As a result of this and of the work already cited we believe that small amounts of highly unsaturated fatty acids occur quite generally in animal fats.

Summary

1. Several animal fats and oils have been examined chemically for the presence of highly unsaturated fatty acids.

2. Linolenic acid was definitely indicated in two specimens of goose oil; it probably occurred along with highly unsaturated acids in another specimen of goose oil and in one of turkey oil.

3. Eight other specimens of avian oils were shown to contain 0.21 to 1.16% of highly unsaturated acid which was mostly arachidonic.

4. The four specimens of animal fats contained traces of highly unsaturated acids other than arachidonic.

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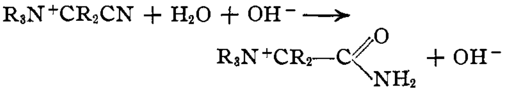
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

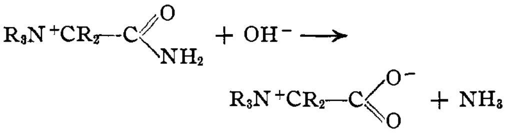
The Kinetics of the Alkaline Hydrolysis of the Betaine Amides

BY DANIEL B. LUTEN, JR., AND T. D. STEWART

In a recent paper Stewart and Korpi[1] reported the results of a study of the rates of hydrolysis to betaines of the corresponding betaine nitriles. The reaction proceeds according to the equations



$$R_3N^+CR_2CN + H_2O + OH^- \longrightarrow R_3N^+CR_2{-}C\begin{smallmatrix}\nearrow O\\ \searrow NH_2\end{smallmatrix} + OH^- \quad (1)$$



$$R_3N^+CR_2{-}C\begin{smallmatrix}\nearrow O\\ \searrow NH_2\end{smallmatrix} + OH^- \longrightarrow R_3N^+CR_2{-}C\begin{smallmatrix}\nearrow O^-\\ \searrow O\end{smallmatrix} + NH_3 \quad (2)$$

They assumed that in this case, as in the case of the ordinary aliphatic nitriles, the first of these steps is the slower so that it alone was being measured. They found that the rates were describable by differential equations involving fractional exponents, but which could not be derived from a reasonable mechanism for the reaction.

It has now been found for these betaine derivatives that, of the two steps in the hydrolysis, the first is actually much the faster. This paper presents the evidence for this statement and gives additional kinetic data which are relevant to the mechanism of Reaction (2) above. The description of most of the compounds used and the determination of their reactivities will be deferred to a later paper.

The First Step in the Hydrolysis, Nitrile to Amide.—The evidence proving that the reaction proceeds in two stages, of which the first is much the faster and has for its product the amide, may be summarized as follows

(1) In very dilute alkali the nitrile reacts with water to form a compound which gives the correct elementary analysis for the amide, has the same melting point as the amide prepared by an independent method, and whose melting point, when mixed with the independently prepared amide, suffers no depression.

(2) The product of the reaction of the nitrile in very dilute alkali is a solution which has the same refractive index as has a solution of the amide and alkali in the same concentrations, respectively.

(3) The independently prepared amide hydrolyzes to give ammonia at the same rate as the nitrile.

Experimental

(1) **Preparation of Betaine Amides.**—Iodoacetamide was prepared as described by von Braun[2] and with it trimethylamine and triethylamine were quaternized.

Anal. Calcd. for $C_5H_{13}ON_2I$: I, 52.01. Found: I, 51.80, 51.79. Calcd. for $C_8H_{19}ON_2I$: I, 44.37. Found: I, 43.98, 44.09.

For the trimethylbetaine amide iodide, the observed m. p. was 196°; the value in the literature[3] is 191°. For the triethyl derivative the observed m. p. was 155°, the value in the literature[3] is 150.5–152.5°.[4]

A substance having the same characteristics as the first

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(1) Stewart and Korpi, THIS JOURNAL, **54**, 3977 (1932).

(2) J. von Braun, *Ber.*, **41**, 2144 (1908).

(3) A. G. F. A. German Patent 292,545; *Chem. Zentr.*, 11, 207 (1916).

(4) These derivatives and nearly all the others considered in this work decompose at or near the melting point. If the melting points are determined in the usual manner, the results obtained are dependent upon the time required for heating. Reasonably reproducible results were obtained only by making very rapid determinations, the sample being heated at the rate of fifteen degrees per minute until near the melting point and then at ten degrees per minute until fusion took place. As a check on all values, the melting point of $(C_2H_5)_2(CH_3)N^+CH_2CNI^-$ was always determined simultaneously. The values obtained are reproducible to within two or three degrees.

of the above amides was prepared from the corresponding nitrile. A weighed amount of the nitrile dissolved in barium hydroxide solution was allowed to react for ten or twelve times the half-life of the reaction. The half-life was determined by observing the change in refractive index of the reacting solution. At the end of this time the solution was neutralized with sulfuric acid, the barium sulfate filtered off, and the water evaporated on the steam-bath. The residue was a yellow sirup which crystallized on cooling and stirring. The yield of the crude product corresponded closely to the theoretical yield for the amide. It was recrystallized from propyl alcohol and analyzed for iodide ion. The same procedure was followed for two other derivatives. The results are summarized in Table I.

TABLE I

BETAINE AMIDES FROM THE CORRESPONDING NITRILES

	Half-life of reaction, min.	Alkali used, N	Yield, g.		Iodine, %		M. p., °C.	
			Calcd.	Actual	Calcd.	Found	Pure	Mixed
$(CH_3)_3N^+CH_2CNI^-$	7	0.0025	18.29	18.38	52.01	51.73	198–199	196–198
$(C_2H_5)_3N^+CH_2CNI^-$	2.8	.0163	9.57	9.61	44.37	43.94	154–156	154–156
	10	15 (NH_4OH)			44.37	44.23		
$(CH_3)_3N^+C(CH_3)_2CNI^-$	180	0.05	13.61	13.60	46.65	46.52	234–236	

(2) In a Rayleigh liquid interferometer one may determine the difference between the refractive indices of two solutions, the smallest observable difference being about 2×10^{-7} with a Zeiss instrument and 40 mm. chambers. The total contribution of the nitrile to the refractive index of its 0.03 N aqueous solution is $14{,}000 \times 10^{-7}$. The uncertainty in this contribution due to uncertainties in the preparation of the solution is a few tenths of one per cent. The difference in refractive index between a solution 0.03 N in nitrile and 0.0045 N in sodium hydroxide and a solution 0.03 N in amide and 0.0045 N in sodium hydroxide is 1300×10^{-7} before reacting, and only 15×10^{-7} after reacting. This final difference is of the order of magnitude of the experimental error. In the time required for the reaction the refractive index of an alkaline solution of amide changes but very slightly.

(3) The results of rate determinations at 25° upon the nitriles and the corresponding amides prepared from iodoacetamide are given below. The empirical rate expression is

$$d(NH_3)/dt = k'[(RCN_0) - (NH_3)]^{1.3} \qquad (3)$$

where (RCN_0) is 0.1 N and the initial hydroxide-ion concentration is five-fold greater. The value of k' (in presence of 0.9 N potassium iodide to reduce the rates) for $(CH_3)_3N^+CH_2CNI^-$ is 0.0366, and for $(CH_3)_3N^+CH_2CONH_2I^-$ it is 0.0355. For $(C_2H_5)_3N^+CH_2CNI^-$ k' is 0.00312, and for $(C_2H_5)_3N^+CH_2CONH_2I^-$ it is practically the same, 0.00314.

The Hydrolysis of the Amide

The Rate Functions.—In the discussion of the second stage of the reaction, which proceeds according to Equation (2), the concentration of ammonia will be represented by P, the concentration of the amide by A and its initial concentration in any run by A_0; correspondingly, hydroxide-ion concentrations will be represented by B and B_0. In the greater part of the work the analytic methods depended upon the determination of ammonia, as described by Stewart and Korpi,[1] so that $A_0 - P$ is the analytically determined quantity which appears in the rate equations.

In general the data were first organized by means of the empirical equation

$$dP/dt = k(B_0 - P)^m(A_0 - P)^n \qquad (4)$$

where m and n may have any values. From the values of m, n and k, the data may be interpreted in terms of some reasonable mechanism.

A more common method of interpreting such complex data has been to analyze them in terms of equations involving integral exponents only, and then to examine the "drifts," or variations, in the resulting rate constants. In this investigation, however, the variations are so large and are so constant that the former method of analysis is more appropriate. We shall restrict ourselves largely to the discussion of the three special cases where the rate equations involving two reactants are somewhat simplified, *viz.*, when

(a) $B_0 = A_0$ (b) $B_0 \gg A_0$ (c) $A_0 \gg B_0$

Equation (4) may be integrated readily only in these three cases. Any data interpreted in terms of the integral equations are then strictly valid only if the conditions for the cases to which those equations apply are strictly fulfilled. No such restrictions are imposed upon data interpreted by means of the differential equations. In general, if the integral equation is used, then the values of m and n are obtained from a number of experimental points, with some increase in reliability resulting therefrom, but at the same time they are average values for the concentration range involved. That is, if $A_0 - P$ diminishes in a particular run from 0.1 to 0.02, and if the appropriate function of $A_0 - P$ is plotted against time, then there are some ten points from which the best value of n is to be obtained. But if the order varies over this range, the value of n obtained will be a rough average. On the other hand, when the data are interpreted in terms of the differential equations, the values of dP/dt are obtained from a plot of $A_0 - P$ or $B_0 - P$ against time, and only one or two values of dP/dt are used from any one run. One of these values at a time t will be dependent mostly upon the two analytical points nearest to t, and only to a lesser extent on those further away. Consequently such values are less reliable, but are dependent on only a very small range of concentrations.

In case (a) the integral equation is

$$\left[\frac{1}{B_0 - P}\right]^{n+m-1} = k(n + m - 1)t + C \qquad (5)$$

in case (b) the integral equation is

$$\left[\frac{1}{A_0 - P}\right]^{n-1} = k(n - 1)(B_0)^m t + C' \qquad (6)$$

Case (c) is perfectly analogous to (b) and the same treatment was accorded it. n for (b) and $(m + n)$ for (a) were determined graphically from the integral equations. m for (b) was determined by the Ostwald isolation method using the differential equation.

The ion $(CH_3)(C_2H_5)_2N^+CH_2CONH_2$ has been investigated most comprehensively. We may summarize the results as follows: (**1**) in case (a) $(m + n)$ is equal to 2.4 in runs over the range 0.10 N to about 0.02 N. Over the range from 0.3 N to 0.08 N the same quantity is 2.6, while from 0.5 N to 0.2 N it is between 2.8 and 3.0.

In case (b) the value of m is first shown to be independent of B; secondly it is shown to be dependent upon A. (**2**) The first result is obtained from the differential equation and a series of ten runs. In each run A_0 is 0.1 N, and the rate is determined when A_0-P equals 0.08 N and 0.04 N. B_0-P varies from 1.0 N down to 0.04 N. Only the runs in the upper half of the concentration range fall in what is generally considered to be case (b). Since we are using the differential equation, this is of no consequence and the order obtained is valid throughout the whole range. The results are given in Table II and Fig. 1. m is equal to the slope of the curve, being 1.64 when $(A_0 - P)$ equals 0.08 N and 1.57 when $(A_0 - P)$ equals 0.04 N.

TABLE II

VARIATION OF RATE WITH HYDROXIDE ION; $T = 35°$; $(I^-) = 1.0\ N$

Run	Ionic strength	$A_0 - P = 0.080$ $B_0 - P$	$dP/dt \times 10^3$	$A_0 - P = 0.040$ $B_0 - P$	$dP/dt \times 10^3$	n
100	2.000	0.980	6.36	0.940	2.88	1.05
99	1.900	.880	5.33	.840	2.33	1.09
98	1.800	.780	4.16	.740	2.01	(0.92)
97	1.700	.680	3.40	.640	1.53	(1.01)
96	1.600	.580	2.76	.540	1.154	1.09
60	1.500	.480	1.98	.440	0.821	1.07
120	1.400	.380	1.45	.340	.573	1.08
121	1.306	.286	0.833	.246	.343	[a]
122	1.200	.180	.392	.140	.130	[a]
20	1.100	.079	.102	.039	.0192	[a]
						1.08

[a] These values of n are not relevant to case (b).

(**3**) m was shown to be dependent upon A by making two series of runs with B_0 equal to 0.5 N in one series and 1.0 N in the other, while A_0 decreases in the same manner through both series.

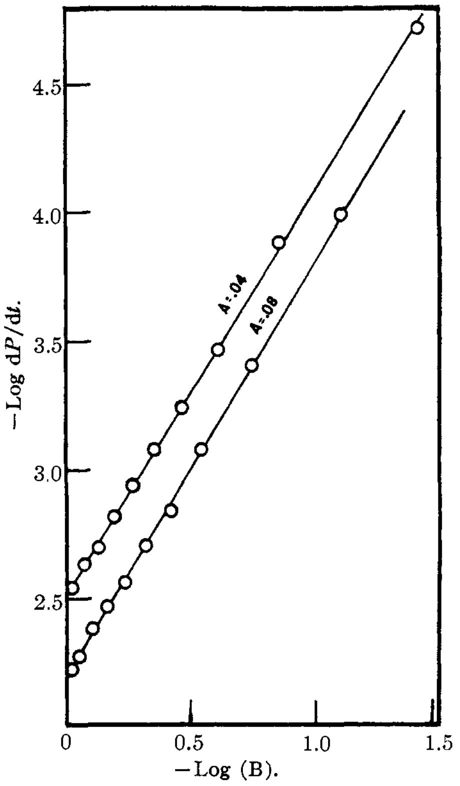

Fig. 1.

By determining the influence of the change in B_0 upon either the rates or the slope constants[5] the order of B over the range of concentration could be determined, as is shown in Table III.

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(5) The slope constant is the product of all the terms which do not vary in a particular run, in this case, $k_s = k(B_0)^m(n - 1)$.

TABLE III

INFLUENCE OF AMIDE CONCENTRATION UPON m IN $(CH_3)(C_2H_5)_2N^+CH_2CONH_2$

Run	Ionic strength	$B_0 - P$	$A_0 - P$	$dP/dt \times 10^4$	Ratio	m	Temp., °C.
111	1.10	0.08	0.48	5.55	2.72	1.45	35 from a run in case (c)
111		.04	.44	1.87			
	2.0 to 1.5	.98 to 0.48	.08			1.64	35 from Table II
	2.0 to 1.5	.94 to .44	.04			1.57	25 from Table II
506	1.02	1.00	.025	17.4	2.63	1.40	25
505	0.52	0.50	.025	6.61			25
511	1.00	1.00	.005	3.70			25
509	1.00	1.00	.005	3.99	2.48	1.31	25
510	0.50	0.50	.005	1.55			25

The value of m falls as A_0 diminishes, becoming 1.3 when A_0 is 0.005 N.

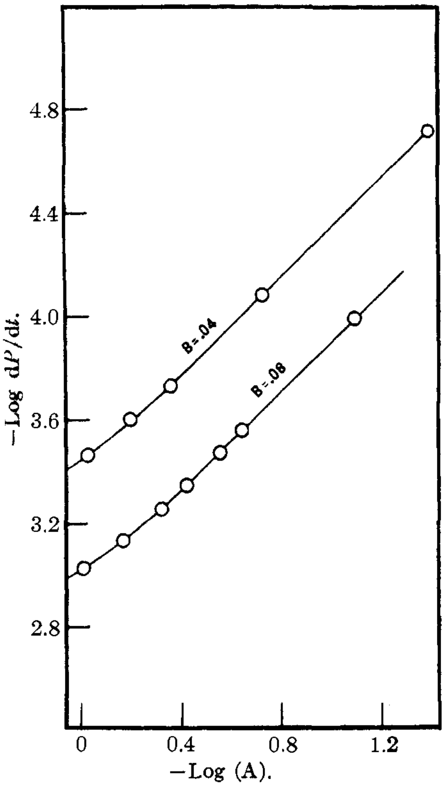

Fig. 2.

(4) At the same time that this latter phenomenon is observed, the value of n also falls, diminishing from a highest value of about 1.10, when A_0 is equal to 0.1 N, to 1.0 when A_0 is less than 0.025 N. In the last column of Table II n is calculated for each run from the values of dA/dt given and the value of m obtained. If the values of n were determined only by means of the integral equation, they would be equal to 1.3 at the highest values of A_0. However, when A_0 is that large the conditions of case (b) are not strictly fulfilled, that is, B_0 is not so much greater than A_0 that it may be considered as a constant. Correcting for this effect, we obtain the results given above.

(5) In case (c) n was determined in precisely the same manner as were the two highest values of m in (b). When (B_0-P) equals either 0.08 N or 0.04 N, n is 0.96 over the range of A_0-P from 0.04 up to 0.5 N. As A_0-P increases further to 1.0 N, n diminishes to about 0.8. This is shown in Table IV and Fig. 2.

TABLE IV

VARIATION OF RATE WITH AMIDE CONCENTRATION, WHEN T = 35°, (I^-) = 1.0 N, IONIC STRENGTH = 1.100

	$B_0 - P$ = 0.080		$B_0 - P$ = 0.040		
Run	$A_0 - P$	$dP/dt \times 10^3$	$A_0 - P$	$dP/dt \times 10^3$	m
116	0.980	0.944	0.940	0.343	1.42
113	.678	.736	.638	.250	1.48
111	.480	.555	.440	.187	1.45
117	.380	.451			
118	.280	.337			
115	.229	.276	.189	.0828	
20	.081	.102	.041	.0192	
					1.45

(6) n, determined from the integral equations, is 1.5 or 1.6 when B_0-P is between 0.1 and 0.02 N. The correct value of m, obtained as n was in case (b), is 1.45. The last column of Table IV gives m for the case (c) runs.

For other derivatives case (c) has not been investigated, and $(m + n)$ has been determined in case (a) only at the lower concentrations. For three other ions of the type $R_3N^+CH_2CONH_2$ $(m + n)$ equals 2.4 as it does with the methyl diethyl derivative.

In case (b) we find for $(CH_3)_3N^+CH_2CONH_2$ a value for m of 1.7 under the conditions where m was 1.6 for the methyl diethyl amide. As A_0 is diminished m again becomes smaller, reaching a value of 1.0 when A_0 equals 0.0025 N, as can be seen from Table V.

The best value of n from the differential equation for this ion is 1.0. The results for other ions

TABLE V

INFLUENCE OF AMIDE CONCENTRATION UPON m IN $(CH_3)_3N^+CH_2CONH_2$ AT 25°

Run	Ionic strength	$B_0 - P$	$A_0 - P$	$dP/dt \times 10^4$	Ratio	m
204	1.50	0.46	0.06	31.0		1.7
207	1.10	.06	.06	1.02		
504	1.02	1.0	.025	55	2.44	
501	0.52	0.5	.025	22.5		1.26
169	1.02	1.0	.025	54.3	2.35	
168	0.52	0.5	.025	23.1		
508	1.00	1.0	.005	10.8	2.23	1.16
507	0.50	0.5	.005	4.85		
	(1.0	1.0	.0025	5.4)	1.94	0.96
514	0.50	0.5	.0025	2.78		

when A_0 is 0.1 N are given in Table VI. There is a rough but persistent correlation between the values of m and n; in general as we go from one ion to another the values of the exponents decrease as the rates decrease.

TABLE VI

THE INFLUENCE OF CONSTITUTION UPON THE ORDERS, $T = 35°$, $B_0 = 0.5$, $A_0 = 0.1$, $P = 0$

	$dP/dt \times 10^4$	m	n
$(CH_3)_3N^+CH_2CONH_2$	187	1.5	1.0
$(C_2H_5)(CH_3)_2N^+CH_2CONH_2$	97.0	1.5	1.1
$(C_2H_5)_2(CH_3)N^+CH_2CONH_2$	49.8	1.6	1.1
$(C_2H_5)_3N^+CH_2CONH_2$	14.5	1.8	1.15
$(p\text{-}CH_3C_6H_5)(CH_3)_2N^+CH_2CONH_2$	50.5	1.7	1.1
$(CH_3)_3N^+CH(CH_3)CONH_2$	1.03	1.3	1.0
$(CH_3)(C_2H_5)_2N^+CHCH_3CONH_2$	0.21	1.2–1.3	1.0
$(CH_3)_3N^+C(CH_3)_2CONH_2$	.13	0.9	1.0

TABLE VII

VARIATION OF RATE WITH HYDROXIDE ION AT 35° IN HIGH SALT CONCENTRATIONS; $(I^-) = 4.0\ N$

		$A_0 - P = 0.08$, $m = 1.67$			$A_0 - P = 0.04$, $m = 1.68$			
Run	Ionic strength	$B_0 - P$	$dP/dt \times 10^3$, obs.	$dP/dt \times 10^3$, calcd.	$B_0 - P$	$dP/dt \times 10^3$, obs.	$dP/dt \times 10^3$, calcd.	n
95	4.99	0.971	3.06	3.12	0.931	1.37	1.39	1.06
94	4.90	.880	2.71	2.64	.840	1.20	1.165	1.06
93	4.80	.780	2.16	2.16	.740	0.925	0.941	1.10
92	4.70	.680	1.64	1.71	.640	.750	.738	(0.99)
91	4.60	.580	1.29	1.32	.540	.542	.555	1.08
44	4.50	.480	1.036	0.96	.440	.396	.394	(1.18)
								1.08

Salt Effect.—As is to be expected in a reaction between two oppositely charged ions there is a negative salt effect. It has not been possible to determine this at the low concentrations where activity expressions become simple, but it has been examined over a wide range of high ionic strength, in order to determine its influence on the order of the reaction.

In case (b) the only influence on $(CH_3)(C_2H_5)_2N^+CH_2CONH_2$ of added potassium iodide in so high concentrations as 5.9 N is to increase just perceptibly the value of m from 1.6 to almost 1.7. For $(CH_3)_3N^+CH_2CONH_2$ n increases from 1.0 to nearly 1.1. In case (a) there is no appreciable effect upon the order; however, the smallest detectable change at this high value of $(m + n)$ is 0.2 unit.

The influence of iodide ion upon the rate of the reaction may be expressed for the two derivatives considered by the following equations

$$\text{for } (CH_3)_3N^+CH_2CONH_2,\ k_s = 0.0581[1 - 0.853 \log(I^-)] \tag{7}$$

$$\text{for } (CH_3)(C_2H_5)_2N^+CH_2CONH_2,\ k_s = 0.0163[1 - 0.860 \log(I^-)] \tag{8}$$

k_s is determined from the integral equation for (b), where $B_0 = 0.5\ N$; it is $(n-1)(k\ )(B_0)^m$ and has the dimensions min.$^{-1}$ mole$^{-0.3}L^{-0.3}$.

These empirical equations hold quite well at the higher concentrations (see Fig. 3) but must break down at lower iodide concentrations. As is to be expected, the salt effect is much less than the effect predicted by the Bronsted theory, using the limiting Debye–Hückel equation. Under the same conditions other negative ions appear to be slightly less effective than iodide ion. However, carbonate ion accelerates the reaction. Lithium ion has the same effect as potassium ion.

TABLE VIII

INFLUENCE OF ADDED SALTS ON $(CH_3)(C_2H_5)_2N^+CH_2CONH_2$

Run (Mean of 3 runs)	Added salt in moles per liter		Total ionic strength	k_s
		0	0.60	0.0288
60	KI	0.90	1.50	.0162
71	KBr	1.00	1.60	.0184
72	KNO_3	1.00	1.60	.0196
101	KCl	3.00	3.60	.0144
[Calcd.]	KCl	1.00	1.60	[.0192]
102	KCl	0.50	1.10	.0215
103	KCl	.20	0.80	.0230
104	K_2SO_4	.40	1.70	.0223
105	K_2SO_4	.25	1.35	.0238
106	K_2SO_4	.10	0.90	.0249
107	LiCl	.50	1.10	.0221
110	K_2CO_3	.50	2.10	.0328

Influence of Temperature.—Stewart and Korpi were able to use the same rate laws over a temperature range of 90°. The variation with temperature for $(CH_3)_3N^+CH(CH_3)CONH_2$, an ion of convenient reactivity, has been determined over a range of temperature of 95°. Two runs in case (b) were made at each temperature and from them m was determined. The results are given in Table IX.

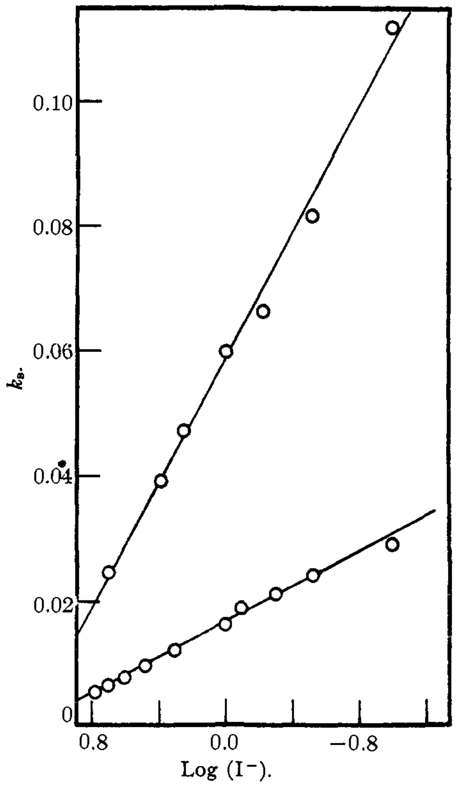

Fig. 3.

TABLE IX

VARIATION WITH TEMPERATURE OF k_s AND m FOR $(CH_3)_3N^+CHCH_3CONH_2$

A_0 = 0.1 N, ionic strength = 0.6 or 1.1

Run	Temp., °C.	B_0	$k_s \times 10^4$	m	k_s calcd. $\times 10^4$ E = 13,400 a = 8.15 $\times 10^6$	k_s calcd. $\times 10^4$ E = 13,300 a = 2.74 $\times 10^6$
201	0	0.996	1.335	1.11	1.45	
202	0	.498	0.620			0.625
197	25	1.000	12.60	1.33	11.6	
198	25	0.500	5.01			4.91
195	55	1.000	98.5	1.33	91.9	
196	55	0.501	39.2			38.1
194	75	.975	290	1.29	300	
193	75	.489	119.5			123
199	95	1.000	823	1.24	861	
200	95	0.501	349			348

m appears to be quite constant (an estimated probable error of 2–3% in the constants gives a probable error of 4–6% in m), except at 0°, where there is a real deviation. The value of the Arrhenius constant, E, is 13,400 calories at the higher and 13,300 at the lower concentration. The deviation of the points from a straight line is not as great as would ordinarily be expected in a system involving competitive reactions.

The Mechanism of the Reaction

The alkaline hydrolysis of ordinary amides must, in all probability, proceed in essentially the same manner as does the hydrolysis of esters. The only difference in detail is that the complex of amide and hydroxide ion has a real existence, while it is not at all certain that such is the case with the ester-hydroxide ion complex. Branch and Clayton[6] have obtained an approximate value of 8×10^{-16} for K_a for acetamide; this is equivalent to determining the equilibrium constant for the first step in the reaction

$$CH_3CONH_2 + OH^- \rightleftharpoons CH_3CONH^- + H_2O \quad (9)$$

The second step is, then, a relatively slow unimolecular decomposition for amides, whereas for esters there is a strong chance that the corresponding decomposition is so rapid that the preceding association is the rate determining step. On the basis of this mechanism for acetamide and of Branch and Clayton's value for K_a, one would expect the bimolecular rate constants to diminish perceptibly as the concentration of hydroxide ion is increased above 0.5 N. Of two investigators, Reid,[7] and von Peskoff and Meyer,[8] who should have observed such a drift, the former did, and the latter failed to do so. But the salt effects have never been determined and they could easily mask the drift in the latter case, and might have produced it in the former. Moreover, if K_a were a few fold smaller, which is remotely possible, the drift would not appear in the concentration range which has been investigated.

In the mechanism now proposed for the betaine amides we assume that part of the reaction proceeds through the same path as in acetamide, but that there are other rate determining steps whose inclusion is prompted by the considerations below. Thus, the fact that m is often greater than 1.0 requires that any satisfactory mechanism must involve a reaction with more than one hydroxide ion. Since the ion of the betaine amide is a zwitterion with a positive charge which is not

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[6] Branch and Clayton, THIS JOURNAL, **50**, 1680 (1928).

[7] E. E. Reid, *Am. Chem. J.*, **46**, 327 (1911).

[8] Von Peskoff and Meyer, *Z. physik. Chem.*, **82**, 129 (1913).

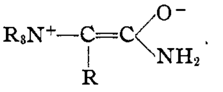
found in acetamide, it is easily conceivable that a path to the final products which involves a reaction with another hydroxide ion might be as easy for the betaine amide as the ordinary path is for acetamide. The complete mechanism proposed is as follows

$$R_3N^+CRR'CONH_2 + OH^- \overset{K}{\rightleftharpoons} R_3N^+CRR'CONH^- + H_2O \quad (9)$$

$$R_3N^+CRR'CONH^- + H_2O \xrightarrow{k_1} R_3N^+CRR'COO^- + NH_3 \quad (10)$$

$$R_3N^+CRR'CONH^- + OH^- + H_2O \xrightarrow{k_2} R_3N^+CRR'COO^- + OH^- + NH_3 \quad (11)$$

$$2(R_3N^+CRR'CONH^-) + H_2O \xrightarrow{k_3} R_3N^+CRR'COO^- + R_3N^+CRR'CONH^- + NH_3 \quad (12)$$

The last reaction is included because the zwitterion is itself a strong base and should be a catalyst of the same order of effectiveness as hydroxide ion. It is to be expected that K will be larger than the corresponding constant would be for acetamide. It is quite possible that the structure of the intermediate is not as represented above. When R$'$ is a hydrogen atom, it may be more highly ionized than the amide hydrogen; in that event the intermediate would have the structure  $R_3N^+{-}\underset{\displaystyle R}{\underset{|}{C}}{=}C\langle^{O^-}_{NH_2}$. It is noteworthy in this connection that high values of m are found only when R$'$ is a hydrogen atom. A third alternative, decidedly improbable, is that the first hydroxide ion is bound in some manner to the quaternary nitrogen.

The differential equations for the cases (a), (b), and (c) are given below. The concentration of the intermediate is represented by X, so that

$$X/BA = K\text{, and} \quad (13)$$

$$dP/dt = k_1X + k_2BX + k_3X^2\text{, or} \quad (14)$$

$$dP/dt = k_1KBA + k_2KB^2A + k_3K^2B^2A^2 \quad (15)$$

In general

$$B = (B_0 -- X - P) \text{ and } A = (A_0 - X - P) \quad (16)$$

In case (b) we assume that $B = B_0$ with the result that

$$A = (A_0 - P)/(1 + KB_0) \quad (17)$$

Equation (15) becomes, after substitution for A

$$\frac{dP}{dt} = \frac{KB_0}{(1 + KB_0)}(A_0 - P)\left[k_1 + k_2B_0 + k_3\frac{KB_0}{(1 + KB_0)}(A_0 - P)\right] \quad (18)$$

The derivation of the equation for case (c) proceeds in the same manner, the only assumption being that $A = A_0$. The equation is

$$\frac{dP}{dt} = \frac{KA_0}{(1 + KA_0)}(B_0 - P)\left[k_1 + k_2\frac{(B_0 - P)}{(1 + KA_0)} + k_3\frac{KA_0}{(1 + KA_0)}(B_0 - P)\right] \quad (19)$$

In case (a) $A = B$, whence

$$dP/dt = KB^2(k_1 + k_2B + k_3KB^2) \quad (20)$$

where

$$B = \frac{-1 \pm \sqrt{1 + 4K(B_0 - P)}}{2K} \quad (21)$$

The significance of the equation can be made clearer by using the binomial expansion for the irrational terms. The higher order terms only represent the contribution of the equilibrium to the lowering of the order, and do not affect the qualitative nature of the equation; moreover, this effect is less in this case than in either of the two discussed above, so for clarity's sake we will omit those terms. The resulting equation is, simply

$$dP/dt = K(B_0 - P)^2[k_1 + k_2(B_0 - P) + k_3K(B_0 - P)^2] \quad (22)$$

In certain combinations of terms in the above equations we find rational explanations for the fractional values of m and n obtained experimentally. The expression $B_0/(1 + KB_0)$ is equal to B_9^x where $0 < x < 1$, and where x diminishes as B_0 is increased. Again, the expression $(B_0 + kB_0^2)$ is equal to B_0^y where $1 < y < 2$, and where y increases as B_0 is increased. Keeping these facts in mind, a good qualitative correlation between the experimental and predicted values of m and n may be obtained in the six sections numbered above in bold-face type. We have not attempted a quantitative evaluation of the agreement between experiment and theory because the manner of propagation of errors from the data into the constants is such that their reliabilities would be small. Small variations in ionic strength which were practically unavoidable, and medium effects in solutions of the same ionic strength but different compositions, might also introduce large errors into the results. Moreover, because there are four constants to be evaluated, it is practically certain than a superficially satisfactory solution could be obtained. The significance of such a solution would be just as small as the probability that it could be obtained is large.

It will be necessary to point out some of the less obvious points of agreement. As k diminishes through a series of derivatives the diminution of m and n is to be attributed to the diminution of K, k_2 and k_3 relative to k_1, which are logical consequences of the masking of the effect of the quaternary nitrogen atom's charge. The fact that this diminution is not regular (Table VI) is evidence that the effect is due to the interaction of more than one factor. The constancy of m at 1.6 in Fig. 1 may be explained as a nice balancing of opposed effects. It may be explained, but it is none the less remarkable that the constants should assume values resulting in such a special solution. This fact and the fact that m for another derivative, a less sensitive case, to be sure, was found to be practically independent of temperature, constitute the strongest arguments against the proposed mechanism.

Carbonate ion in the presence of added hydroxide ion accelerates the reaction pronouncedly (Table VIII) although carbonate ion in the absence of added base gives only a very slow production of ammonia. This indicates that in addition to the equilibrium there is a follow reaction for which carbonate ion is a reasonably effective catalyst, while at the same time it is not sufficiently strong a base to shift the equilibrium to a favorable point.

In the consideration of the influence of changing ionic strength upon the order of the reaction (Table VII and accompanying discussion), we are brought to the interesting problem of salt effects in zwitterion reactions. In equation (11) hydroxide ion reacts with the zwitterion at some ill-defined point in the ion; in equation (12) the negative end of the zwitterion reacts with another zwitterion in the same manner. The theory on which salt effects are predicted is not worked out for such cases, but it can be said that at infinite dilution the zwitterion will behave as a neutral molecule, while at the other extreme of concentration it will behave essentially as two separate unrelated ions. As we proceed from the former to the latter condition the salt effect will increase from that of a neutral molecule to that of an independent ion. The transition appears to be at its maximum at ordinary concentrations. Equation (10) presents an even more baffling case, for here two ions react to form a zwitterion. At low concentrations the zwitterion may, as before, be treated as a neutral molecule but at high concentrations it must be treated as an ion. It is unfortunate that the complexity of the mechanism precludes any treatment of this effect.

In view of these manifold complexities it is not surprising that variation of ionic strength fails to have its usual effect of increasing pronouncedly the rates of some of the steps at the expense of others.

In conclusion we may say that in postulating a mechanism requiring four steps we have made only one innovation—the assumption that there is a reaction between the negative amide ion (the zwitterion) and another basic ion. The evidence that hydroxide ion is involved in more than one rate determining step is overwhelmingly strong. The reaction in equation (12) is a necessary consequence of equation (11), of recent theories of generalized acidic and basic catalysis, and of the fact that the zwitterion must be a strong base. The existence of the equilibrium is a consequence of the mechanism of ester hydrolysis and of Branch and Clayton's value of K_a for acetamide. Finally, important sections of the data could not be explained if any of the four steps were omitted.

Experimental Procedure

In all except the runs at very low amide concentration the analytical method described by Stewart and Korpi was used, with but minor variations. In the runs at low amide concentration the interferometric method[9] was used.

Summary

1. The betaine nitriles hydrolyze rapidly in alkaline solution to the corresponding amides. These amides hydrolyze relatively slowly to the acid salts.

2. The simpler betaine amides hydrolyze according to complex rate laws which involve fractional exponents; the more complex, less reactive, derivatives hydrolyze at a rate which is nearly first order with respect to each reactant.

3. Variation of ionic strength and of temperature has been found to have but little effect on the rate functions.

4. A mechanism has been proposed which, on a qualitative basis, accounts satisfactorily for the observed phenomena.

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[9] Luten, *J. Phys. Chem.*, to be published.