Acyl Substituent Effects in the General Base Catalyzed Ammonolysis Reactions of Esters[1]

Jack F. Kirsch and Adrianne Kline

Contribution from the Department of Biochemistry, University of California, Berkeley, California 94720. *Received August 16, 1968*

Abstract: The reactions of ammonia with series of *p*-chlorophenyl and of *p*-nitrophenyl benzoates have been investigated in 33% acetonitrile–water (v/v) at 25° and ionic strength 0.3. The rates of reaction of the latter series of esters with ammonia are dependent only upon the first power of the ammonia concentration, k_1, while those of the *p*-chlorophenyl benzoates have an additional term in the rate equation dependent upon $[NH_3]^2$, k_2. Under the conditions of these experiments terms dependent on $[OH^-][NH_3]$ or $[NH_4^+][NH_3]$ did not contribute to the observable kinetics. The values of ρ for the k_1 and k_2 terms for the reactions of the *p*-chlorophenyl benzoates are 1.08 ± 0.12 and 1.876 ± 0.011, respectively, indicating that the general base catalyzed reactions of these compounds are more sensitive to electron withdrawal in the acyl position than are the uncatalyzed. The ρ value for the k_1 term for the reactions of the *p*-nitrophenyl esters is 1.426 ± 0.015, demonstrating that the uncatalyzed ammonolysis reactions of these compounds are more sensitive to acyl electron withdrawal than are the corresponding reactions of the *p*-chlorophenyl esters. The integration of these observations into the currently held position that the transition state for the rate-determining step in these reactions resembles amine attack upon the ester rather than alcohol expulsion is accomplished by consideration of both the developing charge on the nucleophilic atom and the contribution to the over-all free energy of the reaction made by carbon–oxygen bond loosening in the transition state. Increasing the stability of the leaving group and the negative charge on the nucleophile both lead to larger ρ values for acyl substituents.

It was clearly demonstrated in 1960 that the aminolysis of esters is subject to catalysis by a second molecule of amine.[2-4] Many investigators, stimulated in part by the suggestions involving general base catalysis of enzymatic acyl transfer reactions,[5] have since carried out extensive studies on this system.[6] It has recently been established that a tetrahedral intermediate is formed in the aminolysis of at least one ordinary ester, methyl formate. The rate-determining step for the over-all reaction is amine attack on the ester at high pH, and breakdown of the tetrahedral intermediate at low pH.[7]

Structure–reactivity studies have been particularly useful in helping to clarify what is now known about the mechanism of these reactions. Jencks and Carriuolo measured the rates of both uncatalyzed and general base catalyzed reactions of glycine, glycine ethyl ester, and hydroxylamine with phenyl acetate but were unable to detect a general base catalyzed reaction of any of these with *p*-nitrophenyl acetate.[2] Bruice and Mayahi found from a Hammett series of substituted phenyl acetates that the general base catalyzed ammonolysis reaction is less sensitive to electron withdrawal in the leaving group than is the uncatalyzed reaction with ammonia.[3] Many workers have studied the kinetics of the aminolysis of phenyl acetate as a function of amine basicity.[2,6,8,9] It has generally been found that a Brønsted plot for the uncatalyzed reactions of structurally related amines has a slope of approximately 0.8, although it is now known that the reaction of very basic amines with reactive esters is nearly independent of basicity.[8] Brønsted plots can also be constructed for the general base catalyzed reactions of amines with phenyl acetates. The slopes of these lines are about 0.9.[6b,9] The important generalities that have thus far emerged from these studies are (1) the rates of reaction with a common nucleophilic amine are increased by a decrease in the pK_a of the leaving group of the ester; and (2) except for the limiting case noted above, increases in the basicity of the attacking amine increase the rates of both the uncatalyzed and general base catalyzed reactions as indicated by the positive Brønsted coefficients. The general acid catalyzed aminolysis reactions of phenyl acetate have also been investigated in some detail.[9] The third-order rate constants for this mode of catalysis are considerably less than those for the corresponding general base catalyzed reactions of the same amine, and the plots correlating the rate constants for the former reactions with those for the uncatalyzed ones or with the pK_a of the amine show a considerably greater scatter than do those constructed for the latter.[9] The poor correlation might be explained in terms of the two components of the catalysis, nucleophilic and general acid, having an opposing dependency upon the pK_a of the amine, *i.e.*, a lowering of the pK_a will result in a stronger general acid but in a poorer nucleophile.

It is not clear what to expect to happen to the rate of reaction when an electron-withdrawing substituent is placed in the acyl moiety of the ester, since both the

---

(1) Supported by National Institutes of Health Grant No. GM 12278 and National Science Foundation Grant No. GB 4606.

(2) W. P. Jencks and J. Carriuolo, *J. Amer. Chem. Soc.*, **82**, 675 (1960).

(3) T. C. Bruice and M. Mayahi, *ibid.*, **82**, 3067 (1960).

(4) J. F. Bunnett and G. T. Davis, *ibid.*, **82**, 665 (1960).

(5) L. C. Cunningham, *Science*, **125**, 1145 (1957); B. M. Anderson, E. H. Cordes, and W. P. Jencks, *J. Biol. Chem.*, **236**, 455 (1961); M. L. Bender and F. J. Kézdy, *Ann. Rev. Biochem.*, **34**, 49 (1965); J. F. Kirsch and M. Igelström, *Biochemistry*, **5**, 783 (1966).

(6) (a) A particularly comprehensive review has been prepared by T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. I, W. A. Benjamin, Inc., New York, N. Y., 1966, Chapter 1. (b) Further aspects of the reaction have been discussed by S. L. Johnson, *Advan. Phys. Org. Chem.*, **5**, 237 (1967).

(7) G. M. Blackburn and W. P. Jencks, *J. Amer. Chem. Soc.*, **90**, 2638 (1968).

(8) W. P. Jencks and M. Gilchrist, *ibid.*, **90**, 2622 (1968).

(9) T. C. Bruice, A. Donzel, R. W. Huffman, and A. R. Butler, *ibid.*, **89**, 2106 (1967).

ground state and the tetrahedral intermediate should have the same net charge.[10] One study of the rates of reaction of acyl-substituted phenyl esters with amines in anhydrous dioxane has been reported, where it was found that the rates of the catalyzed reactions are more sensitive to electron withdrawal in the acyl position than are the rates of uncatalyzed aminolysis.[11] Because of the presumed importance of proton transfer in some of these reactions, as indicated by deuterium isotope effects,[2] and the fact that the vast majority of studies on this system have been conducted in aqueous solution, it was considered of importance to gather more extensive data on rates of aminolysis reactions in water as a function of electron withdrawal in the acyl group. We report here a study of the rates of ammonolysis of two related series of esters, one, *p*-chlorophenyl benzoates, exhibiting both a general base and an uncatalyzed ammonolysis reaction, and the other, *p*-nitrophenyl benzoates, where the catalyzed reaction was of no kinetic importance.

Experimental Section

Materials. *p*-Chlorophenyl *p*-trifluoromethylbenzoate was prepared by the addition of $SOCl_2$ to a pyridine solution of the reactants according to the method previously described,[12] mp 80–81°. *Anal.*[13] Calcd for $C_{14}H_8ClF_3O_2$: C, 56.0; H, 2.66. Found: C, 55.92; H, 2.80.

The remaining esters were available from the same study. Commercial NH_4OH (Baker and Adamson, reagent) was used without further purification. Concentrations of ammonia were determined by titration to methyl red end points. Selected kinetic runs were titrated after completion and no reduction in ammonia concentration was ever observed during the course of the reaction. ND_4OD was purchased from Columbia Organic Chemicals Co., Inc., Columbia, S. C. Hydrogen assay by nmr showed 0.4% H. D_2O was obtained from Bio-Rad Laboratories, Richmond, Calif., and was distilled before use. DCl was made by the addition of $POCl_3$ to D_2O followed by distillation. Distilled acetonitrile and CO_2-free glass-distilled H_2O were used for all kinetic determinations.

Kinetics. The methods for determining rates of alkaline hydrolysis have been described.[12] Reaction mixtures for the ammonolysis experiments were generally prepared in 5-ml volumes and thermostated at 25° in glass-stoppered tubes. Readings of optical density, at the wavelengths given in Table I, were taken at suitable intervals after the addition of ester by transferring aliquots to 3-ml Teflon-stoppered glass cuvettes and placing them in a thermostated brass block in the cell compartment of a Zeiss PMQ II spectrophotometer. Mixtures for the faster reactions were prepared directly in the stoppered cuvette and were not transferred during the course of the run. Infinity readings were usually taken after ten half-lives but were estimated for a few of the slowest reactions by averaging the infinity readings for those reactions in the same series which were studied at higher concentrations of ammonia. All reactions were followed under pseudo-first-order conditions and the observed rate constants obtained from semilogarithmic plots of the data and the equation, $k_{obsd} = 0.693/t_{1/2}$. The values of k_{obsd} were corrected for the known rates of alkaline hydrolysis under these conditions.[12,14] Measurements of pH were made at 25° with a Radiometer PHM4-c pH meter employing a G200b glass electrode. Hydroxide ion concentrations were determined from the equation: $pH = \log [OH^-] + 14.58$, valid at 25°; ionic strength, 0.3 and 33% (v/v) CH_3CN.[12]

Analysis of Data. All rate constants were calculated by least-squares regression analyses fitted to eq 1 for the *p*-nitrophenyl esters and to eq 2 in the case of the *p*-chlorophenyl esters.[15] Hammett plots for the *p*-nitrophenyl esters were constructed by plotting $\log (k_{obsd} - k_{OH^-}[OH^-])$ for each experimental observation against σ. Contributions from the term in the rate expression dependent on the second power of the ammonia concentration obviated this method in the case of the *p*-chlorophenyl esters. In these instances the Hammett plots were computed using the rate constants given in Table I. Approximate standard errors for the logarithmic plots were determined from the equation

$$r^2 = \left(\frac{d \log k}{dk}\right)^2 s^2$$

where s is the standard error of the rate constant and r is the approximate standard error of the logarithm of the rate constant.[16] Weighting factors equal to n/r^2 were assigned to each point used in Figure 4 where n is equal to the number of observations.[17]

Results

The rates of reaction of a typical *p*-nitrophenyl ester, *p*-nitrophenyl benzoate, with ammonia, at two different buffer ratios, are shown in Figure 1. The over-all reaction, for each of the nitrophenyl esters, corrected for the rates of alkaline hydrolysis, could be satisfactorily accommodated by a rate expression proportional only to the first power of the free-base fraction of the ammonia buffer (eq 1).[18]

$$k_{obsd} - k_{OH^-}[OH^-] = k_1[NH_3] \qquad (1)$$

The rates of reaction of the *p*-chlorophenyl benzoates, by contrast, are clearly dependent on terms both first and second order in ammonia free base (Figure 2a, b) and are satisfactorily accommodated by eq 2. The slopes of the upper straight lines, drawn according to eq 3 from rate constants derived from the least-squares fits to eq 2, show the second order, and the intercepts, the first-order rate constants.

$$k_{obsd} - k_{OH^-}[OH^-] = k_1[NH_3] + k_2[NH_3]^2 \qquad (2)$$

$$\frac{k_{obsd} - k_{OH^-}[OH^-]}{[NH_3]} = k_1 + k_2[NH_3] \qquad (3)$$

The rate constants for the ammonolysis reactions and associated standard errors are collected in Table I. The values of k_{OH^-} under these conditions were available from a previous study.[12] The rates of alkaline hydrolysis of *p*-chlorophenyl *p*-trifluoromethylbenzoate in water and in deuterium oxide are reported in Table II. The ratio k_{OD^-}/k_{OH^-} is 1.10 ± 0.04.

The rate constants for the ammonolysis of *p*-chlorophenyl *p*-trifluoromethylbenzoate in deuterium oxide are also reported in Table I. The ratio, k_H/k_D, for the un-

---

(10) Since the pK_a's of the tetrahedral intermediates formed in these reactions are not known, it is conceivable that an anionic intermediate might be formed in some cases. It has been shown, however, that tertiary amines, which must form neutral intermediates, behave very similarly to primary and secondary amines with respect to the dependency of the rates of reaction of certain esters on amine basicity.[8]

(11) A. Sami, S. Shawal, and S. S. Biechler, *J. Amer. Chem. Soc.*, **89**, 3020 (1967).

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

(13) Microanalysis by Microchemical Analytical Laboratory, University of California, Berkeley, Calif.

(14) See Table II.

(15) Programs for multiple regression analysis were written according to the computing forms described in E. C. Bryant, "Statistical Analysis," 2nd ed, McGraw-Hill Book Co., Inc., New York, N. Y., 1966, pp 220–237.

(16) W. J. Blaedel and V. W. Meloche, "Elementary Quantitative Analysis," Row, Peterson, and Co., Evanston, Ill., 1957, p 577.

(17) Weighted least-squares methods are described in N. R. Draper and H. Smith, "Applied Regression Analysis," John Wiley & Sons, Inc., New York, N. Y., 1966, p 77 ff.

(18) When the data were analyzed for a possible second term by fitting to eq 2, it was found that the standard errors for this term were no less than one-half the value of the calculated rate constant indicating that this constant does not significantly differ from zero.

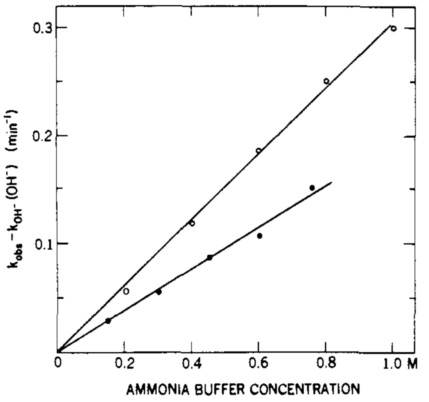


Figure 1. Observed pseudo-first-order rate constants for the reactions of ammonia buffers with *p*-nitrophenyl benzoate at 25°, 33% acetonitrile (v/v), and ionic strength 0.3: ○, 90% free base; ●, 60% free base. The slopes of the straight lines were determined by least-squares analysis with the origin fixed as the constant term.

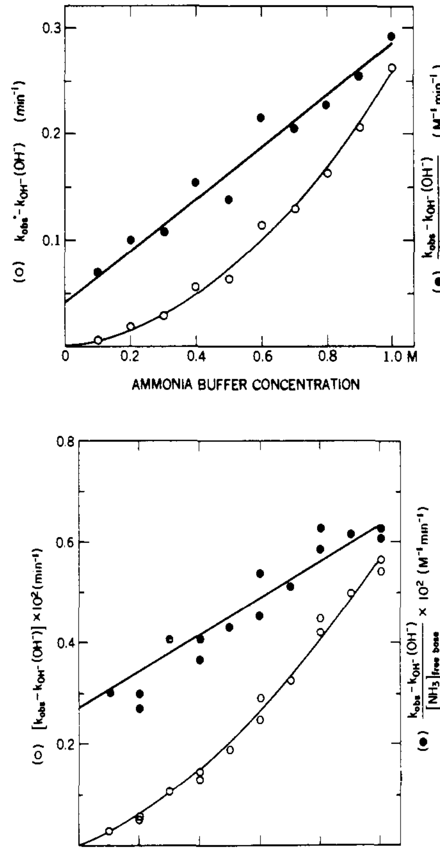


Figure 2. Observed pseudo-first-order rate constants for the reactions of ammonia with representative sustituted *p*-chlorophenyl benzoates. Conditions as in Figure 1 with 90% free base buffer ratio. The lines represent the least-squares fits to the equation: $k_{\text{obsd}} - k_{\text{OH}^-}[\text{OH}^-] = k_1[\text{NH}_3] + k_2[\text{NH}_3]^2$ (see text): (a, top) *p*-chlorophenyl *p*-nitrobenzoate, (b, bottom) *p*-chlorophenyl *p*-toluate.

catalyzed term was not determined very accurately ($k_H/k_D = 0.8 \pm 0.4$). The second-order term has $k_H/k_D = 1.6 \pm 0.2$. These figures may be compared with the corresponding ratios of 1.0 and 1.5 for the uncatalyzed and ammonia-catalyzed ammonolysis of phenyl acetate.[2]

The rate constants obtained for the ammonolysis of the *p*-nitrophenyl esters were generally in close agreement whether measured at 60 or 90% free base buffer ratios. A limited number of measurements were made at both buffer ratios for the more complicated reactions of the *p*-chlorophenyl esters. Although the results obtained were in fair agreement, the values from the lower free base ratio were considerably less precise than those derived from measurement at 90% free base, reflecting in part the relatively larger contribution of the uncatalyzed ammonolysis term at lower ammonia free base concentrations. In addition, specific salt effects are minimized at 90% free base ratio, where the total potassium chloride concentration varied only from 0.29 to 0.19 *M*. However, no significant change in the second-order rate constant for the reactions of *p*-chlorophenyl *p*-nitrobenzoate was observed at this free base ratio when tetramethylammonium chloride was substituted for KCl; or, in fact, when salt other than that contributed from the buffer was omitted altogether (Table I). The general base catalyzed reactions of phenyl acetate with a number of amines are reported to be somewhat greater in KCl than in tetramethylammonium chloride.[19,20]

In addition to exhibiting catalysis by a second molecule of amine, the reactions of certain amines with phenyl acetate are catalyzed by hydroxide ion, giving rise to a term in the rate expression dependent upon the product of the first powers of the ester, hydroxide ion, and amine concentration.[2,3,9,19-21] A search was made for hydroxide ion catalyzed ammonolysis by measuring the rates of release of *p*-chlorophenoxide ion from *p*-chlorophenyl *p*-nitrobenzoate at pH 12.2-12.4 in the presence and absence of added 1 *M* NH_4OH at 25° and ionic strength 0.3 in stoppered cuvettes. No difference in rates was detected, and the maximum value for such a term could be calculated as 40 M^{-2} min^{-1} assuming a 15% rate increase would have been noted.

Discussion

Structure-Reactivity Correlations. Hammett plots constructed by weighted least-squares analysis for the reactions of the substituted *p*-nitrophenyl and *p*-chlorophenyl benzoates are shown in Figures 3 and 4, respectively. The values of ρ, associated standard errors and intercepts at $\sigma = 0$ are given in Table III. Only the *p*-chlorophenyl esters exhibited a significant rate of reaction dependent upon the second power of the ammonia concentration. It was shown earlier that only the ammonolysis reactions of the less reactive phenyl acetates are subject to general base catalysis by a second molecule of NH_3.[3] The presence of a term in the rate expression for ammonolysis dependent on $[OH^-][NH_3]$ in the reactions of five substituted phenyl acetates has also been reported,[3] but was not detectable with *p*-chlorophenyl *p*-nitrobenzoate.

The Significance of the ρ Values and the Nature of the Rate-Determining Step. Although a fairly large number of studies of the aminolysis reactions of ordinary esters have been made, very few of these have given direct

---

(19) W. P. Jencks and M. Gilchrist, *J. Amer. Chem. Soc.*, **88**, 104 (1966).

(20) T. C. Bruice and R. G. Willis, *ibid.*, **87**, 531 (1965).

(21) J. F. Kirsch and W. P. Jencks, *ibid.*, **86**, 833 (1964).

Table I. Rates of Reactions of Esters with Ammonia Buffers[a]

A. p-Nitrophenyl Benzoates[b]				
Benzoyl substituent	Total ammonia,[d] M	Fraction free base	No. detns	k_{NH_3},[c] M^{-1} min^{-1}
p-NO$_2$	0.18–0.90	0.9	5	4.32 ± 0.10
	0.09–0.36	0.6	4	4.11 ± 0.07
m-NO$_2$	0.18–0.90	0.9	4	2.92 ± 0.07
	0.09–0.45	0.6	5	2.75 ± 0.04
p-Cl	0.18–0.90	0.9	5	0.646 ± 0.022
	0.09–0.45	0.6	5	0.566 ± 0.005
p-H	0.18–0.90	0.9	5	0.339 ± 0.004
	0.09–0.45	0.6	5	0.319 ± 0.009
p-CH$_3$	0.18–0.90	0.9	5	0.169 ± 0.003
	0.09–0.45	0.6	5	0.161 ± 0.002

B. p-Chlorophenyl benzoates[d]					
Benzoyl substituent	Init ester concn, $M \times 10^4$	No. detns	k_1,[e] M^{-1} min^{-1} × 10^2	k_2,[e] M^{-2} min^{-1} × 10^2	Wavelength, mμ
p-NO$_2$	0.6	10	4.1 ± 1.7	27.0 ± 2.4	258
	0.6	10[f]	1.3 ± 2.3	29.4 ± 3.3	258
	0.6	10[g]	3.3 ± 2.4	25.9 ± 3.2	258
m-NO$_2$	1.2	15	1.9 ± 0.6	19.2 ± 0.9	282
p-CF$_3$	2.2	9[h]	1.3 ± 0.4	9.88 ± 0.50	302
	2.2	10[i]	1.7 ± 0.7	6.34 ± 0.92	302
p-Cl	2.2	10	0.86 ± 0.13	2.26 ± 0.17	290
p-H	2.4	15	0.362 ± 0.065	0.98 ± 0.09	290
p-CH$_3$	2.4	15	0.271 ± 0.037	0.41 ± 0.05	302

[a] At 25°, 33% CH$_3$CN (v/v), and ionic strength maintained at 0.3 with KCl. [b] Initial ester concentrations were 3×10^{-5} M. Reactions were followed at 400 mμ. [c] Values and standard errors determined by least-squares fit to the equation, $k_{obsd} - k_{OH^-}[OH^-] = k_{NH_3}[NH_3]$. [d] Ammonia buffer concentration varied from 0.09 to 0.90 M, 0.9 fraction free base except where noted. [e] Determined by least-squares fit to the equation, $k_{obsd} - k_{OH^-}[OH^-] = k_1[NH_3] + k_2[NH_3]^2$. [f] Ionic strength maintained at 0.3 with tetramethylammonium chloride replacing KCl. [g] No added salt. Ionic strength varied from 0.01 at the lowest concentration of ammonia to 0.11 at the highest. [h] Ammonia buffer concentration, 0.18–0.90 M. [i] ND$_3$ in D$_2$O.

Table II. Rates of Alkaline Hydrolysis of p-Chlorophenyl p-Trifluoromethylbenzoate[a]

No. obsd	Init ester concn, $M \times 10^5$	Hydroxide ion concn, $M \times 10^4$	k_2[b]	Std error
9	22	50–150	68.9	1.7
9	22	50–150[c]	76.6	1.6

[a] At 25°, 33% (v/v) CH$_3$CN, and ionic strength 0.3. Reactions were followed at 302 mμ. [b] k_{obsd}/lyate ion concentration. [c] OD$^-$ in D$_2$O.

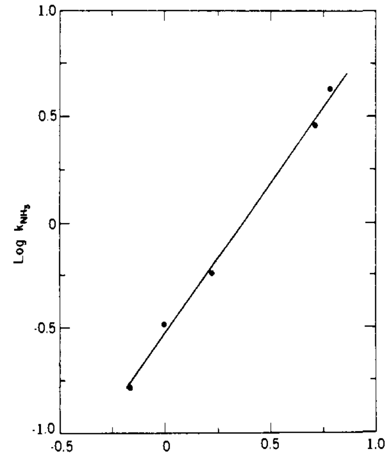


Figure 3. Rates of reaction of substituted p-nitrophenyl benzoates with ammonia as a function of σ. The points represent the average values from Table I.

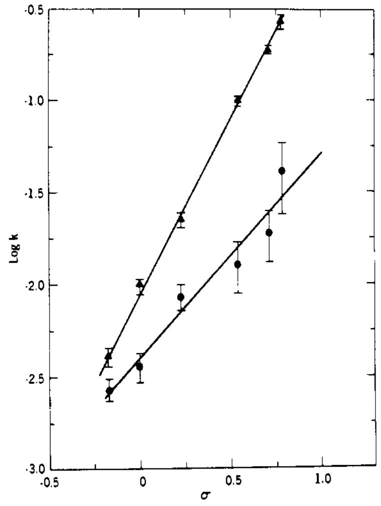


Figure 4. Hammett plots of the rates of reaction of substituted p-chlorophenyl benzoates with ammonia: (●) rate constants for reactions first order in [NH$_3$] free base, (▲) rate constants for reactions second order in [NH$_3$] free base. The lines were determined by weighted least-squares regression anayses (see Experimental Section). Standard errors of the individual rate constants are shown by flags.

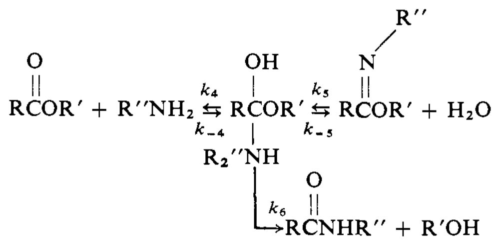
information on whether or not an obligatory tetrahedral addition intermediate is formed or of the critical bond-making and -breaking processes in the transition state for the rate-determining step. The facts relevant to these points which can be considered to be clearly estab-

Table III. ρ Values for the Reactions of Esters with Ammonia

Esters	ρ	Std error of ρ	Intercept at σ = 0.0	Correl coeff	No. of compd
p-Nitrophenyl benzoates	1.426[a]	0.015	−0.529	0.997	5[b]
p-Chlorophenyl benzoates	1.08[a]	0.10	−2.39	0.999	6[c]
	1.876[d]	0.038	−2.04	0.998	6[c]

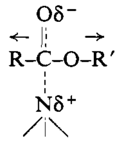
[a] For the rate constants dependent on the first power of ammonia concentration. [b] Representing 48 independent measurements of the rate constants. See text. [c] Data for each compound were grouped before least-squares analysis. See text. [d] For the rate constants dependent on the second power of ammonia concentration.

lished are as follows. (1) A tetrahedral intermediate is formed in the aminolysis of methyl formate and has a sufficiently long lifetime to allow complete proton-transfer equilibrium to be attained among the various ionic forms of the intermediate, and the rate-determining step in this reaction at high pH is the attack of the amine on the ester.[7] (2) The hydrolysis of phenyl N-methylacetimidate above neutral pH leads exclusively to N-methylacetamide and phenol as products, again indicating that amine attack is the rate-determining step in the reaction of methylamine with phenyl acetate.[8,22] The reasoning behind these and similar experiments with cyclic systems[23,24] can be visualized with the aid of the diagram



from which it is seen that the same tetrahedral intermediate, if one is formed (assuming complete proton-transfer equilibrium), will arise from the attack of water upon the imidate and from the amine upon the ester. The imidate experiments show that at neutral or slightly basic pH and in the absence of perturbing buffer effects the product of the hydrolysis of the imidate is exclusively the amide, implying $k_6 > k_{-4}$, and, therefore, that the rate-determining step in ester aminolysis under these conditions is measured by the rate of amine attack, k_4.

The present results on the relative sensitivity of the ρ values for the ammonolysis of acyl-activated esters, taken together with earlier ones on alcohol activation,[3] do not fit in an uncomplicated manner into a mechanism involving simple rate-determining attack, as this does not readily account for the observations that the sensitivities of the k_1 and k_2 terms to inductive electron withdrawal, as measured by the values of ρ, depend on whether the esters are activated in the acyl or in the alcohol moieties. Thus, ρ for k_2 in the reactions of *p*-chlorophenyl benzoates is 1.876 ± 0.011, and for k_1 it is 1.08 ± 0.12 (Table III). In the case of alcohol-substituted phenyl acetates, ρ for $k_2 = 0.56$, which is smaller than ρ for $k_1 = 1.81$.[3] In general, the rates of uncatalyzed nucleophilic displacement reactions of substituted phenyl acetates are more sensitive to electron withdrawal in the alcohol moiety of the ester than are the corresponding general acid or general base catalyzed reactions of the same nucleophile.[25,26] It is not easy to see why the *relative* order of sensitivity of the catalyzed and uncatalyzed components of the reaction should be reversed by changing the position of activation of the substrate if the rate-determining step involved simple addition of the amine to the ester. The ρ* for the k_2 term for the *n*-butyl aminolysis of acyl-substituted phenyl esters in



anhydrous dioxane is also greater than the ρ* value for the k_1 term.[11] Similarly general base catalyzed reactions of imidazole with the acyl-substituted series of *p*-nitrophenyl benzoates are more sensitive to electron withdrawal than are the uncatalyzed reactions,[27] but general base catalysis by a second molecule of imidazole is only detectable for the least reactive esters in the alcohol-substituted series of phenyl acetates[21,25] indicating a lower sensitivity of the catalyzed reaction for the latter compounds. It was not possible to detect a k_2 term for the reactions of *p*-nitrophenyl benzoates, in agreement with earlier results on *p*-nitrophenyl acetate.[3] It is clear from Table III that ρ for the uncatalyzed ammonolysis of the nitrophenyl esters is distinctly higher than that for the same rate constant of the *p*-chlorophenyl benzoates. The ρ values for the alkaline hydrolysis reactions of the five series of acyl-substituted *p*-CH_3-, *p*-H-, *p*-Cl-, *m*-NO_2-, and *p*-NO_2-phenyl benzoates where the rate-determining step is clearly attack, are all virtually identical.[12]

The recent demonstration by Jencks and Gilchrist that the bond between the acyl carbon and the leaving-group oxygen atoms is partially broken in the transition state of aminolysis reactions, even though the rate-determining step involves amine attack,[8] makes it possible to rationalize the present data in a qualified manner. Some of the possible transition states within this framework for the uncatalyzed or solvent-catalyzed reaction are shown in I, below, and in II for the catalyzed reaction. Alternative kinetically indistinguishable arrangements of atoms corresponding to general acid catalyzed breakdown of the tetrahedral intermediate are not included, as this mode of reaction appears to have been ruled out.[7,8] The main difference visualized between catalyzed and uncatalyzed reactions is that while carbon–oxygen bond breaking occurs in both cases, it makes a less important contribution to the total free energy of activation of the catalyzed reaction. This process might be aided by proton transfer from the second molecule of amine,[3,11] a role which may either be omitted entirely (Ia), or be played by water (Ib) or a four-center process (Id). Tran-

---

(22) M. Kandel and E. H. Cordes, *J. Org. Chem.*, **32**, 3061 (1967).

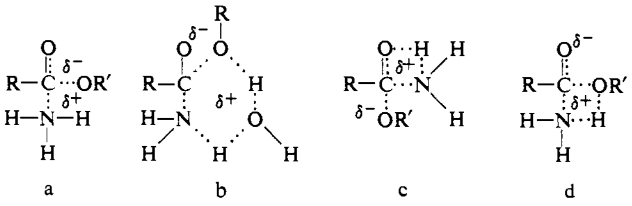
(23) B. A. Cunningham and G. L. Schmir, *J. Amer. Chem. Soc.*, **89**, 917 (1967), and references therein.

(24) G. L. Schmir, *ibid.*, **90**, 3478 (1968).

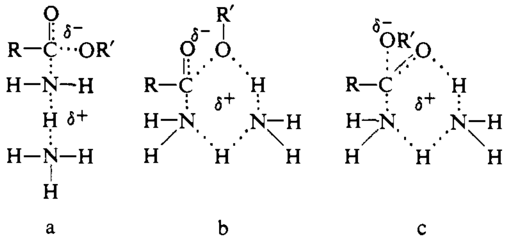
(25) T. C. Bruice and S. J. Benkovic, *ibid.*, **86**, 418 (1964).

(26) L. do Amaral, K. Koehler, D. Bartenbach, T. Pletcher, and E. H. Cordes, *ibid.*, **89**, 3537 (1967).

(27) M. Caplow and W. P. Jencks, *Biochemistry*, **1**, 883 (1962).



I



II

sition state Ic is formally analogous to the hydrogen-bond bridged tetrahedral intermediate that has been suggested to account for the relative difficulty of displacing OH^- relative to alkoxide ions of similar basicity from the intermediate.[28] Transition states Ib, c, and d are less likely representations of the uncatalyzed reaction than Ia because of the lack of a solvent deuterium isotope effect[2,29] and the fact that tertiary amines react in substantially the same manner as do primary amines.[8] Jencks and Gilchrist have shown that the reactivity of very basic amines toward active esters of acetic acid is only slightly dependent upon the basicity of the amine, while the slope of the Brønsted plot for nonbasic amines is approximately 0.8.[8] They have concluded from this result that the rate-determining step is not the same in both instances. Since a proton is partially removed from the nucleophile and general acid catalysis may stabilize the developing negative charge on the adduct (IIb, c) in the transition state, the general base activated attack of ammonia might be considered to be in the basic amine-reactive ester category, while the uncatalyzed attack corresponds to a nonbasic amine reacting with an ordinary ester. The various σ–ρ correlations can be understood in terms of the above discussion in the following manner.

a. The ρ Values for the k_1 and k_2 Terms for the *p*-Chlorophenyl Benzoates. Koehler, *et al.*,[30] have demonstrated that a number of oxyanions as well as F^- and mercaptoacetate exhibit enhanced nucleophilic reactivities toward acyl-activated esters when compared with neutral nitrogen nucleophiles. These results have been extended in this laboratory and the effect has been shown to be dependent more or less exclusively upon the charge of the nucleophilic atom, and to be independent of the nucleophilic element. Thus, for example, the ρ values for the attack of N_3^- on a series of *p*-nitrophenyl benzoates is 1.82,[31] which is closer to that of OH^-, 2.02,[12] than to that of NH_3, 1.43. Since the general base catalyzed attack of ammonia on an ester involves removal of a proton from the attacking NH_3 in the transition state, the nucleophile can be considered to have a partial anionic character, and from the above experiments should be more sensitive to electron withdrawal in the acyl substituent when the leaving group is held constant.

b. ρ Values for the k_1 Terms of *p*-Chlorophenyl- and *p*-Nitrophenyl Benzoates. Although charge effects similar to those discussed above, mediated this time from the alcohol rather than the acyl portion of the ester, might be invoked to explain the fact that the reactions of *p*-nitrophenyl benzoates are more sensitive to electron withdrawal than those of *p*-chlorophenyl esters, the situation in this case is probably more complex. It is, for example, as noted above, not at all obvious that the reaction of a neutral nucleophile with a neutral ester, to give an uncharged tetrahedral intermediate, should be subject to rate acceleration by electron withdrawal. In order to understand why this is so, it is necessary to postulate that the most important component of the free energy required to reach the transition state is the nucleophilic attack of the amine nitrogen atom on the electron-deficient acyl carbon atom, and that other factors such as carbon–oxygen bond breaking and proton transfer, while undoubtedly important, are secondarily so. Nucleophilic attack for all esters is aided by electron withdrawal in the acyl moiety of the ester; but carbon–oxygen bond breaking is correspondingly hindered. Where both components of the reaction are important smaller ρ values are to be expected, since these effects would tend to cancel each other out. Since nitrophenyl esters have better leaving groups than chlorophenyl esters, the bond-breaking process would be expected to contribute less significantly to the free energy of activation required for the formation of the rate-determining transition state than amine attack for the former series of esters and thus the full effect of electron withdrawal can be expressed in enhancement of the nucleophilic attack process. The same considerations would apply to the explanations for the ρ values for the k_1 and k_2 terms for the *p*-chlorophenyl benzoates described above to the extent that proton transfer to the leaving group contributes to the carbon–oxygen bond loosening in the catalyzed reaction (IIb).

c. The Relative Values of ρ for the k_1 and k_2 Terms in Reactions of Alcohol-Substituted Esters. If the displacement of the departing phenol were assisted in the catalyzed reaction by a second molecule of amine as suggested by Bruice[3] (IIb) then the effects of electron withdrawal in the alcohol would more or less cancel out, since carbon–oxygen bond breaking is aided by electron withdrawal, whereas protonation of the incipient phenolate ion is inhibited. Higher ρ values should be observed in the uncatalyzed reactions if this protonation does not make a significant contribution to the energy barrier.

---

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

(29) G. E. Lienhard and W. P. Jencks, *ibid.*, **88**, 3982 (1966), have summarized evidence indicating that general acid–base catalysis of nucleophilic carbonyl addition reactions need not be accompanied by large solvent isotope effects. An additional argument against the blanket use of solvent isotope effects as a definitive criterion of mechanism can be gleaned from the observation that k_{H_2O}/k_{D_2O} for the nucleophilic attack of acetate on 2,4-dinitrophenyl acetate is 1.8 while the general base catalyzed hydrolysis of *p*-tolyl acetate by acetate exhibits a k_{H_2O}/k_{D_2O} of only 2.4 (D. G. Oakenfull, T. Riley, and V. Gold, *Chem. Commun.*, 385 (1966)). It has been generally observed, however, that the ratios of k_{H_2O}/k_{D_2O} for general acid or general base catalyzed attack of amines on phenyl acetate is greater than 1.5 while the corresponding ratios for the uncatalyzed reactions are between 0.9 and 1.1.[9]

(30) K. Koehler, R. Skora, and E. H. Cordes, *J. Amer. Chem. Soc.*, **88**, 3577 (1966).

(31) J. F. Kirsch and L. Brock, unpublished results.

In summary the transition-state representations most readily reconciled with the experimental observations are Ia for the uncatalyzed ammonolysis reaction and IIb for the catalyzed. The main factors taken into account in reaching these conclusions are (1) the fractional charge on the attacking nucleophile and (2) the extent to which carbon–oxygen bond breaking contributes to the over-all free energy of activation. Increased developing negative charge on the nucleophile and stabilization of the leaving group either by electron withdrawal or by general acid catalysis both lead to larger values of ρ for acyl substituents.

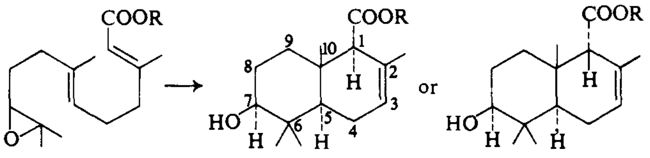
Communications to the Editor

Terpene Terminal Epoxides. Mechanistic Aspects of Conversion to the Bicyclic Level

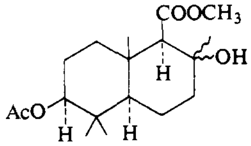
Sir:

In order to assess the requirements for enzyme control in the biosynthesis of lanosterol (I) from squalene 2,3-oxide (II), it is informative to compare and contrast the results of enzymic and nonenzymic reactions of this epoxide or suitable models.[1,2] For these reasons and also to understand more completely the purely organic aspects of such cyclizations, we have taken up physical organic studies which pertain to the mechanism of A,B ring formation.

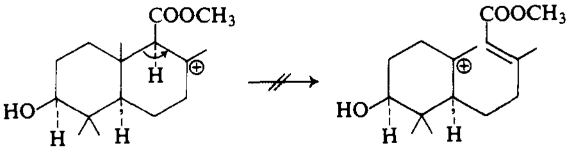
Previous work[3] has revealed that, depending upon reaction conditions, cyclization of *trans,trans*-10,11-oxidofarnesic ester (III) produces predominantly either the C-1,C-10 *trans dl*-bicyclic hydroxy ester IV or the corresponding *cis* isomer V, the latter being of particular interest because this stereochemical arrangement at a comparable pair of chiral centers is deemed necessary for isomerization of tetracyclic intermediate in the bioconversion II → I.[4] That such behavior is general is indicated by the similar specificity exhibited by 10,11-oxidofarnesyl acetates,[3c] and by $\Delta^{2,6}$-*cis,trans*-farnesyl ether.[3b] Of value in this connection are the following new observations. Both $\Delta^{2,6}$-*trans,trans*- and $\Delta^{2,6}$-*trans,cis*-farnesic esters are geometrically stable under the reaction conditions (cold phosphoric acid) used for cyclization of epoxide III. Isomer IV is at least 80% unchanged under these conditions, which induce conversion of epoxide III to bicyclic hydroxy ester comprising as much as 62% of V. Isomer V is largely recovered from the reaction medium (boron trifluoride etherate in benzene) which serves to convert starting epoxide to a mixture rich (75–90%) in isomer IV. A mixture of tertiary alcohols VI (obtained by hydration of ester IV),[5] on being subjected to reaction conditions used for cyclization of epoxide III to hydroxy ester V (presumably the more stable of the IV–V pair),[6] dehydrated—presumably *via* carbonium ion VII—to give exclusively the hydroxy ester isomer IV. On the basis of the foregoing, it seems certain that neither starting material nor product undergoes stereochemical change under cyclization conditions. Also, it appears likely that bicyclic carbonium ion VII does *not* suffer bond cleavage to monocyclic carbonium ion VIII which then recloses to the more stable bicyclic type (V), and thus carbonium ion VII is not an intermediate in the over-all phosphoric acid promoted cyclization of epoxide III to bicyclic ester V. In light of these aspects of epoxide cyclizations, it seems likely that the stereochemical outcome at C-1/C-10 in IV and V is determined by the *solvent-dependent conformation of reacting epoxide.*



III IV V



VI



VII VIII

When *trans,trans*-epoxy ester III was cyclized in trideuteriophosphoric acid under the usual conditions, no deuterium incorporation into product V was observed (mass spectral determination). This result rules out monocyclic, dienoid intermediates which require repro-

---

[1] For a review of earlier investigations along these lines see E. E. van Tamelen, *Accounts Chem. Res.*, **1**, 111 (1968).

[2] For example, by such means we have been able to demonstrate biochemical overriding of normal chemical tendencies in the construction of a six-membered C-ring: E. E. van Tamelen, J. Willett, M. Schwartz, and R. Nadeau, *J. Am. Chem. Soc.*, **88**, 5937 (1966). See also K. B. Sharpless and E. E. van Tamelen, *ibid.*, **91**, 1848 (1969).

[3] (a) E. E. van Tamelen, M. Schwartz, and A. Storni, *Chem. Commun.*, **13**, 409 (1966); (b) E. E. van Tamelen and R. C. Coates, *ibid.*, **13** (1966); (c) E. E. van Tamelen, A. Storni, E. J. Hessler, and M. Schwartz, *J. Am. Chem. Soc.*, **85**, 3295 (1963); (d) J. P. McCormick, unpublished observations.

[4] A. Eschenmoser, L. Ruzicka, O. Jeger, and D. Arigoni, *Helv. Chim. Acta*, **38**, 1890 (1955).

[5] Conversion of bicyclic ester IV to VI was accomplished by treatment with mercuric acetate, followed by reductive cleavage of the intermediary acetoxy mercury compound with $NaBH_4$. Assignment of structure VI rests upon consonant ir, uv, nmr, and mass spectral data, as well as satisfactory elemental analysis.

[6] Because of steric interaction of the pseudoequatorial ester function with both the neighboring olefinic methyl and axial angular methyl, the substituent is considered to be more stable in the pseudo-axial conformation.