Methylene Derivatives of Nitrogen, Oxygen, and Sulfur. Cationic *N,N'*-Methylenediamine Formation and Thermodynamic Parameters for Equilibria for the Reaction of Morpholine with Formaldehyde and Protons[1,2]

Roland G. Kallen,* Richard O. Viale, and Linda K. Smith

Contribution from the Department of Biochemistry, School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania 19104.

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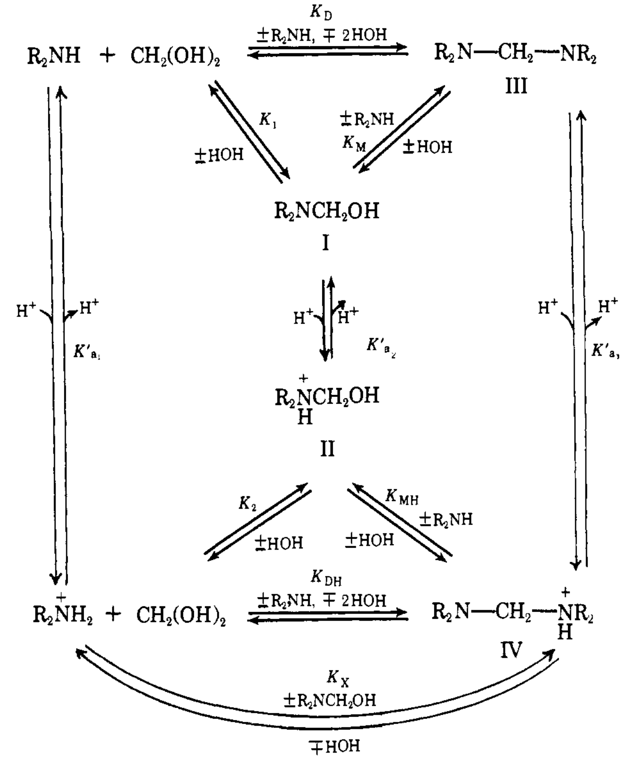
Abstract: The equilibrium constants for the formation of protonated and neutral *N,N'*-methylenedimorpholine and *N*-hydroxymethylmorpholine have been measured by potentiometric determinations of hydrogen ion activity in morpholine buffers containing formaldehyde. The pK_a' values for protonated morpholine, *N*-hydroxymethylmorpholine, and *N,N'*-methylenedimorpholine are 8.88, 6.09, and 7.38, respectively, and agree with calculated values based on Condon's general equation, which quantitatively relates amine ionization constants with polar, hydration, and statistical factors. A comparison of pK_a' values for linear and cyclic methylenediamines of aliphatic and aromatic amines, including heterocyclic amines, indicates that the pK_a' value for the protonated methylenediamine is, in general, 0.4–1.5 units below that of the parent amine. Estimates of pK_a' values for major O, N, and S methylene derivatives are presented.

Equilibrium constants have been reported[3] for the formation of neutral and cationic *N*-hydroxymethyl derivatives of amines (carbinolamines, I and II of Scheme I, respectively), and neutral *N,N'*-methylenediamines[4] (methylenebisamines, III of Scheme I) from aqueous solutions of amines and aldehydes. Methylenediamines and their hydrohalide salts have been isolated under nonaqueous conditions.[5,6] In view of the stability of noncyclic methylenediamines[3] and the small $\Delta pK_a'$ between *N,N'*-diphenylethylenediamine-H$^+$ and *N,N'*-diphenylimidazolidine-H$^+$,[7] cationic linear methylenediamines (IV, Scheme I) are expected to form in aqueous solutions of neutral and cationic amines and formaldehyde. The equilibria between amines and carbonyl compounds in Scheme I are relevant to interactions of aldehydes[8,9] with proteins[8a,10,11] and nucleic acids,[12] reactions of pyridoxal phosphate,[11] the Mannich reaction,[5,6,8c,8d,13] and nucleophilic catalysis of the formation of many nitrogen derivatives of carbonyl compounds.[11,14]

Scheme I



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(2) Abbreviations: F_F and F_T are free and total formaldehyde hydrate; N_{AF} and N_{AT} are free and total cationic morpholine; N_B is bound amine; N_{BF} and N_{BT} are free and total morpholine free base; N_D and N_{DH} are neutral and cationic methylenediamine; N_H and N_{HH} are neutral and cationic hydroxymethylamine; N_T is total amine.

(3) (a) R. G. Kallen and W. P. Jencks, *J. Biol. Chem.*, **241**, 5864 (1965); (b) P. Le Hénaff, *Bull. Soc. Chim. Fr.*, **11**, 3113 (1965); (c) P. Le Hénaff, *C. R. Acad. Sci.*, **258**, 896 (1964), and references therein; (d) J. De Luis, "The Chemistry of Formaldehyde Amine Condensation Products," Ph.D. Thesis, Pennsylvania State University, 1964; *Chem. Abstr.*, **63**, 8184d (1965). Values of K_M (called K_2 in ref 3d) for other amines, determined by an nmr method, are contained in this thesis.

(4) Hydroxymethylamine and methylenediamine refer to the nitrogen adducts.

(5) J. R. Feldman and E. C. Wagner *J. Org. Chem.*, **7**, 31 (1942).

(6) (a) W. C. Hunt and E. C. Wagner, *J. Org. Chem.*, **16**, 1792 (1951); (b) E. Knoevenagel, *Ber.*, **31**, 2585 (1898).

(7) L. Jaenicke and E. Brode, *Justus Liebigs Ann. Chem.*, **624**, 120 (1959). The unexpectedly small $\Delta pK_a'$ values for the most acidic proton dissociation between the dicationic imidazolidine and the dicationic parent ethylenediamine derivatives for the more electron-withdrawing substituents may result from the difficulty in obtaining accurate data in the pH range required: the relevant pK_a' values for dicationic substituted *N,N'*-diphenylimidazolidines are 1.9, 1.6, 0.8, and 0.3 for CH_3CH_2O, CH_3, H, and Br, respectively.

(8) (a) D. French and J. T. Edsall, *Advan. Protein Chem.*, **2**, 277 (1945); (b) E. C. Wagner, *J. Org. Chem.*, **19**, 1862 (1954); (c) B. Reichert, "Die Mannich Reaktion," Springer-Verlag, Berlin, 1959; (d) H. Hellmann and G. Opitz "α-Aminoalkylierung," Verlag Chemie, Weinheim, Germany, 1960.

(9) J. F. Walker, "Formaldehyde," 3rd ed, American Chemical Society Monograph, Reinhold, New York, N. Y., 1964.

(10) F. M. Richards and J. R. Knowles, *J. Mol. Biol.*, **37**, 231 (1968).

(11) R. G. Kallen, *J. Amer. Chem. Soc.*, **93**, 6227, 6236 (1971).

(12) H. Boedtker, *Biochemistry*, **6**, 2718 (1967), and references therein.

(13) J. H. Burckhalter, J. N. Wells, and W. J. Mayer, *Tetrahedron Lett.*, **21**, 1353 (1964).

(14) R. G. Kallen and W. P. Jencks, *J. Biol. Chem.*, **241**, 5851 (1966).

Table I. Temperature Dependence of Equilibrium Constants[a] for Morpholine, Formaldehyde, and Protons at Ionic Strength 1.0 *M*, Water Activity 1.0

T, °C	K_1, M^{-1}	K_2, M^{-1}	K_M, M^{-1}	K_{MH}, M^{-1}	pK_{a_1}' [b]	pK_{a_2}' [b,c]	pK_{a_3}' [c]
6	1980	1.80	27.9	532	9.30	6.26	7.53
15	1390	1.64	23.6	494	9.11	6.18	7.50
25	925	1.51	18.2	362	8.88	6.09	7.38
35	660	1.44	14.0	232	8.66	6.00	7.22
44	455	1.37	11.6	188	8.46	5.93	7.14
58	310	1.26	8.5		8.22	5.83	

[a] F = formaldehyde hydrate. [b] $\log(K_1/K_2) = pK_{a_1}' - pK_{a_2}'$. [c] $\log(K_M/K_{MH}) = pK_{a_2}' - pK_{a_3}'$; $K_1 = [R_2NCH_2OH][HOH]/[R_2NH][F]$; $K_2 = [R_2^+NHCH_2OH][HOH]/[R_2^+NH_2][F]$; $K_M = [R_2NCH_2NR_2][HOH]/[R_2NCH_2OH][R_2NH]$; $K_{MH} = [R_2HN^+CH_2NR_2][HOH]/[R_2^+NHCH_2OH][R_2NH]$; $K_{a_1}' = a_{H^+}[R_2NH]/[R_2^+NH_2]$; $K_{a_2}' = a_{H^+}[R_2NCH_2OH]/[R_2NH^+CH_2OH]$; $K_{a_3}' = a_{H^+}[R_2NCH_2NR_2]/[R_2NCH_2NH^+R_2]$.

However, neither the formation constant nor the pK_a' value for noncyclic cationic methylenediamines has appeared despite their essentiality for the complete description of the composition of solutions of aliphatic amines and formaldehyde in the physiologic pH range. The present communication provides equilibrium constants for the quantitative evaluation of the composition of solutions of morpholine and formaldehyde over wide pH and temperature ranges and includes estimates of pK_a' values for major O, N, and S methylene derivatives of formaldehyde.

Experimental Section

Materials. Reagent grade formaldehyde (36.6–37.2% containing 10 to 12% methanol, Fisher) was diluted to 4.0 and 1.0 *M* stock solutions and the concentration was determined by sulfite titration.[9] The concentrated formaldehyde was found to contain a titratable acidity, presumably formic acid, of about 2×10^{-3} *M* and to have a pH between 3 and 4. The acid in the formaldehyde solutions was neutralized with sodium hydroxide; sodium formate does not affect equilibrium constant determinations that were restricted to the pH range above pH 5.

Morpholine was redistilled under nitrogen before use. The concentration of morpholine solutions was determined gravimetrically and by titration with HCl. Reagent grade inorganic reagents were used without further purification. Deionized water with specific resistance greater than 0.5×10^6 ohm cm was used.

Measurements of pH were made in thermostated vessels with a G-2021B combined glass electrode and a Radiometer 25 or 26 SE pH meter standardized with Beckman pH 4, 7, and 10 buffers at the designated temperatures.

Methods. Methods for the determination of the equilibrium constants for hydroxymethylmorpholine and protonated hydroxymethylmorpholine formation by the formol titration technique have been described.[3a]

The equilibrium constants for methylenedimorpholine formation from hydroxymethyl-and neutral morpholine, K_M, were determined from the final pH values of solutions obtained by adding increasing amounts of a solution containing equimolar morpholine and formaldehyde to a solution of known pH prepared from morpholine, morpholine hydrochloride, and formaldehyde.[3a] At pH > 8.5 the concentrations of the protonated forms of hydroxymethylmorpholine and methylenedimorpholine were insignificant.

With values for equilibrium constants K_1, K_2, K_{a_1}', and K_M (Scheme I), the equilibrium constant for protonated methylenedimorpholine formation, K_{MH}, was determined at pH < 8.5 from the final pH of solutions formed by addition of formaldehyde to concentrated morpholine buffers of rather small fractions of free base. Ionic strength was maintained at 1.0 *M* with KCl.

The maximal changes in pH occurred within 5 min and were constant for 60 min, which indicates that equilibrium is attained rapidly in this system.[3a]

Results

Neutral and Cationic Hydroxymethylmorpholine Formation. The change in pH of relatively dilute morpholine buffer solutions that results from the addition of formaldehyde is described by eq 1, where F_F is free

$$\text{antilog}\,(pH_0 - pH_{obsd}) = \text{antilog}\,\Delta pH = (1 + K_1[F_F])/(1 + K_2[F_F]) \quad (1)$$

formaldehyde hydrate, $K_1 = [R_2NCH_2OH]/[R_2NH][F_F]$, $K_2 = [R_2NHCH_2OH^+]/[R_2NH_2^+][F_F]$, and pH_0 and pH_{obsd} are pH values in the absence and presence of formaldehyde, respectively. The concentration of free formaldehyde was calculated iteratively from eq 1 until self-consistency obtained. Plots of antilog ΔpH against free formaldehyde hydrate concentration have the forms of rectangular hyperbolae (see Figure 2 in ref 3a) due to the formation of the protonated hydroxymethyl adduct of morpholine, K_2, as well as the neutral hydroxymethyl adduct, K_1. Under the conditions employed, $K_1[F_F] \gg 1.0$, and eq 1 may be rearranged to eq 2; double reciprocal plots (Figure 1) give K_1 and K_2 (Table I). Values of 925 and 1.51 M^{-1} for K_1 and K_2, respectively, at 25° and ionic strength 1.0 *M* agree with values of 1100 ± 200 and 1.9–2.1 M^{-1}, respectively, obtained by Le Hénaff at 20°[3b,c] and 899 M^{-1} for K_1 obtained by Skell and coworkers.[3d]

$$1/\text{antilog}\,\Delta pH = K_2/K_1 + 1/(K_1[F_F]) \quad (2)$$

Methylenediamine Formation. At pH > 8.5 there should be an insignificant change in pH if methylenediamine formation from added hydroxymethylamine does not occur, while formation of methylenediamine will result in a decrease in pH because it will decrease the concentration of free amine and the $[R_2NH]/[R_2NH_2^+]$ ratio. The observed decrease in pH upon addition of hydroxymethylmorpholine to morpholine buffers is evidence for the formation of methylenedimorpholine in these solutions.[3a]

Under conditions in which the amount of free formaldehyde is negligible compared to the amount combined with amine, eq 3 holds,[3a] where $[N_B]$, the concentration of amine which is bound as hydroxymethylamine and methylenediamine, is obtained from total and free base amine concentrations. The concentration of free base amine is known from the pH and the concentration of $R_2NH_2^+$. The slope of plots of the left side of eq 3 against $[N_F]$ gives K_D or K_M (Table I, Figure 2).

$$[N_B]/(2[F_T]) - [N_B]) = 1 + 2K_D[N_F]/K_1 = 1 + 2K_M[N_F] \quad (3)$$

The value of K_D for methylenediamine formation from morpholine and formaldehyde was previously reported[3a] as 15,200 M^{-1} largely the result of a lower K_1 of 800 M^{-1} for ionic strength 0.05 *M* at 25°. Difference in ionic strength accounts for only a portion of the

Table II. Experimental Data and Calculated Cationic Methylenedimorpholine Proton Dissociation Constants (pK_{a_3}')[a] at Various Temperatures, Ionic Strength, 1.0 *M*

pH								Total formaldehyde, *M*		pK_{a_3}'							
Temp, °C										Temp, °C							
6[b]	15[b]	25[b]	25[c]	25[d]	25[e]	35[c]	44[c]	1	2	6[b]	15[b]	25[b]	25[c]	25[d]	25[e]	35[c]	44[c]
7.77	7.54	7.36	7.31	7.63	7.58	7.15	6.93										
5.97	5.84	5.89	5.75		5.80	5.80	5.70	0.1192	0.1517	7.52	7.52	7.41	7.38		7.39	7.16	7.11
5.80	5.69	5.69	5.60	5.76	5.66	5.61	5.52	0.1509	0.2490	7.55	7.51	7.41	7.38	7.42	7.40	7.24	7.17
5.71	5.60	5.61	5.52	5.50	5.47	5.54	5.46	0.1748	0.3890	7.56	7.52	7.40	7.36	7.41	7.35	7.20	7.11
5.63	5.53	5.54	5.45	5.37	5.26	5.47	5.39	0.1986	0.502	7.58	7.52	7.40	7.35	7.42	7.34	7.20	7.11
5.55	5.44	5.41	5.35	5.22	5.14	5.33	5.25	0.2463	0.700	7.50	7.47	7.37	7.38	7.43	7.36	7.25	7.16
5.45	5.34	5.32	5.26	5.08	5.02	5.24	5.16	0.2979	1.04	7.52	7.48	7.36	7.36	7.44	7.42	7.24	7.15
5.37	5.26	5.24	5.18			5.16	5.08	0.3495		7.53	7.49	7.38	7.37			7.25	7.16
5.31	5.21	5.18	5.12			5.10	5.03	0.3972		7.53	7.48	7.38	7.38			7.25	7.15
									Av pK_{a_2}'	7.53	7.50	7.38				7.22	7.14
									Stand. dev	±0.03	±0.02	±0.03				±0.03	±0.03

[a] See Appendix for the equation for the calculation of pK_{a_3}'. [b] Morpholine buffer 2.0 *M*, 0.0524 *M* free base, [F_T] of column 1. [c] Morpholine buffer 2.0 *M*, 0.0587 *M* free base, [F_T] of column 1. [d] Morpholine buffer 1.952 *M*, 0.1034 *M* free base, [F_T] of column 2. [e] Morpholine buffer 0.976 *M*, 0.0517 *M* free base, [F_T] of column 2.

difference in K_1 values and the value of 925 M^{-1}, based upon a greater number of experiments, yields a value of K_D of 16,800 M^{-1} at 25°. These results may be compared to values of K_D of 18,300 ± 3000 M^{-1}, corrected to 25°,[3b,c] and 11,600–12,300 M^{-1} in deuterium oxide.[3d]

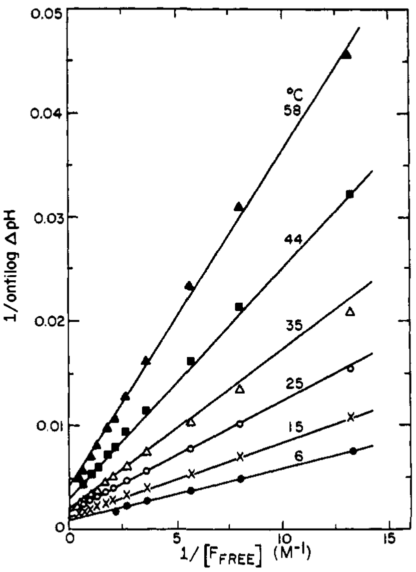

Figure 1. Graphical method for evaluation of equilibrium constants for neutral and cationic hydroxymethyl adducts of morpholine, K_1 and K_2, respectively, at ionic strength 1.0 *M* and various temperatures: ●, 6°; ×, 15°; ○, 25°; △, 35°; ■, 44°; and ▲, 58°. Solid lines are calculated lines from eq 2 and the values of K_1 and K_2 contained in Table I. Morpholine buffers 0.05 *M*, 50% free base, and formaldehyde hydrate concentrations *ca.* 0.06–2.0 *M*.

Cationic Methylenedimorpholine Formation. The complete description of the formaldehyde and proton equilibria with morpholine in the pH range 3–11 (Scheme I) involves nine equations and nine unknown parameters only eight of which, however, are independent (see Appendix). With knowledge of the five equilibrium constants previously determined, K_1, K_2, K_{a_1}', K_{a_2}' and K_M, pH, the free base and protonated morpholine concentrations (in the absence of formaldehyde), and the total formaldehyde concentration, the system is uniquely determined. Solution of eq 9a (see Appendix) for the protonated morpholine concentration at equilibrium (or the analogous cubic equation for the free base morpholine concentration at equilibrium) enables the calculation of both K_{MH} and K_{a_3}'. The experimental conditions, pH measurements, K_{MH}, and pK_{a_3}' values are contained in Tables I and II.

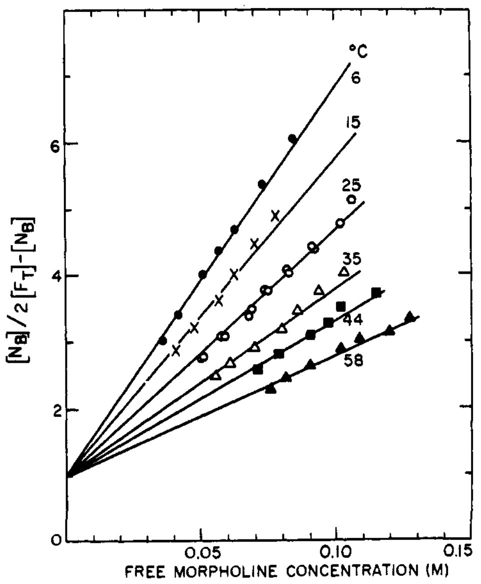

Figure 2. Graphical method for evaluation of equilibrium constant for methylenedimorpholine formation, K_D, at ionic strength 1.0 *M* and various temperatures: ●, 6°; ×, 15°; ○, 25°; △, 35°; ■, 44°; and ▲, 58°. The solid lines are calculated from eq 3 and the values of K_1 and K_M contained in Table I.

Logarithmic plots of the equilibrium constants in Table I against the reciprocals of the absolute temperatures are linear. The enthalpies of reaction were calculated from the slopes obtained from the least-squares fits of the data (Table III). These results may be compared with ΔH_1 and ΔH_M values of −8.0 and −5.5 kcal/mol, respectively, for morpholine and formaldehyde obtained by Le Hénaff.[15]

Optimization of Conditions for Determination of Proton Dissociation Constant of Cationic Methylenedimorpholine (pK_{a_3}'). Exploration of the properties of the system of equilibria of Scheme I by computing

(15) P. Le Hénaff, personal communication.

Table III. Free Energy, Enthalpy, and Entropy Parameters for Equilibria[a] between Morpholine, Formaldehyde, and Protons

Equilibrium	$\Delta G°$, kcal/mol	$\Delta H°$, kcal/mol	$\Delta S°$, eu
K_1	-4.04^b	-6.6	-8.6
K_2	-0.24^b	-1.2	-3.2
K_M	-1.73^b	-4.3	-8.6
K_{MH}	-3.49^b	-5.2	-6.0
K_{a_1}'	$+12.1^b$	$+8.9$	-10.6
K_{a_2}'	$+8.30^b$	$+3.5$	-16.0
K_{a_3}'	-10.1^b	$+4.4$	-18.6

[a] For definition of constants see Table I. [b] 25°.

the solutions of the appropriate cubic equation (see Appendix) for different hypothetical conditions revealed a rather narrow range of experimental conditions which permit the pK_{a_3}' value to be determined with reasonable accuracy by the potentiometric method. The ratio of [base]/[acid] must be quite low, the total buffer and the total formaldehyde concentrations quite high, and the total formaldehyde concentration greater than the total free base amine for optimal results.

Discussion

Effect of Structure on Equilibrium Constants. Hydroxymethylamines. The equilibrium constants for the formation of neutral and cationic hydroxymethylamines, K_1 and K_2 (Scheme I), from amines and formaldehyde are relatively insensitive to the polar character of the amine.[3a] This is a reflection of the similar polar properties of hydrogen and the hydroxymethyl group (σ^* values are 0.49 and 0.56, respectively), and has been discussed in detail elsewhere.[3a,16]

The pK_a' values for protonated morpholine and hydroxymethylmorpholine (determined potentiometrically in this study) of 8.88 and 6.09,[17] respectively, correlate well with calculated values (8.88 and 6.07,[19] respectively) from the generalization of Hall's work[18] by Condon,[20] which correlates the basicity of amines with polar, solvation, and statistical factors. In Condon's equations the major term contributing to the difference in pK_a' values between secondary and tertiary amines of a given $\Sigma\sigma^*$ value (for substituents on nitrogen) results from the effects of hydration. The agreement between the measured and calculated values is consistent with a previous suggestion[3a] that the differences in the solvation energy of the cations are largely responsible for the differences in pK_a' of 2–3 between protonated aliphatic amines and their protonated hydroxymethyl derivatives.

The cationic imine, the zwitterionic form of hydroxymethylmorpholine[21] ($>N^+HCH_2O^-$) and cationic dihydroxymethylmorpholine[3d,11] ($>N^+(CH_2OH)_2$) have been omitted from Scheme I since calculations indicate that these species constitute minor and negligible fractions of the total morpholine under the experimental conditions employed.[3d,11,21]

Methylenediamines. The equilibrium constant, K_M, for the formation of methylenedimorpholine from hydroxymethylmorpholine and a second molecule of morpholine[22] is 36.4 M^{-1}. The value of K_1 is 463 M^{-1} for the formation of hydroxymethylmorpholine from morpholine and formaldehyde.[23] Comparison of these values indicates that the tendency of a hydroxymethylamine molecule to combine with an amine is about tenfold less than that of methylene glycol. The tenfold difference in affinity has been accounted for elsewhere.[24]

Comparison of the values of K_M[22] and K_{MH} of 36.4 and 300 M^{-1}, respectively, indicates that the tendency of a protonated hydroxymethylamine to combine with an amine is some tenfold greater than that of neutral hydroxymethylmorpholine. This is equivalent to a decreased acidity of cationic methylenediamine relative to cationic hydroxymethylmorpholine because the proton dissociation equilibria are different expressions of the same free-energy differences (Scheme I). An alternative view from comparison of K_1/K_M with K_2/K_X (Scheme I) indicates that $[N_H]/[N_D] > [N_{HH}^+]/[N_{DH}^+]$. To account for this inequality (i) solvation, (ii) steric, and (iii) polar effects may be considered.

(i) The pK_{a_3}' value of 7.49 calculated[25] for the ionization of protonated methylenedimorpholine from the equation[19] by Condon[20] agrees with the observed value of 7.38. A portion of the small discrepancy between calculated and measured values may be attributed to the ether group of morpholine for which no allowance was made. The close agreement of calculated pK_a' values for cationic hydroxymethylmorpholine and methylenedimorpholine with the measured values suggests that there exists neither unusual solvation nor intramolecular hydrogen bonding, and that the solvation energies of the cations II and IV in Scheme I are not very different.

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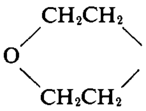
[16] (a) R. W. Taft, "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956; (b) T. N. Hall, *J. Org. Chem.*, **29**, 3587 (1964); (c) J. Hine and R. D. Weimar, Jr., *J. Amer. Chem. Soc.*, **87**, 3387 (1965); (d) E. G. Sander and W. P. Jencks, *ibid.*, **90**, 6154 (1968).

[17] The pK_a' values at 25° for protonated morpholine at ionic strengths 0.005 and 1.0 M are 8.54 and 8.88, respectively. A correction of +0.34 was applied in the calculation of pK_a' values to account for the greater ionic strength in this work (*cf.* ref 18).

[18] H. K. Hall, Jr., *J. Amer. Chem. Soc.*, **79**, 5441 (1957).

[19] (a) The pK_a' values were calculated from eq 2, ref 20, p 4485, with σ^* values of 0.49, 0.55, and 0.62[19b] for H, $HOCH_2$, and



i

respectively. (b) A σ^* value for i was recalculated from eq b, Table II' ref 18, based upon a pK_a' value of 8.54 for morpholinium ion at 25°, ionic strength 0.005 M (*cf.* 8.35 at zero ionic strength, ref 18).

[20] F. E. Condon, *J. Amer. Chem. Soc.*, **87**, 4481, 4485 (1965).

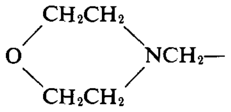
[21] J. Hine and F. C. Kokesh, *ibid.*, **92**, 4383 (1970).

[22] A statistical correction of 2 has been applied to K_M in this discussion for the symmetry of the methylenediamine from which compound the hydroxymethylamine can be formed by cleavage of either of two C–N bonds.

[23] A statistical correction of 0.5 has been applied to K_1 in this discussion since hydroxymethylamine can form by the cleavage of either of two equivalent C–O bonds of formaldehyde hydrate.

[24] An influence of steric factors in the formation of methylenediamines is indicated by the decrease in K_D values from 26,700 to 14.3 M^{-1} for dimethyl- and diethylamine, respectively,[3d] and the fact that values of K_D could not be obtained by this method for either diisopropyl- or di-*n*-butylamine.[3d]

[25] The calculation of the pK_a' value for monoprotonated methylenedimorpholine employs σ^* values of +0.62[19b] for i and +0.22 for



(the latter based on +0.62 for NH_2 and the factor 2.8 for the effect of an interposed CH_2 group[16a]) and eq c, Table II, ref 18, with an allowance of 0.34 in the pK_a' for ionic strength 1.0 M.

(ii) The lone pair of electrons on nitrogen probably has slightly smaller steric requirements than a hydrogen atom.[26] Any direct steric effect is almost certainly not large and would be in the opposite direction that that required to account for the inequality noted above.

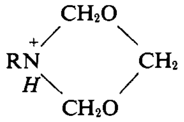
(iii) Since, however, there are large differences in the polar nature of R_2N^+H–, R_2N–, and HO– (based on σ^I values[27] of 0.7, 0.1, and 0.25, respectively), the explanation for the inequality $[N_H]/[N_D] > [N_{HH}^+]/[N_{DH}^+]$ probably resides in greater sensitivity of $R_2NH^+CH_2$– than of R_2NCH_2– to destabilization by electron withdrawal. Thus, the equilibria represented by K_M and K_{MH} are expected to be differently sensitive to polarity, which may be related to orbital electronegativity differences of the groups bonded to the central methylene moiety.[28] There are no satisfactory data for assessment of polar effects on the equilibria represented by K_{MH} and, in particular, the predicted different polar effects on K_M and K_{MH} (*cf.* ref 3d).

Analysis of enthalpic and entropic contributions to the free energies of equilibria in aqueous solution is complicated by contributions to these parameters from the solvent[29] and the assessment of solvent contributions has been attempted for aliphatic ammonium ionizations in only a few cases.[30] Extraordinarily large changes in enthalpy and entropy with much smaller changes in free energy for equilibria in aqueous solution involving either ionic[31a] or hydrophobic groups[31b,c] indicate that the decrease in entropy, due to increased solvent order, can be almost entirely offset by a favorable increase in solvent hydrogen bonding. The present difficulty[29] in separating internal from external (solvent) contributions to thermodynamic quantities[32a] leads us to defer further discussion of the data in Table III.

Diprotonated methylenedimorpholine has been omitted from Scheme I as no evidence exists that accumulation to significant levels occurs under the experimental conditions employed. Insignificant accumulation is consistent with estimates for the pK_a' value for $(CH_3)_2NH^+CH_2NH^+(CH_3)_2$ of 2.2 from Taft's treatment and 3.3 from nmr measurements of the rate of decomposition of this compound in 80% sulfuric acid.[3d] The pK_a' value of diprotonated methylenedimorpholine is about 1.0–1.3, using Hall's equation.[18,19]

The difference in pK_a' values between morpholinium ion and cationic methylenedimorpholine of 1.5 is similar to the range of differences of pK_a' values of 0.4–1.5[7] between monoprotonated substituted ethylenediamines and their monoprotonated cyclic methylene derivatives, imidazolidines.[32b] Thus, monoprotonated cyclic and linear methylene derivatives of aliphatic and aromatic amines with pK_{a_1}' values of 3–9 have pK_{a_2}' values 0.4–1.5 units lower than those of their parent monoprotonated amines.

Table IV. Proton Dissociation Constants for Methylene Derivatives of Oxygen, Nitrogen and Sulfur

Compd	pK_a'	Ref	Method[a]
$\mathrm{HOCH_2O}H$	13.3	*m*	P
$\mathrm{R}\underset{H}{\mathrm{N}}\mathrm{CH_2OH}$	~22	*n*	
$\mathrm{(CH_3)_2NCH_2O}H$	14.8^b	*c*	C
$\mathrm{CH_3SCH_2O}H$	14.1^b	*c*	C
	13–14	*o*	C
$\mathrm{HOCH_2}\underset{H}{\overset{+}{\mathrm{O}}}\mathrm{H}$	$<-2.3^d$	*c*	A
$\mathrm{(CH_3)_2}\underset{\mathrm{H}}{\overset{+}{\mathrm{N}}}\mathrm{CH_2O}H$	9.33^e	*p*	A, P
$\mathrm{R_2}\underset{H}{\overset{+}{\mathrm{N}}}\mathrm{CH_2OH}$	6.09^f	*c*	P
$\mathrm{R_2NCH_2}\underset{H}{\overset{+}{\mathrm{O}}}\mathrm{H}$	$<-2.3^d$	*c*	A
$\mathrm{RSCH_2}\underset{H}{\overset{+}{\mathrm{O}}}\mathrm{H}$	$<-2.3^d$	*c*	A
$\mathrm{R_2}\underset{H}{\overset{+}{\mathrm{N}}}\mathrm{CH_2NR_2}$	7.38^g	*c*	P
	$1.5–3.8^k$	*q*	P
	3.2^l	*r*	S
$\mathrm{R_2}\underset{H}{\overset{+}{\mathrm{N}}}\mathrm{CH_2SR}$	6.24^h	*o*	A, P
$\mathrm{R_2}\underset{\mathrm{H}}{\overset{+}{\mathrm{N}}}\mathrm{CH_2}\underset{H}{\overset{+}{\mathrm{N}}}\mathrm{R_2}$	$1.1–1.3^i$	*c*	C
	2.2^j	*s*	C
	3.3^j	*s*	K
	5–6	*s*	P

[a] A = analogy, C = calculation, K = kinetic, P = potentiometric, S = spectrophotometric. [b] From Hammett plot for substituted alcohols of the type XCH_2OH using σ^I values for $(CH_3)_2N$ and CH_3S of 0.10 and 0.19, respectively (R. E. Barnett, "Diffusion Limited Rate Determining Steps in Carbonyl and Acyl Group Reactions," Ph.D. Thesis, Brandeis University, 1969; R. P. Bell, *Advan. Phys. Org. Chem.*, **4**, 15 (1966)). [c] This work. [d] Analogy to *n*-butyl alcohol (E. M. Arnett and J. N. Anderson, *J. Amer. Chem. Soc.*, **85**, 1542 (1963)) with no allowance made for inductive effects. [e] Analogy to formocholine. [f] For morpholine; for other aliphatic amines the pK_a' value for cationic hydroxymethylamines is 2–3 units below that of the parent ammonium compound (ref 3a). [g] For morpholine. [h] Analogy to thiazolidine-4-carboxylate. [i] Fromeq c, Table II, ref 18 for dicationic methylenedimorpholine. [j] For dicationic methylenedimethylamine. [k] Substituted diphenylimidazolidines. [l] N_5,N_{10}-methylene tetrahydrofolate, N_5 site. [m] R. P. Bell and D. P. Onwood, *Trans. Faraday Soc.*, **58**, 1557 (1962). [n] J. E. Reimann and W. P. Jencks, *J. Amer. Chem. Soc.*, **88**, 3973 (1966). [o] Reference 11. [p] Reference 21. [q] Reference 7. [r] Reference 32b. [s] Reference 3d.

Measurements by Fernandez and Butler[33] of relative heat evolution (ΔT) upon mixing 2 equiv of amine with two successive additions of 1 equiv of formaldehyde led to the conclusion that the predominant adduct is the methylenediamine. From the enthalpy values, ΔH_I and ΔH_M (Table III), and estimates, presented elsewhere,[3a] of the composition of solutions employed in the

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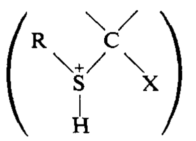
experiments, very little heat evolution is expected upon the second addition of formaldehyde and this is in accord with the observations of Fernandez and Butler. This is *not* due to the fact that morpholine is almost entirely as the methylenediamine, the concentration of which does not significantly change upon addition of an additional equivalent of formaldehyde as concluded by Fernandez and Butler,[33] but the ΔT differences are due to large alterations in the composition of the solution with mutually compensating enthalpic changes. Thus, the method of heat evolution[33] is not applicable for the determination of the composition of solutions of amines and formaldehyde in the absence of knowledge of the heats of the several reactions which may occur in such solutions.[3a]

Measured or estimated pK_a' values from this work and other reports for major methylene derivatives of oxygen, nitrogen, and sulfur are contained in Table IV. Sulfonium ion derivatives



are not included since protonation of methylene derivatives containing a single sulfur atom occurs first on oxygen and nitrogen as a result of their greater basicity.[34]

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Appendix

At equilibrium, solutions containing morpholine buffers and formaldehyde may be described by the following equations,[2] where i = initial and f = final.

$$K_1 = [\mathrm{N_H}]/[\mathrm{N_{BF}}][\mathrm{F_F}] \tag{1a}$$

$$K_M = [\mathrm{N_D}]/[\mathrm{N_H}][\mathrm{N_{BF}}] \tag{2a}$$

$$K_{a_1} = [\mathrm{N_{BF}}]a_H/[\mathrm{N_{AF}}] \tag{3a}$$

$$K_{a_2} = [\mathrm{N_H}]a_H/[\mathrm{N_{HH}}] \tag{4a}$$

$$\begin{aligned}[\mathrm{N_{AT}}] &= [\mathrm{N_{AF}}]_i + a_{H_i} + [\mathrm{OH^-}]_f - a_{H_f} - [\mathrm{OH^-}]_i \\ &= [\mathrm{N_{AF}}]_f + [\mathrm{N_{HH}}] + [\mathrm{N_{DH}}]\end{aligned} \tag{5a}$$

$$[\mathrm{N_{BT}}] = [\mathrm{N_{BF}}]_f + [\mathrm{N_H}] + [\mathrm{N_{DH}}] + 2[\mathrm{N_D}] \tag{6a}$$

$$[\mathrm{N_T}] = [\mathrm{N_{AT}}] + [\mathrm{N_{BT}}] \tag{7a}$$

$$[\mathrm{F_T}] = [\mathrm{F_F}] + [\mathrm{N_H}] + [\mathrm{N_{HH}}] + [\mathrm{N_D}] + [\mathrm{N_{DH}}] \tag{8a}$$

These equations can be combined to yield the cubic polynomial in eq 9a, where $P = [\mathrm{N_{BF}}]_f = [\mathrm{N_{AF}}]_f K_{a_1}/a_{H_f}$. Equation 9a and equations used to derive it will determine all of the final equilibrium concentrations and unknown equilibrium constants.

$$\begin{aligned}&P^3(K_{a_1} + a_{H_f})K_1K_M/K_{a_1} + \\ &\quad P^2\{(2[\mathrm{F_T}] - [\mathrm{N_T}])K_M + 1 - a_{H_f}{}^2/K_{n_1}K_{a_2}\}K_1 + \\ &\quad P\{1 + ([\mathrm{F_T}] - [\mathrm{N_{BT}}])K_1 + \\ &\quad ([\mathrm{N_{AT}}] - [\mathrm{F_T}])a_{H_f}K_1/K_{a_2} - a_{H_f}/K_{a_1}\} + \\ &\quad ([\mathrm{N_{AT}}] - [\mathrm{N_{BT}}]) = 0\end{aligned} \tag{9a}$$

(34) The pK_a' values for $CH_3CH_2SH_2^+$, $CH_3(CH_2)_3OH_2^+$, and $CH_3CH_2NH_3^+$ are −6.72,[35] −2.3 (see Arnett and Anderson, Table IV, footnote *d*), and 10.63,[36] respectively.

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A Steady State Technique for Measuring Phenoxy Radical Termination Constants

Steven A. Weiner

Scientific Research Staff, Ford Motor Company, Dearborn, Michigan 48121.
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Abstract: A new, steady state technique for measuring radical termination rate constants is described. This technique involves photolysis of an α-diketone together with a hydrogen atom donor in the cavity of an esr spectrometer to produce steady state concentrations of two different radicals, one from the diketone and the other from the donor. The technique is applied to phenoxy radicals in benzene and chlorobenzene solution. Analysis of the results leads to values of the termination constants in benzene ranging from $1.7 \times 10^7\ M^{-1}\ \mathrm{sec}^{-1}$ for 4-methoxyphenoxyl to $4.5 \times 10^9\ M^{-1}\ \mathrm{sec}^{-1}$ for 2-naphthoxyl. In general, the termination constants in chlorobenzene are an order of magnitude lower than in benzene.

It has been reported that phenol quenches both the fluorescence and phosphorescence of biacetyl.[1,2] The mechanism suggested was one of reversible hydrogen atom transfer.[1] Thus it was felt that this system might provide a convenient photolytic source of phenoxy radicals. Previously a technique for obtaining absolute termination constants by direct photolysis in an electron spin resonance (esr) spectrometer cavity has been reported.[3]

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