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KINETICS AND MECHANISM OF THE REACTION OF 4(5)-FORMYLIMIDAZOLE WITH HYDROXYLAMINE

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Abstract—The kinetics of the reaction of 4(5)-formylimidazole with hydroxylamine have been determined at 25° in the pH range 0·4–7·4. The complex rate-pH profile has been analysed and interpreted by extending the Jencks mechanism of oxime formation to take account of the ionization of the substrate. The rate maximum at pH 4·75, by contrast with similar maxima found in the rate-pH profiles for oxime formation by non-ionizing carbonyl compounds, is not the result of a change in the rate-limiting step of the reaction from elimination to addition but is a consequence of the effect of substrate ionization on the rate of the elimination step. A change in the rate-limiting step appears to occur at pH *ca* 1. Spectrophotometric titration of 4(5)-formylimidazole at $I = 0{\cdot}1$ yields the following spectroscopic and ionization constants: 4(5)-formylimidazolium cation, λ_{max} 238 mμ, ε_{max} 7300; neutral 4(5)-formylimidazole, λ_{max} 257 mμ, ε_{max} 11,900; 4(5)-formylimidazole anion, λ_{max} 281 mμ, ε_{max} 16,900; first pK = 2·90; second pK = 10·66.

INTRODUCTION

The reactions of carbonyl compounds with nitrogen bases such as hydroxylamine and semicarbazide are characterized by striking maxima in their rate-pH profiles.[1-4] These maxima have been attributed to the opposing effects of general acid catalysis and the decrease of the concentration of free nitrogen base, consequent upon conversion to the conjugate acid at low pH.[3,5] More recently, however, Jencks[6] pointed out that this interpretation is not consistent with the position of the maxima on the pH axis and demonstrated that at neutral pH the attack of the nitrogen base on simple aldehydes and ketones such as furfural and acetone is fast and the observed reaction rate is dependent upon the equilibrium concentration of an addition compound and on the rate of its acid-catalysed dehydration. The maxima in the rate-pH profiles for oxime formation by simple carbonyl compounds are the result of a change in the rate-limiting step of the reaction from acid-catalysed elimination of water from the intermediate carbinolamine addition compound to attack of free hydroxylamine on the carbonyl compound.

The kinetic analysis of the interaction of 4(5)-formylimidazole and hydroxylamine here reported is part of a study of the influence on reactions of nitrogen bases at carbonyl centres, of groups associated with the carbonyl centre which change their state of ionization both inside and outside the range of pH over which the rate-limiting step of the reaction changes. The imidazole moiety is of particular interest in this connection because the imidazole moiety of a histidine residue has been implicated[7] in the active centres of a number of hydrolytic enzymes where it is thought to possess a catalytic role in reactions at the carbonyl centres of substrates.

RESULTS AND DISCUSSION

Spectrophotometric titration of 4(5)-*formylimidazole*. Spectrophotometric data have been reported previously for 4(5)-formylimidazole in 0·1N HCl, in 0·1N NaOH, at pH 7·0,[8] and in 95% ethanol[9] but these data do not permit assignment of values of the absorption parameters to specific structures.

The UV spectrum of 4(5)-formylimidazole above 220 mμ consists in a single high intensity band, the wavelength of maximum absorption (λ_{max}) and the corresponding molecular extinction coefficient (ε_{max}) of which vary with pH (Table 1 and Fig. 1).

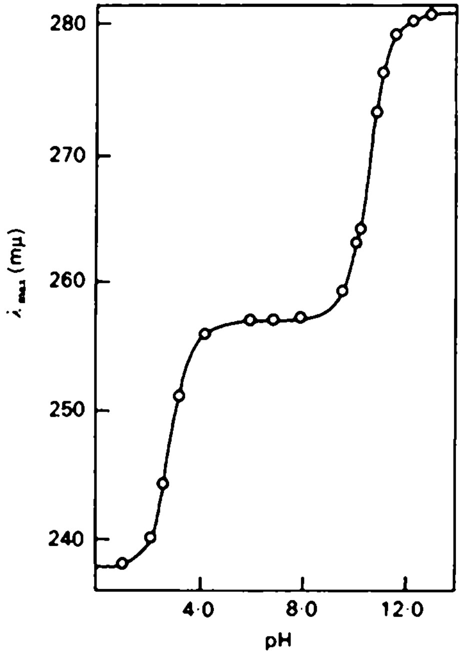
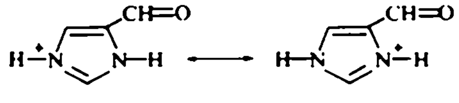
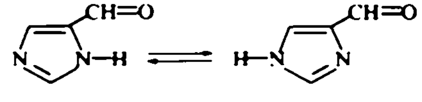
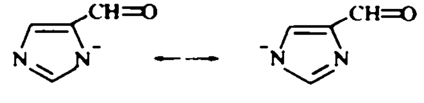


FIG. 1 Variation of the wavelength of maximum absorption of 4(5)-formylimidazole with pH in aqueous solution (I = 0·1) at 25·0°. The points are experimental and the curve is theoretical for p*K*s 2·90 and 10·66

TABLE 1. UV SPECTRAL DATA FOR 4(5)-FORMYLIMIDAZOLIUM ION, 4(5)-FORMYLIMIDAZOLE, AND 4(5)-FORMYLIMIDAZOLE ANION IN AQUEOUS SOLUTION

	λ_{max}, mμ	ε_{max}
	238	7,300
	257	11,900
	281	16,900

The intensity of the absorption band indicates that it arises from a $\pi \rightarrow \pi^*$ transition of the K-band type.[10] That K-bands shift bathochromically as the polarity of the conjugated system is increased and that the pH-dependence of λ_{max} takes the form of a titration curve for two ionizing groups (Fig. 1) makes possible the assignment of the bands to the structures given in Table 1.

A knowledge of the pH-dependence of λ_{max} permits the calculation of the p*K*s of 4(5)-formylimidazole. The values obtained in this way are 2·90 and 10·66. These are apparent p*K*s at $I = 0{\cdot}1$. Closely similar values were obtained from a study of the pH-dependence of the absorbance at 260 mμ and 280 mμ severally.

Kinetics and mechanism. The second order rate constants obtained by dividing the pseudo first-order rate constants for the formation of the oxime of 4(5)-formylimidazole, observed at various pH values, by the total concentration of hydroxylamine (i.e. free hydroxylamine and the hydroxylammonium ion) are presented as a function of pH in Fig. 2.

By contrast with the pH-dependence of the rate of formation of the oxime of furfural[6] which consists in a bell-shaped curve in the pH range 0–7, the rate-pH

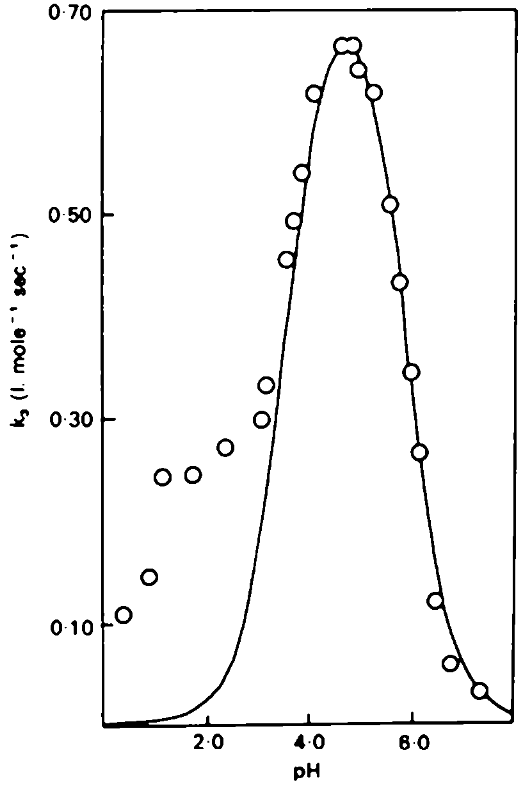


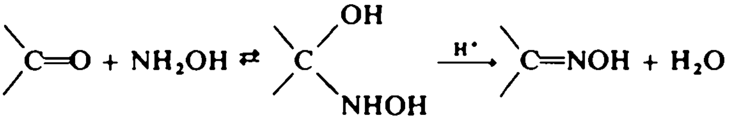
FIG. 2 pH-Dependence of the rate of oxime formation by 4(5)-formylimidazole at 25·0° and $I = 0{\cdot}6$. The points are experimental and the curve is theoretical for (12),

$$k_3 = \bar{k}_3/(1 + [H^+]/K_1 + K_2/[H^+])$$

where $\bar{k}_3 = 0{\cdot}749$ l. mole^{-1} sec^{-1}, p$K_1 = 3{\cdot}55$ and p$K_2 = 5{\cdot}95$.

profile in Fig. 2 is complex. Fig. 2 may be analysed in terms of the Jencks[6] mechanism of oxime formation by extending it to take account of the ionization of the substrate.

In approximately neutral media a carbonyl compound, such as furfural, reacts rapidly with hydroxylamine to form an addition compound which subsequently, in the rate-limiting step, undergoes an acid-catalysed elimination reaction to produce the oxime and water as in (1).



$$>C{=}O + NH_2OH \rightleftharpoons >C(OH)(NHOH) \xrightarrow{H^+} >C{=}NOH + H_2O \quad (1)$$

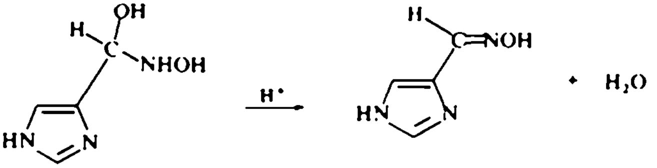
At low hydroxylamine concentrations, when the carbonyl compound is present to only a small extent as the adduct, the rate of oxime formation is given by (2).

$$\text{Rate} = \bar{k}\,[>C{=}O]\,[NH_2OH]\,[H^+] \quad (2)$$

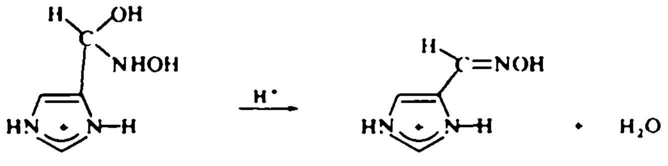
If a similar mechanism obtains for 4(5)-formylimidazole, the rate of oxime formation, when the fraction of the substrate present as the adduct is small, will be given by (3) where FI represents neutral 4(5)-formylimidazole and $\bar{k}_1$ and $\bar{k}_2$ are pH-independent rate constants. The two terms in (3)

$$\text{Rate} = \bar{k}_1\,[FI]\,[NH_2OH]\,[H^+] + \bar{k}_2\,[FI]\,[NH_2OH]\,[H^+]^2 \quad (3)$$

represent acid-catalysed elimination reactions from the unprotonated adduct (4) and from the protonated adduct (5).



(4)



(5)

That the reaction is first order in total hydroxylamine at the hydroxylamine concentration used to determine the rate constants in Fig. 2, at pHs 3·8 and 6·5 is shown in Fig. 3. The rapid formation of the addition compound when 4(5)-formylimidazole and hydroxylamine are mixed has been demonstrated conclusively at pH 6·5 (see Table 2). At pH 3·8 the initial rapid formation of adduct cannot be detected at low hydroxylamine concentrations but in 0·5M hydroxylamine there is an indication that a low concentration of adduct forms rapidly (see Table 2). The detection of the adduct (see Ref. 6) depends upon the fact that when 4(5)-formylimidazole reacts with hydroxylamine to form the oxime the UV absorption in the region of the wavelength of maximum absorption of the K-band increases. Any initial fall in absorbance

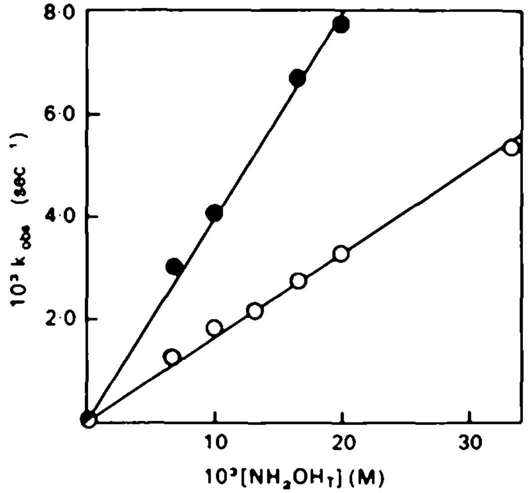


FIG 3 Dependence of the rate of oxime formation by 4(5)-formylimidazole on the total hydroxylamine concentration at 25·0° and I = 0·6; ● pH 3·8; ○ pH 6·5.

in this region therefore must be due to a reaction which destroys the conjugated system responsible for the UV absorption. The intermediates detected spectrophotometrically[6] in oxime and semicarbazone formation by simple carbonyl compounds were assigned the carbinolamine, $R_2C(OH)NHR$, structure by analogy with known addition compounds of hydroxylamine and semicarbazide with carbonyl compounds which contain strongly electron withdrawing groups.[11-14]

TABLE 2. SPECTROPHOTOMETRIC DETECTION OF THE 4(5)-FORMYLIMIDAZOLE-HYDROXYLAMINE ADDUCT

$10^3[NH_2OH_T]$[b] M	Initial absorbance at 250 mμ[a]	
	pH 6·5	pH 3·8
0	0·70	0·52
6·67	0·68	0·52
33·35	0·61	0·52
500	0·23	0·46

[a] Values of the difference absorbance vs hydroxylamine of mixtures of 4(5)-formylimidazole ($6·67 \times 10^{-5}$ M) and hydroxylamine at zero time extrapolated from plots of log $(A_\infty - A_t)$ vs t; 25·0°; I = 0·6. A fall in absorbance from that of the substrate in the absence of hydroxylamine represents the formation of a non-absorbing adduct

[b] $[NH_2OH_T]$ = concentration of hydroxylamine free base + hydroxylammonium ion

Thus in approximately neutral media, 4(5)-formylimidazole reacts rapidly and reversibly with a dilute solution of hydroxylamine to yield a low concentration of the carbinolamine addition compound which subsequently, in the rate-limiting step, undergoes an elimination reaction to produce the oxime and water. That the elimination step is rate-limiting also on the acidic side of the rate maximum in Fig. 2 is suggested by the rapid initial fall (albeit small) in absorbance observed when the substrate is mixed with 0·5M hydroxylamine at pH 3·8 (Table 2). It is suggested that elimination is rate-limiting in the pH range 8–1 since only by making this assumption can the rate-pH profile at low pH be accounted for satisfactorily. The inability to detect unambiguously the adduct at pH 3·8 is the result of the low equilibrium constant for the formation of the adduct, the low concentration of hydroxylamine free base at this pH and the necessity to use relatively low concentrations of total hydroxylamine because of the high rate constant for the elimination step.

Eq. (3) may be rewritten for convenience as (6) in which FIH^+ represents the 4(5)-formylimidazolium cation and $\bar{k}_3$ and $\bar{k}_4$ are pH-independent rate constants.

$$\text{Rate} = \bar{k}_3[FI][N^+H_3OH] + \bar{k}_4[FIH^+][N^+H_3OH] \tag{6}$$

The relevant ionization constants of the substrate and hydroxylamine severally are K_1 and K_2 respectively where

$$K_1 = [FI][H^+]/[FIH^+] \quad \text{and} \quad K_2 = [NH_2OH][H^+]/[N^+H_3OH].$$

If $\bar{k}_3 > \bar{k}_4$ and $pK_1 \ll pK_2$ (in fact $pK_1 = 2·9$ and $pK_2 = 6·0$[15]) there should be a region of pH (in this case >pH ca. 5) in which the second term in (6) may be neglected and the rate of oxime formation is then given by (7).

$$\text{Rate} = \bar{k}_3[FI][N^+H_3OH] \tag{7}$$

$$[FI] + [FIH^+] = [FI_T] \tag{8}$$

$$[NH_2OH] + [N^+H_3OH] = [NH_2OH_T] \tag{9}$$

By making use of the conservation Eqs (8) and (9), (7) may be written:

$$\text{Rate} = \bar{k}_3K_1[FI_T][NH_2OH_T][H^+]/([H^+] + K_1)([H^+] + K_2)$$
$$= k_3[FI_T][NH_2OH_T] \tag{10}$$

where k_3 is the pH-dependent rate constant. Thus the pH-dependent rate constant is related to the pH-independent rate constant by (11).

$$k_3 = \bar{k}_3/(1 + [H^+]/K_1 + K_2/[H^+] + K_2/K_1] \tag{11}$$

When $K_1 \gg K_2$, (11) becomes (12).

$$k_3 = \bar{k}_3/(1 + [H^+]/K_1 + K_2/[H^+]) \tag{12}$$

Fig. 2 shows that in the pH range ca. 7·4–5·0 the experimental results are in a good agreement with (12) in which $\bar{k}_3$, pK_1 and pK_2 have the values given in Table 3. Below pH 4·7 the rate is greater than that predicted by (12). Eq (6) predicts that the rate will be greater than that given by (12) under conditions where the second term in (6) becomes important, i.e. at pH values close to pK_1.

If the rate of oxime formation is controlled by the second term in (6) this equation becomes:

$$\text{Rate} = \bar{k}_4[FIH^+][N^+H_3OH] \tag{13}$$

Eq. (13) may be written:

$$\text{Rate} = \bar{k}_4\,[\mathrm{FI_T}]\,[\mathrm{NH_2OH_T}]\,[\mathrm{H^+}]^2/([\mathrm{H^+}] + K_1)([\mathrm{H^+}] + K_2) = k_4\,[\mathrm{FI_T}]\,[\mathrm{NH_2OH_T}] \qquad (14)$$

where k_4 is the pH-dependent rate constant. Thus these pH-dependent and pH-independent rate constants are related by (15).

$$k_4 = \bar{k}_4/(1 + K_1/[\mathrm{H^+}] + K_2/[\mathrm{H^+}] + K_1K_2/[\mathrm{H^+}]^2) \qquad (15)$$

If $[\mathrm{H^+}] \gg K_2$ and $K_1 \ll 1$, this simplifies to (16).

$$k_4 = \bar{k}_4/(1 + K_1/[\mathrm{H^+}]) \qquad (16)$$

TABLE 3. DISSOCIATION CONSTANTS OF 4(5)-FORMYLIMIDAZOLE AND HYDROXYLAMINE AND KINETIC CONSTANTS FOR THEIR INTERACTION AT 25·0°

$\bar{k}_3$ $\mathrm{l\ mole^{-1}\ sec^{-1}}$	$\bar{k}_4$ $\mathrm{l\ mole^{-1}\ sec^{-1}}$	pK_1	pK_2	Method of determination[a]	Ref[b]
	-	-	6·0	titration of hydroxylamine hydrochloride with alkali	(i)
	—	2·90	-	spectrophotometric titration	(ii)
0·749		3·55	5·95	regression analysis of (12) $k_3 = \bar{k}_3/(1 + [\mathrm{H^+}]/K_1 + K_2/[\mathrm{H^+}])$ for the values in the pH range 4·8–7·5	(ii)
	0·246	3·01		regression analysis of (16) $k_4 = \bar{k}_4/(1 + K_1/[\mathrm{H^+}])$ for the values in the pH range 1–4.	(ii)

[a] Values of k_3 were obtained by dividing the pseudo first order rate constants for the formation of the oxime by the total concentration of hydroxylamine free base and hydroxylammonium ion. Values of k_4 were obtained by subtracting from the experimental values of k_3 those computed from (12)

[b] (i) Ref 15; (ii) this work

Fig. 4 shows that in the pH range ca. 4–1 the pH dependence of the second order rate constant obtained by subtracting from the experimental values (Fig. 2) the values computed from (12) using the values of the constants given in Table 3, is in accord with (16) using the values of $\bar{k}_4$ and pK_1 given in Table 3. Below pH ca. 1 the rate falls below that predicted by (16).

Thus the pH-dependence of the rate of oxime formation in the pH range ca. 7–1 is predicted satisfactorily by (6). This rate equation is composed of terms which represent the acid-catalysed elimination of water from both the unprotonated and protonated 4(5)-formylimidazolehydroxylamine adducts as in (4) and (5). As with simple (non-ionizing) carbonyl compounds,[6] the contribution to the rate of an uncatalysed elimination reaction is negligible. The rate Eq. (6) written in its most general form (3) states that elimination of water can occur from an adduct composed of 1 molecule of 4(5)-formylimidazole, 1 molecule of hydroxylamine and either one or two protons. It can be predicted that the rate equation for the addition of hydroxylamine to 4(5)-formylimidazole to form the adduct will be:

$$\text{Rate} = \bar{k}_5\,[\mathrm{FI}]\,[\mathrm{NH_2OH}]\,[\mathrm{H^+}] + \bar{k}_6\,[\mathrm{FI}]\,[\mathrm{NH_2OH}]. \qquad (17)$$

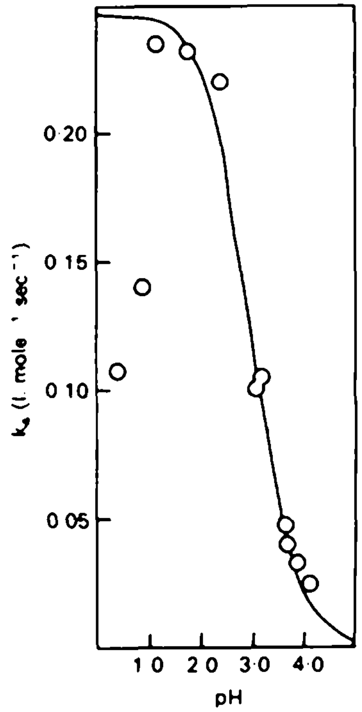


FIG 4 pH-Dependence of the second order rate constant for the reaction of 4(5)-formylimidazole with hydroxylamine at 25·0° and $I = 0·6$ obtained by subtracting from the values determined experimentally the values computed from (12), $k_3 = \mathbf{k}_3/(1 + [H^+]/K_1 + K_2/[H^+])$ where $\mathbf{k}_3 = 0·749$ l. mole^{-1} sec^{-1}, pK_1 = 3·55, and pK_2 = 5·95. The curve is theoretical for (16). $k_4 = \mathbf{k}_4/(1 + K_1/[H^+])$ where $\mathbf{k}_4 = 0·246$ l. mole^{-1} sec^{-1} and pK_1 = 3·01

Eq. (17) assumes that hydroxylamine free base will add to either neutral 4(5)-formylimidazole or to its cation but that a transition state for the addition reaction composed of 1 molecule of 4(5)-formylimidazole, 1 molecule of hydroxylamine and two protons will not be attained, i.e. the hydroxylammonium ion will not act as a nucleophile. This is in agreement with the rate Eq. (18) which obtains for the addition of hydroxylamine to unionized substrates.[6]

$$\text{Rate} = \mathbf{k}[\,{>}C{=}O][NH_2OH] \qquad (18)$$

Since the attack of a hydroxylamine molecule at the electrophilic center of 4(5)-formylimidazole will be facilitated by protonation of the imidazole ring, $\mathbf{k}_5$ will be greater than $\mathbf{k}_6$ {Eq. (17)}. This facilitation of rate would be expected on electronic grounds[16] and also because of the possibility of general acid catalysis by intramolecular hydrogen bonding.

The pH-dependence of the rate of addition of hydroxylamine to 4(5)-formylimidazole as predicted by (17) making the assumption that $\mathbf{k}_5 > \mathbf{k}_6$ is shown schematically in Fig. 5.

The fall in rate in Fig. 4 at pH values < 1 below that predicted by (16) is interpreted as a change in the rate-limiting step from elimination to addition. Such a change in the rate-limiting step in the region of the rate maximum at pH 4·75 would not account for the fact that the observed rates in the pH-range ca. 5–1 are greater than those predicted by (12). The interpretation of the maximum in the rate-pH profile (Fig. 2) is therefore fundamentally different from that which obtains for the maxima in the rate-pH profiles for the reactions of non-ionizing carbonyl compounds with hydroxylamine[6]

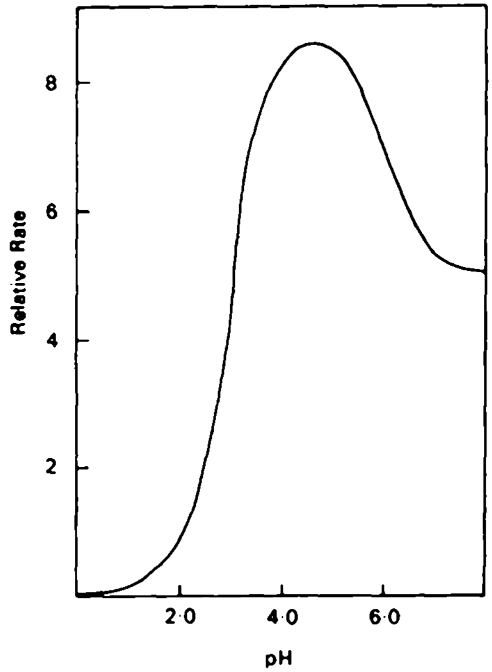


FIG 5 Schematic representation of the pH-dependence of the rate of addition of hydroxylamine to 4(5)-formylimidazole as predicted by (17) i.e. rate $= \mathbf{k}_5 [\mathrm{FI}][\mathrm{NH_2OH}][\mathrm{H^+}] + \mathbf{k}_6 [\mathrm{FI}][\mathrm{NH_2OH}]$ in which $\mathbf{k}_5 > \mathbf{k}_6$.

In considering detailed mechanisms for the elimination step in oxime formation by 4(5)-formylimidazole it must be born in mind that the rate constants in the rate equations used above are composed of true pH-independent rate constants for the acid-catalysed elimination of water from the adducts and equilibrium constants for the formation of the adducts (both protonated and unprotonated). By analogy with the known substituent effects on the rate constants for the addition and elimination steps and on the equilibrium constant for adduct formation in the case of semicarbazone formation by simple carbonyl compounds,[16] the effect of protonation of the imidazole ring of 4(5)-formylimidazole or its hydroxylamine adduct should be, on electronic considerations, to (a) increase the rate of addition of hydroxylamine, (b) increase the equilibrium constant for adduct formation and (c) decrease the rate of the elimination reaction.

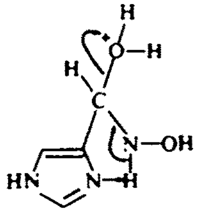
The p*K* of the imidazole group concerned in the elimination step as determined kinetically (see Table 3) assumes a value between that for 4(5)-formylimidazole and that for the imidazole group in the adduct (which should be similar to the value[17] for imidazole itself, i.e. ca. 7). The value is much closer to that for the imidazole group in 4(5)-formylimidazole than to that for the imidazole group in the adduct in agreement with the fact that the adduct is present only in low concentrations. This phenomenon of variability of kinetically determined p*K*s is analogous to that encountered frequently in enzyme kinetics. If a pH-activity profile for an enzyme-catalysed reaction reflects ionizations in the active site of the enzyme, the p*K*s determined kinetically will approximate to those of the free enzyme (E) at low substrate (S) concentrations and to those of the enzyme-substrate complex (ES) at high substrate concentrations.

$$E + S \rightleftarrows ES \rightarrow E + \text{products}.$$

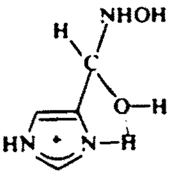
At intermediate substrate concentrations the kinetically determined p*K*s will lie between the two extreme sets of values.

The following mechanisms are consistent with the data. For the system with one proton: (a) specific acid catalysis and intramolecular general base catalysis (I); (b) intramolecular general acid catalysis (II); (c) specific acid catalysis of elimination from the adduct in which the imidazole group is not protonated but without participation of the imidazole group as a general base.

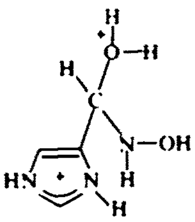
For the system with two protons: specific acid catalysis of elimination from the adduct in which the imidazole group is protonated (III).



I



II



III

An extension of this work to assess the contributions which the various effects such as intramolecular general base catalysis and electronic conjugation of the imidazole ring to the incipient carbonyl carbon atom in the adduct make to the reactivity of the carbonyl compound towards hydroxylamine and other nitrogen bases is in progress.

EXPERIMENTAL

Materials

4(5)-Formylimidazole was prepared from 4(5)-hydroxymethylimidazole according to the method of Turner *et al.*[18] After resublimation it melted at 171–172° (lit.[18] m.p. 173–174°).

4(5)-Formylimidazole oxime was prepared by allowing the aldehyde (0·5 g) to react with a soln of hydroxylamine hydrochloride (0·35 g) and Na_2CO_3 (0·25 g). On keeping the soln, the oxime (0·5 g) crystallized out. After recrystallization from aqueous EtOH it melted at 180–181° (lit.[19] m.p. 181–183°).

Stock solns of 4(5)-formylimidazole in water, containing 10^{-3} M EDTA to retard heavy metal catalysed decomposition and 3% spectroscopic EtOH to assist solubility, were made up just before use. Stock solns of hydroxylamine hydrochloride (Analar grade) were neutralized to the required pH with NaOH immediately before use. Deionized water was used throughout.

Spectrophotometric and kinetic measurements were made on a Cary 15 recording spectrophotometer using the 0·1·0 and 0·0·1 absorbance slidewires. Water from a thermostat at 25·0 ± 0·1° was circulated through the jacketed cell compartments.

All kinetic determinations were carried out with the concentration of hydroxylamine greatly in excess of that of the aldehyde so that pseudo first-order kinetics were obtained. The first order rate constants (k_{obs}) were determined from conventional infinity plots or from half reaction times using the formula $k_{obs} = 0{\cdot}693/t_{\frac{1}{2}}$. In some cases both methods were used and concordant results were obtained. The pH values reported are the apparent pH values measured with the glass electrode of the pH meter of a Radiometer TTT1 titrator. The formation of the oxime was followed at a wavelength in the range 240–250 mμ (depending upon the pH) near to the wavelength of maximum absorption of the aldehyde where an increase in absorbance occurs consequent upon conversion of the aldehyde to its oxime. In the determination of the effect on the rate of varying the hydroxylamine concentration at fixed values of pH, the buffers used were acetate and phosphate. In the other kinetic experiments the hydroxylamine-hydroxylamine hydrochloride system was used as the buffer according to the method of Stempel and Schaffel[20] except at low pH where chloride-HCl buffer was used.

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