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# THEORETICAL CONSIDERATIONS ON THE PREFERENCE OF ALKYL/PHENYL APPROACHED CONFORMATIONS IN 1-ALKYL-2-PHENYL COMPOUNDS Ar-CH($CH_3$)-X-R

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The preferred conformations of *t*-butyl 1-phenylethyl sulfoxide, *t*-butyl 1-phenylethyl ketone, 2,2,4-trimethyl-4-phenylpentane-3-ol, and related compounds were estimated by the empirical molecular force field approach. The results are in accordance with the experiments, showing that the conformation in which the *t*-butyl group is trans to the methyl and gauche to the phenyl group is the most stable. The repulsive force between the *t*-butyl and the methyl groups is the main factor and the attractive van der Waals force is the secondary factor in determining the favored conformation.

Recent investigations on the conformations of 1-phenyl-2-*t*-butyl compounds 1 revealed the preference of a conformation in which bulky *t*-butyl group is located gauche to the phenyl group on the vicinal atom. As to 1-phenylethyl *t*-butyl sulfoxide 1a, Iitaka and co-workers[1] have determined the crystal structures of (*RR/SS*) and (*RS/SR*) diastereomers of its p-bromo-derivative, showing that the *t*-butyl group orients itself trans to the methyl and gauche to the phenyl group. The conformations of these and similar sulfoxides in solution have been concluded to be the same from the LIS[2] and the dipole moment[3] measurements. Moreover, the diastereotopos-differentiating deuteration reaction suggested that the phenyl/*t*-butyl gauche conformation is favorable even in benzyl *t*-butyl sulfoxide.[4,5]

$C_6H_5$-CH($CH_3$)-X-C($CH_3$)$_3$

1 a: X = SO, b: X = CO, c: X = CHOH, d: X = $CH_2$

The phenyl/alkyl gauche conformations (2) are also shown to be the most preferable with alkyl 1-phenylethyl ketones[6] and with 1-alkyl-2-phenyl-1-propanols[7] by the LIS measurements. The results suggest the presence of a considerable amount of the second stable conformation 4 in addition to 2 when the alkyl group (R) is methyl or ethyl.[2,7] In the conformation 4, the alkyl group (R) is flanked by the phenyl and the methyl

groups.

In order to estimate the most stable conformation and to interprete the reason for its stability, empirical molecular force field calculations were carried out with these compounds by use of MMI and MM2 programs.[8] Steric energies of 1 were calculated as a function of dihedral angles (w) around the $C_{benzyl}$-X bond. In these calculations, all coordinates other than the dihedral angle were optimized. The results are illustrated as the potential energy curves in Fig. 1. The energies at the potential minima of the curve were calculated without any restriction of the coordinates. In general, three conformations corresponding to a trans and two gauche conformers[5] were shown to be stable. The stable conformers and their steric energies are given in Table 1.

As to *t*-butyl 1-phenylethyl ketone, the curve has three minima which correspond to the three conformers taking the torsional angles of 79°, 178°, and 308°. It is very remarkable that the *t*-butyl group is gauche to the phenyl group and trans to the methyl group in the most stable conformer 2(X = CO).[9] Similar results were obtained with alcohols and hydrocarbon (1c and 1d). The potential energy curve of (*RR/SS*)-*t*-butyl 1-phenylethyl sulfoxide also has a minimum when w is near 100°. Again the most stable conformer has a *t*-butyl group which is located nearly anti to the methyl group and gauche to the phenyl group. Thus, with respect to the most preferred conformation, the results on 1a-1d are always in line with the conclusions from the experiments. Moreover, the observed energy difference(1.05 kJ/mol) between the trans and the gauche conformers of benzyl *t*-butyl ketone agrees with the theoretical value(0.75 kJ/mol) very well.

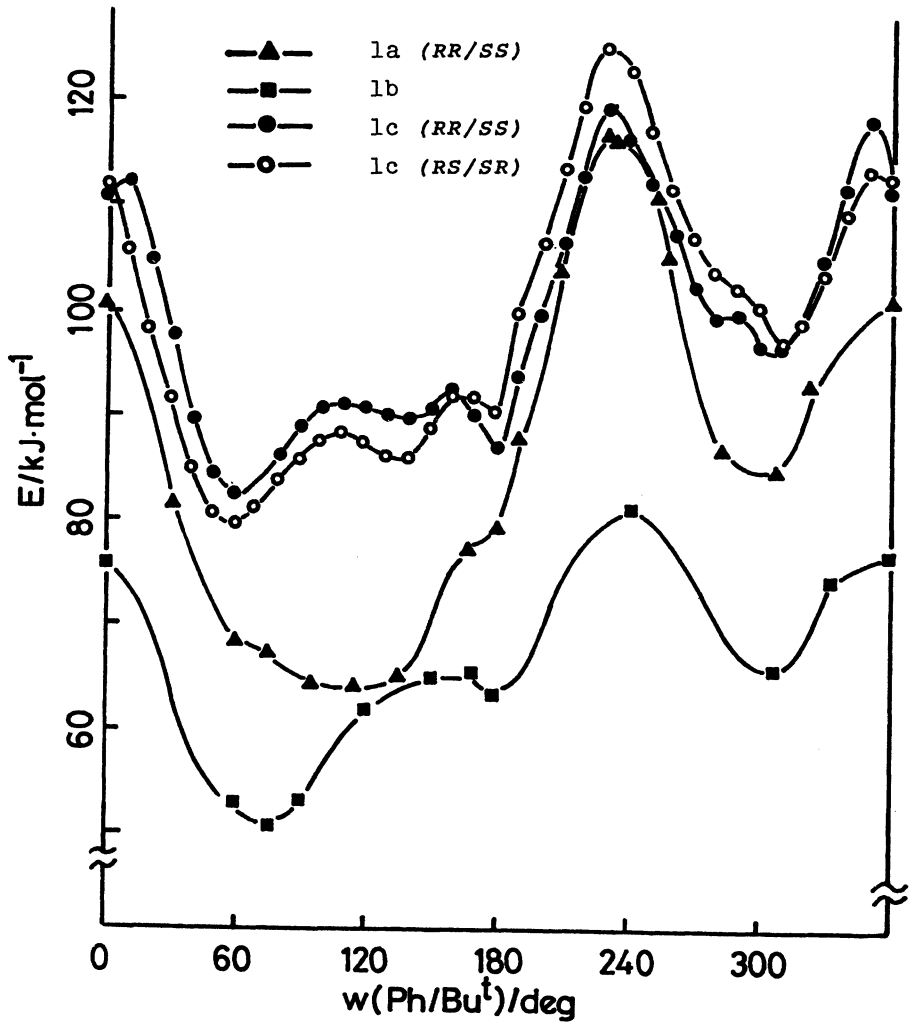
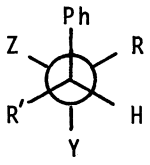


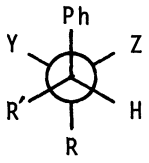

Fig. 1. The potential energy curve as a function of dihedral angles w around the C-X bond of 1.

In order to make clear why the gauche conformation is the most stable in 1a-1d, intramolecular forces effective in each conformer were analyzed in detail. In the

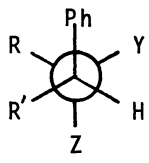
Table 1. Steric energies of the stable conformations



(2)



(3)



(4)

| R | Y | Z | E/kJ·mol$^{-1}$ (w/deg) | E/kJ·mol$^{-1}$ (w/deg) | E/kJ·mol$^{-1}$ (w/deg) |
|---|---|---|---|---|---|
| 1-Phenylethyl Derivatives (R' = Me) | | | | | |
| $Bu^t$ | H | H | 69.62 (60) | 77.99 (172) | 84.35 (308) |
| $Bu^t$ | H | OH | 83.30 (61) | 86.32 (175) | 92.63 (305) |
| $Bu^t$ | OH | H | 77.15 (58) | 84.85 (172) | 90.58 (307) |
| $Bu^t$ | =O | | 50.38 (79) | 62.95 (178) | 66.90 (308) |
| $Bu^t$ | (S)O | lone pair | 63.60 (99) | 76.57 (170) | 83.68 (308) |
| Me | H | OH | 58.95 (58) | 59.45 (174) | 63.26 (300) |
| Et | H | OH | 65.67 (57) | 66.65 (178) | 68.91 (301) |
| $Pr^i$ | H | OH | 71.13 (54) | 72.63 (180) | 79.37 (303) |
| Me | OH | H | 55.23 (53) | 61.17 (172) | 61.67 (307) |
| Et | OH | H | 62.63 (52) | 68.49 (172) | 69.28 (304) |
| $Pr^i$ | OH | H | 67.99 (48) | 74.06 (175) | 79.08 (303) |
| Benzyl Derivatives (R' = H) | | | | | |
| $Bu^t$ | H | OH | 73.85 (65) | 68.20 (179) | 70.00 (297) |
| $Bu^t$ | =O | | 47.36 (80) | 46.61 (180) | 47.36 (280) |

molecular force field calculations, the total steric energy (E) of a molecule is expressed as the sum of compression ($E_s$), bending ($E_b$), torsional ($E_w$), attractive and repulsive van der Waals ($E_v$), and other energy terms including some of their cross terms.[10] When each energy term was compared among the conformers, the intramolecular forces which act to favor the gauche conformer were found. The most predominant factor in determining the most stable conformation is the repulsive force between the methyl and the *t*-butyl groups, since these groups are expected to be approached within their van der Waals radii. This force causes the bending of $C_{t\text{-Bu}}\text{-}C_{carbonyl}\text{-}C_{benzyl}$ and $C_{carbonyl}\text{-}C_{benzyl}\text{-}C_{Me}$ bond angles in 1b, for example. As a consequence, a considerable increase in $E_b$ and lesser increases in $E_s$ and $E_{sb}$ (stretch-bend cross term) were observed in addition to the increase in repulsive van der Waals energy in the conformations 3 and 4, where R is *t*-butyl. As to the example of 1b, the increase in $E_b$ is 4.77 kJ/mol and the total increase of these three terms is 5.65 kJ/mol. Secondly the attractive van der Waals energy is always larger in the gauche conformers than in the trans conformer. The molecule get additional stabilization energy as large as about -2.0 kJ/mol in the case of the gauche conformation in which the two methyl groups

of the *t*-butyl moiety are estimated to be located just above the aromatic nucleus to have maximal attractive van der Waals contact. On the other hand, the alkyl/phenyl contact is impossible in the trans conformer, resulting smaller attractive $E_v$ term. It is remarkable that the gauche conformation is also favorable to the hypothetical CH···$\pi$ attractive interaction.[11]

After all, compounds 1a-1d generally prefer the conformations in which the *t*-butyl group is trans to the methyl group and, consequently, gauche to the phenyl group. The repulsive force between the two alkyl group is the main factor and the attractive van der Waals force is the secondary factor in determining the favored conformation. The conclusion is apparently contradictory to the generally accepted sequence of the bulkiness of substituent groups ($CH_3 < C_6H_5$). The bulkiness in this sequence is estimated from the conformational free energy difference between equatorial and axial substituted cyclohexanes,[12] however. Preference of the alkyl/phenyl gauche conformer is quite reasonable when the arrangement of the phenyl and alkyl groups in the molecule is carefully examined by taking their shapes into account.

The overall feature of the conformational preference in these compounds is thus explained by the general intramolecular forces accounted in the molecular force field approach without assuming the specific CH···$\pi$ attractive interaction. However, small and delicate discrepancies are sometime observed between the theoretical and the experimental results,[7] most of which can be interpreted more adequately by accounting an additional small attractive force assumed in the CH···$\pi$ interaction hypothesis.[11]

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5) Hereafter, w refers to the *t*-Bu/Ph, or more generally R/Ph, dihedral angle. Similarly the terms gauche and trans are used in reference to this dihedral angle.
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