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STERIC SUBSTITUENT CONSTANT Ω_s BASED ON MOLECULAR MECHANICS CALCULATIONS. II. DIRECTIONALLY WEIGHTED STERIC CONSTANTS AND THEIR APPLICATION TO THE ANALYSIS OF THE STERIC COURSE OF REACTIONS

IKUO AKAI, SHIN-ICHI KURODA, KAZUHISA SAKAKIBARA AND MINORU HIROTA*
Department of Synthetic Chemistry, Faculty of Engineering, Yokohama National University, Hodogaya-ku, Yokohama 240, Japan

The directionally weighted steric substituent constant Ω_{jk} was introduced to evaluate the anisotropic steric hindrance effect to the reaction centre. The correlation of the rates with a series of directionally weighted Ω_{jk} is useful for characterizing the feature of steric effect. The difference between the hydrolyses of carboxylic esters and carboxamides was shown by this method.

1. INTRODUCTION

Since the linear free energy relationship was extended to the steric effect by Taft,[1] a variety of steric substituent constants[2–3] have been proposed in order to evaluate the steric effect caused by the substituent. Among these steric constants, E_s and its modifications[1–5] are most widely used in the aim of evaluating steric substituent effects quantitatively. It was defined on the basis of the rates of acid hydrolysis of various carboxylic esters RCOOMe by assuming Taft–Ingold hypothesis. Thus, E_s is dependent on the characteristic habit of the hydrolysis reaction. E_s was shown to be considerably anisotropic by Dubois and *et al.*[12] The E_s^c constant[3] often used in quantitative structure–activity relationship (QSAR), must have been modified to be more isotropic, since it was calculated on the basis of a linear equation connecting E_s with the van der Waals radius of the substituent.

We recently proposed a new steric substituent constant Ω_s[13] (use of solid angle as a steric parameter was recently reported by Chauvin and Kagan[14]). It was originally defined as the solid angle, divided by 4π for normalization, of the shadow of the substituent when an infinitesimal light source was placed at the reaction centre, and the shadow of the substituent was projected on the circumscribing sphere. As the shadow area depends on the conformation of the substituent, the population-weighted mean was used as Ω_s in the cases of substituents having more than one conformers. The geometry and steric free energies of the conformers were calculated by MM2, and then the contour of the substituent was modelled assuming that each atom is a sphere whose radius is equal to its van der Waals radius. The computer program for the calculation (OMEGAS 90)[15] was subsequently modified so as to facilitate the calculation of Ω_s values taking into account the radii of both the reaction centre and the reagent.

Steric effects of the alkyl (R) groups on the nucleophilic substitution reactions of alkylamines (RNH_2) and alcohols (ROH) were generally correlated better with more isotropic steric constants Ω_s of the alkyl group than with their E_s.[13,16]

However, the isotropy is not everything to the steric substituent constant. The reaction rates of carboxylic acid derivatives (RCOX) were correlated far better with E_s than Ω_s. The correlations using Ω_s are usually good but not excellent in most cases. This intimates that the reactions are essential anisotropic, depending on the nature of the interaction between the reaction centre atom and the reagent. As is easily understood from its definition, $\Omega_s(CH_3)$ should be explicitly isotropic.

To consider more fundamentally on the problem of anisotropy, it was reduced to the evaluation of the angular dependency of the reactivity or the reaction probability. In the case of non-spherical reaction centre, the probability of inducing the reaction by the collision of the reagent molecule can be dependent, in principle, on the direction of the approach of the reagent. In fact, all the reaction centre atoms bearing substitutents have a non-symmetrical environment. For this reason, the

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[*] Author for correspondence.

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probability should be a function of angles defined properly with reference to the vertex reaction centre atom.

In this paper, we propose a method to donate anisotropic character to the steric constant Ω_s and its application to the diagnosis of the sterochemical features of the reaction.

THEORY

Definition of weighted Ω_{jk}

In the definition of Ω_s, reactions are assumed to take place between a substrate molecule RX and a reagent Y: the former is assumed to consist of a substituent (R) and a reaction centre (X) directly bonded to each other and the latter to be spherically symmetric. In this model reaction in which spherical reagent (Y) collides with the reaction centre (X) of RX, the solid angular probability of the reaction is assumed to be equal ($\omega = 1$) in the illuminated area, when X is assumed to be a light source:

$$\Omega_s = (1/4\pi) \int \sigma(\omega)\, \mathrm{d}\omega \qquad (1)$$

$\sigma(\omega) = 1$ in the shadow area

$\sigma(\omega) = 0$ in the illuminated area

With the aim of incorporating the angular dependency of the reactivity with Ω_s, we introduced a weighting function in the calculation of Ω_s.[17] In order to donate the angular dependence to Ω_s, $\sigma(\omega)$ in equation (1) was multiplied by a weighting function $f(\theta, \phi)$ at each element of solid angle ($\mathrm{d}\omega$) and then integrated over the whole solid angle range [equation (2)], where ω is the solid angle defined by the latitudinal angle θ and the longitudinal angle ϕ in the polar coordinate system of which z-axis coincides with the R—X bond with X at the origin:

$$\Omega_s = (1/4\pi) \int \sigma(\omega) f_{jk}(\theta, \phi)\, \mathrm{d}\omega \qquad (2)$$

In practice, the integral in equation (2) was replaced by the summation and calculated numerically.

The weighting function can be expressed as the product of periodic functions of θ and ϕ [$g_j(\theta)$ and $h_k(\theta)$]:

$$f_{jk}(\theta, \phi) = g_j(\theta) h_k(\phi) \qquad (3)$$

where

$$g_j(\theta) = [\pm\cos(n\theta)]/2 \qquad n = 0, 1, 2, 3 \qquad (4)$$

$$g_j(\theta) = [\pm\sin(n\theta)]/2 \qquad n = 1, 2, 3 \qquad (4')$$

$$h_k(\theta) = [\pm\cos(n\theta)]/2 \qquad n = 0, 1, 2, 3 \qquad (5)$$

$$h_k(\theta) = [\pm\sin(n\theta)]/2 \qquad n = 1, 2, 3 \qquad (5')$$

where n refers to the periodicity of the functions. In order to simulate the tetrahedral and trigonal reaction centre atoms satisfactorily with a limited number of weighting functions, thirteen $g_j(\theta)$ and $h_k(\phi)$ functions were employed (Table 1).

Various types of weighting functions

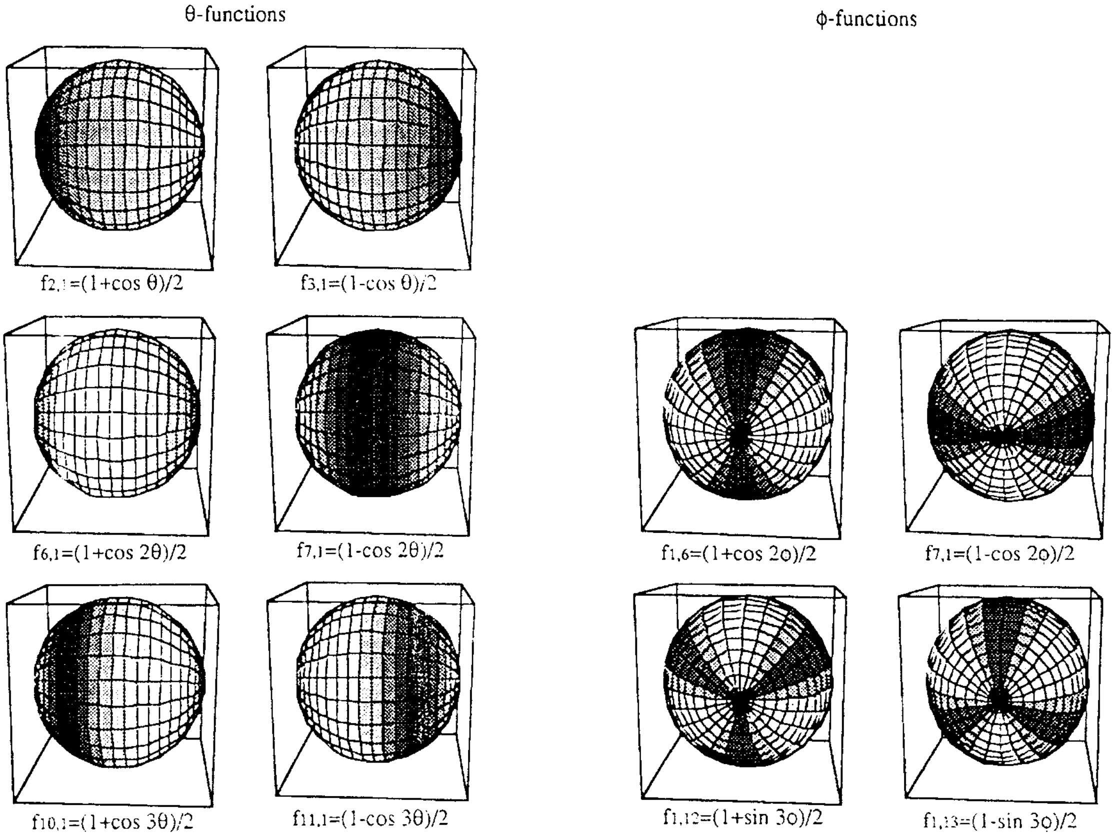
Weighting functions are illustrated in Figure 1 by showing the weighted shadow projected on the surrounding sphere. (a dense shadow refers to a larger $f(\theta, \phi)$ value.)

The meanings of the weighting functions can be explained as follows. As mentioned previously, calculations of Ω_s were carried out on the two models, namely the tetrahedral RCH_3 model and trigonal RCOOH

Table 1. $g_j(\theta)$ and $h_k(\phi^*)$ components of the weighting functions $f_{jk}(\theta, \phi)$

	$g_j(\theta)$			$f_{jk}(\theta, \phi)$		
j or k	n	Sign[a]	Equation	n	sign[a]	Equation
1	0	+	(4)	0	+	(5)
2	1	+	(4)	1	+	(5)
3	1	-	(4)	1	-	(5)
4[b]	1	+	(4′)	1	+	(5′)
5[b]	1	-	(4′)	1	-	(5′)
6	2	+	(4)	2	+	(5)
7	2	-	(4)	2	-	(5)
8	2	+	(4′)	2	+	(5′)
9	2	-	(4′)	2	-	(5′)
10	3	+	(4)	3	+	(5)
11	3	-	(4)	3	-	(5)
12	3	+	(4′)	3	+	(5′)
13	3	-	(4′)	3	-	(5′)

[a] Choice of plus or minus sign in equations (4) to (5′).
[b] Functions g_4, g^5, h^4 and h^5 are not necessary in practice.



$f_{2,1}=(1+\cos\theta)/2$ $f_{3,1}=(1-\cos\theta)/2$

$f_{6,1}=(1+\cos 2\theta)/2$ $f_{7,1}=(1-\cos 2\theta)/2$ $f_{1,6}=(1+\cos 2\phi)/2$ $f_{7,1}=(1-\cos 2\phi)/2$

$f_{10,1}=(1+\cos 3\theta)/2$ $f_{11,1}=(1-\cos 3\theta)/2$ $f_{1,12}=(1+\sin 3\phi)/2$ $f_{1,13}=(1-\sin 3\phi)/2$

Figure 1. Schematic illustrations of simple weighting functions

model. The former is more suitable for general use, but the latter is suitable for trigonal reaction centres, especially carboxylic acid derivatives. As a matter of course, weighting functions were applied to both types of models.

First, the latitudinal θ-functions are shown. For example, $f_{2,1}$ becomes unity at the positive (R side) pole (where $\theta=0$), and zero at the opposite (X side) end (where $\theta=180°$). This emphasizes the steric effect for the rear-side attack of the reagent. Similarly, $f_{3,1}$ emphasizes the steric hindrance for the front-side attack. The 2θ function $f_{6,1}$ emphasizes the steric hindrance of the axial directions and $f_{7,1}$ emphasizes the steric hindrance in the directions perpendicular to the bond. $f_{10,1}$ emphasizes the steric hindrance in the directions of a cone including the three non-axial (not on the x-axis) bonds at a tetrahedral centre. $f_{11,1}$ emphasizes the steric hindrance in the directions of a cone stretching just between the axial bond (on the x-axis) and the other three bonds; the direction corresponds approximately to the directions of the three α-substituents.

Next, the longitudinal ϕ-functions are shown briefly. The 2ϕ function $f_{1,6}$ emphasizes the steric hindrance in the directions vertical to the carbonyl plane. On the other hand, $f_{1,7}$ emphasizes the steric hindrance for the attack from the in-plane directions; $f_{1,12}$ emphasizes the steric hindrance in the directions of dihedral angles eclipsing α-substituents, and $f_{1,13}$ emphasizes the steric hindrance in the directions of dihedral angles eclipsing the tetrahedral substituents on the reaction centre atom. Simultaneously they are the dihedral angles bisecting the directions of α-substituents.

Multiplication of the θ and ϕ functions generates a new weighting function. If we multiply the perpendicular function $f_{1,7}$ and the vertical function $f_{1,6}$ [more strictly by the multiplication of a θ-function $g_7(\theta)$ and a ϕ-function $h_6(\phi)$, a p-orbital-shaped function $f_{7,6}$ is generated. This procedure is illustrated in Figure 2. Similarly, the multiplication of $f_{10,1}$ and $f_{1,13}$ gives a tetrahedral function $f_{10,13}$ featuring (mimicking) bonds at the tetrahedral centre.

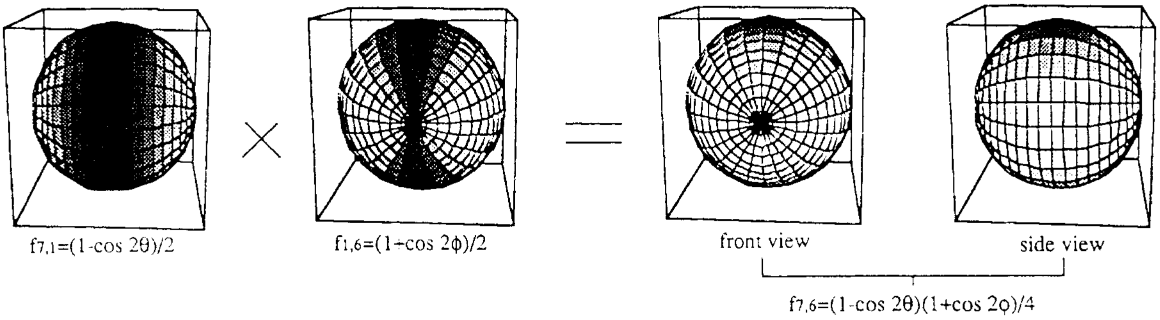


Figure 2. Complex weighting functions generated by the multiplication of simple θ and ϕ functions. $f_{7,1} \times f_{1,6} = f_{7,6}$

Relationship with the shape of the frontier orbital at the reaction centre

Reactions are thought to be induced by the orbital interaction between reactants. The interaction usually occurs between the HOMO and the LUMO of the two reactants. Factors determining the stereochemical course of reactions seemed more complicated, but the shape of the frontier orbital sometimes determines the directional dependency of the probability of reactions. In these cases, the anisotropy can be expressed by the overlap integral between the two reactants, which can be approximated by the angular part of frontier orbital wavefunction at the reaction centre X. This idea can be illustrated by the following typical examples in Figure 3. If we assume that the frontier orbital is s-like, the reaction should be isotropic; hence the weighting function $f(\theta, \phi) = 1$. In the case of a p(y)-type frontier orbital, the function $f(\theta, \phi)$ is expected to be dumb-bell shaped, similar to the angular part of a p-orbital except for its sign. In the case of an sp(x)^n-hybrid orbital, the function has a pear-like shape and is only dependent on θ (axially symmetric).

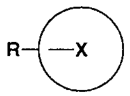
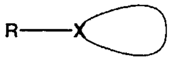
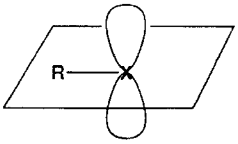
$f_{kl}(\theta,\phi)$	Orbital	Shape
$f_{1,1}(\theta,\phi)$	s	
$f_{3,1}(\theta,\phi)$	sp^n	
$f_{7,6}(\theta,\phi)$	p	

Figure 3. Similarity in shapes of some weighting functions with frontier orbitals

Applications of Ω_{jk} to the analysis of the steric effect

By introducing weighting functions to the calculations of Ω_s, the steric constant can be modified to reproduce the directional dependence of the reactions. This provides a new approach to the understanding of the stereochemical pathway of the access of reagents in reactions. For this purpose, several test reactions were subjected to linear correlation analyses [equation (6)] using a series of systematically weighted Ω_{jk} constants. The degree of conformity of a variety of Ω_{jk} was evaluated by referring to their correlation coefficients (r-values) or other appropriate parameters representing the fitting of the correlations. These Ω_{jk} can be a probe to elucidate the stereochemical course and mechanism of the reaction. Needless to say, a better conformity implies that we are nearer to the true mechanism.

$$\log k = a \log (1 - \Omega_{jk}) + b \qquad (6)$$

RESULTS AND DISCUSSION

Analysis on the preferred direction of access of the reagent: esterification of carboxylic acids and hydrolysis of carboxylate esters

The Ω_{jk} constants calculated on the RCOOH models were applied in order to characterize the steric effect on the reactions of carboxylic acid derivatives (Tables 2 and 3). Even if not very quantitative, the correlation coefficients can be a useful measure to evaluate the relative importance of the steric hindrance by the substituent stretching over the largely weighted

Table 2. Correlation coefficients of log *k* vs log[1-Ω_{jk}(COOH)] plots

j, *k*	Reaction (1)[a]	Reaction (2)[b]
1,1	0·942(3)	0·959(3)
2,1	0·930	0·944
3,1	*0·959*(1)	*0·975*(1)
6,1	0·883	0·865
7,1	*0·952*(2)	*0·966*(2)
1,6	0·918	0·944
1,7	0·917	0·945
6,7	0·876	0·860
7,6	0·918	0·949

[a] RCOOMe + OH^- in 40% dioxane at 20 °C.[3]
[b] RCOOH + CH_3OH + H_3O^+ at 40° C (reference reaction of E_s'[4]).

Table 3. Correlation coefficients of log *k*k vs log[1-Ω_{jk}(COOH)] plots

j, *k*	Reaction (3)[a]	Reaction (4)[b]	Reaction (5)[c]
1,1	0·787	0·845	0·750
2,1	0·736	0·812	0·731
3,1	*0·875*(1)	*0·902*(2)	*0·811*(3)
6,1	0·572	0·740	0·519
7,1	*0·822*(3)	*0·865*(4)	*0·785*(4)
1,6	*0·815*(4)	*0·900*(3)	*0·819*(2)
1,7	0·632	0·716	0·621
6,7	0·531	0·690	0·508
7,6	*0·840*(2)	*0·919*(1)	0·858(1)
E_s	0·923	0·897	0·867
E_s'	0·934	0·901	0·911

[a] $RCONH_2$ + H_3O^+ in H_2O at 85 °C.[18]
[b] $RCONH_2$ + OH^- in H_2 at 85 °C.[18]
[c] N-acyl(RCO)imidazole + H_2O at 30 °C.[18]

direction. Better correlation coefficients than the isotropic Ω_s ($\Omega_{1,1}$) are given in italics and ranked from the best: the numerals in the parentheses following the correlation coefficient values refers to the rank of fitting (1 refers to the best correlation and so on).

Tables 2 and 3 show that the correlations using $\Omega_{3,1}$ are considerably better than those using $\Omega_{2,1}$ 1 in both series of the reactions of carboxylic acids investigated. This implies that the steric hindrance on the opposite side of the substituent ($z<0$, front-side steric hindrance) affects the rate more than the rear-side steric hindrance. In other words, the substituent stretching its branches over the carbonyl function must hinder the reaction more seriously.

Similarly, the relative importance of the steric hindrance in the axial (parallel to the R—X bond) and the perpendicular directions to the R—X bond can be estimated by comparison of the correlations using $\Omega_{6,1}$ and $\Omega_{7,1}$. The steric importance in reference to the carboxyl plane can be estimated by use of longitudinal $h_k(\phi)$ functions. Hence we can evaluate the contribution by the steric effect from in-plane and vertical directions (with reference to the carboxyl plane), respectively, by $\Omega_{1,6}$ and $\Omega_{1,7}$.

Hydrolysis of carboxylate esters and esterification of carboxylic acids are well known and has been investigated in detail as the reference reaction to define E_s and similar steric substituent constants. Concerning to the directional dependences with reference to the molecular axis and the carboxyl plane, esters (Table 2) and amides (Table 3) were shown to behave considerably different in the processes of their hydrolyses and esterifications. As deduced from the almost identical *r*-values for $\Omega_{1,6}$ and $\Omega_{1,7}$ correlations (Table 2), ester hydrolyses and esterifications are almost isotropic with the rotation about the R—X axis, i.e., axially symmetric. [This apparently disagrees with the conclusion from the correlation analysis on $R_1R_2R_3CCOOH$ by Dubouis and co-workers,[19] which showed that the esterification is considerably anisotropic in reference to carbonyl group. However, their analysis was carried out only on the most stable conformation assuming that one of the α-alkyl groups (R_3) is synperiplanar to carbonyl and the other two groups (R_3 and R_2, alkyl or H) occupy anticlinal positions in this conformation. Actually, many alkyl groups prefer this conformation, but some do not. In addition, the second and third stable conformations are populated significantly in many of them. Thus more accurate MM calculations tend to average out the 'conformational effect' pointed out by Dubois and co-workers.] Their rates are slightly more significantly affected by the front-side than the rear-side steric hindrance. However, the difference is not great, since the *r*-values for $\Omega_{2,1}$ (rear-side) and $\Omega_{3,1}$ (front-side) are not very different. The Ω_{jk} analysis showed, in conclusion, that the hydrolysis and the esterification reactions are rather isotropic, which ensures the wide applicability of E_s and similar steric substituent constants defined from the rates of these reactions.

In contrast, hydrolyses of amides showed a very significant dependence on the longitudinal angle ϕ. The steric hindrance from the vertical direction to the carboxyl plane (measured by $\Omega_{1,6}$) affects the rates very significantly whereas the steric effect of the in-plane direction ($\Omega_{1,7}$) has much less significance. This fact, together with the considerable importance of the steric effect in the perpendicular direction ($\Omega_{7,1}$) to R—X, suggests the p-orbital-shaped preference of the amide hydrolyses. In fact, their rates were best correlated using $\Omega_{7,6}$ constants, which are weighted by the p-orbital-shaped function $f_{7,6}$ (θ, ϕ) (Figure 3).

We have no unambiguous explanation for this inclination of anisotropy (angular dependence). However, either or both of the factors given below might play a role in determining this tendency. The first is the difference in the transition state. If we assume that the amide hydrolysis has an early sp^2-like transition state, the p-orbital-shaped angular dependency can be rationalized. The second is the difference in their rotational barriers. As shown with trimethylacetic acid derivatives in Figure 4, the rotational barriers about the C_α—$C_{carbonyl}$ bonds of carboxamides from molecular orbital calculations (PM3) are considerably higher than the corresponding barriers for acids and esters. The higher rotational barrier of the amide is caused by the eclipsing of CH_3 and planar NH_2 groups and common to all alkyl groups bearing an α-alkyl group, i.e. all alkyl groups other than methyl. According to the Boltzmann equi-distribution law, the conformers whose energies are higher than kT (ca 0·6 kcal mol^{-1} at room temperature) can be assumed not to be considerably populated. This, in turn, restricts the range of effective torsional angle (ω) and increases the populations of alkyl/carbonyl eclipsed conformations. In contrast, the lower rotational barriers of carboxylic acids and esters can cause the loss of longitudinal anisotropy by averaging out the conformational distribution.

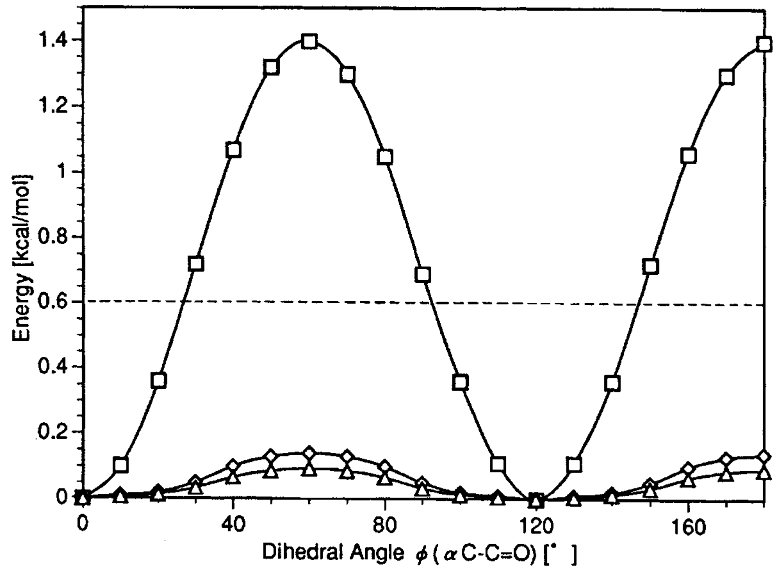


Figure 4. Conformational energies and rotational barriers of $(CH_3)_3CCOX$ [X = (△)OH, (◇)OCH_3 and (□*NH_2] by PM3 calculations

Table 4. Correlation coefficients of log *k*k vs log[1-$\Omega_{jk}(CH_3)$] plots

j, k	Reaction (6)[a]	Reaction (7)[b]	Reaction (8)[c]	Reaction (9)[d]
1,1	0·967	0·912	0·937	0·970(5)
2,1	*0·978*(4)	*0·935*(5)	*0·955*(5)	*0·973*(2)
3,1	0·942	0·866	0·898	0·956
6,1	*0·975*(5)	*0·936*(4)	*0·960*(3)	0·961
7,1	0·962	0·903	0·927	0·967
10,1	0·674	0·400	0·588	0·787
11,1	*0·983*(2)	*0·948*(2)	*0·964*(2)	*0·973*(2)
1,12	*0·979*(3)	*0·939*(3)	*0·960*(2)	*0·971*(4)
1,13	0·950	0·879	0·914	0·963
11,12	*0·985*(1)	*0·949*(1)	*0·968*(1)	*0·985*(1)
E_s	0·868	0·852	0·755	0·916
E'_s	0·900	0·845	0·748	0·914

[a] $RNH_2 + CH_2{=}CH_2Br$ in benzene at 100 °C.[20]
[b] RNH_2 + 2,4-$(NO_2)_2C_6H_3Cl$ in ethanol.[21]
[c] $RNH_2 + CH_3COOMe$ in dioxane at 25 °C.[22]
[d] ROH + 4-$NO_2C_6H_4COCl$ in diethyl ether at 25 °C.[23]

Analysis of the reactions involving substituted amines and alcohols

Results of Ω_{jk} analyses on some typical reactions on amino nitrogen and alkoxy oxygen atoms are given in Table 4. In the cases of amines (RNH_2) and alcohols (ROH), Ω_{jk} were calculated on the basis of the RCH_3 model, which had been shown more isotropic.[13] In our previous investigations, the RCH_3 model was shown to be more appropriate to reproduce the steric substituent effect by R on the reactions occurring on the nitrogen and the oxygen atoms. This might arise from the fact that the conformations of alkylamines and alcohols are more similar to RCH_3 than to RCOOH.

In Table 4, $\Omega_{2,1}$ 1 is always better than $\Omega_{3,1}$ and also than isotropic Ωs ($=\Omega_{1,1}$). This leads to the deduction that the rear-side steric effect has greater effect on the rates. Further, the very good performance by $\Omega_{11,1}$ and $\Omega_{1,12}$ suggests the importance of the steric hindrance around the R_1, R_2 and R_3 substituents. It should be noted that the $\sin(3\phi)$ term in $f_{1,12}$ becomes maximum when ϕ takes either of the torsional angles directing the orientations of R_1, R_2 and R_3 groups. Therefore, we calculated the $\Omega_{11,12}$ (as the product of $f_{11,1}$ and $f_{1,12}$). This represents approximately the steric hindrance in the directions of the three α-substituents. The best performance of $\Omega_{11,12}$ showed that the steric hindrance in the directions of three α-substituents (R_1, R_2 and R_3) is the most important in this series of reactions.

This deduction apparently conflicts with the earlier assumption that Ω_{jk} must be related to the shape of the orbital at the reaction centre. However, it is not surprising since the rates of the nucleophilic substitution of alkylamines and alcohols are strongly dependent on the structure of alkyl group. The reactions had been proved to be retarded by the branching of the alkyl group at the α-position.[24] This can be very clear evidence for the significant contribution of steric crowdedness in the direction of the α-substituents, which is reflected in the correlation analysis using the weighted Ω_{jk} constants. It seemed quite strange from the shape and direction of lone pair electrons, but it is reasonable if we consider the substantial effect of α-branching on the rates of these reactions

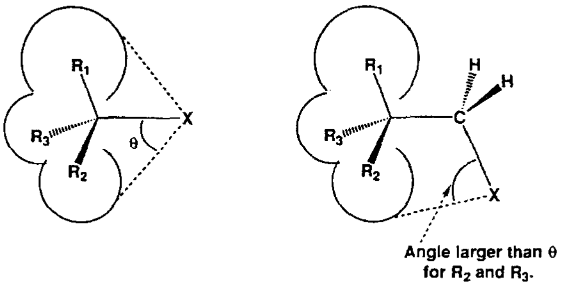


Figure 5. Steric hindrance caused by the substituent R on the α-carbon atom

For the reactions cited in Table 4 it was previously shown by DeTar[25] that their rates were far better correlated with E_s of the RCH_2 group than with E_s of the R group. Our results revealed that the rear-side steric hindrance plays a more important role than the forward steric hindrance. This can be rationalized if we assume that the angle looking up the substituent from the reaction centre X controls the steric hindrance. This is shown schematically in Figure 5. When we compared the two models (RX and RCH_2X models), the latitudinal angles θ become larger with two of the alkyl groups (R_1, R_2 and R_3) in the RCH_2 model than the corresponding angles in the RX model. The $R_1R_2R_3CCH_2X$ molecule has three rotamers about the C_α—C_β bond. The effective θ (population-averaged) for at least two of the three α-alkyl groups (R1, R2 and R3) in the RCH2X model becomes larger than the corresponding θ of the RX model. The magnitude of steric hindrance caused by the α-alkyl groups should depend both on the distance from X and the angle θ. In this case, the angle θ is more important than the distance.

In conclusion, our weighted Ω_{jk} functions provide a method for analysing the angular dependence of the steric effect on reaction rates by a correlation analysis

Table 5. Best-fit correlations [equation (6)] for reactions (1)–(9)

Reaction	Best-fit Ω_{jk}	*n*	*a*	*b*
(1) $RCOOMe + OH^-$	$\Omega_{3,1}$(COOH)	8	17·8 ± 2·5	−17·76 ± 0·15
(2) $RCOOMe + H^+$	$\Omega_{3,1}$(COOH)	29	40·2 ± 1·8	−36·9 ± 0·6
(3) $RCONH_2 + H_3O^+$	$\Omega_{3,1}$ (COOH)	9	35·0 ± 7·2	1·05 ± 0·34
(4) $RCONH_2 + OH^-$	$\Omega_{7,6}$(COOH)	8	8·4 ± 1·5	0·54 ± 0·14
(5) RCO-imiazole	$\Omega_{7,6}$(COOH)	7	12·7 ± 3·4	1·33 ± 0·64
(6) $RNH_2 + CH_2{=}CHCH_2Br$	$\Omega_{11,12}(CH_3)$	8	5·2 ± 0·4	−3·40 ± 0·10
(7) $RNH_2 + (NO_2)_2C_6H_3Cl$	$\Omega_{11,12}(CH_3)$	8	10·6 ± 1·4	−6·76 ± 0·31
(8) $RNH_2 + CH_3COOMe$	$\Omega_{11,12}(CH_3)$	8	13·0 ± 1·4	−8·55 ± 0·23
(9) $ROH + NO_2C_6H_4COCl$	$\Omega_{11,12}(CH_3)$	14	7·9 ± 0·5	−5·03 + 0·16

approach. The best-fit correlations for reactions (1)–(9) are given in Table 5. This analysis could give a deeper insight into the stereochemical course of reactions.

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