A NEW STERIC SUBSTITUENT CONSTANT Ωs. CHARACTERISTIC FEATURE
AND COMPARISON WITH SOME OTHER STERIC CONSTANTS

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A new steric substituent constant, Ωs, was proposed in order to evaluate the kinetic steric effect. Ωs is isotropic and dependent most significantly on the number of β-carbon atoms. The rates of several reactions were shown to be correlated with Ωs better than with Es.

The correlation of molecular structure with chemical reactivity is one of the ultimate objects of organic chemistry. Statistical analysis is one of the most versatile and widely applicable approaches in this field. Since the pioneering work was reported by Hammett,[1] many investigations revealed that the substituent electronic effect could be correlated linearly with a few constants intrinsic to the electronic properties of the substituent.[2] The relationship between kinetic rates and substituent constants (such as σ) was rationalized in terms of linear free energy relationship(LFER).[3]

LFER was extended to the steric effect of the substituent. The Taft steric constant, Es,[4] is the first widely-applicable substituent constant *defined on the basis of the reaction rates.* It is based on the rates of hydrolysis of variously substituted carboxylic esters under acidic conditions assuming the Taft-Ingold hypothesis. Then, a variety of steric substituent constants were proposed in order to evaluate the steric effect caused by substituents.[5-8] On the other hand, precise geometries of a large number of molecules have been determined by spectroscopic and diffraction studies in cooperation with sophisticated quantum mechanical calculations. Thus accumulated knowledge on the molecular structure provides us sufficient data for the theoretical evaluation of sterical shape and bulkiness of organic molecules. Several steric substituent constants were defined on the basis of the progress in this field. The molecular volume and parachor,[9] as well as van der Waals volume Vw[10] and van der Waals surface area Aw,[10] are the prototypes of the steric substituent constant defined in reference to the bulkiness. The idea of the

molecular contour defined by van der Waals radii has been developed further to the STERIMOL parameters[11] used frequently in QSAR studies. Charton[12] defined the V constant from the size of substituent measured by assuming that the atom has a contour defined by van der Waals radius. Seeman and coworkers[13] found an excellent correlation of the bond length or the bond angle around the reaction center with the nonadditive kinetic effect on the methylation of 2,x-dialkyl pyridines. He also evaluated the geometric accessibility factors for nitrogens of several pyridines by evaluating the accessible solid angle. Tolman[14] defined the cone angle θ in order to evaluate quantitatively the steric effects of phosphorus ligands by use of CPK molecular models.

In recent decades, molecular force field method became known as a versatile tool for the quantitative estimation of steric effects. A variety of reactions have been studied by this method in the aim of predicting or justifying their steric courses and stereoselectivity. In most cases, the method was applied individually on a particular reaction system or, at most, a series of reactions of a similar type.[15] In contrast, relatively few applications have been reported for the purpose of evaluating general steric substituent constants. Wipke and Gund[16] evaluated the steric congestion for the nucleophilic attack towards carbonyl carbons of 52 cyclic ketones, reproducing the stereoselectivity of hydride attack on ketones. Beckhaus's ψf constant[17] for the evaluation of F strain is the steric substituent parameters which is developed by use of molecular mechanics. Meyer[18] recently proposed the volume in the anchor sphere V^a and the globularity G as steric substituent constants derived by molecular mechanics calculations. Meanwhile, the model caluculations by DeTar[19] have shown that the molecular mechanics calculations reproduce the Taft's Es parameters.

In order to evaluate the steric hindrance by a substituent to the access of the reagent, we have contrived a new method based on the molecular force field calculation and defined a new steric substituent constant Ωs,[20] and its calculation has been reported.[21] The outline of its definition is as follows. If we assume that a molecule has a contour defined by the van der Waals radii of constituting atoms, the steric hindrance by a substituent could be estimated from the area of its shadow projected to the surrounding sphere of an appropriate radius(R) when the substrate molecule was placed in a manner to coincide its reaction center with the center of the sphere where a light source was placed. The new steric constant Ωs is defined as the area of the shadow divided by the total surface area of the projected sphere. Since the substituent actually exists as an equilibrium mixture of several conformations, the area of

shadow has been calculated as the population-weighted mean of the shadow area of every conformer. Thus, Ωs should represent the probability of the access of a reagent to the reaction center. From this point of view, it is a measure for the pre-exponential factor of the Arrhenius equation and is expected to have entropic nature.

In this paper, we intended to examine the characteristic features of Ωs and to compare its performance in the actual correlation analysis to other steric substituent constants.

Calculations

The Ωs constants were calculated by use of the OMEGAS90 program on the geometries optimized by the conventional MM2 and BIGSTRN-3 programs.[22] Revised carboxyl parameters were used in the calculations on R-COOH models.[23] Threshold values of the convergence were set as 0.003 for conventional MM2 and 1×10^{-6} kcal/mol for BIGSTRN. Mass of unshared electron pair was assumed to be $2m_e$ (m_e = mass of an electron) in calculating the normal vibrational frequency of carboxylic acids in the RCOOH model.[24] The OMEGAS90 parameters: $r_c = 0$, T = 313.15K (40°C), $r_{vdw}(H) = 1.20A$, $r_{vdw}(C) = 1.70A$.[25] The radius of the sphere circumscribing the substituent is chosen as r_s, and d is optimized by MM2.

Results and Discussion

The Ωs values for 37 alkyl groups were calculated with the two different model molecules, namely R-COOH and R-CH$_3$ employing the two different methods for estimating the populations of conformers (the one from steric energy and the other from free energy). The results are given in Table 1. A little larger Ωs(R-COOH) value than the corresponding Ωs(R-CH$_3$) was observed with almost all substituents. This can be ascribed to the shorter C-X bond length in R-COOH model; i. e., $C_{sp}3(\alpha)-C_{sp}2(X)$ in R-COOH is shorter than $C_{sp}3(\alpha)-C_{sp}3(X)$ in R-CH$_3$. In most cases, conformations of R group are similar in the two model molecules. As the Ωs(R-COOH) and Ωs(R-CH$_3$) were closely correlated to each other (r=0.992), both of them can equally be used as steric substituent constants. We have proposed the Ωs(R-CH$_3$,G) as the standard Ωs constant for substituent R because it was calculated elaborately by use of BIGSTRN-3 and it has isotropic character (discussed later). Relatively large differences between Ωs from the two models were observed with α-neopentyl substituted alkyl group and a few other groups having relatively large freedom of motion, and shown to be caused by the conformational change between R-CH$_3$ and R-COOH models.

Characteristic Feature of Ωs Constant. In order to shed light on the implication of Ωs, the characteristic feature of Ωs was examined from the following two points of view: (i) whether it is a measure for the

Table 1. The $\Omega_s(R-CH_3)$ and $\Omega_s(R-COOH)$ Values for Various Alkyl Substituents. Numbers are common to the publication by R. W. Taft (ref. 4) except for some newly calculated substituents.

No	Substituent R	$\Omega_s(R-CH_3)$		$\Omega_s(R-COOH)$	
		SE[a]	G(FE)[a]	SE	G(FE)
	[Primary Alkyl]				
2	Me-	0.206	**0.206**	0.211	0.211
3	Et-	0.256	**0.256**	0.259	0.259
10	$^nPr-$	0.269	**0.273**	0.274	0.274
11	$^nBu-$	0.269	**0.272**	0.276	0.275
12	$^nPent-$	0.270	**0.272**	0.278	0.275
13	$Me_2CHCH_2CH_2-$	0.271	**0.267**	0.282	0.278
14	$Me(CH_2)_5-$	0.271	**0.271**	0.280	0.279
15	$^{neo}PentCH_2-$	0.263	**0.263**	0.279	0.273
26	$^iBu-$	0.298	**0.295**	0.305	0.303
35	$^tBuCH_2-$	0.331	**0.331**	0.338	0.338
	[Secondary Alkyl]				
20	$^iPr-$	0.304	**0.304**	0.306	0.305
28	$^sBu-$	0.326	**0.325**	0.334	0.333
39	Et_2CH-	0.356	**0.355**	0.373	0.368
41	$^nPr_2CH-$	0.361	**0.360**	0.384	0.377
42	$^iBu_2CH-$	0.382	**0.378**	0.399	0.403
46	$^tBuMeCH-$	0.383	**0.383**	0.391	0.391
55	$^iPrEtCH-$	0.386	**0.389**	0.401	0.402
58	$^iPr_2CH-$	0.418	**0.419**	0.431	0.431
63	$^tBu^iPrCH-$	0.453	**0.454**	0.459	0.460
64	$^tBu_2CH-$	0.473	**0.473**	0.483	0.483
37	$^{neo}PentMeCH-$	0.358	**0.358**	0.400	0.401
45	$(^{neo}Pent)_2CH-$	0.408	**0.411**	0.468	0.438
	[Tertiary Alkyl]				
32	$^tBu-$	0.352	**0.352**	0.354	0.354
54	$EtMe_2C-$	0.378	**0.378**	0.387	0.387
57	$^iPrMe_2C-$	0.404	**0.404**	0.410	0.408
47	$^tBuMe_2C-$	0.434	**0.434**	0.440	0.440
68	Et_2MeC-	0.402	**0.405**	0.414	0.412
48	Et_3C-	0.429	**0.429**	0.437	0.437
59	$^iPrEt_2C-$	0.459	**0.460**	0.463	0.464
66	$^tBuEt_2C-$	0.491	**0.491**	0.492	0.494
60	$^iPr_2MeC-$	0.461	**0,461**	0.474	0.475
61	$^iPr_2EtC-$	0.478	**0.482**	0.491	0.491
62	$^iPr_3C-$	0.522	**0.522**	0.515	0.515
65	$^tBu^iPrMeC-$	0.490	**0.495**	0.498	0.498
67	$^tBu^iPrEtC-$	0.514	**0.519**	0.522	0.522
44	$^{neo}PentMe_2C-$	0.417	**0.417**	0.448	0.447
49	$^{neo}Pent^tBuMeC-$	0.505	**0.505**	0.529	0.529

a) SE and G(FE) refer to the Ω_s values calculated on the basis of steric energy and free energy, respectively.

local steric hindrance or a measure for the global bulkiness of the sub-stituent; and (ii) whether it is an anisotropic constant specific to the individual reaction (model molecule) or a general isotropic constant. Topological treatment often serves in characterizing steric constants.

As easily understood from its definition, the Ωs constant can be expected to be a measure for the local steric hindrance around the reaction center which should affects the chemical reactivity most signifi-cantly. Alternatively, the characteristics from the total shape of the substituent must be reflected to a lesser extent in this constant. For example, the Ωs values for the straight chain alkyl groups tend to converge to a constant value with the increase in the number of carbon atoms of the substituents. This tendency also holds for other steric constants (such as Es) defined empirically from the chemical reactivity. In order to characterize Ωs from this view point, the Ωs values were correlated with several important kinetic steric constants and bulk parameters previously proposed by several authors.

Van der Waals volume (Vw) and van der Waals surface area (Aw) are known to represent the size and the shape of whole molecule [10] and their approximate values can be calculated by use of a simple additivity rule. In the first place, these bulk parameters were chosen as a criteria to examine the correlation of our Ωs with the total size and shape of the substituent group. The results of linear regression analyses (Table 2) showed, as expected, that the Ωs-values are correlated only fairly with both Vw and Aw.

Table 2. The correlation of Ωs(R-Me) with the van der Waals volume Vw and surface area Aw, as well as the Beckhaus's Ψf, by the linear regression equation Es' = a Cs + b. Standard errors are given in ( ).

Cs	a	b	n	r
Vw	3.77(0.38)	-0.18(0.15)	37	0.856
Aw	4.90(0.50)	-0.12(0.19)	37	0.856
Ψ f	34.85(2.83)	-8.51(0.99)	21	0.943

In order to characterize the Ωs further, it was tested topologically by a correlation analytical approach. Firstly, effect of branching of R on the Ωs value was examined by using the branching equation proposed by Charton.[27] The branching of alkyl chain has been treated topologically by classifying the carbon atoms with respect to the number of intervening bonds between the reaction center and the relevant carbon atom. Thus, the number of carbon atoms (N_j) which is separated by j-bonds from C_α was chosen as a parameter to represent the topological characteristics of

substituent (and denoted class j, hereafter). As previously reported [27] a steric substituent constant(Cs) can be approximated by eq. 1 as the sum of the contribution of each class (j), where coefficient a_j represent the relative importance of the class j. The equation 1' was applied to Ωs, and the contribution of the each class of carbon atoms to Ωs was evaluated.

$$Cs = a_0 + \sum_j (a_j N_j) \qquad Cs = Es' \qquad (1)$$

$$Cs = \Omega s \qquad (1')$$

Data from this regression analysis are given in Table 3. Carbon atoms at the β-position (class j=1) were shown to contribute predominantly to Ωs in contrast to Es' which depends almost equally upon the number of both β- and γ-carbon atoms (j=1 and 2).[28,29]

Table 3. Regression analysis of Ωs(R-CH$_3$) and Ωs(R-COOH) using eq.1. ($C_s = a_0 + a_1 N_1 + a_2 N_2 + a_3 N_3$). r and s refer to the correlation coefficient and the standard deviation, respectively.

Cs	a_0	a_1	a_2	a_3	n	r	s
Ωs(R-CH$_3$)	0.1909	0.0535	0.0282	(0.0076)	35	0.9935	0.0100
Ωs(R-COOH)	0.1950	0.0550	0.0278	0.0145	35	0.9879	0.0137
Es'	1.584	-1.074	-1.040	(0.0114)	35	0.9684	0.6944

Secondly, the conformational effect on Ωs was examined in the aim of clarifying whether it measures the steric effect isotropically or not.

The preferred conformation arising from the internal rotation about the C_{alpha}-$C_{carbonyl}$ bond of carboxylic acids and other carbonyl compounds has been studied rather extensively. Most of spectroscopic and diffraction experiments[30a] concluded that the most stable conformations of primary-alkyl(RCH$_2$) carbonyl compounds are syn-periplanar, i. e. alkyl(R)-carbonyl eclipsed (R$_1$=R$_2$=H, R$_3$=alkyl). The molecular orbital calculations, including ab initio calculations,[30b] supported the preferred conformation from experimental evidence. Molecular mechanics calculations also reproduce sp-conformation as the most stable minimum of energy surface,[26] proving its availability to the conformational search about the C_{alpha}-$C_{carbonyl}$ bond. As anticipated, considerable number of primary and tertiary carboxylic acids were shown by molecular mechanics calculations to take sp-conformations most preferably.

For a series of carboxylic acids which have common alkyl-carbonyl ecipsed conformations, Dubois and coworker[26] found out the fact that the magnitude of Es' value is mainly determined by the steric crowdedness

hindering the access of the reagent from the perpendicular direction to carbonyl plane. They did it by the correlation analytical approach (using eq.2) showing that the ac-substituent(R_1) reaching out perpendicular from the plane towards the less hindered side contributes most predominantly and the one (R_2) reaching towards the more hindered side contributes second predominantly to the Es' value. In eq. 2, the whole steric effect by $-CR_1R_2R_3$ group is partitioned into the contributions by Es' and six-numbers[31] of sub-groups R_1, R_2, and R_3.
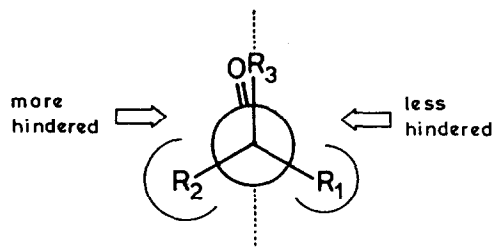
In order to know further about the nature of Ωs, we also tried to estimate the contribution of each alkyl sub-group to Ωs by use of Dubois method (eq. 2'),

$$Cs(CR_1R_2R_3-) = \sum_{k}(a_k Es'(R_k) + b_k \Delta 6_k) + c$$

$$Cs = Es' \quad (2) \qquad\qquad Cs = \Omega s \quad (2')$$

where Es'(R_k) and $\Delta 6_k$ refer to the Dubois' Es'[5] and the Newman's six-number,[31] respectively, for each sub-group (k = 1, 2, or 3). Here, H, Me, Et, ^{i}Pr, and ^{t}Bu are chosen as R_k's, whose Es' values increase monotonously with the successive substitution by a methyl group ("telescopic effect")[3] and are independent of the conformational effect. The coefficients a_k and b_k represent the relative importance of Es' and $\Delta 6_k$ for the substituent R_k in comparison with others. The results of the correlation analysis by eq. 2' are shown in Table 4.

Table 4. Relative contribution to Ωs of the sub-groups(R_1, R_2, and R_3) in the substituents having the most stable alkyl(R_3)-carbonyl eclipsed conformation (by eq. 2'). The coefficients x 10 of eq. 2 and the coefficients x 10^{-2} of eq. 2' are given. Figures in the parentheses are the standard errors.

Cs	c	a_1	a_2	a_3	b_1	b_2	b_3	r
Es'	-13.8	7.96	4.21	0.35	-8.13	-3.18	-1.38	0.999
	(1.17)	(1.60)	(1.66)	(1.70)	(0.68)	(0.35)	(0.41)	
Ωs(R-CH$_3$)	35.4	-4.52	-4.22	-4.40	1.28	0.55	0.35	0.9997
	(0.32)	(0.44)	(0.46)	(0.47)	(0.18)	(0.10)	(0.11)	
Ωs(R-COOH)	35.8	-4.84	-3.91	-4.38	1.33	0.59	0.36	0.999
	(0.62)	(0.84)	(0.87)	(0.90)	(0.34)	(0.18)	(0.21)	

In contrast to eq. 2 for E_S', the best fit regression coefficients of a_k of eq. 2' for Ωs are nearly identical irrespective of the direction of the sub-group relative to the C=O plane (shown by the thin broken line). Judging from rather small b_k coefficients, Ωs seemed less influenced by the six-number than Es'. The a_k coefficients of eq. 2' become more similar to each other for Ωs from R-CH$_3$ model than those from R-COOH model. The similarity of the a_k coefficients should guarantee the isotropic nature of the Ωs(R-CH$_3$) constant corroboratively.

Comparison of Ωs with Es'   Substituent steric effect on reactivity has been evaluated very frequently by using empirical constants based on kinetic substituent effect. Thus, the new steric constant Ωs was compared with some of them by correlation analytical approach.

The most typical of such substituent steric constants is the Taft's E_S which was defined as given by eq. 3 from the rates of the acid-catalyzed hydrolysis of esters.[4]

Table 5. Correlation of the new steric constants with Es' assuming a linear relationship (Es' = a Cs + b.)[a] Standard errors are given in ( ).

Cs	set	a	b	n	r
Ωs(R-Me)	prim(1)	-13.6(2.5)	3.2(0.7)	9	0.896
	prim(2)	-20.4(1.0)	5.2(0.3)	8	0.993
	sec	-41.3(3.4)	12.4(1.3)	9	0.993
	tert	-45.6(2.8)	14.6(1.2)	11	0.980
	all	-31.7(1.7)	8.5(0.6)	29	0.962
log(1-Ωs(R-Me))	prim(1)	10.1(1.7)	2.7(0.5)	9	0.910
	prim(2)	14.3(0.7)	4.2(0.2)	8	0.993
	sec	24.9(1.9)	8.8(0.9)	9	0.973
	tert	25.8(1.7)	9.6(0.8)	11	0.982
	all	19.9(0.9)	6.8(0.4)	29	0.974
log(1-Ωs(R-Me)-0.422)[b]		6.3(0.2)	7.1(0.4)	29	0.985
Ωs(R-COOH)	prim(1)	-13.4(2.5)	3.2(0.7)	9	0.895
	prim(2)	-20.3(0.7)	5.3(0.2)	8	0.996
	sec	-39.9(2.9)	12.3(1.1)	9	0.982
	tert	-45.6(2.4)	14.9(1.1)	11	0.988
	all	-31.0(1.7)	8.5(0.6)	29	0.962
log(1-Ωs(R-COOH))	prim(1)	9.9(1.7)	2.7(0.6)	9	0.910
	prim(2)	14.2(0.5)	4.2(0.2)	8	0.997
	sec	24.0(1.5)	8.8(0.8)	9	0.987
	tert	25.7(1.4)	9.9(0.8)	11	0.986
	all	19.6(0.9)	6.2(0.4)	29	0.974
log(1-Ωs(R-COOH)-0.419)[b]		6.0(0.2)	6.8(0.3)	29	0.987

a) The plots exclude the substituents having neopentyl group(s) (except $^{neo}C_5H_{11}CH_2$-), $^iBu_2CH$-, $^iPr_3C$-, and $^tBu^iPrEtC$- groups whose reliable Es values were inaccessible. The set of prim(1) includes all prim-alkyls, while the set of prim(2) excludes methyl.
b) The log(1-Ωs-Ωx) vs. Es' plots with the best fit Ωx values for "all-R" sets[,where Ωx(R-Me)=0.422 and Ωx(R-COOH)=0.419].

$$E_s = -\log k_{rel} = -\log(k/k_0) \qquad\qquad (3)$$

In this equation, k is the rate constant of the hydrolysis of ester RCOOEt and k_0 for ethyl acetate as the reference. Afterwards, Dubois and co-workers became doubtful on the kinetic data from which Es was derived. Accordingly, a revised Es constant, denoted Es', was defined by the same equation as Es (eq. 3) on the basis of standardized and controlled kinetic experiments on the acid-catalyzed esterification of carboxylic acids in methanol at 40°C. In addition, the Dubois Es' constant covers a wider range of alkyl substituents than Es. Therefore, the Es' values were employed for the purpose of comparing with Ωs. The Es' vs. Ωs plots are shown in Fig. 1. The gradient of the regression lines and their reliablity data are given in Table 5.

DeTar[32] threw doubt on the accuracy of Es' values for several bulky substituents. He pointed out that the Es' of ^{i}Pr$_3$C-(62) and ^{t}Bu^{i}PrEtC-(67) deviated largely from his estimation from the calculation. Plotted points for these substitents in Fig. 1 also deviated considerably from the regression line.

The correlation between Ωs and Es' is fairly good even when all classes of substituents were treated together. The correlation became better when treated within each class of primary, secondary, and tertiary alkyl substituents. The separation of the plotted points into such classes must arise from the conformation-dependent nature of Es'.[30] A similar separation of the plotted points was also reported with the Es vs. φ_f plot, where φ_f is a steric constant measuring the F strain of alkyl group. In this case, plotted points tend to be separated into three lines classified by the number of H atoms on the α-C atom of the substituent. This trend was suspected to be originated from the conformational feature of the aliphatic esters. The Es' vs. Ωs plot in Fig. 1 is very similar to the reported Es vs. φ_f plot, both of them consisting of three separate lines corresponding to the classes of alkyl groups. Thus the separation of the plotted points into primary to tertiary alkyl groups in the Es' vs. Ωs plot should also be caused by the conformational effect included in Es'. The excellent linear regression within each class (Table 5) renders a support on the usefulness of Ωs constant for the evaluation of steric hindrance when the conformational effect is absent. The fact that the plotted point for methyl group is occupying a position away from the regression line for primary groups is quite reasonable, since it has three, instead of two, hydrogen atoms on the α-carbon atom. In addition, its conformational behavior is expected to be essentially different because of its three-fold axis of symmetry.
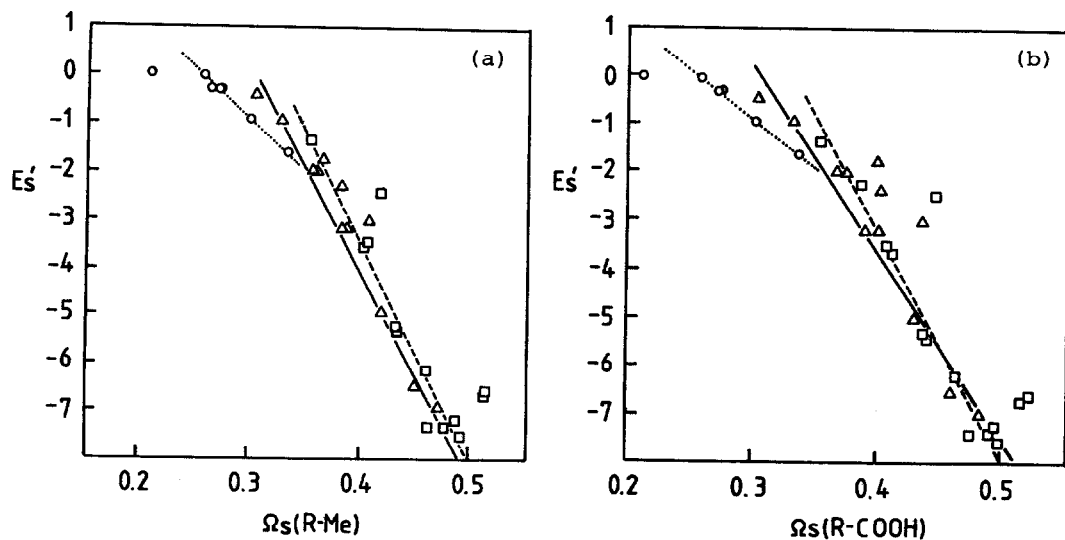
Fig. 1. Plots of Es' vs. Ωs plots using (a) Ωs(R-Me) and (b) Ωs(R-COOH). Open circles, triangles, and squares represent primary, secondary, and tertiary alkyl substitents, respectively.
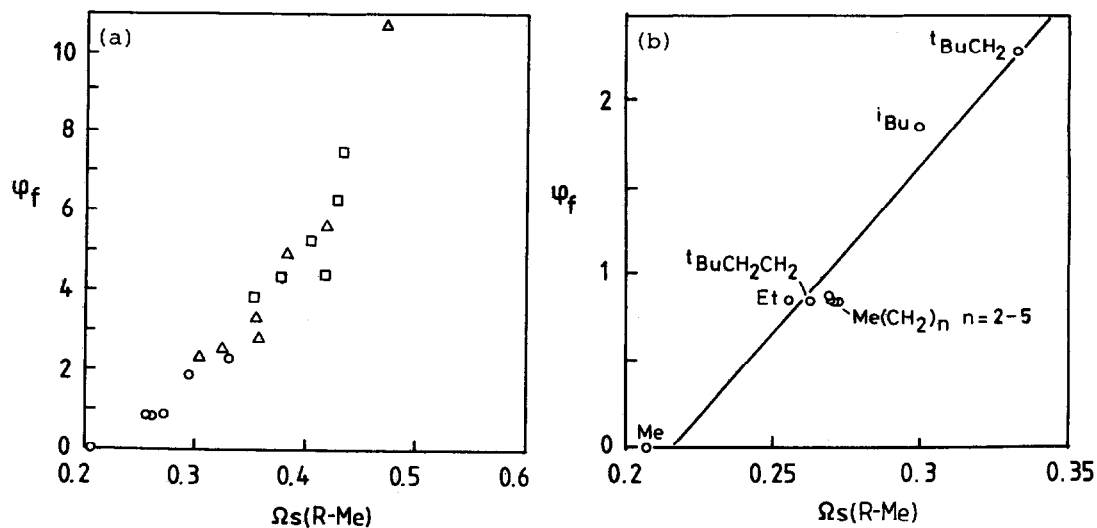

Fig. 2. Plots of Beckhaus's φ_f vs. Ωs(R-Me): (a) the plot including all substituents, and (b) the enlarged plot in the region of primary alkyl groups. The marks have the same meaning as in Fig. 1.

The φ_f vs. Ωs plot is given in Fig. 2. The plotted points consist a somewhat concave line reflecting excessively large frontal strain for $^tBu_2CH-$ and $^tBuCMe_2$-groups. As expected from the isotropic nature of the both steric parameters, the plotted points showed no tendency of separating into groups of primary to tertiary alkyl substituents. As φ_f was designed to estimate the F strain in the close vicinity of the reaction center, it is a measure for the very short-range steric effect in the neighborhood of α-carbon atom. As a result, φ_f's for all $R(CH_2)_n$-groups (R=alkyl) converge to a nearly same value. This trend is revealed more clearly in the enlarged φ_f vs. Ωs plot (Fig. 2b) for primary alkyl groups. In fig. 2b, plots for long chain n-alkyl groups ($CH_3(CH_2)_n$-: n = 2-5) deviate from the regression line apparently. The regression coeficient of Fig. 2b (r=0.949, ψ=0.358) was improved considerably when these groups were excluded (r=0.993, ψ=0.166). This implies that Ωs can perceive the steric effect of longer range than φ_f.

Use of log(1 - Ωs) as a Steric Substituent Constant. From the definition of Ωs, (1 - Ωs) should represent the probability of the reaction and, hence, be proportional to the pre-exponential factor of the Arrhenius equation. Thus log(1- Ωs) can be expected to be proportional to $\log(k/k_0)$ when the rate is controlled by steric effect. For this reason, log(1 - Ωs) was plotted against Es'. (Fig. 3, see also the correlation data in Table 5.) The use of log(1- Ωs) improved the correlation with Es' slightly. Thus the log(1- Ωs) value can be another steric substituent constant. Nevertheless, Ωs itself is still an appropriate steric constant in the linear correlation analyses, since its availability is rationalized by the fact that the Taylor expansion of ln(1-Ωs) gives -Ωs as the first term of the power series (eq. 4) and the second and subsequent terms are much smaller than the first term.

$$\ln(1 - \Omega s) = -\Omega s - (1/2)\Omega s^2 - (1/3)\Omega s^3 - \cdots \qquad (4)$$

If we proceed further the discussion on the log(1- Ωs) model, the access of the reagent must be hindered by other substituent atoms linking to the reaction center (OH and =O in the case of R-COOH) just like by R. Thus the probability factor (1- Ωs) should be subtracted by Ωx, which corresponds to the solid angle occupied by other substituent atoms and groups on X (Fig. 4).[33] The most suitable Ωx value for a series of similar reactions at the similar reaction center can be estimated by searching for the best fit Ωx value for the $\log(k/k_0)$ vs. log(1- Ωs-Ωx) plot. By this method, the Ωx value was estimated to be 0.422 for the esterification of RCOOH on which Es' is based. Thus obtained Ωx value is

rather larger than expected from the size of OH and =O groups. This might
imply the fact that the reaction center is more crowded than estimated by
(1- Ωs). Both the sizes of the reaction center (X) and the reagent (Y)
were assumed to be infinitesimal in the calculation in the expectation
that they should be cancelled out each other. This assumption seemed

necessary to define the
Ωs as a general sub-
stituent steric con-
stant not dependent on
any particular reaction
system, i. e., not
dependent on r_Y.
However, the reagent
can be bulkier than the
atom at the reaction
center (i. e.,$r_Y > r_X$)
in many cases. Such
situations might result
an exaggerated Ωx
reflecting the crowded-
ness around the reac-
tion center.
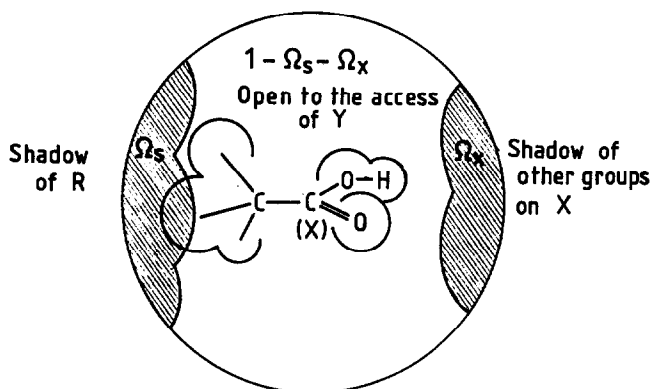
FIg. 4.   Implication of Ωx.
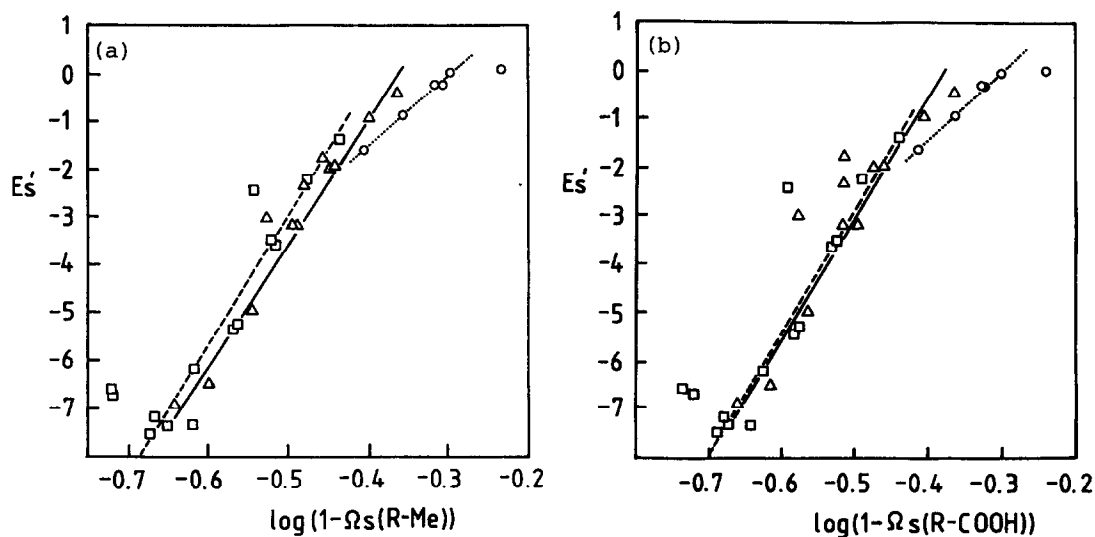
Fig. 3.   Plots of Es' vs. log(1-Ωs) using (a) Ωs(R-Me) and (b)
Ωs(R-COOH). The marks have the same meaning as in Fig. 1.

Some Quantitative Structure-Reactivity Relationship by use of Ωs

The Ωs constants were then correlated with the rates of several series of reactions (Fig. 5) in order to examine the extent of their applicability.[34] All of the trial reactions [(1) to (8) in Fig. 5] were cited from literature.[36-42] In most cases, their rates had been carefully determined by the original authors in view of evaluating the substituent steric effect by correlation analyses. These kinetic data were correlated with Ωs by applying eq. 5' which was derived from the Taft equation (eq. 5) by replacing Es by Ωs. Quite analogous to the $\log(k/k_0)$ vs. Es plots, the $\log(k/k_0)$ vs. Ωs plot was shown to regress to eq. 5' with good reliability.

$$\log(k/k_0) = \rho_s Es \qquad\qquad (5)$$

$$\log(k/k_0) = \rho_s \Omega_s + a' \qquad\qquad (5')$$
$$\text{or} \quad \log k = \rho_s \Omega_s + \log k_r$$

The slope ρ_s and correlation coefficient r of these plots (eq. 5') are given together with the corresponding parameters for the $\log(k/k_0)$ vs. Es plots (eq. 5) in Table 6. Except for the alkaline hydrolysis of RCOOMe (reaction 4) which is very similar to the reference reactions used to define the Es' (and Es) constant, the relative rates ($\log(k/k_0)$) are always better correlated with Ωs than with Es when we compared the correlation coefficients and standard deviations of the two series of plots.

In eq. 5', ρ_s represents the sensitivity of the rates to the steric effect. The ρ_s values from the log k vs. Ωs plots could be correlated very excellently with those from the log k vs. Es plots (r = 0.991 for Ωs(COOH) and r = 0.989 for Ωs(Me)). Thus the ρ_s values from both the log k vs. Es and the log k vs. Ωs plots should have a common significance. If we compare the three reactions of RNH$_2$ (reactions No. 1, 2, and 5), the Ωs value tends to increase as the steric hindrance around the reaction center becomes more stringent. The constant a' can be related to the logarithm of the rate (k_r) of an ideal substrate which has a substituent of infinitesimal radius (a' = $\log k_r$ - $\log k_0$).

The rates of the S_N2 reactions of primary alkylamines (RNH$_2$) with 2,4-dinitrochlorobenzene in ethanol (reaction 1)[37] and with allyl bromide in benzene (reaction 2)[38] were first analyzed by DeTar and coworkers[35] using the Taft equation. They found that the rates could be correlated very excellently with the E_s values for RCH$_2$ groups (denoted hereafter as Es(RCH$_2$)). In sharp contrast, the correlations became rather poor when the E_s for R group (denoted as Es(R)) were used in place of the E_s(RCH$_2$).
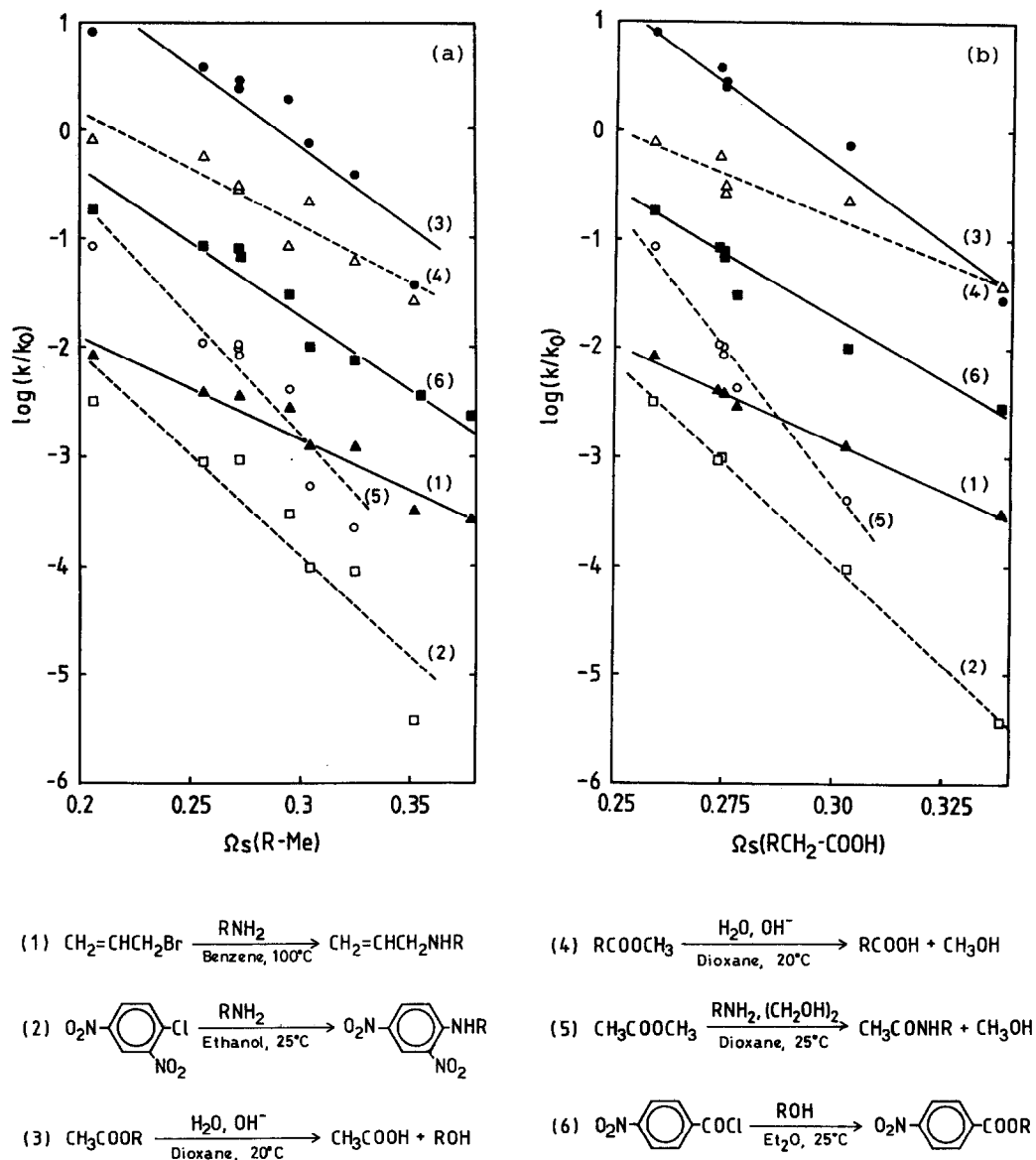
Fig. 5. Plots of the relative rates $\log(k/k_0)$ vs. Ωs(R-X) for reactions 1 to 9 [Figs. 5(a) and 5(c)] and the $\log(k/k_0)$ vs. Ωs(RCH$_2$-X) plots for reactions 1 to 6 [Fig. 5(b)]. The numbers in paretheses correspond to those of the reactions. The $\log(k_A/k_B)$ values were used in place of $\log(k/k_0)$ in reactions 8 and 9.
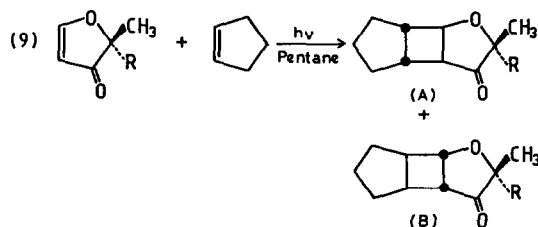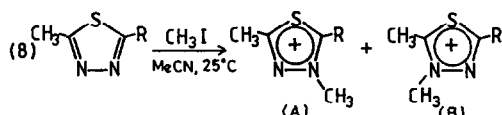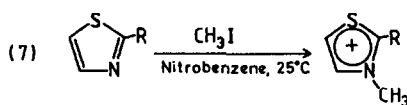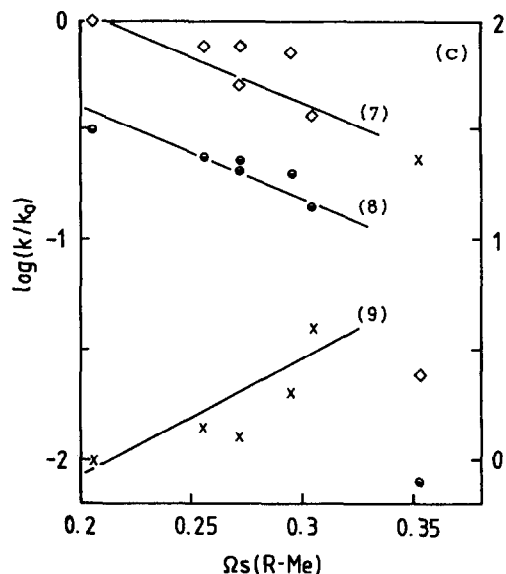
Table 6. Correlation of Several Rate Data with $\Omega s(R-X)$ and $\Omega s(RCH_2-X)$. (X = COOH and Me)

Ref. No	Steric const(Cs)	R			RCH₂		
		ρs	n	r (s)	ρs	n	r (s)
(1)[37]	Es	0.70	7	0.868 (0.251)	0.81	6	0.986 (0.093)
	Ωs(COOH)	-9.1	8	0.954 (0.171)	-17.4	6	0.995 (0.054)
	Ωs(Me)	-9.3	8	0.959 (0.157)	-17.9	6	0.979 (0.112)
(2)[38]	Es	1.47	8	0.852 (0.524)	1.75	7	0.997 (0.084)
	Ωs(COOH)	-18.4	8	0.888 (0.460)	-36.9	7	0.999 (0.051)
	Ωs(Me)	-18.5	8	0.898 (0.434)	-38.7	7	0.992 (0.088)
(3)[36]	Es	1.24	8	0.905 (0.340)	1.36	7	0.987 (0.137)
	Ωs(COOH)	-15.1	8	0.910 (0.331)	-28.9	7	0.988 (0.133)
	Ωs(Me)	-15.1	8	0.916 (0.316)	-29.4	7	0.985 (0.194)
(4)[36]	Es	0.93	8	0.997 (0.045)	0.72	7	0.807 (0.326)
	Ωs(COOH)	-10.6	8	0.942 (0.182)	-15.9	7	0.832 (0.306)
	Ωs(Me)	-10.5	8	0.937 (0.202)	-15.7	7	0.779 (0.346)
(5)[39]	Es	1.62	8	0.755 (0.589)	2.56	6	0.921 (0.229)
	Ωs(COOH)	-21.2	8	0.927 (0.338)	-51.8	6	0.989 (0.043)
	Ωs(Me)	-21.8	8	0.932 (0.326)	-54.7	6	0.931 (0.303)
(6)[40]	Es	0.84	12	0.914 (0.285)	1.07	7	0.914 (0.207)
	Ωs(COOH)	-12.9	14	0.961 (0.197)	-23.3	7	0.976 (0.151)
	Ωs(Me)	-13.6	14	0.967 (0.183)	-23.8	7	0.941 (0.232)
(7)[41]	Es	0.49	7	0.602 (0.488)	0.95	7	0.963 (0.166)
	Ωs(COOH)	-8.1	7	0.703 (0.435)	-20.0	7	0.950 (0.192)
	Ωs(Me)	-8.3	7	0.722 (0.423)	-20.5	7	0.943 (0.203)
(8)[41]	Es	0.48	7	0.609 (0.476)	0.94	7	0.966 (0.156)
	Ωs(COOH)	-8.1	7	0.715 (0.420)	-19.7	7	0.955 (0.179)
	Ωs(Me)	-8.2	7	0.734 (0.408)	-20.1	7	0.946 (0.195)
(9)[42]	Es	-0.81	6	0.936 (0.199)	-0.76	5	0.950 (0.200)
	Ωs(COOH)	9.6	6	0.919 (0.222)	17.1	6	0.950 (0.176)
	Ωs(Me)	9.4	6	0.921 (0.477)	17.3	6	0.949 (0.210)

Thus, the $\log(k/k_0)$ were also plotted against the Ωs for RCH_2 groups. His results were again reproduced in our $\log(k/k_0)$ vs. Ωs plots. The reactions of alcohols (reactions 3 and 6) again behave similarly, but to a lesser extent. This fact could be accounted by assuming that the ROH and RNH_2 molecules react at the reaction center located on the robe of unshared electron pair. The unshared electron pair of RNH_2 occupies a position topologically similar to the X group of RCH_2-X molecule. However, we could assume alternatively that the reactions do proceed on the oxygen and nitrogen atoms just like the carbonyl reactions. Since the substituent R is directly linked with the nitrogen and oxygen reaction centers in the latter assumption, Es(R) should also give a good correlation. In fact, our Ωs(R) could be correlated with the rates of reactions 1 to 6 considerably better than Es(R). In order to make a better use of Ωs, how to search the location of the actual reaction center X becomes a very important problem to which we are pursuing further.

As revealed by the analyis using eq. 2,[31] Es', as well as Es, includes some anisotropic effects depending on the mechanism of the reference reaction used in definition. This is reflected in the fact that a very close linear correlation of steric effect measured by Es' and reaction rates holds only among the reactions in the series of carboxylic acids RCOOH and carboxylate esters RCOOR' of which transition states are expected to take similar conformations as that of the reaction used in its definition. Some fluctuations and deviations were observed when Es' was applied to other kinds of reactions. The origin of such anisotropic effects can be one or several of conformational effect,[17,31] hyperconjugation effect,[6a] directional effect to the access attacking reagent,[13,16,26] etc. Generally speaking, they tend to injure the good correlation whatever their origin can be. On defining our new steric constant Ωs, the steric effect was evaluated by the calculations on an idealized system free from such effects originating from the individual reactions used for the definition. In this respect, Ωs can be expected to be more isotropic and, hence, more generally applicable.

However, its application should be limited to the rates of reactions giving strainless products as easily understood from its definition. Additional strain energy in the transition state must retard the reaction manifesting an exaggerated steric hindrance effect more than expected from Ωs. In order to check the limit of the applicabilty of Ωs, it was applied to the rates of reactions 7 to 9[41,42] [Fig. 5(c)]. Their reaction centers are separated by more bonds from the substituent R than reactons 1 to 6. In these reactions, the orientation of R is fixed relative to the site of reaction so as to oppose the access of reagent. Therefore,

considerable increase in steric energy is expected in the transition state
when the substituent is bulky (ex. t-butyl). This trend can be seen
apparently with reactions 7 and 8 in which the ortho-substituent hinders
the frontal attack inducing the F strain. Plotted points for ^{t}Bu (and
^{i}Pr, sometimes) deviate apparently downward from the regression line [Fig.
5(c)]. Similar deviationwere also observed with the $\log(k/k_0)$ vs. Es
plots of these reactions. The concave plots for reaction 9 is another
example of exaggerated effect. This beffect is also seen to a lesser
extent with reaction 1 [Fig 5(a)], which is expected to be hindered
considerably by the ortho-nitro group.

Conclusion

A new steric substituent constant Ωs was shown to provide an appro-
priate measure for the kinetic steric effect around the reaction center.
It is usually more accurate than conventional steric substituent constants
defined on the basis of kinetic experiments. The Ωs value calculated on
the model $R-CH_3$ molecule can be expected to be used very generally, since
it is isotropical and free from the effect of the habit of the reference
reactions used for definition.

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