A General Preference for *gauche* Alkyl–Phenyl Interactions. The Use of Lanthanide Shift Reagents in determining the Preferred Conformations of Some Alkyl 1-Phenylethyl Sulphoxides

By **Yoshio Kodama, Shoji Zushi, Ken Nishihata,** and **Motohiro Nishio,*** Central Research Laboratories, Meiji Seika Kaisha Ltd., Morooka, Kohoku, Yokohama 222, Japan
Jun Uzawa, The Institute of Physical and Chemical Research, Wako 351, Japan

The conformations of alkyl *threo*- and *erythro*-1-phenylethyl sulphoxides have been studied by means of n.m.r. spectroscopy, largely by the computer simulation of the lanthanide-induced shifts. It has been demonstrated that, in the most populated conformation, the achiral alkyl group is oriented *gauche* to the phenyl and *anti* to the methyl group, irrespective of the nature of the alkyl group (Me, Et, Pr^i, or Bu^t) and irrespective of the configuration of the sulphoxide. A considerable contribution from a second stable rotamer is suggested for the lower alkyl homologues (Me, Et, or Pr^i), whereby the alkyl group is flanked by the phenyl and methyl groups.

EARLIER work from these laboratories have shown that the conformations of 1-phenylethyl t-butyl sulphide (1), *threo*- † (2) and *erythro*-1-phenylethyl t-butyl sulphoxide (3), and of 1-phenylethyl t-butyl sulphone (4) are like those illustrated in Figure 1: the t-butyl group in these compounds lies *gauche* to the phenyl group and *anti* to the methyl group. This conclusion has been drawn from *X*-ray,[1,2] n.m.r.,[2,3] o.r.d.–c.d.,[2] and dipole-moment studies [4] of the relevant molecules and from consideration of the stereoselectivities in certain reactions.[5,6] It follows, therefore, that this situation (*gauche* Bu^t–Ph conformation) holds not only in the crystal, but also in solution. The conformations of (3*R*,4*S*/3*S*,4*R*)- (6) and (3*S*,4*S*/3*R*,4*R*)-2,2-dimethyl-4-phenylpentan-3-ol (7) were also studied,[7] and the t-butyl group in these compounds has been shown to orient itself close to the phenyl group in the preferred conformation (Figure 1). Moreover, there is evidence that, in the corresponding

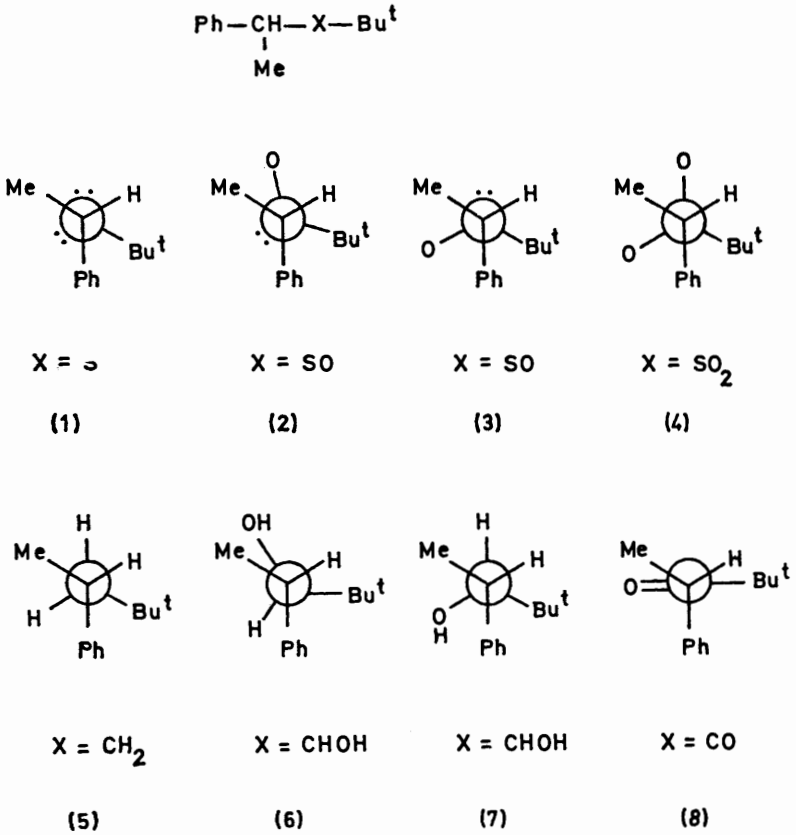


FIGURE 1

† In order to avoid confusion, we employ here the *threo–erythro* notation for describing configurations. The sequence-rule symbols do not necessarily relate to the stereochemically corresponding structures. Thus, Bu-*th* (see Figure 2) and Me-*th* (and Et-*th* and Pr-*th*) are configurationally related, but have different sequence-rule symbols: (α*R*,*sS*/α*S*,*sR*) for (2; R = Bu^t) but (α*R*,*sR*/α*S*,*sS*) for the lower alkyl homologues.

ketone (8) [8,9] as well as in the hydrocarbon (5),*[,9] the *gauche* t-butyl–phenyl conformation is energetically favoured over the *anti*-conformation. In an attempt to explore the generality of the phenomenon (favoured *gauche* alkyl–phenyl interaction) we have now studied

FIGURE 2

the conformations of the lower alkyl homologues of the sulphoxide diastereoisomers where the t-butyl group in (2) and (3) is replaced by the methyl, ethyl, or isopropyl group (Figure 2).†

RESULTS

Tables 1 and 2 summarize the ^1H and ^{13}C n.m.r. chemical shifts, respectively, for the diastereoisomeric sulphoxides. For comparison, the data recorded for the t-butyl derivatives (2) and (3) and for the structurally related sulphides and sulphones are also included. Table 3 lists the lanthanide induced shifts (LIS) for the proton resonances of the sulphoxide pairs.

The relative LIS for the benzylic proton (H_a) in Table 3 is always much greater in the *threo*-sulphoxides than in the respective *erythro*-isomers. The reverse is true for the LIS of the *ortho*-hydrogens (H_o) in the phenyl ring. This leads to the expectation that the preferred conformation of a series of sulphoxides with the same configuration is similar in each case. In order to ascertain this and to establish more exactly the conformations of these sulphoxides, we carried out computer simulation of the LIS of these compounds.

The procedure of the computer simulation was reported previously.[3,7] We adopted the approximations usually made in the LIS-simulation method: [10] (1) the use of the McConnell–Robertson equation (1) for an axially symmetric dipolar field (neglect of the non-axial term) where r_i is the

$$\Delta\nu_i = K(3\cos^2\chi_i - 1)r_i^{-3} \quad (1)$$

length of a vector joining the paramagnetic centre and the ith proton and χ_i is the angle between this vector and the principal magnetic axis; (2) the conformation of the substrate is described by a single set of co-ordinates; and (3) for the protons of the methyl, ethyl, isopropyl, t-butyl, and aromatic groups, the contribution of the individual protons in a number of conformers was calculated and averaged. After several trials, the lanthanide (Ln)-O-S angle was fixed at 120°. The reliability function as described in equation (2) was used to assess the agreement between the calculated and the observed LIS.‡

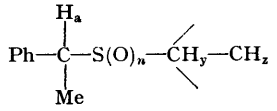
$$AF(\%) = 100\left(\sum_i|LIS_{obs.,i} - LIS_{calc.,i}|\right)/\sum LIS_{obs.,i} \quad (2)$$

The structural parameters were collected from our X-ray data on *erythro*-1-(*p*-bromophenyl)ethyl t-butyl sulphoxide (10),[3] or assumed to have the usual values when necessary.

A comment is required on the use of the lanthanide distribution parameter A. At an earlier stage of this study, computations were carried out on the basis of the assumption that the lanthanide shift reagent (LSR) rotates freely around the S–O bond. This procedure gave rather good results for *threo*-1-(*p*-bromophenyl)ethyl t-butyl sulphoxide (9), where the simulated value (as well as the X-ray

TABLE 1

Proton chemical shifts of alkyl 1-phenylethyl sulphides, sulphoxides, and sulphones



	Ph	H_a	H_y	H_z	Me
Sulphides PhCH(CH$_3$)SR					
R = Me	7.15	3.70	1.70		1.47
R = Et	7.18	3.87	2.15	1.10	1.48
R = Pr^i	7.19	3.90	2.68	1.03, 1.17	1.45
R = Bu^t	7.20	3.95		1.17	1.47
Sulphoxides (*threo*) PhCH(CH$_3$)SOR					
R = Me	7.24	3.64	2.18		1.67
R = Et	7.27	3.67	2.29	1.21	1.68
R = Pr^i	7.23	3.66	2.32	1.12, 1.17	1.63
R = Bu^t	7.24	3.75		1.07	1.55
Sulphoxides (*erythro*) PhCH(CH$_3$)SOR					
R = Me	7.27	3.66	1.98		1.65
R = Et	7.29	3.65	2.32	1.16	1.67
R = Pr^i					
R = Bu^t	7.26	3.64		0.97	1.71
Sulphones PhCH(CH$_3$)SO$_2$R					
R = Me	7.44	4.21	2.62		1.78
R = Et	7.38	4.13	2.61	1.20	1.74
R = Pr^i	7.37	4.18	2.69	1.17, 1.20	1.69
R = Bu^t	7.40	4.38		1.22	1.78

* The evidence for this has been provided by molecular mechanics calculations by Professor M. Hirota.

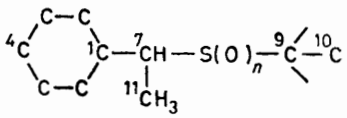
† Racemic compounds were used, but only one enantiomer is illustrated.

‡ The data were normalized to the largest LIS value in the computational process.

evidence [1]) demonstrated that the S–O oxygen group (the site of co-ordination) lies *anti* to (and therefore remote from) the phenyl group.[3] Good agreement was no longer available by the simple procedure, however, for the *erythro*-sulphoxide (10). For this compound, the *X*-ray study demonstrated that the sulphoxide oxygen lies close to the phenyl ring [2] (see Figure 3). In this conformation it is not

TABLE 2

C-13 Chemical shifts of alkyl 1-phenylethyl sulphides, sulphoxides, and sulphones



	C(1)	C(4)	C(7)	C(9)	C(10)	C(11)
(a) Sulphides PhCH(CH$_3$)SR						
R = Me	143.3	126.7	45.6	14.5		22.0
R = Et	143.8	126.6	45.6	25.1	14.4	22.5
R = Pr^i	144.2	126.6	43.0	34.0	23.0, 23.5	23.0
R = Bu^t	146.1	126.3	42.3	43.6	31.3	25.3
(b) Sulphones PhCH(CH$_3$)SO$_2$R						
R = Me	134.1	128.8	64.5	37.7		13.6 (−8.4) [a]
R = Et	134.1	128.6	62.4	44.2	6.0	13.6 (−8.9)
R = Pr^i	134.5	128.5	59.8	49.6	14.1, 16.2	14.1 (−8.9)
R = Bu^t	136.1	128.5	59.7	61.5	24.2	16.4 (−8.9)
(c) Sulphoxides [c] (*threo*)						
	C(1)	C(4)	C(7)	C(9)	C(10)	C(11)
R = Me	136.2	128.0	64.7	36.0		15.6 (+2.6) [b]
R = Et	136.5	128.0	62.1	42.7	6.7	16.1 (+2.0)
R = Pr^i	137.3	127.9	59.2	45.9	12.4, 18.1	16.4
R = Bu^t	140.0	127.8	56.9	55.1	23.7	17.8 (−1.8)
(d) Sulphoxides (*erythro*)						
R = Me	134.6	128.4	60.4	33.9		13.0
R = Et	135.0	128.3	58.9	41.9	7.4	14.1
R = Pr^i						
R = Bu^t	137.3	127.9	54.8	55.1	23.6	19.6

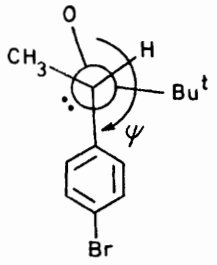
[a] δ(SO$_2$) − δ(S). [b] δ(*threo*) − δ(*erythro*). [c] Data for the t-butyl derivatives are from Table 3 of ref. 7.

reasonable to assume an equally populated lanthanide distribution around the S–O bond axis. A modified procedure was therefore sought for describing a localized distribution of the LSR. Thus we adopted a Gaussian weight factor (w) for the distribution of the rotamers of the LSR–substrate complex as in equation (3).[11] In equation (3), A is the

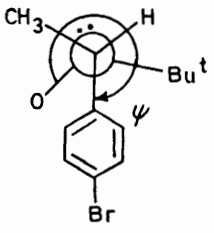
$$w(\theta) = \frac{A}{\sqrt{\pi}} \exp[-A^2(\theta - \theta_0)^2] \qquad (3)$$

distribution coefficient and θ is the torsional angle for the rotation of the LSR around the S–O bond. In this program (PSCONT) θ_0 is set so that the position of the LSR to be always furthest from the centre of the phenyl group. The free rotation of the LSR–substrate complex corresponds to $A = 0$, whereas a higher value of A corresponds to a more localized distribution of the LSR. The Ln–O distance R and the O–Ph dihedral angle ψ were then varied incrementally at a given distribution index in order to search for a reasonable fit with the experimental LIS.

Figure 4 illustrates plots of the AF (agreement factor) against the O–Ph torsional angle ψ for *threo*-1-phenylethyl methyl sulphoxide (Me-*th*); good agreement was obtained at ψ *ca.* 180°. The results are not sensitive to changes in A. However, this is not the case for the *erythro*-isomer (Me-*er*).



(9)



(10)

ψ (O - Ph dihedral angle)

(9)	(10)
ca. 192° (*X*-ray)	*ca.* 310° (*X*-ray)
ca. 190° (n.m.r.)	*ca.* 300° (n.m.r.)

FIGURE 3 Conformations of *threo*- (9) and *erythro*-1-(*p*-bromophenyl)ethyl t-butyl sulphoxide (10) from *X*-ray and n.m.r. data

An acceptable fit was found for ψ 300°, but only when a higher distribution index was employed.

Essentially the same trend is also observed for the AF–ψ profiles of sulphoxides containing the other alkyl groups. Thus, for the *threo*-isomers the shape of the curve is not significantly affected by the change in A. For the *erythro*-isomers, on the other hand, the shape of the curve is sensitive to the value of the distribution index; an acceptable AF has been obtained only at higher values of A. The results are summarized in Figures 5 and 6.

TABLE 3

Lanthanide shift reagent induced shifts [a] for *threo*- and *erythro*-alkyl 1-phenylethyl sulphoxides PhCH(CH$_3$)SOR

	H$_o$	H$_m$	H$_a$	H$_y$	H$_z$	Me
threo-Isomers						
R = Me (Me-*th*)	0.49	0.19	1.20	1.00		0.81
R = Et (Et-*th*)	0.51	0.23	1.36	1.00	0.94	1.02
R = Pr^i (Pr-*th*)	0.95	0.39	2.03	1.00	1.06, 1.24	1.69
R = Bu^t (Bu-*th*)	0.47	0.19	1.50		1.00	1.57
erythro-Isomers						
R = Me (Me-*er*)	0.69	0.30	0.69	1.00		0.87
R = Et (Et-*er*)	0.73	0.15	0.60	1.00 [b]	0.70	0.91
R = Pr^i (Pr-*er*)						
R = Bu^t (Bu-*er*)	1.15	0.19	0.84		1.00	1.14

[a] Relative chemical shifts induced by the addition of Eu(fod)$_3$ in CCl$_4$ solution. These data are normalized to the value of H$_y$ (or H$_z$, LIS$_{rel}$ = 1.00). [b] Average for diastereotopic protons, 1.31 for one proton, 0.69 for the other.

The agreement is not necessarily good for the *threo* sulphoxides with an ethyl or isopropyl group.* We

* The agreement is fair for Et-*er*. We have, at present, no explanation for this discrepancy.

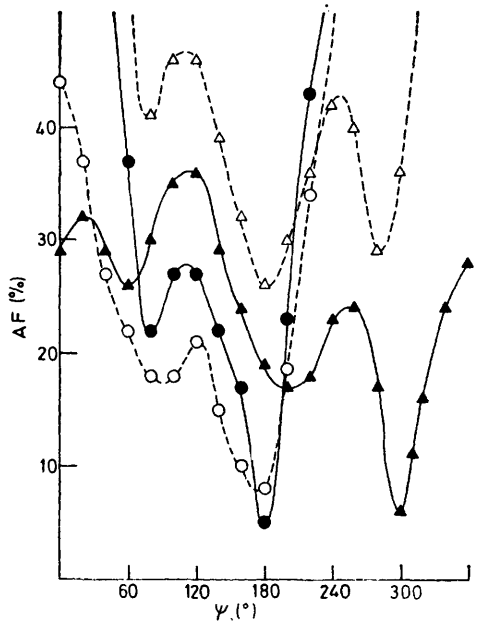


FIGURE 4 Plots of AF *versus* the O–Ph dihedral angle (ψ) for Me-*th* (●, *A* 0.4; ○, *A* 0.8) (*R* 0.34 nm) and Me-*er* (*R* 0.40 nm) (△, *A* 0.4; ▲, *A* 0.8)

attribute this to the lack of symmetry of these groups. In these calculations, the contributions of all possible rotamers (with respect to rotation around the S–alkyl bond) have been estimated and averaged. Obviously, this is a good approximation for groups with C_3 symmetry (Me or Bu^t), but not for compounds with an ethyl or isopropyl group. In fact, neglect of the H_y and/or H_z LIS data significantly improved the agreements and did not displace the position of the torsional angle ψ at the best fit.

Compared with the AF–ψ profiles, the AF–*R* profiles are rather flat. However, we found that there is a tendency for the better fit to be recorded at a longer Ln–O distance for the *erythro*-isomers than for the *threo*-sulphoxides. This is reasonable, since, in the *erythro*-compounds, the S–O oxygen is flanked by the phenyl and methyl groups. The Ln–O distance *R* in the complex is expected, for steric reasons, to shift toward larger values for *erythro*- than for the *threo*-sulphoxides.

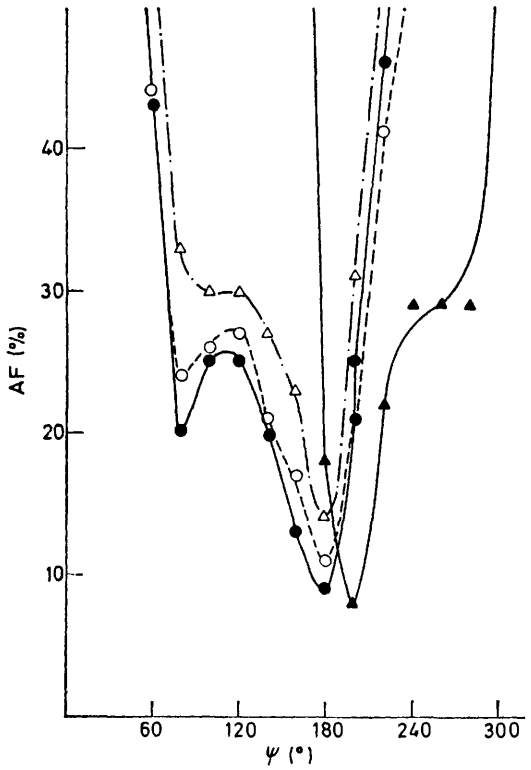


FIGURE 5 Plots of AF *versus* ψ for sulphoxides with the *threo*-configuration. *A* and *R* are kept constant at 0.4 and 0.36 nm, respectively. ●, Me-*th*; ○, Et-*th*; △, Pr-*th*; ▲, Bu-*th*

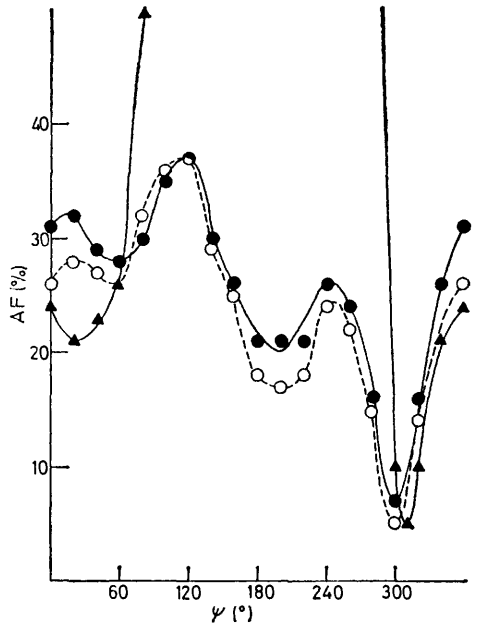


FIGURE 6 Plots of AF *versus* ψ for sulphoxides with the *erythro* configuration. *A* and *R* are kept constant at 0.8 and 0.38 nm, respectively. ●, Me-*er*; ○, Et-*er*; ▲, Bu-*er*

DISCUSSION

The possibility of conformational change upon formation of the complex is a serious problem. This, however, can be safely assumed to be unimportant in the present case. Thus, in the case of the t-butyl sulphoxides (9) and (10), we have already found that the conformation in the crystal [1,2] is maintained in solution.[2-4] Perturbation of the conformational equilibrium by coordination with an LSR has been shown to be unimportant in this case. Further support for this assumption is provided from our studies on the structurally related alcohols (6), (7),[7] and their lower alkyl homologues,[12] where we found that little perturbation of the conformational equilibrium occurs upon complex formation. In these alcohols the conformational change can be monitored with confidence by inspection of the vicinal coupling constant of the relevant protons. In all cases studied so far, the coupling constant has been found to be insensitive to the addition of the lanthanide species.

The model used in the simulation procedure assumes

that the conformation of the substrate can be described by a single set of co-ordinates (*i.e.* that there is an unique solution for ψ). This is a good approximation if there is only one highly preferred rotamer. This is probably the case when there is a t-butyl group in the molecule. In fact, the AF–ψ profiles are sharp enough almost to allow

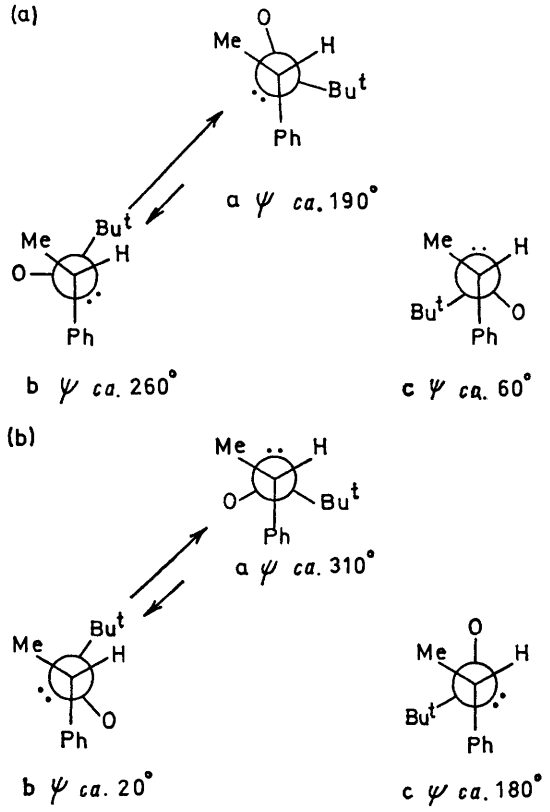


FIGURE 7 Conformational equilibria for (a) Bu-*th* and (b) Bu-*er*

a single conformation. The result is consistent with the presence of a highly populated rotamer with a t-butyl–phenyl dihedral angle of *ca.* 70° for both diastereoisomers. This is illustrated in Figure 7.

This conclusion is supported by the ^{13}C n.m.r. data. Compared with the respective sulphides, the methyl-carbon chemical shifts are significantly shifted in sulphoxides and sulphones to higher magnetic field. This is understood in terms of the presence of a γ-effect [13] in the sulphoxides and sulphones. In view of the differing geometrical disposition of the S–O oxygen atom with respect to the α methyl group, the *γ-gauche* effect * might well be expected to be more pronounced for the *threo*-sulphoxide (O–CH_3 dihedral angle *ca.* 50°) than for the *erythro* isomer (*ca.* 70°).† The chemical shift for the methyl carbon is 1.8 p.p.m. higher for Bu-*th* than for Bu-*er*; this is consistent with the above considerations.‡[7]

With regard to the most populated conformation, essentially the same conclusion is reached for the lower alkyl homologues. Thus, in the preferred rotamer, the sulphoxide oxygen has been suggested to be *anti* (ψ 180°) to the phenyl group in the *threo*-sulphoxides, but flanked by the methyl and phenyl groups (ψ 300°) in the *erythro*-isomers. The result implies that *the alkyl group in the preferred rotamer is always* gauche *to the phenyl and* anti *to the methyl group, irrespective of the nature of the alkyl group and irrespective of the configuration at the sulphur atom.* Compared with the t-butyl homologues, however, somewhat different AF–ψ profiles obtain in cases where we have an alkyl group other than a t-butyl group. In general, the curves are broader and have several minima. In the profile of Me-*er* (see Figure 6), for instance, a second minimum is seen at ψ 200° and a third one at ψ 60°, in addition to best fit position (AF 7% at ψ 300°). The AF values at these ψ values (21 and 28%) are too

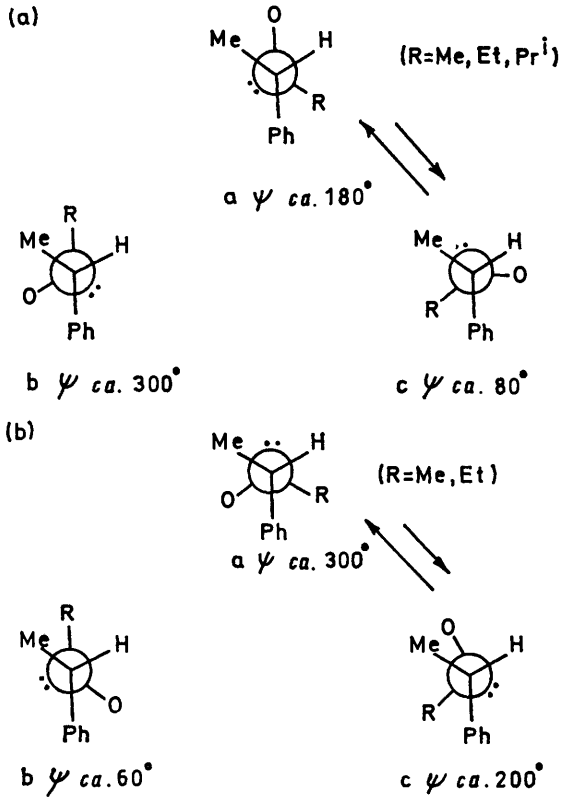


FIGURE 8 Conformational equilibria for the lower alkyl sulphoxides PhCHMeSOR: (a) *threo*-series; (*b*) *erythro*-series

large to be acceptable. It should be remembered that these values merely correspond to the reliability maxima and by no means represent the energy minima of the respective rotamers. We believe, however, that the

* For this we suggest an important contribution from a $CH_3 \cdots O$ hydrogen bond.[7,14]

† *X*-Ray studies show that the $O \cdots C(CH_3)$ interatomic distance is 0.30 and 0.32 nm, respectively, for (9) and (10) (Figure 3), in support of the above consideration. The short contacts suggest a contribution from the $CH_3 \cdots O$ hydrogen bond.[14a] (*cf.* D. J. Sutor, *J. Chem. Soc.*, 1963, 1105).

‡ The result is also rationalized by considering a partial contribution from rotamer b (see Figure 7; rotamer corresponds to an inflection at ψ 260° for Bu-*th* and the second minimum at ψ 20° for Bu-*er*). This is supported by a dipole-moment study of these sulphoxides.[4]

presence of local minima or inflections is not necessarily an artefact. It is likely that it reflects some physical basis as to the contribution of other rotamers. In this regard, it is noteworthy that, for the lower alkyl homologues, the second minimum in every case is at ψ *ca.* 80° for the *threo*-series and *ca.* 200° for the *erythro*-sulphoxides. Figure 8 illustrates the rotamers which correspond to these ψ values. Note that *in these conformations the alkyl group is flanked by the phenyl and methyl groups.*

We suggest that there is an appreciable contribution from rotamer c in Figure 8 for the lower alkyl sulphoxides. Support for this suggestion is provided from consideration of the γ-effect. Thus, quite in contrast to the observation for the t-butyl compounds, the n.m.r. peaks for the methyl carbon are at higher magnetic field for the *erythro*- compared with the *threo*-isomers; the difference in chemical shift [$\Delta = \delta$ (*threo*) $- \delta$ (*erythro*)] is 2.6 and 2.0 p.p.m., respectively, for the methyl and ethyl sulphoxides (Table 2). This can be understood if we take into account a contribution from rotamer c (in addition to rotamer a). In this conformation, the sulphoxide oxygen is *gauche* to the methyl group in the *erythro*-isomers, whereas in the *threo*-sulphoxides it is *anti* (see Figure 8). In the lower alkyl homologues, therefore, a more pronounced γ-effect is expected for the *erythro*-sulphoxides if an appreciable portion of rotamer c contributes to the conformational equilibria.

In view of this and other evidence,[6,7] we conclude that the interaction between an alkyl and a phenyl group (more generally, a π-system) is attractive. The nature of this attractive interaction is not yet clear. However, we believe that it probably originates from a kind of weak hydrogen bond, the donor being the π-electron system and the acceptor being the very weakly acidic hydrogens in the alkyl group.* The presence of a weak hydrogen bond has long been recognized in the case of the OH–π interaction.[15] Also, the benzene π-system has been known to interact with the acidic C–H hydrogen atom of chloroform, *etc.*[16] It would therefore be not unreasonable, by extrapolation, to expect the presence of an interaction between the hydrogens of simple alkyl groups with a π-system. In fact, the presence of a weak attractive force has been suggested by MO calculations (CNDO/2) of a benzene–methane model system; the stabilization energy is estimated to be *ca.* 3.5 kJ mol^{-1} in this case.[6,7] Support for this comes from *X*-ray evidence, where we found a short interatomic contact between a methyl carbon and a carbon atom in the phenyl group in (9) and (10).[6]

The stabilization energy is very small for a CH–π interaction. In spite of this, we suggest the possibility that interactions of this nature (CH_3–π as well as CH_3–*n* where *n* represents lone pair electrons) can play an important role in certain systems. In general, C–H groups are not present in an isolated manner, but are arranged normally in a certain chemical structure. It might well be that, in certain molecular environments, the total interaction energy becomes appreciable by accumulation of the effects of multiple CH–π (or CH–*n*) interactions. We suggest further that interactions of this type are entropically advantageous in that the probability of interaction increases upon arrangement of the C–H groups into certain symmetric structures such as methyl and isopropyl groups, *etc.*[7,14a] The effect would be most noticeable in the dynamic interactions of reacting species.† These include the selectivity in some reactions and the efficacy of molecular recognition.

The possible implications of this concept (CH–π interaction) in chemical [6b,7] as well as in certain biochemical systems [14a,17] have been commented upon briefly in our earlier papers and will form the subject of a future paper.

EXPERIMENTAL

Materials.—Compounds‡ were prepared according to procedures reported elsewhere.[2,5,18] Me-*th* and Et-*th* were contaminated with a small amount of their diastereoisomeric congeners. The influence on the n.m.r. data of small quantities of contaminants is considered to be negligible. This is supported by the consistency of the results on the conformational preferences (see text).

N.M.R. Measurements.—N.m.r. spectra were determined for 0.2 mol l^{-1} solutions in carbon tetrachloride on a JEOL MH-100 instrument (^{1}H) and for deuteriochloroform solutions of equal concentration on a JEOL FX-100 spectrometer (^{13}C). Chemical shifts are given in p.p.m. relative to tetramethylsilane as internal reference (δ 0) and are accurate to $\pm$0.01 p.p.m. for ^{1}H and $\pm$0.04 p.p.m. for ^{13}C data. LIS Values were obtained by incremental addition of $Eu(fod)_3$ to substrates dissolved in CCl_4 and subsequent determinations of the proton chemical shifts. A least-squares fit to the experimental points was used to obtain the LIS data. These values were found to be directly proportional to the LSR : substrate ratio up to a value of *ca.* 0.2 equiv. mol^{-1}.

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* This might also be regarded as hyperconjugation through space.

† A selectivity of *ca.* 100 : 1 can be brought about by a difference in the activation free energy ($\Delta\Delta G^{\ddagger}$) of only *ca.* 11 kJ mol^{-1} (at 25°), for a kinetically controlled competitive reaction.

‡ The sulphoxide corresponding to Pr-*er* was not prepared.

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