed. The mechanism of 1,2-asymmetric induction (Cram's open-chain model) was suggested to be explained on the basis of a simple premise that the geometries of the transition state resemble those of the ground state conformation of reactants.

Introduction

Recently, we studied by *ab initio* MO calculations the conformation of diastereoisomers of alkyl 1-phenylethyl sulfoxides $C_6H_5CHCH_3SOR$ **1** and **2** (Fig. 1).[1] It has been shown that the geometry whereby the alkyl group is synclinal to C_6H_5 (Ph) and antiperiplanar to the benzylic methyl group (Ph/R torsional angle $\phi \cong 60°$: rotamer **a**) is the most stable in every case. The computational results agreed with earlier conclusions from X ray[2] and NMR experiments.[3] Rotamer **c** ($\phi \cong 180°$) has been shown the least stable except for isopropyl and *tert*-butyl analogs.



1: X = O, Y = lone pair
2: X = lone pair, Y = O
3: X = Y = lone pair
4: X = Y = O

Fig. 1 Possible conformations of alkyl 1-phenylethyl sulfoxides $C_6H_5CHCH_3SOR$ **1** and **2**, sulfides $C_6H_5CHCH_3SR$ **3**, and sulfones $C_6H_5CHCH_3SO_2R$ **4**.

To accommodate the above findings, we suggested that weak molecular forces, attractive as well as repulsive, control the rotameric abundance of these compounds. Thus, in rotamers **a** ($\phi \cong 60°$) and **b** ($\phi \cong 300°$), R is close to Ph and is capable of interacting favourably with the π-system. The attractive forces may include the CH/π interaction.[4–8] In rotamers **a** and **c** of **1** and **a** and **b** of **2**, the CH/O hydrogen bond[9–11] may work between the benzylic methyl (Me) and the oxygen atom in S–O. The unfavourable interactions, which may destabilize rotamer **c**, are of steric (R *vs.* Me) and electrostatic (O *vs.* Ph) origin.

Previously, Nishihata and Nishio reported on the stereochemistry of an oxidation of aralkyl sulfides to give sulfoxides.[12] On treatment with peroxyacetic acid, sulfides $C_6H_5CHCH_3SR$ **3** produced diastereoisomeric sulfoxides **1** and **2** in differing yields (Fig. 2). The product ratio **1**/**2** was 3.1, 3.2, 3.6 and 49, respectively, for R = CH_3, C_2H_5, *i*-C_3H_7 and *t*-C_4H_9. They interpreted the result by assuming that the geometry of the transition-state is reactant like and the reagent approaches from the less hindered side of the most prevailed conformer.

Hirota and coworkers estimated the stereochemical outcome of the above reaction[13] on the basis of the conformational energy of sulfides **3** calculated by the MM2 method.[14] In Fig. 3(a), the relative ease of the reagent attack on **3** is defined as *x* and *y*, respectively, from the lone pairs flanked by H and Me, and Me and Ph. They assumed, on steric grounds, that the reagent prefers approaching from the H side and that the attack does not occur from the side of the lone pairs flanked by Me and Ph ($x \gg y = 0$). A fair agreement was

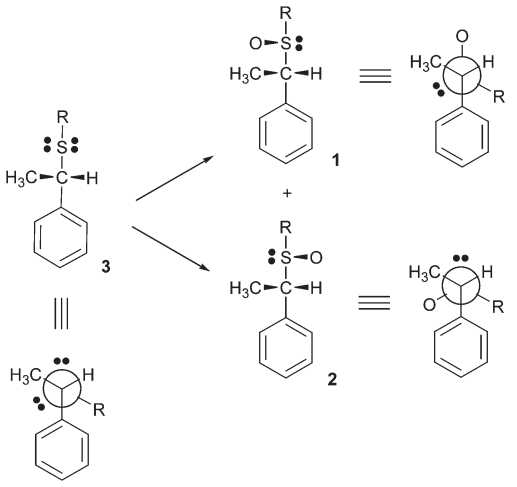


Fig. 2 Oxidation of alkyl 1-phenylethyl sulfides **3** to diastereoisomeric sulfoxides **1** and **2**.

obtained with the experimental data by this procedure: 3.1, 3.4, 4.3 and 18, respectively, for R = CH_3, C_2H_5, *i*-C_3H_7 and *t*-C_4H_9.

Exact information about the rotameric abundance of **3** is indispensable in considering the stereochemical course of the oxidation of sulfides to sulfoxides. Since the conformational equilibrium of **1** and **2** determined by the MO method[1] differs significantly from the earlier MM2 result,[13] the conclusion by Hirota *et al.* may not be valid. We therefore examined, by *ab initio* MO calculations, the conformational energy of 1-phenylethyl sulfides $C_6H_5CHCH_3SR$ **3** (Fig. 1).[15] The conformation of related sulfones $C_6H_5CHCH_3SO_2R$ **4** were also examined for comparison. The oxygen atom, which may be involved in the CH/O hydrogen bond and the unfavourable O/Ph interaction, is absent in **3**. Therefore, the net effect of the CH/π hydrogen bond may be estimated by comparing the rotameric abundance of **3** with that of **4**.

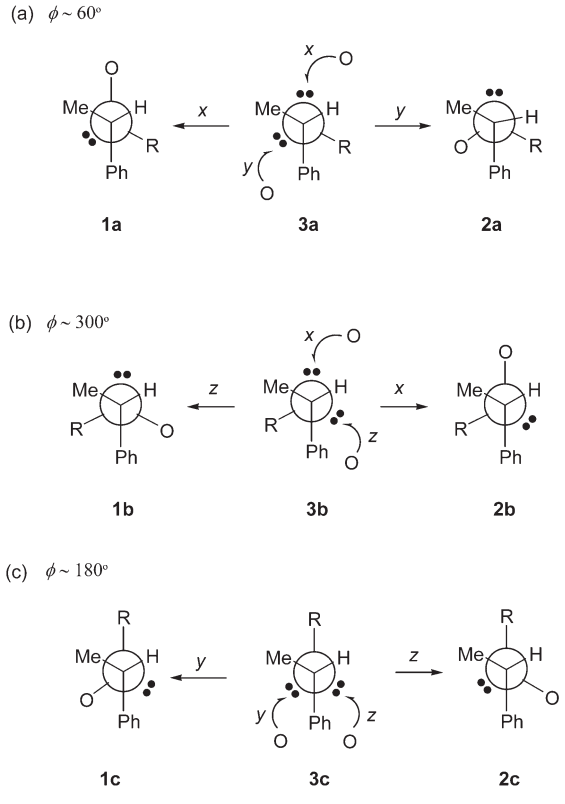


Fig. 3 Possible mechanism of the oxidation of alkyl 1-phenylethyl sulfides **3** to diastereoisomeric sulfoxides **1** and **2**.

Method

The Gaussian 98 program[16] was used. Electron correlation energies were calculated by applying the second order Møller-Plesset (MP2) perturbation theory. Geometry of the molecules was optimized at the MP2/6-31G(d) level of approximation. Using these geometries, single point calculations were performed at the MP2/6-311G(d,p) level to estimate the energies of the conformers. To confirm the validity of the MP2 method, single point calculations at the MP4/6-311G(d,p) level were carried out for the methyl analog of **3**. Vibrational frequencies were calculated using the analytical second derivatives at the same level of the geometry optimization for each conformer and were scaled to 0.9434.[17] Using these results, the thermal energy corrections were added to the total energy at 298.15 K and 1 atmosphere of pressure.

Results and discussion

Conformation of sulfides and sulfones

Fig. 4 gives the energy profile obtained for **3** (R = CH_3) at the MP2/6-31G(d) level. The energy potential shows that **3** is in three stable conformations around the rotation (ϕ) about C_6H_5–C–S–R: rotamers **a**, **b** and **c**.

Table 1 lists the relative Gibbs energy of the stable conformations of alkyl 1-phenylethyl sulfides **3** and sulfones **4** (three rotamers for R = CH_3 and *t*-C_4H_9 and nine rotamers for R = C_2H_5 and *i*-C_3H_7). Data calculated for compounds with no alkyl group (R = H) are included for comparison. Results from the MP4/6-311G(d,p) level calculations are given for methyl analog of **3**. No appreciable difference has been found between the data from the different levels of approximation. We therefore think the results obtained by the MP2 method give a correct picture of the rotameric equilibrium of these compounds. For ethyl and isopropyl derivatives, three stable geometries are possible with respect to the rotation around the S–Cα(alkyl) bond; the number of stable rotamer increases to 9, accordingly. The number in the bracket indicates the number of atoms (5- or 6-membered) forming the intramolecular CH/C_{ipso} interaction.

Rotamer **a** has been found to be the most stable in every case. In this rotamer, R is synclinal to Ph and antiperiplanar to Me (ϕ 50 ~ 63° for **3**, 46 ~ 56° for **4**). Rotamer **b** (-synclinal: ϕ 305 ~ 322° for **3**, 307 ~ 319° for **4**) is slightly more stable than rotamer **c** (ϕ 169 ~ 178° for **3**, 167 ~ 174° for **4**) in methyl and ethyl derivatives. In isopropyl and *t*-butyl analogs of **3**, rotamer **c** is slightly more stable than **b**. The difference between the conformational energies of **b** and **c** is insignificant in **4**.

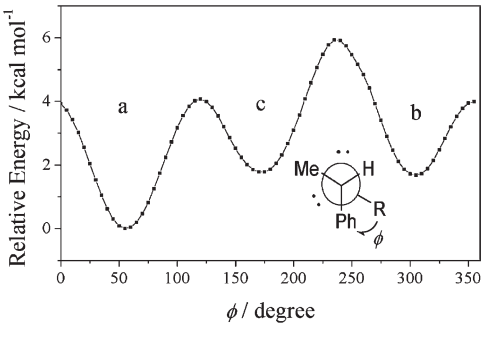


Fig. 4 Potential energy profile of alkyl 1-phenylethyl sulfides **3** (R = CH_3) around the rotation of the central C–S bond (ϕ).

Table 1 Relative Gibbs energy (in kcal mol^{-1}, as compared to the most stable one in each series) at 298.15 K and 1 atmosphere pressure of the stable conformations of (a) alkyl 1-phenylethyl sulfides **3** and (b) alkyl 1-phenylethyl sulfones **4** calculated by the *ab initio* method [MP2/6-311G(d,p)//MP2/6-31G(d)]. For sulfide **3** (R = CH_3) data obtained from the MP4/6-311G(d,p) level calculations are also given. Optimized torsion angles R–S–C–Ph (ϕ/°) are given in the parentheses. Results for unsubstituted derivatives (R = H) are also given for comparison. The number in the bracket indicates the number of atoms forming the intramolecular CH/π interaction. Three rotamers are present for R = H, CH_3 and *t*-C_4H_9, but nine rotamers are possible for the ethyl and isopropyl derivatives: 3 for rotation around the C–S bond $\phi \times 3$ for rotation around S–Cα(alkyl) bond Ψ

(a) Alkyl 1-phenylethyl sulfides $C_6H_5CHCH_3SR$ **3**

R	Rotamer **a**	Rotamer **b**	Rotamer **c**
H	0.00 (51)	0.23 (302)	0.22 (178)
CH_3	0.00 (55) [5]	1.54 (305) [5]	1.63 (173)
CH_3 (MP4)	0.00	1.39	1.40
C_2H_5	0.00 (50) [5]	1.84 (306) [5]	1.94 (172)
	0.26 (56) [5]	2.39 (308) [6]	1.98 (178)
	0.67 (58) [6]	2.99 (308) [5]	2.90 (174)
i-C_3H_7	0.00 (50) [5]	2.46 (307) [6]	2.08 (178)
	0.79 (60) [6]	3.20 (322) [5]	3.07 (173)
	2.06 (61) [6]	6.17 (312) [6]	4.62 (170)
t-C_4H_9	0.00 (63) [6]	4.26 (310) [6]	2.73 (169)

(b) Alkyl 1-phenylethyl sulfones $C_6H_5CHCH_3SO_2R$ **4**

R	Rotamer **a**	Rotamer **b**	Rotamer **c**
H	0.00 (42)	0.35 (307)	1.12 (172)
CH_3	0.00 (49) [5]	0.92 (307) [5]	1.97 (169)
C_2H_5	0.00 (47) [5]	1.23 (308) [5]	1.88 (172)
	0.23 (49) [5]	1.69 (309) [6]	2.18 (167)
	0.49 (52) [6]	2.48 (318) [5]	3.44 (172)
i-C_3H_7	0.00 (47) [5]	1.99 (307) [6]	1.96 (174)
	0.78 (54) [6]	2.68 (319) [5]	3.98 (172)
	1.41 (54) [6]	4.34 (312) [6]	4.16 (169)
t-C_4H_9	0.00 (56) [6]	3.06 (311) [6]	2.97 (167)

Fig. 5 gives stereo views of the stable rotamers **a**, **b** and **c** of **3** (R = CH_3).

In sulfoxides, formation of an intramolecular 1,5 CH/O hydrogen bond[18] is possible between Me and the S–O oxygen atom. This may enhance the stability of rotamers **1a** and **2a** (Fig. 3) since in these geometries Me and O are close to each other. Rotamer **a** of sulfones **4** may also be stabilized by the CH_3/O hydrogen bond since both the oxygen atoms are close to Me (see Fig. 1). It is noteworthy that rotamer **a** also is the most stable in **3**, despite the absence of the favourable CH_3/O interaction. This, along with earlier computational results of related benzylic compounds,[19] suggests that the CH/π hydrogen bond plays an important role in determining the conformational equilibrium of these aralkyl compounds.[20] Interatomic CH/π distances between the relevant CH and C_{ipso} in **3** are listed in Table 2. Short CH/π distances recorded in rotamers **a** and **b** are compatible with the suggestion that CH/π interaction is effective in stabilizing these conformations.[21]

Stereochemical mechanism of the oxidation of alkyl 1-phenylethyl sulfides to sulfoxides

We re-calculated the ratio of the oxidation products of sulfides **3** to diastereoisomeric sulfoxides **1** and **2**, on the basis of the present energetic data. In Table 3 are given the relative abundance of rotamers **a**, **b**, and **c** estimated for **3** according to the Boltzmann distribution law. Approach of the reagent to the

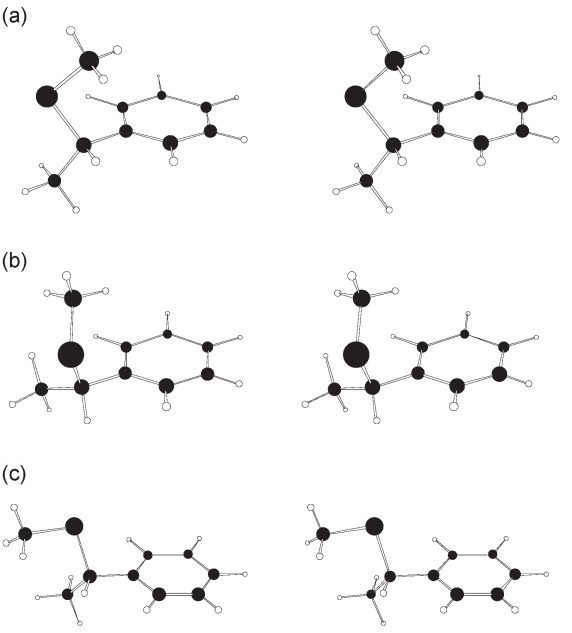


Fig. 5 Stereo views of the three stable rotamers (**a**, **b**, **c**) of methyl 1-phenylethyl sulfide $C_6H_5CHCH_3SCH_3$ **3**. (a) Rotamer **a** of **3**. (b) Rotamer **b** of **3**. (c) Rotamer **c** of **3**.

Table 2 Interatomic CH···π(Ph) distances (Å) of the stable conformations of (A) alkyl 1-phenylethyl sulfides $C_6H_5CHCH_3SR$ **3** and (B) alkyl 1-phenylethyl sulfones $C_6H_5CHCH_3SO_2R$ **4**, calculated by the *ab initio* method [MP2/6-311G(d,p)//MP2/6-31G(d)]. Numbers in brackets indicate the number of atoms forming the intramolecular CH/π hydrogen bond

(A) $C_6H_5CHCH_3SR$ **3**	CH/π distance/Å	ϕ/°
CH_3	2.732 [5]	55 (**a**)
	2.738 [5]	305 (**b**)
C_2H_5	2.682 [5]	50 (**a**)
	2.705 [5]	58
	2.699 [6]	56
	2.722 [5]	308 (**b**)
	2.706 [5]	306
	2.613 [6]	308
i-C_3H_7	2.658 [5]	50 (**a**)
	2.683 [6]	60
	2.649 [6]	61
	2.703 [6]	307 (**b**)
	2.556 [5]	322
	2.625 [6]	312
t-C_4H_9	2.599 [6]	63 (**a**)
	2.576 [6]	310 (**b**)
(B) $C_6H_5CHCH_3SO_2R$ **4**		
CH_3	2.784 [5]	49 (**a**)
	2.802 [5]	307 (**b**)
C_2H_5	2.753 [5]	47 (**a**)
	2.680 [5]	52
	2.745 [6]	49
	2.696 [5]	309 (**b**)
	2.760 [5]	308
	2.700 [6]	318
i-C_3H_7	2.726 [5]	47 (**a**)
	2.602 [6]	54
	2.674 [6]	54
	2.626 [6]	307 (**b**)
	2.681 [5]	319
	2.680 [6]	312
t-C_4H_9	2.585 [6]	56 (**a**)
	2.591 [6]	311 (**b**)

Table 3 Relative abundance of rotamers **a**, **b**, and **c** of alkyl 1-phenylethyl sulfides **3** and the ratio of the oxidation products **1** and **2**

	Relative abundance (%)			Product ratio **1**/**2**		
					Calculated[a]	
R	**a**	**b**	**c**	Observed	Method 1	Method 2
CH_3	87.9	6.6	5.5	3.1	*3.0* (74.7[b]/25.3[c])	9.4 (90.4/9.6)
C_2H_5	92.4	3.2	4.4	3.2	*3.2* (76.4/23.6)	13.5 (93.1/6.9)
i-C_3H_7	95.1	2.3	2.6	3.6	*3.5* (77.8/22.3)	20.4 (95.3/4.7)
t-C_4H_9	99.0	0.1	0.9	49.0	3.9 (79.5/20.7)	*49.1* (98.1[d]/2.0[e])

[a] Simulated values which agreed with the experimental data are italicized. [b] $87.9 \times 0.8 + 6.6 \times 0.2 + 5.5 \times 0.5$ [c] $87.9 \times 0.2 + 6.6 \times 0.8 + 5.5 \times 0.5$ [d] $99.0 \times 0.99 + 0.1 \times 0.01 + 0.9 \times 0.5$ [e] $99.0 \times 0.01 + 0.1 \times 0.99 + 0.9 \times 0.5$

sulfur lone pairs is, as usual, expected to take place more easily from the less hindered side of the reactant sulfides (Fig. 3). Thus, rotamer **3a** will give **1** as the predominant product ($x > y$). Attack of the reagent to rotamer **3c**, on the contrary, will result in the predominant formation of **2** ($z > y$). Rotamer **3b** will give the diastereoisomers in a comparable yield ($x = z$). If we assume that $x = z = 4y$,[22,23] the proportion of the diastereomeric products is predicted as shown in Table 3 (method 1). The results agree with the experimental data for the lower alkyl analogs. For the *tert*-butyl analog, however, this method does not give results compatible with the experimental data. *A priori* assumption of a much greater ratio ($x = z = 99y$)[24] of the reagent attack, predicts the product ratio of 49 for the *tert*-butyl analog (method 2). This procedure, on the other hand, did not give results consistent with the experimental data for the lower alkyl analogs.

The reason remains unclear why the difference between these two cases (lower alkyls *vs.* *tert*-butyl) is exceptionally large. A rationalization, however, may be provided on the basis of the following consideration. If we assume that x is equal to z, the ratio x/y ($= z/y$) is calculated, by using the experimental product ratios, to be 4.7, 4.1, 4.6 and 105.4, respectively, for R = CH_3, C_2H_5, *i*-C_3H_7 and *tert*-C_4H_9 compounds. The results agree with the above *a priori* assumptions. To accommodate this, the torsional angle in the prevalent rotamer is much larger in *tert*-butyl **3** (ϕ 63°) than in the lower alkyl sulfides (50 ~ 55°).[25] Hence it is reasonable to envisage a differing ratio, for the approach of the reagent, in these sulfides. In this regard, it is pertinent to point out that orientation of the phenyl ring to the alkyl group is different in the above two cases. In alkyl sulfides other than *tert*-butyl-**3**, formation of a 5-membered CH/π bonding is possible, whereas in *tert*-butyl sulfide only a 6-membered CH/π interaction is viable. In rotamer **a** of *tert*-butyl-**3**, the phenyl group must rotate, to make an effective 6-membered CH/π bond. One of the two *ortho* CHs, consequently, orients itself toward one of the lone pairs on the sulfur atom. The torsion angle defined by C^2–C^1–C^7–S^8 in rotamer **a** (Fig. 6) is in fact found smaller in the *tert*-butyl sulfide (55.1°) than in the methyl derivative (57.5°). Approach of the reagent from this side of *tert*-butyl **3** will be much disturbed.

The above interpretation bears implications for stereochemistry of the nucleophilic addition to carbonyl compounds (Cram's open-chain model).[26] Thus, Felkin and coworkers studied the hydride reduction of chiral ketones to give diastereoisomeric alcohols in differing yields.[27] The proportion of the product secondary alcohols was reported to be 2.9, 3.2, 5.0 and 49, respectively, for $LiAlH_4$ reduction of CH_3, C_2H_5, *i*-C_3H_7 and *t*-C_4H_9 1-phenylethyl ketones. The similarity in the stereochemical outcome of this reaction with that of the oxidation of sulfides is noteworthy in view of the difference in nature of these two reactions (electrophilic *vs.* nucleophilic; oxidation *vs.* reduction; solvent polarity: acetic acid *vs.* ethyl ether, *etc.*). This suggests that the stereochemical course of these reactions includes a common mechanism; the ground state conformation of the compounds may be a key factor.

Conclusion

To summarize, *ab initio* MO calculations have demonstrated that rotamers with alkyl/phenyl synclinal geometry preponderate in the conformational equilibrium of aralkyl sulfides and sulfones. The CH/π hydrogen bond has been suggested to be a key factor in bringing stability to these conformations.

The above finding may provide a simple interpretation for the stereoselective oxidation of aralkyl sulfides. We suggest the present result has implications for the mechanism of nucleophilic additions to chiral carbonyl compounds to give diastereoisomeric products in differing yields. The above suggestion is open to criticism and must await examination, experimental as well as theoretical. The origin of the diastereofacial selectivity may involve many factors such as electrostatic,[28] steric,[29] inductive,[30] conformational[31] or electronic (orbital interaction)[32] effects. At all events, re-consideration of the mechanism of 1,2-asymmetric induction reactions[33] is necessary in the light of more recent theory and more exact structural data.

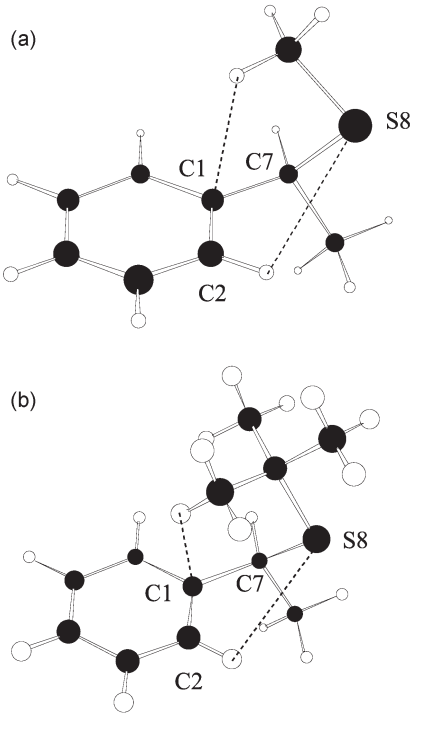


Fig. 6 Rotamer **a** of (a) methyl 1-phenylethyl sulfide and (b) *tert*-butyl 1-phenylethyl sulfide.

Acknowledgements

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