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The Nature and Composition of Taft–Hancock Steric Constants

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The Taft steric, E_s, and the Hancock corrected steric, E_s^c, constants of a set of various alkyl- and heteroatom-substituted groups were analyzed as to whether they are separable into components. The analyses were carried out by means of the equation $E_s(CR_1R_2R_3) = aE_s(R_1) + bE_s(R_2) + cE_s(R_3) + d$, where $E_s = E_s$ or E_s^c and $E_s(R_1) \geqq E_s(R_2) \geqq E_s(R_3)$. For the set of 37 groups, the correlation was surprisingly good for E_s^c values, 98% of variance of the data being elucidated. The finding that the linear combination of three α substituents is capable of describing the steric constant of the parent group indicates that the relative importance of the steric repulsion effect and steric hindrance of motions in any one of the E_s^c values is unchanged so that an isokinetic relationship holds between relative enthalpies and entropies of activation for the steric course of ester reactions.

In order to estimate the steric effect in aliphatic reactions quantitatively, the Taft E_s constants defined by eq 1 are most widely used.[1] The expression $(k_R/k_{Me})_A$ refers to the ratio of the rate constant of acid-catalyzed hydrolysis of esters of the type RCOOEt to that of MeCOOEt.

$$E_s = \log(k_R/k_{Me})_A \qquad (1)$$

Since the E_s value is determined by the relative activation free energy from the unsaturated initial state to the saturated transition state of the ester hydrolysis, Hancock and his coworkers considered that a hyperconjugation effect of α hydrogen may contribute to the estmate of E_s values.[2] They defined an E_s^c (corrected steric) constant as shown in eq 2, separating the hyperconjugation effect from the "true steric effect." In eq 2, n_H is the number of α hydrogen atoms.

$$E_s^c = E_s - 0.306(3 - n_H) \qquad (2)$$

In the course of structure–reactivity studies on various sets of aliphatic amines with various lone-pair electron acceptors, we have found that the steric and polar effects of three N substituents of amines can be separated in the form of eq 3, where k is either a rate or an equilibrium constant, ρ^*, a, b, c, and d are constants, and $\Sigma\sigma^*$ is the summation of the Taft σ^* values of three N substituents. E_s^c1, E_s^c2, and E_s^c3 relate to the N substituents R_1, R_2, and R_3, denoted according to the sequence of their magnitude, *i.e.*, $E_s^c1 \geqq E_s^c2 \geqq E_s^c3$. The use of E_s instead of E_s^c values was found to yield poorer results.[3]

$$\log k = \rho^*\Sigma\sigma^* + aE_s^c1 + bE_s^c2 + cE_s^c3 + d \qquad (3)$$

The total steric effect of three N substituents, R_1, R_2, and R_3, on a certain electron acceptor is similar in nature, if not identical, to that of three α substituents R_1, R_2, and R_3 on the reaction center in the transition state of ester hydrolysis as suggested by Taft (Figure 1).[4] We have assumed that the E_s^c value of a certain group, $CR_1R_2R_3$, may be expressed by a linear combination of those of three α substituents, R_1, R_2, and R_3, as shown in eq 4, where $E_s^c1 \geqq E_s^c2 \geqq E_s^c3$ and a, b, c, and d are constants which are determined by means of the method of least squares.

$$E_s^c(CR_1R_2R_3) = aE_s^c1 + bE_s^c2 + cE_s^c3 + d \qquad (4)$$

The purpose of the work in this paper is to obtain supporting evidence on the above assumption by analyzing the mutual relationship among E_s^c values expressed in terms of eq 4 and to contribute to a better understanding of the nature and composition of steric constants. Since the particular use of E_s^c values has been viewed with skepticism by some workers,[5] we have compared the quality of correlation between eq 4 and its counterpart for E_s values.

Analyses.—First, we have analyzed E_s and E_s^c values directly with those of three α substituents for 26 primary, secondary, and tertiary alkyl groups from the Taft's original tabulation.[1] Equations 5 and 6 are derived for E_s and E_s^c values, respectively. In these and the following equations, n is the number of data points used for the correlation, s is the standard deviation, and r is the correlation coefficient. The figures in

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[1] R. W. Taft, Jr., "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, p 597.

[2] K. Hancock, E. A. Meyers, and B. J. Yager, *J. Amer. Chem. Soc.*, **83**, 4211 (1961).

[3] T. Fujita, C. Takayama, and M. Nakajima, to be published.

[4] Reference 1, p 673.

[5] K. Bowden, N. B. Chapman, and J. Shorter, *J. Chem. Soc.*, 5239 (1963).

$$\begin{array}{lccccr} & n & s & r & F_{3,26} & \\ E_s(\mathrm{CR_1R_2R_3}) = \underset{(\pm0.655)}{-2.467} + \underset{(\pm0.554)}{0.924\,E_s1} + \underset{(\pm0.319)}{0.774E_s2} + \underset{(\pm0.334)}{0.438E_s3} & 26 & 0.613 & 0.898 & 30.4 & (5) \end{array}$$

$$\begin{array}{lccccr} E_s^c(\mathrm{CR_1R_2R_3}) = \underset{(\pm0.586)}{-2.347} + \underset{(\pm1.598)}{4.589E_s^c1} + \underset{(\pm0.425)}{0.958E_s^c2} + \underset{(\pm0.318)}{0.630E_s^c3} & 26 & 0.647 & 0.917 & 38.9 & (6) \end{array}$$

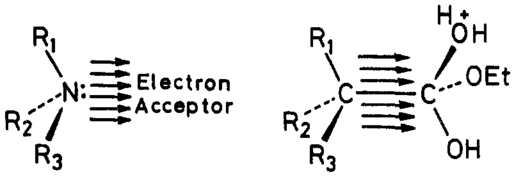

Figure 1.—Resemblance of total steric effect of three substituents.

parentheses are the 95% confidence intervals. Both eq 5 and 6 are significant at better than the 99.5% confidence level ($F_{3,26,0.005}$ = 5.41). The quality of correlation is slightly better for E_s^c values than for E_s values in terms of the F value. Although the correlations are far from complete, the E_s and E_s^c values can be separated into their components much better than we might anticipate. With increasing substitutions at the α carbon, the steric effect is increased "telescopically" in such series as Me, Et, *i*-Pr, and *t*-Bu. However, the telescoping effect is not general and is not observed with successive α-methyl substitutions on neo-Pent and neopentylmethyl groups. Thus, we might expect that the composition of steric constants is too complex to be expressed by a simple relationship such as eq 5 or 6. Almost 80% of variance in the steric constant data is elucidated by eq 5 and 6.

In elaborating the correlations, we have considered that E_s or E_s^c values of some α substituents could not always represent their steric effects properly. The E_s and E_s^c values of primary alkyl groups are generally well predicted by eq 5 and 6 except for those of *i*-Pent and neopentylmethyl groups where the calculated values are considerably lower than their original values. For these two groups, the steric constants of the component R_3 may not represent the true situation. The *i*-Bu and neo-Pent groups at the α carbon could rotate around the C_α–C_β axis so that the effect of *i*-Pr and *t*-Bu groups at the β carbon might be minimized. We assume that the steric effect of *i*-Bu and neo-Pent substituents at the α carbon can be simulated by that of the *n*-Pr group.

If the components at the α carbon are congested in secondary and tertiary groups, their orientation would be limited and "effective" steric constants might differ from their original values. For these groups, the total number of hydrogens at β carbon atoms could be taken as a measure of congestion. The maximum number is six for secondary groups at *i*-Pr and nine for tertiary group at *t*-Bu. The less the number of β hydrogens, *i.e.*, the more substituted the β carbon atoms by other alkyl groups, the more congested would be the α substituents. We have assumed that, when the number of β hydrogens becomes less than four for secondary and less than six for tertiary alkyl groups, the steric effect of α components, in particular, that of groups of CH_2R' type, is represented by a different E_s or E_s^c value.

If the steric effects of both the groups R_2 and R_3 of CH_2R' type are originally moderate, one of these groups would be forced to direct its R′ moiety forward so as to exaggerate its steric effect. Thus, in diethylcarbinyl, di-*n*-propylcarbinyl, and triethylcarbinyl groups, the effective steric effect of one of the component Et and *n*-Pr groups could be expressed by the E_s or E_s^c value of the *i*-Pr group. If the steric effect of the group R_3 is large enough, the group R_2 of the CH_2R' type would be oriented in such a way as to minimize the effect of R′ on the group R_3 and the reaction center. For *i*-Bu and neo-Pent groups as the component R_2 in diisobutylcarbinyl, dineopentylcarbinyl, and methylneopentyl-*tert*-butylcarbinyl groups, the steric effect could be similar to that of the *n*-Pr group.

For methyl-*tert*-butylcarbinyl and dimethyl-*tert*-butylcarbinyl groups both the groups R_2 and R_3 are of the symmetrical top type. It is difficult to choose other substituents the E_s or E_s^c values of which are capable of describing the effective steric effects of groups R_2 and R_3. Probably, the effect of the *t*-Bu group would be much greater than that anticipated by its usual E_s and E_s^c values. These two groups are not submitted to further correlations. In Table I, the above assumptions are summarized.

TABLE I

CONFORMATIONALLY LIMITED GROUPS

	Original groups[a]			No. of	Groups which exhibit "effective" steric effect[b]		
	R_1	R_2	R_3	β H	R_1	R_2	R_3
Primary	H	H	*i-Bu*	2	H	H	*Pr*
	H	H	*neo-Pent*	2	H	H	*Pr*
Secondary	H	Et	*Et*	4	H	Et	*i-Pr*
	H	Pr	*Pr*	4	H	Pr	*i-Pr*
	H	*i-Bu*	*i*-Bu	4	H	*Pr*	*i*-Bu
	H	*neo-Pent*	neo-Pent	4	H	*Pr*	neo-Pent
	H	Me	*t-Bu*	3	H	Me	(*t*-Bu)
Tertiary	Et	Et	*Et*	6	Et	Et	*i-Pr*
	Me	Me	*t-Bu*	6	Me	Me	(*t*-Bu)
	Me	*neo-Pent*	*t*-Bu	5	Me	*Pr*	*t*-Bu

[a] The component group the conformation of which is significantly limited is italicized. [b] The group the steric constant of which is taken to simulate the "effective" steric effect is italicized. *t*-Bu group is shown with parentheses; see text.

With the use of effective E_s or E_s^c values for conformationally limited α substituents in Table I, the correlations are repeated. The results are shown in Table II and eq 7 and 8. The correlation for E_s values is still not acceptable. By eq 7, E_s values of secondary and tertiary groups are only very poorly predicted. On the other hand, the correlation for E_s^c values is much improved. Equation 8 is able to interprete 98% of the variance in E_s^c data. Thus, the assumptions made above for conformations of α substituents appear to be justified and the E_s^c value seems to be better than E_s for the scale of steric effects. Encouraged by this result, we have attempted to extend the analyses to other groups the α substituents of which include heteroatoms. To this end, the steric constants of heteroatoms should be evaluated.

Recently, Charton has analyzed quantitatively the dependence of E_s values on group dimensions expressed in terms of van der Waals radii.[6] For example, the

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(6) M. Charton, *J. Amer. Chem. Soc.*, **91**, 615 (1969).

TABLE II

STERIC CONSTANTS OF ALKYL GROUPS

Groups	Component α substituents[a]			Component E_s values			E_s values		Component E_s^c values			E_s^c values	
	R_1	R_2	R_3	E_s1	E_s2	E_s3	Orig[d]	Calcd[e]	E_s^c1	E_s^c2	E_s^c3	Orig	Calcd[f]
Me	H	H	H	1.24	1.24	1.24	0.00	0.53	0.32	0.32	0.32	0.00	−0.17
Et	H	H	Me	1.24	1.24	0.00	−0.07	−0.27	0.32	0.32	0.00	−0.38	−0.37
Pr	H	H	Et	1.24	1.24	−0.07	−0.36	−0.32	0.32	0.32	−0.38	−0.67	−0.62
Bu	H	H	Pr	1.24	1.24	−0.36	−0.39	−0.51	0.32	0.32	−0.67	−0.70	−0.81
Pent	H	H	Bu	1.24	1.24	−0.39	−0.40	−0.52	0.32	0.32	−0.70	−0.71	−0.83
i-Pent	H	H	*i*-Bu*	1.24	1.24	−0.36	−0.35	−0.51	0.32	0.32	−0.67	−0.66	−0.81
n-Oct	H	H	*n*-Hept	1.24	1.24	−0.33[b]	−0.33	−0.49	0.32	0.32	−0.64[b]	−0.64	−0.79
	H	H	neo-Pent*	1.24	1.24	−0.36	−0.34	−0.51	0.32	0.32	−0.67	−0.65	−0.81
i-Bu	H	H	*i*-Pr	1.24	1.24	−0.47	−0.93	−0.58	0.32	0.32	−1.08	−1.24	−1.07
neo-Pent	H	H	*t*-Bu	1.24	1.24	−1.54	−1.74	−1.27	0.32	0.32	−2.46	−2.05	−1.97
	H	H	Bz[c]	1.24	1.24	−0.38	−0.38	−0.52	0.32	0.32	−0.69	−0.69	−0.82
	H	H	$BzCH_2$	1.24	1.24	−0.38	−0.45	−0.52	0.32	0.32	−0.69	−0.76	−0.82
	H	H	c-Hex	1.24	1.24	−0.79	−0.98	−0.78	0.32	0.32	−1.40	−1.29	−1.28
i-Pr	H	Me	Me	1.24	0.00	0.00	−0.47	−1.30	0.32	0.00	0.00	−1.08	−1.01
sec-Pent	H	Et	Et*	1.24	−0.07	−0.47	−1.98	−1.67	0.32	−0.38	−1.08	−2.59	−2.46
sec-Hept	H	Pr	Pr*	1.24	−0.36	−0.47	−2.11	−1.91	0.32	−0.67	−1.08	−2.72	−3.03
	H	*i*-Bu*	*i*-Bu	1.24	−0.36	−0.93	−2.47	−2.21	0.32	−0.67	−1.24	−3.08	−3.14
	H	neo-Pent*	neo-Pent	1.24	−0.36	−1.74	−3.18	−2.73	0.32	−0.67	−2.05	−3.79	−3.66
sec-Bu	H	Me	Et	1.24	0.00	−0.07	−1.13	−1.35	0.32	0.00	−0.38	−1.74	−1.25
	H	Me	neo-Pent	1.24	0.00	−1.74	−1.85	−2.43	0.32	0.00	−2.05	−2.46	−2.34
t-Bu	Me	Me	Me	0.00	0.00	0.00	−1.54	−2.28	0.00	0.00	0.00	−2.46	−2.10
	Et	Et	Et*	−0.07	−0.07	−0.47	−3.80	−2.70	−0.38	−0.38	−1.08	−4.72	−4.86
	Me	Me	neo-Pent	0.00	0.00	−1.74	−2.57	−3.41	0.00	0.00	−2.05	−3.49	−3.43
	Me	neo-Pent*	*t*-Bu	0.00	−0.36	−1.54	−4.00	−3.58	0.00	−0.67	−2.46	−4.92	−5.03

[a] Conformationally limited groups are indicated with asterisk. Their steric constants are taken as shown in Table I. [b] Steric constants of *n*-Hept are taken as those of *n*-Oct. [c] Bz = benzyl. [d] Original values from ref 1. [e] Calculated by eq 7. [f] Calculated by eq 8.

$$\begin{array}{lccc} & n & s & r \\ E_s(CR_1R_2R_3) = -2.282 + 0.789E_s1 + 0.832E_s2 + 0.648E_s3 & 24 & 0.499 & 0.921 \\ \qquad (\pm 0.596) \quad (\pm 0.510) \quad (\pm 0.363) \quad (\pm 0.340) & & & \end{array} \tag{7}$$

$$\begin{array}{lccc} E_s^c(CR_1R_2R_3) = -2.104 + 3.429E_s^c1 + 1.978E_s^c2 + 0.649E_s^c3 & 24 & 0.191 & 0.992 \\ \qquad (\pm 0.195) \quad (\pm 0.516) \quad (\pm 0.252) \quad (\pm 0.118) & & & \end{array} \tag{8}$$

E_s values of CH_2X, CHX_2, and CX_3 groups including the group of X = H are linearly dependent on van der Waals radius, $r_v(X)$, of the heteroatom, X, such as halogens and O and S in OCH_3 and SCH_3 groups. Equations 9–11 indicate the situation where a, a', a'',

$$E_s(CH_2X) = ar_v(X) + c \tag{9}$$

$$E_s(CHX_2) = a'r_v(X) + c' \tag{10}$$

$$E_s(CX_3) = a''r_v(X) + c'' \tag{11}$$

c, c', and c'' are constants. He also pointed out that, for symmetrical top-type groups such as CX_3 and CH_3, either a maximum or a minimum value of the group van der Waals radius, $r_v(CX_3, \max)$ or $r_v(CX_3, \min)$, calculated by means of trigonometry can be used to correlate with their E_s value. With the use of an average of Charton's $r_v(\max)$ and $r_v(\min)$ values, Kutter and Hansch have derived eq 12 for symmetrical top-type groups including H.[7] Substituting the $r_v(X)$ values of halogens, O, and S into eq 12, they have estimated E_s values of symmetric monoatomic substituents as well as of OCH_3 and SCH_3, as shown in Table III.

$$\begin{array}{lccc} & n & s & r \\ E_s = 3.484 - 1.839\, r_v(CX_3, \text{ave}) & 6 & 0.132 & 0.996 \\ \quad (\pm 0.55) \quad (\pm 0.22) & & & \end{array} \tag{12}$$

TABLE III

E_s AND E_s^c VALUES OF HALOGENS OCH_3, OPh, AND SCH_3

Functions	$r_v(X)$	E_s[b]	E_s^c [c]
F	1.47	0.78	−0.02
Cl	1.75	0.27	−0.18
Br	1.85	0.08	−0.23
I	1.98	−0.16	−0.31
OCH_3[a]	1.52	0.69	−0.05
OC_6H_5[a]	1.52	0.69	−0.05
SCH_3[a]	1.80	0.17	−0.21

[a] Calculated using oxygen or sulfur radius only. [b] Calculated by eq 12. [c] Calculated by eq 17.

Adopting these E_s values for α-heteroatom substituents, eq 13 is derived for 37 groups including 24 alkyl- and 13 heteroatom-substituted groups. Although E_s values of the heteroatom-substituted groups are well predicted in general, the situation for some of the secondary and tertiary alkyl groups is not improved much above eq 7, as shown in Table IV.

For evaluating E_s^c values of heteroatom substituents, the procedure using the relationship between E_s^c and r_v(ave) for symmetrical top-type groups including H cannot be applied. While both E_s and E_s^c values of CH_3 are equal to each other, being zero, the E_s^c values of H and CX_3 (X = halogen and CH_3) are taken to be 0.306 $(3 - n_H)$ = 0.92 unit lower than the corresponding E_s values. Thus, the correlation of E_s^c with r_v(ave) is obviously poorer than that in eq 12. If the E_s^c is really free from the hyperconjugation effect and a measure of the "true" steric effect, the apparent lack of linear correlation with the van der Waals radius might

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[7] E. Kutter and C. Hansch, *J. Med. Chem.*, **12**, 647 (1969).

$$E_s(\mathrm{CR_1R_2R_3}) = \underset{(\pm 0.382)}{-2.532} + \underset{(\pm 0.371)}{0.739E_s1} + \underset{(\pm 0.276)}{0.926E_s2} + \underset{(\pm 0.215)}{0.440E_s3} \qquad \begin{array}{ccc} n & s & r \\ 37 & 0.429 & 0.925 \end{array} \qquad (13)$$

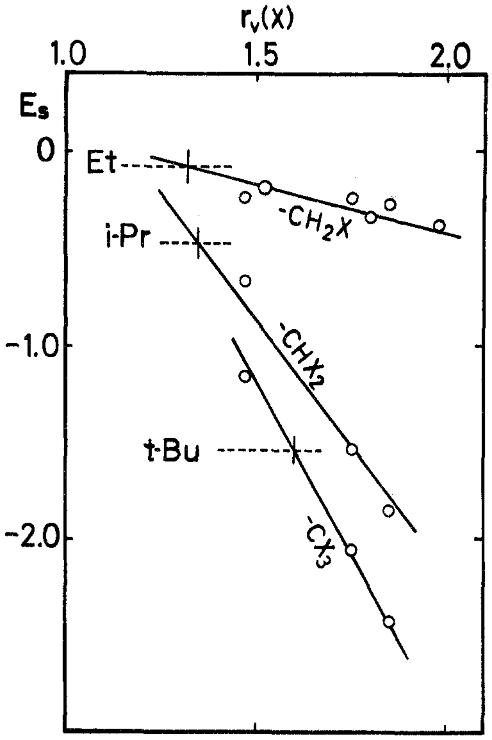

Figure 2.—Plot of E_s vs. r_v (X).

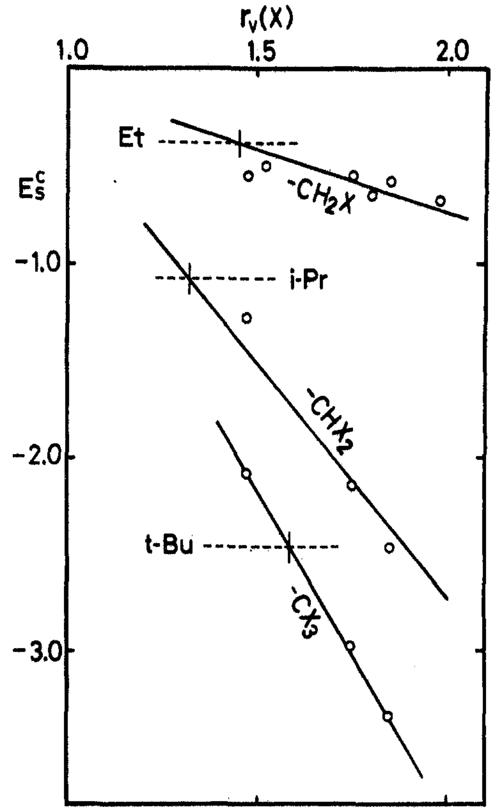

Figure 3.—Plot of E_s^c vs. r_v (X).

be due to the fact that the r_v(ave) values such as those used for eq 12 do not represent the "effective" steric dimensions for some groups.

There are some conflicts in the estimate of r_v(ave) or r_v(X) of the CH_3 group (X = CH_3), even for the relation with E_s values. The E_s value of $C(CH_3)_3$ is 0.89 unit larger than that of CBr_3, indicating that the effective steric size of CH_3 is considerably smaller than that of Br. Yet, from eq 12, the E_s value of Br is estimated as being quite close to that of CH_3, since r_v(X) of Br and r_v(ave) of CH_3 are taken as 1.85 and 1.97 Å, respectively. Moreover, the linear relationships between $E_s(CH_2X, CHX_2, CX_3)$ and r_v(X) as shown in eq 9–11 do not hold for the groups of X = CH_3. The E_s values of Et, *i*-Pr, and *t*-Bu groups are too large to be elucidated by r_v(ave) and even by r_v(min) of the Me group. The effective size of Me should be considerably smaller than that represented by r_v(min), 1.76 Å.

Figures 2 and 3 indicate the situation, showing that the effective value of $r_v(CH_3)$ might be estimated as 1.3–1.5 Å. The three lines in these figures which correlate E_s or E_s^c values with r_v(X) should intersect the abscissa at the same point when X = H; *i.e.*, CH_2X = CHX_2 = CX_3 = CH_3. The most probable r_v(X) values for X = CH_3 and X = H are estimated by means of the relation expressed as eq 14. In this equation, *a*, *b*, *c*, and

$$r_v(X) = aE_s(CH_2X) + bE_s(CHX_2) + cE_s(CX_3) + d \qquad (14)$$

d are constants and each of the E_s terms is applied only to each type of group; *i.e.*, for CH_2X type groups, $a \neq 0$ and $b = c = 0$. For 12 groups in Table V where X = halogen, OCH_3, and SCH_3, eq 15 and 16 are derived. The correlation coefficients of these equations are not very high. However, the standard deviations are rather small and the *F* tests show that the correlations are significant at better than 99% level of probability ($F_{3,8,0.01}$ = 7.59).

From eq 15, r_v(H) is 1.16 Å on the basis of E_s values, which agrees with its usually adopted value, 1.20 Å. However, eq 16 with E_s^c values show that the effective radius of H is around 0.87 Å. By substituting the E_s value of Et, *i*-Pr, and *t*-Bu groups into the first, second, and third term of eq 15, respectively, the values 1.31, 1.34, and 1.60 Å are obtained for r_v(Me). The average of these three is 1.41 Å, which could be regarded as the most probable effective radius of Me. Similarly, from eq 16, the values 1.43, 1.31, and 1.55 Å are derived. The average, 1.43 Å, can be taken as r_v(Me) on the basis of E_s^c values. The effective value of r_v(Me), 1.41–1.43 Å, seems rather low compared with the usually adopted value, 2.00 Å, or r_v(ave), 1.97 Å. Charton has recognized that r_v(min), 1.72 Å, is always a better scale for elucidating the steric effect of Me than r_v(max) or r_v(ave).[6] The dimensions of the hydrogen atom are so small that the net effect of Me could be represented by the one even lower than the r_v(min) value. Since the effective value of r_v(Me) is close to the van der Waals radius of a naked carbon atom, 1.60 Å,[8] the group Me could be regarded as having the character of a single atom type substituent. Thus, the correlation between E_s and r_v(ave) shown as eq 12 seems to require reexamination, at least for ester reactions. For inter-

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[8] "Handbook of Biochemistry," H. A. Sober, Ed., Chemical Rubber Co., Cleveland, Ohio, 1970, p J-3.

TABLE IV

STERIC CONSTANTS OF ALKYL- AND HETEROATOM-SUBSTITUTED GROUPS

	Component α-substituents[a]			Component E_s values			E_s values		Component E_s^c values			E_s^c values	
Groups	R_1	R_2	R_3	E_s1	E_s2	E_s3	Orig[d]	Calcd[e]	E_s^c1	E_s^c2	E_s^c3	Orig	Calcd[f]
Me	H	H	H	1.24	1.24	1.24	0.00	0.15	0.32	0.32	0.32	0.00	−0.29
Et	H	H	Me	1.24	1.24	0.00	−0.07	−0.40	0.32	0.32	0.00	−0.38	−0.47
Pr	H	H	Et	1.24	1.24	−0.07	−0.36	−0.43	0.32	0.32	−0.38	−0.67	−0.69
Bu	H	H	Pr	1.24	1.24	−0.36	−0.39	−0.56	0.32	0.32	−0.67	−0.70	−0.85
Pent	H	H	Bu	1.24	1.24	−0.39	−0.40	−0.57	0.32	0.32	−0.70	−0.71	−0.87
i-Pent	H	H	*i*-Bu*	1.24	1.24	−0.36	−0.35	−0.56	0.32	0.32	−0.67	−0.66	−0.85
n-Oct	H	H	*n*-Hept	1.24	1.24	−0.33[b]	−0.33	−0.55	0.32	0.32	−0.64[b]	−0.64	−0.84
	H	H	neo-Pent*	1.24	1.24	−0.36	−0.34	−0.56	0.32	0.32	−0.67	−0.65	−0.85
i-Bu	H	H	*i*-Pr	1.24	1.24	−0.47	−0.93	−0.61	0.32	0.32	−1.08	−1.24	−1.09
neo-Pent	H	H	*t*-Bu	1.24	1.24	−1.54	−1.74	−1.08	0.32	0.32	−2.46	−2.05	−1.88
	H	H	Bz[c]	1.24	1.24	−0.38	−0.38	−0.57	0.32	0.32	−0.69	−0.69	−0.87
	H	H	$BzCH_2$[c]	1.24	1.24	−0.38	−0.45	−0.57	0.32	0.32	−0.69	−0.76	−0.87
	H	H	c-Hex	1.24	1.24	−0.79	−0.98	−0.75	0.32	0.32	−1.40	−1.29	−1.27
i-Pr	H	Me	Me	1.24	0.00	0.00	−0.47	−1.55	0.32	0.00	0.00	−1.08	−1.16
sec-Pent	H	Et	Et*	1.24	−0.07	−0.47	−1.98	−1.82	0.32	−0.38	−1.08	−2.59	−2.60
sec-Hept	H	Pr	Pr*	1.24	−0.36	−0.47	−2.11	−2.09	0.32	−0.67	−1.08	−2.72	−3.23
	H	*i*-Bu*	*i*-Bu	1.24	−0.36	−0.93	−2.47	−2.29	0.32	−0.67	−1.24	−3.08	−3.32
	H	neo-Pent*	neo-Pent	1.24	−0.36	−1.74	−3.18	−2.65	0.32	−0.67	−2.05	−3.79	−3.78
sec-Bu	H	Me	Et	1.24	0.00	−0.07	−1.13	−1.58	0.32	0.00	−0.38	−1.74	−1.38
	H	Me	neo-Pent	1.24	0.00	−1.74	−1.85	−2.31	0.32	0.00	−2.05	−2.46	−2.33
t-Bu	Me	Me	Me	0.00	0.00	0.00	−1.54	−2.53	0.00	0.00	0.00	−2.46	−2.12
	Et	Et	Et*	−0.07	−0.07	−0.47	−3.80	−2.86	−0.38	−0.38	−1.08	−4.72	−4.69
	Me	Me	neo-Pent	0.00	0.00	−1.74	−2.57	−3.30	0.00	0.00	−2.05	−3.49	−3.29
	Me	neo-Pent*	*t*-Bu	0.00	−0.36	−1.54	−4.00	−3.54	0.00	−0.67	−2.46	−4.92	−4.97
CH_2OMe	H	H	OMe	1.24	1.24	0.69	−0.19	−0.10	0.32	0.32	−0.05	−0.50	−0.50
CH_2Cl	H	H	Cl	1.24	1.24	0.27	−0.24	−0.28	0.32	0.32	−0.18	−0.55	−0.58
CH_2F	H	H	F	1.24	1.24	0.78	−0.24	−0.06	0.32	0.32	−0.02	−0.55	−0.48
CH_2Br	H	H	Br	1.24	1.24	0.08	−0.27	−0.37	0.32	0.32	−0.23	−0.58	−0.60
CH_2SMe	H	H	SMe	1.24	1.24	0.17	−0.34	−0.33	0.32	0.32	−0.21	−0.65	−0.59
CH_2I	H	H	I	1.24	1.24	−0.16	−0.37	−0.47	0.32	0.32	−0.31	−0.68	−0.65
CH_2OPh	H	H	OPh	1.24	1.24	0.69	−0.33	−0.10	0.32	0.32	−0.05	−0.64	−0.50
CHF_2	H	F	F	1.24	0.78	0.78	−0.67	−0.48	0.32	−0.02	−0.02	−1.28	−1.22
$CHCl_2$	H	Cl	Cl	1.24	0.27	0.27	−1.54	−1.18	0.32	−0.18	−0.18	−2.15	−1.66
$CHBr_2$	H	Br	Br	1.24	0.08	0.08	−1.86	−1.44	0.32	−0.23	−0.23	−2.47	−1.79
CF_3	F	F	F	0.78	0.78	0.78	−1.16	−0.85	−0.02	−0.02	−0.02	−2.08	−2.23
CCl_3	Cl	Cl	Cl	0.27	0.27	0.27	−2.06	−1.95	−0.18	−0.18	−0.18	−2.98	−3.15
CBr_3	Br	Br	Br	0.08	0.08	0.08	−2.43	−2.36	−0.23	−0.23	−0.23	−3.35	−3.43

[a] Conformationally limited groups are shown with asterisk. For their steric constants, see Table I. [b] Taken as those of *n*-Oct. [c] Bz = benzyl. [d] From ref 1. [e] Calculated by eq 13. [f] Calculated by eq 19.

TABLE V

$r_v(X)$ *vs.* E_s AND E_s^c VALUES, DATA FOR EQUATIONS 15 AND 16

				$r_v(X)$					$r_v(X)$	
Groups	$E_s(CH_2X)$	$E_s(CHX_2)$	$E_s(CX_3)$	Orig	Calcd[a]	$E_s^c(CH_2X)$	$E_s^c(CHX_2)$	$E_s^c(CX_3)$	Orig	Calcd[b]
CH_2F	−0.24			1.47	1.66	−0.55			1.47	1.68
CH_2Cl	−0.24			1.75	1.66	−0.55			1.75	1.68
CH_2Br	−0.27			1.85	1.72	−0.58			1.85	1.73
CH_2I	−0.37			1.98	1.93	−0.68			1.98	1.88
CH_2OMe	−0.19			1.52	1.56	−0.50			1.52	1.61
CH_2SMe	−0.34			1.80	1.87	−0.65			1.80	1.83
CHF_2		−0.67		1.47	1.42		−1.28		1.47	1.39
$CHCl_2$		−1.54		1.75	1.75		−2.15		1.75	1.75
$CHBr_2$		−1.86		1.85	1.87		−2.47		1.85	1.89
CF_3			−1.16	1.47	1.49			−2.08	1.47	1.48
CCl_3			−2.06	1.75	1.74			−2.98	1.75	1.74
CBr_3			−2.43	1.85	1.85			−3.35	1.85	1.85

[a] Calculated by eq 15. [b] Calculated by eq 16.

$$\begin{array}{lcccl} & n & s & r & \\ r_v(X) = \underset{(\pm 0.235)}{1.164} - \underset{(\pm 0.873)}{2.065}E_s(CH_2X) - \underset{(\pm 0.176)}{0.379}E_s(CHX_2) - \underset{(\pm 0.132)}{0.281}E_s(CX_3) & 12 & 0.095 & 0.892 & F_{3,8} = 10.3 \quad (15) \end{array}$$

$$\begin{array}{lcccl} r_v(X) = \underset{(\pm 0.414)}{0.865} - \underset{(\pm 0.721)}{1.485}E_s^c(CH_2X) - \underset{(\pm 0.210)}{0.413}E_s^c(CHX_2) - \underset{(\pm 0.151)}{0.295}E_s^c(CX_3) & 12 & 0.107 & 0.861 & F_{3,8} = 7.60 \quad (16) \end{array}$$

molecular interactions such as enzyme-inhibitor and drug-receptor complex formations where the thickness of substituents on an aromatic ring plays a critical role, the E_s values, being linearly related to the thickness of substituents, have been found to be useful parameters.[7]

The effective value, 0.87 Å, for hydrogen on the basis of E_s^c values is also considerably lower than its usually adopted value, 1.20 Å. As shown in Figure 4, for CX_3 type substituents, the variation in their dimension is largest toward a direction which takes 70.5° (= 180° − 109.5°) with the central axis. In this case, the $r_v(CX_3$, ave) values take care of the variation in the covalent bond radii of X. On the other hand, for single-atom substituents, the variation in their dimension is largest along the central axis, being determined by their covalent and van der Waals radii. In this case, the increase in the van der Waals radius which is necessarily accompanied with the elongation of the C–X bond would not be reflected on the increase in the steric effect so remarkably as that for CX_3 type substituents. The situation can be illustrated in Figure 5, where the plot of E_s^c values *vs.* effective or average r_v values for H-, CH_3-, and CX_3-type substituents, regarding CH_3 as having characters of CX_3 type and also single atom type substituent, results in biphasic lines. In Figure 5, the line connecting points for H and CH_3 is regarded as representing the relation of E_s^c with effective r_v value of single-atom substituents. The slope is −0.57, as shown in eq 17. This value is about $^1/_3$ of that of the regression line expressed as eq 18 for CX_3-type substituents. The ratio is acceptable since it is close to the cosine of 70.5°, the angle between two directions along which the variations in dimensions of X and CX_3 substituents are most sensitive. On this basis, the effective value of an H-substituent radius, 0.87 Å, would not be considered as an unreasonable estimate.

$$E_s^c(X) = 0.821 - 0.571 r_v(X) \qquad (17)$$

$$\begin{array}{lccc} & n & s & r \\ E_s^c(CX_3) = \underset{(\pm 0.756)}{2.610} - \underset{(\pm 0.285)}{1.860} r_v(\text{ave}) & 5 & 0.126 & 0.997 \end{array} \qquad (18)$$

The E_s^c values of single-atom substituents, including OCH_3 and SCH_3, which are shown in Table III are estimated by means of eq 17. With these values for α-heteroatom substituents, the E_s^c values of 37 groups shown in Table IV are analyzed to give eq 19. The quality of correlation is slightly poorer than that of eq 8 but still good enough to be acceptable. The values of the slope of each E_s^c term and intercept are practically identical with those of eq 8. Although the E_s^c values of $CHCl_2$ and $CHBr_2$ are poorly predicted (*vide infra*), it would be reasonable to conclude that, on the whole, the steric constants are separable into components even for the heteroatom substituents.

$$\begin{array}{lccc} & n & s & r \\ E_s^c(CR_1R_2R_3) = \underset{(\pm 0.151)}{-2.118} + \underset{(\pm 0.468)}{2.982} E_s^c 1 + \underset{(\pm 0.273)}{2.160} E_s^c 2 + \underset{(\pm 0.116)}{0.570} E_s^c 3 & 37 & 0.232 & 0.985 \end{array} \qquad (19)$$

Discussion

The above analyses strongly support the hypothesis that the steric constant of aliphatic groups is composed of three components. Although the relative merits of two sets of constants, E_s and E_s^c, should be compared with the use of reactivity and equilibrium data involving steric effects, E_s^c values, in particular those of alkyl groups, are suggested to be superior to E_s values as the scale of steric effect. The failure in predicting those of secondary and tertiary alkyl groups is the most serious drawback in E_s values.

We have adopted in this work E_s^c values which are estimated assuming that the hyperconjugation effect is −0.306 log unit per α hydrogen.[2] Whether or not the hyperconjugation effect of α hydrogen is unchanged regardless of substituents being alkyl- or heteroatom-substituted groups is still open to further discussions. However, the good correlations obtained for eq 8 and 19 would indicate that the value −0.306 is reasonable at least as a first approximation. The concept of CF hyperconjugation, which was suggested at one time, has been proved to be fallacious recently.[9]

For the acid hydrolysis of esters, the step of attack of a water molecule on the protonated ester at the sp^2 carbon atom is rate limiting. The stable conformations of esters and also of protonated esters have been generally considered to be the eclipsed forms.[10,11] The most stable form is shown in Figure 6, where the bulkiest α substituent, R_3, is eclipsed with the carbonyl or ^+C–OH except for dihalo acetates.[11] The water molecule would attack the sp^2 carbon from the side sterically least hindered. In this situation, the steric effect of the R_1 group would play a dominant role. At the same time as the attack of water molecule, the coordination number of the sp^2 carbon is increased from three to four and the resultant sp^3 structure would take a staggered form, as shown in Figure 7. The larger the size of the component R_2, the less favorable would be the process, since nonbonded repulsion with R_2 becomes greater in the sp^3 structure than before. When the size of the R_3 group increases, two opposed effects would emerge. One is that the attack of a water molecule is less favored and the other is that the release of the ^+C–OH group from the eclipsed form to the less hindered staggered conformation would be facilitated. These two effects would be more or less compensated by each other. Thus, the activation process would be most sensitive to the steric effect of R_1 and least to that of R_3. The coefficient of E_s^c terms in eq 8 and 19 can be understood on this basis. Although each of the component E_s^c values can be further separable into three subcomponents, it should represent the "total" steric effect for each of the α substituents in the right side of these equations.

The most poorly predicted E_s^c values in eq 19 are those of dihalomethyl (CHX_2) groups. For dihaloacetic acid esters, Brown has proposed that they exhibit a two-fold barrier to internal rotation and the form I is more stable than the form II in Figure 8.[11] Thus, the situation where a water molecule attacks the sp^2 carbon is different from that shown in Figure 7. If the protonated esters also maintain the same conformations as shown in Figure 8, the groups R_1, R_2, and R_3 would

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(9) D. Holtz, *Progr. Phys. Org. Chem.*, **8**, 1 (1971).

(10) G. J. Karabatsos and D. J. Fenoglio, *Top. Stereochem.*, **5**, 167 (1970).

(11) T. L. Brown, *Spectrochim. Acta*, **18**, 1615 (1962).

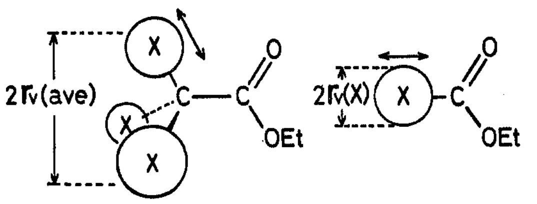


Figure 4.—The direction along which the variation in group dimensions is most sensitive to structural variation (←→).

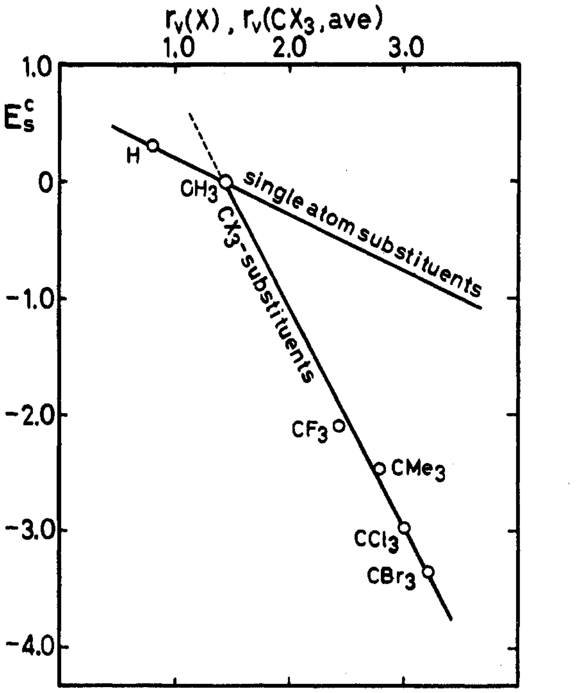


Figure 5.—Plot of E_s^c vs. effective r_v(X) or r_v(CX_3, ave) value of symmetric top-type groups.

correspond to X, X, and H, respectively, in either of these two conformations, so that the component E_s^c values should be taken as $E_s^c1 = E_s^c2 = E_s^c(X)$ and $E_s^c3 = E_s^c(H)$, the sequence of magnitude being $E_s^c1 = E_s^c2 < E_s^c3$. The calculated values by means of eq 19 with the use of these component values are, in effect, smaller than the values earlier predicted, but even smaller than the actual values. Thus, it could be anticipated that the dihalo acetates are attacked by the water molecule partly in these conformations.

In Taft's orginal tabulation of steric constants, 50 groups are included.[1] Out of these, the cycloalkyl groups and groups where at least one of the α components is phenyl are excluded from the analyses, since steric constants of cyclic polymethylene and phenyl groups are not available. We are now able to calculate E_s^c values of tri-, tetra-, penta-, and hexamethylene cyclic groups by substituting E_s^c values of H and cyclobutyl, -pentyl, -hexyl, and -heptyl groups into eq 8, and combining the E_s^c2 and E_s^c3 terms. As shown in Table VI, the steric effects of polymethylene groups are generally low. At the most, the E_s^c value of one of two bidentate hexamethylene ligands, −0.27, is still higher than that of Et, −0.38. In cyclohexyl and cycloheptyl groups, the reaction center is located at the equatorial position with regard to the ring system, so that the effect of the tied-up polymethylene chain would be minimized. The steric constant for the phenyl group as the α components could be compared with that of Et, as shown in Table VII. The E_s^c value of the diphenylmethyl group can be explained by the congestion of two α-phenyl groups.

TABLE VI

E_s^c VALUES OF POLYMETHYLENE CYCLIC GROUPS

Groups	$E_s^c/2$
$(CH_3)_4<$	0.13
$(CH_2)_4<$	−0.04
$(CH_2)_5<$	−0.15
$(CH_2)_6<$	−0.27

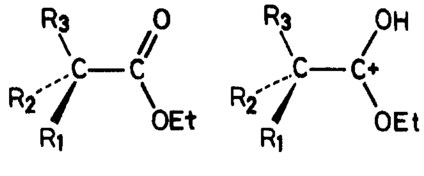


Figure 6.—The most stable form of esters and their protonated intermediates.

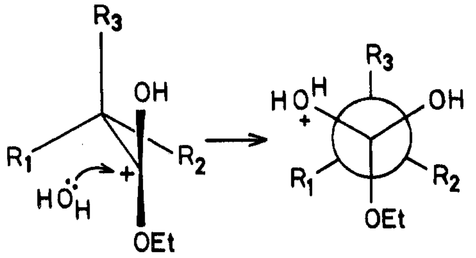
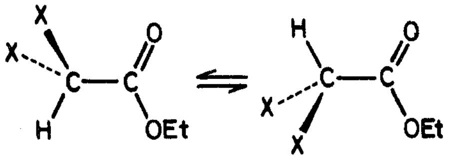


Figure 7.—The rate-determining step of ester hydrolysis.



I II

Figure 8.—Rotamers of dihalo acetates.

TABLE VII

COMPARISON OF STERIC EFFECTS IN Ph AND Et GROUPS

Component α substituents			E_s^c value	Components of equivalent steric effect			E_s^c value calcd[a]
H	H	Ph	−0.69	H	H	Et	−0.62
H	Me	Ph	−1.80	H	Me	Et	−1.25
H	Et	Ph	−2.11	H	Et	Et	−2.01
H	Ph	Ph	−2.37	H	Et	*i*-Pr	−2.59

[a] Calculated by eq 8.

The steric constants of $ClCH_2CH_2$– and $CH_3OCH_2CH_2$– groups are also not included in the analyses, since they are only very poorly predicted on preliminary calculations. For these groups, the steric effect is much higher than expected. Probably, β-Cl and $-OCH_3$ groups would be directed toward the reaction center as shown in Figure 9. The positive charge at the reaction center would attract the lone-pair-carrying substituents at the β-carbon atom.

It is interesting to test the applicability of eq 8 by examining the steric constants of alkyl-*o*-biphenylylcarbinyl groups determined by Bowden and his associates recently.[5] Their E_s values, listed in Table VIII,

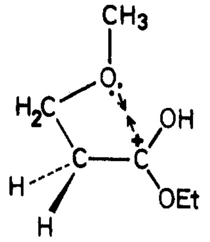
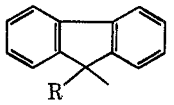


Figure 9.—Interaction of β substituents with the reaction center.

TABLE VIII
STERIC CONSTANTS OF
ALKYL-*o*-BIPHENYLYLCARBINYL GROUPS



No.	R	$E_s{}^a$	$E_s{}^c$ Orig	$E_s{}^c$ Calcd^b
1	H	−1.10	−1.71	−1.55
2	Me	−1.73	−2.65	−2.65^c
3	Et	−1.97	−2.89	−3.49
4	*i*-Pr	−3.30	−4.22	−3.94
5	*t*-Bu	−4.12	−5.04	−4.83

[a] Taken from ref 5. [b] Calculated by eq 8. [c] Taken as the standard.

are obtained from the rate constants of acid-catalyzed esterification of acids. From the $E_s{}^c$ value of group 2 in Table VIII, we can calculate that of one of two ligands of *o*-biphenylyl as being −0.21 by using eq 8. With this value, the $E_s{}^c$ values of homologous groups are calculated. Except for group 3, the predictions by means of eq 8 are fairly good. The steric effect of the conformationally fixed phenyl group can be considered quite low, being between those of methyl and ethyl.

According to Taft, the steric effect in ester reactions is, in fact, a combination of two effects, *i.e.*, steric strain effect and steric hindrance of motions.[12] The activation energy due to repulsive interactions of component α substituents with the reaction center would be increased by an increase in the steric strain effect of substituents. The entropy of activation would be decreased by a loss of internal motions in the transition state relative to the initial state. It has been generally considered that "no substituent leads to increased steric strain without an accompanying increased steric hindrance of motions, *i.e.*, that the parallel retarding effects are usually observed in relative enthalpies and entropies of activation, $\Delta\Delta H^\ddagger$ and $\Delta\Delta S^\ddagger$, resulting from structural variation."[12] The two parallel effects are not necessarily linearly related with each other.

The present work indicates that, although a simple additive principle does not hold for the steric constant of any substituent, the constants expressed in terms of $E_s{}^c$ can be expressed by a linear combination of those of three α components. Thus, the relative importance of two effects, steric strain and steric hindrance of motions, in any one of $E_s{}^c$ values should be kept constant, at least for ester reactions. The variation in the steric repulsion effect and steric hindrance of motions according to the structural variation, which are formulated by $\Delta\Delta H^\ddagger$ and $-T\Delta\Delta S^\ddagger$, are related proportionally so that an isokinetic relationship would hold between two parallel effects.

The above discussions present possible rationale for the linear relationship among steric constants of aliphatic groups. The critical assumptions used for the analyses, such as conformational restrictions for some α substituents and biphasic relations between $E_s{}^c$ and r_v for symmetrical top-type groups, would be plausible enough as far as the present discussions are concerned. However, it is emphasized that, in the absence of theoretical knowledges, the present result should be taken as an empirical relationship among steric effect constants for ester reactions. In fact, we have found that the total steric effect of three N substituents on various types of electron acceptors is similarly expressed by a linear combination of $E_s{}^c$ constants but the values of slope associated with each $E_s{}^c$ term are different from those of eq 8 or 19, and substituents for which conformational restrictions should be considered are not identical with those in Table I.[3] Here, a relationship such as eq 8 or 19 cannot be extended directly to estimate the total steric effect of N substituents. It might be also possible that further studies on steric mechanisms for other reactions reveal deviations from the simple linear combinations. As Miller has pointed out, multiple variations which give rise to linear relationships such as eq 8 or 19 are special cases of more generally expected ones which contain cross terms.[13] Thus, it is urgently desirable for further work to establish the realm of validity of this type of quantitative approach to the steric course of reaction mechanisms.

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(12) Reference 1, p 665.

(13) S. Miller, *J. Amer. Chem. Soc.*, **81**, 101 (1959).