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Mechanisms for the Solvolytic Decompositions of Nucleoside Analogues. II. Acidic Hydrolysis of 1-(1-Alkoxyethyl)-benzimidazoles

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Some 1-(1-alkoxyethyl)benzimidazoles have been prepared and the rate constants for their hydrolyses measured at various oxonium ion concentrations. The increasing electron-attracting character of the alkoxy group greatly retards the decomposition of the protonated substrate, but exerts only a slight effect on the ionization of this species. The former influence is quantitatively comparable to the effect that the nondeparting alkoxy group has on the rate for the hydrolysis of acetals of formaldehyde. This finding strongly suggests that 1-(1-alkoxyethyl)benzimidazoles are hydrolyzed in acidic conditions analogous to acyclic acetals, *i.e. via* formation of an oxocarbenium ion from the 1-alkoxyethyl group.

In a previous paper,[1] concerning the solvolytic decompositions of model nucleosides, we suggested that 2-substituted 1-(1-ethoxyethyl)benzimidazoles are hydrolyzed in acidic solutions by a mechanism involving a rapid initial protonation of the imidazole ring and a subsequent rate-limiting cleavage of the protonated substrate to form free benzimidazole and an oxocarbenium ion derived from the 1-ethoxyethyl group. According to this mechanism the reaction rate should be highly sensitive to the structural factors that affect the stability of the developing oxocarbenium ion. For example, the polar nature of the alkoxy group would be expected to have a prominent influence on the hydrolysis rate. Most likely this influence would be comparable to the effect that the nondeparting alkoxy group exerts on the rate for the acid-catalyzed cleavage of acyclic acetals, also reacting *via* similar oxocarbenium ions.[2] To ascertain the mechanistic

Table 1. First-order rate constants for the hydrolyses of some 1-(1-alkoxyethyl)benzimidazoles in aqueous acid and buffer solutions at 353.15 K.

Reaction solution			$k/10^{-4}$ s^{-1}			
HA	[HA] / mol dm^{-3}	[NaA] / mol dm^{-3}	Isopropoxy	Ethoxy[a]	Methoxy	2-Chloroethoxy
HCl	0.10	–	67.3(8)	21.1(3)	6.92(5)	0.610(4)
HCl	0.010	0.090	66.6(4)	22.3(4)	7.25(7)	0.643(8)
HCl	0.0020	0.098	61.8(7)	21.3(3)	6.65(8)	0.559(6)
HCOOH	0.10	0.10	49.4(2)	17.17(26)	5.05(3)	0.422(4)
CH_3COOH	0.20	0.10	25.3(2)	7.82(10)	2.30(2)	0.1605(30)
CH_3COOH	0.10	0.10	15.01(24)	5.47(6)	1.791(30)	0.1087(7)
CH_3COOH	0.050	0.10	9.30(18)	3.03(4)	0.902(13)	0.0588(7)

[a] See Ref. 1.

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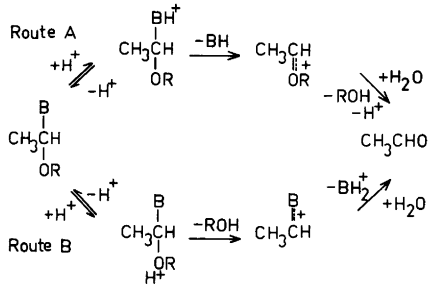
proposal presented above for the hydrolysis of 1-(1-ethoxyethyl)benzimidazoles we went on to investigate the dependence of the hydrolysis rates of 1-(1-alkoxyethyl)benzimidazoles on the nature of the alkoxy substituent and compared the observed structural effect with those in the acid-catalyzed cleavage of the correspondingly substituted acetals of formaldehyde.[3]

RESULTS AND DISCUSSION

Table 1 summarizes the first-order rate constants obtained for the hydrolysis of 1-(1-alkoxyethyl)-benzimidazoles in aqueous acid and buffer solutions at 353.15 K. Each compound behaves similarly. The hydrolysis rate remains almost unchanged as the oxonium ion concentration is decreased from 0.10 mol dm^{-3} to 0.0020 mol dm^{-3} and undergoes a sharp diminution thereafter with less acidic solutions (Fig. 1). If a mechanism involving rate-limiting departure of the protonated benzimidazolyl group (Route A in Scheme 1) is followed, as



Scheme 1.

suggested in a previous discussion,[1] the observed rate constants are in the range of the plateau of the pH-profile equal to the rate constants for the decomposition of the protonated substrates. The fact that these values are strongly decreased with the increasing electronegativity of the alkoxy substituent is in good agreement with the assumed mechanism. The increasing electron-withdrawal by the alkoxy group destabilizes the developing oxocarbenium ion by lowering the electron density at C1 of the ethyl group, which results in a marked retardation of rate. To obtain a quantitative estimation for this kind of structural effect the acid-catalyzed hydrolysis of acylic acetals, proceeding *via* oxo-

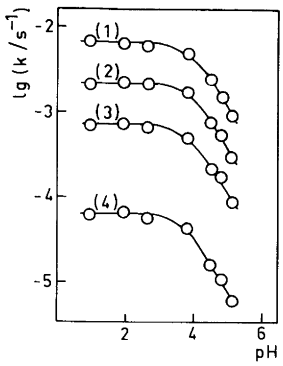
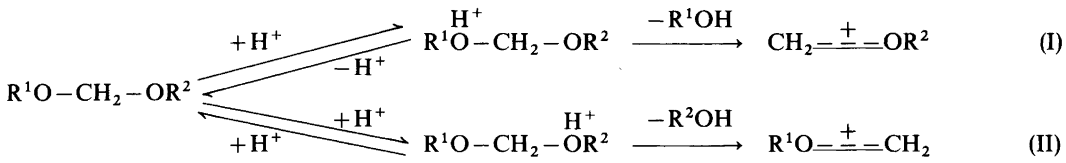


Fig. 1. Acid-catalyzed hydrolysis of 1-(1-alkoxyethyl)benzimidazoles at 353.13 K. Dependence of the observed first-order rate constants on the oxonium ion concentration of the reaction mixture. (1) Isopropoxy, (2) ethoxy, (3) methoxy and (4) 2-chloroethoxy derivatives.

carbenium ion intermediates,[2] is considered in the following.

Salomaa has shown[3] that the acidic hydrolysis of acyclic acetals proceeds by two different routes depicted in the heading of Table 2. The rate constants, k(I), for the partial reaction (I) describe the influence of the nondeparting alkoxy group, R^2, on the hydrolysis of acetals of formaldehyde. This influence reflects predominantly the effect of R^2 on the stability of the oxocarbenium ion intermediate. The influence on the pre-equilibrium protonation is presumably small, since the inductive effect of R^2 must be transmitted *via* three carbon-oxygen bonds to the site of protonation. In Fig. 2 the effects of various alkoxy groups on the acidic hydrolysis of 1-(1-alkoxyethyl)benzimidazoles have been compared with the effects that the same groups have on the stability of the oxocarbenium ion intermediate in the hydrolysis of formaldehyde acetals. Plotting of the rate constants for the former reaction in 0.10 mol dm^{-3} aqueous hydrogen chloride against the values of k(I) for the hydrolysis of acetals of formaldehyde yields a strictly linear correlation line with the slope close to unity. In other words, the susceptibility to polar effects is in both reactions almost the same. The latter finding strongly suggests that the decomposition of the protonated 1-(1-alkoxyethyl)benzimidazoles proceeds *via* an intermediate closely related to that in reaction (I) of acetals of formaldehyde, *viz.* the oxocarbenium ion formed from the 1-alkoxyethyl group.

Table 2. Relative rate constants for the partial reactions (I) and (II) of acetals of formaldehyde at 298.2 K.[3]



R^2 [a]	k(I)	k(II)
Isopropyl	22.1	2.27
Ethyl	4.48	1.21
Methyl	1	1
2-Chloroethyl	0.0480	1.96

[a] R^1 is a simple alkyl group (methyl, ethyl, isopropyl, or 2-chloroethyl) the structure of which remains unvaried as the structure of R^2 changes.

A few pyrimidine nucleosides have been shown to undergo in aqueous acid anomerization reactions concurrent with hydrolysis, which suggests that their hydrolytic decomposition might involve protonation of the glycon ring and subsequent cleavage of the carbon–oxygen bond.[4] Analogously, the hydrolysis of 1-(1-alkoxyethyl)benzimidazoles could be expected to proceed by Route B in Scheme 1. The structural effects indicated above do not, however, support this possibility. As described previously,[1] the rate constants for this reaction under strongly acidic conditions, k_B^H(obs), can be expressed by eqn. (1), where K_A and K_B are the ionization constants for the substrates protonated on the imidazole ring and the oxygen atom, respectively, and k_B is the first-order rate constant for the heterolysis of the latter species. If Route B were utilized, k_B^H(obs) would be rather sensitive to the polar nature of the alkoxy group. The increasing electron-attracting ability of this group, for example, facilitates its departure considerably, but, at the same time, increases the acidity of the substrate protonated on the oxygen atom. Accordingly, both k_B and K_B are increased and the increments, at least partially, cancel each other. The influence on K_A can be neglected for the reasons given below. Consequently, the situation is analogous to the hydrolysis of acyclic acetals as the effect of the departing alkoxy group is considered. Table 2 clearly shows that the latter effect contrasts strongly with that observed in the hydrolysis of benzimidazole derivatives.

$$k_B^H(\text{obs}) = k_B K_A / K_B \qquad (1)$$

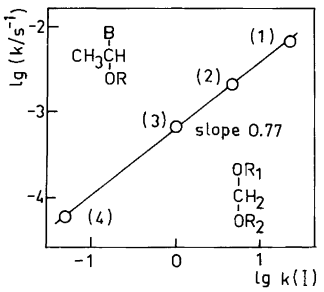


Fig. 2. Comparison of structural effects in the acidic hydrolysis of 1-(1-alkoxyethyl)benzimidazoles with those in partial reaction (I) of acetals of formaldehyde (see Table 2). (1) Isopropoxy, (2) ethoxy, (3) methoxy and (4) 2-chloroethoxy derivatives.

As described previously,[1] the ionization constant, K_A, can be calculated by eqn. (2) from the kinetic data irrespective of which one of the routes in Scheme 1 is followed. Here k(obs) is the observed rate constant in a given oxonium ion concentration and k^H(obs) is the rate constant in the plateau of the pH profile. The ionization constants obtained by this method for protonated 1-(1-alkoxyethyl)benzimidazoles are collected in Table 3. The values are quite insensitive to the

$$\lg(K_A/\text{mol dm}^{-3}) = \lg\left(\frac{k^H(\text{obs})}{k(\text{obs})} - 1\right) + \lg([H^+]/\text{mol dm}^{-3}) \qquad (2)$$

Table 3. Kinetically determined ionization constants at 353.15 K for some 1-(1-alkoxyethyl)benzimidazoles protonated on the imidazole ring.

pH of reaction solution at 353.15 K	$-\lg (K_A/\text{mol dm}^3)$			
	Isopropoxy	Ethoxy [a]	Methoxy	2-Chloroethoxy
3.88	4.32	4.52	4.31	4.23
4.58	4.36	4.35	4.28	4.13
4.88	4.34	4.42	4.42	4.22
5.18	4.38	4.40	4.36	4.21
The mean	4.35	4.42	4.34	4.20

structure of the alkoxy group, as assumed in the preceding discussion. This is expected on the basis of the long distance between the alkoxy substituent and the site of protonation.

In summary, the results of this paper in part corroborate the suggestion of Zoltewicz,[5] according to which the acidic hydrolysis of nucleosides proceeds by unimolecular departure of the protonated nitrogen base in the rate-limiting stage. This mechanism can probably be extended to all related compounds capable of forming a reasonably stable oxocarbenium ion.

EXPERIMENTAL

Preparation of materials. 1-(1-Alkoxyethyl)benzimidazoles were prepared by treating benzimidazole at room temperature in DMF solution with a slight excess of appropriate alkyl 1-chloroethyl ethers. Triethylamine was added to neutralize the hydrogen chloride liberated in the condensation reaction. Triethylamine hydrochloride was removed by filtration and the solvent was evaporated under reduced pressure. The products were crystallized from methanol as their picric acid salts. Of the alkyl 1-chloroethyl ethers, employed as starting materials, 1-chloroethyl methyl ether was obtained by treating the mixture of methanol and acetaldehyde with hydrogen chloride at −10 °C.[6] 1-Chloroethyl isopropyl ether and 1,2′-dichloroethyl ether were prepared by conducting dry hydrogen chloride into isopropyl and 2-chloroethyl vinyl ethers, respectively.[7] Before kinetic measurements, 1-(1-alkoxyethyl)benzimidazoles were regenerated from their picrates as described earlier.[1] The syrupy products obtained were characterized by ^{1}H NMR spectroscopy (Jeol JNM PMX60 spectrometer) in CCl_4. The following compounds were prepared.

1-Methoxyethyl derivative: m.p. of the picrate 174−175 °C; NMR signals (δ values) at 1.63 d (3H), 3.01 s (3H), 5.34 q (1H), 6.95−7.65 m (4H), 7.73 s (1H).

1-Isopropoxyethyl derivative: m.p. of the picrate 154−155 °C; NMR signals at 0.83 d (3H), 1.04 d (3H), 1.56 d (3H), 3.33 q (1H), 5.57 q (1H), 6.95−7.65 m (4H), 7.77 s (1H).

1-(2-Chloroethoxy)ethyl derivative: m.p. of the picrate 152−155 °C; NMR signals at 1.74 d (3H), 3.40−3.62 m (4H), 5.84 q (1H), 7.00−7.65 m (4H), 8.25 s (1H).

Kinetic measurements. Kinetic measurements were performed as described earlier.[1]

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