

## Dimethylformamide Dimethyl Acetal in Methanol Solution; Probable Reversible Formation of Carbonium Ion and Carbene Intermediates

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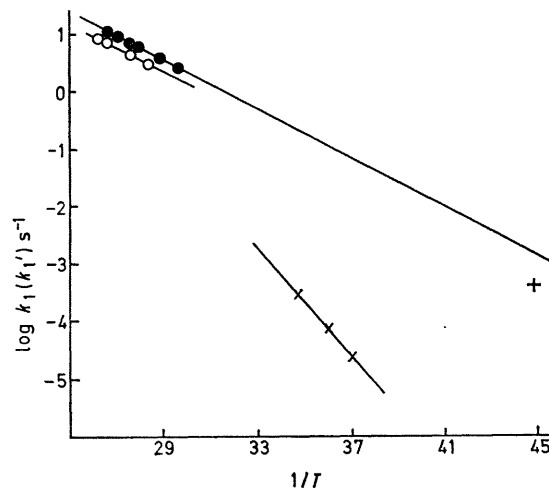
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**Summary** Both methoxy and methine protons of  $(\text{MeO})_2\text{-CHNMe}_2$  exchange with  $\text{CD}_3\text{OD}$  at low temperatures, and n.m.r. signal coalescence between methoxy and solvent methanol protons is achieved at higher temperatures.

It has been reported<sup>1</sup> that the methine hydrogens of dimethylformamide dimethyl acetal (**1**) are rapidly replaced by deuterium in  $\text{CD}_3\text{OD}$  solution and a mechanism involving an N-ylide (**4**) as key intermediate has been suggested. Since there is no notable acidity enhancement for the methine proton in acetals relative to a paraffinic C-H bond, this mechanism would predict ready isotope exchange at the  $\alpha$ -position in tertiary amines, which clearly does not occur. We report that methoxy protons in (**1**) exchange much more rapidly than methine protons and suggest that the two processes are interrelated. Thus at  $-50^\circ$  in  $\text{CD}_3\text{OD}$ † solution, decay of the  $^1\text{H}$  n.m.r. methoxy signal of (**1**) and concomitant appearance of the methoxy signal of methanol ( $\delta H$  1.8 Hz) may be followed, and occurs at within 5% of the same rate for solutions containing 20, 30 or 90  $\mu\text{l}$  of substrate in 500  $\mu\text{l}$  of  $\text{CD}_3\text{OD}$ . In a reaction mixture containing 30  $\mu\text{l}$  of (**1**) and 30  $\mu\text{l}$  of triethylamine, the rate was depressed by a factor of 1.15. At  $-50^\circ$  no exchange of methine protons was observed, but in separate experiments conducted at *ca.*  $5^\circ$  it was confirmed that this latter process occurred. Through runs in which 20  $\mu\text{l}$ , 48  $\mu\text{l}$ , and 100  $\mu\text{l}$  of (**1**) were dissolved in 500  $\mu\text{l}$  of  $\text{CH}_3\text{OD}$ , the rate was shown to decrease as concentration increased in ratio 1.29:1.00:0.86. In 1.0M-methanolic NaOMe, the reaction rate was depressed to 0.65 of its initial value. Additional information on the methoxy exchange was gained from the observation of temperature dependent reversible line broadening and coalescence of the -OMe signals ( $\delta H$  4.0 Hz) in a mixture of (**1**) and a two-molar excess of methanol. The exchange rate was calculated at a variety of temperatures by total line-shape analysis.‡ Similar exchange rates (within experimental error) were observed for solutions in which methanol was 0.1M in NaOMe, or if 2  $\mu\text{l}$  of  $\text{CF}_3\text{CO}_2\text{H}$ § was added; if the methanol was 1.0 molar in base ( $\delta H$  4.7 Hz) the rate became 0.60 of its original value at  $90^\circ$ .

An explanation of these results is given in the Scheme. Ionisation of substrate would be expected to be rapid since a highly stabilised carbonium ion (**2**) is being formed; this agrees with our observation that (**1**) is hydrolysed to dimethylformamide and methanol within seconds at room temperature, and with the easy alkoxy exchanges which form the basis of the synthetic utility of amide-acetals.<sup>3</sup> In the related system (**5**) in methanol both benzyloxy/methoxy exchange and deuteration were observed to occur rapidly at room temperature, but methine exchange was assumed to occur in every ionisation event.<sup>3</sup> Additionally the pH independent H/D exchange at  $\text{C}_2$  in thiazole near neutrality involves the ylide (**6**),<sup>4</sup> and several examples of

conversion of stabilised carbonium ions into carbenes are recorded which include the very ready exchange observed in oxazolium salts (**7**) and related species.<sup>5</sup>



FIGURE

Least-squares Arrhenius plots for exchange reactions. Both methoxy and methine exchange were shown to follow good first-order kinetics through more than one half-life. X: Methine exchange  $\frac{d[(1)]}{dt} = \frac{-k_1 k_2 [(1)]}{k_1^{-1}} = k_1$ ; +: Methoxy exchange with  $-\text{OCD}_3$ ;  $\frac{d[\text{MeOD}]}{dt} = \frac{k_1^{-1} [(1)]}{2}$ . ●: Methoxy exchange by n.m.r. line broadening;  $k_1 = \frac{1}{\tau}$ . O: Methoxy exchange by n.m.r. line broadening with methanol 1.0M in NaOMe.

The line-shape data, analysed on the assumption of a first-order rate-determining ionisation give Arrhenius parameters  $\log_{10} A$  7.3, and  $E_a$  10.650 kcal mol<sup>-1</sup>. Kinetic analysis on n.m.r. exchange processes often provides misleading Arrhenius parameters, particularly when closely spaced signals are involved.<sup>6</sup> However the extrapolated rate constant at  $-50^\circ$  is within a factor of four of the isotopic exchange rate at that temperature, notwithstanding the effects of deuterated solvent and differing concentration on the latter experiments. The pre-exponential factor is very low for an  $\text{S}_{\text{N}}1$  solvolysis in a polar solvent<sup>7</sup> and is explicable in terms of the specific solvation demands of a highly basic methoxide ion at the transition-state. The minor decrease in rate at high concentrations of methoxide ion is most probably a common-ion effect.<sup>8</sup>

The majority of ions (**2**) are attacked by solvent with resultant isotope exchange or signal coalescence. Methine exchange is *ca.*  $10^3$  slower at  $+5^\circ$  and has Arrhenius parameters  $\log_{10} A$  14.3 and  $E_a$  23.400 kcal mol<sup>-1</sup>. This suggests that an essentially neutral transition-state with no

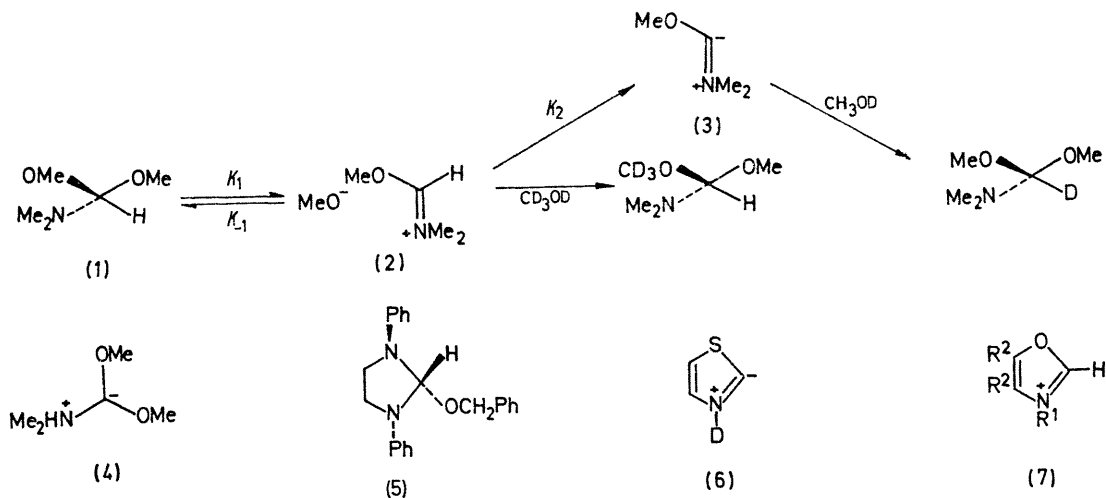
† N.m.r. spectra were recorded on a Perkin-Elmer R.10 machine and temperatures quoted are correct to  $\pm 0.5^\circ$ .

‡ Program NMREX 2-SITE kindly provided by Dr. I. O. Sutherland was used.

§ Presumably under these conditions all the acid is present as  $\text{MeOCHNMe}_2^+$ ,  $\text{CF}_3\text{CO}_2^-$

requirement for methoxide solvation is involved. The depression of rate caused by sodium methoxide is in line with a similar depression of methoxy exchange rate and

strongly acidic conditions are required to exchange the methine proton of ortho-acetals.<sup>1</sup> The spontaneous methoxy migration of tropone dimethyl-acetal<sup>9</sup> may be better



SCHEME

gives no information on whether deprotonation is achieved by the ionising methoxide, or by the solvent; we favour the former.

Dimethoxy-carbene is formed less easily than (3), since

explained by an ionisation–return mechanism than by the concerted processes proposed.

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<sup>4</sup> R. A. Coburn, J. M. Landesberg, D. S. Kemp, and R. A. Olofson, *Tetrahedron*, 1970, **26**, 685, these authors report that C<sub>2</sub> exchange decreases in rate as the concentration of thiazole increases.

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