ESTIMATION OF THE STEREOSELECTIVITY OF SOME REACTIONS ON ALKYL 1-PHENYL-ETHYL SULFIDES AND KETONES BY MOLECULAR FORCE FIELD CALCULATIONS

Minoru HIROTA,* Kazuhisa ABE, Hiroshi TASHIRO, and Motohiro NISHIO+

Department of Applied Chemistry, Faculty of Engineering,

Yokohama National University, Hodogaya-ku, Yokohama 240

+ Central Research Laboratories, Meiji Seika Kaisha Ltd.,

Kohoku-ku, Yokohama 222

The stereoisomeric(threo/erythro) ratios of the reaction products were estimated from the conformational ratios of the reactant calculated by molecular force field approach. Examples of the oxidation to sulfoxides of alkyl 1-phenylethyl sulfides and the hydride reduction of alkyl 1-phenylethyl ketones were given.

Molecular force field calculations have been widely applied to the evaluation of steric energies of the stable and labile conformations of many organic molecules.[1,2] Since the method is more practical than the molecular orbital method in the calculations of the conformational energies of rather complex organic molecules, the application is becoming popular in organic chemistry. In the earlier stage of its development, it is mainly applied on hydrocarbon molecules. However, recently improved version of the computer program[3] enables us to estimate the steric energies of hetero-atom containing compounds considerably well. For example, our recent calculation on benzyl t-butyl ketone reproduced the conformational energy difference $(E_g - E_t)$ from infrared measurement very closely (calcd., 0.75 kJ·mol^{-1} and obsd., 1.05 kJ·mol^{-1}).[4]

Rates of many organic reactions are often influenced by the pre-equilibrum among conformers of the reactant, when the reaction proceeds selectively with either

Table 1. Conformational Energies and Expected Oxidation Products of Alkyl 1-Phenylethyl Sulfides

| | Conformer | | | Product Ratio (threo/erythro) | | |
	(1a)	(1b)	(1c)	Estimated by Method A	Method B	Observed
CH$_3$	0 (72.3%)	0.94 (15.1%)	1.05 (12.6%)	3.1	2.9	3.1
C$_2$H$_5$	0 (74.5%)	1.03 (13.4%)	1.09 (12.1%)	3.4	3.2	3.2
i-C$_3$H$_7$	0 (79.8%)	1.16 (11.5%)	1.32 (8.8%)	4.3	3.8	3.6
t-C$_4$H$_9$	0 (94.5%)	1.92 (3.85%)	2.43 (1.65%)	18	17	49
Expected Product	(2)	(3)	(2) + (3)			

(1a)   (2)

(1b)   (3)

(1c)   (2) + (3)
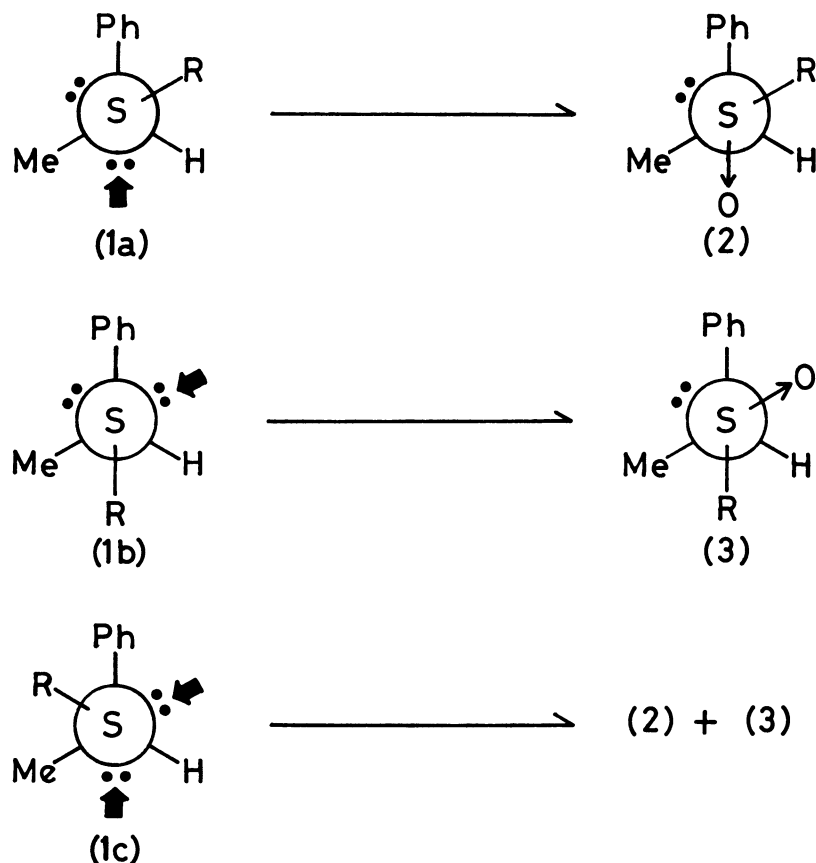
of the conformers. One of the present authors (M. Nishio) has reported the oxidation of alkyl 1-phenylethyl sulfides to produce the corresponding sulfoxides.[5] In these reactions, the threo (2) to erythro (3) ratios of the produced sulfoxides become gradually large when the alkyl moiety is altered from methyl to t-butyl (as shown in the last column of Table 1). The reaction was explained qualitatively that the oxygen attacks to the sulfur atom from the less crowded side of the stable conformer (1a) forming the threo sulfoxide 2 as the major product. The stability of the Ph/alkyl approached conformer 1a has been ascribed to the CH···π attractive interaction between the vicinal phenyl and alkyl groups.[6]

The steric energies of these alkyl 1-phenylethyl sulfides were evaluated as a function of the Ph/R torsional angle around the C_{benzyl}-S bond by the molecular force field approach using the most recent version of MM2 program by Allinger and co-workers.[3] The calculation gives three energy minima corresponding to the conformers 1a, 1b, and 1c for every sulfide. The steric energies of these three conformers were re-calculated by the full minimization without any restriction of coordinates. Relative steric energies with reference to the most stable conformer are given in Table 1 together with the abundances (%) at 25°C of the conformers calculated by the Boltzmann's law of distribution (P = P_0 exp(-ΔE/RT)) in the parentheses. If we assume a priori that the reactivities of the sites scissored by H and Me and scissored by H and Ph are identical and that scissored by Me and Ph is negligibly low,[7] the product ratios could be estimated as given in the fourth column of Table 1 (Method A). In spite of rather rough assumption, the calculated product ratios are in accord with the tendency of the steric effect by the alkyl

Table 2. Conformational Energies and Expected Products by $NaBH_4$
Reduction of Alkyl 1-Phenylethyl Ketones.

| R | Conformer | | | Product Ratio (threo/erythro) | | |
| | | | | Estimated by | | |
	(4a)	(4b)	(4c)	Method A	Method B	Observed
CH_3	0 (88.9%)	1.34 (9.5%)	2.44 (1.5%)	9.3	3.0	2.9
C_2H_5	0 (90.7%)	1.47 (7.8%)	2.48 (1.5%)	11.6	3.7	3.2
$i\text{-}C_3H_7$	0 (93.1%)	1.64 (6.1%)	2.78 (0.9%)	15.4	5.0	5.7
$t\text{-}C_4H_9$	0 (99.1%)	2.92 (0.76%)	3.95 (0.14%)	130	43	49
Expected Product	(5)	(6)				

(4a) (4b) (4c)

(5) (6)
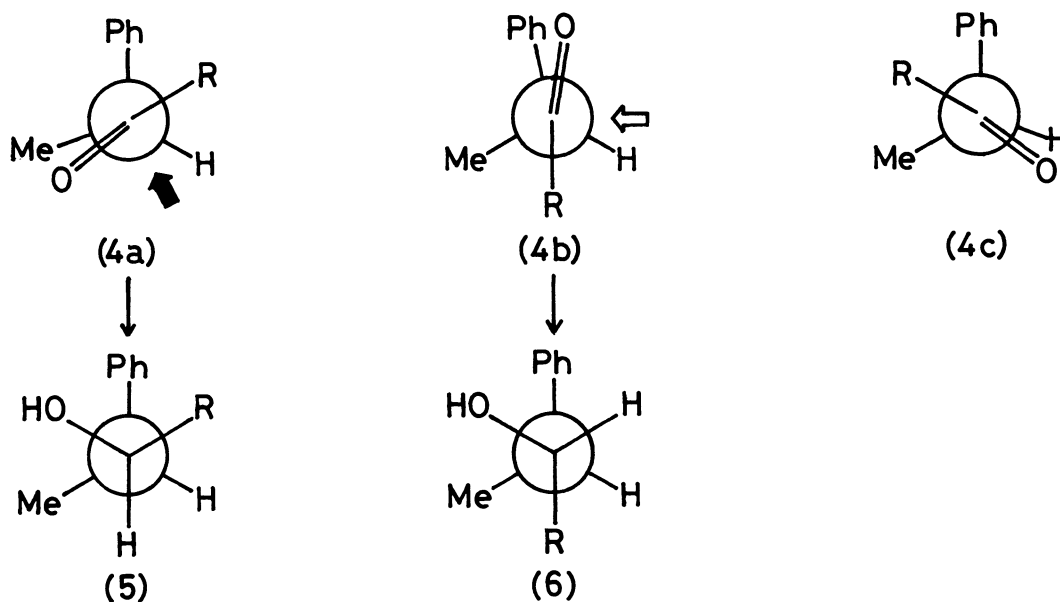
moiety observed in the experiment. If we take into account the difference between the lone pair electrons scissored by H and Ph and those scissored by H and Me in the reactivity towards the oxidant assuming that the former conformer is 1.07 times[8] more reactive than the latter, the agreement becomes better than the results by method A (Mehtod B). In this case, however, the improvement was not remarkable.

Quite similarly, the metal hydride reduction of alkyl 1-phenylethyl ketones was explained by the molecular force field calculations on these compounds. The reduction of these ketones by sodium borohydride were reported by Felkin and co-workers.[9] The isomeric(threo/erythro) ratio is affected by the bulkiness of the alkyl substituent in the way similar to the oxidation of alkyl 1-phenylethyl sulfides. The observed change in the isomeric ratios of the produced alcohols was again reproduced by the calculations[10] assuming the equal reactivity for the attack of the reagent towards the faces opposing H atom of carbonyl group (indicated by

arrows in 4a and 4b)(Method A). If we assume that the attack of the reagent towards the face of carbonyl/Ph eclipsed conformation (4b) is 3.0 times faster than the attack to the face of carbonyl/Me eclipsed conformation (4a), the calculated isomeric ratios of the products agree quantitatively with those from experiments[8] (Method B).

References
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7) This assumption is, in a sense, another expression of the Cram's law which has been successfully applied to interprete many stereoselective reactions.
8) The difference in reactivities at two non-equivalent sites was estimated as the value fittest to the experiments from the least squares calculation on the methyl to isopropyl derivatives of the sulfides or the ketones. The t-butyl derivative was excluded because considerable distortion is expected in the molecule.
9) M. Cherest, H. Felkin, and N. Prudent, Tetrahedron Lett., 1968, 2199.
10) However, the populations of the conformers predicted by force field calculations of the ketones are not completely consistent with those from computer simulation of the lanthanoid induced shifts. See S. Zushi, Y. Kodama, K. Nishihata, K. Umemura, M. Nishio, J. Uzawa, and M. Hirota, Bull. Chem. Soc. Jpn., 53, 3631 (1980).