Direct Observation of a Mannich Intermediate in Solution[1]

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Summary A new polarographic reduction wave observed for aqueous solutions of formaldehyde and secondary amines is ascribed to the aminomethylcarbonium ion.

A POLAROGRAPHIC reduction wave observed in the presence of formaldehyde and secondary amines in solution was ascribed to the reduction of aminomethylcarbonium ion, a so-called Mannich intermediate.[2]

When formaldehyde was reduced at a dropping mercury electrode in the presence of secondary amine in aqueous solution, a new polarographic reduction wave was observed near −1·2 v *vs* S.C.E. The height of the reduction wave, which did not change with time, was very small relative to the concentration of formaldehyde and of the amine. The wave-height depended on the pH of the solution, and the wave height attained a maximum at a pH between 10 and 11. The wave disappeared at low pH.

The reduction wave was examined further by using dimethylamine and formaldehyde in the pH region where the maximum wave-height was observed, with the following results (a) The continuous variation method[3] showed that the maximum wave-height was obtained when the molar ratio of dimethylamine to formaldehyde was 2 : 1. (b) The wave-height was independent of the height of the mercury column, but increased by 6—12% per degree with increase in temperature in the range 15—35°. The wave is, therefore, a kinetic one. (c) Large scale controlled-potential electrolysis[4] was carried out on a solution containing dimethylamine and formaldehyde (2 : 1 molar ratio) at the potential at which the plateau of the polarographic reduction wave was reached (−1·45 v *vs* S.C.E.). The electrolysis current decreased very slowly even in the first stage of the run, and *ca.* 26 hr. was required for completion of the electrolysis. The number of electrons required per molecule was calculated to be 1·9. Analysis of the reduction products by g.l.c.† showed that the final solution contained equimolar amounts of dimethylamine and trimethylamine.

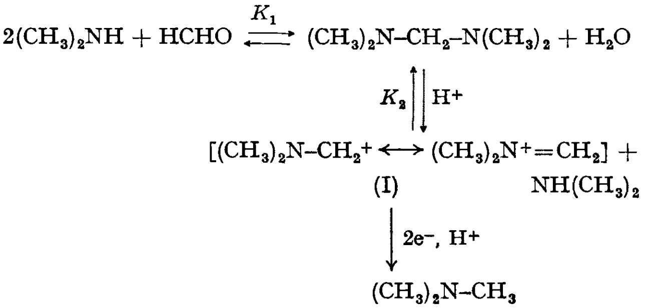
The polarographic behaviour of methylenebisdimethylamine[5] in aqueous solution was essentially the same as that of the mixture of dimethylamine and formaldehyde (in molar ratio 2 : 1) when both solutions had the same concentration. In acetonitrile, methylenebisdimethylamine also exhibited a very small reduction wave at −1·28 v *vs* S.C.E. (with tetraethylammonium perchlorate as supporting electrolyte), which cannot be ascribed to the reduction of methylenebisdimethylamine, because of the unusually small wave-height. The wave-height increased sharply with the addition of proton donors such as phenol, acetic acid, and formic acid. In acetonitrile, essentially the same results were obtained when a solution (2 : 1 in molar ratio) of dimethylamine and formaldehyde was used.

Polarographic data for formaldehyde–secondary amine mixtures in aqueous solution at 25°[a]

Amine	pH[b]	$E_{1/2}$(v) *vs* S.C.E.	Wave-height (μA)
Dimethylamine	10·0	−1·18	1·10
Diethylamine	11·0	−1·18	0·78
Di-isopropylamine ..	11·0	−1·17	0·10

[a] Formaldehyde conc. 1·5 × 10^{-2} M. Amine conc. 5 × 10^{-2} M.
[b] Maximum wave-height was observed at this pH.

These results strongly suggest the following reaction scheme.



$$\begin{tikzcd}
2(CH_3)_2NH + HCHO \arrow[r, shift left, "K_1"] & (CH_3)_2N\text{-}CH_2\text{-}N(CH_3)_2 + H_2O \arrow[l, shift left] \arrow[d, shift left, "H^+"] \\
& {[\underset{(I)}{(CH_3)_2N\text{-}CH_2^+} \longleftrightarrow (CH_3)_2N^+{=}CH_2] + NH(CH_3)_2} \arrow[u, shift left, "K_2"] \arrow[d, "{2e^-,\ H^+}"] \\
& (CH_3)_2N\text{-}CH_3
\end{tikzcd}$$

In aqueous solution at low pH, the equilibrium K_1 is far to the left because of protonation of the amine, but in acetonitrile the proton donors although too weak to protonate dimethylamine, favour the equilibrium K_2 in the direction of aminomethyl carbonium ion. The new reduction wave cannot be ascribed to reductive fission of the C–N bond in methylenebisdimethylamine because of the result obtained from the experiment in acetonitrile. Therefore, the reduction wave is ascribed to the reduction of (I), though the wave-height corresponds to the total amount of (I) present, including that supplied kinetically.

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† Recovery of both dimethylamine and trimethylamine, based on the amount of formaldehyde, was more than 80%. Acetone was used as an internal standard.

[1] A part of this report was read at the Annual Meeting of the Pharmaceutical Society of Japan, Nagoya, April 1969.

[2] B. B. Thompson, *J. Pharm. Sci.*, 1968, **57**, 715; W. L. Nobles and N. D. Potti, *ibid.*, p. 1097.

[3] W. C. Vosburgh and G. R. Cooper, *J. Amer. Chem. Soc.*, 1941, **63**, 437.

[4] Controlled potential electrolysis was carried out as previously employed in our laboratory: see, *e.g.*, M. Masui and H. Ohmori, *Chem. and Pharm. Bull. (Japan)*, 1964, **12**, 877.

[5] L. W. Jones and H. F. Whalen, *J. Amer. Chem. Soc.*, 1925, **47**, 1351.