ure at these concentrations would remove most of the significance which might be attached to the temperature coefficient of the diffusion process in glacial acetic acid.

A gap in the 25° data, about $\bar{c} = 14$, exists because in this region both the density and refractive index of this system go through a maximum.

Acknowledgments.—This investigation was the direct result of a general discussion with Professor J. G. Kirkwood and Dr. I. Tinoco of the relationship between the transport and thermodynamic properties of partially dissociated proteins. Our thanks are due also to Professor H. S. Harned for some pertinent comments on this problem. The work was supported in part by Atomic Energy Commissions contract AT (30-1)-1375. V. Vitagliano is indebted to the Fondazione A. Beneduce, Napoli, for a foreign study fellowship.

NEW HAVEN, CONN.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE ROHM AND HAAS COMPANY]

The Kinetics and Mechanism of the Aminolysis of Ethyl Formate with *n*-Butylamine

BY WARREN H. WATANABE AND LESTER R. DEFONSO

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The kinetics of the reaction of *n*-butylamine with ethyl formate to give *n*-butylformamide and ethanol have been measured in approx. 4 *M* ethylene glycol in dioxane, and in absolute ethanol. In both solvents the initial rates are represented to a good approximation by the rate equation $-d[\text{Amine}]/dt = k[\text{Amine}]^{3/2}[\text{Ester}]$. This result is shown to correspond to a mechanism in which the sole reaction is between the anion of the amine, RNH^-, and the ester. Abnormally high positive neutral salt effects have been observed in both solvents. The strong retarding effect of *n*-butylamine hydrochloride at constant ionic strength on the reaction in ethanol supports this mechanism; however there is still a residual rate at extrapolated infinitely high concentration of the amine acid salt. This residual rate indicates that a reaction of molecular amine with ester provides a minor but nevertheless distinct portion of the over-all reaction. The complete rate equation is thus shown to be $-d[\text{Amine}]/dt = k[\text{Amine}]^{3/2}[\text{Ester}] + k'[\text{Amine}][\text{Ester}]$ in harmony with the mechanism of ammonolysis first proposed by Betts and Hammett. The relationship of the present results with those of previous investigators, notably Hawkins, is discussed.

Of the large variety of reactions into which amines enter as nucleophilic reagents, perhaps the most thoroughly studied from the standpoint of kinetics and mechanism are those of aminolysis, in which an amine and an ester react to form an amide and an alcohol. It is therefore the more surprising that with but two recent exceptions,[1] none of these studies have dealt with the detailed kinetics of a single such aminolysis reaction, although in most of the earlier reports there have been strong indications that the rate of aminolysis does not follow the simple second-order kinetics so often assumed. Previous studies have dealt with the effect of structure on reactivity in aminolysis,[2] on the effect of solvents on rates,[3,4] on the effect of base[3] and of acid salts,[3,5] and on the accelerating influence of water[6] and hydroxylic solvents.[2] In this earlier work it has been the practice to calculate rate constants as over-all second order, first order in amine and first order in ester. Hawkins has shown, however, that in the simultaneous aminolysis and hydrolysis of ethyl thioacetate and β-acetaminoethyl thioacetate in water with *n*-butylamine[1a] the only term in the rate equation attributable to aminolysis is

$$\text{Rate} = k[RNH^-][\text{Ester}] \qquad (1)$$

and in the simultaneous aminolysis and hydrolysis of α-naphthyl acetate in water with *n*-butylamine[1b] there are two terms in the rate equation describing the aminolysis

$$\text{Rate} = k[RNH^-][\text{Ester}] + k'[RNH_3^+][\text{Ester}] \qquad (2)$$

In the fundamentally important study of the ammonolysis of methyl phenylacetate in anhydrous methanol carried out by Betts and Hammett[7] the rate equation was found to contain two terms

$$\text{Rate} = k[NH_3][\text{Ester}] + k'[NH_2^-][\text{Ester}] \qquad (3)$$

Thus the only relevant detailed investigations have shown that the order with respect to the amine (or ammonia) is greater than one, and that the rate must then be a function of the amine concentration if the rate constant is calculated as first order in amine.

The present study of the kinetics of aminolysis was undertaken as a preliminary to a determination of the effects of certain metal salts on the rate of a typical nucleophilic reaction of an amine.[8] For this purpose the aminolysis of ethyl formate with *n*-butylamine was chosen as the model reaction both

$$n\text{-}C_4H_9NH_2 + HCOOC_2H_5 \longrightarrow n\text{-}C_4H_9NHCHO + C_2H_5OH \qquad (4)$$

because of its high rate, which would allow measurements to high conversion, and its presumed freedom from complicating side reactions. As solvents were used 4.137 *M* ethylene glycol in dioxane, claimed to be a particularly good solvent mixture for aminolyses by primary amines,[2] and absolute ethanol, in which it was found rates were also rapid. Our kinetic results substantiate those of

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[1] (a) P. J. Hawkins and D. S. Tarbell, THIS JOURNAL, **75**, 2982 (1953); (b) P. J. Hawkins and I. Piscalnikow, *ibid.*, **77**, 2771 (1955).

[2] E. M. Arnett, J. G. Miller and A. R. Day, *ibid.*, **72**, 5635 (1950); **73**, 5393 (1951).

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

[4] M. Grunfeld, *Ann. chim.*, **20**, 351 (1933).

[5] P. K. Glasoe, J. Kleinberg and L. F. Audrieth, THIS JOURNAL, **61**, 2387 (1939).

[6] P. K. Glasoe, L. D. Scott and L. F. Audrieth, *ibid.*, **63**, 2965 (1941).

[7] R. L. Betts and L. P. Hammett, *ibid.*, **59**, 1569 (1937).

[8] This work will be the subject of a future communication.

Hawkins in showing that at least for reaction (4) aminolysis is a relatively complex reaction. The kinetics of (4) in both solvents follow equation 1 to a good approximation, but evidence was also found to indicate some reaction of molecular amine to give an over-all reaction similar to (3). No contribution of an acid-catalyzed portion was found as in (2), but this was not surprising since nucleophilic reactions on ethyl formate are far more susceptible to basic catalysis than to acid catalysis.

Experimental

Materials.—Every effort was made to exclude water from the solvents and reactants in order to keep hydrolysis to a minimum. Ethyl alcohol was dehydrated by the method of Lund and Bjerrum.[9] *n*-Butylamine was first kept over calcium hydride for several days until reaction ceased, then distilled out of fresh calcium hydride. A midcut from this fractionation was refractionated out of fresh calcium hydride, and another midcut, b.p. 77.0–77.2°, $n^{25}\text{D}$ 1.3976, $d^{30}{}_4$ 0.7302, purity by titration to methyl red end-point, 100.1%, was used. Ethyl formate was treated in an identical manner, and a midcut from the second fractionation, b.p. 54.0–54.2°, $n^{52}\text{D}$ 1.3565, $d^{30}{}_4$ 0.9096, purity by saponification, 100.8%, was used. Dioxane was purified by the method of Fieser.[10] Ethylene glycol was dried over anhydrous magnesium sulfate and distilled, b.p. 60–61° (10 mm.). *n*-Butylamine hydrochloride, m.p. 213.6–214.0° dec., was dried before use. Lithium chloride, lithium nitrate and sodium iodide were reagent grade materials, dried before use. Lithium ethoxide solution was prepared by dissolving reagent grade lithium metal in absolute ethanol under a nitrogen atmosphere, titrating with acid to determine base content, and diluting with absolute ethanol to obtain the very dilute solutions required. The mixed dioxane–ethylene glycol solvent was prepared by diluting 513.56 g. of ethylene glycol to 2 liters with dioxane at 23.4°, giving at this temperature a solution 4.137 *M* in ethylene glycol. All runs made in this solvent medium were carried out using this single stock.

Kinetic Measurements.—Stock solutions of *n*-butylamine and ethyl formate were made up in the appropriate solvent and the strengths of each of these solutions determined by analysis. *n*-Butylamine was determined by pipetting an aliquot into excess standard acid and back-titrating to the methyl red end-point with standard base. Ethyl formate was saponified by pipetting an aliquot into excess standard base, letting stand at room temperature until reaction was complete (experimentally determined to be within 2 minutes), and back-titrating to the phenolphthalein end-point with standard acid. When neutral salts or other materials were to be added to the reaction mixture, these were usually dissolved in the stock solutions.

The stock solutions and surplus solvent were thermostated at 30.00 ± 0.02°, the temperature of all the rate runs here reported, and the reaction mixtures then made up by mixing the requisite quantities of stock solution and solvent to provide the desired concentrations of reactants. The rate was followed by withdrawing aliquots at measured time intervals, stopping the reaction by adding to excess standard acid, and then determining the concentration of unreacted amine by back-titration to the methyl red end-point with standard base. Rates generally were measured through at least one half-life (more often to two or three half-lives) of the reactant present in lower concentration.

The over-all second-order rate constants (first order in amine and first order in ester) were calculated using the usual integrated equation

$$k_2t = \frac{2.303}{(b - a)} \log \frac{a(b - x)}{b(a - x)} \qquad (5)$$

where a = initial concentration of ethyl formate, b = initial concentration of *n*-butylamine, and x = concentration of product at time t. The over-all third-order constants (second order in amine and first order in ester) were obtained from the equation

$$k_3t = \frac{1}{(a - b)} \left[\frac{1}{(b - x)} - \frac{1}{b} + \frac{2.303}{(a - b)} \log \frac{a(b - x)}{b(a - x)}\right] \qquad (6)$$

Integration of the rate expression for the reaction 3/2 order in amine and first order in ester led to the following expressions, which were used to calculate the over-all 5/2 order rate constants

$$k_{5/2}t = \frac{2}{(a - b)} \left[\frac{1}{(b - x)^{1/2}} - \frac{1}{b^{1/2}} + \frac{1}{(a - b)^{1/2}} \tan^{-1} \frac{(b - x)^{1/2}}{(a - b)^{1/2}} - \frac{1}{(a - b)^{1/2}} \tan^{-1} \frac{b^{1/2}}{(a - b)^{1/2}}\right] \qquad (7)$$

for a > b

$$k_{5/2}t = \frac{2}{(b - a)} \left\{\frac{1}{b^{1/2}} - \frac{1}{(b - x)^{1/2}} + \frac{2.303}{2(b - a)^{1/2}} \log \left[\frac{(b - x)^{1/2} + (b - a)^{1/2}}{(b - x)^{1/2} - (b - a)^{1/2}}\right]\left[\frac{b^{1/2} - (b - a)^{1/2}}{b^{1/2} + (b - a)^{1/2}}\right]\right\} \qquad (8)$$

for $b > a$

In the treatment of data from this work only the limiting initial rate constants ($k^0{}_2$, $k^0{}_{5/2}$ and $k^0{}_3$) were used. These initial rates were obtained by plotting, for each run, the values of k_2, $k_{5/2}$ or k_3 calculated from eq. 5–8 against time and extrapolating to zero time.[11] The errors reported are standard errors.

Representative data for reactions in each of the solvents are given below in Tables I, II and III.

TABLE I

REPRESENTATIVE RATE RUN IN DIOXANE–ETHYLENE GLYCOL

$[n\text{-C}_4\text{H}_9\text{NH}_2]_0$ = 0.6545 *M*, $[\text{HCOOC}_2\text{H}_5]_0$ = 0.5976 *M*

$t \times 10^{-2}$ (sec.)	$(a - x)$ (mole/l.)	$(b - x)$ (mole/l.)	$k_2 \times 10^3$, (mole/l.)$^{-1}$ sec.$^{-1}$	$k_{5/2} \times 10^3$, (mole/l.)$^{-3/2}$ sec.$^{-1}$
5.23	0 4511	0.5080	0.927	1.24
8.94	.3849	.4418	.922	1.27
15.29	.3073	.3642	.906	1.32
21.09	.2601	.3170	.892	1.36
29.87	.2101	.2670	.879	1.42
43.82	.1611	.2180	.849	1.48
54.82	.1371	.1940	.821	1.66
71.40	.1115	.1684	.791	1.53

$k_2^0 = 0.937 \times 10^{-3}$ (mole/l.)$^{-1}$ sec.$^{-1}$

$k_{5/2}^0 = 1.23 \times 10^{-3}$ (mole/l.)$^{-3/2}$ sec.$^{-1}$

TABLE II

REPRESENTATIVE RATE RUN IN ETHANOL

Run 92. $[n\text{-C}_4\text{H}_9\text{NH}_2]_0 = b = 0.3880$ *M*, $[\text{HCOOC}_2\text{H}_5]_0 = a = 0.2319$ *M*, $\mu = 0.100$

$t \times 10^{-2}$ (sec.)	$(a - x)$ (mole/l.)	$(b - x)$ (mole/l.)	$k_3 \times 10^3$ (mole/l.)$^{-2}$ sec.$^{-1}$	$k_{5/2} \times 10^3$, (mole/l.)$^{-3/2}$ sec.$^{-1}$
1.00	0.2005	0.3566	10.6	6.43
2.86	.1619	.3180	10.3	6.08
4.62	.1345	.2906	10.7	6.15
6.71	.1129	.2690	10.7	6.00
9.47	.0951	.2512	10.3	5.63
12.37	.0815	.2376	9.96	5.33
16.61	.0683	.2244	9.43	4.95
21.30	.0549	.2110	9.52	4.87
27.20	.0447	.2008	9.24	4.61

$k^0{}_3 = 10.8 \times 10^{-3}$ (mole/l.)$^{-2}$ sec.$^{-1}$

$k^0{}_{5/2} = 6.70 \times 10^{-3}$ (mole/l.)$^{-3/2}$ sec.$^{-1}$

Stoichiometry and Product Isolation.—The stoichiometry of the aminolysis reaction was shown to correspond with equation 4 by analyzing for amine at long reaction times in a reaction mixture containing an excess of amine over the ester.

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

(10) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., New York, N. Y., 1941, pp. 368–369.

(11) This method of determining the initial rate has the disadvantage that undue weight is placed on the earlier titration values which are the least accurate. We have nevertheless used this procedure since the results are freer from subjective preferences than the determination of the initial slopes by inspection from plots of eq. 5–8.

TABLE III

REPRESENTATIVE RATE RUN IN ETHANOL, *n*-BUTYLAMINE HYDROCHLORIDE ADDED

$[n\text{-}C_4H_9NH_2]_0 = b = 0.5084\ M$, $[HCOOC_2H_5]_0 = a = 0.4685\ M$, $[n\text{-}C_4H_9NH_2\cdot HCl] = 0.00677\ M$, $\mu = 0.100$

$t \times 10^{-2}$ (sec.)	$(a - x)$ (mole/l.)	$(b - x)$ (mole/l.)	$k_3 \times 10^3$, (mole/l.)$^{-2}$ sec.$^{-1}$
2.97	0.3995	0.4394	2.41
5.95	.3581	.3980	2.27
8.95	.3257	.3656	2.24
12.18	.2973	.3372	2.25
15.12	.2773	.3172	2.25
19.39	.2533	.2932	2.26
24.05	.2345	.2744	2.22

$k^0_3 = 2.28 \times 10^{-3}$ (mole/l.)$^{-2}$ sec.$^{-1}$

TABLE IV

STOICHIOMETRY OF THE REACTION

Solvent, ethanol; room temperature, $\mu = 0.100$

Time (hr.)	Ester (mole/l.)	Amine (mole/l.)	Ratio, amine reacted to ester originally present
0	0.2368	0.4738	...
72	.0058	.2428	0.976
96	.0024	.2404	.986
120	.0020	.2400	.987

Reaction product in amount sufficient for isolation was prepared by allowing 200 cc. of an ethyl alcohol solution 0.4734 *M* in ethyl formate and 0.4954 *M* in *n*-butylamine, made to $\mu = 0.100$ with lithium nitrate, to stand at room temperature for 30 days. This solution was then vacuum flash-distilled to separate the neutral salt and the distillate then stripped of ethyl alcohol. Fractionation of the residue through a small Vigreux column gave 8.40 g. (88% yield) of *n*-butylformamide, b.p. 68–69° (0.3 mm.), n^{25}_D 1.4386, d^{25}_4 0.9098.

Anal.[12] Calcd. for $C_5H_{11}ON$: C, 59.37; H, 10.96; N, 13.85. Found: C, 59.27; H, 10.84; N, 13.85.

An authentic sample of *n*-butylformamide (prepared by reaction of *n*-butylamine with carbon monoxide) kindly supplied by Dr. J. LoCicero, redistilled through the same Vigreux column, had the following constants: b.p. 69–69.5° (0.3 mm.), n^{25}_D 1.4385, d^{25}_4 0.9080.

Results

The experiments dealing with stoichiometry and product isolation together indicate that reaction (4) occurs in high yield in a one-to-one mole ratio, unaccompanied by any reverse ethanolysis of the product, *n*-butylformamide. All rate data except those from runs in which *n*-butylamine hydrochloride was added were plotted according to the rate expression

$$-d[\text{Amine}]/dt = k_{5/2}[\text{Amine}]^{3/2}[\text{Ester}] \qquad (9)$$

the rate constants $k_{5/2}$ being obtained by use of equations 7 or 8. As can be seen from the data of Tables I and II, within any single run the values of $k_{5/2}$ either rise (as in dioxane–ethylene glycol) or fall (as in ethanol), thus making it necessary to use only the limiting initial rate constants $k^0_{5/2}$. For reasons which will become clear in the later discussion, these constants were multiplied by the square root of the alcohol concentration, where the alcohol was ethylene glycol (considered to act as a monohydric alcohol) in dioxane–ethylene glycol, and ethanol when the solvent was ethanol. The concentration of these alcohols was adjusted for the dilution caused by solution of the amine and ester, using the appropriate densities and assuming additivity of volumes. Since only the initial rate constants were used, no corrections were necessary for alcohol formed during the aminolysis. Data from reactions in dioxane–ethylene glycol were also calculated as first order in amine and first order in ester and the limiting initial rates determined. A similar over-all second-order calculation of data obtained in ethanol was found to be unsatisfactory because of the strong downward curvature in these plots, making it impossible to obtain reliable initial rates. This set was therefore calculated as second order in amine and first order in ester and the initial rates thereby determined.

Dioxane–Ethylene Glycol.—The range of concentrations covered was tenfold in amine and fourfold in ester. The results are given in Table V.

TABLE V

RATE MEASUREMENTS IN DIOXANE–ETHYLENE GLYCOL

$(k^0_{5/2})\ [\text{ROH}]^{1/2}$ (av.) $= 2.46 \pm 0.21 \times 10^{-3}$ (mole/l.)$^{-1}$ sec.$^{-1}$

Run no.	Amine (mole/l.)	Ester (mole/l.)	$k^0_2 \times 10^3$, (mole/l.)$^{-1}$ sec.$^{-1}$	$[\text{ROH}]^{1/2}$ (mole/l.)$^{1/2}$	$(k^0_{5/2})\cdot[\text{ROH}]^{1/2} \times 10^3$ (mole/l.)$^{-1}$ sec.$^{-1}$
56	0.1085	0.4680	0.240	1.976	(1.50)
52	.2023	.1875	.480	1.990	2.39
50	.2023	.4688	.515	1.967	2.22
48	.2023	.7500	.645	1.945	2.60
49	.4046	.4688	.745	1.945	2.18
45	.5058	.4688	.865	1.935	2.63
46	.5058	.4688	.850	1.935	2.63
53	.5200	.4600	.890	1.935	2.42
62	.6490	.6120	.960	1.906	2.36
59	.6545	.5976	.937	1.907	2.35
51	.7605	.4688	1.046	1.907	2.36
54	1.0400	.4680	1.305	1.877	2.87
55	1.0400	.4680	1.220[a]		

[a] Contained 0.039 mole/l. water.

The last run in Table V shows that water retards the rate slightly. There is a particularly large effect of neutral salt on rates in this solvent (Fig. 1). It is of course to be expected that rates in solvents of low dielectric constant would be strongly affected by changes in ionic strength, but the acceleration observed here is nevertheless quite large. Thus log $(k/k_0)_{5/2}$ becomes 1.24 at $\sqrt{\mu} = 0.2$, corresponding to a decrease in half-life of amine from about 30 minutes to less than 2 minutes.

Ethanol.—The concentration of amine was varied eighteen-fold and that of the ester fivefold. The results are presented in Table VI. All measurements were made at an ionic strength of 0.100, maintained with lithium chloride.

Decreases in rate caused by water, as shown in Fig. 2, are much sharper in this solvent than in dioxane–ethylene glycol. Figure 1 illustrates the increase in rate effected by neutral salt. Three different salts, lithium chloride, lithium nitrate and sodium iodide, are represented in these data, but all fall on the same smooth curve. When *n*-butylamine hydrochloride is added in varying amount as the ionic strength is kept constant, there results a marked decrease in rate with increasing concentration of the amine acid salt.[3] At the same time the usual downward drift of the rate constants is eliminated and the fit to third-order kinetics becomes

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[12] Microanalyses by Mr. C. W. Nash and associates.

TABLE VI

RATE MEASUREMENTS IN ETHANOL AT μ = 0.100
$(k^0{}_{5/2})\,[\mathrm{ROH}]^{1/2}$ (av.) = 2.99 ± 0.31 × 10^{-2} (mole/l.)$^{-1}$ sec.$^{-1}$

Run no.	Amine (mole/l.)	Ester (mole/l.)	$k^0{}_3 \times 10^3$ (mole/l.)$^{-2}$ sec.$^{-1}$	$[\mathrm{ROH}]^{1/2}$ (mole/l.)$^{1/2}$	$k^0{}_{5/2}\cdot[\mathrm{ROH}]^{1/2} \times 10^2$, (mole/l.)$^{-1}$ sec.$^{-1}$
97	0.0547	0.1160	27.9	4.086	2.80
93	.1749	.2319	16.6	4.041	3.64
98	.2532	.1204	14.9	4.043	3.17
96	.3038	.2318	11.7	4.013	2.85
92	.3880	.2319	10.8	3.996	2.68
91	.4850	.2319	11.0	3.976	2.79
80	.4907	.5326	10.5	3.924	2.87
99	.5020	.4775	10.4	3.930	2.70
95	.7595	.4815	9.52	3.873	3.02
94	1.0127	.4815	9.71	3.817	3.34

quite accurate (compare Tables II and III). The results are given in Table VII.

TABLE VII

EFFECT OF n-BUTYLAMINE HYDROCHLORIDE ON RATES IN ETHANOL, μ = 0.100

Amine (m./l.)	Ester (mole/l.)	n-$C_4H_9NH_2 \cdot HCl$ (mole/l.)	$k^0{}_3 \times 10^3$, (mole/l.)$^{-2}$ sec.$^{-1}$
0.5084	0.4685	0.00481	2.75
.4907	.5326	.00500	2.27
.5084	.4685	.00677	2.28
.4907	.5326	.00743	2.96
.5084	.4685	.00990	1.95
.4907	.5326	.0102	2.04
.5084	.4685	.0198	1.50
.4907	.5326	.0200	1.51
.5084	.4685	.0404	1.17
.5084	.4685	.1000	0.905
.4907	.5326	.1000	0.936

Discussion

In view of the several different expressions that have been derived for the kinetics of aminolysis[1a,1b] and ammonolysis,[7] we have examined our results carefully and find the best correlation of data with theory when the mechanism proposed by Betts and Hammett[7] for ammonolysis is applied to the present case of aminolysis. The over-all aminolysis reaction is presumed to proceed through two simultaneous competing reactions, reaction (4) and (10)

$$n\text{-}C_4H_9NH^- + HCOOC_2H_5 \longrightarrow n\text{-}C_4H_9NHCHO + C_2H_5O^- \quad (10)$$

The total rate would be

$$-d[RNH_2]/dt = k_m[RNH_2][Ester] + k_a[RNH^-][Ester] \quad (11)$$

where k_m and k_a are the second-order rate constants for the reaction of ester with molecular amine and amine anion, respectively. The present aminolysis reaction differs from the Betts and Hammett case, however, in that by far the larger proportion of the reaction proceeds through (10) and only a minor (and difficultly demonstrable) proportion through (4). The concentration of RNH^- in hydroxylic solvents is determined by the equilibria

$$2RNH_2 \rightleftharpoons RNH_3^+ + RNH^- \quad K_{am} \quad (12)$$

$$RNH_2 + R'OH \rightleftharpoons RNH_3^+ + R'O^- \quad K_b \quad (13)$$

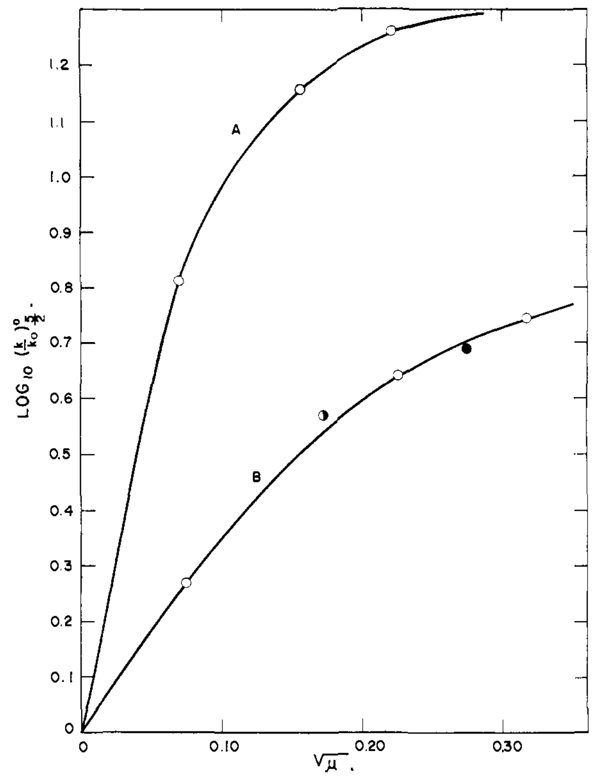

Fig. 1.—Effect of ionic strength. Curve A for dioxane–ethylene glycol: $[n\text{-}C_4H_9NH_2]_0$ = 0.6490 mole/l.; $[HCOOC_2H_5]_0$ = 0.6120 mole/l. Curve B for ethanol: $[n\text{-}C_4H_9NH_2]_0$ = 0.4907 mole/l.; $[HCOOC_2H_5]_0$ = 0.5328 mole/l. Neutral salt: O, lithium chloride; ◑, sodium iodide; ●, lithium nitrate.

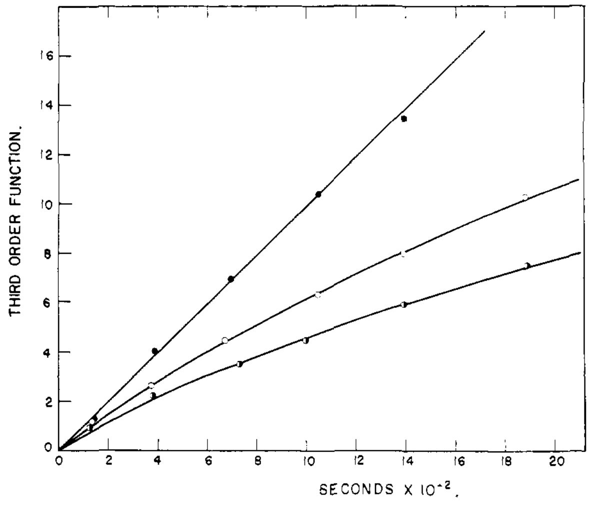

Fig. 2.—Effect of water on rate in ethanol. $[n\text{-}C_4H_9NH_2]_0$ = 0.5020 mole/l.; $[HCOOC_2H_5]_0$ = 0.4775 mole/l. Right-hand side of eq. 6 plotted against time. ●, No water; O, 0.0549 mole/l. water; ◑, 0.1675 mole/l. water.

Since $K_b >> K_{am}$, in the absence of amine acid salts and base catalysts the second equilibrium (13) governs the concentration of RNH_3^+. We may then set

$$RNH_3^+ = R'O^- \quad (14)$$

and obtain from (14) and the expressions for K_b[13] and K_{am} the concentration of RNH^-

$$[RNH^-] = \frac{K_{am}[RNH_2]^{3/2}}{K_b^{1/2}[R'OH]^{1/2}} \qquad (15)$$

If the aminolysis proceeds solely through (10), the total rate would then be

$$\frac{-d[RNH_2]}{dt} = \frac{k_a K_{am}[RNH_2]^{3/2}[Ester]}{K_b^{1/2}[R'OH]^{1/2}} = k_{5/2}[RNH_2]^{3/2}[Ester] \qquad (16)$$

where

$$\frac{k_a K_{am}}{K_b^{1/2}} = k_{5/2}\ [R'OH]^{1/2} \qquad (17)$$

However, if there is a term involving molecular amine (reaction 4) then

$$\frac{-d[RNH_2]}{dt} = k_m\ [RNH_2][Ester] + \frac{k_a K_{am}\ [RNH_2]^{3/2}[Ester]}{K_b^{1/2}[R'OH]^{1/2}} \qquad (18)$$

Dioxane–Ethylene Glycol.—The values in the fifth column of Table V are constant within experimental error over the entire range of reactant concentrations, and indicate that the rate expression (16) is followed and that the aminolysis therefore proceeds solely through reaction (10). There are however quite obvious upward drifts in the rate constants in any single run (Table I) which suggest that a term of order lower than 3/2 in amine (or one in ester) is being neglected. To determine the presence of such a term the data were therefore recalculated as first order in amine and first order in ester and the initial slopes of these plots measured to give the k_2^0 values of Table V.

$$\frac{-d[RNH_2]}{dt} = k_2[RNH_2][Ester] \qquad (19)$$

From (18) and (19) it follows that

$$k_2^0 = k_m + \frac{k_a K_{am}[RNH_2]_0^{1/2}}{K_b^{1/2}[R'OH]^{1/2}} \qquad (20)$$

Equation 20 requires that a plot of k_2^0 against $([RNH_2]_0/[R'OH])^{1/2}$ be a straight line with slope equal to $k_a K_{am}/K_b^{1/2}$ and intercept equal to k_m. The resulting plot (Fig. 3) is reasonably linear, with deviations only at the lower amine concentrations. Least squares calculations give for this plot a slope of 2.49 ± 0.16 × 10^{-3} (mole/l.)$^{-1}$ sec.$^{-1}$ (*cf.* average value of $k_{5/2}^0$ $[R'OH]^{1/2}$ from Table V of 2.46 ± 0.21 × 10^{-3} (mole/l.)$^{-1}$ sec.$^{-1}$) and an intercept indistinguishable from zero of −0.07 ± 0.06 × 10^{-3} (mole/l.)$^{-1}$ sec.$^{-1}$. Thus from these data alone, the reaction of molecular amine cannot be firmly established.

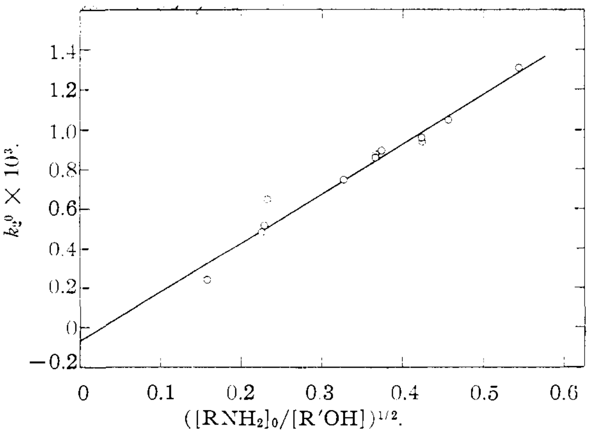

Fig. 3.—Plot of eq. 20, rates in dioxane–ethylene glycol.

Ethanol.—In ethanol the data (Table VI) also fit the rate expression (16) to a very good approximation. A procedure similar to that above was carried out to search for a term involving molecular amine. In this solvent it was found more convenient in obtaining initial rates to recalculate the rate data as second order in amine and first order in ester

$$\frac{-d[RNH_2]}{dt} = k_3[RNH_2]^2[Ester] \qquad (21)$$

Then from (18) and (21)

$$[RNH_2]_0\ k_3^0 = k_m + \frac{k_a K_{am}[RNH_2]_0^{1/2}}{K_b^{1/2}[R'OH]^{1/2}} \qquad (22)$$

Hence a plot of $[RNH_2]_0 k_3^0$ against $([RNH_2]_0/[R'OH])^{1/2}$ should be linear, with slope equal to $k_a K_{am}/K_b^{1/2}$ and intercept equal to k_m. The data obtained in ethanol showed some scatter in such a plot, owing to uncertainties in obtaining initial rates from the very rapid reactions which resulted at high amine concentrations. Thus the most rapid run (last one, Table VI) was not included in this plot (Fig. 4). The resulting slope was 3.28 ± 0.19 × 10^{-2} (mole/l.)$^{-1}$ sec.$^{-1}$ (*cf.* average value of $k_{5/2}^0 \cdot [R'OH]^{1/2}$ from Table VI of 2.99 ± 0.31 × 10^{-2} (mole/l.)$^{-1}$ sec.$^{-1}$), and the intercept −0.56 ± 0.33 × 10^{-3} (mole/l.)$^{-1}$ sec.$^{-1}$. Thus again the intercept k_m is very nearly zero within the experimental error of these data.

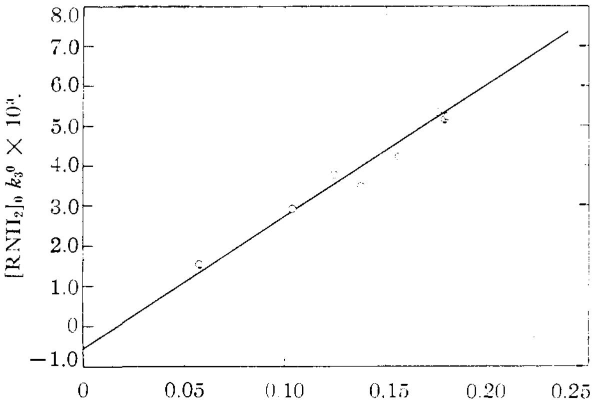

Fig. 4.—Plot of eq. 22, rates in ethanol.

Reaction of molecular amine could, however, be demonstrated through the quantitative determination of the retarding effect of acid. When an amine acid salt is added to the reaction, the concentration of RNH^- becomes determined by equilibrium (12) and the expression (16) becomes

$$\frac{-d[RNH_2]}{dt} = \frac{k_a K_{am}[RNH_2]^2[Ester]}{[RNH_3^+]} \qquad (23)$$

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[13] We define K_b = $[RNH_3^+][R'O^-]/[RNH_2][R'OH]$. This formulation is used since R'OH varies by about 5% between the extreme ranges of concentrations of the amine and ester. The ionization constant of the amine in R'OH is defined as $K_B = [RNH_3^+][R'O^-]/[RNH_2]$. Then $K_B = [R'OH]K_b$. For pure ethanol at 30°, [R'OH] = 16.95 mole/l.

and likewise (18) becomes

$$\frac{-\mathrm{d}[\mathrm{RNH_2}]}{\mathrm{d}t} = k_{\mathrm{m}}\,[\mathrm{RNH_2}][\mathrm{Ester}] + \frac{k_{\mathrm{a}}K_{\mathrm{am}}\,[\mathrm{RNH_2}]^2[\mathrm{Ester}]}{[\mathrm{RNH_3}^+]} \qquad (24)$$

Since (23) should describe the over-all reaction to a good approximation, it is to be expected that when an amine acid salt is present the reaction will now follow third-order kinetics quite accurately; that this is indeed the case is shown in Table III. Following the previously established procedures we now find that from (21) and (24)

$$[\mathrm{RNH_2}]_0\,k_3^0 = k_{\mathrm{m}} + \frac{k_{\mathrm{a}}K_{\mathrm{am}}[\mathrm{RNH_2}]_0}{[\mathrm{RNH_3}^+]} \qquad (25)$$

Thus a plot of $[\mathrm{RNH_2}]_0k_3$ against $[\mathrm{RNH_2}]_0/[\mathrm{RNH_3}^+]$ should be linear, with a slope of $k_{\mathrm{a}}K_{\mathrm{am}}$ and an intercept of k_{m}. Figure 5 shows this relation to hold reasonably well. The least squares slope is $9.55 \pm 0.47 \times 10^{-6}$ (mole/l.)$^{-1}$ sec.$^{-1}$ and the intercept is $4.72 \pm 0.27 \times 10^{-4}$ (mole/l.)$^{-1}$ sec.$^{-1}$. This value for the intercept k_{m} (*cf.* value of $-5.6 \pm 3.3 \times 10^{-4}$ (mole/l.)$^{-1}$ sec.$^{-1}$ for k_{m} from Fig. 5) is now within experimental error greater than zero and thus establishes that there is indeed a small but distinct reaction of molecular amine.

From the slopes of the two plots (Figs. 4 and 5) a value can be calculated for K_{b}. Thus

$$\frac{k_{\mathrm{a}}K_{\mathrm{am}}}{K_{\mathrm{b}}^{1/2}} = 3.28 \pm 0.19 \times 10^{-2}\,(\mathrm{mole/l.})^{-1}\,\mathrm{sec.}^{-1} \qquad (26)$$

$$k_{\mathrm{a}}K_{\mathrm{am}} = 9.55 \pm 0.47 \times 10^{-6}\,(\mathrm{mole/l.})^{-1}\,\mathrm{sec.}^{-1} \qquad (27)$$

and therefore K_{b} is $0.85 \pm 0.15 \times 10^{-7}$. The ionization constant, K_{B}, of *n*-butylamine in ethanol at 30° and $\mu = 0.100$, is then $1.44 \pm 0.25 \times 10^{-6}$ and pK_{B} (expt.) $= 5.84 \pm 0.08$.[13] For comparison with this value of pK_{B} (expt.), we have the determination of the ionization constant of *n*-butylamine in ethanol at 25° by Goodhue and Hixon[14] from e.m.f. measurements, in which pK_{B} is reported to be 7.40. We estimate that at the higher ionic strength and temperature of our measurements the true pK_{B} would be lower by about one unit than the reported value,[15] or about 6.4. The difference between our result and the independently determined ionization constant is then within an order of magnitude, and thus not entirely unsatisfactory in view of the indirect manner in which K_{B} was derived from the present study.

Ionic Strength Effects.—The large increases in rate caused by the neutral salts (Fig. 1) are entirely consistent with a mechanism in which RNH^- is the primary reactant. The salt effect is too large to be a primary salt effect; its magnitude and the manner in which these data plot (log (k/k_0) is linear with $\sqrt{\mu}$ at low μ and linear with $1/\sqrt{\mu}$ at high μ) indicate that this is an effect acting on ionic equilibria. Equation 15 shows that the concentration of RNH^- is determined by the ratio $K_{\mathrm{am}}/K_{\mathrm{b}}^{1/2}$, $[\mathrm{RNH_2}]$ and $[\mathrm{R'OH}]$ remaining constant. This ratio clearly must increase with increasing ionic strength since any deviations from ideal behavior should affect K_{am} and K_{b} in the same manner. Thus $[\mathrm{RNH}^-]$ will increase with increasing neutral salt concentration, with a resulting sharp increase in rate.[16]

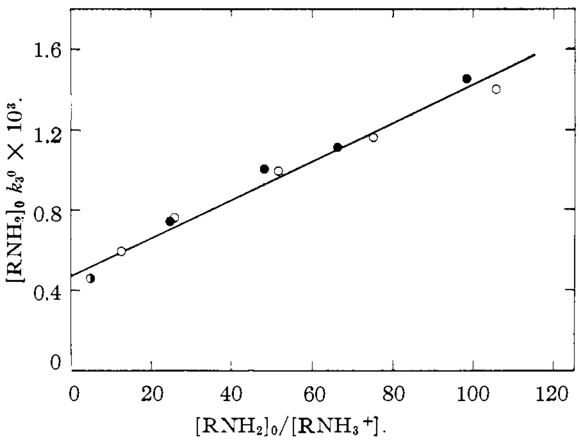

Fig. 5.—Effect of *n*-butylamine hydrochloride on rates in ethanol, plotted according to eq. 25: ○, $[n\text{-}\mathrm{C_4H_9NH_2}]_0 = 0.5084$ mole/l.; $[\mathrm{HCOOC_2H_5}]_0 = 0.4685$ mole/l.; ●, $[n\text{-}\mathrm{C_4H_9NH_2}]_0 = 0.4907$ mole/l.; $[\mathrm{HCOOC_2H_5}]_0 = 0.5326$ mole/l.; ◑, values for the two sets coincide.

Base Catalysis.—Since the rate is almost entirely dependent on $[\mathrm{RNH}^-]$, there should be an especially strong base catalysis. Results of several runs made to measure this effect are given in Table VIII.

TABLE VIII

CATALYSIS BY LITHIUM ETHOXIDE IN ETHANOL, $\mu = 0.100$ $[n\text{-}\mathrm{C_4H_9NH_2}] = 0.5040$ *M*, $[\mathrm{HCOOC_2H_5}] = 0.5348$ *M*

Concn. $\mathrm{LiOC_2H_5}$ (mole/l.)	$k_3 \times 10^3$ (mole/l.)$^{-2}$ sec.$^{-1}$
0.000170	10.4
.000389	12.4
.000678	15.2
.0044	26.1

These data could not be treated quantitatively since the accelerations caused by base were so pronounced that measurements could be made only at very low base concentrations. In this range, the added alkoxide concentration is of the same order of magnitude as the alkoxide produced in equilibrium (13), and thus K_{b} must be known quite accurately in order to calculate total alkoxide. Such a value of K_{b} was not available. Rough calculations indicate, however, that the data of Table VIII may not fit equation 11, the rate constants at high base concentrations being lower than would be expected. One explanation might be that there are side reactions which consume base, some possibilities being alkyl–oxygen fission of the type[17]

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

[15] L. S. Guss and I. M. Kolthoff, *ibid.*, **62**, 249 (1940); J. R. Schaefgen, M. S. Newman and F. H. Verhoek, *ibid.*, **66**, 1847 (1944).

[16] The strong accelerating effect of neutral salt has also been noted in an earlier study of aminolysis,[6] where it is pointed out that the catalysis by amine acid salt previously reported by these investigators[5] may have been a neutral salt effect rather than an actual catalysis. This explanation agrees with our own observation that if the ionic strength is not maintained at a constant fixed high value by the addition of neutral salt, *n*-butylamine hydrochloride added alone causes an apparent slight increase in rate. This increase is the resultant of an increase in rate arising from the neutral salt effect and a decrease in rate caused by the reduction in RNH^- concentration by the acid salt. However at constant ionic strength the effect of the acid salt is isolated from the neutral salt effect and is shown to result in a decrease in rate (Table VII and Fig. 5).

[17] *Cf.* J. F. Bunnett, M. M. Robison and F. C. Pennington, THIS JOURNAL, **72**, 2378 (1950); L. P. Hammett and H. L. Pfluger, *ibid.*, **55**, 4079 (1933).

$$HCOOC_2H_5 + C_2H_5O^- \longrightarrow HCOO^- + C_2H_5OC_2H_5 \quad (28)$$

$$HCOOC_2H_5 + n\text{-}C_4H_9NH^- \longrightarrow HCOO^- + C_2H_5NHC_4H_9\text{-}n \quad (29)$$

Side Reactions.—We wish again to point out that the key relations (16), (20) and (22) have been verified only by the use of the limiting initial rate constants, *i.e.*, those obtained by extrapolating the calculated rate constants in any given run to zero time. The fit of these rate constants to theory is satisfactory and, taken together with the results of the amine hydrochloride experiments, provides strong evidence for the mechanism (4), (10). It should however be equally possible, at least in principle, to apply the same analysis to the data of a single run and obtain therewith the same values of k_m and k_aK_{am}/K_b. From (18) we have that

$$\frac{-d[RNH_2]/dt}{[Ester][RNH_2]} = k_m + \frac{k_aK_{am}[RNH_2]^{1/2}}{K_b^{1/2}[R'OH]^{1/2}} \quad (30)$$

From a smoothed curve of amine concentration against time we can determine for different values of the time t, the values of the instantaneous rate $(d[RNH_2]/dt)$, and the concentrations of amine and ester. Then a plot of the left-hand side of (30) against $([RNH_2]/[R'OH])^{1/2}$ should be a straight line with intercept k_m and slope $k_aK_{am}/K_b^{1/2}$.

Reactions in dioxane–ethylene glycol were found to give no fit to equation (30). The plots showed a distinct curvature, concave downwards, indicating the perturbing effect of some other reaction upon the aminolysis. This result, as well as a fit of the data to second order kinetics which is better than should be expected from the very low contribution of k_m, and the strongly increasing values of $k_{5/2}$ within a single run (see Table I, columns 4 and 5), show that this side reaction causes an acceleration in rate as the reaction proceeds. We feel this must be a transesterification between ethyl formate and ethylene glycol, leading to the hydroxyethyl ester, which then aminolyzes more rapidly than the ethyl ester.[18] Support for this proposal is provided in the observation of Davis and Ross[19] that the alkaline hydrolysis of hydroxyethyl acetate proceeds ten times faster than the hydrolysis of ethyl acetate. It may be expected that rates of aminolysis will be affected in the same manner by changes in structure as are rates of alkaline hydrolysis, and it is therefore reasonable that hydroxyethyl formate will aminolyze more rapidly than ethyl formate. It is indeed probable that the "catalytic" effect of glycols upon rates of aminolysis, reported by Day,[2] is simply due to a similar transesterification to a more rapidly aminolyzed ester.

Application of (30) to data obtained in ethanol gave better, but still not entirely satisfactory, results. Here a linear plot was obtained, but the slopes and intercepts were different from the values obtained from Fig. 5. Thus run 92 (see Tables II and VI) gave 0.62×10^{-2} (mole/l.)$^{-1}$ sec.$^{-1}$ for k_m and -5.3×10^{-3} (mole/l.)$^{-1}$ sec.$^{-1}$ for $k_aK_{am}/K_b^{1/2}$ (*cf.* the respective values of $3.28 \pm 0.19 \times 10^{-2}$ (mole/l.)$^{-1}$ sec.$^{-1}$ and $-0.56 \pm 0.33 \times 10^{-3}$ (mole/l.)$^{-1}$ sec.$^{-1}$ from Fig. 4). Since in any single run there are drops in both k_3 and $k_{5/2}$ (see Table II), there is obviously a decrease in rate as the reaction proceeds which is not reconcilable with the mechanism (4), (10). This is undoubtedly due either to traces of water, or to reactions such as (28) and (29), any of which in the absence of any added base have the net effect of producing acid. The data of Table VII show how striking the retarding effect of small amounts of acid can be. Addition of 0.00481 mole/l. *n*-butylamine hydrochloride causes a drop in k_3^0 from 10.4×10^{-3} (mole/l.)$^-$ sec.$^{-1}$ (see Table VI, run 99) to 2.75×10^{-3} (mole/l.)$^{-2}$ sec.$^{-1}$. Since the amine concentration in these runs is about 0.50 mole/l., this amount of the acid salt is equivalent to a conversion of only 1% of the amine to the acid salt. Thus it is entirely reasonable that the rate constants drift downward as the reaction proceeds, and it is also clear why even the initial rate constants are subject to such large random errors.

Other Possible Mechanisms.—From the preceding discussion it is clear that the predominant feature of the aminolysis of ethyl formate with *n*-butylamine in each of the two solvents is a good fit of the initial rate constants to a reaction which is 3/2 order in amine and first order in ester. A second limiting condition is a retardation by acid, expressed as in equation 25. These observations are necessary and sufficient to define uniquely a term $k_a[RNH^-][Ester]$. There is also evidence from Fig. 5 for a second minor term, and we have shown that our data are consistent with a choice of $k_m \cdot [RNH_2][Ester]$ as this second term. We must, however, consider whether this identification of the second term is unique and, moreover, whether there may be still further terms in the complete rate equation.

We can make a limited analysis of possible mechanisms as follows. The three species arising from amine likely to be present in an aminolysis reaction are RNH_2, RNH^-, and RNH_3^+; the most likely kinetic terms including these species, together with the order with respect to amine which these terms would be equivalent to (derived as was equation 15) are shown in Table IX.

TABLE IX

POSSIBLE KINETIC TERMS IN AMINOLYSIS

Number	Term	Order in aminolysis
1	$k_1[RNH_2]$	1
2	$k_2[RNH^-]$	3/2
3	$k_3[RNH_3^+]$	1/2
4	$k_4[RNH_2][RNH^-]$	5/2
5	$k_5[RNH_2][RNH_3^+]$	3/2
6	$k_6[RNH^-][RNH_3^+]$	2

There are fifteen possible combinations of these terms taken two at a time and twenty combinations taken three at a time, a total of thirty-five combinations to choose from. Our requirement that term 2 be included in any mechanism to be considered reduces the number of possible combinations to fifteen.

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[18] Baltzly, *et al.*,[3] report that in the aminolysis of ethyl esters in methanol the second-order rate constants increase with time. This acceleration is similarly ascribed to transesterification to give the methyl ester, which is more reactive.

[19] W. Davis and W. C. J. Ross, *J. Chem. Soc.*, 3056 (1950).

Nine of these fifteen combinations can be checked against our data. We have already shown how the combination we consider most probable, 1 + 2, satisfies the data. None of the remaining eight mechanisms that we can handle is, however, consistent with our data. As an example, we consider the case of 2 + 3, which is the mechanism found to be operative in the aminolysis of α-naphthyl acetate.[1b] Here, by operations entirely analogous to those whereby equations 22 and 25 were derived, we find

$$[\mathrm{RNH_2}]_0{}^{1/2}\, k_3{}^0 = \frac{k_2 K_{\mathrm{am}}}{K_{\mathrm{b}}{}^{1/2}[\mathrm{R'OH}]^{1/2}} + \frac{k_3 K_{\mathrm{b}}{}^{1/2}[\mathrm{R'OH}]^{1/2}}{[\mathrm{RNH_2}]_0} \quad (31)$$

$$[\mathrm{RNH_3}^+]k_3{}^0 = k_2 K_{\mathrm{am}} + \frac{k_3[\mathrm{RNH_3}^+]^2}{[\mathrm{RNH_3}]_0} \quad (32)$$

When the data of Tables VI and VII are fed into these equations, the appropriate plot for (31) is found not to be linear, thereby showing that these data do not fit mechanism 2 + 3. In like manner, we eliminate the seven combinations 2 + 4, 2 + 5, 2 + 6, 2 + 3 + 4, 2 + 3 + 5, 2 + 4 + 5, and 2 + 5 + 6. We are thus left with six possible mechanisms that we cannot either accept or reject on the basis of our present treatment of our data: 1 + 2 + 3, 1 + 2 + 4, 1 + 2 + 5, 1 + 2 + 6, 2 + 3 + 6 and 2 + 4 + 6. Three of these combinations contain the term 3 or 5, corresponding to acid catalysis, and we must then conclude that if there is an acid catalysis term in the rate equation, it will appear in one of these combinations.

The foregoing analysis has thus disclosed no simple mechanism other than 1 + 2 which satisfactorily accounts for our results, and consequently has furnished no positive evidence for acid catalysis in the reaction under study. It has, however, led to a list of six other mechanisms which our treatment does not test, and thus has shown that our present assignment of mechanism, even though most reasonable chemically, nevertheless may not be uniquely demanded by the experimental results.

The formal similarity among ammonolysis, aminolysis, and hydrolysis has been remarked upon by several previous authors.[1b,3,20] Hydrolysis, however, has been considered either as separately base catalyzed or separately acid catalyzed,[21] and it has not been experimentally demonstrated that both processes may be operative in the same reaction. Such a demonstration should be possible when both base and acid are present at approximately the same concentrations as, for example, in neutral aqueous solution, and when the susceptibility of the ester to acid hydrolysis is of the same order of magnitude as its susceptibility to base catalysis. Rates of hydrolysis under such conditions are generally low and often complicated by changes in mechanism to alkyl–oxygen fission.[21] A more ideal situation exists in aminolysis, however, since $\mathrm{RNH^-}$ has undoubtedly much greater nucleophilic reactivity toward carbonyl carbon than $\mathrm{OH^-}$ and thus rapid rates may be realized without added catalysts. Since it is generally the case that in hydrolysis the acceleration afforded by a given level of base is greater than that resulting from the same concentration of acid, it is not unexpected that in aminolysis the reaction of $\mathrm{RNH^-}$ may far overshadow the effect of $\mathrm{RNH_3^+}$ upon the ester. Thus it is possible that only in those instances in which base catalysis is relatively ineffective, as is probably the case with α-naphthyl acetate, would a term involving $\mathrm{RNH_3^+}$ be large enough to detect. This would mean that our results are by no means in contradiction with those of Hawkins[1b] but represent a more restricted, but probably more common, aspect of the mechanism of aminolysis.

Acknowledgment.—We are indebted to Dr. S. Gratch, Dr. L. P. Hammett, and Dr. C. Huggett for many stimulating discussions during the course of this work.

(20) C. K. Ingold, "Structure and Mechanism in Organic Chemistry" Cornell University Press, Ithaca, N. Y., 1953, pp. 782–784.

(21) Reference 20, p. 752, *et seq.*

PHILADELPHIA, PA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA AT DAVIS]

The Kinetics of the Zinc Chloride-catalyzed Bromination of Polymethylbenzenes in Acetic Acid Solution

BY L. J. ANDREWS AND R. M. KEEFER

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Partial rate factors for substitution at positions *ortho*, *meta* and *para* to a methyl substituent on the benzene ring have been determined through an investigation of the kinetics of the zinc chloride-catalyzed bromination of a series of methylbenzenes in acetic acid solution. Evidence has been obtained that not only the *ortho* partial rate factors but also the *meta* and *para* factors are subject to steric influences of ring methyl substituents. The bromination reactions are first order with respect to halogen, to aromatic hydrocarbon and to catalyst. The reactions are inhibited by $\mathrm{HZnCl_2Br}$ which accumulates in the medium as the reaction proceeds. This substance has no catalytic activity but can react with a reaction intermediate to regenerate the starting materials. Ethyl-, isopropyl- and *t*-butylbenzene are only slightly less reactive than toluene, but *p*-di-*t*-butyl- and *sym*-tri-*t*-butylbenzene brominate very slowly.

Partial rate factors for nuclear halogenation of the benzene ring at positions *ortho*, *meta* or *para* to methyl substituents have been calculated.[1] These calculations were based on the known isomer distribution of products resulting from the chlorination of toluene in the presence of antimony pentachloride and iodine[2] and on values reported for the relative rates of chlorination of benzene and toluene in 80% acetic acid.[3] These partial rate factors

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(1) F. E. Condon, THIS JOURNAL, **70**, 1963 (1948).

(2) E. Wertyporoch, *Ann.*, **493**, 153 (1932).

(3) P. B. D. de la Mare and P. W. Robertson, *J. Chem. Soc.*, 279 (1943).