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Analysis of Ortho Effects with a Steric Parameter Defined by the Acidic Hydrolysis Rate of Ortho-Substituted Benzamides

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The applicability of our new steric parameter for ortho substituents, E_s(AMD), in evaluation of organic reactivity and physicochemical data was examined. The E_s(AMD) constant was derived from the rate constants for acidic hydrolysis of ortho-substituted benzamides, and its scale was put as close as possible to that of the E_s steric parameter of Taft, and Kutter and Hansch (TKH). For alkyl and halogen substituents, the E_s(AMD) value was very close to the TKH E_s value, but for methoxyl, isopropoxyl, and such planar π-bonded substituents as NO_2 and Ph, it was not. Reactivity and physicochemical data taken from the literature were analyzed quantitatively by use of steric and electronic parameters, and the results obtained by E_s(AMD) and E_s were compared. The E_s(AMD) value gave better results than TKH E_s in various reactions including those of benzoic acids and their derivatives, if the change in the hybridization geometry of the reaction center between the initial and intermediate states was similar to that of the reference reaction.

Steric effects of substituents strongly affect organic reactivity and physicochemical properties. As a scale of steric effects, the E_s parameter set of Taft,[1] Kutter and Hansch[2] (TKH) is widely used.[3] The TKH E_s is, however, a set of parameters combined from different sources; Taft originally defined the E_s value for alkyl groups from chemical reactivity data,[1] and Kutter and Hansch estimated the value for non-alkyl substituents by using a linear relationship between the appropriate van der Waals dimension and the Taft E_s value for alkyl groups with symmetric tops.[2]

We have recently proposed a steric parameter for ortho substituents, E_s(AMD), derived from the rate constant data of the acidic hydrolysis of ortho-substituted benzamides.[4] For alkyl and halogen substituents, the E_s(AMD) value is very close to the TKH E_s value. For alkoxyl, alkylthio, and such π-bonded (planar) substituents as NO_2 and Ph, the E_s(AMD) parameter provides a certain constant, whereas the E_s value of Kutter and Hansch is evaluated based on assumptions about molecular geometry.[2] For example, the TKH E_s parameters of alkoxyl and alkylthio groups are estimated for their minimum effect from the van der Waals radius of oxygen and sulfur atoms, respectively. Two E_s values are defined for each of planar NO_2 and Ph groups from their half-thickness to represent the minimum steric effect and from their half-width to express the maximum steric effect.

The applicability of E_s(AMD) has recently been examined in studies of the quantitative structure–activity relationship of biologically active compounds.[5] For several series of compounds, the set of E_s(AMD) values gives statistically better correlation than the TKH E_s values. In this paper, as an extension of our studies on the ortho effect, the applicability of E_s(AMD) to organic reactivity and physicochemical data was examined by use of our procedure to deal with the effect of the aromatic ortho susbstituents by the same standards as that of meta and para substituents.[6] The data, including those for substituents other than alkyl and halogen, were selected from the literature, and the performances of E_s(AMD) and TKH E_s were compared.

Procedure for Analysis

Our procedure to deal with the ortho effect[6] is based on the assumptions that (a) the effect of ortho substituents is composed of "ordinary" electronic, "proximity" electronic, and steric components, (b) the ordinary electronic effect of ortho substituents is equivalent to that of the corresponding para substituents, i.e., $\sigma_{ortho}=\sigma_{para}$, (c) the steric effect is represented by the E_s constant, and (d) the proximity electronic effect is factored by the σ_I constant,[7] although the Swain–Lupton–Hansch F constant is used originally.[6] Thus, the data for ortho substituted derivatives can be analyzed by Eq. 1, in which K is either the equilibrium or rate constant value.

$$\log K = \rho\sigma_o + \delta[E_s(\text{AMD}) \text{ or } E_s]^\circ + \rho_I\sigma_I^\circ + c \qquad (1)$$

The data for meta and para substituted isomers can be combined under conditions of $E_s=\sigma_I=0$ for meta and para substituents to afford Eq. 2. In other words, the second and third terms of the right side of Eq. 2 are not applicable to the data only for meta and para substituted isomers, so Eq. 2 is reduced to the regular Hammett equation.

$$\log K = \rho\sigma_{o,m,p} + \delta[E_s(\text{AMD}) \text{ or } E_s]^\circ + \rho_I\sigma_I^\circ + c \qquad (2)$$

ρ, δ, ρ_I, and c are the susceptibility constants and the intercept to be calculated by regression analysis.

Analysis was done with the use of Eqs. 1 and 2 when data for ortho, meta, and para derivatives were available. For data on ortho derivatives only, Eq. 1 was used. The unsubstituted parent compound was included whenever available, because it is regarded as the ortho-hydrogen-substituted compound, and also because its absence often results in high collinearity between some pairs of independent variables.[8] Not all parameter terms in Eqs. 1 and 2 were always necessary, and their significance

was judged statistically. The regular Hammett equation was not shown for the meta and para derivatives only. In general, the ρ and intercept values in the regular Hammett equation are very close to the corresponding values in the correlation equation according to Eq. 2.[6]

For the ordinary electronic effect, one of the Hammett-type parameters such as σ, σ^+, σ^-, or σ° was examined according to the reaction type. The TKH E_s parameter set including the value for NO_2 and Ph estimated from the half-thickness of the groups to represent the minimum steric effect was designated E_s(S), and that with the value for NO_2 and Ph estimated from the half-width to express the maximum steric effect was designated E_s(L).

Multiple correlation analyses were done with the use of any one of the E_s(AMD), E_s(S), and E_s(L) parameter sets along with various kinds of electronic parameters. The quality of the correlation equation derived with E_s-(AMD) was compared with that formulated with the TKH E_s constants. The electronic parameters, the E_s(AMD) value, and the TKH E_s constant are given in Table 1 and reactivity data are given in Table 2.

The criteria for selection of data sets were as follows: (a) at least one of NO_2, Ph, and alkoxyl or phenoxyl substituents is included, because the TKH E_s value for these substituents is different from the corresponding E_s(AMD), (b) the steric effect should govern the reaction sufficiently so that the significance of the steric parameter term can be evaluated, (c) the number of compounds per the number of independent variables used in the correlation equation is at least 4 for data sets including ortho as well as meta and para derivatives. With data sets that include ortho derivatives only, this ratio is greater than or close to 3.

Results and Discussion

Applicability of E_s(AMD). Table 3 lists the correlation in which E_s(AMD) worked better than E_s(S) and E_s(L). Either the E_s(S) or E_s(L) equation, whichever was of better quality, is shown for comparison with the E_s(AMD) equation.

Set 1 was for the alkaline hydrolysis of substituted benzamides, including three derivatives with oxy groups (OMe, OEt, OPh) at the ortho position. Note that the E_s values of Kutter and Hansch for oxy groups were calculated from the van der Waals radius of the oxygen

Table 1. Physicochemical Parameters Used for Correlation Analyses[a]

Substituents	σ[b]	σ°[c]	σ^-[c]	σ^+[d]	σ_I[e]	E_s(S)[f]	E_s(L)[f]	E_s(AMD)[g]
H	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
p-Cl	0.23							
p-Br	0.23							
p-I	0.18							
p-Me	−0.17							
p-OMe	−0.27		−0.20					
p-NO_2	0.78		1.24					
p-NH_2	−0.66							
m-Cl	0.37							
m-Br	0.39							
m-I	0.35							
m-Me	−0.07							
m-OMe	0.12	0.06						
m-NO_2	0.71	0.70						
m-NH_2	−0.16							
m-O^-	−0.71							
o-F	0.06	0.17		−0.07	0.54	−0.46	−0.46	−0.32
o-Cl	0.23	0.27		0.11	0.47	−0.97	−0.97	−0.98
o-Br	0.23	0.26		0.15	0.47	−1.16	−1.16	−1.12
o-I	0.18	0.27		0.14	0.40	−1.40	−1.40	−1.44
o-Me	−0.17	−0.12		−0.31	−0.01	−1.24	−1.24	−1.16
o-Et	−0.15	−0.13			−0.01	−1.31	−1.31	−1.33
o-*i*-Pr	−0.15	−0.16			0.01	−1.71	−1.71	−1.66
o-OMe	−0.27	−0.16		−0.78	0.30	−0.55	−0.55	−0.40
o-NO_2	0.78	0.82		0.79	0.67	−1.01[h]	−2.52[i]	−1.65
o-Ph	−0.01	0.04			0.12	−1.01[h]	−3.82[i]	−2.19
o-OEt	−0.24			−0.78	0.28	−0.55	−0.55	−0.55
o-OPh	−0.32				0.40	−0.55	−0.55	−0.59
o-SMe	0.00				0.30	−1.07	−1.07	−1.14
o-*n*-Pr	−0.15				−0.01	−1.60	−1.60	−1.62
o-*n*-Bu	−0.15				−0.01	−1.63	−1.63	−1.64

a) Values used in this work are listed only. b) From Ref. 9. c) From Ref. 8. When σ_p is used as σ^- for a substituent that does not undergo the electron-attracting through-resonance, it is not shown. d) From Ref. 10. σ_m^+ equated to σ_m is not listed. e) From Ref. 7. f) From Ref. 11. g) From Ref. 4. h) For the minimum perpendicular dimension. i) For the maximum coplanar dimension.

Table 2. Compounds Included in Correlation Analyses[a]

Set No.	Reactivity data
1	Alkaline hydrolysis of *o,m,p*-X-$C_6H_4CONH_2$ in aq $Ba(OH)_2$ at 100°C, 10^4k (min^{-1} mol^{-1})[b] H (944), *p*-Cl (1800), *p*-Br (1800), *p*-I (1590), *p*-Me (623), *p*-NO_2 (6300), *p*-NH_2 (178), *p*-OMe (462), *m*-Br (2820), *m*-I (2450), *m*-Me (752), *m*-NO_2 (5300), *m*-NH_2 (885), *m*-O^- (165), *o*-Cl (489), *o*-Br (291), *o*-I (130), *o*-OMe (528), *o*-OEt (360), *o*-OPh (427), *o*-Me (50.5) [*o*-O^- (60), *o*-NMe_2 (152)]
2	Acidic esterification of *o,m*-X-C_6H_4COOH with MeOH at 25°C, 10^5k (min^{-1})[c] H (19.2), *o*-F (19.9), *o*-Cl (7.83), *o*-Br (5.55), *o*-I (3.31), *o*-Me (6.41), *o*-OMe (83.0), *o*-NO_2 (0.546), *o*-OEt (66.1), *m*-NO_2 (7.28), *m*-F (13.1), *m*-Cl (12.4), *m*-Br (12.5), *m*-I (13.7), *m*-Me (21.7), *m*-OMe (19.1), *m*-OEt (21.1) [*p*-F (7.56), *p*-Cl (11.4), *p*-Br (12.3), *p*-Me (19.7), *p*-OMe (10.4), *p*-OEt (11.3), *p*-NO_2 (8.67)]
3	Alkali-catalyzed methanolysis of *o,m,p*-X-C_6H_4COO-*l*-menthyl at 40°C, 10^4k (sec^{-1})[d] H (1.294), *p*-Cl (5.74), *p*-Br (6.72), *p*-Me (0.560), *p*-OMe (0.296), *p*-NO_2 (127.4), *m*-Cl (13.50), *m*-Br (13.45), *m*-Me (0.972), *m*-OMe (1.704), *m*-NO_2 (93.1), *o*-Cl (0.891), *o*-Br (0.659), *o*-Me (0.0998), *o*-OMe (0.248), *o*-NO_2 (3.57), *p*-CN (73.3)
4	Acidic hydrolysis of *o*-X-$C_6H_4CON(Me)OH$ in water at 90°C, $-\log k$ (sec^{-1})[e] *o*-Me (4.359), *o*-OMe (3.964), *o*-Cl (4.585), *o*-Br (4.713), *o*-I (4.793), *o*-NO_2 (5.237)
5	Substitution of *o,m,p*-X-$C_6H_4NH_2$ by C_6H_5COCl in benzene at 25°C, 10^2k (min^{-1} mol^{-1})[f] H (7.48), *o*-Cl (0.0486), *o*-Me (2.81), *o*-OMe (9.07), *o*-NO_2 (0.00030), *p*-Cl (1.57), *p*-Me (31.6), *p*-NO_2 (0.00421), *m*-Cl (0.436), *m*-Br (0.396), *m*-Me (13.8), *m*-NO_2 (0.0444)
6	Taft E_S^0[g] *o*-Me (0.00), *o*-Cl (0.18), *o*-Br (0.00), *o*-I (−0.20), *o*-OMe (0.99), *o*-OEt (0.90), *o*-NO_2 (−0.75), *o*-Ph (−0.90) [*o*-F (0.49)]
7	pK_a of *o,m,p*-X-C_6H_4COOH in water at 25°C[h] *p*-F (4.14), *p*-Cl (3.98), *p*-Br (3.97), *p*-I (3.93), *p*-Me (4.37), *p*-Et (4.35), *p*-*i*-Pr (4.35), *p*-OMe (4.47), *p*-NO_2 (3.43), *m*-F (3.87), *m*-Cl (3.83), *m*-Br (3.81), *m*-I (3.85), *m*-Me (4.27), *m*-OMe (4.09), *m*-NO_2 (3.49), *o*-F (3.27), *o*-Cl (2.94), *o*-Br (2.85), *o*-I (2.86), *o*-Me (3.91), *o*-Et (3.79), *o*-*i*-Pr (3.64), *o*-OMe (4.09), *o*-NO_2 (2.17), *o*-Ph (3.46), *m*-CN (3.60), *m*-Ac (3.83), *m*-OPh (3.95), *p*-CN (3.55), *p*-Ac (3.70), *p*-OPh (4.52), H (4.20), *p*-*t*-Bu (4.39), *o*-OPh (3.53) [*o*-*t*-Bu]
8	Nucleophilic substitution of $C_6H_5COCH_2Br$ by *o*-X-$C_6H_4COO^-$ in 90% acetone–water at 35°C, 10^3k (sec^{-1} mol^{-1})[i] H (14.1), *o*-F (10.0), *o*-Cl (13.1), *o*-Br (14.0), *o*-I (18.0), *o*-Me (28.1), *o*-OMe (15.4), *o*-NO_2 (8.18), *o*-SMe (20.7) [*o*-SO_2Me (10.5)]
9	Rearrangement of *o,m,p*-X-C_6H_4COOH to anilines with NaN_3 in $CHCl_3$ at 20°C, 10^3k (sec^{-1} mol^{-1})[j] H (0.72), *o*-Cl (17.2), *o*-Br (37.5), *o*-I (109), *o*-Me (145), *o*-Et (272), *o*-*i*-Pr (903), *o*-NO_2 (2.6), *p*-Cl (0.31), *p*-Br (0.25), *p*-Me (0.84), *p*-NO_2 (0.002), *m*-Cl (0.10), *m*-Br (0.13), *m*-Me (0.81), *m*-NO_2 (0.004) [*o*-*t*-Bu (1558)]

a) The original reactivity and physicochemical data are shown. Whenever necessary, they were transformed into log values. The ortho substituents in brackets were excluded in analyses, because their E_s (AMD) value was unavailable except for in Set 6. For Set 2 where para substituents were excluded, see text. b) From Ref. 14. c) From Ref. 15. d) From Ref. 16. e) From Ref. 17. f) From Ref. 18. g) From Ref. 1. h) From Ref. 19. i) From Ref. 20. j) From Ref. 21.

atom. No π-bonded planar ortho substituent was included, so there was no difference between the E_s(L) and E_s(S) parameter sets in this data set. The E_s(L) column is used in Table 3.

The quality of correlation for Eqs. 3 and 5 was better than that for Eqs. 4 and 6, respectively. This coincides with the previous findings that the steric effect of alkoxyl and OPh groups is not represented by that of the oxygen atom alone but is somewhat affected by the bulkiness of the alkyl and phenyl moieties.[4] The ρ values in Eqs. 3 and 4 are considerably smaller than those in Eqs. 5 and 6. This may be mainly due to the fact that the range of variations in the σ value for ortho substituents is much lower (0.55) than that for the whole substituents set (1.44). Even a small experimental error tends to destabilize the value in the ortho compound set. The ρ and the intercept values for the set of meta and para compounds are shown to be 1.077 and 2.993[6] that are almost equal to the corresponding values in Eqs. 5 and 6. The σ_I and E_s(AMD) terms and the intercept value are very stable in Eqs. 3 and 5, as the σ_I and E_s(L) terms in Eqs. 4 and 6. The δ value for the E_s(AMD) term is very close to unity. This indicates that the steric effect of ortho substituents in the acidic hydrolysis of benzamides[4] is almost equivalent to that in their alkaline hydrolysis.

Set 2, the acid-catalyzed esterification of benzoic acids, was selected to examine the applicability of E_s(AMD) to the NO_2 group. In our previous study, the *p*-F, *p*-alkoxy, *o*-OMe and *o*-OEt derivatives were excluded, and σ and F were used as the electronic parameters.[6] In this study, *o*-OMe and *o*-OEt derivatives were included. Instead, all para isomers were omitted, because the data set including only para isomers did not give any reasonable correlation equation with any σ parameter. For the ordinary electronic effect of ortho substituents, the σ^+ value of the corresponding para substituents worked better than σ, and neither σ_I nor the Swain–Lupton–Hansch F term was a significant in Eqs. 7 and 8. In Eqs. 9 and 10, a composite set of σ^+ for ortho and σ for meta substituents was used. E_s(AMD) in Eqs. 7 and 9 gave better results than E_s in Eqs. 8 and 10. The exclusion of all of para isomers in this study seemed more straightforward than the exclusion of some para and ortho

Table 3. Correlation Results in Which E_s (AMD) is Better than TKH E_s[a]

$\rho^{(\sigma)}$	$\rho_I^{(\sigma_I)}$	$\delta[E_s(\text{AMD})]$	$\delta[E_s(\text{S})]$	$\delta[E_s(\text{L})]$	c	n[b]	n_{ortho}[c]	s[d]	r[e]	F[f]	Eq. No.
Set 1: Alkaline hydrolysis of *o,m,p*-X-$C_6H_4CONH_2$											
0.637	1.077	0.987			2.970	8	8	0.036	0.998	292.21	3
(0.189)	(0.215)	(0.095)			(0.094)						
0.550	0.995			0.960	2.989	8	8	0.071	0.991	71.70	4
(0.374)	(0.427)			(0.186)	(0.192)						
1.022	1.067	1.027			3.007	21	8	0.072	0.992	369.43	5
(0.087)	(0.294)	(0.113)			(0.040)						
1.006	0.987			0.983	3.011	21	8	0.089	0.988	235.19	6
(0.109)	(0.361)			(0.137)	(0.050)						
Set 2: Acidic esterification of *o,m*-X-C_6H_4COOH with MeOH											
−0.895		0.542			1.387	9	9	0.129	0.986	106.35	7
(0.281)		(0.249)			(0.248)						
−0.829				0.431	1.357	9	9	0.154	0.980	73.37	8
(0.367)				(0.248)	(0.294)						
−0.848		0.555			1.399	17	9	0.096	0.984	206.70	9
(0.120)		(0.087)			(0.064)						
−0.782				0.449	1.377	17	9	0.107	0.979	163.34	10
(0.135)				(0.080)	(0.070)						
Set 3: Alkali-catalyzed metanolysis of *o,m,p*-X-C_6H_4COO-*l*-menthyl											
1.943		0.674			0.142	6	6	0.040	0.998	467.96	11
(0.206)		(0.131)			(0.112)						
1.456			0.630		0.128	6	6	0.105	0.989	66.20	12
(0.415)			(0.334)		(0.297)						
2.385		0.823			0.200	17	6	0.115	0.9933	520.18	13
(0.173)		(0.113)			(0.078)						
2.477				0.641	0.165	17	6	0.120	0.9928	478.50	14
(0.182)				(0.092)	(0.079)						
Set 4: Acidic hydrolysis of *o*-X-$C_6H_4CON(Me)OH$											
	−0.762	0.764			−3.457	6	6	0.053	0.995	163.51	15
	(0.358)	(0.190)			(0.215)						
	−0.593			0.475	−3.761	6	6	0.191	0.939	11.14	16
	(1.401)			(0.482)	(0.625)						
Set 5: Substitution of *o,m,p*-X-$C_6H_4NH_2$ by C_6H_5COCl											
−3.126		1.173			0.874	12	5	0.213	0.991	246.57	17
(0.383)		(0.251)			(0.183)						
−2.972				0.868	0.810	12	5	0.246	0.988	183.17	18
(0.449)				(0.218)	(0.206)						
Set 6: Taft E_s°											
		1.141			1.381	8	8	0.163	0.975	115.47	19
		(0.260)			(0.339)						
				0.546	0.860	8	8	0.330	0.893	23.66	20
				(0.274)	(0.507)						
−0.430		1.013			1.266	8	8	0.093	0.993	184.48	21
(0.301)		(0.180)			(0.218)						
−0.696				0.460	0.793	8	8	0.249	0.951	23.53	22
(0.761)				(0.237)	(0.408)						

a) The susceptibility constants and the intercept according to Eqs. 1 and 2 are listed. Figures in parentheses are the 95% confidence intervals. b) Number of compounds. c) Number of ortho-substituted derivatives including the unsubstituted compound. d) Standard deviation. e) Multiple correlation coefficient. f) F ratio between regression and residual variances.

derivatives somewhat arbitrarily in our previous paper.[6]

Set 3 was for the base-catalyzed solvolysis of *l*-menthyl benzoates. For ortho-substituted derivatives, E_s(S) worked better than E_s(L) in Eq. 12. When substituents at other positions were included, E_s(L) was better than E_s(S) in Eq. 14. The NO_2 group was the only ortho substituent with different E_s(S) and E_s(L) values included in the correlations, so the stability of the TKH E_s term was low. With the E_s(AMD) value, this ambiguity was not found, and better and consistent correlation was found with Eqs. 11 and 13. In addition, the ρ values in Eqs. 11 and 13 were much closer to each other than those in Eqs. 12 and 14.

Set 4 was for the acidic hydrolysis of ortho-substituted benzenecarbohydroxamic acids, including the *o*-NO_2 derivative. In spite of the limited number of derivatives, E_s(AMD) gave high correlation. The resonance effect of ortho substituents was very low, so only the inductive

Table 4. Correlation Results in Which TKH E_s (S) is Better than E_s (AMD)[a)]

$\rho^{(\sigma)}$	$\rho_I^{[(\sigma_I)]}$	$\delta[E_s(S)]$	$\delta[E_s(AMD)]$	c	n	n_{ortho}	s	r	F	Eq. No.
Set 7: log K_a of o,m,p-X-C_6H_4COOH										
0.941	1.349	−0.439		−4.218	12	12	0.136	0.981	67.61	23
(0.431)	(0.527)	(0.210)		(0.287)						
0.741	1.447		−0.342	−4.189	12	12	0.147	0.978	58.10	24
(0.504)	(0.586)		(0.180)	(0.302)						
0.989	1.303	−0.427		−4.195	35	12	0.072	0.991	569.64	25
(0.082)	(0.157)	(0.059)		(0.033)						
0.930	1.350		−0.341	−4.177	35	12	0.084	0.988	419.51	26
(0.093)	(0.180)		(0.056)	(0.037)						
Set 8: Nucleophilic Substitution of $C_6H_5COCH_2Br$ by o-X-$C_6H_4COO^-$										
−0.219	−0.429	−0.230		1.144	9	9	0.028	0.991	86.43	27
(0.121)	(0.158)	(0.059)		(0.068)						
−0.408	−0.355		−0.220	1.140	9	9	0.034	0.986	58.19	28
(0.165)	(0.191)		(0.069)	(0.084)						
Set 9: Rearrangement of o,m,p-X-C_6H_4COOH to anilines with NaN_3										
−1.466		−1.711		−0.124	8	8	0.075	0.998	668.38	29
(0.233)		(0.148)		(0.182)						
−2.515			−1.589	0.027	8	8	0.260	0.978	53.68	30
(0.818)			(0.489)	(0.605)						
−2.745	1.398	−1.579		−0.181	16	8	0.253	0.991	214.32	31
(0.562)	(0.876)	(0.302)		(0.237)						
−3.019	0.862		−1.552	−0.093	16	8	0.263	0.990	198.00	32
(0.555)	(0.986)		(0.310)	(0.236)						

a) The susceptibility constants and the intercept according to Eqs. 1 and 2 are listed. Figures in parentheses are the 95% confidence intervals. For n, n_{ortho}, s, r, and F, see Table 3.

(field) electrical σ_I term was significant.

Set 5 was for the reaction of substituted anilines with benzoyl chloride, and included the o-OMe and o-NO_2 derivatives. There were only five ortho derivatives in this set. Therefore, analyses were done with Eq. 2 only. This example shows the applicability of E_s(AMD) to reactions other than benzoyl transfer.

Set 6 was of the Taft steric parameter for ortho substituents, E_s°.[1)] This parameter has been defined on the assumption that the rates of the acid-catalyzed hydrolysis of ortho-substituted benzoic acid esters and the acid-catalyzed esterification of ortho-substituted benzoic acids are a function mostly or entirely of the steric effect of ortho substituents. When all of the data available were included, fairly good correlation was found with the E_s(AMD) and σ-parameter terms (n=9, r=0.976), with the most significant deviant being F. Correlations reexamined by deletion of the F substituent are shown here. The Taft E_s° set includes the values for OMe, OEt, OPh, NO_2, and Ph groups, and correlation with E_s(AMD) was much better than with E_s(S) and E_s(L). Equation 21 indicates that the Taft E_s° value is indeed a composite parameter of steric and electronic effects. After separation of the electronic effect, the slope of the E_s(AMD) term was close to unity. This is reasonable because reactivities used to define the Taft E_s° value are considered to suffer a nearly equivalent steric effetc of substituents with that on the acid-catalyzed hydrolysis of ortho-substituted benzamides in aqueous media.[4)]

Owing to the lack of a series of consistent data including enough ortho substituents, Taft combined data sets from different sources to estimate the E_s° value.[1)] The significance of the σ term in Eq. 21 seems to be due to his selection of data sets. In some data sets he selected, the electronic effect could not be neglected. Charton has reported that the Taft E_s° value is not correlated with the size of substituents, but mainly with the resonance component of the electronic effect.[12)] In his analysis, however, planar π-bonded substituents were excluded. Exclusion of such substituents as NO_2 and Ph leads to high collinearity between σ_R and the van der Waals radius of the substituents, as pointed out by Mager el al.,[13)] resulting in the overestimation of the σ_R effect.

The slope of the E_s(AMD) term is generally higher than the slope of the E_s(L) term in the above examples. This is due to the fact that the E_s(AMD) value is less negative than the E_s(L) for most substituents included in the above sets. The difference is most conspicuous in Set 6, in which the o-Ph substituent is included, leading to about two times higher and physicochemically more reasonable slope of the E_s(AMD) term than that of the E_s(L) term.

The above examples tend to reinforce the versatility of the E_s(AMD) value for alkoxyl, OPh, NO_2, and Ph groups. The deviations of the data of compounds having these groups from the regression analyses are generally reduced with use of the E_s(AMD) value.

Conditions Required for Correlation with E_s(AMD). As shown in Table 3, examples in which E_s(AMD) gave better results than the TKH E_s mostly involved esterification and hydrolysis of ortho-substituted benzoic acids and their derivatives. In these reactions, the transition

state with sp^3 hybridization at the carbonyl carbon is formed from the initial state with sp^2 hybridization. The E_s(AMD) value was originally derived from the rate constants for acidic hydrolysis of ortho-substituted benzamides, and reflects the free-energy difference between the trigonal initial and tetrahedral intermediate states. It is reasonable that the E_s(AMD) value represents the steric effect in reactions in which the change in the hybridization geometry of the reaction center is similar to that occurring in the acidic hydrolysis of ortho-substituted benzamides. Another thing to be noted is that the coefficients with E_s(AMD) and E_s are positive in every example in Table 3. Thus, the reactions in Table 3 are retarded by the bulkiness of ortho substituents, as in the acidic hydrolysis of benzamides. The results for Set 5 may be fortuitous, but the steric effect of an ortho substituent of anilines on benzanilide formation could be similar to that of an ortho substituent on benzoyl transfer reactions. In fact, the initial and intermediate states of this reaction have sp^2 and sp^3 geometry, respectively.

For comparison, we listed in Table 4 some data sets for which TKH E_s(S) gave better results than E_s(AMD): the proton-transfer reaction of substituted benzoic acids (pK_a value; Set 7), the nucleophilic attack by ortho-substituted benzoate anions on phenacyl bromide (Set 8), and the Schmidt reaction of ortho-substituted benzoic acids (Set 9). For Sets 7 and 8, the hybridization type at the carbonyl carbon remains unchanged during the course of the reactions. For Set 9, the formation of the sp-hybridized acylium ions from the initial sp^2-hybridized carbonyl carbon is the rate-determining step. The change in the hybridization symmetry in the reactions in Table 4 is different from that occurring in the acidic hydrolysis of benzamides. The steric bulkiness of ortho substituents favors the reactions in Table 4.

In the literature, the number of data sets that could be used in this kind of analyses is limited; the number of ortho derivatives, especially the number of ortho substituents with a sufficiently high steric effect, is small in each data set. Therefore, intensive analysis with the use of a large number of ortho data sets could not be done. Nevertheless, the correlations found here showed the role of ortho substituents in the acceleration or inhibition of the reaction and that the changes in the hybridization type of the reaction center greatly influence the ortho steric effect.

To summarize, the E_s(AMD) defined by the acid-catalyzed hydrolysis rate of ortho-substituted benzamides satisfactorily represented the steric effect of ortho substituents in reactions including those of benzoic acids and their derivatives if the change in the hybridization geometry of the reaction center during the reaction course was similar to that of the reference reaction.

References

1) R. W. Taft, "Steric Effects in Organic Chemistry," ed by M. S. Newman, Wiley, New York (1956), p. 556.
2) E. Kutter and C. Hansch, *J. Med. Chem.*, **12**, 647 (1969).
3) T. Fujita and H. Iwamura, *Top. Curr. Chem.*, **114**, 119 (1983).
4) T. Sotomatsu and T. Fujita, *J. Org. Chem.*, **54**, 4443 (1989).
5) T. Sotomatsu and T. Fujita, *Quant. Struct.-Act. Relat.*, **9**, 295 (1990).
6) T. Fujita and T. Nishioka, *Progr. Phys. Org. Chem.*, **12**, 49 (1976).
7) M. Charton, *Progr. Phys. Org. Chem.*, **13**, 119 (1981).
8) J. Shorter, "Advances in Linear Free Energy Relationships," ed by N. B. Chapman and J. Shorter, Plenum Press, London (1972), p. 72.
9) D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, **23**, 420 (1958).
10) H. C. Brown and Y. Okamoto, *J. Am. Chem. Soc.*, **80**, 4979 (1958).
11) C. Hansch and A. J. Leo, "Substituent Constants for Correlation Analysis in Chemistry and Biology," Wiley, New York (1979), p. 13.
12) M. Charton, *Progr. Phys. Org. Chem.*, **8**, 235 (1971).
13) H. Mager, P. P. Mager, and A. Barth, *Tetrahedron*, **1979**, 1953.
14) E. Reid, *Am. Chem. J.*, **24**, 397 (1900).
15) R. J. Hartman and A. M. Borders, *J. Chem. Soc.*, **1937**, 2107; **1940**, 1559.
16) R. W. Taft, M. S. Newman, and F. H. Verhoek, *J. Am. Chem. Soc.*, **72**, 4511 (1950).
17) D. C. Berndt and I. E. Ward, *J. Org. Chem.*, **43**, 13 (1978).
18) F. J. Stubbs and C. Hinshelwood, *J. Chem. Soc.*, **1949**, S71.
19) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," Methuen, London (1962), p. 121.
20) A. J. de Koning, *Recl. J. R. Neth. Chem. Soc.*, **98**, 548 (1979).
21) C. Srinivasan, A. Shunmugasundaram, M. Roja, and N. Arumugam, *Indian J. Chem., Sect. B*, **23**, 555 (1984).