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Evaluation of the steric substituent effect by Ω_S: reinvestigation of the reaction dependency of the steric substituent constant

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ABSTRACT: Using the OMEGAS program, two sets [$\Omega_S(0.5,0.5)$ and $\Omega_S(0.9,0.5)$] of steric substituents were calculated by assuming different sizes of effective radii for the reaction center atom. The former set reproduces the steric substituent effect on the nucleophilic reactions of carboxylic acid derivatives better; the latter set is far better for the reactions of amines and alcohol derivatives. Our results clearly show that the effective size of the reaction center atom is another important factor in characterizing the steric effect in addition to the bulkiness of the substituent. This can be rationalized by the fact that such a general steric constant cannot be used to evaluate all sorts of steric effects using a single set of substituent constants. Copyright © 2001 John Wiley & Sons, Ltd.
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KEYWORDS: steric effect; steric substituent constant; E_S; Ω_S; reactions of carboxylic acid derivatives; reactions of amines and alcohol derivatives

INTRODUCTION

Since the linear free energy relationship equations were first applied to steric effects by Taft,[1] various attempts at searching for steric substituent constants have been reported. Earlier steric constants[1–6] were evaluated from the kinetic steric effects on reactions. On the other hand, computational methods to measure the steric effect have been proposed by several authors.[7–12] Most of the calculations on steric constants were carried out by modeling atoms by the spheres of van der Waals radii.

As molecular mechanics is one of the best methods to estimate the shapes and steric energies of molecules very precisely without the perturbation of electronic effects, it has been applied to many stereochemical problems. We used molecular mechanics in order to define our steric substituent constant Ω_S.[13] As has been reported previously, Ω_S is defined by Eqn. (1) as the normalized area of the shadow of the substituent seen from the reaction center atom (X) (see Fig. 1):

$$\Omega_S(r_c, r_r, r_s, \theta, \phi) = \frac{1}{4\pi {r_s}^2} \frac{1}{N} \int f(\theta, \phi)\ \mathrm{d}S \qquad (1)$$

Here, 'normalized' implies that the area of shadow is divided by the total surface area of the surrounding screen sphere ($4\pi {r_s}^2$). This makes Ω_s dimensionless. If we

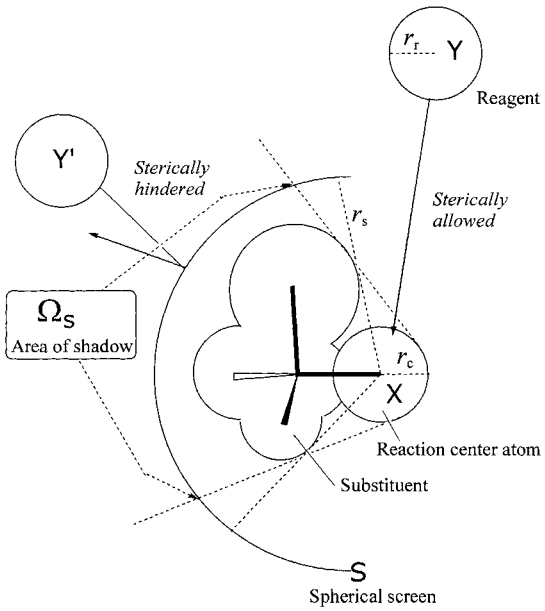

Figure 1. Schematic illustration of the definition of $\Omega_S(r_c,r_r)$. If we assume that the reaction center atom (X) is the light source, the reagent (Y′) coming from the direction of the shadow area on the screen sphere (S) is sterically hindered and cannot reach the reaction center. Reagent (Y) coming from the sunny area can reach the reaction center

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assume that $r_c = 0$ and $f(\theta,\phi)$, Ω_s is equal to the solid angle of the shadow area divided by 4π for normalization. Ω_s is calculated numerically as the shadow area in Fig. 1. Details of this procedure are reported in Ref. 13b.

The integration in Eqn. (1) is carried out over all elemental shadow areas (dS), and N is the normalization factor of the weighting function $f(\theta,\phi)$. In the calculations of Ω_S, the direction of the access of the reagent is defined by the angles θ and ϕ (the latitudinal angle θ and longitudinal angle ϕ of the polar coordinate system about the C_α—X bond axis).[13d,f] The function $f(\theta,\phi)$ is used to take the direction dependency effect into account explicitly and is defined as $f(\theta,\phi) = g(\theta)h(\phi)$, where $g(\theta) = \pm\cos(n\theta)/2$ or $\pm\sin(m\theta)/2$ and $h(\phi) = \pm\cos(n\phi)/2$ or $\pm\sin(n\phi)/2$, where $n = 0, 1, 2, 3$ and $m = 1, 2, 3$. The stereochemical meanings of the function are given in Ref. 13e. The geometric parameters r_c, r_r, and r_s are, respectively, the effective radii of the reaction center atom and the reagent, and the radius of the surrounding spherical screen S on which the shadow is projected. Note, if we intend to rationalize the radius of the surrounding screen r_s as a parameter to characterize the steric constant, it should be the distance of migration of the reagent within its directional correlation time, and should be closely related to the mean free path of the reagent. The steric constant Ω_S could easily be modified by altering these geometric and direction-dependency parameters.[13b]

When the substituent has more than one stable conformer, the population-weighted mean p_i (Eqn. (2)) of the Ω_S (i) of each conformer i over all conformers was used as the Ω_S of the substituent. The calculations were carried out numerically using the OMEGAS program.[13b,e]

$$\Omega_S = \sum p_i \Omega_S(i) \qquad (2)$$

The Ω_S value calculated in this way is expected to be a quantitative scale for the steric hindrance of the substituent on the reaction. Thus, $(1 - \Omega_S)$ can be related to the pre-exponential factor of the Arrhenius equation. This implies that the logarithm of $(1 - \Omega_S)$ can be expected to correspond linearly to the activation entropy and other steric parameters, such as E_S.

In the flood of various steric constants, several authors were aware of the reaction dependency of steric constants[14] and multiparametric steric effect models were proposed by Charton.[15] In this paper, the reaction dependency of the performance of the steric constants was reinvestigated by using the Ω_S methodology.

RESULTS AND DISCUSSION

Calculations of $\Omega_S(r_c,r_r)$

The calculations considering the dependency of rates on the direction of the attack of the reagent are useful for characterizing the anisotropy of the reaction. However, the reactions of carboxylic acids and esters are shown to be rather isotropic.[13e] The reactions involving the unshared electrons of alkylamino and alkoxy compounds are also shown to be considerably isotropic with respect to the steric effect by the alkyl group.[13d,e] These isotropic reactions (for which we can assume that $f(\theta,\phi) = 1$ in Eqn. (1)) are chosen as the samples throughout this paper in order to decrease the complication and the ambiguity due to the increase in the degree of freedom in the calculation of Ω_S.

The effective radii, r_c and r_r, were explicitly included in the calculation of Ω_S in order to evaluate the effects of the sizes of the reaction center atom (X) and the reagent (Y). Hereafter, the calculated Ω_S is denoted as $\Omega_S(r_c,r_r)$ in order to distinguish it from the original Ω_S.[†] In addition, the radius of the surrounding spherical screen r_s becomes necessary in the calculations where r_c takes a finite value. The $\Omega_s(0.5,0.5)$ and $\Omega_s(0.9,0.5)$ values for some important substituents are given in Table 1.

In this paper, $\log_{10}(1 - \Omega_s)$ was employed so as to evaluate the steric effect more quantitatively. This quantity is expected to be linearly correlated with log$k$ as discussed before.

Procedure in search for the best $\Omega_s(r_c,r_r)$

The contour map method. In the first place, we tried to search out the r_c and r_r values that give the best-fit in the E_S[1,2a,b] versus $\log_{10}[1 - \Omega_s(r_c,r_r)]$ correlation; in other words, to find the best $\Omega_s(r_c,r_r)$ for the hydrolysis and the esterification of carboxylic acid derivatives. This process is illustrated by the contour maps of correlation coefficients R in Fig. 2. In this investigation, the correlation coefficient R is used as a criterion to evaluate the performance of each steric constant. The maximum value of R (peak) is indicated by circles in the contour maps. The best-fit r_c and r_r values should correspond to the r_c and r_r coordinates of the peak in the contour map. In this way, the best-fit $\Omega_s(r_c,r_r)$ for the esterification reactions used to define E_s was shown to be $\Omega_s(0.5,0.5)$. As can be seen from the rather flat ridge along the line of $r_c = 0.5$ Å in Fig. 2, R is rather insensitive to r_r and does not seems important in characterizing the steric effect in this sort of reaction. On the other hand, R is very sensitive to the change in r_c. The three maps of R assuming that r_s is 4, 6, and 8 Å are very similar to each other. Similar trends were observed with other contour maps, and the r_s value was shown to be not an important factor in the performance of Ω_s which was measured by the change in

[†]E.g. Ω_S calculated by assuming that $r_c = 0.9$ Å and $r_r = 0.5$ Å is $\Omega_s(0.9,0.5)$. The original Ω_s is calculated by assuming that $r_c = r_r = r_{\alpha-C} = 0$. In this case, the ratio of the area of shadow to the total area of the surrounding sphere ($4\pi r_s$) becomes independent of r_s.

Table 1. Isotropic $\Omega_S(0.5,0.5)$ and $\Omega_S(0.9,0.5)$ constants for some alkyl, cycloalkyl, and aralkyl groups.[a]

Substituent	$\Omega_S(0.5,0.5)$	$\Omega_S(0.9,0.5)$
H—	0.2046	0.0967
CH_3—	0.3138	0.2081
CH_3CH_2—	0.3338	0.2585
$CH_3CH_2CH_2$—	0.3460	0.2730
$CH_3(CH_2)_3$—	0.3469	0.2744
$CH_3(CH_2)_4$—	0.3475	0.2754
$(CH_3)_2CHCH_2CH_2$—	0.3484	0.2767
$C(CH_3)_3CH_2$—	0.4074	0.3480
$(CH_3)_2CHCH_2$	0.3736	0.3075
$(CH_3)_2CH$	0.3604	0.3128
$CH_3CH_2C(CH_3)H$—	0.3646	0.3171
$(CH_3CH_2)_2CH$—	0.4248	0.3842
$C(CH_3)_3C(CH_3)H$—	0.4469	0.4082
$[(CH_3)_2CH]_2CH$—	0.4925	0.4591
$C(CH_3)_3$—	0.3909	0.3668
$(CH_3CH_2)(CH_3)_2C$—	0.4226	0.3989
$(CH_3CH_2)_2(CH_3)C$—	0.4613	0.4378
$(CH_3CH_2)_3C$—	0.4839	0.4600
cyclo-C_5H_9—	0.3553	0.3044
cyclo-C_6H_{11}—	0.3631	0.3158
cyclo-$C_6H_{11}CH_2$—	0.3723	0.3047
$C_6H_5CH_2$—	0.3540	0.2972
$C_6H_5CH_2CH_2$—	0.3729	0.3060
$C_6H_5(CH_2)_3$—	0.3638	0.2943
$C_6H_5C(CH_3)H$—	0.3952	0.3477
$(C_6H_5)_2CH$—	0.4215	0.3848

[a] The $\Omega_s(r_c,r_r)$ values of 38 alkyl substituents are available as supplementary material. The list covers the simple and the directionally weighted $\Omega_s(r_c,r_r)$ values in the ranges of r_r from 0 to 3.0 Å (at intervals of 0.5 Å) and of r_c from 0.3 to 0.9 Å (at intervals of 0.1 Å). The $\Omega_s(r_c,r_r)$ values outside this range can be calculated easily using the OMEGAS program. The list of the original Ω_s is given in Ref. 13c.

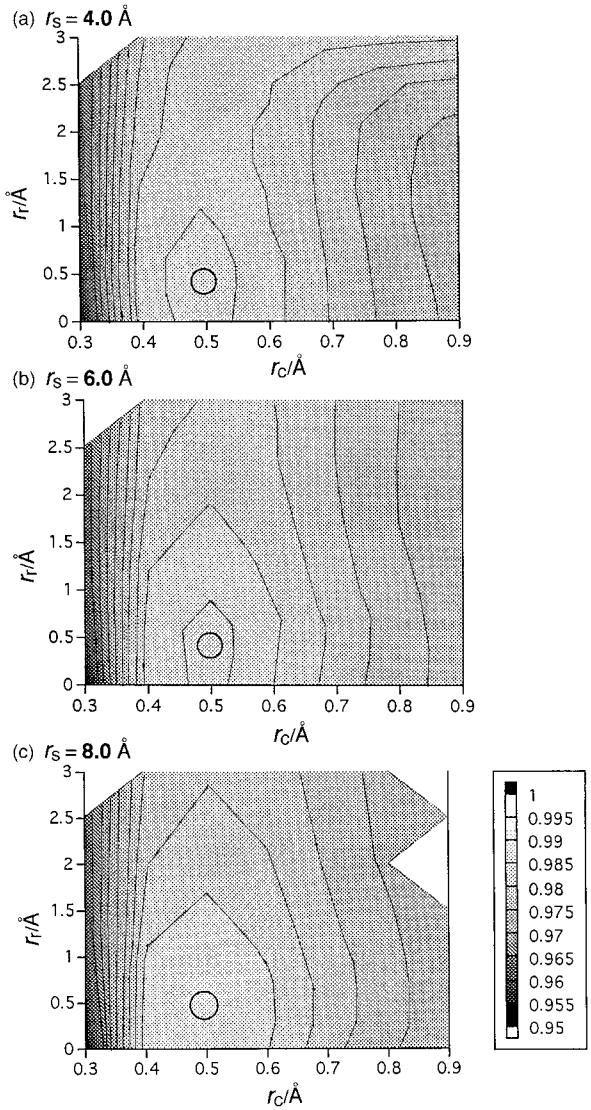


Figure 2. Contour maps of correlation coefficient (R) of the E_S versus Ω_S linear regressions using various $\Omega_S(r_c,r_r)$: (a) r_S = 4.0 Å; (b) r_S = 6.0 Å; (c) r_S = 8.0 Å

R. Thus, all other calculations hereafter were carried out by assigning 4 Å to the r_s value.

Even if the contour map procedure is rather cumbersome, it is useful to find out the most appropriate $\Omega_s(r_c,r_r)$, since the pattern of the contour map is characteristic of the type of the reaction and tends to be similar among similar reactions.

Simplified cross-section method. Next we wish to describe a simplified method to find out the best-fit $\Omega_s(r_c,r_r)$. Regression lines (a and b) and correlation coefficients R at several points along the two perpendicular vertical sections passing the peak of the contour map are given in Table 2. Reaction (a) of Table 2 is the same as the reaction whose contour map is shown in Fig. 2(a).

As to the acid hydrolysis rates of series of amides (b) and alkyl phenylacetates (c), again R is rather insensitive to r_r. If R is generally insensitive to r_r, the r_c value for the 'best-fit $\Omega_s(r_c,r_r)$' can be located tentatively as the peak of R along a cross-section at an appropriate r_r value in the contour map. This can be done quite easily by assuming tentatively that r_r is 0.5 Å and by varying r_c at intervals of 0.1 Å. After determining the peak along the r_c axis, the search along the r_r axis at this r_c value gives a nearly best $\Omega_s(r_c,r_r)$. By this procedure, we can reach the best-fit $\Omega_s(r_c,r_r)$ with these three examples in Table 2. A few repetitions of this procedure have given the best-fit $\Omega_s(r_c,r_r)$ in all cases investigated.

Reaction dependency of the steric constant

Both the esterification of carboxylic acids (RCOOH) and the hydrolysis of amides ($RCONH_2$) in acidic media (given in Table 2) have been shown to behave quite similarly on the contour map. The r_c for the best-fit $\Omega_s(r_c,r_r)$ is in the range 0.4–0.5 Å in both cases. In contrast, the $\log_{10} k$ versus $\log_{10}[1 - \Omega_s(r_c,r_r)]$ correlation of the hydrolysis of alkoxy esters ($C_6H_5CH_2COOR$)

Table 2. Correlation coefficients R for the linear regression log $k = a\log(1-\Omega_S(r_c,r_r)) + b$

r_c/Å	r_r/Å	a	b	R
(a) RCOOH + CH_3OH esterification in methanol at 40 °C ($n = 31$)[a]				
0.3	**0.5**	58.9	13.7	0.959
0.4	**0.5**	49.8	10.0	0.984
0.5	**0.5**	45.1	8.1	**0.9865**
0.6	**0.5**	42.1	7.0	0.984
0.7	**0.5**	40.1	6.2	0.980
0.8	**0.5**	39.1	5.7	0.976
0.5	0.0	59.4	8.4	0.9862
0.5	**0.5**	45.1	8.1	**0.9865**
0.5	1.0	36.1	8.2	0.985
0.5	1.5	29.4	8.2	0.984
0.5	2.0	23.8	8.3	0.984
(b) $RCONH_2 + H_3O^+$ reaction in H_2O at 75 °C ($n = 13$)[b]				
0.3	**0.5**	74.89	11.19	0.885
0.4	**0.5**	73.23	8.32	**0.965**
0.5	**0.5**	59.72	4.40	0.932
0.6	**0.5**	50.94	1.09	0.852
0.7	**0.5**	43.38	−0.76	0.805
0.4	0.0	102.28	9.42	0.964
0.4	**0.5**	73.23	8.32	**0.965**
0.4	1.0	57.19	7.93	0.963
0.4	1.5	45.78	7.68	0.962
0.4	2.0	38.69	7.47	0.960
(c) $C_6H_5CH_2COOR + OH^-$ reaction in 56% acetone at 25 °C ($n = 11$)[c]				
0.5	**0.5**	109.88	20.54	0.875
0.6	**0.5**	89.15	15.32	0.924
0.7	**0.5**	76.10	12.20	0.942
0.8	**0.5**	69.34	10.54	0.947
0.9	**0.5**	65.38	9.50	**0.9492**
1.0	**0.5**	62.23	9.17	0.947
0.9	0.0	84.55	9.16	0.9491
0.9	**0.5**	65.38	9.50	**0.9492**
0.9	1.0	53.73	10.13	0.945
0.9	1.5	44.80	10.85	0.942
0.9	2.0	37.18	11.60	0.941

[a] Correlation with the E_S constant. The data are shown more completely in Fig. 2. See Refs. 1, 2a,b.
[b] R = Me, Et, *n*-Pr, i-Bu, t-$BuCH_2$, i-Pr, *s*-Bu, Et_2CH, t-Bu, $PhCH_2$, *cyclo*-$C_6H_{11}CH_2$, *cyclo*-C_5H_9, and *cyclo*-C_6H_{11}. See Ref. 19.
[c] R = Me, Et, *n*-Pr, i-Bu, i-$BuCH_2$, *n*-C_6H_{13}, i-Pr, *s*-Bu, t-Bu, *cyclo*-C_5H_9, and *cyclo*-C_6H_{11}. See Ref. 21.

becomes a best fit when r_c is 0.9 Å. The facts allow us to assume that $\Omega_s(0.9,0.5)$ shows improved performance for the reactions involving alkoxy- and presumably alkylamino-compounds. On the other hand, E_s and $\Omega_s(0.5,0.5)$ are better for the alkylcarbonyl compounds.

With the aim of confirming this assumption, we examined more extensively the performance of these modified Ω_s in the correlation analysis. The various rate data[16–31] were plotted against the three modifications of Ω_s, namely $\Omega_s(0.5,0.5)$, $\Omega_s(0.9,0.5)$ and the original Ω_s, as well as against E_s for the purpose of comparison. In order to suppress the electronic and stereoelectronic effects to a minimum, only alkyl (and a few aralkyl) substituted derivatives of the series of compounds were employed in this investigation. Results are given in Table 3.

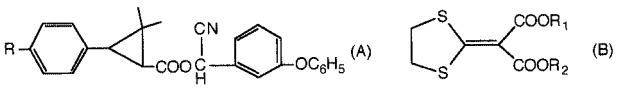
The performance of $\Omega_s(0.5, 0.5)$ with the rates of carboxylic acid derivatives were considerably improved in comparison with the correlations using $\Omega_s(0.9,0.5)$ and the original Ω_s, even if it is still considerably worse than E_s. In contrast, the rates concerning the alkylamino(R—NX—) and alkoxy(R—O—) compounds could be correlated with $\Omega_s(0.9,0.5)$ far better than with $\Omega_s(0.5,0.5)$ and E_s. In short, the set of steric substituent constants most suitable to evaluate the steric interaction at the carboxyl carbon is entirely different from the set evaluating the interaction at the nitrogen and oxygen atoms of amines and alcohols. As shown in the last four rows in Table 3, the $\Omega_s(0.9,0.5)$ constant also gave better performance than E_s in many correlations concerning biological activities.

Our results clearly showed that the effective size of the reaction center atom r_c should be another important factor characterizing the steric effect, in addition to the bulkiness of the substituent itself. This provides us a stereochemical interpretation for the reaction dependency of the steric constant. Reactions of carboxylic acid

Table 3. Performance of E_S and three modifications of Ω_S as the steric substituent constant[a]

Reaction or biological activity	Ref.	n[b]	E_S	$\log(1-\Omega^{0.5})$[c]	$\log(1-\Omega_S)$	$\log(1-\Omega^{0.9})$[c]
Nucleophilic reactions of RCOX compounds						
RCOOH + MeOH in HCl/MeOH	16	18	**0.994**	0.931	0.922	0.928
RCOO(β-$C_{10}H_7$) + MeOH in HCl/MeOH	17	6	**0.992**	0.964	0.947	0.956
RCOOEt + H_2O in HCl/70% MeAc aq.	18	12	**0.970**	0.963	0.929	0.949
$RCONH_2 + H_3O^+$ in H_2O	19	14	**0.925**	0.913	0.722	0.718
RCOSMe + OH^- in 40% dioxane aq.	20	9	**0.974**	0.922	0.911	0.874
Reactions of ROX and RNHX compounds						
$PhCH_2COOR + OH^-$ in 50% MeAc aq.	21	12	0.826	0.839	0.884	**0.899**
$AcOR + OH^-$ in 70% MeAc aq.	22	9	0.913	0.888	0.942	**0.952**
ROH + 4-$NO_2C_6H_4CH_2Cl$ in Et_2O	23	19	0.818	0.826	0.870	**0.882**
$RO^- + PhCH_2Cl$ in ROH	24	9	0.783	0.745	0.845	**0.846**
$RNH_2 + CH_2{=}CHCH_2Br$ in PhH	25	11	0.875	0.884	0.946	**0.958**
RNH_2 + 2,4-$(NO_2)_2C_6H_3Cl$ in $PhNO_2$	26	8	0.853	0.842	0.912	**0.928**
2-*R*-2-Oxo-3,1,2-dioxaphosphorinane + OH^-	27	8	0.707	0.791	**0.928**	0.925
RPhCHCN + OH^- in *iso*-AmOH	28	13	0.717	0.740	**0.886**	0.882
Biological activity						
$-\log LC_{95}$ to an acarus of (A)[d]	29	10	0.850	0.849	**0.888**	0.887
$-\log LC_{50}$ to another acarus of (A)[d]	29	10	0.831	0.840	**0.903**	0.889
$-\log ED_{50}$ of $RNHCH_2CN$	30	13	0.813	0.859	0.742	**0.884**
Hydrolysis (log k) of (B)[d] by a rat liver esterase	31	8	0.826	0.832	0.921	**0.982**

[a] The correlation coefficients (R) are given as a measure of the performance. The bold figures represent the best of four steric constants. Kinetics and activity data reported in the Refs 16–31 were used in the regression analysis.
[b] n: number of samples (substituents R) used in the linear regression analysis.
[c] $\Omega^{0.5}$ and $\Omega^{0.9}$ refer to $\Omega(0.5,0.5)$ and $\Omega(0.9,0.5)$ respectively.
[d] The formulas of compounds (A) and (B):



derivatives proceed *via* cationic intermediates and the reaction center atom is expected to have a relatively small radius. In contrast, oxygen and nitrogen atoms of the alkoxy- and alkylamino-derivatives have lone pairs of electrons that are rather loosely bound and spread widely into the space. The difference in the effective radius of the reaction center atom r_c for the two series of reactions can be accounted for qualitatively in this way. However, further sophistication and accumulation of data are necessary before the r_c parameter can be used for quantitative purposes and as evidence for the reaction mechanism.

The effect of effective radius r_c was shown to be closely related to the different contributions of the β-, γ-, and δ-carbon atoms of the substituent group to the steric effect. The correlation analytical treatment using Eqn. (3), proposed by Charton,[32] gives C_β, C_γ, C_δ, … values that can serve as a measure of their relative importance to the steric effect:

$$E_s(\text{or } \log(1-\Omega_s)) = C_0 + C_\beta N_\beta + C_\gamma N_\gamma + C_\delta N_\delta + \ldots \quad (3)$$

where N_β, N_γ, and N_δ are the numbers of β-, γ- and δ-carbon atoms, and C_β, C_γ, and C_δ are the coefficients giving the best-fit correlation of Eqn. (3).

In order to characterize various Ω_s from this point of view, they were analyzed using this equation. The results show that the C_β to C_γ ratio is closely dependent on our best-fit r_c values (Table 4). If we compare the C_γ/C_β ratios among the four steric constants under discussion, then it is found that $\Omega_s(0.5,0.5)$ is more similar to E_s, whereas $\Omega_s(0.9,0.5)$ is more similar to the original Ω_s.

Table 4. The best-fit C_0, C_β, C_γ, and C_δ values for Eqn. (3)

Steric constant	C_0	C_β	C_γ	C_δ	C_γ/C_β
E_S	1.584	−1.074	−1.040	0.011	0.97
Ω_S(original)[a]	0.191	0.0535	0.0282	0.0076	0.53
$\Omega_S(0.5,0.5)$	0.095	0.0842	0.0795	0.0067	0.94
$\Omega_S(0.9,0.5)$	0.075	0.1007	0.0601	0.0059	0.60

[a] Calculated by assuming that $r_c = r_r = r_{\alpha-C} = 0$.[13]

This trend is consistent with their performances in the correlations of the rates in Table 4.

Our original Ω_s[13a,c] values were calculated by assuming that both the reaction center atom X and the α-carbon atom are very small ($r_c = r_r = r_{\alpha-C} = 0$) for technical feasibility reasons. However, as a consequence of the small α-carbon, the relative contribution of the β-atoms in comparison to the γ-atoms is somewhat exaggerated.

CONCLUSION

The effective size of the reaction center atom X affects the characteristic feature of the steric effect; this is in addition to the bulkiness of the substituent itself. This effect comes essentially from the nature of the reaction, which implies that the steric substituent constant should be chosen by taking into account the mechanism. In agreement with previous studies by Charton[15] and others,[14] our analysis using modified Ω_s showed clearly that no single set of steric constants is very good at describing all the various sorts of steric substituent effect. In this situation, we must examine the nature of the relevant reaction closely and choose the most suitable set of steric substituent constants. Our OMEGAS program[13b] can serve to generate the statistically most appropriate set of steric constants. Alternatively, the analysis using various Ω_s, including anisotropic ones, helps us to find out the critical factors governing the steric effect (the diagnosis of the steric effect) and can give a deeper insight into the stereochemical course of reactions, providing a new strategy to elucidate the reaction mechanism.

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