Deuterium Isotope Effects and the Bunnett *w* Factor in Elimination Reactions of 4-Alkoxyimino-5,6-dihydro-6-alkoxyaminopyrimidin-2(1*H*)-one in Strong Acid Media

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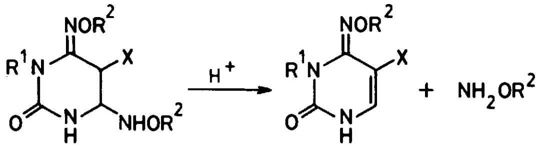
Rate coefficients for the elimination of hydroxylamines from 4-alkoxyimino-5,6-dihydro-6-alkoxyaminopyrimidin-2(1*H*)-ones (1a) show maxima at H_0 values of −1.8 (for *O*-benzylhydroxylamine) and −0.8 (for hydroxylamine) in a variety of mineral acids. The hitherto unknown values of H_0 for trifluoromethanesulphonic acid are reported and this acid also gives a rate maximum at −1.8 for the elimination of *O*-benzylhydroxylamine from (1a; R^2 = Bz). Bunnett *w* values for these eliminations fall in the range 6.0—16.0 (dependent upon the acid) implying that water is involved as a proton transfer agent. In contrast, eliminations in formic acid show low and variable *w* values and formate ion is involved as the proton transfer agent which explains the lack of a rate maximum in this acid. Deuterium isotope effects reveal a highly stereoselective elimination and support the proposal of an *E*1cB (irreversible) mechanism. The inhibition of elimination by the 5-fluoro-substituent [as in (1b)] is probably due to destabilisation of the intermediate carbanion by the lone pair electrons on fluorine.

We recently published kinetic details on the elimination of hydroxylamines from dihydropyrimidinones (1a) to yield hydroxyiminouracils (2) in strong acid media.[1] It was shown that the rate coefficients were dependent upon the nature of the hydroxylamine and the H_0 value of the medium and for (1a; R^1 = H, R^2 = Bz) a maximum rate coefficient was observed at H_0 −1.8 in a number of mineral acids. The results were explained in terms of a mechanism involving elimination from the doubly protonated form of the substrate with the triply protonated form being unreactive due to conformational changes induced by the third protonation. Conformational effects were also offered as a tentative explanation for hydrolysis of the hydroxyimino-function of 5-fluoropyrimidinones (1b; R^1 = H, R^2 = Bz) in preference to elimination. It was recognised however that variations in the activity of water might play an important role in the mechanism and this aspect has now been investigated more thoroughly. The results, together with a detailed report of the deuterium isotope effects for the eliminations, form the basis of this paper.



(1) (2)

a; X = H
b; X = F
R^1 = H or Me
R^2 = H, alkyl, or aralkyl

EXPERIMENTAL

The acid materials and kinetic techniques used throughout this work have been described previously.[1] Trifluoromethanesulphonic acid was a gift from I.C.I. (Mond Division) and had a specified purity of ⩾99%. The 5,6-dihydropyrimidinones were prepared as reported previously [1] and 5-deuteriocytosine was obtained by cysteine-catalysed exchange with D_2O.[2]

RESULTS AND DISCUSSION

The H_0 *Values of Trifluoromethanesulphonic Acid.*—The H_0 values of trifluoromethanesulphonic acid were determined spectrophotometrically [3] using *o*-nitroanilines as indicators and the results are shown in Table 1. A graph of $[CF_3SO_3H]$ *versus* $-H_0$ gave a rectilinear correlation up to 7M-CF_3SO_3H which conformed to equation (1). At higher acid concentrations however a pronounced (positive) deviation from linearity was observed.

$$-H_0 = 0.66\,[CF_3SO_3H] - 0.72\ (r\ 0.993) \quad (1)$$

TABLE 1

Values of H_0 against the molarity of CF_3SO_3H at 25 °C

$[CF_3SO_3H]$/M	$-H_0$	Indicator
0.50	−0.34	*o*-Nitroaniline
1.00	0.15	
1.50	0.37	
2.00	0.51	4-Chloro-2-nitroaniline
2.50	0.93	
3.00	1.16	
3.50	1.46	
4.00	1.65	*p*-Nitrodiphenylamine
4.50	2.09	
5.00	2.40	
5.50	2.89	
6.00	3.62	
6.50	3.66	2,4-Dinitroaniline
7.00	3.86	
7.50	4.49	
8.00	5.05	
8.50	6.18	

The Elimination of Hydroxylamines from (1a).—The reactions were followed spectrophotometrically at *ca.* 280 nm and in each case, as in the earlier work, an isosbestic point was observed showing that there was no detectable build-up of intermediate. Using (1a; R^1 = R^2 = H) as substrate and a temperature of 38 °C, maximum rate coefficients were observed at H_0 *ca.* −0.8 for HCl,[1] $HClO_4$, H_2SO_4, CF_3CO_2H, and CF_3SO_3H (Table 2).

TABLE 2

Rate constants for the elimination of hydroxylamine from (1a; $R^1 = R^2 = H$) in $HClO_4$, H_2SO_4, CF_3CO_2H, and CF_3SO_3H at 38.0 °C

Perchloric acid

M	$-H_0$ [a]	$10^4k_{obs}/s^{-1}$	$-\log a_{H_2O}$ [b]
1.00	0.32	9.8 ± 0.1	0.018
1.50	0.57	11.5 ± 0.2	0.030
2.00	0.82	11.9 ± 0.1	0.043
2.50	1.07	11.0 ± 0.2	0.060

Sulphuric acid

M	$-H_0$ [c]	$10^4k_{obs}/s^{-1}$	$-\log a_{H_2O}$ [b]
0.50	0.02	11.9 ± 0.2	0.008
1.00	0.25	16.8 ± 0.4	0.018
1.50	0.56	19.5 ± 0.4	0.030
2.00	0.85	20.2 ± 0.7	0.043
2.50	1.12	18.6 ± 0.6	0.063
3.00	1.37	15.9 ± 0.3	0.085

Trifluoroacetic acid

M	$-H_0$ [d]	$10^4k_{obs}/s^{-1}$	$-\log a_{H_2O}$
1.04	0.02	8.9 ± 0.2	0.003
2.38	0.21	13.7 ± 0.2	0.008
4.19	0.43	16.5 ± 0.2	0.021
6.71	0.68	20.0 ± 0.8	0.048
8.41	0.91	20.0 ± 0.7	0.076
9.62	1.25	18.3 ± 0.7	0.130
10.50	1.65	16.2 ± 0.8	0.235
11.20	2.10	15.6 ± 0.1	0.470
11.80	2.50	15.2 ± 0.1	0.720
12.30	2.70	15.3 ± 0.3	1.00
13.00	2.70	14.5 ± 0.1	2.10

Trifluoromethanesulphonic acid

M	$-H_0$ [f]	$10^4k_{obs}/s^{-1}$
0.50	−0.034	7.12
1.00	0.150	8.60
1.50	0.370	10.2
2.00	0.510	10.5
2.50	0.930	11.5
3.00	1.16	10.4
3.50	1.46	7.02
4.00	1.65	5.50
4.50	2.09	5.09
5.00	2.40	3.80

[a] H_0 Values from K. Yates and H. Wai, *J. Am. Chem. Soc.*, 1964, **86**, 5408 and ref. *c*. [b] a_{H_2O} Values from J. F. Bunnett, *J. Am. Chem. Soc.*, 1961, **83**, 4956. [c] H_0 Values from R. H. Boyd, 'Solute–Solvent Interactions,' eds. J. F. Coetzee and C. D. Ritchie, Marcel Dekker, New York, 1969, ch. 3. [d] H_0 Values from U. A. Spitzer, T. W. Toone, and R. Stewart, *Can. J. Chem.*, 1976, **54**, 440. [e] a_{H_2O} Values from N. G. Zarakhoni and N. P. Vorobeva, *Russ. J. Phys. Chem.*, 1972, **46**, 9. [f] H_0 Values from Table 1; no a_{H_2O} values available.

Maximum rate coefficients at the same value of H_0 (*ca.* —0.8) were also observed at 25 °C in $HClO_4$ and CF_3CO_2H and rate data in 1M-$HClO_4$ (H_0 *ca.* —0.3) over a temperature range of 18 °C are shown in Table 3 together with the derived activation parameters.

It is immediately obvious that in contrast to the elimination of *O*-benzylhydroxylamine from (1a; $R^1 = H$, $R^2 = Bz$)[1] trifluoroacetic acid gives a rate coefficient maximum with (1a; $R^1 = R^2 = H$) at the anticipated H_0 values, despite the fact that the α-conformation of the molecule is maintained as evidenced by the retention of the AB quartet up to an H_0 value of —2.0. Furthermore, the structurally analogous CF_3SO_3H gives a similar result and with (1a; $R^1 = H$, $R^2 = Bz$) gives a rate coefficient maximum at H_0 —1.8 (Table 4). Thus the hypothesis[1] that conformational changes in the triply protonated species are responsible for the rate decrease beyond certain $-H_0$ values is suspect.

TABLE 3

Rate constants for the elimination of hydroxylamine from (1a; $R^2 = R^2 = H$) in 1M-$HClO_4$ at various temperatures

T (°C)	25.6	28.8	32.0	38.0	43.0
$10^4k_{obs}(\pm 0.2)/s^{-1}$	2.85	3.35	6.23	11.4	20.0

E_a 91 ± 2 kJ mol⁻¹
$\Delta G^‡$ 94 ± 2 kJ mol⁻¹
$\Delta S^‡$ −25 ± 20 J mol⁻¹ K⁻¹

TABLE 4

Rate constants for the elimination of *O*-benzylhydroxylamine from (1a; $R^1 = H$, $R^2 = Bz$) in CF_3SO_3H at 38 °C

M	$-H_0$	$10^4k_{obs}/s^{-1}$
1.13	0.15	3.8 ± 0.2
2.26	0.80	6.1 ± 0.3
2.82	1.10	8.5 ± 0.3
3.39	1.42	8.7 ± 0.3
3.95	1.72	9.6 ± 0.4
4.52	2.10	9.6 ± 0.1
5.65	2.85	3.5 ± 0.2
6.78	3.72	0.65 ± 0.02

An alternative explanation may be found in terms of a balance between increasing rate with acid strength and decreasing rate as the activity of water within the medium falls. As an initial test of this proposal, Bunnett *w* values[4] were derived from plots of ($\log k_{obs} + H_0$) *versus* $\log a_{H_2O}$ for eliminations from (1a; $R^1 = H$, $R^2 =$ H or Bz) and are shown in Table 5. The linear plots with *w* >6.0 for the inorganic acids imply that water is involved as a proton transfer agent in the reaction which in turn implies that a_{H_2O} has an important influence on the reaction rate. With trifluoroacetic acid and elimination of *O*-benzylhydroxylamine the value of *w*, although variable, does not exceed 2.0 which suggests a minor role for water and may explain the absence of a rate coefficient maximum in this acid. With trifluoroacetic acid and the elimination of hydroxylamine, however, the *w* values are again high (though variable) and accordingly a rate coefficient maximum is seen as the decrease in a_{H_2O} begins to predominate. Further confirmation was obtained through studies of the effect of lyate ion on the rate coefficients (Table 6). Here, although the numerical value of $-H_0$ increases through the expected optimum, the value of k_{obs} decreases slightly, but steadily, with a_{H_2O} and the Bunnett plot is again linear with *w* 8.3.

TABLE 5

Bunnett *w*-parameters for the elimination of hydroxylamines from (1a) with a variety of acids at 38 °C

From (1a; $R^1 = R^2 = H$)

Acid	HCl	$HClO_4$	H_2SO_4	CF_3CO_2H [a]
w	9.6	15.9 (15.6) [b]	16.0	1.0—6.2 (4.3—7.8) [b]

For (1b; $R^1 = H$, $R^2 = Bz$)

w	*ca.* 7	6.6	6.3	0.2—2.0

[a] Plots not linear. Figures represent minimum — maximum slopes. [b] Values from data at 25 °C.

With formic acid a slightly different picture emerges. For the elimination of *O*-benzylhydroxylamine from (1a; R^2 = Bz) the rate coefficients reached a plateau around H_0 −1.5 [1] and since the maximum obtainable H_0 value was −2.2 it was not clear whether or not the rate was decreasing beyong H_0 −1.8. For (1a; R^2 = H) however, the elimination rate coefficients showed a sudden increase at H_0 *ca.* −0.7 and than increased more slowly beyond H_0 −1.0 (Table 7). The *w* values at 38 °C for the two substrates were 0.8 (for R^2 = Bz) and 0.97 (for R^2 = H) showing clearly that water is *not* involved as a proton transfer agent in this medium. Hence the rate coefficients do not fall with decreasing a_{H_2O} and the reaction (at least for R^2 = H) shows an 'ionisation type' rate profile (Figure). In order to confirm this result, the elimination of *O*-benzylhydroxylamine was studied in mixtures of formic acid and sodium formate (Table 8). Despite the increase in H_0 with added formate ion, the rate coefficients remained virtually constant but a plot of the difference between the observed rate coefficients and the rate coefficients expected for the particular value of H_0 (Δk_{obs}) against [HCO_2Na] was linear [equation (2)] demonstrating that, in this case, the formate ion

$$\Delta k_{obs} = 62.7\,[HCO_2Na] + 11.1 \quad (r\ 0.998) \qquad (2)$$

acts as the proton transfer agent. Thus a proton is lost to water or the lyate ion either prior to or during the rate-limiting step of the elimination and hence the mechanism must be either *E*2 or *E*1cB from the doubly- or triply-protonated substrate. The activation parameters are consistent with bimolecular eliminations from 'onium salts [5] and hence are compatible with either.

TABLE 6

Rate constants for the elimination of hydroxylamine from (1a; $R^1 = R^2$ = H) in perchloric acid (1.0M)-sodium perchlorate mixtures at 38 °C

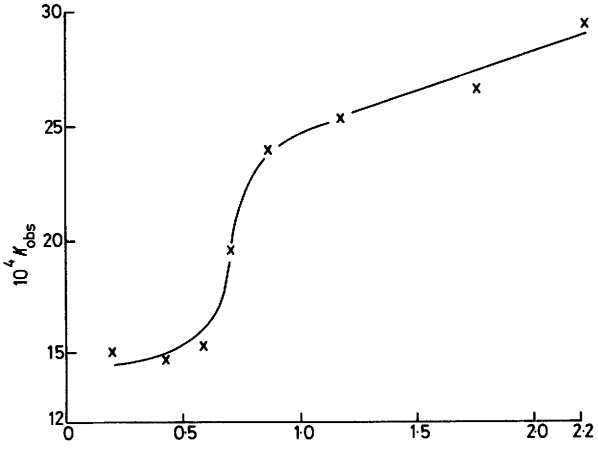
[$NaClO_4$]/M	$10^4k_{obs}/s^{-1}$	$-H_0$ [a]	$-\log a_{H_2O}$ [b]
1.00	10.0 ± 0.1	0.49	0.042
1.50	8.5 ± 0.1	0.60	0.058
2.00	8.3 ± 0.1	0.72	0.076
2.50	8.3 ± 0.1	0.84	0.094
3.00	7.6 ± 0.1	0.95	0.112
3.50	6.8 ± 0.2	1.08	0.130

[a] Data from B. C. Challis and J. H. Ridd, *J. Chem. Soc.*, 1962, 5209; M. A. Paul and F. A. Long, *Chem. Rev.*, 1957, **57**, 1. [b] Data from C. Perrin, *J. Am. Chem. Soc.*, 1963, **85**, 2773; 1964, **86**, 256; J. F. Bunnett, *ibid.*, 1961, **83**, 4956.

TABLE 7

Rate constants for the elimination of hydroxylamine from (1a; $R^1 = R^2$ = H) in formic acid at 38 °C

[HCO_2H]/M	$-H_0$	$10^4k_{obs}/s^{-1}$	$-\log a_{H_2O}$
20.0	0.19	15.2 ± 0.3	0.495
21.0	0.41	14.9 ± 0.2	0.590
22.0	0.58	15.4 ± 0.3	0.690
23.0	0.68	19.6 ± 0.3	0.800
24.0	0.85	24.1 ± 0.5	0.930
25.0	1.16	25.4 ± 0.1	1.27
26.0	1.75	26.7 ± 0.3	1.70
26.6	2.22	30.1 ± 1.2	



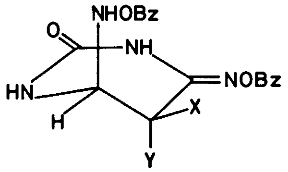
Plot of k_{obs} *versus* H_0 for the elimination of hydroxylamine from (1a; R^1, R^2 = H) in formic acid at 38 °C

TABLE 8

Rate constants for the elimination of *O*-benzylhydroxylamine from (1a; R^1 = H, R^2 = Bz) in neat formic acid -sodium formate mixtures at 38 °C

[HCO_2Na]/M	$10^4k_{obs}/s^{-1}$	$-H_0$ [a]	$10^4\Delta k_{obs}/s^{-1}$
0	26.3 ± 0.3	2.22	
0.010	27.6 ± 0.7	0.63	11.8
0.025	25.2 ± 0.3	0.39	12.8
0.050	23.5 ± 1.2	0.16	14.8
0.075	22.9 ± 1.2	0.05	15.8
0.100	26.3 ± 1.0	−0.18	17.5

[a] Data from L. P. Hammet and A. J. Deyrup, *J. Am. Chem. Soc.*, 1932, **54**, 4242.



(3) X = Y = H
(4) X = H, Y = D
(5) X = D, Y = H
(6) X = Y = D

In order to probe the alternatives further, deuterium isotope effects were studied in a variety of acids and substrates (3)—(6) and the results are reported in Table 9.

These data give rise to the k_H/k_D values shown in Table 10 which show clearly that, within experimental error, thee limination is *highly stereoselective* and involves removal of the proton at C-5 derived from the addition. The k_H/k_D values of *ca.* 2.1 in mineral acids are low for an *E*2 process [6] and point to an *E*1cB mechanism of the irreversible type, *i.e.* no exchange before elimination.*

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* Very recent results reveal that with certain substrates [*e.g.* (1a; R^1 = Me, R^2 = Bz)] exchange does occur to some extent prior to elimination giving, in this case, k_H/k_D *ca.* 1.1, and indicating a change to an E_1cB (reversible) mechanism.

TABLE 9

Rate constants for the elimination of *O*-benzylhydroxylamine from (1a; R^1 = H, R^2 = Bz) and its deuteriated derivatives in a variety of acids at 38 °C

[Acid]/M	$10^4k_{obs}/s^{-1}$ Substrate [a] (3)	(4)	(5)	(6)
$HClO_4$ (4.2)	11.5	5.1	9.6	6.2
H_2SO_4 (4.0)	17.5	8.4	14.6	7.3
HCl (5.1)	9.9	4.7	9.0	4.9
CF_3CO_2H (10.5)	32.9	12.8	39.2	10.3
HCO_2H (26.0)	25.1	13.6	24.8	15.4

[a] (3) From cytosine (C) + $BzONH_2$; (4) from (C) + $BzOND_2$; (5) from 5-deuterio-(C) + $BzONH_2$; (6) from 5-deuterio-(C) + $BzOND_2$.

A mechanism which is consistent with the data involves an *E*1cB elimination from the doubly- or triply-protonated species (7) or (8) with water or the lyate ion as base (Scheme). The differential rate equation based on this Scheme (see ref. 1 for derivation) gives an expression for k_{obs} [equation (3)] which can be shown by

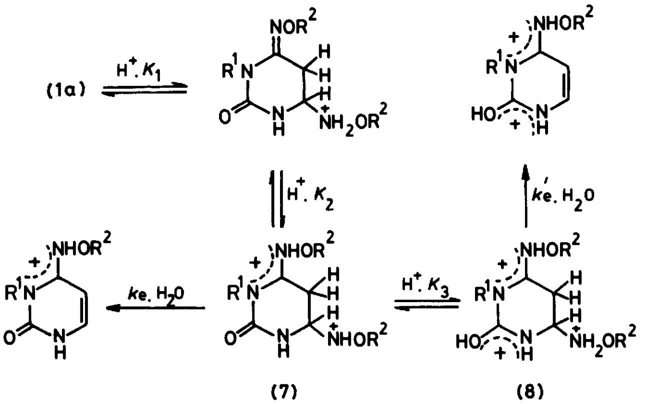
TABLE 10

Deuterium isotope effects (k_H/k_D values) for the elimination of *O*-benzylhydroxylamine from (1a; R^1 = H, R^2 = Bz) in various acids at 38 °C

Acid	$k_{obs}(3)/k_{obs}(5)$	$k_{obs}(3)/k_{obs}(4)$	$k_{obs}(3)/k_{obs}(6)$
$HClO_4$ H_2SO_4 HCl	1.1 ± 0.1	2.2 ± 0.1	2.1 ± 0.1
CF_3CO_2H	0.8	2.6	3.2
HCO_2H	1.0	1.8	1.6

$$k_{obs} = \frac{(k_eK_3[H^+]^2 + k'_e[H^+]^3)a_{H_2O}}{[H^+]^3 + K_3[H^+]^2 + K_2K_3[H^+] + K_1K_2K_3} \quad (3)$$

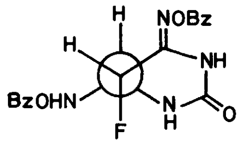
graphical methods to be in qualitative agreement with the observed H_0 profiles.



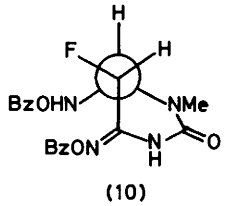
(7) (8)

SCHEME

The *E*1cB (irreversible) mechanism requires development of a negative charge at C-5 which would be stabilised by interaction with the protonated hydroxyimino-function at C-4 (see ref. 1). This stabilization would be maximised by removal of the proton which is perpendicular to the plane of the protonated hydroxyimino-function (*i.e.* proton Y in (3)] and, as we have shown elsewhere,[2] this proton is *trans*-antiperiplanar to the protonated 6-alkoxyamino-group. The *E*1cB hypothesis receives support from the results with (1b) which gave hydrolysis at C-4 rather than elimination.[1] The rate of hydrolysis increased steadily with $-H_0$ and a *w* value of *ca.* 6.0 was derived from the data, showing that water was also an important factor in this reaction. The inhibition of the elimination was attributed [1] (at least in part) to the β-conformation of (1b; R^1 = H, R^2 = Bz) *i.e.* (9) preventing the proton at C-5 and the alkoxyamino-group at C-6 adopting the *trans*-antiperiplanar conformation necessary to achieve elimination.



(9)



(10)

However, the reaction of 1-methyl-(1b; R^1 = H, R^2 = Bz) has now been studied in 10.2M-hydrochloric acid and showed u.v. spectra similar to those observed for (1b; R^1 = H, R^2 = Bz) [1] indicating that hydrolysis is again taking place in preference to elimination. Since it has been established by n.m.r. that 1-methyl-(1b) exists as the α-conformer (10) of *trans*-addition [2] and this conformation is maintained in 9M-D_2SO_4, the inhibition of the elimination reaction cannot be due to the conformation of the molecule. Thus triple protonation and molecular conformation have been ruled out as factors responsible for hydrolysis in preference to elimination. Hydration remains a possibility but a more likely explanation appears by consideration of the relative ease of formation of the carbanion in the proposed *E*1cB mechanism. The rates of formation of carbanions are known to be inhibited by highly electronegative atoms attached directly to the potential carbanion [7,8] and with fluorine this effect has been attributed to repulsive interaction between the non-bonding electrons on fluorine and the carbanion.[9] Thus the formation of the necessary carbanion intermediate is retarded and hydrolysis becomes the dominant reaction.

In conclusion, all the evidence for these acid-catalysed eliminations points to an *E*1cB (irreversible) mechanism which involves rate-limiting proton abstraction by water or the conjugate base of the acid catalyst. If formation of the carbanion is inhibited, however, hydrolysis of the hydroxyimino function may occur in preference to elimination.

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