β-Ureido Acids and Dihydrouracils. Part 15.[1] Effect of Allylic Strain on Ring Opening of 1,6-Disubstituted Dihydrouracils

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The rate profiles for the alkaline hydrolysis of some dihydrouracil and dihydro-orotic acid derivatives have been measured in order to assess the effect of allylic strain on the ring opening of 1,6-disubstituted dihydrouracils. The introduction of a 1-nitrogen-substituent in the 6-substituted compounds brings about a substantial decrease (40—500 times) in the observed rate constant which is second order in hydroxide ion (k_1k_3/k_{-1}). The rate decreases of the addition step, k_1, are moderate and in the range expected from the observed shifts in conformational equilibria towards the axial conformation which gives rise to a hindered transition state. The major contributions to the rate decreases arise from the ring-opening step, k_3/k_{-1}, and have been attributed to strains of the type associated with the *gem*-dimethyl effect upon ring closure.

Steric effects on reactivity caused by groups in axial conformations enforced by allylic strain have long been recognized in carbocyclic systems.[2] The shifts of the conformational equilibria brought about by nitrogen-substitution in heterocycles containing *endo*-amide groupings vary depending on the system [1,3,4] and their effect on reactivity has generally not been studied. In this respect, the alkaline hydrolysis of dihydrouracils is a particularly suitable model since substituents at C-6† readily adopt an axial conformation in the presence of substituents at N-1.[1,4]

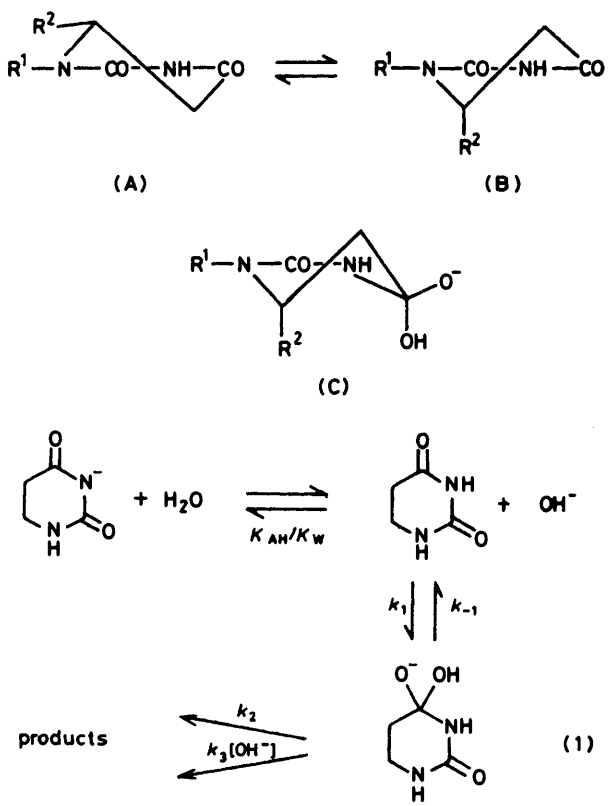
On the other hand, it is axial substituents at C-6 that very strongly affect the rate of alkaline hydrolysis. Thus, 6,6-dimethyldihydrouracil, with one of the methyl groups necessarily axial, opens its ring at pH 13 *ca.* 200 times more slowly than 6-methyldihydrouracil where the methyl group is mainly equatorial.[5] This has been interpreted as due to the severe diaxial Me–OH interaction in the tetrahedral intermediate (C).

The hydrolysis of dihydrouracils proceeds according to equation (1).[6] In the pH range 11—14, a change of mechanism usually takes place. This allows the steric effects on the addition step, k_1, and on the partitioning ratios k_2/k_{-1} and k_3/k_{-1} for the ring-opening steps to be elicited separately as these constants can be obtained from the rate profiles.

The ring opening of compounds (1)—(10) will be discussed. The rate profiles for compounds (1),[6a,c] (2),[6b] (3),[6b] and (8) [6a] have been published previously. We now report those of the remaining compounds. The rate profiles of (2) and (8) were repeated for the sake of better comparison.

The pyrimidine derivatives studied are of some biological interest since in many addition reactions of pyrimidine nucleosides 1,6-disubstituted dihydrouracils are obtained. Recently Atkins *et al.* studied the effect induced by an axial 1-methyl group in the acid-catalysed elimination of 6-alkoxyamino-5,6-dihydro-4-alkoxyiminopyrimidin-2(1*H*)-one.[7]

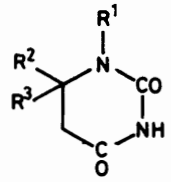
† The compounds discussed in this paper are derivatives of hexahydropyrimidine-2,4-dione (1) and hexahydro-2,6-dioxopyrimidine-4-carboxylic acid (8). To avoid confusion with the different numbering in the systematic nomenclature only that of the former is used in conjunction with the trivial names dihydrouracil and dihydro-orotic acid, respectively.



Results

Dihydrouracils are weak acids and are deprotonated at N-3 in the pH range studied. In order to account for the effect of ionization on the apparent rates, the pK values were determined spectrophotometrically in standard buffers. The pK values obtained are listed in Table 1.

The rate profiles obtained at 25 °C in sodium hydroxide solutions (I = 1M-KCl) for the dihydrouracils are presented



	R^1	R^2	R^3		R^1	R^2	R^3
(1)	H	H	H	(6)	H	Ph	H
(2)	Me	H	H	(7)	Me	Ph	H
(3)	H	Me	H	(8)	H	CO_2H	H
(4)	H	Me	Me	(9)	Me	CO_2H	H
(5)	Me	Me	H	(10)	Et	CO_2H	H

Table 1. pK Values for ionization of dihydrouracils at 3-NH

Compound	pK_{AH}	Compound	pK_{AH}
(1)	11.74 [a]	(6)	11.22
(2)	11.86	(7)	11.25
(3)	11.60 [a]	(8)	11.60 [b]
(4)	11.44 [a]	(9)	12.11
(5)	11.71	(10)	12.22

[a] From ref. 14. [b] From ref. 6*a*.

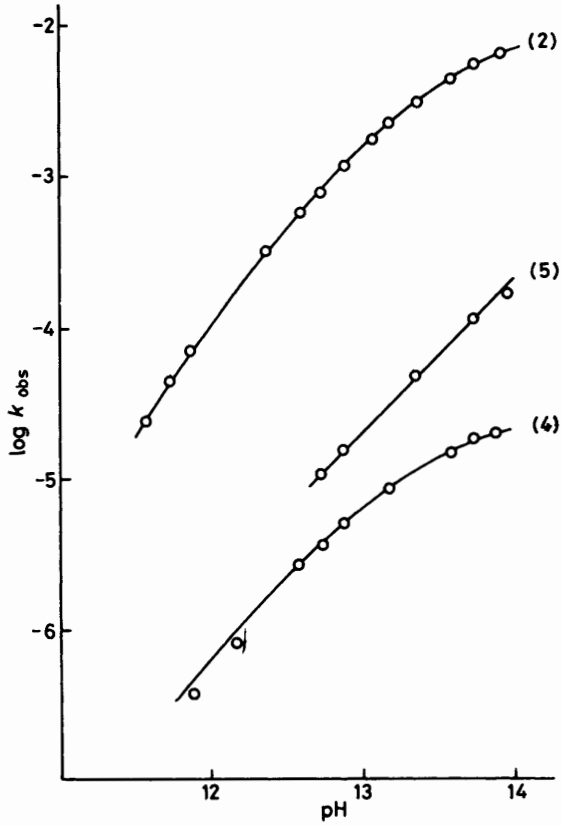


Figure 1. Plots of log k_{obs} against pH for the hydrolysis of methyl-substituted dihydrouracils. The solid lines are calculated with the constants from Table 2 and pK values from Table 1

in Figures 1—3. According to the rate law (2) of equation (1) the observed changes in the slopes from 1 towards 0 result

$$k_{obs.} = \frac{k_1[OH^-](k_2/k_{-1} + k_3[OH^-]/k_{-1})}{(1 + K_{AH}[OH^-]/K_W)(1 + k_2/k_{-1} + k_3[OH^-]/k_{-1})} \quad (2)$$

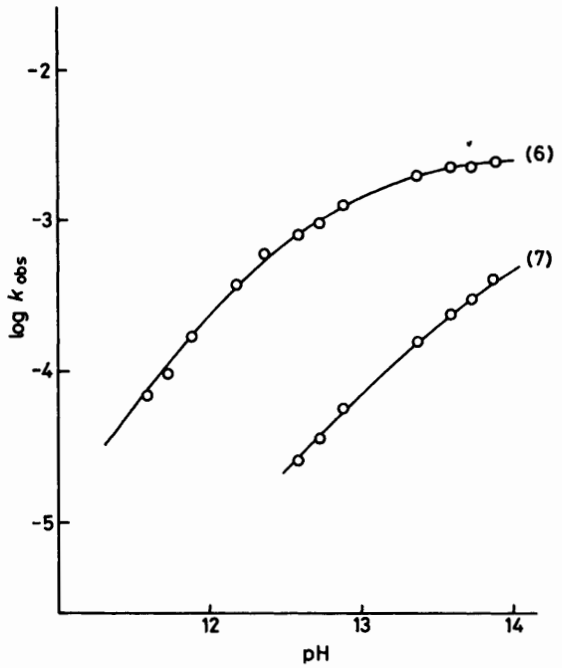


Figure 2. Plots of log k_{obs} against pH for the hydrolysis of 6-phenyl-dihydrouracils. The solid lines are calculated with the constants from Table 2 and pK values from Table 1

from $K_{AH}[OH^-]/K_W$ and $k_3[OH^-]/k_{-1}$ terms in the denominator becoming >1 with the increase in $[OH^-]$ (k_2/k_{-1} is usually $\ll 1$). The individual rate constants were calculated from the rate profiles corrected for ionization. Because of the difference in ionic strength in the pK and rate measurements, the hydroxide ion concentrations used in the latter were converted into activities with a coefficient of 0.759 determined from pH measurements of the solutions used. The constants k_1 and k_3/k_{-1} were calculated from the upper curved portion of the plots by means of equation (3).

$$a_{OH^-} = k_1 (a_{OH^-})^2/k_{corr} - k_{-1}/k_3 \quad (3)$$

In the case of compounds (5) and (10), plots of log k_{corr} against log$[OH^-]$ retained their slopes of 2 up to 1M-NaOH and only the overall rate constant k_1k_3/k_{-1} could be determined. Rate data obtained from experiments in more concentrated hydroxide solutions were not used in the calculations because of the rather strong salt effect observed. The k_1k_2/k_{-1} term was observable at lower hydroxide concentrations with the *N*-substituted dihydro-orotic acids (9) and (10) and calculated from equation (4). The rate constants shown in Table 2 have been recalculated in concentration units.

$$k_{corr}/a_{OH^-} = k_1k_3a_{OH^-}/k_{-1} + k_1k_2/k_{-1} \quad (4)$$

Discussion

Before discussing the rate constants for ring opening of the compounds studied, an outline of the conformational equilibrium (A) $\rightleftharpoons$ (B) should be given. The relevant J values of the couplings of the *trans*-protons at C-5 and -6 of the dihydrouracils are shown on Table 3.[1,4] The populations are calculated using the previously suggested values of 11.5 and 2 Hz for (A) and (B) respectively [8] and are subject to the usual limitations. According to that scale, nitrogen substitution in 6-methyldihydrouracil (3) and in dihydro-orotic acid

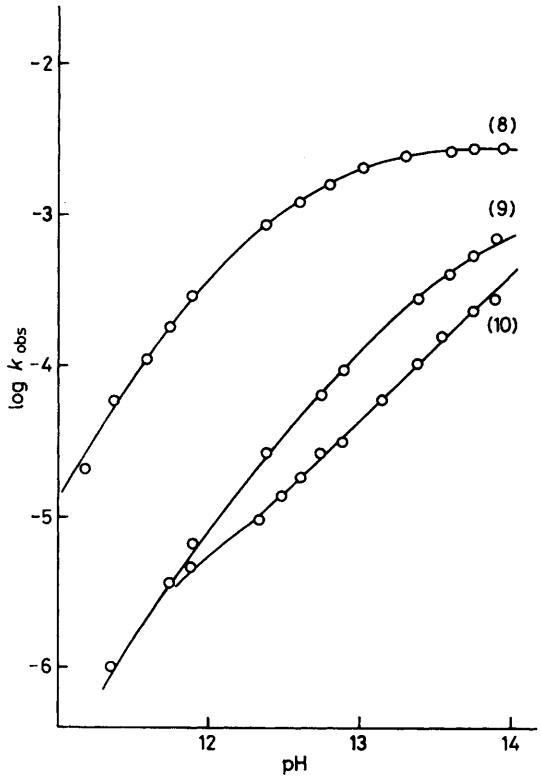


Figure 3. Plots of log k_{obs} against pH for the hydrolysis of dihydro-orotic acids. The solid lines are calculated with the constants from Table 2 and pK values from Table 1

(8) and its salts shifts the equilibrium to >90% population of (B) [see compounds (5), (9), and (10)]. The axial conformation is apparently more strongly preferred with the nitrogen-substituted dihydro-orotic acids but these start from an already favoured axial conformation in the unsubstituted compound (8) so that it is not possible to assess where allylic strain is more efficient. The conformations of the phenyl-substituted dihydrouracils (6) and (7) are strongly solvent dependent. The conformations in water can be assumed to be similar to those observed in trifluoroacetic acid since dihydrouracils are too weak as bases to be protonated in the latter solvent.[9] As can be seen from the percentages in Table 3, the shift to the axial conformation (B) in the pair (6) and (7) is appreciably less than that in the 6-methyl compounds (3) and (5).

The ' neat ' effect of a N-methyl group is demonstrated by the rate constants observed for (2) (Table 2). The overall rate k_1k_3/k_{-1} is much smaller than that of dihydrouracil (1), the decrease being mainly contributed by k_3/k_{-1}. Although this could be attributed to an inductive effect on the doubly negatively charged transition state for k_3, this is hardly the case as the changes brought about in the pK values by an N-methyl group are very slight as can be seen in Table 1 for the pairs (1) and (2), (3) and (5), and (6) and (7). Rather this is most probably steric hindrance to ring opening. It has been shown recently [10] that upon cyclization of the respective ureido acids, the accelerations caused by the methyl groups increase in the order (1), (3), (4), (2) and this is exactly the order of the decreases in rate observed for the k_3/k_{-1} process. As the *gem*-dimethyl effect in the case of ring closure was found to correlate with the steric strains in the open-chain compounds apparently released upon ring formation this suggests that the strains caused by the substituents in the

Table 2. Rate constants for the hydrolysis of dihydrouracils in NaOH solutions at 25 °C (I = 1M-KCl)

Compound	$k_1k_3k_{-1}$/ dm^6 mol^{-2} s^{-1}	k_1/dm^3 mol^{-1} s^{-1}	k_3k_{-1}/ dm^3 mol^{-1}
(1) [a]	17.3	1.83	9.44
(2)	1.56	1.21	1.29
(3) [b]	3.09	0.645	4.79
(4)	0.0176	0.007 97	2.21
(5)	0.0245		
(6)	11.0	1.20	9.18
(7)	0.258	0.487	0.531
(8)	9.78	0.589	16.6
(9) [c]	0.0783	0.0819	0.956
(10) [d]	0.0200		

[a] From ref. 6c. [b] From ref. 6b, k_2 1.61 × 10^{-3}. [c] k_2 1.2 × 10^{-3}. [d] k_1k_2/k_{-1} 5.00 × 10^{-4} dm^3 mol^{-1} s^{-1}.

Table 3. ^{1}H Vicinal coupling constants of *trans*-protons at C-5 and -6 in dihydrouracils

Compound	Solvent	J/Hz	% conformation (A)
(2) [a]	CF_3COOD	9.9	84
	[$^2H_6$]DMSO	9.5	79
(5) [a]	CF_3COOH	2.8	8
	[$^2H_6$]DMSO	2.6	6
(6) [b]	CF_3COOH	16.0 [c]	82
	DMSO	5.8 (6.8)	41 (50)
(7) [a]	CF_3COOD	3.9	20
	Pyridine	2.2	<5
(8) [d]	D_2O	5.1	33
	$NaHCO_3$–D_2O	6.8	50
(9) [d]	D_2O	1.4	<5
	$NaHCO_3$–D_2O	1.8	<5
(10) [d]	D_2O	2.1	<5

[a] J Values from ref. 4. [b] From ref. 8. [c] The sum of the two vicinal couplings. [d] J Values from ref. 1.

transition state of the ring-opening step k_3/k_{-1} in some respects resemble those arising in the open-chain compounds.

The effect of allylic strain on the observed third-order rate constant k_1k_3/k_{-1} is strongly pronounced in the case of 1,6-dimethyldihydrouracil (5) where the rate of hydrolysis is almost as low as that of 6,6-dimethyldihydrouracil (4). With this compound however, the individual rate constants could not be obtained so that their contributions can only be estimated. The individual constants observed for the reference compounds (1)—(4) would suggest that the main effect is due, as for the 6,6-dimethyl derivative, to a large decrease of k_1 because of the steric hindrance caused by the axial methyl group as depicted in structure (C). The addition step, k_1, with 6,6-dimethyldihydrouracil (4) is 80 times slower than with 6-methyldihydrouracil (3). However, the observation that the plot of log k_{corr} against log[OH$^-$] for (5) is a straight line of slope 2 in the interval 0.07—1M-NaOH signifies according to equation (2) that k_3[OH$^-$]/k_{-1} remains smaller than 1 + k_2/k_{-1}. As k_2/k_{-1} in these systems is much smaller than unity, k_3/k_{-1} can be detected from the curvature in the rate profile when k_3[OH$^-$]/k_{-1} is *ca.* 1. Setting the detectable limit of k_3/k_{-1} as 0.2 dm^3 mol^{-1} indicates, from the observed overall rate, a k_1 value not smaller than 0.12 dm^3 mol^{-1} s^{-1}. These limiting values of the individual constants for (5) correspond to a situation where the overall 125-fold decrease in rate compared with that of (3) is brought about by a factor of 25 in the ring-opening step, k_3/k_{-1}, and only of 5 in the addition step k_1.

An *N*-methyl group causes a smaller decrease in the overall rate of the phenyl derivatives (6) and (7), which correlates with the smaller tendency of (7) to adopt an axial conformation. As can be seen from Table 2 the contribution of the individual rate constants is similar to (5), the major effect being due to the ring-opening step.

The observed smaller decreases in the addition step k_1 are actually expected from the Winstein–Holness relationship assuming that the equatorial form reacts as the 6-substituted derivative while the axial conformation adds OH^- very slowly as for (4). The population of the equatorial conformation decreases *ca.* 6 times in the pair (3) and (5) and *ca.* 4 times in the phenyl derivatives (6) and (7) which is in rough accord with the lowest estimate of k_1 in (5), and the observed value of k_1 for (7).

The effect of nitrogen substituents on the ring-opening step k_3/k_{-1} of (5) and (7) is apparently much larger than can be accounted for by the shifts in the conformational equilibria. In any case steric hindrance associated with the tetrahedral intermediate and an axial group at C-6 is expected to cancel to a large extent in the partitioning ratio k_3/k_{-1}. So a reason, apart from the increased population of the axial form, has to be sought for the observed decreases in the rate constants k_3/k_{-1}. We consider this to be the reverse action of the *gem*-dimethyl effect, *i.e.* the increase of strain upon ring opening with substitution discussed already in the case of 1-methyldihydrouracil (2). The leaving ureido group is a rigid moiety and this in all probability increases the steric requirements of the *N*-methyl group. As shown recently [11] in the more extreme case of tetramethylhydantoin, the presence of a 1-*N*-methyl group and two vicinal methyl groups not only makes the ring stable to base but in addition the parent hydantoic acid cyclizes in base by the reverse of the k_3 process. One of the first to discuss the hindrance of substituents in the actual process of breaking the ring was Bordwell in a study of sultone hydrolysis.[12] He viewed it, however, as a case where the staggered conformations in the ring became eclipsed in the transition state while it should be considered as part of the general strain which is released in the opposing process of ring closure.

The dihydro-orotic acids studied present a more complicated case since the polar effect of the charged carboxylate group is also involved. In spite of this negative charge dihydro-orotic acid (8) is a slightly stronger 3-NH acid than dihydrouracil (Table 1). The nitrogen-substituted derivatives (9) and (10) are, however, 0.5 p*K* units weaker acids, demonstrating the direct field effect of an axial carboxylate group. Sterically the carboxy-group is similar to phenyl but has a smaller conformational energy in cyclohexanes.[13] The rate decrease brought about by an *N*-methyl group in (9) compared with (8) in k_1k_3/k_{-1} is greater than that observed with the phenyl derivatives (6) and (7) which is due to a larger drop in k_1. Since the combined steric and polar effect of an axial carboxylate group most probably strongly reduces k_1 this could be attributed to a greater decrease in the population of the equatorial conformation. The *J* values of the *N*-alkyl derivatives are, however, too close to the reference values for any quantitative determination of the equilibrium position. Compared with the phenyl compounds the axial carboxylate group appears to have little effect on the extra negative charge involved in the k_3/k_{-1} process. According to the kinetics of the base-catalysed cyclization of tetramethylhydantoic acid this is a general base-catalysed step (k_3) and as such will have a more dispersed charge in the transition state and be less sensitive to polar effects. Even in the case of a small β coefficient intramolecular catalysis could have been expected. The rate decrease in k_1k_3/k_{-1} of almost 500 times observed with the *N*-ethyl derivative (10) is greatest in the series studied and is most likely related to steric hindrance to ring opening. The *N*-isopropyl derivative of dihydro-orotic acid hydrolysed still more slowly but cyclized simultaneously to 1-isopropyl-5-hydantoinacetic acid and discussion of this result is deferred until a more detailed study is completed.

To summarise, the above study shows that allylic strain in 1,6-disubstituted dihydrouracils affects the rates of hydrolysis in two ways: one is by increasing the population of the axial conformations which hinders the formation of the tetrahedral intermediate, the k_1 step, and the second one by hindering the process of ring opening, the k_3/k_{-1} step. The second, more important in dihydrouracils, appears to be related to the strains involved in the *gem*-dimethyl effect upon cyclization.

Experimental

Materials.—The preparation of compounds (1),[9] (2),[6b] (3),[5] (4),[14] (6),[8] (7),[4] and (8)—(10) [1] has been described previously.

Methyl 3-(1-*methylureido*)*butanoate*. To a slurry of methyl 3-methylaminobutanoate (5 g) and water (13 ml) cooled to −1 to 5 °C, concentrated HCl (5 ml) was added followed by powdered potassium cyanate (5 g). The solution was left at this temperature for 1 h and then ethanol (50 ml) added. The precipitate was filtered off and the residue evaporated *in vacuo*. The dry residue was refluxed in acetone (80 ml), the mixture filtered, and carbon tetrachloride (50 ml) added to the hot filtrate. Upon cooling the crude product was filtered, washed with ether, and recrystallized from acetone to yield pure *ureido ester* (1.3 g, 20%), m.p. 131—132 °C (Found: C, 48.4; H, 8.1; N, 16.0. $C_7H_{14}N_2O_3$ requires C, 48.3; H, 8.1; N, 16.1%).

1,6-*Dimethylhexahydropyrimidine*-2,4-*dione*. A solution of methyl 3-(1-methylureido)butanoate (1.0 g) in 10% HCl (20 ml) was boiled for 1 h. Upon cooling the dihydrouracil was deposited. Recrystallization from acetone yielded *dione* (5) 10.40 g, 49%), m.p. 148—149 °C (Found: C, 50.6; H, 7.1; N, 19.2. $C_7H_{12}N_2O_2$ requires C, 50.7; H, 7.1; N, 19.7%).

pK_{AH}-*Measurements*.—These were carried out on a Unicam SP 800 spectrophotometer at $\lambda_{max.}$ of the anion (*ca.* 232 nm for the 1-H and *ca.* 240 nm for the 1-alkyl compounds) in thermostatted cells at 25.0 °C. The standard buffers of Bates and Bower [15] were used: 0.05M-$NaHCO_3$ for pH 9.60—11.00, 0.05M-Na_2HPO_4 for pH 10.90—12.00, and mixtures of NaOH and KCl for p*K* 12.00—13.00, *I* of the buffers varying between 0.035 and 0.131. The absorbances were extrapolated where necessary from plots of log *A* against time. The pK_{AH}-values were obtained from least-squares fitting of equation (5)

$$A = -\frac{a_{H^+}}{K_{AH}}(A - A_{AH}) + A_{A^-} \qquad (5)$$

where *A* is the absorbance at a given pH value, A_{AH} the absorbance in distilled water, and A_{A^-} the absorbance of the anion treated as an unknown because of rapid hydrolysis in some cases and stray light problems in more concentrated NaOH solutions. The pK_{AH} values in Table 1 are averages of at least two measurements, the reproducibility being, as found before,[14] better than ±0.05 p*K* units.

Rate Measurements.—These were carried out on the same instrument following the decrease of absorbance of the dihydrouracil as described in ref. 6*b*.

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