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

The Preparation and the Quaternary Ammonium Decomposition of Formocholine

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Formocholine chloride, $(CH_3)_3NCH_2OH^+Cl^-$, is interesting as a quaternary ammonium compound since a hydrogen attached to an atom in the β position to the nitrogen should be to some extent ionized. According to the theory[1] of quaternary ammonium decompositions such an ionization should result in the reaction

$$(CH_3)_3N^+{-}CH_2OH \overset{A}{\rightleftharpoons} (CH_3)_3N^+{-}CH_2O^- + H^+ \xrightarrow{B} (CH_3)_3NH^+ + CH_2O \quad (1)$$

This is analogous to the reaction

$$(CH_3)_3N^+{-}CH_2{-}CH_2{-}C_6H_5 + OH^- \longrightarrow (CH_3)_3N + C_6H_5CH{=}CH_2 + H_2O \quad (2)$$

which takes place with unusual ease, due to the activation of the β hydrogen by the phenyl group. In these reactions three situations may occur: (1) the decomposition is preceded by a relatively rapid ionization, as in Equation (1); (2) the decomposition proceeds only in the presence of highly basic ions, such as hydroxide ion, and then by a path whose rate is dependent upon the number of collisions of the two ions (Equation (2)); and (3) the reaction rate is independent of the hydroxide ion concentration and first order in the quaternary ion concentration, suggesting that the rate determining step is the rate of ionization (or rate of activation) of the quaternary ion. Evidence for this was looked for by Stewart and Korpi[2] among the α-amino nitrile derivatives, $R_3NCH_2CN^+OH^-$. Hughes and Ingold[3] report facts regarding the decomposition of the ion $(CH_3)_3N^+$-$CH(C_6H_5)_2$ which they interpret in this way. Formocholine belongs to the case (1), a rapid reversible ionization followed by the decomposition of the neutral residue as the rate determining step.

The Preparation of Formocholine Chloride.—The preparation has been reported by various authors, whose methods have failed in our hands.

Hofmann[4] and later Schmidt and Litterschied[5] heated a mixture of silver oxide and iodomethyltrimethylammonium iodide for several days, and isolated gold and platinum double salts, presumably of formocholine chloride.

$$(CH_3)_3N^+{-}CH_2I + AgOH \longrightarrow (CH_3)_3N^+{-}CH_2OH + AgI \quad (3)$$

The yield was apparently small, and in view of the extremely rapid decomposition of formocholine in alkali, as described below, we feel safe in saying that their product was not formocholine. It could have been the ether, $[(CH_3)_3N{-}CH_2{-}O{-}CH_2{-}N$-

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[1] (a) v. Braun, *Ann.*, **382**, 1 (1911); (b) Lewis, "Valence and the Structure of Atoms and Molecules," The Chemical Catalog Co., Inc., New York, 1923, p. 135; (c) Stewart and Aston, THIS JOURNAL, **49**, 1720 (1927); (d) Hanhart and Ingold, *J. Chem. Soc.*, 997 (1927).

[2] Stewart and Korpi, THIS JOURNAL, **54**, 3977 (1932).

[3] Hughes and Ingold, *J. Chem. Soc.*, 69 (1933).

[4] Hofmann, *Jahresb.*, 377 (1859).

[5] Schmidt and Litterschied, *Ann.*, **377**, 74 (1904).

$(CH_3)_3]^{++}Cl_2^-$, whose platinum double salt contains one molecule of water of crystallization. The platinum double salts of formocholine and of the above hydrated ether are described by Litterschied as decomposing at 230 and 232°, respectively; the true formocholine double salt decomposes sharply at 246° if the bath temperature is raised rapidly, otherwise the decomposition temperature is 252°, corresponding to that of the double salt of trimethylammonium chloride. The above ether does not decompose in boiling dilute alkali.

Renshaw and Ware[6] reported formocholine formed by the reactions

$$(CH_3)_3N + ClCH_2{-}O{-}CO{-}CH_3 \longrightarrow (CH_3)_3N^+{-}CH_2{-}O{-}CO{-}CH_3 + Cl^- \tag{4}$$

$$(CH_3)_3N^+{-}CH_2{-}O{-}CO{-}CH_3 + C_2H_5OH \xrightarrow[\text{Alc.}]{\text{Dil. HCl}} (CH_3)_3N^+{-}CH_2OH + CH_3{-}CO_2C_2H_5 \tag{5}$$

They heated the acetylformocholine with "very dilute" alcoholic hydrochloric acid at 56° for twenty-four hours. The only fractions of the product formed by their procedure which we have found to correspond to their chlorine analysis proved to be approximately equal molal mixtures of unchanged acetylformocholine chloride and trimethylammonium chloride. Moreover, the pure formocholine chloride decomposes completely in one hour at 40° in 0.03 *N* alcoholic hydrochloric acid, and in twenty-four hours at any low concentration of acid would be largely decomposed at 56°.

Experimental

The method of Renshaw and Ware has been modified.

Acetylformocholine Chloride.—Fifty-eight grams of chloromethyl acetate b. p. (60 mm.) 49° and 29 g. of trimethylamine in 68 g. of propyl alcohol stood for twenty hours in an ice-bath. The crystals which separated (55% yield) were almost pure acetylformocholine chloride; a second crop containing some trimethylamine hydrochloride was precipitated from the mother liquor with ether; total yield 72 g. Recrystallization from hot propyl alcohol gave the pure salt of the composition $(CH_3)_3NCH_2OCOCH_3Cl \cdot {}^1/_2H_2O$. Cl found, 20.3; calcd. 20.1. Drying in a vacuum desiccator over phosphorus pentoxide gave the pure anhydrous salt.

Bis-dimethylaminomethylether-bis-methyl chloride occurred as a by-product in the above preparation, due to the presence of dichloromethyl ether as an impurity in the chloromethyl acetate. It was isolated by treating the last fractions of the crude acetylformocholine with excess 0.1 *N* sodium hydroxide on the steam-bath until all the liberated trimethylamine had been driven off, acidifying with hydrochloric acid and evaporating to dryness. The salt was extracted from the sodium chloride with hot propyl alcohol and recrystallized. Equivalent weights (by chlorine analysis) 125.0 and 125.3, calculated for $[(CH_3)_3N{-}CH_2]_2O \cdot Cl_2 \cdot H_2O$, 125.5. After four days in a vacuum desiccator over phosphorus pentoxide the equivalent weights found were 116.3 and 116.5.

Formocholine Chloride.[7]—Three grams of acetyl formocholine chloride was dis-

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(6) Renshaw and Ware, THIS JOURNAL, **47**, 2990 (1925).

(7) The only other acyclic salts of this structure known to us were prepared by Ingold and Rothstein [*J. Chem. Soc.*, 8 (1929)] by the reaction

$$CH_2Cl{-}CH{=}CH{-}N^+(CH_3)_3 \xrightarrow{+O^-C_2H_5} CH_2{=}CH{-}CH(OC_2H_5){-}N^+(CH_3)_3 \xrightarrow[\text{HCl}]{\text{concd.}} CH_2{=}CH{-}CH(OH)N^+(CH_3)_3$$

The α-hydroxyallyl derivative was ozonized in acetic acid, and the ozonide decomposed in boiling 30% acetic acid to yield $CHO{-}CH(OH){-}N^+(CH_3)_3$. Compared to formocholine, this is evidence of surprising stability. Similar attempts to hydrolyze the compound $CH_2(OR){-}N^+R_3$, derived from α-amino ethers [*cf.* Stewart and Aston, *loc. cit.*, and Robinson and Robinson, *J. Chem. Soc.*, **123**, 532 (1923)] resulted only in the corresponding tertiary amine salt.

solved in 50 cc. of 5 *N* hydrochloric acid, and the solution allowed to stand at room temperature until the hydrolysis was complete. In this experiment a larger amount of aqueous acid was used than necessary, which permitted the withdrawal of portions for analysis to determine the extent of the hydrolysis. The samples were diluted with ice-cooled water and the free acid neutralized by 0.1 *N* sodium hydroxide to the bromo thymol blue end-point. A known excess of standard alkali was then added to each, and the solution allowed to stand for one and a half hours at room temperature. The alkali was then back titrated and the amount of acetyl compound remaining in the sample calculated from the alkali consumed. The hydrolysis was practically complete within ten hours. The remaining stock solution was evaporated at room temperature *in vacuo* over soda lime and calcium chloride. The resulting sirup was taken up with 10 cc. of propyl alcohol, and the addition of ether brought down the salt as a viscous solution. To obtain the crystalline salt, the precipitate was dissolved in 20 cc. of butyl alcohol at 25–30°, and the solution cooled to ice temperature. The yield of this crop of salt was about 34% of the theoretical. Additional salt was recovered from the mother liquor by slow addition of ether, but was contaminated by trimethylamine hydrochloride.

Anal. Calcd. for $C_4H_{12}ONCl$: Cl, 28.23. Found: Cl (Volhard), 28.20, 28.23.

When dissolved in water, the salt decomposed very rapidly according to the equation

$$(CH_3)_3N^+CH_2OH + Cl^- = (CH_3)_3NH^+ + Cl^- + CH_2O \qquad (6)$$

The formaldehyde produced by this decomposition was determined by the bisulfite method; yield in two samples, 94.5 and 97.0%. Trimethylamine was determined by distilling a weighed sample with an excess of 0.1 *N* sodium hydroxide in a Kjeldahl apparatus; yield 98.7%.

The chloroplatinate of formocholine was made by dissolving the salt in absolute alcohol, and immediately precipitating with chloroplatinic acid. The orange-yellow precipitate was analyzed: calcd. for $(C_4H_{12}ON)_2PtCl_6$, Pt, 33.2; found, 32.9, 33.1. This chloroplatinate is very little soluble in alcohol. When dissolved in warm water, it decomposes to give a strong odor of formaldehyde. It decomposes sharply at 246° when it is heated very rapidly. This is accomplished by heating the bath to 245° before placing the melting point tube in it. Whenever the temperature was raised slowly, the chloroplatinate gave the decomposition temperature of 252°, which is the decomposition temperature of trimethylammonium chloroplatinate.[8]

The Hydrolysis and Alcoholysis of Acetylformocholine.—At *P*H 8.8 the hydrolysis is half complete in about seven minutes at room temperature, yielding trimethylamine, formaldehyde and acetate ion; in *N*/2 hydrochloric acid the hydrolysis is half complete in about nineteen hours at room temperature, as followed by the acetic acid produced; in water only 33% had hydrolyzed in ten days at room temperature. Alcoholysis, with the formation of ethyl acetate, trimethylamine and formaldehyde is catalyzed by both hydrogen chloride and trimethylamine. In concentrations of acid of the order *N*/10 the alcoholysis is very slow; mixtures of unchanged acetylformocholine with trimethylamine hydrochloride were obtained.

Decomposition of Formocholine Chloride in Slightly Acidified Alcoholic Solution.—0.32 g. of formocholine chloride was dissolved in 20 cc. of absolute alcohol; 10 cc. of the solution was run into an excess amount of chloroplatinic acid. Calcd. for $(C_4H_{12}ON)_2$-$PtCl_6$, Pt, 33.2; found, 33.5. The other 10 cc. of the solution was acidified with 0.05 cc. of 5 *N* hydrochloric acid and heated at 40–50° for an hour. After the resulting

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[8] Two isomeric platinum complexes exist, one being mentioned in the introduction. The other is the double salt of the amine oxide derivative, $(CH_3)_3NOCH_3{\cdot}Cl$. A sample was prepared and purified: Pt found, 32.9; calcd., 33.2. It decomposed sharply at 236° when put into the bath at 230° or above. When heated in water no odor of formaldehyde could be detected; the salt may be recrystallized from hot water.

solution had cooled to room temperature, it was precipitated with excess chloroplatinic acid. The analysis of the precipitate indicated trimethylammonium chloroplatinate: calcd. for $(C_3H_{10}N)_2PtCl_6$, Pt, 37.0; found, 37.1, 37.0. The compound would be more stable in more acidic solutions, but this was sufficient to show the difficulty of obtaining it through the slow alcoholysis of the acetyl derivative.

Acetylation of Formocholine Iodide.—One and one-half grams (crude) was treated with about 15 cc. of acetic anhydride (in which it is not soluble) and allowed to stand at room temperature for two weeks with occasional shaking. During this time some long needle crystals separated from the brown solution. The solution was diluted with ether, filtered, and the product recrystallized once from hot propyl alcohol, yield 1.0 g.; decomposed at 150–152° (decomposition temperature of acetylformocholine iodide is 152°); I, calcd. for acetylformocholine iodide 49.0; calcd. for formocholine iodide 58.5; found, 51.0. Acetic acid produced by alkaline hydrolysis: calcd. for acetylformocholine iodide, 0.00386 mole/g.; found, 0.00341 mole/g. From the above two determinations it is calculated that the sample contains 85.0 mole per cent. of acetylformocholine iodide.

Triethyl-hydroxymethyl-ammonium Chloride.—This was prepared from triethyl-acetoxymethylammonium chloride, which was in turn prepared from chloromethyl acetate and triethylamine in equivalent amounts. The latter reaction requires two weeks at room temperature or about ten hours at 70°, and the product was identified as the chloroplatinate double salt: calcd. for $(C_9H_{20}NO_2)_2PtCl_6$, Pt, 25.8; found, 25.9, 25.6. No attempt was made to isolate the acetoxy compound; it was converted to the hydroxy compound through the same procedure used for formocholine chloride.

Anal. (Volhard) Calcd. for $C_7H_{18}NOCl$: Cl, 21.15. Found: 21.4.

This salt also decomposes rapidly when dissolved in water, and the formaldehyde produced in the process when determined by the bisulfite method was 95.5% of the theoretical amount.

The Decomposition of Formocholine and its Triethyl Homolog.—The decomposition was followed in buffered solutions through the change in the refractive index as measured by a Zeiss interferometer. This instrument cannot be used at temperatures far from room temperature.

Interferometer Measurements.—The reference solution was a mixture, in equal volumes, of the buffer salt solution and 0.3 *N* potassium chloride. The reacting solution was made up by diluting the same buffer solution with an equal volume of water and adding a measured amount of mixture, usually 10 cc., to about 0.09 g. of the formocholine chloride. The first reading could be taken within three minutes after preparing the solutions in the thermostat. The buffer solutions were made up as described by Sørensen,[9] of twice the desired concentration to allow for dilution as described above. The citrate solution contained 41.016 g. of citric acid and 400 cc. of 1.0 *N* sodium hydroxide, diluted to one liter; the hydrogen chloride solution was made up of 200 cc. of 1.0 *N* acid diluted to one liter. The *P*H value of the reacting solution with possible salt effect neglected was taken from Sørensen's tables. The small constant drift at the end of a run (Table I) was assumed to have also occurred throughout the run, and correction made for it.

To show that the interferometer readings were a measure of the reaction, the half-life at *P*H 1.418 was obtained colorimetrically with Schiff's reagent, using an empirical procedure. This was found to be 300 ± 15 minutes. Extrapolation of the curve in Fig. 1 to this *P*H value indicated a half-life of 285 minutes. Data for a typical experiment are given in Table I.

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[9] Clark, "The Determination of Hydrogen Ions," third ed., p. 209.

TABLE I

THE RATE OF DECOMPOSITION OF FORMOCHOLINE CHLORIDE AT CONSTANT HYDROGEN-ION CONCENTRATION

Expt. 6; *P*H, 3.364. Temperature, 25.00 ± 0.02°; concn. 0.198 g. of formocholine chloride in 20 cc. of buffer solution

Time, t, minutes	Readings	Corr. readings (R_t)	$R_f - R_t$	Log ($R_f - R_t$)	Time, t, minutes	Readings	Corr. readings (R_t)	$R_f - R_t$	Log ($R_f - R_t$)
3	455	454.8	84.2	1.9253	13	530.0	527.3	9.8	0.9912
4	472	471.7	67.3	1.8280	14	532.0	531.1	7.9	.8976
5	484	483.7	55.3	1.7427	15	533.0	532.0	7.0	.8451
6	494	493.6	45.4	1.6580	18	536.5	535.2	3.8	.5798
7	503	502.5	36.5	1.5623	21	537.5	536.1	2.9	.4624
8	510	509.5	29.5	1.4698	24	540.0	538.4	0.6	
9	516.5	515.9	23.1	1.3636	30	541.0	539.0(R_f)		
10	520.0	519.4	19.6	1.2923	60	543.0	539.0		
11	524.0	523.3	15.7	1.1959	90	545.0	539.0		
12	527.5	526.7	12.3	1.0899					

Column three gives the readings of the instrument corrected for a small constant change due to unequal evaporation from the reference and reacting solutions. Column four gives the change in reading based upon the final corrected reading. This was shown to be proportional to the amount of reacting material present; when the logarithm of this quantity is plotted against the corresponding time, the points are found to lie on a straight line, indicating a rate law of the form

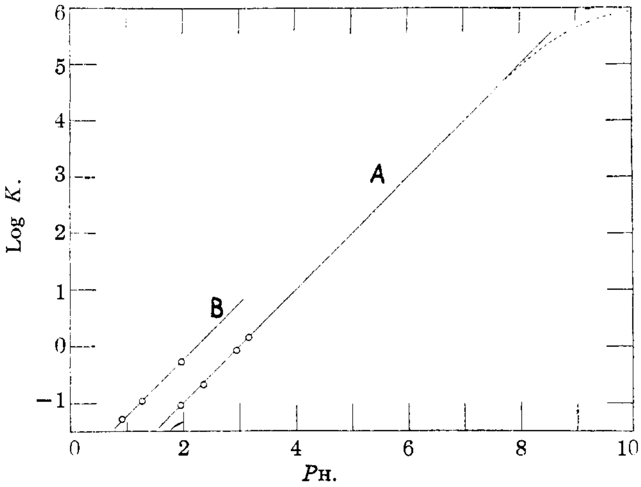

Fig. 1.—The change in rate of decomposition with *P*H at 25°. Curve A, formocholine chloride; Curve B, hydroxymethyltriethylammonium chloride.

$$-d(C)/dt = k(C) \qquad (7)$$

at constant hydrogen-ion concentration. The slope of the line has a value

-0.908 and $K = 0.209$ (min.$^{-1}$). Table II summarizes similar data at different *P*H values, for both formocholine chloride and triethylhydroxymethylammonium chloride.

TABLE II

THE DECOMPOSITION IN DIFFERENT BUFFERS

Formocholine chloride			Triethylhydroxymethylammonium chloride		
*P*H	*K* (min.$^{-1}$)	Log *K*	*P*H	*K* (min.$^{-1}$)	Log *K*
2.972	0.0934	−1.03	1.925	0.0514	−1.289
3.364	.209	−0.68	2.274	.1255	−0.902
3.948	.855	− .068	2.972	.533	− .273
4.158	1.420	.152			

The data in Table II are plotted in Fig. 1. The slope of the drawn lines is unity, indicating that the specific reaction rate constant is inversely proportional to the hydrogen-ion concentration:

$$\log K = a + P\text{H} \qquad (8)$$

The constant a has a value characteristic of each compound; for formocholine chloride it is -4.017, for triethylhydroxymethyl ammonium chloride it is -3.213. At 25° and at a given *P*H the specific reaction rate of the latter is 5.75 times that of formocholine chloride. The salt effect on the reaction rate is small. A three-fold dilution of the buffer salt caused a decrease of only 2.2% in the specific reaction rate. The *P*H value of the buffered solution was considered unchanged by the dilution.

Discussion of Results.—The relative stability, compared to formocholine chloride, of its O-ethyl and O-acetyl derivatives strongly indicates that the presence of the hydroxyl hydrogen is essential to the rapidity of the decomposition. The inverse proportionality of the rate to hydrogen-ion concentration could be interpreted as a direct proportionality to hydroxide-ion concentration, but the fact that the reaction proceeds so rapidly in acid solution makes it improbable that a second order reaction involving hydroxyl ion could be concerned.

This conclusion could best be tested by determining the rate in more alkaline media. If step B in Equation (1) is the rate determining step, then the rate law should be

$$-\frac{d(C)}{dt} = \frac{k_r \cdot K_a \cdot (C)}{K_a + (H^+)} \qquad (9)$$

where K_a is the equilibrium constant of step A (Equation (1)), or the acid dissociation constant of formocholine, k_r the specific reaction rate constant of step B and C the sum of the concentrations of the dissociated and undissociated reactant. If K_a is small compared to (H^+), Equation (8) takes the form of Equation (6), at constant (H^+). When K_a equals (H^+), then the observed rate constant k is equal to $^1/_2k_r$. At higher alkalinity, k approaches k_r and the slope of the curve in Fig. 1 becomes zero. The dotted line in Fig. 1 is calculated from the relation $k = k_r \cdot K_a/(K_a +$

(H^+)) assuming a value of 1×10^{-10} for K_a. The rapidity of the reaction in neutral or alkaline solution prevents a direct determination of the form of the curve in this region. The constant a (Equation (7)) is equal to log $K_a \cdot k_r$. K_a is probably of the order of 1×10^{-10}, for formocholine, in which case k_r is of the order 1×10^6 (min.$^{-1}$) at 25°.[10]

The effect of the alkyl groups is interesting and will be further studied. The same difference between methyl and ethyl groups was found by Stewart and Bradley[11] for the reaction $R_2N^+H—CH_2—SO_3^- \longrightarrow R_2N^+{=}CH_2 + HSO_3^-$. The ratio of the rates of the diethyl and dimethyl derivation was 2.6 at 30°, with very nearly the same heats of activation, as compared to a ratio of 5.75 in the formocholines. This suggests possible similarities in these apparently different types of reaction and points to the importance of the intensity and distribution of the charge on the nitrogen as one governing factor in the rate of reaction.

Summary

Trimethylhydroxymethylammonium chloride (formocholine) and triethylhydroxymethylammonium chloride have been prepared. The rates of decomposition in dilute acid have been measured and the rate law found to conform to the equation

$$R_3N^+—CH_2OH \overset{\text{Fast}}{\rightleftharpoons} R_3N^+—CH_2O^- + H^+ \xrightarrow{\text{Slow}} R_3NH^+ + CH_2O$$

The reaction is first order at constant P_H and the rate is inversely proportional to the hydrogen-ion concentration in dilute acid. The bearing of these facts on quaternary ion decomposition is discussed. The specific reaction rates are given by the equation $\log K = a + P_H$, where a has the values -4.017 and -3.213 for the trimethyl and triethyl derivatives, respectively, at 25° and when K is given in min.$^{-1}$.

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(10) A plot of $1/k$ against (H^+) should give $1/k_r$ at the intercept where (H^+) is zero. The accuracy of the data is not sufficient to make this extrapolation reliable, since $1/k_r$ is such a small number. Such a plot gives an intercept at the origin

(11) Stewart and Bradley, THIS JOURNAL, **54,** 4183 (1932)