The Methoxylaminolysis of Methyl Thiolformate: Rate-determining, Diffusion-controlled Proton Transfer

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Summary Under appropriate conditions, four different transition states control the rate of methoxylaminolysis of methyl thiolformate: one of these involves a diffusion-controlled proton transfer.

THE reaction† between methoxylamine and methyl thiolformate exhibits complex dependence on pH. The transition state for the reaction is seen to undergo three changes with increasing acidity: a neutral transition state at high pH gives way to a cationic one below pH 7 which in turn is superseded by a neutral state[1] below pH 5 and finally displaced by an anionic transition state below pH 4 (Figure 1).

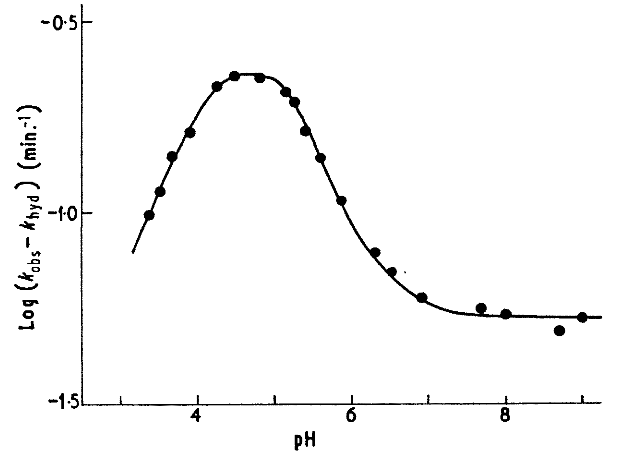

FIGURE 1. *Reaction of methoxylamine with methyl thiolformate* (0·05M *free amine*). (*Rate constants above* pH 7 *obtained by extrapolations to zero* [N-*ethylmorpholine*] *buffer*).

General acid–base catalysis of the aminolysis of methyl thiolformate is displayed by a wide variety of compounds. A detailed study of the reaction in methoxylamine buffers at several pH's (Figure 2) demonstrates general base and water catalysis at high pH. General acid catalysis is observed below pH 7 and becomes acid-inhibited below pH 5. At low pH the reaction approaches first-order dependance on amine though some general catalysis persists. A Brønsted plot for catalysis by other general acids, measured in the pH range 4·5—6, shows a sharp transition from zero to unit slope at pK_a 7·5 (Figure 3). The catalysis by methoxylammonium ion is more effective than that of

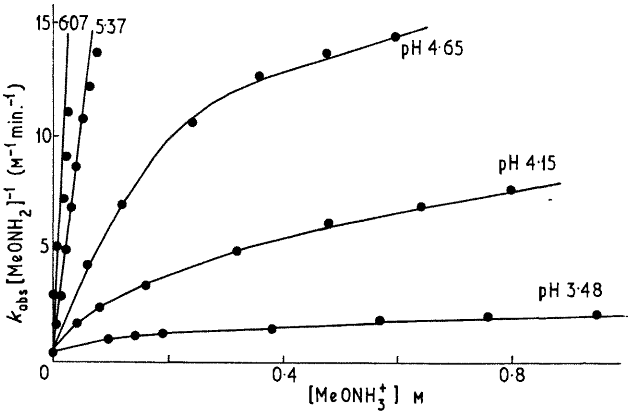

FIGURE 2. *Apparent second-order rate constants for the methoxylaminolysis of methyl thiolformate as a function of* [*methoxylammonium hydrochloride*].[a]

[a] The rate equation above pH 5 is $k_{obs} = 0{\cdot}4[B] + 14[B]^2 + 1{\cdot}5 \times 10^7[B]^2[H^+]$ min^{-1}.

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† All reactions performed in water at 25° ionic strength 1·0M.

other general acids[2] though less than that of the solvated proton, suggesting that it shares in some measure the capacity of the latter for rapid proton transfer in water [3]

A qualitative interpretation of these results leads to the following mechanism for the aminolysis of a thiolester which is compatible with data for reactions between other amines and methyl thiolacetate and thiolformate [4]

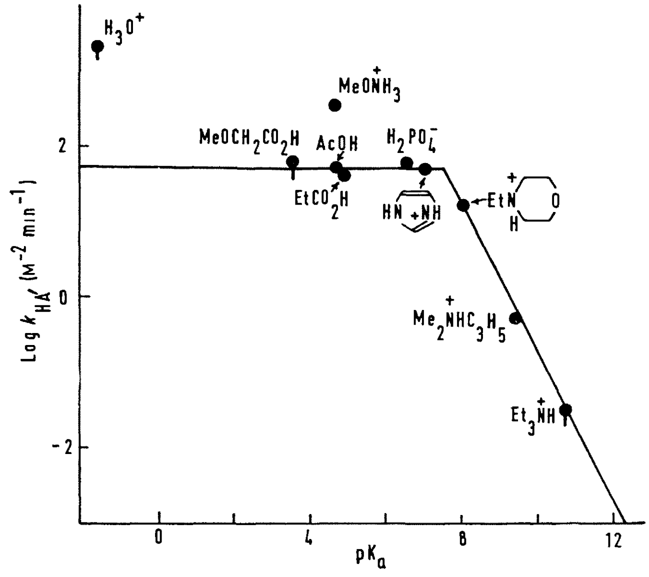
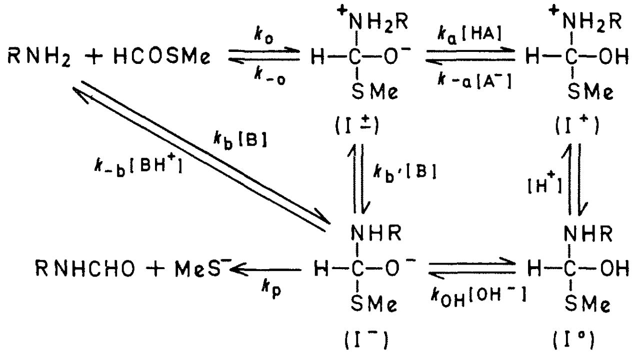


FIGURE 3 *Brønsted plot for the methoxylaminolysis of methyl thiolformate showing the catalytic efficiency of general acids as a function of their acidities (The change in rate determining step below* pH 5 *restricts the evaluation of catalysis by methoxyacetic acid and the solvated proton maximum estimated values are indicated*)

The kinetic behaviour below pH 6 reveals two changes in rate-limiting step for a reaction in which there are only two bond-making and -breaking processes involving carbon Therefore, one rate limiting step must involve a proton transfer The pattern of Brønsted catalysis (Figure 3) for the aminolysis reaction at pH 5—6 is characteristic of a diffusion-controlled proton transfer[3,5] to a base of pK_a 7 5 Studies on the hydrolysis of thioimidate esters[4,6] and on the intramolecular aminolysis of *S*-acetylmercaptoethylamine[5] show that general acid–base catalysis of similar behaviour can be identified with rate-limiting proton transfers between zwitterionic and cationic tetrahedral intermediates (I± and I+, respectively) Thus the transition state for aminolysis between pH 5 and 6 can be identified with the interconversion of (I±) and (I^0)

Below pH 5, the reaction rate falls below that of the proton transfer step and carbon bond-making and -breaking processes become rate limiting Again, studies on thioimidate hydrolyses[4-6] show that slowly-formed, tetrahedral intermediates (I^0) are rapidly converted into thiolesters at low pH but give only amides at higher pH It follows that the addition of amine to the thiolester is the rate-limiting process at pH 4—5 while hydroxide-catalysed breakdown of the intermediate (I^0) corresponds to the anionic transition state of the reaction seen at low pH



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Two possible mechanisms exist for the general-base catalysed aminolysis which is predominant above pH 7. In the first, reversible, base-catalysed addition of amine to the thiol ester gives the anionic intermediate (I⁻) which is in equilibrium through rapid proton transfers with the neutral (I^0) and zwitterionic (I±) forms and which gives products by expulsion of sulphur In the second, the addition of amine to the thiolester is concerted with carbon–sulphur bond breaking in the transition state and the aminolysis does not involve a tetrahedral intermediate of sufficient stability to accept a proton from its immediate environment This would formally constitute a concerted, S_N2-like substitution reaction at a trigonal centre [7] It is expected that a quantitative analysis of the kinetic data will distinguish between these alternatives

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[1] These two changes have also been described for the methoxylaminolysis of n butyl thiolacetate by T C Bruice and L R Fedor *J Amer Chem Soc* 1964 **86** 4886

[2] Methoxylamine also shows enhanced general acid–base catalysis of the hydrolysis of ethyl trifluorothiolacetate (L R Fedor and T C Bruice *J Amer Chem Soc* 1965 **87** 4138)

[3] M Eigen *Angew Chem Internat Edn* 1964 **3** 1, *Discuss Faraday Soc* 1965 **39**, 7

[4] D J Shire Thesis Sheffield University 1969

[5] R E Barnett and W P Jencks *J Amer Chem Soc* 1969 **91** 2358

[6] R K Chaturvedi and G L Schmir *J Amer Chem Soc* 1969 **91** 736

[7] *cf* J. M Briody and D P N Satchell *J Chem Soc* 1965 168, D K Neville and F D Foss, *J Amer Chem Soc* 1969 **91**, 5054