Tetrahedron Vol. 39, No. 19, pp. 3091 to 3099, 1983
Printed in Great Britain

0040-4020/83 \$3.00+.00

THEORETICAL DESCRIPTION OF THE PREFERENCE OF VICINAL ALKYL/PHENYL GAUCHE CONFORMATION BY MOLECULAR MECHANICS. AN ALTERNATIVE INTERPRETATION FOR THE CH · · · π ATTRACTIVE INTERACTION

MINORU HIROTA,* TOSHIYUKI SEKIYA, KAZUHISA ABE, HIROSHI TASHIRO and MAKOTO KARATSU
Department of Applied Chemistry, Faculty of Engineering, Yokohama National University, Hodogaya-ku, Yokohama 240, Japan

MOTOHIRO NISHIO
Central Research Laboratories, Meiji Seika Kaisha Ltd., Kohoku-ku, Yokohama 222, Japan

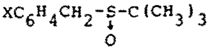
and

EIJI OSAWA
Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo 060, Japan.

(*Received in Japan* 27 *December* 1982)

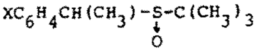
Abstract—Molecular mechanics calculations on alkyl benzyl carbinols, ketones, sulphides and sulphoxides were carried out as a function of the torsional angle about the benzyl C–O, C–S, or C–SO bond by use of the MM2 program. Theoretical consequences generally agree with the experimental results showing that the phenyl/alkyl gauche conformer is the most preferred for all 1-phenylethyl compounds and also for some of benzyl compounds investigated. Detailed examination on the energy terms revealed the contribution of attractive non-bond interaction between the alkyl and phenyl groups vicinally located in stabilizing the phenyl-alkyl gauche conformer. Thus the preference of CH · · · π conformation can be interpreted by the contribution of the dispersive force. Possible participation of other attractive forces is discussed briefly.

Recent investigations on the conformations of 1-aryl-2-t-butyl compounds revealed the preference of a conformation in which bulky t-butyl group is gauche (or syn-clinal) to the aryl group on the vicinal atom. This is especially true when the compound has a methyl (or other alkyl) group located geminal to the aryl group. Thus the 1-methyl-1-phenyl-2-t-butyl compounds PhCHMe-XCMe$_3$ generally take a conformation in which t-butyl group is gauche to the phenyl and anti (more exactly anti-periplanar) to the methyl group. For example, Iitaka *et al.*[1] determined the molecular structure of 1-(p-bromophenyl)ethyl t-butyl sulfoxide by X-ray crystallographic method and showed that the bulky t-butyl group orients itself anti to the methyl and gauche to the p-bromophenyl group. Conformations of related sulfoxides were determined by the present authors[2] by measurement of their dipole moments in benzene solutions. Results showed that the anti conformer is the most stable in benzylic sulfoxides **1a**, **1b**, and **1c** and that, in contrast, the conformation in which t-butyl group is gauche to the phenyl and anti to the methyl is preferred in 1-phenylethyl sulfoxides **2a**, **2b**, and **2c**. The same conclusion was also obtained from the stereochemistry of some reactions.[3] The dipole moments of t-butyl p-chlorobenzyl ketone and its α-methyl derivative again support the preference of the conformations similar to those of the corresponding sulfoxides.[4] In other words, the benzyl and the 1-phenylethyl ketones 3 and 4 take the phenyl/t-butyl anti conformation and the phenyl/t-butyl gauche and methyl/t-butyl anti conformation, respectively. Furthermore, Nishio *et al.* have shown the general occurrence of alkyl/phenyl gauche conformer from the detailed analysis on lanthanoid induced shifts of proton and ^{13}C NMR spectra of alcohols,[5–7] ketones,[8] and sulfoxides[9] of this series. In these reports, the benzylic alcohols PhCH$_2$CH(OH)R were also suspected to take the Ph/R gauche conformations most probably.[7] Evidences in favor of the preference of phenyl/alkyl gauche conformation even in benzylic sulfoxides were obtained by the kinetic and mechanistic considerations on their deuterium isotope exchange and methylation reactions.[10] After all, the preference of alkyl/phenyl gauche conformer is quite common among vicinal alkyl aryl compounds.



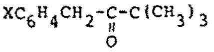
$XC_6H_4CH_2\text{-}\underset{\overset{\downarrow}{O}}{S}\text{-}C(CH_3)_3$

(1a) X = H
(1b) X = p-Br
(1c) X = p-NO$_2$



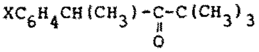
$XC_6H_4CH(CH_3)\text{-}\underset{\overset{\downarrow}{O}}{S}\text{-}C(CH_3)_3$

(2a) X = H
(2b) X = p-Br
(2c) X = p-NO$_2$



$XC_6H_4CH_2\text{-}\underset{\overset{\|}{O}}{C}\text{-}C(CH_3)_3$

(3a) X = H
(3b) X = p-Cl



$XC_6H_4CH(CH_3)\text{-}\underset{\overset{\|}{O}}{C}\text{-}C(CH_3)_3$

(4a) X = H
(4b) X = p-Cl

Based on the evidence from experiments, we assumed a weak attractive interaction between C–H group and π-electrons. At an early stage of investigation, the interaction was supposed to be similar to OH · · · π and other weak hydrogen bond in nature, just assumed in the case of complex formation between chloroform and aromatic hydrocarbons. In this point of view, one of the present authors (M. N.) has proposed "the CH · · · π interaction hypothesis"[11] and tried to interpret apparently unusual behavior of vicinal alkyl aryl compounds.

As another trial in order to estimate the most stable conformers of these and similar compounds and to interpret the reason for their stability, empirical molecular force field calculations[12] were carried out. Empirical force field calculations were first proposed by Westheimer.[13] Since then many versions for the calculation have been tried by many investigators. Those by Allinger,[14] by von Schleyer,[15] by Scheraga,[16] and by Bartell[17] are the typical examples. All these versions have been applied to the conformational researches on organic molecules either in general or in specialized fields. Among these methods of calculation, MM2/MMP2 program is one of the most versatile and widely applicable to organic molecules. Thus the MM2 program by Allinger *et al.*[14] was employed throughout the molecular force field calculations in this investigation.

The theoretical consequences from these calculations were compared with the experimental results and discussed in this paper.

RESULTS AND DISCUSSION

Prediction of the preferred conformation by molecular mechanics calculations

Steric energies of $PhCH_2XR$ and PhCHMeXR (where X is CH_2, CH(OH), C=O, S, or $S \rightarrow O$) were calculated as a function of torsional angle (w) around the benzyl carbon-X bond. In these calculations, all coordinates other than the torsional angle were optimized. Some of the results are illustrated in Fig. 1. Energies at the potential minima of the curve (in Fig. 1) were re-calculated without any restriction of the coordinates. Steric energy values for the stable conformers were thus obtained and are given together with the corresponding torsional angle realizing the stable conformers in Table 1. As seen from Fig. 1 and Table 1, three conformations corresponding to one Ph/R anti and two Ph/R gauche conformers were shown to be realized.

In the series of 1-phenyl-2-alkyl compounds PhCHMeXR, the most stable conformer has an alkyl group (R) gauche to the phenyl and anti to the methyl group without exception. It is remarkable that the estimated conformer generally agrees with the one deduced from experiment. In order to elucidate the reason why the gauche conformer (A) is the most stable in this series of compounds, intramolecular forces operating in each conformer were examined in detail. In molecular mechanics calculations, total steric energy of a molecule is calculated by summing stretching (E_s), bending (E_b), torsional (E_w), van der Waals (E_v), and other energy terms, as well as some of their cross terms. If each energy term, as well as displacement from optimal geometry, is examined with care, intramolecular forces which act to favor the Ph/R gauche conformer should be found out. In practice, the energy difference between the most stable Ph/R gauche conformer (A) and the second stable Ph/R anti conformer (B) is mainly determined by the difference in E_b, E_v, and E_w terms, the most important term among them being dependent on the structure of the compound. The bending term (E_b) of conformer (B) is usually higher than that of conformer (A) when the alkyl group (R) is bulky.

The E_b term of a molecule is expressed as the sum of the contributions from all bond angles. When the contribution from each bond angle was examined, the increase in E_b term of these compounds was shown to be due to the contributions by the deformation of C_R–$C_{carbonyl}$–C_{benzyl} and $C_{carbonyl}$–C_{benzyl}–C_{methyl} bond angles. For example, the bending energy term concerning these

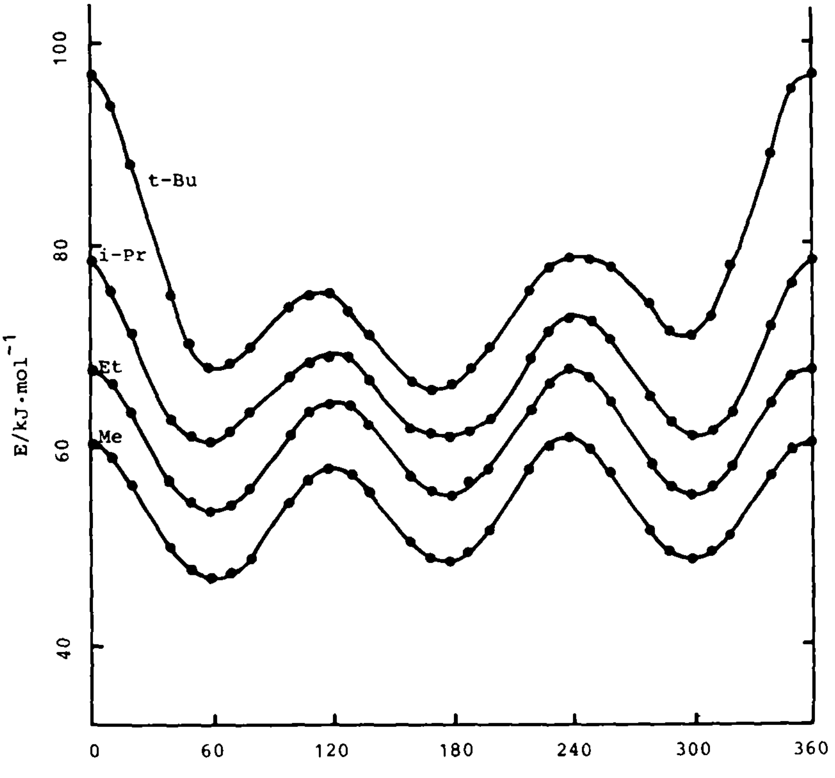
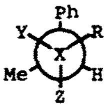
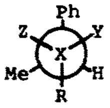
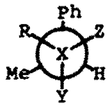


Fig. 1. Total steric energy (E) vs torsional angle (w) plots for $C_6H_5CH_2CHROH$, where R is methyl (Me), ethyl (Et), isopropyl (i-Pr), or t-butyl (t-Bu).

Table 1. Relative steric energies of the stable conformers in kJ mol^{-1}. Optimized torsional angle w(Ph/R) are given in parentheses

(a) $C_6H_5CH(CH_3)XR$

						
X	Y	Z	R	(A)	(B)	(C)
C	H	H	Me	0 (56)	2.68 (173)	6.15 (302)
			Et	0 (57)	2.85 (173)	6.28 (303)
			Pr^i	0 (53)	3.56 (178)	11.17 (306)
			Bu^t	0 (60)	8.33 (172)	15.27 (308)
C	OH	H	Me	0 (58)	0.50 (174)	4.31 (300)
			Et	0 (57)	0.96 (178)	3.22 (301)
			Pr^i	0 (54)	1.51 (180)	8.24 (303)
			Bu^t	0 (61)	3.01 (175)	14.02 (308)
C	H	OH	Me	0 (53)	5.94 (173)	6.44 (307)
			Et	0 (52)	5.86 (172)	6.65 (304)
			Pr^i	0 (48)	6.07 (175)	11.09 (303)
			Bu^t	0 (57)	8.12 (172)	13.85 (308)
C	=O*		Me	0 (56)	5.61 (178)	10.21 (314)
			Et	0 (58)	6.15 (178)	10.38 (314)
			Pr^i	0 (51)	6.86 (176)	11.63 (283)
			Bu^t	0 (79)	12.22 (178)	16.53 (309)
S	-	-	Me	0 (59)	3.93 (174)	4.39 (309)
			Et	0 (59)	4.31 (164)	4.56 (309)
			Pr^i	0 (59)	4.85 (180)	5.52 (306)
			Bu^t	0 (63)	8.03 (172)	10.17 (307)
S	-	O	Bu^t	0 (63)	10.54 (139)	14.43 (309)
S	O	-	Bu^t	0 (115)	13.14 (166)	20.25 (308)

(b) $C_6H_5CH_2XR$

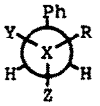
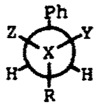
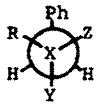
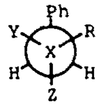
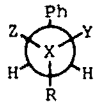
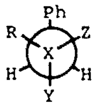
						
X	Y	Z	R	(D)	(F)	(G)
C	H	H	Me	0.29 (62)	0 (180)	0.29 (298)
			Et	0.29 (62)	0 (180)	0.29 (298)
			Pr^i	0.08 (62)	0 (180)	0.08 (298)
			Bu^t	3.31 (63)	0 (180)	3.31 (297)
C	H	OH	Me	0 (61)	1.72 (178)	2.01 (301)
			Et	0 (60)	1.63 (177)	1.84 (300)
			Pr^i	0 (60)	1.09 (179)	1.21 (299)
			Bu^t	1.38 (62)	0 (171)	4.64 (299)

Table 1 (*Contd*)

(b) $C_6H_5CH_2XR$

X	Y	Z	R	 (D)	 (F)	 (G)
C	=O*		Me	0.54 (58)	0 (180)	0.54 (302)
			Et	0.54 (60)	0 (180)	0.54 (300)
			Pr^i	0 (53)	0.59 (173,187)**	0 (307)
			Bu^t	0.75 (80)	0 (180)	0.75 (280)
S	-	O	Bu^t	0 (106)	1.34 (160)	3.56 (294)

* The C=O bond stretches toward the direction bisecting YXZ angle.

** One of the methyl groups in isopropyl moiety is eclipsed with carbonyl group in the stable conformer.

bond angles and the Ph/t-Bu and Me/t-Bu non-bond interaction energy terms of t-butyl 1-phenylethyl ketone (**4a**) were given in Table 2. Here, the local non-bond interaction terms were calculated as the sum of the E_v terms between the atom consisting the phenyl (or methyl) group and the atoms consisting the t-butyl group. Since the strain in one part of molecule is relaxed in the whole molecule, the energy difference in Table 2 can not be straightforwardly related by the energy difference between the two conformers. However, the comparison of the local energy terms is effective in the qualitative interpretation on the preference among the conformers. In short, the steric repulsion between the vicinal alkyl groups (α-methyl and R) is the most predominant factor to disfavor the Ph/R anti (hence, Me/R gauche) conformer (B) in comparison with the Ph/R gauche conformer (A). As a consequence of the steric crowdedness of this sort, a considerable increase in stretching energy and stretch-bend cross term were also observed in several cases.

Secondly the attractive van der Waals energy, or the dispersion energy is always larger in the alkyl(R)/phenyl gauche conformer than in the anti-conformer. The molecule seems to gain additional stabilization energy of at most 2 kJ/mol when it takes the Ph/R gauche conformer due to the contribution of the attractive E_v terms. As to t-butyl 1-phenylethyl ketone, for example, two methyl groups of the t-butyl moiety are estimated to be located just above the aromatic nucleus to have largest attractive van der Waals contact and, probably, to minimize the distortion of bond angles.

Conclusions from molecular mechanics calculations on the compounds of benzyl series $PhCH_2XR$ are considerably different from those on the compounds of 1-phenylethyl series. The most stable conformers in this series are dependent both on the bulkiness of alkyl

Table 2. Some E_b and E_v terms affecting the conformational preference of t-butyl 1-phenylethyl ketone

Conformer	(D) 79°		(F) 178°		Difference $E_F - E_D$*
Bending term	Bond angle	E_b*	Bond angle	E_b*	
$C_{Bz}-C_{CO}-C_{Bu}$	120.4°	0.852	122.3°	1.592	
$C_{Ph}-C_{Bz}-C_{CO}$	110.4°	0.000	109.2°	0.132	
$C_{Me}-C_{Bz}-C_{CO}$	112.6°	0.154	117.1°	1.471	
Total		1.006		3.195	2.19
Non-bond interaction	E_v*		E_v*		
$Ph\cdots Bu^t$	-3.35		-1.34		
$Me\cdots Bu^t$	-0.67		+1.05		
Total	-4.02		-0.29		3.73

*) $kJ\cdot mol^{-1}$.

substituent and on the nature of X moiety. Moreover, the energy difference between the gauche and anti conformers is extremely low in most cases. Therefore the both conformers are expected to coexist as an equilibrium mixture. The equilibrium might shift to either of the conformers very sensitively to the experimental conditions, such as polarity of solvent, complex formation, etc. Since the methyl group on α-carbon atom is absent in the compounds of benzyl series, no repulsive force between vicinal alkyl groups (Me/R repulsive interaction) can act to disfavor the anti conformer. Thus, the main factor in determining the most stable conformation is the attractive van der Waals interaction most predominantly operating between alkyl and phenyl groups. When the alkyl group on the X moiety is t-butyl, a measurable steric hindrance is present between alkyl and phenyl groups. In molecular mechanics calculations, this effect is reflected on the E_b terms. In other words, distortions of some bond angles (evaluated by E_b) contribute to disfavor t-butyl/phenyl gauche conformers.

Interpretation of several experimental facts by the preferred conformations from molecular mechanics calculations

The most probable conformations of these compounds ($PhCH_2XR$ and $PhCH(CH_3)XR$) were determined by measurement of the lanthanoid induced shifts (LIS) of their ^1H and ^{13}C NMR chemical shifts.[5–9,19] In these investigations, Ln–O distance was assumed to be 3.0 Å (=0.30 nm) and the agreement factors were calculated as a function of torsional angle (w) about C_{benzyl}–X bond. The results are shown in Fig. 2 for 1-alkyl-2-phenylethanols as an example.

The deepest trough of the curve corresponds to the most predominant conformer. On the other hand, the population of each conformation can easily be derived from steric energy obtained by molecular methanics calculation by use of Boltzmann's theorem relating energy and population. In order to compare the results with those from LIS (Fig. 2a). the inverse of the relative population ($\exp(\Delta E/RT)$) was plotted as a function of the same torsional angle (Fig. 2b). The two plots are very similar. The similarity of the two plots can be related straightforwardly with the close agreement of the theoretical consequence with the experimental results, since the agreement factor is not rigorously related with the population of the conformer. At least the most probable conformers were correctly predicted in all cases, however. The alkyl/phenyl gauche conformer is shown to be the most probable, except when alkyl is t-butyl. Analogously, the most probable conformers of threo- and erythro-1-alkyl-2-phenyl-1-propanols were predicted correctly in most cases by molecular mechanics calculations (Table 3). In this table, the most probable conformer is denoted by 1 and the least probable by 3. In some cases (when R is CH_3, C_2H_5, and $CH(CH_3)_2$ of the threo alcohols and R is CH_3 and C_2H_5 of the erythro alcohols), the conformer in which the alkyl group is flanked by methyl and phenyl groups is predicted to be more stable than the Ph/R anti conformer from LIS

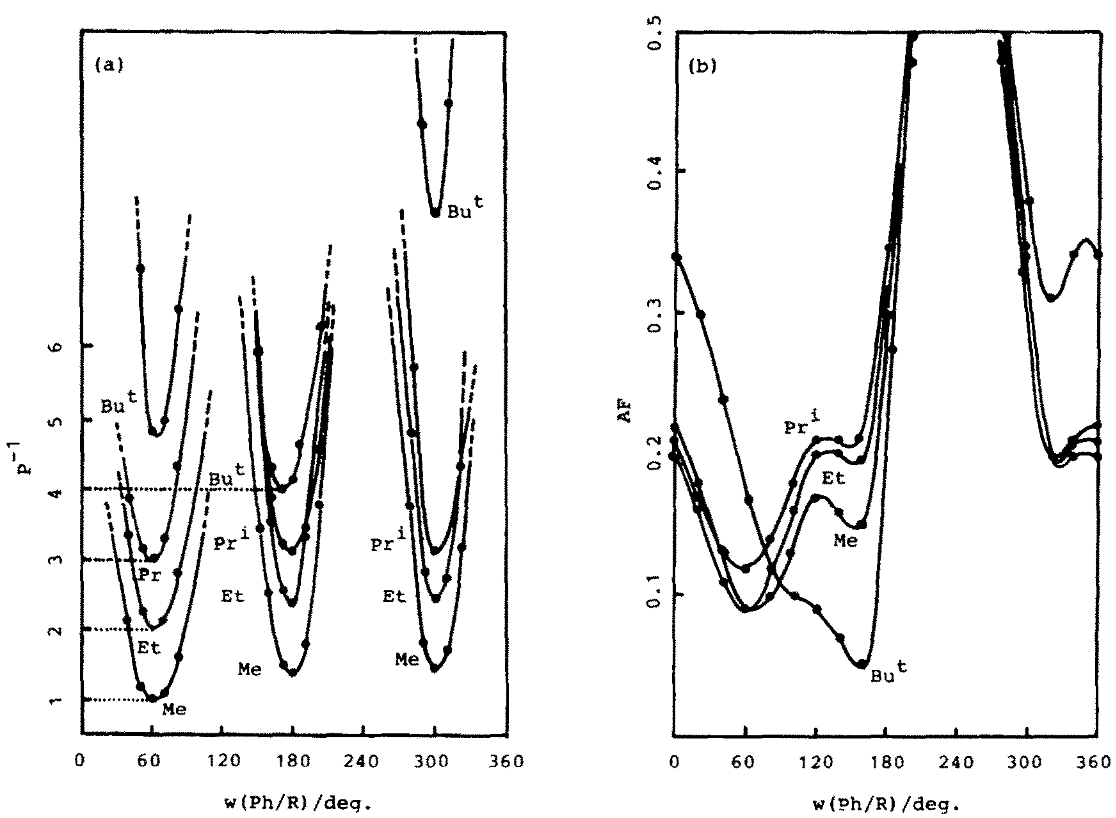


Fig. 2. (a) Relative populations of conformations (P) and (b) agreement factors (AF) as functions of torsional angles (w(Ph/R)) of $C_6H_5CH_2CHROH$, where R is methyl (Me), ethyl (Et), isopropyl (Pr^i), or t-butyl (Bu^t). Inverse of population (P^{-1}) is plotted in order to compare with the results from LIS measurement, since the agreement factor is a quantity which is least when most probable.

Table 3. The conformational preference predicted from the LIS measurement of threo- and erythro-$C_6H_5CH(CH_3)CHROH$. Relative steric energies from MM2 are given in parentheses

R	Conformer		
	(A)	(B)	(C)
threo (X=C, Y=OH, Z=H)			
Me	2 (0)	3 (0.50)	1 (4.31)
Et	1 (0)	3 (0.96)	2 (3.22)
Pr^i	1 (0)	3 (1.51)	2 (8.24)
Bu^t	1 (0)	2 (3.01)	3(14.02)
erythro (X=C, Y=H, Z=OH)			
Me	1 (0)	3 (5.94)	2 (6.44)
Et	1 (0)	3 (5.86)	2 (6.65)
Pr^i	1 (0)	2 (5.86)	3(11.09)
Bu^t	1 (0)	2 (8.12)	3(13.85)

measurement. This disagreement between the theory and the LIS experiment can be interpreted if we assume an extra attractive interaction between phenyl and alkyl groups on the vicinal atoms. The nature of the attractive force will be discussed later. An alternative explanation that the coordinating ability of each conformer is uneven and that the conformer (C) is more favorable in forming the shift reagent-substrate complex than other conformer is also possible. Uneven coordination was shown to occur in the case of sterically hindered pyridines and related azaheterocycles.[21] The uneven coordination seems less probable because the steric circumstances of the hydroxyl groups in conformers (A)-(C) of the threo alcohols are not expected to be remarkably different.

The most preferable conformers of benzyl and 1-phenylethyl t-butyl ketones and sulfoxides were determined by measurement of their dipole moments.[2,4,20] Since the dipole moments of the unsubstituted ketones and sulfoxides are rather insensitive to the conformational change, the measurement was carried out also on some of their p-substituted derivatives. The conclusions from dipole moments (given in Table 4) agreed with the theoretical consequences from molecular mechanics calculations again. As to t-butyl 1-phenylethyl ketone, three conformers having the torsional angles of 79°, 178° and 308° were estimated to be stable by the calculations. Of the three conformers, the most stable conformer has a torsional angle of 79°. t-Butyl group is again gauche to the phenyl and anti to the methyl group in this conformer. Even if the anti conformer is more stable than the gauche one in benzyl t-butyl ketone, the energy difference between them is unexpectedly small. The energy difference was estimated experimentally by measurement of their carbonyl absorption bands at

Table 4. Dipole moments of benzyl t-butyl sulfoxides (**1a**–**1c**), t-butyl 1-phenylethyl sulfoxides (**2a**–**2c**), benzyl t-butyl ketones (**3a**, **3b**), and t-butyl 1-phenylethyl ketones (**4a**, **4b**) and the most probable conformers estimated by several methods

Compound	Dipole moment (D)		Estimated conformer		
	Obsd.	Calcd.	Dipole	X-ray	MM
1a	3.90	3.85	F		D
1b	4.72	4.61	F	F	
1c	6.44	6.62	F		
2a (RR/SS)	3.84	3.75	A		A
2b (RR/SS)	4.23	4.23	A	A	
2c (RR/SS)	5.69	5.91	A		
2a (RS/SR)	3.86	3.28**	A*+B(C)		A
2b (RS/SR)	3.42	3.31**	A*+B(C)	A	
2c (RS/SR)	4.26	3.29**	A*+B(C)		
3a	2.57	2.81**	F*+D		F
3b	3.68	3.82**	F*+D		
4a	2.49	2.51	A		A
4b	2.55	2.53	A		

*) The most predominant conformer.

**) Calculated value for the most predominant conformer.

various temperatures. Intensities of the two overlapping bands at 1716.5 and 1704.5 cm^{-1} (assigned to the anti and the gauche conformers, respectively) were dependent on temperature, thereby giving the enthalpy difference between the conformers from log(ϵ_g/ϵ_a) vs 1/T plot (in Fig. 3b). The observed ΔH value (1.05 kJ mol^{-1} in CCl$_4$ solution) agrees with the calculated value (0.75 kJ mol^{-1}) rather very well. The very low energy difference admits the existence of the both conformers as evidenced by the infrared C=O absorption in Fig. 3(a).

Molecular mechanics calculations gave an explanation for the stereoselective reactions which had been cited as evidence favorable to the CH $\cdots$ π attractive interaction hypothesis.[19] The first example (Table 5a) is the oxidation of alkyl 1-phenylethyl sulfides by peroxyacetic acid producing the corresponding sulfoxides.[3] In these reactions, the threo to erythro ratio of the produced sulfoxide becomes gradually large as the alkyl group becomes bulky (as given in the last column of Table 5a). The nomenclature (RR/SS) and (RS/SR), instead of threo and erythro, respectively, designate more unambiguously the configurations of these sulfoxides. However, the nomenclature for those having t-butyl as alkyl on sulfur atom are reversed. In cases of oxidations by peroxy acids and other hydroperoxides, the reaction is supposed to proceed by the initial nucleophilic attack on an electrophilic oxygen atom in the peroxide molecule, forming the less hindered sulfoxide as the major product.[22] So the reaction (in Table 5a) was interpreted qualitatively that the oxygen in the peroxide reacts with sulfur atom from the less crowded side of the most stable and, hence, the most predominant conformer (A) forming the threo-sulfoxide as the major product. The populations of the three conformers of these sulfides were easily estimated from the steric energies (In Table 1) and given in Table 6(a). If we assume tentatively that the reactivities of the sites, i.e. the unshared electron pairs which can react with electrophilic oxygen atom, flanked by H and Me and flanked by H and Ph are identical while the one flanked by Me and Ph is negligibly low owing to steric hindrance, the isomeric (threo to erythro) ratio of the products could be estimated (method A). In spite of rather rough assumption, the calculated ratios are in accord with the observed ratios. The agreement should be better if the difference in reactivity of the two dissimilar sites is taken into account. The difference was evaluated as the best fit factor for the experimental and the theoretical ratios were corrected as given in the last column of Table 6a. In this case, the

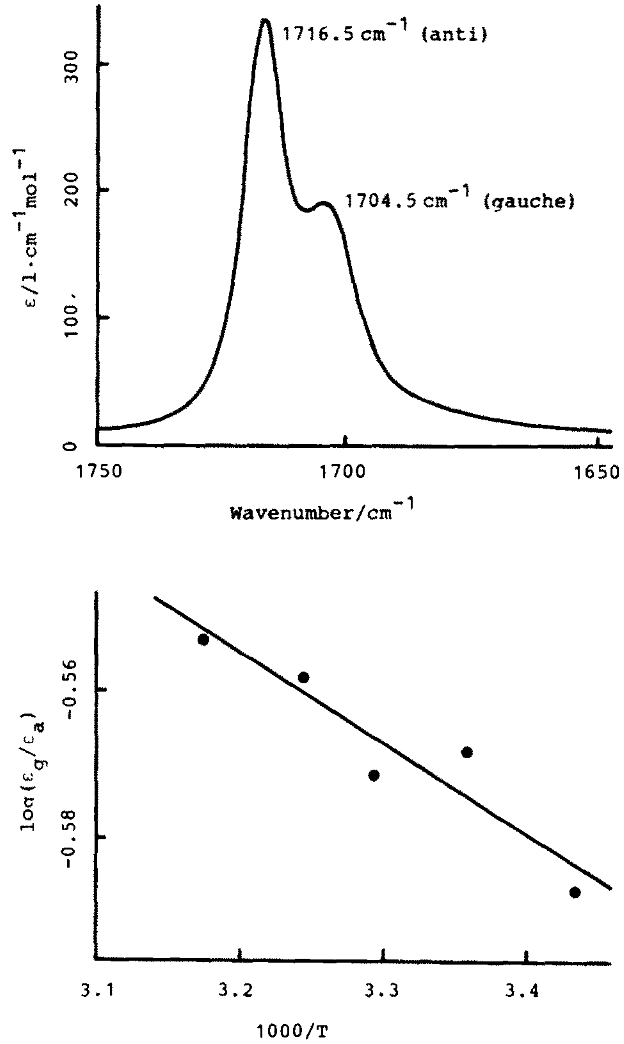


Fig. 3. (a) IR carbonyl absorption bands and (b) the temperature dependence of their intensities for benzyl t-butyl ketone.

Table 5. Prediction of the rates of some reactions from the conformational populations calculated by MM2

a) Oxidation of PhCHMeSR to PhCHMeSOR.

R	Population of conformers of starting sulfides (%)			Product ratio (threo/erythro)		
				Estimated* by		Observed
	(A)	(B)	(C)	Method A	Method B	
Me	72.3	15.1	12.6	3.1	2.9	3.1
Et	74.5	13.4	12.1	3.4	3.2	3.2
Pr^i	79.8	11.5	8.8	4.3	3.8	3.6
Bu^t	94.5	3.8	1.7	18	17	49
Expected product	threo	erythro	threo + erythro			

*) Method A, (A + C)/(B + C); method B, (A + C)/(1.07(B + C).

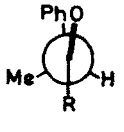
b) Hydride reduction of PhCHMeCOR to PhCHMeCH(OH)R.

R	Population of conformers of starting ketones (%)			Product ratio (threo/erythro)		
				Estimated* by		Observed
	(A)	(B)	(C)	Method A	Method B	
Me	88.9	9.4	1.5	9.3	3.0	2.9
Et	90.7	7.8	1.5	11.6	3.7	3.2
Pr^i	93.1	6.1	0.9	15.4	5.0	5.7
Bu^t	99.1	0.76	0.14	130	43	49
Expected product	threo	erythro	No reaction			

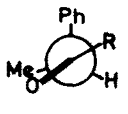
*) Method A, A / B ; method B, A /(3.0 B).

difference is only slight (1.07 times) and the improvement was not remarkable by the sophistication of the calculation (method B).

The stereoisomeric ratios of the alcohols formed by the metal hydride reduction of alkyl 1-phenylethyl ketones[23] were also explained by the population of the conformers of the starting ketones from molecular mechanics calculations. In this case, the difference in reactivity of the dissimilar sites is estimated to be considerably large. The observed stereoisomeric ratios were reproduced best when the attack of the hydride towards the less hindered face of carbonyl/phenyl eclipsed conformation (H) is assumed to be 3.0 times faster than the attack towards the less hindered face of carbonyl/methyl eclipsed conformation (J) (method B).



(H)



(J)

In both cases, the Ph/R gauche and Me/R anti conformer is the most stable. From the general sequence of the bulkiness of substituents which suggests that phenyl is bulkier than methyl, stability of the conformer was apparently anomalous. Molecular mechanics calculations have given the correct populations of the conformers even in these cases.

As we have illustrated by several examples, alkyl groups are liable to be located gauche to the vicinal aryl group. The overall feature of this conformational preference can be reproduced by molecular mechanics calculations. In organic chemistry, the magnitude of steric effect is thought to be transferable and has been evaluated from the standpoint of repulsive force alone. Thus, steric hindrance of substituent is often estimated by conformational free energy difference defined by the difference in free energies of equatorially and axially substituted cyclohexanes,[24] and by van der Waals radii of atoms and groups.[25] However, the preference of Ph/R gauche conformation, especially in $C_6H_5CH_2XR$ series, cannot be rationalized without taking into account the attractive interaction between these groups. As an empirical explanation for the preference of alkyl/phenyl approached conformations shown above, the $CH\cdots\pi$ interaction hypothesis was formerly suggested, in which the attractive force was assumed to be hydrogen bond-like in nature. Direct evidence for such a specific interaction is lacking yet.

The preference of alkyl/phenyl gauche conformation can be predicted, at least semiquantitatively, without taking into account any contribution of specific attractive force between CH group and π-electrons by molecular mechanics calculations. Dispersion force, or van der Waals attractive force, is the only general attractive force included in the calculation. Therefore, it should be the controlling factor to realize the stable Ph/R gauche conformer. Small discrepancies are sometimes observed between the theoretical consequences and the experimental results. Most of them can be interpreted more adequately by assuming additional weak attractive interaction between the alkyl and the phenyl groups. They might arise from experimental errors or directed deviation inherent to the method of measurement. Otherwise, they might arise from the contribution of either of the following factors: (a) solvent effect in the observed system; (b) underestimation of van der Waals attraction in molecular mechanics calculations; (c) hydrogen bond-like CH $\cdots$ π interaction; (d) excess polarizability effect of π-electron system; and (e) electrostatic interactions by quadrupole and other higher multipoles. The solvent effect usually favors the more polar conformer. The dipole moments are similar among the conformers of the alcohols, and no relationship between the discrepancy and the dipolar nature of the conformers. The underestimation is not probable, since the MM2 program and the parameters used has been tested by a large number of compounds and highly trustworthy. Hydrogen bond-like interaction is possible in principle. However, the orientation of the C–H bond relative to the aromatic nucleus plays a crucial role. The overlap populations from *ab initio* calculations on the alcohols did not support such interactions. In order to examine the possibility of such hydrogen bond-like interaction, infrared C-D stretching absorptions of 2-methyl-4-phenyl-3-pentanone-2d and some of its p-substituted derivatives were measured. At present, it is not conclusive but the substituent effect on the intensities seems favorable to the CH $\cdots$ π hydrogen bond, though the enthalpies of interaction were estimated to be extremely small. Dipole-quadrupole and other higher multipole interactions are usually small. Moreover, they might average out to nearly zero by the molecular motion of alkyl group. Recently some experimental results suggesting similar attractive interaction between vicinal aryl groups have been reported.[26] Therefore, some contribution of the excess polarizability is also probable, since polarizable aryl group is always particpating when the proximity of the substituents is remarkable.

Acknowledgements—Molecular mechanics calculations were carried out by a HITAC M200H computer of the Institute for Molecular Science to which the authors are grateful. We also thank Prof. N. L. Allinger, the University of Georgia, for his valuable suggestion on molecular mechanics calculations.

REFERENCES

[1] Y. Iitaka, Y. Kodama, K. Nishihata and M. Nishio, *J. Chem. Soc., Chem. Commun.* 389 (1974); *J. Chem. Soc.* Perkin II 1490 (1976).
[2] M. Hirota, Y. Takahashi, M. Nishio and K. Nishihata, *Bull. Chem. Soc. Jpn.* **51**, 2358 (1978).
[3] K. Nishihata and M. Nishio, *Tetrahedron Letters* 1041 (1977).
[4] M. Hirota, T. Sekiya, M. Nishio and K. Nishihata, Presented to the *ACS/CSJ Chemical Cong.* April 1979, Honolulu, Abstracts.
[5] Y. Kodama, K. Nishihata, S. Zushi, M. Nishio, J. Uzawa, K. Sakamoto and H. Iwamura, *Bull. Chem. Soc. Jpn.* **52**, 2666 (1979).
[6] J. Uzawa, S. Zushi, Y. Kodama, Y. Fukuda, K. Nishihata, K. Umemura, M. Nishio and M. Hirota, *Ibid.* **53**, 3623 (1980).
[7] S. Zushi, Y. Kodama, K. Nishihata, K. Umemura, M. Nishio, M. Hirota and J. Uzawa, *Ibid.* **54**, 2113 (1981).
[8] S. Zushi, Y. Kodama, K. Nishihata, K. Umemura, M. Nishio, J. Uzawa and M. Hirota, *Ibid.* **53**, 3631 (1980).
[10] K. Nishihata and M. Nishio, *J. Chem. Soc.* Perkin II 1136 (1972).
[11] M. Nishio, *Kagaku no Ryoiki* **33**, 68 (1979).
[12] N. L. Allinger, *Adv. Phys. Org. Chem.* **13**, 1 (1976); E. Osawa, *Yuki Gosei Kagaku Kyokai Shi* **36**, 812 (1978).
[13] F. H. Westheimer, *Steric Effects in Organic Chemistry* (Edited by M. S. Newman), p. 523. Wiley, New York (1956).
[14] N. L. Allinger, *J. Am. Chem. Soc.* **99**, 8127 (1977).
[15] K. Mislow and P. von R. Schleyer, BIGSTRAN, QCPE #348.
[16] F. A. Momany, R. F. McGuire, A. W. Burgess and H. A. Scheraga, *J. Phys. Chem.* **79**, 2361 (1975); M. J. Brown and H. A. Scheraga, ECEPP, QCPE #286.
[17] S. Fitzwater and L. S. Bartell, *J. Am. Chem. Soc.* **98**, 5107 (1976).
[18] M. Nishio, Kagaku no Ryoiki **33**, 422 (1979).
[19] M. Nishio, *Ibid* **36**, 190 (1982).
[20] M. Hirota and H. Tashiro, Unpublished data, some given in Table 4.
[21] Y. Nagawa, M. Ono, M. Hirota, Y. Hamada and I. Takeuchi, *Bull. Chem. Soc. Jpn* **49**, 1322 (1976).
[22] C. R. Johnson and D. McCants, Jr., *J. Am. Chem. Soc.* **87**, 1109 (1965).
[23] M. Cherest, H. Felkin and N. Prudent, *Tetrahedron Lett.* 2199 (1968).
[24] E. L. Eliel, N. L. Allinger, S. J. Angyal and G. A. Morrison, *Conformational Analysis*, p. 42. Interscience, New York (1965).
[25] M. S. Leslie and E. E. Turner, *J. Chem. Soc.* 1588 (1933); C. C. Li and R. Adams, *J. Am. Chem. Soc.* **57**, 1565 (1935).
[26] P. Ivanov, I. Pojarlieff and N. Tyutyulkov, *Tetrahedron Letters* 775 (1976); J. Jacobus, *Ibid.* 2979 (1976).