130 pH meter with combination electrode, and then dissolving the needed amount of NaCl to achieve the desired ionic strength. The solutions of acetonitrile in deuterium oxide were prepared as above except that the solutions were adjusted to pD 2.0 (pH meter reading 1.6) with deuterium chloride. The solutions for the proton inventory studies at each volume fraction of acetonitrile in H_2O–D_2O mixtures of atom fraction deuterium n were prepared by mixing appropriate volumes of the corresponding H_2O–CH_3CN and D_2O–CH_3CN solutions. The atom fraction of deuterium of exchangeable protons was calculated from the results of an analysis by Josef Nemeth (see footnote in Table I) on a sample of "100%" D_2O–CH_3CN solution.

Kinetics. The equilibrium hydration of 2-acetyl-3,4-dimethylthiazolium iodide was monitored by following the decrease in absorbance at 295 nm on a Cary 118C UV–vis spectrophotometer equipped with a constant temperature cell compartment and cell holder. Runs were initiated by 100-μL injections of a stock solution of **2** (4×10^{-3} M in CH_3CN) into a cuvette containing 3.0 mL of the appropriate HCl–DCl–CH_3CN solution. A timer was started at the moment of injection to allow extrapolation back to time zero. Runs were followed for at least 5 half-lives and exhibited good first-order kinetics. First-order rate constants were determined from linear regression analysis of plots of $(A_t - A_\infty)$ versus time using the linear regression program on an HP-11C. Equilibrium constants and rate constants for the hydration of **2** were determined from these first-order rate constants by using the equation described previously.[3a] Thermodynamic activation parameters were calculated from the rate constants of the forward step of the equilibrium hydration obtained at four temperatures between 16 and 32 °C. The activation parameters were determined from Eyring plots of ln (k/T) versus $1/T$.

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The Steric Effect of Ortho Substituents on the Acidic Hydrolysis of Benzamides

Tomoko Sotomatsu and Toshio Fujita*

Department of Agricultural Chemistry, Kyoto University, Kyoto 606, Japan

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The rate constant, k, for the acidic hydrolysis of a number of substituted benzamides in water and in a dioxane–water mixture (1:1, v/v) was measured. The reaction conditions were selected to exclude the electronic effects of substituents on the overall rate as far as possible. The log k value for meta derivatives was almost independent of the electronic effects of substituents. Although the log k value for para derivatives was weakly affected by the through-resonance effect of electron-donating substituents, the value for ortho derivatives was almost linear with the Taft–Kutter–Hansch (TKH) E_s steric parameter except for NO_2 and Ph. The effective steric effects of these π-bonded planar substituents were approximated by the averaged value of the two TKH E_s constants estimated from the thickness and width of each group. The log k value was also analyzed by using the Charton υ steric parameter. The differences in definition of the υ from the TKH E_s parameter seriously distorted the analysis of the ortho substituent effects on the hydrolytic reaction.

We have proposed a procedure to analyze the effects of ortho substituents on the reactivity of aromatic compounds on the same basis as those of para and meta substituents. In this procedure, the Taft–Kutter–Hansch (TKH) E_s parameter was used to represent the steric effect of ortho substituents.[1,2] The original Taft E_s parameter for mostly alkyl substituents is defined by the reactivity data of the acidic hydrolysis of aliphatic esters.[3] For such substituents as halogens, alkoxy, alkylthio, and π-bonded planar groups, the E_s value cannot be evaluated experimentally under the same conditions as that for alkyls. Charton has found that the Taft E_s value of alkyl groups of a similar structural type is quantitatively related to their van der Waals dimensions.[4] On the basis of this finding, Kutter and Hansch have extended the E_s value to non-alkyl substituents by using their appropriate van der Waals dimensions.[5] The TKH E_s is a combined set of parameters of the original Taft E_s and those extended by Kutter and Hansch. Although the Taft E_s is defined for aliphatic substituents, the TKH E_s has been shown to apply in certain cases to substituents at various positions of aromatic molecules in correlation analysis of biological activities with structural properties[5-8] besides the above-mentioned aromatic ortho substituent effects.

Two types of TKH E_s values are estimated from the half-width and the half-thickness of each π-bonded planar substituent.[5] In our previous analysis of ortho effects, either of the two E_s parameters was selected, depending upon the situation, but the criterion for the selection was somewhat arbitrary.[2] We also noticed that occasionally neither of the two parameters rationalizes the ortho steric effect satisfactorily. In addition, the TKH E_s value for OR, NHR, and SR groups, which is evaluated from the van der Waals radius (r_v) of O, N, and S atoms, sometimes does not predict the reactivity well, especially when the R group

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Table I. Reaction Conditions and the Electronic Effects on the Acidic Hydrolysis of Meta- and Para-Substituted Benzamides:[a] $\log k = \rho\sigma + c$

eq no.	concn, M H^+	concn, M benzamide	$\rho\sigma$[b]	c[c]	n[d]	s[e]	r[f]	F[g]	solvent	temp, °C	substituents	ref
1	0.025	0.025	−0.375 (0.263)σ	−3.704 (0.109) (s^{-1} M^{-1})	4	0.044	0.974	37.6	60% EtOH	100.0	H, *p*-Me, *p*-Cl, *p*-NO_2	*h*
2	7.19	0.17	0.862 (0.127)σ^+	−0.574 (0.063) (h^{-1})	8	0.071	0.989	274.2	H_2O	95.0	H, *m*-Me, *m*-Br, *m*-NO_2, *p*-Me, *p*-OMe, *p*-Br, *p*-NO_2	*i*
3	ca. 0.5	0.02–0.04	0.160 (0.059)σ^+	−1.708 (0.025) (min^{-1} M^{-1})	9	0.031	0.924	40.8	H_2O	100.0	H, *m*-Me, *m*-Br, *m*-NO_2, *p*-Me, *p*-OMe, *p*-Cl, *p*-Br, *p*-NO_2	*j*

[a] Footnotes *d–g* apply to the correlation equations appearing later. [b] Regression coefficient ρ and the type of electronic parameters used. The σ and σ^+ values used are taken from ref 12. The figures in parentheses are the 95% confidence intervals. [c] Intercept of the correlation equation. [d] Number of substituents. [e] Standard deviation. [f] Correlation coefficient. [g] F value for significance of the correlation. [h] From ref 13. The log k value for each compound at 100 °C was estimated from the least-squares Arrhenius equation derived from those measured at various temperatures. [i] From ref 14. [j] From ref 15. *p*-NH_2 and *m*-NH_2 derivatives were excluded because of a possibility of protonation of the amino group. The *m*-I, *p*-I, *p*-NO_2, and *p*-OMe derivatives were omitted since the data for these compounds seemed to be perturbed in part by the rate of solution.[13]

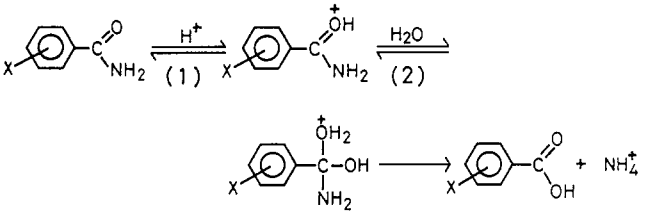
in these substituents is large and congested.

This study was directed to experimentally reexamine the TKH E_s parameters, especially for non-alkyl substituents. We selected the acidic hydrolysis of ortho-substituted benzamides as the standard system. The rate of this reaction under certain conditions has been shown to be largely governed by the ortho steric effect.[2,3] We measured the rate not only for ortho- but also for meta- and para-substituted derivatives to examine whether the electronic effect was excluded as far as possible.

Experimental Section

Materials. Most of the benzamides were commercially purchased and purified by recrystallization from water before use. Some benzamides were prepared from the corresponding benzoyl chlorides or benzonitriles by the usual methods. 2-Isopropyl-, 2-*n*-propyl-, and 2-*n*-butylbenzonitriles were synthesized from the corresponding anilines by the Sandmeyer reaction. 2-*n*-Butylaniline was obtained from *n*-butylbenzene by nitration,[9] followed by reduction with ammonium chloride and iron powder in a methanol–water mixture. The ortho and para isomers were separated by fractional distillation and alumina column chromatography. 2-Isopropoxybenzamide was prepared by the addition of isopropyl iodide into a dimethyl sulfoxide solution containing 2-hydroxybenzamide and potassium hydroxide. All compounds thus obtained were recrystallized from water or water–methanol and identified by IR spectra and elemental analyses for C, H, and N. The analytical data of synthesized compounds were as follows. 2-Isopropoxybenzamide: mp 61–62 °C; IR ($CHCl_3$) 3500, 3390, 1661 cm^{-1}. Anal. Calcd: H, 7.31; C, 67.01; N, 7.81. Found: H, 7.25; C, 67.09; N, 7.87. 2-*n*-Butylbenzamide: mp 120–122 °C; IR ($CHCl_3$) 3500, 3390, 1677 cm^{-1}. Anal. Calcd: H, 8.52; C, 74.54; N, 7.90. Found: H, 8.47; C, 74.62; N, 7.84. 2-*n*-Propylbenzamide: mp 104–105 °C; IR ($CHCl_3$) 3500, 3390, 1677 cm^{-1}. Anal. Calcd: H, 8.03; C, 73.59; N, 8.58. Found: H, 8.11; C, 73.50; N, 8.54. 2-Isopropylbenzamide: mp 173–174 °C; IR ($CHCl_3$) 3500, 3390, 1676 cm^{-1}. Anal. Calcd: H, 8.03; C, 73.59; N, 8.58. Found: H, 8.09; C, 73.46; N, 8.64. 2-(Methylthio)benzamide: mp 210–212 °C; IR ($CHCl_3$) 3500, 3390, 1670 cm^{-1}. Anal. Calcd: H, 5.42; C, 57.46; N, 8.38. Calcd: H, 5.43; C, 57.23; N, 8.29. 2-Ethylbenzamide: mp 164–165 °C; IR ($CHCl_3$) 3500, 3390, 1677 cm^{-1}. Calcd: H, 7.43; C, 72.46; N, 9.39. Found: H, 7.55; C, 72.54; N, 9.33. 2-Bromobenzamide: mp 204–206 °C; IR ($CHCl_3$) 3500, 3390, 1682 cm^{-1}. Calcd: H, 3.02; C, 42.03; N, 7.00. Found: H, 2.90; C, 42.27; N, 6.93. 2-Iodobenzamide: mp 215–216 °C; IR ($CHCl_3$) 3500, 3390, 1682 cm^{-1}. Calcd: H, 2.45; C, 34.03; N, 5.67. Found: H, 2.53; C, 34.23; N, 5.96. 2-Phenoxybenzamide: mp 117 °C; IR ($CHCl_3$) 3500, 3390, 1667 cm^{-1}. Calcd: H, 5.19; C, 73.22; N, 6.56. Found: H, 5.12; C, 73.29; N, 6.60. 2-Phenylbenzamide: mp 162 °C; IR ($CHCl_3$) 3500, 3390, 1671 cm^{-1}. Calcd: H, 5.62; C, 79.17; N, 7.10. Found: H, 5.47; C, 79.08; N, 6.99. 2-(Trifluoromethyl)benzamide: mp 185 °C; IR ($CHCl_3$) 3500, 3390, 1690 cm^{-1}. Calcd: H, 3.20; C, 50.80; N, 7.41. Found: H, 3.03; C, 51.04; N, 7.42. Dioxane was of spectroscopic grade. The standard solutions of hydrochloric acid were commercially obtained.

Scheme I



Measurement of the Rate Constants. The reaction was done at 90 ± 0.05 °C. Water or a dioxane–water mixture (1:1, v/v) was used as the solvent, because some of the benzamides were scarcely soluble in water. Stock solutions were made by dissolving weighed benzamides into water or dioxane. The reaction solution was prepared at 0 °C by mixing the stock solution with an equal volume of hydrochloric acid of an appropriate concentration. The reaction solution (0.2 mL) was sealed in a borosilicate glass tube (diameter, 6 mm). Five to seven tubes were used for each rate constant measurement. At different times, one of the reaction tubes was cooled at 0 °C to quench the reaction, and its contents were diluted with a certain amount of water. After coloration by the indophenol method,[10] the concentration of ammonia evolved during the reaction was measured with a Shimadzu UV 360 spectrophotometer. The indophenol method was sensitive to ammonia of the concentration 10^{-4}–10^{-6} M. Benzoic acids and benzamides in the reaction solution did not interfere with the coloration.

The rate constant, k, was estimated according to the conventional second-order kinetics by using the least-squares method. Usually, the time needed to evaluate the rate constant was about 2–3 h for unsubstituted and meta- and para-substituted compounds and about 1–2 days for ortho-substituted derivatives. Reproducibility of the rate constant was generally within 5% for 2–4 experimental runs except for *o*-CF_3 and *o*-Ph derivatives, where it was within 10%.

Results and Discussion

Electronic Effects and Reaction Conditions. The acid hydrolysis of benzamides proceeds by the mechanism shown in Scheme I.[11] In this mechanism, electron-donating substituents accelerate the protonation (step 1), and electron-withdrawing substituents facilitate the attack of water molecules on the protonated amide (step 2). Table I shows the analyses of the literature data for the acidic hydrolysis of meta- and para-substituted benzamides.

In eq 1 (Table I), where the concentration of hydrogen ion is low, electron-donating substituents accelerate the

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Table II. Second-Order Rate Constant k(min^{-1} M^{-1}) × 10^3 for Acidic Hydrolysis of Unsubstituted Benzamide in Aqueous Hydrochloric Acid of Various Concentrations

benzamide concn, M	HCl concn, M				
	1.00	0.50	0.25	0.05	0.01
0.005	4.00	4.18	4.15	4.15	4.20
0.025	4.05	4.18	4.18	4.15	

Table III. log k(min^{-1} M^{-1}) for Acidic Hydrolysis of Meta- and Para-Substituted Benzamides

compd	log k(H_2O)	log k(diox)	σ_R[a]
H	−2.38	−2.75	0.00
m-F		−2.76	
m-NO_2		−2.70	
m-OMe		−2.74	
p-Cl	−2.49		−0.25
p-NO_2	−2.31	−2.64	0.10
p-OMe	−2.63	−3.04	−0.58
p-Br		−2.83	−0.25
p-I		−2.84	−0.16

[a] From ref 16.

rates; the protonation is the rate-determining step. On the other hand, when the concentration of hydrogen ion is high and much in excess, electron-withdrawing substituents facilitate the reaction as shown by eq 2; the attacking step of water molecules determines the rate. There could be a certain hydrogen ion concentration where the opposite electronic effects in the two steps are canceled.

In eq 3, the concentration of hydrogen ion is much lower than that in eq 2, but is still in excess relative to that of the substrates. The reactivity data used for eq 3 may be perturbed by the rate of solution of amides into the aqueous solution under these experimental conditions, as pointed out by Meloche and Laidler.[13] By deleting the dubious data, the coefficient with the electronic parameter in eq 3 is positive, but much lower than that in eq 2. This shows that step 2 is slightly more dominant than step 1, and the electronic effect on the overall rate is much reduced.

Table II summarizes the second-order rate constants of the unsubstituted benzamide measured here under various conditions. Within the concentration range 0.01–1.00 M for hydrogen ion, and within the range 0.005–0.025 M for benzamide, the second-order rate constants agree within experimental error, indicating no notable change in the reaction mechanism.

On the basis of the results in Tables I and II, the reaction conditions for series experiments in this study were chosen so as to make the contribution of the electronic effects of substituents on the overall rate as low as possible. Owing to the limited solubility of some benzamides in water, their concentration was set as 0.005 M, and both water and dioxane–water mixture (1:1, v/v) were used as the solvents. Dioxane was inert under our experimental conditions and permitted the rate measurement for prolonged lengths of time. Equation 3 suggests that a hydrogen ion concentration lower than 0.5 M is suitable for our purpose. The concentration of hydrochloric acid was set as 0.25 M for the water medium. A higher hydrogen ion concentration of 0.50 M was used for the water–dioxane mixture, because some sterically hindered ortho-substituted benzamides were hard to dissolve in water as well as to hydrolyze in the water–dioxane mixture.

Electronic Effects of Substituents. Table III shows the rate constants for meta- and para-substituted benzamides newly measured. The log k(diox) values in water–dioxane for meta derivatives are practically unchanged from that of the unsubstituted benzamide. In these meta derivatives, both electron-donating and -withdrawing substituents are included. Thus, for meta derivatives, the electronic effect of substituents on the overall rate was almost canceled under these reaction conditions, as we expected.

The rate for para compounds was, however, affected by the resonance electronic effect, as shown in eq 4 and 5, where the unsubstituted compound is included as the reference. σ_R is the resonance electronic parameter defined

$$\log k(H_2O) = \underset{(0.110)}{0.459}\sigma_R - \underset{(0.035)}{2.369} \quad (4)$$

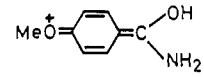
$$n = 4,\ s = 0.013,\ r = 0.997,\ F = 324.1$$

$$\log k(\text{diox}) = \underset{(0.172)}{0.553}\sigma_R - \underset{(0.051)}{2.726} \quad (5)$$

$$n = 5,\ s = 0.028,\ r = 0.986,\ F = 104.9$$

by Charton.[16] In eq 4 and 5, the addition of the inductive electronic parameter σ_I and the use of σ instead of σ_R did not improve the correlations. The slope of σ_R is positive, so the critical step is the attack of water on the protonated amide.

The inductive component of the electronic effect was almost completely canceled out for both meta and para derivatives. The resonance effect remained for para derivatives but not for meta derivatives. This may be because the positively charged reaction center is in part stabilized by electron-donating para substituents with an extra through-resonance effect. As shown below, for instance, the through-resonance effect of the *p*-methoxy group would delocalize the positive charge, leading to a canonical structure less susceptible to the attack of water on the carbonyl carbon:



The use of the σ_R^+ parameter[16] representing the resonance electronic effect on the electron-deficient center instead of σ_R in eq 4 and 5 gave poorer results than that of σ_R (data not shown). Perhaps the σ_R^+ parameter overestimates the contribution of the through-resonating canonical form.

The through-resonance interaction as shown in the structure above requires the coplanar structure. The bulk of ortho substituents forces the protonated carbonyl group out of the plane of the aromatic ring and inhibits the through-resonance interaction to various extents. The contribution of the through-resonance effect should be less important for ortho derivatives than that for para derivatives. We have shown that the through-resonance interaction of ortho substituents with functional groups is generally much less significant than that of the corresponding para derivatives.[2] The rate constant for ortho-substituted benzamides would be, therefore, only weakly affected by the resonance electronic effect like that for meta derivatives.

Steric Effects of Ortho Substituents. In Figure 1, the Δ log k(diox) for para and ortho derivatives is plotted against σ_R, where Δ log k(diox) is the value relative to that of unsubstituted benzamide. The Δ log k value is listed

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Table IV. Relative log k (min^{-1} M^{-1}) Value for Acidic Hydrolysis of Ortho-Substituted Benzamides and Physicochemical Parameters of Substituents Used for Correlation Analysis

substituents	Δ log k(H_2O)	Δ log k(diox)	σ_R[a]	σ[b]	E_s[b]	v[c]	E_s(AMD)[d]
H	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Me	−1.07	−0.88	−0.16	−0.17	−1.24	0.52	−1.16
Et	−1.21	−1.01	−0.14	−0.15	−1.31	0.56	−1.33
n-Pr		−1.23	−0.16	−0.15	−1.60	0.68	−1.62
i-Pr	−1.38	−1.26	−0.16	−0.15	−1.71	0.76	−1.66
n-Bu		−1.24	−0.15	−0.16	−1.63	0.68	−1.64
F	−0.23	−0.24	−0.48	0.06	−0.46	0.27	−0.32
Cl	−0.85	−0.74	−0.25	0.23	−0.97	0.55	−0.98
Br	−1.00	−0.85	−0.25	0.23	−1.16	0.65	−1.12
I	−1.22	−1.09	−0.16	0.18	−1.40	0.78	−1.44
OMe	−0.16	−0.30	−0.58	−0.27	−0.55	0.36	−0.40
OEt	−0.23	−0.42	−0.57	−0.24	−0.55	0.48	−0.55
O-*i*-Pr		−0.63	−0.72	−0.45	−0.55	0.75	−0.83
Ph	−1.97	−1.66	−0.11	−0.01	−1.01[e]		−2.19
					−3.82[f]		
OPh	−0.43	−0.45	−0.48	−0.30	−0.55		−0.59
SMe	−1.00	−0.86	−0.38	0.00	−1.07	0.64	−1.14
CF_3	−2.14	−1.86	0.11	0.54	−2.40	0.90	−2.46
NO_2	−1.52	−1.25	0.10	0.78	−1.01[e]		−1.65
					−2.52[f]		

[a] From ref 16. [b] From ref 12. [c] From ref 17. [d] Calculated from eq 11. [e] E_s from the half-thickness. [f] E_s from the half-width.

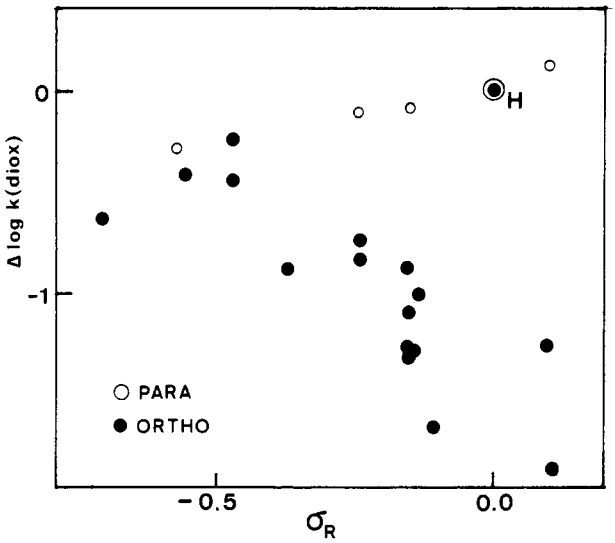

Figure 1. Plot of the relative log k(diox) value for para- and ortho-substituted benzamides against the resonance electronic parameter σ_R of substituents.

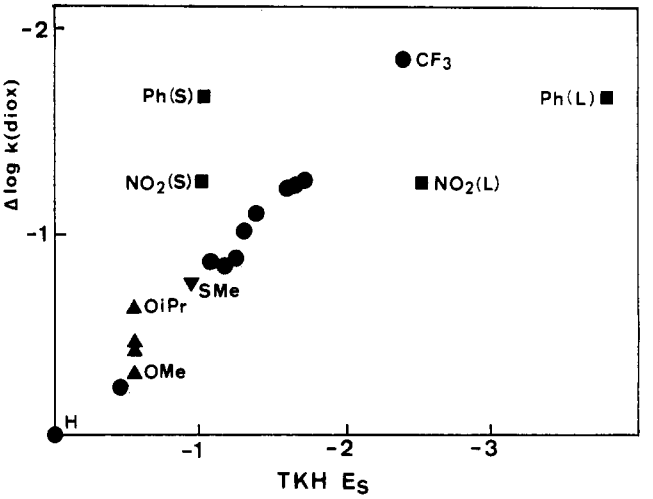

Figure 2. Plot of the relative log k(diox) value for ortho-substituted benzamides against the Taft–Kutter–Hansch E_s parameter. ●: unsubstituted, alkyl, CF_3, and halogen. ▲: alkoxy. ▼: thioalkyl. ■: planar π-bonded groups. S in the parentheses signifies the plot against the E_s for the half-thickness and L for the half-width.

in Table IV. Contrarily to the linear relationship for para derivatives, no clear correlation is observed for ortho derivatives including the unsubstituted (*o*-H substituted) benzamide. All ortho derivatives are less reactive than the unsubstituted compound. The variations in the rate constant are large, covering almost 2 log units. The origin of the large variations should be sought in effects other than electronic ones. A similar plot was obtained for the rate constant in water, Δ log k(H_2O). In fact, Δ log k(H_2O) is linear with Δ log k(diox) for ortho and unsubstituted derivatives, as shown in eq 6. That the slope of the Δ log

$$\Delta \log k(\text{diox}) = \underset{(0.060)}{0.796}(\Delta \log k(H_2O)) - \underset{(0.068)}{0.093} \quad (6)$$

$$n = 15,\ s = 0.067,\ r = 0.992,\ F = 833.6$$

k(H_2O) term is lower than 1 shows some differences in solvation effects between the two solvent systems. The aqueous system without perturbations from the organic solvent molecules would be preferable for the mechanism analysis, because the step of the attack by water molecules participates in the rate process. The number of the Δ log k(H_2O) values was limited, so we use the Δ log k(diox) values hereafter for discussions.

In Figure 2, the Δ log k(diox) value of ortho derivatives is plotted against the corresponding TKH E_s listed in Table IV, the reference point of which was shifted to that of H. At least for alkyl, CF_3, and halogen substituents, an almost linear correlation is observed for which eq 7 was formulated. The E_s values for alkyl and CF_3 are those defined by Taft,[3] and those for halogens are estimated from their r_v by Kutter and Hansch.[5] Although the rate

$$\Delta \log k(\text{diox}) = \underset{(0.046)}{0.790}E_s + \underset{(0.064)}{0.052} \quad (7)$$

$$n = 11,\ s = 0.041,\ r = 0.997,\ F = 1528.5$$

for para derivatives was correlated with σ_R (eq 4 and 5), the addition of the σ_R or other electronic parameter term in eq 7 did not improve the correlation. The rates for the ortho derivatives were considered as being almost completely controlled by the steric effect at least for alkyl, CF_3, and halogen substituents.

The TKH E_s value for OR is evaluated from the r_v of the oxygen atom. As shown in Table IV, the log k(diox)

value varies with the bulkiness of R (alkyl and phenyl) in OR substituents. Apparently, the steric effects of OR substituents are not represented by that of the oxygen atom alone. Nevertheless, combining OR and SMe derivatives with those included in eq 7, eq 8 was obtained.

$$\Delta \log k(\text{diox}) = \underset{(0.070)}{0.765}E_s + \underset{(0.085)}{0.004} \quad (8)$$

$$n = 16,\ s = 0.077,\ r = 0.988,\ F = 553.3$$

Again, the addition of any electronic parameter term was insignificant. Although eq 8 is slightly worse than eq 7, a still good quality of correlation indicates that the TKH E_s value for OR and SMe can be used as a first approximation. It is interesting to note that the log k(diox) value of O-*i*-Pr is more negative than that of OPh. Their steric effect is not entirely decided by the apparent bulkiness of R in OR substituents.

For NO_2 and Ph substituents, neither of the two E_s values evaluated from the half-thickness and half-width rationalizes the Δ log k(diox) values in Figure 2. Their steric effect is apparently expressible by a certain value in between. Using the averaged value of the two E_s constants for NO_2 and Ph, eq 9 was formulated for all derivatives studied here. The addition of an electronic parameter term was insignificant in eq 9. Although the procedure to average the half-thickness and half-width parameters has no a priori physicochemical background, the correlation of eq 9 is almost as good as that of eq 8. These planar substituents perhaps exert their steric effect on the amide group in a moderately twisted conformation.

$$\Delta \log k(\text{diox}) = \underset{(0.064)}{0.728}E_s - \underset{(0.086)}{0.024} \quad (9)$$

$$n = 18,\ s = 0.083,\ r = 0.987,\ F = 583.2$$

The above analyses show that the steric effect of ortho substituents can be rationalized by the TKH E_s parameter as a first approximation except for planar π-bonded groups for which the "effective" E_s value was estimated by averaging the two TKH scales. The "averaged" E_s value for planar substituents may be applicable to their steric effect on the reactivity of similar reaction mechanisms, but it may not be applicable to that on the reactivity of different mechanisms.

For the steric effect of OR substituents apparently depending upon the bulk of R as well as of SMe and planar substituents, the present correlations could be used to estimate an improved E_s scale. We used eq 7 where the OR, SMe, and planar substituents are not included, and the quality of the correlation is excellent. The reference compound is the unsubstituted benzamide, so that its E_s value should be 0. Thus, a counterpart of eq 7 from which the adjustable constant was deleted was formulated as shown in eq 10. Then, the improved TKH E_s constants,

$$\Delta \log k(\text{diox}) = \underset{(0.174)}{0.757}E_s \quad (10)$$

$$n = 11,\ s = 0.045,\ r = 0.997,\ F = 2377.8$$

E_s(AMD), can be estimated from eq 11 not only for OR, SMe, and planar groups but also for other groups from which eq 10 was derived. In eq 11, the Δ log k value is

$$E_s(\text{AMD}) = \Delta \log k(\text{diox})/0.757 \quad (11)$$

divided by 0.757, the slope of the E_s term in eq 10, to put the scale of the improved parameter as close as possible to that of the original TKH E_s. The E_s(AMD) values calculated from eq 11 are listed in Table IV. The value generated for alkoxy groups progressively shifted in the negative direction as the size of the alkyl increased, but that of OPh is almost equal to that of OEt. The value of SMe is practically the same as the TKH E_s value evaluated from the r_v of S.

The Charton υ steric parameter has been recently used in correlation analyses of ortho effects with various degrees of success.[17,18] It is then worth comparing the above analyses with those done using υ. The υ values are listed in Table IV. They are defined so that the more positive the value, the bulkier the substituent. For NO_2, Ph, and OPh substituents, the υ value is unavailable.[17] Without including these substituents, eq 12 was derived for 15 substituents. For the same set of 15 compounds, eq 13

$$\Delta \log k(\text{diox}) = \underset{(0.293)}{-1.698}\upsilon - \underset{(0.290)}{0.928}\sigma_R - \underset{(0.205)}{0.120} \quad (12)$$

$$n = 15,\ s = 0.114,\ r = 0.976,\ F = 118.3$$

was obtained by using the TKH E_s, which is practically the same as eq 8. In eq 12, the σ_R term is significant, but

$$\Delta \log k(\text{diox}) = \underset{(0.074)}{0.769}E_s + \underset{(0.093)}{0.010} \quad (13)$$

$$n = 15,\ s = 0.079,\ r = 0.987,\ F = 498.9$$

not in eq 13. Although the correlation of eq 12 is slightly poorer than that of eq 13, eq 12 seems to provide us with another interpretation on the ortho effect in the benzamide hydrolysis. Thus, we examined the correlation with υ more closely by separating the substituents into subsets according to the procedures for defining the υ values. The unsubstituted derivative was included in each subset as the reference. The results are listed in Table V.

For alkyl and CF_3 compounds, eq 14 and 15 were given (Table V). In this set, the υ values for symmetric-top Me and CF_3 groups are simply the minimum r_v relative to r_v of H. The υ value for nonsymmetric alkyl groups is estimated from the logarithmic rate constant, log k, of standard acyl transfer reactions. A linear relationship between the log k and the minimum r_v for symmetric-top substituents (e.g., H, Me, *t*-Bu, CCl_3, and CF_3) is used to estimate the "effective" r_v for nonsymmetric alkyl groups from their log k value on the same scale of the minimum r_v for symmetric-top substituents.[19]

Equations 16 and 17 were derived for halogen derivatives. The υ value of halogens is defined as their r_v relative to that of H.[4] Equations 18 and 19 were obtained for alkoxy compounds. The υ value of the alkoxy group is estimated with an approximation that the υ(OR) is parallel with the $\upsilon(CH_2R)$, i.e., υ(OR) = $\upsilon(CH_2R)$ + constant, the υ(OMe) value being assigned as 0.36.[20] In this set, the υ value of alkoxy groups is highly collinear with σ_R (r = 0.937), and the use of υ and σ_R at the same time was insignificant. These correlations were compared with those derived with the original (not improved) TKH E_s, and the results are listed in Table V. Using E_s, any electronic parameter term was insignificant at the 95% level in each subsets.

As shown in Table V, even when the σ_R term is statistically significant, the coefficient of the υ term in eq 14 and 16 does not change much from that in eq 15 and 17, respectively, showing a great importance of the steric effect

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(18) Magee, P. S. In *Computer-Assisted Drug Design*; Olson, E. C., Christoffersen, R. E., Eds.; ACS Symposium Series 112; American Chemical Society: Washington, DC, 1979; p 319.
(19) Charton, M. *J. Am. Chem. Soc.* **1975**, *97*, 1552.
(20) Charton, M. *J. Org. Chem.* **1977**, *42*, 3531.

Table V. Correlation Equations for $\Delta \log k(\text{diox}) = \delta(E_s \text{ or } \upsilon) + \rho\sigma_R + c$

substituent set	δ	ρ	c	n^a	s^b	r^c	F^d	eq
Charton υ								
alkyl, CF_3	−1.941 (0.215)	−0.867 (0.577)	−0.014 (0.147)	7	0.054	0.997	318.4	14
	−1.926 (0.412)		0.059 (0.265)	7	0.113	0.983	114.7	15
halogen	−1.457 (0.126)	−0.322 (0.227)	−0.002 (0.077)	5	0.018	1.000	1241.8	16
	−1.423 (0.311)		0.056 (0.175)	5	0.065	0.992	187.6	17
alkoxy	−0.845 (0.085)		−0.002 (0.041)	4	0.011	0.999	1814.2	18
		0.772 (0.880)	0.023 (0.478)	4	0.113	0.937	14.3	19
TKH E_s								
alkyl, CF_3	0.771 (0.052)		0.021 (0.082)	7	0.036	0.998	1440.9	20
halogen	0.793 (0.161)		0.049 (0.152)	5	0.057	0.994	245.1	21
alkoxy, OPh, SMe	0.804 (0.434)		−0.005 (0.272)	6	0.118	0.932	26.5	22

[a] Number of substituents. In all subsets, the unsubstituted benzamide is included. [b] Standard deviation. [c] Correlation coefficient. [d] F value for significance of the correlation.

in each subset. Nevertheless, when υ is used as the steric parameter, the coefficient of the term significantly differs among subsets. On the other hand, the slope of the E_s term is almost unchanged (eq 20–22) for the corresponding subsets. It is also almost equal to that of eq 9 including planar substituents.

The TKH E_s values of alkyl and CF_3 substituents are the original Taft values. The TKH E_s values of halogens are estimated from their r_v based on a linear correlation between the Taft E_s and the averaged (not minimum) r_v for symmetric-top substituents.[5] The same correlation is used to estimate E_s for OR and SR from r_v of O and S. The greatest differences in definition between E_s and υ are as follows. First, for equiscaling the parameters for alkyl and halogen substituents, the TKH E_s value uses the relationship between E_s and the averaged r_v of symmetric-top substituents, but the υ scale uses the relationship with the minimum r_v. Secondly, for alkoxy groups, E_s is calculated from the r_v of the oxygen atom, but υ is defined by certain assumptions as mentioned above.

In fact, we found a linear relationship between the "improved" E_s(AMD) value for OR (R = alkyl and Ph) according to eq 11 and the corresponding Taft E_s for CH_2R (R = alkyl and Ph). Including E_s(H) (=0) in both sides, the coefficient with $E_s(CH_2R)$ was 0.353 and r was 0.995. In eq 23, the addition of the σ_R parameter was insignificant at the 95% level. This equation shows that the steric

$$E_s(\text{AMD,OR}) = \underset{(0.211)}{0.387}E_s(CH_2R) + \underset{(0.372)}{0.074} \quad (23)$$

$$n = 4,\ s = 0.039,\ r = 0.984,\ F = 62.4$$

effect of OR (R = alkyl) and OPh substituents is indeed linear but not parallel with that of CH_2R and CH_2Ph; the steric effect of CH_2R and CH_2Ph is more susceptible to the bulkiness of R and Ph than that of OR and OPh. This is reasonable because CH_2R substituents, having two extra C–H bonds, are more crowded than OR. Although the scale of steric parameters should be common throughout differing types of substituents, there seems to be some discrepancy in procedures defining υ among subsets of substituents.

According to eq 12, where the negative σ_R term is significant, the protonation step in Scheme I could be critical in the overall rate. This is, however, not in accord with the observation for para derivatives, where the attack of water molecules on the protonated amide is the rate-determining step (eq 4 and 5). Additionally, the resonance interaction should be sterically inhibited in ortho-substituted benzamides, as Katritzky and co-workers reported.[21] We have also shown a much weakened resonance effect of ortho substituents in the protonation of substituted benzoic acids.[2] Thus, the negative σ_R term in eq 12 seems to show up just statistically without physicochemical meaning. It may mainly compensate for the overestimated υ for alkoxy groups as well as the underestimated υ value for alkyl and CF_3 groups using the scale of minimum r_v values.

The above discussions definitely indicate the importance of the equiscaling procedure in defining steric parameters for various types of substituents. We believe that the improved TKH E_s scale is much clearer in definition and easier in understanding the steric effect of ortho substituents than the υ parameter.

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