Aminolysis Reactions. I. Mechanism of Aminolysis and Amidinolysis of *p*-Nitrophenyl Acetate in Chlorobenzene

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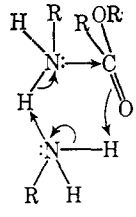
Abstract: The kinetics of aminolysis and amidinolysis of *p*-nitrophenyl acetate (*p*-NPA) in chlorobenzene at 25.0° were investigated. With diamines the pseudo-first-order rate constants fit the equation $k_{1,\,obsd} = k_2(\text{diamine}) + k_3(\text{diamine})^2$ with k_2 values of 0.0634 and 0.0474 M^{-1} sec^{-1} and k_3 values of 0.903 and 0.349 M^{-2} sec^{-1} for 1,3-diaminopropane and N,N-dimethyl-1,3-diaminopropane, respectively. Because the *n*-butylaminolysis exhibits only the third-order term, the k_2 terms observed with the diamines represent intramolecular catalysis by the amino and dimethylamino groups. The tertiary amine 1,4-diazabicyclo[2.2.2]octane, although 150 times less basic, is a 1.3 times better catalyst of the *n*-butylaminolysis of *p*-NPA than *n*-butylamine. These results show that the tertiary amino groups are effective catalysts of the aminolysis of *p*-NPA in chlorobenzene if steric interactions are minimized. The aminolyses are therefore not solely bifunctionally catalyzed, transition state I, as previously proposed. Similarly, the proposal that bifunctional catalysis, transition state II, results in the facile benzamidinolysis of *p*-NPA is shown to be unlikely by the second-order rate constant (162 M^{-1} sec^{-1}) for the reaction with 1,4,5,6-tetrahydropyrimidine being 46 times larger than that with benzamidine. More definitive means of differentiating between bifunctional and general base catalysis are suggested.

Aminolysis reactions, especially when performed in low dielectric aprotic solvents, are often third order, second order in amine. The observation of little or no catalysis by tertiary amines and the expected unfavorability of charge separation in poor ionizing solvents have been employed as evidence for a six-membered cyclic transition state and bifunctional catalysis by the second amine molecule.[1-3]

Because polar reactions do occur in poor ionizing solvents[4] and general base catalysis is subject to steric hindrance,[5,6] we considered this type of data to be insufficient to establish bifunctional catalysis or to eliminate general base catalysis. We report here an investigation of the aminolysis and amidinolysis of *p*-nitrophenyl acetate (*p*-NPA) in chlorobenzene and the methods we employed to disprove the proposal that these reactions are bifunctionally catalyzed and proceed *via* transition states I and II.[1]



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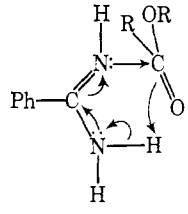


II

Experimental Section

Materials. All distillations were performed under nitrogen and only the middle 50% of the constant-boiling fraction was retained for further use. Reagent grade chlorobenzene was dried (P_2O_5) overnight and distilled from P_2O_5 through a 90 × 1.2 cm column filled with Raschig rings. The diamines and *n*-butylamine were twice distilled from KOH and zinc dust: 1,3-diaminopropane, bp 137–138° (lit.[7] bp 135–136 (738 mm)); N,N-dimethyl-1,3-diaminopropane, bp 133° (lit.[8] bp 132–133°); *n*-butylamine, bp 77° (lit.[8] bp 77.0–77.5°). The 1,4,5,6-tetrahydropyrimidine (THP) was synthesized from 1,3-diaminopropane and hydrogen cyanide,[9] bp 129–130° (15 mm) (lit.[9] 125° (18 mm)). The 1,4-diazabicyclo-[2.2.2]octane (DABCO) was recrystallized from benzene and sublimed, mp 157–159° (lit.[10] 157–158°).

Gas chromatographs (5-ft Carbowax and polyethylenamine columns) of the amines and THP showed only single peaks and equivalent-weight determinations (HCl and methyl red indicator) agreed with the calculated values to better than 0.8%. The nmr of neat THP was consistent with its structure: singlet, τ 1.58 (1.0 H); singlet, 3.05 (0.96 H); triplet, 6.85 (4.2 H); and quintuplet, 8.5 (2.1 H).

All the kinetics were performed in stoppered cuvettes contained in the thermostated (25.0 ± 0.1°) cell holder of a Cary 14 or 15 spectrophotometer. The release of *p*-nitrophenol was followed by the increase in absorbance at 335 mμ. The reactions were initiated by placing the appropriate volume of 4.0 × 10^{-2} *M* *p*-NPA in chlorobenzene on the rim of the flattened end of a stirring rod and vigorously and quickly stirring the thermostated amine or amidine solution with the rod. In the majority of the runs the amines and

Table I. The Observed Second-Order Rate Constants for the Diaminolysis of *p*-Nitrophenyl Acetate[a]

(Diamine), *M*	$k_{2,\,obsd}$, 10^{-3} M^{-1} sec^{-1}	
	1,3-Diaminopropane	N,N-Dimethyl-1,3-diaminopropane
0.100	155.0	82.4
0.070	126.0	71.7
0.050	107.0	64.4
0.030	89.2	58.7
0.010	71.9	51.7
0.0030	68.0	47.6

[a] 25.0°, in chlorobenzene.

(1) F. M. Menger, *J. Am. Chem. Soc.*, **88**, 3081 (1966).
(2) P. J. Lillford and D. P. N. Satchell, *Chem. Ind.* (London), 1750 (1967); *J. Chem. Soc., B*, 360 (1967).
(3) S. T. McDowell and C. J. M. Stirling, *ibid.*, 343 (1967).
(4) R. E. Pincock, *J. Am. Chem. Soc.*, **86**, 1820 (1964); **87**, 1274 (1965).
(5) F. Covitz and F. H. Westheimer, *ibid.*, **85**, 1773 (1963); R. P. Bell, M. H. Rand, and K. M. A. Wynne-Jones, *Trans. Faraday Soc.*, **52**, 1093 (1956).
(6) W. P. Jencks and M. Gilchrist, *J. Am. Chem. Soc.*, **88**, 104 (1966); T. C. Bruice, A. Donzel, R. W. Huffman, and A. R. Butler, *ibid.*, **89**, 2106 (1967).
(7) I. Heilbron, "Dictionary of Organic Compounds," Eyre and Spottiswoode, London, 1965, p 877.
(8) A. S. Shawali and S. S. Biechler, *J. Am. Chem. Soc.*, **89**, 3020 (1967).
(9) W. Jentzsch and M. Seefelder, *Chem. Ber.*, **98**, 1342 (1965).
(10) M. Lichtenwalter and H. G. Muhlbauer, *Chem. Abstr.*, **61**, 670*d* (1964).

the THP were in considerable excess over the *p*-NPA (9×10^{-5} *M* for the aminolyses). The pseudo-first-order plots were linear in all cases.

The observed second-order rate constants ($k_{2,obsd}$) listed in Tables I, II, and III were obtained by dividing the pseudo-first-order rate constants by the amine or amidine concentration.

Table II. The Observed Second-Order Rate Constants for the Reaction of 1,4,5,6-Tetrahydropyrimidine with *p*-NPA[a]

(THP), 10^{-4} *M*	(*p*-NPA), 10^{-4} *M*	k_2, M^{-1} sec^{-1}
3.87	0.078	171.0
2.61	0.062	165.0
2.44	0.062	164.0
2.27	0.062	154.0
1.85	0.062	166.0
1.60	0.052	171.0
1.43	0.055	164.0
1.26	0.052	151.0
1.01	0.055	152.0
0.84	0.049	162.0
0.69	0.045	161.0
		Av 162 ± 6

[a] 25.0°, in chlorobenzene.

Table III. The Rate Expression and $k_{2,obsd}$ Values for the *n*-Butylaminolysis of *p*-NPA in the Presence of DABCO

(Butylamine), *M*	(DABCO), *M*	$k_{2,obsd}$, 10^{-3} M^{-1} sec^{-1}
0.111	0.107	16.3
0.111	0.0514	11.0
0.111	...	7.12
k_3^a = 6.4 M^{-2} sec^{-1}, $k_3'^a$ = 8.4 M^{-2} sec^{-1}		
0.111	0.107	16.3
0.051	0.107	12.5
...	0.107	Nr[b]
k_3^a = 6.4 M^{-2} sec^{-1}, $k_3'^a$ = 8.6 M^{-2} sec^{-1}		

[a] k_3 and k_3' values for best fit of the data. [b] No reaction in 3 hr.

Results

Table I lists the $k_{2,obsd}$ values for the aminolysis of *p*-NPA with N,N-dimethyl-1,3-diaminopropane and 1,3-diaminopropane. Figure 1 shows that the data may be fitted to the expression

$$k_{2,obsd} = k_2 + k_3(\text{diamine})$$

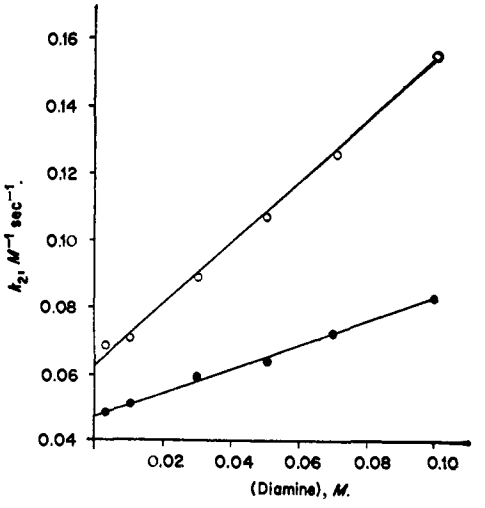


Figure 1. Plot of $k_{2,obsd}$ *vs.* diamine concentration for the aminolysis of *p*-NPA with 1,3-diaminopropane, ○, and with N,N-dimethyl-1,3-diaminopropane, ●, in chlorobenzene at 25.0°.

The $k_{2,obsd}$ values (Table II) for the reaction of *p*-NPA with 1,4,5,6-tetrahydropyrimidine (THP) are, within the experimental error, independent of the THP concentration.[11]

The $k_{2,obsd}$ values of the *n*-butylaminolysis of *p*-NPA in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) fits the expression $k_{2,obsd} = k_3(\text{butylamine}) + k_3'(\text{DABCO})$. The $k_{2,obsd}$ values and the k_3 and k_3' values which give the best fit of the data are listed in Table III. The k_3 values are in reasonable agreement with the reported value[1] of 0.062 ± 0.002 M^{-2} sec^{-1}.

Discussion

It has been reported[1] that the *n*-butylaminolysis of *p*-NPA chlorobenzene is purely third order and that the addition of 0.26 *M* *n*-methylpiperidine to 0.1 *M* *n*-butylamine increased the rate of aminolysis of *p*-NPA by only 30%. The benzamidinolysis of *p*-NPA was found to be second order,[11] with a second-order rate constant at least 15,000 times larger than the undetectable second-order rate constant for the *n*-butylaminolysis. These data, along with the expected unfavorability of charge separation in chlorobenzene, were taken as evidence for bifunctional catalysis, transition states I and II. The small rate increase observed with N-methylpiperidine was attributed to a medium effect rather than to N-methylpiperidine being one-ninth as strong a general base catalyst as *n*-butylamine.

Because heterolytic reactions do occur in poor ionizing solvents[4] and general base catalysis is subject to steric hindrance,[5,6] this is not sufficient evidence to eliminate general base catalysis. The aminolysis of phenyl acetate in water exhibits an amine-catalyzed term, k_3, and a solvent-catalyzed term, k_2. For methyl-, ethyl-, *n*-butyl-, and isopropylamines, the k_3/k_2 ratios are 6.6:1.3:0.8:0.0 indicating that even for primary amines steric hindrance to amine catalysis of ester aminolysis is significant.[6] Consequently we have investigated intramolecular general base catalysis and catalysis by DABCO in order to minimize steric effects.

The pure third-order kinetics of the *n*-butylaminolysis of *p*-NPA in chlorobenzene justifies the attribution of a second-order term in the aminolysis with a diamine to intramolecular catalysis by the second amino group. The bifunctional catalysis mechanism requires that this second-order term for the aminolysis with 1,3-diaminopropane be considerably larger than that with N,N-dimethyl-1,3-diaminopropane because the dimethylamino group, lacking a transferable proton, is incapable of bifunctional catalysis.

The k_2 terms listed in Table IV show that the dimethylamine group is not only an effective intramolecular catalyst but is a slightly better one than the amino group after correction for a statistical factor of 2. The greater catalytic ability of the dimethylamino group is consistent with the increase in kinetic and thermodynamic basicity along the series primary < secondary < tertiary amine when hydrogen bond donation to the solvent and steric effects are small.[12]

In contrast to our results, intramolecular catalysis

(11) The decrease in $k_{2,obsd}$ for the reaction of *p*-NPA with benzamidine at the lower benzamidine concentrations[1] may be due to a change in the rate-determining step.

(12) R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959, p 176.

Table IV. Rate Constants for the Aminolysis and Amidinolysis of *p*-NPA[a]

	k_2, M^{-1} sec^{-1}	k_3, M^{-2} sec^{-1}
n-Butylamine[b]	$<2 \times 10^{-4}$	0.062
1,3-Diaminopropane	0.0634	0.903
N,N-Dimethyl-1,3-diaminopropane	0.0474	0.349
Benzamidine[b]	3.54	
1,4,5,6-Tetrahydropyrimidine	162.0	

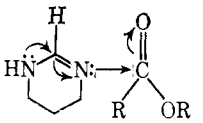
[a] 25.0°, in chlorobenzene. [b] From ref 1.

was not detected in the reaction of phenyl acetate with 1,3-diaminopropane in water.[13]

The data of Table III further demonstrate that tertiary amines are effective catalysts of the aminolysis of *p*-NPA if steric interactions are minimal. Although DABCO (pK_a = 8.6)[14] is approximately 150 times less basic than *n*-butylamine (pK_a = 10.77)[13] and 30 times less basic than N-methylpiperidine (pK_a = 10.08),[14] it is 1.3 and 12 times more effective than these amines in catalyzing the *n*-butylaminolysis of *p*-NPA.

These results indicate that bifunctional catalysis can not be the sole mechanism of aminolysis of *p*-NPA in chlorobenzene and that other proposals of bifunctional catalysis[2,3] based only on third-order kinetics in poor ionizing solvents and the low catalytic ability of tertiary amines must be considered suspect unless steric effects are explicitly considered and shown to be too small to account for the observed differences in catalytic abilities.

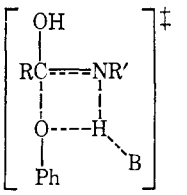
Although the aminolysis results are suggestive, they are not sufficient to eliminate bifunctional catalysis in the benzamidinolysis of *p*-NPA in chlorobenzene. The reaction of THP with *p*-NPA was therefore investigated. The geometry of this amidine makes bifunctional catalysis impossible for nucleophilic attack by



(13) T. C. Bruice and R. G. Willis, *J. Am. Chem. Soc.*, 87, 531 (1965).
(14) J. Hine, J. G. Houston, J. H. Jensen, and J. Mulders, *ibid.*, 87, 5050 (1965).

the imine nitrogen. The data of Tables II and IV show that the reaction with THP is second order and is 46 times faster than the benzamidinolysis. The bifunctional catalysis mechanism, transition state II, if it occurs, is therefore at most competitive with one or more nonconcerted, polar mechanisms for the benzamidinolysis of *p*-NPA in chlorobenzene. The high reactivity of the amidines is most reasonably attributed to high electron density on the imine nitrogen and stabilization of the transition state by dispersal of the positive charge over three atoms rather than to bifunctional catalysis.[1]

It has been proposed that the aminolysis of phenyl esters in dioxane involve four-membered cyclic transition states of the type[8]



The second-order kinetics and the relative reactivities of THP and benzamidine rule out similar cyclic transition states for the amidinolysis of *p*-NPA in chlorobenzene and suggest that such processes are unimportant in the aminolysis reaction.

We propose that in attempting to differentiate between bifunctional catalysis and general base catalysis by determining the relative catalytic abilities of tertiary and primary or secondary amines that steric effects be minimized by studying intramolecular catalysis or intermolecular catalysis with a tertiary amine of low steric requirements (DABCO, quinuclidine, or trimethylamine). In appropriate cases the relative reactivities of acyclic and cyclic amidines may be employed to the same end.

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