Kinetics and Mechanism of Base Catalysed Hydrolysis of Barbituric Acid

By **M. Niyaz Khan** and **A. Aziz Khan,*** Department of Chemistry, Aligarh Muslim University, Aligarh 202001, U.P., India

A kinetic study of base catalysed hydrolysis of barbituric acid by 0.02—3.00M-sodium hydroxide solution at different temperatures was found to follow the irreversible first-order consecutive reaction path (i).

$$\text{Barbituric acid} \xrightarrow{k_{1,\text{obs}}} \text{Malonuric acid} \xrightarrow{k_{2,\text{obs}}} \text{Ammonia} \quad \text{(i)}$$

The observed pseudo-first-order rate constants, $k_{1,\text{obs}}$ and $k_{2,\text{obs}}$, showed three regions of hydroxide ion dependence. (a) The reciprocal of the rate constants was linearly dependent on the reciprocal of hydroxide ion concentration at low concentration. (b) At relatively higher concentration of hydroxide ion the rate constants were found to be independent of the concentration of hydroxide ion. (c) At high concentration of hydroxide ion the rate constants were found to follow the general relationship (ii).

$$k_{\text{obs}} = a + b[\text{OH}^-] + c[\text{OH}^-]^2 \quad \text{(ii)}$$

The empirical parameters *a*—*c* were evaluated using a least-squares technique. A trianionic tetrahedral intermediate is proposed to account for the second power of hydroxide ion in the relationship.

THE alkaline hydrolysis of substituted barbituric acids has been studied by Eriksson [1,2] and his co-workers with the aim of establishing the influence of substituents at the 5 position on rate constants and activation parameters. These workers [3,4] extended their studies and concluded that the mechanism of ring opening was similar to that of anilides.[5-9] Bojarski [10] reviewed the studies concerned with characterization of the products of barbituric acid and its derivatives. The neutral and alkaline hydrolysis of barbituric acid and its derivatives was studied by Garrett *et al.*[11] up to the stage of ring opening using a spectrophotometric method. The hydrolysis of *NN*-dimethyl-barbital [12] and -thiobarbital [13] was studied recently by Bojarski up to the ring-opening stage and a possible mechanism for this step was suggested. The reasons for the limitation of these studies to the ring-opening stage are the hydrolytic stability of the intermediates and the difficulty of solving the kinetic equations from two or more consecutive rate-determining steps. The studies reported here are mainly concerned with the determination of the consecutive rate constants for the hydrolysis of barbituric acid up to the stage of evolution of ammonia. A possible mechanism is proposed.

EXPERIMENTAL

Barbituric acid (B.D.H.) was used as received and the other materials employed were of analytical reagent grade. Nessler's reagent was prepared by the method described by Vogel.[14]

Kinetic Measurements.—The requisite volumes of solutions of all the reactants except sodium hydroxide were placed in a two-necked reaction vessel fitted with a double surface condenser to prevent evaporation. The mixture was thermostatted in an oil-bath to ±0.1 °C. The reaction was then started by adding the requisite volume of sodium hydroxide solution and zero time was taken when half the base solution had been added. The ionic strength was maintained with sodium nitrate. The ammonia evolved was swept out by a constant current of nitrogen gas and was absorbed in hydrochloric acid [15-17] at intervals. The concentration of absorbed ammonia was determined spectrophotometrically by Nesslerization.[18-23] Spectrophotometric measurements were taken with a Bausch and Lomb spectronic-20 instrument.

RESULTS

In the alkaline hydrolysis of barbituric acid, the kinetic data were found to fit equation (1) which can be derived by an irreversible first-order consecutive reaction scheme of

$$[\text{X}] = [\text{A}]_0\left[1 + \frac{1}{(k_{1,\text{obs}} - k_{2,\text{obs}})}(k_{2,\text{obs}}\,\text{e}^{-k_{1,\text{obs}}t} - k_{2,\text{obs}}\,\text{e}^{-k_{1,\text{obs}}t})\right] \quad (1)$$

type (2) where A, B, and X represent barbituric acid,

$$\text{A} \xrightarrow{k_{1,\text{obs}}} \text{B} \xrightarrow{k_{2,\text{obs}}} \text{X} \qquad (2)$$

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malonuric acid,[11] and ammonia, respectively. $[A]_0$ is the initial concentration of barbituric acid and $k_{1,obs}$ and $k_{2,obs}$ are the observed pseudo-first-order rate constants.

Mathematically it is not possible to differentiate between $k_{1,obs}$ and $k_{2,obs}$ but it has been shown qualitatively that $k_{1,obs}$ is greater than $k_{2,obs}$ for the following reasons. (a) It is a known fact [24] that an imide bond is more easily hydrolysed than amide and since the production of ammonia in the second step of hydrolysis is due to amide bond cleavage, therefore $k_{1,obs}$ should be greater than $k_{2,obs}$. (b) It has been found that the ratio $k_{2,obs} : k_{1,obs}$ falls within 0.20—0.15 for many sets of observations. Hence in the final stage of the reaction where the concentration of barbituric acid is no more than 1% of the original, the first step of reaction (2) may be neglected by comparison with the second. Thus $k_{2,obs}$ must be very close to k_f, the pseudo-first-order rate constant obtained from the one-step irreversible first-order rate equation (3). Here $[B]_0$ and $[X]_0$ are the concentration

$$k_f = \frac{1}{(t - t_0)} \ln \frac{[B]_0}{[B]_0 - ([X]_t - [X]_0)} \qquad (3)$$

of intermediate product and ammonia, respectively, at time t_0 when the concentration of barbituric acid has become negligible. $[X]_t$ is the concentration of ammonia at any time t. The values of $k_{2,obs}$ and k_f as evaluated by equations (1) and (3) for a kinetic run are summarized in Table 1 which indicates good agreement between $k_{2,obs}$ and k_f.

TABLE 1

Comparison of rate constants evaluated for a kinetic run [a]

$$\frac{k_{2,obs}}{k_{1,obs}} = 0.15$$

t/min	$10^4[X]_{obs}$[b]/M	$10^4[X]_{calc}$/M	$10^4[A]^{c}_{calc}$/M	$10^4k_{2,obs}$[d]/min^{-1}	$10^4k_f'$[e]/min^{-1}	10^4k_f[f]/min^{-1}
125	4.10	4.10	7.32	18.31	8.65	
210	10.06	10.06	2.30	20.95	13.79	
255	12.59	12.59	1.25	20.92	14.82	
315	16.02	16.02	0.55	21.30	16.24	
360	17.89	17.89	0.30	20.93	16.47	18.48
412	19.76	19.76	0.15	20.45	16.53	17.93
465	21.94	21.94	0.07	20.59	17.10	19.42
525	23.72	23.72	0.03	20.22	17.12	18.97
600	25.90	25.90	0.01	20.09	17.38	19.22

[a] 0.004M-Barbituric acid; 2.8M-NaOH; ionic strength 3.0; 95 °C. [b] Calculated using equation (1) with $k_{1,obs}$ and $k_{2,obs}$ obtained from the method described in the text. [c] $[A]_{calc} = [A]_0e^{-k_{1,obs}t}$. [d] Calculated from the method described in the text. [e] $k_f' = t^{-1} \ln [A]_0/([A]_0-[X]_{obs})$. [f] $k_f = (t - t_a)^{-1} \ln [B]_0/\{[B]_0 - ([X]_t - [X]_0)\}$ with $[B]_0 = 23.43 \times 10^{-4}$M, $t_0 = 315$ min, and $[X]_0 = 16.02 \times 10^{-4}$ M.

Equation (1) reduces to (4) on substitution of ρ for $k_{2,obs}/k_{1,obs}$. Equation (4) has been solved for $k_{1,obs}$ by introducing various trial values of ρ using the Newton–Raphson method.[25] The best possible value of ρ was

$$[X] = [A]_0\left[1 + \frac{1}{1 - \rho}(\rho e^{-k_{1,obs}t} - e—\rho k_{1,obs}t)\right] \qquad (4)$$

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 FORTRAN IV program for an I.B.M. 1130 computer. The value of $k_{2,obs}$ was obtained from the values of ρ and $k_{1,obs}$.

A series of kinetic runs was carried out at different temperatures with hydroxide ion concentration ranging from 0.02 to 3.0M. The ionic strength was kept constant at 3.0M with sodium nitrate. The results of plotting the observed pseudo-first-order rate constants against hydroxide ion concentration for both consecutive steps are shown in Figure 1. From these results it has been found that in the lower concentration range of hydroxide ion $k_{1,obs}$ and $k_{2,obs}$ vary according to the equations (5) and (6). These results are

$$1/k_{1,obs} = B_1 + B_2[OH^-]^{-1} \qquad (5)$$

$$1/k_{2,obs} = C_1 + C_2[OH^-]^{-1} \qquad (6)$$

shown graphically in Figure 2. The linear unknown parameters B_1, B_2, C_1, and C_2 were determined using least-squares technique. The results are summarised in Table 2.

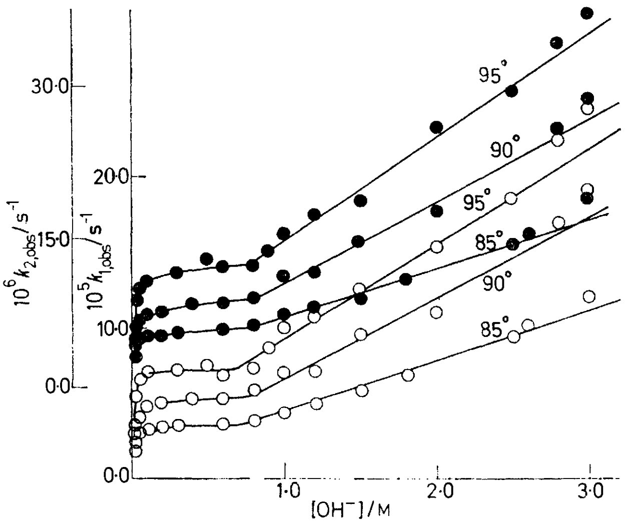

FIGURE 1 Variation of $k_{1,obs}$ (○) and $k_{2,obs}$ (●) with hydroxide ion

In the concentration range *ca.* 0.2—*ca.* 0.8M the values of $k_{1,obs}$ and $k_{2,obs}$, as shown in Figure 1, are found to be independent of hydroxide ion concentrations while at higher concentration $k_{1,obs}$ and $k_{2,obs}$ begin to increase. This vari-

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TABLE 2

Linear constants corresponding to equations (5) and (6) [a]

T/°C	$10^{-3}B_1$/s	$10^{-2}B_2$/mol s l^{-1}	Max [b] dev. (%)	$10^{-4}C_1$/s	$10^{-3}C_2$/mol s l^{-1}	Max [b] dev. (%)
85	25.1 ± 1.9 [c]	5.2 ± 0.7 [c]	8.4	16.5 ± 1.3 [c]	2.6 ± 0.5 [c]	9.4
90	17.3 ± 1.0	3.9 ± 0.3	−2.9	11.5 ± 0.5	2.0 ± 0.2	2.2
95	8.4 ± 3.1	3.9 ± 1.0	−15.5	7.0 ± 1.3	1.8 ± 0.4	10.1

[a] 0.004M-Barbituric acid; ionic strength 3.0. [b] Maximum deviation between observed and calculated values. [c] Error limits are standard deviations.

ation as shown by Figure 3 was found to follow the empirical equations (7) and (8). The unknown parameters D_1—D_3

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

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

and E_1—E_3 were evaluated using a least-squares method and the results are summarized in Tables 3 and 4, respectively.

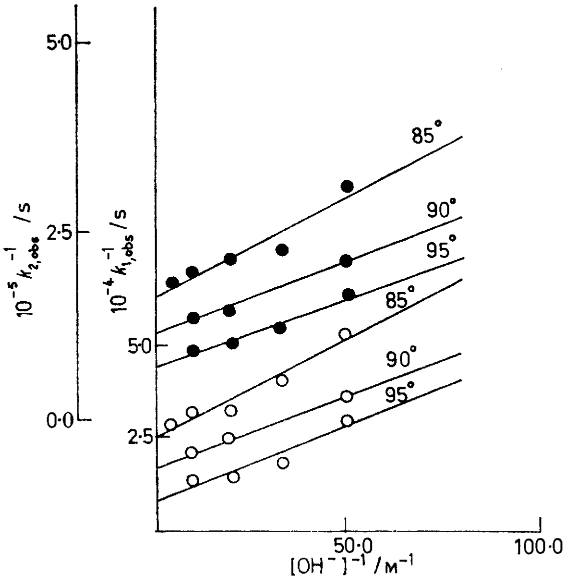


FIGURE 2 Variation of $k^{-1}_{1,\mathrm{obs}}$ (○) and $k^{-1}_{2,\mathrm{obs}}$ (●) with $[\mathrm{OH^-}]^{-1}$ solid lines are drawn from the values of pseudo-first-order rate constants calculated from equations (5) and (6)

TABLE 3

Empirical constants corresponding to equation (7) [a]

T/°C	10^6D_1/s^{-1}	10^6D_2/ l mol^{-1} s^{-1}	10^6D_3/ l^2 mol^{-2} s^{-1}	Max [b] dev. (%)
85	22.2 ± 1.2 [c]	16.8 ± 1.4 [c]	5.1 ± 0.4 [c]	1.3
90	48.2 ± 15.5	6.0 ± 18.8	13.5 ± 4.8	8.3
95	51.6 ± 17.4	28.1 ± 1.8	11.9 ± 5.8	−13.3

[a–c] As Table 2.

TABLE 4

Empirical constants corresponding to equation (8) [a]

T/°C	10^7E_1/s^{-1}	10^7E_2/ l mol^{-1} s^{-1}	10^7E_3/ l^2 mol^{-2} s^{-1}	Max [b] dev. (%)
85	53.9 ± 7.7 [c]	2.1 ± 9.3 [c]	14.2 ± 2.4 [c]	3.1
90	63.5 ± 17.4	25.6 ± 21.1	15.8 ± 5.4	5.6
95	58.5 ± 21.0	80.3 ± 26.2	7.4 ± 6.9	−5.7

[a–c] As Table 2.

The effect of temperature on hydrolysis was studied over the range 75—95°. The observed results are shown graphically in Figure 4. The various activation parameters were determined by using the Arrhenius and Eyring equations with a linear least-squares treatment. These results are summarized in Table 5. The reproducibility of the observed rate constants is evident from the root-mean-square deviations and maximum deviations between observed and calculated values as recorded in Table 5.

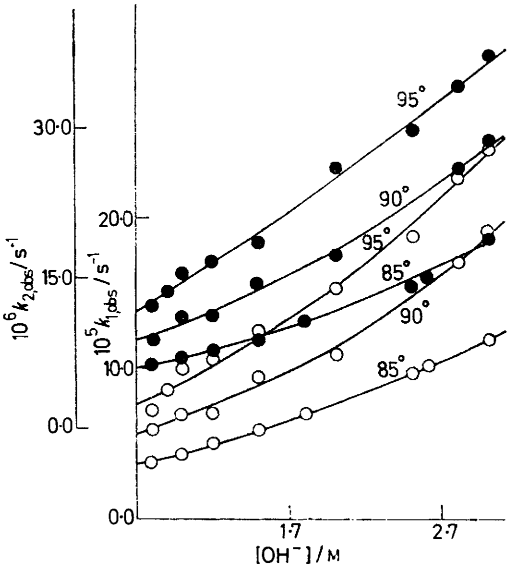


FIGURE 3 Variation of $k_{1,\mathrm{obs}}$ (○) and $k_{2,\mathrm{obs}}$ (●) with $[\mathrm{OH^-}]$. Solid lines are drawn from the values of pseudo-first-order rate constants calculated from equations (7) and (8)

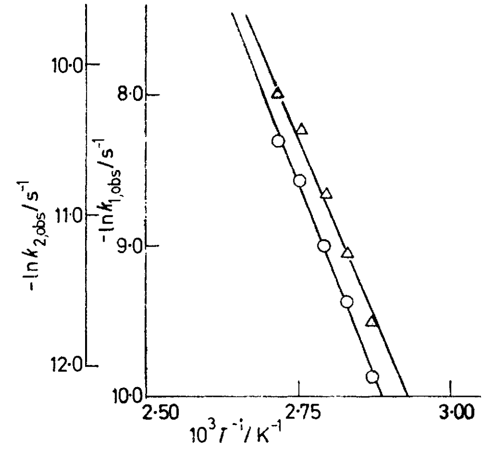


FIGURE 4 Effect of temperature on pseudo first-order rate constants for hydrolysis of barbituric acid: ○, $k_{1,\mathrm{obs}}$; △, $k_{2,\mathrm{obs}}$

DISCUSSION

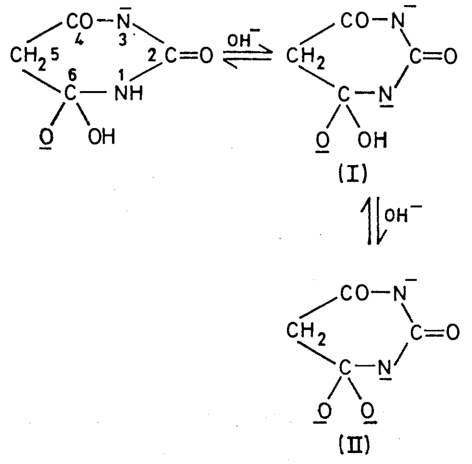
The rate profile shown in Figure 1 cannot be explained by the dissociation of protons at the 1- and 3-positions in the pyrimidine ring, and indicates a multistep reaction path in which the rate-determining steps change with hydroxide ion concentration. Similar results had been recently observed by Sander[26] in the hydrolysis of dihydropyrimidines under strongly alkaline medium. In an extensive study of hydrolysis of anilides[27-29] the usual change from second- to first-order kinetics has been explained by the formation of a tetrahedral addition intermediate between a nucleophilic reagent and an acyl compound which then reacts further to expel the leaving group with formation of products.

TABLE 5

Activation parameters[a]

Reaction step	ΔH^*/kcal mol^{-1}	$-\Delta S^*$/cal K^{-1} mol^{-1}	E_a/kcal mol^{-1}	ln (A/s^{-1})	10^4R_{ms}[b]	Max[c] dev. (%)
$A \xrightarrow{k_{1,obs}} B$	19.4 ± 0.5[d] 21.0[e]	22.7 ± 1.3[d] 17.3[e]	20.1 ± 0.5[d]	19.2 ± 1.3[d] 20.9[e]	5.576	6.3
$B \xrightarrow{k_{2,obs}} X$	18.8 ± 0.5	28.2 ± 1.3	19.5 ± 0.5	16.4 ± 1.3	0.811	−6.0

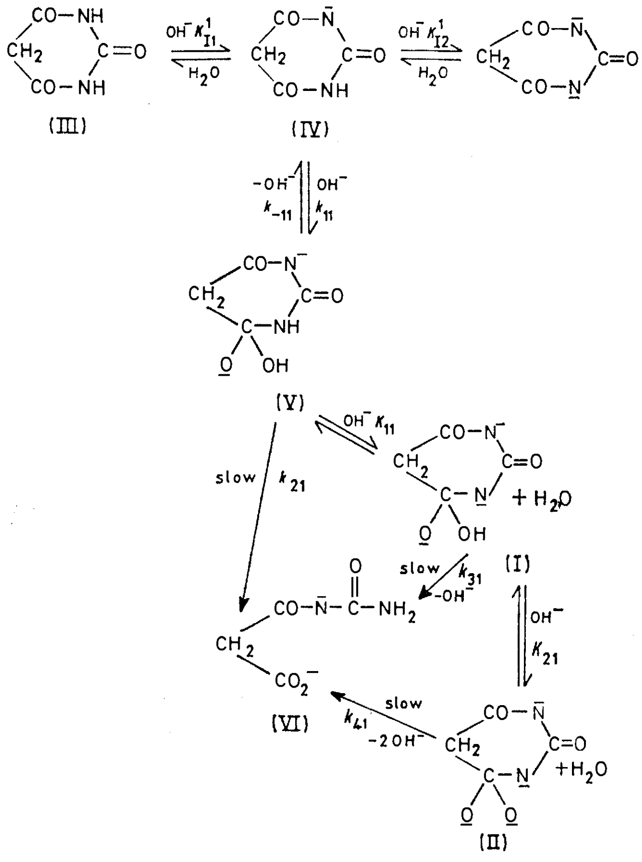
[a] 0.004M-Barbituric acid; 3.0M-NaOH. [b] Root mean square deviation between observed and calculated values of rate constant. [c] Maximum deviation between observed and calculated values of rate constants. [d] Error limits are standard deviations. [e] Ref. 11, conditions: 0.4M-NaOH.



(I)

(II)

The transition from a pH dependent rate to an independent one does not, however, occur around a pH corresponding to the pK_a of barbituric acid as expected from a simple first-order dependence of rate on hydroxide ion concentration, but occurs at a much higher pH. The observed results show that at low hydroxide ion concentration the decomposition of tetrahedral addition intermediate is rate determining whereas at higher concentration the rate becomes linearly dependent on the second and third powers in addition to the first power of the concentration of hydroxide ion. This is reasonable because previous studies[30-32] indicate that the existence or non-existence of an additional dianionic tetrahedral addition intermediate along with the monoanionic intermediate in the rate-determining steps depends upon the strength of hydroxide ion concentration and the nature of the substrate. The requirement of two and three hydroxide ions demands that a total of two and three negative charges be accumulated in the transition state. Apparently this is the first report for imide hydrolysis in which the rate is found to be a function of first, second, and third powers of hydroxide ion. The existence of a trianionic species in imide hydrolysis is not surprising because of the resonance stabilization due to presence of



SCHEME 1

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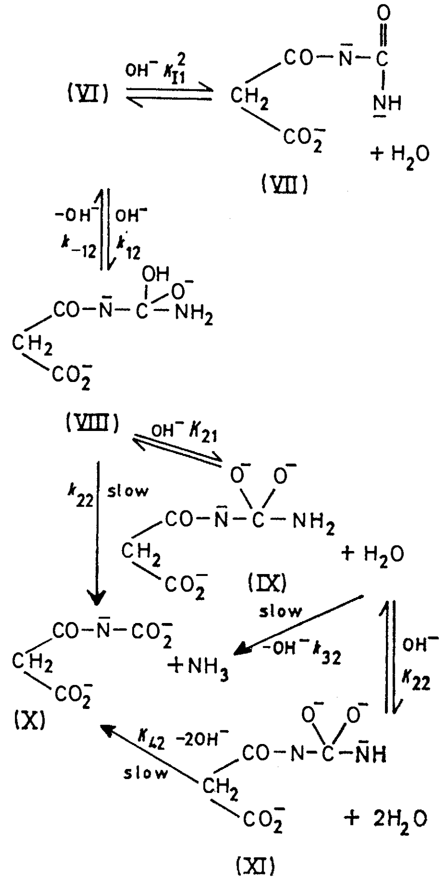
[32] A. Bruylants and F. Kezdy, *Rec. Chem. Progr.*, 1960, **21**, 213.

the adjacent carbonyl group as shown for the case of the tetrahedral intermediate of monoanionic barbituric acid.

Structure (I) is preferred over (II) because the hydrogen atom at the 1-position is more acidic than the hydrogen of the added hydroxy-group due to resonance stabilization.

The simplest mechanism which accounts for the rate data for alkaline hydrolysis of barbituric acid for both consecutive steps of reaction (2) is given by Schemes 1 and 2.

Ring opening at the 1,6- or the 3,4-positions of the pyrimidine ring produces malonuric acid (Scheme 1) was reported by Garrett *et al.*[11] These workers studied[1] the first step of the hydrolysis of barbituric acid in the alkali concentration range 0.01—0.4M and could not detect kinetically the existence of di- and tri-anionic tetrahedral addition intermediates because their concentration range was low.



SCHEME 2

Since our experiments were done at a higher pH than the pK_{a2} of barbituric acid, the equilibrium concentration of undissociated barbituric acid is negligible by comparison with those of mono- and di-anionic barbituric acids. Thus in Scheme 1 the assumption that the concentration of tetrahedral addition intermediate (V) is in the steady state leads to equation (9) for the first stage of

$$k_{1,\mathrm{obs}} = \frac{k_{11}K^1_{i1}[OH^-]^2}{1 + K^1_{i1}[OH^-] + K^1_{i1}K^1_{i2}[OH^-]^2} \; \frac{k_{21} + k_{31}K_{11}[OH^-] + k_{41}K_{11}K_{21}[OH^-]^2}{k_{-11} + k_{21} + k_{31}k_{11}[OH^-] + k_{41}K_{11}K_{21}[OH^-]^2} \qquad (9)$$

the reaction. Similarly Scheme 2 leads to equation (10) for the second step of the reaction.

$$k_{2,\mathrm{obs}} = \frac{k_{12}[OH^-]}{1 + K^2_{i1}[OH^-]} \; \frac{k_{22} + k_{32}K_{12}[OH^-] + k_{42}K_{12}K_{22}[OH^-]^2}{k_{-12} + k_{22} + K_{12}[OH^-] + k_{42}K_{12}K_{22}[OH^-]^2} \qquad (10)$$

Here $K_i(K_I/[H_2O])$ is the ionization constant of acid (III) and (VII) in Schemes 1 and 2, respectively, and is equal to K_a/K_w where K_a is the acidity constant of the acid.

At low hydroxide ion concentration the breakdown of the tetrahedral addition intermediate to the product through di- and tri-anionic species is negligible by comparison with its direct conversion to the product, *i.e.* $(k_{31}K_{11}[OH^-] + k_{41}K_{11}K_{21}[OH^-]^2) \ll k_2$ and $(k_{-11} + k_{21})$. Also since $1 \ll (K^1_{i1}[OH^-] + K^1_{i1}K^1_{i2}[OH^-]^2)$, equation (9) reduces to (11). Similarly equation (10) reduces to

$$k_{1,\mathrm{obs}} = \frac{k_{11}k_{21}[OH^-]}{(1 + K^1_{i2}[OH^-])(k_{-11} + k_{21})} \qquad (11)$$

(12). Equations (11) and (12) are similar to (5) and (6)

$$k_{2,\mathrm{obs}} = \frac{k_{12}k_{22}[OH^-]}{(1 + K^2_{i1}[OH^-])(k_{-12} + k_{22})} \qquad (12)$$

with $B_1 = K^1_{i2}(k_{-11} + k_{21})/k_{11}k_{21}$, $B_2 = (k_{-11} + k_{21})/k_{11}k_{21}$, $C_1 = K^2_{i1}(k_{-12} + k_{22})/k_{12}k_{22}$, and $C_2 = (k_{-12} + k_{22})/k_{12}k_{22}$.

At relatively higher hydroxide ion concentration the conditions $1 \ll K^1_{i2}[OH^-]$ and $K^2_{i1}[OH^-]$ become more probable and thus the rate becomes independent of alkali concentration. Under these conditions equations (11) and (12) reduce to (13) and (14). A closely related

$$k_{1,\mathrm{obs}} = \frac{k_{11}k_{21}}{K^1_{i2}(k_{-11} + k_{21})} \qquad (13)$$

$$k_{2,\mathrm{obs}} = \frac{k_{12}k_{22}}{K^2_{i1}(k_{-12} + k_{22})} \qquad (14)$$

conclusion has been reached by Mader,[8] Sander,[26] and Menger[33] for the alkaline hydrolysis of trifluoroacetanilide, dihydropyrimidines, and *N*-acylpyrroles, respectively.

Beyond 0.8M-hydroxide ion the condition $(k_{31}k_{11}[OH^-] + k_{41}K_{11}K_{21}[OH^-]^2) \ll k_{21}$ no longer exists but still $(k_{31}K_{11}[OH^-] + k_{41}K_{11}K_{21}[OH^-]^2) \ll (k_{-11} + k_{21})$. This condition is reasonable because in previous studies[30-32] the breakdown of the tetrahedral intermediate *via* a dianionic intermediate was observed only in strongly alkaline solution. Applying these conditions, equation

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[33] F. M. Menger, *J. Amer. Chem. Soc.*, 1973, **95**, 432

(9) reduces to (15) and similarly equation (10) reduces to

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

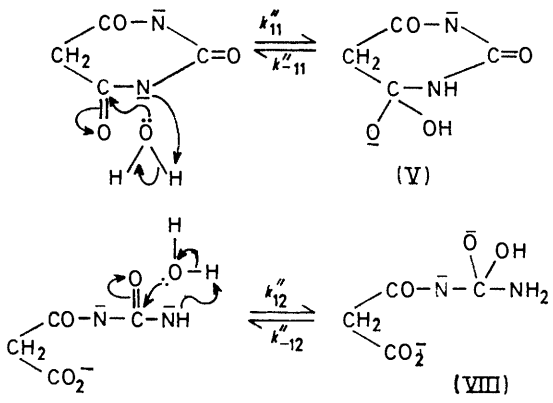
(16). Equations (15) and (16) are similar to the empirical

$$k_{2,\mathrm{obs}} = \frac{k_{12}}{K_{i1}^{2}(k_{-12} + k_{22})}(k_{22} + k_{32}K_{12}[\mathrm{OH}^-] + k_{42}K_{12}K_{22}[\mathrm{OH}^-]^2) \quad (16)$$

equations (7) and (8) with $D_1 = k_{11}k_{21}/K_{i2}^{1}(k_{-11} + k_{21})$, $D_2 = k_{11}k_{31}K_{11}/K_{i2}^{1}(k_{-11} + k_{21})$, $D_3 = k_{11}k_{41}K_{11}K_{21}/K_{i2}^{1}(k_{-11} + k_{21})$, $E_1 = k_{12}k_{22}/K_{i1}^{2}(k_{-12} + k_{22})$, $E_2 = k_{12}k_{32}K_{12}/K_{i1}^{2}(k_{-12} + k_{22})$, and $E_3 = k_{12}K_{42}K_{12}K_{22}/K_{i1}^{2}(k_{-12} + k_{22})$.

Although Schemes 1 and 2 are sufficient to account for the rate data, the additional kinetically indistinguishable paths in Scheme 3 cannot be completely excluded in strongly alkaline medium. The kinetic equations derived by including the additional steps in Scheme 3 will have the same dependence of [OH⁻] as equations (7) and (8).

The activation parameters for the first step of hydrolysis (Table 5) indicate close agreement with the results of Garrett *et al.*[11] A slight difference in the values of these parameters may be attributed to the difference in hydroxide ion concentrations as is evident from the results of Garrett *et al.* which show a decrease in the values of enthalpy and entropy of activation with the increase in hydroxide ion concentrations.



SCHEME 3

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