down were shown by chromatography to be 5'-amino-5'-deoxyadenosine and trimetaphosphate.

The 5'-amino-5'-deoxyadenosine 5'-triphosphate was shown in preliminary experiments to replace ATP itself as a substrate in the rabbit muscle creatine kinase reaction. The coupled assay procedure of Tanzer and Gilvarg[70] as modified by Rotthauwe and Cerqueiro-Rodriguez[71] was used. Also, formation of phosphocreatine as well as the loss of the ATP analog and formation of what appears to be 5'-amino-5'-deoxyadenosine 5'-diphosphate in the enzymatic reaction were followed using PEI cellulose thin-layer chromatography as described elsewhere.[43] Further details concerning the isolation and biological activity of this ATP analog will be published at a later date.

(70) M. L. Tanzer and C. Gilvarg, *J. Biol. Chem.*, 234, 3201 (1959).
(71) H. Rotthauwe and M. Cerqueiro-Rodriguez, *Clin. Chim. Acta*, 10, 134 (1964).

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Mechanism of Ester Aminolyses in Aprotic Solvents

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Abstract: The reaction of pyrrolidine with esters in acetonitrile and chlorobenzene is much more sensitive to substituents on the leaving group of the esters (ρ = 4–6) than to substituents on the acyl portion of the esters (ρ = 1–2). This is the reverse order of sensitivity found in reactions of esters with hydroxide ion in water. We conclude from the ρ values (and from the effects on the aminolysis rates of tertiary amine, pyrrolidinium ion, azide ion, and pyrrolidine-*d*) that collapse of a tetrahedral intermediate is rate determining. Possible structures of the tetrahedral intermediate are considered, and the impact of our results on the conclusions of previous work in the area is discussed.

In 1834 Liebig[2] discovered that amines react with esters to form amides. About a century later Hinshelwood[3] and Day[4] became interested in the mechanism of this reaction in aprotic solvents, but they decided not to pursue the subject upon finding that simple alkyl esters react slowly in media lacking water or alcohol. Although a great deal of attention was subsequently given to ester aminolyses in aqueous solvents,[5-8] not until recently has the mechanism in aprotic solvents been explored in detail.[9-18] This latter work has generated an unusual number of conflicting conclusions. For example, the overall third-order aminolysis of esters in aprotic media has been considered both a cyclic concerted[9,10] and a general base[11] process. Aminolysis mechanisms have usually entailed a tetrahedral intermediate,[12] although a direct displacement without an intermediate may be preferable.[13] Overall second-order aminolyses have been discussed in terms of both four-membered cyclic transition states[14] and ionic processes.[11] It has been suggested[14] and denied[13] that primary and secondary amines react in aprotic solvents by different mechanisms. Tertiary amine catalysis has been ascribed to both nucleophilic[15] and general base[16] catalysis. Acceleration by the hydroxyl group in the aminolysis of salicylate systems in nonhydroxylic media has been viewed as a general acid catalysis[16] and as an ion-pair effect.[17] In the present paper we describe experiments that lead to a unifying mechanistic theory for ester aminolyses in aprotic solvents.[19]

(1) Recipient of a Camille and Henry Dreyfus Foundation Teacher–Scholar Grant and a National Institutes of Health Career Development Award.
(2) A. W. Hofmann, *Chem. Ber.*, 15, 977 (1882), ref 3.
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(4) M. Gordon, J. G. Miller, and A. R. Day, *J. Amer. Chem. Soc.*, 70, 1946 (1948).
(5) P. J. Hawkins and I. Piscalnikow, *ibid.*, 77, 2771 (1955).
(6) J. F. Bunnett and G. T. Davis, *ibid.*, 82, 665 (1960).
(7) W. P. Jencks and J. Carriuolo, *ibid.*, 82, 675 (1960).
(8) T. C. Bruice, A. Donzel, R. W. Huffman, and A. R. Butler, *ibid.*, 89, 2106 (1967).
(9) F. M. Menger, *ibid.*, 88, 3081 (1966).
(10) N. Nakamizo, *Bull. Chem. Soc. Jap.*, 42, 1071 (1969).
(11) H. Anderson, C. Su, and J. W. Watson, *J. Amer. Chem. Soc.*, 91, 482 (1969).
(12) P. R. Rony, *ibid.*, 91, 6090 (1969).
(13) D. P. N. Satchell and I. I. Secemski, *J. Chem. Soc. B*, 130 (1969).
(14) A. Sami, A. S. Shawali, and S. S. Biechler, *J. Amer. Chem. Soc.*, 89, 3020 (1967).
(15) D. P. N. Satchell and I. I. Secemski, *J. Chem. Soc. B*, 1013 (1970).
(16) F. M. Menger and J. H. Smith, *J. Amer. Chem. Soc.*, 91, 5346 (1969).
(17) R. L. Snell, W. Kwok, and Y. Kim, *ibid.*, 89, 6728 (1967).
(18) H. J. Gold, *ibid.*, 90, 3402 (1968).

Experimental Section

Materials. Acetonitrile was distilled twice over phosphorus pentoxide and once over anhydrous potassium carbonate using a 30-cm Vigreux column. Chlorobenzene was washed successively with concentrated sulfuric acid, aqueous sodium carbonate, and water. The chlorobenzene was then dried over anhydrous magnesium sulfate and distilled over calcium hydride using a 30-cm Vigreux column. Heptane was distilled over lithium aluminum hydride.

Pyrrolidine and *n*-butylamine were distilled over calcium hydride prior to use. Triethylenediamine (Dabco) was crystallized twice from heptane and sublimed twice at room temperature (0.1–0.2 mm) to afford colorless crystals, mp 158–159° (lit.[11] mp 157–159°).

We prepared tetraethylammonium azide as follows. A 10% aqueous solution of tetraethylammonium hydroxide was concentrated with the aid of a rotary evaporator. After diluting with absolute methanol, we neutralized the solution with a two–threefold excess of hydrazoic acid in ether.[20] The solvent was removed,

(19) For a preliminary report of this work, see F. M. Menger and J. H. Smith, *Tetrahedron Lett.*, 4163 (1970).
(20) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1968, p 446.

and the residue was dried under vacuum and crystallized several times from acetone giving a hygroscopic crystalline solid, mp 255–260° dec (lit.[21] mp 250° dec), which was always handled under nitrogen.

Pyrrolidinium perchlorate was prepared by adding 70% perchloric acid (5.2 ml, 0.06 mol) to pyrrolidine (5.9 ml, 0.07 mol) in 20 ml of 2-propanol under nitrogen (0°). Volatile material was removed under reduced pressure, and the solid residue was crystallized from 2-propanol–ether. The salt contained solvent of crystallization (determined by nmr) which we removed by heating for several hours at 100° under vacuum. The product, mp 240–242°, burned explosively when ignited but did not appear to be shock sensitive.

n-Butylamine-d_2 was obtained by mixing *n*-butylamine (30 ml) with D_2O (17 ml), and reisolating the amine by distillation through a 20-cm Vigreux column. After repeating this procedure three more times, we dried the amine over calcium hydride and distilled the material. The isotopic purity, estimated by nmr and ir, was greater than 95%. We prepared pyrrolidine-*d* in a similar manner.

Aryl acetates (secured commercially or by synthesis[22]) were purified by distillation or crystallization; boiling and melting points agreed well with literature values.

Phenyl benzoates were prepared by combining equimolar amounts of the corresponding substituted benzoyl chloride and substituted phenol in dry pyridine. The mixtures were heated to dissolve the reagents, allowed to stand for several hours, and poured into a five–tenfold excess of water. We removed the precipitates by filtration and crystallized them twice from acetone, methanol, or a mixture of the two solvents. Melting points[13,23,24] and analytical data for the esters are listed in Table I.

Kinetics. The following procedure, given for the one particular run, is typical of that used throughout. A solution of 0.28 *M* pyrrolidine in acetonitrile was equilibrated at 25.0 ± 0.1° in a stoppered cuvette placed within the thermostated chamber of a Cary 14 spectrophotometer. A small amount (50 μl) of an acetonitrile solution of *p*-chlorophenyl acetate was added rapidly to the cuvette (with the aid of a stirring rod flattened at one end) such that the initial ester concentration was 3.6×10^{-4} *M*. The change in absorbance at 290.0 mμ was traced as a function of time until the reaction was complete (greater than eight half-lives).

The choice of wavelength and amine concentration depended upon the ester. In all runs the amine was in large excess over the ester, so that pseudo-first-order conditions prevailed. First-order plots were linear to at least two half-lives. Difficulties were encountered with reactions between pyrrolidine and several phenyl acetates in heptane. Apparently, small amounts of carbon dioxide reacted with the amine to form a carbamic acid which catalyzed the aminolyses. There were no such problems with experiments involving acetonitrile or chlorobenzene; observed rate constants for reactions in these two solvents were reproducible to ± 3%.

Reactions of tetraethylammonium azide in acetonitrile were well behaved only when the esters had leaving groups less basic than *p*-nitrophenoxide. Otherwise the phenoxide product, whose formation we were following spectrophotometrically, was partially neutralized by trace impurities in the solvent, resulting in an apparent induction period prior to the absorbance increase.

Results

Aminolyses of aryl esters in aprotic solvents under pseudo-first-order conditions obey a two-term rate law (eq 1). We determined the rate constants k_1 and k_2 by

$$k_{obsd} = k_1[\text{amine}] + k_2[\text{amine}]^2 \qquad (1)$$

plotting $k_{obsd}/[\text{amine}]$ *vs.* [amine] and measuring the intercepts and slopes of the straight lines. In a few cases the k_1 term was not observed, while in others the k_2 term was absent. This reflects the experimental difficulty of using a range of amine concentrations large enough to evaluate both competing processes. The overall second-order and third-order rate constants for the reactions of substituted aromatic esters with pyrrolidine in acetonitrile are compiled in Tables II–IV. From these data we obtained the Hammett ρ values listed in Table V.[25] Clearly, both the k_1 and k_2 aminoly-

(21) V. Gutmann, G. Hample, and O. Leitman, *Monatsh. Chem.*, **95**, 1034 (1964).

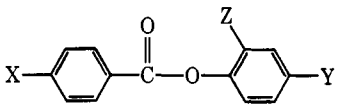
(22) M. L. Bender and K. Nakamura, *J. Amer. Chem. Soc.*, **84**, 2577 (1962).

(23) J. F. Kirsch, W. Clewell, and A. Simon, *J. Org. Chem.*, **33**, 127 (1968).

(24) Y. Akahori, *Chem. Pharm. Bull.*, **13**, 368 (1965).

(25) ρ values in Table V were obtained using Hammett σ constants. Correlations were good, although small improvements were sometimes

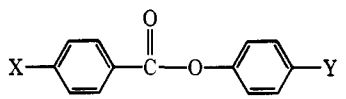
Table I. Analytical Data for a Series of Substituted Phenyl Benzoates



X	Y	Z	Mp, °C	Lit. mp, °C	Ref or analysis
NO_2	NO_2	H	158.5–159.5	158.5–159	23
H	NO_2	H	142–143	142–143	23
OCH_3	NO_2	H	165–166	167	13
CH_3	NO_2	H	119.5–120	120.3–121.3	23
Cl	NO_2	H	138–139	137–138.5	23
NO_2	CN	H	189–191		*a*
NO_2	Cl	H	171.5–172.5	171–172	23
NO_2	H	H	128–129	128–129	23
H	Cl	H	87–88.5	88–89	23
OCH_3	Cl	H	91.5–92.5		*b*
NO_2	$COCH_3$	H	197–198		*c*
NO_2	NO_2	NO_2	139–140		*d*
OCH_3	NO_2	NO_2	135–136		*e*
H	NO_2	NO_2	130–131.5	128–129	24
CH_3	NO_2	NO_2	159–160		*f*
Cl	NO_2	NO_2	145–147		*g*
NO_2	H	NO_2	140–140.5		*h*
OCH_3	H	NO_2	96.5–97.5		*i*
H	H	NO_2	54–55	58	24
H	Cl	NO_2	113–114.5		*j*

[a] Calcd for $C_{14}H_8NO_4$: C, 62.69; H, 3.01; N, 10.44. Found: C, 62.81; H, 3.04; N, 10.49. [b] Calcd for $C_{14}H_{11}ClO_3$: C, 64.01; H, 4.22. Found: C, 63.90; H, 4.44. [c] Calcd for $C_{15}H_{11}NO_5$: C, 63.16; H, 3.89; N, 4.91. Found: C, 63.51; H, 3.81; N, 4.82. [d] Calcd for $C_{13}H_7N_3O_8$: C, 46.86; H, 2.12; N, 12.61. Found: C, 46.89; H, 2.06; N, 12.73. [e] Calcd for $C_{14}H_{10}N_2O_7$: C, 52.84; H, 3.17; N, 8.80. Found: C, 52.77; H, 3.08; N, 8.82. [f] Calcd for $C_{14}H_{10}N_2O_6$: C, 55.64; H, 3.33; N, 9.27. Found: C, 55.58; H, 3.27; N, 9.29. [g] Calcd for $C_{13}H_7ClN_2O_6$: C, 48.39; H, 2.19; N, 8.68. Found: C, 48.21; H, 2.27; N, 8.72. [h] Calcd for $C_{13}H_8N_2O_6$: C, 54.18; H, 2.80; N, 9.72. Found: C, 53.81; H, 2.71; N, 9.54. [i] Calcd for $C_{14}H_{11}NO_5$: C, 61.54; H, 4.06; N, 5.13. Found: C, 55.97; H, 3.97; N, 5.01. [j] Calcd for $C_{13}H_8ClNO_4$: C, 56.23; H, 2.90; N, 5.04. Found: C, 55.97; H, 2.98; N, 5.00.

Table II. Values of k_1 and k_2 (Eq 1) for the Reaction of Substituted Phenyl Benzoates with Pyrrolidine in Acetonitrile at 25.0°



X/Y	NO_2	CN	Cl	H
		k_1, M^{-1} sec^{-1}		
NO_2	3.61×10^1	1.98	5.60×10^{-3}	5.39×10^{-4}
Cl	1.21×10^1		8.00×10^{-4}	
H	8.00		5.14×10^{-4}	
CH_3	5.14			
OCH_3	2.39		*a*	
		k_2, M^{-2} sec^{-1}		
NO_2	*b*	2.87×10^1	1.68×10^{-1}	2.19×10^{-2}
H	*b*		3.99×10^{-3}	
OCH_3	*b*		1.20×10^{-3}	

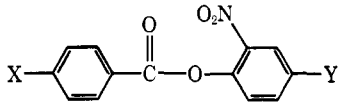
[a] No detectable k_1 term. [b] No detectable k_2 term.

Table III. Values of k_1 and k_2 (Eq 1) for the Reaction of Para-Substituted Phenyl Acetates with Pyrrolidine at 25.0°

Substituent	Chlorobenzene	Acetonitrile
	k_1, M^{-1} sec^{-1}	
NO_2	2.71×10^{-1}	2.38×10^{1}
CN	4.68×10^{-2}	5.61
Cl	1.33×10^{-3}	5.85×10^{-3}
H		2.62×10^{-4}
CH_3		4.34×10^{-5}
	k_2, M^{-2} sec^{-1}	
NO_2[b]	1.84×10^{1}	[a]
CN	3.57	[a]
Cl	8.84×10^{-3}	6.55×10^{-2}
H		2.21×10^{-3}
CH_3		5.55×10^{-4}

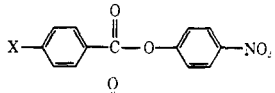
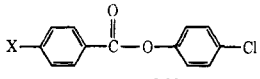
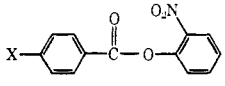
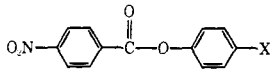
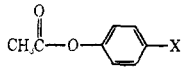
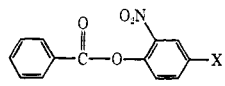
[a] No detectable k_2 term. [b] $k_2 = 7.22$ in heptane.

Table IV. Values of k_1 in M^{-1} sec^{-1} (Eq 1) for the Reaction of Substituted *o*-Nitrophenyl Benzoates with Pyrrolidine in Acetonitrile at 25.0°



X/Y	NO_2	Cl	H
NO_2			3.88×10^{1}
Cl	1.97×10^{3}		
H	8.66×10^{2}	3.35×10^{1}	5.70
CH_3	5.20×10^{2}		
OCH_3	2.77×10^{2}		1.48

Table V. Hammett ρ Values for Reactions of Esters with Pyrrolidine in Acetonitrile at 25.0°

Ester	ρ k_1[a]	ρ k_2[a]
	1.02 ± 0.12[b]	[c]
	1.01 ± 0.06	2.06 ± 0.02
	1.4 ± 0.2	[c]
	6.07 ± 0.33	4.78 ± 0.15
	6.24 ± 0.17[d]	5.29 ± 0.23[d]
	2.7 ± 0.2	[c]

[a] Equation 1. [b] Standard deviation. [c] Third-order kinetics were not observed with nitrophenyl esters. [d] ρ values for aminolyses in chlorobenzene are 4.02 ± 0.21 and 6.02 ± 0.01 for k_1 and k_2, respectively.

ses are much more sensitive to substituents on the leaving group than to substituents on the acyl portion of the esters. For example, k_1 has a ρ of 6.24 for para-substituted acetates in acetonitrile, whereas k_1 has a ρ of only 1.02 for substituted benzoates in the same solvent. This is the *reverse* order of sensitivity found in reactions of esters with hydroxide ion in aqueous media. Thus, basic hydrolyses of para-substituted aryl esters and substituted methyl benzoates have ρ values of 1.1[26] and 1.93,[27] respectively. Aqueous ester aminolyses also display a sensitivity to substituents different from that of aminolyses in aprotic solvents (Table V). ρ values for the reaction in water of ammonia with substituted phenyl acetates are only 2.1 for k_1 and 0.55 for k_2;[26] with substituted benzoates the values are 1.08 for k_1 and 1.88 for k_2.[28] We know of no aqueous ester aminolysis which has a ρ approaching the magnitude of the fourth and fifth entries of Table V. The value of 2.7 for *o*-nitrophenyl derivatives of benzoic acid (sixth entry, Table V) also appears large when we consider that the nitro group should diminish sensitivity to structural changes (a statement of the "reactivity–selectivity" principle).

Pyrrolidine possesses a mobile proton on its nitrogen which is transferred to another atom when the amine reacts with an ester to form an amide. Proton transfer is an important, possibly rate-determining,[29] component of any aminolysis mechanism. Consequently, we were interested in comparing pyrrolidine with an anionic nucleophile, azide ion, which has no proton to donate. We treated tetraethylammonium azide in acetonitrile with two classes of esters: (a) *o*-nitrophenyl benzoates substituted in the para position of the phenyl portion and (b) *p*-nitrophenyl benzoates substituted in the para position of the benzoate portion. Both types of substrates display overall second-order kinetics; the former has a ρ of 4.0, the latter has a ρ of 2.7. The rate of the azide reaction, like that of the aminolysis, is very sensitive to the nature of the leaving group in the ester.

We determined kinetic isotope effects in three aprotic solvents for reactions of *p*-nitrophenyl acetate with primary and secondary amines deuterated on the nitrogen (Table VI). The isotope effects are near unity for both the second-order and the third-order processes.

Table VI. Kinetic Isotope Effects at 25.0° for Reactions of *p*-Nitrophenyl Acetate with Amines Deuterated on the Nitrogen

Amine	Solvent	k_H/k_D[a] k_1[b]	k_H/k_D[a] k_2[b]
Pyrrolidine	CH_3CN	1.09	
Pyrrolidine	C_6H_5Cl	0.93[c]	
Pyrrolidine	*n*-C_7H_{16}		1.57
n-Butylamine	CH_3CN	1.04	
Benzamidine	C_6H_5Cl	1.08	
Tetrahydropyrimidine	C_6H_5Cl	1.09	

[a] ±5%. [b] Equation 1. [c] In the presence of Dabco, a kinetic term is observed which is first order in ester, pyrrolidine, and Dabco. The value of k_H/k_D for this third-order term is 0.99.

Aminolyses of esters in aprotic solvents are known to be catalyzed by the unhindered tertiary amine, triethylenediamine (Dabco).[11,13,15,16] Catalyzed reactions follow the general rate expression given in eq 2. Values

$$k_{obsd} = k_1[\text{amine}] + k_2[\text{amine}]^2 + k_3[\text{amine}][\text{Dabco}] \quad (2)$$

of k_2, k_3, and k_2/k_3 for the reaction of *p*-nitrophenyl

possible by using σ^+ for acyl-substituted esters and σ^- for esters substituted in the leaving group. For the sake of consistency, σ constants were used throughout.

(26) T. C. Bruice and M. F. Mayahi, *J. Amer. Chem. Soc.*, **82**, 3067 (1960).
(27) M. L. Bender and R. J. Thomas, *ibid.*, **83**, 4189 (1961).
(28) J. F. Kirsch and A. Kline, *ibid.*, **91**, 1841 (1969).
(29) R. Barnett and W. P. Jencks, *ibid.*, **90**, 4199 (1968).

Table VII. Values of k_2 (M^{-2} sec^{-1}), k_3 (M^{-2} sec^{-1}), and k_2/k_3 of Eq 2 for the Aminolysis of Esters in Aprotic Solvents at 25.0°

Ester	Amine	Solvent	k_2	k_3	k_2/k_3	Ref
p-Nitrophenyl acetate	Pyrrolidine	C_6H_5Cl	1.84×10^1	1.89×10^1	0.97	*a*
p-Nitrophenyl acetate	*n*-Butylamine	C_6H_5Cl	6.4×10^{-2}	8.4×10^{-2}	0.76	11
p-Nitrophenyl acetate	*n*-Butylamine	$(CH_3CH_2)_2O$	5.85×10^{-2}	7.63×10^{-2}	0.77	15
Phenyl *o*-methoxybenzoate	*n*-Butylamine	CH_3CN	4.98×10^{-4}	4.32×10^{-4}	1.15	16

[a] This work.

acetate with pyrrolidine–Dabco in chlorobenzene are presented in Table VII along with pertinent literature data. Although the values of k_2 and k_3 change by more than 10^4 when substrate, solvent, and amine are varied, k_2/k_3 changes by less than a factor of 2. The mechanistic implications of this result will be discussed in the next section.

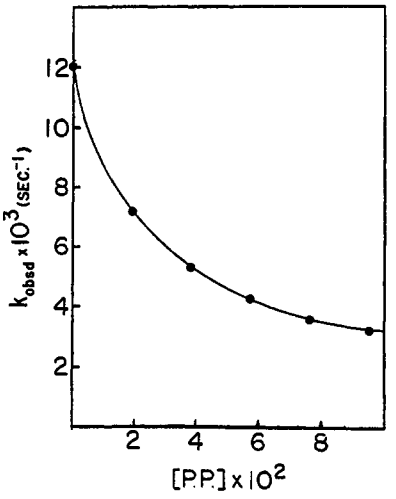


Figure 1. Plot of k_{obsd} *vs.* concentration of pyrrolidinium perchlorate (P.P.) for the reaction of *p*-cyanophenyl *p*-nitrobenzoate with 6.02×10^{-3} *M* pyrrolidine in acetonitrile at 25.0°.

Aminolyses of esters and acid chlorides in aprotic solvents are accelerated by carboxylic acids.[10,12,13,30] However, it is unclear whether the catalysis is caused by the carboxyl group, protonated amine, carboxylate anion, or acid–amine pair. To obviate this uncertainty, we determined the effect of a different acidic additive, pyrrolidinium perchlorate, upon the reaction of esters with pyrrolidine in acetonitrile. Pyrrolidinium perchlorate was selected because pyrrolidinium cation is the strongest possible acid in a pyrrolidine solution; moreover, perchlorate anion is known not to perturb aminolysis rates.[16] We found that pyrrolidinium perchlorate *inhibits* the reactions of pyrrolidine with *p*-nitrophenyl *p*-nitrobenzoate and *p*-cyanophenyl *p*-nitrobenzoate (Figure 1). The data in Figure 1 for the *p*-cyano compound are consistent with eq 3 in which $K = 48\ M^{-1}$, $k = 2.03\ M^{-1}$, and $k_c = 0.18\ M^{-1}$ sec^{-1} (determined by a nonlinear regression analysis). Since k is larger than k_c, addition of pyrrolidinium perchlorate lowers the rate of the aminolysis.

(30) L. M. Litvinenko and N. M. Oleinik, *Zh. Obshch. Khim.*, 33, 2287 (1963).

$$\text{amine} + \text{acid} \overset{K}{\rightleftharpoons} \text{complex}$$
$$\text{ester} + \text{amine} \xrightarrow{k} \text{products} \qquad (3)$$
$$\text{ester} + \text{complex} \xrightarrow{k_c} \text{products}$$

In contrast to the above results, the reactions of pyrrolidine with *p*-chlorophenyl *p*-nitrobenzoate and phenyl *p*-nitrobenzoate are catalyzed by pyrrolidinium perchlorate (Figure 2). Thus, catalysis is observed with poorer leaving groups while inhibition occurs with the better ones.

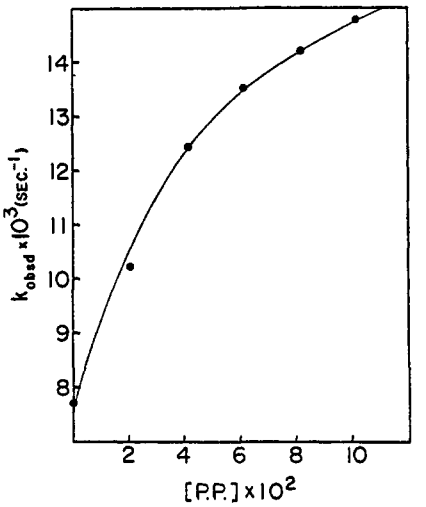


Figure 2. Plot of k_{obsd} *vs.* concentration of pyrrolidinium perchlorate (P.P.) for the reaction of *p*-chlorophenyl *p*-nitrobenzoate with 0.198 *M* pyrrolidine in acetonitrile at 25.0°.

Discussion

Kinetic studies never prove a mechanism; they only remove mechanisms from consideration. We begin this discussion by eliminating several mechanisms which have been proposed for aminolyses of aryl esters in aprotic solvents.

Cyclic mechanisms leading directly to product (Figure 3)[13,14] do not account for the prodigious ρ values of 4–6 in Table V. Both transition states in Figure 3 feature delivery of a proton to a departing oxygen. An electron-withdrawing substituent would enhance carbon–oxygen cleavage but impede oxygen protonation. (The reverse is true for an electron-donating substituent.) Since the effects of a substituent more or less cancel, we would expect *small* ρ values if the cyclic mechanisms were correct.[31]

(31) Small ρ values for the aminolysis of phenyl acetates in water have been used as evidence *supporting* a cyclic mechanism.[26]

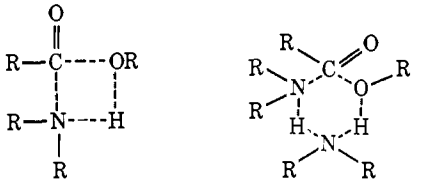
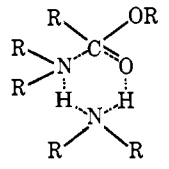


Figure 3. Transition states for one-step cyclic concerted mechanisms for k_1 and k_2 of eq 1.

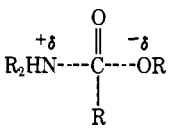
Nor do the observed ρ values justify a rate-determining cyclic concerted mechanism leading to a neutral tetrahedral intermediate (transition state A);[9-11] the



transition state A

bond between the carbonyl carbon and the phenolate oxygen in A breaks only slightly (if at all) in the transition state.[32] Similarly, a rate-determining addition of amine to form a charged tetrahedral intermediate (Figure 4)[11] fails to explain the extreme sensitivity of the rate constants to the phenol portion of the aryl esters.

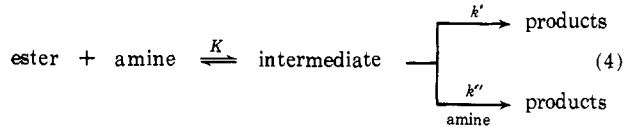
What mechanisms *are* consistent with the ρ values of 4–6? The simplest one is a direct displacement reaction with no intermediate (transition state B). Rates of aminolyses proceeding by this mechanism would indeed respond to changes in substituents on the leaving group. Such substituents can alter the partial positive charge on



transition state B

the carbonyl carbon and hence perturb the rate of bond formation between the carbon and nucleophile. More importantly, substituents either increase or diminish the developing negative charge on the departing phenol oxygen. The effect on the aminolysis rates should be appreciable, particularly since the anionic oxygen is poorly solvated in aprotic media. Note that the simultaneous bond breakage and bond formation of the carbonyl carbon in B accord with the small ρ values (1–2) for acyl-substituted esters (Table V).

Another possible mechanism emerges: reversible formation of a tetrahedral addition intermediate followed by rate-determining collapse of the intermediate (eq 4). For the moment we will be concerned with the



(4)

gross features of eq 4 rather than with the detailed structure of the unstable intermediate. The intermediate in eq 4 forms products with and without the aid of a second amine molecule, leading to a two-term rate expression (eq 5) which is kinetically equivalent to our observed rate law, eq 1.

$$\text{rate} = k'K[\text{ester}][\text{amine}] + k''K[\text{ester}][\text{amine}]^2 \quad (5)$$

ρ values for the aminolysis are comprised of contributions from both steps of the two-stage mechanism.[33] An electron-withdrawing substituent in the leaving group of the ester shifts the equilibrium to the right and accelerates the second step, resulting in a large ρ value. An electron-withdrawing substituent in the acyl portion, while having a favorable effect on the first step, inhibits the loss of a negatively charged leaving group. The net ρ value should be small, and this is what we observe.

A series of runs were performed using an unhindered tertiary amine, triethylenediamine (Dabco), as an additional component of the system. The tertiary amine was found to catalyze the ester aminolyses according to eq 2. Although the absolute values of k_2 and k_3 changed by more than 10^4 when the substrate, solvent, and amine were varied, the ratio k_2/k_3 remained constant within a factor of two (Table VII). Equation 4 predicts these results. Any type of amine (primary, secondary, or tertiary) can serve as a proton acceptor in the catalyzed decomposition of the tetrahedral intermediate. The data in Table VII are also consistent with a direct displacement (transition state B) catalyzed by a general base. However, cyclic mechanisms in which the nitrogen of *both* participating amine molecules bear at least one hydrogen (Figure 3 and transition state A) are shown to be invalid (as we also demonstrated from the ρ values).

We have no data bearing on the merits of a two-step mechanism involving a tetrahedral intermediate as opposed to a direct displacement mechanism. Unfortunately, negative deviations from pH–rate profiles and other lines of evidence used to support tetrahedral intermediates in aqueous systems[34] cannot be applied to reactions in acetonitrile and chlorobenzene. Nevertheless, since addition intermediates are common in acyl transfer reactions in water, [35] we favor their presence in aprotic solvents.[36] If this is correct, then our ρ values demand that collapse of the intermediates be rate determining.[37]

Let us now turn our attention to possible structures of the tetrahedral intermediate. We know that the inter-

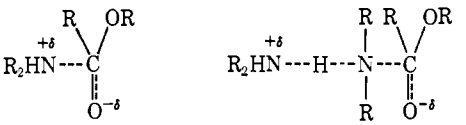


Figure 4. Transition states for rate-determining addition of an amine (uncatalyzed for k_1 and general base catalyzed for k_2) to form charged tetrahedral intermediates.

(32) Some bond breakage is possible even if formation of the tetrahedral intermediate is rate determining: W. P. Jencks and M. Gilchrist, *J. Amer. Chem. Soc.*, **90**, 2622 (1968).

(33) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," Wiley, New York, N. Y., 1963, p 187.

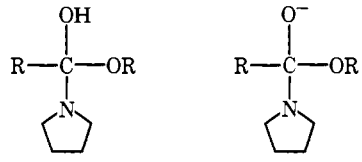
(34) S. A. Shain and J. F. Kirsch, *J. Amer. Chem. Soc.*, **90**, 5848 (1968).

(35) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969.

(36) S. D. Ross, *J. Amer. Chem. Soc.*, **92**, 5998 (1970).

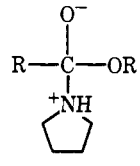
(37) The rate-limiting step is determined by the highest point on the energy profile. When ΔF^* for conversion of a steady state intermediate into products exceeds that for conversion into reactants, the former is rate determining.

mediate expels the leaving group in an unprotonated state (*i.e.*, as phenoxide rather than phenol). Otherwise, the ρ values of 4–6 for esters substituted in the leaving group would be much smaller (a substituent that promotes carbon–oxygen cleavage also impedes oxygen protonation, and the effects cancel). Phenoxide expulsion is confirmed by the similarity between ρ values for the reactions of pyrrolidine and azide ion with esters in acetonitrile. Since the leaving group is certainly anionic in the azide reaction, we infer that the same is true for the aminolysis. Note also that the tetrahedral intermediate must revert back to reactants faster than it forms products (collapse of the intermediate to products is rate determining[37]). From these considerations we exclude two addition intermediates, I and II. If I or II were directly involved, then the reverse reaction of the intermediate in eq 4 would be *slower* than the forward ones because the amine anion is a poorer leaving group than phenoxide.



I II

On the other hand, structure III is an acceptable steady state intermediate.[38] Partitioning of III would



III

favor the reactants over products because the reverse reaction of III dissipates charge and because pyrrolidine is a weaker base in acetonitrile than even our best leaving group, *p*-nitrophenoxide.[39]

In the third-order aminolyses of esters, a second amine molecule accepts the proton from the nitrogen of III (k'' step of eq 4), thereby impairing the back reaction of the intermediate. If this amine catalysis became important enough, the rate-determining step could change. We added large amounts of a tertiary amine, triethylenediamine, to solutions of constant pyrrolidine concentration, hoping to reach a point where product formation was the fast step. This would be manifested by a downward curvature in a plot of k_{obsd} *vs.* [triethylenediamine].[40] However, the plots were linear even at 2 *M* tertiary amine.

The pyrrolidine-*d* isotope effects in Table VI for the k_1 and k_2 terms of eq 1 are consistent with the small values expected from the "solvation rule"[41] (which says that proton transfer between two heteroatoms leads to no primary isotope effect in reactions where bond changes on a carbon are rate-determining). We will let the matter of isotope effects rest here, because we doubt the value in this case of drawing detailed conclusions about complex transition states from small rate differences of diverse origin.[42]

Pyrrolidinium ion modestly accelerates reactions of pyrrolidine with esters having poor leaving groups (Figure 2). Perhaps the acid assists the collapse of the intermediate by donating a proton to the departing oxygen. When the leaving group is *p*-nitrophenoxide or *p*-cyanophenoxide, pyrrolidinium ion inhibits the aminolyses (Figure 1). Complexation of pyrrolidinium ion with pyrrolidine (eq 3),[43,44] which reduces the nucleophilicity of the amine, predominates over possible catalytic effects.

Previously proposed mechanisms for ester aminolyses in aprotic solvents[9–18] should be assessed in light of the main conclusion of the present study, namely that collapse of a tetrahedral intermediate is rate determining. Of course, we cannot categorically dismiss these other mechanisms, many of which involve reactants and solvents different from ours. Finally, we must point out that the details of the rate-determining collapse of the tetrahedral intermediate are unknown; indeed, they may never be known with certainty.[45]

Acknowledgment. We thank the National Science Foundation for support of this work.

(38) Formation of ionic intermediates from neutral reactants in aprotic solvents is common. For example, see E. Gelles, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 2918 (1954); M. J. S. Dewar and R. C. Fahey, *J. Amer. Chem. Soc.*, **85**, 3645 (1963).

(39) J. F. Coetzee, *Progr. Phys. Org. Chem.*, **4**, 45 (1967).

(40) C. F. Bernasconi, *J. Org. Chem.*, **32**, 2947 (1967).

(41) C. G. Swain, D. A. Kuhn, and R. L. Schowen, *J. Amer. Chem. Soc.*, **87**, 1553 (1965).

(42) In this connection, see F. G. Bordwell and W. J. Boyle, *ibid.*, **93**, 512 (1971).

(43) J. F. Coetzee and G. R. Padmanabhan, *ibid.*, **87**, 5005 (1965).

(44) M. M. Davis, "Acid-Base Behavior in Aprotic Organic Solvents," National Bureau of Standards Monograph 105, Washington, D. C., 1968.

(45) T. C. Bruice and S. Benkovic, "Bioorganic Mechanisms," Vol. 1, W. A. Benjamin, New York, N. Y., 1966, p 258.