

Effect of Hydroxide Ion Concentration on the Partitioning of a Mono-anionic Tetrahedral Intermediate into Di- and Tri-anionic Reactive Intermediates in the Alkaline Hydrolysis of Alloxan

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The alkaline hydrolysis of alloxan was studied within the hydroxide ion concentration range 0.02–3.0M at a constant ionic strength. The rate of hydrolysis was found to follow an irreversible first-order consecutive reaction path

of the type $A \xrightarrow{k_{1\text{obs.}}} B \xrightarrow{k_{2\text{obs.}}} X$ where $k_{1\text{obs.}}$ and $k_{2\text{obs.}}$ are pseudo-first-order rate constants and A, B, and X stand for alloxanic acid, intermediate, and ammonia, respectively. Three distinct regions were found to exist in the rate profiles. In the lower region, rate constants were found to follow the relations $\frac{1}{k_{1\text{obs.}}} = B_1 + \frac{B_2}{[\text{OH}^-]}$ and $\frac{1}{k_{2\text{obs.}}} = C_1 + \frac{C_2}{[\text{OH}^-]}$. At relatively higher concentration the rate was independent of hydroxide ion concentration and at much higher concentration the rate constants followed the relations $k_{1\text{obs.}} = D_1 + D_1[\text{OH}^-] + D_3[\text{OH}^-]^2$ and $k_{2\text{obs.}} = E_1 + E_2[\text{OH}^-] + E_3[\text{OH}^-]^2$. In these relations $B_1, B_2, C_1, C_2, D_1, D_2, D_3, E_1, E_2,$ and E_3 are arbitrary constants. On the basis of observed kinetic data, a possible mechanism has been proposed and various kinetically indistinguishable kinetic paths have also been discussed.

In our earlier studies on the hydrolysis of many acyl group-containing substrates¹⁻⁴ it was shown, on the basis of purely kinetic observations, that the partitioning of the tetrahedral intermediate which, in fact, controls the nature of the rate-determining steps depends usually on two factors: (i) the nature of the leaving group and (ii) the alkalinity of the reaction medium. In continuation of our work on the hydrolysis of barbituric acid⁵ in highly alkaline medium the study on the kinetics and mechanism of hydrolysis of alloxan was undertaken. Although extensive biological studies of alloxan have been reported in literature, no kinetic study of its alkaline hydrolysis has been described. Here the consecutive nature of the base-catalysed hydrolysis of alloxan up to the stage of evolution of ammonia is described and a detailed mechanism is proposed.

EXPERIMENTAL

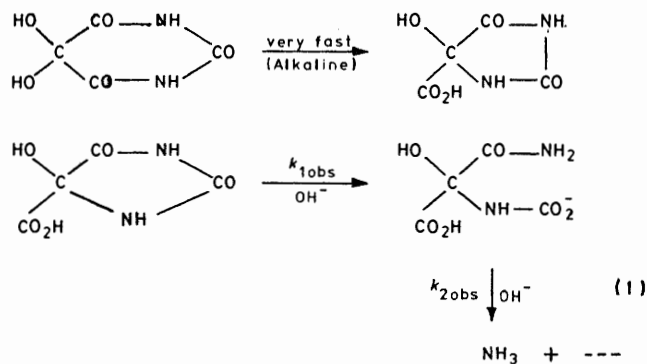
Powdered alloxan (B.D.H.) which is known to be in the dihydroxy-form⁶ was used. All other reagents were of AnalaR grade and the solutions were prepared in doubly distilled water. Nessler's reagent was prepared as described by Vogel⁷ and was always kept in the dark after use.

The kinetic procedure used was the same as described in earlier studies.⁵

RESULTS

Kinetic studies of the conversion of alloxan into alloxanic acid have been carried out in detail by other workers^{8,9} and the half-life of this reaction under their conditions is reported as 3.2 min⁸ and 7 s,⁹ respectively. On the basis of these studies it is obvious that under our experimental conditions the formation of alloxanic acid would be much faster than the other consecutive steps of the hydrolytic cleavage of alloxan. Thus the production of ammonia in the alkaline hydrolysis of alloxan, as observed to be followed

by irreversible first-order consecutive reaction, may be shown as follows:



SCHEME 1

Kinetic studies on the alkaline hydrolysis of alloxan carried out by Seligson *et al.*⁸ revealed that there was almost no formation of urea during the course of hydrolysis.

In equation (1) $k_{1\text{obs.}}$ and $k_{2\text{obs.}}$ are the *pseudo*-first-order rate constants. Equation (1) leads to kinetic equation (2)¹⁰ for a concentration of ammonia (X) as a function of $k_{1\text{obs.}}$, $k_{2\text{obs.}}$, and time t , where A_0 is the initial concentration

$$X = A_0 \left[1 + \frac{1}{k_{1\text{obs.}} - k_{2\text{obs.}}} (k_{2\text{obs.}} e^{-k_{1\text{obs.}} t} - k_{1\text{obs.}} e^{-k_{2\text{obs.}} t}) \right] \quad (2)$$

of alloxan. By substituting a parameter ρ for k_2/k_1 in equation (2), we get:

$$X = A_0 \left[1 + \frac{1}{1 - \rho} (\rho e^{-k_{1\text{obs.}} t} - e^{-\rho k_{2\text{obs.}} t}) \right] \quad (3)$$

Equation (3) has been solved for $k_{1\text{obs.}}$ various trial values of ρ being introduced using the Newton-Raphson method.¹¹

The best possible value of ρ was obtained by selecting one of those trial values for which the sum of the squares of the difference of observed and calculated values was found to be minimum. This fitting was done using a computer program developed for I.B.M.-1130. The value of $k_{2\text{obs}}$ was determined from the exact values of ρ and $k_{1\text{obs}}$. In equation (2) $k_{1\text{obs}}$ is considered to be greater than $k_{2\text{obs}}$, because the hydrolysis of the imide bond is faster than the amide bond. This fact was further confirmed by studying the reaction near completion when the concentration of alloxan became less than $\sim 1.0\%$. Under these conditions the first step was neglected in comparison to the second one and $k_{2\text{obs}}$ must be very close to k_t which is given by the pseudo-first-order rate equation (4), where B_0 and X_0 are the

$$k_t = \frac{1}{(t_i - t_0)} \ln \left(\frac{B_0}{(B_0 - (X_t - X_0))} \right) \quad (4)$$

concentrations of the intermediate and ammonia respectively at time t_0 where the concentration of alloxan is negligible and X_t is the concentration of ammonia at any time t_i . The values of $k_{2\text{obs}}$ and k_t as evaluated by equations (2) and (3) are summarized in Table 1, which indicate good agreement between $k_{2\text{obs}}$ and k_t .

TABLE 1

Comparison of rate constants as evaluated for kinetic run ^a

Time min	$10^4 x_{\text{obs}}$ M	$\frac{k_{2\text{obs}}}{k_{1\text{obs}}} = 0.081$		$10^4 k_{2\text{obs}}^c$ min ⁻¹	$10^4 k_t^d$ min ⁻¹	$10^4 k_t^e$ min ⁻¹
		$10^4 A_{\text{calc}}^b$ M	$10^4 k_{2\text{obs}}^c$ min ⁻¹			
90	5.46	2.49	24.99	16.31		
156	9.56	0.49	22.83	17.51		
255	15.96	0.03	23.28	19.97		
316	19.33	0.00	23.56	20.89	24.79	
377	22.61	0.00	24.34	22.10	26.58	
435	25.63	0.00	25.48	23.53	28.63	
505	27.90	0.00	25.35	23.68	27.51	
580	30.00	0.00	25.36	23.90	27.04	

^a Conditions: $40.00 \times 10^{-4}\text{M}$ -alloxan, 2.30M -NaOH, $\mu = 3.00\text{M}$, 90°C . ^b $A_{\text{calc}} = A_0 e^{-k_{1\text{obs}} t}$ where A_0 is the initial concentration of alloxan. ^c Calculated from the method in ref. 1.

$$^d k_t' = \frac{1}{t} \ln \left(\frac{A_0}{A_0 - x_{\text{obs}}} \right)$$

^e $k_t = \frac{1}{(t_i - t_0)} \ln \left(\frac{B_0}{(B_0 - (X_t - X_0))} \right)$ with $10^4 B_0 = 24.01\text{M}$, $t_0 = 255$ min, and $10^4 x_0 = 15.96\text{M}$.

The kinetics of alkaline hydrolysis of alloxan was studied at different temperatures with sodium hydroxide in the concentration range 0.02 – 3.0M . The ionic strength was kept constant by potassium chloride. The plots of $k_{1\text{obs}}$ and $k_{2\text{obs}}$ against hydroxide ion concentrations are shown in Figure 1. There are three noteworthy features of these plots: first, in the lower concentration range of sodium hydroxide, there is an increase in $k_{1\text{obs}}$ and $k_{2\text{obs}}$ with increase in hydroxide ion concentration. This variation

was found to be well-fitted by the empirical equations (5) and (6), and is also shown graphically in Figure 2. The

$$\frac{1}{k_{1\text{obs}}} = B_1 + \frac{B_2}{[\text{OH}^-]} \quad (5)$$

$$\frac{1}{k_{2\text{obs}}} = C_1 + \frac{C_2}{[\text{OH}^-]} \quad (6)$$

linear unknown parameters B_1 , B_2 , C_1 , and C_2 were evaluated using the least-squares technique and the results are summarized in Tables 2 and 3, respectively. Secondly, at

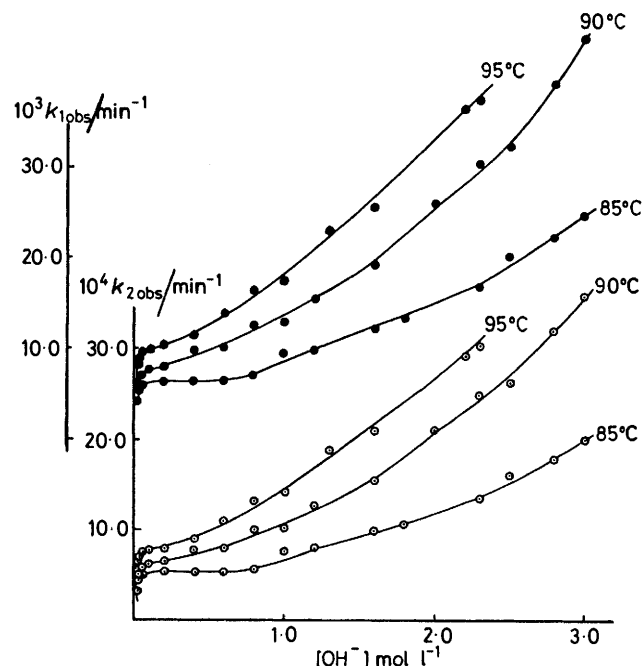


FIGURE 1 Sodium hydroxide ion concentration dependence of $k_{1\text{obs}}$ and $k_{2\text{obs}}$ at $\mu = 3.0\text{M}$: \bullet , $k_{1\text{obs}}$; \circ , $k_{2\text{obs}}$.

relatively higher concentrations the values of $k_{1\text{obs}}$ and $k_{2\text{obs}}$ are independent of the concentration of hydroxide ion. Thirdly, a further increase in concentration results in the corresponding increase in $k_{1\text{obs}}$ and $k_{2\text{obs}}$. The variation of $k_{1\text{obs}}$ and $k_{2\text{obs}}$ with hydroxide ion concentration in this region is shown graphically in Figures 3 and 4 and was found to follow the empirical equations (7) and (8). The

$$k_{1\text{obs}} = D_1 + D_2[\text{OH}^-] + D_3[\text{OH}^-]^2 \quad (7)$$

$$k_{2\text{obs}} = E_1 + E_2[\text{OH}^-] + E_3[\text{OH}^-]^2 \quad (8)$$

unknown parameters D_1 , D_2 , D_3 , E_1 , E_2 , and E_3 were evaluated using a least-square treatment and are summarized in

TABLE 2

The linear adjustable parameters to the empirical relationship $\frac{1}{k_{1\text{obs}}} = B_1 + \frac{B_2}{[\text{OH}^-]}$

t $^\circ\text{C}$	$10^{-1} B_1$ min	B_2 mol l min ⁻¹	$10^7 \Sigma d_1^2$ ^c min ⁻¹	Max. ^d dev. (%)	$10^3/B_1$ min ⁻¹	(B_1/B_2) l mol ⁻¹	$10^3 k_{1\text{obs}}$ min ⁻¹
85	13.96 ± 1.57 ^b	1.78 ± 0.49 ^b	4.52	8.30	7.16	78.50	6.38 ^{e1}
90	11.43 ± 0.38	1.46 ± 0.10	0.50	2.20	8.69	78.10	7.68 ^{e2}
95	9.82 ± 0.13	0.47 ± 0.05	0.58	-1.80	10.18	208.00	9.84 ^{e2}

^a Conditions: $40.00 \times 10^{-4}\text{M}$ -alloxan, $\mu = 3.0\text{M}$. ^b Error limits are standard deviations. ^c Sum of the squares of the difference between observed and calculated values. ^d Maximum deviation between observed and calculated values. ^{e1, e2} Observed rate constants within the $[\text{OH}^-]$ range of 0.2 – 0.6 and 0.1 – 0.2M , respectively, where the rate is independent of $[\text{OH}^-]$.

TABLE 3

The linear adjustable parameters to the empirical relationship $a \frac{1}{k_{2\text{obs}}} = C_1 + \frac{C_2}{[\text{OH}^-]}$

$t/^\circ\text{C}$	$\frac{10^2 C_1}{\text{min}}$	$\frac{C_2}{\text{mol l}^{-1} \text{min}^{-1}}$	$\frac{10^8 \Sigma d_i^{2e}}{\text{min}^{-1}}$	Max. d dev. (%)	$\frac{10^4}{C}$ min^{-1}	$\frac{C_1}{C_2}$ l mol^{-1}	$\frac{10^4 k_{2\text{obs.}}}{\text{min}^{-1}}$
85	16.98 ± 2.13^b	22.96 ± 6.72^b	3.77	8.60	5.89	74.00	5.15^{e1}
90	14.29 ± 0.41	18.30 ± 1.27	0.31	2.20	6.99	78.90	6.16^{e1}
95	12.30 ± 0.16	5.73 ± 0.55	0.35	-1.60	8.13	214.00	7.86^{e1}

^a All the symbols have their usual meanings as described in Table 2.

TABLE 4

The best fitted parameters to the empirical equation $a k_{1\text{obs.}} = D_1 + D_2[\text{OH}^-] + D_3[\text{OH}^-]^2$

$t/^\circ\text{C}$	$\frac{10^3 D_1}{\text{min}^{-1}}$	$\frac{10^3 D_2}{\text{l mol}^{-1} \text{min}^{-1}}$	$\frac{10^3 D_3}{\text{l mol}^{-2} \text{min}^{-1}}$	$\frac{10^8 \Sigma d_i^{2e}}{\text{min}^{-1}}$	Max. dev. d (%)
85	6.24 ± 3.18^b	0.68 ± 3.19^b	1.83 ± 0.75^b	1.45	4.50
90	7.85 ± 1.53	2.08 ± 1.97	3.29 ± 0.54	5.18	6.50
95	7.61 ± 3.59	9.49 ± 5.56	1.52 ± 8.47	6.98	8.30

^a All the symbols have their usual meanings as described in Table 2.

TABLE 5

The best fitted parameters to the empirical equation $a k_{2\text{obs.}} = E_1 + E_2[\text{OH}^-] + E_3[\text{OH}^-]^2$

$t/^\circ\text{C}$	$\frac{10^4 E_1}{\text{min}^{-1}}$	$\frac{10^4 E_2}{\text{l mol}^{-1} \text{min}^{-1}}$	$\frac{10^4 E_3}{\text{l mol}^{-2} \text{min}^{-1}}$	$\frac{10^8 \Sigma d_i^{2e}}{\text{min}^{-1}}$	Max. dev. d (%)
85	4.999 ± 2.34^b	0.69 ± 2.35^b	1.41 ± 0.55^b	0.78	4.20
90	6.39 ± 1.21	1.51 ± 1.56	2.74 ± 4.30	3.24	6.60
95	5.76 ± 2.84	8.38 ± 4.41	0.99 ± 1.46	4.38	8.30

^a All the symbols have their usual meanings as described in Table 2.

Tables 4 and 4. Equations (7) and (8) indicate the partitioning of a monoanionic tetrahedral intermediate into di- and tri-anionic tetrahedral intermediates and thus there is addition of two further parallel rate-determining steps along with the breakdown of monoanionic tetrahedral intermediate. The mono-, di-, and tri-anionic tetrahedral intermediates have been defined on the basis of the charges introduced in the substrate without considering the charges already present on it.

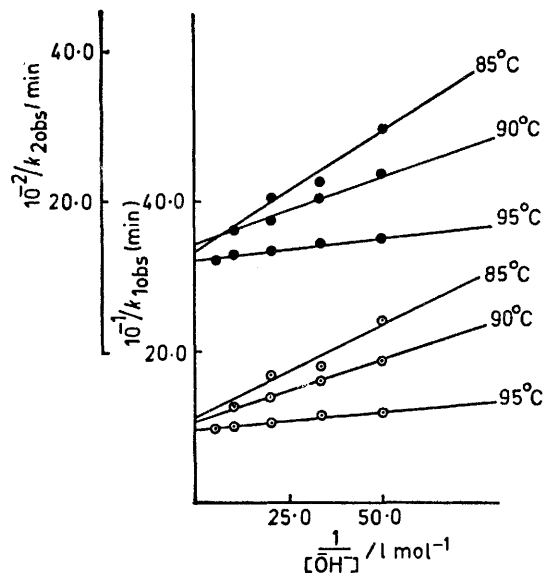


FIGURE 2 Plots of $\frac{1}{k_{1\text{obs.}}}$ and $\frac{1}{k_{2\text{obs.}}}$ vs. $\frac{1}{[\text{OH}^-]}$ respectively. Solid lines are drawn from the calculated values of rate constants from equations (4) and (5) respectively: \circ , $k_{1\text{obs.}}$; \bullet , $k_{2\text{obs.}}$.

DISCUSSION

The variation of $k_{1\text{obs.}}$ and $k_{2\text{obs.}}$ with hydroxide ion concentration indicates a multistep reaction path in

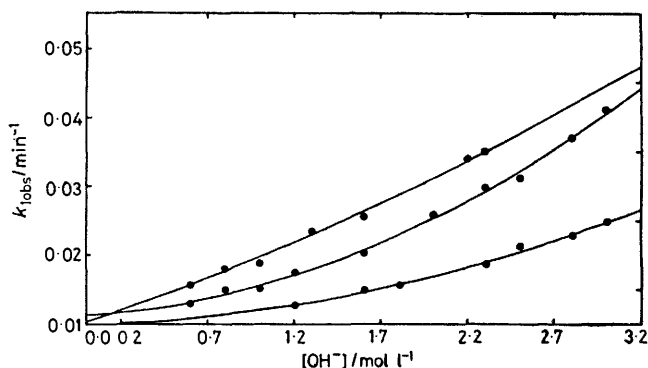


FIGURE 3 Plots showing the relationship: $k_{1\text{obs.}} = D_1 + D_2[\text{OH}^-] + D_3[\text{OH}^-]^2$ solid lines are drawn from the calculated values of rate constants

which the rate-determining steps change with change in alkali concentration. This shows that the hydrolysis of alloxan follows a stepwise mechanism. The transition from pH dependent rate to an independent one did not occur around the pH corresponding to pK_a of alloxanic acid as expected for a simple first-order dependence of rate on hydroxide ion concentration, but occurred at a much higher pH. The observed linearity of the plot of $\frac{1}{k_{1\text{obs.}}}$ vs. $\frac{1}{[\text{OH}^-]}$ (Figure 2), reveals that at the lower hydroxide ion concentrations, the breakdown of the monoanionic tetrahedral intermediate is the only rate-determining step.^{1,2,5,12-16} At relatively higher concen-

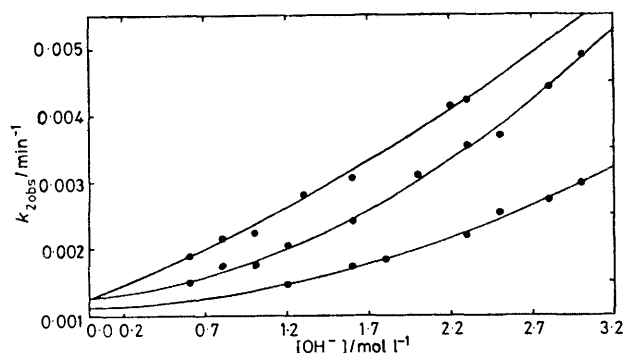
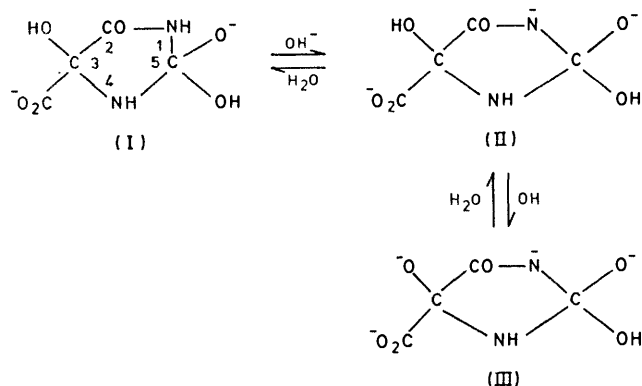


FIGURE 4 Plots showing the relationship: $k_{2\text{obs.}} = E_1 + E_2[\text{OH}^-] + E_3[\text{OH}^-]^2$ solid lines are drawn from the calculated values of rate constants

trations of hydroxide ion the rate constants are given by equations (7) and (8). These equations require that one, two, and three more negative charges must be accumulated on the reacting species to form the transition states of three parallel discrete rate-determining steps. The existence of a trianionic tetrahedral intermediate was first reported in the hydrolysis of barbituric acid⁵ along with the existence of mono- and di-anionic ones. The trianionic tetrahedral intermediate is stabilized by resonance due to the presence of an adjacent carbonyl group as shown in Scheme 2. Structure (II) should be more stable than (III) because the hydrogen atom at 1-position is more acidic than the hydrogen of the added hydroxy group, a result of the resonance-stabilizing effect of the carbonyl group.

The mechanism accounting for the observed rate-data for alkaline hydrolysis of alloxan corresponding to two consecutive steps may be represented by Schemes 3 and 4, respectively.

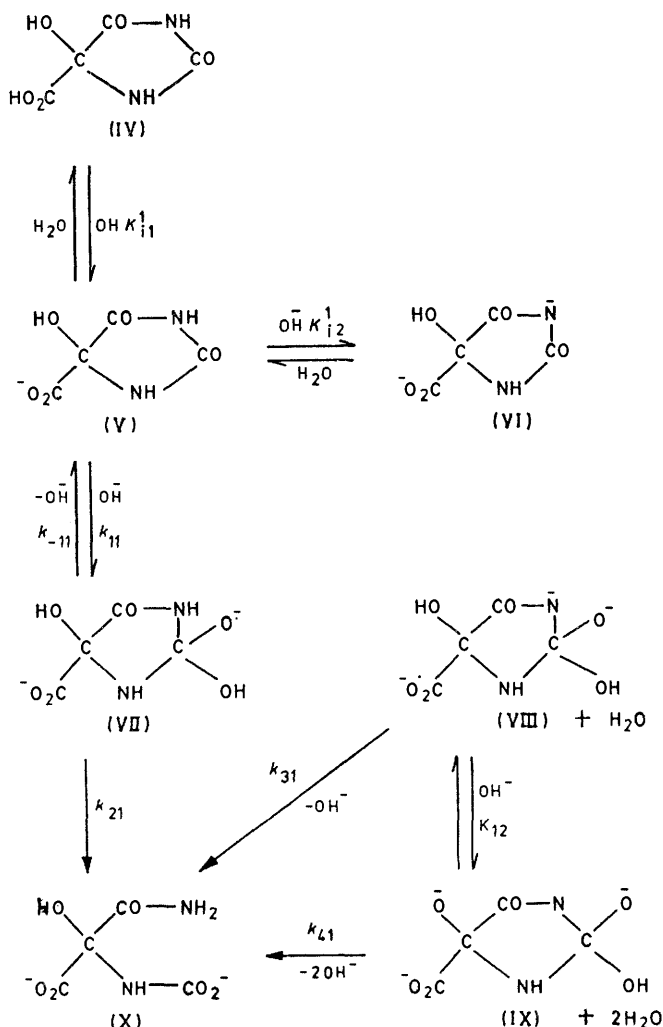
The above mechanisms include the major postulated hydrolytic step as reviewed by Bojarski.¹⁷ The previous studies on the hydrolysis of various substituted barbiturates were mainly concerned with the characterization of various intermediates formed during hydrolysis and it was concluded that the ring opening is controlled by both the pH and steric effects produced by the substituents at 5-position. Mono- and oxy-dianionic tetrahedral intermediates have been reported in the studies on the hydrolysis of dihydrouracil.¹⁸ In the present



SCHEME 2

studies the tetrahedral intermediates (VII)—(IX) and (XII)—(XIV) are found to be extremely unstable and the steady-state treatment led to the kinetic equations (9) and (10) for the first and second steps of hydrolysis, respectively. Here $K'_{i,s} = K'_{a,s}/K_w$, where $K'_{a,s}$ are the acidity constants for sth acids (IV), (V), and (X) and K_w is autoprotolytic constant of water.

In the lower region of hydroxide ion concentration the rate is only controlled by the breakdown of monoanionic tetrahedral intermediates (VII) and (XII) and therefore



SCHEME 3

it tends to assume that $k_{21} \gg k_{31}K_{11}[\text{OH}^-] + k_{41}K_{11}K_{12}^{-1}[\text{OH}^-]^2$ and $k_{22} \gg k_{32}k_{21}[\text{OH}^-] + k_{42}K_{21}K_{22}[\text{OH}^-]^2$

$$k_{1\text{obs.}} = \frac{k_{11}K_{i1}^4[\text{OH}^-]^2}{1 + K_{i2}^4[\text{OH}^-] + K_{i1}^4K_{i2}^4[\text{OH}^-]^2} \times \frac{k_{21} + k_{31}K_{11}[\text{OH}^-] + k_{41}K_{11}K_{12}[\text{OH}^-]^2}{k_{-11} + k_{21} + k_{31}K_{11}[\text{OH}^-] + k_{41}K_{11}K_{12}[\text{OH}^-]^2} \quad (9)$$

$$k_{2\text{obs.}} = \frac{k_{21}[\text{OH}^-]^2}{1 + K_{i1}^2[\text{OH}^-]} \times \frac{k_{22} + k_{32}K_{21}[\text{OH}^-] + k_{42}K_{21}K_{22}[\text{OH}^-]^2}{k_{-21} + k_{22} + k_{32}K_{21}[\text{OH}^-] + k_{42}K_{21}K_{22}[\text{OH}^-]^2} \quad (10)$$

Following these conditions and that $1 < (K_{i1}^1[\text{OH}^-] + K_{i1}^1K_{i2}^1[\text{OH}^-]^2)$ equations (9) and (10) reduce to (11) and (12), respectively.

$$k_{1\text{obs.}} = \frac{k_{11}k_{21}[\text{OH}^-]}{(1 + K_{i2}^1[\text{OH}^-])(k_{-11} + k_{21})} \quad (11)$$

$$k_{2\text{obs.}} = \frac{k_{22}k_{21}[\text{OH}^-]}{(1 + K_{i1}^2[\text{OH}^-])(k_{-21} + k_{22})} \quad (12)$$

Equations (11) and (12) are similar to those empirically best fitted equations (5) and (6) with

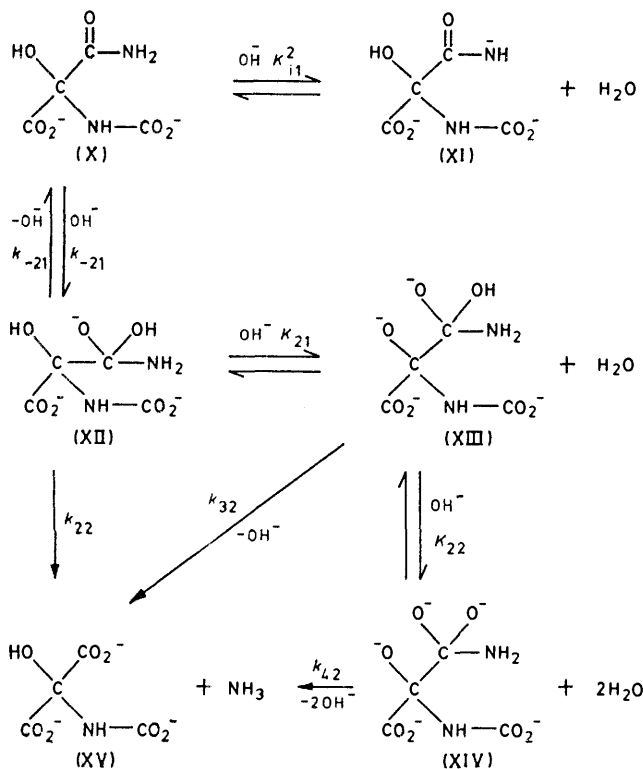
$$B_1 = \frac{(k_{-11} + k_{21})K_{i2}^1}{k_{11}k_{21}}$$

$$B_2 = \frac{k_{-11} + k_{21}}{k_{11}k_{21}}, \quad C_1 = \frac{(k_{-21} + k_{22})K_{i1}^2}{k_{22}k_{21}}$$

and

$$C_2 = \frac{(k_{-21} + k_{22})}{k_{21}k_{22}}$$

The values of B_1/B_2 and C_1/C_2 stand for $K_{i2}^1 (= K_{a2}^1/K_w)$ and $K_{i1}^2 (= K_{a1}^2/K_w)$, respectively, where K_{a2}^1 and



K_{a1}^2 represent the acidity constants for ionization of (V) and (X). These values at different temperatures are summarized in Tables 2 and 3 and are compared with those of barbituric acid.⁵ The Tables indicate that the K_{a2}^1/K_w and K_{a1}^2/K_w values for alloxanic acid are higher than those for barbituric acid. This difference is probably due to the presence of an additional electron-withdrawing carbonyl group which enhances the acidity of ionizable protons.

An independent rate of hydroxide ion is evident from rate-pH profiles (Figure 1). In this region the con-

ditions $1 < K_{i2}^1[\text{OH}^-]$ and $1 < K_{i1}^2[\text{OH}^-]$ are found to hold good and equations (11) and (12) are further reduced to equations (13) and (14). These equations

$$k_{1\text{obs.}} = \frac{k_{11}k_{21}}{K_{i2}^1(k_{-11} + k_{21})} \quad (13)$$

$$k_{2\text{obs.}} = \frac{k_{21}k_{22}}{K_{i1}^2(k_{-21} + k_{22})} \quad (14)$$

reveal kinetically the identity of the independent character of the pH-rate profiles. Equations (11)–(14) also indicate that $1/B_1$ and $1/C_1$ must be equal to $k_{1\text{obs.}}$ and $k_{2\text{obs.}}$ obtained in the region where the rate was independent of hydroxide ion concentration. Tables 2 and (3) indicate that $1/B_1$ and $1/C_1$ within their standard deviations are comparable with $k_{1\text{obs.}}$ and $k_{2\text{obs.}}$.

There is an increase in $k_{1\text{obs.}}$ and $k_{2\text{obs.}}$ with a further increase in hydroxide ion concentration (Figure 1) which requires that conditions $k_{21} \gg (k_{31}K_{i1}[\text{OH}^-] + k_{41}K_{i1}K_{i2}[\text{OH}^-]^2)$ and $k_{22} \gg (k_{32}k_{21}[\text{OH}^-] + k_{42}K_{i2}[\text{OH}^-]^2)$ no longer exist but still $(k_{21} + k_{-11}) > (k_{31}K_{i1}[\text{OH}^-] + k_{41}K_{i1}K_{i2}[\text{OH}^-]^2)$ and $(k_{22} + k_{-21}) > (k_{32}K_{i2}[\text{OH}^-] + k_{42}K_{i2}[\text{OH}^-]^2)$ hold good. Such assumptions are fairly valid on the basis of previous studies^{2,5,18,19} on the hydrolysis of acyl-transfer reactions where the existence of oxydianionic tetrahedral intermediates are kinetically established. Thus these conditions simplify equations (9) and (10) to (15) and (16). These equations are

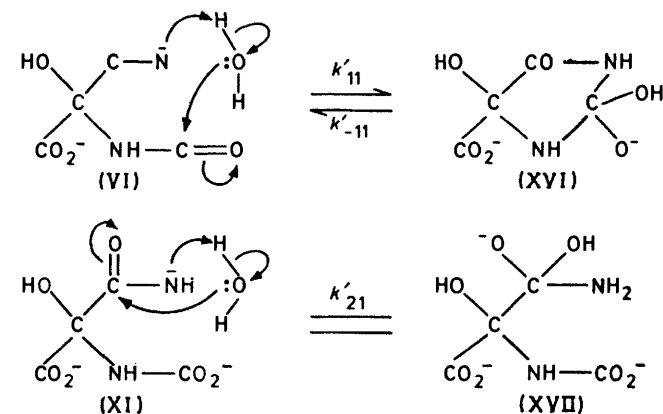
$$k_{1\text{obs.}} = \frac{k_{11}}{K_{i2}^1(k_{-11} + k_{21})} (k_{21} + k_{31}K_{i1}[\text{OH}^-] + k_{41}K_{i1}K_{i2}[\text{OH}^-]^2) \quad (15)$$

and

$$k_{2\text{obs.}} = \frac{k_{21}}{K_{i2}^2(k_{-21} + k_{22})} (k_{22} + k_{32}K_{i2}[\text{OH}^-] + k_{42}k_{21}K_{i2}[\text{OH}^-]^2) \quad (16)$$

similar to the empirically well-fitted equation (7) and (8) with $D_1 = k_{11}k_{21}/\alpha$, $D_2 = k_{11}k_{31}K_{i1}/\alpha$, $D_3 = k_{11}k_{41}K_{i1}K_{i2}/\alpha$ and $E_1 = k_{22}k_{21}/\beta$, $E_2 = k_{21}k_{32}K_{i2}/\beta$, $E_3 = K_{i2}^2K_{i2}/\beta$ where $\alpha = K_{i2}^1(k_{-11} + k_{21})$ and $\beta = K_{i1}^2(k_{-21} + k_{22})$.

Though the mechanisms given in Schemes 3 and 4 are sufficient to account completely for the observed rate data, the following indistinguishable kinetic steps cannot be completely ruled out. Intermediates



(XVI) and (XVII) are the same as (VII) and (XII), respectively. Thus the kinetic equations derived including these additional steps will have the same dependence on hydroxide ion concentrations as shown throughout equations (9)—(16).

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