The ethereal distillate was analyzed using an Autoprep Mode A-700 glpc apparatus with a 20-m SE/30 column operating at 80°. Two major fractions were obtained and were identified as ether and benzene. The proportion of benzene to ether was determined by comparison of the peak areas with those of known mixtures of benzene and ether.

The quantity of benzene already present in the phenylmagnesium bromide solution used was determined similarly. The quantity of benzene produced in the reaction was then calculated and was found to be 0.28 g, 3.6 mmoles

Experiment 2. Methyl chloromethylphosphinate (1.3 g, 10.1 mmoles) in ether (10 ml) was slowly added to a solution of phenylmagnesium bromide in ether (20 ml of 3 *N* solution). The ether was distilled off and the residue was decomposed with D_2O (40 ml). Methyldiphenylphosphine oxide was isolated by the usual method. Benzene (0.29 g, 3.8 mmoles) was identified in the ethereal distillate.

Experiment 3. A sample of pure methyldiphenylphosphine oxide (1.5 g) in ether (50 ml) was added to phenylmagnesium bromide solution (20 ml of 3 *N* solution). The ether was evaporated off and the residue was hydrolyzed with D_2O (40 ml); the methyldiphenylphosphine oxide was isolated by the usual procedure.

The amount of deuterium incorporated in the methyldiphenylphosphine oxide obtained from experiments 1, 2, and 3 was determined by ^{1}H nmr spectroscopy. The results are summarized in Table I.

Secondary Valence Force Catalysis. III. The Apparent Abnormal Reactivity of Anionic Nucleophilic Reagents toward Acyl-Activated Esters[1,2]

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Contribution No. 1395 from the Department of Chemistry, Indiana University, Bloomington, Indiana. *Received February 26, 1966*

Abstract: Second-order rate constants for reaction of a variety of charged and uncharged nucleophilic reagents with *p*-nitrophenyl chloroacetate, phenyl dichloroacetate, and 2,4-dinitrophenyl acetate have been measured in water at 25° and ionic strength 1.0. The Brønsted plot for the last substrate qualitatively resembles that for *p*-nitrophenyl acetate while those for the first two substrates are reminiscent of that for acetylimidazolium ion. That is, anions are abnormally reactive, compared to a series of uncharged amines, toward esters possessing an electron-withdrawing substituent in the acyl portion of the molecule. This finding is *tentatively* ascribed to electrostatic stabilization of the transition state resulting from ion–dipole or dipole–dipole interactions between acyl-activated substrate and anionic nucleophilic reagent.

An increase in the rate of an organic reaction resulting from noncovalent interactions between two reactants or a reactant and a catalyst is termed secondary valence force catalysis. Weak interactions may influence rates either by serving to approximate and orient appropriate reacting groups, largely an entropy effect, or by directly affecting ground and/or transition state stabilities, largely an enthalpy effect. Rather little attention has been directed toward examination of rate alterations which result from weak interactions. Available evidence does indicate that rather substantial rate effects may result from charge transfer interactions,[4–6] London dispersion forces,[7] and electrostatic effects. Many pertinent cases have been compiled and critically reviewed by Jencks.[8]

Of particular relevance to the present communication are those examples of secondary valence force catalysis that involve electrostatic interactions. A number of studies has revealed that the incorporation of substrates into or onto micelles formed from ionic detergents frequently results in considerable rate accelerations or retardations.[9–13] Similarly, the effects of certain organic anions, cations, and detergent salts on the rate of reaction of methyl 1-naphthoate with hydroxide ion apparently result from electrostatic factors.[14] Such effects may also account for the abnormal reactivity of anions toward acetylimidazolium ion[15] and for the abnormal reactivity of cationic nucleophilic reagents toward the *p*-nitrophenyl phosphate dianion,[16] isopropyl methylphosphonofluoridate,[17] and the *o*-nitrophenyl oxalate anion.[18] Finally, it has been argued that the rates of reaction of anionic nucleophilic reagents with *ortho*-substituted phenacyl chlorides are augmented by ion–dipole interactions in the transition state.[19]

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(1) Supported by Grant AM 08232 from the National Institutes of Health.

(2) For paper II in this series, see M. T. A. Behme, J. G. Fullington, R. Noel, and E. H. Cordes, *J. Am. Chem. Soc.*, 87, 266 (1965).

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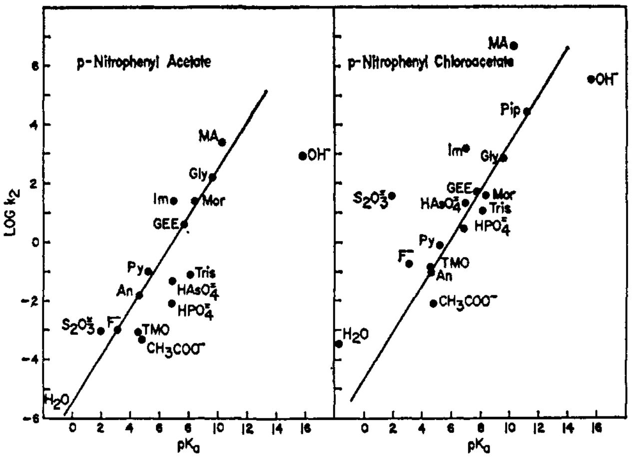

Figure 1. Brønsted plots for reaction of *p*-nitrophenyl chloroacetate and *p*-nitrophenyl acetate with a series of nucleophilic reagents in aqueous solution at 25°. Data for the latter plot have been taken from the compilation in ref 15. The abbreviations employed are defined in Table I.

Weak interactions between enzyme and substrate certainly occur in the course of enzyme-catalyzed reactions and it has frequently been suggested that such interactions are responsible for an appreciable fraction of the over-all catalytic effect.[8] In an effort to provide additional information regarding the susceptibility of organic reactions to secondary valence force catalysis and, ultimately, to assess the role of such catalysis in enzymatic processes, we have initiated a general series of studies in this field. This manuscript reports the apparent abnormal reactivity of anionic nucleophilic reagents toward acyl-activated esters.

Experimental Section

Materials. *p*-Nitrophenyl chloroacetate was synthesized by the dropwise addition of 4.05 ml of pyridine to a stirred solution of 5.0 g of *p*-nitrophenol and 5.65 g of chloroacetyl chloride dissolved in 65 ml of dry ether. Following completion of the addition, the mixture was refluxed for 30 min. The pyridinium chloride was removed by filtration, the filtrate was evaporated, and the residue was recrystallized from benzene, mp 95–97° (lit.[20] mp 97–98°). Phenyl dichloroacetate was synthesized by the dropwise addition of 4.05 ml of pyridine to a stirred solution of 3.5 g of phenol and 7.5 g of dichloroacetyl chloride in 65 ml of ether cooled in an ice–salt bath. The reaction was permitted to proceed in the cold for 1 hr and filtered, and the solvent was removed under reduced pressure. The residue was recrystallized three times from *n*-hexane, mp 45–47°. Phenyl acetate and 2,4-dinitrophenyl acetate were synthesized from the appropriate phenol and acetic anhydride according to the procedure of Bender and Nakamura.[21] Trimethylamine N-oxide hydrochloride was prepared according to a published procedure.[22] Other materials were obtained commercially and, with the exception of reagent grade inorganic salts and mercaptoacetaic acid, were recrystallized or redistilled prior to use. Distilled water was employed throughout.

Kinetic measurements were carried out spectrophotometrically with a Zeiss PMQ II spectrophotometer equipped with a thermostated cell compartment as described by Jencks and Carriuolo.[15] In each case, the reaction was followed by observing the appearance of the appropriate phenol or phenolate ion. For relatively rapid reactions, half-times of 1 hr or less, the reactions were conducted directly in silica cells housed within the cell compartment of the spectrophotometer. For slower reactions, the reaction mixtures were maintained in a thermostated water bath and the optical density was determined with aliquots at appropriate time intervals. In all cases, the reactions were initiated by the addition of $^1/_{30}$ volume of ester dissolved in ethanol or acetonitrile. Thus, the reaction mixtures contained about 3% organic solvent. Second-order rate constants were evaluated from the slopes of plots of first-order rate constants against the concentration of nucleophilic reagent in the reactive form. In all cases, good straight lines were obtained. No evidence was found for general acid–base catalysis in any of the reactions. Where possible, pH was maintained by employing the nucleophilic reagent and its conjugate acid as the buffer system; in other cases an appropriate dilute buffer was added to the system. Values of pH were measured with a glass electrode and a Radiometer Model 4c pH meter. All reactions were carried out at 25° and, except where noted, at an ionic strength of 1.0, maintained with KCl.

Results

Second-order rate constants for reaction of 17 nucleophilic reagents with *p*-nitrophenyl chloroacetate in aqueous solution are collected in Table I. These data are presented schematically in Figure 1 in which each of these rate constants is plotted against the pK_a in water of the corresponding conjugate acid. For the sake of comparison, a similar plot has been included in this figure for reaction of the same nucleophilic reagents with *p*-nitrophenyl acetate. Data for the latter Brønsted plot has been collected from the extensive compilation of Jencks and Carriuolo.[15] In each case a line of slope 0.8 has been drawn through points for several typical amines. Examination of Figure 1 reveals that the two Brønsted plots are quite distinct in the respect that

Table I. Second-Order Rate Constants for the Reaction of a Series of Nucleophilic Reagents with *p*-Nitrophenyl Chloroacetate in Aqueous Solution at 25° and Ionic Strength 1.0

Nucleophilic reagent	pK_a[a]	pH	Concn range, M	k_2, M^{-1} min^{-1}
Water[b]	−1.74	1.3, 3.0	55	3.6×10^{-4}
Fluoride[c]	3.17	7.2	0.2–0.8	0.17
Acetate	4.76	5.3	0.2–1.0	0.0086
Phosphate	6.9	6.9	0.01–0.05	2.8
Aniline[d] (An)	4.62	4.7	0.06–0.30	0.099
Pyridine[d] (Py)	5.14	5.4	0.02–0.40	0.81
Glycine ethyl ester (GEE)	7.75	6.8	0.005–0.5	50
Imidazole[d,e] (Im)	6.95	4.8	0.1–0.5	1700
		7.0	0.001–0.004	1500
Glycine[d,f] (Gly)	9.76	7.6	0.004–0.08	720
Morpholine[d] (Mor)	8.36	7.4	0.01–0.20	44
Piperidine[g] (Pip)	11.22	7.2	0.005–0.25	28500
Tris(hydroxymethyl)aminomethane (Tris)	8.1	8.3	0.05–0.80	11
Mercaptoacetate[h] (MA)	10.3	7.1	0.0002–0.001	4.9×10^6
Arsenate	6.98	7.2	0.004–0.04	23
Thiosulfate[i]	1.9	7.2	0.002–0.02	40
Trimethylamine N-oxide (TMO)	4.6	4.9	0.02–0.16	0.18
Hydroxide[j]	15.74	6.97–8.54		3.55×10^5

[a] Of the conjugate acid. [b] Measured in dilute solutions of hydrochloric acid. [c] Carried out in 0.02 M phosphate buffer. [d] Ionic strength 0.50 [e] Carried out in 0.06 M acetate buffer. [f] Unbuffered medium. [g] Carried out in 0.05 M phosphate buffer. [h] Carried out in 0.01 M phosphate buffer. [i] Carried out in 0.02 M phosphate buffer. [j] Carried out in 0.01 M triethanolamine buffer.

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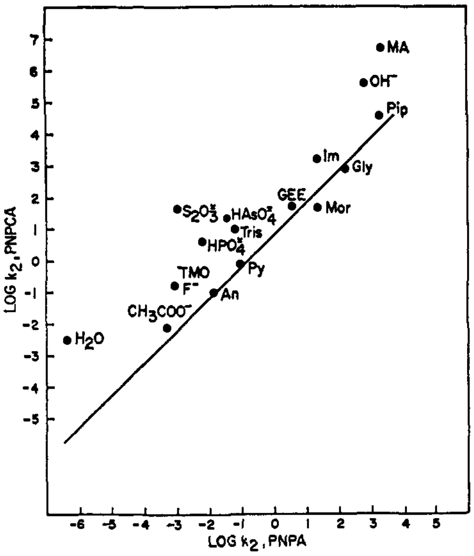

Figure 2. A double logarithmic plot of second-order rate constants for reaction of *p*-nitrophenyl chloroacetate and *p*-nitrophenyl acetate with a series of nucleophilic reagents in aqueous solution at 25°. The abbreviations employed are defined in Table I.

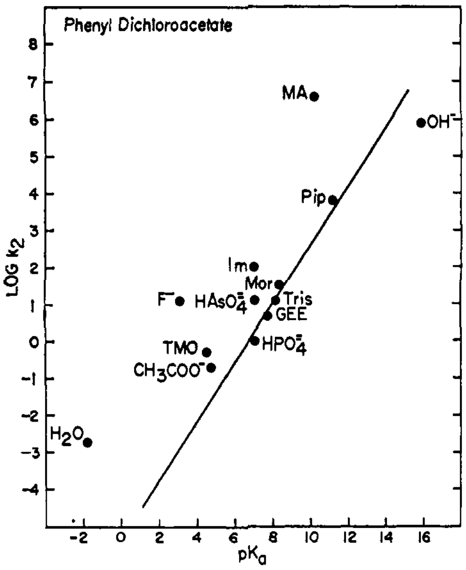

Figure 3. A Brønsted plot for reaction of phenyl dichloroacetate with a series of nucleophilic reagents in aqueous solution at 25°. Abbreviations employed are defined in Table II.

nucleophilic reagents which react as anions are relatively more reactive toward the chloroacetate compared to the acetate. Note, for example, the relative positions of thiosulfate, phosphate, mercaptoacetate, and hydroxide ion in the two plots. The Brønsted plot for *p*-nitrophenyl chloroacetate is strongly reminiscent of that for acetylimidazolium ion as regards the relative positions of anionic and uncharged nucleophilic reagents.[15] In the latter case, the abnormal reactivity of anions has been attributed to electrostatic interactions between substrate and nucleophilic reagent. We develop a related thesis to account for the present results below.

The relative reactivity of anions and neutral molecules toward the *p*-nitrophenyl esters of acetic and chloroacetic acids is most readily illustrated in the form of a double logarithmic plot as indicated in Figure 2. A straight line of unit slope in this plot passes through or near most of the points for amines although those for imidazole and tris(hydroxymethyl)aminomethane fall somewhat above this line. In contrast, all of the points, with but a single exception, for nucleophilic reagents which react as anions fall one to four orders of magnitude above this line as does the point for water. The single exception, acetate, may be accounted for in terms of the function of this species as a general base catalyst for the attack of water rather than as a nucleophilic reagent.[23]

Second-order rate constants for reaction of a series of 13 nucleophilic reagents with phenyl dichloroacetate in aqueous solution are collected in Table II. For the most part, these reagents are the same as those studied with *p*-nitrophenyl chloroacetate. The data of Table II are presented in the form of a Brønsted plot in Figure 3 in which a straight line of slope 0.8 has been drawn through the points for several amines. This Brønsted plot closely resembles those for *p*-nitrophenyl chloroacetate and acetylimidazolium ion and is distinct from that for *p*-nitrophenyl acetate. Thus, the point for fluoride, which is on the line in the plot for the acetate, is nearly four orders of magnitude above the line in the plot for the dichloroacetate. Similar behavior is noted for the remainder of the anions as well. In addition, water and tris(hydroxymethyl)aminomethane are unexpectedly reactive toward the dichloroacetate as in the case of the chloroacetate.

Table II. Second-Order Rate Constants for Reaction of a Series of Nucleophilic Reagents with Phenyl Dichloroacetate in Aqueous Solution at 25° and Ionic Strength 1.0

Nucleophilic reagent	pK_a[a]	pH	Concn range, M	k_2, M^{-1} min^{-1}
Water[b]	−1.74	1.0, 3.0	55	1.9×10^{-3}
Fluoride[c]	3.1	7.3	0.004–0.04	14
Acetate	4.76	5.2	0.02–1.0	0.19
Phosphate	6.9	7.1	0.05–0.5	0.91
Arsenate	6.98	7.2	0.004–0.04	14
Glycine ethyl ester[d] (GEE)	7.75	7.3	0.1–0.5	5.1
Imidazole[d] (Im)	6.95	7.3	0.005–0.20	97
Morpholine (Mor)	8.36	8.8	0.025–0.25	31
Piperidine[d,e] (Pip)	11.22	6.6	0.005–0.25	6700
Tris(hydroxylmethyl) aminomethane (Tris)	8.1	7.7	0.05–0.8	13
Mercaptoacetate[f] (MA)	10.3	7.2	0.0002–0.001	4.1×10^{6}
Trimethylamine N-oxide (TMO)	4.6	4.9	0.02–0.16	0.50
Hydroxide[g]	15.74	7.0–8.5		7.7×10^{5}

[a] Of the conjugate acid. [b] Carried out in dilute solutions of hydrochloric acid. [c] Carried out in 0.02 M phosphate buffer. [d] Ionic strength 0.50 M. [e] Carried out in 0.05 M phosphate buffer. [f] Carried out in 0.01 M phosphate buffer. [g] Carried out in 0.01 M triethanolamine buffer.

In Table III, second-order rate constants for reaction of ten nucleophilic reagents with 2,4-dinitrophenyl acetate in aqueous solution are collected and these data are presented in the form of a Brønsted plot in Figure 4.

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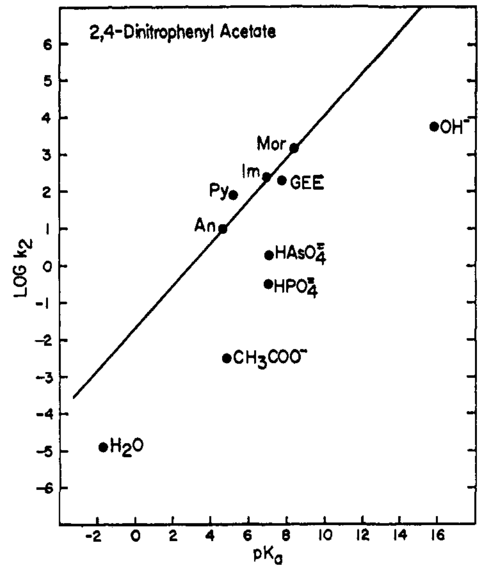


Figure 4. A Brønsted plot for reaction of 2,4-dinitrophenyl acetate with a series of nucleophilic reagents in aqueous solution at 25°. Abbreviations employed are defined in Table III.

The best straight line through the points for the uncharged amines has a slope of 0.6, somewhat less than those for the plots previously discussed. The qualitative conclusions to be drawn from this plot are not appreciably dependent on the slope of this line. Examination of this Brønsted plot reveals that the position for the points for anions with respect to the line drawn through the points for the amines resembles that for *p*-nitrophenyl acetate and is distinct from that for the acyl-activated esters. Thus arsenate and phosphate, for example, fall well below the line in this Brønsted plot rather than on or above the line.

Table III. Second-Order Rate Constants for Reaction of a Series of Nucleophilic Reagents with 2,4-Dinitrophenyl Acetate in Aqueous Solution at 25° and Ionic Strength 1.0

Nucleophilic Reagent	pK_a[a]	pH	Concn range, M	k_2, M^{-1} min^{-1}
Water[b]	−1.74	4.6	55	1.2×10^{-5}
Acetate	4.76	4.6	0.2–1.0	0.028
Phosphate	6.9	6.6	0.001–0.03	0.28
Arsenate	6.98	6.4	0.004–0.08	1.8
Aniline (An)	4.6	4.8	0.02–0.10	9.9
Pyridine (Py)	5.17	5.4	0.001–0.05	90
Glycine ethyl ester (GEE)	7.75	7.2	0.001–0.005	190
Imidazole (Im)	6.95	7.2	0.001–0.02	240
Morpholine (Mor)	8.36	8.0	0.0005–0.005	1700
Hydroxide[c]	15.74	8.6		5640

[a] Of the conjugate acid. [b] Value obtained from the intercept of a plot of first-order rate constants against the concentration of a series of dilute acetate buffers. [c] Measured in dilute solutions of triethanolamine buffers.

The qualitative distinctions inferred from examination of Figures 1 through 4 receive a quantitative statement in Table IV. In this table, values of log $(k_{\text{ester}}/k_{\text{PNPA}})_{\text{N}} - \log (k_{\text{ester}}/k_{\text{PNPA}})_{\text{GEE}}$ are presented for each of the nucleophilic reagents and esters studied. In this expression, ester refers to each substrate, PNPA to *p*-nitrophenyl acetate, N to the nucleophilic reagents, and GEE to glycine ethyl ester. The first term in this expression simply gives the relative reactivity of "ester" and *p*-nitrophenyl acetate toward N and the second term gives the same quantity with N specifically chosen as glycine ethyl ester, a substrate for which abnormal behavior was not observed. Thus, the entire expression yields a quantitative measure for abnormal reactivity of N toward "ester" as compared with *p*-nitrophenyl acetate. Thus, the entry of 2.32 for reaction of mercaptoacetate with *p*-nitrophenyl chloroacetate simply means that this nucleophilic reagent is $10^{2.32} = 210$ times as reactive toward this ester as would have been predicted from (a) its reactivity toward *p*-nitrophenyl acetate, and (b) the relative reactivities of these two esters toward glycine ethyl ester.

Table IV. A Quantitative Summary of Relative Reactivities of Neutral and Anionic Nucleophilic Reagents toward Esters[a]

Nucleophilic reagent	$\log\left(\frac{k_{\text{ester}}}{k_{\text{PNPA}}}\right)_{\text{N}} - \log\left(\frac{k_{\text{ester}}}{k_{\text{PNPA}}}\right)_{\text{GEE}}$		
	PNPCA	PDCA	DNPA
Aniline	−0.15		0.27
Pyridine	−0.06	0.61	1.40
Glycine ethyl ester	0.00	0.00	0.00
Glycine	−0.21		
Morpholine	−0.74	0.12	0.28
Piperidine	0.26		
Imidazole	0.84	0.61	−0.57
Tris(hydroxymethyl)-aminomethane	1.23	2.29	
Acetate	0.26	2.59	0.19
Fluoride	1.26	4.17	
Phosphate	1.61	2.11	0.03
Arsenate	1.79	2.53	0.09
Thiosulfate	3.59		
Trimethylamine N-oxide	1.34	2.77	
Hydroxide	1.63	2.96	−0.74
Mercaptoacetate	2.32	3.23	−0.25
Water	1.81	3.52	

[a] Abbreviations: PNPA, *p*-nitrophenyl acetate; PNPCA, *p*-nitrophenyl chloroacetate; PDCA, phenyl dichloroacetate; DNPA, 2,4-dinitrophenyl acetate.

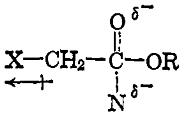
Discussion

Previously published data reveals that the Brønsted plots for reaction of nucleophilic reagents with *p*-nitrophenyl acetate and acetylimidazolium are distinct as a result of the fact that anionic species are relatively more reactive toward the latter compound, a finding rationalized on the basis of electrostatic interactions between such reagents and the positively charged substrate.[15] The principal experimental finding reported herein is directly related to this observation; that is, 2,4-dinitrophenyl acetate exhibits a Brønsted plot similar to that for *p*-nitrophenyl acetate while *p*-nitrophenyl chloroacetate and phenyl dichloroacetate exhibit plots similar to that of acetylimidazolium ion. The abnormal reactivity of anions toward the acyl-activated esters seems to primarily reflect just the fact that they are anions and is not dependent on their basicity, polarizability, or reactivity toward *p*-nitrophenyl acetate. Prior to examining possible explanations for these observations, a few comments regarding the comparability of Brønsted plots are in order.

Provided a sufficiently broad spectrum of nucleophilic reagents is investigated, Brønsted plots for esters with different leaving groups are certain to exhibit differences in detail. This conclusion follows directly from two considerations. First, the nature of the rate-determining step for certain nucleophilic reagents may change from formation to decomposition of the tetrahedral intermediate as the nature of the leaving group is altered.[24] Since those factors which influence reactivity are likely to be a function of the rate-determining step, such a transition in the rate-determining step would alter the relative reactivities of nucleophilic reagents toward different esters. Second, the fact that the Hammett ρ values for nucleophilic reactions with a series of phenyl acetates are a function of the nature of the nucleophilic reagent[25] requires that different reagents exhibit distinct relative reactivities toward various phenyl acetates. In consequence, the most satisfactory evidence for abnormal reactivity due to weak interactions comes from comparison of the data for the *p*-nitrophenyl esters of acetic and chloroacetic acids (Figures 1 and 2). For this pair of substrates, the reservations noted above do not, of course, apply. Thus, attention is focused primarily on the pair of *p*-nitrophenyl esters, keeping in mind that the data for the other substrates are consistent with and support the arguments developed below and suggests their generality.

Those factors which affect nucleophilic reactivity toward esters and thus account for the character of the individual Brønsted plots have been discussed in detail by Jencks and Carriuolo[15] and by Bruice and Lapinski.[26] We are not so much interested in the individual cases themselves as in the distinctions between them noted above. That the relative reactivities of a series of nucleophilic reagents is a function of the substrate toward which they are measured has been recognized for several years. The present results do emphasize that minor changes in substrate structure can markedly influence the order of nucleophilicity. Thus, toward *p*-nitrophenyl acetate we have the order fluoride < phosphate dianion < aniline < pyridine while toward the corresponding chloroacetate we have aniline < fluoride < pyridine < phosphate dianion. Bunnett,[27] Hudson,[28] and Edwards and Pearson[29] have proposed explanations to account for the influence of the substrate in establishing orders of nucleophilic reactivity. Two factors appear to be of particular relevance to the present case. First, Edwards and Pearson have argued that the negative potential at the nucleophilic center may be of particular importance in determining nucleophilicity toward those substrates which possess a high positive charge at the atom upon which attack occurs.[29] Thus we might interpret the heightened reactivity of anions toward acyl-activated esters as reflecting enhanced electrostatic interactions between nucleophilic reagent and substrate in the transition state. In terms of this explanation, it is somewhat surprising that anions are not abnormally reactive toward 2,4-dinitrophenyl acetate compared to *p*-nitrophenyl acetate since, naively, the degree of carbonium ion character at the acyl carbon atom should largely be a function of the reactivity of the ester. Thus anions would be expected to react abnormally rapidly with any particularly reactive ester and not only with those which are activated in the acyl moiety. It is difficult to arrive at a clear-cut conclusion, however, since the transition state structure, upon which interactions of the sort under consideration will depend, may vary somewhat from substrate to substrate.

Second, the abnormal reactivity of anions toward acyl-activated esters may be accounted for in terms of ion–dipole or dipole–dipole interactions, depending on the nature of the nucleophilic reagent, between substrate and nucleophile. Such interactions have been alluded to by Bunnett.[27] As depicted below, the transition state for attack of anionic species on acyl-activated esters (I) involves an attractive interaction between the partial negative charge on the attacking atom and the C–Cl dipole while the corresponding interaction is repulsive for the case of an uncharged nucleophilic reagent (II). Thus the transition state for reactions involving anions will be stabilized relative to those involving uncharged species by the presence of a properly oriented dipole in the acyl moiety. Substantially the same conclusion is reached provided decomposition of the tetrahedral intermediate is rate determining; compare transition states III and IV. In terms of this explanation, one might have expected that rather larger effects would have been observed with the dichloroacetate compared to the chloroacetate. Again, ion–dipole interactions of the sort envisaged will depend in a sensitive fashion on the geometry of the transition state. Lack of precise knowledge of transition state geometries precludes a sophisticated analysis of the data.



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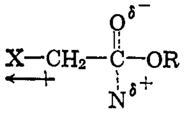

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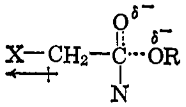
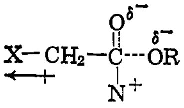


$\underset{\longleftarrow\!+}{X-CH_2}-\underset{\underset{N}{|}}{\overset{\overset{O^{\delta-}}{\|}}{C}}\cdots\overset{\delta-}{OR}$

III



$\underset{\longleftarrow\!+}{X-CH_2}-\underset{\underset{N^{+}}{|}}{\overset{\overset{O^{\delta-}}{\|}}{C}}\cdots\overset{\delta-}{OR}$

IV

No ready explanation is available to account for the abnormally rapid uncatalyzed hydrolysis of acyl-activated esters.

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