Concerted Push–Pull Catalysis in Thiol Ester Aminolysis

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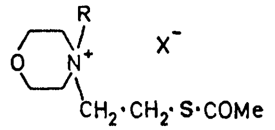
Summary The aminolysis of 4-(2-acetylthioethyl)morpholine hydrochloride by methoxylamine proceeds by four independent routes, one of which combines both general acid and general base catalysis in the same transition state.

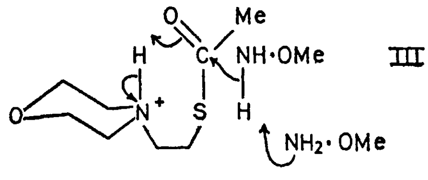
The accelerated mutarotation of 2,3,4,6-tetra-*O*-methylglucose in the presence of 2-pyridone[1] has long remained the classical example of concerted general acid–base catalysis. Nonetheless, as a model for polyfunctional catalysis in enzyme behaviour, it is limited both by the tautomeric system connecting the acid and base functions[2] and by the absence of similar bifunctional catalysis of mutarotation of glucose in water[3]—the solvent essential for enzyme and enzyme-model processes alike.[4] Other searches for bifunctional catalysis, especially of esterolytic reactions, have proved unrewarding[5,6] with the possible exception of the special case of tautomeric catalysis.[2]

Three features of the methoxylaminolysis of *S*-methyl thioformate suggested that a suitably designed thioester might exhibit push–pull catalysis. First, the aminolysis at pH 6 responds equally and independently to general acid and general base catalysis, secondly the former shows the behaviour characteristic of a diffusion-controlled process, and lastly all transition states for reactions at pH greater than 3 involve rate-determining attack of the amine on the carbonyl group.[7] Accordingly we investigated the reaction between methoxylamine and 4-(2-acetylthioethyl morpholine hydrochloride† (I), prepared[8] by acetylation of the corresponding thiol.



(I) (R = H; X = Cl)

(II) (R = Me; X = Br)



III

The notable features of the pH–rate profile for this reaction‡ (Figure 1) are the marked acid catalysis at low pH and the inflexion at pH 6·7, corresponding to the observed dissociation constant of (I), pK_a 6·7, which separates two pH-independent regions. The importance of the internal amino-function in the reaction is shown by the pH-rate profile for aminolysis of the quaternary ammonium ester (II), obtained by the action of methyl bromide on (I). This is much less reactive towards methoxylamine (Figure 1) except at low pH where the response of (II) to acid catalysis is similar to, though less than, that of (I). A detailed description of the kinetic behaviour is made possible by analysis of the dependence of the apparent second-order rate constant on methoxylamine concentration and on pH (Figure 2). The dominant observation is that at pH below 7 the reaction rate shows greater than first-order dependence on amine concentration. The overall reaction between (I) and methoxylamine is well fitted by equation (1) which accords with the following mechanistic analysis.

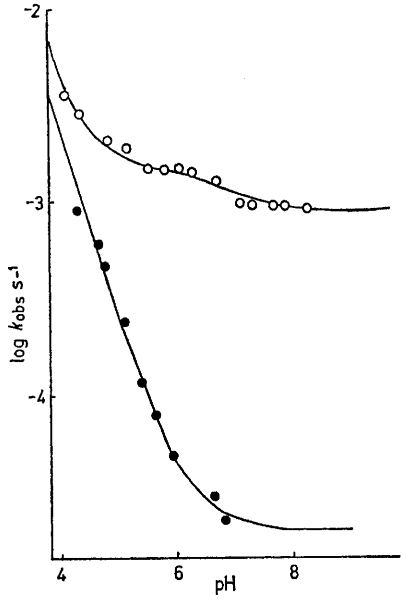


Figure 1. *Reaction of methoxylamine* (0·2M-*free amine*) *with thioesters* (I) (*open symbols*) *and* (II) (*closed symbols*). *Upper curve calculated from equation* (1), *lower curve from equation* (2).

$$k_{\mathrm{I(obs)}}/(\mathrm{s}^{-1}) = [\mathrm{MeONH_2}]\left\{\frac{k_1 + (k_2 + k_3[\mathrm{H^+}])[\mathrm{MeONH_2}]}{1 + 2{\cdot}0 \times 10^{-7}[\mathrm{H^+}]^{-1}} + \frac{k_4}{1 + 5{\cdot}0 \times 10^{6}[\mathrm{H^+}]}\right\}\mathrm{s}^{-1} \quad (1)$$

$k_1 = (3{\cdot}5 \pm 0{\cdot}2) \times 10^{-3}\mathrm{M}^{-1}\mathrm{s}^{-1}$; $k_2 = (2{\cdot}1 \pm 0{\cdot}2) \times 10^{-2}\mathrm{M}^{-2}\mathrm{s}^{-1}$; $k_3 = 700 \pm 100\mathrm{M}^{-3}\mathrm{s}^{-1}$; $k_4 = (4{\cdot}5 \pm 0{\cdot}3) \times 10^{-3}\mathrm{M}^{-1}\mathrm{s}^{-1}$.

$$k_{\mathrm{II(obs)}} = [\mathrm{MeONH_2}]\{k_5 + (k_6 + k_7\,[\mathrm{H^+}])\,[\mathrm{MeONH_2}]\}\,\mathrm{s}^{-1} \quad (2)$$

$k_5 = (2{\cdot}0 \pm 0{\cdot}2) \times 10^{-5}\mathrm{M}^{-1}\mathrm{s}^{-1}$; $k_6 = (4{\cdot}4 \pm 0{\cdot}4) \times 10^{-4}\mathrm{M}^{-2}\mathrm{s}^{-1}$; $k_7 = (585 \pm 50)\mathrm{M}^{-3}\mathrm{s}^{-1}$

At the lowest pH studied, the methoxylaminolyses of both (I) and (II) proceed at similar rates and involve

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† Full analytical and spectroscopic data have been obtained for (I) and (II).

‡ All reactions performed in glass-distilled water at 25° and ionic strength 1·0 (KCl). Spectroscopic data were recorded at 237 nm through at least three half-lives and first-order kinetic behaviour was observed for all reactions below pH 9.

intermolecular general acid catalysis by methoxylammonium hydrochloride [k_3 in equation (1) and k_7 in equation (2) respectively], which is a characteristic feature of thiol ester aminolysis.[9] At high pH, the aminolysis of the conjugate base of (I) requires only 1 mol. of methoxylamine [k_4 of equation (1)] but is over 200 times faster than the corresponding reaction (k_5) of (II). It follows that this process must use the morpholinyl nitrogen as an intramolecular general base catalyst. At pH 4—6 the reaction of (I) shows both first- and second-order dependence on methoxylamine. Since the former process [k_1 of equation (1)] is over 100 times faster than the bimolecular reaction of (II) and exhibits a kinetic solvent isotope effect§ of 3·5, the protonated morpholinyl residue must in this case act as an intramolecular general acid catalyst.

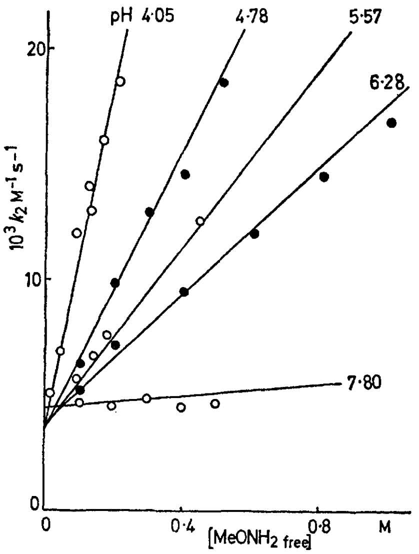

FIGURE 2. *Apparent second-order rate constants for methoxylaminolysis of* (I) *as a function of methoxylamine concentration. Curves calculated from equation* (1).

The fourth and last kinetic process [k_2 of equation (1)] involves the cation (I) and two molecules of methoxylamine and is 50 times faster than the termolecular reaction (k_6) of (II). It is strongly retarded above pH 6 corresponding to the ionisation of an acidic function of pK_a 6·7. In addition, it displays a kinetic solvent isotope effect§ of 3, characteristic of a general acid–base catalytic process.[4] We conclude that this reaction must involve a transition state in which both inter- and intra-molecular catalyses operate concertedly.

It is practicable to represent this mechanistically as classical intramolecular general acid *plus* intermolecular general base catalysis (III) or by any equivalent formulation. However, since the reaction is unquestionably a 'one-encounter' phenomenon,[10] no meaning derives from the attempt to formalise the location of the proton in the transition state. The reaction stands as an example of 'push–pull' catalysis not heretofore observed.

(*Received, 29th October* 1971; *Com.* 1882.)

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§ $k(H_2O)/k(D_2O)$ corrected for glass-electrode and pK_a effects.

[1] C. G. Swain and J. F. Brown, *J. Amer. Chem. Soc.*, 1952, **74**, 2534, 2538.
[2] P. R. Rony, *J. Amer. Chem. Soc.*, 1969, **91**, 6090.
[3] R. P. Bell, 'The Proton in Chemistry,' Methuen, London, 1959, p. 152.
[4] W. P. Jencks, 'Catalysis in Chemistry and Enzymology,' McGraw-Hill, New York, 1969, p. 201.
[5] R. F. Pratt and J. M. Lawlor, *Chem. Comm.*, 1968, 522.
[6] T. Maugh and T. C. Bruice, *J. Amer. Chem. Soc.*, 1971, **93**, 3237.
[7] G. M. Blackburn, *Chem. Comm.*, 1970, 249.
[8] J. W. Haefele and R. W. Broge, *Proc. Sci. Sect. Toilet Goods Assoc.*, 1959, No. **32**, 52 (*Chem. Abs.*, 1960, **54**, 17233g).
[9] T. C. Bruice and L. R. Fedor, *J. Amer. Chem. Soc.*, 1964, **86**, 4886.
[10] M. Eigen, *Angew. Chem. Internat. Edn.*, 1964, **3**, 1; *Discuss. Faraday Soc.*, 1965, **39**, 7.