toxy-Δ^5-bisnorcholenate, 0.1 ml. of absolute ethanol and 0.1 ml. of liquid ammonia was sealed and then heated at 68° for two hours. The tube was opened and the volatiles removed to give 48 mg. (100%) of the amide,[12] m.p. 221–226°; 5.77, 6.02, and 6.09 μ (KBr). Crystallization of 6 mg. from methanol at 5° gave 5 mg. (80%), m.p. 226–227°.

Attempts to prepare the diethylamide were unsuccessful. The reaction was incomplete after heating the ester with diethylamine for two hours at 140° in a sealed tube; after 12 hours, no ester remained but ammonolysis of the acetate group seemed to have occurred to a considerable extent.

1-Methoxyvinyl *p*-Nitrobenzoate. With Hg^{++}.—*p*-Nitrobenzoic acid (167 mg., 1 mmole), 0.3 mg. (0.001 mmole) of mercuric acetate and 2.8 mmoles of methoxyacetylene in 2 ml. of methylene chloride were stirred together at room temperature for one hour. The acid is not very soluble in the solvent and the end of the reaction was evident when the solution clarified. Removal of the volatiles gave 215 mg. (96%) of crude 1-methoxyvinyl *p*-nitrobenzoate, m.p. 67–72°, containing a little anhydride, 5.54 μ (CH_2Cl_2). The crude ester (130 mg.) was dissolved in 4 ml. of hot ethanol and the solution cooled rapidly and allowed to stand at room temperature for five minutes, after which it was centrifuged from the small amount of deposited solid. The clear filtrate was stored at −20° and gave 89 mg. (66%) of long, pale yellow needles, m.p. 75–78°, 5.72 and 5.94 μ (KBr). A further crystallization from ethanol gave analytical material, m.p. 76.5–78°.

Anal. Calcd. for $C_{10}H_9NO_5$: C, 53.81; H, 4.06; N, 6.28. Found: C, 53.72; H, 4.28; N, 6.36.

***p*-Nitrobenzamide.**—A tube containing 37.8 mg. (0.17 mmole) of 1-methoxyvinyl *p*-nitrobenzoate, m.p. 75–78°, 0.2 ml. of absolute ethanol and 0.2 ml. of liquid ammonia was sealed, heated momentarily to dissolve the solid, and then left at room temperature for 10 minutes. Removal of the volatiles gave 28.2 mg. (100%) of crude amide, m.p. 192–199°. Crystallization of 5.4 mg. from 0.5 ml. of water at 5° gave 4.6 mg. (85%), m.p. 198–202°, raised to 201–202.5° by a further crystallization; 6.01 μ (KBr).

1-Methoxyvinyl 3,5-Dinitrobenzoate.—A suspension of 217 mg. (1.02 mmoles) of 3,5-dinitrobenzoic acid in 1.8 ml. of methylene chloride, containing 0.9 mg. (0.0028 mmole) of mercuric acetate and 2.5 mmoles of methoxyacetylene, was stirred at room temperature. The reaction was complete in 12 minutes (evident from the clearing of the solution). Removal of the volatiles gave 267 mg. (97%) of crystalline 1-methoxyvinyl 3,5-dinitrobenzoate, m.p. 93.5–95.5°, containing only small amounts of anhydride, *ca.* 5.5 μ (CH_2Cl_2). Attempts to crystallize the ester led to extensive decomposition. Analytical material was obtained in another run, using 106 mg. (0.5 mmole) of acid and 7 mmoles of methoxyacetylene in 5 ml. of methylene chloride (no mercuric salt was added). The reaction was complete in 15 minutes. Removal of the volatiles gave 135 mg. (101%) of crystalline ester, 93.5–95.5°, 5.71 and 5.94 μ (KBr).

Anal. Calcd. for $C_{10}H_8N_2O_7$: C, 44.78; H, 3.01; N, 10.45. Found: C, 45.03; H, 3.24; N, 10.29.

1-Methoxyvinyl *p*-Phenylazobenzoate. With Hg^{++}.—A suspension of 41 mg. (0.18 mmole) of *p*-phenylazobenzoic acid in 3 ml. of methylene chloride, containing 0.8 mmole of methoxyacetylene, was stirred at room temperature for 12 hours. The infrared spectrum of the filtered solution showed that the acid was sparingly soluble in the solvent and negligible reaction had occurred. After the addition of 2.7 mg. (0.0085 mmole) of mercuric acetate, the reaction proceeded rapidly and was complete in half an hour (evident from the clearing of the solution). Removal of the volatiles gave 51 mg. (96%) of crude 1-methoxyvinyl *p*-phenylazobenzoate, m.p. 76–80°. With rapid heating and cooling of the solution, 32 mg. was crystallized from ethanol at 5° to give 26.5 mg. (80%) of pure ester, 5.72 and 5.97 μ (KBr). If heated slowly from 70°, a transition with partial melting, followed by solidification, occurred at 81°, m.p. (sharp) 94.5–95.5°. If immersed in the oil-bath at 85°, the ester melted completely before solidifying and finally remelting at 94.5–95.5°.

Anal. Calcd. for $C_{16}H_{14}N_2O_3$: C, 68.07; H, 5.00; N, 9.92. Found: C, 68.03; H, 5.09; N, 9.94.

***p*-Phenylazobenzamide.**—A tube containing 6.0 mg. (0.021 mmole) of 1-methoxyvinyl *p*-phenylazobenzoate, 0.2 ml. of ethanol and 0.1 ml. of liquid ammonia was sealed and left at room temperature for 10 minutes. Removal of the volatiles gave 4.9 mg. (100%) of amide, m.p. 226–227°, unchanged after crystallization from ethanol; 6.04 μ (KBr).

1-Methoxyvinyl 3β-Hydroxy-Δ^5-cholenate. Without Hg^{++}.—A suspension of 53 mg. (0.14 mmole) of 3β-hydroxy-Δ^5-cholenic acid in 5 ml. of methylene chloride was stirred overnight with 0.4 ml. (5.7 mmoles) of methoxyacetylene. Removal of the volatiles gave 61 mg. (100%) of crude ester, m.p. 125–127° (capillary tube inserted at 120°), 5.70 and 5.96 μ (KBr). An attempt to crystallize the crude material from methanol resulted in crystals melting less sharply below 110°. The crude product was not further characterized.

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[12] W. Cole and P. L. Julian, THIS JOURNAL, **67**, 1369 (1945).

[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY OF THE UNIVERSITY OF NORTH CAROLINA AND OF BROWN UNIVERSITY]

The Mechanism of Aminolysis of Esters[1,2]

BY J. F. BUNNETT AND GEORGE T. DAVIS

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The reaction of ethyl formate with *n*-butylamine in ethanol solution to form *n*-butylformamide is general base catalyzed. The rate law contains terms second order in amine (representing amine catalysis) and 3/2 order in amine (representing alkoxide ion catalysis) but no detectable term first order in amine. Addition of *n*-butylammonium chloride affects the rate law and the rate in a fashion consistent with this interpretation. The results are best represented by the mechanism of equations 23–25. The mechanism of equations 1–4, formerly generally accepted, is untenable. This work constitutes additional evidence for the intermediate complex mechanism as a general mechanism for substitution at carbonyl carbon.

The reactions of carboxylic esters with amines to form carboxamides have been extensively studied.[3,4] Careful kinetic researches[5,6] have revealed that such reactions are susceptible to base catalysis.

Ester aminolyses are in the category of nucleophilic substitutions at unsaturated carbon. An-

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[1] The portion of this work performed at the University of North Carolina was supported in part by the Office of Ordnance Research, U. S. Army, and the portion performed at Brown University by the National Science Foundation (Grant No. N.S.F. G6210).

[2] Preliminary results of this research were presented to the Kekulé Symposium on Theoretical Organic Chemistry, London, September, 1958; J. F. Bunnett, Proceedings of the Kekulé Symposium, p. 144.

[3] (a) P. K. Glasoe, L. D. Scott and L. F. Audrieth, THIS JOURNAL, **61**, 2387 (1939), and preceding papers; (b) R. N. Washburne, J. G. Miller and A. R. Day, *ibid.*, **80**, 5963 (1958), and preceding papers; (c) G. H. Grant and C. N. Hinshelwood, *J. Chem. Soc.*, 1351 (1933); (d) N. T. Vartak, N. L. Phalnikar and B. V. Bhide, *J. Indian Chem. Soc.*, **24**, 131A (1947); (e) P. J. Hawkins and I. Piscalnikow, THIS JOURNAL, **77**, 2771 (1955).

[4] R. Baltzly, I. M. Berger and A. A. Rothstein, *ibid.*, **72**, 4149 (1950).

[5] R. L. Betts and L. P. Hammett, *ibid.*, **59**, 1568 (1937).

[6] W. H. Watanabe and L. R. DeFonso, *ibid.*, **78**, 4542 (1956).

other aminolysis reaction within this category, that of N-methylaniline with 2,4-dinitrofluorobenzene to form N-methyl-2,4-dinitrodiphenylamine, is also sensitive to base catalysis, and a study[7] of the catalysis phenomenon indicated a mechanism substantially different from that which had been advanced to explain base catalysis of ester aminolysis. A re-examination of the latter effect was therefore undertaken.

Betts and Hammett,[5] on the basis of their kinetic study of ester aminolysis, proposed the mechanism

$$RNH_2 + RNH_2 \rightleftarrows RNH_3^+ + RNH^- \quad K_{Am} \quad (1)$$

$$RNH_2 + R'OH \rightleftarrows RNH_3^+ + R'O^- \quad K_B \quad (2)$$

$$R''COOR' + RNH_2 \longrightarrow R''CONHR + R'OH \quad k_a \quad (3)$$

$$R''COOR' + RNH^- \longrightarrow R''CONHR + R'O^- \quad k_b \quad (4)$$

They were careful to point out that this mechanism was not the only one consistent with their data,[8] but this mechanism was clearly favored by them. It has come to be generally accepted.

The experiments of Betts and Hammett concerned the reactions of ammonia (R = H) with methyl esters ($R' = CH_3$) of phenylacetic acid and some of its ring-substituted derivatives. The observations which called for the above mechanism or a mathematically equivalent one were: (a) the reactions were approximately 3/2 order in ammonia as well as first order in ester, (b) the reactions were accelerated by added sodium methoxide, and (c) the reactions were retarded by added RNH_3Cl in such a way that a plot of the apparent second-order rate coefficient (first order in ester and first order in ammonia) against $1/[RNH_3^+]$ was linear.

It will now be shown how these observations were reconciled with the mechanism of equations 1–4. The over-all rate (from equations 3 and 4) should be

$$\text{rate} = k_a[E][RNH_2] + k_b[E][RNH^-] \quad (5)$$

From equation 1

$$[RNH^-] = K_{Am}[RNH_2]^2/[RNH_3^+]$$

and therefore

$$\text{rate} = k_a[E][RNH_2] + k_bK_{Am}[E][RNH_2]^2/[RNH_3^+] \quad (6)$$

In the absence of added RNH_3^+, the concentrations of RNH_3^+ and R'O are equal (equation 2) and hence

$$[R'O^-] = K_B^{1/2}[RNH_2]^{1/2} \quad (7)$$

Equation 6 is then transformed into

$$\text{rate} = k_a[E][RNH_2] + k_bK_{Am}[E][RNH_2]^{3/2}/K_B^{1/2} \quad (8)$$

Equation 8 was said to explain observation (a) and equation 6 to explain (c). The accelerating effect of added sodium methoxide was interpreted as due to a shift of equation 2 to the left and a resulting shift of equation 1 to the right, causing an increase in $[RNH^-]$.

Watanabe and DeFonso[6] studied the kinetics of reaction of *n*-butylamine with ethyl formate in ethanol solution and in *ca.* 4 *M* ethylene glycol in dioxane. Kinetics first order in ester and approximately 3/2 order in amine were observed. However, the over-all 5/2 order rate coefficients were not constant throughout any run and the data were treated in terms of limiting values at zero time. When *n*-butylamine hydrochloride was present in constant amount, the kinetics in any run were accurately third-order over-all (first order in ester, second order in amine). When *n*-butylamine hydrochloride concentration was varied but total salt concentration was kept constant by compensation with lithium chloride, the rate coefficient decreased about threefold with change of $[RNH_3Cl]$ from 0.005 to 0.100 *M*. Strong catalysis (in ethanol) by added sodium ethoxide also was noted. These observations are similar to those of Betts and Hammett and were interpreted in terms of the same mechanism. Watanabe and DeFonso emphasized, however, that the mechanism of Betts and Hammett was not uniquely required by their data.

The results of the foregoing authors[5,6] are also compatible with this type of mechanism

$$R''COOR' + RNH_2 \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} R''COOR'{\cdot}RNH_2 \quad (9)$$

$$R''COOR'{\cdot}RNH_2 \xrightarrow{k_2} R''CONHR + R'OH \quad (10)$$

$$R''COOR'{\cdot}RNH_2 + B \xrightarrow{k_3} R''CONHR + R'OH + B \quad (11)$$

To our knowledge, this type of mechanism for ester aminolysis was first suggested by Hawkins and Tarbell[9] as an interpretation of the base catalysis of thiolester aminolysis which they observed. The kinetic expression for this type of mechanism,[7] derived with reliance on the steady state assumption, is

$$\text{rate} = \frac{k_1k_2 + k_1k_3[B]}{k_{-1} + k_2 + k_3[B]}[E][RNH_2] \quad (12)$$

if k_{-1} greatly exceeds both k_2 and $k_3[B]$, the denominator simplifies to k_{-1}. Then, taking account of the presence of three bases in an alcoholic solution of an amine—the alcohol, the amine and the alkoxide ion—one may write

$$\text{rate} = [E][RNH_2]\left[\frac{k_1k_2}{k_{-1}} + \frac{k_1k_3'}{k_{-1}}[R'O^-] + \frac{k_1k_3''}{k_{-1}}[RNH_2]\right] \quad (13)$$

Letting $k_{R'O^-}$ stand for k_1k_3'/k_{-1} and k_{RNH_2} for k_1k_3''/k_{-1}, we may rewrite this equation as

$$\text{rate} = (k_1k_2/k_{-1})/[E][RNH_2] + k_{R'O^-}[E][RNH_2][R'O^-] + k_{RNH_2}[E][RNH_2]^2 \quad (14)$$

When no RNH_3^+ salt is present this equation becomes (see equation 7)

$$\text{rate} = (k_1k_2/k_{-1})[E][RNH_2] + k_{R'O^-}K_B^{1/2}[E][RNH_2]^{3/2} + k_{RNH_2}[E][RNH_2]^2 \quad (15)$$

And when RNH_3^+ salt is present, equation 14

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[7] J. F. Bunnett and J. J. Randall, THIS JOURNAL, **80**, 6020 (1958).

[8] Betts and Hammett[5] said, "The obvious mechanism for such a [base] catalysis would involve amide ion as the actual reactant, and we shall discuss it in terms of this mechanism. The same conclusions can, however, be obtained from other mechanisms. Thus the reaction might be a truly termolecular one involving ester, ammonia and methylate ion, or the initial equilibrium might involve the ester and methylate ion."

[9] P. J. Hawkins and D. S. Tarbell, THIS JOURNAL, **75**, 2982 (1953).

becomes (see equation 2)

$$\text{rate} = (k_1k_2/k_{-1})[\mathrm{E}][\mathrm{RNH_2}] + k_{\mathrm{R'O^-}}K_\mathrm{B}[\mathrm{E}][\mathrm{RNH_2}]^2/[\mathrm{RNH_3^+}] + k_{\mathrm{RNH_2}}[\mathrm{E}][\mathrm{RNH_2}]^2 \quad (16)$$

Equation 15 contains terms in which the kinetic order in amine is one, 3/2 and two, respectively. Hence ester aminolysis might be any of these three orders in amine, or a mixture of orders, depending on the relative magnitudes of the three terms. If alkoxide catalysis were dominant, the second term which is 3/2 order in amine would account for most of the reaction. The observation of approximately 3/2 order in amine is thus understandable. If an $\mathrm{RNH_3^+}$ salt were present, equation 16 would obtain and at any fixed $\mathrm{RNH_3^+}$ concentration the second and third terms would merge as a term second order in amine. Thus the mechanism of equations 9–11 gives an adequate account of the observations of kinetic order reported by Betts and Hammett and by Watanabe and DeFonso. Acceleration by alkoxide ion, as observed, is obviously called for by equation 14.

When two chemically different mechanisms are both compatible with a set of kinetic data, a means of distinguishing them experimentally is desirable. In the present case, further kinetic tests can be applied. Foremost is determination of the type of base catalysis which prevails. The mechanism of equations 1–4 requires specific lyate ion catalysis whereas that of equations 9–11 demands general base catalysis.[10]

Choice of Experimental Conditions

The classic experiment for distinguishing general base catalysis from specific lyate ion catalysis involves determining the reaction rate in a series of buffers of constant buffer ratio but varying absolute buffer concentration, and at constant ionic strength.[10] Water is customarily the solvent for such a study. In this research, water was eschewed in order to avoid possible hydrolysis complications. An amphoteric solvent, in the Brönsted sense, was desired; the obvious choice was the alcohol represented in the alkyl group of the ester. If any other alcohol were used, *Umesterung* would be a possible complication, as Watanabe and DeFonso have pointed out. Bearing in mind the possibility that general base catalysis might be confused with nucleophilic catalysis,[11] we wanted a catalyzing base unable to effect nucleophilic displacement of ester alkoxy groups or which, if it did displace the alkoxy group, would not complicate the over-all reaction. The special bases which meet the latter requirement are the amine reactant itself and the alkoxide ion corresponding to the alkoxy group. These special bases were in fact the only ones studied in this work. In order that the progress of the reaction in any run should not disturb the buffer ratio, it was desired to have the amine and buffer components in large excess over the ester. This meant that the ester need be at very low concentration and therefore that a sensitive analytical method be used. Photometric analysis in the ultraviolet, depending on the difference in absorptivity between ester and amide functions, was found to be feasible.

Several ester–amine combinations were found to lack sufficient reactivity to be useful for our purposes. These included aniline–ethyl acetate, piperidine–ethyl acetate, aniline–ethyl benzoate, aniline–ethyl *p*-nitrobenzoate, *n*-butylamine–ethyl benzoate and *n*-butylamine–ethyl acetate. Eventually we settled on the system studied by Watanabe and DeFonso, the reaction of *n*-butylamine with ethyl formate in ethanol solution. The kinetic effects of varying concentrations of *n*-butylamine, of *n*-butylammonium chloride, of lithium chloride and of sodium ethoxide, in various combinations, were studied.

Because of the specificity of salt effects in ethanol solutions, owing largely to the prevalence of ion pairing, the ionic strength is not in itself an adequate representation of salt effects in this solvent. Therefore no effort was made to maintain constant ionic strength, and salt effects were studied separately.

Experimental

Materials.—Absolute ethanol was prepared by distillation of 95% ethanol from calcium oxide and then distillation from magnesium ethoxide.[12] This method was found to give ethanol of highest optical purity for measurements at 220 mμ.

Commercial butylamine was precipitated as the hydrochloride, m.p. 213–213.5°, from ether.[6] After three reprecipitations from ethanol by addition of ether, the free amine was liberated with excess strong base. After ether extraction and separation, the material was distilled (b.p. 77.3–77.8°) several times from solid potassium hydroxide and stored in a desiccator over solid sodium hydroxide.

Butylamine hydrochloride was prepared as described above and stored over Drierite and paraffin chips. Weighings of the hygroscopic hydrochloride were conducted in a dry-box.

Stock solutions of lithium chloride in ethanol were prepared from reagent grade material redried *in vacuo* over phosphorus pentoxide and weighed in a dry-box. The solutions were standardized by potentiometric chloride determination.

Ethyl formate was dried, distilled (b.p. 54.0–54.6°) and stored over phosphorus pentoxide.

n-Butylformamide was prepared from chloral and butylamine[13] in 24% yield, b.p. 121–122° (21 mm.) (uncor.), $n^{26}\mathrm{D}$ 1.4387 (lit.[13] b.p. 122–123° (16 mm.), $n^{26}\mathrm{D}$ 1.4385). This material was employed in initial spectral studies, and in preparation of mock infinity solutions.

A sample of *n*-butylamine was purified through the *o*-chlorobenzoyl derivative, m.p. 79–80°.

Anal. Calcd. for $\mathrm{C_{11}H_{14}ClNO}$: C, 62.40; H, 6.67. Found[14]: C, 62.62; H, 6.33.

n-Butylamine liberated from this material by basic hydrolysis was kinetically indistinguishable from amine purified through the hydrochloride.

Sodium ethoxide solutions were prepared by dissolving clean, freshly cut sodium in absolute ethanol, and standardizing the solution against standard acid.

Methanol was treated with magnesium metal and distilled from magnesium methoxide.

The methyl benzoate used was a commercial product, redistilled, b.p. 197.8–199.5°.

N-*n*-Butylbenzamide was prepared from benzoyl chloride and *n*-butylamine by the Schotten–Baumann reaction, b.p. 194–195° (25 mm.). After solidification in an ice-chest, the material was recrystallized three times from ethanol with seeding, m.p. 40–42° (lit.[15a] b.p. 182–184° (12 mm.), m.p.[15a] 68–70°, m.p.[15b] 41–42°). This material was used for spectral studies and preparation of infinity solutions.

Spectral studies of formic acid were made on solutions containing weighed quantities of sodium formate in acidified aqueous alcoholic media.

Methods.—The aminolysis reaction solutions were prepared from pipetted aliquots of standard stock solutions which were mixed and diluted at the reaction temperature. At appropriate time intervals, 10-ml. aliquots were quenched in 25-ml. volumetric flasks containing excess cold alcoholic hydrochloric acid (0.2–1.5 *M*). The samples then were diluted to the mark and measured at 220 mμ.

Slow decrease in absorption on standing required photometric measurements to be made without delay. Measurements were made on a Beckman DU spectrophotometer in matched 1-cm. quartz cells against a blank of quenching solution. Care was taken to use the same quenching medium

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(10) L. P. Hammett, "Physical Organic Chemistry," McGraw–Hill Book Co., Inc., New York, N. Y., 1940, p. 215.

(11) M. L. Bender and B. W. Turnquest, This Journal, **79**, 1652, 1656 (1957); M. L. Bender, Y.-L. Chow and F. Chloupek, *ibid.*, **80**, 5380 (1958); T. C. Bruice and R. Lapinski, *ibid.*, **80**, 2265 (1958); E. R. Garrett, *ibid.*, **79**, 5206 (1957).

(12) H. Lund and J. Bjerrum, *Ber.*, **64**, 210 (1931).

(13) F. F. Blicke and Chi Jung Lu, This Journal, **74**, 3933 (1952).

(14) Analysis by Micro-Tech Laboratories, Skokie, Ill.

(15) (a) J. v. Braun and J. Weismantel, *Ber.*, **55**, 3170 (1922); (b) H. W. Grimmel, A. Guenther and J. F. Morgan, This Journal, **68**, 539 (1946).

throughout a given run, as variations in solvent absorbances were found to be appreciable at 220 mμ. Yields based on the infinity absorbances for the unbuffered runs appeared to vary considerably and in an irregular manner. Undoubtedly, this contributed to the low precision of these runs.

In the most rapid runs containing added sodium ethoxide, special techniques were used to follow the reaction. The reactants were prepared to known volumes and concentrations in separate flasks and mixed by rapid introduction into a glass-stoppered erlenmeyer flask. Samples were withdrawn by means of a rapid-delivery syringe having a metal stop over the plunger. By this technique, it was possible to obtain samples at intervals of five seconds.

The runs involving methyl benzoate were followed by increase in absorption at 250 mμ due to production of N-butylbenzamide; 1-cc. aliquots were taken from reaction solutions containing 0.0100 *M* initial ester. These were quenched in 0.100 *M* 50% aqueous ethanolic hydrochloric acid.

Plots of log (O.D.$_\infty$ − O.D.) *versus* time gave good straight lines (*cf.* Fig. 1). The slope of such a line, selected by eye, was multiplied by 2.303 to give the total pseudo-first-order rate coefficient, k_ψ.

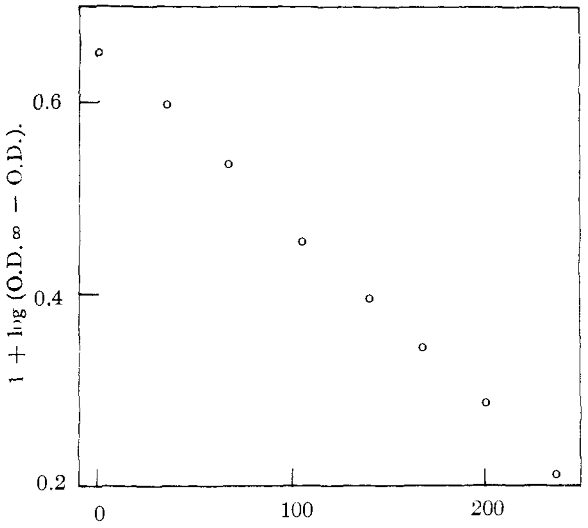

Fig. 1.—Representative kinetic run. Plot of the data in Table I.

In some runs, especially those involving sodium ethoxide catalysis, the infinity optical density was significantly less than that expected for quantitative conversion to the amide. In such cases hydrolysis or other reaction leading to the formation of formate ion was assumed. It was necessary to dissect the total pseudo-first-order coefficient into its components, a coefficient (k_A) for amide formation and another (k_F) for formate formation.

The dissection was performed as follows[7,16]: Let O.D.$_\infty$ be the experimental infinity value and let O.D.$_A$ and O.D.$_F$ be the theoretical infinity values on the assumptions, respectively, of complete conversion to amide and to formate. From the expressions

$$k_{tot} = k_A + k_F, \text{ and } O.D._\infty = (k_A/k_{tot})O.D._A + (k_F/k_{tot})O.D._F$$

one can derive by simple algebra that

$$k_A = k_{tot}(O.D._\infty - O.D._F)/(O.D._A - O.D._F)$$

This derivation involves the reasonable assumptions that the competing reaction is first order in ester and that the ratio $k_A : k_F$ is constant throughout any run.

Data from a typical run are displayed in Table I. Tables II and III present rate coefficients from several sets of supposedly identical runs. It will be noted that reproducibility in buffered runs (Table III) is better than in unbuffered runs (Table II); this same characteristic was mentioned by Betts and Hammett.

TABLE I

BUFFERED REACTION OF BUTYLAMINE WITH ETHYL FORMATE IN ABSOLUTE ETHANOL AT 24.6°. A REPRESENTATIVE RUN

Initial concentrations: RNH_2, 0.200 *M*; RNH_3Cl, 1.00 *M*; HCOOEt, 0.0100 *M*

Time, min.	Optical density (O.D.)	(O.D.$_\infty$ − O.D.)	1 + log (O.D.$_\infty$ − O.D.)
0.5	0.422	0.452	0.655
35.0	.477	.397	.599
67.0	.530	.344	.537
105.0	.588	.286	.456
140.0	.624	.250	.398
168.0	.652	.222	.346
200.5	.680	.194	.288
237.5	.710	.164	.215
1200	.874		

TABLE II

REPRODUCIBILITY OF UNBUFFERED RUNS. BUTYLAMINOLYSIS OF ETHYL FORMATE AT 24.60°

Initial concentration of ethyl formate: 0.0100 *M*

[BuNH$_2$], *M*	$k_\psi \times 10^4$, sec.$^{-1}$	Yield of aminolysis product,[a] %
0.600	5.38	73
.600	5.63	88
.600	5.30	104
.600	5.48	96
.600	6.72	104
.600	6.60	86
Average	5.85	

[a] From photometric measurements.

TABLE III

REPRODUCIBILITY OF BUFFERED RUNS. BUTYLAMINOLYSIS OF ETHYL FORMATE AT 24.60°

Initial concentration of ethyl formate: 0.0100 *M*

[RNH$_2$], *M*	[RNH$_3$Cl], *M*	$k_\psi \times 10^4$, sec.$^{-1}$
0.800	0.800	9.54
.800	.800	8.94
.800	.800	8.73
.600	.600	4.18
.600	.600	3.63
1.000	1.000	17.3
1.000	1.000	16.8

One run was made with simultaneous chemical and photometric analysis to verify the photometric method of analysis. The chemical analysis involved back-titration of samples quenched in excess standard methanolic hydrochloric acid. Nearly simultaneous samples were taken for photometric determination. In this run, the initial ester concentration was equal to the initial amine concentration. In agreement with Watanabe and DeFonso, the second-order plot of $1/(a - x)$ *versus* time was not linear. Significantly, however, the estimates of the extent of reaction by photometric

TABLE IV

COMPARISON OF PHOTOMETRIC AND CHEMICAL ANALYSIS

Initial concentrations of butylamine and of ethyl formate: 0.250 *M*; temperature, 25°

Chemical run		Photometric run	
Time, min.	$1/(a - x)$, l./mole	Time, min.	$1/(a - x)$, l./mole
0	4.06	0.5	4.07
30	4.72	30.5	4.50
63.5	5.25	64.5	5.28
90	5.71	91.5	5.65
121.5	6.05	123.5	6.26
192	7.06	195	7.26
225	7.63	227	7.80

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(16) J. F. Bunnett and K. M. Pruitt, *J. Elisha Mitchell Sci. Soc.*, **73**, 297 (1957).

and chemical measurements were of similar magnitude throughout the run. Detail on this run is shown in Table IV.

Results and Interpretation

Runs in the Absence of Added Substances.—A series of runs was made in which the *n*-butylamine concentration was varied tenfold, from 0.1 to 1.0 *M*. Reproducibility was not all that might have been desired, but the resulting pseudo-first-order rate coefficients (Table V) lay on a smooth curve when plotted against amine concentration. The curvature of this plot (which is not reproduced here) confirms that the reaction is not simply second order (first order in amine).[6] Division of the pseudo-first-order rate coefficient, k_ψ, by $[\mathrm{RNH_2}]$, by $[\mathrm{RNH_2}]^{3/2}$ and by $[\mathrm{RNH_2}]^2$ gives, respectively, over-all second-order, 5/2-order and third-order rate coefficients. These are given in Table V, and none of these pure order coefficients is constant over the range of amine concentrations represented.

TABLE V

BUTYLAMINOLYSIS OF ETHYL FORMATE IN ABSOLUTE ETHANOL AT 24.60°. UNBUFFERED RUNS

Initial concentration of ethyl formate: 0.010 *M*

$[\mathrm{RNH_2}]$, *M*	$k_\psi \times 10^4$, sec.$^{-1}$, obsd.	Yield of amide,[a] %	$k_\psi/[\mathrm{RNH_2}] \times 10^4$	$k_\psi/[\mathrm{RNH_2}]^{3/2} \times 10^4$	$k_\psi/[\mathrm{RNH_2}]^2 \times 10^4$	$k_\psi \times 10^4$ calcd.[b]
0.100	0.257	97	2.57	8.13	25.7	0.268
.250	1.29	99.5	5.16	10.3	20.6	1.27
.500	4.42	103	8.84	12.5	17.7	4.27
.600	5.85[c]	73–104	9.75	12.6	16.2	5.87
.750	8.75[d]	89–102	11.7	13.5	15.6	8.75
1.00	14.0	103	14.0	14.0	14.0	14.7

[a] Determined from infinity absorbances. [b] Calculated from the expression: $k_\psi \times 10^4 = (9.0[\mathrm{RNH_2}]^2 + 5.7 \cdot [\mathrm{RNH_2}]^{3/2})$ sec.$^{-1}$. [c] See Table II. [d] Average of 3 determinations.

Equation 15 is the rate expression expected under these conditions. If the first term is neglected, equation 15 is easily transformed into

$$k_\psi/[\mathrm{RNH_2}]^{3/2} = K_{\mathrm{B}}{}^{1/2}k_{\mathrm{OEt^-}} + k_{\mathrm{RNH_2}}[\mathrm{RNH_2}]^{1/2} \quad (17)$$

A plot of $k_\psi/[\mathrm{RNH_2}]^{3/2}$ against $[\mathrm{RNH_2}]^{1/2}$ should therefore be linear. It is, as shown in Fig. 2. The intercept should be $k_{\mathrm{B}}{}^{1/2}k_{\mathrm{OEt^-}}$ and it has the value 5.7×10^{-4} l. mole$^{-3/2}$ sec.$^{-1}$; the slope should be $k_{\mathrm{RNH_2}}$ and it has the value 9.0×10^{-4} l.^{2} mole^{-2} sec.$^{-1}$ (at 24.6°). These values were inserted into a rearranged form of equation 17 and the pseudo-first-order rate coefficient was calculated for each amine concentration at which rate measurements were made. The agreement of calculated with observed rate coefficients (Table V) is satisfying.[17]

The decisiveness of this resolution into terms 3/2 order and second order in amine stands in contrast to earlier studies[5-6] in which reaction orders could only be approximated. The success of the present treatment supports the assumption that the uncatalyzed (or solvent catalyzed) term is of insignificant magnitude. It should be noted, though, that the apparent validity of an expression with the mathematical form of equation 13 does not prove the correctness of the mechanism of equations 8–10 since other conceivable mechanisms have the same mathematical requirements.

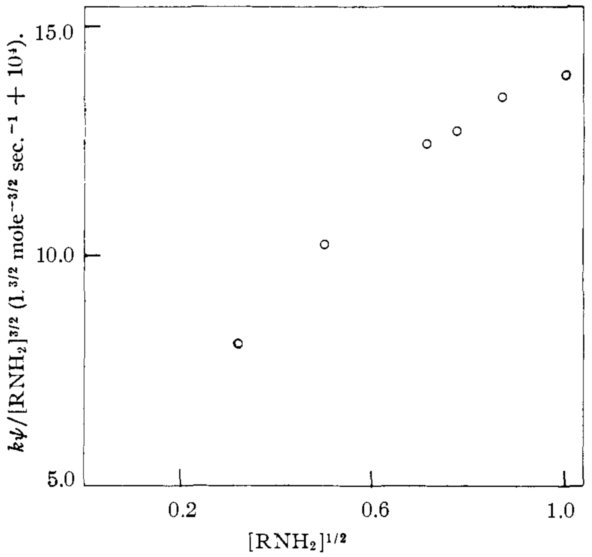

Fig. 2.—Reaction of ethyl formate with *n*-butylamine. Plot used in resolution of unbuffered rates into components 3/2 order and second order in amine.

If the terms 3/2 order and second order in amine do indeed represent alkoxide and amine catalysis, it follows from the analysis summarized in Table V that the reaction is 33% catalyzed by amine at 0.1 *M* *n*-butylamine and 61% catalyzed by amine at 1.0 *M*. The remainder in either case represents alkoxide catalysts. Thus the range of amine concentrations investigated covers a change from predominating alkoxide catalysis at lower amine concentrations to predominating amine catalysis at higher concentrations.

The Effect of Added *n*-Butylammonium Chloride.—A series of runs was made in which $[\mathrm{RNH_2}]$ was held constant at 0.2 *M* and *n*-butylammonium chloride was added in concentrations up to 1.0 *M*. Results are displayed in the top part of Table VI. This salt had a moderate decelerating effect which was less pronounced at higher concentrations. The initial drop in rate is expected from equations 14–16 because the addition of $\mathrm{RNH_3Cl}$ should repress formation of ethoxide ion (equation 2) and essentially eliminate the term which is 3/2 order in amine. This point is discussed further below. The remaining term at 0.2 *M* amine concentration is reckoned, with use of $k_{\mathrm{RNH_2}}$ as evaluated in the preceding section, to have the magnitude 0.36×10^{-4} sec.$^{-1}$. This agrees with the pseudo-first-order coefficients observed at the lowest $\mathrm{RNH_3Cl}$ concentrations. The validity of this treatment based on equations 14–16 is thus further substantiated.

The gradual increase in rate coefficient with increasing $\mathrm{RNH_3Cl}$ concentration is presumably a positive salt effect. A plot of the third-order rate coefficients, $k_\psi/[\mathrm{RNH_2}]^2$, against $\mathrm{RNH_3Cl}$ concentration is linear as shown in Fig. 3.

The Effect of Added Lithium Chloride.—A series of runs was made in which varying amounts of lithium chloride were present along with constant

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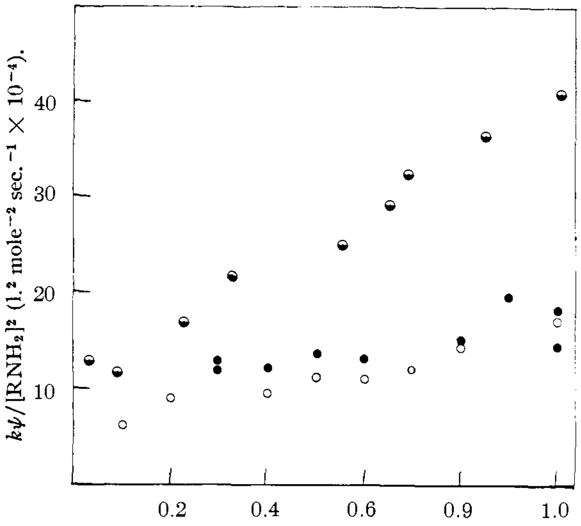
[17] Actually, the values of the two parameters can be varied considerably without seriously disturbing the goodness of the fit of calculated with observed rate coefficients.



Added salt concentration, *M*.

Fig. 3.—Salt effects in the reaction of ethyl formate with *n*-butylamine. The horizontal scale is the concentration of salt added in addition to 0.2 *M* *n*-butylammonium chloride: ◒ added LiCl (with $[RNH_2] = [RNH_3Cl] = 0.2$ *M*); ●, added RNH_3Cl (with $[RNH_2]$ constantly 0.2 *M*); ○, added RNH_3Cl (with $[RNH_2]$ constantly equal to $[RNH_3Cl]$).

amounts of *n*-butylamine and *n*-butylammonium chloride ($[RNH_2] = [RNH_3Cl] = 0.2$ *M*). Results are set forth in the lower part of Table VI. Lithium chloride has a strong accelerating effect; a plot of the third-order rate coefficients from these runs against [LiCl] is linear, as shown in Fig. 3. In the spirit of equations 14–16, this is interpreted as a positive salt effect on the term which is second order in amine, the other term having been eliminated by the RNH_3Cl present.

TABLE VI

SALT EFFECTS. BUTYLAMINOLYSIS OF ETHYL FORMATE IN ABSOLUTE ETHANOL AT 24.60°

Initial concentrations: RNH_2, 0.200 *M*; ethyl formate, 0.0100 *M*

$[RNH_3Cl]$, *M*	[LiCl], *M*	Total salt concn., *M*	$k_\psi \times 10^4$, sec.$^{-1}$	$k_\psi/[RNH_2] \times 10^4$, l. mole^{-1} sec.$^{-1}$	$k_\psi/[RNH_2]^2 \times 10^4$, l.^{2} mole^{-2} sec.$^{-1}$
Nil		Nil	0.870^a		
0.0100		0.0100	.323	1.62	8.08
.00100		.00100	.370	1.85	9.25
.200		.200	.362	1.84	9.08
.300		.300	0.521; 0.471	2.62; 2.37	13.1; 11.8
.400		.400	0.485	2.44	12.2
.500		.500	.540	2.70	13.5
.600		.600	.523	2.62	13.1
.800		.800	.588	2.96	14.8
.900		.900	.748	3.75	19.7
1.000		1.000	0.724; 0.580	3.63; 2.90	18.2; 14.5
0.200	0.04606	0.246	0.516	2.58	12.9
.200	.0921	.292	.471	2.36	11.8
.200	.2303	.430	.676	3.38	17.0
.200	.325	.525	.867	4.35	21.8
.200	.553	.753	1.00	5.00	25.0
.200	.650	.850	1.14	5.68	28.5
.200	.691	.891	1.30	6.51	32.5
.200	.848	1.048	1.43	7.13	36.7
.200	1.060	1.260	1.63	8.15	40.8

^{a} Calculated; see footnote *b*, Table V.

Buffered Runs.—A series of runs was made in which the concentration of *n*-butylammonium chloride was constantly equal to that of *n*-butylamine but in which the absolute concentrations of these substances were varied tenfold. Results are displayed in Table VII. The over-all third-order rate coefficients, $k_\psi/[RNH_2]^2$, were linearly dependent on RNH_3Cl concentration; the plot appears in Fig. 3. The line defined by these points is within experimental error the same as defined by the experiments in which $[RNH_2]$ was held constant and $[RNH_3Cl]$ was varied (Table VI, top part). This is reasonable with respect to equation 16. When RNH_3Cl is present, both the first and second terms are of insignificant magnitude so that the third term alone accounts for the rate. The third-order rate coefficient ought to be constant at all amine concentrations except for salt effects, and the same salt (RNH_3Cl) is present in both series of runs.

TABLE VII

BUTYLAMINOLYSIS OF ETHYL FORMATE IN ABSOLUTE ETHANOL AT 24.60°

1:1 buffered runs; initial concentration of ethyl formate, 0.0100 *M*

$[RNH_2]$, *M*	$[RNH_3Cl]$, *M*	$k_\psi \times 10^4$, sec.$^{-1}$	$k_\psi/[RNH_2] \times 10^4$, l. mole^{-1} sec.$^{-1}$	$k_\psi/[RNH_2]^2 \times 10^4$, l.^{2} mole^{-2} sec.$^{-1}$
0.100	0.100	0.0616	0.616	6.16
.200	.200	0.362^a	1.82	9.07
.400	.400	1.52	3.80	9.48
.500	.500	2.77^a	5.55	11.1
.600	.600	3.92^a	6.51	10.9
.700	.700	5.93	8.46	12.1
.800	.800	9.07^a	11.9	14.8
1.000	1.000	17.2^a	17.2	17.2

^{a} Tabulated values are average of several runs.

The data of Table VII provide further evidence that the uncatalyzed or solvent catalyzed term of equations 14–16 is of negligible magnitude. If enough RNH_3Cl is present to obliterate the alkoxide catalyzed term, the over-all *second-order* rate coefficient ($k_\psi/[RNH_2]$) should be the sum of k_1k_2/k_{-1} plus $k_{RNH_2}[RNH_2]$. In a plot of the second-order rate coefficient against $[RNH_2]$, the intercept should be k_1k_2/k_{-1}, the rate coefficient for the uncatalyzed term. When the data of Table VII are plotted in this fashion (Fig. 4) the extrapolated intercept at zero $[RNH_2]$ is zero. There is no evidence for an uncatalyzed term.

Catalysis by Sodium Ethoxide.—A series of runs was made in which sodium ethoxide was present in concentrations as high as 0.44 *M*.

Infinity optical densities showed the yield of *n*-butylformamide to be less than quantitative (Table VIII). A competing reaction was indicated, and the data showed the degree of competition to increase with increasing sodium ethoxide concentration. Hydrolysis owing to traces of water in the solvent was suspected, but it seemed unlikely that the extent of hydrolysis would increase regularly as the sodium ethoxide concentration increased. The competing reaction is more apt to be displacement on ethyl carbon forming diethyl ether[18] or β-elimination forming ethylene and, in either case, sodium formate. Whatever its

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[18] J. F. Bunnett, M. M. Robison and F. C. Pennington, THIS JOURNAL, **72**, 2378 (1950).

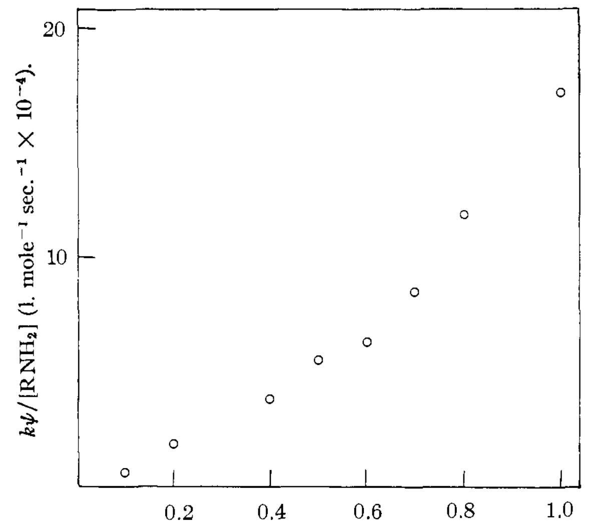

Fig. 4.—Variation of second-order rate coefficient with amine concentration in 1:1 buffered runs, reaction of ethyl formate with *n*-butylamine.

nature, the competing reaction did not interfere with the obtaining of rate coefficients for the ester aminolysis reaction; the method of calculation is outlined in the Experimental section.

TABLE VIII

ETHOXIDE CATALYSIS. BUTYLAMINOLYSIS OF ETHYL FORMATE AT 24.60° IN ABSOLUTE ETHANOL

Initial concentrations: ethyl formate, 0.0100 M; RNH_2, 0.100 M

$[NaOC_2H_5]$, M	$k_\psi \times 10^4$, sec.$^{-1}$	$k_A \times 10^4$, sec.$^{-1a}$	$k_F \times 10^4$, sec.$^{-1}$	Yield of aminolysis product, %
0.00928	7.33	6.72	0.61	91.6
.00928	6.68	6.05	.63	90.5
.00464	5.06	4.65	.41	91.8
.02320	11.1	9.77	1.3	88.5
.02784	15.0	12.6	2.4	84.0
.03248	16.4	13.5	2.9	82.4
.04640	25.7	21.0	4.7	81.8
.0978	48.7	35.5	13.2	72.9
.1712	90.0	66.2	23.8	73.5
.3667	163	123	40	76.0
.4401	173	141	32	81.2
.4401	179	121	58	67.5

[a] Corrected for competing reaction (see Experimental).

Rate coefficients for the ester aminolysis reaction are listed in Table VIII. The reaction is strongly accelerated by sodium ethoxide, and the acceleration is linearly dependent on the sodium ethoxide concentration as Fig. 5 shows. From equation 14, the slope of the line as plotted should be $k_{OEt^-}[RNH_2]$; k_{OEt^-} is thus evaluated as 0.33 l.^{2} mole^{-2} sec.$^{-1}$.

As detailed above, the product $K_B{}^{1/2}k_{OEt^-}$ was evaluated from the data of Table V as 5.7 × 10^{-4} l.$^{3/2}$ mole$^{-3/2}$ sec.$^{-1}$ From this and the above k_{OEt^-} value, K_B is reckoned to be 3.1 × 10^{-6} mole/l. This compares with 4.0 × 10^{-8} mole/l. as determined by Goodhue and Hixon[19] from e.m.f. measurements.

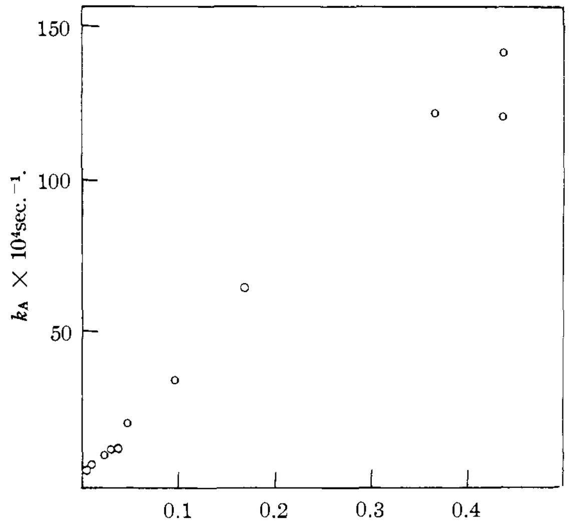

Fig. 5.—Sodium ethoxide catalysis of the reaction of ethyl formate with *n*-butylamine.

The Methoxide Catalyzed Reaction of *n*-Butylamine with Methyl Benzoate.—The reaction of *n*-butylamine with methyl benzoate in methanol, in the absence of additional substances, was so slow as to escape our notice in preliminary experiments. The strong catalysis by sodium ethoxide portrayed in Fig. 5 suggested that very slow aminolyses might be accelerated to a measurable rate by addition of alkoxide ions. This expectation was fulfilled, as shown by the data in Table IX. The rate of reaction of butylamine with methyl benzoate is appreciable in the presence of sodium methoxide and is proportional to methoxide concentration. The constancy of the third-order rate coefficient (based on the assumption of first order in amine) shows that this reaction, like the butylaminolysis of ethyl formate, is first order in alkoxide ion.

TABLE IX

METHOXIDE CATALYSIS. BUTYLAMINOLYSIS OF METHYL BENZOATE IN ANHYDROUS METHANOL AT 46.27°

[Me Benzoate]$_0$ = 0.100 M; $[BuNH_2]$ = 0.500 M

Sodium methoxide (m./l.)	$k_\psi \times 10^4$, sec.$^{-1}$	$k_\psi/[RNH_2][OCH_3^-]$ $\times 10^4$, l.^{2} mole^{-2} sec.$^{-1}$
0.311	0.199	1.28
.622	.400	1.29
.932	.656	1.41

Strong catalysis of ester aminolysis reactions by alkoxide ions has been noted before.[4-6] It can be of utility in preparative work, as Russell[20] has shown.

Attempted Interpretation in Terms of the Mechanism of Betts and Hammett.—It has been demonstrated that the mechanism of equations 9–11 leads to an interpretation of our results which is qualitatively satisfying and which meets several quantitative requirements. It will now be shown that the mechanism of Betts and Hammett cannot be made the basis of an acceptable interpretation.

The first shortcoming of the older mechanism is that it does not provide for mixed 3/2 and second order in amine, in the absence of added RNH_3^+ salt, as were observed (Table V).

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(19) L. D. Goodhue and R. M. Hixon, THIS JOURNAL, **57**, 1688 (1935).

(20) P. B. Russell, *ibid.*, **72**, 1853 (1950).

Another deficiency has to do with the kinetic effect of added RNH_3^+ ions. Both the mechanism of equations 1–4 and that of equations 9–11 call for a term sensitive to RNH_3^+ ions. This is the second term in equation 6 or 8 (for the older mechanism) and also the second term in equation 15 or 16 (for the newer one). Moreover, each mechanism calls for the same magnitude of change in this term upon the addition of RNH_3^+ ions. From equations 6 and 8 or from equations 15 and 16, the change in the RNH_3^+-sensitive term should be

$$\frac{\text{second term } (RNH_3^+ \text{ present})}{\text{second term } (RNH_3^+ \text{ absent})} = K_B^{1/2}[RNH_2]^{1/2}/[RNH_3^+] \quad (18)$$

Therefore the sharp drop in rate on addition of RNH_3^+ ions noted above is intelligible in terms of either mechanism. By equation 18, if K_B is 4.0×10^{-8} as given by Goodhue and Hixon[19] and if the *n*-butylamine concentration is 0.2 *M*, the addition of 0.01 *M* *n*-butylammonium chloride should cause the RNH_3^+-sensitive term to drop to 1% of its value in the absence of added salt. This would render it kinetically undetectable if it were combined additively with another term of significant magnitude as required by either interpretation. Even if K_B is 3.1×10^{-6} as given above by an indirect derivation from kinetic data, 0.01 *M* RNH_3Cl would still reduce the term in question to but 8% of its former value.

Both interpretations agree, then, that added RNH_3Cl should effectively eliminate the second term. They do not agree, however, on what should be left. The older mechanism would call for the remainder to be an uncatalyzed, over-all second-order term; the mechanism of equations 9–11 calls for it to be an amine-catalyzed, over-all third-order term. We have remarked on the lack of evidence for an uncatalyzed term and on the fact that in the presence of RNH_3Cl the reaction is third order with a superimposed salt effect (Fig. 3). Thus the part of the reaction which is not suppressed by added RNH_3Cl has the characteristics called for by the newer mechanism.

Had the experiments with the 1:1 buffered reagents (Table VII and Figs. 3 and 4) been performed in water solution at constant ionic strength, the plot corresponding to Fig. 4 would have been a horizontal line for specific lyate ion catalysis or a straight line of positive slope for general base catalysis. Because ionic strength was not maintained constant in our experiments, for reasons which have been stated, the interpretation of Fig. 4 is not quite so simple. The curved line of Fig. 4 is, however, easily interpreted as a linear dependence on $[RNH_2]$ plus a salt effect, as shown by the relevant plot in Fig. 3. Interpretation as an unusual positive salt effect on some persistent lyate-ion dependent term is not tenable because such a term should not disappear on extrapolation to zero buffer concentration.

Further evidence that specific lyate ion catalysis does not prevail is the fact that third-order rate coefficients for runs in which RNH_2 and RNH_3Cl concentrations were equal fall on the same line as those for runs in which RNH_2 and RNH_3Cl concentrations were decidedly unequal, when plotted in the manner of Fig. 3.

Criticism of the Interpretation of Watanabe and DeFonso.—It has been mentioned that many of the kinetic consequences of the older mechanism are shared by the mechanism of equations 9–11. Therefore it suffices to say, concerning many of Watanabe and DeFonso's observations, that they can be interpreted equally well in terms of the newer mechanism. The older mechanism did not provide an interpretation for the tendency, which they observed, for the kinetics in ethanol solvent to be intermediate between 3/2 and second order in amine, whereas the newer mechanism makes full provision for this.

The only aspect of their work to which real exception can be taken is their interpretation of a series of runs in which $[RNH_2]$ was held essentially constant and $[RNH_3Cl]$ was varied over a 20-fold range with maintenance of constant salt concentration by compensation with lithium chloride. The result was, in effect, a linear plot of the third-order rate coefficient against $1/[RNH_3^+]$, the rate being lower at higher RNH_3^+ concentrations. This is the plot in Fig. 5 of their paper. With reference to the relationship which appears as equation 6 in this paper, they took the substantial intercept in this plot as evidence for an uncatalyzed term, although other tests for an uncatalyzed term were negative. The slope was considered to be $k_b K_{Am}$ and was used in a computation of K_B.

We consider this interpretation to be incorrect. Its fault is the assumption that the kinetic salt effects of *n*-butylammonium chloride and lithium chloride in ethanol are equal. It is known that ion pairing in ethanol is extensive but that lithium chloride is one of the more highly dissociated salts.[21] Our work (Fig. 3) shows that the kinetic salt effect of lithium chloride is considerably greater than that of *n*-butylammonium chloride. The decrease in rate as lithium chloride is progressively replaced by *n*-butylammonium chloride is therefore to be understood as a consequence of replacing a good salt with a mediocre one. The data plotted in Watanabe and DeFonso's Fig. 5 do not constitute evidence for repression of reaction rate by RNH_3Cl within the range of RNH_3Cl concentrations represented in that plot.

Comment on the Experiments of Betts and Hammett.—A detailed analysis[22] shows that the results of these authors are equally consistent with the mechanism originally favored (equations 1–4) and with the mechanism of equations 9–11. This is not to deny the *possibility* of distinguishing the two mechanisms by kinetics; it is just that the data of Betts and Hammett, as published, do not allow a distinction to be made. In the situation that exists, the newer mechanism is nevertheless to be favored because of its now proven superiority for the aminolysis of ethyl formate.

The Reaction Mechanism

We have shown that our kinetic results are consistent with a rate law of the form of equation 14 or the subsidiary equation 15 or 16. The uncatalyzed (or solvent catalyzed) term is not detectable. General base catalysis has been demonstrated, and equation 14 provides separately for catalysis by each base in the system.

After our experimental work was completed, we learned that Dr. William P. Jencks had also observed general base catalysis of ester aminolysis in another system.[23] Susceptibility to general base catalysis appears to be a general characteristic of ester aminolysis reactions.

Equation 14 was derived with reference to the chemical equations 9–11, but other conceivable mechanisms could lead to the same rate law. Also, equations 9–11 are not very specific and there is need to consider some of the particular mechanisms which they might represent. Of the many conceivable mechanisms which would call for a rate law such as equation 14, three are sufficiently in accord with existing chemical theory to warrant close attention.

The first is closely related to that of equations 1–4. It calls for prior association of base with amine, as

$$RNH_2 + B \overset{\text{fast}}{\rightleftharpoons} RNH_2{\cdot}B \quad (19)$$

$$RNH_2{\cdot}B + R''COOR' \longrightarrow R''CONHR + R'OH + B \quad (20)$$

The complex $RNH_2{\cdot}B$ would be thought of as an RNH^- ion carrier, a species of especially high nucleophilic reactivity with an unusual capacity to displace the alkoxy group from an ester. We disfavor this mechanism on the grounds that if complexes of the type $RNH_2{\cdot}B$ did exist in sig-

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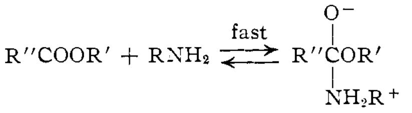
(21) J. R. Graham, G. S. Kell and A. R. Gordon, THIS JOURNAL, **79**, 2352 (1957). These data have been recalculated by Dr. R. L. Kay (Brown University) using the theory of Onsager and Fuoss; *cf.* R. M. Fuoss, *ibid.*, **79**, 3301 (1957). Both the original and the refined calculations indicate the order of association: KCl > NaCl > LiCl.

(22) Omitted from this paper in the interest of economy of space.

(23) See the accompanying paper: W. P. Jencks and J. Carriuolo, THIS JOURNAL, **82**, 675 (1960).

nificant concentration and/or did have exceptional nucleophilic reactivity, base catalysis ought to be universal in nucleophilic displacements induced by amines. But base catalysis is not universal in such reactions. Specifically, the reactions of several amines (piperidine, aniline, N-methylaniline, *n*-butylamine) with 2,4-dinitrochlorobenzene have been found to be insensitive (within experimental error) to catalysis by the very strong base, hydroxide ion.[7,16,24] Indeed, on an earlier occasion[16] this very insensitivity to catalysis by hydroxide ion generated doubts concerning the mechanism of equations 1–4 for ester aminolysis. It is because equations 19 and 20 imply that all nucleophilic displacements involving amines ought to be sensitive to base catalysis, whereas some are not, that we disfavor this representation of the base catalysis phenomenon.

The second possibility is a variation of the mechanism of equations 9–11. This mechanism is



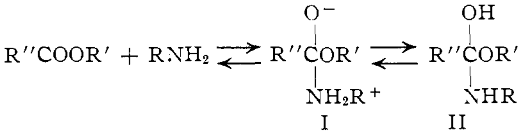
$$R''COOR' + RNH_2 \overset{\text{fast}}{\rightleftarrows} R''\overset{\overset{O^-}{|}}{\underset{\underset{NH_2R^+}{|}}{C}}OR' \qquad (21)$$

$$R''\overset{\overset{O^-}{|}}{\underset{\underset{NH_2R^+}{|}}{C}}OR' + B \xrightarrow{\text{slow}} R''CONHR + R'O^- + BH \qquad (22)$$

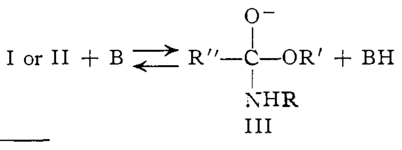
No step corresponding to equation 10 is included because of the undetectability of an uncatalyzed term. The action of the base on the tetrahedral intermediate might be thought of as an E2 elimination, the removal of a proton from the nitrogen atom being concerted with departure of the alkoxy group as an alkoxide ion. It was this mechanism that Hawkins and Tarbell[9] suggested as an interpretation of base catalysis of thiolester aminolysis.

The mechanism of equations 21–22 assigns to the catalyzing base a function, that of assisting departure of the leaving group (the alkoxy group), which is of no kinetic importance in the reactions of amines with 2,4-dinitrochlorobenzene. It is thus compatible with the fact that the latter reactions are not base catalyzed. However, the absence of an uncatalyzed term is difficult to understand in terms of this mechanism. One would expect the ubiquitous solvent to be able to accept protons from the nitrogen of the intermediate frequently enough to account for a detectable amount of uncatalyzed aminolysis.

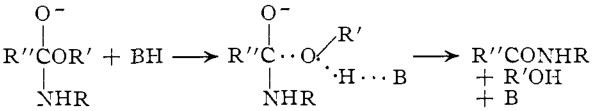
The third and most attractive possibility is also a variation of the mechanism of equations 9–11. It is



$$R''COOR' + RNH_2 \rightleftarrows \underset{\text{I}}{R''\overset{\overset{O^-}{|}}{\underset{\underset{NH_2R^+}{|}}{C}}OR'} \rightleftarrows \underset{\text{II}}{R''\overset{\overset{OH}{|}}{\underset{\underset{NHR}{|}}{C}}OR'} \qquad (23)$$



$$\text{I or II} + B \rightleftarrows \underset{\text{III}}{R''\text{—}\overset{\overset{O^-}{|}}{\underset{\underset{NHR}{|}}{C}}\text{—}OR'} + BH \qquad (24)$$



$$R''\overset{\overset{O^-}{|}}{\underset{\underset{NHR}{|}}{C}}OR' + BH \longrightarrow \underset{\text{transition state}}{R''\overset{\overset{O^-}{|}}{\underset{\underset{NHR}{|}}{C}}\cdot\cdot O\overset{R'}{\underset{\cdot H\cdots B}{\diagup}}} \longrightarrow R''CONHR + R'OH + B \qquad (25)$$

This mechanism comprises a series of prior equilibrium steps followed by a slow step in which the alkoxy group is lost. The formation of intermediate I by the addition of an amine molecule to the carbonyl function of the ester finds analogy in the reaction of acetaldehyde with ammonia and in the formation of oximes and semicarbazones from aldehydes.[25] Intermediate II differs from I only in proton disposition and is thermodynamically more probable. It is reasonable that either I or II should yield a proton to a base to form III and that this process should be rapidly reversible. The final slow step (equation 25) is a general *acid*-catalyzed removal of alkoxide ion from intermediate III.[26]

This mechanism is the most satisfactory of those which have been considered. It is consistent with the kinetics, it gives a good account of why ester aminolysis requires base catalysis whereas reactions of amines with 2,4-dinitrochlorobenzene do not[27] and it renders intelligible the absence of an uncatalyzed term.

The mechanism of equations 23–25 also facilitates understanding of the surprisingly low reactivity of carboxylic esters with alkali metal amides in liquid ammonia. The amide ion (NH_2^-) in liquid ammonia is a powerful nucleophile; a recent demonstration is the facile cleavage of *o*-fluorobenzophenone to form fluorobenzene and benzamide.[28] Yet carboxylic esters do not react exceptionally fast with the amide ion to form carboxamides. Although carboxamides are indeed formed, esters are sometimes recovered unchanged from treatment with lithium, sodium or potassium amide and often they undergo some other reaction such as elimination or loss of a proton from an α-carbon.[29] It is unlikely that the amide ion is slow in attacking esters to form tetrahedral intermediates of type III, and therefore it seems probable that the expulsion of an alkoxide ion from such an intermediate is significantly slow. If

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[24] S. D. Ross, THIS JOURNAL, **80**, 5319 (1958).

[25] W. P. Jencks, *ibid.*, **81**, 475 (1959).

[26] It is legitimate for a general *base*-catalyzed reaction to involve general *acid* catalysis in its slow step. From equation 25

$$d[R''CONHR]/dt = k[III][BH]$$

and from equations 23 and 24

$$[III][BH] = K[E][RNH_2][B]$$

where K is an over-all equilibrium constant. It follows that

$$d[R''CONHR]/dt = kK[E][RNH_2][B]$$

[27] A mechanism of this type, involving general acid-catalyzed removal of the leaving group from the conjugate base of the intermediate complex, is also possible in the general base-catalyzed reaction of 2,4-dinitrofluorobenzene with N-methylaniline.[7] A rate-determining E2-type elimination of HF from the intermediate complex, as previously suggested,[7] is equally reasonable.

[28] J. F. Bunnett and B. F. Hrutfiord, Absts. Am. Chem. Soc. Meeting, Boston, Mass., April, 1959, p. 94-O.

[29] R. Levine and W. C. Fernelius, *Chem. Revs.*, **54**, 523 (1954); C. R. Hauser, J. C. Shivers and P. S. Skell, THIS JOURNAL, **67**, 409 (1945); C. R. Hauser and W. J. Chambers, *ibid.*, **78**, 3837 (1956); W. W. Leake and R. Levine, *ibid.*, **81**, 1627 (1959); C. R. Hauser, M. T. Tetenbaum and D. S. Hoffenberg, *J. Org. Chem.*, **23**, 861 (1958).

general acid catalysis is needed to assist expulsion of the alkoxy group, the slowness of this reaction in liquid ammonia solutions containing metal amides is understandable in view of the poor quality of the acids available in such systems.

This slowness of reactions of esters with amide ion in ammonia is, incidentally, an argument against both the mechanism of equations 19–20 and that of equations 21–22.

The probability that the mechanism of equations 23–25 prevails in the butylaminolysis of ethyl formate does not, however, exclude mechanisms such as those of equations 21–22, 19–20 or even 1–4 for related reactions. If the structure of the carbonyl compound were changed so as to provide a better leaving group, the need for acid catalysis of its departure from III would decrease. In such a case the departure of the leaving group might follow immediately upon or be concerted with the removal of a proton from intermediate 1; the result would be the mechanism of equations 21–22. If the reagent were changed so as to become more acidic, the tendency for prior association with a base would increase so that, if the leaving group were good, the mechanism of equations 19–20 might be approached. With a distinctly acidic reagent and a very good leaving group, the mechanism of equations 1–4 would be expected. An extreme case of the last would be the reaction of a phenol with an acid chloride. Thus a spectrum of sub-mechanisms is conceivable, all of them involving the formation of tetrahedral intermediate complexes but differing in the relative kinetic significance of the various reaction steps and/or in the timing of the proton transfers.

The mechanism of equations 23–25 implies, by the principle of microscopic reversibility, that the reverse of ester aminolysis, the alcoholysis of amides, should be general base catalyzed. The reaction is certainly base catalyzed,[30] but the question of general base catalysis *versus* specific lyate ion catalysis does not appear to have been probed. The mechanism implied for the reverse reaction is, it will be noted, much like the mechanism of equations 19–20 which is disfavored for the forward reaction when an alkyl ester is involved. This does not constitute a logical inconsistency because of the differences in acidity and nucleophilic reactivity of alcohols and amines. Actually, as discussed in the preceding paragraph, such changes are expected. Amines are good nucleophiles and weak acids; they do not need the sort of help by a base which is represented in equations 19–20. Alcohols are poor nucleophiles but fairly strong acids and they have much to gain from the same sort of help.

General Significance.—Aside from their specific relevance to the mechanism of ester aminolysis, our results also have significance in respect to more general problems. Our work constitutes evidence that a tetrahedral complex of type I or II (equation 23) is an intermediate in ester aminolysis. Bender[31] and Bunton[32] have proposed, from study of exchange of carbonyl oxygen-18 with the medium during hydrolysis of esters, amides, acid chlorides, etc., that the hydrolysis of these various carboxylic acid derivatives proceeds through tetrahedral intermediates of similar type. Our work serves to increase the probability that such tetrahedral intermediates are general for bimolecular nucleophilic substitution at carbonyl carbon.

Nucleophilic substitution at carbonyl carbon falls within the general category of substitution at unsaturated carbon. Studies of bimolecular nucleophilic substitution at aromatic carbon and at vinylic carbon have indicated an intermediate complex mechanism for these reactions. Our results are therefore additional support for the general proposition that bimolecular nucleophilic substitution at unsaturated carbon proceeds through tetrahedral intermediate complexes.[2]

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(30) B. M. Wepster and P. E. Verkade, *Rec. trav. chim.*, **67**, 411, 425 (1948); P. E. Verkade and B. M. Wepster, *Belg. chem. Industrie*, **20**, 1281 (1955).

(31) M. L. Bender, THIS JOURNAL, **73**, 1626 (1951); M. L. Bender, R. D. Ginger and K. C. Kemp, *ibid.*, **76**, 3350 (1954).

(32) C. A. Bunton, R. A. Lewis and D. H. Llewellyn, *Chemistry & Industry*, 1154 (1954).