Rate and Equilibrium Constants for Each Step in the Reaction of Trimethylammonium Ions with Formaldehyde to Give Formocholine Cations in Aqueous Solution[1a,b]

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Abstract: The equilibrium constant for the formation of the hydroxymethyltrimethylammonium (formocholine) cation from the trimethylammonium ion and formaldehyde hydrate in deuterium oxide at 30 ± 5° was found by proton magnetic resonance measurements to be $0.5 \pm 0.1\ M^{-1}$. The formocholine cation was found to be more acidic than the trimethylammonium ion, having a pK of 9.33. These measurements and data from the literature permitted the calculation or reliable estimation of the rate constants for every step in the equilibration. These rate constants explain the observation that in the pmr spectrum of the equilibrium mixture at pD 7 the methyl peak of the trimethylammonium ion is merged with the methyl peak of formocholine, but the methylene peak of formaldehyde hydrate is not merged with the methylene peak of formocholine; at pD 2, neither pair of peaks is merged. At pD 7, the rate-controlling step in the transformation of formocholine to trimethylammonium ions is heterolysis of the zwitterion $Me_3N^+CH_2O^-$, but the rate-controlling step in the formation of formaldehyde hydrate is the subsequent hydration of the aldehyde. It is also concluded that certain hydroxymethylamines may exist to a significant extent (10% or more) in the form of their zwitterionic tautomers in aqueous solution.

Carbonyl reactions, like many other types of organic reactions, often appear to proceed by multistep mechanisms. In rationalizing reaction rates and positions of equilibrium in such processes, it is much more desirable to be able to make a step-by-step comparison of rate and equilibrium constants than to be able to compare only data for the overall reactions. Such a detailed comparison may also shed light in some cases on whether a given pair of steps that can be written as proceeding consecutively are actually fused into a single concerted step. There are not many multistep reactions for which values of the rate and equilibrium constants have been reported for every step. The reaction of aqueous formaldehyde (present largely as the the hydrate) with trimethylammonium salts to give salts of formocholine (eq 1) seemed to be a case in

$$CH_2(OH)_2 + Me_3NH^+ \rightleftharpoons H_2O + Me_3NCH_2OH^+ \qquad (1)$$

which it might be possible to obtain or estimate reliably all the desired data.

The Equilibrium Constant for the Formation of Formocholine Cations. Le Hénaff[2,3] and Kallen and Jencks[4] have measured equilibrium constants for the formation of hydroxymethylammonium ions from formaldehyde and ammonium ions by cryoscopic measurements and pH measurements, among other ways. For our purposes, proton magnetic resonance (pmr) measurements seemed most suitable. Such measurements in protium oxide solution were not very useful because of interference by the solvent. In deuterium oxide solution, however, mixtures of formaldehyde and trimethylammonium chloride at pD 2 showed singlets with chemical shifts[5] of 0.29 and 1.88 ppm in addition to the singlets at 0.18 (trimethylammonium ions), 1.92 (residual protons in the solvent), 2.08 (formaldehyde hydrate), and 2.15 ppm [bis(hydroxymethyl) ether] attributable to the aldehyde and trimethylammonium chloride solutions. The peak at δ 1.88 ppm had a chemical shift very near that observed for the methylene group of methoxymethyltrimethylammonium chloride and had about two-ninths the area of the peak at δ 0.29 ppm. Hence the 1.88-ppm peak was attributed to the methylene group and the 0.29-ppm peak to the methyl groups of formocholine cations. The pmr spectra obtained at pD 7 were similar, except that the methyl peaks at 0.29 and 0.18 ppm were merged and the width at half-height of the singlet due to the methylene group of formocholine had decreased markedly (for reasons to be considered later in discussing the reaction mechanism). From the areas of the relevant peaks at 30 ± 5°, it was calculated that K_f' equals $0.5 \pm 0.1\ M^{-1}$.

$$K_f' = \frac{[Me_3NCH_2OD^+]}{[Me_3ND^+][CH_2(OD)_2]}$$

The Acidity Constant of Formocholine Cations. The positively charged trimethylammonio group should make the oxygen-bound hydrogen atom of the formocholine cation much more acidic than the oxygen-bound hydrogen of an alcohol without electron-withdrawing substituents. If this hydrogen atom is more acidic than the nitrogen-bound hydrogen in a trimethylammonium cation, the addition of formaldehyde to a solution of trimethylammonium chloride (which transforms a significant fraction of the trimethylammonium cations to formocholine cations) should increase the effective acidity of the solution. We have used this fact to determine the acidity constant of formocholine cations by potentiometric titrations, adding standard sodium hydroxide to solutions made up from trimethylammonium chloride and formaldehyde. Equilibrium constants are defined as

$$K_{af} = \frac{[H^+][Me_3N^+CH_2O^-]}{[Me_3NCH_2OH^+]}$$

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[2] P. Le Hénaff, *C. R. Acad. Sci., Paris*, 258, 896 (1964).

[3] P. Le Hénaff, *Bull. Soc. Chim. Fr.*, 3113 (1965).

[4] R. G. Kallen and W. P. Jencks, *J. Biol. Chem.*, 241, 5864 (1966).

[5] Downfield from internal dimethyl sulfoxide.

$$K_{at} = \frac{[H^+][Me_3N]}{[Me_3NH^+]}$$

$$K_d = \frac{[(HOCH_2)_2O]}{[CH_2(OH)_2]^2}$$

$$K_f = \frac{[Me_3NCH_2OH^+]}{[Me_3NH^+][CH_2(OH)_2]}$$

From the amounts of material used in making up the solutions, the values of $[CH_2O]_t$, the total concentration of formaldehyde in all forms, and $[Me_3N]_t$, the total concentration of trimethylamine in all forms, are known. The concentration of free formaldehyde is only 0.05% that of formaldehyde hydrate;[6,7] the pmr absorption characteristic of higher polymers of formaldehyde hydrate was not observed in any of our solutions at the concentrations used for acidity measurements, and according to the observations of Skell and Suhr,[8] the amount of such polymers present should never be as large as 0.3% of that of the monomer at these concentrations; from the ionization constant of formaldehyde hydrate[9] the concentration of the conjugate base ($HOCH_2O^-$) may be calculated to be less than 0.1% that of the hydrate under any of our conditions. A third equation may be based on the electrical neutrality of the solutions (eq 4). Substituting from the equilibrium constant expressions and noting that $[Me_3N]_t$ is equal to $[Cl^-]$ transforms eq 2, 3, and 4 to eq 5, 6, and 7

$$[CH_2O]_t = [CH_2(OH)_2] + 2[(HOCH_2)_2O] + [Me_3N^+CH_2O^-] + [Me_3NCH_2OH^+] \quad (2)$$

$$[Me_3N]_t = [Me_3NH^+] + [Me_3N] + [Me_3N^+CH_2O^-] + [Me_3NCH_2OH^+] \quad (3)$$

$$[Na^+] + [Me_3NH^+] + [Me_3NCH_2OH^+] + [H^+] = [Cl^-] + [OH^-] \quad (4)$$

$$[CH_2O]_t = [CH_2(OH)_2]\left(1 + 2K_d[CH_2(OH)_2] + K_f[Me_3NH^+] + \frac{K_fK_{af}[Me_3NH^+]}{[H^+]}\right) \quad (5)$$

$$[Me_3N]_t = [Me_3NH^+]\left(1 + \frac{K_{at}}{[H^+]} + K_f[CH_2(OH)_2] + \frac{K_fK_{af}[CH_2(OH)_2]}{[H^+]}\right) \quad (6)$$

$$C = [Me_3NH^+] + K_f[Me_3NH^+][CH_2(OH)_2] \quad (7)$$

where $C = [Me_3N]_t - [Na^+] + [OH^-] - [H^+]$. Experimentally determined or satisfactorily approximated values are available for all the terms in these equations except for the three unknowns, $[Me_3NH^+]$, $[CH_2(OH)_2]$, and K_{af}. Elimination of the latter two unknowns gives eq 8. This equation may be solved for $[Me_3NH^+]$ to any desired degree of accuracy by various iterative processes, and from the result values of $[CH_2(OH)_2]$ and K_{af} may be calculated.

$$[Me_3N]_t - [CH_2O]_t = [Me_3NH^+] + \frac{K_{at}[Me_3NH^+]}{[H^+]} - \frac{C - [Me_3NH^+]}{K_f[Me_3NH^+]} - 2K_d\left(\frac{C - [Me_3NH^+]}{K_f[Me_3NH^+]}\right)^2 \quad (8)$$

These equations were applied to data on titrations of 1 M trimethylammonium chloride solutions containing various amounts of added formaldehyde with 4 M sodium hydroxide. Fairly concentrated solutions of trimethylammonium chloride and formaldehyde had to be used in order to get significant fractions of transformation to formocholine. The strong sodium hydroxide solution was used to avoid dilution and to minimize the decrease in ionic strength that accompanies the titration. The ionic strength could have been kept constant by addition of a salt to the sodium hydroxide solution, but this did not seem worthwhile since at concentrations around 1 M salt effects are not so much ionic strength effects as they are specific salt effects. To further minimize salt effects, the titrations were not carried above about pH 9.5. In none of our titrations did the ionic strength change by as much as 5%. Equally important, in no case did the new ions introduced by the titration contribute as much as 16% to the ionic strength. Figure 1 contains titration curves in the presence of 0, 0.197, and 0.631 M formaldehyde. Blank experiments showed that addition of 0.63 M formaldehyde to a 1 M solution of trimethylammonium chloride at pH 2 has no effect on the pH, and that at around pH 9 a comparable concentration of ethylene glycol lowers the pH by only about one-tenth as much as formaldehyde does. It therefore seems unlikely that the effect of formaldehyde is largely a solvent effect.

From such curves, values of K_{af} were calculated at intervals of 0.1 pH unit. In these calculations K_f was taken as 0.5 M^{-1}, the value determined in deuterium oxide solution (K_f'). For K_d the value, 0.1 M^{-1}, calculated from the data of Skell and Suhr[8] was used. The value, 10.06, used for pK_{at} was determined by potentiometric titrations of 1 M solutions of trimethylammonium chloride with 4 M sodium hydroxide up to about pH 9.5. From the measurements of Loewenstein and Meiboom at 0.28–2.3 M trimethylammonium chloride concentrations, a value of 10.01 may be interpolated for 1 M salt and 22 ± 1°.[10] An estimated temperature correction[11] gives a value of 9.95 ± 0.02 at 25°. Since K_w appears only in the term for the hydroxide ion concentration, which was always negligible compared to that of the other species present, any value up to ten times the value we used ($10^{-14}M^2$) would give the same results that we obtained. (In the presence of 1 M sodium chloride[12] K_w is $10^{-13.73}$ M^2.) Variations of 20% in K_f, 0.03 in pK_{at}, 0.02 in the observed pH, and 100% in K_d change the calculated value of pK_{af} by 0.05, 0.03, 0.04, and 0.001, respectively. In Figure 2 the ranges of volumes required to reach given pH's are plotted as circles or vertical lines, and the theoretical volumes calculated from pK_{af} values of 9.30 and 9.40 are shown as curves. From such plots for titrations using 0.631 and 0.197 M total formaldehyde, the best value of pK_{af} was taken to be 9.33 ±

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(7) R. P. Bell, *Advan. Phys. Org. Chem.*, **4**, 1 (1966).

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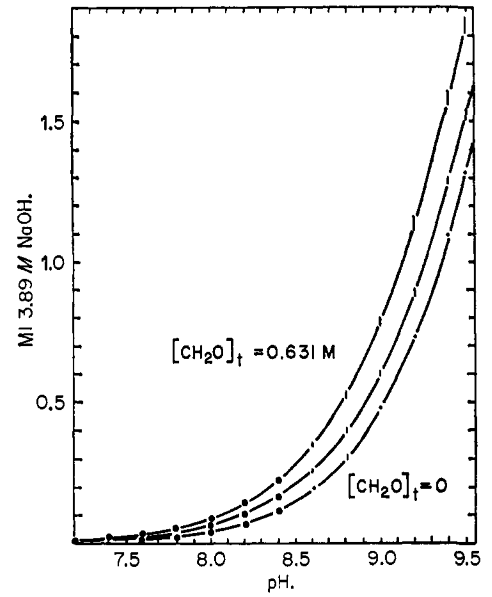

Figure 1. Plot of milliliters of added 3.89 M sodium hydroxide solution *vs.* pH in titration of 25-ml samples of 0.9595 M trimethylammonium chloride containing 0, 0.197, and 0.631 M total formaldehyde.

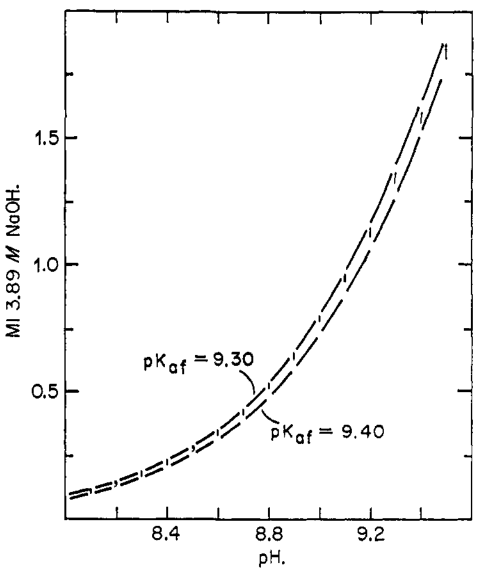

Figure 2. Plot of range of volumes of 3.89 M sodium hydroxide solution *vs.* pH (vertical lines). Theoretical volumes calculated on the basis of pK_{af} values of 9.30 and 9.40 are plotted as broken curves.

0.10 (including the uncertainties in K_f, K_{at}, pH, K_d, etc.).

Discussion of Results

Values of K_f were found in the literature for three other tertiary amines, pyridine,[4] N-methylimidazole,[4] and hexamethylenetetramine.[13] These values, 0.5, 1.6, and 4.3 M^{-1}, as well as those for several secondary amines, are of the same order of magnitude as that which we have found for trimethylamine. The first two values, at least, were determined by measurements of the effect of formaldehyde on the pH of tertiary amine buffers, in which the effect was attributed to the formation of B^+CH_2OH, and the formation of $B^+CH_2O^-$ was neglected. Such neglect seems warranted in the case of the three tertiary amines referred to, whose basicity is so low that at the pH's given by their buffers the ratio $[B^+CH_2O^-]/[B^+CH_2OH]$ should be quite small. Such neglect would not be warranted in the case of more strongly basic amines, however. In general, the addition of formaldehyde to B–BH buffers will raise the pH if BCH_2OH is a weaker acid than BH and lower it if BCH_2OH is a stronger acid (neglecting complications due to the acidity of formaldehyde hydrate itself). If the acidity of BH is too near that of BCH_2OH, the pH method will probably not be useful in determining the equilibrium constant for hydroxymethylation. In the case where B is a tertiary amine, substituents are so much further from the acidic proton in B^+CH_2OH than from the one in BH^+ that the acidity of the former will be much less sensitive to the nature of B. Formaldehyde may change the pH of buffer solutions by a medium effect also, but it seems likely that with some of the tertiary amines studied, particularly N-methylpyrrolidine, for which the pH change was the largest observed, the observed decreases in pH[4] are produced partly by hydroxymethylation. The pK of the monoprotonated form of triethylenediamine is so near that to be expected of its hydroxymethyl derivative that it is not clear whether major amounts of hydroxymethylation are occurring or not.

In reactions with a primary or secondary amine the equilibrium constant for the formation of $R_2N^+HCH_2O^-$ will be a part of the equilibrium constant attributed to the formation of the tautomeric R_2NCH_2OH. Let us estimate whether the zwitterionic forms ever comprise a major fraction of the tautomeric mixture. The largest amount of zwitterion will be present when the acidity of the nitrogen-bound proton of $R_2NHCH_2OH^+$ is the lowest relative to the acidity of the oxygen-bound proton. Since the R groups are closer to the nitrogen-bound than to the oxygen-bound proton, increases in the electron-withdrawing power of R will usually decrease the fraction of zwitterion present in the tautomeric mixture. Hence the more strongly basic amines will tend to form formaldehyde adducts containing a larger fraction of zwitterion. If both components of the tautomeric mixture are included, the constant denoted K_{a2}' by Kallen and Jencks may be rewritten

$$K_{a2}' = \frac{[R_2NCH_2OH][H^+]}{[R_2NHCH_2OH^+]} + \frac{[R_2N^+HCH_2O^-][H^+]}{[R_2NHCH_2OH^+]} \quad (9)$$

The second term on the right should have about the same value for all the cases in which the R groups do not contain significantly electron-withdrawing substituents. Hence the zwitterion will comprise the largest fraction of the tautomeric mixture when the value of K_{a2}' is the smallest. The smallest values that may be calculated from the data of Kallen and Jencks are 3.2×10^{-9} and 3.4×10^{-9} M^{-1} for the proline anion and pyrrolidine, respectively. If the second term on the right side of eq 9 in these cases has a value near 4.7×10^{-10}, the value we have measured for K_{af}, it follows that about 14% of the formaldehyde adducts of these amines is zwitterionic. On going from $R_2NHCH_2OH^+$ to $RNH_2CH_2OH^+$, the acidity of the nitrogen-bound hydrogen should decrease somewhat (secondary amines being stronger bases than the corresponding tertiary amines) while that of the oxygen-bound hydrogen may

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(13) Unpublished work of P. Le Hénaff quoted by Kallen and Jencks.[4]

be relatively unaffected. It therefore seems possible that more than 14% of the monoformaldehyde adducts of some primary amines consists of zwitterions. On the other hand it appears that in at least some cases, *e.g.*, that of glycine and its N-methyl derivatives,[14–16] replacement of the alkyl group on a trimethylammonio substituent by hydrogen decreases the electron-withdrawing power of the substituent. Hence the oxygen-bound proton in a species of the type $RNH_2CH_2OH^+$ may have an acidity constant considerably smaller than 4.7×10^{-10}.

The value of pK_{af} determined is in the vicinity of values that could have been predicted in various ways. The method of Branch and Calvin[17] leads to a value of 10.8 if methanol, whose pK is 15.5,[18] is used as a reference compound. A Taft equation correlation of the acidity of alcohols and a correlation using inductive substituent constants gave values of 8.5 and 10.2, respectively.[1a]

The transformation of formocholine chloride to trimethylammonium chloride and formaldehyde hydrate was studied by Stewart and Kung[19] at concentrations so dilute that the reaction went essentially to completion. The first-order rate constants (in sec^{-1}) obtained at 25° and ionic strengths around 0.3 *M* obeyed eq 10

$$\log k = -5.80 + pH \qquad (10)$$

from pH 1.4 to pH 4.2, above which the rate became too fast to measure. Measurements in the presence of citrate buffers showed no general base or acid catalysis for the reaction. The following mechanism is essentially a more detailed version of the mechanism suggested by Stewart and Kung

$$Me_3N^+CH_2OH \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Me_3N^+CH_2O^- + H^+$$

$$Me_3N^+CH_2OH + OH^- \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} Me_3N^+CH_2O^- + H_2O$$

$$Me_3N^+CH_2O^- \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} Me_3N + CH_2O$$

$$CH_2O + H_2O \underset{k_{-4}}{\overset{k_4}{\rightleftharpoons}} CH_2(OH)_2$$

$$Me_3N + H^+ \underset{k_{-5}}{\overset{k_5}{\rightleftharpoons}} Me_3NH^+$$

$$Me_3N + Me_3N^*H^+ \underset{k_{-6}}{\overset{k_6}{\rightleftharpoons}} Me_3NH^+ + Me_3N^*$$

In discussing this mechanism, all reactions involving, water will be treated as first order. Values of k_5, k_{-5}, k_6, and k_{-6} have been measured.[10,20] The reactions governed by k_{-1} and k_2 are exergonic proton transfers between oxygen atoms and hence should be diffusion controlled. Thus k_{-1} and k_2 may be estimated reliably from data on similar reactions[20] and k_1 and k_{-2} may be calculated from the equilibrium constants K_1 and K_2. Values of k_4 may be calculated from the study of the hydration of formaldehyde by Bell and Evans.[21] Combination of their rate data with equilibrium data[6,7] gives k_{H_2O}, k_{H^+}, and k_{OH} values of 10 sec^{-1} and 5×10^3 and 3×10^6 M^{-1} sec^{-1}, and from their Brønsted plots, values of 2 and 2×10^3 M^{-1} sec^{-1} may be estimated for $k_{Me_3NH^+}$ and k_{Me_3N}, respectively.[21] The value of k_3 may be calculated from the kinetic data of Stewart and Kung. According to the reaction mechanism given, the rate of formation of formaldehyde hydrate may be expressed as shown in eq 11 (neglecting reversibility).

$$\frac{d[CH_2(OH)_2]}{dt} = \frac{k_1k_3k_4[Me_3NCH_2OH^+]}{k_{-1}[H^+](k_{-3}[Me_3N] + k_4)} \qquad (11)$$

From the fact that the reaction rate was not found to be affected by the increasing concentrations of trimethylamine formed as the individual runs progressed, especially at the higher pH's, it follows that k_4 was always considerably larger than k_{-3} $[Me_3N]$ under the conditions of the kinetic runs. This and the fact that k_1/k_{-1} is K_{af} reduces eq 11 to eq 12. Comparison with

$$d[CH_2(OH)_2]/dt = k_3K_{af}[Me_3NCH_2OH^+]/[H^+] \qquad (12)$$

eq 10 shows that in dilute solution at 25° k_3K_{af} equals $10^{-5.80}$ *M* sec^{-1}. If K_{af} has the same value in dilute solution that we have determined in the presence of almost 1 *M* salts, k_3 equals 3.4×10^3 sec^{-1}.

The equilibrium constant for the heterolysis of the formocholine zwitterion may be expressed as shown in eq 13 where $K_h = [CH_2O]/[CH_2(OH)_2] = 5 \times 10^{-4}$ (in

$$\frac{k_3}{k_{-3}} = \frac{K_{at}K_h}{K_{af}K_f} = 2.7 \times 10^{-4} \qquad (13)$$

water at 25°).[6,7] The numerical value shown was calculated from a pK_{at} value (9.90) at ionic strength 0.3 *M* and 25° estimated from data at 20 and 30° and ionic strength 0.07–0.25 *M*[22] and our K_f value determined at 30 ± 5° in heavy water about 1 *M* in salts.

The value of k_{-3} calculated from eq 13 and other rate constants involved in the decomposition of formocholine are listed in Table I. Although there are uncertainties stemming from changes in constants because of changes in ionic strength or because of solvent isotope effects, these numbers are believed to be correct within a factor of 2 at worst. They explain the surprising observation that the decomposition of formocholine to trimethylammonium ions and formaldehyde hydrate (and its reversal) in heavy water at pD 7 is fast enough

Table I. Rate Constants Involved in the Hydrolysis of Formocholine Cations in Water at 25°

n	k_n[a]	k_{-n}[a]
1	1.2×10^1 [b]	2.5×10^{10}
2	2×10^{10}	4×10^5 [b]
3	3.4×10^3	1.3×10^7
5	2.5×10^{10}	4[b]
6	3.1×10^8	3.1×10^8

[a] In M^{-1} sec^{-1} unless otherwise stated. [b] Sec^{-1}.

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(14) B. B. Owen, *J. Amer. Chem. Soc.*, **56,** 24 (1934).

(15) J. Johnson, *Proc. Roy. Soc.* (London), **A78,** 82 (1906).

(16) O. Weider, *Ber.*, **68,** 263 (1935).

(17) G. E. K. Branch and M. Calvin, "The Theory of Organic Chemistry," Prentice-Hall, Inc., New York, N. Y., 1941, p 201.

(18) P. Ballinger and F. A. Long, *J. Amer. Chem. Soc.*, **82,** 795 (1960).

(19) T. D. Stewart and H. P. Kung, *ibid.*, **55,** 4813 (1933). It may be seen from the text that the numbers on the abscissa of Figure 1 of this paper should each be increased by 1.

(20) M. Eigen, *Angew. Chem. Intern. Ed. Engl.*, **3,** 1 (1964).

(21) R. P. Bell and P. G. Evans, *Proc. Roy. Soc.* (London), **A291,** 297 (1966).

(22) D. H. Everett and W. F. K. Wynne-Jones, *ibid.*, **A177,** 499 (1941).

to merge the pmr methyl peaks of formocholine and trimethylammonium ions but not fast enough to merge the pmr methylene peaks of formocholine and formaldehyde hydrate. Under the conditions of the pmr measurements at pD 7, the value of $k_{-3}[\mathrm{Me_3N}]$ is about 10^4 sec^{-1} while that of k_4 is about 14 sec^{-1}. Hence the rate-controlling step in the formation of formaldehyde hydrate from formocholine under these conditions is hydration of the aldehyde. The sum of the first-order rate constants for the transformation of formocholine to formaldehyde hydrate and for the reverse reaction, *i.e.*, the first-order rate constant for approach to equilibrium, is about 2×10^{-2} sec^{-1}. Since this is much smaller than $2\pi(12)$ sec^{-1}, the pmr peak for formaldehyde hydrate is not expected to be merged with the methylene peak of formocholine, which is 12 Hz away from it.[23] In the formation of trimethylammonium ions from formocholine, however, $k_6[\mathrm{Me_3NH^+}]$ (about 3×10^8 sec^{-1}) is so much larger than $k_{-3}[\mathrm{CH_2O}]$ (about 10^3 sec^{-1}) that the rate-controlling step is the heterolysis of the formocholine zwitterion. This conclusion leads to the calculation of about 1×10^2 sec^{-1} as the rate constant for approach to equilibrium in the formocholine–methylammonium reaction. The fact that the methyl peak of formocholine has merged with that of trimethylammonium ions, which had been about 6 Hz away, is therefore not surprising. The rapid exchange of the trimethylammonio groups of formocholine is presumably also responsible for the elimination of the broadening of the methylene peak of formocholine, which was probably caused by the nitrogen atom to which the methylene group was attached. At pD 9.8 the methyl peaks were still merged and the methylene peaks still separate, just as would be expected from the rate constants in Table I.

At pD 2 the heterolysis of the formocholine zwitterion may be shown to be the rate-controlling step in the formation of either formaldehyde hydrate or trimethylammonium ions, but the rate constants for the interconversions at this pD are so small that the pmr peaks would not be expected to be merged.

It is interesting that according to the rate constants in Table I, near the end of a kinetic run in the most basic solutions (~pH 4.2) used by Stewart and Kung, the amount of trimethylamine in equilibrium with the ~0.05 *M* trimethylammonium ions formed would give a value of $k_{-3}[\mathrm{Me_3N}]$ about one-tenth as large as k_4 under these conditions. Apparently if the kinetic study had been carried about one pH unit further toward the basic region, the rate-controlling step of the reaction would have changed and eq 10 would no longer have been applicable.

Experimental Section

Methoxymethyltrimethylammonium Chloride. The reaction of trimethylamine with chloromethyl methyl ether in acetonitrile solution gave methoxymethyltrimethylammonium chloride, which has been referred to by other workers[24] without mention of the method of synthesis. The pmr spectrum[25] of a 1.5 *M* solution of this salt in deuterium oxide containing 0.1 *M* dimethyl sulfoxide showed singlets at 0.37, 0.99, and 1.87 ppm.[5] Addition of protium oxide caused the rather broad singlet at 1.87 ppm to separate into one broad peak (width at half-height 2.3 ppm) and one narrow peak at slightly lower field, which grew upon further addition of protium oxide. Relative areas of the 0.37- and 0.99-ppm peaks and the broader of the 1.87-ppm peaks were 9:3:2.

Determination of the Equilibrium Constant for the Formation of Formocholine Cations. Standard solutions of formaldehyde were prepared by heating trioxane with dilute hydrogen chloride in deuterium oxide, and the concentration was checked in some cases by iodometric titration.[26] The pmr spectra of these solutions showed singlets at 1.98 (residual protium from the solvent), 2.09 (formaldehyde hydrate), and 2.16 ppm[5] [terminal methylene groups in $\mathrm{HO(CH_2O)}_n\mathrm{H}$ polymers], and at higher concentrations than those at which formocholine formation was studied a peak at still lower field, due to internal methylene groups in $\mathrm{HO(CH_2O)}_n\mathrm{H}$ polymers.[8] Solutions of trimethylammonium chloride (recrystallized if necessary to remove acidic impurities) were prepared by dissolving in deuterium oxide, evaporating to remove protium, and adding more deuterium oxide. Their strength was checked by argentometric analysis. The pmr spectra of these solutions showed a singlet at 0.17 ppm[5] in addition to the residual proton peak.

Solutions of formaldehyde and trimethylammonium chloride with a pD of 2 showed singlets at 0.18, 0.29, 1.88 (width at half-height 2.1 Hz), 1.92, 2.08, and 2.15 ppm.[5] The peak at 1.92 ppm grew when protium oxide was added to the solution. The peak at 0.29 ppm had 4.5 times the area of that at 1.88 ppm. Similar solutions to which disodium hydrogen phosphate had been added to give a pD of 7 had singlets at 0.19, 1.88 (width at half-height 0.8 Hz), 1.92, 2.08, and 2.15 ppm.[5]

To determine K_f', concentrations of trimethylammonium ions, formaldehyde hydrate, and formocholine are needed. Since essentially all the formaldehyde originally added is present as formaldehyde hydrate, bis(hydroxymethyl) ether, or formocholine, the concentration of each of these three species may be calculated from the relative areas of the pmr peaks at 2.08, 2.15, and 1.88 ppm. Similarly, at pD 2 the concentrations of trimethylammonium ions and formocholine may be calculated from the total concentration of trimethylammonium ions originally added and the relative areas of the peaks at 0.18 and 0.29 ppm. These two methods of calculating the formocholine concentration give two methods of calculating K_f'. At pD 7, there was only one methyl peak and hence only one way of calculating the formocholine concentration, which was then subtracted from the concentration of trimethylammonium ions originally added to get the concentration at equilibrium. The results from four runs are summarized in Table II. Peak areas in the first three runs shown were integrated electronically, and in the fourth run the areas were measured with a planimeter. Since the concentration of formocholine was more nearly comparable to that of formaldehyde than to that of trimethylammonium ions, the concentration determined from the area of the methylene peak is

Table II. Equilibrium in the Reaction of Trimethylammonium Chloride with Formaldehyde in Aqueous Solution[a]

		pD			
		2	2	7	7
$[\mathrm{CH_2O}]_t$, *M*		0.58	0.58	0.58	0.47
$[\mathrm{Me_3ND^+}]_t$, *M*		1.35	1.35	1.35	1.25
$\mathrm{C}H_2\mathrm{(OD)_2}$		3.39	6.44	12.57	27.3
$\mathrm{(CH_3)_3N^+C}H_2\mathrm{OD}$	*b*	1.67	3.59	6.99	16.0
$\mathrm{O(C}H_2\mathrm{OD)_2}$		0.23	0.56	1.79	*c*
$\mathrm{(C}H_3\mathrm{)_3N^+D}$		12.17	16.55		
$\mathrm{(C}H_3\mathrm{)_3N^+CH_2OD}$	*b*	2.62	4.45		
K_f', M^{-1}		0.44[d] (0.58)[e]	0.52[d] (0.76)[e]	0.48[d]	0.54[d]

[a] At 30 ± 5°. [b] Pmr peak areas. Within a given run, one set of spectrometer settings was used for the methylene peaks and another set for the methyl peaks. [c] This peak was not measured but assumed (on the basis of the other three runs) to be 2.2. [d] Based on a formocholine concentration calculated from areas of methylene peaks. [e] Based on a formocholine concentration calculated from areas of methyl peaks.

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(25) All pmr spectra were determined using Varian spectrometers, Models A-60 and A-60A.

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thought to be more reliable than that determined from the methyl peak. Therefore we have weighted the parenthesized values of K_t' in Table II relatively lightly and taken as an average value and probable uncertainty $0.5 \pm 0.1\ M^{-1}$.

Determination of the Acidity Constant of the Formocholine Cation. Titrations were carried out at 25 ± 0.1° using a Radiometer Model 26 pH meter, G202B (pH 0–14) glass electrode, calomel reference electrode, and 2.5-ml Auto-Burette. It was assumed that in the titration solutions $-\log [H^+] = X + \text{pH}$, where X is a constant and pH is the reading on the meter. The meter was adjusted to read within 0.01 of the correct pH values for standard buffers with pH's of 7.413, 4.01, and 2.044 (0.01 *M* hydrochloric acid). It was then found to read 2.00 ± 0.01 for 0.01 *M* solutions of hydrochloric acid in 1.00 *M* trimethylammonium chloride and in 0.64 *M* formaldehyde plus 1.00 *M* trimethylammonium chloride. Therefore in this case, X is zero and the observed pH is equal to $-\log [H^+]$.

The addition of 0.631 *M* formaldehyde, as shown in Figure 1, increased the amount of sodium hydroxide required to reach a given pH in the titration of 25 ml of 0.96 *M* trimethylammonium chloride by as much as 2.0 mequiv. Blank experiments showed that the addition of 1.0 *M* formaldehyde never increased the amount of sodium hydroxide required to reach a given pH in the titration of 25 ml of water by more than 0.01 mequiv up to pH 9.5. When solutions of trimethylammonium chloride that had been titrated to pH 8.98 and 9.36 were made 0.6 *M* in ethylene glycol, their pH's decreased by 0.03 and 0.02, respectively.

Electron Spin Resonance Studies of the Reactions of Tris(1-naphthalene)phosphine and Its Oxide, Sulfide, and Selenide with Alkali Metals in Tetrahydrofuran and 1,2-Dimethoxyethane

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Abstract: Tris(1-naphthalene)phosphine (I) was allowed to react separately with lithium, sodium, potassium, and sodium–potassium alloy in tetrahydrofuran (THF) and in 1,2-dimethoxyethane (DME). In both solvents the reaction of I with sodium gave the naphthalene radical anion (II) while with potassium, $[(C_{10}H_7)_2PK]\cdot^-$(III) was formed. Reduction with sodium–potassium alloy gave a mixture of II and III. The reaction of I with lithium gave the 1,1′-binaphthyl radical anion, but when the lithium was allowed to react initially with glass and then with I, the perylene radical anion IV was formed. The oxide, sulfide, and selenide derivatives of I all behaved similarly to I in their reactions with the alkali metals in THF and DME. The electron spin resonance (esr) spectra of the 1,1′-binaphthyl radical anion was also studied. The mechanisms of the above reactions are discussed.

The reactions of arylphosphines with alkali metals in THF and DME have yielded interesting results. For example, Wittenberg and Gilman[1] reported the cleavage of triphenylphosphine by lithium to yield diphenylphosphinolithium and phenyllithium. Hanna[2]

$$(C_6H_5)_3P + 2Li \xrightleftharpoons{\text{THF}} (C_6H_5)_2PLi + C_6H_5Li$$

reported that this reaction with alkali metals produces the mononegative ion $[(C_6H_5)_3P]\cdot^-$ identified from its esr spectrum. The cleavage of phenyl groups from $(C_6H_5)_3P$ by alkali metals in THF is a well-known reaction,[1,3,4] and it has been reinvestigated in detail by Britt and Kaiser.[5] They studied the reaction as a function of the concentration of $(C_6H_5)_3P$ for the three alkali metals, K, Na, and Li, and the course of the reaction was followed by chemical methods and esr spectroscopy. They reported that the spectrum of the radical formed, as determined by the hyperfine splittings and the intensities of the lines, belongs to $[(C_6H_5)_2PK]\cdot^-$. Another esr study was reported by Kabachnik, *et al.*,[6] who observed the spectrum of the triphenylphosphine anion radical. This work was not in agreement with previous data on this compound.

In a comparison of the reactions of triphenylphosphine with those of triphenylphosphine oxide, Hein, Plust, and Pohleman[7] reported that triphenylphosphine oxide forms adducts with alkali metals which they formulated as Ar_3POM, Ar_2POM_3, and ArM, respectively. On the other hand, Hoffmann and Tesch[8] reported that solutions of triphenylphosphine oxide react with lithium or sodium to form the biphenyl radical anion in DME solution. A different paramagnetic species was obtained when potassium was used as the reducing agent. The spectrum consisted of eleven lines split by 1.75 G, which slowly disappeared when excess potassium was added due to formation of biphenyl radical anions.

Cowley and Hnoosh[9] reported that the free-radical species derived from $(C_6H_5)_3PO$ depends upon the alkali metal and the solvent. Like Hoffmann and Tesch,[8] they were able to detect only the biphenyl anion radical (*via* phenyl-P cleavage) in the reduction of $(C_6H_5)_3P(O)$ in DME by sodium. They obtained the same result by means of sodium reduction in THF.

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