The Inherent Instability of Dimethylformamide–Water Systems Containing Hydroxide Ion

By E. BUNCEL* and E. A. SYMONS

(*Department of Chemistry, Queen's University, Kingston, Ontario, Canada*)

Summary. Aqueous dimethylformamide (DMF) solutions containing hydroxide ion are unstable, formate ion and dimethylamine being produced fairly rapidly even under mild conditions, with a maximum rate constant at *ca.* 30 mole% DMF.

DIMETHYLFORMAMIDE (DMF) has found increasing use in recent years as a preferred medium for a variety of chemical processes. As a typical dipolar aprotic solvent[1] it has the property of greatly enhancing the rates of many reactions, particularly those between anionic or basic reagents and neutral substrates.[1–4] The use of aqueous DMF media is often dictated by practical considerations (*cf.* ref. 3) such as increased solubility of reagents or, in the case of isotopic (*e.g.* H/D) exchange processes, the requirement of a solvent pool of isotopically enriched material. The stability of such reaction systems appears to have been generally accepted.[5] We now report that aqueous DMF systems containing hydroxide ion are unstable, hydroxide ion being consumed fairly rapidly under mild conditions, with the liberation of dimethylamine and formate ion.

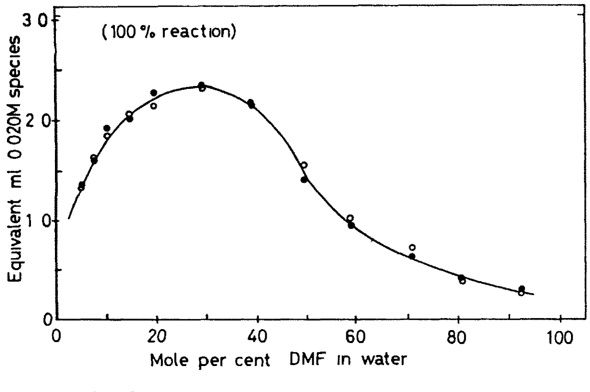

FIGURE. *Alkaline* (0.02 M NaOH) *hydrolysis of DMF as a function of solvent composition at* 23°. *Extent of reaction after* 15 *min. expressed in equivalent ml. of* 0.02M *species* (*theoretical maximum for* 100% *reaction is* 3.03 ml. *using* 3 *ml. portions of reaction mixture*); *open circles* NaOH *consumed, filled circles,* Me_2NH *produced.*

The Figure shows our results for the reaction of sodium hydroxide (0.02N) with DMF over most of the DMF–water composition range at room temperature (23°), in the form of "one-point" kinetic runs. Portions of reaction mixture were quenched with isopropyl alcohol, unreacted hydroxide was titrated with standard acid, and dimethylamine was titrated as the dithiocarbamic acid $(CH_3)_2NC(S)SH$ after addition of carbon disulphide.

Sample kinetic data were obtained at 25.0° by the above procedure for representative DMF–water compositions, *i.e.* 7.6, 29.1, 53.8, and 80.6 mole per cent DMF in water. The pseudo first-order rate constants for these solvent compositions are given in the Table, and are in full accord with data in the Figure.

Pseudo-first-order rate constants for alkaline (0.02M-NaOH) *hydrolysis of DMF in various DMF–water solvent mixtures at* 25.0°

Mole (volume) % DMF	k_{obs} (s^{-1}) (loss of OH^-)	k_{obs} (s^{-1}) (form. of Me_2NH)
7.6 (27)	9.9×10^{-4}	10.1×10^{-4}
29.1 (66)	18.5×10^{-4}	18.2×10^{-4}
53.6 (85)	6.1×10^{-4}	6.7×10^{-4}
80.6 (95)	2.30×10^{-4}	2.08×10^{-4}

The positive identification of sodium formate and of dimethylamine, as products in the reaction of sodium hydroxide with DMF in aqueous solution, was also performed.†

The maximum observed in the rate profile (Figure) in the 30 mole % DMF region is noteworthy. This maximum in rate occurs in the solvent composition region which also shows well defined changes with respect to several physical properties (e.g. the viscosity of aqueous DMF solutions

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† Sodium formate was isolated from a 50 mole % DMF–water system 0.9N NaOH (initially heterogeneous). Dimethylamine was detected by g.l.c. from a 79 mole % DMF–water system, 0.1N-NaOH (heterogeneous initially).

passes through a maximum at *ca.* 30—35 mole % DMF,[6] while distinct changes are also observed in the curves given by the freezing-point, density, and surface tension.[6]) This parallelism suggests that there is a relationship between the hydrolysis rate and solvent structure. An alternative explanation of the observed rate profile may, however, be that the medium changes have a differential effect on the rates of formation and decomposition of the tetrahedral reaction intermediate postulated in amide hydrolysis,[7] thereby resulting in a change in the rate-determining step as the medium is varied. This possibility, which would constitute novel evidence for the two-stage amide hydrolysis mechanism, is under further investigation.

From the practical viewpoint, the results illustrated in the Figure and the Table show that for the purpose of conducting reactions involving hydroxide ion in DMF–water mixtures, the solvent composition of *ca.* 30 mole (67 vol)% DMF is to be avoided in favour of *ca.* 80 mole (95 vol) % DMF.

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[2] J. J. Delpuech, *Bull. Soc. chim. France*, 1966, 1624.
[3] A. J. Parker, *Chem. Rev.*, 1969, **69**, 1.
[4] C. D. Ritchie, "Solute–Solvent Interactions," eds. J. F. Coetzee and C. D. Ritchie, Marcel Dekker, New York, 1969, ch. 4.
[5] The "DMF Product Information Bulletin," E. I. du Pont de Nemours and Co. (Inc.), states that "Alkali catalysis of DMF containing 4·7 to 7·6% water at 95°C, resulted in a maximum hydrolysis of 0·4% after 265 hours."
[6] "DMF Product Information Bulletin" (ref. 5).
[7] W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw Hill, New York, 1969, ch. 10, and references cited therein.