Studies in Heterocyclic Chemistry. Part IV.[1] Kinetics and Mechanisms for the Hydrolysis of Benzoxazoles

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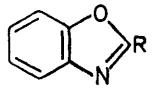
Under acidic conditions simple benzoxazoles hydrolyse principally to the corresponding amidophenols. For benzoxazole and 2-methylbenzoxazole the reactions show acid catalysis for solutions of low acidity but retardation at higher acidities corresponding to a change in rate-determining step from nucleophilic attack on the conjugate acid to fission of the ring C–O bond in the resultant tetrahedral intermediate. A related pathway is observed for 2-trifluoromethylbenzoxazole but the different dependence on pH is attributed to a change as the pH increases from nucleophilic attack on the conjugate acid to attack on the free base and finally to attack by hydroxide ion. The retardation of hydrolysis of 1,2-dimethylbenzoxazolium perchlorate with increasing acidity follows expectation for attack by hydroxide ion and water and confirms that in contrast with other imidates, for benzoxazoles product formation may become rate determining at low pH.

THE formation of imidazole and thiazole ring systems by the cyclisation of the appropriate *o*-amino- and *o*-mercapto-anilides provides a convenient and important synthetic route to the benzimidazoles and benzothiazoles. The kinetics and mechanisms of these reactions are readily studied in aqueous media.[1,2] The analogous benzoxazoles are accessible by similar syntheses though the required conditions are generally more



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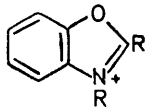


(II)

vigorous. In contrast to the simple benzimidazoles and benzothiazoles, the benzoxazoles are readily hydrolysed under aqueous conditions.[3] Though this instability precludes direct study of their formation in aqueous media it provides the opportunity of examining the ring cleavage under mild conditions. To this end the hydrolysis of a series of benzoxazoles (I; R = H, Me, Ph, and CF_3) and (II; R = Me) has been examined over a range of acidities.

RESULTS

The hydrolysis of benzoxazole, 2-methyl-, 2-trifluoromethyl-, and 2-phenyl-benzoxazole, and 1,2-dimethylbenzoxazolium perchlorate was studied at 25° in aqueous media over the pH range −1·5—5; except for those solutions more acidic than 1M-HCl, the ionic strength was maintained at 1·0. The rates of hydrolysis were followed by u.v. spectroscopy. With 2-trifluoromethylbenzoxazole in 4M-HCl the reaction yielded *o*-aminophenol but at lower acidities and for all the other compounds only the corresponding amide could be detected as the initial product.

The reactions showed good first-order kinetics according to the expression: rate = k_{obs}[benzoxazole], where k_{obs}, the experimentally determined first order rate constant, shows a dependence on pH similar to that for the hydrolysis of other imidates.[4,5] None of the reactions showed significant

[1] Part III, K. J. Morgan and A. M. Turner, *Tetrahedron*, 1969, **25**, 915.
[2] A. J. Collings and K. J. Morgan, *Tetrahedron*, 1964, **20**, 2167.
[3] M. A. Phillips, *J. Chem. Soc.*, 1930, 2685.
[4] J. Stieglitz, *Amer. Chem. J.*, 1908, **39**, 29; E. S. Hand and W. P. Jencks, *J. Amer. Chem. Soc.*, 1962, **84**, 3505.
[5] R. B. Martin, S. Lowey, E. L. Elson, and J. T. Edsall, *J. Amer. Chem. Soc.*, 1959, **81**, 5089.

variation in rate with the concentrations of the phosphate buffers employed.

The plots of observed rate constants against pH for benzoxazole and its 2-methyl derivative exhibit maxima at pH 0·35 and 1·35 respectively (Figure 1), the apparent

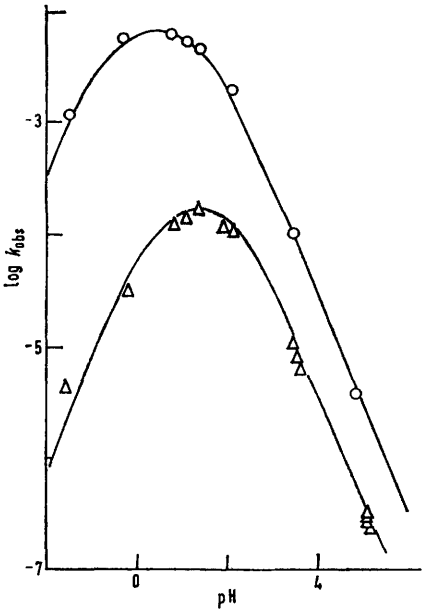


FIGURE 1 Effect of pH on first-order rate constant for the hydrolysis of benzoxazole (○) and 2-methylbenzoxazole (△). Experimental values are marked as points; the curve is calculated from the constants given in Table 2

dependence on acidity being given by $k_{obs} = k'[H^+]$ at low acidities and $k_{obs} = k''/[H^+]$ at higher acidities. The low solubility of 2-phenylbenzoxazole in water precluded a directly comparable study; in 80% aqueous methanol comparison with 2-methylbenzoxazole was possible and showed that the replacement of methyl by phenyl produced a diminution in reactivity of *ca.* 100 for solutions 0·05—1M-HCl (see Table 1).

TABLE 1

First-order rate constants for hydrolysis [a] of 2-methyl- and 2-phenyl-benzoxazole

HCl/M	0·05	0·1	0·2	1·0
2-Methylbenzoxazole, $10^7k/s^{-1}$	242	276	273	250
2-Phenylbenzoxazole, $10^7k/s^{-1}$	1·30	1·44	1·90	3·92

[a] 80% Aqueous methanolic HCl, 25°.

For 2-trifluoromethylbenzoxazole the rate profile adopts a different form, the observed rate constant being independent of pH over the range 2—5 but increasing with acidity at lower pH (Figure 2). Also showing different behaviour is 1,2-dimethylbenzoxazolium perchlorate (Figure 3): the present results are in good agreement with those reported by Oliveros and Wahl [6] and extend the range of measurements to lower pH where the observed rate constants decrease with increasing acidity.

DISCUSSION

The facility with which benzoxazoles hydrolyse in acidic media is in marked contrast to the stabilities of the corresponding benzimidazoles and benzothiazoles. The greater reactivity appears to parallel the lower aromatic stability of the oxazole ring system [7] and suggests that the hydrolytic process may well proceed by nucleophilic attack on the polar carbiminyl bond. The formation in this way of an intermediate 2-hydroxybenzoxazoline was suggested by Skraup and Moser.[8]

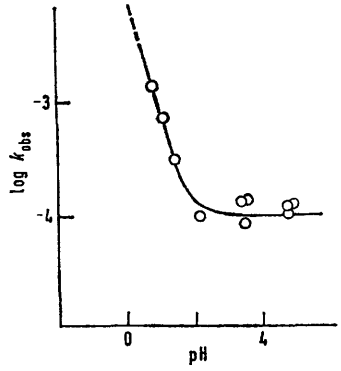


FIGURE 2 Effect of pH on first-order rate constant for the hydrolysis of 2-trifluoromethylbenzoxazole. Experimental values are marked as points; the curve is calculated from the constants given in Table 2.

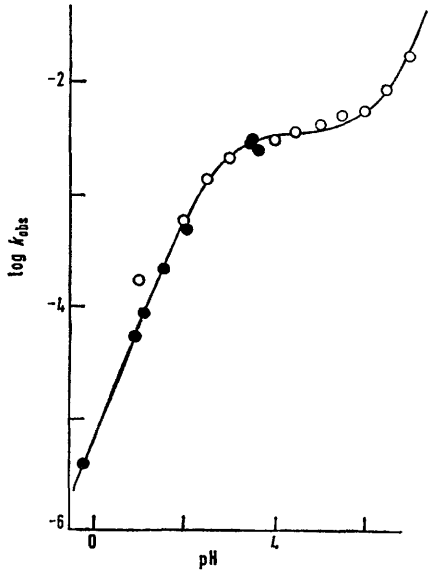
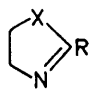


FIGURE 3 Effect of pH on first-order rate constant for the hydrolysis of 1,2-dimethylbenzoxazolium perchlorate. Experimental values from this work (●) and from Oliveros and Wahl [6] (○) are marked as points; the curve is calculated from the constants given in Table 2, and $k_4 = 1{\cdot}6 \times 10^5$ l mol^{-1} s^{-1}

The analogous 2-hydroxyimidazolines have been postulated [1] as intermediates in the formation of imidazoles, a 2-hydroxyimidazolidine has been detected as an intermediate in the hydrolysis of an imidazoline,[9] and 3-acyl-2-hydroxybenzoxazolidines are thought to be similarly involved in both the rearrangement and hydrolysis of *NO*-diacyl-*o*-aminophenols.[10] Moreover the apparently

[6] L. Oliveros and H. Wahl, *Bull. Soc. chim. France*, 1969, 2815.
[7] M. J. S. Dewar, A. J. Harget, and N. Trinajstic, *J. Amer. Chem. Soc.*, 1969, **91**, 6321.
[8] S. Skraup and M. Moser, *Ber.*, 1922, **55**, 1080.
[9] D. R. Robinson, *J. Amer. Chem. Soc.*, 1970, **92**, 3138.
[10] A. M. Turner, Ph.D. Thesis, University of Lancaster, 1967.

closely related hydrolyses of the non-aromatic Δ^2-thiazolines [5,11] (III; X = S) and Δ^2-oxazolines [12] (III; X = O) have been shown to proceed by this route.



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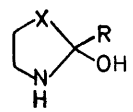


(IV)

The formation and hydrolysis of many carbonyl compounds and their nitrogen derivatives have been extensively studied.[13] The rate of hydrolysis of Schiff's bases [14] at low acidities is determined by the rate of the acid-catalysed hydration. At higher acidities hydration of the protonated Schiff's base attains a limiting value and the kinetically rate-determining step then becomes decomposition of the intermediate carbinolamine.

A similar sequence of steps is established for many nucleophilic reactions at carbiminyl centres incorporated in carbimidates. Thus in the hydrolysis of thiazolines [5,11] and oxazolines [12] nucleophilic attack gives first a tetrahedral carbinolamine (IV), which subsequently collapses to products. The corresponding reaction sequence [5] (Scheme 1) [B = (III); BHOH = (IV)] leads, with the

$$B + H^+ \underset{}{\overset{K}{\rightleftharpoons}} BH^+$$

$$BH^+ + H_2O \underset{k_2}{\overset{k_1}{\rightleftharpoons}} BHOH + H^+$$

$$BHOH \xrightarrow{k_3} \text{Products}$$

SCHEME 1

usual stationary state assumptions, to expression (1),

$$\text{Rate of hydrolysis} = \frac{(k_1k_3/k_2)[B]_T[H^+]}{(K + [H^+])(k_3/k_2 + [H^+])} \quad (1)$$

where $[B]_T$ represents the total concentration of imidate, both free and protonated. Under the limiting conditions when $K \gg [H^+]$ and $(k_3/k_2) \gg [H^+]$ this expression reduces to that of a simple acid-catalysed process (2).

$$\text{Rate of hydrolysis} \simeq (k_1/K)[H^+][B]_T \quad (2)$$

Conversely when the acidity rises so that $[H^+] \gg K$ and $[H^+] \gg (k_3/k_2)$ the rate equation becomes that of an acid-inhibited process (3). The transition from rate-

$$\text{Rate of hydrolysis} \simeq (k_1k_3/k_2)[B]_T/[H^+] \quad (3)$$

determining nucleophilic attack [equation (2)] to rate-determining collapse of the tetrahedral intermediate [equation (3)] gives rise to a maximum in the plot of the observed rate constant against pH at $[H^+] = Kk_3/k_2$.

Benzoxazole and 2-Methylbenzoxazole.—The close formal similarity between benzoxazoles (I) and thiazolines and oxazolines, which extends to a similarity in the variation with pH of the observed rate constants for hydrolysis of benzoxazole (I; R = H) and its 2-methyl derivative (I; R = Me), suggests that a similar kinetic scheme may be appropriate. Using Scheme 1, a satisfactory fit of the experimental points to the curve (Figure 1) calculated from equation (1) is obtained with the parameters listed in Table 2. The dissociation constant of the conjugate acid of 2-methylbenzoxazole, derived from the kinetic results, is in satisfactory agreement with that determined directly (pK_A 0·60) by a spectrometric method; for benzoxazole rapid hydrolysis prevents the use of the normal methods but an estimate of the dissociation constant (pK_A −0·13) was obtained by extrapolating spectrometer readings to zero time.[15] Additionally the decrease in both K and k_1 between benzoxazole and 2-methylbenzoxazole is fully in accord with the changes expected for the substitution of an electron-repelling methyl group; the limited results for the 2-phenyl derivative are also in accord with the stabilisation of the carbiminyl group by the extended conjugation.

TABLE 2

Constants for hydrolysis of benzoxazoles in aqueous solution (I = 1·0) at 25°

	k_1/s^{-1}	$10^3k_3/k_2$/mol l^{-1}	K_a/mol l^{-1}
Benzoxazole	1·06	26·1	3·59
2-Methylbenzoxazole	1·62 × 10^{-2}	5·51	4·26 × 10^{-1}
2-Trifluoromethylbenzoxazole	(10^2)		(10^4)
1,2-Dimethylbenzoxazolium perchlorate	3·47 × 10^{-3}	1·8	

2-Trifluoromethylbenzoxazole.—The anticipated greater ease of nucleophilic attack [16] and lower basicity of the trifluoromethyl derivative (I; R = CF_3) is revealed in a fast reaction showing acid catalysis at low pH; but under conditions of lower acidity the observed rate constant becomes independent of pH (Figure 2). At acidities greater than pH 0·8 the reaction becomes too fast to follow by conventional spectroscopic methods and no attempt was made to observe a maximum in the plot of observed rate constant against pH or to obtain by direct measurement an estimate of the dissociation constant.

An approximate value for the dissociation constant of the conjugate acid of 2-trifluoromethylbenzoxazole can be obtained from the values for the parent compound, its 2-methyl derivative, and the corresponding Hammett σ values.[17] With $\sigma_{CF_3} = 0{\cdot}55$, this gives an estimated dissociation constant of *ca.* 10^4 l mol^{-1}. Then with the assumption that the acid-catalysed reaction follows the usual path (Scheme 1) and that the effective rate law for hydrolysis under these conditions is given by equation (2), the observed rate constants give $k_1/K \simeq 0{\cdot}01$

[11] R. B. Martin and A. Parcell, *J. Amer. Chem. Soc.*, 1961, **83**, 4830.
[12] R. B. Martin and A. Parcell, *J. Amer. Chem. Soc.*, 1961, **83**, 4835.
[13] W. P. Jencks, *Progr. Phys. Org. Chem.*, 1964, **2**, 63.
[14] E. H. Cordes and W. P. Jencks, *J. Amer. Chem. Soc.*, 1963, **85**, 2843.
[15] K. J. Allen, unpublished result.
[16] G. Gavin, O. R. Pierce, and E. T. McBee, *J. Amer. Chem. Soc.*, 1953, **75**, 5622.
[17] D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, 1958, **23**, 420.

l mol^{-1} s^{-1} and hence k_1 *ca.* 10^2 s^{-1}. This estimate for k_1 is of the expected order of magnitude for the introduction of a trifluoromethyl group and corresponds to an acceleration in the rate of nucleophilic attack of *ca.* 100 with respect to benzoxazole.

At lower acidities the rate of reaction becomes independent of pH. Such kinetic behaviour can be attributed either to attack of water on the unprotonated benzoxazole, or of hydroxide ion on the conjugate acid, or to a combination of these processes (see Scheme 2).

$$BH^+ + OH^- \underset{k_5}{\overset{k_4}{\rightleftharpoons}} BHOH$$

$$B + H_2O \underset{k_7}{\overset{k_6}{\rightleftharpoons}} BHOH$$

SCHEME 2

In the related pH-independent hydrolyses of some Schiff's bases the reaction has been identified [14] as attack by hydroxide ion, and similar characteristics have been demonstrated for thiazolines,[18] iminolactones,[19] and acyclic imidates.[20]

The full kinetic expression corresponding to the reaction sequences of Schemes 1 and 2 has the form of equation (4). With the assumption that $k_3 \gg (k_5 + k_7)$

$$k_{obs} = \frac{(k_1k_3[H^+] + k_3k_4K_w + k_3k_6K)}{(k_2[H^+] + k_3 + k_5 + k_7)(K + [H^+])} \quad (4)$$

and that under conditions of low acidity nucleophilic attack is rate determining, *i.e.* that $k_2[H^+] \ll k_3$ this reduces to equation (5). If the reaction over the range

$$k_{obs} = (k_1/K)[H^+] + (k_4K_w/K) + k_6 \quad (5)$$

pH 3—5 were to arise essentially from only the first two terms it is possible to estimate k_4 from the known and estimated values of the other constants. With $k_{obs} = 10^{-4}$, $(k_1/K) = 10^{-2}$, $K_w = 10^{-14}$, and $K = 10^4$ at pH 4, this would give $k_4 =$ *ca.* 10^{14} s^{-1}. This estimate exceeds that for a diffusion-controlled bimolecular process by a factor far greater than the possible error in K that it necessarily excludes the possibility of significant contribution at this pH of rate-determining attack by hydroxide ion. Consequently if rate-determining nucleophilic attack does occur at this acidity it must unusually involve the action of water on the neutral benzoxazole. On this basis, k_6 can be estimated to be *ca.* 10^{-4} s^{-1}, showing an appropriate reduction of 10^{-6} in the reactivity to water for 2-trifluoromethylbenzoxazole with respect to its conjugate acid (*cf.* ref. 20). The qualitative observation that hydrolysis has become fast at pH 9 can then be interpreted as due to the appearance of the corresponding attack by hydroxide ion on neutral 2-trifluoromethylbenzoxazole.

* The observed first-order rate constant for hydrolysis of *o*-acetamidophenyl acetate in 4M-HCl at 25° is $1{\cdot}2 \times 10^{-3}$ s^{-1}; for phenyl trifluoroacetate [21] in 3·3M-$HClO_4$ in 70% dioxan–water the corresponding rate constant at 0° is $1{\cdot}89 \times 10^{-3}$ s^{-1}.

[18] G. L. Schmir, *J. Amer. Chem. Soc.*, 1965, **87**, 2743.

[19] B. A. Cunningham and G. L. Schmir, *J. Amer. Chem. Soc.*, 1965, **87**, 5692; 1966, **88**, 551.

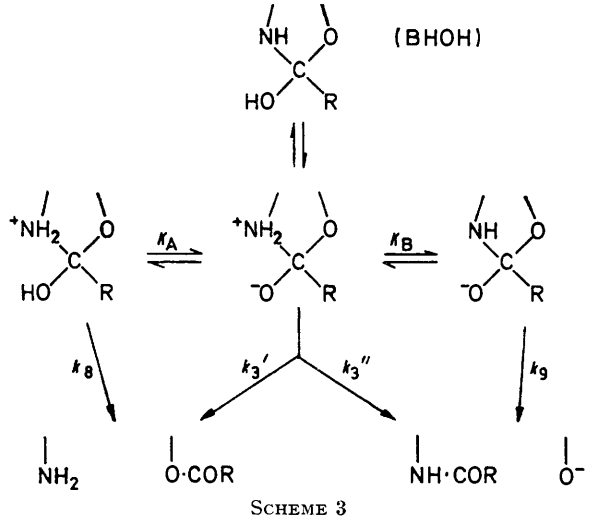
There exists the alternative possibility that the product-forming step is rate determining for pH 3—5 ($k_3 \ll k_2[H^+]$). While this is not inappropriate to the ease of nucleophilic attack on trifluoroacetyl derivatives and qualitatively accommodates the pH-independent rate constant, it does not seem to be capable of accounting simply either for the rate or the products of the acid-catalysed reaction at higher acidities.

In this respect particular interest attaches to the change in product from *o*-hydroxytrifluoroacetanilide to *o*-aminophenol at pH < -1. Although exposure to concentrated hydrochloric acid does lead to hydrolysis of the anilide the observed first order rate constant, $8{\cdot}68 \times 10^{-6}$ s^{-1} for 4M-HCl at 25° is too small to enable this to account for the rapid appearance of aminophenol from the benzoxazole. In contrast the isomeric *o*-aminophenyl trifluoroacetate can be expected to hydrolyse rapidly * and this must provide the route to aminophenol.

The collapse of the intermediate can be expected to yield two products corresponding to C–N (V) and C–O (VI) fission. Imidates generally (*i.e.*, acyclic imino-ethers,[20,22,23] oxazolines,[12] iminolactones,[18,19] and thiazo-

(V) (VI)

lines [5,11,18]) give a mixture of the two products; in this respect benzoxazole and its 2-methyl and 2-phenyl derivatives are abnormal in giving only the product of



SCHEME 3

C–O fission. To accommodate the two modes of collapse, Schemes 1 and 2 require modification of reaction (3) as in Scheme 3. Experience with other

[20] M. Kandel and E. H. Cordes, *J. Org. Chem.*, 1967, **32**, 3061; T. C. Pletcher, S. Koehler, and E. H. Cordes, *J. Amer. Chem. Soc.*, 1968, **90**, 7072.

[21] C. A. Bunton and T. Hadwick, *J. Chem. Soc.*, 1961, 943.

[22] W. P. Jencks and M. Gilchrist, *J. Amer. Chem. Soc.*, 1968, **90**, 2622; G. M. Blackburn and W. P. Jencks, *ibid.*, p. 2638.

[23] R. K. Chaturvedi and G. L. Schmir, *J. Amer. Chem. Soc.*, 1968, **90**, 4413.

imidates [19,20,22] has shown that under conditions of low acidity more C–N fission occurs. This variation in products has been analysed in terms of the effects of pH on the equilibria of Scheme 3 and the relative values of the rate constants k_8, k_9, k_3', and k_3''.[19,20]

For the non-polar benzoxazoles (I; R = H, Me, and Ph) the invariance of the product to the limits of detection over the pH range −2—5 suggests that the decomposition occurs largely through the zwitterion ($k_3' > k_3''$).

In contrast, the change of product from amide to amine for 2-trifluoromethylbenzoxazole suggests that decomposition of the cationic intermediate becomes important at high acidity. While this reaction (k_8) is indeed acid catalysed its appearance only at pH < −1 must exclude any possibility that it is the origin of the kinetically-detected acid catalysis in the observed rate constant at pH < 3. Hence the product-determining reaction cannot be identified with the rate-determining step over the pH range −1 to 3, and so confirms that the latter is properly assigned to the initial nucleophilic attack over the full range of pH (−1 to 5) examined kinetically. By inference this result provides further support for the conclusion from the kinetic results that the nucleophilic attack proceeds largely by attack of water on the protonated (pH −1 to 3) and neutral (pH 3—5) benzoxazole.

1,2-*Dimethylbenzoxazolium Perchlorate*.—From the form of Schemes 1 and 2, the effects of acid retardation become apparent when the substrate is fully converted into the conjugate acid. Strongly acidic conditions are needed to achieve this with the weakly basic benzoxazoles but this restraint does not apply to the benzoxazolium salt (II). Application of Schemes 1 and 2 to the hydrolysis of the salt (II) gives an expression for k_{obs} containing terms for nucleophilic attack by both water and hydroxide ion [equation (6)].

$$k_{obs} = k_1k_3/(k_2[H^+] + k_3) + k_3k_4[OH^-]/(k_2[H^+] + k_3) \quad (6)$$

The observation [6] of an increase in the observed rate constant near pH 7 suggests that the second term becomes important under conditions of low acidity, but this alone does not account for the levelling off and subsequent decrease in k_{obs} at higher acidities. The experimentally-observed rate constants both from this work and from that of Oliveros and Wahl [6] are satisfactorily fitted to equation (6) with the constants in Table 2 together with k_4, $1{\cdot}6 \times 10^5$ l mol^{-1} s^{-1}. The values of the constants k_1 and k_3/k_2 have magnitudes appropriate for benzoxazole hydrolysis, reflecting the influence of the second methyl substituent. The ratio $k_4/k_1 = 5 \times 10^7$ l mol^{-1}, is also in good agreement with those for nucleophilic attack by hydroxide ion and water on the conjugate acids of analogous imidates.[11,23]

[24] J. T. Edward and S. C. R. Meacock, *J. Chem. Soc.*, 1957, 2009; R. Greenhalgh, R. M. Heggie, and M. A. Weinberger, *Canad. J. Chem.*, 1963, **41**, 1662; R. H. De Wolfe and F. B. Augustine, *J. Org. Chem.*, 1965, **30**, 699.

The derived values of the constants k_1 and k_3/k_2 indicate that at pH < 2·5 product formation has become the rate-determining step. This conclusion may be contrasted with that from the hydrolysis of acyclic imino-ethers. For these compounds a change in product ratios occurring at a pH where the overall rate is retarded by increased acidity has provided evidence against a complete change of rate-determining step from nucleophilic attack to product formation.[19,22] In these cases the apparent acid inhibition has been attributed to the reduced activity of water [24] or to a negative salt effect.[20,22] The kinetic characteristics and the products of the hydrolysis of benzoxazoles give no evidence requiring this interpretation and for the *N*-methyl salt the kinetic evidence is for a change in the rate-determining step.

EXPERIMENTAL

2-*Methylbenzoxazole*.—A mixture of acetic anhydride (40·8 g, 0·4 mol) and *o*-aminophenol (21·8 g, 0·2 mol) was boiled under reflux for 1 h and then distilled through a fractionating column. The distillate, b.p. 150°, was dissolved in ether (250 ml) washed with aqueous potassium hydrogen carbonate and water, dried, and distilled yielding 2-methylbenzoxazole (16·5 g, 65%), b.p. 198—201°, n_D^{25} 1·5421. Benzoxazole, b.p. 179—182°, was prepared similarly from *o*-aminophenol (0·2 mol) and formic acid (0·4 mol).

2-*Trifluoromethylbenzoxazole*.[25]—A mixture of trifluoroacetic acid (40 g), *o*-aminophenol (21·8 g), and syrupy phosphoric acid (5 ml) was boiled under reflux for 2 h and then distilled through a short fractionating column. The distillate, b.p. 155—162°, deposited a solid (2 g), m.p. 164·5—165·5°, identified spectroscopically as *o*-trifluoroacetamidophenol. The residual liquor was redistilled giving the oxazole (5 g), b.p. 152°, n_D^{25} 1·4579 (lit.,[25] b.p. 62—63° at 19 mmHg, n_D^{25} 1·4579), *M* (mass spectrum), 187; the i.r. spectrum indicated the absence of carbonyl, amino-, and hydroxy-groups.

2-*Phenylbenzoxazole*.—A mixture of *o*-aminophenol (5 g), benzoic acid (5·1 g), and orthophosphoric acid (1 ml) was heated at 200° for 4 h. After cooling, the mixture was poured into water (200 ml) and the precipitate washed with excess of aqueous sodium carbonate solution giving 2-phenylbenzoxazole (2·4 g), m.p. 102—103° (from ethanol).

o-*Acetamidophenol*.—A solution of *o*-acetamidophenyl acetate (15 g) in excess of 0·2M-potassium hydroxide was filtered and acidified with HCl, precipitating the phenol (10 g), m.p. 205—206°.

o-*Formamidophenol*.—A mixture of *o*-aminophenol (10·9 g) and formic acid (4·6 g) was boiled under reflux for 1 h. After cooling, the product was extracted with hot water yielding the amide (6 g), m.p. 125—127° (from water).

1,2-*Dimethylbenzoxazolium Perchlorate*.[26]—(i) The yellow solid, from heating at 100° for 8 h 2-methylbenzoxazole and methyl iodide in a sealed tube, was washed with ether giving the methiodide (27·3 g, 89%), m.p. 196—198°.

(ii) A concentrated aqueous solution of the methiodide (10 g) was treated with an excess of saturated aqueous sodium perchlorate. The precipitate was washed with

[25] M. Pailer and W. J. Huebsch, *Monatsh.*, 1966, **96**, 1541; C. I. Braz, G. V. Myasnikoya, and A. Ya. Yakubovich, *Khim. geterotsikl. Soedinenie, Akad. Nauk Latv. S.S.R.*, 1965, 147 (*Chem. Abs.*, 1965, **63**, 5622).

[26] L. M. Clark, *J. Chem. Soc.*, 1926, 232.

ether and then shaken repeatedly with an excess of saturated aqueous sodium perchlorate giving the methoperchlorate, m.p. 166—170° (decomp.).

Kinetic Measurements.—For reactions at pH >2 aqueous phosphate or acetate buffer (10 ml) at 25° was added to aqueous solutions (50 ml) of oxazole or amide at 25° containing sufficient potassium chloride to bring the final ionic strength to 1·0. For higher acidities the reactant solution was added to the acid. Aliquot portions (5 ml) were withdrawn at suitable intervals of time and the reaction was quenched by dilution with water. The resultant solutions were analysed on a Unicam SP 800 spectrometer at 200—450 nm. When the reactant was sparingly soluble in water, the reaction was studied for more dilute solutions and the aliquot portions were examined directly; for 2-methyl- and 2-phenyl-benzoxazole the reaction was examined under similar conditions in methanol–water (4 : 1 v/v). The faster reactions ($k_{obs} > 10^{-4}$ s^{-1}) were studied with a thermostatted cell in an SP 700 spectrometer and the changes followed by recording at predetermined fixed wavelengths. First-order rate constants were calculated by standard methods.

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