Studies on Alkoxyheterocyclic Compounds. Part II.[1] Hydrolysis of 2-Methoxy-1-methylbenzimidazoles

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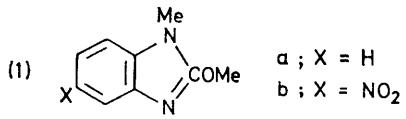
The kinetics of the hydrolysis of 2-methoxy-1-methylbenzimidazole and of the corresponding 5-nitro-derivative have been investigated as a function of pH. The results, together with some evidence from ^{18}O exchange, indicate the presence of several reaction paths which vary in importance with medium acidity.

In a previous paper[1] we have discussed from the mechanistic point of view the transalkylation of some 2-alkoxybenzimidazoles and other ring-nitrogen activated heterocyclic methyl ethers with thiophenol. In connection with this study we report an investigation of the kinetics of the acid, neutral, and base hydrolysis of benzimidazol-2-yl methyl ethers (1) in order to elucidate the

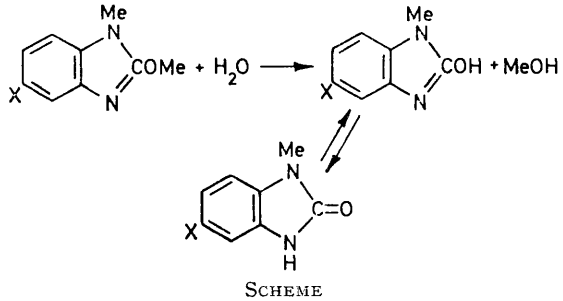


different reaction paths involved and their different importance.

[1] P. Dembech, A. Ricci, G. Seconi, and P. Vivarelli, *J. Chem. Soc.* (*B*), 1971, 2299 is considered to be Part I of the series.

RESULTS

The methoxybenzimidazoles (1a and b) undergo acid, neutral, and base hydrolysis in 80% aqueous dioxan



Scheme

leading almost quantitatively to the benzimidazol-2(3*H*)-ones (Scheme). The reaction can take place by attack

of the nucleophiles present in the system (water and hydroxide ion) at the methoxy or at the heterocyclic carbon atom to give the same products. The different paths have been distinguished by hydrolysis, at different pH values, in ^{18}O enriched water–dioxan and examining the reaction by means of mass spectrometry (Table 1). For the experimental conditions 1-methylbenzimidazol-2(3*H*)-one and the corresponding 5-nitro-derivative contain no oxygen-18.

TABLE 1

Oxygen-18 enrichment of 5-substituted 1-methylbenzimidazol-2(3*H*)-ones obtained from the hydrolysis at different pH values of compounds (1a and b) (0·1—0·7M) in 4 : 1 (v/v) $H_2{}^{18}O$–dioxan at 80°

		5-H		
pH	0·5	3·4	5·9	11·8
^{18}O Enrichment (%)			Trace	35
		5-NO_2		
pH	0·5	4·5	7·0	11·8
^{18}O Enrichment (%)		10	32	87

The kinetics of the title reaction have been investigated as a function of pH in buffered 80% aqueous dioxan at constant ionic strength (see Experimental section). Pseudo-first-order kinetics were observed for all cases

TABLE 2

Specific rate coefficients for the hydrolysis, at different pH values, of 5-substituted 2-methoxy-1-methylbenzimidazoles (1a and b) (1·1—8·6 × 10^{-4}M) at 80 ± 0·05° in 4 : 1 (v/v) H_2O–dioxan at ionic strength 0·5M

				5-H				
pH	0·50	1·18	2·53	3·00	3·78	4·40	4·75	5·90
$10^5k/s^{-1}$	87·1	82·5	41·8	32·1	12·1	4·40	1·90	0·15
				5-NO_2				
pH	0·50	1·18	2·53	3·00	3·78	4·40	4·75	5·90
$10^5k/s^{-1}$	686	457	23·0	8·28	1·82	0·46	0·24	0·02
pH	6·50	6·70	7·00					
$10^5k/s^{-1}$	0·013	0·011	0·014					

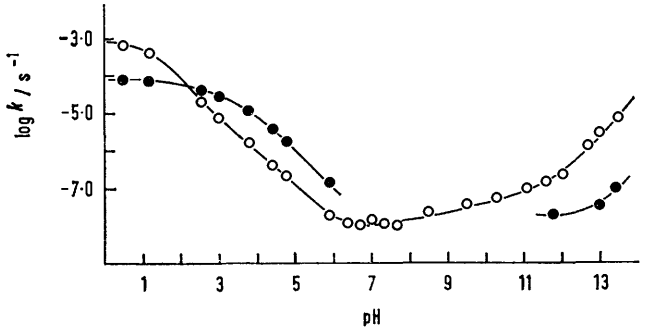


FIGURE 1 The log*k*–pH rate profile for the hydrolysis of benzimidazol-2-yl methyl ethers (1a) (full circles) and (1b) (open circles) in 4 : 1 (v/v) H_2O–dioxan at 80 ± 0·05° and ionic strength 0·5M

by varying the initial concentration of compounds (1) over the range 10^{-2}—10^{-4}M. The reactivity of the system is affected by the medium acidity and by the structural modification in the benzene ring. These effects have been studied in detail at 80°. At this temperature the reaction is sufficiently fast to be followed until high conversions (70—90%). The results are listed in Tables 2 and 3, whereas in Figure 1, the pH–rate profile is shown. The hydrolytic rate has been also measured, for some pH values, at 25° and the results are reported in Table 4 together with second-order rate coefficients for the reaction between compounds (1) and OH^- anion present at the selected acidities.

TABLE 3

Specific rate coefficients for the base hydrolysis, at different pH values, of 5-substituted 2-methoxy-1-methylbenzimidazoles (1a and b) (1·1—9 × 10^{-4}M) at 80 ± 0·05° in 4 : 1 (v/v) H_2O–dioxan at ionic strength 0·5M

			5-H					
pH	11·8	13·0	13·4					
$10^6k/s^{-1}$	0·21	0·38	0·97					
				5-NO_2				
pH	7·30	7·50	8·50	9·50	10·3	11·1	11·6	12·0
$10^6k/s^{-1}$	0·13	0·11	0·22	0·37	0·56	1·00	1·60	2·34
pH	12·7	13·0	13·4					
$10^6k/s^{-1}$	14·7	31·7	80·6					

TABLE 4

Specific rate coefficients for the hydrolysis, at different pH values, of compounds (1a and b) (2·4—6·8 × 10^{-3}M) in 4 : 1 (v/v) H_2O–dioxan at 25 ± 0·01° and ionic strength 0·5M

pH	$[OH^-]$/ g ion l^{-1}	k/s^{-1}	$k[OH^-]^{-1}$/ 1 mol^{-1} s^{-1}
		Compound (1a)	
0·5	6·5 × 10^{-14}	1·2 × 10^{-6}	1·9 × 10^7
5·9	1·6 × 10^{-8}	(1·2 × 10^{-8})	7 × 10^{-1}
		Compound (1b)	
7·0	1·4 × 10^{-7}	(4·2 × 10^{-10})	2·9 × 10^{-3}

Values in parentheses refer to reactions followed below 40% conversion.

TABLE 5

First order rate coefficients for the acid hydrolysis of 2-methoxy-1-methyl-5-nitrobenzimidazole (1·56 × 10^{-3}M) in the presence of different amounts of Na_2HPO_4–citric acid buffers in 4 : 1 (v/v) H_2O–dioxan at 80 ± 0·05° and ionic strength 0·5M

	[Citric acid] = 1·25 [Na_2HPO_4]		
10^2[Citric acid]/M	2·15	4·29	5·72
pH	3·70	3·70	3·73
$10^5k/s^{-1}$	3·29	3·06	2·88

The influence of buffer concentration on the reactivity of our system at constant pH has been studied for compound (1b). The results, collected in Table 5, show that the hydrolysis is a specific acid-catalysed process. Finally the u.v. spectra of (1a) have been recorded at different pH values (Figure 2). This spectral pattern is similar to that previously observed for other benzimidazoles in which the protonation of the pyridine nitrogen atom is well established.[2]

DISCUSSION

The results obtained can be discussed in detail considering that, in the solvent used, the substrate is present as free base in equilibrium with the corresponding conjugate acid [equation (1)] whose concentration

[2] G. Leandri, A. Mangini, F. Montanari, and R. Passerini, *Gazzetta*, 1955, **85**, 769.

obviously depends on the equilibrium constant and on

$$B + H_2O \rightleftharpoons BH^+ + OH^- \quad (1)$$

the medium acidity (B and BH^+ are the unprotonated and protonated methoxybenzimidazole respectively). The protonated and unprotonated substrate has two sites for attack of the nucleophile (H_2O or OH^-): the

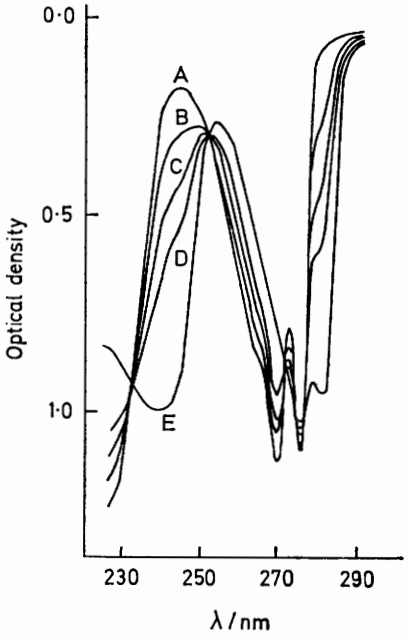


FIGURE 2 U.v. spectra of 2-methoxy-1-methylbenzimidazole (1a) ($1{\cdot}89 \times 10^{-6}$M) in 80% aqueous dioxan at various pH values: A, 0·5; B, 2·53; C, 3·20; D, 3·78; and E, 12·6

methyl carbon (Me) of the methoxy-group or the heterocyclic C-2 atom (C). Therefore in our system there are different processes possible in principle which may be described by the kinetic equations (2)—(9) where k_{Me}

Acid-catalysed processes

$$\text{Rate} = k_{Me}[BH^+][H_2O] \quad (2)$$

$$\text{Rate} = k_C[BH^+][H_2O] \quad (3)$$

pH-Independent processes

$$\text{Rate} = k_{Me}[BH^+][OH^-] \quad (4)$$

$$\text{Rate} = k_C[BH^+][OH^-] \quad (5)$$

$$\text{Rate} = k_{Me}'[B][H_2O] \quad (6)$$

$$\text{Rate} = k_C[B][H_2O] \quad (7)$$

Base-catalysed processes

$$\text{Rate} = k_{Me}''[B][OH^-] \quad (8)$$

$$\text{Rate} = k_C''[B][OH^-] \quad (9)$$

and k_C represent the rate constants for the attack of water or hydroxide ion at the saturated and heterocyclic carbon atom respectively in the protonated or unprotonated substrate.

From the results it appears that the rate coefficient for acid hydrolysis (pH < 6) rapidly increases with the medium acidity but at lower pH values a plateau is reached (see Figure 1). This pH–rate profile, qualitatively similar to that observed for the acid hydrolysis of a number of imidates [3-5] in which the reaction of water and protonated substrate is involved,[6] suggests the presence in our system of the processes (2) and/or (3) where the reacting species, according to the spectroscopic evidence, is the *N*-protonated benzimidazole. The BH^+ concentration, in fact, strongly increases with medium acidity and this accounts for the observed rate enhancement. The different reactivity of compounds (1) at pH $\geqslant$ 2·53 (see Table 2) is also in line with this interpretation since the methoxybenzimidazole (1a) is more protonated [1] and consequently appears to be more reactive than the corresponding nitro-derivative (1b).

In the strongly acidic medium compounds (1) are almost fully protonated (see later) and the concentration of the heterocyclic cation becomes roughly independent of the pH. Therefore the hydrolytic rate must be slightly sensitive to the medium acidity and compound (1b) more reactive than (1a) as really observed. In this case the nitro-group may perform its usual activating role [7] in nucleophilic substitution. The products from hydrolysis in strongly acidic medium do not show any ^{18}O enrichment (see Table 1). Therefore the reaction proceeds exclusively at the methoxy-carbon atom of the protonated system and not only process (3), but also paths (5), (7), and (9) must be unimportant. On the other hand from the pK_a of compound [1] (1a) and from the hydrogen ion concentration at pH 0·5 it follows that only one part in *ca.* $3{\cdot}7 \times 10^3$ of the stoicheiometric benzimidazole is present in the unprotonated form (B). The rate of reaction between the equilibrium concentration of BH^+ and hydroxide ion ($6{\cdot}5 \times 10^{-14}$M at pH 0·5), evaluated on the assumption that this reaction is a diffusion-controlled process, is *ca.* $1{\cdot}6 \times 10^{-7}$ l mol^{-1} s^{-1} at 25°. This value is much smaller than the experimental second-order rate coefficient (see last column in Table 4). Therefore the observed reactivity cannot be ascribed to process (4). Also reactions (6) and (8) seem unimportant when the extremely low concentrations of the unprotonated substrate and of hydroxide ion are considered. The conclusion from the results is that the strongly acid hydrolysis may be described by equation (2). Then the only site for the reaction of protonated benzimidazole with water is the methyl carbon if the methoxy-group and not the heterocyclic C-2 atom.

At pH values of *ca.* 2—6, *i.e.* in the region where the rate constant strongly depends on the medium acidity, we observe some ^{18}O enrichment in the products (see Table 1). Then the reaction proceeds at the saturated

[3] M. Kandel and E. H. Cordes, *J. Org. Chem.*, 1967, **32**, 3061.
[4] T. C. Pletcher, S. Kochler, and E. H. Cordes, *J. Amer. Chem. Soc.*, 1968, **90**, 7072.
[5] R. K. Chaturvedi and G. L. Schmir, *J. Amer. Chem. Soc.*, 1968, **90**, 4413.
[6] R. H. DeWolfe, *J. Org. Chem.*, 1971, **36**, 162.
[7] R. L. Burwell, jun., *Chem. Rev.*, 1954, **54**, 615; C. K. Ingold, 'Structure and Mechanism in Organic Chemistry,' Cornell University Press, London, 1969.

and, in part, at the heterocyclic carbon atom with dealkylation and dealkoxylation of the system, respectively. In this region processes (4) and (5) appear to be unimportant. In fact the rate of reaction between the equilibrium concentration of protonated (1a) and hydroxide ion at pH 5·9, evaluated as above, is *ca.* $5{\cdot}8 \times 10^{-4}$ l mol^{-1} s^{-1} at 25°. This value, *ca.* 1200 times smaller than the experimental one (see last column in Table 4), supports the absence of these reactions. Process (2) should contribute, as already observed for the strongly acid hydrolysis, to the overall reaction together with paths (6) and (7) in which the methoxy-carbon atom together with the heterocyclic carbon atom of the unprotonated benzimidazole is attacked by water. Accordingly, on decreasing the medium acidity the pH-dependent process (2) will become less significant relative to the pH-independent paths (6) and (7). The reaction near pH 7 should therefore become pH-independent as in fact has been experimentally observed for compound (1b) (see Tables 2 and 3, and Figure 1). This pH-independent rate profile also excludes in neutral medium any significant contribution to the overall reaction from processes (8) and (9) which therefore can be even more neglected in acid medium. The above considerations lead to the kinetic equation (10) where $k^* = k_{Me}' + k_C$. Both

$$\text{Rate} = k_{Me}[BH^+][H_2O] + k^*[B][H_2O] \quad (10)$$

terms of equation (10) represent the acid hydrolysis at pH values at *ca.* 2—6, whereas only the second term is responsible for the pH-independent dealkylation and dealkoxylation processes experimentally observed in neutral medium.

In the case of the base hydrolysis the acid-catalysed processes (2) and (3), already absent in the neutral reaction, seem unimportant. On the same basis,† paths (4) and (5) may be neglected. Base hydrolysis most probably takes place *via* the processes (6)—(9). Then the reaction may be described by the kinetic equation (11), where $k^* = k_{Me}' + k_C$ and $k = k_{Me}'' + k_C''$, in which the reactive species is the unprotonated

$$\text{Rate} = k^*[B][H_2O] + k[B][OH^-] \quad (11)$$

benzimidazole. This is in line with the larger reactivity observed for compound (1b) relative to (1a) (see Table 3) taking into account the electronic effects of the nitro-group.

Equation (11) accounts for the obtained pH–rate profile. In fact, on increasing the medium basicity the second, pH-dependent term should increase in importance in respect to the first, pH-independent term. Consequently the hydrolytic rate should increase with pH as observed (see Table 3 and Figure 1). Finally the isotope exchange results (see Table 1) show that base hydrolysis still proceeds with dealkylation and dealkoxylation. On the basis of the above equation these different processes may be ascribed to the attack of a water molecule and of hydroxide ion on the methoxy and heterocyclic carbon atoms of the unprotonated substrate.

† The rate of reaction between the equilibrium concentration of protonated (1b) and hydroxide ion at pH 7 at 25°, evaluated as above, is *ca.* $6{\cdot}5 \times 10^{-6}$ l mol^{-1} s^{-1}. This value is about 450 times smaller than the experimental one (see last column in Table 4).

EXPERIMENTAL

Materials.—Compounds (1a and b) were obtained from the corresponding 2-chloro-derivatives as previously described.[1,8] In the kinetic experiments twice distilled water and dioxan (AnalaR), purified by a published method [9] were used. Buffers employed were HCl (pH 0·5), HCl–sodium acetate [10] (pH 1·18), $Na_2HPO_4,2H_2O$–citric acid [10] (pH 2·5—5·9), KH_2PO_4–sodium hydroxide [10] (pH 6·5—7·5), H_3BO_3–KCl–sodium hydroxide [10] (pH 8·5—9·5), NaCl–NaOH–glycine [10] (pH 10·3—12), and NaOH (0·1—0·5M; pH > 12).

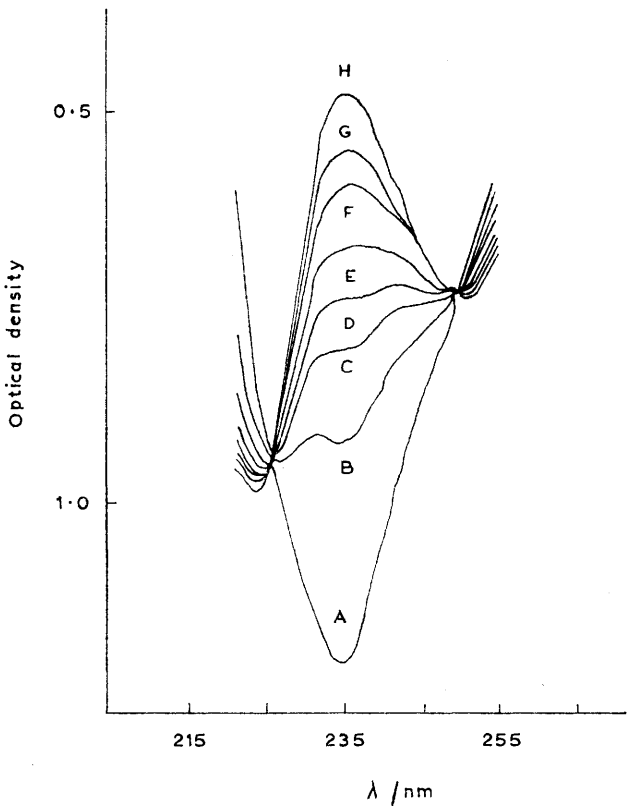


FIGURE 3 Variation of the u.v. spectra with time for the hydrolysis of (1b) ($2{\cdot}83 \times 10^{-3}$M) at pH 2·53 in 80% aqueous dioxan at 80° and μ 0·5M. Spectra were recorded after 50-fold dilution of samples with water. A, 70 s; B, 35 min; C, 55 min; D, 71 min; E, 93 min; F, 125 min; G, 178 min; and H, t_∞.

Products.—The products of the title reaction have been checked at 80° at different pH values, *i.e.* 0·5, 5·9, 7, and 12. At the completion of the reaction, the acid solution (hydrochloric acid was added in the case of the alkaline hydrolysis), on cooling, gives almost quantitatively

[8] A. Ricci and P. Vivarelli, *Gazzetta*, 1967, **97**, 741.
[9] L. F. Fieser, 'Experiments in Organic Chemistry,' Heath, New York, 1955, 3rd edn., p. 284.
[10] A. I. Vogel, 'Textbook of Quantitative Inorganic Analysis,' Longmans, London, 2nd edn., 1951.

1-methylbenzimidazol-2(3*H*)-one,[11] m.p. 192—193° (from ethanol), and the corresponding 5-nitro-derivative,[12] m.p. 300—301° (from ethanol), identical with authentic samples. In the filtrate, methanol was detected by g.l.c. analysis (LAC 10% on Cromosorb W; 60—80 mesh). The oxygen-18 exchange experiments were carried out as above, employing 3·68 atom % $H_2{}^{18}O$.

Kinetics.—Known volumes of thermostatted solutions of benzimidazolyl ethers in dioxan and of the selected buffer in water, were mixed at zero time in a flask. If necessary, NaCl was added to the buffer solution in order to have a final ionic strength of 0·5. Aliquot portions were removed at intervals from the solution and quenched in known volumes of water. Samples of each portion were analysed spectrophotometrically at room temperature following, in the case of compound (1a), the appearance of the corresponding benzimidazol-2(3*H*)-one at 280 nm. In the case of compound (1b) the disappearance of the ether (235 nm; pH 0·5—11·6) or the appearance of the product (270 nm; pH > 11·6) was followed. A typical kinetic run is shown in Figure 3. The quantitative nature of the reaction is indicated by the close superimposition upon the t_∞ spectrum (reached in many cases) by the u.v. spectra of the benzimidazol-2(3*H*)-ones recorded for the same experimental conditions. The pseudo-first-order rate constants, calculated from the analytical data by the usual methods,[13] are averages of three or more independent runs. The experimental error is *ca.* ±3%. The rate of reaction between the equilibrium concentration of protonated benzimidazoles and hydroxide ion, has been evaluated by a literature method.[14] The pK_a of compounds (1) and pK_w values at 25° and ionic strength 0·5M, used for the calculations are those previously reported.[1,15]

The u.v. spectra were recorded on a Perkin-Elmer 402 spectrophotometer. The pH values in the range 0·5—12 were measured as previously described,[1] and estimated from the stoicheiometric concentration of OH^- anion in the other cases.

Mass Spectra.†—Oxygen-18 analyses were carried out on an Hitachi–Perkin-Elmer RMU-7 instrument. Measurements were done by repetitive scanning and averaging of the M^+ region for the following conditions: 70 eV (electron beam energy), 180° (source temperature), and 1800 V (acceleration voltage). The insertion of samples was directly at 60° and indirectly through an all glass inlet at 200°. Relative standard deviations were ±2%.

We thank Professor J. H. Ridd, University College of London, for helpful discussions and for reading the manuscript.

[2/1417 *Received*, 19*th June*, 1972]

† Analyses were performed by Dr. J. Seibl, Eidg. Tech. Hochschule, Zurich, Switzerland.

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[13] A. A. Frost and R. G. Pearson, ' Kinetics and Mechanism,' Wiley, New York, 2nd edn., 1961.

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[15] A. Liberti and T. S. Light, *J. Chem. Educ.*, 1962, **39**, 236.