Acid and Base Catalysis of the Mutarotation of D-Arabinose Oxime

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The mutarotation of *Z*-D-arabinose oxime is subject to general acid and to specific base catalysis and is proposed to proceed by an addition–elimination pathway involving cyclic *N*-arabinosylhydroxylamine intermediates. It is suggested that general acid catalysis (Brönsted α 0.54) proceeds *via* a prior equilibrium proton transfer followed by a rate-determining reaction with conjugate base.

D-ARABINOSE OXIME adopts acyclic structures in aqueous solution and in the crystalline state;[1,2] dissolution of the *Z*-form leads to an equilibrium mixture of *Z*- and *E*-forms in the ratio 1 : 4, the formation of which can be monitored by ^{1}H n.m.r. spectroscopy and by polarimetry.[1] We have investigated the effects of acids and bases on this kinetically simple mutarotation and propose on the basis of the results and other evidence that the process involves the formation of cyclic *N*-arabinosylhydroxylamines which are analogous to the carbinolamine intermediates (1) established[3,4] in the reactions of carbonyl compounds

$$R_2C{=}O + H_2NOH \rightleftharpoons R_2C(OH)NHOH \rightleftharpoons R_2C{=}NOH + H_2O \quad (1)$$

(1)

with hydroxylamine [equation (1)]. The measurement of mutarotation rates of this carbohydrate oxime thus allows the study of addition to a >C=NOH system, for which some of the characteristics have previously been inferred from studies of the formation (dehydration) reaction.[5,6]

The configurational instability of oximes and the accelerating effects † of Brönsted–Lowry [8] and Lewis [9] acids, and u.v. radiation [10] on the isomerisation have long been known. The few kinetic studies [11,12] made have been on the thermal, uncatalysed reaction, and theoretical studies and review discussions [13,14] have also concentrated on this in terms of lateral inversion at nitrogen or restricted rotation about the C=N bond. Other possible mechanisms involve the reversible formation of the oximate anion [15,16] ($R_2C{=}N{-}O^- \leftrightarrow R_2C^-{-}N{=}O$), the nitrone ($R_2C{=}^+NH{-}O^- \leftrightarrow R_2C^+{-}NH{-}O^-$), the enamine [17] ($R_2C{=}CR{-}NH{-}OH$), the conjugate acid [18] ($R_2C{=}^+NH{-}OH \leftrightarrow R_2{}^+C{-}NH{-}OH$), and an addition compound [19] [$R_2C(OR)NH{-}OH$, *e.g.* carbinolamine, reverse of equation (1)].

In the case of the carbohydrate oximes the carbinolamine intermediate may take the form of a cyclic structure formed by intramolecular reaction of a hydroxy-group; such a structure has been observed directly for D-glucose oxime [1,2] and inferred to be present in aqueous solutions of D-arabinose oxime to account for its activity as a substrate of yeast hexokinase.[20]

† The retarding effect of (non-aqueous) trifluoroacetic acid on the isomerisation of *p*-benzoquinone mono-oxime [7] is a special case and can be explained by the conjugation of the C=N$^+$ bond with the benzene ring.

The mutarotation of D-arabinose oxime behaves kinetically as a two-component, first-order, reversible reaction (2) with an observable rate constant equal to

$$E \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Z \quad (2)$$

$k_1 + k_{-1}$. k_1 and k_{-1} are complex constants which incorporate the rates of formation and destruction of any intermediates, *e.g.* C [equation (3)] Any catalyst will

$$E \underset{k_E}{\overset{k_{-E}}{\rightleftharpoons}} C \underset{k_{-Z}}{\overset{k_Z}{\rightleftharpoons}} Z \quad (3)$$

affect k_E and k_{-Z} equally, and k_E and k_{-Z} equally, but each pair of rate constants need not necessarily be affected to the same extent. However since the partitioning of the catalytic effect between the *E* and *Z* pairs of rate constants cannot be known, and the ratio of k_1 and k_{-1} is of course constant, the results will be discussed in terms of observable effects on $k_1 + k_{-1}$.

RESULTS

The observed rate constants for the mutarotation of *Z*-D-arabinose oxime at different pH values and extrapolated to zero buffer concentration are given in Table 1, and plotted logarithmically in Figure 1. The results show that hydrogen ion and hydroxide ion catalyses operate in the pH ranges 4.6—6.0 and 7.0—9.0, respectively. The values of the catalytic coefficients for H_3O^+ and OH^- obtained from plots of k_{obs} at zero buffer concentration *versus* H_3O^+ and OH^- are given in Table 2.‡ No buffer species catalysis was observed in the alkaline region in 1,2-dimethylimidazole and amino-tris(hydroxymethyl)methane buffers, but buffer catalysis was observed in phosphate (pH 7.0) and acidic buffer solutions. The buffer catalytic coefficients were derived from the slopes (k_{app} in Table 2) of plots (*e.g.* Figure 2, trimethylacetate buffers) of k_{obs} *versus* the concentration of base component replotted (*e.g.* Figure 3) against the buffer

TABLE 1

Observed first-order rate constant at different pH values for the mutarotation of *Z*-D-arabinose oxime at 25 °C in water (*I* 0.2, KCl)

pH	4.40	4.60	4.80	5.00	5.17	5.20	5.40	6.09
$10^3 k_{obs}/s^{-1}$	4.09	2.01	1.06	0.763	0.517	0.386	0.234	0.248
pH	6.27	6.47	6.64	7.00	7.10	8.00	9.00	
$10^3 k_{obs}/s^{-1}$	0.126	0.107	0.026	0.081	0.097	0.525	0.605	

‡ No significant reaction with water was observed.

TABLE 2

Catalysis of the mutarotation of *Z*-D-arabinose oxime in water at 25 °C and *I* 0.2 (KCl)

Catalyst or buffer	pK_a	Concentration/M [a]	Buffer ratio [acid] : [base]	k_{app}/l mol^{-1} s^{-1} [b]	k_{HA}/l mol^{-1} s^{-1}
H_3O^+	−1.74	0.4×10^{-5}—2.53×10^{-5}			80.5
Glycolate	3.83	0.04—0.20	0.269	1.49×10^{-2}	
		0.04—0.20	0.170	1.17×10^{-2}	
		0.04—0.20	0.107	8.41×10^{-3}	
		0.04—0.20	0.0676	6.64×10^{-3}	
		0.04—0.20	0.0427	3.37×10^{-3}	6.14×10^{-2}
Acetate	4.76	0.044—0.175	1.445	2.17×10^{-2}	
		0.046—0.184	0.575	6.81×10^{-3}	
		0.048—0.192	0.229	2.40×10^{-4}	1.59×10^{-2}
Trimethylacetate	5.05	0.010—0.05	2.24	3.48×10^{-2}	
		0.012—0.095	1.58	2.05×10^{-2}	
		0.045—0.178	1.12	1.32×10^{-2}	
		0.040—0.20	0.753	9.04×10^{-3}	
		0.049—0.193	0.562	6.69×10^{-3}	1.43×10^{-2}
Cacodylate	6.27	0.04—0.16	2.34	7.55×10^{-3}	
		0.04—0.20	1.50	6.58×10^{-3}	
		0.04—0.20	1.000	3.11×10^{-3}	
		0.04—0.20	0.631	2.68×10^{-3}	
		0.04—0.20	0.429	2.21×10^{-3}	4.01×10^{-3}
Phosphate monoanion	7.20	0.0085—0.034	1.58	1.40×10^{-2}	
OH^-		10^{-7}—10^{-5}			6.07×10^2

[a] Refers to the species given in the first column. [b] Apparent rate constant in terms of concentration of basic buffer component.

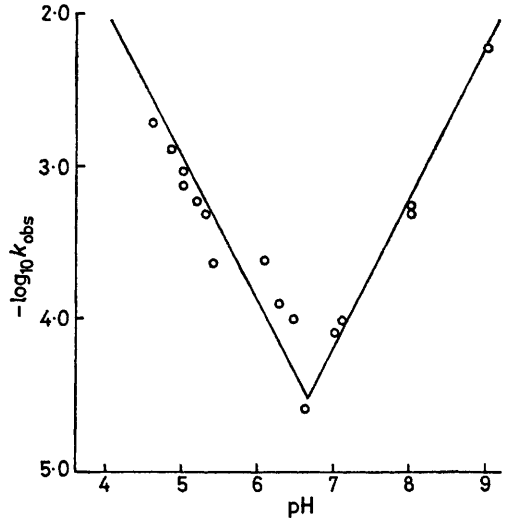


FIGURE 1 pH–log rate profile for the mutarotation of *Z*-D-arabinose oxime at 25 °C in water (*I* 0.2, KCl). Rate constants at pH <7 were obtained by extrapolation of values at different concentrations of buffers to zero buffer concentration. The lines are drawn with slopes of +1 and −1

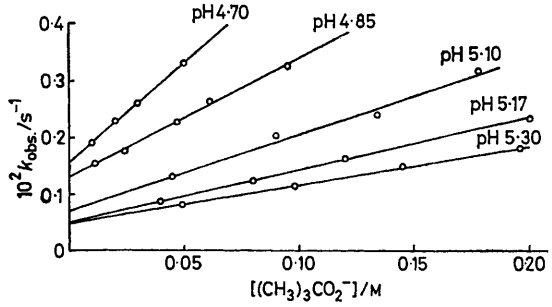


FIGURE 2 Observed first-order rate constants for the mutarotation of *Z*-D-arabinose oxime as a function of the concentration of trimethylacetate buffer (base component) at the pH values shown at 25 °C and *I* 0.2 (KCl)

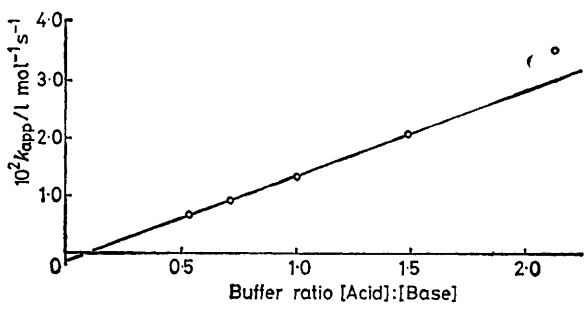


FIGURE 3 Dependence of the apparent second-order rate constants for catalysis of the mutarotation of *Z*-D-arabinose oxime by trimethylacetate on the buffer ratio, *i.e.* [acid component] : [base component]

ratio [acid component]/[base component]. In such plots the catalytic coefficients for the acid and base components of the buffer are given by the slope and intercept, respectively.[21] In all cases negligible catalysis by the base components of the buffers was observed; the catalytic constants are given in Table 2 and as a Brönsted plot in Figure 4.

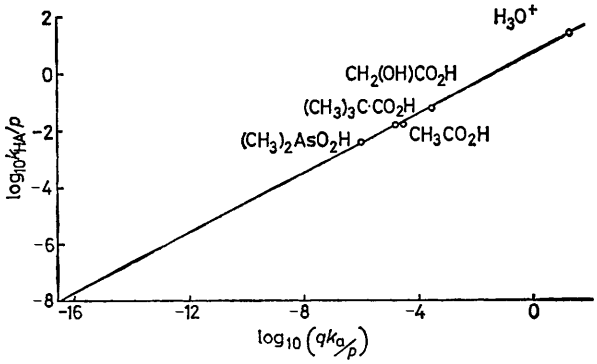
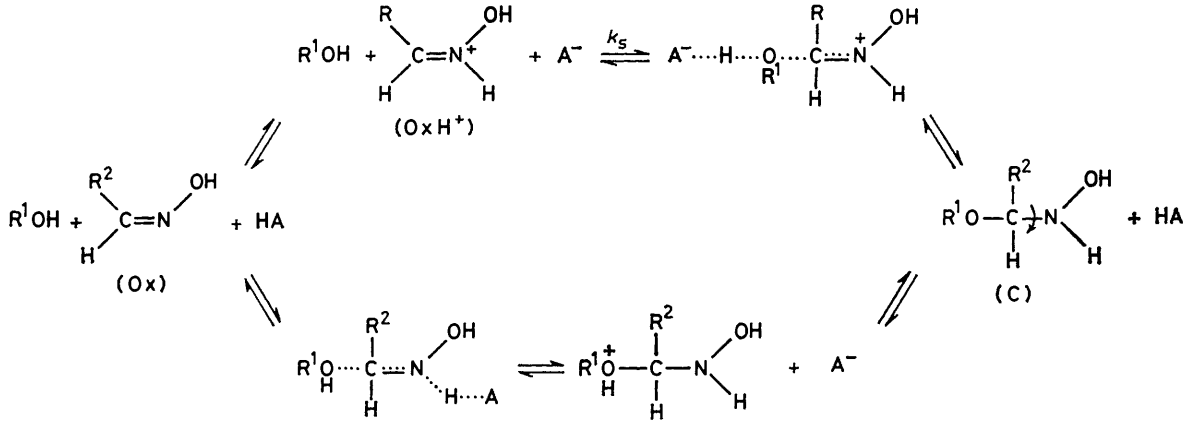


FIGURE 4 Brönsted plot for the general acid-catalysed mutarotation of *Z*-D-arabinose oxime at 25 °C. Statistical corrections have been made according to R. P. Bell and P. G. Evans, *Proc. R. Soc. London, Ser. A*, 1966, **291**, 297

DISCUSSION

The Acid-catalysed Reaction.—The observation of general acid catalysis shows that the mutarotation of D-arabinose oxime proceeds by an addition–elimination pathway (enamine formation can be discounted because no hydrogen exchange or loss of chirality at C-2 is observed). The acid catalysis can be accounted for by the mechanisms shown in Scheme 1 in which the upper pathway describes general base catalysis of the attack of



SCHEME 1

water (or an alcohol) on a cationic imine and the lower pathway describes general acid catalysis of the attack of water (or an alcohol) on a neutral oxime. The lower pathway is ruled out by the work of Reimann and Jencks [22] who showed that the formation of the oxime and the *N*-methylnitrone of *p*-chlorobenzaldehyde are subject to general acid catalysis in a similar manner. In both cases the dehydration of a carbinolamine intermediate is involved, but proton removal from the nitrogen atom is not possible in nitrone formation [equation (4)]. The type of transition state shown in the lower pathway was also rejected, although not without objection,[23] for the general base catalysis of the hydrolysis of imines.[24,25]

The feasibility of the conjugate acid of the oxime (OxH^+) as a reaction intermediate in Scheme 1 can be tested by calculating the rate constant for the rate-limiting step and comparing it to the rate of a reaction limited by diffusion.[26] The rate of formation of carbinolamine (C) is given by equation (5) where K_{HA} and K_{OxH^+}

$$k_s[H_2O][OxH^+][A^-] = k_s[H_2O][Ox][HA]K_{HA}/K_{OxH^+} \quad (5)$$

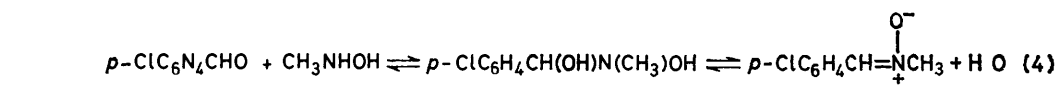
are the dissociation constants of the acid catalyst and the conjugate acid of the oxime, respectively. The observed rate is given by $k_{HA}[HA][Ox]$ where k_{HA} is the catalytic constant, and therefore equation (6) applies. The

$$k_s = k_{HA}K_{OxH^+}/K_{HA}[H_2O] \quad (6)$$

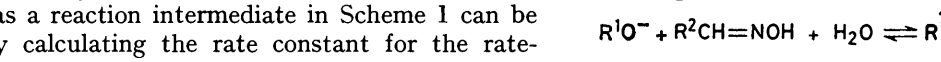
dissociation constant (K_{OxH^+}) of the conjugate acid of the oxime will be of the order of 10^{-1} mol l^{-1} [27] and so k_s can be calculated for different catalysts (Table 3). In the calculations in Table 3 water is assumed to be hydrogen bonded to the catalyst, *i.e.* $[H_2O]$ is set at unity. If $[H_2O]$ is 55.5M the k_s values are reduced further below the value for the diffusion-controlled limit.

A reaction sequence which consists of a prior equilibrium between oxime and hydrogen ion followed by a rate-determining base-catalysed nucleophilic addition is suggestive of a concerted mechansim [28] for the second step which avoids the formation of the species $R^1\dot{O}\dot{H}$–CHR^2NHOH. Catalysis by reaction of this intermediate with buffer anion (trapping) is unlikely because of its low pK (*ca.* −3), trapping by proton donation to 55M-water would be far more efficient.[29,30]

The Base-catalysed Reaction.—The specific base catalysis of mutarotation can be described by attack of OH^- or RO^- (intramolecular) on the neutral oxime as shown



in Scheme 2. This reaction must involve proton donation *via* a hydrogen bonding or concerted mechanism because the protonation of a discrete anionic intermediate (pK_a *ca.* 27) * would have to be faster than the



SCHEME 2

diffusion-controlled limit. The proton donor is shown as water in Scheme 2; no general acid catalysis was observed at pH >7. From studies of the dehydration

* The rate constant k_b for reaction of the anionic intermediate $RCH(OH)\bar{N}OH$ with 55.5M-water is given by [29] K_wk_{-b}/K_a where K_w is the dissociation constant of water, k_{-b} is the rate constant for the diffusion-controlled abstraction of a proton by hydroxide ion (10^{10} l mol^{-1} s^{-1}), and K_a is the acid (NH) dissociation constant of a carbinolamine (10^{-27} mol l^{-1}), and would thus equal 10^{21} l mol^{-1} s^{-1}.

of various carbinolamines Sayer and Jencks [6] concluded that the transition state for this type of reaction is reached by an initial rehybridisation of the C and N atoms from sp^2 to sp^3 and possesses unit negative charge on the N atom.

TABLE 3

Rate constants for rate-determining step in oxime mutarotation calculated from equation (6)

Catalyst	H_3O^+	CH_3CO_2H	$(CH_3)_2AsO_2H$
$k_{s,calc}$/ l mol^{-1} s^{-1}	1.4×10^{-1}	0.91×10^{-2}	7.7×10^{2}

Comparison with Other Systems.—The reversible hydrations of carbon–nitrogen double bonds in a number of structures have been subjected to detailed kinetic analysis, and at the appropriate pH values the data are satisfactorily accounted for by the mechanisms of acid and base catalysis presented above. The present results for D-arabinose oxime and rate constants calculated from studies [3,31] of acetone oxime formation under conditions where carbinolamine dehydration is rate limiting are given in Table 4. Oxime formation under these conditions has been shown to be subject to general acid catalysis although with derivatives of aromatic carbonyl compounds it is difficult to detect ($\alpha > 0.75$).[22,25]

TABLE 4

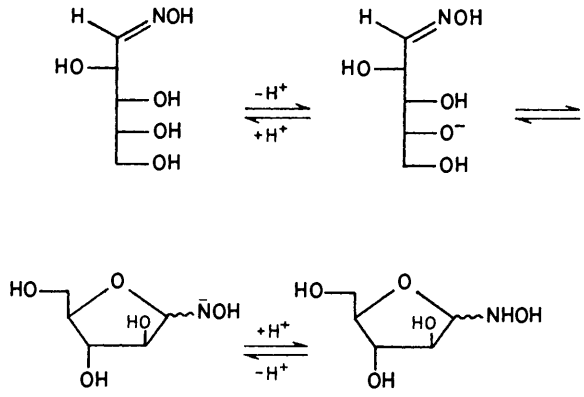
Catalytic constants for hydration of C=N structures

	D-Arabinose oxime	Acetone oxime
$k_{H_3O^+}$/l mol^{-1} s^{-1}	80.5	1.43
k_{OH^-}/l mol^{-1} s^{-1}	607	1.18×10^{-4}
General acid catalysis, α	+, 0.54	+, 0.6
General base catalysis, β	?	+?

The hydrolysis of Schiff's bases shows a similar susceptibility to catalysis which is observed [25] as general base catalysis (β *ca.* 0.25) since the substrate is essentially completely protonated under the reaction conditions. General acid catalysis of oxime formation from aliphatic carbonyl compounds has been reported on a number of occasions [3,31–33] and from limited data Williams and Bender [31] calculated a Brönsted α value of *ca.* 0.6.

One general feature of the results which deserves comment is the sensitivity of the catalytic constants to variations in structure; hydronium-ion catalysis is relatively insensitive whereas specific base catalysis is very sensitive to structural variation (see Table 4). The behaviour of the hydronium-ion constants is readily interpreted in terms of the mechanism proposed (Scheme 1, upper pathway). Thus any structure variation which (by electron donation) increases the equilibrium concentration of the conjugate acid will decrease the rate of its attack by a nucleophile and these two effects will tend to compensate one another.

We believe that the difference between the k_{OH^-} values for D-arabinose oxime and acetone oxime can be largely attributed to the fact that the carbohydrate derivative can react by intramolecular attack of alkoxide oxygen (*e.g.* see Scheme 3 in which a furanosyl ring is depicted) rather than intermolecular attack of hydroxide ion. If the alcohol group and water are of comparable acidity [34] this implies a rate acceleration for the intramolecular process of 5×10^6, which may be compared with a factor of *ca.* 60 for the acid-catalysed reaction. Large values for the rates of intramolecular



SCHEME 3

nucleophilic reactions in comparison to their base-catalysed counterparts have been observed previously and discussed convincingly by Jencks [35] and by Kirby and Lloyd.[36,37] These authors attribute the smaller rate acceleration of a catalysed reaction to a looser transition state, *i.e.* the transition stage for an acid- or base-catalysed reaction possesses a higher residual entropy than for a nucleophilic reaction where fewer bonds are being made or broken simultaneously. However, under both acidic and basic conditions the more rapid isomerisation of carbohydrate oximes than that of simple oximes [13] can be attributed to structural features, *i.e.* appropriately positioned hydroxy-groups which allow the formation of cyclic carbinolamine intermediates.

EXPERIMENTAL

Z-D-Arabinose oxime was synthesised as described previously, the assignment of configuration made by n.m.r. spectroscopy [1] was subsequently confirmed by *X*-ray crystallographic analyses of both the *E*- and *Z*-forms.[2]

Kinetics of Mutarotation.—Rates of mutarotation were measured at 25 °C using a Perkin-Elmer 141 polarimeter with a jacketted cell and operating at 589 nm. Buffer solutions were made up in deionised water at a constant ionic strength of 0.2 obtained by adding potassium chloride. Solutions (0.08M) of *Z*-D-arabinose oxime were made up immediately before taking measurements. First-order rate constants were calculated from values of ln $(\alpha_t - \alpha_\infty)$ and t using a linear least-squares method and were correlated to the data by a coefficient of 0.99 or greater. The rate of isomerisation of 0.303M-*Z*-D-arabinose oxime in D_2O solution was also measured by ^1H n.m.r. spectroscopy at 60 MHz (Varian EM360 instrument). The integrated areas of the signals from 1-H of the *E*- and *Z*-forms were measured after various times using the signal from sodium 3-(trimethylsilyl)propanesulphonate as an internal stan-

dard. The changes in peak areas followed first-order kinetics with a rate constant of 0.57×10^{-4} s^{-1}; the same value was obtained by polarimetry in water and D_2O solutions.

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