position of the band is less sensitive to the amount of 1,2-dimethoxyethane when there is a substantial amount present. It is concluded that local environmental factors play an important role in determining the energy of the visible transition of the ketyl ion pairs.

Solvent Polarity.—It is possible that the ketyl spectral shifts reflect solvent properties to a greater extent than solute properties or properties which depend on both solvent and solute (such as the degree of solute–solvent steric interaction). If this should be the case, these spectral variations might have value as measures of the "polarity" of ethereal solvents toward ionic or ionoid species, particularly organometallic compounds. In order to be empirically useful and possibly theoretically significant, such a measure of polarity would have to be shown to correlate, qualitatively or quantitatively, with other chemical phenomena dependent on the same kind of "polarity." The fact that spectral shifts in another solvent dependent system have been successful in correlating spectra and reaction parameters

in a wide range of solvents is justification for seeking a similar application of the present results.[55] Moreover, it is possible that deviations from otherwise consistent correlational behavior may be significant in establishing the details of theories related to ionic aggregation and ethereal solvent effects in organometallic systems.

Data against which to make quantitative tests of correlations are not plentiful, but those which are available are, for the most part, consistent, and will be discussed in detail later.
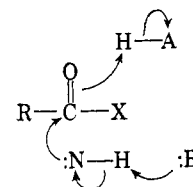

The Compensation in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ Accompanying the Conversion of Lower Order Nucleophilic Displacement Reactions to Higher Order Catalytic Processes. The Temperature Dependence of the Hydrazinolysis and Imidazole-Catalyzed Hydrolysis of Substituted Phenyl Acetates

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The hydrazinolysis and imidazole-catalyzed hydrolysis of a series of substituted phenyl acetates were found to be dependent on the concentration of the conjugate acid and base species of the nitrogen bases in the following manner: $-\mathrm{d}(\text{ester})/\mathrm{d}t = [k_n(\mathrm{H_2NNH_2}) + k_{gb}(\mathrm{H_2NNH_2})^2 + k_{ga}(\mathrm{H_2NNH_2})(\mathrm{H_2NNH_3^{\oplus}})](\text{ester})$ and $-\mathrm{d}(\text{ester})/\mathrm{d}t = [k_n(\mathrm{C_3H_4N_2}) + k_{gb}(\mathrm{C_3H_4N_2})^2](\text{ester})$, respectively. The terms k_n are second-order rate constants for nucleophilic displacement at the ester bond, and the k_{gb} and k_{ga} terms are third-order rate constants for general-base and general-acid assisted nucleophilic displacement reactions at the ester bond. The $k_n - \rho$ value for hydrazine is considerably greater than that for ammonia, so that the α-effect is greatest with the best leaving group. Also, the α-effect is of greater importance in k_{gb} and in k_{ga} than in k_n. The ρ-values for the k_{gb} and k_{ga} terms are very much smaller than those for the k_n terms, as previously found for general base-catalyzed ammonolysis reactions. The consistent finding that the ρ-values for the third-order, generally assisted reactions are always much less than the ρ-values for the simple unassisted bimolecular reactions has the result that the assisted reactions are always of much greater importance for nucleophilic displacement reactions on esters with poorer leaving groups. The k_{gb} term for hydrazine, as previously found for ammonia, exhibits no deuterium solvent kinetic isotope effect; however, the k_{gb} term for imidazole does. Unlike the k_{gb} term, the k_{ga} term for hydrazine does exhibit a deuterium solvent isotope effect. The $\Delta H^{\ddagger}$ for the k_n term does not appear to be simply related to the nature of the nucleophile nor the substituent on the phenyl ester. With change in the electronic nature of substituent groups on the ester, the $T\Delta S^{\ddagger}$ term may follow a consistent pattern of decrease, of increase, or a random variation. The electronic effects on $T\Delta S^{\ddagger}$ may be considered to be secondary perturbations of that value determined by the nucleophile and the kinetic order of the reaction. By averaging the $T\Delta S^{\ddagger}$ values for the series of esters for a particular term ($i.e.$, k_n, k_{gb}, or k_{ga}) with a particular nucleophile, the electronic effects of substituent groups may be compensated for. The kinetic order of the reaction when multiplied by 5 ± 1 kcal. mole^{-1} provides in each case (eleven reactions) the value of $T\Delta S^{\ddagger}_{av}$. This result is discussed on the basis of the arbitrary division of $T\Delta S^{\ddagger}$ into a component ($T\Delta S^{\ddagger}_{t.r.}$) determined by the number of species which must be brought to a position of close approach in order to enter the transition state and a component ($T\Delta S^{\ddagger}_{e}$) which relates to the kinetic energy terms in taking the reactants from a position of close approach to the transition state. The expected lowering of $\Delta H^{\ddagger}$ and $T\Delta S^{\ddagger}$ accompanying the conversion of a lower order displacement reaction to a higher order catalytic process has been examined. The values of $\Delta H^{\ddagger}$ and $T\Delta S^{\ddagger}$ for k_n, k_{gb}, and k_{ga} for the hydrazinolysis reactions are found to behave in a compensatory manner so that $\Delta F^{\ddagger}$ becomes only slightly more negative for the catalytic reactions.

The displacement of a leaving group (–X) by a nucleophile (:NH) may be assisted by general-acid (AH) and by general-base (BH) catalysis.[2,3] It is anticipated that the conversion of a bimolecular nucleophilic attack by :NH into one of the higher order catalytic processes ($i.e.$, general acid or general base) should be accompanied by a compensatory change in potential and kinetic energy terms. Assuming that

(1) Predoctoral Fellow of the National Institutes of Health (1960–1963). A portion of the Ph.D. thesis of S. J. B.

(2) T. C. Bruice, *Brookhaven Symposia in Biology*, **No. 15**, 52 (1962).

(3) M. L. Bender, *Chem. Rev.*, **60**, 53 (1960).

$\Delta H^{\ddagger}$ and $T\Delta S^{\ddagger}$ reflect simply potential energy and kinetic energy parameters, respectively, it is reasonable to suppose that the necessity of incorporating extra species into the transition state should decrease $T\Delta S^{\ddagger}$.

Table I
Kinetic Data for the Hydrazinolysis of Substituted O-acetyl phenols ($\mu = 1.0$ M KCl; Solv. H_2O)

p-NO$_2$C$_6$H$_4$OCOCH$_3$

°C = 10

pH	H$_f$ (M)	k$_{obs}$ (min.$^{-1}$)
7.40	0.000595	0.140
7.40	0.00119	0.288
7.40	0.00119	0.271
7.40	0.00179	0.405
7.40	0.00248	0.564

°C = 18

pH	H$_f$ (M)	k$_{obs}$ (min.$^{-1}$)
7.20	0.000694	0.219
7.20	0.00129	0.408
7.20	0.00178	0.599
7.20	0.00248	0.810

°C = 25

pH	H$_f$ (M)	k$_{obs}$ (min.$^{-1}$)
6.93	.000757	0.331
6.94	.00141	0.594
6.95	.00195	0.797
6.95	.00270	01.16

°C = 34

pH	H$_f$ (M)	k$_{obs}$ (min.$^{-1}$)
7.13	0.000218	0.133
7.13	0.000328	0.216
7.13	0.000437	0.284
7.13	0.000546	0.353

m-NO$_2$C$_6$H$_4$OCOCH$_3$

°C = 10

pH	H$_f$ (M)	k$_{obs}$ (min.$^{-1}$)
8.57	0.00297	0.0652
8.57	0.00297	0.0642
8.58	0.00593	0.141
8.59	0.00900	0.229
8.59	0.0124	0.337

°C = 18

pH	H$_f$ (M)	k$_{obs}$ (min.$^{-1}$)
8.37	0.00342	.128
8.37	0.00586	.245
8.39	0.00878	.342
8.39	0.0122	.502
8.39	0.0122	.503

°C = 25

pH	H$_f$ (M)	k$_{obs}$ (min.$^{-1}$)
8.19	0.0060	0.352
8.19	0.0120	0.736
8.21	0.0180	1.02
8.20	0.0250	1.51

°C = 34

pH	H$_f$ (M)	k$_{obs}$ (min.$^{-1}$)
6.76	0.00318	0.326
6.77	0.00441	0.443
6.77	0.00612	0.621

C$_6$H$_5$OCOCH$_3$

°C = 4

pH	H$_f$ (M)	k$_{obs}$ (min.$^{-1}$)
8.88	0.0777	0.0553
8.88	0.133	0.165
8.89	0.200	0.306
8.89	0.200	0.281
8.89	0.278	0.661
8.49	0.0474	0.0257
8.49	0.0814	0.0648
8.50	0.122	0.145
8.48	0.170	0.274
8.48	0.0468	0.0257
8.48	0.0802	0.0669
8.48	0.120	0.142
8.49	0.167	0.265
8.49	0.167	0.263
8.30	0.0349	0.0165
8.30	0.0598	0.0434
8.30	0.0896	0.0932
8.30	0.125	0.179

°C = 10

pH	H$_f$ (M)	k$_{obs}$ (min.$^{-1}$)
8.60	0.060	0.0437
8.60	0.120	0.156
8.61	0.180	0.361
8.60	0.250	0.721
8.60	0.250	0.701
8.41	0.115	0.154
8.42	0.143	0.240
8.43	0.199	0.499
8.43	0.199	0.479
8.20	0.0821	0.0955
8.20	0.103	0.144
8.21	0.143	0.285
8.21	0.143	0.286

°C = 18

pH	H$_f$ (M)	k$_{obs}$ (min.$^{-1}$)
8.72	0.0614	0.0624
8.72	0.123	0.204
8.73	0.184	0.464
8.74	0.256	0.874
8.39	0.0600	0.0631
8.39	0.120	0.212
8.39	0.180	0.481
8.39	0.250	0.925
8.20	0.0470	0.0438
8.21	0.0941	0.153
8.21	0.141	0.340
8.21	0.196	0.615
8.00	0.0342	0.0292
8.00	0.0684	0.0958
8.00	0.103	0.201
8.00	0.143	0.391

°C = 25

pH	H$_f$ (M)	k$_{obs}$ (min.$^{-1}$)
8.29	0.0401	0.0461
8.29	0.0802	0.153
8.30	0.120	0.277
8.30	0.167	0.524
8.11	0.0436	0.0504
8.12	0.0872	0.165
8.12	0.131	0.339
8.12	0.182	0.621
7.90	0.0467	0.0628
7.90	0.0801	0.155
7.90	0.120	0.345
7.90	0.167	0.616
7.90	0.167	0.600
7.80	0.0347	0.0385
7.81	0.0694	0.188
7.81	0.104	0.258
7.81	0.145	0.468

°C = 34

pH	H$_f$ (M)	k$_{obs}$ (min.$^{-1}$)
8.13	0.0423	0.0654
8.13	0.0845	0.195
8.13	0.127	0.383
8.13	0.176	0.682
7.76	0.0445	0.0761
7.76	0.0890	0.231
7.75	0.134	0.466
7.74	0.186	0.835
7.63	0.0365	0.0549
7.62	0.0730	0.166
7.61	0.109	0.334
7.61	0.152	0.600

°C = 41

pH	H$_f$ (M)	k$_{obs}$ (min.$^{-1}$)
7.96	0.0420	0.0981
7.96	0.0719	0.217
7.94	0.108	0.416
7.96	0.150	0.687
7.54	0.0348	0.0717
7.54	0.0596	0.152
7.52	0.0894	0.289
7.53	0.124	0.514
7.30	0.0349	0.0758
7.30	0.0599	0.169
7.30	0.0901	0.337
7.33	0.125	0.568
7.30	0.0336	0.0768
7.29	0.0577	0.180
7.30	0.0864	0.346
7.29	0.120	0.598

p-CH$_3$C$_6$H$_4$OCOCH$_3$

°C = 10

pH	H$_f$ (M)	k$_{obs}$ (min.$^{-1}$)
8.60	0.0603	0.0295
8.60	0.120	0.109
8.61	0.180	0.231
8.61	0.250	0.449
8.42	0.116	0.111
8.43	0.145	0.165
8.43	0.181	0.251
8.44	0.202	0.320
8.20	0.0832	0.0694
8.21	0.104	0.107
8.22	0.121	0.141
8.22	0.145	0.205

°C = 18

pH	H$_f$ (M)	k$_{obs}$ (min.$^{-1}$)
8.72	0.0614	0.0408
8.72	0.123	0.141
8.73	0.185	0.320
8.74	0.256	0.613
8.39	0.0600	0.0442
8.40	0.120	0.152
8.40	0.180	0.315
8.40	0.180	0.328
8.41	0.250	0.666
8.41	0.250	0.637
8.20	0.0471	0.0304
8.21	0.0941	0.105
8.21	0.141	0.239
8.21	0.196	0.452
8.00	0.0342	0.0201
8.00	0.0684	0.0705
8.00	0.103	0.142
8.00	0.143	0.286

°C = 25

pH	H$_f$ (M)	k$_{obs}$ (min.$^{-1}$)
8.29	0.0401	0.0285
8.29	0.0802	0.0805
8.30	0.120	0.177
8.30	0.167	0.322
8.10	0.0425	0.0301
8.10	0.0850	0.111
8.10	0.128	0.227
8.10	0.177	0.383
8.10	0.177	0.373
7.92	0.0331	0.0230
7.92	0.0662	0.0710
7.92	0.0992	0.148
7.91	0.138	0.276
7.81	0.0347	0.0273
7.81	0.0695	0.0879
7.80	0.104	0.168
7.80	0.104	0.177
7.80	0.145	0.341

°C = 34

pH	H$_f$ (M)	k$_{obs}$ (min.$^{-1}$)
8.13	0.0423	0.0429
8.13	0.0845	0.118
8.13	0.0845	0.128
8.13	0.127	0.255
8.13	0.176	0.488
7.76	0.0445	0.0472
7.76	0.0890	0.146
7.75	0.134	0.331
7.74	0.186	0.590
7.63	0.0365	0.0389
7.62	0.0730	0.123
7.61	0.109	0.247
7.61	0.152	0.445

p-CH$_3$OC$_6$H$_4$OCOCH$_3$

°C = 10

pH	H$_f$ (M)	k$_{obs}$ (min.$^{-1}$)
8.60	0.060	0.0299
8.60	0.120	0.117
8.61	0.180	0.257
8.61	0.250	0.493
8.42	0.116	0.115
8.43	0.145	0.186
8.43	0.181	0.300
8.44	0.202	0.383
8.20	0.0832	0.0728
8.21	0.104	0.113
8.22	0.121	0.152
8.22	0.145	0.221
8.22	0.145	0.229

°C = 18

pH	H$_f$ (M)	k$_{obs}$ (min.$^{-1}$)
8.72	0.0614	0.0409
8.72	0.123	0.142
8.73	0.185	0.321
8.74	0.256	0.589
8.40	0.0600	0.0430
8.40	0.120	0.160
8.41	0.180	0.357
8.41	0.250	0.665
8.20	0.0471	0.0290
8.21	0.0941	0.103
8.21	0.141	0.228
8.21	0.196	0.452
8.02	0.0353	0.0193
8.02	0.0705	0.0676
8.02	0.106	0.148
8.02	0.147	0.286

°C = 25

pH	H$_f$ (M)	k$_{obs}$ (min.$^{-1}$)
8.26	0.160	0.314
8.26	0.187	0.427
8.26	0.213	0.552
8.26	0.240	0.726
8.26	0.267	0.842
8.10	0.0425	0.0287
8.10	0.0850	0.100
8.10	0.128	0.217
8.10	0.177	0.411
7.92	0.0331	0.0206
7.92	0.0662	0.0658
7.92	0.0993	0.149
7.92	0.0993	0.143
7.91	0.138	0.265
7.81	0.0347	0.0236
7.81	0.0694	0.0811
7.80	0.104	0.178
7.80	0.145	0.354
7.80	0.145	0.336

It then follows that the change in $\Delta F^{\pm}$ would depend on whether $\Delta H^{\pm}$ or $T\Delta S^{\pm}$ exhibited the greater sensitivity to the conversion of the lower order reaction to a higher order catalytic process.

It is both of organic and biochemical interest to determine how much of the cost of incorporating an extra species is returned *via* the catalytic process. Thus, most proposals for enzymatic catalysis envisage a polyfunctional "active site" for the enzyme. The active site would then have the advantage of a prior restriction of the nucleophilic and catalytic functional groups resulting in a lowering of $\Delta F^{\pm}$ by an amount $(n - 1)y$ over the same reaction in aqueous solution, (where n is the number of nucleophilic and catalytic groups, and y the kinetic energy cost in $\Delta F^{\pm}$ in bringing each species into the transition state).
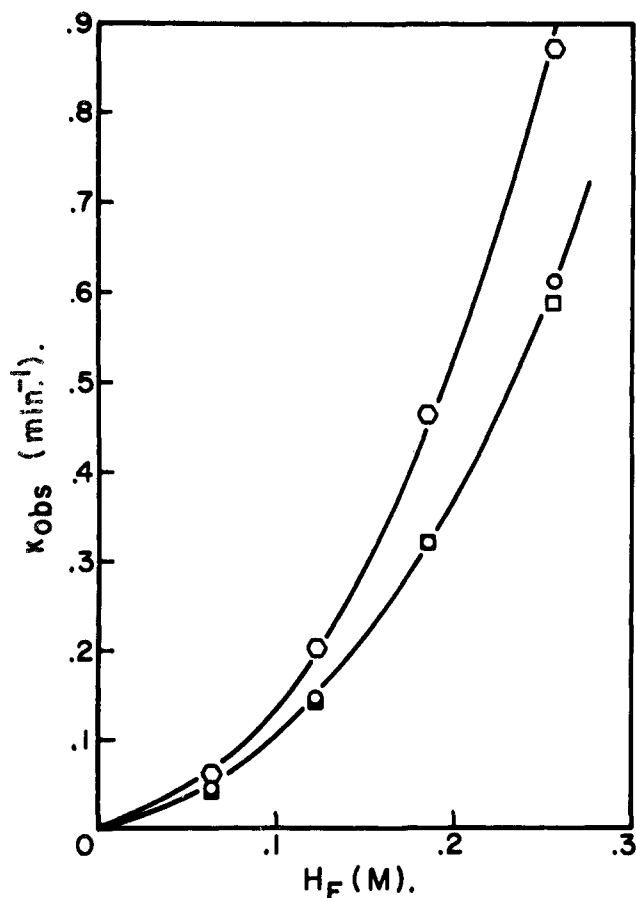
Fig. 1.—The observed rates of disappearance of (□) p-methyl-, (O) p-methoxy-, and (⊡) unsubstituted phenyl acetate as a function of hydrazine concentration.

For the purpose of determining the anticipated compensatory relationship in $\Delta H^{\ddagger}$ and $T\Delta S^{\ddagger}$, we have determined these parameters for the nucleophilic, general-acid and general-base catalyzed nucleophilic hydrazinolysis of substituted phenyl acetates. We have also determined the activation parameters for the catalysis of the hydrolysis of a series of substituted phenyl acetates by imidazole and for one case of general-base catalyzed nucleophilic catalysis of the hydrolysis of a substituted phenyl acetate by imidazole. These studies have been carried out in aqueous solution at a calculated ionic strength of 1.0 M (with KCl).

Experimental

Materials.—p-Nitro-, m-nitro-, p-chloro-, p-methylphenyl acetate as well as phenyl acetate itself were samples employed in a recent study.[4] p-Methoxyphenyl acetate was prepared by a conventional method.[5]

Kinetics.—The hydrazine and imidazole solutions were prepared in water, and KCl was added to give a constant (calculated) ionic strength of 1.0 M. Aliquots of the desired solution (3 ml.) were introduced into two matched (1-cm. path) silica cuvettes. The cuvettes were then thermally equilibrated at the desired temperature before adding 1 drop of the desired ester as an ethereal solution. The resultant solutions were rapidly mixed and placed in a thermostated (±0.1°) brass block in the cell compartment of a Zeiss PMQ II spectrophotometer. After a few minutes of re-equilibration the appearance of phenoxide ion was followed spectrophotometrically. The following wave lengths were employed to follow the reactions: p-NO₂, 400 mμ; m-NO₂, 350 mμ; p-Cl, 285 mμ; p-H, 275 mμ; p-CH₃, 280 mμ; and p-CH₃O, 288 mμ. All first-order rate constants were determined by the method of Guggenheim.[6] This procedure was found to provide more reproducible results than the employment of the integrated form of the first-order rate equation which depends on an accurate knowledge of the absorbance at $t\infty$.

(1) T. C. Bruice and S. J. Benkovic, J. Am. Chem. Soc., 85, 1 (1963).

(5) G. Cilento and W. F. Walker, ibid., 76, 4470 (1954).

(6) E. A. Guggenheim. Phil. Mag., 2, 538 (1926).

The pH of solutions were determined prior to and at the completion of the reactions at the reaction temperature. pH measurements were made with a Radiometer EK 2021 B combined glass calomel electrode and a Radiometer Model 22 pH meter with a Radiometer Model PHA 630 Pa scale expander. The electrode was kept at the temperature of the reaction being investigated, and reaction solutions were prepared to a tolerance of ±0.01 pH unit.

In the calculation of the rate constants the heats of ionization of hydrazine and imidazole were taken into account. The pK_2 value for hydrazine and pK_1 value for imidazole (both at $\mu = 1.0$ M with KCl) were determined by the method of half neutralization.

pK_2'	Temp., °C.	pK_1'	Temp. °C.
8.60	10	7.54	10
8.40	18	7.36	18
8.20	25	7.20	26
7.98	34	7.02	34

From the pK_2' values a ΔH_i of 10.4 kcal. mole⁻¹ was calculated for hydrazine. The predicted pK_2' value at 30° is 8.08 in good agreement with a previously determined value of 8.07 at this temperature.[7] From the pK_1' values a ΔH_i of 8.4 kcal./mole was calculated for imidazole and was found to compare favorably to those previously recorded for imidazole and imidazole compounds.[8,9]

Deuterium Solvent Isotope Effects.—For hydrazine reactions carried out in D₂O at 18° the pD values were taken as the pH meter readings plus the proper electrode correction.[10] The pK_2' (18°) value for hydrazine in D₂O was determined to be 9.11 ($\mu = 1.0$ M with KCl).

For imidazole reactions carried out in D₂O at 34° the pD values were also taken as the pH meter readings plus the proper electrode correction. The pK_1' value at 34° for imidazole in D₂O was determined to be 7.38 ($\mu = 1.0$ M with KCl). For experiments at 10 and 25° half-neutralized imidazole was employed, thus obviating the determination of pK_1' and electrode corrections.

Results[11]

Hydrazinolysis.[12]—The hydrazine reactions were carried out under conditions in which hydrazine was in great excess over ester so that pseudo-first-order kinetics were obtained (solvent H₂O; $\mu = 1.0$ M with KCl). In Table I are recorded the determined first-order rate constants. For p-nitrophenyl acetate the reaction was found to be first order in hydrazine from the linear dependence of k_{obsd} on the hydrazine concentration. However, for m-nitro-, p-methoxy-, p-methylphenyl acetate and phenyl acetate itself the reactions were found to be dependent on a higher than the first power of the hydrazine concentration. In the case of the m-nitro ester the higher order dependency on the hydrazine concentration was only observed at the lowest temperature employed for this ester (10°). In Fig. 1 the pseudo-first-order rate constants for p-methyl-, p-methoxy-, and phenyl acetate have been plotted vs. the concentration of free hydrazine base in the reaction solutions (18°). The decided upward curvature of the plots of Fig. 1 suggests that the disappearance of these esters contains a contribution proportional to H_f^2. At constant pH

$$-d(\text{ester})/dt = k_3(\text{ester})(H_f)^2 + k_n(\text{ester})(H_f) \qquad (1)$$

$$k_{obsd} = k_3(H_f)^2 + k_n(H_f)$$

$$k_{obsd}/(H_f) = k_3(H_f) + k_n \qquad (2)$$

(7) R. Hinman, J. Org. Chem., 23, 1587 (1958).

(8) E. J. Cohn and J. T. Edsall, "Proteins, Amino Acids and Peptides," Reinhold Publ. Corp., New York, N. Y., 1943, p. 89.

(9) (a) J. T. Edsall, G. Felsenfeld, D. S. Goodman, and F. R. N. Gurd, J. Am. Chem. Soc., 76, 3054 (1954); (b) Y. Nozaki, F. R. N. Gurd, R. F. Chen, and J. T. Edsall, ibid., 79, 2123 (1957).

(10) T. H. Fife and T. C. Bruice, J. Phys. Chem., 65, 1079 (1961).

(11) Abbreviations employed are: H_f = concentration of H₂NNH₂; $H_h^\oplus$ = concentration of H₂NNH₃⊕; IM_f = concentration of imidazole free base; $IMH^\oplus$ = concentration of imidazolium ion; a_H = hydrogen ion activity as determined by the glass electrode. The rate constants are abbreviated as: k_s = the apparent third-order rate constant determined at a particular pH; k_n = the second-order rate constant for the reaction of nitrogen base with ester; k_{gb} = the third-order rate constant for the general-base catalyzed reaction of a nitrogen base with ester; k_{ga} = the third-order rate constant for the general-acid catalyzed reaction of a nitrogen base with ester.

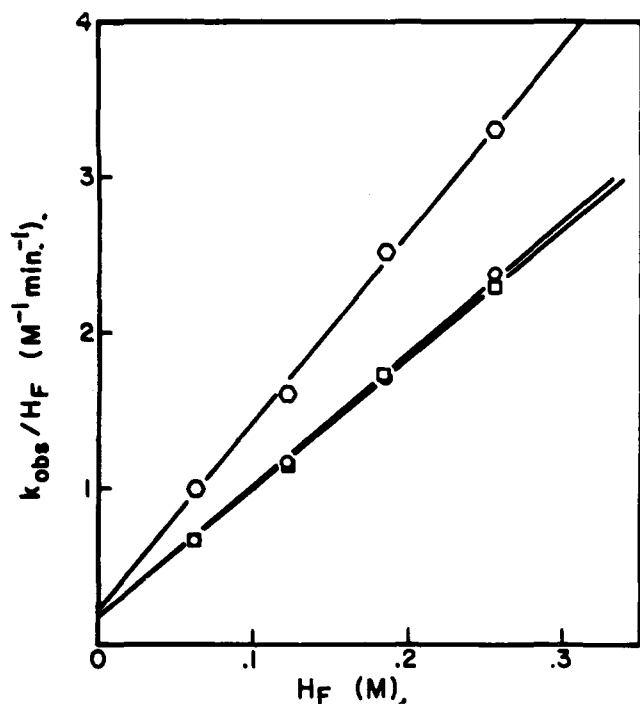(12) W. P. Jencks and J. Carriuolo, J. Am. Chem. Soc., 82, 1778 (1960).

Fig. 2.—Plots of eq. 2 for ($\square$) p-methyl-, ($\bigcirc$) p-methoxy-, and ($\langle\underline{}\rangle$) unsubstituted phenyl acetate.

The data of Fig. 1 have been plotted in the form of eq. 2 in Fig. 2 (pH 8.73). The values of k_3 are obtained as the slope and the value of k_n as the intercept of plots such as Fig. 2. When the experiments were extended to various pH values it was found that k_3 was dependent on pH and k_n independent of pH. The dependence of k_3 on a_H was determined to be

$$k_3 = k_{ga}(a_H/K_2') + k_{gb} \qquad (3)$$

In Fig. 3 the values of k_3 have been plotted vs. a_H/K_2', where a_H is the hydrogen ion activity as measured by the glass electrode and K_2' the dissociation constant of the conjugate acid of hydrazine. The general acid rate constant k_{ga} is obtained as the slope and the general base rate constant k_{gb} as the intercept at $a_H/K_2' = 0$. Thus, the over-all kinetic expression for the reaction of p-methyl-, p-methoxy-, and phenyl acetate (and m-nitrophenyl acetate at 10°) with hydrazine is given by (4).[13]

$$-\mathrm{d(ester)}/\mathrm{d}t = [k_n(H_f) + k_{gb}(H_f)^2 +$$
$$k_{ga}(H_f)(H_h\oplus)](\text{ester}) \quad (4)$$

The values of k_n, k_{gb}, and k_{ga} at 18° are provided in Table II. The relative proportion of product arising from k_n and the third-order terms is of course dependent on the hydrazine concentration and the pH of the experiment. Also included in Table II are the deuterium solvent isotope effects determined for the reaction of phenyl acetate with hydrazine.

(13) Kinetically equivalent expressions for the hydrazine reaction (i.e., $k_{ba}(H_f)^2 a_H$) representing the actually reacting species rather than $k_{ga}(H_f)$ ($H_h\oplus$) may be ruled out since the constants would exceed those for diffusion controlled process. For example

$$k_{ga}(H_f)(H_h\oplus)(\text{ester}) = k_{ba}a_H(H_f)^2(\text{ester})$$

where

$$k_{ga}/K_2' = k_{ba}$$

Since K_2' for hydrazine is ca. 10^{-9} and $k_{ga} \cong 2$, $k_{ba} = 2 \times 10^9$. A kinetic process for the specific acid-general base catalyzed term such as

$$\text{ester} + H_3O\oplus \underset{k_r(H_f)}{\overset{K_a}{\rightleftharpoons}} \text{ester-H}\oplus + H_2O$$

$$\text{ester-H}\oplus + H_f \longrightarrow \text{prod.}$$
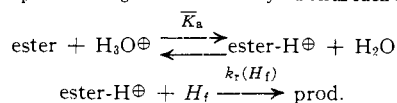
yields k_{ba} as $k_r/\overline{K}_a$. Assuming a reasonable value of $\overline{K}_a$ to be 10^6, k_r would have to be 10^{15}, a value 10^6 greater than that observed for a diffusion controlled process.
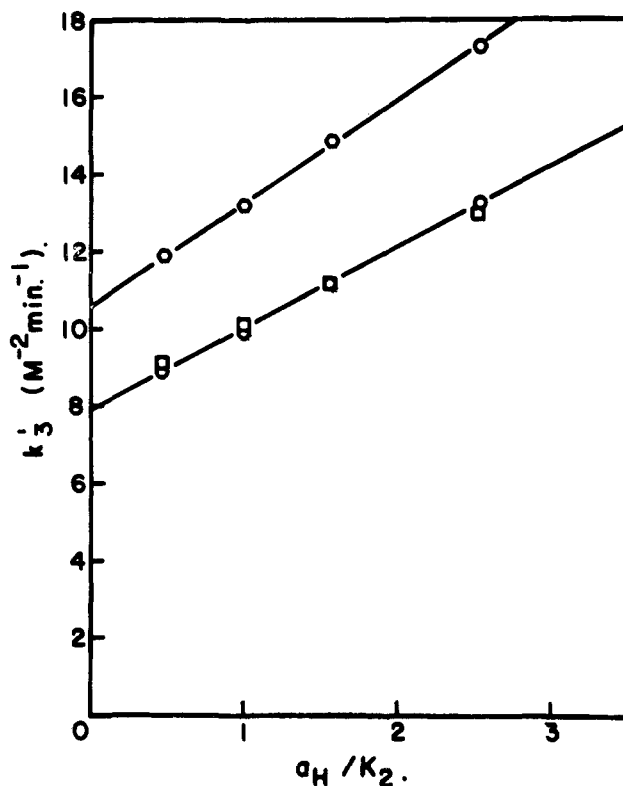
Fig. 3.—Plots of eq. 3 for ($\square$) p-methyl-, ($\bigcirc$) p-methoxy-, and ($\langle\underline{}\rangle$) unsubstituted phenyl acetate.

In Fig. 4 are plotted the log k_n, log k_{gb}, and log k_{ga} values vs. $1/T$ for the hydrazinolysis of p-cresol acetate and phenyl acetate. The $\Delta H^{\ddagger}$ and $T\Delta S^{\ddagger}$ values calculated from this plot along with those for the other esters of the series are presented in Table III.

TABLE II

RATE CONSTANTS FOR THE REACTION OF HYDRAZINE WITH SUBSTITUTED PHENYL ACETATES (H_2O; $\mu = 1$ 0 M WITH KCl, 18°)

Sub-stituent	k_n, l. mole^{-1} min.$^{-1}$	k_{ga}, l.^{2} mole^{-2} min.$^{-1}$	k_{gb}, l.^{2} mole^{-2} min.$^{-1}$
p-NO$_2$	327		
m-NO$_2$	39.7		
H	0.245	2.62	10.75
p-CH$_3$	.130	1.98	7.86
p-OCH$_3$	.097	1.82	8.20
H	k_H/k_D in k_n 1.1	k_H/k_D in k_{ga} 2.3	k_H/k_D in k_{gb} 1.2

TABLE III

ACTIVATION PARAMETERS[a] FOR THE REACTION OF HYDRAZINE WITH SUBSTITUTED PHENYL ACETATES

Sub-stituent	k_n $\Delta H^{\ddagger}$	$T\Delta S^{\ddagger}$	k_{gb} $\Delta H^{\ddagger}$	$T\Delta S^{\ddagger}$	k_{ga} $\Delta H^{\ddagger}$	$T\Delta S^{\ddagger}$
	kcal. mole^{-1}		kcal. mole^{-1}		kcal. mole^{-1}	
p-NO$_2$	6.8	−9.7				
m-NO$_2$	10.9	−6.5				
H	11.3	−9.0	4.1	−14.2	ca. 0.9	−18.4
p-CH$_3$	12.0	−8.6	5.8	−12.7	ca. 0.3	−19.1
p-OCH$_3$			5.0	−13.4	1.5	−17.9

[a] Calculated from $\Delta H^{\ddagger} = E_a - RT$, $-T\Delta S^{\ddagger} = \Delta F^{\ddagger} - \Delta H^{\ddagger}$, and $\Delta F^{\ddagger} = RT 2.303 \log(KT/hk_r)$ (A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," John Wiley and Sons, Inc., New York, N. Y., 1953, pp. 95–97), standard states of 1 M and 1 M^2; $T = 25°$ and time in sec. Slopes of linear plots were determined by method of least squares.

For k_n the activation enthalpy does not appear to be as constant as previously noted in the bir molecular and intramolecular nucleophilic displacement reaction at
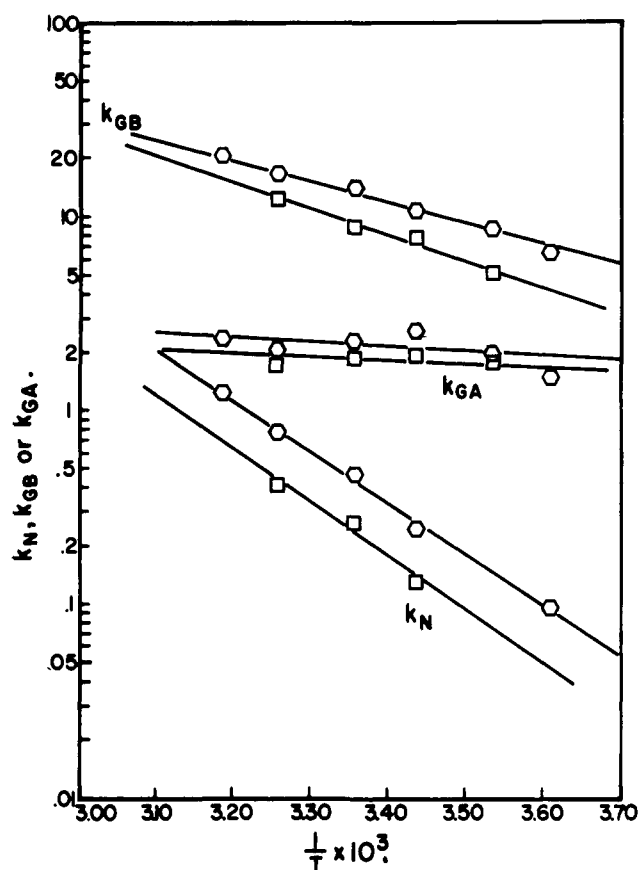
Fig. 4.—Plots of log k_n, log k_{gb}, and log k_{ga} vs. $1/T$ for the reactions of (⬡) unsubstituted and (□) p-methylphenyl acetate with hydrazine.
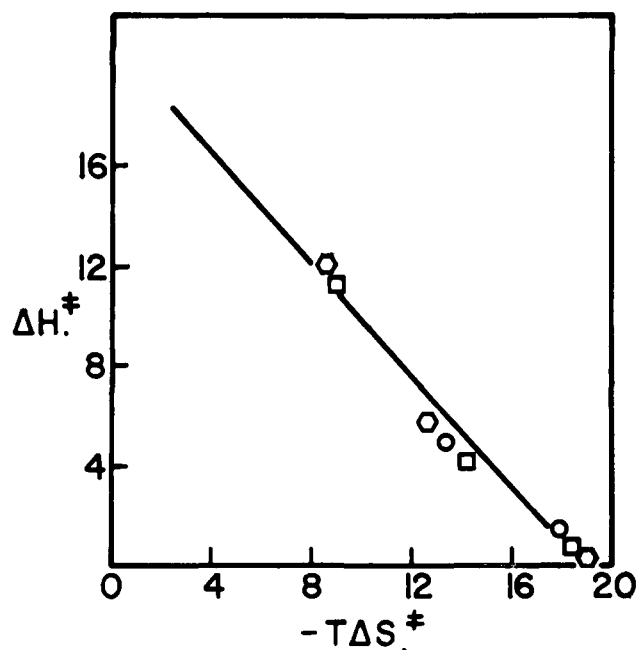
Fig. 5.—Plot of $\Delta H^{\pm}$ vs. $-T\Delta S^{\pm}$ for the reaction of hydrazine with (□) p-methyl-, (○) p-methoxy-, and (⬡) unsubstituted phenyl acetate depicting compensation.

phenyl ester bonds.[4,14]   Instead, $\Delta H^{\pm}$ increases as the substituent becomes less electron attracting. In addition there is no regular trend observable in the $T\Delta S^{\pm}$ term. However, the high reactivity of p-nitrophenyl acetate with hydrazine seems to be due to a more

(14) E. Gaetjens and H. Morawetz, J. Am. Chem. Soc., **82**, 5328 (1960).
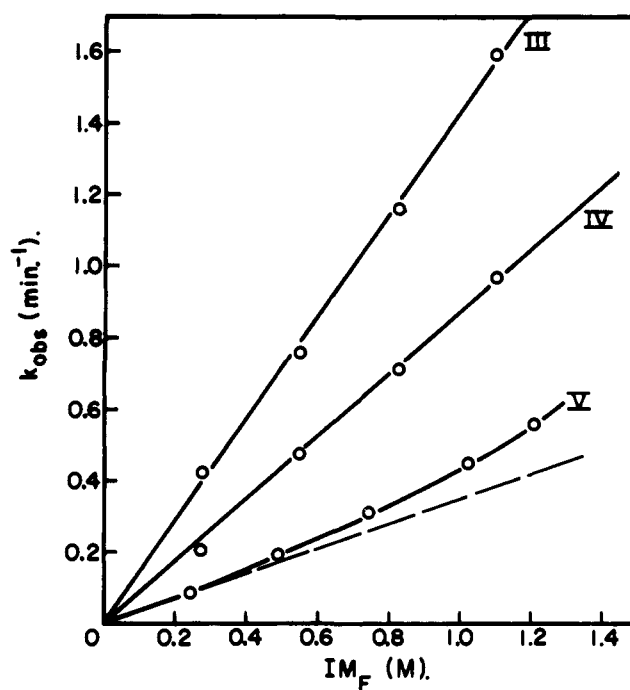
Fig. 6.—The observed rates of disappearance of (III) p-chloro-, (IV) unsubstituted, (V) p-methyl phenyl acetate as a function of imidazole concentration.

favorable enthalpy term than that associated with other esters in the series. The activation enthalpy associated with both general base and general acid catalysis is significantly less than that associated with simple nucleophilic attack. General-acid catalysis appears to be the most efficient form of catalysis in terms of lowering the activation enthalpy. The small values of $\Delta H^{\pm}$ found for p-methyl-, p-methoxy-, and phenyl acetate reflect essentially a temperature independent general-acid constant.

The general-acid and general-base mechanisms indicate catalytic processes which are somewhat more favorable in terms of free energy than the uncatalyzed reaction. Since the catalytic processes represent the higher order reactions, it would be anticipated that they would be less probable. On the other hand, the assistance to nucleophilic attack by the general-base and general-acid species should bring about a lowering of the potential energy barrier. These two opposing effects on $\Delta F^{\pm}$ should result in compensation in the $\Delta H^{\pm}$ and $T\Delta S^{\pm}$ for the k_n, k_{gb}, and k_{ga} terms of Table III. Examination of Fig. 5 reveals a good linear relationship between the two activation parameters, and the slope of the line indicates that a decrease of 1 kcal. mole^{-1} in $T\Delta S^{\pm}$ is accompanied by a decrease in $\Delta H^{\pm}$ of 1.15 kcal. mole^{-1}. From this result it follows that the decrease in $\Delta F^{\pm}$ brought about by the catalytic processes is almost completely lost in the gain in $\Delta F^{\pm}$ necessitated by the loss in the entropy of activation associated with the higher order reactions.

Imidazole.[15]—The reactions of imidazole with substituted phenyl acetates were studied under the same pseudo-first-order conditions employed for hydrazine (solv. H_2O; $\mu = 1.0$ M with KCl). For p-nitro-, m-nitro-, p-chloro-, and unsubstituted phenyl acetate the reactions were found to be first order in imidazole. However, for p-methyl- and p-methoxy-substituted phenyl acetates the hydrolytic reactions were found to

(15) For pertinent references on the catalysis of the hydrolysis of phenyl acetate by imidazoles, see: (a) M. L. Bender and B. W. Turnquest, ibid., **79**, 1652, 1656 (1957); (b) T. C. Bruice and G. L. Schmir, ibid., **79**, 1663 (1957); (c) ibid., **80**, 148 (1958).
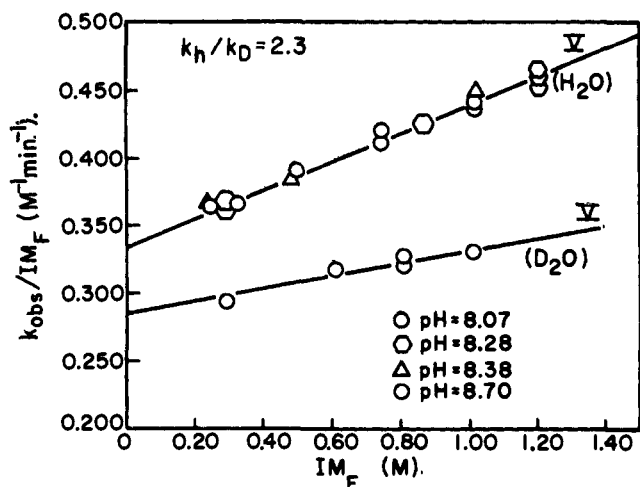
Fig. 7.—Plot of eq. 7 for the reaction of (V) p-methylphenyl acetate in H_2O and D_2O with imidazole.

be dependent on a higher than the first power of imidazole concentration. These conclusions may be verified by inspection of Fig. 6. In Fig. 6 the pseudo-first-order rate constants for the disappearance of the unsubstituted and the p-chloro- and p-methylphenyl acetates have been plotted $vs.$ the concentration of free imidazole base in the reaction solutions (34°). Inspection of Fig. 6 reveals that for p-chloro- and unsubstituted phenyl acetate the values of k_{obsd} are linearly dependent on the concentration of the free base. However, in the case of p-cresol acetate there is a decided upward curvature in the plot of k_{obsd} $vs.$ IM_f. For p-nitro- and m-nitrophenyl acetates k_{obsd} was found to be linearly dependent on the concentration of IM_f as in the case of the p-chloro ester of Fig. 6. In the case of p-methoxyphenyl acetate the plot of k_{obsd} $vs.$ IM_f is virtually superimposable on that of p-cresol acetate. The plots of k_{obsd} for p-cresol acetate and p-methoxyphenyl acetate suggest that the catalysis of ester hydrolysis for these esters might contain a contribution proportional to $IM_f{}^2$.

$$-d(\text{ester})/dt = k_{gb}(\text{ester})(IM_f)^2 + k_n(\text{ester})(IM_f) \quad (5)$$

$$k_{obsd} = k_{gb}(IM_f)^2 + k_n(IM_f) \quad (6)$$

and

$$k_{obsd}/IM_f = k_{gb}(IM_f) + k_n \quad (7)$$

In Fig. 7 are plotted the values of k_{obsd}/IM_f $vs.$ IM_f at several pH values for p-cresol acetate in H_2O and D_2O. The third-order rate constant k_{gb} is obtained as the slope and the second-order rate constant k_n as the intercept at $IM_f = 0$. The observed isotope effect in k_{gb} is consistent with general base catalysis $(k_H/k_D = 2.2)$. The values of k_n and k_{gb} at 34° are provided in Table IV, the proportion of hydrolytic products arising from the third-order terms being $ca.$ 30% at 1.0 M imidazole.

TABLE IV

RATE CONSTANTS FOR THE REACTION OF IMIDAZOLE WITH SUBSTITUTED PHENYL ACETATES (SOLVENT H_2O; $\mu = 1.0$ M WITH KCl; 34°)

Substituent	k_n, 1. mole^{-1} min.$^{-1}$	k_{gb}, 1.^{2} mole^{-2} min.$^{-1}$
p-NO$_2$	47.4	
m-NO$_2$	17.2	
p-Cl	1.60	
H	0.960	
p-CH$_3$	.333	0.105
p-OCH$_3$	.323	0.095
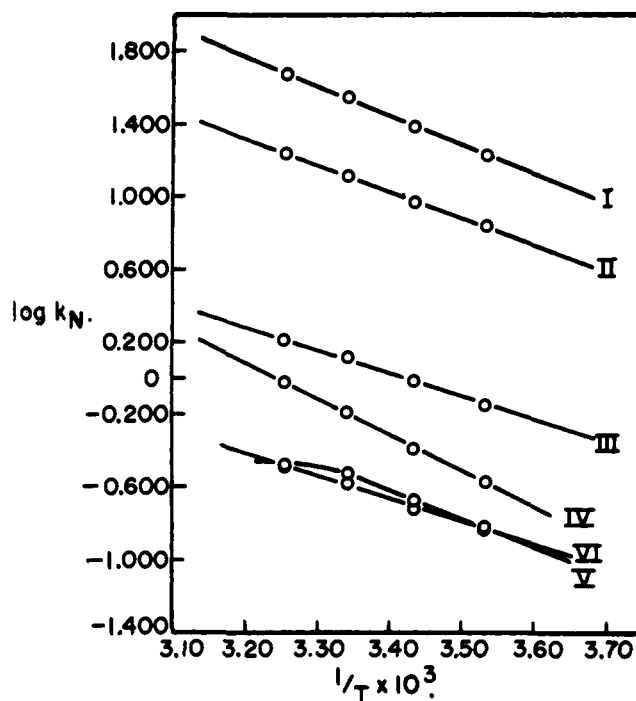
Fig. 8.—Plot of log k_n $vs.$ $1/T$ for the reactions of (I) p-nitro-, (II) m-nitro-, (III) p-chloro-, (IV) unsubstituted, (V) p-methoxy-, (VI) p-methylphenyl acetate with imidazole.
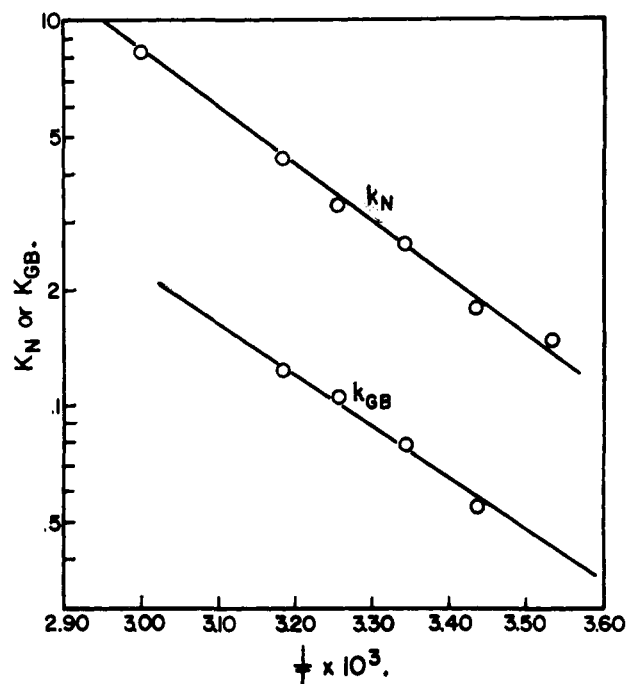
Fig. 9.—Plots of log k_n and log k_{gb} $vs.$ $1/T$ for the reaction of (VI) p-methylphenyl acetate with imidazole.

In Fig. 8 are plotted the log k_n values $vs.$ $1/T$ for the temperature range of 10 to 34°. It should be noted that linear relationships exist for the log k_n values of all esters with one exception. For p-methoxyphenyl acetate a sharp curvature is encountered. The plotted value at 34° represents the separately determined value of k_n, while the values at all lower temperatures where k_{gb} could not be experimentally distinguished must represent composite constants of k_n and k_{gb}. The value of k_n at 10° should reflect little or no contribution from k_{gb}, a supposition that is justified by the negligible contribution of k_{gb} to k_{obsd} for p-cresol acetate at 10° as illustrated in Fig. 9. The activation

parameters for p-methoxyphenyl acetate were then calculated employing the determined values of k_n at 34 and 10° only. In Table V are recorded the values of $\Delta H^{\ddagger}$ and $T\Delta S^{\ddagger}$ for k_n and k_{gb} as calculated from Fig. 8 and 9.

Inspection of the values of Table V reveals that the electronic influence of the substituent group on k_n is characterized by shifts of $\Delta H^{\ddagger}$ and $T\Delta S^{\ddagger}$ in the same direction. The incursion of general base catalysis does not result in a significant lowering of $\Delta F^{\ddagger}$ as was noted in general-base catalyzed reactions with hydrazine. Thus simple nucleophilic attack is more favored in terms of free energy when imidazole serves as the nucleophile.

Also included in Table V are the observed deuterium solvent isotope effects associated with k_n. For nucleophilic attack no solvent isotope effect is anticipated. However, the reaction of phenyl acetate was found to exhibit a deuterium solvent isotope effect that appears to depend on ionic strength. The values of k_H/k_D for k_n at various ionic strengths and temperatures are included in Table V.

Table V

ACTIVATION PARAMETERS AND DEUTERIUM SOLVENT ISOTOPE EFFECTS FOR THE REACTION OF IMIDAZOLE WITH SUBSTITUTED PHENYL ACETATES (SOLVENT H$_2$O; $\mu = 1.0$ M; $T = 10$–$34°$)

	k_n		k_{gb}		
Substituent	$\Delta H^{\ddagger}$	$T\Delta S^{\ddagger}$ [a]	$\Delta H^{\ddagger}$	$T\Delta S^{\ddagger}$	k_H/k_D for k_n
p-NO$_2$	7.0	-10.7			
m-NO$_2$	6.0	-12.3			1.0[c]
p-Cl	5.4	-14.4			1.2[d]
H	8.4	-11.6			1.5–1.8,[e] 1.3,[f] 1.07[g]
p-CH$_3$	6.2	-14.4	5.5	-15.8	1.2[h]
p-OCH$_3$	4.9	-15.7[b]			

[a] Calculated from $\Delta H^{\ddagger} = E_a - RT$, $-T\Delta S^{\ddagger} = \Delta F^{\ddagger} - \Delta H^{\ddagger}$, and $\Delta F^{\ddagger} = RT2.303 \log(KT/hk_r)$ (A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," John Wiley and Sons, Inc., New York, N. Y., 1953, pp. 95–97) standard state used was 1 M; $T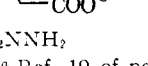 = 25°$; with time in sec. Least squares method employed. [b] Calculated from the determined value of k_n at 34° and the assumption that k_n at 10° does not contain any significant contribution from k_{gb}. [c] M. L. Bender, E. J. Pollock, and M. C. Neveu, J. Am. Chem. Soc., **84**, 596 (1962); 5% dioxane–H$_2$O, 25°. [d] At 34°, $\mu = 1.0$; this study. [e] 1.6 at 34°, 1.5 at 25°, 1.8 at 10°, $\mu = 1.0$; this study. [f] 1.3 at 25°, $\mu = 0.50$; this study. [g] B. M. Anderson, E. H. Cordes, and S. P. Jencks, J. Biol. Chem., **236**, 455 (1961); $\mu = 0.35$ at 25°. [h] At 34°, $\mu = 1.0$; this study.
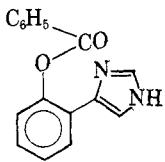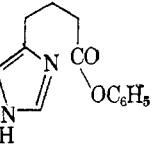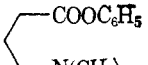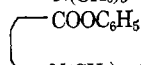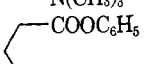
Discussion

$\Delta H^{\ddagger}$ and the pK_a of the Nucleophile.—At present the dependence of $\Delta H^{\ddagger}$ on the nature of the nucleophile and on the electronic effects of ester substituents is not understood. The previously suggested[14] linear relationship between $\Delta H^{\ddagger}$ and pK_a of the nucleophile has been proved unsound on the basis of this study. The reactions upon which the correlation was based exhibited $\Delta H^{\ddagger}$ values independent of the electronic nature of the substituent groups but dependent upon the pK_a of the nucleophile. In the present study the values of $\Delta H^{\ddagger}$ are not only dependent on the nucleophile, but also on the nature of the electronic substituents. Nevertheless, it is obvious that the determined $\Delta H^{\ddagger}$ values deviate widely from those anticipated from the suggested correlation. For example, a $\Delta H^{\ddagger}$ of ca. 16 kcal. mole^{-1} for the bimolecular reaction of imidazole with substituted phenyl acetates is predicted on the basis of the previously determined linear dependence of $\Delta H^{\ddagger}$ on pK_a', whereas a value of 7 to 5 kcal. mole^{-1} is observed.

Hammett ρ-Values and the "α-Effect."—Because of the very high reactivity of hydrazine with esters (the α-effect[16]), it is of interest to compare the Hammett

Table VI

ρ-VALUES FOR REACTIONS OF VARIOUS NUCLEOPHILES WITH A SERIES OF SUBSTITUTED PHENYL ACETATES

Nucleophile	Catalyst	Kinetic order	ρ	Ref.
NH$_2$NH$_2$	NH$_2$NH$_2$	3	0.55	d
NH$_3$	NH$_3$	3	0.55	a
Imidazole	Imidazole	3	0.5	d
NH$_2$NH$_2$	NH$_2$NH$_3^{\oplus}$	3	0.65	d
CH$_2$O$^{\ominus}$ HOCH$_2$CNH$_2$ CH$_2$OH (as oxyanion)		2	0.64	b
CH$_2$OH HOCH$_2$CNH$_2$ CH$_2$OH (as amine)		2	0.71	b
OH$^-$		2	0.8	a
CH$_2$OH HOCH$_2$CCH$_2$O$^{\ominus}$ CH$_2$OH		2	0.98	b
		1	1.5	e
		1	1.3	f
Imidazole		2	1.8	d
NH$_3$		2	2.1	a
(CH$_3$)$_3$N		2	2.6	c
		1	2.6	c
		1	2.6	c
		1	2.6	g
H$_2$NNH$_2$		2	2.9	d

[a] Ref. 19 of paper. [b] Ref. 17 of paper. [c] Ref. 14 of paper. [d] This study. [e] T. C. Bruice and U. K. Pandit, J. Am. Chem. Soc., **82**, 3386 (1960). [f] T. C. Bruice and J. M. Sturtevant, ibid., **81**, 2860 (1959). [g] Ref. 15 of this paper.

ρ-value of this nucleophile to values determined for other nucleophiles with the same series of esters. A re-evaluation of Hammett plots for nucleophilic displacement reactions on phenyl esters has shown that much better plots are obtained when a σ-value of 1.0 is employed for the p-NO$_2$ group. For certain nucleophiles the conventional values of 1.27 and 0.78 are quite satisfactory. However, all the data collected to date appear to correlate with the value of 1.0, and we prefer to employ a single σ-constant for comparative purposes. The use of 1.0 as the σ for the p-NO$_2$ group removes the cases of curvature previously encountered for certain nucleophiles (i.e., pentaerythritol and tris-(hy-

(16) J. O. Edwards and R. G. Pearson, J. Am. Chem. Soc., **84**, 16 (1962).

droxymethyl)-aminomethane).[17] Justification for the use of a σ-value of 1.0 for the p-NO_2 group stems from the consideration that the displacement reactions considered are two-step mechanisms. In the first step the nucleophile attacks the ester carbonyl group (requiring the nonconjugative σ of 0.78) and in the second step the phenoxide ion leaves the tetrahedral intermediate (requiring a σ of 1.27). The accumulated data are presented in Fig. 10 and Table VI along with the related ρ-constants using $\sigma = 1.0$ for p-nitrophenyl acetate.

The ρ-value for k_n for hydrazine is the largest (+)-value yet obtained for nucleophilic displacement reactions at the phenyl ester bonds. A comparison of the k_n values for hydrazine and ammonia is provided in Table VII.

<div align="center">

TABLE VII

Comparison of the Rate Constants for the Second-Order Reaction of Hydrazine and Ammonia with Substituted Phenyl Acetates

($30°$; Solvent H_2O; $\mu = 1.0$ M with KCl)

</div>

	k_n		
	H_2NNH_2	$NH_3{}^a$	
Substituent	1. mole^{-1} min.$^{-1}$		$k_{H_2NNH_2}/k_{NH_3}$
p-NO_2	534	29.2	18.2
m-NO_2	82.2	10.5	7.82
H	0.65	0.245	2.65
p-CH_3	0.36	0.13	2.77

^{a} Data of T. C. Bruice and M. F. Mayahi; see ref. 19 of paper

Inspection of the values of $k_{H_2NNH_2}/k_{NH_3}$ of Table VII reveals that the α-effect decreases with decreasing electron withdrawal by the substituent groups and thus the ρ-value reflects this sensitivity to the α-effect. The slope of the Brönsted plots for the reaction of nitrogen bases with p-nitrophenyl acetate is $ca.$ 0.8[18] and the pK_a of hydrazine and ammonia at 30° have been determined to be 8.11 and 9.5, respectively. If no special effect were in operation it would be anticipated that the ratio of $k_{H_2NNH_2}/k_{NH_3}$ would be 0.077 so that hydrazine can be seen to react with p-nitrophenyl acetate some 236 times more rapidly than expected. For the general-base catalyzed ammonolysis and hydrazinolysis of phenyl acetate and p-cresol acetate the ratio of $k_{H_2NNH_2}/k_{NH_3} = 21.0$ and 21.6, so that the α-effect is approximately ten times as important in the general base term (k_{gb}) as in the nucleophilic term (k_n).

The small ρ-value obtained for the k_{gb} terms with hydrazine and imidazole is identical with that obtained for the same term with ammonia.[19] Like most other general-base assisted aminolysis reactions, the hydrazine general-base reaction exhibits no deuterium solvent isotope effect.[20] However, the general-base catalyzed reaction of imidazole with p-cresol acetate exhibits a deuterium solvent isotope effect of 2.2. This finding is similar to that reported for the imidazole catalysis of the hydrolysis of a series of m- and p-substituted p-nitrophenyl benzoates in 27% acetonitrile–water solution where there is, in addition to the second-order nucleophilic catalysis term, a third-order term which is first order in ester and second order in imidazole.[21] The latter general-base term was associated with a deuterium solvent isotope effect of 1.81.

$\Delta S^{\ddagger}$ **and the Kinetic Order.**—Possibly more can be said about the entropy of activation than about the enthalpy of activation. This is so since $\Delta H^{\ddagger}$ possesses both potential and kinetic energy terms, whereas $\Delta S^{\ddagger}$

(17) T. C. Bruice and J. L. York, $J. Am. Chem. Soc.$, **83**, 1382 (1961).

(18) T. C. Bruice and R. Lapinski, $ibid.$, **80**, 2265 (1958).

(19) T. C. Bruice and M. F. Mayahi, $ibid.$, **82**, 3067 (1960).

(20) W. P. Jencks and J. Carriuolo, $ibid.$, **82**, 675 (1960).

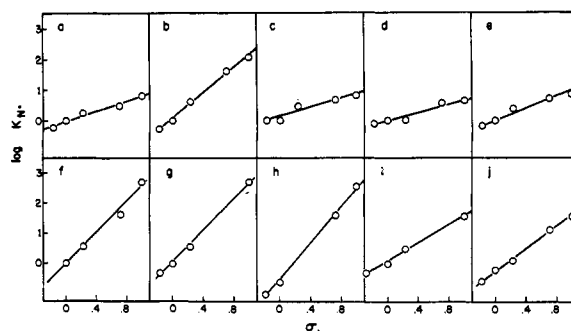(21) M. Caplow and W. P. Jencks, $Biochem.$, **1**, 883 (1962).

Fig. 10.—Hammett type plots for the reactions of substituted phenyl acetates with the various nucleophiles of Table VIII, utilizing $\sigma_{p-NO_2} = 1.0$. The plots refer to the nucleophiles in Table VIII as: a-7, b-2, c-6, d-5, e-8, f-13, g-14, h-17, i-9, j-11.

is composed of only kinetic energy terms.[22] Values of $\Delta H^{\ddagger}$ and $T\Delta S^{\ddagger}$ have now been amassed for eleven different nucleophilic displacement reactions each on series of phenyl ester bonds. These reactions share in common the fact that the same series of bonds are being broken but differ in the nucleophiles involved and also in the kinetic order and mechanism of the reactions. Thus, with various nucleophiles we have collected activation parameters for simple intramolecular displacement reactions which are kinetically first order, simple bimolecular nucleophilic displacement reactions, and third-order general-acid and general-base assisted nucleophilic displacement reactions. Though electronic effects may produce erratic (as with H_2NNH_2) or systematic (as with $N(CH_3)_3$)[14] alterations in $T\Delta S^{\ddagger}$ these may be considered as secondary perturbations on a value which is that of the average entropy of activation ($T\Delta S^{\ddagger}_{av}$) for the series of phenyl ester bonds investigated with a particular nucleophilic displacement reaction.

We may conveniently divide the $T\Delta S^{\ddagger}_{av}$ term into two parts: (1) the first part may be considered to be that involved with the translation of the nucleophile and catalytic species (if any) to a position of very close approach to the ester bond, ($\Delta S^{\ddagger}_{t.r.}$) and (2) the second part of the entropy term ($\Delta S^{\ddagger}_e$) may be considered to be that involved in the bond breaking and making processes.

$$T\Delta S^{\ddagger}_{av} = T(\Delta S^{\ddagger}_{t.r.} + \Delta S^{\ddagger}_e) \qquad (8)$$

The term $\Delta S^{\ddagger}_{t.r.}$ should be due to translational and in part rotational entropy factors while $\Delta S^{\ddagger}_e$ should be determined by those kinetic energy terms involved in the formation of the transition state when the ground state of the reactants is that of very close approach. We may include entropy terms associated with solvent striction or solvent reacting, and electronic effects in $\Delta S^{\ddagger}_e$. First-order spontaneous processes shou'd then be favored over higher order reactions provided that the bringing together of reactants alters $T\Delta S^{\ddagger}_{t.r.}$ much more than $T\Delta S^{\ddagger}_e$. For nucleophilic displacement reactions on phenyl acetates the cost in proceeding from spontaneous first-order reactions to higher order processes appears to be between 4–6 kcal. mole^{-1} for each increase in order by one (see Table VIII). As a result, $when\ the\ kinetic\ order\ of\ the\ displacement\ reaction\ is\ multiplied\ by\ 4\ to\ 6\ kcal.\ mole^{-1}$, $the\ determined\ average\ T\Delta S^{\ddagger}\ value\ is\ obtained.$ The value of 4–6 kcal. mole^{-1} compares favorably with a value of 5.4 kcal. mole^{-1} suggested by Long and Schaleger as a reasonable value for the loss of entropy from incorporation of a water molecule into a transition state.[23] On the other hand,

(22) R. W. Taft, "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, pp. 556–675.

(23) L. L. Schaleger and F. A. Long, "Advances in Physical Organic Chemistry," V. Gold, Ed., Academic Press, Inc., New York, N. Y., 1963, p. 26.

a smaller value (2–3 kcal. mole^{-1}) is calculated for the translation of two molecules to form a complex by the Sackur and Tetrode equation.[24]

Reaction	Kinetic order	$T\Delta S^{\neq}$ / kinetic order[a]	Number of esters investi- gated	Ref.[b]
$(CH_3)_3N$ + Ph esters	2	4	4	c
γ-(N,N-Dimethylamino)- butyrate Ph esters	1	4	5	c
δ-(N,N-Dimethylamino)- valerate Ph esters	1	4–5	5	c
OH$^-$ + Ph esters	2	3	4	c
AcO$^-$ + Ph esters	2	4	2	g
Monophenyl glutarates	1	4	4	g
H_2NNH_2 + Ph esters	2	4	4	d
$2(H_2NNH_2)$ + Ph esters	3	4–5	3	d
H_2NNH_2 + $H_2NNH_3^+$ + Ph esters	3	6	3	d
Imidazole + Ph esters	2	6–7	6	d
2(Imidazole) + Ph esters	3	5	1	d

[a] Values rounded to one significant figure. [b] References are the same as in Table VII.

Bimolecular complex formation is characterized by values of $T\Delta S^{\circ}$ of 0.6 to 6.0 kcal. mole^{-1} with the most common values of $ca.$ 2 to 3 kcal. mole^{-1}.[25] In the correlations of $T\Delta S^{\neq}{}_{av}$ to the kinetic order of the reactions the standard states of M^{-1} and time units of seconds were employed. The experimentally determined relationship is of course dependent on the standard states employed. That the kinetic order (disregarding solvent) is obtained on dividing $T\Delta S^{\neq}{}_{av}$ by 4–6 kcal. mole^{-1} implies that $T\Delta S^{\neq}{}_{t.r.}$/species and $T\Delta S^{\neq}{}_{e}$ average out to be 4–6 kcal. mole^{-1}. The intramolecular reactions may be considered as reactions where $T\Delta S^{\neq}{}_{e}$ is more important than $T\Delta S^{\neq}{}_{t.r.}$. The two of course cannot be rigorously separated.

Compensation of $\Delta H^{\neq}$ and $T\Delta S^{\neq}$ Accompanying Catalysis.—Examination of Fig. 5 reveals that the decrease in $T\Delta S^{\neq}$ in the hydrazine reactions in passing from nucleophilic through general-base to general-acid catalysis is systematic; a decrease of $ca.$ −4 kcal. mole^{-1} is observed upon each transition. The general-base and general-acid catalyzed reactions possess more favorable $\Delta H^{\neq}$ values than the simple nucleophilic displacement reaction. However, as the slope of the plot of Fig. 5 reveals, a decrease in $\Delta H^{\neq}$ of 1.15 kcal. mole^{-1} due to the catalytic processes is compensated by a decrease of 1.0 kcal. mole^{-1} in $T\Delta S^{\neq}$. On the basis of the determination of only a single set of activation parameters for the general-base catalyzed imidazole reaction it is not possible to determine if $\Delta H^{\neq}$ and

$T\Delta S^{\neq}$ do compensate. As a result of the nature of the compensation in the hydrazinolysis reactions, the general-base and general-acid catalyzed reactions are slightly favored over the noncatalytic process. From the results at 34° the general base mechanism for the imidazole reaction is less favorable than the noncatalyzed reaction.

It would appear, therefore, that the increase in complexity of the reaction in going to higher order catalytic processes costs as much or more in kinetic energy as paid back in potential energy due to the catalytic process—the net result being very little change in the free energy of activation for the reaction. In most postulations of the mechanism of enzymatic catalysis the catalytic process is envisaged as one involving two or more functional groups of the enzyme. In enzymatic reactions the substrate is adsorbed to the catalytic site of the enzyme to form the Michaelis complex. Within this complex the nucleophile and catalytic groups are sterically oriented toward the bonded substrate. With the formation of the Michaelis complex there results a cancelling of $\Delta S^{\neq}{}_{t.r.}$ terms so that the entropy of activation is made up of only $\Delta S^{\neq}{}_{e}$. What this might signify can be seen by inspection of the activation parameters for the general-acid catalyzed hydrazinolysis of p-cresol acetate. For this reaction values of $\Delta H^{\neq}$ = $ca.$ 0.3 kcal. mole^{-1} and $T\Delta S^{\neq}$ = −19.1 kcal. mole^{-1} were observed ($\Delta F^{\neq}$ = 19.4 kcal. mole^{-1}). Now, if the molecules of hydrazine, ester, and the conjugate acid of hydrazine could be incorporated into a single species, one might anticipate that $\Delta H^{\neq}$ = 0.3 kcal. mole^{-1}, $T\Delta S^{\neq}$ = −11.1 kcal. mole^{-1}, and $\Delta F^{\neq}$ = 11.4 kcal. mole^{-1}. A $\Delta F^{\neq}$ of 11.4 kcal. mole^{-1} is attributable to a first-order rate constant of 10^3 to 10^4 sec.$^{-1}$. This value is at the ultimate limit for a rate constant involving proton abstraction in the rate-limiting step.[26] Similar considerations applied to the general-base catalyzed hydrozinolysis of p-cresol acetate predict a $\Delta F^{\neq}$ value of 10.5 kcal. mole^{-1}. Again the anticipated rate constant would be at the theoretical limit for a reaction involving proton abstraction. *No rate constant for any hydrolytic enzyme exceeds these values.* The above treatment presupposes that $\Delta H^{\neq}$ would not increase when $T\Delta S^{\neq}$ is increased through the ordering of the catalytic functions in the ground state. This is a most reasonable supposition but it must be admitted that the compensation in activation parameters is not completely understood. The only model investigated to date[14] has shown no alteration of $\Delta H^{\neq}$ to occur when $T\Delta S^{\neq}$ is increased on converting a bimolecular to an intramolecular reaction.

(24) I. Steinberg and H. A. Scheraga, *J. Biol. Chem.*, **238**, 172 (1963).

(25) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1963, p. 52.

(26) M. Eigen and G. C. Hammes, "Elementary Steps in Enzyme Reactions," to appear in *Advan. Enzymol.*