

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

THE RATES OF THE HYDROLYSIS TO BETAINES OF SOME QUATERNARY BASES OF ALPHA-AMINONITRILES. A STUDY OF QUATERNARY AMMONIUM BASES

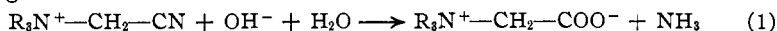
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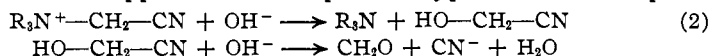
Introduction

A. Klages and S. Margolinsky¹ reported the preparation of betaines through the reaction



The hydrolysis takes place rapidly in dilute alkali, without appreciable side reactions, so a study of the kinetics of the reaction has been undertaken in an attempt to determine, first, the nature of the rate-determining step, and, second, what connection, if any, exists between this reaction and quaternary ammonium base decomposition.

Since these are quaternary ammonium compounds it would not have been surprising to find an appreciable decomposition typical of such compounds



The only evidence we have observed of the formation of a tertiary amine is in the case of the acetone derivative, $[(CH_3)_3N-C(CH_3)_2CN]^+OH^-$, which yields easily detectable amounts of trimethylamine during the betaine formation.² The question arises as to whether this lack of quaternary decomposition is due to a fundamental stability of these quaternary ammonium hydroxides, or to the existence of the faster reaction of betaine formation. In the latter case the same factors which affect quaternary ion decomposition might also affect betaine formation, and point to a common initial step in the reaction mechanisms.

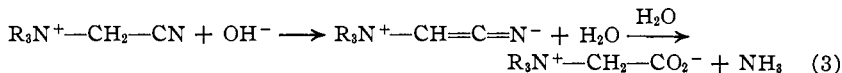
According to Stewart and Aston³ the position and intensity of charge on a quaternary ammonium ion affect the ease of activation of the bonds concerned in its decomposition and hence affect the rate of the reaction. A decrease in the intensity of the charge by means of solvation, conjugation with neighboring atoms, or association with negative ions would hinder the reaction. The fact that in water solution only strongly basic negative ions bring about quaternary decomposition indicates that the point of attack is a hydrogen atom, presumably upon either the α or β position to the nitrogen. The cyanide group might well have contributed to the ease of quaternary decomposition through its influence upon the

¹ Klages and Margolinsky, *Ber.*, **36**, 4189 (1903).

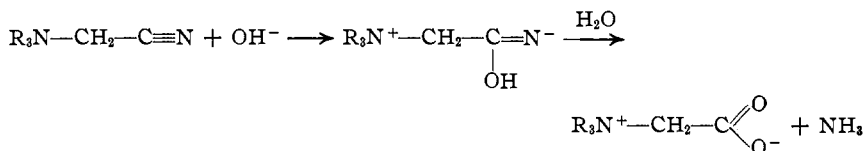
² The betaines yield trimethylamine with concentrated hot sodium hydroxide, but do not decompose detectably under the conditions of this nitrile hydrolysis.

³ Stewart and Aston, *THIS JOURNAL*, **49**, 1718 (1927).

reactivity of the hydrogen atom adjacent to it. We shall then presume that the initial step in the present case is the same as that in quaternary ammonium ion decomposition, namely, loss of hydrogen ion, but that the following reaction involves the cyanide instead of the ammonium radical



Without this alternative reaction the hypothetical intermediate would have rapidly undergone quaternary decomposition. A second path for the reaction, likewise fostered by the positive charge, would be the direct addition of the hydroxyl ion to the cyanide triple bond



According to either of the above mechanisms, the rate determining step might involve either (1) quaternary and hydroxide ions each to the first power or (2) an activation step of the quaternary ion alone. Neither of these assumptions seems justified from a simple analysis of the reaction kinetics. Other ions, particularly negative ions, could be expected to exert a strong influence upon the reaction rate.

The Specific Reaction Rate Law.—In each of the experiments made the total ionic strength of the solutions was high, and for purposes of comparison the effect of changing ionic strength, as such, has been disregarded. The reactants are considered to be completely ionized, so that uncorrected formula concentrations by volume of the ions have been used. The remarkable insensitivity of our rate law to changes in concentration, temperature and the presence of inert salts demands this simple treatment as a first approximation.

The quaternary nitrile ion will be represented by A , hydroxide ion by B and ammonia by x . Assuming the concentration of the water constant, the general rate expression for the hydrolysis reaction represented by equation (1) may be written

$$\frac{dx}{dt} = K(A - x)^n(B - x)^m \quad (I)$$

in which $(A - x)$ and $(B - x)$ are the concentrations of the reactants at any time, derived from the corresponding initial concentrations, (A) and (B) . By keeping B in large excess it may be considered constant, and the best value of n may then be obtained by plotting $(1/A - x)^{n-1}$ against the corresponding values of t , using various values of n until a straight line may be drawn through the points. The value of m could similarly be obtained when A is in large and constant excess.

The Reaction in Excess Hydroxide Ion and Varying Iodide Ion.⁴—
Table I gives the initial and final conditions of a number of experiments;

TABLE I

EXPERIMENTAL CONDITIONS FOR THE HYDROLYSIS IN EXCESS HYDROXIDE ION B, AND VARYING IODIDE ION, OF DIETHYLMETHYLAMMONIUM ACETONITRILE ION, A. TEMP., 35°

Expt.	Concn. of A		Concn. of B		Other concentrations			Elapsed time, min.
	Initial	Final	Initial	Final	Na ⁺	I ⁻	K ⁺	
28	0.0990	0.0099	0.5000	0.4110	0.5000	0.0990	...	74.5
34	.1019	.0125	.5000	.4106	.5000	0.5084	0.4065	103.8
33	.1020	.0130	.5000	.4110	.5000	1.000	.898	128.0
37	.1024	.0034	.6000	.5010	.600	0.4024	.300	102.0
31	.1003	.0065	.950	.8562	.950	.980	.880	57.6

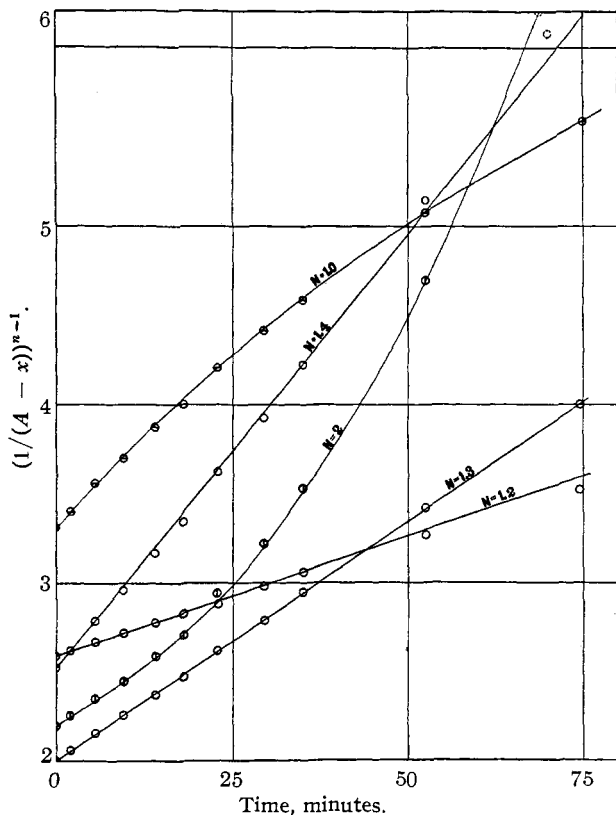


Fig. 1.—Plot of $(1/(A-x))^{n-1}$ against time in minutes for Expt. 28.

⁴ Only a few experiments are included here. In others the analytical work was not as accurate or the reaction was not carried near enough to completion. In every case the results were consistent with these subsequent experiments.

Figs. 1 and 2 give the corresponding plots of $(1/(A - x))^{n-1}$. All concentrations are in moles per liter of solution.

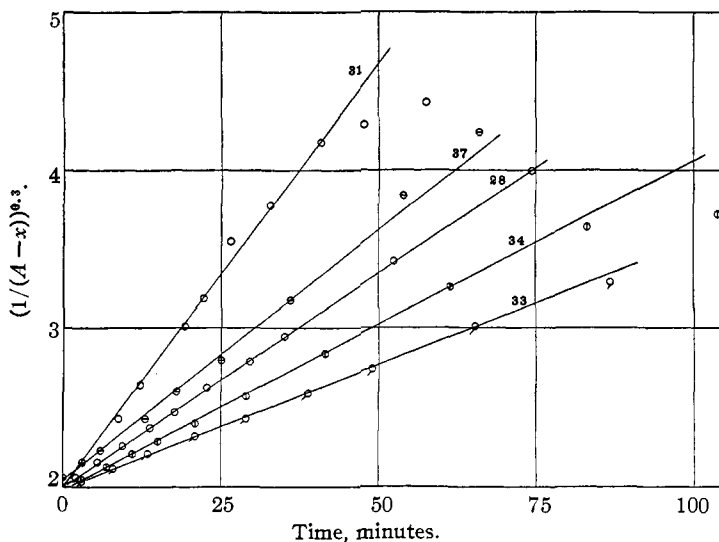


Fig. 2.—Plot of $(1/(A - x))^{n-1}$ when $n = 1.3$, against time.

It is seen from the plots that with a five to ten-fold excess of hydroxide ion, the rate of betaine formation is proportional to neither a first nor second power of the ammonium nitrile ion concentration, but is between the two. When n is about 1.3, a very good straight line is obtained in the plots for 80% or better of the total reaction during which the concentration of A changes five-fold. This power law ($n = 1.2$ to 1.4) holds over the following variations of the experimental conditions: (1) addition of betaine or ammonia, or both; (2) addition of potassium iodide, potassium chloride, potassium perchlorate, lithium chloride, potassium sulfate, potassium nitrite and potassium carbonate, from $0.1 M$ to $5 M$; (3) variation of temperature over a range of 100° ; (4) variation of proportional excess of hydroxide ion; (5) removal of ions other than A and B ; (6) use of homologs varying the substituents on the nitrogen and substituting methyl for hydrogen on the carbon.

This fractional power naturally suggests a combination of first and second order reactions, but all attempts to approximate these extremes throughout application of the above variables have failed. Analytical difficulties have not permitted measurements at concentrations of the nitrile below 0.01 molal, in which range some other exponent or rate law may serve.

No attempt will be made in this paper to give physical significance to this fractional exponent. Its use gives a means of comparing one experiment with another and of ascertaining the effect upon the specific reaction

rate of changing conditions. Taking the value 1.3 for n in all experiments where hydroxyl ion is in excess, we may use the slope of the plot of $(1/(A - x))^{n-1}$ against time as the specific reaction rate when the concentration of A is the sole variable, and compare the effect of changing salt and hydroxyl-ion concentrations. The results are given in Table II.

TABLE II
RATES OF THE REACTIONS TAKEN FROM TABLE I AND FIG. 2 WHEN $n = 1.3$;
TEMPERATURE, 35°

Expt.	A (Initial)	Concentration B (Average)	Na ⁺ + K ⁺	I ⁻	Slope (K_s)	$\frac{K_s}{B}$
28	0.0990	0.455	0.5000	0.0990	0.0269	0.0591
34	.1019	.455	.9064	.5084	.0202	.0444
33	.1020	.455	1.398	1.000	.0157	.0345
37	.1024	.550	0.900	0.4024	.0315	.0573
31	.1003	.903	1.830	.980	.0540	.0598

It is seen that the specific reaction rate decreases with increasing iodide (Expt. 28, 34, 33) and is not proportional to the first power of the hydroxide-ion concentrations (Expt. 33, 31). It would thus appear that the exponent m in Equation I is also greater than unity.

The Effect of the Products Formed upon the Reaction.—Ammonia alone produces too slow a reaction to be readily measured. Ammonia (0.0926 N) in strong base (0.500 N) gave for the same fractional exponent for $(A - x)$, the same slope (K_s) throughout as for a comparative reaction without ammonia present. Similarly the presence of 0.102 N ammonia together with 0.102 N betaine in one of two parallel experiments caused no perceptible difference in the rate.

The Reaction in Excess Quaternary Ammonium Ion.—Under these conditions the concentration of A (Equation I) is constant and that of B variable. Plotting $(1/(B - x))^{m-1}$ against time as before no straight line corresponding to values of m between one and two could be found. The closest approach to a straight line was given by a value of 1.6 for m , which agrees closely with the value of 1.84 taken from Expts. 31 and 33, Table II. In the latter case a correction for the effect of the difference in the iodide ion concentrations would lower the value of m . It is believed that the salt effect in these experiments takes the form of a ratio of the reacting ion to the sum of all ions of the same sign (a mole fraction) and this ratio changes markedly in these experiments during the progress of the reaction. In the case of excess hydroxide ion this ratio is nearly constant. An analysis of these and other data from this standpoint will be presented in another paper.

The Reaction in Equal Concentrations of the Reactants. The Effect of Temperature.—When (A) and (B) (Equation I) are equal the values of $(1/(A - x))^{n+m-1}$ plotted against time should lie on a straight line for the

correct values of m and n . This is true for 80% of the reaction when $m + n$ is taken as 2.4 (Fig. 3), and regardless of the presence or absence of sodium and iodide ions. Solutions made up from the quaternary iodide salt and silver oxide conformed to the same rate law (same exponent) as those made up of the quaternary iodide and sodium hydroxide. The reaction was slower in the presence of the iodide. A series of solutions about 0.1 M each in the quaternary iodide and sodium hydroxide was subjected to temperatures from 25 to 115°. There was no apparent change in the best value of $m + n$ (2.4). When the logarithm of the slope taken from each plot was plotted (Fig. 4) against the reciprocal of the temperature, a straight line was obtained, indicating that the heat of activation was constant over this range of temperature.

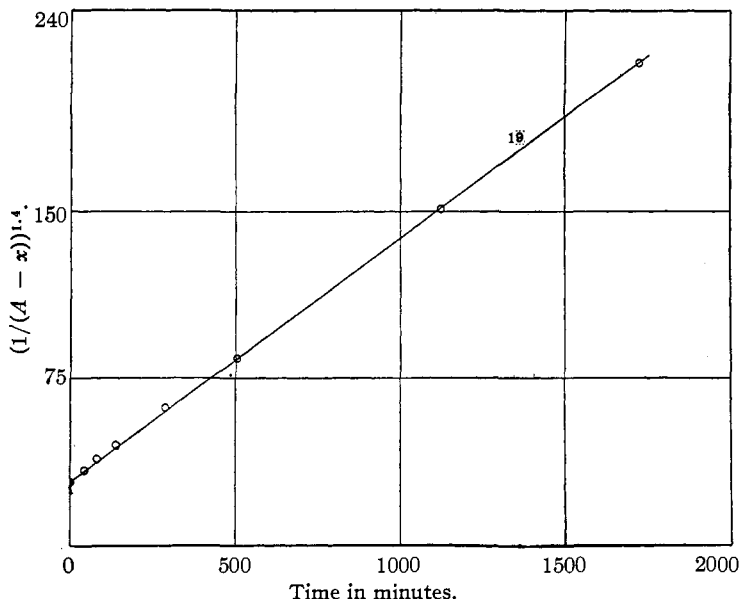


Fig. 3.—The reaction when (A) and (B) are equal (Expt. 19), plotting $(1/(A-x))^{n+m-1}$ against time, with $n + m$ equal to 2.4.

Table III summarizes the data. The final times and concentrations are given, but in the actual plotting to obtain the slopes (K_s) these last points received little weight because of the error in assuming $(A-x)$ equal to $(B-x)$ at all times. Actually even these points fell very close to the ruled line, with most of the points directly on the line. Reproducibility is indicated by the Experiments 23 and 24. A numerical average of the two concentrations was used.

The heat of activation, as calculated from the plot by the usual formula, is 13,000 calories.

TABLE III

RATES OF THE REACTION OF DIETHYLMETHYLAMMONIUMACETONITRILE ION WITH HYDROXIDE ION IN EQUAL AMOUNT, AT VARIOUS TEMPERATURES, ASSUMING $m + n = 2.4$

Expt.	Concentration		B (Initial)	Na ⁺	I ⁻	Time, min.	Temp., °C.	K _s
	A (Initial)	A (Final)						
18	0.0910	0.0258	0.0895	0.0985	0.1000	2670	25	0.0575
19	.0918	.0225	.0898	.0985	.1000	1728	35	.110
20	.0911	.0158	.0891	.0985	.1005	1612	45	.212
21	.0822	.0109	.0815	.0985	.0992	345	75	1.34
22	.0903	.0080	.0882	.0985	.1006	1751	60	0.528
23	.0798	.0119	.0781	.0985	.1002	180	90	2.67
24	.0845	.0104	.0828	.0985	.1002	201	90	2.65
25	.0825	.0082	.0805	.0985	.1005	198	100	4.63
26	.0666	.0065	.0645	.0985	.1006	135	115	11.3

Whereas no physical interpretation can be given this heat of activation, it is apparent that this exponential rate law represents some very simple process rather than a summation of several rate-determining steps, as otherwise either the law itself would probably fail to hold with change of temperature or the apparent heat of activation would have changed.

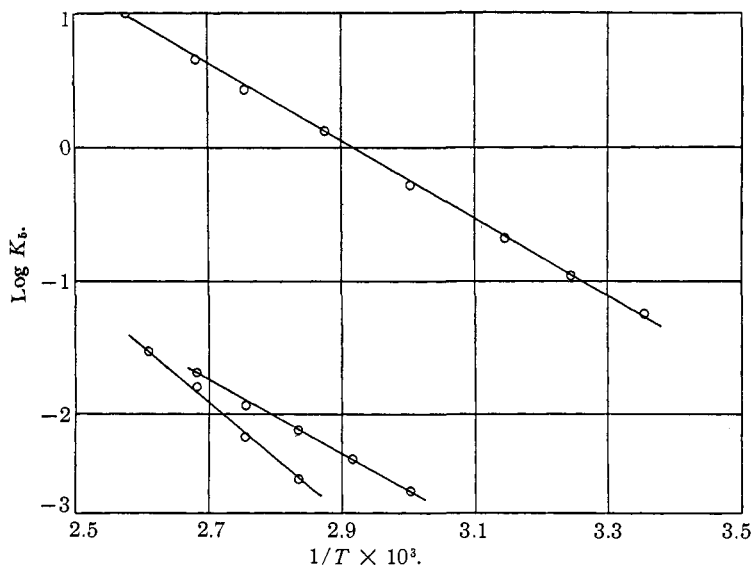


Fig. 4.—The change in reaction rate with the temperature. Upper curve, acetoneitrile derivative; middle curve, propionitrile derivative; lower curve, isobutyronitrile derivative.

If the best value of n is 1.3 and the best value of m about 1.8 when B is in excess, but the best value of $m + n$ when the hydroxyl-ion concentration is equal to that of the quaternary ion is 2.4, the values of both m and n cannot be constant, except under the restricted conditions of one

experiment. Therefore this fractional power has no real physical significance but is simply a close approximation to, but not an equivalent of, the real rate law.

The Effect of the Removal of All Negative Ions except Hydroxide Ion.—Two experiments were made at 17.3° in which the solutions were prepared by adding silver oxide in slight excess to an aqueous solution of the iodide, and filtering off the silver iodide. In each case some silver was left in solution, partially due to ammonia formed. In one experiment excess potassium hydroxide was added to this solution. Table IV describes the conditions and results.

TABLE IV

RATES OF HYDROLYSIS OF DIETHYLMETHYLAMMONIUMACETONITRILE HYDROXIDE IN THE ABSENCE OF IODIDE ION

Temp., 17.3°; K_s taken from plots of $(1/(A - x))^{1.4}$ and $(1/(A - x))^{0.3}$ against time in Experiments 11 and 14, respectively.

Expt.	Concentration		B (Initial)	Ag ⁺	K ⁺	Time, min.	K_s
	A (Initial)	A (Final)					
11	0.2011	0.0270	0.2175	0.016	...	6157	0.0342
14	.1842	.0289	.5605	.036	0.340	210	.0060

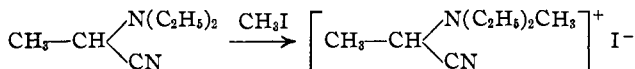
In the absence of iodide ion just as good plots were obtained as in its presence, using the same fractional power law, showing that the nature of the exponent is not affected by other electrolytes. Since the temperature is different⁵ and the temperature coefficient in the absence of iodide ion has not been determined, the effect of iodide ion upon the rate has not been calculated. The salt effect is being studied in more detail. A rough comparison of these experiments with Experiments 19 and 28 indicates that the effect of a given concentration of iodide ion (0.1 *M*) depends upon the hydroxide-ion concentration, being relatively less when the latter is in excess. These two experiments may be used to determine the rate law with respect to hydroxide ion in the absence of iodide ion. The reaction rate in each case was taken graphically at the point where the concentration of the positive ion was 0.05 *M* and those of hydroxide ion were 0.0639 *M* and 0.4230 *M*, respectively. The specific rates were 1.96×10^{-5} and 4×10^{-4} , respectively, in corresponding units. Assuming the same exponent for *A* in the two cases, the exponent *m* for hydroxide ion is 1.6, in good agreement with the exponent found in the presence of high concentrations of iodide ion.

The conclusion is drawn that the fractional exponent is due to some property of the reacting system, and that the actual reaction rate, but not the rate law, is affected by other electrolytes present.

The Effect of the Substitution of Methyl Groups for Hydrogens in Trialkylammoniumacetoneitrile Ion.—The theory presented in the

⁵ Other experiments at the same temperature were made earlier, but the analyses were not as accurate.

introduction involved the hydrogens near the ammonium radical. Therefore the effect on the rate and on the form of the rate law of substitution of these hydrogens by carbon groups was studied. One methyl was introduced by means of starting with the acetaldehyde derivative.



This quaternary compound reacted so slowly that the temperature range used was from 60 to 120°. Table V gives the experimental conditions and results.

TABLE V

RATES OF THE REACTION OF α -DIETHYLMETHYLAMMONIUMPROPIONITRILE ION (A') WITH HYDROXIDE ION (B)

$n = 1.3$. K_s corrected to B = 0.95 M, assuming $m = 1.8$

Expt.	A' (Initial)	Concentrations A' (Final)	B (Average)	Na ⁺	I ⁻	Time, min.	Temp., °C.	K_s (corr.)
5A	0.0925	0.0070	0.866	0.913	0.100	641	70	0.00450
6A	.0869	.0118	.869	.913	.100	282	80	.00749
7A	.0417	.0098	.883	.913	.050	155	80	.0106
8A	.0872	.0160	.871	.913	.100	146	90	.0115
9A	.0716	.0043	.952	1.000	.100	151	100	.0198
10A	.0901	.0054	.953	1.000	.099	1687	60	.00260

In the plots of $(1/A' - x)^{0.3}$ against time, the eight or ten points fell on the ruled line well within experimental error, except in Experiment 10A, in which the excessive time required probably allowed a reaction with the glass bombs. In this case only the first six points were used, involving about 75% of the total reaction. In Fig. 4, K_s is plotted against $1/T_{\text{Abs}}$ as before. The calculated activation energy is 12,650 calories, or the same within experimental error as for the unsubstituted derivative.

An experiment was made in which the concentrations of reactants were equal, and, as before, the value of $m + n$ of 2.4 gave a straight line plot.

The amino nitrile from acetone yielded diethylmethylammonium-isobutyronitrile ion. Table VI describes the experiments and results using this substance.

TABLE VI

EXPERIMENTS WITH THE ISOBUTYRONITRILE DERIVATIVE, A'', WITH K_s TAKEN FROM PLOTS WITH $n = 1.4$

Expt.	A'' (Initial)	Concentrations A'' (Final)	B (Average)	Na ⁺	I ⁻	Time, min.	Temp., °C.	K_s
1B	0.0387	0.0113	0.983	1.000	0.0453	164	100	0.0158
2B	.0354	.0062	.984	1.000	.0395	1245	80	.00320
3B	.0403	.0100	.983	1.000	.0453	447	90	.00672
4B	.0381	.0131	.984	1.000	.0453	75	110	.0306

Each of these experiments as reported involved five or six samples, the last one of which in each case plotted off the ruled line. Subsequent

samples gave points which deviated widely. Consequently no clear distinction could be drawn between an exponent of 1.3 and 1.4. The latter seemed to yield the better results, and since there was abundant evidence of tertiary amine in the samples taken at higher temperatures, it was concluded that the discrepancy lay in a simultaneous decomposition of the quaternary type, which forbade utilizing much of the possible reaction. Whether this reaction follows the betaine formation or is independent of it is not known, as the amount of the tertiary amine formed was small.

It is interesting to observe that the quaternary amine decomposition is found only in this case, in which both methylene hydrogens are substituted, and that the formal heat of activation (Fig. 4) is much higher (20,500 calories). The fact that the quaternary amine decomposition was greater at the higher temperatures means that the temperature coefficient of that reaction is even greater, and that the two reactions do not have the same rate determining step as postulated in the introduction. It is hoped that some derivatives may be found that yield the two reactions at some reasonable temperature at more nearly the same rate, in order that the rate laws, salt effects and temperature coefficients of both reactions may be compared.

There was no evidence of ethylene formation during any of these experiments, indicating that at the temperatures employed this type of quaternary ion decomposition was very slow compared to the other possible reactions.

The three derivatives then differ in rate and formal activation energy as follows

		E	K_s at 120°
1	$[\text{R}_3\text{N}-\text{CH}_2-\text{CN}]^+$	13,200	14.1
2	$[\text{R}_3\text{N}-\text{CH}(\text{CH}_3)-\text{CN}]^+$	12,600	0.327
3	$[\text{R}_3\text{N}-\text{C}(\text{CH}_3)_2-\text{CN}]^+$	20,500	0.144

The comparison in rate (K_s) above was made with the quaternary ion equal in concentration to the hydroxide ion, each 0.0992 M , with iodide and sodium ions also 0.0992 M and $m + n$ equal to 2.4. It is also interesting to observe that von Peskoff and Meyer⁶ found the activation energy for the alkaline hydrolysis of simple alkyl nitriles to be 19,400 calories, with the kinetics of the reaction a simple second order. From this it would follow that the third compound above corresponds in mechanism closely to simple nitriles, that in the others the rate and activation energy are markedly influenced by the ammonium ion present, and that the transmission of this effect depends upon the presence of hydrogens on the carbon adjacent to the nitrogen.

Cryoscopic Study of the Salt Solutions.—To ascertain that the structures of the compounds used involved no anomalies, the freezing points

⁶ Von Peskoff and Meyer, *Z. physik. Chem.*, **82**, 167 (1913).

of aqueous solutions at concentrations varying from 0.2 *M* to 0.01 *M* were determined, and the apparent degree of ionization calculated, assuming a molecular freezing point lowering of 1.86° for 1000 grams of solvent. Above 0.1 *M* the iodides were between 60 and 70% ionized, and the apparent dissociation increased rapidly upon dilution until at 0.01 *M* it was over 95%.

Experimental Part

Preparation of Materials.—Diethylaminoacetonitrile was prepared by the method of Knoevenagel and Mercklin⁷ from a saturated sodium formaldehyde bisulfite solution, anhydrous diethylamine and a saturated solution of potassium cyanide. The oil which separates was dried with anhydrous potassium carbonate and treated with methyl iodide to form the *methiodide*. The reaction is rapid; the crystals were recrystallized from propyl iodide, yield about 80%.

Diethylaminopropionitrile and Diethylaminoisobutyronitrile (b. p. 730 at 12 mm.) are best made from the cyanhydrins of acetaldehyde and acetone, respectively, and anhydrous diethylamine. In the first case the reaction is rapid, with evolution of heat, and drying with anhydrous sodium sulfate suffices. In the second case the reaction requires several hours at 40 to 50° with lime as a dehydrating agent. In both cases addition of methyl iodide was carried out in bombs at 80° until a solid mass of crystals formed, which were recrystallized from propyl alcohol. Analyses made for both nitrogen and iodine indicated 100% purity.

Procedure.—The solutions for measurement were prepared by dissolving weighed quantities of the salt in a known volume of water and diluting with known base to the desired concentrations. Where the iodide ion was removed, the known salt solutions were treated with the required amount of silver oxide and the silver iodide was filtered off. This left only the two reacting ions in solution.

For the faster reactions the solutions that were to be mixed (the base and the salt solutions) were brought to the temperature of the bath beforehand. The base solution was then poured into the reaction bottle and thoroughly mixed to ensure homogeneity. The bottle was then stoppered. Ten-cc. samples were taken from this at intervals and run into a slight excess of acid which stopped the reaction.

Bombs made from test-tubes were used for the slower reactions and for those at higher temperatures. Various kinds of glass were tried to see whether the surface affected the reaction in any way. It was found necessary to use Pyrex glass at the higher temperatures to reduce the action of the alkali on the glass.

When bombs were used, the stock solutions were mixed without preheating and a 10-cc. sample was placed in each bomb. After sealing, the bombs were placed in a wire basket and completely immersed in the bath. By trial it was found to require about eight minutes for the samples to reach temperature equilibrium. When a bomb was taken out, it was agitated violently in a freezing bath to reduce the reaction to a negligible rate. Time was taken at this point. The bomb was opened and excess acid was run into it to reduce the chance of losing ammonia. The sample was poured into a beaker for titration and the bomb was rinsed with distilled water.

Analytical Method.—The method of Rouchese⁸ was used. The acidified sample taken from the reaction mixture was first neutralized to methyl red. Ten cc. of 20% formaldehyde solution, neutral (to methyl red), was then added, and the mixture titrated with standard sodium hydroxide to phenolphthalein. Small amounts of methyl

⁷ Knoevenagel and Mercklin, *Ber.*, **37**, 4087 (1904).

⁸ A. Rouchese, *J. pharm. chim.*, [6] **25**, 611; *Chem. Abstracts* **1**, 2355 (1907).

red do not obscure the end-point, which can be found to 0.05 cc. of 0.1 *N* alkali in volumes of less than 50 cc. The equivalents of alkali used are equal to the equivalents of ammonia present.

Summary

The alkaline hydrolysis of quaternary ammonium substituted acetonitrile to the betaine cannot be expressed as a simple second order reaction between positive and negative ions. In excess hydroxide ion the rate is proportional to the 1.3 power of the ammonium ion and to the 1.6 to 1.8 power of the hydroxide ion. When in equal concentrations the sum of the necessary exponents is about 2.4. These facts are unchanged by changes in salt concentration, temperature and in the homolog used, and should furnish a useful system for the study of electrolyte solutions.

The effect upon nitrile hydrolysis of the presence of the ammonium group has been studied, together with the effect of alkyl substitutions.

BERKELEY, CALIFORNIA

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF THE
PUNJAB]

STUDIES IN CHEMOTHERAPY: ATTEMPTS TO FIND ANTIMALARIALS. II. PYRRYL INDOLES

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The most prolific method for the synthesis of indoles has been the well-known Fischer reaction¹ but the exact mechanism of this excellent reaction is still uncertain. However, the application of this method to the aliphatic and aromatic ketones has resulted in the synthesis of a large class of indoles mostly substituted in the α -position. This explanatory piece of research was undertaken with a view to ascertain whether pyrrolyl methyl ketones would respond to the Fischer reaction and yield α -pyrrolyl indoles (III) and also to decide if possible between the rival theories of the reaction. These α -pyrrolyl indoles are likely antimalarials because of their analogy to harmine; moreover, the pyrrole nucleus might endow a certain amount of local anesthetic property to the compounds because of the partial resemblance to the tropine structure.²

The only heterocyclic ketone which hitherto has been found to give the Fischer reaction is 2-thionyl methyl ketone.³ Tetrahydroquinolone,⁴ also has been converted into an indole.

¹ Fischer, *Ber.*, **16**, 2245 (1883).

² Blicke and Blake, *THIS JOURNAL*, **53**, 1015 (1931).

³ Brunck, *Ann.*, **272**, 201-208 (1893).

⁴ Clemo and Perkin, *J. Chem. Soc.*, **125**, 1612 (1924).