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Mechanisms for the Solvolytic Decompositions of Nucleoside Analogues. VI. Acidic Hydrolysis of 2-Substituted 1-(3-Chlorotetrahydro-2-furyl)benzimidazoles

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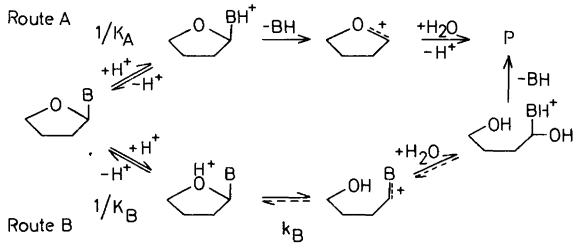
A few 2-substituted 1-(3-chlorotetrahydro-2-furyl)-benzimidazoles have been prepared and the rate constants for their hydrolysis measured in aqueous perchloric acid of various concentrations. The great rate-enhancing effects of electronegative 2-substituents suggest that the rate-limiting step for the hydrolysis reaction involves a departure of the protonated base moiety and formation of a cyclic oxocarbenium ion from the 3-chlorotetrahydro-2-furyl group.

It is widely accepted[1–6] that the acid-catalyzed hydrolysis of purine nucleosides proceeds by unimolecular rate-limiting heterolysis of the mono- and dications of the substrate with formation of a free base and a cyclic oxocarbenium ion from the glycosyl moiety (Route A in Scheme 1). Some pyrimidine nucleosides, however, have been shown to undergo isomerization to pyranoid and α-furanoid derivatives concurrent with the hydrolysis.[7] This finding strongly suggests that the hydrolytic decomposition takes place through formation of an acyclic Schiff base intermediate,[7] *i.e.* analogously to the hydrolysis of glycosylamines (Route B in Scheme 1). Thus, the mechanism for the acidic hydrolysis of nucleosides may depend on the structure of the base moiety.

We have previously approached the problem by examining the effects that polar substituents in the base moiety of relatively simple acyclic nucleoside analogues, 1-(1-ethoxyethyl)benzimidazoles, exert on the rate and mechanism of their hydrolytic decomposition.[8] All the compounds studied have been shown to react by a mechanism as depicted by Route A in Scheme 1.[8,9] However, the extension of these results to nucleoside hydrolysis is not quite straightforward. The formation of a cyclic oxocarbenium ion from the β-D-ribofuranosyl moiety of nucleosides is a far more difficult process than the formation of an acyclic oxocarbenium ion from the 1-ethoxyethyl group. In other words, the observation that Route A is followed during the hydrolysis of acyclic benzimidazole derivatives may not necessarily mean that this mechanism is generally valid for the hydrolysis of nucleosides. For this reason, the investigation is now extended to cyclic nucleoside analogues as 2-substituted 1-(3-chlorotetrahydro-2-furyl)benzimidazoles which contain a strongly elec-



Scheme 1.

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tronegative chloro substituent in the α-position to the anomeric carbon making the formation of a cyclic oxocarbenium ion, and hence Route A, rather unfavorable. The hydrolysis mechanism for these compounds can be established by comparing the structural effects with those observed in the hydrolysis of the corresponding 1-(1-ethoxyethyl)benzimidazoles.

RESULTS AND DISCUSSION

Table 1 records the first-order rate constants for the hydrolysis of the isomeric 2-substituted 1-(3-chlorotetrahydro-2-furyl)benzimidazoles in aqueous hydrogen chloride. Unfortunately, a configurational problem arises with regard to the two isomers, since the available data do not allow a definite assignment of which of the isomers are the *cis*-2,3 or the *trans*-2,3 anomers. However, for the following reasons we believe that the more reactive isomers have the *trans*-2,3-arrangement. The C1 carbon of several 1,2-di-substituted five-membered rings has been shown to resonate at 5–10 ppm higher field in the *cis* than in the *trans* isomer.[10–12] Since the anomeric carbon of the less reactive 1-(3-chlorotetrahydro-2-furyl)-2-methylbenzimidazole is about 5 ppm more shielded than the anomeric carbon of the more reactive anomer, it appears reasonable to assign the latter as *trans*-2,3-anomer. Additional support for this suggestion comes from the ^{1}H NMR measurements.

The vicinal coupling constants, ^3J(H,H), for the cisoidal protons of a five-membered ring generally vary from 4.5 to 10 Hz and those for the *trans* oriented protons from 0 to 11 Hz.[10] The coupling constants, ^3J(H2′,H3′), for the anomeric protons of the more reactive isomers are about 3.5 Hz, thus being slightly smaller than would be expected for a *cis*-2,3-arrangement. The corresponding values for the less reactive isomers are about 4.5 Hz. Furthermore, the anomeric protons of nucleosides,[13] aldofuranosides,[14] and 3-substituted 2-phenyltetrahydrofurans[15] resonate at a higher field when the adjacent proton is *trans* than when *cis*. Consistent with this general trend, the more readily hydrolyzed isomers exhibit their anomeric proton signals at about 0.15 ppm higher field than the less reactive counterparts. Finally, purine and imidazole nucleosides having the *trans*-1,2-configuration display H8 and H2 signals, respectively, at lower field than

Table 1. First-order rate constants, $k/10^{-5}$ s^{-1}, for the hydrolysis of isomeric 2-substituted 1-(3-chlorotetrahydro-2-furyl)benzimidazoles in aqueous hydrogen chloride. The temperature is 363.2 K if not otherwise stated.

Substituent at C2	$[H^+]$/mol dm^{-3}	*trans*-2,3	*cis*-2,3
CH_3	0.010	0.516(9)	0.322(5)
	0.10	0.511(12)	0.274(9)
	1.0	0.512(4)	0.321(8)
H	0.010		0.459(4)
	0.10		0.425(8)
	1.0		0.422(10)
	5.0		0.449(12)
CH_2OH	0.010	6.07(7)	3.90(13)
	0.10	6.06(11)	3.98(9)
	1.0	5.69(10)	3.58(10)
CH_2Cl	0.010	53.4(11)	28.7(9)
	0.050	76.2(9)	36.9(7)
	0.10	79.0(12)	40.7(4)
	1.0	80.6(9)	40.2(5)
	0.10	26.0(5)[a]	12.5(2)[a]
	0.10	7.44(8)[b]	3.68(4)[b]

[a] 353.2 K. [b] 343.2 K.

the corresponding *cis* compounds,[13] as observed for the proton signals of the C2 substituents in isomeric 1-(3-chlorotetrahydro-2-furyl)benzimidazoles in the present study.

The rate constants for the hydrolysis of 1-(3-chlorotetrahydro-2-furyl)benzimidazoles are apparently independent upon the oxonium ion concentration as the latter exceeds $\sim 10^{-2}$ mol dm^{-3}, *i.e.* when the substrates are expected to be almost completely protonated.[8,9,16] Accordingly, mechanisms involving diprotonated forms of the substrate as intermediates can be refuted. In particular, the hydrolysis cannot proceed *via* a dication bearing a proton at both the N3 and the O1′ atoms. Introduction of electronagetive substituents as hydroxymethyl and chloromethyl groups at the C2-carbon of the benzimidazole ring greatly accelerates the hydrolysis, as expected when Route A in Scheme 1 is followed. Electron-attracting groups at C2 lower the electron density at N1 facilitating the rupture of the carbon–nitrogen bond. The effect on the basicity of the substrate can be ignored under conditions where the substrates are completely protonated. Fig. 1 clearly indicates that in both isomeric series of 1-(3-chlorotetrahydro-2-furyl)-benzimidazoles the dependence of the hydrolysis rate on the structure of the C2 substituents is of the same order of magnitude was with 2-substituted 1-(1-ethoxyethyl)benzimidazoles. This finding strongly suggests that Route A, shown to be utilized in the hydrolysis of the latter compounds,[8,9] also is followed during the hydrolysis of the former nucleoside analogues. The entropies of activation, (23 ± 6) J K^{-1} mol^{-1} and (23 ± 2) J K^{-1} mol^{-1} for the *trans* and *cis* isomers of the chloromethyl substituted compound, respectively, agree with the unimolecular nature of the rate-limiting step of the assumed mechanism.[17]

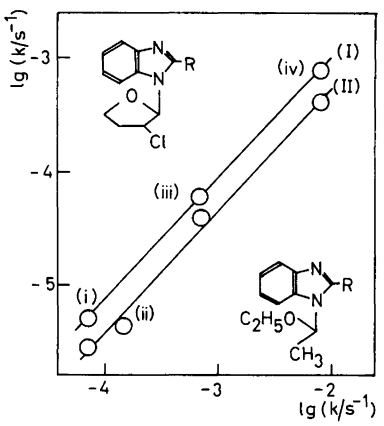

Fig. 1. A comparison of structural effects in the acidic hydrolysis of isomeric 2-substituted 1-(3-chlorotetrahydro-2-furyl)benzimidazoles at 363.2 K with those for acidic hydrolysis of 2-substituted 1-(1-ethoxyethyl)benzimidazoles at 333.2 K.[8] Lines I and II refer to the *trans*-2,3 and *cis*-2,3 isomers, respectively. The substituents at C2 are (i) methyl, (ii) hydrogen, (iii) hydroxymethyl and (iv) chloromethyl.

In contrast, the available kinetic data cannot be accounted for by Route B in Scheme 1. This mechanism involves three possible rate-limiting steps; opening of the protonated tetrahydrofuryl ring, nucleophilic addition of water to the cationic Schiff base, and, finally, heterolysis of the amino-alcohol intermediate. We have previously shown[8] that at moderate oxonium ion concentration the observed first-order rate constant, k_B(obs), for reaction *B* involving rate-limiting ring-opening can be expressed by eqn. (1) where the partial rate and

$$k_B(\text{obs}) = k_B(K_A/K_B) \quad (1)$$

equilibrium constants are those indicated in Scheme 1. The increasing electronegativity of the substituent at C2 increases both K_A and K_B, but the influence on the latter is presumably smaller owing to the longer distance to the site of protonation. At the same time, k_B is decreased, since increased electron-withdrawal of the C2 substituent lowers the electron density at N1, retarding the developing of the positively charged carbonium ion. Accordingly, the gross effect on k_B(obs) can be expected to be much smaller than that observed. The second alternative, the rate-limiting attack of water at the carbonium ion center, appears improbable since positive entropies of activation are observed. If water were to participate as a nucleophile in the rate-limiting stage, the $\Delta S^{\neq}$ values would be negative.[17] This would also be the case if the attack of water would take place prior to cleavage of the carbon–oxygen bond. The third alternative, the rate-limiting decomposition of the aminoalcohol intermediate, can be excluded on the basis of the pH-rate profiles, since removal of the proton from the hydroxyl group of the aminoalcohol probably needs base catalysis.[18] For this reason, hydrolysis reactions known to proceed by this mechanism show at high oxonium ion concentrations inverse dependence of rate on acidity.[18–22] As seen from Table 1, this is not the

case in the hydrolysis of 1-(3-chlorotetrahydro-2-furyl)benzimidazoles; the first-order rate constant for the unsubstituted compound remains constant up to an oxonium ion concentration of 5 mol dm^{-3}. If formation or decomposition of the aminoalcohol intermadiate were to be the rate-limiting step, anomerization of the substrate would be expected to take place concurrent with the hydrolysis and first-order kinetics would not be strictly obeyed.

The slightly higher reactivity of the *trans*-2,3 isomers of the 1-(3-chlorotetrahydro-2-furyl)benzimidazoles compared to the *cis*-2,3 anomers is difficult to explain on the basis of the available data. Possibly a weak electrostatic attraction between the protonated benzimidazole group and the electron-rich chloro substituent makes the protonated *cis*-2,3 anomers more stable than their *trans*-2,3 counterparts.

The present results may be extended to the hydrolysis of purine nucleosides with varying polar properties of the base moiety, provided the reaction *via* the monoprotonated substrate is concerned. The formation of a cyclic oxocarbenium ion from the 3-chlorotetrahydro-2-furyl group may well be compared to the corresponding process of the β-D-ribofuranosyl group. Comparison of the rate constants for the acidic hydrolysis of 1-(1-ethoxyethyl)-benzimidazoles [8] with that for the monocation of 9-(1-ethoxyethyl)adenine [23] reveals that protonated benzimidazole having an electronegative substituent at C2 is approximately as good leaving group as the monocation of adenine.

EXPERIMENTAL

2-Substituted 1-(3-chlorotetrahydro-2-furyl)benzimidazoles were prepared by treating the appropriate benzimidazole in refluxing *m*-xylene with *trans*-2,3-dichlorotetrahydrofuran, prepared as described earlier.[24] Triethylamine was added to neutralize the hydrogen chloride liberated. The cooled solution was filtered and concentrated to a syrup under reduced pressure. The product was extracted into carbon tetrachloride and washed with aqueous sodium hydroxide and water to remove traces of unreacted benzimidazole. The *cis*-2,3 and *trans*-2,3 isomers formed were separated by preparative TLC on Silica gel 60 (acetone–$CHCl_3$ 1:4). The R_F values, melting points of the picrates and relevant ^1H NMR chemical shifts are given in Table 2. In addition to the listed signals each compound exhibited H4′ at 2.1–2.7 (m,2H), H3′ at 4.1–4.7 (m, 3H), and aromatic protons at 7.1–7.3 (m,2H) and 7.6–7.9 (m,2H). The *trans*-2,3 isomer of 1-(3-chlorotetrahydro-2-furyl)-2-methylbenzimidazole gave the following ^{13}C chemical shifts (ppm from TMS in CCl_4): δ(C2′) 93.3, δ(C3′) 58.5, δ(C4′) 35.4, δ(C5′) 67.3, δ(C2–CH_3) 14.8, δ(C2) 151.2, δ(C4,7) 110.8 and 119.6, δ(C5,6) 122.7, and δ(C8,9) 132.8 and 142.9. The corresponding signals of the *cis*-2,3 anomer were: δ(C2′) 88.8, δ(C3′) 59.7, δ(C4′) 35.6, δ(C5′) 66.6, δ(C2–CH_3)

Table 2. R_F values[a] and characteristic ^1H NMR signals[b] for 2-substituted 1-(3-chlorotetrahydro-2-furyl)-imidazoles, and melting points for their picric acid salts.

R	R_F	δ(R)	δ(H2′)	^3J(H2′,H3′)/Hz	M.p./°C
CH_3	0.47[c]	s 2.57	d 6.00	3.8	168–170
	0.24[d]	s 2.52	d 6.15	4.8	173–175
H	0.36[d]	s 7.97	d 6.08	4.5	162–163
CH_2OH	0.56[c]	d 4.90	d 6.17	3.5	160–161
	0.43[d]	d 4.86	d 6.33	4.5	137–139
CH_2Cl	0.63[c]	s 4.78	d 6.08	3.5	152–154
	0.54[d]	s 4.74	d 6.22	4.5	158–160

[a] On silica gel 60 (acetone-$CHCl_3$ 1:4). [b] As ppm in CCl_4 rel. to TMS; for chemical shifts not listed see text. [c] The *trans*-2,3 isomer. [d] The *cis*-2,3 isomer.

15.9, δ(C2) 151.4, δ(C4,7) 111.1 and 119.3, δ(C5,6) 122.1 and 122.3, and δ(C8,9) 133.0 and 142.8. Kinetic measurements were performed as described earlier.[8]

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