Conclusions

Reactions 2–4 appear to proceed without the loss of ring position identity in contrast to reaction 1. Reactions 1, 2, and 4 appear to be similar in that each involves the cleavage of an OY′ bond in $YC_6H_4OY'\cdot^+$; however simple fission, which is the major pathway when Y′ = NO or CH_3, is insignificant when Y′ = C_2H_5, for which the rearrangement formation of $(M - C_2H_4)\cdot^+$ ions predominates. This observation seems inconsistent with the isomerization mechanisms proposed for reaction 1;[1] such mechanisms by analogy should be of considerable if not more importance in reactions 2 and 4. Possibly there is initial fast hydrogen rearrangement to yield a form such as $YC_6H_4{}^+OHC_2H_4\cdot$ that has sufficient stability to permit isomerization of the ring positions[2,4] before decomposition. Studies of other systems which are possibly analogous are in progress.

Experimental Section

Spectra were recorded on a Hitachi RMU-6D mass spectrometer at Purdue University and a Hitachi RMU-6E mass spectrometer at the University of North Carolina. In both cases 75 ev was used for the high-voltage spectra; the ionizing current was 80 μa. For low-voltage spectra a trap current of 2 μa was maintained, and the ionization potential obtained by the vanishing current technique. Several spectra at energies approximately 5 v (measured by a digital voltmeter readable to ±0.02 v) above the ionization potential were then recorded, and the intensities at the desired voltage were determined by interpolation of data.

Inlet system and ion source temperatures were approximately 180°.

Compounds used in this study were either gifts or commercial samples.

Acknowledgments.—We thank the National Institutes of Health (GM 12755 and FR 00354) for generous support of this work and the National Science Foundation for funds for purchase of the Hitachi RMU-6D mass spectrometer at Purdue University. We are also grateful to Dr. Herbert C. Brown for donations of chemicals and to Mr. Laurence R. Dusold for assistance with the computer program used.

Multiple Structure–Reactivity Correlations. The Alkaline Hydrolyses of Acyl- and Aryl-Substituted Phenyl Benzoates[1]

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The rates of alkaline hydrolysis of acyl-substituted *p*-nitrophenyl, *m*-nitrophenyl, *p*-chlorophenyl, phenyl, and *p*-tolyl benzoates have been determined in 33% acetonitrile-water at 25°. Each of the substituted phenols generated an independent $\sigma-\rho$ plot which was correlated very precisely with the Hammett equation (r = 0.998 – 0.999). The values of ρ so obtained show no tendency either to increase or to decrease with the intrinsic reactivity of the parent phenol and are all within ±0.040 of the mean of 2.021. Poorer correlations were obtained with the Hammett plots made by varying the aryl moieties of the esters while holding the acyl fractions constant. These could only be improved if the σ of the *p*-nitrophenyl derivative was allowed to assume a "best" value of 0.89, which is intermediate between σ and σ^-. Ground-state destabilization of *p*-nitrophenyl esters by resonance is suggested as a possible explanation for the enhanced value of σ. The constancy of the ρ values is considered in relationship to a recently proposed multiple structure–reactivity equation.

The Hammett equation (eq 1) has been one of the most successful and most widely used of the linear free-energy relationships which have been applied in physical organic chemistry[2] in the resolution of structure reactivity problems. Several parameters which influence

$$\log k_i = \sigma_i\rho + \log k_0 \qquad (1)$$

the values of ρ for a given set of substrates and reaction conditions have been investigated; among these are temperature and solvent composition,[3] distance of substituent from the reacting center,[4] and changes in the rate-determining step in proceeding from the most reactive to the least reactive members of the series.[5,6] However, the effect of the reactivity of the reactants themselves upon ρ has received scanty consideration, the main efforts in this direction being those of Brown and coworkers in an extensive series of studies on electrophilic aromatic substitution reactions. They have shown that the ratio of the rate constants for the reactions of an electrophile with toluene and with benzene ($k_{\text{tol}}/k_{\text{benz}}$) approaches unity as the strength of the electrophile is increased, indicating that the absolute value of ρ decreases with increasing reactivity. The increasing reactivity is accompanied by a decrease in positional selectivity, the more highly reactive electrophiles producing greater quantities of *meta*-substituted products in addition to the usual *ortho* and *para* ones. This behavior is quantitatively reflected in the ρ values, which proceed from –12.1 in the highly selective, uncatalyzed bromination reaction where essentially no *meta*-substituted product is formed to ρ of –2.4 in the rather unselective Friedel–Craft ethylation reaction where appreciable quantities of *meta* isomers are produced.[7] These experiments can be considered

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[1] Supported by National Institutes of Health Grant Number GM 12278 and National Science Foundation Grant Number GB 4606.

[2] For recent discussions, see (a) P. R. Wells, *Chem. Rev.*, **63**, 171 (1963); (b) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1963.

[3] An extensive compilation of relevant data is given in (a) H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953). Theoretical discussions of the effect of temperature on ρ are given by (b) C. C. Price, *ibid.*, **29**, 37 (1941), and in (c) ref 2b, p 177 ff.

[4] R. W. Taft, Jr., and I. C. Lewis, *J. Am. Chem. Soc.*, **80**, 2436 (1958).

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[6] J. F. Kirsch and W. P. Jencks, *ibid.*, **86**, 837 (1964).

[7] (a) L. M. Stock and H. C. Brown, *Advan. Phys. Org. Chem.*, **1**, 35 (1963). See also (b) G. A. Olah, S. J. Kuhn, S. H. Flood, and B. A. Hardie, *J. Am. Chem. Soc.*, **86**, 2203 (1964), and earlier papers by G. A. Olah.

against the background of the Hammond postulate[8] which implies a decreasing selectivity as the energy content of the ground state approaches that of the transition state.

In this work the problem of the effect of the reactivity of the substrate upon the magnitude of ρ was approached through a study of the alkaline hydrolysis of phenyl benzoates which were substituted in both the acyl and aryl moieties. Each aryl derivative was used to generate an independent Hammett plot by systematic substitutions on the acyl groups. Rates of alkaline hydrolysis of substituted methyl and ethyl benzoates and of phenyl acetates have been reported by Tommila and Hinshelwood.[3a,9] Later workers have reported further measurements on the alkaline hydrolysis rates of substituted phenyl acetates,[6,10] and Bender and Thomas have made an additional study of methyl benzoates.[11] We report here the results of an investigation of the rates of alkaline hydrolysis of 24 substituted phenyl benzoates, ranging in reactivity from *p*-nitrophenyl *p*-nitrobenzoate to *p*-tolyl *p*-dimethylaminobenzoate.

Experimental Section

Materials.—The substituted phenyl benzoates were generally prepared by the addition of one equivalent of $SOCl_2$ to an equimolar mixture of carboxylic acid and phenol dissolved in excess pyridine with stirring at 0°. The products were precipitated by pouring the reaction mixture into a tenfold excess of cold water, and the solid precipitates were collected by filtration, washed with 5% Na_2CO_3, crystallized from 95% ethanol, and dried over P_2O_5 in a vacuum dessicator. The following compounds were prepared by this procedure.

p-Tolyl *p*-dimethylaminobenzoate, mp 156–158°, was recrystallized from acetone and gave an analytical sample, mp 160–161°.

Anal.[12] Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.16; H, 6.65; N, 5.57.

Phenyl *p*-dimethylaminobenzoate was recrystallized from acetone–water, mp 180–181° (lit.[13] mp 180–181°).

m-Nitrophenyl *p*-dimethylaminobenzoate was recrystallized from acetone–water, mp 139.5–141°. Recrystallization from methanol yielded an analytical sample, mp 139.5–140.5.

Anal. Calcd for $C_{15}H_{14}N_2O_4$: C, 62.92; H, 4.94; N, 9.79. Found: C, 62.81; H, 5.06; N, 9.68.

p-Nitrophenyl *p*-dimethylaminobenzoate was crystallized from acetone rather than ethanol, mp 195–196.5°.

Anal. Calcd for $C_{15}H_{14}N_2O_4$: C, 62.92; H, 4.94; N, 9.79. Found: C, 62.90; H, 5.11; N, 9.73.

p-Tolyl *p*-toluate had mp 89.0–90.5° (lit. mp 91–92°,[14] 90.8°[15]).

p-Chlorophenyl *p*-toluate had mp 89.2–90.7 (lit.[16] mp 91.6–92.1°).

p-Nitrophenyl *p*-toluate had mp 120.3–121.3.

Anal. Calcd for $C_{14}H_{11}NO_4$: C, 65.36; H, 4.31; N, 5.44. Found: C, 65.10; H, 4.27; N, 5.66.

p-Tolyl benzoate had mp 70.4–71.2° (lit. mp 71°,[17] 72°[16]).

p-Chlorophenyl benzoate had mp 88–89° (lit.[18] mp 88–89°).

p-Nitrophenyl benzoate had mp 142–143° (lit.[19] mp 143°).

Alternatively some of the esters were prepared by the slow addition of 1 equiv of the acyl chloride dissolved in toluene to a solution of the phenol in excess pyridine. After the addition was completed, the reaction mixture was evaporated to dryness; the products were taken up in chloroform. The chloroform solution was washed with Na_2CO_3 followed by H_2O and dried over Na_2SO_4. The esters were crystallized from 95% ethanol after removal of the solvent. The following compounds were prepared in this manner.

Phenyl *p*-toluate had mp 75–76.5 (lit.[20] 83°).

Anal. Calcd for $C_{14}H_{12}O_2$: C, 79.22; H, 5.70. Found: C, 79.65; H, 6.10.

m-Nitrophenyl *p*-toluate had mp 106–107.5°.

Anal. Calcd for $C_{14}H_{11}NO_4$: C, 65.36; H, 4.31; N, 5.44. Found: C, 65.42; H, 4.48; N, 5.54.

m-Nitrophenyl benzoate had mp 92.5–94° (lit.[21] mp 95°).

p-Tolyl *p*-chlorobenzoate had mp 97.5–98.5° (lit.[16] mp 98–98.5°).

Phenyl *p*-chlorobenzoate had mp 103.5–104.5 (lit.[22] mp 107).

Anal. Calcd for $C_{13}H_9ClO_2$: C, 67.09; H, 3.90; Cl, 15.25. Found: C, 66.84; H, 4.10; Cl, 15.09.

p-Chlorophenyl *p*-chlorobenzoate had mp 96–96.5° (lit.[14] mp 96.3).

m-Nitrophenyl *p*-chlorobenzoate had mp 135–136.5°.

Anal. Calcd for $C_{13}H_8ClNO_4$: C, 56.22; H, 2.90; Cl, 12.78. Found: C, 55.70; H, 2.99; Cl, 12.99.

p-Nitrophenyl *p*-chlorobenzoate had mp 137–138.5° (lit.[23] mp 138°).

p-Tolyl *p*-nitrobenzoate had mp 98–99° (lit.[20] mp 96.5–97.5°).

Phenyl *p*-nitrobenzoate had mp 128–129° (lit. mp 129°,[24] 127.5°[25]).

p-Chlorophenyl *p*-nitrobenzoate had mp 171–172° (lit.[26] mp 171°).

m-Nitrophenyl *p*-nitrobenzoate had mp 176.5–177° (lit.[23] mp 174–175°).

p-Nitrophenyl *p*-nitrobenzoate had mp 158.5–159° (lit. 150°,[27] 158–159°[23]).

Phenyl benzoate was purchased from Eastman and recrystallized from ethanol. Acetonitrile was redistilled. The preparation of triethylamine buffers has been described.[28] Carbon dioxide-free glass distilled water was used throughout. The normality of the KOH solutions was checked by titration against primary standard potassium acid phthalate.

Methods.—All reactions were followed in a Zeiss PMQ II spectrophotometer equipped with a thermostated brass cell holder. The wave lengths used are given in the last column of Table I. The slower reactions were followed by the method described by Jencks and Carriuolo.[29] Acetonitrile solutions of the esters were added directly with a polyethylene spoon to the cuvettes in the spectrophotometer cell compartment when the half-lives of the reactions were less than 1 min. All reactions were studied under pseudo-first-order conditions, and the rate constants were obtained from the equation $k_1 = 0.693/t_{1/2}$. Second-order rate constants were obtained as described in the Results section. The OH^- concentrations were obtained directly from the known amount of added KOH where the concentration of base exceeded 0.004 *N*. The faster reactions required the use of triethylamine buffers. The following procedure allowed the determination of hydroxide ion concentration from the measured pH under the conditions used in these studies. Twenty solutions were made in 33% acetonitrile and ionic strength 0.3 containing concentrations of KOH ranging from 0.005 *N* to 0.3 *N*, and the pH of these solutions measured at 25°. A plot of measured pH against log $[OH^-]$ for these solutions fit the empirical equation: $pH = \log [OH^-] + 14.58$. This equation was used in calculating the hydroxide ion concentration from the measured pH in triethylamine buffers. In addition, the rate

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TABLE I

RATES OF ALKALINE HYDROLYSIS OF SUBSTITUTED PHENYL BENZOATES[a]

Acyl substituent	Registry No.	Alcohol substituent	No. obsd	Initial ester concn, $M \times 10^5$	Hydroxide ion $M \times 10^4$ [b]	k_2,[c] M^{-1} min^{-1}	Std error	Wavelength, mμ
p-N(CH$_3$)$_2$	15024-07-4	*p*-CH$_3$	9	2.0	1000–3000	0.0478	0.0005	322
p-CH$_3$	15024-08-5	*p*-CH$_3$	8	24	1000–3000	0.836	0.020	298
p-H	614-34-6	*p*-CH$_3$	18	25	1000–3000	1.993	0.057	298
p-Cl	15024-10-9	*p*-CH$_3$	8	30	300–800	5.83	0.12	298
p-NO$_2$	15024-11-0	*p*-CH$_3$	17	40	50–150	89.7	1.5	261
p-N(CH$_3$)$_2$	15024-12-1	*p*-H	9	2.0	1000–3000	0.0725	0.0009	327
p-CH$_3$	1900-85-2	*p*-H	9	20	1000–3000	1.41	0.034	292
p-H	93-99-2	*p*-H	12	20	600–1800	3.345	0.040	292
p-Cl	1871-38-1	*p*-H	9	4.0	200–600	10.50	0.31	253
p-NO$_2$	1429-05-6	*p*-H	26	2.5	1.07–150	117.7	1.9	232[d]
p-CH$_3$	15023-58-2	*p*-Cl	9	24	300–1200	3.072	0.020	302
p-H	2005-08-5	*p*-Cl	9	12	300–900	7.453	0.072	300
p-Cl	6961-42-8	*p*-Cl	8	22	70–200	18.33	0.28	302
p-NO$_2$	7511-31-1	*p*-Cl	27	45	1.07–150	272.9	5.8	243[e]
p-N(CH$_3$)$_2$	15023-62-8	*m*-NO$_2$	9	2.0	1000–3000	0.5086	0.0088	330
p-CH$_3$	15023-63-9	*m*-NO$_2$	9	40	100–300	11.22	0.18	390
p-H	1523-13-3	*m*-NO$_2$	8	40	100–300	27.57	0.44	390
p-Cl	15026-13-8	*m*-NO$_2$	18	40	50–150	68.1	1.1	390
p-NO$_2$	15023-65-1	*m*-NO$_2$	17	40	0.86–5.0	986	19	390
p-N(CH$_3$)$_2$	15023-66-2	*p*-NO$_2$	9	3.0	1000–3000	0.897	0.017	400
p-CH$_3$	15023-67-3	*p*-NO$_2$	9	3.3	100–300	20.95	0.34	400
p-H	959-22-8	*p*-NO$_2$	16	3.3	50–150	48.40	0.75	400
p-Cl	6264-29-5	*p*-NO$_2$	7	3.5	50–120	109.6	2.8	400
p-NO$_2$	1037-31-6	*p*-NO$_2$	9	3.0	0.95–4.40	1596	21	400

[a] In 33% acetonitrile, ionic strength 0.3 at 25°. [b] Hydroxide ion concentrations less than 0.005 *M* were determined from the measured pH as described in the Experimental Section. Higher concentrations were determined directly from the known amount of added KOH. [c] $k_{obsd}/[OH^-]$. [d] At the lower concentrations of hydroxide ion this reaction was studied in 0.05 *M* triethylamine buffers and followed at 259 mμ. [e] Reactions in 0.05 *M* triethylamine buffers were followed at 265 mμ.

constants for several of the esters were measured both in triethylamine buffers and in unbuffered solutions containing a known added amount of KOH. The rate constants obtained by the two methods were in close agreement.

Measurements of pH were made with a Radiometer PHM4c pH meter employing a G200B glass electrode. Least squares analyses were performed on an I.B.M. 7094 computer.

Results

Neutral Hydrolysis of *p*-Nitrophenyl *p*-Nitrobenzoate.—The uncatalyzed rate of hydrolysis of *p*-nitrophenyl *p*-nitrobenzoate was measured at 25°, 33% CH$_3$CN, and ionic strength 0.3 in the the presence of added 0.001, 0.0015, and 0.002 *N* HCl. The rate of ester hydrolysis was unaffected by increasing concentration of acid and the average pseudo-first-order rate constant measured under these conditions was 1.154×10^{-5} min^{-1} with an average deviation from the mean of 0.018×10^{-5} min^{-1} (five determinations). Division by the molar concentration of water ($^2/_3 \times 55.5$ *M*) gives a second-order rate constant of 3.1×10^{-7} M^{-1} min^{-1} for this compound.

Rates of Alkaline Hydrolysis.—The observed half-lives corresponding to the uncatalyzed rates of hydrolysis of *p*-nitrophenyl *p*-nitrobenzoate were of the order of 1000 hr for this, the most reactive compound employed in this study. Since the slowest half-lives for any measured alkaline hydrolysis rate were *ca.* 2 hr, the neutral rates could be neglected by comparison. Therefore, the regression lines of k_{obsd} *vs.* [OH$^-$] were forced through the origin.[30] The rate constants for the alkaline hydrolyses determined in this manner and the associated standard errors for the 24 substituted phenylbenzoates are collected in Table I. The average value of the standard error is on the order of 2% of the second-order rate constant.

Since the uncatalyzed solvolysis rates were negligible, each value of k_{obsd} was divided by the hydroxide ion concentration and plotted as a function of the σ of the acyl group, holding the alcohol moiety constant. Five independent regression lines were thus generated (Figure 1). The σ values used were taken from the compilation of McDaniel and Brown[31] and are given in Table II. The values of ρ are given together with the standard errors and correlation coefficients as well as the intercepts of the lines at $\sigma = 0.0$ in Table III. There is no apparent tendency of the ρ values either to increase or to decrease as the p*K*′ of the phenol decreases. All of the ρ values are within two standard deviations from the mean value of 2.021, with the exception of that derived for the esters of unsubstituted phenol.

TABLE II

σ VALUES[a]

Substituent	σ
p-N(CH$_3$)$_2$[b]	−0.83
p-CH$_3$	−0.17
p-H	0.00
p-Cl	0.227
m-NO$_2$[c]	0.710
p-NO$_2$	0.778[d]

[a] Reference 31. [b] This substituent was present only in the acyl group. [c] This substituent was present only in the alcohol group. [d] Value used only for esters of *p*-nitrobenzoic acid. The σ value for *p*-nitrophenyl esters is discussed in the text.

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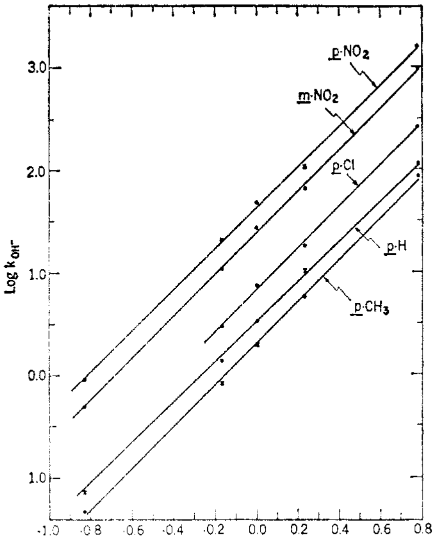

Figure 1.—Hammett plots for the alkaline hydrolysis of substituted phenyl benzoates. The particular phenyl derivative was fixed for each line as indicated, and log k_{OH^-} plotted as a function of the varying acyl σ value. Standard errors as indicated by the flags are taken from Table I. No flags are shown where the standard error is less than ±3%.

Table III

ρ Values for the Alkaline Hydrolysis of Acyl-Substituted Phenyl Benzoates

Alcohol	ρ	Intercept at σ = 0.0	Std error of ρ	Correlation coefficient	No. obsd	No. of compd
p-Methylphenol	2.032	0.328	0.013	0.999	60	5
Phenol	1.982	0.521	0.009	0.999	65	5
p-Chlorophenol	2.044	0.835	0.016	0.998	53	4
m-Nitrophenol	2.041	1.395	0.012	0.999	61	5
p-Nitrophenol	2.006	1.644	0.012	0.999	50	5

Caplow and Jencks[32] have previously studied the alkaline hydrolysis of *p*-nitrophenyl benzoates at 25° in 33% acetonitrile and ionic strength 1.0. Their reported ρ value of 2.04 is in excellent accord with that given in Table III.

Discussion

σ–ρ Plots Derived by Varying the Aryl Groups.—Figure 1 was constructed by varying the acyl moiety of each series of esters while holding the phenol derivative constant. The data could be plotted, alternatively, as a function of the σ of the aryl group while holding the acyl functions constant. It was observed, when this method was attempted, that the correlation coefficients were far poorer than those given in Table III. This was true even if the σ^- value of 1.27[3a] were used for the *p*-nitrophenyl group in place of 0.78. As σ^- values, with the exception of the *p*-nitrophenyl substituent, are virtually identical with the usual σ constants for the derivatives used in this study, it seemed reasonable to assume that the major cause of the poor correlation lay with the choice of σ for the *p*-nitrophenyl compounds. Bruice and Benkovic[33] have previously noted that much better Hammett plots for nucleophilic displacement reactions on substituted phenyl esters are obtained when a σ value of 1.0 is employed for the *p*-nitrophenyl group. Since the experiments reported here generated a relatively large amount of data for the reactions of a single nucleophile, hydroxide ion, a more quantitative approach to the problem of the best choice of σ for the *p*-nitrophenyl derivative became possible. In order to accomplish this the ordinary σ constants were assigned to all the aryl substituents except the *p*-nitro, and a computer program was written to assign a σ value to the *p*-nitrophenyl group which would meet the criterion that the sum of the sums of the squares of the deviations from all of the five lines (one generated by each acyl substituent) was at a minimum. No restraints were placed on the values of ρ. The final σ value of 0.89 represents that which best fits the data for all the alkaline hydrolysis rate constants reported here. The plots derived from this treatment are shown in Figure 2, and the values of ρ, intercepts at σ = 0, standard errors, and correlation coefficients for the lines are given in Table IV. The mean value of ρ for the five lines is 1.238, and the mean standard error is 0.013. The significance of the σ of 0.89 is considered below.

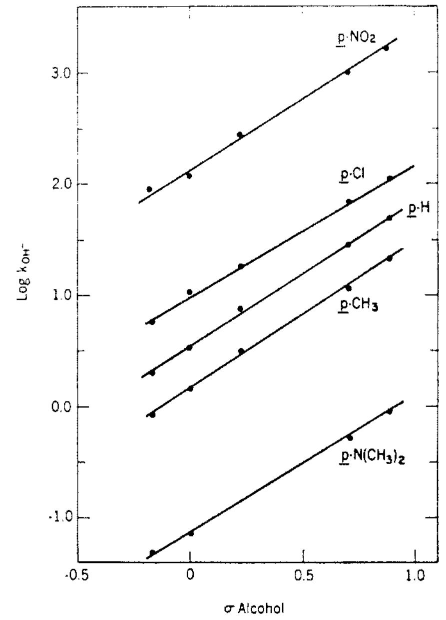

Figure 2.—Hammett plots as in Figure 1 but shown with constant acyl derivatives and varying alcohol. Standard errors are not indicated. The σ value used for the *p*-nitrophenyl esters is 0.89 (see text).

A comparison of the results reported in Table III and Table IV reveals that the rate of alkaline hydrolysis of an ester is far more sensitive to electron withdrawal in the acyl portion than in the alcohol. The earlier measurements of Tommila and Hinshelwood on the rates of alkaline hydrolysis of methyl benzoates and of phenyl acetates[9] also show a greater sensitivity to acyl than to aryl activation. Since the rate-determining step for these reactions almost certainly involves only the rate of addition of hydroxide ion to the acyl carbon atom[6] this greater sensitivity can be understood in terms of the reacting bond being one atom closer to the acyl substituent than it is to the alcohol. Taft and Lewis have shown empirically, from a consideration of substituent effects upon the dissociation constants of acids, that the transmission of elec-

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TABLE IV

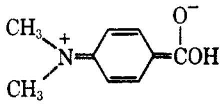
ρ VALUES FOR THE ALKALINE HYDROLYSIS OF ARYL-SUBSTITUTED PHENYL BENZOATES

Substituted benzoic acid	ρ	Intercept at σ = 0.0	Std error of ρ	Correlation coefficient[a]	No. obsd	No. of compd
p-Dimethylamino-	1.200	−1.112	0.010	0.999	36	4
p-Methyl-	1.278	0.170	0.014	0.997	44	5
p-H-	1.275	0.535	0.011	0.998	63	5
p-Chloro-	1.181	0.974	0.014	0.997	50	5
p-Nitro-	1.254	2.113	0.016	0.992	96	5

[a] The correlation coefficients have not been corrected for the reduction in the number of degrees of freedom caused by setting σ (*p*-NO_2) to 0.89.

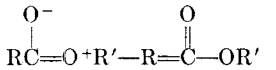
tronic effects through saturated atoms falls off according to the equation $\rho_I \cong (2.8 \pm 0.5)^{1-i}$ "where i = the number of saturated atoms between the benzene ring and the atom at which the unit decrease in formal charge takes place."[4]

The Significance of the Enhanced σ of the *p*-Nitro Substituent.—Apparent enhancements of the classical σ values frequently occur where direct resonance conjugation of a substituent with the reacting center is possible. Hammett suggested that a σ value of 1.27 be used for the *p*-nitro group when studying reactions of phenols or anilines.[34] The value of σ used for the *p*-$N(CH_3)_2$ derivative can be considered to be enhanced in a negative sense by the above criterion, since McDaniel and Brown[31] assigned the value of −0.83 to it on the basis of Johnston's data for the ionization of *p*-dimethylaminobenzoic acid,[35] where the undissociated acid would be expected to be stabilized to a greater degree than the anion by electron donation of the form



This resonance structure should contribute to the stability of the ground state in ester hydrolysis as well.

Van Bekkum, *et al.*, and Taft, *et al.*,[36] have persuasively demonstrated that the concept of a duality of σ values, particularly with respect to the *p*-nitro substituent, is a gross oversimplification and that a near continuum of values can be found, reflecting in the main differing resonance contributions to the ground-state–transition-state or ground-state product, free-energy differences for the various types of reactions investigated. The following two reasons may be suggested as explanations for enhanced σ values in the alkaline hydrolysis of esters, the first invoking ground-state destabilization and the second increased stability of the transition state. (1) Since the ground state of



$$\overset{O^-}{\overset{|}{R\text{C}}}{=}O^+R'—R{=}\overset{O}{\overset{\|}{\text{C}}}—OR'$$

esters is stabilized by resonance contributions of the type accounting for as much as 24 kcal/mole of resonance energy,[37] the electron-withdrawing *p*-nitrophenyl group should destabilize the ground state by cross-conjugation competition for the nonbonded electrons on the ether oxygen atom. (2) Any fractional negative charge residing on the ether oxygen in the transition state would be stabilized by electron withdrawal from the *p*-nitrophenyl substituent, the enhancement of σ being a measure of the degree of bond breaking between the acyl carbon atom and the departing oxygen atom. Neither of these resonance interactions is possible in the series of *para*- and *meta*-substituted benzoic acids originally used to define σ values. A plausible choice between the alternative explanations can be arrived at from a consideration of the most likely rate-determining step in the alkaline hydrolysis of esters. The fact that log k_{OH^-} is linearly related to the pK_a of the departing alcohols for all acetate esters ranging in reactivity from ethyl acetate to acetic anhydride provides good evidence for a common rate-determining step which in the case of hydroxide ion almost certainly represents the attack of the nucleophile upon the ester.[6] This conclusion along with the fact that tetrahedral addition intermediates have been demonstrated in many nucleophilic displacement reactions at acyl carbon[38] mitigates against the existence of a great deal of ether carbon–oxygen bond breaking in the transition state and leaves the first explanation, ground-state destabilization, as the more likely one to account for most of the observed enhancement in the σ value. Gerstein and Jencks have noted that the equilibrium addition of substituted phenolate ions to the acetylium ion is more sensitive to substituents than is the addition of a proton.[39] When the logarithms of the equilibrium constants for acetate ester formation were plotted against the pK_a's of the phenol, a line of slope 1.72 was obtained. This result cannot easily be explained by purely inductive effects, but rather may serve to emphasize the role of the nonbonded electrons on the ether oxygen in stabilizing the ground state. This result of Gerstein and Jencks can be rationalized if it is allowed that the addition of a proton requires only the free negative charge on the phenolate ion, but addition of an acylium ion demands, in addition, a contribution from the nonbonded electrons residing on the ether oxygen atom. This point further tends to emphasize the importance of the nonbonded electrons in stabilizing the ground state, and to strengthen the argument that the principal explanation for the enhanced σ of the *p*-nitrophenyl derivative is due to ground-state destabilization. This cross-conjugation effect apparently contributes even more noticeably to the instability of acetic anhydride.[40] Bruice and Benkovic have explained their observation of an improved correlation in nucleophilic displacements of phenolic esters when a σ value of 1.0 is used for the *p*-nitrophenyl derivative on the basis that attack at the acyl carbon atom requires the unconjugated σ value of 0.78, while expulsion of the alcohol requires that assigned to phenols, 1.27. In general, however, the rate-determining step will be one or the other, *i.e.*, either attack of hydroxide ion or expulsion of the

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(34) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p 188.

(35) J. Johnston, *Proc. Roy. Soc.* (London), **A78**, 82 (1906).

(36) (a) H. Van Bekkum, P. E. Verkade, and B. M. Wepster, *Rec. Trav. Chim.*, **78**, 815 (1959); (b) R. W. Taft, Jr., S. Ehrenson, I. C. Lewis, and R. E. Glick, *J. Am. Chem. Soc.*, **81**, 5352 (1959).

(37) L. Pauling, "The Nature of the Chemical Bond," 3rd ed, Cornell University Press, Ithaca, N. Y., 1960, p 275.

(38) (a) G. E. Lienhard and W. P. Jencks, *J. Am. Chem. Soc.*, **87**, 3855 (1965), and references therein; (b) L. R. Fedor and T. C. Bruice, *ibid.*, **87**, 4138 (1965); (c) G. L. Schmir and B. A. Cunningham, *ibid.*, **87**, 5692 (1965).

(39) J. Gerstein and W. P. Jencks, *ibid.*, **86**, 4655 (1964).

(40) W. P. Jencks, F. Barley, R. Barnett, and M. Gilchrist, *ibid.*, **88**, 4464 (1966).

alcohol, and the enhanced σ value should only be a function of the sensitivity of that single step to electron withdrawal by resonance; and in particular the rate-determining step in alkaline hydrolysis is almost certainly the attack (see above) of the nucleophile, and the value of σ giving the best fit for the *p*-nitrophenyl group is 0.89. It is further seen from the data collected by Bruice and Benkovic that the value of σ assigned to the *p*-nitrophenyl derivative is independent of nucleophile even though the rate-determining step progresses from being attack of the nucleophile in the case of hydroxide ion to a combination involving both formation and breakdown of the tetrahedral intermediates with imidazole[6] and with ammonia[10] as nucleophiles. Even intra- and intermolecular reactions of carboxylate ions are correlated best by this intermediate value. Only intramolecular nucleophilic displacements of phenyl esters by carboxylate ions are known,[41] and the slow step for these reactions is almost certainly the rate of breakdown of the tetrahedral intermediate. The bimolecular pathway proceeds predominantly through classical general base catalysis.[42]

The constancy of the best choice of σ values for *p*-nitrophenyl derivatives for reactions that proceed with different rate-determining steps and even different mechanisms further supports the hypothesis that the primary explanation for enhanced σ values in nucleophilic reactions of esters is ground state destabilization of the ester. The above arguments are based on a reaction mechanism involving a tetrahedral intermediate, but would also apply if the reactions involved concerted displacements with asymmetric transition states.[6] More recently Ryan and Humffray[43] have measured the rates of alkaline hydrolysis of a series of substituted phenyl acetates which included a number of substituents with σ^- not equal to σ and obtained a good Hammett plot using a modification of the equation proposed by Yukawa and Tsuno which allows a variable amount of mixing of enhanced and normal σ values depending on the reaction.[44]

The destabilization energy of the *p*-nitrophenyl group can be estimated from the equation of Van Bekkum, *et al.*[36a] (eq 2), where $\sigma - \sigma^n$ is equal to 0.89–0.78 or 0.11. The value obtained for $-\Delta\Delta F$ is -180 cal/mole, which may be compared with a typical free energy of activation of -17 kcal/mole.[45]

$$-\Delta\Delta F = 2.303RT\rho(\sigma - \sigma^n) \qquad (2)$$

Selectivity–Reactivity Considerations.—The σ–ρ plots shown in Figures 1 and 2 are excellent approximations to straight lines. If the alkaline hydrolysis rates for increasingly reactive esters approach the diffusion control limit[46] of approximately 10^{12} M^{-1} min^{-1}, the slope of the Hammett plots would at that point decrease to 0. This rate would be reached for a *p*-nitrophenyl ester if the acyl substituent had a σ value greater than or equal to 5.4, assuming the ρ of 2.0 is maintained up to this point. No evidence exists at present to indicate whether or not this slope would exhibit a gradual curvature approaching a horizontal line as the diffusion control limit is approached. It is interesting to note in this connection that the Hammett equation is followed in reactions of the hydrated electron with substituted aromatic nuclei where this limit is nearly attained.[47] Eigen and his coworkers have found that the change from $\alpha = 1$ to $\alpha = 0$ in the Brønsted equation is usually fairly sharp when there is no major electronic or spatial molecular rearrangement accompanying the proton transfer, but the change may be quite gradual, occurring over a variation of many p*K* units in the catalyzing acid or base when the converse is true.[48]

Cordes and Jencks, *et al.*,[49,50] have proposed a series of equations based on the Hammett, Brønsted, and Swain–Scott relationships for correlating multiple-structure reactivity series. In the case at hand their treatment would give

$$\frac{\log k_1 - \log k_2}{\rho_1 - \rho_2} = C \qquad (3)$$

where the log k terms refer to the alkaline hydrolysis rates for two substituted phenyl esters sharing a common acyl group, the ρ values are generated by varying the acyl portion of the ester while holding the alcohol moieties constant and C is a constant. It can be concluded from the data presented in Table III that a trend representing a decrease in ρ, representing a decreasing substrate selectivity by hydroxide ion, of approximately 0.05 in proceeding from *p*-tolyl to *p*-nitrophenyl esters would have been detected. The absence of such a trend indicates that C is greater than 25 for these reactions. Similar reasoning based on the data in Table IV leads to the conclusion that C must be greater than 50, both results emphasizing the insensitivity of the ρ values to the reactivity of the esters over the range studied.

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[41] (a) E. Gaetjens and H. Morawetz, *J. Am. Chem. Soc.*, **82**, 5328 (1960); (b) J. W. Thanassi and T. C. Bruice, *ibid.*, **88**, 747 (1966).

[42] A. R. Butler and V. Gold, *J. Chem. Soc.*, 1334 (1962).

[43] J. J. Ryan and A. A. Humffray, *J. Chem. Soc., Sect. B*, 842 (1966).

[44] Y. Yukawa and Y. Tsuno, *Bull. Soc. Chem. Japan*, **32**, 965, 971 (1959).

[45] Obtained from the equation $\Delta F^* = -2.303 \log k_B T/hk_r$. See A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1961, pp 98, 99). Calculated for 1 M hydroxide ion, $T = 25°$, and a pseudo-first-order rate constant of 100 min^{-1}.

[46] E. F. Caldin, "Fast Reactions in Solution," John Wiley and Sons, Inc., New York, N. Y., 1964, pp 10–13.

[47] M. Anbar and E. J. Hart, *J. Am. Chem. Soc.*, **86**, 5633 (1964).

[48] M. Eigen, *Angew. Chem. Intern. Ed. Engl.*, **3**, 1 (1964).

[49] E. H. Cordes and W. P. Jencks, *J. Am. Chem. Soc.*, **84**, 4319 (1962).

[50] L. do Amaral, W. A. Sandstrom, and E. H. Cordes, *ibid.*, **88**, 2225 (1966).