

Linear Free Energy Models for Ester Solvolysis with a Critical Examination of the Alcohol and Phenol Dissociation Model

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Abstract □ Rate constants for the alkaline hydrolysis of *para*-substituted benzoate esters, with a variety of aliphatic and aromatic leaving groups, were determined under constant reaction conditions. It was found that acyl variation encompassing both aliphatic and aromatic leaving groups could be correlated using the Hammett equation, since the interaction mechanisms involved in both rate processes are apparently proportional to those involved in the equilibrium process. Application of either the Hammett equation or phenol dissociation model to aromatic substituents in the alkyl portion of the ester resulted in nonlinearity. The incomplete success observed in the comparison of the rate processes to these models was not due to a change in mechanism or in rate-determining step, as was shown by solvent isotope, temperature, and catalytic studies, but was apparently due to differences in resonance and solvation interactions in rate and equilibrium processes. Aromatic substituent effects in the alkyl portion of the ester could be quantitated by using a linear combination of the Hammett and phenol dissociation model analogous to the Yukawa-Tsuno equation. In addition, the Swain and Lupton approach quantitated the effect of the alkyl substituent on the rate of reaction. Application of the alcohol dissociation model for aliphatic substituents in the alkyl portion of the ester was not totally effective in correlating rates of reaction with pK_a of the leaving group because curvature was noted, when substituents with low pK_a were employed, in the plot of rate constant versus pK_a. In this case the nonlinearity was ascribed to mesomeric stabilization of the anion in the equilibrium process. Besides the nonlinearity in the free energy plots of rate against phenol or alcohol dissociation, there was a dispersion of approximately 5 pK_a units between the lines for aliphatic and aromatic leaving groups; this was attributed to the resonance differences observed in the pK_a's of alcohols and phenols.

Keyphrases □ Benzoate esters, *p*-substituted—alkaline hydrolysis □ Hydrolysis rates—*p*-substituted benzoate esters □ Deuterium isotope solvent effects—alkaline hydrolysis rates, esters □ Activation parameters—alkaline hydrolysis, benzoate esters □ Alcohol, phenol dissociation models, Hammett relationship—structure-reactivity relationship, benzoate esters □ UV spectrophotometry—ester hydrolysis monitoring

The quantitative prediction of rates and equilibria of organic reactions has long plagued physical chemists due to the complexity of organic molecules. Numerous treatments utilizing the extrathermodynamic approach (1) have been partially successful in analysis of structural and medium effects on reactivity. This approach usually involves a comparison of the free energies in a specific rate or equilibrium process with that of a suitable model or set of models.

The choice of the appropriate model for linear free energy relationships has been mainly dependent upon the specific reaction considered. In the case of ester hydrolysis, substituent effects in the acyl portion of the molecule have been successfully correlated with reactivity using either the Hammett or Taft relationship, depending upon the type of ester involved in the series. Substituent variations in the alkyl portion of the ester molecule have been investigated in the past by several

groups; attempts to correlate structure with reactivity using either the Hammett or Taft relationship have not been successful (2–7). A variety of approaches (6, 8, 9) have been used to develop linear relationships between structure and reactivity for substituents in the alkyl portion, most of which deal with the free energy of ionization of the conjugate acid of the leaving group.

Kirsch and Jencks (8) and Bruice *et al.* (9) demonstrated that the rates of solvolysis of some acetate esters could be correlated with the pK_a of the conjugate acid of the leaving groups; however, the two studies disagree as to whether a single correlation, encompassing both aromatic and aliphatic leaving groups, or a dual correlation, one for each type, is necessary. Robinson and Matheson (6) showed that dissociation of aliphatic alcohols is an excellent model for ester hydrolysis involving aliphatic substituents in the alkyl portion of the ester molecule. Additional results were reported concerning the effectiveness of the alcohol dissociation model in correlating structure with reactivity for a variety of *para*-substituted benzoates with aliphatic leaving groups (10).

Recently, a number of investigators (3, 4, 7, 11) reported the observation of nonlinear correlations of the free energy of activation with the free energy of ionization of the conjugate acid of the leaving group or nucleophile. Ryan and Humffray (3, 4) observed that a linear combination of σ and σ^- constants was required to give linearity in the plot of rate of alkaline hydrolysis for aryl benzoates and aryl acetates. Kirsch *et al.* (5) also observed nonlinearity in Hammett plots for the alkaline hydrolysis of aryl benzoates and suggested that a special value of σ for the *p*-NO₂ substituent be used to attain linearity. Milton *et al.* (7) also observed nonlinearity in the $\Delta G^\ddagger - \Delta G^0$ plot for the basic methanolysis of aryl acetates and carbonates; they suggested the nonlinearity may be due to differences in resonance interactions in the two processes or changes in the structure of the transition state as the reactant structure is altered. Nonlinear $\Delta G^\ddagger - \Delta G^0$ relations have also been observed for carbonyl displacement reactions involving variations in nucleophile and have been explained by either a change in rate-determining step or a change in transition state configuration (12).

The present study examines some linear free energy relationships that have been used in ester solvolysis, with a thorough exploration of the use of alcohol and phenol dissociation as a model process for ester solvolysis. The intents are to evaluate the extent to which both dissociation processes would serve as effective models and to offer explanations for the curvature in such structure-reactivity free energy correlations.

EXPERIMENTAL

Reagents—Fisher certified acetonitrile was used in all reaction mixtures and stock solutions without further purification after it was established that it had no effect on the rate of alkaline hydrolysis and that it was spectrally pure (from 230 to 400 nm.). All other chemicals were of analytical or reagent grade. The reaction mixture for the solvent deuterium isotope studies was prepared with 99.8% D₂O¹ and NaOD (minimum 99% purity)². Water was doubly distilled from acid permanganate in an all-glass distillation apparatus.

All esters were prepared according to procedures outlined by Shriner *et al.* (13) with slight modification. The acyl chloride was reacted with the appropriate alcohol by heating under reflux for 30 min. The reaction mixture was then dissolved in chloroform, extracted with 5% sodium carbonate followed by water, and finally dried with magnesium sulfate. After removal of chloroform under vacuum, the remaining ester was purified by repeated recrystallization from mixtures of water and the alcohol representing the alkyl portion of the ester or, in the case of liquids, by vacuum distillation. In the case of esters derived from phenols, the acid chloride was added either directly to the phenol, with subsequent heating above the melting point of the phenol for about 30 min., or to an ethyl ether solution of pyridine followed by addition of an ethereal solution of the phenol and refluxed for about 1 hr. Purification of these esters involved the same procedures as described for the esters of alcohols, with the modification that repeated recrystallization was carried out from aqueous methanol solutions. The identification and purity of the esters were determined by melting-point or boiling-point comparison with literature values and by spectral properties.

Apparatus—The pH measurements and adjustments were made using a Corning model 12 pH meter with an expanded scale and a Beckman type E3 wide-range glass electrode. The pH meter and electrode system was standardized against phosphate buffer, as described by Bates (14). To ensure accuracy of pH measurements, particularly at elevated temperatures, adjustment of pH of the reaction mixture as well as standardization of the pH meter was carried out at the reaction temperature, using a water-jacketed beaker at the appropriate temperature. Water bath temperatures for the pH measurements and also the kinetic measurements were maintained to $\pm 0.1^\circ$ with Sargent Thermomonitor electronic relays. Progress of the reaction was followed using either a Cary model 11, 14, or 15 recording spectrophotometer equipped with thermostated cell compartments.

Procedures—*Solvent System*—Fifty milliliters of acetonitrile was added to an equal volume of 0.02 M dibasic phosphate buffer, and the resulting solution was brought to the appropriate pH with a few drops of concentrated NaOH solution. It was determined that phosphate buffer did not catalyze the reaction. The acetonitrile-phosphate buffer solution gave a volume somewhat less than 100 ml. and was used as such for all kinetic determinations. For the solvent deuterium isotope studies, the phosphate buffer was eliminated since the pD was sufficiently high to act as a buffer by itself; consequently, pseudo-first-order conditions were maintained since the pD change was negligible during the course of the reaction.

The reaction media for the solvent study were composed of various combinations of acetonitrile and 0.02 M phosphate buffer (acetonitrile-phosphate buffer, 5:95, 30:70, and 50:50). These solutions were adjusted to the appropriate pH as described previously. The reaction medium for the imidazole study was prepared by dissolving an appropriate amount of imidazole in a 50% v/v solution of acetonitrile-water such that the final concentration of imidazole would be 0.05 or 0.1 M. The resulting solution was adjusted to the appropriate pH with a few drops of saturated NaOH solution.

Continuous Spectrophotometric Procedure—For rapid reactions, the following procedure was used: after temperature equilibration of the buffer system in a 1- or 2-cm. photometer cell, 50 μ l. of a stock solution of ester in acetonitrile was introduced and mixed thoroughly within the cell. A 1×10^{-2} M stock solution was used for esters derived from alcohols, while a variety of concentrations varying from 6×10^{-3} to 5×10^{-2} M in acetonitrile was used as a

stock solution for esters derived from phenols. The reaction progress was monitored by following the disappearance of ester at an appropriate wavelength: benzoates at 244 nm., toluates at 250 nm., *p*-chlorobenzoates at 254 nm., *p*-fluorobenzoates at 244 nm., and *p*-cyanobenzoates at 250 nm., and by the appearance of the acid anion at 290 nm. in the *p*-nitrobenzoate case for all esters derived from alcohols. For the esters of phenols, the appearance of the phenolate anion was monitored at 300 nm. for all cases except for the *p*-nitrophenolate and 2,4-dinitrophenolate anions which were monitored at 400 nm.

Discontinuous Spectrophotometric Procedure—For esters with inconveniently slow rates of reaction, the following procedure was used: 100 ml. of buffer solution was prepared and adjusted to the appropriate pH. Two milliliters of a 1×10^{-2} M ester stock solution was added to the buffer solution after temperature equilibration, and the resulting mixture was placed in 5-ml. volumetric flasks which were then placed in a water bath at the appropriate temperature. At periodic time intervals, two flasks were removed from the bath and quenched in an ice-brine solution, and their absorbances were determined at an appropriate wavelength. The average absorbance of the two solutions was used, and the data were treated using either a $\log(A_t - A_\infty)$ versus time plot or the method described by Guggenheim (15).

Data Treatment—All experiments were carried out with a large excess of hydroxide ion; thus, pseudo-first-order kinetics were observed. Pseudo-first-order rate constants were converted to second-order rate constants using hydroxide-ion activity as calculated from the measured pH and the appropriate pK_w (16).

For the solvent deuterium isotope studies, second-order rate constants were determined using Eq. 1 as described by Bates (14):

$$pD = \text{pH meter reading} + 0.40 \quad (\text{Eq. 1})$$

with subsequent conversion to deuterioxide-ion activity using a value of 14.955 for the ionization constant of deuterium oxide at 25° (16).

Kinetics studies using imidazole were done at two concentrations of imidazole (0.05 and 0.1 M). Rate constants due to imidazole catalysis (k_{IM}) were calculated from the pseudo-first-order rate constants using Eq. 2, after establishing that catalysis was first order with respect to imidazole over the pH range used in this study:

$$k_{obs.} = k_{OH}(OH) + k_{IM}(IM) \quad (\text{Eq. 2})$$

The activation parameters, ΔG^\ddagger , ΔH^\ddagger , and ΔS^\ddagger , were calculated at 25° using Arrhenius plots for the determination of E_a and the following equations:

$$\Delta H^\ddagger = E_a - RT \quad (\text{Eq. 3})$$

$$\Delta G^\ddagger = 2.303RT \left(\log \frac{kT}{h} - \log k_r \right) \quad (\text{Eq. 4})$$

$$\Delta S^\ddagger = \frac{\Delta H^\ddagger - \Delta G^\ddagger}{T} \quad (\text{Eq. 5})$$

RESULTS

Although the literature abounds with rate data on solvolysis of esters, there are insufficient data, under constant conditions (temperature, solvent composition, buffer composition, *etc.*) to carry out the analysis described in the introduction. Thus, second-order alkaline hydrolytic rate constants were determined for a variety of acyl- and alkyl-substituted benzoate esters under constant conditions, and they are presented in Table I together with standard deviations and number of determinations. Rate constants for some of these esters were presented in an earlier publication (10) but, for the sake of completeness, they are reproduced here. At least two rate determinations were made for each ester, and these were carried out at more than one pH value to ensure that the reaction was first order with respect to hydroxide ion. The pH range employed for all esters was 11–13.4 since the buffer capacity of the solvent system, for the concentration of ester employed in this study, was satisfactory over this range.

Solvent deuterium isotope effects on the rate of alkaline hydrolysis of some benzoate esters were determined, and the results are

¹ Stohler Isotope Chemicals.

² Brinkmann Instruments, Inc.

Table I—Second-Order Rate Constants for Alkaline Hydrolysis of Some Benzoate Esters^a

Ester Series	$k \times 10^4$, $M^{-1} \text{ sec.}^{-1}$	SD^b	Number of Determinations
<i>p</i>-Toluates			
Methyl	2.65	0.002	4
Ethyl	0.879	0.001	2
<i>n</i> -Propyl	0.671	0.049	3
Isopropyl	0.168	0.015	2
<i>n</i> -Butyl	0.568	0.044	2
Isobutyl	0.449	0.013	2
Phenyl	15.1	0.4	3
<i>p</i> -Chlorophenyl	33.7	0.5	5
<i>p</i> -Nitrophenyl	232	3	5
<i>p</i> -Fluorophenyl	26.2	0.1	4
<i>p</i> -Cyanophenyl	158	3	3
<i>p</i> -Tolyl	10.5	0.5	4
Benzoates			
Methyl	6.08	0.08	2
Ethyl	1.98	0.04	2
<i>n</i> -Propyl	1.67	0.08	3
Isopropyl	0.319	0.07	2
<i>n</i> -Butyl	1.41	0.02	2
Isobutyl	1.18	0.13	2
Phenyl	33.6	1.4	4
<i>p</i> -Chlorophenyl	77.9	3.9	4
<i>p</i> -Nitrophenyl	536	18	5
<i>p</i> -Fluorophenyl	56.5	1.2	4
<i>p</i> -Cyanophenyl	414	4	3
<i>p</i> -Tolyl	22.5	1.2	4
<i>m</i> -Cyanophenyl	226	9	3
Monochloroethyl	12.4	0.1	2
Dichloroethyl	31.9	0.3	4
Trichloroethyl	57.8	0.7	6
2,4-Dinitrophenyl	3580	37	4
<i>p</i>-Fluorobenzoates			
Methyl	12.1	0.2	3
Ethyl	4.05	0.08	3
<i>n</i> -Propyl	2.65	0.09	3
Isopropyl	0.623	0.04	3
<i>n</i> -Butyl	2.44	0.06	3
Isobutyl	1.90	0.24	3
Phenyl	67.3	1.2	5
<i>p</i> -Chlorophenyl	115	2	3
<i>p</i> -Nitrophenyl	772	15	4
<i>p</i> -Fluorophenyl	89.3	6.8	4
<i>p</i> -Cyanophenyl	552	13	4
<i>p</i> -Tolyl	35.6	0.8	4
<i>p</i>-Chlorobenzoates			
Methyl	19.1	0.1	3
Ethyl	6.51	0.39	3
<i>n</i> -Propyl	5.11	0.65	2
Isopropyl	1.21	0.02	2
<i>n</i> -Butyl	3.49	0.29	4
Isobutyl	3.36	0.08	2
Phenyl	103	2	4
<i>p</i> -Chlorophenyl	235	3	3
<i>p</i> -Nitrophenyl	1460	15	3
<i>p</i> -Fluorophenyl	191	3	4
<i>p</i> -Cyanophenyl	1070	9	4
<i>p</i> -Tolyl	71.9	1.6	4
2,4-Dinitrophenyl	7430	44	4
<i>p</i>-Cyanobenzoates			
Methyl	195	2	4
Ethyl	79.7	1.4	5
<i>n</i> -Propyl	52.6	0.3	3
Isopropyl	12.6	0.2	5
<i>n</i> -Butyl	41.9	1.2	3
Isobutyl	39.4	1.5	4
Phenyl	736	14	4
<i>p</i> -Chlorophenyl	1660	26	5
<i>p</i> -Nitrophenyl	12,700	150	5
<i>p</i> -Fluorophenyl	1310	28	4
<i>p</i> -Cyanophenyl	7630	110	5
<i>p</i> -Tolyl	518	10	4
2,4-Dinitrophenyl	100,600	200	4

Table I—(continued)

Ester Series	$k \times 10^4$, $M^{-1} \text{ sec.}^{-1}$	SD^b	Number of Determinations
<i>p</i>-Nitrobenzoates			
Methyl	276	7	6
Ethyl	98.8	3.9	6
<i>n</i> -Propyl	76.0	1.8	5
Isopropyl	19.6	1.2	4
<i>n</i> -Butyl	63.4	0.8	3
Isobutyl	60.0	2.0	4
Phenyl	1140	21	3
<i>p</i> -Chlorophenyl	2570	11	4
<i>p</i> -Nitrophenyl	20,900	290	4
<i>p</i> -Fluorophenyl	2000	36	3
<i>p</i> -Cyanophenyl	10,800	250	4
<i>p</i> -Tolyl	752	29	4
<i>m</i> -Cyanophenyl	8450	200	6
Monochloroethyl	504	50	10
Dichloroethyl	1816	22	5
Trichloroethyl	3220	22	8

^a In a 50% (v/v) acetonitrile–0.02 M phosphate buffer at 25°. ^b Standard deviation.

shown in Table II. A suitable correction for the pK_a of deuterium oxide was employed in the calculation of the rate constants, as described in the *Experimental* section. Also included in Table II are the second-order rate constants for imidazole catalysis of the same benzoate esters. The imidazole studies were carried out at more than one concentration of imidazole and at different pH's to ensure that the catalytic constant for imidazole was first order with respect to imidazole. For both the solvent deuterium isotope studies and the imidazole studies, a minimum of three determinations was carried out for each ester; the standard deviations for these rate constants are in the range of 2–4% of the rate constants.

The effect of solvent composition on the rate of alkaline hydrolysis of some benzoate esters was investigated, and the results are presented in Table III. Due to solubility problems associated with the esters, it was not possible to carry out the reactions in a fully aqueous system. A minimum of three determinations was employed for each ester at each solvent composition. The standard deviations for the rate constants are in the range of 2–4% of the rate constants.

Temperature effects on the rate of alkaline hydrolysis of some benzoate esters were also investigated, and the results are shown in Table IV. Determination of the appropriate pH at the various temperatures, as well as calculation of the activation parameters, was discussed in the *Experimental* section. At least three determinations were made for each ester at each temperature. Standard deviations for these rate constants are in the range 3–5% of the rate constants. The activation parameters calculated from the temperature studies are presented in Table V.

DISCUSSION

Acyl Variation—The success of the Hammett relationship in correlation of structure with reactivity for acyl variations in benzoates has been widely known and accepted since its conception (17, 18). Hence, successful correlations for *para*-substituted ben-

Table II—Solvent Deuterium Isotope Effects and Imidazole Catalytic Effects Relative to Alkaline Hydrolysis of Some Benzoate Esters

Benzoate Esters	k_{OD}/k_{OD}	k_{OH}/k_{TM}	$k_{OH} \times 10^4$, $M^{-1} \text{ sec.}^{-1}$
2,4-Dinitrophenyl	0.650	2.01	3580
<i>p</i> -Nitrophenyl	0.745	1.37	536
<i>m</i> -Cyanophenyl	0.820	2.14	227
<i>p</i> -Tolyl	0.875	1.86	22.5
Methyl	0.360	2.02	6.08
Ethyl	0.408		1.98
<i>n</i> -Propyl	0.441		1.67

Table III—Effect of Solvent Composition upon the Second-Order Rate Constants for Alkaline Hydrolysis of Some Benzoate Esters

Benzoate Esters	$k_{OH} \times 10^4 (M^{-1} \text{ sec.}^{-1})$		
	50% ^a	30% ^a	5% ^a
2,4-Dinitrophenyl	3,580	15,900	150,000
<i>p</i> -Nitrophenyl	536	2,740	28,200
<i>m</i> -Cyanophenyl	227	1,220	21,500
<i>p</i> -Tolyl	22.5	144.0	3,200
Ethyl	1.98	21.4	267

^a Percent v/v acetonitrile in 0.02 M phosphate buffer.

zoates with alcoholic and phenolic leaving groups are expected. Treatment of the data in the present study using this procedure gives excellent results, as shown by the slopes, standard deviations of points from the line, and correlation coefficients for all of the benzoates (Table VI). The fact that the rates of hydrolysis may be correlated successfully suggests that all factors operative in the rate process are the same as, or at least parallel to, those involved in the equilibrium process.

Comparison of the ρ -values for the two types of leaving groups, aliphatic and aromatic, reveals that the sensitivity of alkaline hydrolysis to polar effects is relatively independent of the type of leaving group, since the ρ -values are approximately the same (2.2 for aliphatic leaving groups as compared to 2.1 for aromatic leaving groups). This slight difference in the ρ -values may conceivably be a result of inductive or resonance differences involved in the two types of leaving groups rather than a steric effect; in the case of aliphatic leaving groups, the ρ -values are insensitive to a wide variety of steric variations when considering the series of methyl through isopropyl leaving groups.

Treatment of the present data for variations in the acyl component of the ester molecule, using the Swain and Lupton approach (19), is demonstrated in Fig. 1. The average percent resonance (%R) contribution for each type of leaving group was determined from the slopes and intercepts in this figure. The %R for the alkaline hydrolysis of *para*-substituted benzoates with aromatic leaving groups was calculated to be 51; while for *para*-substituted benzoates with aliphatic leaving groups, the %R was 50. Since the %R involved in the benzoic acid ionization in water is 53, based on the Hammett substituent constants (19), one might expect that substituent effects in the acyl component of the benzoate esters would be successfully correlated with σ and this is indeed the case.

Alkyl Variation—Neither Hammett's substituent constant, σ , nor σ^- could successfully correlate rates of alkaline hydrolysis when variations were made in the alkyl portion of aryl benzoates, suggesting some factor or factors may not be taken into account when the comparison is made. A variety of approaches have been used to linearize Hammett plots when curvature in the line exists. Several authors (5, 11) suggested that the σ -values for strong electron-withdrawing substituents be adjusted to fit the line defined on the basis of other weaker electron-withdrawing substituents. This forced linearization of Hammett plots, however, might lead to erroneous mechanistic interpretation of the reaction at hand.

Another approach involves a linear combination of model processes, benzoic acid dissociation and phenol dissociation, as proposed by Ryan and Humfray (3, 4), who suggested that the Hammett

Table IV—Effect of Temperature on the Second-Order Rate Constants for Alkaline Hydrolysis of Some Benzoate Esters

Benzoate Esters	$k_{OH} \times 10^4 (M^{-1} \text{ sec.}^{-1})$			
	20°	25°	30°	35°
Methyl	4.40	6.08	11.0	15.0
Ethyl	1.35	1.98	3.41	4.20
<i>n</i> -Propyl	1.18	1.67	2.43	3.88
<i>p</i> -Tolyl	12.2	22.5	23.7	31.7
Phenyl	17.8	33.6	39.1	50.7
<i>p</i> -Fluorophenyl	32.5	56.5	64.8	84.9
<i>p</i> -Chlorophenyl	40.7	77.9	86.2	113
<i>m</i> -Cyanophenyl	132	227	252	326
<i>p</i> -Cyanophenyl	218	412	425	546
<i>p</i> -Nitrophenyl	302	533	592	845
2,4-Dinitrophenyl	2930	3580	4770	5040

Table V—Activation Parameters for Alkaline Hydrolysis of Some Benzoate Esters as a Function of the Alkyl Component

Substituent	$\Delta G_{\ddagger}^{\ddagger 25^\circ}$, kcal./mole	$\Delta H_{\ddagger}^{\ddagger 25^\circ}$, kcal./mole	$\Delta S_{\ddagger}^{\ddagger 25^\circ}$, cal./mole-deg.
Methyl	21.8	14.7	-23.8
Ethyl	22.5	13.5	-30.2
<i>n</i> -Propyl	22.6	14.1	-28.5
<i>p</i> -Tolyl	21.1	10.5	-35.6
Phenyl	20.8	12.2	-28.9
<i>p</i> -Fluorophenyl	20.5	11.5	-30.2
<i>p</i> -Chlorophenyl	20.3	12.1	-27.5
<i>m</i> -Cyanophenyl	19.7	10.1	-32.2
<i>p</i> -Cyanophenyl	19.3	10.8	-28.5
<i>p</i> -Nitrophenyl	19.2	11.5	-25.8
2,4-Dinitrophenyl	18.1	6.5	-38.9

substituent constant (σ) is associated with nucleophilic attack of the hydroxide ion at the carbonyl carbon of the ester while the phenol dissociation constant (σ^-) is most closely associated with decomposition of the tetrahedral intermediate. Treatment of the present data using this procedure is shown in Fig. 2. Table VII indicates the slopes, standard deviations, and correlation coefficients for the ester data using this approach. The magnitude of the proportionality constant, r , required for the linear combination of σ and σ^- has been used to indicate the rate-determining step. The value of r necessary to linearize the Hammett plot for the data in this study is 0.3, which suggests that attack of hydroxide ion is rate limiting in the reaction sequence, which coincides with the observation of Ryan and Humfray (3, 4).

Comparisons of the slopes in the two plots, as seen in Table VIII, for acyl and alkyl variation show that the acyl component has a greater sensitivity to polar effects than does alkyl variation. Kirsch *et al.* (5) and Tommila and Hinshelwood (20) also observed that a greater sensitivity exists in the acyl portion than in the alkyl portion. If the rate-determining step for all of these reactions involves only the addition of hydroxide ion to the ester carbonyl carbon, this greater sensitivity can be understood in terms of the reacting bond being one atom closer to the substituent.

Treatment of the data in this study for alkyl variations, using the Swain and Lupton approach, is exemplified in Fig. 3 and Table IX. The correlation coefficients for each series of leaving groups are quite good; that linear correlations using this concept could be obtained suggests that at least two interaction mechanisms are involved as in the case for acyl variation. However, some factor(s)

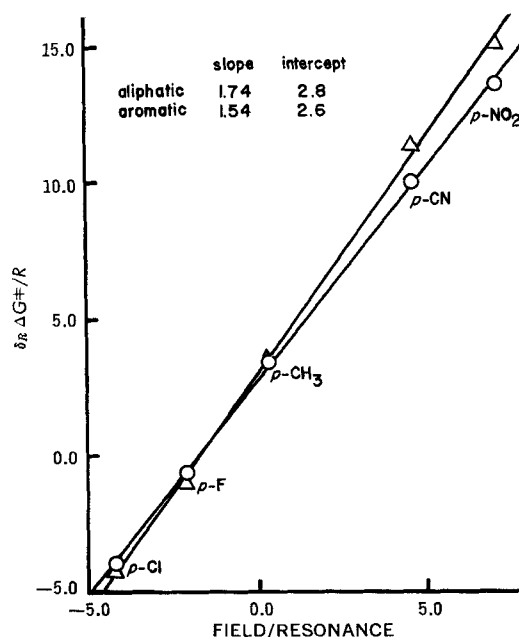


Figure 1—Graphical representation of Swain and Lupton's treatment for acyl variations on the alkaline hydrolysis of benzoate esters with aromatic and aliphatic leaving groups. Key: \circ , aromatic leaving groups; Δ , aliphatic leaving groups.

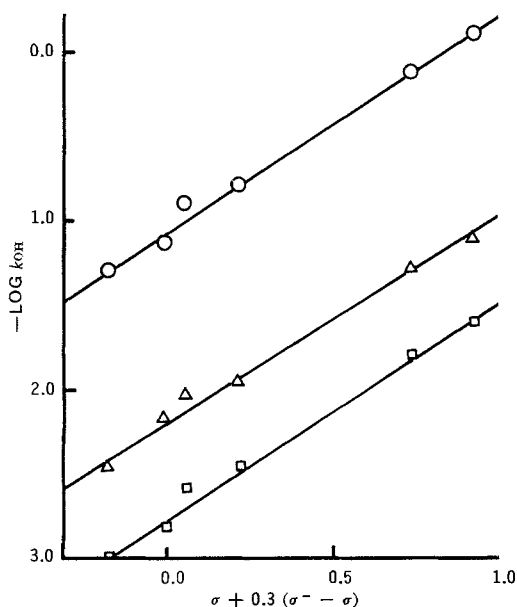


Figure 2—Plot of the second-order rate constants for alkaline hydrolysis of some benzoate esters with variations in the aromatic leaving group versus a modified form of the Yukawa and Tsuno equation. Key: \circ , *p*-cyanobenzoates; Δ , *p*-fluorobenzoates; and \square , *p*-methylbenzoates.

is not contributing equally to the overall interaction mechanism involved in the rate process in comparison to benzoic acid (σ) or phenol (σ^-) dissociation. No correlation is apparent between the %*R* involved in the reaction series and the acyl substituent; however, a striking difference in %*R* is observed when comparing the %*R* involved in the rate process, 43%, with that of the two equilibrium processes (53% for benzoic acid dissociation and 56% for phenol dissociation). There is a 10–15% difference in resonance contributions in the rate process as compared with either dissociation model, suggesting that this difference may account for the nonlinearity observed in the Hammett plot or $\log k_{OH}$ versus σ^- plot. Milton *et al.* (7) observed an average of 46% resonance for the methoxide-catalyzed methanolysis of aryl acetates and carbonates; they also observed nonlinearity for both series when the rate data were plotted against σ or σ^- .

Successful correlations of alkyl variations in structure and reactivity for *para*-substituted benzoate esters derived from alcohols were reported previously (10), but over a limited range of substituents involving small polar effects. Expansion of the series of substituent variation to encompass more polar groups, such as the halogenated ethyl substituents, did not result in the continued linearity of the correlation, as evidenced by the lines on the right-hand side of the $pK_a - \log k_{OH}$ plot shown in Fig. 4. This non-

Table VI—Correlation of Relative Rates of Alkaline Hydrolysis ($\log k/k_0$) with Hammett Substituent Constants (σ) for Some Benzoate Esters

Ester Series ^a	ρ^b	<i>SD</i> ^c	<i>R</i> ^d
Methyl benzoates	2.138	0.079	0.996
Ethyl benzoates	2.213	0.093	0.995
<i>n</i> -Propyl benzoates	2.184	0.049	0.999
Isopropyl benzoates	2.233	0.061	0.998
<i>n</i> -Butyl benzoates	2.158	0.077	0.996
Isobutyl benzoates	2.243	0.055	0.998
<i>p</i> -Tolyl benzoates	1.910	0.093	0.992
Phenyl benzoates	1.973	0.079	0.995
<i>p</i> -Fluorophenyl benzoates	2.020	0.056	0.998
<i>p</i> -Chlorophenyl benzoates	1.990	0.091	0.998
<i>p</i> -Cyanophenyl benzoates	2.095	0.117	0.998
<i>p</i> -Nitrophenyl benzoates	2.095	0.028	0.999

^a Each series was composed of the following acyl substituents: *p*-methyl, hydrogen, *p*-fluoro, *p*-chloro, *p*-cyano, and *p*-nitro. ^b ρ is the least-squares fitted slope of a $\log(k/k_0)$ versus σ plot. ^c Standard deviation of the points from the line. ^d Correlation coefficient for the line.

Table VII—Correlation of Relative Rates of Alkaline Hydrolysis ($\log k/k_0$) with Substituent Constants for Some Aryl Benzoate Esters Using the Modified Yukawa and Tsuno Equation

Ester Series ^a	ρ^b	<i>SD</i> ^c	<i>R</i> ^d
<i>p</i> -Toluates	1.409	0.095	0.992
Benzoates	1.495	0.104	0.998
<i>p</i> -Fluorobenzoates	1.400	0.128	0.982
<i>p</i> -Chlorobenzoates	1.340	0.139	0.986
<i>p</i> -Cyanobenzoates	1.383	0.100	0.989
<i>p</i> -Nitrobenzoates	1.445	0.094	0.993

^a Each series was composed of the following phenolic leaving groups: *p*-methyl, hydrogen, *p*-fluoro, *p*-chloro, *p*-cyano, and *p*-nitro. ^b ρ is the least-squares fitted slope of a $\log(k/k_0)$ versus $\sigma + 0.3(\sigma^- - \sigma)$ plot. ^c Standard deviation of the points from the line. ^d Correlation coefficient for the line.

linearity might arise from the mesomeric effects associated with stabilization of the anion of the alcohol in the dissociation process.

As can be seen from Fig. 4, there are two distinct families of curves, depending on the types of leaving group; both types of leaving groups show definite curvature in the free energy plots. Kirsch and Jencks (8) also observed two separate correlations as a function of leaving group, but they did not observe the curvature since a limited number of substituents were used in the correlation. Two questions are apparent: (a) Why is there curvature in the free energy plot? (b) Why are there two families of curves, one for aromatic leaving groups and one for aliphatic leaving groups, and what accounts for the separation between these curves?

Nonlinearity in the $\Delta G^\ddagger - \Delta G^0$ Plot—The nonlinearity observed in the $\Delta G^\ddagger - \Delta G^0$ plot may result from nonlinearity in either the rate process or the comparison of the rate process to the equilibrium process. When considering the rate process, three possible explanations may be postulated involving: (a) a change in rate-determining step, (b) a change in mechanism, and (c) a change in the transition state structure as a result of substituent variations. When comparison of the rate process to the equilibrium process is considered, nonlinearity may arise from: (a) the differences in the interaction mechanisms involved in the two processes, or (b) a solvent effect since the rate process was carried out in 50% acetonitrile–water and the dissociation process in water.

If a change in rate-determining step or mechanism is the explanation for the nonlinearity, then the transition state for nucleophilic attack of hydroxide ion at the carbonyl carbon of the ester must be stabilized by the substituent variation to a degree such that the transition state associated with decomposition of the tetrahedral intermediate would have a greater energy of activation and thus be rate determining in the reaction mechanism. Bender and Thomas (21) showed that the ratio of hydrolysis to exchange (k_H/k_{EX}) varied with the electron-withdrawing power of the acyl substituent in a series of *para*-substituted methyl benzoates, but in all cases k_H/k_{EX} was greater than unity, thus implying that the rate-determining step in all instances was the formation of the tetrahedral intermediate.

It has been suggested that a change in mechanism occurs as the leaving group is varied in the case of imidazole-catalyzed hydrolysis of esters (22, 23). General base catalysis occurs for esters with poor leaving groups, while nucleophilic catalysis occurs for esters with good leaving groups, as deduced from the order associated with the imidazole concentration in the rate expression. Solvent deuterium isotope effects and imidazole catalysis studies are important tools

Table VIII—Effect of Substituents in the Acyl Component Relative to the Alkyl Component

Substituent	$\rho_{Acyl}^a / \rho_{Alkyl}^b$
<i>p</i> -Nitro	1.469
<i>p</i> -Cyano	1.391
<i>p</i> -Chloro	1.485
<i>p</i> -Fluoro	1.442
Hydrogen	1.319
<i>p</i> -Methyl	1.355

^a ρ_{Acyl} is the value of the least-squares fitted slope of $\log(k/k_0)$ versus σ plot for acyl variations. ^b ρ_{Alkyl} is the value of the least-squares fitted slope of $\log(k/k_0)$ versus $\sigma + 0.3(\sigma^- - \sigma)$ plot for alkyl variations.

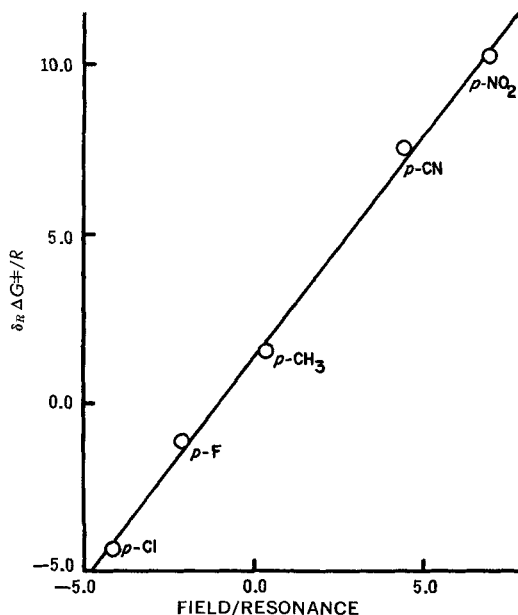


Figure 3—Graphical representation of Swain and Lupton's treatment for variations in aromatic leaving group on the alkaline hydrolysis of benzoate esters.

in suggesting the mechanism involved in ester hydrolysis, and both were investigated in the present study. The results of these studies are tabulated in Table II as a function of leaving group. As can be seen from the table, the rates of deuteroxide-catalyzed hydrolysis are greater than that of hydroxide ion; this inverse isotope effect suggests that the reaction involves specific base catalysis rather than general base catalysis. Similarly, the imidazole catalysis study implies that the mechanism involved in all cases of ester variations is nucleophilic attack rather than general base catalysis, since the ratio of rate constants associated with each ester is quite small. Milton *et al.* (24) observed similar solvent deuterium isotope effects in their study of basic methanolysis of aryl acetates and carbonates and suggested that a change in rate-determining step was not in

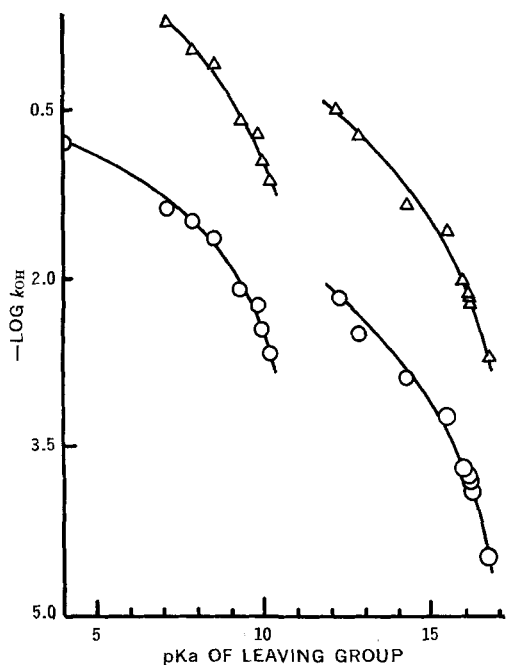


Figure 4—Plot of the second-order rate constants for alkaline hydrolysis of benzoates and *p*-nitrobenzoates with variations in the leaving groups versus the *pK_a* of the corresponding leaving group. Key: Δ , *p*-nitrobenzoates; and \circ , benzoates.

Table IX—Correlation of Free Energy of Activation for Alkaline Hydrolysis of Some Benzoate Esters with the Field (*F*) and Resonance (*R*) Constants of Swain and Lupton

Ester Series ^a	Slope ^b	Intercept	<i>R</i> ^c	% <i>R</i> ^d
<i>p</i> -Toluates	1.226	1.403	0.990	42
Benzoates	1.244	1.591	0.987	44
<i>p</i> -Fluorobenzoates	1.037	1.713	0.981	50
<i>p</i> -Chlorobenzoates	1.291	1.040	0.994	34
<i>p</i> -Cyanobenzoates	1.223	1.345	0.987	41
<i>p</i> -Nitrobenzoates	1.264	1.458	0.988	42

^a Each series is composed of the following phenolic leaving groups: -methyl, *p*-fluoro, *p*-chloro, *p*-cyano, and *p*-nitro. ^b Value of the least-squares fitted slope of $\delta_R \Delta G^\ddagger/R$ versus *F/R* plot, where $\delta_R \Delta G^\ddagger$ is the effect of substituent *R* on the free energy of activation. ^c Correlation coefficient for the line. ^d Percent resonance involved in the reaction series as calculated by the method of Swain and Lupton.

order for the explanation of the nonlinearity observed in the $\Delta G^\ddagger - \Delta G^0$ plot.

Exner (25, 26) suggested that if a linear correlation of the free energies of activation at two temperatures can be obtained for a reaction, then the reaction is occurring *via* the same mechanism at the two temperatures throughout the series of substituent variations. Temperature effects on the rates of alkaline hydrolysis reveal that a linear correlation may be obtained; this is demonstrated by Fig. 5 for benzoate esters with both aromatic and aliphatic leaving groups. The slope and correlation coefficient for this plot are 0.933 and 0.999, respectively, providing additional evidence that the nonlinearity in the free energy plots is not due to a change in mechanism or rate-determining step. Also, the %*R* as calculated from the Swain and Lupton approach is not affected to any appreciable extent by the temperature.

Another possible explanation for nonlinearity might involve changes in the structure of the transition state as the substituent is varied. Fersht and Jencks (27) recently investigated the reactions of nucleophilic reagents with acylating agents of extreme reactivity and unreactivity, and they suggested that the symmetry of the transition state involved in the reaction may account for the nonlinearity observed in the free energy plot. This, however, cannot be applied to the case of ester hydrolysis since a relatively stable tetrahedral intermediate is involved in the mechanism, and asymmetry in the transition state would be reflected in a change in rate-determining step. The effect of the leaving group on the solvation cage around the carbonyl carbon in the ester molecule as the hydroxide ion approaches it may conceivably be a more appropriate explanation for the nonlinearity. Since the dispersal of the developing negative charge in the transition state is affected by the electron-withdrawing power of the leaving group, the effects of substituents

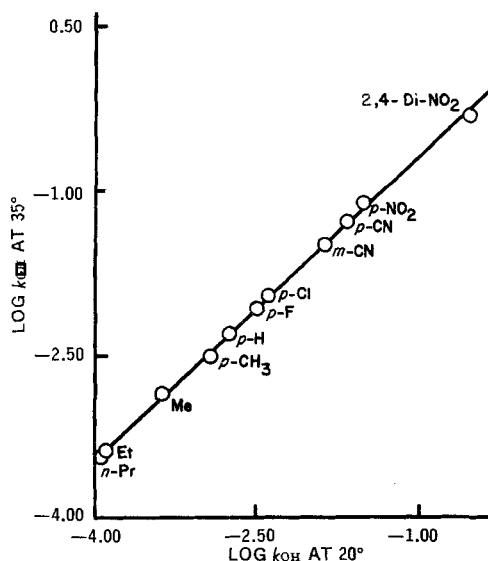


Figure 5—Linear dependence of the substituent effects on the second-order rate constants for alkaline hydrolysis of benzoate esters at 20° and 35°, encompassing both aromatic and aliphatic leaving groups.

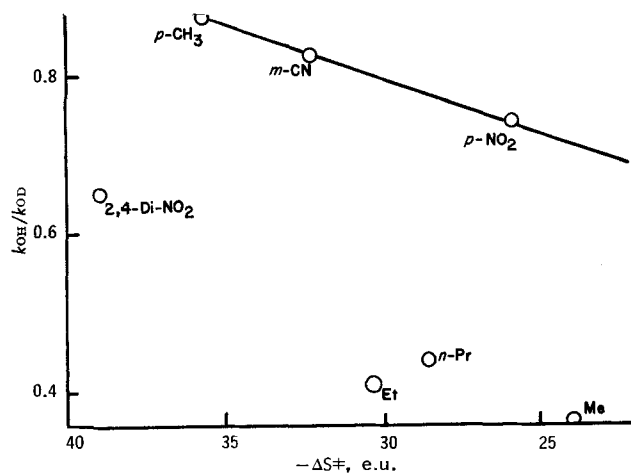


Figure 6—Plot of substituent effects on the solvent deuterium isotope effects versus entropies of activation for the alkaline hydrolysis of benzoate esters with variations in leaving group.

on the entropy of activation and the magnitude of the inverse solvent deuterium isotope effect would be related since both are dependent on the hydrogen bonding of the solvent in the transition state. Figure 6 indicates that this is indeed the case for leaving groups with similar steric requirements at the carbonyl carbon. The deviations from the line may be attributed to either variation in steric parameters or resonance.

Solvent effects on the second-order rate constants were correlated using the Kosower Z values for solvent polarity, and linear correlations were obtained as shown in Table X. Generally, the rate of reaction increased as the dielectric constant of the medium increased, suggesting that the activated complex is more polar than the ground state of the ester and the values of the slopes of this plot are dependent on the electron-donating or withdrawing power of the leaving group. These sensitivities to medium changes parallel the entropies of activation and the inverse solvent deuterium isotope effects as a function of leaving group involved in the ester. Figure 7 demonstrates the linearity of the entropies of activation to the slope from the $\log k_{OH}$ versus Z plot for *para*-substituted aromatic leaving groups, with the deviations from the line reflecting the steric differences involved in the ethyl and 2,4-dinitrophenyl leaving group. Figure 8, on the other hand, illustrates the linear dependence of the inverse solvent deuterium isotope effects on the slope from the $\log k_{OH}$ versus Z plot for all the aromatic leaving groups and the displacement from the line for the aliphatic leaving group.

Comparison of the rate process to the equilibrium process may involve either differences in the interaction mechanisms involved

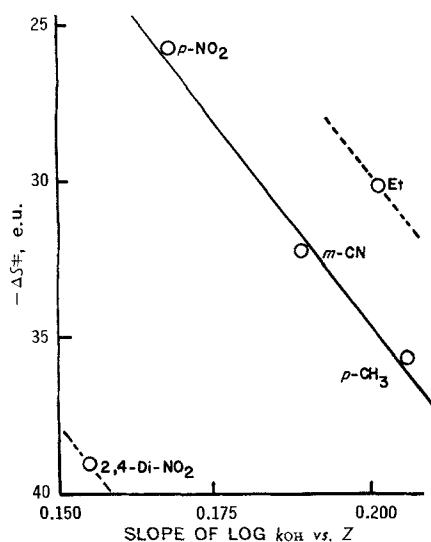


Figure 7—Plot of the entropies of activation versus the slope of the Kosower plot for alkaline hydrolysis of benzoates with variations in leaving group.

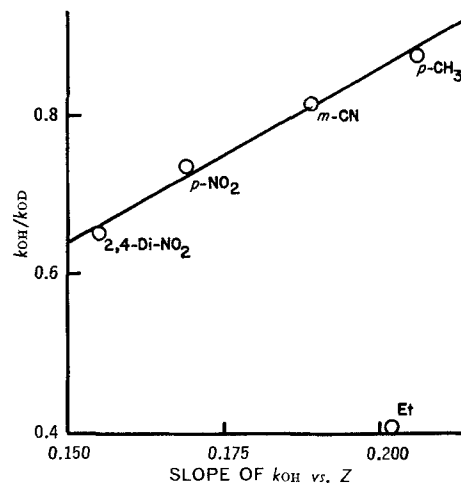


Figure 8—Plot of the linear dependence of the solvent deuterium isotope effect on the slope of the Kosower plot for alkaline hydrolysis of benzoate esters with variations in leaving group.

in the two processes or a solvent phenomenon, since the rate process was carried out in a semiaqueous system and compared to the equilibrium process in a completely aqueous system. Considering the interaction mechanisms involved in the two processes first, resonance effects in the phenol dissociation process are definitely known to exist and result from stabilization of the anion. Calculations show that there is 56% R in the dissociation of the phenols (19) as compared to 43% for the alkaline hydrolysis of esters with variations in the aromatic leaving group. In the case of alcohol dissociation, no resonance is capable of stabilizing the anion, since there are no π -electrons present in the saturated alcohol. However, for halogenated ethanols, the mesomeric effects of the halogen may result in stabilization of the anion. Hence the nonlinearity in the $\Delta G^\ddagger - \Delta G^0$ plot may be a result of the differences in resonance involved in the two processes. Furthermore, the enthalpies of ionization of phenols in water are approximately one-half of the enthalpies of activation involved in the alkaline hydrolysis of the esters with corresponding leaving groups, while the entropies involved in both processes are very similar.

No distinct relationship was observed in the ΔH^\ddagger versus ΔS^\ddagger plot, as shown in Fig. 9, as a function of leaving group for the alkaline hydrolysis of these esters; however, if the enthalpies and entropies of activation are a result of external and internal contributions as suggested by Hepler for ionization of phenols (28), a line may be drawn in the plot with a slope corresponding to a value of the isokinetic temperature of 340°K. The deviations from this

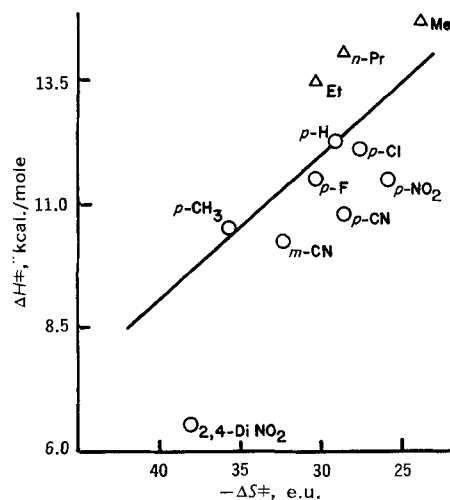


Figure 9—Enthalpies of activation versus entropies of activation for the alkaline hydrolysis of benzoate esters with variations in the leaving group. The line drawn on the plot has a value of 340°K. for the slope. Key: \circ , aromatic leaving groups; and Δ , aliphatic leaving groups.

Table X—Correlation of Solvent Effect on the Alkaline Hydrolysis of Some Benzoate Esters with Kosower's Z Values

Benzoate Ester	Slope ^a	Intercept ^b	R ^c
2,4-Dinitrophenyl	0.155	1.32	0.999
<i>p</i> -Nitrophenyl	0.168	0.68	0.999
<i>m</i> -Cyanophenyl	0.189	0.47	0.996
<i>p</i> -Tolyl	0.206	0.34	0.997
Ethyl	0.202	-1.30	0.999

^a Slope of the least-squares fitted line of $\log k_{OH}$ versus Z plot. ^b Intercept value of $\log k_{OH}$ corresponding to 100% water. ^c Correlation coefficient for the line.

line would then reflect the internal contributions to the enthalpies of activation exhibited by the substituted aromatic leaving groups, and a linear plot of these substituent effects on the internal contributions to enthalpy of activation versus Hammett's substituent constants is obtained (Fig. 10). The substituent effects on the free energies of ionization of phenols is defined by:

$$\delta_R \Delta G^0 = \delta_R \Delta H_i^0 + (280^\circ - T)\delta_R \Delta S^0 \quad (\text{Eq. 6})$$

while the free energies of activation for the alkaline hydrolysis of esters with the corresponding leaving groups is defined by:

$$\delta_R \Delta G^\ddagger = \delta_R \Delta H_i^\ddagger + (340^\circ - T)\delta_R \Delta S^\ddagger \quad (\text{Eq. 7})$$

suggesting that differences in the solvation may be responsible for the nonlinearity since the substituent effect on ΔG^0 in the ionization of phenols is primarily dependent on the internal contributions to enthalpy, with minor solvation contributions as reflected by the temperature differential.

A solvent effect may also explain the nonlinearity in the ΔG^\ddagger - ΔG^0 plot if nonlinearity exists in the plot of the pKa of the leaving groups in water as compared to the pKa of the leaving group in the buffer system. Extrapolation of the rate constants to 100% water for each leaving group was performed, and the logarithms of these extrapolated values were plotted versus the pKa of the conjugate acid of the leaving group (Fig. 11). Included in Fig. 11 are the logarithms of the rate constants at a variety of other water concentrations; nonlinearity has not been eliminated, suggesting that a solvent effect is not the cause for the nonlinearity.

SEPARATION OF AROMATIC AND ALIPHATIC LEAVING GROUP CURVES IN THE ΔG^\ddagger - ΔG^0 PLOT

Kirsch and Jencks (8) observed two distinct correlations as a function of the type of leaving group in the alkaline hydrolysis of

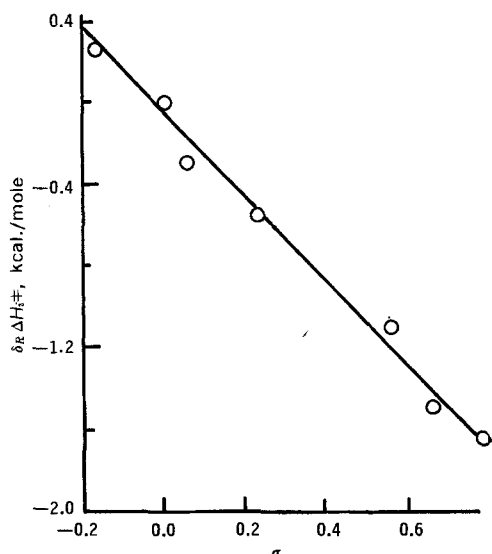


Figure 10—Hammett plot of substituent effects in the internal contributions to enthalpy of activation for the alkaline hydrolysis of benzoates with aromatic leaving groups.

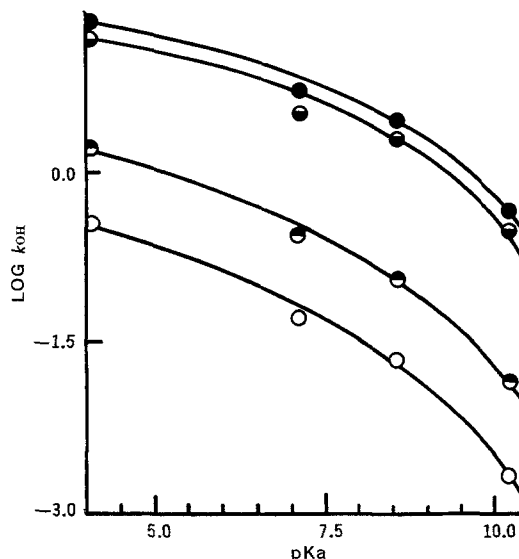


Figure 11—Effect of solvent composition on the second-order rate constants for alkaline hydrolysis of benzoate esters with aromatic leaving groups versus the pKa of the corresponding phenol. Key: ●, 100% water; ◐, 5% (v/v) acetonitrile in water; ○, 50% (v/v) acetonitrile in water.

acetate esters and suggested that the phenolic esters were less reactive than alcoholic esters of comparable pKa because of steric hindrance of the bulky benzene ring. Bruice *et al.* (9), however, observed a single correlation for the alkaline hydrolysis of acetates as a function of the pKa of the leaving group. According to Jencks, this could be explained by the fact that their results were obtained under a variety of conditions and could not be compared directly. If a steric effect is operative in determining this separation between the two types of leaving groups, the entropies of activation involved in each type should reflect this.

As can be seen in Table V, no apparent trend or regularity in ΔS^\ddagger for either the phenolic or alcoholic esters is evident. However, the ΔH_i^\ddagger 's for the alcoholic esters apparently are several kilocalories greater than those of the phenolic esters, suggesting that resonance effects play a greater role in determining the rate than steric effects; resonance effects would be reflected in ΔH_i^\ddagger whereas steric effects would primarily be reflected in ΔS^\ddagger . Furthermore, if comparisons of the pKa's of the alcohols and phenols with that of the corresponding acids are made, as in Fig. 12, one observes two distinct correla-

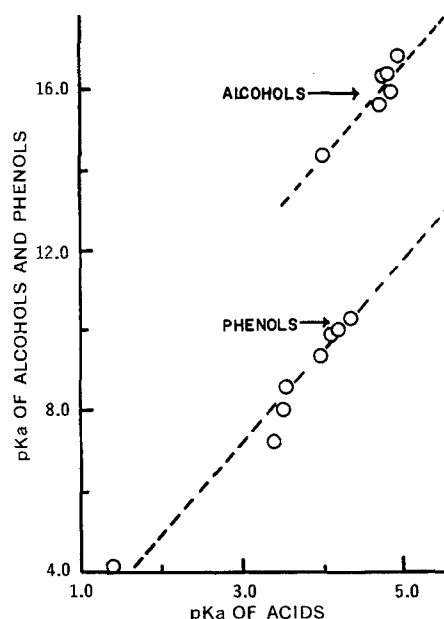


Figure 12—Plot of the pKa of alcohols and phenols (ROH) versus the pKa of the corresponding acids (RCOOH).

tions separated by approximately 5 pKa units, which coincides with the 5 pKa unit displacement between the rates of hydrolysis of esters with alcoholic and phenolic leaving groups in the $\Delta G^\ddagger - \Delta G^0$ plot. Thus, the separation observed in the $\Delta G^\ddagger - \Delta G^0$ plot may be a result of the differences involved in comparing the two equilibrium processes to the rate process.

CONCLUSIONS

Correlation of substituent effects with reactivity for acyl-substituted benzoate esters, composed of both aliphatic and aromatic leaving groups, is successfully accomplished using the Hammett equation. This successful correlation is apparently due to equivalent contributing factors involved in both the rate and the equilibrium processes. One of these factors is the resonance interaction, which was found to be essentially equal in the equilibrium process (dissociation of *para*-substituted benzoic acids) and in the rate process (alkaline hydrolysis of acyl-substituted benzoate esters).

Neither the Hammett equation nor the alcohol and phenol dissociation model is entirely effective in correlating structure with reactivity for variation in the alkyl portion of the ester molecule. However, the alcohol dissociation model is effective over a larger range of substituents than either the Hammett relationship or the phenol dissociation model.

Plotting the rate constant for alkaline hydrolysis of some benzoates *versus* the dissociation constant of the conjugate acid of the leaving group yields two distinct families of curves, one for aliphatic and one for aromatic leaving groups, and each ester series shows distinct curvature. The curvature in the $\Delta G^\ddagger - \Delta G^0$ plot is not due to a change in mechanism or rate-determining step in the rate process, based on the evidence presented here, but rather is due to multiple interaction mechanisms which are apparently not involved to the same extent when comparing the two processes. One of these interaction mechanisms, resonance, may account for the nonlinearity since the resonance contributions are approximately 10–15% less in the alkaline hydrolysis of aryl benzoates than are involved in the dissociation of benzoic acids or phenols.

Another interaction mechanism that must be considered to account for the nonlinearity is the solvation differences that exist between the rate and equilibrium processes. Substituent effects on ΔH^\ddagger and ΔS^\ddagger can be divided into internal and external contributions; it has been shown here that only the internal contributions to ΔH^\ddagger can be successfully correlated with Hammett's polar substituent constant, σ , suggesting that the nonlinearity in $\Delta G^\ddagger - \Delta G^0$ plots might be a result of the external contributions arising from solvation of the transition state. However, when the entropies involved in the two processes are considered, evidence suggests that the nonlinearity involved may not be a result of solvation differences since the ΔS^\ddagger for the rate process are very similar to the ΔS^0 for the equilibrium process. Hence, the resonance interaction mechanism is favored as an explanation of the nonlinearity observed in the $\Delta G^\ddagger - \Delta G^0$ plot.

The two families of curves observed by plotting the rate constant for alkaline hydrolysis against the pKa of the leaving group may best be explained on the basis of resonance involved in the dissociation process. In phenol dissociation, there is resonance stabilization of the anion; in alcohol dissociation, no such stabilization is possible. Thus, the 5 pKa unit difference between the two families of curves, one for aliphatic and one for aromatic, is the same as is observed when plotting the pKa of phenols and alcohols against the pKa of the corresponding aliphatic and aromatic acids.

In summary, the alcohol and phenol dissociation model does not linearly correlate with rate of ester solvolysis when large ranges of substituent leaving groups are employed. Moreover, the incomplete correlation can be used to provide mechanistic insight into alkaline hydrolysis of esters. The alcohol dissociation model is effective

over a larger range of substituents than phenol dissociation, conceivably because of the general lack of resonance interaction mechanism involved in alcohol dissociation as compared to phenol dissociation.

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