References and Notes

(1) (a) Previous paper in this series: Y. Pocker and R. F. Buchholz, *J. Am. Chem. Soc.*, **93**, 2905 (1971). (b) Supported in part by grants from the U.S. Public Health Service and the National Science Foundation.
(2) Taken in part from the Ph.D. Dissertation of David L. Ellsworth, University of Washington, Seattle, Wash., 1976.
(3) B. R. Sundheim, "Fused Salts", McGraw-Hill, New York, N.Y., 1964.
(4) M. Blander, "Molten Salt Chemistry", Interscience, New York, N.Y., 1964.
(5) C. G. Swain, A. Ohno, D. K. Roe, R. Brown, and T. Maugh III, *J. Am. Chem. Soc.*, **89**, 2648 (1967).
(6) Y. Pocker and R. F. Buchholz, *J. Am. Chem. Soc.*, **92**, 2075 (1970).
(7) Y. Pocker and R. F. Buchholz, *J. Am. Chem. Soc.*, **92**, 4033 (1970).
(8) H. H. Willard and G. F. Smith, *J. Am. Chem. Soc.*, **45**, 286 (1923).
(9) K. Ekelin and L. G. Sillén, *Acta Chem. Scand.*, **7**, 987 (1953).
(10) J. C. H. Chu, Ph.D. Thesis, University of Michigan, Ann Arbor, Mich., 1949; *Chem. Abstr.*, **43**, 8790 (1949).
(11) O. Johnson, Ph.D. Thesis, Universtiy of Michigan, Ann Arbor, Mich., 1948, *Chem. Abstr.*, **43**, 4543 (1949).
(12) S. Winstein, S. Smith, and D. Darwish, *J. Am. Chem. Soc.*, **81**, 5511 (1959).
(13) S. Winstein, E. C. Friedrich, and S. Smith, *J. Am. Chem. Soc.*, **86**, 305 (1964).
(14) Y. Pocker, *Proc. Chem. Soc., London*, 240 (1958).
(15) Y. Pocker, *J. Chem. Soc.*, 386 (1959).
(16) E. D. Hughes, C. K. Ingold, S. F. Mok, S. Patai, and Y. Pocker, *J. Chem. Soc.*, 1265 (1957), and accompanying papers.
(17) M. M. Markowitz, W. N. Hawley, D. A. Boryta, and R. F. Harris, *J. Chem. Eng. Data*, **6**, 325 (1961).
(18) (a) G. Valkanas and E. S. Waight, *J. Chem. Soc.*, 2720 (1959); (b) G. Valkanas, E. S. Waight, and M. Weinstock, *J. Chem. Soc.*, 4248 (1963); (c) D. J. Rawlinson and R. M. Noyes, *J. Chem. Soc.*, 1793 (1963).
(19) M. Y. Shandala, E. S. Waight, and M. Weinstock, *J. Chem. Soc.*, 590 (1966).
(20) (a) W. G. Young, F. Caserio, and D. Brandor, *Science*, 117, 473 (1953); (b) F. Caserio, G. E. Dennis, R. H. DeWolfe, and W. G. Young, *J. Am. Chem. Soc.*, 77, 4182 (1955).
(21) A. Frost and R. Pearson, "Kinetics and Mechanism", Wiley, New York, N.Y., 1953, p 95.
(22) J. E. Leffler, *J. Org. Chem.*, **20**, 1202 (1955).
(23) D. A. Blackadder and C. N. Hinshelwood, *J. Chem. Soc.*, 2720 (1958).
(24) D. A. Blackadder and C. N. Hinshelwood, *J. Chem. Soc.*, 2728 (1958).
(25) H. S. Venkataraman and C. N. Hinshelwood, *J. Chem. Soc.*, 4977 (1960).
(26) H. S. Venkataraman and C. N. Hinshelwood, *J. Chem. Soc.*, 4986 (1960).
(27) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions", Wiley, New York, N.Y., 1963, pp 386–402.
(28) American Petroleum Institute Research Project 44, Pittsburgh, Carnegie Institute of Technology, Catalogue of Ultraviolet Spectral Data (1948–1950): (a) Serial No. 339; (b) Serial No. 328.
(29) A. E. Eastham, *J. Chem. Soc.*, 1936 (1952).
(30) B. Rickborn and R. M. Gerkin, *J. Am. Chem. Soc.*, **90**, 4193 (1968).
(31) B. Rickborn and R. M. Gerkin, *J. Am. Chem. Soc.*, **93**, 1693 (1971).
(32) J. H. Kennedy and C. Buse, *J. Org. Chem.*, **36**, 3135 (1971).
(33) S. Searles, Jr., and M. Tamres, "The Chemistry of the Ether Linkage", S. Patai, Ed., Interscience, New York, N.Y., 1967, Chapter 6.
(34) A. F. Diorio, E. R. Lippincott, and L. Mandelkern, *Nature (London)*, **195**, 1296 (1962).
(35) W. E. Bull, S. K. Madan, and J. E. Willis, *Inorg. Chem.*, **2**, 303 (1963).
(36) W. G. Young, H. L. Goering, and S. Winstein, *J. Am. Chem. Soc.*, **73**, 1958 (1951).
(37) C. A. Bunton, Y. Pocker, and H. Dahn, *Chem. Ind. (London)*, 1516 (1958).
(38) Y. Pocker, *J. Chem. Soc.*, 4323 (1958).
(39) Y. Pocker, *J. Chem. Soc.*, 4318 (1958).
(40) Y. Pocker, *Chem. Ind. (London)*, 195 (1959).
(41) The repeated finding that $\Delta\Delta H^{\ddagger} = 0$ for these powerful salt effects is fascinating and important. We wish to postpone a more detailed analysis of these data until our physico-chemical studies of these unusual electrolytic solutions are more complete. One line of reasoning would be that the negative enthalpy term for electrostatic stabilization is apparently offset by a positive enthalpy term for the release of ether molecules, but no such compensatory effect occurs with the respective terms in the entropy of activation. Clearly, the overall entropic effect is more complex and results in $\Delta\Delta S^{\ddagger}$ becoming more positive as the concentration of salt increases. It has not escaped our attention that, in some sense, this change in $\Delta\Delta S^{\ddagger}$ represents a partial "utilization" of electrostatic energy to drive the isomerization of **1** to **2**.

Electrostatic Catalysis by Ionic Aggregates. 5.[1] Aminolysis Reaction of *p*-Nitrophenyl Acetate with Imidazole and the Proton Transfer from *p*-Nitrophenol in Lithium Perchlorate–Diethyl Ether Solutions[2]

Y. Pocker* and David L. Ellsworth

Contribution from the Department of Chemistry, University of Washington, Seattle, Washington 98195.

Received July 26, 1976

Abstract: The equilibrium constant associated with the proton transfer from *p*-nitrophenol to imidazole in diethyl ether solutions is shown to be highly sensitive to the amount of added $LiClO_4$. For example, in pure ether $K_{eq_{PNP}}^{0} = 1.87 \times 10^{-7}$, while in the presence of 4.58 M $LiClO_4$, it rises to a value of $K_{eq_{PNP}} = 1.21 \times 10^{-1}$, an apparent increase of 647 000-fold. The experimental results indicate that we are dealing with a dissociation into *p*-nitrophenolate and imidazolium ions rather than with an ionization into ion pairs. While the *p*-nitrophenolate and imidazolium ions act as if they are separated from one another, each probably exists as an ionic aggregate with $LiClO_4$ and solvent, consistent with the fact that K_{eq} shows a third-order dependence on the concentration of lithium perchlorate. The aminolysis reaction of *p*-nitrophenyl acetate by imidazole in lithium perchlorate–diethyl ether solution exhibits good second-order kinetics; in pure ether, $k_2 = 7.13 \times 10^{-7}\ M^{-1}\ s^{-1}$, and in solutions containing 4.96 M salt, $k_2 = 4.14 \times 10^{-2}\ M^{-1}\ s^{-1}$, an increase of 58 000-fold. Temperature dependence studies reveal that the energy of activation remains essentially constant throughout the increase in $LiClO_4$ concentration, while the entropy of activation increases steadily. A possible choice of mechanisms for the aminolysis reaction is discussed in terms of the available experimental evidence. Catalysis by ionic aggregates of $LiClO_4$ in diethyl ether is clearly documented and possible transition states are presented.

Introduction

In Part 4,[1] we showed that when anhydrous lithium perchlorate is dissolved in solvents of low ionizing capacity such as diethyl ether, tetrahydrofuran, propylene oxide, and diethyl carbonate, the resulting solutions exhibit a powerful catalysis with respect to the rearrangement of 1-phenylallyl chloride to cinnamyl chloride and that this catalysis appears to be essentially electrostatic in nature. In the case of dimethylformamide, a solvent of much higher dielectric constant and greater ionizing capacity, the catalysis was not so marked, but was exhibited nonetheless. A study of the activation parameters in each of these various lithium perchlorate–solvent systems revealed that the progressive decreases in the free energy of re-

arrangement were due to respective increases in the entropy of activation.

It has been noted in Part 4 that ion pair interactions are responsible for the observed acceleration in rate of ionization processes occurring in aprotic solvents through extra stabilization of the transition state relative to the ground state.[3,4] In fact, even in enzymatic catalysis, contributions from this effect have been postulated. The single displacement reactions of β-amylase and the hydrolytic processes of lysozyme have been interpreted in terms of a cooperative ion pair stabilization in the hydrophobic cleft.[5-7] If the substrate is held in a hydrophobic cavity by the enzyme, its heterolysis could be subject to powerful electrostatic catalysis similar to that in aprotic solvents.[8] It is of considerable interest to evaluate to what extent the electrostatic catalysis arising from ion pairs alone might offset the disadvantage of an unfavorable hydrophobic environment.

In the present paper, we describe the role of electrostatic catalysis in the aminolysis of *p*-nitrophenyl acetate by imidazole. The reaction of amines with esters to form amides was first discovered in 1834 by Liebig.[9] It was nearly a century later when Hinshelwood[10] and Day et al.[11] studied the mechanism of this reaction in aprotic solvents. Their results with simple alkyl esters were not promising, and it was not until the last 10 years that the mechanism of the reaction in aprotic solvents was studied in detail.[12-15] It has long been suggested that imidazole was an important or essential part of the active site of hydrolytic enzymes, such as α-chymotrypsin, trypsin, and acetylcholinesterase.[16-18] Phenyl acetates have been found to serve as nonspecific substrates for esterases,[18] and, in particular, the hydrolysis of *p*-nitrophenyl acetate has been found to be catalyzed by imidazole.[16] Menger and co-workers[12,13] have proposed that the breakdown of a dipolar tetrahedral intermediate is the rate-limiting step in ester aminolysis in aprotic solvents. In the present work, we have used the aprotic electrostatic environment of $LiClO_4$–diethyl ether solutions (LPDE) to study the possible rate enhancement of the aminolysis reaction of *p*-nitrophenyl acetate by imidazole. The LPDE solutions were chosen because their behavior has been delineated earlier in some detail[19] and also because they seem to exhibit the highest rate enhancements.[1,19-21] In order to better understand the kinetic data, we felt it would be valuable to first study the effect of lithium perchlorate on the dissociation of the corresponding phenol. Consequently, we undertook a determination of the equilibrium constant of *p*-nitrophenol in LPDE solutions, using imidazole as the base.

In our investigation of the aminolysis reaction, we have determined the activation parameters, E_a, $\Delta H^{\ddagger}$, $\Delta G^{\ddagger}$, and $\Delta S^{\ddagger}$, as a function of lithium perchlorate concentration and have thereby delineated the specific energy requirements of the accompanying electrostatic catalysis.

Experimental Section

Materials. All methods of preparation and purification of materials used have been previously described,[1] except for *p*-nitrophenol, *p*-nitrophenyl acetate, imidazole, and *N*-acetylimidazole.

***p*-Nitrophenol.** Reagent grade *p*-nitrophenol (Eastman) was recrystallized from diethyl ether.

***p*-Nitrophenyl Acetate.** Reagent grade *p*-nitrophenyl acetate (Aldrich Chemical Co.) was recrystallized from anhydrous diethyl ether to a constant melting point of 79.5–81.0 °C.

Imidazole. Reagent grade imidazole (Aldrich Chemical Co.) was recrystallized three times from benzene.

***N*-Acetylimidazole.** *N*-Acetylimidazole was prepared by following exactly the method of Wieland and Schneider:[22] white needles, mp 102.5–103.5 °C. These data are in accord with literature values.[22]

Kinetic Measurements. The reaction of *p*-nitrophenyl acetate (PNPA) with imidazole was studied by following the increase of absorbance at 400 nm, resulting from the formation of the *p*-nitrophenolate ion (ε 18 400).[23] All spectral measurements were made on a Beckman DU-2 equipped with a constant temperature bath set at 25.0 ± 0.05 °C controlled by a Sargent Thermonitor. In the case of temperature dependence studies, temperatures below 20 °C were achieved by use of a Formatemp Jr., Model 2095-2, in place of the Sargent Thermonitor. The imidazole was in 100-fold excess and pseudo-first-order rates were obtained by plotting log $(A_\infty - A_i)$ against time. In general, the pseudo-first-order rate constants for the aminolysis were obtained with an accuracy of ±2%. The first-order plots were linear to at least 2 half-life times, and, in some cases where $\tau_{1/2} \leq 2$ h, the plots were linear up to 3 half-lives. Reactions in pure solvent or dilute salt solution with very long half-life times ($\tau_{1/2} > 24$ h) necessitated the calculation of "initial" rate constants associated with the first 10–25% of reaction.

Equilibrium Constant for *p*-Nitrophenol. The equilibrium constant of *p*-nitrophenol (PNP) was determined by addition of the phenol to various solutions of LPDE and imidazole. The absorbance of the *p*-nitrophenolate ion was measured at 400 nm [experimental, ε 23 040 (lit.,[23] ε 18 400)], using a Beckman DU-2 equipped with a constant temperature bath set at 25.0 ± 0.05 °C controlled with a Sargent Thermonitor. The value for K_{eqPNP} was calculated using the relationship: $K_{eqPNP} = [p\text{-}O_2NC_6H_4O^-][ImH^+]/[p\text{-}O_2NC_6H_4OH]\cdot[Im]$.

Thermodynamic Activation Parameters. The effect of temperature on the reaction of *p*-nitrophenyl acetate with imidazole in LPDE was determined, using the same method as previously described in Part 4.[1] The values for E_a and $\Delta H^{\ddagger}$ were obtained with an accuracy of ±0.5 kcal/mol. The corresponding values of $\Delta S^{\ddagger}$ were found to be accurate to within ±1.5 cal/(deg mol).

Results

Equilibrium Constant for *p*-Nitrophenol. An investigation of the dissociation of *p*-nitrophenol was made in LPDE over the lithium perchlorate concentration range of 0.0 to 5.05 M. When *p*-nitrophenol (PNP) is dissolved in dry ether, there is virtually no *p*-nitrophenolate ion formed. Addition of the base imidazole in approximately 70-fold excess still produces only a small amount of the phenolate ion. As lithium perchlorate is added to the solution of the phenol and the base, the characteristic yellow color of the *p*-nitrophenolate ion appears as an intense peak at 400 nm. As more lithium perchlorate is added, the yellow color progressively becomes more intense. At any particular concentration of lithium perchlorate, an apparent equilibrium constant, K_{eqPNP}, can be calculated for the dissociation of *p*-nitrophenol as shown below:

$$p\text{-}O_2NC_6H_4OH + Im \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} p\text{-}O_2NC_6H_4O^- + ImH^+ \quad (1)$$

$$K_{eqPNP} = \frac{k_1}{k_{-1}} = \frac{[p\text{-}O_2NC_6H_4O^-][ImH^+]}{[p\text{-}O_2NC_6H_4OH][Im]} \quad (2)$$

where $p\text{-}O_2NC_6H_4OH$ is *p*-nitrophenol and Im is imidazole. The values for K_{eqPNP} are listed in Table I.

The results show that the overall effect is quite substantial. The apparent equilibrium constant increases from $K_{eqPNP}{}^0 = 1.87 \times 10^{-7}$ in pure ether to $K_{eqPNP} = 1.21 \times 10^{-1}$ at 4.58 M lithium perchlorate, with added imidazole in each case, for an apparent increase of 647 000 fold. It is of interest to note that the value of the equilibrium constant reaches a limiting value, as shown by the fact that the value at 4.58 M LPDE is nearly the same as that at 5.05 M LPDE and appears to be the maximum value in this case. When one compares the ratio $K_{eqPNP}{}^{5\ M\ LiClO_4}/K_{eqPNP}{}^0 = 578\ 000$ for *p*-nitrophenol with the ratio $K_{eqTCl}{}^{5\ M\ LiClO_4}/K_{eqTCl}{}^0 = 7\ 000\ 000$ obtained by Pocker and Buchholz[19] in the study of the equilibrium constant for the dissociation of trityl chloride (TCl), it may be seen that TCl exhibits a change in K_{eq} which is about 10 000 times greater than that for *p*-nitrophenol.

It is informative to determine the dependence of the increase in K_{eqPNP} on the concentration of lithium perchlorate. Values of the log $(K_{eqPNP} - K_{eqPNP}{}^0)$ where $K_{eqPNP}{}^0 = 1.87 \times 10^{-7}$ at 0.0 M LPDE were plotted against the log $[LiClO_4]$. The order was found to remain the same throughout the range of lithium

Table I. The Equilibrium Constant for the Proton Transfer from *p*-Nitrophenol to Imidazole in LPDE at 25.0 °C[a]

[$LiClO_4$], M	[Imidazole], M[b]	[*p*-Nitrophenol], M[c]	[*p*-Nitrophenolate], M	$K_{eq_{PNP}}$
0.00	5.89×10^{-3}	8.39×10^{-5}	3.04×10^{-7}	1.87×10^{-7}
0.349	5.89×10^{-3}	8.06×10^{-5}	3.64×10^{-6}	2.80×10^{-5}
0.698	5.88×10^{-3}	7.79×10^{-5}	6.42×10^{-6}	9.11×10^{-5}
1.05	5.87×10^{-3}	6.61×10^{-5}	1.81×10^{-5}	8.45×10^{-4}
1.40	5.86×10^{-3}	5.90×10^{-5}	2.52×10^{-5}	1.84×10^{-3}
1.74	5.86×10^{-3}	5.43×10^{-5}	2.99×10^{-5}	2.81×10^{-3}
2.09	5.85×10^{-3}	4.64×10^{-5}	3.78×10^{-5}	5.26×10^{-3}
2.44	5.85×10^{-3}	3.99×10^{-5}	4.43×10^{-5}	8.41×10^{-3}
2.83	5.84×10^{-3}	3.39×10^{-5}	5.33×10^{-5}	1.43×10^{-2}
3.13	5.83×10^{-3}	2.77×10^{-5}	5.65×10^{-5}	1.98×10^{-2}
3.58	5.83×10^{-3}	2.00×10^{-5}	6.42×10^{-5}	3.54×10^{-2}
4.02	5.82×10^{-3}	1.17×10^{-5}	7.25×10^{-5}	7.72×10^{-2}
4.58	5.81×10^{-3}	0.82×10^{-5}	7.60×10^{-5}	1.21×10^{-1}
5.05	5.81×10^{-3}	0.90×10^{-5}	7.52×10^{-5}	1.08×10^{-1}
3.14	0.00	8.39×10^{-5}	3.47×10^{-7}	1.44×10^{-9} M[d]
0.00	0.00	8.40×10^{-5}	2.16×10^{-7}	5.55×10^{-10} M[d]

[a] $[Imidazole]_0 = 5.89 \times 10^{-3}$ M, $[p\text{-nitrophenol}]_0 = 8.42 \times 10^{-5}$ M. [b] Concentration of free imidazole. [c] Concentration of free *p*-nitrophenol. [d] Calculated from $K = [p\text{-}O_2NC_6H_4O^-][Et_2OH^+]/[p\text{-}O_2NC_6H_4OH]$.

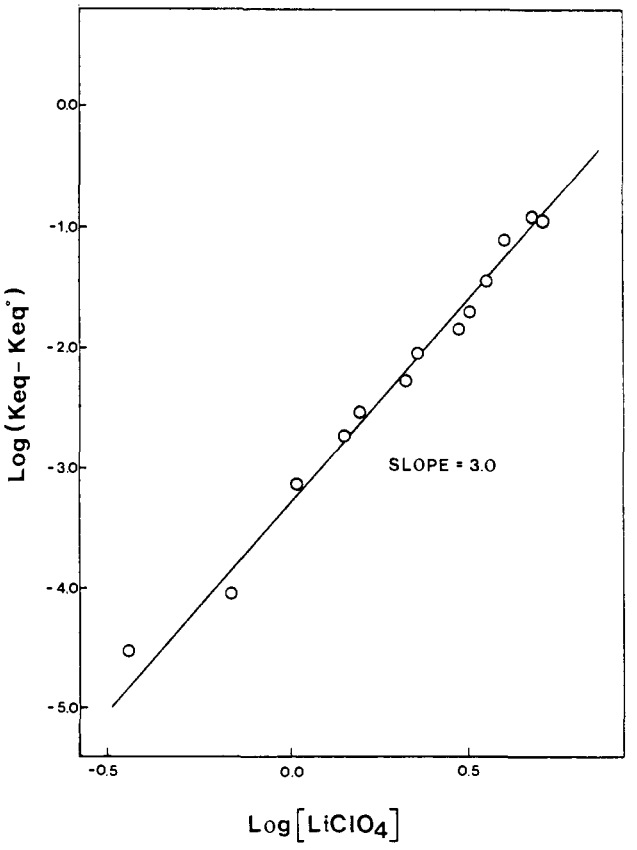


Figure 1. Plot of the log ($K_{eq} - K_{eq}^0$) vs. log [$LiClO_4$] for the dissociation of *p*-nitrophenol with imidazole in LPDE at 25.0 °C.

perchlorate concentrations studied and was equal to 3.0 as shown in Figure 1. By comparison, Pocker and Buchholz[19] found that, in the case of TCl, the order varied and showed every change from 2 to 12. Thus, the dissociation of *p*-nitrophenol must have a different capacity for lithium perchlorate than the corresponding process for TCl.

Kinetic Results of the Aminolysis Reaction of *p*-Nitrophenyl Acetate with Imidazole. The aminolysis reaction of *p*-nitrophenyl acetate (PNPA) with imidazole was studied in LPDE solutions in the lithium perchlorate concentration range of 0.0 to 4.96 M. The values for the rate constant k_{obsd} are listed in

Table II. Values of k_{obsd} and k_2 for the Reaction of *p*-Nitrophenyl Acetate with Imidazole in LPDE at 25.0 °C[a,b]

[$LiClO_4$], M	k_{obsd}, s^{-1}	k_2, M^{-1} s^{-1}
0.00	4.20×10^{-9}	7.13×10^{-7}
0.266	5.30×10^{-8}	9.00×10^{-6}
0.532	1.53×10^{-6}	2.60×10^{-4}
1.01	4.41×10^{-6}	7.49×10^{-4}
1.51	9.98×10^{-6}	1.69×10^{-3}
2.02	1.80×10^{-5}	3.06×10^{-3}
2.39	2.44×10^{-5}	4.14×10^{-3}
2.98	5.30×10^{-5}	9.00×10^{-3}
3.99	9.20×10^{-5}	1.56×10^{-2}
4.25	1.68×10^{-4}	2.85×10^{-2}
4.50	2.09×10^{-4}	3.55×10^{-2}
4.96	2.44×10^{-4}	4.14×10^{-2}

[a] [*p*-Nitrophenyl acetate] = 5.54×10^{-5} M. [b] [Imidazole] = 5.89×10^{-3} M.

Table II. If we express the rate equation in the same form as Satchell and Secemski[24] in their study of the aminolysis of *p*-nitrophenyl acetate in diethyl ether, it would have the form of

$$-d[ester]/dt = (k_2[amine] + k_3[amine]^2)[ester] = k_{obsd}[ester] \quad (3)$$

In our study in 2.98 M LPDE, we found no evidence for an order in amine greater than 1, over a change in imidazole concentration of 100-fold. This is shown in Figure 2 with a plot of log k_{obsd} vs. log [imidazole]. Thus, we may rewrite eq 3 to give the following equation, which is applicable to our work in LPDE:

$$-d[ester]/dt = k_2[imidazole][ester] = k_{obsd}[ester] \quad (4)$$

where $k_2 = k_{obsd}/[imidazole]$. The values for k_2 are found listed in Table II. On the other hand, other groups who have studied this particular reaction in the absence of added $LiClO_4$ have reported that the aminolysis has a term in the rate equation which is second order in amine[24-26] and under certain conditions shows evidence of a higher order in amine.[24]

It is of interest to examine the overall catalytic effect of the LPDE system on the reaction. The results of the comparison of k_{obsd} at 0.0 M lithium perchlorate with k_{obsd} at various higher concentrations of lithium perchlorate are shown in Table III. The LPDE solutions produce an apparent increase

Table III. The Catalytic Effect of Lithium Perchlorate in Ether at 25.0 °C

Range of $[LiClO_4]$, M	Increase in k_{obsd}
0.0 to 0.532	3.64×10^2
0.0 to 1.51	2.34×10^3
0.0 to 2.98	1.26×10^4
0.0 to 4.96	5.81×10^4

in k_{obsd} which is over 58 000 fold with a change in lithium perchlorate concentration of 4.96 M.

It is informative to compare our results in LPDE solutions with those obtained by other groups for the aminolysis of *p*-nitrophenyl acetate in aprotic solvents of low ionizing capacity. Table IV presents a summary of some of these results. The solvents used range from toluene with a dielectric constant of 2.38[28] to acetonitrile with a dielectric constant of 37.5.[28] All the amines have fairly basic pK_a values, except imidazole (see Table IV). Tlhe most striking feature of the comparison is that the reaction of imidazole in pure ether (0.0 M LPDE) with *p*-nitrophenyl acetate is very slow compared with any of the others, and yet it is one of the fastest when carried out in an ether solution containing 4.96 M LPDE. If the differences in concentration are considered, only the reaction in chlorobenzene with benzamidine, a base with a pK_a value about 4.5 units higher than that of imdazole and with unusual bifunctional capacity,[25] exceeds the value for k_{obsd} in 4.96 M LPDE. This is even more easily seen by comparing the values of the second-order rate constant, k_2, in Table IV. These comparisons demonstrate once again the remarkable catalytic efficiency of LPDE solutions.

The determination of the dependence of the increase in k_{obsd} on the concentration of lithium perchlorate was obtained by plotting the values of log $(k_{obsd} - k_{obsd}^0)$, where $k_{obsd}^0 = 4.20 \times 10^{-9}$ s^{-1} ($[LiClO_4] = 0.0$ M), against log $[LiClO_4]$ for the various LPDE solutions. The results are shown in Figure 3. This plot shows every order from 1 to 4 and means that as lithium perchlorate is added to diethyl ether, raising the concentration from 0.0 to 4.96 M, the order in lithium perchlorate changes from 0 to 4.

It is possible to state something about the products of the aminolysis reaction as some of them are detectable by spectrophotometric means. A typical run with the [PNPA] = 5.54×10^{-5} M, [imidazole] = 5.89×10^{-3} M, and the concentration of LPDE = 2.94 M was scanned from 200 to 450 nm at several time intervals during the reaction, using a Varian Techtron, Model 635, spectrophotometer. The rate of appearance of the *p*-nitrophenolate ion at a UV max 400 nm

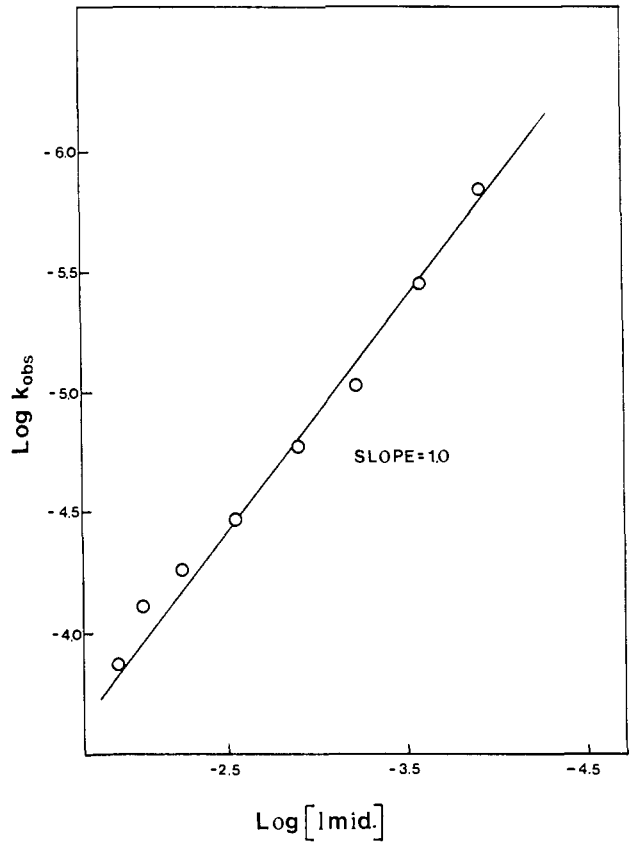


Figure 2. Determination of the order of imidazole in the reaction with *p*-nitrophenyl acetate in 2.98 M LPDE at 25.0 °C.

coincided with the disappearance of the *p*-nitrophenyl acetate at a UV max 266 nm (lit.[16] UV max 278 nm), and the appearance of *N*-acetylimidazole at UV max 238 nm (lit.[29] UV max 245 nm). The values of UV max for the acetate and acetylimidazole are apparently shifted to lower wavelengths by the LPDE solution. When the reaction is complete (>10 half-lives), the absorption peaks for *p*-nitrophenolate ion and *N*-acetylimidazole are at about 94% of their calculated value using Beer's Law, and the absorption peak for *p*-nitrophenyl acetate has virtually disappeared. It might also be noted that at no time was an absorption peak for *p*-nitrophenol detected, UV max 309 nm in LPDE (experimental value). *N*-Acetylimidazole has been detected and reported as the most likely intermediate in the hydrolysis of PNPA catalyzed by imidazole.[16]

Table IV. Comparison of Aminolysis Reactions of *p*-Nitrophenyl Acetate by Various Amines in Aprotic Solvents with That by Imidazole in LPDE at 25.0 °C

Solvent	Amine	pK_a	[Amine], M	[PNPA], M	k_{obsd}, s^{-1}	k_2, M^{-1} s^{-1} [e]
0.0 M LPDE[a]	Imidazole	6.97[f]	5.89×10^{-3}	5.54×10^{-5}	4.20×10^{-9}	7.13×10^{-7}
4.96 M LPDE[a]	Imidazole		5.89×10^{-3}	5.54×10^{-5}	2.44×10^{-4}	4.14×10^{-2}
Diethyl ether[b]	*n*-Butylamine	10.7	1.97×10^{-2}	$\sim 10^{-4}$	1.25×10^{-4}	6.35×10^{-3}
Diethyl ether[b]	*tert*-Butylamine	10.7	9.5×10^{-2}	$\sim 10^{-4}$	9.83×10^{-7}	1.03×10^{-5}
Diethyl ether[b]	Piperidine	11.1	2.27×10^{-2}	$\sim 10^{-4}$	4.33×10^{-4}	1.91×10^{-2}
Diethyl ether[b]	Diethylamine	11.0	3.84×10^{-2}	$\sim 10^{-4}$	7.33×10^{-6}	1.91×10^{-4}
Chlorobenzene[c]	Benzamidine	11.6	2.15×10^{-3}	1.07×10^{-5}	7.42×10^{-3}	3.45
Chlorobenzene[c]	*n*-Butylamine		2.21×10^{-2}	3.25×10^{-4}	2.91×10^{-5}	1.32×10^{-3}
Toluene[d]	Piperidine		5.60×10^{-3}	2.53×10^{-5}	6.90×10^{-5}	1.23×10^{-2}
Toluene[d]	Imidazole		1.04×10^{-2}	2.53×10^{-5}	7.80×10^{-6}	7.50×10^{-4}
Acetonitrile[b]	*n*-Butylamine		3.13×10^{-3}	$\sim 10^{-4}$	7.67×10^{-4}	2.45×10^{-1}

[a] Data was taken from Table II. [b] Data was taken from ref 24. [c] Data was taken from ref 25. [d] Data was taken from ref 26. [e] Values calculated from the relationship $k_2 = k_{obsd}/[amine]$. [f] Reference 27.

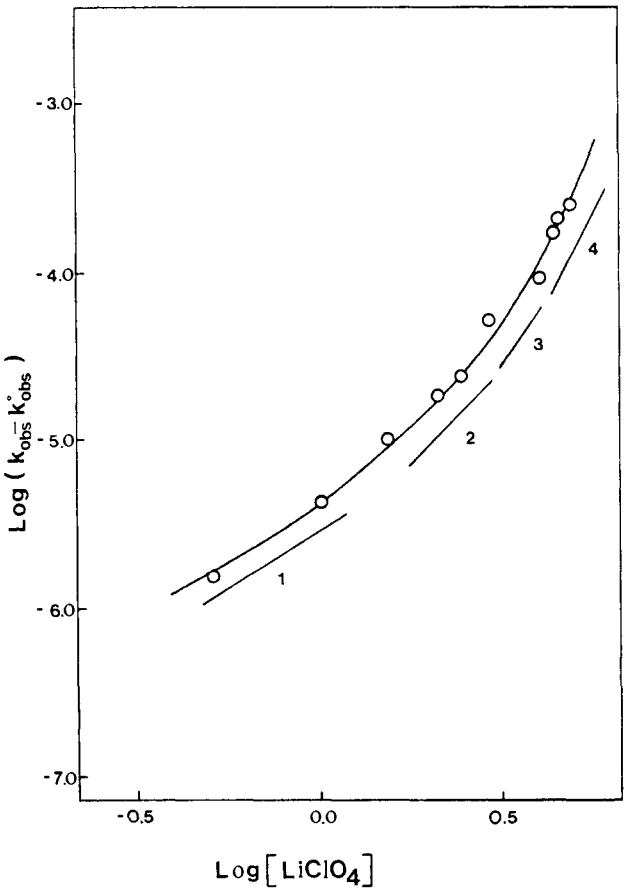


Figure 3. Plot of log ($k_{obsd} - k_{obsd}^{0}$) for *p*-nitrophenyl acetate and imidazole vs. log [$LiClO_4$] in LPDE at 25.0 °C.

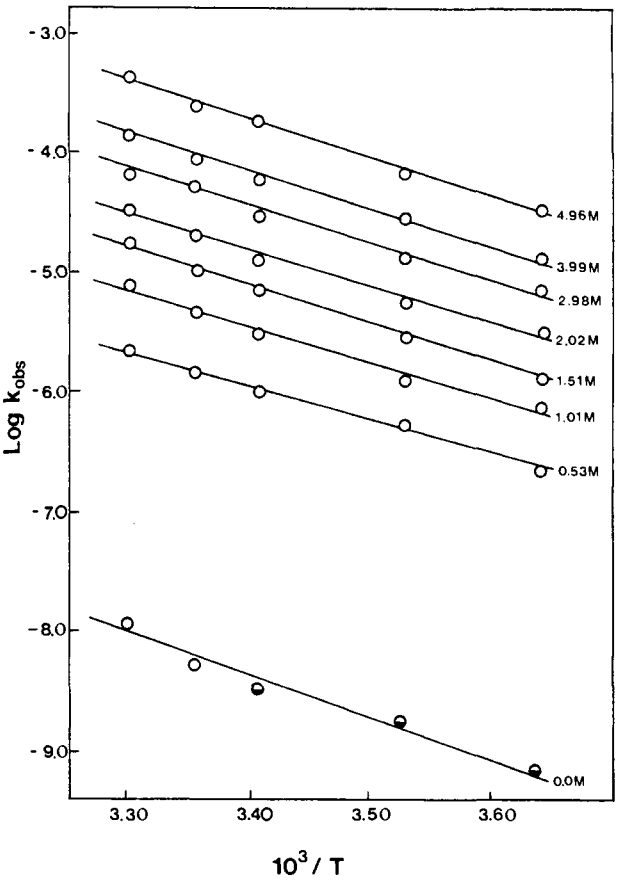


Figure 4. Determination of the temperature dependence of the rate constant for the reaction of *p*-nitrophenyl acetate with imidazole in LPDE at 25.0 °C: (◒) extrapolated value.

Activation Parameters of the Aminolysis Reaction of *p*-Nitrophenyl Acetate by Imidazole. The temperature dependence of the observed rate constant, k_{obsd}, for the reaction of *p*-nitrophenyl acetate with imidazole was determined by the rate of appearance of *p*-nitrophenolate ion at various temperatures and in various LPDE solutions. Arrhenius plots were constructed from the data and were used to determine the energy of activation, E_a, and then the other activation parameters were calculated using the values of k_2 for the rate constant, employing the standard equations.[30] The results are shown in Table V, and the corresponding Arrhenius plots are shown in Figure 4. From the data it is apparent that the decrease in the free energy of activation, $\Delta G^{\ddagger}$, with increasing lithium perchlorate concentration is primarily dictated by an increase in the entropy of activation, $\Delta S^{\ddagger}$. Thus, as the molar concentration of lithium perchlorate is increased, the values of E_a and the enthalpy of activation, $\Delta H^{\ddagger}$, remain essentially constant while the rate constant, k_2, increases and the major change in the activation parameters is a large increase in $\Delta S^{\ddagger}$. This same observation was made concerning the results for the isomerization of 1-phenylallyl chloride which were reported in Part 4.[1] An examination of the Arrhenius plots in Figure 4 shows the lines to be very nearly parallel in all cases, demonstrating visually that the slopes are virtually the same, thus giving rise to very similar values of E_a.

The value of $\Delta S^{\ddagger}$ increases with an increase in the lithium perchlorate concentration. This may be seen more clearly by an examination of Figure 5. It may be seen from the curve that results from the plot of $\Delta S^{\ddagger}$ vs. [$LiClO_4$] that a very large increase occurs in $\Delta S^{\ddagger}$ as the [$LiClO_4$] rises from 0.0 to 1.0 M. The effect then becomes less dramatic as the concentration is increased by increments of 0.5 M. From Table VI this trend may be seen numerically. In Figure 5, the corresponding curve of the change in $\Delta S^{\ddagger}$ vs. [$LiClO_4$] for the isomerization reaction in LPDE from Part 4 is shown for comparison with the plot for the aminolysis. It may be seen that the general shape of the two curves is very similar. Both reactions show a very large change in $\Delta S^{\ddagger}$ with the addition of lithium perchlorate, increasing the concentration from 0.0 to 0.5 M. This is followed by a concomitant decrease in change in $\Delta S^{\ddagger}$ as the molar concentration of lithium perchlorate is increased.

Table V. Activation Parameters for the Reaction of *p*-Nitrophenyl Acetate with Imidazole in LPDE at 25.0 °C

[$LiClO_4$], M	E_a, kcal/mol	$\Delta H^{\ddagger}$, kcal/mol	$\Delta G^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, cal/(deg mol)
0.00	+14.8	+14.2	+25.8	−38.9
0.53	+14.2	+13.6	+22.3	−29.2
1.01	+14.5	+13.9	+21.7	−26.2
1.51	+14.9	+14.3	+21.2	−23.2
2.02	+14.9	+14.3	+20.8	−21.8
2.98	+14.9	+14.3	+20.2	−19.8
3.99	+14.9	+14.3	+19.9	−18.8
4.96	+14.9	+14.3	+19.3	−16.8

Discussion

We have demonstrated that the dissociation of *p*-nitrophenol in ether may be effectively enhanced by the addition of lithium perchlorate. The thermodynamic pK_a of this weak acid in water is 7.15 at 25 °C.[31] The pK_a value of the phenol in pure ether with no added base or lithium perchlorate may be calculated from the relationship: $-\log [p\text{-}O_2NC_6H_4O^-][Et_2O^+H]/[p\text{-}O_2NC_6H_4OH] = pK_a$, using the data from

Table VI. The Relationship of $\Delta S^{\ddagger}$ with Increasing Lithium Perchlorate Concentration for the Reaction of *p*-Nitrophenyl Acetate with Imidazole in LPDE[a]

Change in $[LiClO_4]$, M	$\Delta(\Delta S^{\ddagger})$, cal/(deg mol)
0.0 to 0.5	8.7
0.5 to 1.0	4.1
1.0 to 1.5	2.6
1.5 to 2.0	1.9
2.0 to 3.0	2.0
3.0 to 4.0	1.4
4.0 to 5.0	1.1

[a] These results are deduced from Figure 5.

Table I. Such a calculation gives the value of $pK_a = 9.26$. Employing the same method and using data from the same Table, it may be seen that the addition of 3.14 M lithium perchlorate lowers the pK_a to 8.84.

Addition of the base, imidazole, in the absence of perchlorate gives a K_{eqPNP} of 1.87×10^{-7}; but addition of both imidazole and lithium perchlorate increases the apparent K_{eqPNP} until at 4.58 M $LiClO_4$ a limiting value is obtained, $K_{eqPNP} = 1.21 \times 10^{-1}$. This means that the maximum catalytic effect on the dissociation of *p*-nitrophenol in LPDE solutions with imidazole acting as the base is about 647 000. One of the questions which must be considered with regard to this interesting result is whether the ionic products obtained from the interaction of *p*-nitrophenol with imidazole in LPDE solutions should be treated as tight ion pairs or as separated ions. In the determination of K_{eqPNP}, either one of two relationships may be used. The tight ion pair ionization scheme may be expressed in terms of eq 5 and the corresponding K_{eqPNP}' calculated from eq 6:

$$p\text{-}O_2NC_6H_4OH + Im \underset{k_{-1}'}{\overset{k_1'}{\rightleftharpoons}} p\text{-}O_2NC_6H_4O^-, ImH^+ \quad (5)$$

$$K_{eqPNP}' = \frac{k_1'}{k_{-1}'} = \frac{[p\text{-}O_2NC_6H_4O^-, ImH^+]}{[p\text{-}O_2NC_6H_4OH][Im]} \quad (6)$$

where $p\text{-}O_2NC_6H_4OH$ represents free *p*-nitrophenol and Im, free imidazole. The dissociation to form separated ions may be expressed by eq 7 and the K_{eqPNP} calculated from eq 8:

$$p\text{-}O_2NC_6H_4OH + Im \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} p\text{-}O_2NC_6H_4O^- + ImH^+ \quad (7)$$

$$K_{eqPNP} = \frac{k_1}{k_{-1}} = \frac{[p\text{-}O_2NC_6H_4O^-][ImH^+]}{[p\text{-}O_2NC_6H_4OH][Im]} \quad (8)$$

Two different methods were used to vary the concentrations of both the base and the phenol over a 100-fold range while holding the LPDE concentration constant. In the first method, the concentration of the base is held constant at 5.89×10^{-3} M, while the concentration of the phenol is varied from 1.68×10^{-4} to 1.68×10^{-6} M (method IA). The process is then repeated holding the concentration of the phenol constant at 8.42×10^{-5} M and varying that of the base from 1.18×10^{-2} to 1.18×10^{-4} M (method IB). In the second method (method II), a solution containing the phenol at a concentration of 1.68×10^{-4} M and the base at a concentration of 1.18×10^{-2} M is successively diluted over a 100-fold range of concentrations. In each set of experiments, it was found that eq 8 led to a constant value for K_{eq} at 2.09 M $LiClO_4$. Clearly, then, the scheme represented by eq 7 appears to be more nearly correct.[32] Thus, in ether, in the presence of a substantial concentration of lithium perchlorate, ionized *p*-nitrophenol behaves like free *p*-nitrophenolate ion, and the protonated base acts like a free imidazolium ion. It is most likely, however, that while these ions act like they are separated from one another, each probably exists as an ionic aggregate with lithium perchlorate and solvent. Pocker and Buchholz, in their study of the ionization and dissociation of trityl chloride (TCl), pointed out that, in the presence of lithium perchlorate, ionized TCl behaves like free T^+, but is actually present as $T^+ClO_4^-(Li^+ClO_4^-)_n$. Furthermore, their observations ruled out the existence of detectable concentrations of T^+Cl^- ion pairs[19] in LPDE solutions.

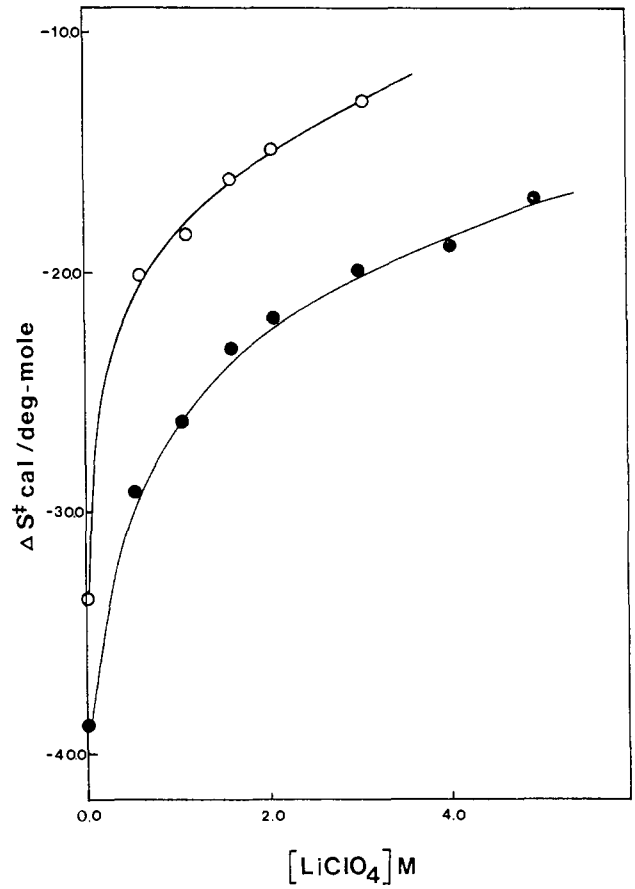


Figure 5. Plot of $\Delta S^{\ddagger}$ for the isomerization of 1-phenylallyl chloride vs. the molar concentration of lithium perchlorate in LPDE (○) (data taken from ref 1). Plot of $\Delta S^{\ddagger}$ for the reaction of *p*-nitrophenyl acetate with imidazole vs. the molar concentration of lithium perchlorate in LPDE (●).

From Figure 1 we know that the order in $LiClO_4$ for the dissociation of *p*-nitrophenol is 3.0. Thus, we may formulate a catalytic path consistent with this observation of third-order dependence as shown in the following equation:

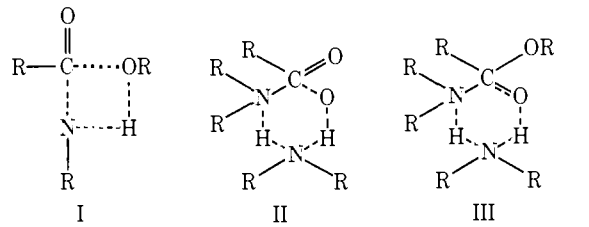
$$p\text{-}O_2NC_6H_4OH + Im + 3Li^+(OEt_2)_xClO_4^- \underset{k_{-1}^*}{\overset{k_1^*}{\rightleftharpoons}} ImH^+ClO_4^-, Li^+(OEt_2)_xClO_4^- + Li^+(OEt_2)_x{}^-OC_6H_4NO_2\text{-}p, Li^+(OEt_2)_xClO_4^- \quad (9)$$

The value of *x* is equal to 2 below concentrations of 4.25 M LPDE and may be 1 or 2 above 4.25 M LPDE.[19] Thus, when *p*-nitrophenol is dissolved in LPDE solutions with imidazole present, we may envision it being under the influence of the Coulombic fields that surround the ionic aggregates of lithium perchlorate in ether. The final state for the dissociation consists of the fully ionized phenolate and imidazolium ions and should be stabilized to a greater extent by the LPDE system than the initial state consisting of neutral molecules. Therefore, it might be postulated that the LPDE system stabilizes the dissociated state by virtue of the much stronger interaction of the Coulombic fields of its ionic aggregates with the much more polar final state than with the weakly polar initial state. The orien-

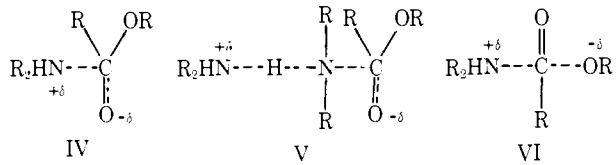
tation of the LPDE ionic aggregates in the final state is unknown and may only be expressed in a statistical manner as being a total of three.

We have also demonstrated that the aminolysis reaction of *p*-nitrophenyl acetate with the amine base imidazole may be effectively catalyzed by the addition of lithium perchlorate to diethyl ether. We have also shown by comparison with other aprotic solvents of low ionizing capacity that LPDE solutions can produce remarkable rate enhancements which produce a rate constant, k_2, that is greater in magnitude than can be produced even by the use of much more basic amines and solvents of higher dielectric constant such as acetonitrile. It is of interest, therefore, to examine a possible rationale for these results and endeavor to propose a suitable explanation and mechanism.

The mechanism of the aminolysis of esters in aqueous solution has long been a subject of investigation and debate, and several attempts have been made in recent years to propose mechanistic paths and possible transition states for the various aminolysis paths.[33,34] Satchell and Secemski[24] have pointed out that in hydroxylic solvents the rate equation for ester aminolysis is rather complex as a rule, but in aprotic solvents of low ionizing power, such as diethyl ether, it is rather simple by comparison. Complications arising from solvolysis and the catalytic contributions of solvent species are absent. Despite this, Menger and Smith[12] point out that an unusual number of conflicting conclusions have arisen. They point to examples such as (1) overall third-order aminolysis of esters in aprotic solvents has been considered both a cyclic concerted and a general base process; (2) overall second-order aminolyses have been discussed in terms of both four-membered cyclic transition states and ionic processes; (3) primary and secondary amines have been assigned different mechanisms in aprotic solvents, and this suggestion has been criticized; and (4) tertiary amine catalysis has been ascribed to both nucleophilic and general base catalysis.[12] Menger and co-workers have made an attempt to explain these various disagreements by suggesting a unifying mechanistic theory of their own.[12,13] Several possible transition states were considered and are shown below. Transition states I and II are for one-step cyclic concerted mechanisms; III is for a cyclic concerted mechanism leading to a neutral tetrahedral intermediate; IV and V are for rate-determining addition of an amine, where IV is uncatalyzed and V is general base catalyzed; and VI is a direct displacement

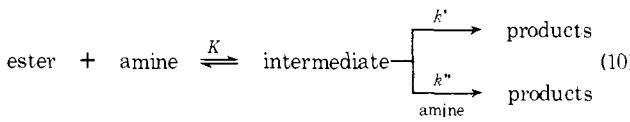


I II III



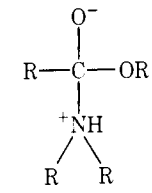
IV V VI

reaction with no intermediate. All of these were rejected for various reasons.[12] Another possibility was proposed as shown in the following equation:



ester + amine $\overset{K}{\rightleftharpoons}$ intermediate $\xrightarrow{k'}$ products; intermediate $\xrightarrow[\text{amine}]{k''}$ products (10)

This represents the reversible formation of a tetrahedral addition intermediate, followed by a rate-determining collapse of the intermediate to products. A possible structure for such an intermediate would be VII. Thus, Menger and co-workers



VII

propose that collapse of a tetrahedral intermediate such as VII is rate determining in ester aminolyses in aprotic solvents.[12,13]

In our particular case, we have expressed our rate law as shown in the following equation:

$$-\mathrm{d[ester]}/\mathrm{d}t = (k_2[\text{amine}] + k_3[\text{amine}]^2)[\text{ester}] = k_{\text{obsd}}[\text{ester}] \quad (11)$$

Since we found no evidence for any order of amine greater than 1 (Figure 2) at a concentration of 2.98 M LPDE, we may rewrite eq 11 to give

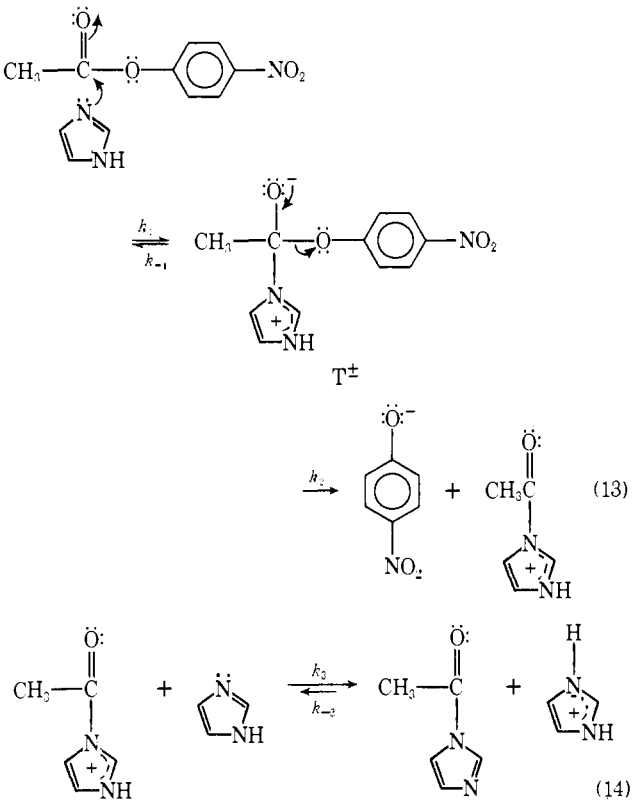
$$-\mathrm{d[ester]}/\mathrm{d}t = k_2[\text{imidazole}][\text{ester}] = k_{\text{obsd}}[\text{ester}] \quad (12)$$

Since the reaction of *p*-nitrophenyl acetate with imidazole in 2.98 M LPDE is first order in amine, we may now examine the possible transition states suggested by Menger and co-workers to see which may be eliminated. Transition states II, III, and V require two amine molecules in the transition state and so may be eliminated. Likewise, the pathway of k'' in eq 10 represents the collapse of intermediate VII aided by a second amine and so must also be discarded.

By examination, we see that I is also removed from consideration as it requires the concerted transfer of a proton to the leaving group, and our system prohibits this. We are left, then, with the three possibilities of IV, VI, and pathway k' for VII.

Transition state VI, which represents the direct displacement reaction with no intermediate, will be considered first. This type of reaction is kinetically indistinguishable from the other two possibilities, and we have no evidence which bears on the merits of this mechanism as opposed to the other two. But Menger and Smith point out that addition intermediates are common in acyl transfer reactions in water, and they favor their presence in aprotic solvents.[12] We, likewise, favor the formation of such an addition intermediate in LPDE solutions, especially at substantial concentrations where the charges or partial charges may be effectively stabilized by the coulombic fields of the ionic aggregates. For this reason, we suggest the elimination of VI as a possible transition state for our reaction.

If this is true, we must turn our attention to the relative merits of IV vs. VII. Both of these possibilities may be effectively represented by the scheme shown in eq 13 and 14. Transition state IV requires the rate-determining addition of imidazole to ester to give a tetrahedral intermediate, followed by rapid breakdown to products. In this mechanism $k_{\text{obsd}} = k_1$, and the transition state is actually somewhere between the reactants and the tetrahedral intermediate, $T^{\pm}$, having a partial charge development which will be stabilized by the ionic aggregates of LPDE. Evidence in favor of rate-limiting addition of imidazole is the fact that the reaction is first order in imidazole with no indication at all of any presence of a higher order. Thus, above 2.98 M LPDE we would expect this condition to hold and below 2.98 M LPDE we would expect this condition to at least predominate until concentrations of lithium perchlorate begin to approach 1.50 M where the order in lithium



(13)

(14)

perchlorate begins to change from 2 to 1. As stated above, the observed catalytic effect could possibly occur from the greater stabilization of the partially charged transition state relative to the weakly polar initial state of the reactants. For this mechanism to be reasonable, one must be able to rationalize $k_2 > k_{-1}$ which means that the tetrahedral intermediate, $T^{\pm}$, decomposes to give *p*-nitrophenolate faster than it decomposes to give imidazole. In reality, the pK_a of imidazole in water is 6.97[27] and that of *p*-nitrophenol is 7.15,[31] which might lead to the prediction that $k_2 \simeq k_{-1}$. On the other hand, previous studies of the reaction of imidazole with *p*-nitrophenyl acetate in aqueous solutions have indicated that nucleophilic attack by imidazole could be rate limiting.[16,35,36] Bruice and Bruice[37] in some recent work on the aminolysis of substituted quinoline-8-carboxylates and quinoline-6-carboxylates with primary and secondary amines in aqueous solution point out that in the case of very good leaving groups, collapse of the tetrahedral intermediate in the direction of products is so rapid that the rate-limiting step becomes attack of amine on the carbonyl carbon, and they also observe that lowering of the pK_a of the leaving group increases the breakdown rate of the intermediate or, in other words, k_2 becomes greater than k_{-1}. Their work demonstrates that when the leaving group is 2,4-dinitrophenolate ion, the attack of amine is always rate limiting. This observation is not surprising since in water 2,4-dinitrophenol has a pK_a of 4.11.[38]

In view of the extra stabilization of the ions produced by the k_2 step in LPDE solutions, it is perhaps not unreasonable to suggest that in the presence of high concentrations of lithium perchlorate the breakdown of the tetrahedral intermediate, $T^{\pm}$, to *p*-nitrophenolate ion may be faster than its breakdown to imidazole and ester ($k_2 > k_{-1}$). Thus, the nucleophilic attack of imidazole, k_1, would be the rate-limiting step and IV would be the preferred transition state. It might be noted that, in this mechanism, the k_3 step is very fast, as it involves the removal of a proton from acetylimidazolium ion by imidazole (which is in at least 100-fold excess) to give the observed product acetylimidazole. In fact, acetylimidazolium ion is a much better acid than imidazolium ion in water,[36] so that $k_3 \gg k_{-3}$.

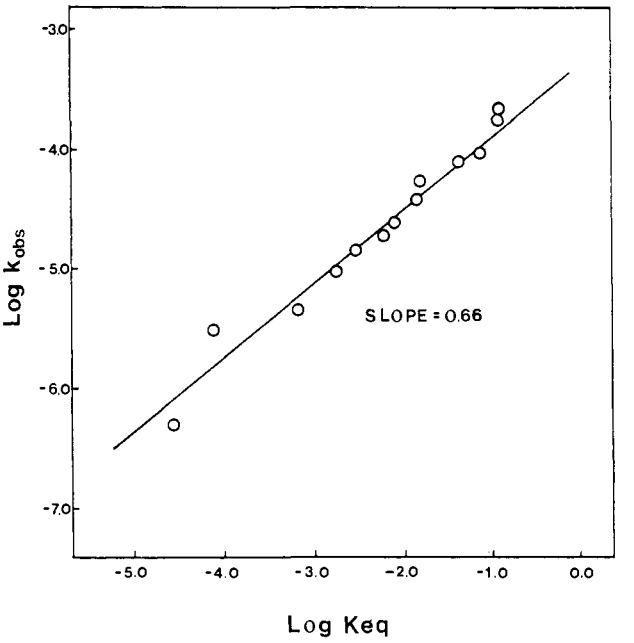


Figure 6. Plot of log k_{obsd} for *p*-nitrophenyl acetate and imidazole vs. log K_{eq} for *p*-nitrophenol in LPDE at 25.0 °C.

Now, let us consider the merits of a rate-determining step involving the breakdown of VII to products. This mechanism would require that $k_{obsd} = k_1k_2/k_{-1}$ where $k_{-1} > k_2$. Thus, the catalytic effect of LPDE solutions would be to increase both k_1/k_{-1} and k_2. This type of rate-limiting step represented by k_2 is actually the one favored by Menger and co-workers for ester aminolysis in aprotic solvents.[12,13] In this mechanism, imidazole must be envisioned as a better leaving group than *p*-nitrophenolate ion since $k_{-1} > k_2$. Thus, it appears that this is also a plausible mechanism.

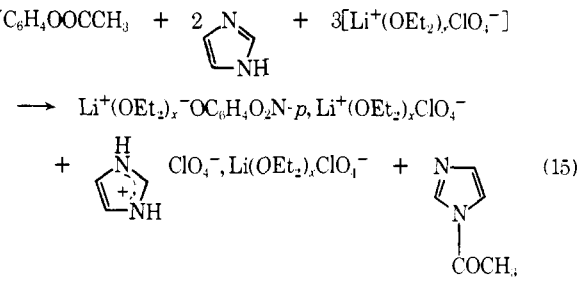
It is of interest to consider two ways it might be possible to decide which mechanism is most likely to be the correct one. One such way is to examine a plot of log k_{obsd} vs. log K_{eq}. Figure 6 shows such a plot for our data. Unfortunately, the slope of 0.66 is undecisive. The value we have is not conclusive for either mechanism. Another way to decide the issue is a comparison of the rates of the aminolysis of the 2,4-dinitro ester with those we already have for the *p*-nitro ester. A consistently large difference in rate (about 1000-fold) between the two esters as the concentration of lithium perchlorate is increased would argue in support of k_2 being rate limiting, while a smaller difference (<100-fold) would indicate k_1 was rate limiting.[13] These data are not available as yet. The problem is under investigation in our laboratories, but is complicated by the fact that the 2,4-dinitro ester appears to complex with $LiClO_4$. Thus, at this point we cannot say with any degree of certainty which is the rate-determining step—the formation of a dipolar intermediate from two neutral molecules (k_1) or the formation of two separate charged species from the dipolar intermediate (k_2). It is conceivable that both mechanisms operate. One mechanism, $k_{-1} > k_2$, may operate in pure ether and also dilute LPDE solutions. An intermediate situation with $k_{-1} \simeq k_2$ may prevail at slightly higher concentrations of lithium perchlorate. Finally, a mechanism involving $k_2 > k_{-1}$ may be operating at more concentrated lithium perchlorate solutions. We hope further investigation will lead to a more definitive conclusion.

With either mechanism, it is not difficult to envisage the transition state as being greatly influenced by the Coulombic fields surrounding the lithium and perchlorate ions. It would seem reasonable at first glance to propose that the free energy of activation, $\Delta G^{\ddagger}$, of the aminolysis would be lowered as a

result of a lowering of E_a and consequently a lowering of $\Delta H^{\ddagger}$ as the molar concentration of lithium perchlorate is steadily increased, thereby causing an apparent increase in the rate constant, k_2. However, this is not what is observed. The E_a and $\Delta H^{\ddagger}$ remain virtually constant and the entropy of activation, $\Delta S^{\ddagger}$, shows the marked change which affects the lowering of the free energy of activation. This is precisely what was observed in Part 4 in the rearrangement of 1-phenylallyl chloride.[1]

Combining these observations with data in Table VI and Figures 3 and 5, it may be possible to formulate some conclusions about how the catalysis of the aminolysis reaction occurs. Consider first that, at moderate concentrations of lithium perchlorate, further association may occur. Thus, $Li^+(OEt_2)_x$, ClO_4^- ion pairs may associate in diethyl ether to neutral pairs of ion pairs $[Li^+(OEt_2)_x, ClO_4^-]_2$. Such associations, as well as still higher clusters, have been suggested to exist in moderately concentrated LPDE solutions.[39] Clearly then, the formal kinetic orders depicted in Figure 3 represent the *minimum apparent molecularity* of such catalytic processes. Pocker and Buchholz have demonstrated that LPDE exists primarily as dietherate ions, $Li^+(OEt_2)_2ClO_4^-$, at concentrations below 4.25 M and as a mixture of both dietherate and monoetherate, $Li^+(OEt_2)ClO_4^-$, above 4.25 M.[19] With this in mind, as one increases the molar concentration of lithium perchlorate from 0.0 to about 0.5 M, the order in lithium perchlorate changes from 0 to 1. Then it might be proposed that the transition state of the aminolysis becomes stabilized by one $Li^+(OEt_2)_2ClO_4^-$ ionic aggregate, increasing the $\Delta S^{\ddagger}$ by 8.7 cal/(deg mol) thereby lowering $\Delta G^{\ddagger}$ and increasing the value of k_2. Increasing the concentration of lithium perchlorate to about 1.50 M brings an order change of 1 to 2. Thus, one might propose that in this region the transition state is stabilized by $2[Li^+(OEt_2)_2ClO_4^-]$ ionic aggregates, increasing the $\Delta S^{\ddagger}$ by another 6.7 cal/(deg mol), lowering the $\Delta G^{\ddagger}$, and increasing the value of k_2. The next order change from 2 to 3 occurs at a lithium perchlorate concentration of about 2.80 M. This increase in lithium perchlorate concentration provides an increase of about 3.5 cal/(deg mol) as the transition state is stabilized by $3[Li^+(OEt_2)_2ClO_4^-]$ ionic aggregates. The final order change from 3 to 4 takes place when the perchlorate concentration reaches about 4.00 M, providing a further increase in $\Delta S^{\ddagger}$ of about 1.8 cal/(deg mol), and the transition state is now stabilized by $4[Li^+(OEt_2)_xClO_4^-]$, where $x = 1$ or 2.[19] Thus, it may be seen that, as the molar concentration of lithium perchlorate is steadily increased, it complexes with the diethyl ether solvent molecules, forming ionic aggregates which then orient themselves around the transition state in some fashion in increasing numbers. This stabilizes the polar transition state and decreases $\Delta G^{\ddagger}$ for the aminolysis, thereby leading to the observed rate enhancement.[40] The LPDE ionic aggregates, as was suggested in Part 4,[1] may be envisioned as pieces of an electrostatic "blanket" surrounding the activated complex. Each change in order represents the addition of another piece of the electrostatic "blanket" in place, until all the available positions are occupied leading to a progressive increase in the value of the rate constant, k_2. As a result, it is possible to formulate an apparent stoichiometric equation for the aminolysis reaction of *p*-nitrophenyl acetate with imidazole, under various conditions in LPDE solutions. The case for the order of 3 in lithium perchlorate is shown in eq 15, where $x = 1$ or 2.

This work taken as a whole supports the original observations of Pocker and Buchholz[19-21] as to the striking catalytic efficiency of LPDE solutions and their utility in studying organic reactions which are too slow in aprotic solvents of low ionizing capacity. It also lends credence to the hypothesis that the catalytic efficiency of certain enzymes is dependent, in part, upon some cooperative ion pair stabilization in the hydrophobic cavity.[5-8] Future work on proton transfer and on aminolysis reactions in LPDE solutions may provide a more complete understanding of the great penetration of electrostatic forces in hydrophobic media.



(15)

References and Notes

(1) (a) Previous paper in this series: Y. Pocker and D. L. Ellsworth, preceding paper in this issue. (b) Supported in part by grants from the U. S. Public Health Service and the National Science Foundation.
(2) Taken in part from the Ph.D. Dissertation of David L. Ellsworth, University of Washington, Seattle, Wash., 1976.
(3) S. Winstein, S. Smith, and D. Darwish, *J. Am. Chem. Soc.*, **81**, 5511 (1959).
(4) E. D. Hughes, C. K. Ingold, S. F. Mok, S. Patai, and Y. Pocker, *J. Chem. Soc.*, 1265 (1957), and accompanying papers.
(5) D. E. Koshland, Jr., J. A. Yankeelov, Jr., and J. A. Thoma, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **21**, 1031 (1962).
(6) C. C. F. Blake, D. F. Koenig, G. A. Mair, A. C. T. North, D. C. Phillips, and V. R. Sharma, *Nature (London)*, **206**, 757 (1965).
(7) C. C. F. Blake, L. N. Johnson, G. A. Mair, A. C. T. North, D. C. Phillips, and V. R. Sharma, *Proc. R. Soc. London, Ser. B*, **167**, 348 (1967).
(8) D. E. Koshland, Jr., and K. E. Neet, *Annu. Rev. Biochem.*, 37, 359 (1968).
(9) A. W. Hofmann, *Chem. Ber.*, **15**, 977 (1882), ref 3.
(10) G. H. Grant and C. N. Hinshelwood, *J. Chem. Soc.*, 1351 (1933).
(11) M. Gordon, J. G. Miller, and A. R. Day, *J. Am. Chem. Soc.*, **70**, 1946 (1948).
(12) F. M. Menger and J. H. Smith, *J. Am. Chem. Soc.*, **94**, 3824 (1972), and references quoted therein.
(13) F. M. Menger and A. C. Vitale, *J. Am. Chem. Soc.*, **95**, 4931 (1973).
(14) C. W. Su and J. W. Watson, *J. Am. Chem. Soc.*, **96**, 1854 (1974).
(15) T. D. Singh and R. W. Taft, *J. Am. Chem. Soc.*, **97**, 3867 (1975).
(16) M. L. Bender and B. W. Turnquest, *J. Am. Chem. Soc.*, 79, 1652 (1957).
(17) M. L. Bender and B. W. Turnquest, *J. Am. Chem. Soc.*, 79, 1656 (1957), and references quoted therein.
(18) T. C. Bruice and G. L. Schmir, *J. Am. Chem. Soc.*, 79, 1663 (1957), and references quoted therein.
(19) Y. Pocker and R. F. Buchholz, *J. Am. Chem. Soc.*, **92**, 2075 (1970).
(20) Y. Pocker and R. F. Buchholz, *J. Am. Chem. Soc.*, **92**, 4033 (1970).
(21) Y. Pocker and R. F. Buchholz, *J. Am. Chem. Soc.*, **93**, 2905 (1971).
(22) T. Wieland and G. Schneider, *Justus Liebigs Ann. Chem.*, **580**, 159 (1953).
(23) Y. Pocker and J. Stone, *Biochemistry*, **6**, 668 (1967).
(24) D. P. N. Satchell and I. I. Secemski, *J. Chem. Soc., Ser. B*, 130 (1969).
(25) F. M. Menger, *J. Am. Chem. Soc.*, **88**, 3081 (1966).
(26) F. M. Menger and A. C. Vitale, *J. Am. Chem. Soc.*, **95**, 4931 (1973).
(27) Y. Nozaki, F. R. N. Gurd, R. F. Chen, and J. T. Edsall, *J. Am. Chem. Soc.*, **79**, 2123 (1957).
(28) M. M. Markowitz, W. N. Hawley, D. A. Boryta, and R. F. Harris, *J. Chem. Eng. Data*, **6**, 325 (1961).
(29) E. R. Stadtman, "The Mechanism of Enzyme Action", W. D. McElroy and B. Glass, Ed., Johns Hopkins Press, Baltimore, Md., 1954, pp 581–598.
(30) A. Frost and R. Pearson, "Kinetics and Mechanism", Wiley, New York, N.Y., 1953, p 95.
(31) L. P. Fernandez and L. G. Helper, *J. Am. Chem. Soc.*, **81**, 1783 (1959).
(32) We have also considered the possibility that the initial state may, in fact, consist of a hydrogen bonded complex between *p*-nitrophenol and imidazole. An ionization scheme leading from the hydrogen bonded complex to ion pairs is represented by eq 5A, and the corresponding values of $K_{eq_{PNP}}{}^{A'}$ were calculated from eq 6A:

$$p\text{-}O_2NC_6H_4OH\cdots Im \underset{k_{-1}^{A'}}{\overset{k_1^{A'}}{\rightleftharpoons}} p\text{-}O_2NC_6H_4O^-, ImH^+ \qquad (5A)$$

$$K_{eq_{PNP}}{}^{A'} = \frac{k_1^{A'}}{k_{-1}^{A'}} = \frac{[p\text{-}O_2NC_6H_4O^-, ImH^+]}{[p\text{-}O_2NC_6H_4OH\cdots Im]} \qquad (6A)$$

Similarly, a dissociation scheme leading from the hydrogen bonded complex to free ions is represented by eq 7A and the corresponding values of $K_{eq_{PNP}}{}^{A}$ were calculated from eq 8A:

$$p\text{-}O_2NC_6H_4OH\cdots Im \underset{k_{-1}^{A}}{\overset{k_1^{A}}{\rightleftharpoons}} p\text{-}O_2NC_6H_4O^- + ImH^+ \qquad (7A)$$

$$K_{eq_{PNP}}{}^{A} = \frac{k_1^{A}}{k_{-1}^{A}} = \frac{[p\text{-}O_2NC_6H_4O^-][ImH^+]}{[p\text{-}O_2NC_6H_4OH\cdots Im]} \qquad (8A)$$

Comparisons of equilibrium constants obtained for the various schemes represented by eq 5, 5A, 7, and 7A lead to a definitive conclusion. For example, employing method IA with the base concentration held constant

at 5.89 × 10^{-3} M and varying the concentration of the phenol from 1.68 × 10^{-4} M (IA_1) to 1.68 × 10^{-6} M (IA_2), we obtain the following ratios of equilibrium constants: $K_{eqPNP}(IA_1)/K_{eqPNP}(IA_2)$ = 1.08, $K_{eqPNP}'(IA_1)/K_{eqPNP}'(IA_2)$ = 1/46.6, $K_{eqPNP}^{A}(IA_1)/K_{eqPNP}^{A}(IA_2)$ = 1.01, $K_{eqPNP}^{A'}(IA_1)/K_{eqPNP}^{A'}(IA_2)$ = 1/49.9. If method IB is employed, with the phenol concentration held constant at 8.42 × 10^{-5} M and the base concentration is varied from 1.18 × 10^{-2} M (IB_1) to 1.18 × 10^{-4} M (IB_2), we obtain the ratios: $K_{eqPNP}(IB_1)/K_{eqPNP}(IB_2)$ = 1/2.5, $K_{eqPNP}'(IB_1)/K_{eqPNP}'(IB_2)$ = 1/10.9, $K_{eqPNP}^{A}(IB_1)/K_{eqPNP}^{A}(IB_2)$ = 22.5, $K_{eqPNP}^{A'}(IB_1)/K_{eqPNP}^{A'}(IB_2)$ = 7.22. Use of the second method (II) where the concentration of the base at 1.18 × 10^{-2} M and the phenol at 1.68 × 10^{-4} M (II_1) is diluted 10-fold to a base concentration of 1.18 × 10^{-3} M and phenol concentration of 1.68 × 10^{-5} M (II_2) followed by a subsequent dilution of 10-fold to concentrations of 1.18 × 10^{-4} M for the base and 1.68 × 10^{-6} M for the phenol (II_3) gave rise to the following ratios: $K_{eqPNP}(II_1)/K_{eqPNP}(II_2)$ = 1/1.19, $K_{eqPNP}'(II_1)/K_{eqPNP}'(II_2)$ = 1/11.1, $K_{eqPNP}^{A}(II_1)/K_{eqPNP}^{A}(II_2)$ = 8.6, $K_{eqPNP}^{A'}(II_1)/K_{eqPNP}^{A'}(II_2)$ = 1.11; and $K_{eqPNP}(II_2)/K_{eqPNP}(II_3)$ = 1.08, $K_{eqPNP}'(II_2)/K_{eqPNP}'(II_3)$ = 1/9.6, $K_{eqPNP}^{A}(II_2)/K_{eqPNP}^{A}(II_3)$ = 10.6, $K_{eqPNP}^{A'}(II_2)/K_{eqPNP}^{A'}(II_3)$ = 1.05. It appears, then that the selection of the dissociation scheme represented by eq 7 as the one which is more nearly correct can be successfully sustained.

(33) T. C. Bruice, A. F. Hagarty, S. M. Felton, A. Donzel, and N. G. Kundu, *J. Am. Chem. Soc.*, **92**, 1370 (1970).
(34) A. C. Satterthwait and W. P. Jencks, *J. Am. Chem. Soc.*, **96**, 7018 (1974), and references quoted therein.
(35) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms", Vol. I, W. A. Benjamin, New York, N.Y., 1966, p 46.
(36) W. P. Jencks, "Catalysis in Chemistry and Enzymology", McGraw-Hill, New York, N.Y., 1969, pp 67, 484.
(37) P. Y. Bruice and T. C. Bruice, *J. Am. Chem. Soc.*, **96**, 5533 (1974).
(38) H. A. Sober, Ed., "Handbook of Biochemistry Selected Data for Molecular Biology", The Chemical Rubber Co., Cleveland, Ohio, 1968, p J158.
(39) K. Ekelin and L. G. Sillén, *Acta Chem. Scand.*, **7**, 987 (1953).

(40) The LPDE system strongly catalyzes the aminolysis of *p*-nitrophenyl acetate by virtue of the much stronger interaction of its ion pairs and higher ionic aggregates with the highly polar transition state than with the weakly polar initial state. The repeated finding that $\Delta\Delta H^{\ddagger} \simeq 0$ for these powerful salt effects is both fascinating and important. We wish to postpone a more detailed analysis of the data until our physico-chemical characterization of these unusual electrolytic solutions is more complete. One line of reasoning would be that the negative enthalpy term for electrostatic stabilization is apparently offset by a positive enthalpy term for the release of ether molecules but no such complete compensatory effect occurs in the respective entropy of activation terms. In some sense, the increase in $\Delta\Delta S^{\ddagger}$ represents a partial utilization of electrostatic energy in such a way as to facilitate the attainment of the transition state. The group of observations as a whole reveals a number of features which could provide mechanisms for rate acceleration and specificity.[41]

(41) W. P. Jencks, *Adv. Enzymol. Relat. Areas Mol. Biol.*, **43**, 219 (1975).

Some Acyclic Pentaalkoxyphosphoranes

Lydia L. Chang, Donald B. Denney,* Dorothy Z. Denney, and Richard J. Kazior

Contribution from Wright and Rieman Chemistry Laboratories, Rutgers, The State University of New Jersey, New Brunswick, New Jersey 08903.

Received August 26, 1976

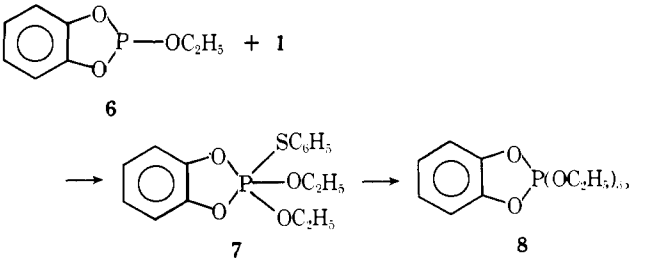
Abstract: Methyl, ethyl, isopropyl, neopentyl, cyclopentyl, cyclohexyl, and benzyl benzenesulfenates have been allowed to react respectively with trimethyl, triethyl, triisopropyl, trineopentyl, tricyclopentyl, tricyclohexyl, and tribenzyl phosphites. In all cases pentaalkoxylphosphoranes were formed. Varying degrees of stability have been found for these substances. They have been characterized by ^{1}H, ^{31}P, and ^{13}C NMR. Several of them have been investigated by variable-temperature ^{1}H and ^{13}C NMR. In no case was it possible to detect a nonequivalency of any particular group of atoms.

Methods for the preparation of acyclic pentaalkoxyphosphoranes have been few in number. It has been shown that dialkyl peroxides such as dimethyl and diethyl peroxide will react with trialkyl phosphites to give pentaalkoxyphosphoranes.[1-12] This reaction is limited by the availability of the peroxides and their inherent danger. Pentaphenoxyphosphorane has been prepared by allowing phenol to react with phosphorus pentachloride in the presence of organic bases.[13] Attempts to form pentaethoxyphosphorane from tetraethoxyphosphonium tetrafluoroborate and ethoxide ion have never led to the production of an observable amount of phosphorane.[14] The dialkyl peroxide-trialkyl phosphite reaction is thought to proceed by a biphilic insertion of the phosphorus into the oxygen-oxygen bond.[8] This route by-passes a tetraethoxyphosphonium ethoxide ion pair which would most probably decompose into diethyl ether and triethyl phosphate.

Because of the instability of acyclic pentaalkoxyphosphoranes, it seems that only high-energy reactants can offer much potential for their synthesis. Secondly, only paths which do not offer the opportunity for phosphate formation can be used. In a search for reactants that can provide the potential for phosphorane formation, a number of substances with weak σ bonds have been investigated. One of these materials was ethyl benzenesulfenate (**1**). When **1** was allowed to react with triethyl phosphite (**2**), a rapid reaction occurred with the production of pentaethoxyphosphorane (**3**) and diphenyl disulfide (**4**):[15]

$$2C_6H_5SOC_2H_5 + (C_2H_5O)_3P \rightarrow (C_2H_5O)_5P + (C_6H_5S)_2$$
1 **2** **3** **4**

This rather remarkable reaction presumably involves the initial production of a mixed phosphorane, $(C_2H_5O)_4PSC_6H_5$ (**5**), which rapidly reacts with another mole of **1** to yield **3** and **4**. In fact, **5** has never been observed. A mixed thiooxyphosphorane **7** was observed when ethyl 1,2-phenylene phosphite (**6**) was allowed to react with **1**. An absorption was found at δ +22 relative to 85% phosphoric acid in the ^{31}P NMR spectrum. This material is assigned the structure **7** primarily on the basis of its ^{31}P NMR spectrum. It is known that substitution of sulfur for oxygen in an oxyphosphorane leads to a downfield shift of the ^{31}P NMR resonance. The pentaalkoxyphosphorane **8** which resulted from the further reaction of **7** with **1** absorbs at δ +50.



6 **7** **8**

These rather remarkable results prompted an investigation of the general utility of the reaction as a means of preparing phosphoranes.

Results and Discussion

A series of alkyl benzenesulfenates, **1, 9–14,** was prepared by condensation of benzenesulfenyl chloride with the appro-