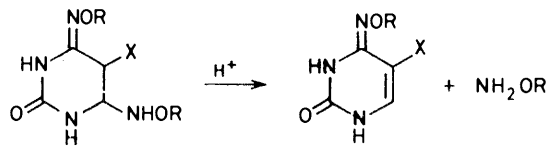
Elimination and Hydrolysis Reactions of 4-Alkoxyimino-5,6-dihydro-6-alkoxyaminopyrimidin-2(1*H*)-ones and 4-Alkoxyimino-5-fluoro-5,6-dihydro-6-alkoxyaminopyrimidin-2(1*H*)-ones in Strong Acid Media

By **David J. Palling, Peter M. Schalke, Paul J. Atkins,** and **C. Dennis Hall,*** Department of Chemistry, King's College, Strand, London WC2R 2LS

The rate of elimination of hydroxylamines from 4-alkoxyimino-5,6-dihydro-6-alkoxyaminopyrimidin-2(1*H*)-ones (Ia) in a number of acids is shown to be maximal at a H_0 value of −1.8, with the exception of trifluoroacetic acid for which a linear increase in rate constant is observed with increasing acid strength. The results are explained by a mechanism involving the doubly protonated form of the substrate. With 4-alkoxyimino-5-fluoro-5,6-dihydro-6-alkoxyaminopyrimidin-2(1*H*)-ones (Ib), acid-catalysed hydrolysis to form 5-fluoro-5,6-dihydro-6-alkoxyaminopyrimidine-2,4(1*H*,3*H*)-diones (V) occurs in preference to the elimination reaction which in this case is *ca.* 750 times slower than with (Ia). The rate differences for elimination are explained by differences in conformation between the two substrates (Ia and b).

It has been known since 1965 [1] that dihydropyrimidinones of type (Ia) decompose in acid to yield 4-hydroxyiminouracils (IIa) but no detailed kinetic information has been published. An understanding of the mechanism



(I) R = H, alkyl, aralkyl (II)

a; X = H
b; X = F

of this reaction is relevant to synthetic work directed towards the preparation of molecules of type (II) and hence, in conjunction with our studies on the hydroxylaminolysis of cytosines,[2] we have investigated this elimination in a number of different acid media.

EXPERIMENTAL

AnalaR grade sulphuric, hydrochloric, perchloric, formic, acetic, and trifluoroacetic acid were used. Formic and trifluoroacetic acid were redistilled before use. The dihydropyrimidinones were prepared by the general procedure reported previously.[3] Rates of reaction were followed by monitoring the appearance of the absorption of hydroxyiminouracils at 280 nm using 10 mm cuvettes thermostatted at 38.0 °C in the cell housing of a Pye–Unicam SP1700 spectrophotometer. In reactions with 5-fluorodihydropyrimidinones the disappearance of the 235 nm band was also monitored. Good straight lines ($r \geqslant 0.999$) were obtained from semi-logarithmic plots of the results and rate constants were calculated either from plots of $\ln(A_\infty - A_t)$ *versus* time or by the Guggenheim method, over at least three half-lives. The H_0 values of the acid solutions were taken from suitably constructed calibration curves by using published results. No temperature corrections were made. N.m.r. spectra were recorded on a Bruker HFX 90 instrument operating in the Fourier transform mode with a deuterium lock. The pK_a values of hydroxylamines were determined by automatic titration (Radiometer).

RESULTS AND DISCUSSION

Investigation of the Reaction of Pyrimidinones (Ia) *in Acid.*—A typical set of u.v. scans with time is shown in Figure 1 and the presence of an isosbestic point indicates that build-up of an intermediate cannot be detected. Except for trifluoroacetic acid, bell-shaped rate profiles were obtained when the observed rate constants for the elimination of *O*-benzylhydroxylamine from 4-benzyloxyimino-5,6-dihydro-6-benzyloxyaminopyrimidin-2(1*H*)-one (Ia; R = CH_2Ph) in acid were plotted against the H_0 values of the acid. The results are presented in Table 1 and typical plots are shown in Figure 2. It can be seen that the maximum rate constant in sulphuric, hydrochloric, formic, and perchloric acid is at a H_0 value of *ca.* −1.8, and that the rate constants at any particular H_0 value are comparable although an order, formic > sulphuric > hydrochloric > perchloric is discernible.

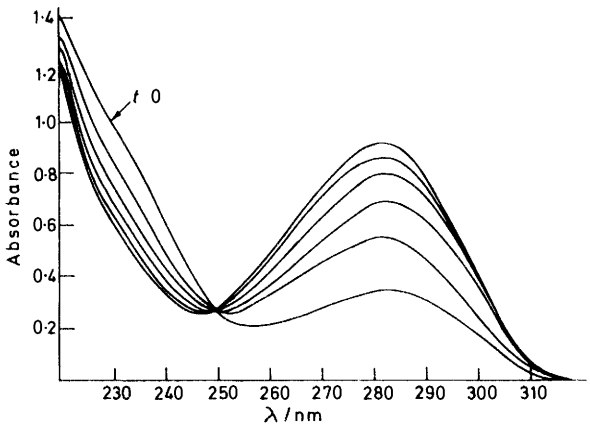


FIGURE 1 U.v. scans *versus* time for the reaction of (Ia; R = CH_2Ph) in 5.5M-sulphuric acid at 38 °C; intervals of 5 min

In acetic acid (H_0 *ca.* 0.0) [4] a rate constant of 7.9×10^{-6} s^{-1} was obtained. In trifluoroacetic acid however, a maximum rate of *ca.* 4.0×10^{-3} s^{-1} was reached at a mole fraction of *ca.* 0.8 and the rate did not decrease in more concentrated acid. This maximum is about twice

TABLE 1

Rate constants for the elimination of *O*-benzylhydroxylamine from (Ia; R = CH_2Ph) in acid at 38.0 °C

Hydrochloric acid [a]

M	$-H_0$	$10^4k_{obs}/s^{-1}$
1.0	0.20	3.02
2.0	0.69	7.67
3.1	1.06	12.3
4.1	1.42	14.8
4.6	1.60	15.9
5.1	1.79	18.2
5.6	1.98	16.2
6.1	2.18	15.5
7.1	2.55	9.28
8.1	2.90	7.37
9.2	3.27	3.98
10.2	3.66	2.47

Perchloric acid [b]

M	$-H_0$	$10^4k_{obs}/s^{-1}$
1.16	0.42	4.08
2.32	1.00	10.5
2.90	1.26	10.5
3.48	1.51	12.3
3.63	1.58	12.6
3.92	1.71	13.1
4.18	1.82	13.5
4.35	1.90	14.2
4.74	2.08	13.7
5.22	2.31	13.7
5.48	2.46	10.5
6.09	2.79	9.09
6.96	3.36	2.70
8.70	4.48	0.19

Formic acid [c]

M	$-H_0$	$10^4k_{obs}/s^{-1}$
17.7	−0.24	1.69
21.3	0.30	10.9
22.4	0.49	13.9
24.6	0.98	15.9
25.2	1.15	16.4
25.9	1.46	18.6
26.2	1.72	20.1
26.6	2.22	18.5

Sulphuric acid [d]

M	$-H_0$	$10^4k_{obs}/s^{-1}$
0.9	0.2	4.48
1.8	0.7	9.68
2.7	1.2	14.4
3.6	1.6	17.1
4.1	1.85	18.2
4.55	2.05	16.9
5.5	2.5	11.5
6.6	3.0	5.93
7.3	3.35	4.04
9.1	4.3	0.72

Trifluoroacetic acid [e]

$X_{CF_3CO_2H}$	$-H_0$	$10^4k_{obs}/s^{-1}$
0.1	0.44	6.96
0.2	0.73	11.9
0.3	1.03	17.1
0.4	1.47	22.5
0.5	2.00	28.7
0.6	2.38	33.1
0.8	2.78	39.8
1.0	2.71	39.7

[a] H_0 values from M. A. Paul and F. A. Long, *Chem. Rev.*, 1957, **57**, 1. [b] From K. Yates and H. Wai, *J. Amer. Chem. Soc.*, 1964, **86**, 5408. [c] From R. Stewart and T. Matthews, *Canad. J. Chem.*, 1960, **38**, 602. [d] From P. Tickle, A. G. Briggs, and J. M. Wilson, *J. Chem. Soc.* (*B*), 1970, 65, and E. M. Arnett and G. W. Mach, *J. Amer. Chem. Soc.*, 1966, **88**, 1177. [e] From U. A. Spitzer, T. W. Toone, and R. Stewart, *Canad. J. Chem.*, 1976, **54**, 440.

the maximum obtained for sulphuric acid, and when the k_{obs} values are plotted against the H_0 values a linear relationship is obtained between H_0 −0.4 and −2.8 (the H_0 value of trifluoroacetic acid above a mole fraction of 0.8).

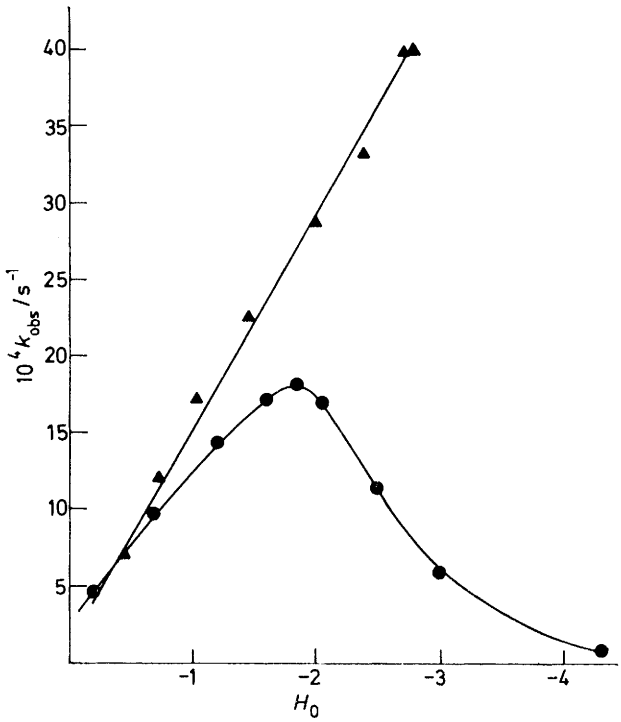


FIGURE 2 Observed rate constants at 38 °C for the elimination of *O*-benzylhydroxylamine from (Ia; R = CH_2Ph) in trifluoroacetic acid (▲) and sulphuric acid (●) *versus* the H_0-value of the acid

A bell-shaped rate profile was also obtained from a plot of k_{obs} *versus* H_0 for the elimination of hydroxylamine from 4-hydroxyimino-5,6-dihydro-6-hydroxyaminopyrimidin-2(1*H*)-one (Ia; R = H) in hydrochloric acid. In this case the rate constant maximum is at a H_0 value of −0.7 (Table 2 and Figure 3).

U.v. spectra run at the end of the *O*-benzyl reactions showed $\lambda_{max.}$ 277 nm (log ε 4.01) in 5.1M-HCl. Uracil,

TABLE 2

Rate constants for the elimination of hydroxylamine from (Ia; R = H) in hydrochloric acid at 38.0 °C

[HCl]/M	$-H_0$	$10^4k_{obs}/s^{-1}$
0.25	−0.55	2.77
0.50	−0.20	5.48
1.00	0.20	9.55
2.00	0.69	12.6
3.10	1.06	11.4
4.10	1.42	8.99
5.10	1.79	7.87
6.10	2.18	5.00
7.10	2.55	3.64

which would have been formed by hydrolysis of (IIa) has $\lambda_{max.}$ 260 nm (log ε 3.92) in 5.1 M-HCl.

The kinetics of the elimination of *O*-benzylhydroxylamine from (Ia; R = CH_2Ph) in 5.1M-DCl were also followed by ^1H n.m.r. spectroscopy. At time 0 the

spectrum showed an AB quartet of an ABX system (centred at δ 3.35, range 52 Hz) due to the two 5-H protons, singlets at δ 4.63 and 5.01 due to the 6-OCH_2 and 4-OCH_2 protons, respectively, and a multiplet at δ 5.62 due to the 6-H proton (the X proton of the ABX

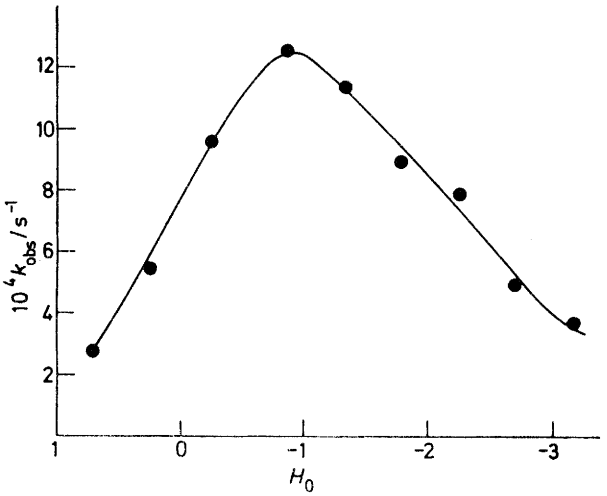


FIGURE 3 Observed rate constants at 38 °C for the elimination of hydroxylamine from (Ia; R = H) in hydrochloric acid *versus* the H_0 value of the acid

system) plus, of course, the phenyl resonances. During 24 h the 5-H_AH_B, the 6-OCH_2, and the 6-H_X peaks disappeared completely and a new pair of doublets at δ 7.65 and 6.06 (J 7.8 Hz) appeared for the 6 and 5-H, respectively, of the hydroxyiminouracil product (IIa; R = CH_2Ph). The OCH_2 peak of the *O*-benzylhydroxylamine was superimposed on that of the 4-OCH_2 peak of (IIa) and no other new products were detected. The rate of disappearance of the 5-H_AH_B peaks equalled the rate of appearance of the 5-H product doublet (Figure 4)

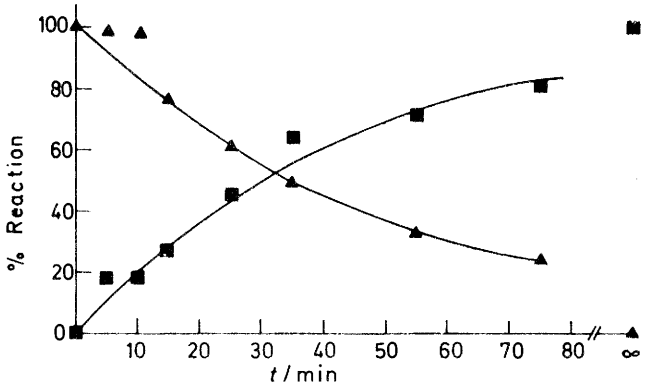


FIGURE 4 Percentage appearance of the 5-H doublet of (IIa; R = CH_2Ph) (■) and percentage disappearance of the 5-H_AH_B quartet of (Ia; R = CH_2Ph) (▲) *versus* time for (Ia; R = CH_2Ph) in 5.1M-DCl at 24.0 °C followed by ^1H n.m.r.

and the build-up of a reaction intermediate was not detectable by n.m.r. which confirmed the observation of an isosbestic point by u.v. (Figure 1).

The shape of the 5-H_AH_B resonance pattern of 5,6-dihydropyrimidinones provides valuable information about the conformation of these molecules.[3] For the *O*-benzyl derivative (Ia) in 5.1M-DCl and trifluoroacetic [^2H]acid at $X_{CF_3CO_2D} = 1$ and 0.6, and also in $CDCl_3$, a typical AB quartet pattern is seen (Figure 5a). In 10.2M-DCl however this collapses to a much more simple pattern (Figure 5b). Unfortunately, the *O*-benzyl derivative is not sufficiently soluble in 1M-DCl for n.m.r. purposes. However, the *O*-methyl derivative is soluble and this also shows the typical AB quartet centred at δ 3.06 (range 52 Hz) (Figure 5c).

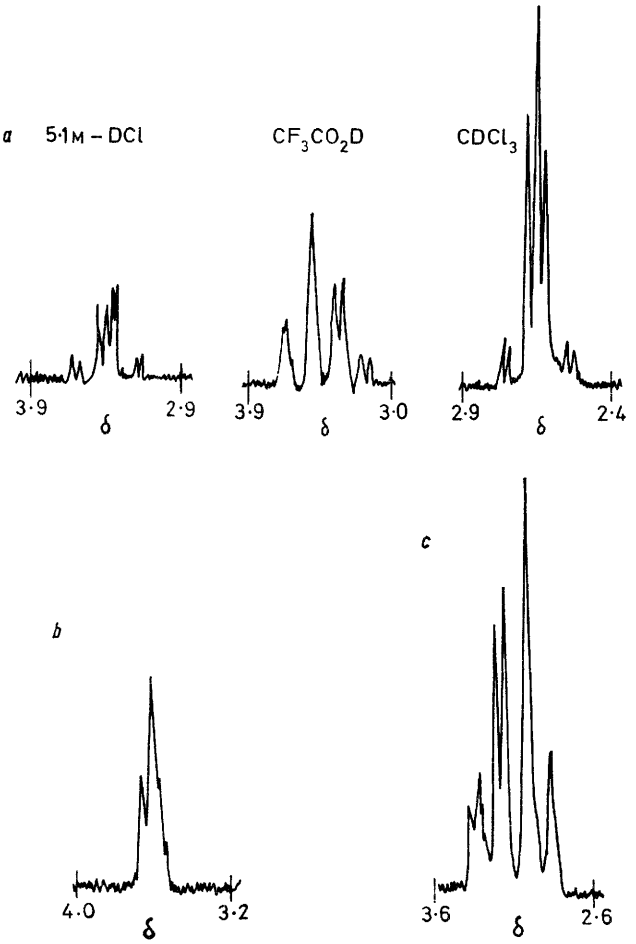


FIGURE 5 a, 5-H_AH_B quartet of (Ia; R = CH_2Ph) in 5.1M-DCl, CF_3CO_2D, and $CDCl_3$; b, 5-H_AH_B quartet of (Ia; R = CH_2Ph) in 10.2M-DCl; c, 5-H_AH_B quartet of (Ia; R = Me) in 1M-DCl

Investigation of the Reaction of Pyrimidinones (Ib) *in Hydrochloric Acid.*—With the 5-fluoro-*O*-benzyldihydropyrimidinone (Ib; R = CH_2Ph), in contrast to the unfluorinated compound, the absorbance at 235 nm disappears quickly compared with the slow appearance of a band at longer wavelength formed by loss of *O*-benzylhydroxylamine across the 5,6-bond; furthermore an isosbestic point is not seen (Figure 6). The rate of disappearance of the absorbance at 235 nm increases with acid strength over the range 1.0—10.2M (Figure 7 and Table 3). The band at longer wavelength initially has $\lambda_{max.}$ 292 nm, but this eventually shifts to shorter wavelength, the final $\lambda_{max.}$ being at 270 nm. 5-Fluorouracil

TABLE 3

Rate constants for the hydrolysis (disappearance of 235 nm band) of (Ib; R = CH_2Ph) in hydrochloric acid at 38.0 °C

[HCl]/M	$-H_0$	$10^5 k_{obs}/s^{-1}$
1.0	0.20	1.02
3.1	1.06	5.10
4.1	1.42	4.65
5.1	1.79	5.65
6.1	2.18	6.86
7.1	2.55	10.1
8.1	2.90	12.3
10.2	3.66	17.9

under the same condition (8.1M-HCl) has $\lambda_{max.}$ 267 nm (log ε 3.78). The appearance of the longer wavelength band is very slow and analysis is complicated by the shift in $\lambda_{max.}$. Therefore no attempt has been made to obtain rate constants for this process, although a rough estimate reveals that elimination from the fluorinated compound is *ca.* 750 times slower than for the unfluorinated compound in 5.1M-HCl.

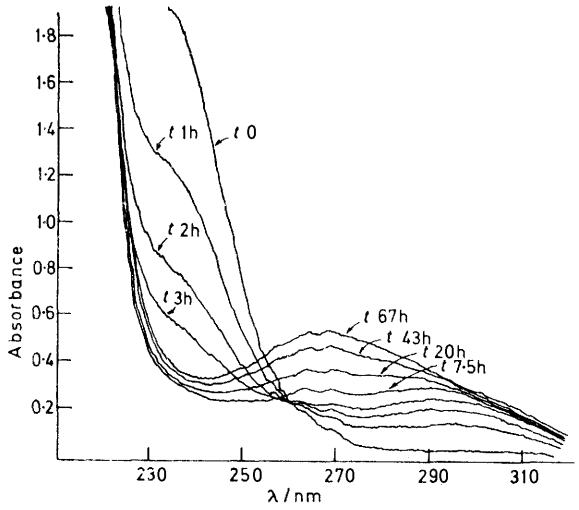


FIGURE 6 U.v. scans *versus* time for the reaction of (Ib; R = CH_2Ph) in 10.2M=HCl at 38 °C

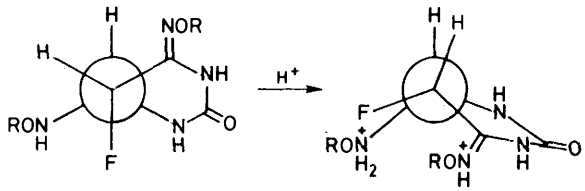
We have previously shown that in DMSO and in $CHCl_3$ the 5-F,6-H coupling constant of the fluorinated addition–substitution compound is *ca.* 18 Hz. This is compatible only with a *trans*-disposition about the C(5)–C(6) bond [2,5] and we referred to the structure responsible for this coupling as the β-conformer (III). In aqueous media, however, the value of $J_{F,6\text{-}H}$ is reduced as is shown in Table 4. It will be noted that the smallest values of $J_{F,6\text{-}H}$ are for the most acidic media and this we can imagine as being due to an acid-promoted flip to a

TABLE 4

Values of $J_{5\text{-}F,6\text{-}H}$ in (Ib; R = H and Me)

R	Solvent system	$J_{5\text{-}F,6\text{-}H}$/Hz
H	DMSO	20
H	D_2O–DCl (pH 0)	<2
H	D_2O–DCl (8M)	<2
Me	DMSO	17.1
Me	D_2O–NaOD (pH 12.4)	12.2
Me	D_2O (pH 7.3)	7.32
Me	D_2O–DCl (pH 1.5)	4.88

conformer such as (IV) in which F · · · $\overset{+}{H}$–N(6) hydrogen bonding is probably important as is shown in the expanded structure (IV). The shortest F–H distance is in the eclipsed conformer (IV) and it is reasonable to



(III) (IV)

expect the doubly protonated form to approach this conformation as the planarity of the ring increases.

By analogy with the Karplus diagram for vicinal fluorine–hydrogen coupling in substituted ethanes [6] we would expect this conformer to have a very small vicinal

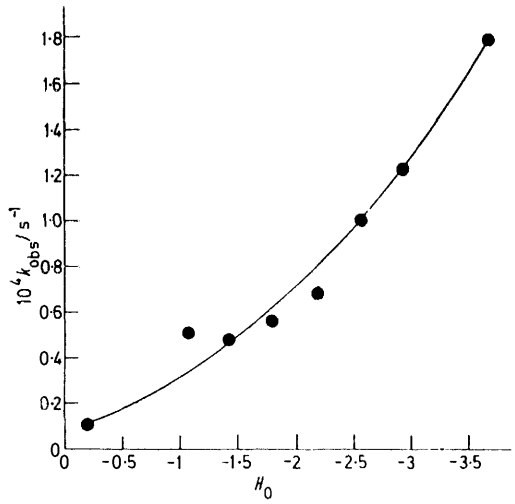
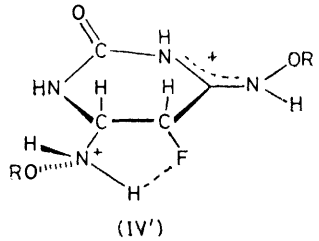


FIGURE 7 Observed rate constant at 38 °C for the hydrolysis reaction of (Ib; R = CH_2Ph) in HCl *versus* the H_0 of the acid

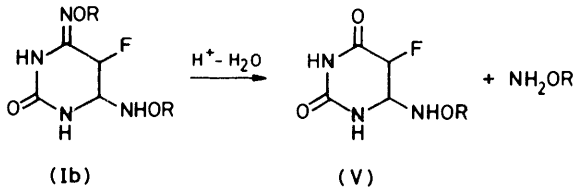
coupling constant at a dihedral angle of *ca.* 90°. The ^{19}F spectrum of (Ib; R = H) in 8.1M-DCl was run immediately after mixing the components and again after 1 h. Initially a doublet was seen at δ −210.2 p.p.m. (standard $CFCl_3$) ($J_{F,5\text{-}H}$ 43.9, $J_{F,6\text{-}H} < 2$ Hz).



(IV')

After 1 h a second doublet had appeared at δ −214.5 p.p.m. with the same coupling constants. 5-Fluorocytosine shows a 5-F,6-H coupling of only 4.88 Hz and it is evident therefore that no elimination had occurred

across the C(5)–C(6) bond. This n.m.r. evidence, along with the disappearance of the 235 nm band in the u.v. indicates that in acid the primary reaction which occurs is conversion of (Ib) into (V). To test this theory, a



(Ib) (V)

larger scale reaction was carried out using the *O*-benzyl derivative in 5.7M-HCl. After a day a new spot which could not be detected by u.v. light was seen on t.l.c. with a different R_F value from either the starting material, *O*-benzylhydroxylamine, or 5-fluorouracil. After 3 days a u.v. detectable spot at the same R_F value as an authentic sample of 5-fluorouracil was also seen. The non-u.v. detectable spot was presumably due to the 5,6-dihydrouracil derivative (V) (see Table 5 for R_F values).

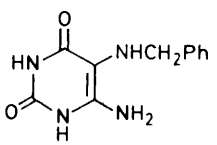
TABLE 5

R_F Values on Merck t.l.c. plastic sheets pre-coated with silica gel 60 F_{254}. Eluant, chloroform–methanol (5 : 1 v/v)

	R_F
5-Fluorouracil	0.25
6-Benzyloxyamino-5,6-dihydrouracil	0.44
O-Benzylhydroxylamine	0.64
(Ib; R = CH_2Ph)	0.69

Mechanism of the Reaction of Pyrimidinones (Ia) *in Acid.*—A mechanism which is consistent with the kinetic data is shown in Scheme 1.

In strong acid media dihydropyrimidinones of type (Ia) will be protonated, and the order of protonation is almost certainly that shown in Scheme 1. This can be justified by analogy with the pK_a values of known compounds. *O*-Benzylhydroxylamine has a pK_a of 4.1 and NH_2OH 5.78. Oximes have pK_a values of *ca.* 1 [7] (*e.g.* Me_2C=NOH, pK_a 0.99) and it is reasonable to expect the pK_a of the 4-hydroxyimino-function to be in this region,* with the OH derivative being more basic than the OCH_2Ph derivative. The pK_a of the N-1,2-oxo-

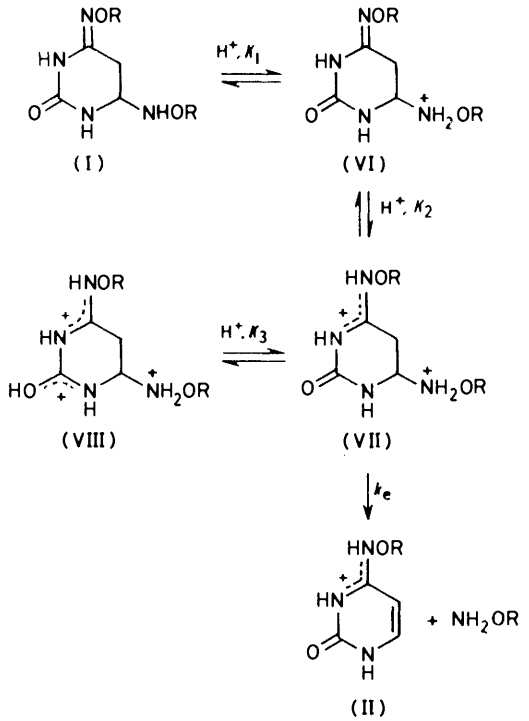


(IX)

functionality of (Ia) can be estimated by comparison with uracil which has a basic pK_a of −3.38 [8] or 6-amino-5-benzylaminopyrimidine-2,4(1*H*,3*H*)-dione (IX) which has a basic pK_a of −4.1.[7]

* Janion and Shugar (*Acta Biochim. Polonica*, 1965, **12**, 337; 1972, **19**, 261) estimate a pK_a of 2.8 for 4-hydroxyimino- and 1.9 for 4-methoxyimino-uracil.

Furthermore, 4-amino-2-hydroxypyridine, which bears some structural resemblance to (Ia) has a basic pK_a of −5.14.[7] Thus we can estimate the three pK_a values of (Ia; R = H) to be 5.5, 1, and −4 and for (Ia; R = CH_2Ph) 4, 0, and −4.



(I) (VI) (VIII) (VII) (II)

SCHEME 1

The differential rate equation (11) for Scheme 1 can be derived as shown below. In equation (2) $[S]_T$ is the total concentration of the dihydropyrimidinone. The equilibrium constants K_1, K_2, and K_3 are defined by equations (3)—(5).

$$v = k_e\,[(VII)] \quad (1)$$

$$[(VII)] = [S]_T - [(I)] - [(VI)] - [(VIII)] \quad (2)$$

$$K_1 = [(VI)]/[H^+][(I)] \quad (3)$$

$$K_2 = [(VII)]/[(VI)][H^+] \quad (4)$$

$$K_3 = [(VIII)]/[(VII)][H^+] \quad (5)$$

$$\therefore \quad [(I)] = [(VII)]/K_1K_2[H^+]^2 \quad (6)$$

$$\therefore \quad [(VII)] = [S]_T - \frac{[(VII)]}{K_1K_2[H^+]^2} - \frac{[(VII)]}{K_2[H^+]} - K_3[(VII)][H^+] \quad (7)$$

$$\therefore \quad [S]_T = [(VII)]\left\{1 + \frac{1}{K_1K_2[H^+]^2} + \frac{1}{K_2[H^+]} + K_3[H^+]\right\} \quad (8)$$

$$\therefore \quad v = k_e[(VII)] = \frac{k_e[S]_T}{\left\{1 + \frac{1}{K_1K_2[H^+]^2} + \frac{1}{K_2[H^+]} + K_3[H^+]\right\}} \quad (9)$$

$$\therefore \quad k_{obs} = \frac{v}{[S]_T} =$$

$$\frac{k_e}{\left\{1 + \frac{1}{K_1K_2[H^+]^2} + \frac{1}{K_2[H^+]} + K_3[H^+]\right\}} \quad (10)$$

$$= \frac{K_1K_2[H^+]^2k_e}{1 + K_1[H^+] + K_1K_2[H^+]^2 + K_1K_2K_3[H^+]^3} \quad (11)$$

It can be shown that the general form of the curve of equation (11) (with k_{obs} and $[H^+]$ being the variables y and x) has only one maximum when $[H^+]$ and all constants are positive (the conditions in this system). Thus the differential rate equation is in qualitative agreement with experiment when the acidity function H_0 is used to indicate $[H^+]$. The anomalous behaviour in trifluoroacetic acid will be discussed at the end of this section.

The acidity function H_0 is a quantitative measure of the ability of the solvent to donate protons to a base [9] and is defined so that for certain weakly basic amines the concentrations of free base (A) and conjugate acid (HA) are given by equation (12). It follows therefore,

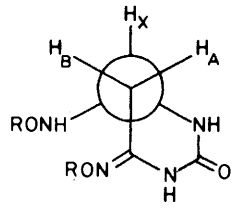
$$H_0 = pK_a - \log_{10}([HA]/[A]) \quad (12)$$

that a plot of $\log_{10}([HA]/[A])$ against H_0 should be linear with unit gradient. It has often been pointed out that bases of different types need not obey this rule (*e.g.* ref. 4). Katritzky and Waring [8] found that for a number of pyrimidines rectilinear plots *were* obtained but the gradients were often much less than unity. This implies that the extent of protonation of pyrimidines *is proportional* to H_0 functions but that the ratio of [base] to [conjugate acid] at any given H_0 value in our system cannot be calculated accurately.

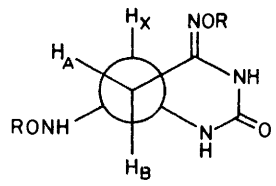
It is significant that for (Ia; R = CH_2Ph) the maximum rate of elimination of $PhCH_2ONH_2$ in the different acids occurs at a H_0 value of *ca.* −1.8 and that this value lies between our estimates of the second and third pK_a values. This implies that the major factor controlling the rate of the reaction is the degree of protonation, and that it is from the doubly protonated form (VII) that elimination occurs. It is evident that little or no elimination occurs from the singly protonated form (VI) since the 6-NH will be 100% protonated at pH 2 where the elimination rate is very slow. If we were to assume *equal* gradients for plots of log ([HA]/[A]) *versus* H_0 for (VII) and (VIII), then the maximum concentration of (VII) would occur at a H_0 value midway between the second and third pK_a values. However, as already discussed, this assumption is not justified, although it can be concluded that the maximum concentration of (VII) will be in this region. The H_0 value of −1.8 falls sensibly between our estimates of 0 and −4 as the values of the second and third pK_a values.

The shift to lower acidity (H_0 −0.7) for the maximum rate of elimination of NH_2OH from (Ia; R = H) may be due to the slightly higher second pK_a of this substrate compared to the R = CH_2Ph derivative, as already discussed. No attempt to calculate the value of k_e can be made since the values of $[H^+]$ at any given value of H_0 cannot be calculated.

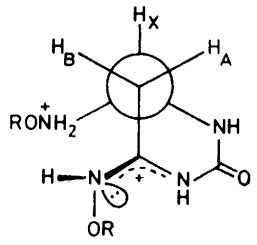
It has been shown previously that of the two possible conformers of (Ia), pictured as their Newman projections down the C(5)–C(6) bond [(X) and (XI)], the α-conformer



(X) α



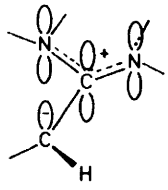
(XI) β



(XII)

(X) is predominant. This conformer is responsible for the AB quartet pattern seen in chloroform, in 1M- and 5M-DCl and in trifluoroacetic acid (see Figure 5a). It can also be seen that the 5-H and 6-RONH group are antiperiplanar in (X) but not in (XI) and therefore elimination of $RONH_2$ is more likely from a type (X) conformer, *i.e.* the doubly protonated conformer (XII).

The question now arises—why should elimination from the doubly protonated form be more favourable than from either the singly or triply protonated forms? We suggest that the mechanism resembles the ' irreversible ' *E*1cB mechanism as discussed by McLennan [10] and by Bordwell,[11] in which removal of the 5-H_A atom is slow compared with the loss of the $\overset{+}{R}ONH_2$ group. This would involve the development of a negative charge on the C(5) of the ring and this is more likely to be stabilized by a positive charge delocalized about N(4)–C(4)–N(3) as in the doubly protonated form [see (XIII)]



(XIII)

but not in the singly protonated form. This type of mechanism is also supported by kinetic isotope work carried out in this laboratory. A k_H/k_D value of *ca.* 2.5 was observed [12] and this aspect of the problem is currently under more intensive investigation. A ' pre-equilibrium ' type *E*1cB mechanism involving proton removal in a fast pre-equilibrium step does not appear likely in view of the fact that no deuterium incorporation was observed in the reactant (Ia) at 10.2M-DCl or in the

product (IIa) at 5.1M-DCl. The possibility of intermolecular attack on 5-H_A by an $E2$ type mechanism was investigated by the addition of increasing amounts of potassium formate to formic acid. No rate enhancement was detected (see Table 6) and this suggests the mechanism is not E_2. On the other hand, addition of sodium formate to formic acid is known to reduce the $-H_0$ values [13] and since there is little effect on the rote, formate ion may be involved in the removal of the proton at C–5 and hence be compensating for the fall in $-H_0$.

TABLE 6

Investigation of effect of added formate ion on rate of elimination of *O*-benzylhydroxylamine from (Ia; R = CH_2Ph) at 38.0 °C. Concentration of HCO_2H maintained at 23.9M

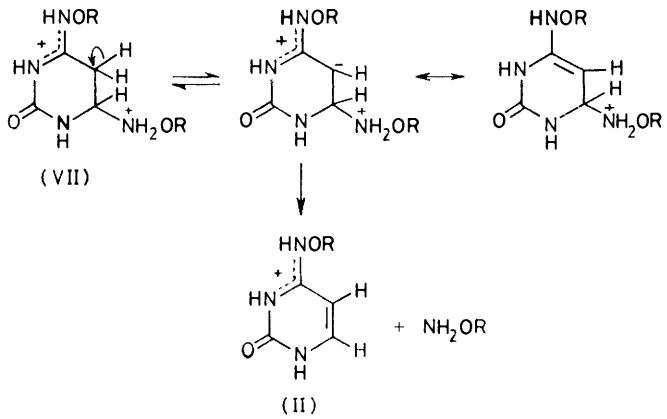
A Ionic strength maintained constant by making solutions up with a suitable solution of KCl

$[HCO_2K]$/M	$10^3k_{obs}/s^{-1}$
0.1	1.42
0.083	1.51
0.067	1.52
0.05	1.53

B Ionic strength not maintained. Solutions made up to volume with H_2O

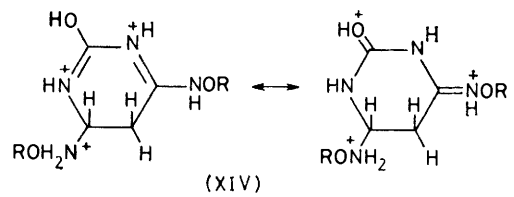
0.083	1.41
0.050	1.47

Thus, as shown in Scheme 2, it appears that double protonation is required to provide the driving force for cleavage of the C(5)–H bond. It is evident from the



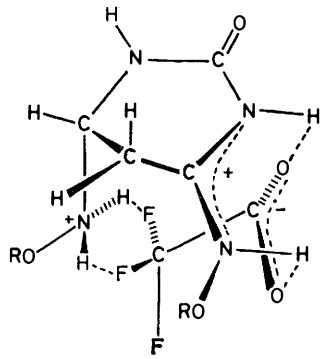
SCHEME 2

n.m.r. spectrum (Figure 5b) that in 10.2M-DCl compound (Ia) exists either entirely as a different conformer [*e.g.* the almost planar (XIV)] or as a number of rapidly equilibrating conformers. Either way this will reduce the effective concentration of the α-conformer and will thus inhibit the elimination. However, the decrease in rates beyond



certain $-H_0$ values, at least in mineral acids, may also be associated with a concomitant decrease in the activity of water and this possibility is also receiving further attention.

We now turn to the anomalous behaviour seen in trifluoroacetic acid. It is evident from Figure 2 that the rate constant for elimination does not decrease beyond the H_0 value corresponding to the maximum concentration of the doubly protonated form. Furthermore, n.m.r. evidence shows that even in 100% CF_3CO_2H the α-conformer is preserved. Thus in CF_3CO_2H the energy barrier to interconversion of the α- and β-conformers is greater than in other acids at comparable H_0 values. Molecular model studies indicate that the $CF_3CO_2^-$ anion is of just the correct dimensions to hold

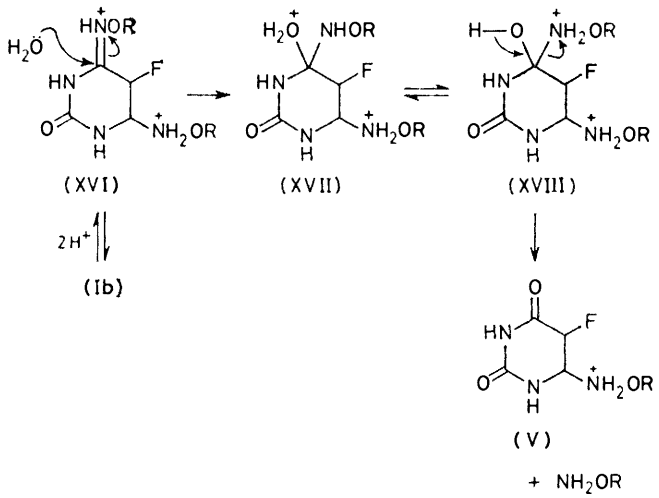


the dihydropyrimidine as the α-conformer through hydrogen-bonding to oxygen and fluorine within the ion-pair (XV).

The difference in maximum rate constants in the various acids represents a $\delta\Delta G^{\ddagger}$ of *ca.* 7 kJ mol^{-1} between the fastest and slowest. As this figure is less than the strength of an average hydrogen bond there seems little point in attempting to rationalize the variations although there is a reasonable correlation between the rate order and the basicity of the anion *i.e.* $HCO_2^- \sim CF_3CO_2^- > HSO_4^- > Cl^- \sim ClO_4^-$.

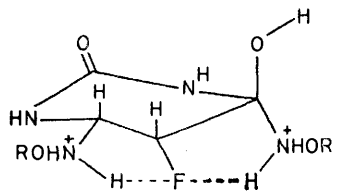
Mechanism of the Reaction of Pyrimidinones (Ib) *in Acid.*—As indicated in the results section a different reaction occurs with the 5-fluoro-derivative, the major product being the 5,6-dihydrouracil (V), with elimination occurring very slowly. The rate of the hydrolysis increases with acid strength and the mechanism is presumably that in Scheme 3, with no inhibition of the reaction by triple protonation.

A number of explanations can be put forward for this behaviour with the fluorinated compound. (1) Fox [14] has found that introduction of the fluorine atom at the 5-position of cytosines causes a decrease in the basic strength by nearly 2 pK_a units (the same is true regarding the pK_a of uracil as an acid). In our system this would have the effect of bringing the second and third pK_a values closer to one another thereby decreasing the concentration of the doubly protonated form, from which



SCHEME 3

elimination occurs, at any given H_0 value. This would therefore reduce the extent of elimination and allow the hydrolysis to compete successfully. (Hydrolysis of the 4-hydroxyimino-function was found to occur in the non-fluorinated compound, but at a very much lower rate



(XVIII)

than the elimination, so that it did not interfere). (2) Stereochemical evidence from the n.m.r. experiments indicates that the fluorinated dihydropyrimidine does not have the 5-H and 6-NHOR antiperiplanar and this would also lower the rate of elimination at the expense of hydrolysis. (3) It is possible that the doubly protonated form (XVI) exists as a hydrate [(XVII) ⇌ (XVIII)] stabilized by two hydrogen bonds as shown above. The hydrogen at C-5 is now no longer labile (no stabilization of the carbanion) but this is the intermediate which leads to hydrolysis at C-4. Both (XVIII) and (IV) have the eclipsed conformation which would produce the very low $J_{F,6\text{-}H}$ coupling constant. For the unfluorinated compound the doubly protonated intermediate (VII) could also, in principle, exist as a hydrate but this would receive no stabilization by hydrogen-bonding.

We thank the Cancer Research Campaign for financial support.

[0/618 *Received*, 28*th April*, 1980]

REFERENCES

1 D. M. Brown and P. Schell, *J. Chem. Soc.*, 1965, 208.
2 D. J. Palling, P. J. Atkins, and C. D. Hall, *J.C.S. Perkin II*, 1980, in the press.
3 P. M. Schalke and C. D. Hall, *J.C.S. Perkin I*, 1975, 2417.
4 C. H. Rochester, 'Acidity Functions,' Academic Press, London, 1970, ch. 2.
5 P. M. Schalke and C. D. Hall, *J.C.S. Chem. Comm.*, 1976, 391.
6 J. W. Emsley, L. Phillips, and V. Wray, ' Fluorine Coupling Constants,' Pergamon, Oxford, 1977, p. 108.
7 D. D. Perrin, ' Dissociation Constants of Organic Bases in Aqueous Solution,' Butterworths, London, 1965, and 1972 Supplement.
8 A. R. Katritzky and A. J. Waring, *J. Chem. Soc.*, 1962, 1540.
9 J. Hine, ' Physical Organic Chemistry,' McGraw-Hill, New York, 1956.
10 D. J. McLennan, *Quart. Rev.*, 1967, **21**, 490.
11 F. G. Bordwell, *Accounts Chem. Res.*, 1972, **5**, 374.
12 P, J. Atkins, unpublished results.
13 L. P. Hammett and A. J. Deyrup, *J. Amer. Chem. Soc.*, 1932, **54**, 4239.
14 I. Wempen, R. Duscinsky, L. Kaplan, and J. J. Fox, *J. Amer. Chem. Soc.*, 1961, **83**, 4755.