and upon the nature of the functional alcoholic groups and to a smaller extent on the position of the benzene ring in the molecule.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Acid Catalysis in Amines. II. The Catalytic Effect of Various Butylammonium Salts on the Aminolysis of Ethyl Phenylacetate in Anhydrous *n*-Butylamine

BY PAUL K. GLASOE, J. KLEINBERG AND L. F. AUDRIETH

Experimental evidence already has been presented to demonstrate that the ammonolysis of esters in anhydrous liquid ammonia is markedly catalyzed by the presence of ammonium salts.[1-4] The catalytic effect of equimolar concentrations of different ammonium salts has been found to decrease in the following order: $C_2H_3O_2^- > C_6H_5COO^- > Cl^- > Br^- > NO_3^- > I^- > ClO_4^-$.[2,4] This result is quite unexpected, especially if this effect is to be interpreted as an example of acid catalysis in a non-aqueous solvent. This anion order is exactly opposite from what might be expected from a consideration of those physical properties of ammonium salts in liquid ammonia which presumably permit a quantitative estimation of the ammonium ion concentration.

In extending these studies from ammonia to amines it has been shown that aminolytic reactions are also catalyzed by the solvated proton, introduced into the reaction mixture in the form of the amine salt.[5] In view of the anomalous behavior of ammonium salts in accelerating the ammonolysis of esters it became of distinct interest to determine whether the catalytic effect of equimolar concentrations of different amine salts also varied with the nature of the anion, as observed in the case of liquid ammonia. The present investigation was therefore undertaken to study the influence of various butylammonium salts on the rate of the reaction between anhydrous butylamine and ethyl phenylacetate.

Experimental

Procedure.—Due to the excessive solubility of the various butylammonium salts in anhydrous butylamine, and their hygroscopicity, the method used in the actual isolation and preparation of analogous cyclohexylammonium salts[5] could not be employed satisfactorily.[6] Consequently, butylammonium salts were in most instances not isolated, but prepared in butylamine by adding a definite quantity of ammonium salt to an excess of amine. The resulting mixtures were then warmed on the steam-bath under slightly reduced pressure to effect removal of ammonia, yielding solutions of known content of butylammonium salts.

In preparing standard solutions for reaction velocity studies a definite quantity of ester was added to the amine solution of the specific salt and the mixture diluted with amine to exactly 25 cc. Two-cc. samples of this mixture were transferred to small Pyrex test-tubes which were immediately sealed and placed in a thermostat at 25°. At definite intervals of time tubes were removed, broken into an excess of standard hydrochloric acid and back titrated with standard sodium hydroxide using a methylene blue–methyl red indicator. The difference between these titrations and an initial one carried out at the beginning of each series of runs gave a measure of the amount of amine used and therefore a measure of the amount of ester which had reacted to form the N-substituted amide.

Discussion of Results

Ethyl phenylacetate reacts with butylamine in accordance with the equation: $C_6H_5CH_2COOC_2H_5 + C_4H_9NH_2 \longrightarrow C_6H_5CH_2CONHC_4H_9 + C_2H_5OH$. The reaction is very slow, as is evident from Curve 11, Fig. 1, in which the % yield of amide is plotted as a function of time. Addition of butylammonium salts, presumably acting as acids in butylamine because of the presence of the $C_4H_9NH_2.H^+$ ion, accelerates aminolysis markedly. However, the magnitude of the cata-

(1) Slobutsky and Audrieth, *Proc. Natl. Acad. Sci.*, **23**, 611 (1937).
(2) Fellinger and Audrieth, THIS JOURNAL, **60**, 579 (1938).
(3) Audrieth and Kleinberg, *J. Org. Chem.*, **3**, 312 (1938).
(4) Shatenshtein, THIS JOURNAL, **59**, 432 (1937).
(5) Glasoe and Audrieth, *J. Org. Chem.*, **4**, 34 (1939).

(6) It was also observed in the attempted preparation of butylammonium nitrate from butylamine and ammonium nitrate that aminolysis with evolution of ammonia was limited to dilute solutions and that further quantities of ammonium nitrate could be dissolved subsequently in the amine without reaction.

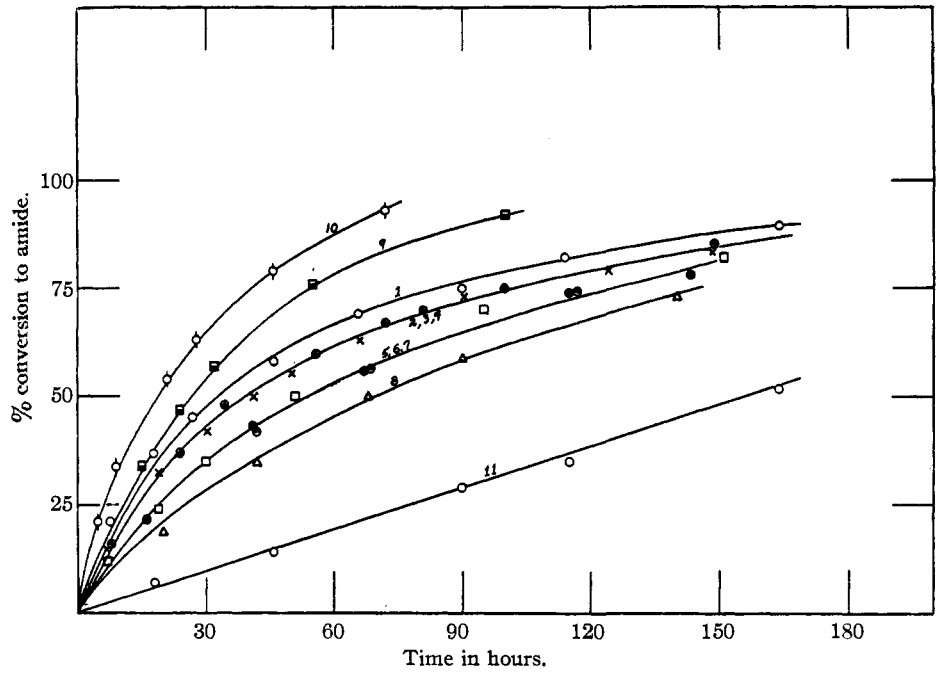

Fig. 1.—Catalytic effect of various butylammonium salts on the reaction between *n*-butylamine and ethyl phenylacetate (see Table I for specific data). Curves represent the use of equimolar quantities of different catalysts (S = $C_4H_9NH_2$): 1, S·HCl; 2, 3, 4, S·HBr, S·$HC_2H_3O_2$, S·$HOOCC_6H_5$; 5, 6, 7, S·HNO_3, S·HSCN, S·HI; 8, S·$HClO_4$; 11, no catalyst. Curves 4, 9, and 10 show the effect of increasing the molar ratio of amine to ester using $C_4H_9NH_2$·HBr as catalyst.

lytic effect is definitely dependent upon the nature of the anion.

A plot of the function log $(a - x)/(b - x)$ against time indicates that these reactions are pseudo-second order, but it is obvious that the butylammonium salt plays a definite part in the reaction, since the values of the specific reaction rate constants as given in Table I vary with the nature of the salt. The data in Table I indicate a specific anion effect which for equimolecular concentrations of added butylammonium salts decreases in the order

$$Cl^- > C_2H_3O_2^- > C_6H_5COO^- > Br^- > NO_3^- > CNS^- > I^- > ClO_4^-$$

No information is available in the literature concerning the physical properties (conductivity, degree of ionization, etc.) of the respective butylammonium salts in butylamine. It is significant, however, that the above order parallels, except for the position of the chloride, the order of cata-

TABLE I

AMINOLYSIS OF ETHYL PHENYLACETATE IN ANHYDROUS *n*-BUTYLAMINE AT 25°

Concentration of catalyst = 0.1 mole per liter; a = concentration of amine in moles per liter; b = concentration of ester in moles per liter.

Curve no. (see Fig. 1)	Catalyst used	a	b	$K \times 10^3$	t 1/2 (calcd.)	t 1/2 (exptl.)
1	$C_4H_9NH_2$·HCl	5.35	2.80	4.65	33	33
2	$C_4H_9NH_2$·$HC_2H_3O_2$	5.36	2.80	3.87	39.5	40
3	$C_4H_9NH_2$·$HOOCC_6H_5$	5.35	2.80	3.85	40	40
4	$C_4H_9NH_2$·HBr	5.37	2.80	3.85	40	40
5	$C_4H_9NH_2$·HNO_3	5.34	2.80	2.93	51	52
6	$C_4H_9NH_2$·HSCN	5.36	2.80	2.81	54	53
7	$C_4H_9NH_2$·HI	5.34	2.80	2.57	59	57
8	$C_4H_9NH_2$·$HClO_4$	5.40	2.80	2.09	73	70
9	$C_4H_9NH_2$·HBr	7.02	1.80	4.04	26	27
10	$C_4H_9NH_2$·HBr	7.78	1.33	5.27	18	18
11	None	5.45	2.80	0.87	171	158

lytic activity of the corresponding ammonium salts upon the ammonolysis of esters in liquid ammonia. Like ammonia, butylamine is a strongly basic solvent in which ionization of weak acids is presumably enhanced. On the other hand, however, the low dielectric constant ($\epsilon = 5.4$)[7] of the solvent undoubtedly promotes formation of inactive ion pairs, or even larger aggregates, with the consequence that stoichiometric concentrations give little or no insight into the concentrations of either the butylammonium ions or the negative ions in solution.

It also should be pointed out that the presence of a fairly large mole fraction of ester in the solutions under investigation undoubtedly influences the ionization of the butylammonium salts. Actually, very concentrated solutions of ester in amine were used in all experiments.

It is also apparent from a comparison of the experimental series 4, 9 and 10, that the ratio of amine to ester affects the rate of the reaction very appreciably. In the first eight series the molar ratios of amine, ester and catalyst are given approximately by the numbers 380:200:7. As the mole ratio of amine to ester is increased, the value for the specific reaction rate constant also becomes larger. It is obvious, therefore, that the reaction is not even pseudo-bimolecular in character, except for specified conditions. To obtain more rapid reaction it is advisable to use quantities of amine considerably in excess of those required stoichiometrically.

The tremendous effect of the addition of the relatively small quantity of butylammonium salt is emphasized by a comparison of the half-life times of the first ten series, with that for the uncatalyzed reaction. These findings again emphasize our contention[5] that the mechanism of all solvolytic reactions, whether they be hydrolytic, ammonolytic or aminolytic, is fundamentally the same as illustrated by the reaction

$$\left.\begin{matrix}\mathrm{HOH}\\ \mathrm{HNH_2}\\ \mathrm{R''NH_2}\end{matrix}\right\} + \mathrm{RCOOR'} \xrightarrow{\mathrm{S{\cdot}H^+}} \mathrm{RCO}\left\{\begin{matrix}\mathrm{OH}\\ \mathrm{NH_2}\\ \mathrm{NHR''}\end{matrix}\right. + \mathrm{R'OH}$$

(7) Schlundt, *J. Phys. Chem.*, **5**, 503 (1901).

Summary

1. The aminolysis of ethyl phenylacetate in *n*-butylamine to yield the N-butylamide of phenylacetic acid is catalyzed by butylammonium salts.

2. The catalytic effect of equimolar concentrations of various butylammonium salts decreases with the anion in the following order: $Cl^- > C_2H_3O_2^- > C_6H_5COO^- > Br^- > NO_3^- > CNS^- > I^- > ClO_4^-$.

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[CONTRIBUTION FROM THE SAMSON LABORATORIES]

The Relation of Cuprous Creatinine to Tests for Sugar in Urine[1]

BY MEYER SAMSON

It is almost a hundred years since Trommer[2] published the first practical directions for a copper reduction test for sugar. Of the hundreds of modifications[3] subsequently proposed, only the methods of Trommer, Fehling[4] and Benedict are largely used today.

Most of the proposed modifications were designed to avoid interference. Creatinine soon was recognized as the principal source of trouble, which arose from its own reducing powers, as well as from its property of holding in solution the cuprous oxide formed in the presence of glucose.[5-7]

Benedict,[8] in reviving the forgotten idea of Possoz[9] of using carbonate in place of hydroxide as alkali, believed he had found a copper solution on which creatinine was without appreciable effect.[10] When he later proposed the copper carbonate–citrate mixture in the solution[11] known by his name, he claimed it to be more sensitive to glucose either in pure solution or in urine than is Fehling's fluid. This is not correct, since

(1) Presented before the Division of Biological Chemistry, 96th meeting, American Chemical Society, Milwaukee, Wis., September 5–9, 1938.

(2) Trommer, *Ann.*, **39**, 360 (1841).

(3) Dehn, Jackson and Ballard, *Ind. Eng. Chem., Anal. Ed.*, **4**, 413 (1932).

(4) Fehling, *Ann.*, **72**, 106 (1849).

(5) Von Babo and Meissner, *Z. Rat. Med.*, **3**, 329 (1858).

(6) Winogradoff, *Arch. Path. Anat.*, **27**, 533 (1863).

(7) MacLean, *Biochem. J.*, **2**, 156 (1907).

(8) Benedict, *J. Biol. Chem.*, **3**, 101 (1907).

(9) Possoz, *Compt. rend.*, **75**, 1836 (1872).

(10) Benedict, *J. Am. Med. Assoc.*, **57**, 1193 (1911).

(11) Benedict, *J. Biol. Chem.*, **5**, 484 (1908).