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

# ACID CATALYSIS IN AMINES. I. THE CATALYTIC EFFECT OF CYCLOHEXYLAMMONIUM SALTS ON THE REACTION BETWEEN CYCLOHEXYLAMINE AND ESTERS

PAUL K. GLASOE AND L. F. AUDRIETH

*Received January 14, 1939*

Experimental evidence has already been presented to demonstrate that the ammonolysis of esters in liquid ammonia is susceptible to catalysis by ammonium salts.[1, 2, 3] Since ammonium salts have been shown to behave as acids in liquid ammonia,[4] these findings have been interpreted as possible examples of acid catalysis. In extending these studies to other basic solvents it was regarded as highly probable that related reactions involving the aminolysis of esters, resulting in the formation of *N*-substituted acid amides, could be accelerated by addition of the corresponding amine salts. Equations (1), (2), and (3), representing reactions of hydrolysis, ammonolysis, and aminolysis, respectively, of esters are all strictly analogous and may be regarded broadly as solvolytic reactions.

$$\text{(1)}\qquad RCOOR' + HOH \longrightarrow RCOOH + R'OH$$

$$\text{(2)}\qquad RCOOR' + HNH_2 \longrightarrow RCONH_2 + R'OH$$

$$\text{(3)}\qquad RCOOR' + HNHR'' \longrightarrow RCONHR'' + R'OH$$

Cyclohexylamine was chosen for this preliminary study because of its unusual physical and chemical properties,[5] as well as its ready availability on the market. It is a strongly basic solvent and appears to be a much more powerful proton acceptor than ammonia. It can readily be prepared in a state of high purity. On the basis of the modern concept of acidity it may be predicted that cyclohexylammonium salts will behave as acids in cyclohexylamine:

$$\underset{\text{(base)}}{C_6H_{11}NH_2} + \underset{\text{(acid)}}{HX} \longrightarrow \underset{\text{(acid)}}{C_6H_{11}NH_2\cdot H^+} + \underset{\text{(base)}}{X^-}$$

---

[1] SLOBUTSKY AND AUDRIETH, *Proc. Nat. Acad. Sci.*, **23**, 611 (1937).

[2] FELLENGER AND AUDRIETH, *J. Am. Chem. Soc.*, **60**, 579 (1938).

[3] AUDRIETH AND KLEINBERG, J. ORG. CHEM., **3**, 312 (1938).

[4] FRANKLIN, "The Nitrogen System of Compounds," A.C.S. Monograph. Reinhold Publishing Corporation, New York City, **1935**, p. 26.

[5] CARSWELL AND MORRELL, *Ind. Eng. Chem.*, **29**, 1247 (1937).

## EXPERIMENTAL

*Preparation of materials.*—The cyclohexylamine used in this study was purified by dehydration over solid caustic potash and repeated fractional distillation. All esters were dried carefully, and purified by distillation under reduced pressure.

*Preparation of cyclohexylammonium salts.*—During the course of a preliminary study of solubility relationships in cyclohexylamine as solvent it was observed that ammonium salts react with the solvent with evolution of ammonia. Further study of this reaction led to the development of a simple method for the preparation of cyclohexylammonium salts. These reactions, which may be regarded as simple cases of solvolysis, specifically aminolysis, may best be represented by the following type equation:

$$C_6H_{11}NH_2 + NH_4X \rightarrow C_6H_{11}NH_2 \cdot HX + NH_3$$

It is interesting to note, in this connection, that the rate of solvolysis, as evidenced by the effervescence of the solutions due to the evolution of ammonia, varies in the decreasing order:

$$NH_4NO_3 > NH_4I > NH_4Br > NH_4Cl.$$

TABLE I

CYCLOHEXYLAMMONIUM SALTS

(Prepared by interaction of cyclohexylamine and the ammonium salt.)

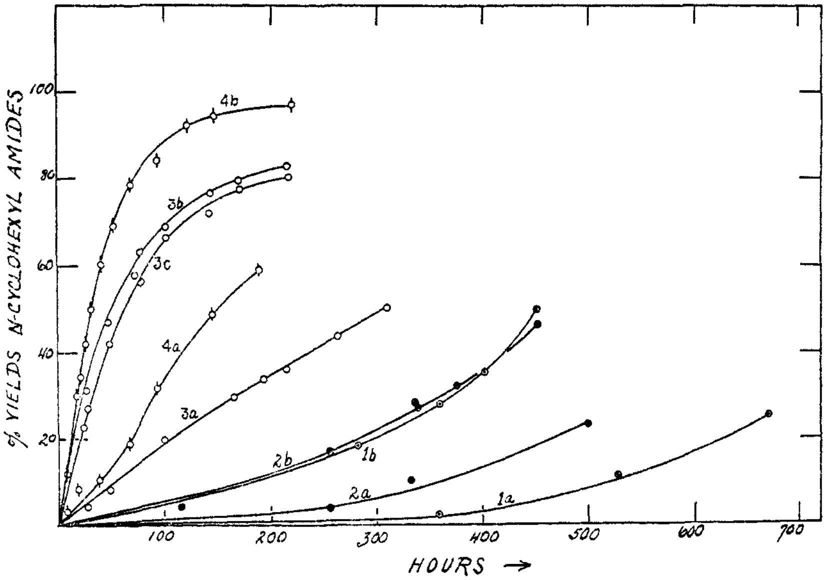
| FORMULA | MELTING POINT (UNCORR.) | N ANAL. | |
|---|---|---|---|
| | | Calc'd | Found |
| $C_6H_{11}NH_2 \cdot HBr$ | 196–197° | 7.77 | 7.68 |
| $C_6H_{11}NH_2 \cdot HNO_3$ | 156 | 17.29 | 17.06 |
| $C_6H_{11}NH_2 \cdot HI$ | 193–194 | 6.15 | 6.12 |
| $(C_6H_{11}NH_2)_2 \cdot HI$ | 185–187 | 8.59 | 8.40 |

The solubility of the resulting cyclohexylammonium salts in cyclohexylamine at 25° also decreases in the same order, the chloride and the bromide being but slightly soluble. A qualitative knowledge of these solubilities was of interest in the present investigation, since it precluded the use of the bromide and chloride as catalysts at 25°.

In preparing cyclohexylammonium salts the solid ammonium salt was added to an excess of cyclohexylamine, and the solution was heated on the steam cone under slightly reduced pressure until evolution of ammonia had ceased. The solutions were then cooled, cooling resulting, in the case of the chloride and bromide, in the formation of the solid salts, which were removed by filtration. The addition of ether to the solution, or filtrate, resulted in further precipitation of the desired cyclohexylammonium salt.

In the case of the nitrate, chloride, and bromide, the normal salts, $C_6H_{11}NH_2 \cdot HX$, were obtained. However, the product obtained by the addition of ether to a solution of the iodide in cyclohexylamine was found by analysis to be the solvated salt containing an extra molecule of cyclohexylamine. Recrystallization of this product from ethanol was found to give the normal iodide. Salts prepared by this method, with melting points and analyses, are listed in Table I.

*Procedure.*—Two methods were used to determine the rate of reaction between cyclohexylamine and the dissolved ester. In both cases stock solutions containing definite quantities of amine and ester were made up, either with or without cyclohexylammonium salt. In some runs the whole solution was kept in a thermostat at 25°, and samples were withdrawn at definite time intervals. In other experiments, especially in the case of the reaction between ethyl malonate and cyclohexylamine, where the solid reaction product precipitates from solution, aliquot portions of the stock solution were at the very beginning pipetted into separate containers, which were then placed in the thermostat for definite time periods.



Aminolysis of Esters in Cyclohexylamine (Concn. of ester = $0.5M$)

| CURVE | ESTER | CATALYST | CONCN. OF CATALYST IN MOLES PER LITER |
|---|---|---|---|
| 1A | Ethyl acetate | None | 0.00 |
| 1B | Ethyl acetate | $C_6H_{11}NH_2 \cdot HI$ | 0.20 |
| 2A | Ethyl phenylacetate | None | 0.00 |
| 2B | Ethyl phenylacetate | $C_6H_{11}NH_2 \cdot HI$ | 0.20 |
| 3A | Ethyl lactate | None | 0.00 |
| 3B | Ethyl lactate | $C_6H_{11}NH_2 \cdot HI$ | 0.20 |
| 3C | Ethyl lactate | $C_6H_{11}NH_2 \cdot HNO_3$ | 0.20 |
| 4A | Ethyl malonate | None | 0.00 |
| 4B | Ethyl malonate | $C_6H_{11}NH_2 \cdot HI$ | 0.10 |

After a certain time had elapsed samples were removed from the thermostat and treated immediately with an excess of standard hydrochloric acid; the excess was back-titrated with standard alkali. From a knowledge of the acid requirement of equal volumes of the solution at the beginning of the reaction and again at various time intervals, it was possible to calculate the extent to which the reaction had proceeded. The amount of cyclohexylamine disappearing is equivalent to the quantity of ester used up and also equivalent to the molar quantity of *N*-cyclohexyl amide formed. No difficulty was encountered in carrying out titrations, as cyclohexylamine is a strong base in aqueous solution.

Quantitative studies of this sort were carried out using the ethyl esters of acetic, phenylacetic, lactic and malonic acids. The formation of the corresponding *N*-cyclohexyl amides was verified by actual isolation of these derivatives from the reaction mixture. In view of the limited solubilities of the cyclohexylammonium bromide and chloride in cyclohexylamine at 25°, the catalytic effects of the nitrate and iodide only were investigated.

The composite experimental material is depicted graphically in the accompanying figure. The percentage conversion of the esters into the corresponding *N*-cyclohexyl amides is plotted against the time in hours. In every case 0.05 mole of the ester was diluted with cyclohexylamine to give 100 cc. of solution. The explanatory legend with the figure also indicates the moles of "onium" salt added where experiments were carried out to determine the effect of adding cyclohexylammonium salts.

TABLE II

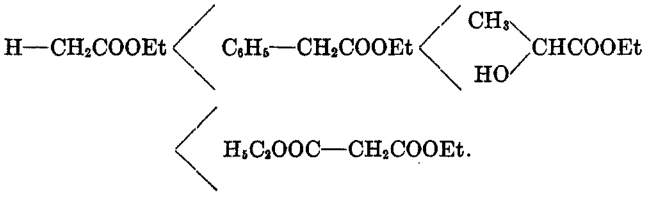
Aminolysis of Esters at 25°

(0.05 mole ester diluted to 100 cc. with $C_6H_{11}NH_2$)
Catalyst, 0.02 mole $C_6H_{11}NH_2\cdot HI$

| Ester | Conversion | | | |
|---|---|---|---|---|
| | 100 Hours | | 200 Hours | |
| | No Catalyst | With Catalyst | No Catalyst | With Catalyst |
| Ethyl acetate | 0.5 | 5.0 | 1.0 | 11.0 |
| Ethyl phenylacetate | 1.2 | 5.7 | 3.0 | 12.0 |
| Ethyl lactate | 20. | 69.0 | 52.0 | 81.0 |
| Ethyl malonate | 34.0 | 88.5* | 61.0 | 97.0* |

* Only 0.01 mole of catalyst was employed in the experiments with ethyl malonate.

*Discussion.*—The relative reactivities of the various ethyl esters towards cyclohexylamine may be compared from the summary presented in Table II. These data were obtained by interpolation from the curves given in the figure, and refer to the percentage conversions of the esters into the corresponding *N*-cyclohexyl amides after 100 and 200 hours at 25°. The effect of the α-substituent on the reactivity of the ethyl esters is given by the series:



$$\mathrm{H{-}CH_2COOEt} < \mathrm{C_6H_5{-}CH_2COOEt} < \begin{matrix}\mathrm{CH_3}\\ \mathrm{HO}\end{matrix}\!>\!\mathrm{CHCOOEt} < \mathrm{H_5C_2OOC{-}CH_2COOEt}.$$

This order also holds qualitatively for these same esters in so far as their susceptibility to hydrolysis[6] and to ammonolysis[3] is concerned. These findings lend additional weight to our contention that reactions of hydrolysis, ammonolysis, and aminolysis are all similar in character and may be considered broadly as "solvolytic" reactions.

Furthermore, just as reactions of ammonolysis and hydrolysis are catalyzed by the ammonium and hydronium ions, respectively, so solvolytic reactions in cyclohexylamine are catalyzed by the corresponding "onium" ion, the $C_6H_{11}NH_2 \cdot H^+$ ion, furnished by the cyclohexylammonium salt. It is evident that the mechanism which accounts for the catalytic effect of acids upon the rate of hydrolysis of esters may be applied also to ammonolytic and aminolytic reactions. That the catalytic effect is one which may be ascribed to the solvated proton, the $C_6H_{11}NH_2 \cdot H^+$ ion, is apparent from the fact that both the nitrate and iodide exert approximately the same catalytic effect in equimolar concentrations (see curves 3B and 3C in figure).

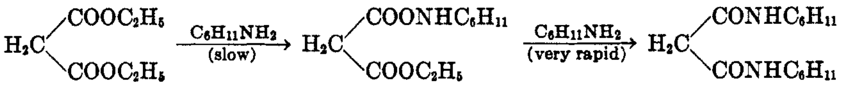
TABLE III

PREPARATION OF SOME *N*-CYCLOHEXYL AMIDES

| FORMULA | MELTING POINT (UNCORR.), °C. | N ANAL. | | SOLUBILITIES* |
|---|---|---|---|---|
| | | Calc'd | Found | |
| 1. $CH_2(CONHC_6H_{11})_2$ | 175 | 10.52 | 10.45 | Insol. $H_2O$; sol. $C_2H_5OH$ |
| 2. $C_6H_5CH_2CONHC_6H_{11}$ | 134 | 6.44 | 6.51 | Insol. $H_2O$; sol. $C_2H_5OH$ |
| 3. $CH_3CHOHCONHC_6H_{11}$ | 59 | 8.17 | 8.33 | Sol. $H_2O$; sol. $C_2H_5OH$ |

* 1 and 2 were recrystallized from alcohol-water, and 3 from acetone by cooling to −30°.

In the case of ethyl malonate the plotted data (see curves 4A and 4B in figure) are based upon the assumption that the amount of amine used up corresponds to the formation of the *N*,*N'*-dicyclohexylmalonamide. The reaction obviously goes through an intermediate stage, involving only partial aminolysis:



$$H_2C\begin{smallmatrix}COOC_2H_5\\COOC_2H_5\end{smallmatrix} \xrightarrow[\text{(slow)}]{C_6H_{11}NH_2} H_2C\begin{smallmatrix}COONHC_6H_{11}\\COOC_2H_5\end{smallmatrix} \xrightarrow[\text{(very rapid)}]{C_6H_{11}NH_2} H_2C\begin{smallmatrix}CONHC_6H_{11}\\CONHC_6H_{11}\end{smallmatrix}$$

Presumably, the circumstances here are similar to those observed in the reaction between liquid ammonia and ethyl malonate.[3] The intermediate compound is very rapidly converted into the completely solvolyzed product, and its concentration in solution is never very great. It may, therefore, be assumed that the first step is relatively slow and that this initial solvolytic action determines the speed of the reaction. The designation of the $C_2H_5OOC$— grouping in the α position as having the greatest effect upon the rate of aminolysis is based upon the overall reaction.

It should be emphasized that the preliminary observations reported in this paper indicate that the concept of "onium" ion catalysis is one which should be of real value in synthetic organic chemistry. In the present case, it has been shown that

---

[6] OLSON, *Z. physik. Chem.*, **133**, 233 (1928).

the yields of *N*-cyclohexyl amides over comparable time periods are increased markedly by adding a relatively small quantity of cyclohexylammonium salt to the reaction mixture. The *N*-cyclohexyl amides of lactic, phenylacetic, and malonic acids were prepared in quantity using this method. Analytical data, solubilities, and melting points are recorded in Table III.

## SUMMARY

The reactions between the ethyl esters of acetic, phenylacetic, lactic, and malonic acids, respectively, and cyclohexylamine, leading to the formation of the corresponding *N*-cyclohexyl amides, are catalyzed by the addition of cyclohexylammonium salts. These findings have been interpreted as examples of acid catalysis in an amine.