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MECHANISMS FOR THE SOLVOLYTIC DECOMPOSITIONS OF NUCLEOSIDE ANALOGUES—*I*

ACIDIC HYDROLYSIS OF 2-SUBSTITUTED 1-(1-ETHOXYETHYL)BENZIMIDAZOLES

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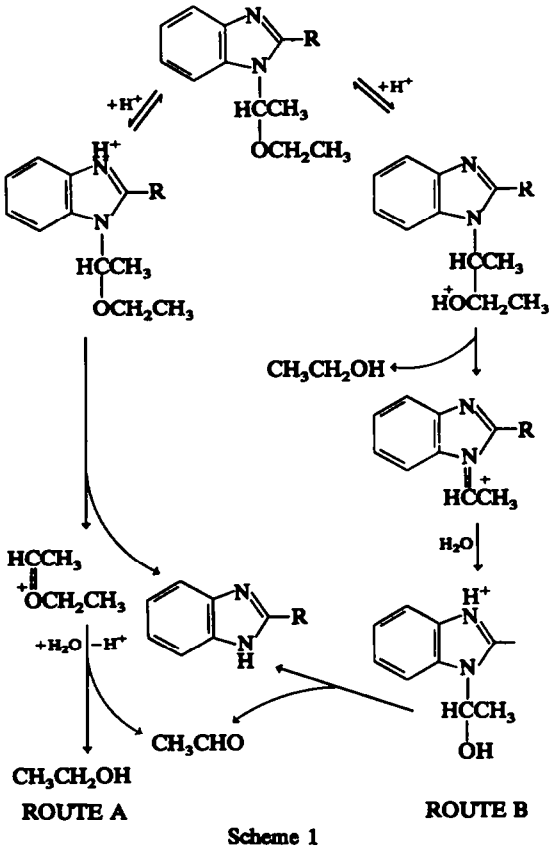
Abstract—A few 2-substituted 1-(1-ethoxyethyl)benzimidazoles have been prepared and the rate constants for their hydrolysis measured at various temperatures and oxonium ion concentrations. The formal kinetics followed and the effect of varying the 2-substitution on the hydrolysis rate suggest that the acid-catalyzed cleavage of these compounds involves a rapid initial protonation of the benzimidazole ring and a subsequent rate-limiting heterolysis of the protonated substrate to form a free nitrogen base and an oxocarbenium ion derived from the ethoxyethyl group. The values obtained for the entropy of activation are consistent with the assumed unimolecular nature of the rate-limiting step. The effects of 2-substituents on the acidities of the protonated substrates and their heterolysis rates have been compared. The latter partial reaction has been suggested to be the subject of steric acceleration.

Reactions of nucleosides and related compounds, containing a heterocyclic nitrogen base bonded through one of its heteroatoms to the anomeric carbon of a furanoid carbohydrate derivative, have been the objects of increasing interest after the discovery that some of these compounds have antitumor[1] or antiviral[2] properties. For example, their hydrolytic decomposition to base and sugar components has been studied quite extensively.[3–17] However, relatively few of the investigations are mechanistically significant. Zoltewicz *et al.* have suggested[5,8] that the acidic hydrolysis of purine nucleosides consists of a rapid initial protonation of the purine ring to give a mono- or dication and a subsequent rate-limiting fission of these species to a free base and a cyclic oxocarbenium ion of the sugar moiety. This proposal has received considerable supporting evidence from several kinetic studies concerning the acid-catalyzed cleavage of a variety of nucleosides. The effects of structure on reactivity,[9,10] the rate-pH profiles,[7,10] the values for the entropy of activation,[9–11] and the secondary deuterium isotope effects[17] are all consistent with the suggested mechanism. Quite recently it has been noticed, however, that two pyrimidine nucleosides, thymidine and deoxyuridine, undergo in aqueous acid anomerization to the corresponding pyranoid and α-furanoid derivatives concurrent with the hydrolysis.[14] The latter finding has been interpreted to indicate that the hydrolytic decomposition occurs, at least partially, by protonation of the glycon moiety at the ring-oxygen followed by rate-limiting opening of the five-membered ring to give a Schiff base intermediate.[14] In other words, the same mechanism as in the hydrolysis of glycosylamines[3] would operate. It should be noted that the majority of the data presented above to support the unimolecular rate-limiting rupture of the CN bond are in accordance with this mechanism, too.

On the basis of the preceding discussion it seems possible that the mechanism of the acid-catalyzed hydrolysis of nucleosides and their analogues may depend on the structure of heterocyclic base component in the substrate. The aim of our studies is to elucidate the structural factors that could possibly favor one of the suggested mechanism over the other, and to further the understanding of the structures of the transition states for these reactions. Simple *N*-(1-alkoxyalkyl) derivatives of various heterocyclic nitrogen bases are used as model compounds. The present paper, comprising the first part of the investigation, deals with the effects of 2-substituents on the hydrolysis of 1-(1-ethoxyethyl)benzimidazoles in aqueous acid solutions.

RESULTS AND DISCUSSION

Analogous to the hydrolysis of nucleosides, two alternative pathways can be formulated for the acid-catalyzed cleavage of 2-substituted 1-(1-ethoxyethyl)benzimidazoles. Either the substrate protonated on the imidazole ring undergoes rate-limiting heterolysis to benzimidazole and an oxocarbenium ion derived from the 1-ethoxyethyl group, all subsequent reactions being fast (Route A in Scheme 1), or a rapid initial protonation of the oxygen atom is followed by cleavage of ethanol to give a resonance stabilized carbonium ion, which is further degraded to benzimidazole and acetaldehyde *via* an aminoalcohol intermediate (Route B in Scheme 1). In the latter pathway the departure of the protonated ethoxy group is the reasonable rate-limiting stage. If the addition of water on the carbonium ion were the slow process the reverse



Scheme 1

for the formation of this species, *i.e.* the attack of ethanol on it, should occur faster than the attack of water on the carbonium ion centre. This can hardly be the case, since the concentration of ethanol is in a dilute aqueous solution extremely low compared to that of water. If the decomposition of the aminoalcohol intermediate were rate-limiting, the liberation of ethanol would take place in a pre-equilibrium stage. Because the reverse of this partial reaction would be of second-order, the formation of final products would not obey simple first-order kinetics. However, in the hydrolysis of 1-(1-ethoxyethyl)benzimidazoles the first-order kinetics is in every investigated case strictly followed. Moreover, the reactions proceeding by rate-limiting heterolysis of an aminoalcohol intermediate generally exhibit in highly acidic solutions inverse dependences of reactivity on acidity, probably due to the fact that general base catalysis is needed to remove proton from the hydroxyl group of the amino-alcohol.[18] For examples, the hydrolyses of benzylidene-*tert*-butylamines,[19] benzylideneanilines[20] and *N*-aryl-glycosylamines[21] are characterized by this kind of behaviour. In contrast, the hydrolysis rate for 1-(1-ethoxyethyl)benzimidazole is completely independent of the acid concentration, as can be seen from the data in Table 1.

Table 1. First-order rate constants for the hydrolysis of 1-(1-ethoxyethyl)benzimidazole in aqueous perchloric acid at 343.15 K.

$[HClO_4]$/mol dm^{-3}	$k/10^{-4}$ s^{-1}
0.10	5.92±0.04
0.50	5.97 0.06
1.0	5.53 0.05
2.0	5.58 0.06
5.0	6.49 0.08
6.0	6.47 0.09

The first-order rate constants obtained for the hydrolyses of 2-substituted 1-(1-ethoxyethyl)-benzimidazoles in aqueous hydrogen chloride and buffer solutions are collected in Table 2. Each compound exhibits a similar reactivity-pH profile. The rate constants remain unchanged in high oxonium ion concentrations and experience sharp decreases on going to less acidic solutions. This kind of pH dependence can be easily explained by either mechanism A or mechanism B involving rate-limiting departure of the protonated ethoxy group. The observed first-order rate constants for these reactions can be expressed by eqn (1) and (2), where K_A and K_B stands for the ionization constants for the substrates protonated on the imidazole ring and the oxygen atom, respectively, and

Table 2. First-order rate constants for the hydrolyses of 2-substituted 1-(1-ethoxyethyl)benzimidazoles in various acid and buffer solutions. The temperature is 353.15 K if not otherwise stated.

Reaction solution			Substituent in position 2									
			CH_3		H		CH_2OH		CH_2Cl		CH_2CN	
HA	[HA]/mol dm^{-3}	[NaA]/mol dm^{-3}	$k/10^{-3}$ s^{-1}									
HCl	0.10	—	1.090	±0.016	2.11	±0.03	9.64	±0.11	8.46	±0.11[a]	3.08	±0.07[b]
HCl	0.010	0.090	1.228	0.014	2.23	0.04	9.64	±0.13	8.78	±0.13[a]	3.21	0.12[b]
HCl	0.0020	0.098	1.006	0.014	2.13	0.03	9.36	0.18	6.34	0.14[a]	1.557	0.070[b]
HCOOH	0.20	0.10									0.707	0.016[b]
HCOOH	0.10	0.10	0.966	0.010	1.717	0.026			1.824	0.071[a]	0.291	0.009[b]
HCOOH	0.050	0.10	0.881	0.011	1.454	0.046	5.70	0.10			0.229	0.008[b]
CH_3COOH	0.20	0.10	0.735	0.010	0.782	0.010	2.70	0.05	0.744	0.013[a]	1.172	0.032[a]
CH_3COOH	0.10	0.10	0.653	0.007	0.547	0.006	2.32	0.02	0.434	0.009[a]	0.592	0.011[a]
CH_3COOH	0.050	0.10	0.548	0.007	0.303	0.004	1.274	0.036	0.234	0.007[a]	0.306	0.008[a]
CH_3COOH	0.020	0.10	0.301	0.004	0.146	0.003	0.657	0.017				

[a] T = 333.15 K.
[b] T = 313.15 K.

k_A and k_B denote the first-order rate constants for the heterolysis of these species. Accordingly, the observed rate constants are linearly related to the oxonium ion concentration as long as $[H^+]$ is negligible compared to K_A, and level off to constant values, given by eqn (3) and (4), when $[H^+]$ becomes greater than K_A.

$$k_A(\text{obs.}) = k_A \cdot \frac{[H^+]}{K_A + [H^+]} \quad (1)$$

$$k_B(\text{obs.}) = k_B \cdot \frac{K_A}{K_B} \cdot \frac{[H^+]}{K_A + [H^+]} \quad (2)$$

$$k_A^H(\text{obs.}) = k_A \quad (3)$$

$$k_B^H(\text{obs.}) = k_B \cdot \frac{K_A}{K_B} \quad (4)$$

Equations (3) and (4) enable us to distinguish between mechanism A and mechanism B with rate-limiting cleavage of ethanol. Table 3 records the first-order rate constants measured for the hydrolysis of 2-substituted 1-(1-ethoxyethyl)benzimidazoles in 0.10 mol dm^{-3} aqueous hydrogen chloride at different temperatures. The values extrapolated to 333.15 K increase considerably with the electron-attracting character of the 2-substituent. Replacing of 2-methyl group by 2-cyanomethyl substituent, for example, results in a 570-fold increase in the hydrolysis rate. In other words, the reaction constant, ρ, is of the order of ten if σ_I constants are used as a measure for the inductive effects. A rate-enhancement of this magnitude can easily be accounted for by mechanism A. The observed rate constant for this reaction is, according to eqn (3), equal to the rate constant for the fission of the protonated substrate. In the latter process the electron density increases at the nitrogen atom in position 1 with the departure of the protonated benzimidazole moiety. Accordingly, electron-withdrawal by the adjacent 2-substituent tends to stabilize the transition state leading to a marked rate acceleration. For example, in the spontaneous hydrolysis of 1-(β-D-galactopyranosyl) pyridinium ions a similar rate-enhancement is observed on going from the unsubstituted to 3-chloro-substituted compound.[16] In contrast, a lower or even opposite susceptibility to inductive effects would be expected if Route B involving rate-limiting cleavage of the protonated ethoxy group were utilized. The observed rate constant for this reaction under acidic conditions is given by eqn (4). As the electronegativity of the 2-substituent increases the ionization constants for both of the protonated forms of the substrate increase, but the effect on K_A is presumably greater owing to the shorter distance to the atom which looses the proton. Consequently, the effect on the ratio K_A/K_B is rate -accelerating. At the same time k_B is, however, considerably decreased, since electron-withdrawal by the 2-substituent lowers the electron density at the developing carboniuin ion centre. Hence the effects on the concentration of the protonated substrate and its decomposition rates are opposite. As a result of partial cancellation of these influences, the susceptibility to the polar nature of the 2-substituent would be expected to be low. However, as will be seen later, the effect on the observed rate constant is even greater than on K_A.

Table 3 also records the entropies of activation for the acid-catalyzed hydrolysis of the 1-(1-ethoxyethyl)benzimidazoles investigated. The values are all positive and of same magnitude, being in good agreement with the proposed unimolecular nature of the rate-limiting step of mechanism A. For the corresponding reactions of nucleosides somewhat smaller values have been reported.[7,9,10]

Besides electronic effects, *ortho*-substituents often exert significant steric effects, too.[22] A possible way to elucidate the latter in the hydrolysis of

Table 3. First-order rate constants at different temperatures and the enthalpies and entropies of activation for the hydrolysis of 2-substituted 1-(1-ethoxyethyl)benzimidazoles in 0.10 mol dm^{-3} aqueous hydrogen chloride.

Substituent in position 2	T/K	k/10^{-3} s^{-1}	k(calc.)[a]/10^{-3} s^{-1}	$\Delta H^{\ddagger a}$/kJ mol^{-1}	$\Delta S^{\ddagger a}$/J K^{-1} mol^{-1}
CH_3	333.15	0.0734±0.0008	0.0743±0.0022	129.2±2.2	63±6
	343.15	0.306 0.003			
	353.15	1.090 0.016			
H	323.15	0.0363±0.0007	0.1545±0.0020	125.4±1.0	58±3
	333.15	0.1590 0.0010			
	343.15	0.592 0.004			
	353.15	2.11 0.03			
CH_2OH	323.15	0.1793±0.0015	0.726 ±0.034	121.5±3.7	59±11
	333.15	0.773 0.010			
	343.15	2.44 0.05			
	353.15	9.64 0.11			
CH_2Cl	313.15	0.592 ±0.008	8.35 ±0.06	112.2±0.4	51±2
	323.15	2.28 0.05			
	333.15	8.46 0.11			
	343.15	27.9 0.5			
CH_2CN	293.15	0.1825±0.0043	42.4 ±3.7	107.5±2.6	51±8
	303.15	0.875 0.011			
	313.15	3.08 0.08			
	323.15	12.77 0.22			

[a] T = 333.15 K.

Table 4. Kinetically determined ionization constants, K_A, for 2-substituted 1-(1-ethoxyethyl)benzimidazoles protonated on the nitrogen in position 3. The temperature is 353.15 K if not otherwise stated.

pH of the reaction solution at 353.15 K	Substituent in position 2				
	CH_3	H	CH_2OH	CH_2Cl	CH_2CN
	$-\lg(K_A/\text{mol dm}^{-3})$				
3.58					2.93[b]
3.88				3.25[a]	2.78[b]
4.18	4.80	4.53	4.34		2.97[b]
4.58	4.90	4.35	4.17	3.49[a]	2.95[a]
4.88	5.05	4.42	4.38	3.54[a]	2.96[a]
5.18	5.18	4.40	4.36	3.56[a]	2.97[a]
5.58	5.16	4.45	4.44		3.11[a]
the mean	5.02±0.16	4.43±0.07	4.34±0.10	3.46±0.14	2.95±0.10

[a] T = 333.15 K.
[b] T = 313.15 K.

2-substituted 1-(1-ethoxyethyl)benzimidazoles is to compare the influences that 2-substituents have on the ionization constant, K_A, for the substrate protonated on the nitrogen in position 3 and on the rate constant, k_A, for the heterolysis of this species. In the former reaction the steric effects do not probably play any important role. For example, the ionization constants for the conjugate acids of 2-substituted imidazoles and benzimidazoles can be correlated with Hammett equation by means of σ_m values,[23] indicating the absence of marked steric effects. That this is the case also with 1-(1-ethoxyethyl)benzimidazoles can be seen from the values in Table 4. These have been calculated from the kinetic data given in Table 2. For this purpose eqn (1) where k_A has been replaced by k_A^H(obs.), in accord with eqn (3), is written in the form (5). As

$$\lg K_A = \lg\left(\frac{k_A^H(\text{obs.})}{k_A(\text{obs.})} - 1\right) - \text{pH} \qquad (5)$$

seen from Fig. 1, a fairly good linear correlation exists between the calculated $\lg K_A$ values and the σ_m constants of the 2-substituents, with the reaction constant, ρ_m, of 9.0±0.3. The points for the 2-chloromethyl and 2-cyanomethyl substituted compounds are included in the plot, although their K_A values refer to lower temperatures than those for the other derivatives. The fact that the basicity of the 2-cyanomethyl compound does not markedly change with temperature, as can be seen from Table 4, gives some justification for this procedure. Fig. 1 also shows the dependence of $\lg k_A$ on δ_m constants. The susceptibility to electronic effects is in this case almost the same as in the ionization of the protonated substrates, but the correlation line exhibits a slight curvature, and the point for the unsubstituted derivative falls below the line the other compounds yield. These findings suggest that the substituents in position 2 exert, besides electronic effects, observable steric accelerations on the decomposition of the protonated substrate. It has been shown[24] that the steric demands of *ortho*-substituents in aromatic systems can be described by Taft's E_s parameters,[25] designated originally for aliphatic compounds. If it is further assumed that δ_m constants adequately measures the electronic effects of 2-substituents on the heterolysis of protonated 1-(1-ethoxyethyl)benzimidazoles, as they do in the ionization of the same species, $\lg k_A$ values would be expected to obey eqn (6), where a and b are adjustable parameters.

$$\lg k_A = \rho(\delta_m + aE_s) + b \qquad (6)$$

Figure 2 clearly shows that this is indeed the situation. The value of −0.033 for a gives the best fit, the reaction constant, ρ, and parameter, b, being 10.8±0.2 and −3.37±0.02, respectively. Accordingly, the hydrolysis of 1-(1-ethoxyethyl)benzimidazoles seems to be to some extent accelerated by bulky *ortho*-substituents, though the electronic effects, no doubt, play much more decisive role.

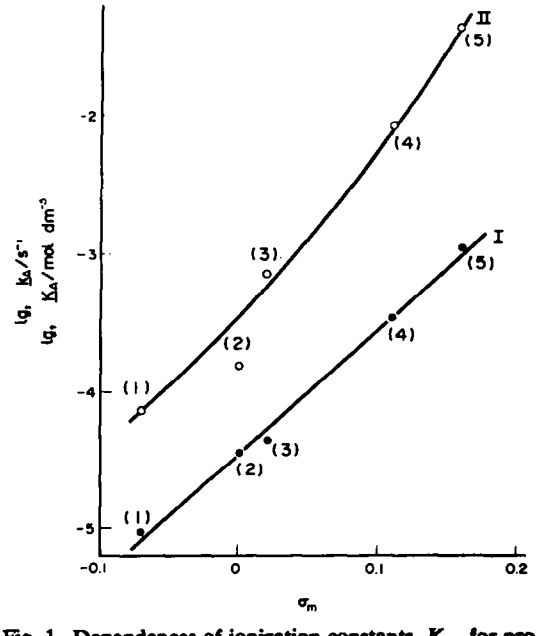
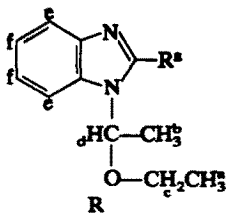


Fig. 1. Dependences of ionization constants, K_A, for protonated 1-(1-ethoxyethyl)benzimidazoles (line I) and first-order rate constants, k_A, for their heterolysis (line II) on the σ_m values of the substituents in position 2. The σ_m values employed are those reported in Ref. 26. Notation:(1) CH_3, (2) H, (3) CH_2OH, (4) CH_2Cl and (5) CH_2CN substituted compound.

Table 5. ^{1}H NMR chemical shifts for the 2-substituted 1-(1-ethoxyethyl)benzimidazole prepared and the melting points for their picric acid salts.



	^{1}H NMR chemical shifts in CCl_4							
	δ_a	δ_b	δ_c	δ_d	δ_e	δ_f	δ_g	M.p./°C
H	t 1.10	d 1.73	q 3.34	q 5.63	m 7.24	m 7.64	s 8.03	145–47
CH_3	t 1.12	d 1.66	q 3.25	q 5.55	m 7.05	m 7.46	s 2.50	156–59
CH_2OH	t 1.18	d 1.75	q 3.43	q 5.84	m 7.08	m 7.58	d 4.78 t 6.01	134–37
CH_2Cl	t 1.16	d 1.75	q 3.38	q 5.70	m 7.05	m 7.48	s 4.72	151–53
CH_2CN	t 1.12	d 1.68	q 3.27	q 5.65	m 7.11	m 7.51	s 4.12	130–31

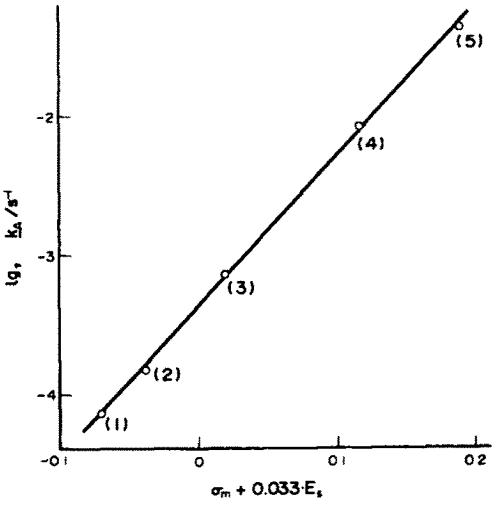


Fig. 2. Dependence of first-order rate constants for the heterolysis of protonated 1-(1-ethoxyethyl)benzimidazoles on the values of $\sigma_m + 0.033 \cdot E_s$ for the substituents in position 2. The values for σ_m are taken from Ref. 26 and those for E_s from Ref. 27. The numbers of the compounds are the same as in Fig. 1.

In summary, the preceding discussion lends some additional support for the suggestion of Zoltewicz[5] according to which the hydrolysis of nucleosides proceeds by unimolecular rate-limiting departure of the protonated heterocyclic base. The rate of this reaction is probably determined by both electronic and steric properties of the leaving group, the former being more important.

EXPERIMENTAL

Preparation of materials. 2-Substituted 1-(1-ethoxyethyl)benzimidazoles were prepared by treating the appropriate benzimidazole in boiling xylene with an equal amount of 1-chloroethyl ethyl ether. Excess of triethylamine was added to neutralize the hydrogen chloride liberated in the condensation reaction. The cooled mixture was filtered and concentrated to a syrup under reduced pressure. The crude product was extracted with diethyl ether. The etheral solution was washed several times with water and dried with $MgSO_4$. The product was characterised by ^{1}H NMR spectroscopy (Jeol JNM PMX60 spectrometer) and converted to its picric acid salt. The ^{1}H NMR chemical shifts are collected in Table 5 together with the melting points of the picrates. 1-Chloroethyl ethyl ether, used as the starting material, was obtained by passing dry hydrogen chloride into cooled (−10°C) ethyl vinyl ether. The product was purified by distillation under reduced pressure.

Before kinetic measurements the compounds were regenerated from their picric acid salts by dissolving the picrate in aqueous sodium hydroxide and extracting the liberated 1-(1-ethoxyethyl)benzimidazole into carbon tetrachloride. The organic layer was washed several times with water, dried with $MgSO_4$ and evaporated to dryness under reduced pressure.

Kinetic measurements. Hydrolyses of 2-substituted 1-(1-ethoxyethyl)benzimidazoles were carried out in stoppered bottles immersed in a thermostated bath, the temperature of which was kept constant within 0.05 K. Reactions were started by adding the substrates as dimethyl sulfoxide solutions into prethermostated reaction media. Aliquots of 2 ml were withdrawn at appropriate intervals and the reaction was stopped by mixing them into 1 ml of 0.5 M sodium hydroxide solution. The progress of the hydrolysis was followed by measuring the absorbances of the alkalized samples at 255 nm. The absorbance of the unreacted substrate did not change with time under the alkaline conditions used in the determinations. The final values were taken after ten half lives. The buffer solutions were prepared by weighing the acidic component into a sodium hydroxide solution of known concentration.

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