The Ortho Effect in Hydrolysis of Phenyl Esters

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The effect of ortho substituents on the alkaline hydrolysis of substituted phenyl esters of acetic acid, *N,N*-dimethylcarbamic acid, diethylphosphoric acid, and *N*-methylcarbamic acid was analyzed using our recently developing method to correlate reactivity data of a set of ortho-, meta-, and para-substituted derivatives. The logarithmic value of the second-order rate constant was excellently correlated using $\log k = \rho\sigma_{o,m,p} + \delta E_s + fF + c$, where E_s and F are the Taft–Kutter–Hansch steric and the Swain–Lupton–Hansch field effect constants of ortho substituents, respectively. By means of the respective susceptibility constants, ρ, δ, and f, the role of ortho substituents in the hydrolysis reaction course was analyzed quantitatively.

Analyses of structure–reactivity relationships of hydrolytic reaction of phenyl phosphates and phenyl carbamates are important in order to gain better insight into their reactivities with acetylcholinesterase (AChE), which is believed to be the target for insecticidal action of these classes of compounds. A number of studies have been performed with the use of Hammett σ constants and related parameters.[1-7] Sometimes, the nature and site of the rate-determining process of the overall hydrolytic reaction sequence can be inferred from the value of the reaction constant ρ.[4-7] This approach is, however, only applicable to meta- and para-substituted derivatives. Since some ortho-substituted derivatives have been shown to be highly reactive with AChE,[8] it seems of significance to analyze the effect of ortho substituents and to know the role of "ortho effect" in the hydrolytic reaction course.

Recently, we have found that the logarithmic value of the alkaline catalyzed hydrolysis rate constant of substituted phenyl *N*-methylcarbamates is linearly related with the log K_A value of the corresponding phenols including ortho derivatives.[7] The effect of ortho substituents on the alkaline hydrolysis can be simulated by that on the acid dissociation of ortho-substituted phenols. However, the same procedure does not apply to other reactions. More recently, we have developed eq 1

$$\log k = \rho\sigma_{ortho} + \delta E_s + fF + c \quad (1)$$

to correlate reactivity data of a set of ortho-substituted derivatives including the unsubstituted parent compound.[9] In this equation, k is either the rate or equilibrium constant, E_s and F are the Taft–Kutter–Hansch steric[10,11] and Swain–Lupton field effect constants,[12] respectively, and ρ, δ, f, and c are susceptibility constants and the intercept which are determined by the method of least squares. It is assumed that (1) the total effect of ortho substituents is composed of ordinary polar, steric, and proximity polar effects, (2) the ordinary polar effect is equal to that of the corresponding para substituents, i.e., $\sigma_{ortho} = \sigma_{para}$, (3) the steric effect is represented by the E_s constant, and (4) the proximity polar effect is factored by the F constant. By mutual comparisons among eq 1, the corresponding Hammett equation (eq 2) and the combined equation (eq 3) for ortho-, meta-, and para-substituted derivatives, it has been shown that the proximity polar and steric effects of ortho substituents are excellently separable from the ordinary polar effect for a number of existing reactivity data.

$$\log k = \rho\sigma_{m,p} + c \quad (2)$$

$$\log k = \rho\sigma_{o,m,p} + \delta E_s^{ortho} + fF_{ortho} + c \quad (3)$$

In this paper, we have applied eq 1, 2, and 3 to the alkaline hydrolysis data of ortho-, meta-, and para-substituted phenyl diethyl phosphates, phenyl *N*-methylcarbamates, and phenyl *N,N*-dimethylcarbamates to analyze the ortho substituent effect on the hydrolytic reaction course. We have included, for comparison, a similar data set for substituted phenyl acetates. Phenyl acetates have been extensively used to delineate mechanisms of ester hydrolysis under various conditions[13-15] as well as with α-chymotrypsin.[16]

Materials and Method

Syntheses of Compounds. The phenyl acetates used are shown in Table I. Appropriate substituted phenol (0.1 mol) was stirred with acetyl chloride (0.2 mol) for 2 hr at room temperature and for 1 hr at 100°. The reaction mixture was poured onto ice and the oil which separated was extracted with ether, washed twice with saturated NaCl, dried over Na_2SO_4, and concentrated. The residual crude sample was purified either by repeated vacuum distillations or by recrystallizations from ethanol. The substituted phenyl dimethylcarbamates shown in Table I were synthesized as follows. To a solution of phosgene (0.12–0.15 mol) in anhydrous toluene (150 ml), an appropriate phenol (0.1 mol) in toluene (50 ml) was added dropwise with stirring at 0–5°. Subsequently anhydrous pyridine (0.11 mol) was added at 5–10°. Pyridine hydrochloride was filtered off and the filtrate was evacuated to remove excess phosgene. To the resulting toluene solution of the substituted phenyl chloroformate, 40% aqueous dimethylamine (22.5 g, 0.2 mol) was added at 10–15°. After the addition was complete, the toluene layer was washed three times with saturated NaCl, dried over Na_2SO_4, and evaporated in vacuo to give a crude sample of dimethylcarbamate which was purified either by repeated vacuum distillation or by recrystallizations from benzene–hexane. The ortho substituents were selected so that the simple correlation between F and E_s values is as low as possible. Some of compounds used which had not been previously reported were confirmed by elementary analysis for C and H.

Rate of Alkaline Hydrolysis. The reaction rate was followed spectrally using a Shimazu UV-200 double-beam spectrophotometer equipped with a thermostated cell at 25.0 ± 0.2°. The rate for phenyl acetates was measured at pH 9.14 ± 0.20 with 0.1 *M* Atkins–Pantin buffer (a mixture of 0.1 *M* Na_2CO_3 and 0.1 *M* H_3BO_3–KCl in a ratio (v/v) of 3.7:6.3), while that for dimethylcarbamates was at pH 13.95 ± 0.20 with 0.9 *N* NaOH. The initial concentration of substrate in the reaction mixture was 10^{-3}–10^{-4} *M*. Because of limited solubility of compounds, a certain amount of ethanol was contained in the reaction mixture: 10 vol % for dimethylcarbamates and 3 vol % for acetates. The pseudo-first-order rate constant, k_{hyd} in min^{-1}, was calculated from the initial rate of increase in the absorbance due to

Table I
Phenyl Esters of Acetic Acids and Dimethylcarbamic Acids[a]

Phenol substituents	Acetates mp or bp (mm), °C	Carbamates mp or bp (mm), °C	Phenol substituents	Acetates mp or bp (mm), °C	Carbamates mp or bp (mm), °C
H	81–82 (12)[b]	44–45[t]	*m*-Me	92–93 (13)[i]	129 (7)
o-F	79–80 (13)	113–114 (7)	*m*-Et	110–112 (19)[j]	
o-Cl	100 (9)[c]	130–131 (6)	*m*-OMe	127–128 (13)[k]	
o-Br	110–111 (13)[c]	148–149 (8)	*m*-NO_2	55[l]	62
o-I	126–127 (13)[d]	163–164 (7)	*m*-CN	58[m]	63–64
o-Me	87–88 (13)[e]	123–124 (7)	*m*-COMe		169–171 (7)
o-Et	105–106 (13)		*p*-F	81–82 (13)[n]	
o-*i*-Pr	103 (9)		*p*-Cl	109 (13)[o]	115 (0.3)[t]
o-*sec*-Bu		131–132 (8)	*p*-Br	120 (13)[p]	
o-*t*-Bu	112 (13)	107	*p*-Me	94 (14)[q]	52[t]
o-CF_3		46–47	*p*-Et	105–106 (13)[r]	
o-OMe	115 (13)[f]	142 (2)	*p*-*t*-Bu	119 (9)[j]	93–94
o-NO_2	41[g]	58	*p*-OMe	122 (14)[j]	66[t]
o-CN	143–144 (22)[h]		*p*-NO_2	79[l]	107–108[t]
m-F	77–78 (13)		*p*-CN	56[j]	67[t]
m-Cl		125–127 (4)	*p*-COMe	53[s]	123
m-Br	142 (34)[c]				

[a] All new compounds provided acceptable elemental analyses. [b] "Handbook of Table for Organic Compound Identification", 3rd ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1967, p 258. [c] W. J. Wohlleben, *Ber.*, **42**, 4369 (1909). [d] S. Buchan and H. McCombie, *J. Chem. Soc.*, 137 (1931). [e] K. Matsumoto and K. Han, *Bull. Chem. Soc. Jpn.*, **8**, 333 (1933). [f] F. Misani and M. T. Bogert, *J. Org. Chem.*, **10**, 347 (1945). [g] F. D. Chattaway, *J. Chem. Soc.*, 2495 (1931). [h] B. Lach, *Chem. Ber.*, **17**, 1501 (1884). [i] K. Ono and M. Imoto, *Bull. Chem. Soc. Jpn.*, **11**, 127 (1936). [j] R. L. Van Etten, J. F. Sebastian, G. A. Clowes, and M. L. Bender, *J. Am. Chem. Soc.*, **89**, 3242 (1967). [k] F. Mauthner, *J. Prakt. Chem.*, **136**, 205 (1933). [l] T. C. Bruice and G. L. Schmir, *J. Am. Chem. Soc.*, **79**, 1663 (1957). [m] A. Clemm, *Ber.*, **24**, 826 (1891). [n] C. M. Suter, E. J. Lowson, and P. G. Smith, *J. Am. Chem. Soc.*, **61**, 161 (1939). [o] E. Klarmann, V. A. Shternov, and L. W. Gates, *ibid.*, **55**, 2576 (1933). [p] W. Autenrieth and P. Mühlinghaus, *Ber.*, **40**, 744 (1909). [q] J. Meisenheimer and L.-H. Chen, *Justus Liebigs Ann. Chem.*, **539**, 78 (1936). [r] W. S. Emerson, J. W. Heyd, V. E. Lucas, W. B. Cook, G. R. Owens, and R. W. Shotridge, *J. Am. Chem. Soc.*, **68**, 1665 (1946). [s] J. A. King and F. H. McMillan, *ibid.*, **68**, 2335 (1946). [t] R. D. O'Brien, B. D. Hilton, and L. Gilmour, *Mol. Pharmacol.*, **2**, 593 (1966).

Table II
Second-Order Rate Constant for the Alkaline Hydrolysis of Substituted Phenyl Acetates and *N,N*-Dimethylcarbamates

Substituent	Acetates[c] 10^{-2} k_2,[a] M^{-1} min^{-1}	Carbamates[d] 10^3 k_2,[b] M^{-1} min^{-1}	Substituent	Acetates[e] 10^{-2} k_2,[a] M^{-1} min^{-1}	Carbamates[f] 10^3 k_2,[b] M^{-1} min^{-1}
H	1.65	2.30	*m*-Me	1.45	2.00
o-F	4.63	3.18	*m*-Et	1.50	
o-Cl	3.35	2.06	*m*-OMe	2.22	2.57
o-Br	3.69	1.78	*m*-NO_2	12.2	14.7
o-I	3.30	1.30	*m*-CN	9.73	11.9
o-Me	0.74	0.64	*m*-COMe		5.62
o-Et	0.67		*p*-F	2.52	
o-*i*-Pr	0.61		*p*-Cl	3.64	5.88
o-*sec*-Bu		0.38	*p*-Br	3.33	
o-*t*-Bu	0.32	0.33	*p*-Me	1.45	1.89
o-CF_3		3.25	*p*-Et	1.21	
o-OMe	1.20	1.15	*p*-*t*-Bu	1.14	1.64
o-NO_2	13.1	4.51	*p*-OMe	1.43	2.11
o-CN	20.2		*p*-NO_2	18.6	25.0
m-F	4.66		*p*-CN	11.9	15.3
m-Cl		6.76	*p*-COMe	5.99	10.7
m-Br	4.70				

[a] 0.1 *M* Atkins-Pantin (Na_2CO_3–H_3BO_3) buffer, 3% ethanol, 25°. [b] 0.9 *N* NaOH, 10% ethanol, 25°. [c] Registry no. are, respectively, 122-79-2, 29650-44-0, 4525-75-1, 1829-37-4, 32865-61-5, 533-18-6, 3056-59-5, 1608-68-0, 3245-25-8, 613-70-7, 610-69-5, 5715-02-6, 701-83-7, 35065-86-2. [d] Registry no. are, respectively, 6969-90-0, 55682-12-7, 7305-01-3, 7305-04-6, 55682-13-8, 7305-06-8, 55379-70-9, 55682-14-9, 55682-15-0, 55682-16-1, 3373-86-2, 7305-02-4. [e] Registry no. are, respectively, 122-46-3, 3056-60-8, 5451-83-2, 1523-06-4, 55682-11-6, 405-51-6, 876-27-7, 1927-95-3, 140-39-6, 3245-23-6, 3056-64-2, 1200-06-2, 830-03-5, 13031-41-9, 13031-43-1. [f] Registry no. are, respectively, 7305-07-9, 7305-09-1, 7304-99-6, 55682-17-2, 2689-47-6, 7305-03-5, 7305-08-0, 5461-74-5, 7305-10-4, 7244-70-4, 14100-44-8, 52916-82-2.

the formation of phenoxide. The decrease in the substrate concentration was negligible and the rate of phenoxide formation was almost constant at least for the first 5 min under the present conditions. The second-order rate constant, k_{OH}, was estimated from k_{hyd} and pH values. The rate experiments were performed at least three times with different substrate concentrations. The average standard deviation in k_{OH} values is estimated as being 4%. k_{OH} values of phenyl acetates and dimethylcarbamates are listed in Table II. The rate constants of substituted phenyl diethyl phosphates are taken from the work of van Hooidonk and Ginjaar.[5] Those of phenyl *N*-methylcarbamates are

Table III
Log k Values Used in Correlations of Phenyl Diethyl Phosphates and Phenyl N-Methylcarbamates

	Substituent and log k, M^{-1} min^{-1}
Phosphates[a]	H: −1.56, o-Cl: −0.81, o-Br: −0.85, o-I: −0.94, o-C_2H_5: −1.94, o-i-C_3H_7: −1.99, o-OCH_3: −1.66, o-NO_2: 0.12, m-Cl: −1.03, m-Br: −1.00, m-CH_3: −1.67, m-OCH_3: −1.43, m-NO_2: −0.42, p-Cl: −1.16, p-Br: −1.12, p-I: −1.11, p-C_2H_5: −1.71, p-i-C_3H_7: −1.70, p-OCH_3: −1.78, p-SCH_3: −1.35, p-NH_2: −1.84, p-$COCH_3$: −0.71, p-CN: −0.42, p-NO_2: −0.18
N-Methyl-carbamates[b]	H: 2.38, o-F: 3.89, o-Cl: 3.92, o-Br: 4.10, o-I: 4.01, o-CH_3: 1.67, o-C_2H_5: 1.67, o-i-C_3H_7: 1.69, o-C_3H_7: 1.66, o-sec-C_4H_9: 0.83, o-t-C_4H_9: 0.83, o-OCH_3: 2.53, o-OC_2H_5: 2.48, o-i-C_3H_7: 2.36, o-CN: 5.44, o-NO_2: 5.79, m-F: 3.30, m-Cl: 3.26, m-Br: 3.54, m-CH_3: 2.28, m-OCH_3: 2.55, m-CN: 4.10, m-NO_2: 4.44, m-$N(CH_3)_2$: 2.15, p-F: 2.40, p-Cl: 3.00, p-Br: 3.10, p-CH_3: 1.98, p-OCH_3: 1.79, p-CN: 5.00, p-NO_2: 5.66, 3,4-$(CH_3)_2$: 1.80

[a] From C. van Hooidonk and L. Ginjaar, *Recl. Trav. Chim. Pays-Bas*, 86, 449 (1967). [b] From T. Fujita, K. Kamoshita, T. Nishioka, and M. Nakajima, *Agric. Biol. Chem.*, 38, 1521 (1974).

previously reported values.[7] Their logarithm values are in Table III.

Substituent Parameters. The E_s value used in this work is not Taft $E_s°$ for the aromatic ortho substituents but the one for the aliphatic system,[10] which is a space-filling parameter as demonstrated by Charton.[17] For heteroatom substituents, the E_s value was estimated by eq 4

$$E_s = 3.484 - 1.839\, r_v \qquad (4)$$

where r_v is the average van der Waals radius according to Kutter and Hansch.[11] For the OR, SR, and NHR substituents, the values were calculated using oxygen, sulfur, and nitrogen radius only. For unsymmetrical top-type o-NO_2 group, two values of E_s were calculated corresponding to the group being either coplanar with or perpendicular to the reaction site by substituting the value of half-width or half-thickness of the group for r_v in eq 4. However, for reaction in this work, the value with the maximum dimension for the coplanar orientation gave much better correlations than the other. For these original E_s values, the point of reference is the methyl group, i.e., E_s(Me) = 0. In this work, however, the reference group is shifted to hydrogen for the sake of simplicity. The F values were first defined by Swain and Lupton,[12] but recently improved and extended by Hansch and coworkers.[18] The scale of the original set was not correct. The Taft σ_I constants[19] show rather small differences from the corresponding F values. The correlations using σ_I have been shown to be almost equivalent to or slightly poorer than those with eq 1 and 3 for various sets of reactivity data.[9] While we have selected here to use the Swain–Lupton–Hansch F constants, this does not necessarily mean that the Taft σ_I constants are not applicable to the current analyses. The relevant sets of substituent parameters are shown in Table IV.

Results

The three types of correlation, cor 1, 2, and 3, derived using eq 1, 2, and 3, respectively, are shown in Table V with some statistical values. The levels of significance of all the correlations presented in Table V are better than 99.5% as examined by the F test. Each term is justified above the 99% level by t test and represents a significant improvement above the 99% level over the corresponding equation minus that variable by F test, except for the E_s term in cor 1 of set 3, which is justified at the 97.5% level by t test and the 98.5% level by F test.

For phenyl acetates (set 1) and dimethylcarbamates (set 2), $\sigma°$ for the "insulated" substituent effect[20] is used to give correlations which are much better than those with σ and σ^-.[20] For meta- and para-substituted phenyl phosphates, a modified Yukawa–Tsuno equation[21] (eq 5)

$$\log k = \rho\sigma° + b\Delta\sigma + c;\ \Delta\sigma = \sigma^- - \sigma° \qquad (5)$$

(considering to a certain extent the through-resonance effect of para substituents) gives an excellent result (set 3, cor 2). The $b\Delta\sigma$ term is also statistically significant in cor 3 where the same effect is allowed for the corresponding ortho substituents. The ordinary polar effect of ortho substituents is expressed as $\sigma° + b(\sigma - \sigma°)/\rho$ in this case. However, in cor 1 for unsubstituted and ortho-substituted derivatives only, this term is statistically not significant. In this correlation, the o-NO_2 and o-OMe derivatives are those for which the values of σ and $\sigma°$ of substituent are different as apparent from Table IV. The value of $\Delta\sigma$ for the other six compounds is zero. The variation in the $\Delta\sigma$ value is so small that the contribution of this term cannot be established with statistical confidence.

The rate constants of meta- and para-substituted phenyl N-methylcarbamates are well correlated with σ^- (set 4, cor 2). However, when those of ortho-substituted derivatives are analyzed by assuming that $\sigma_{ortho} = \sigma_p^-$, the correlations give only poor results. If σ_{ortho} values are taken as σ_p instead of σ_p^-, the correlations are excellent (set 4, cor 1 and 3) where $\sigma\#$ (sigma mixed) is a set of σ_{ortho} (= σ_p), σ_m, and σ_p^-.

It is immediately apparent that, for each of the sets in Table V, ρ and c values of the usual Hammett equation for meta- and para-substituted derivatives (cor 2) are practically identical with those for ortho-substituted derivatives (cor 1) and for the combined data set (cor 3). The terms, δE_s and fF, in cor 1 correspond very well with those in cor 3. Thus, the assumptions which eq 1 is based upon hold generally only with a slight modification in the case of N-methylcarbamates.

Discussion

The hydrolysis of esters is generally regarded as following the addition intermediate path.[6,22] For the alkaline hydrolysis of phenyl esters, it is shown as Scheme I. Under conditions where a steady state is maintained for the addi-

Scheme I

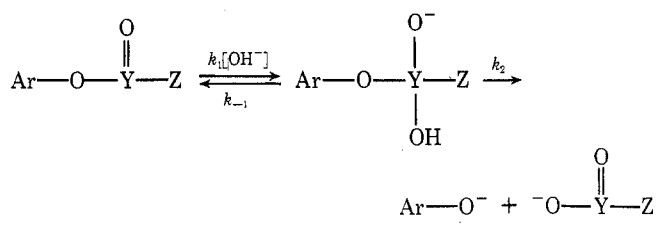


Table IV
Substituent Parameters Used for Correlations[a]

Substituent	σ_m[b]	σ_p[b]	σ_m°[c]	σ_p°[c]	σ_p^-[c]	E_s[d]	F[e]
H	0.0	0.0				0.0	0.0
Me	−0.07	−0.17		−0.12		−1.24	−0.04
Et	−0.07	−0.15		−0.13		−1.31	−0.05
i-Pr	−0.07[f]	−0.15		−0.16		−1.71	−0.05
n-Pr		−0.15[g]				−1.60	−0.06
sec-Bu		−0.15[g]		−0.16		−2.37	−0.05[g]
t-Bu	−0.10	−0.20		−0.17		−2.78	−0.07
OMe	0.12	−0.27	0.06	−0.16	−0.20[f]	−0.55	0.26
OEt	0.07[f]	−0.24	0.04[g]	−0.14[g]		−0.55	0.22
O-*i*-Pr		−0.45				−0.55	0.30
F	0.34	0.06	0.35	0.17	−0.02[f]	−0.49	0.43
Cl	0.37	0.23	0.37	0.27		−0.97	0.41
Br	0.39	0.23	0.38	0.26		−1.16	0.44
I	0.35	0.18	0.35	0.27		−1.40	0.40
CF_3	0.43	0.54			0.65	−2.40	0.38
COMe	0.38	0.50	0.38[f]	0.46	0.87[f]		
CN	0.56	0.66	0.62	0.69	0.90	−0.51	0.51
NO_2	0.71	0.78	0.70	0.82	1.24[f]	−1.01[h]	0.67
						−2.52[i]	
NH_2	−0.16	−0.66	−0.14	−0.38	−0.15		
NMe_2	−0.21[f]			−0.44		−0.61	0.10
SMe	0.15	0.0		0.08			

[a] Values used in this work are listed. When σ_p^- value is taken as σ_p° for substituents which do not undergo electron-withdrawing through-resonance, it is not shown. Likewise, if σ_m° value is equal to σ_m, it is not necessarily listed. [b] From the compilation of D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, **23**, 420 (1958), unless otherwise noted. [c] From ref 20 unless otherwise noted. [d] From ref 10 and 11; the point of reference is shifted to E_s of H; see text. [e] From ref 18. [f] From the compilation of M. S. Tute, *Adv. Drug Res.*, 6, 68 (1971). [g] Estimated from values of closely related substituents. [h] For the minimum steric effect of the perpendicular dimension. [i] For the maximum steric effect of the coplanar dimension.

tion intermediate, the overall second-order rate constant k_{sec} is expressed by the rate constants of elementary steps as eq 6. There are two extreme cases depending on the location of the rate-determining step.

$$k_{sec} = k_1k_2/(k_{-1} + k_2) \quad (6)$$

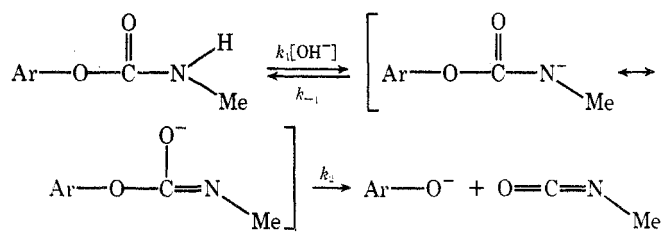
If the rate-determining step is the nucleophilic attack of OH^- on the carbonyl carbon and the phenoxide splitting occurs quickly, k_{sec} is reduced to k_1, since $k_2 \gg k_{-1}$ in eq 6. Since the site of reaction center in the rate-determining step is located at the second atom from the benzene ring, the rate constant k_{sec} is susceptible to the aromatic substituent effect probably to a degree similar to the acid dissociation of substituted benzoic acids (ρ = 1.0).[23] In fact, the ρ values for phenyl acetates and dimethylcarbamates are 1.18 and 1.16, respectively. Thus, for hydrolysis of these two series of esters, the hydroxide attack is rate limiting. The correlations with σ° indicate that the conjugation of the acyloxy group in phenyl acetates and dimethylcarbamates with the benzene ring occurs in neither initial nor intermediate state. Recently, Cohen and Takahashi[15] have shown evidence which supports the lack of the electron-attracting through-resonance effect of para substituents such as *p*-NO_2, -CN, and -$COCH_3$ on the phenoxy oxygen lone pair electrons in the hydrolysis of phenyl acetates. The steric inhibition of the conjugation of acyloxy group due to ortho substituents need not be considered.

The other extreme is the case where the addition occurs in a rapid equilibrium and the phenoxide splitting is rate limiting. Then, the overall second-order rate constant is expressed as $k_{sec} = k_2k_1/k_{-1}$, since $k_2 \ll k_{-1}$ in eq 6. In this case the reaction constant ρ will reflect the sum of those for steps k_1/k_{-1} and k_2. The ρ value for the preequilibrium step, k_1/k_{-1}, is expected to be around 1.0. The step k_2 can be considered to possess a ρ value about 2.0, similar to that for the dissociation of phenols.[23] Since the phenoxide splitting step, k_2, will be facilitated by the electron-attracting through-resonance effect and since it is more susceptible to the aromatic substituent effect than the preequilibrium intermediate formation, the rate constant is probably better correlated with σ^-.

The correlation for phenyl phosphates falls between the above described two extreme cases. Correlation 3 of set 3 indicates that the polar effect is best illustrated as a linear combination of σ° and σ^-: $1.42\sigma^\circ + 0.45(\sigma^- - \sigma^\circ) = 1.42(0.68\sigma^\circ + 0.32\sigma^-)$. The fact that the polar effect contains about 70% σ° character and the ρ value (1.42) is rather close to 1.0 suggests that the overall rate is mostly controlled by the step of hydroxide attack.

The ρ value for *N*-methylcarbamates (set 4) is close to what is expected for rate-determining phenoxide splitting mechanism with the use of σ^- for through-resonating para substituents. Unlike the above-described cases, however, the hydrolysis does not occur through the addition intermediate but via a quick preequilibrium deprotonation as shown in Scheme II.[4,7] Thus, the overall reaction constant,

Scheme II



ρ = 2.5, corresponds to the sum of those for the two consecutive steps. The deprotonation equilibrium seems to have a ρ value around 0.5, similar to the one for the acid dissociation of phenylacetic acids.[23] The fact that the correlations including ortho-substituted derivatives (cor 1 and 3) are

Table V
Correlation of Hydrolysis Data with Eq 1, 2, and 3[a]
$\log k = \rho\sigma + \delta E_s + fF + b\Delta\sigma + c$

Set no.	Esters and condition	Cor[b] no.	ρ	δ	f	b	c	n[c]	n_0[d]	s[e]	r[f]	F[g]
1	Acetates 3% EtOH–H_2O, 25° ($\log k_H$ = 2.22)	1	1.234σ° (±0.234)	0.185 (±0.045)	0.482[h] (±0.295)		2.263 (±0.085)	12	12	0.052	0.997	414.2
		2	1.174σ° (±0.057)				2.258 (±0.022)	18	0	0.037	0.996	1921.5
		3	1.180σ° (±0.054)	0.185 (±0.023)	0.538 (±0.094)		2.258 (±0.021)	29	12	0.041	0.997	1203.3
2	Dimethylcarbamates 10% EtOH–H_2O, 25° ($\log k_H$ = −2.64)	1	1.144σ° (±0.305)	0.232 (±0.102)			−2.684 (±0.168)	11	11	0.128	0.956	42.2
		2	1.145σ° (±0.096)				−2.591 (±0.041)	14	0	0.056	0.991	681.2
		3	1.164σ° (±0.121)	0.271 (±0.043)			−2.610 (±0.057)	24	11	0.095	0.983	302.0
3	Diethyl phosphates 2% i-PrOH–H_2O, 25° ($\log k_H$ = −1.56)	1	1.639σ° (±0.252)	0.090[i] (±0.060)	0.840 (±0.281)		−1.553 (±0.089)	8	8	0.034	0.999	1063.6
		2	1.405σ° (±0.090)			0.472[j] (±0.207)	−1.508 (±0.033)	17	0	0.052	0.996	785.3
		3	1.420σ° (±0.083)	0.134 (±0.047)	0.950 (±0.178)	0.445[j] (±0.181)	−1.510 (±0.028)	24	8	0.051	0.997	732.0
4	Methylcarbamates 10% EtOH–H_2O, 38° ($\log k_H$ = 2.38)	1	2.216σ (±0.349)	0.244 (±0.103)	3.233 (±0.471)		2.477 (±0.200)	16	16	0.133	0.997	605.9
		2	2.690σ^- (±0.161)				2.440 (±0.077)	17	0	0.128	0.994	1262.8
		3	2.541σ# (±0.144)	0.241 (±0.069)	2.989 (±0.285)		2.501 (±0.073)	32	16	0.148	0.994	802.1

[a] Unless otherwise noted, the value of ρ, δ, f, and b are justified by t test at better than the 99.5% level of significance. The figures in parentheses are the 95% confidence intervals. [b] Correlation number; see text. [c] The number of data used in the correlation. [d] The number of data of ortho-substituted derivatives including the unsubstituted ester. [e] Standard deviation. [f] Multiple correlation coefficient. [g] F value of the correlation. [h] Justified at a level between 99.5 and 99%. [i] Justified at a level between 99 and 97.5%. [j] $\Delta\sigma = \sigma^- - \sigma^\circ$.

excellent only when σ_{ortho} is taken as σ_{para} but not as σ^-_{para} indicates that the overlapping of phenoxy oxygen lone pair electrons with those of the benzene ring is seriously limited by ortho substituents and the electron-attracting through-resonance effect of ortho substituents is almost inhibited at the rate-limiting phenoxide splitting step.

It is interesting to compare correlations of set 4 with corresponding ones for log K_A of substituted phenols (eq 7–9). The ortho-substituted phenols are correlated with the use of σ and the whole set compounds are with σ# for the ordinary polar effect of substituents.[9] It is apparent that the correlations are quite similar to those for the *N*-methylcarbamate hydrolysis. In particular, the coefficients of three terms of eq 7 and 9 are nearly proportional to corresponding ones of cor 1 and 3 of set 4. The fact that the log K_A value of phenols is approximately linearly related with the log k value of phenyl *N*-methylcarbamate hydrolysis including ortho-substituted derivatives can be understood on this basis.

For ortho derivatives:

$$\log K_A = 2.196\ (\pm 0.749)\ \sigma + 0.199\ (\pm 0.148)\ E_s + 2.173\ (\pm 0.930)\ F - 9.727\ (\pm 0.308)$$
$$n = 14\ s = 0.203\ r = 0.990 \quad (7)$$

For meta and para derivatives:

$$\log K_A = 2.061\ (\pm 0.099)\ \sigma^- - 9.836\ (\pm 0.055)$$
$$n = 27\ s = 0.097\ r = 0.993 \quad (8)$$

For ortho, meta, and para derivatives:

$$\log K_A = 2.036\ (\pm 0.118)\ \sigma\# + 0.167\ (\pm 0.060)\ E_s + 2.395\ (\pm 0.260)\ F - 9.814\ (\pm 0.065)$$
$$n = 40\ s = 0.134\ r = 0.992 \quad (9)$$

The δ values for sets 1 and 2 are positive and close to each other (0.22 ± 0.03) indicating that the space-filling effect of ortho substituents is inhibitive of the reactivity and is similar between these two sets of phenyl esters. The sterically critical rate-determining step of these reactions is located at a quite similar geometrical position relative to the benzene ring. Since the steric inhibition of resonance does not seem to be important, the ortho substituents probably hinder the approach of nucleophile to the reaction site and/or prevent the formation of space-requiring tetrahedral addition intermediate according to their space-filling dimensions. Recently, the magnitude of δ values has been deduced to be a function of the distance between ortho substituent and the reaction site from 44 sets of analyses.[9] Nearly constant δ values have been found for eight benzoyl transfer (0.63 ± 0.14) and three phenylacetyl transfer (0.39 ± 0.01) reactions.[9]

The transition state of phenyl phosphates is more advanced on the reaction coordinate than that of the above esters as suggested by the polar effect of substituents being expressed as a linear combination of σ° and σ^-. Thus, their phenoxy-oxygen–phosphorus bond seems to be weakened and extended more than the corresponding bond of the above esters. However, this bond extension does not significantly modify the steric course of the hydrolysis, resulting in only slightly smaller δ value.

The δ value for set 4 for *N*-methylcarbamates is similar to values for sets 1 and 2. However, differing in the reaction mechanism from these systems, it probably indicates the susceptibility of critical phenoxide formation to the steric effect of ortho substituents. In fact, it may be taken as rather similar to the values in eq 7 and 9 for log K_A of phenols. The steric effect on the preequilibrium deprotonation

occurring at the third atom from the benzene ring does not seem to be involved in this δ value.

In the present correlations, the steric effect of o-NO_2 group is fit best with the E_s value for its maximum dimension. In the sterically critical step of hydrolysis reactions, the o-NO_2 group seems to remain coplanar with the benzene ring. The conjugation of the o-NO_2 group is not inhibited, while the intergroup through-resonance between o-NO_2 and acyloxy groups is not significant.

Substituent effects on the hydrolytic reaction course of phenyl acetates and dimethylcarbamates are very similar to each other including ortho-substituted derivatives as far as the ordinary polar and steric effects are concerned. However, the proximity polar effect of ortho substituents significantly differs between these two series. A distinct proximity effect appears to be involved for the ortho-substituted phenyl acetates (set 1, cor 1 and 3) while not significant for the ortho-substituted dimethylcarbamates (set 2, cor 1 and 3). As suggested in our recent analyses, the magnitude of f may be subject not only to the distance between reaction site and the benzene ring but also to the side chain structure to some extent.[9] Even though the geometrical location of the rate-limiting reaction site is similar to the above cases, the negative f value (-0.29 ± 0.05) has been found for three phenylacetyl transfer reactions.[9]

The large f value (3.0) for set 4 should come mostly from a high susceptibility of the rate-determining phenoxide formation step to the electron-withdrawing proximity polar effect of ortho substituents, which can be compared with that for the dissociation of phenols, 2.4 in eq 7 and 9. The difference may be attributed to the effect of ortho substituents on the preequilibrium deprotonation step. The f value, 0.90 ± 0.04, for set 3 is larger than that for set 1 of phenyl acetates. It may be mostly attributed to the step of addition intermediate formation, containing in part a component due to the phenoxide splitting.

The above work indicates that the ortho effect on the alkaline hydrolysis of phenyl esters can be analyzed quantitatively by means of δ and f terms of component effects overlapping on the ordinary polar effect of ortho substituents. The component effects participate in the total effect of ortho substituents generally to varying degrees according to reaction systems. We must be careful in discussing mechanism of reactions of these classes of compounds including ortho derivatives with enzyme systems so as to select reference reaction systems and conditions as close as possible to those of the enzymatic reactions.

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3-Cycloalkenylindoles

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A simple method for the preparation of the title compounds 4 is described and demonstrated on a variety of indoles (1) and ketones (2). Some reactions of these new derivatives are discussed.

Reactions of indoles with ketones under acidic conditions are well documented.[1] The general course is electrophilic attack by the carbonyl carbon at the indole 3 position, leading via 3-methyleneindolenines or indolyl-3-carbinols to diindolylmethanes (Scheme I).

We found that cyclic ketones (2), contrary to this general observation, give 1:1 reaction products with 3-unsubstituted indoles (1). This reaction proceeds with a wide variety of cyclic ketones in excellent yields, affording indole derivatives of the general formula 4, hitherto little known[2,3] and accessible only via tedious de novo syntheses. Obviously, the intermediates 3 stabilize by water elimination.

The scope of this reaction was investigated using 1,2-