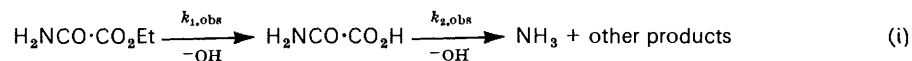# Kinetics and Mechanism of the Alkaline Hydrolysis of Ethyl Oxamate

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The kinetics of hydrolysis of ethyl oxamate in alkaline medium (0.02—1.0M-NaOH solution) were found to follow an irreversible first-order consecutive path of the type (i). Both the kinetic steps involve oxy-mono- and -di-

$$H_2NCO \cdot CO_2Et \xrightarrow[-OH]{k_{1,obs}} H_2NCO \cdot CO_2H \xrightarrow[-OH]{k_{2,obs}} NH_3 + \text{other products} \qquad (i)$$

anionic tetrahedral intermediates which control the rate-determining step in the complete hydrolytic process. The rate profiles for both steps are similar at low hydroxide ion concentrations and differ at higher concentrations. A possible mechanism and many kinetically indistinguishable elementary steps are suggested. The temperature dependence of hydrolysis was studied and activation parameters evaluated.

THE consecutive nature of the hydrolysis of oxamide has been demonstrated by Bruylants et al.[1] who pointed out that oxamic acid was one of the stable intermediates

in this case. In continuation of our work on the hydrolysis of amides and related compounds, a study of alkaline hydrolysis of ethyl oxamate was carried out with the following aims: (i) to establish whether the complete hydrolysis of ethyl oxamate follows an irreversible first-

[1] Vigernon-Voortman, P. Crooy, and A. Bruylants, *Bull. Soc. chim. belges*, 1964, **73**, 753.

order consecutive path and (ii) to examine the effect of alkalinity on the existence of oxydianionic tetrahedral intermediates in both consecutive steps.

EXPERIMENTAL

Ethyl oxamate (Merck) was used without further purification. Nessler's reagent was prepared as described by Vogel.[2] Other common reagents used were of reagent grade. The kinetic procedure was described previously.[3]

RESULTS

In the alkaline hydrolysis of ethyl oxamate, it was observed that the rate of production of ammonia increases initially and reaches a maximum and then decreases continuously towards the end of the reaction (Figure 1). This
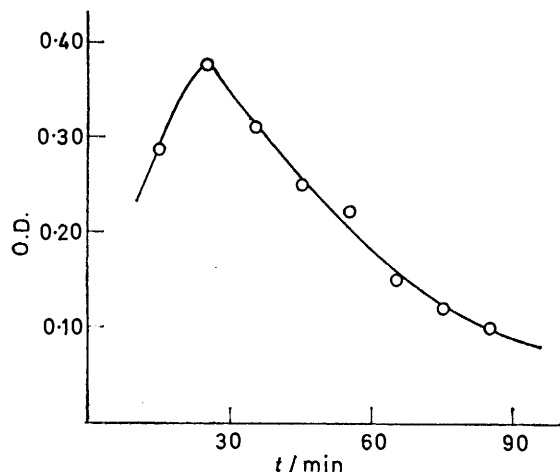
FIGURE 1 Plot of optical density *versus* time for alkaline hydrolysis of ethyl oxamate

indicates that the hydrolysis involves the formation of a stable intermediate which is further hydrolysed to yield ammonia. The stoicheiometry of the reaction in the presence of an excess of alkali may be represented by (1).

The concentration of ammonia (X) as a function of time

(1)
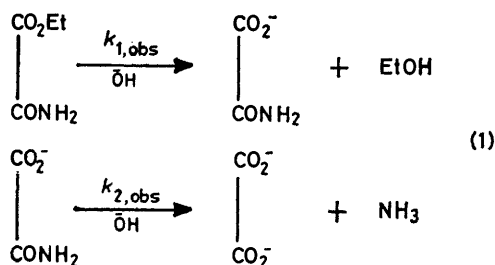
(t) and the pseudo-first-order rate constants $k_{1,obs}$ and $k_{2,obs}$ are given by equation (2) where A_0 stands for the

$$X_{obs} = A_0 \left[1 + \frac{1}{(k_{1,obs} - k_{2,obs})} \right.$$

$$\left. (k_{2,obs}e^{-k_{1,obs}t} - k_{1,obs}e^{-k_{2,obs}t}) \right] \quad (2)$$

initial concentration of ethyl oxamate. The procedure for the evaluation of the rate constants has been described

[2] A. I. Vogel, 'A Text Book of Quantitative Inorganic Analysis,' Longman Green, London, 1955, p. 643.
[3] M. N. Khan and A. A. Khan, *J.C.S. Perkin II*, 1976, 1009.

elsewhere.[3] In these investigations $k_{1,obs} > k_{2,obs}$ which is justified on the basis that the hydrolysis of ester is faster
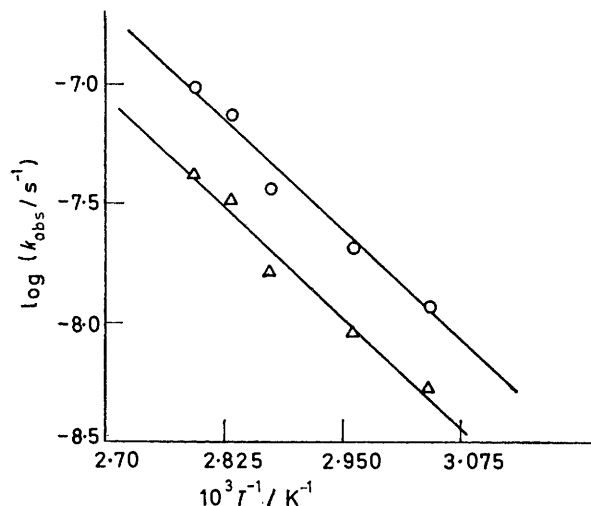
FIGURE 2 Temperature dependence of hydrolysis of ethyl oxamate. Solid lines are drawn from calculated values of rate constants, O, $k_{1,obs}$; △, $k_{2,obs}$

than that of amide. Secondly the values of $k_{2,obs}$ obtained when the concentration of ethyl oxamate had fallen to *ca.* 1.0% of the original were found to be comparable to those of k_f obtained from equation (3) where k_f is the pseudo-

$$k_f = \frac{1}{(t_t - t_0)} \ln \left[\frac{B_0}{B_0 - (X_t - X_0)} \right] \quad (3)$$

first-order rate constant and B_0 and X_0 are the concentrations of oxamic acid and ammonia respectively at time t_0 when the concentration of ethyl oxamate has fallen to *ca.* 1.0% of the original and X_t is the concentration of ammonia at any time t_t.
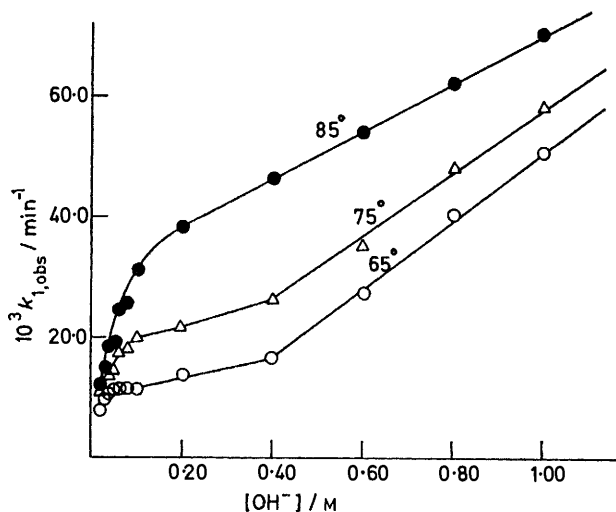
FIGURE 3 Dependence of $k_{1,obs}$ on [⁻OH]

The temperature dependence of hydrolysis was studied over the temperature range 55—85°. The activation parameters were calculated using Arrhenius and Eyring equations [4] by a standard least squares program on an IBM-1130 computer and are summarized in Table 1.

[4] K. J. Laidler, ' Chemical Kinetics,' McGraw-Hill, New York, 1965, p. 89.

A series of kinetic runs were carried out at different temperatures within the sodium hydroxide concentration range 0.02—1.5M. The results are shown graphically in Figures 3 and 4, corresponding to the first and second steps

and are shown in Figures 5 and 6. The linear adjustable parameters B_1, B_2, C_1, and C_2 were evaluated by linear least squares treatment and are summarized in Tables 2 and 3.

Figures 2 and 3 also indicate that the rates of hydrolysis

TABLE 1

Activation paramaters [a]

Reaction	$\Delta F^*/$ kcal mol^{-1} [b]	$\Delta H^*/$ kcal mol^{-1}	$\Delta S^*/$ cal K^{-1} mol^{-1}	$E_a/$ kcal mol^{-1}	$\log(A/s^{-1})$	10^3 R.m.s./ min^{-1} [c]	Maximum deviation (%) [d]
A $\xrightarrow{k_{1,obs}}$ B	26.07	6.88 ±0.36 [e]	55.6 +1.0 [e]	7.56 ±0.36 [e]	3.59 ±1.04 [e]	2.40	−10.2
B $\xrightarrow{k_{2,obs}}$ X	26.34	6.71 ±0.36	5.68 ±1.1	7.39 ±0.36	2.99 ±1.06	1.70	−9.8

[a] Conditions: 4.0×10^{-3}M-ethyl oxamate, 0.6M-NaOH, μ 1.0M. [b] Calculated from $k_{obs} = (k_B T/h) \exp (-\Delta F^*/RT)$ at 85°. [c] R.m.s. is the root mean square deviation between observed and calculated values, given by $[(k_{obs} - k_{calc})^2/(N - 1)]^{1/2}$ when N is the number of k_{obs} values. [d] Maximum deviation between observed and calculated values. [e] Error limit, 1 standard deviation.

TABLE 2

Linear adjustable parameters obtained from the equation [a] $1/k_{1,obs} = B_1 + B_2/[^-OH]$

$T/°C$	$B_1/$min	$B_2/$ mol min l^{-1}	10^4 R.m.s.[c]/ min^{-1}	Maximum deviation (%) [d]	$10^3 B_1^{-1}/$ min^{-1}	$B_1 B_2^{-1}/$ l mol^{-1}	$10^3 k_{1,obs}/$min^{-1}
65	75.66 ±2.60 [b]	0.90 ±0.10 [b]	3.502	3.7	13.21	83.7	12.18 [e] ±1.16
75	42.30 ±3.89	1.11 ±0.15	10.83	−11.1	23.64	38.3	20.82 ±0.91
85	22.38 ±2.45	1.28 ±0.09	14.89	−9.3	44.68	17.5	

[a] Conditions: 4.0×10^{-3}M-ethyl oxamate, $\mu = 1.0$M. [b] Error limits are standard deviations. [c] Root mean square deviation between observed and calculated values. [d] Maximum deviation between observed and calculated values. [e] [$^-$OH] 0.08—0.2M. Mean deviation from the mean. [g] [$^-$OH] 0.1—0.2M.

TABLE 3

Linear adjustable parameters obtained from equation [a] $1/k_{2,obs} = C_1 + C_2/[^-OH]$

$T/°C$	$C_1/$min	$C_2/$ mol min l^{-1}	10^4 R.m.s.[c]/ min^{-1}	Maximum deviation (%) [d]	$10^3 C_1^{-1}/$ min^{-1}	$C_1 C_2^{-1}/$ l mol^{-1}	$10^3 k_{2,obs}/$min^{-1}
65	76.24 ±2.71 [b]	0.94 ±0.10 [b]	3.53	3.8	13.09	81.1	19.95 [e] ±0.44 [f]
75	43.06 ±4.07	1.11 ±0.16	11.70	−10.4	23.25	38.9	25.63 [g] ±0.57 [f]
85	23.11 ±2.64	1.27 ±0.10	16.15	−10.3	42.38	18.3	37.76 [h] ±0.34 [f]

[a–d,f] As Table 2. [e] [$^-$OH] 0.6—1.0M. [g] 0.4—0.84M. [h] 0.2—0.6M.

of hydrolysis, respectively. These results indicate that the rates of both steps increase with an increase in the hydroxide
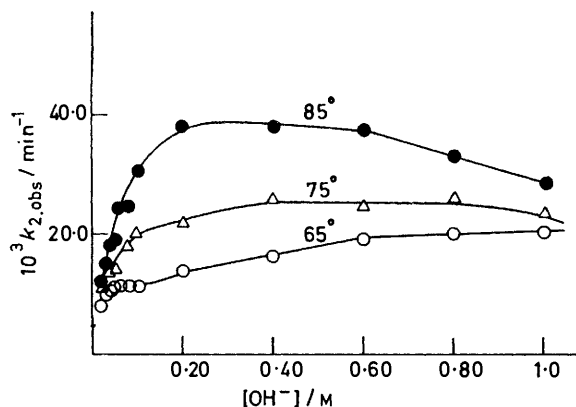

FIGURE 4 Dependence of $k_{2,obs}$ on [$^-$OH]

ion concentration in the lower range. The results for this region were found to follow the empirical equations (4) and (5)

tend to be independent of hydroxide ion concentration above the region where equations (4) and (5) are valid. As the hydroxide ion concentration is increased further, the

$$1/k_{1,obs} = B_1 + B_2/[OH^-] \qquad (4)$$

$$1/k_{2,obs} = C_1 + C_2/[OH^-] \qquad (5)$$

rates again become dependent on it and the rate of the first step was found to follow a linear relationship of the type (6).

$$k_{1,obs} = \alpha + \beta[^-OH] \qquad (6)$$

The values of $k_{2,obs}$ were found to decrease with increase in hydroxide ion concentration. The parameters α and β were evaluated using the least squares treatment and are summarized in Table 4.

DISCUSSION

The breaks in the rate profiles (Figures 3 and 4) indicate that there are changes in the rate-determining step with changes in the hydroxide ion concentration and that the reaction proceeds in a stepwise rather than

concerted manner.[5-8] The ascending limbs of the rate profiles in the low alkaline region reveal that the rate of

It was established that breakdown of the tetrahedral intermediate was the rate-determining step because the

TABLE 4

Linear parameters obtained from equation ^{a} $k_{1,obs} = \alpha + \beta[^-OH]$

$T/°C$	$10^3/\alpha$ min^{-1}	$10^3\beta/$ $1\ mol^{-1}\ min^{-1}$	10^4 R.m.s./ min^{-1} ^{c}	Maximum deviation% ^{d}	$[^-OH]/M$
65	−6.65	57.80	6.23	5.2	0.4—1.0
	±1.25 ^{b}	±1.71 ^{b}			
75	4.23	54.06	9.71	−3.8	0.4—1.0
	±1.95	±2.60			
85	30.34	39.95	1.47	0.39	0.2—1.0
	±0.18	±0.27			

$^{a-d}$ As Table 2.

both steps is controlled by the breakdown of a tetrahedral intermediate. Such results have been found for
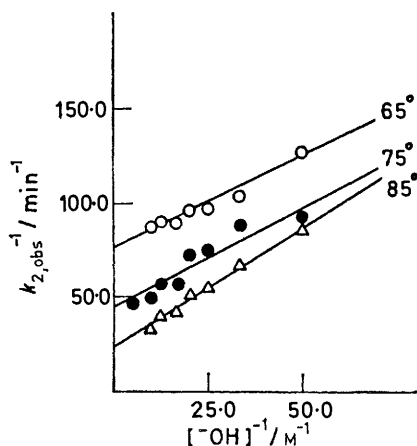

FIGURE 5   Inverse dependence of $k_{1,obs}$ on $[^-OH]$. Solid lines are drawn from the calculated values of rate constants

many acyl transfer reactions [3,9-22] where the acyl substrate contains an ionizable proton. Various studies [16,18,23,24] on the hydrolysis of acyl substrates followed by the breakdown of amide and imide bonds during hydrolysis reveal that an oxydianionic tetrahedral intermediate contributes to the overall reaction in many cases. The linear variation of $k_{1,obs}$ with $[OH^-]$ indicates that an oxydianionic tetrahedral intermediate may be controlling the rate along with the breakdown of a monoanionic tetrahedral intermediate. On the basis of these observations the mechanism for the hydrolysis of ethyl oxamate may be represented by Schemes 1 and 2.

[5] B. Hansen, *Acta Chem. Scand.*, 1963, **17**, 1307.
[6] B. A. Cunningham and G. L. Schmir, *J. Amer. Chem. Soc.*, 1967, **89**, 917.
[7] G. M. Blackburn and W. P. Jencks, *J. Amer. Chem. Soc.*, 1968, **90**, 2638.
[8] A. C. Satterthwait and W. P. Jencks, *J. Amer. Chem. Soc.*, 1974, **96**, 7018, 7031.
[9] M. N. Khan and A. A. Khan, *J. Org. Chem.*, 1975, **40**, 1793.
[10] M. N. Khan and A. A. Khan, *Indian J. Chem.*, 1975, **13**, 485.
[11] M. N. Khan, R. Ahmad, and A. A. Khan, *Indian J. Chem.*, 1976, **14A**, 961.
[12] R. Ahmad, M. N. Khan, and A. A. Khan, *Indian J. Chem.*, 1976, **14A**, 807.
[13] (a) S. O. Eriksson, *Acta Pharm. Suecica*, 1969, **6**, 321; (b) S. O. Eriksson and C. G. Regardh, *ibid.*, 1968, **5**, 457.
[14] C. E. Stauffer, *J. Amer. Chem. Soc.*, 1972, **94**, 7887.
[15] S. S. Biechler and R. W. Taft, jun., *J. Amer. Chem. Soc.*, 1957, **79**, 4927.

basicities of the leaving group, alkoxide ion, and the amine anion are considerably larger than that of hydroxide ion. The rate-determining formation of a tetrahedral intermediate can also be ruled out on the basis of the sufficiently large negative entropy of activation (Table 1) which must be attributed to the orientation of several water molecules in a charged transition state.[25] The tetrahedral intermediates (I)—(IV) are in rapid equilibrium and their concentrations at any moment are constant. Therefore, the steady state treatment was applied to obtain the following kinetic
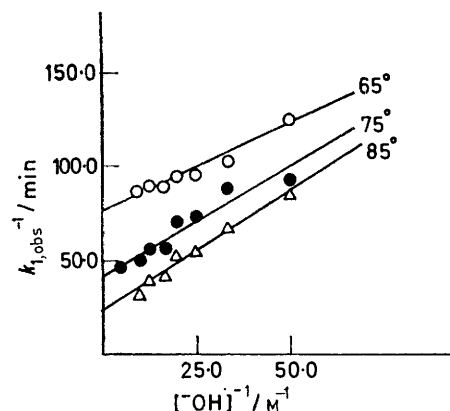

FIGURE 6   Dependence of $k_{2,obs}$ on $[^-OH]$ in the lower region of $[^-OH]$. Solid lines are drawn from the calculated values of rate constants

equations (7) for the first step and (8) for the second. Here $K_1 = K_a/K_w = [EOX^-][H^+]/[EOXH]$ and $K'_1 = K'_a/K_w = [^-OX][H^+]/[OXH]$ where K_w stands for the autoprotolysis of water.

[16] R. M. Pollack and T. C. Dumsha, *J. Amer. Chem. Soc.*, 1973, **95**, 4463.
[17] R. M. Pollack, *J. Org. Chem.*, 1974, **39**, 2108.
[18] R. M. Pollack and M. L. Bender, *J. Amer. Chem. Soc.*, 1970, **92**, 7190.
[19] M. L. Bender and R. J. Thomas, *J. Amer. Chem. Soc.*, 1961, **83**, 4183.
[20] S. O. Eriksson and C. Holst, *Acta Chem. Scand.*, 1966, **20**, 1892.
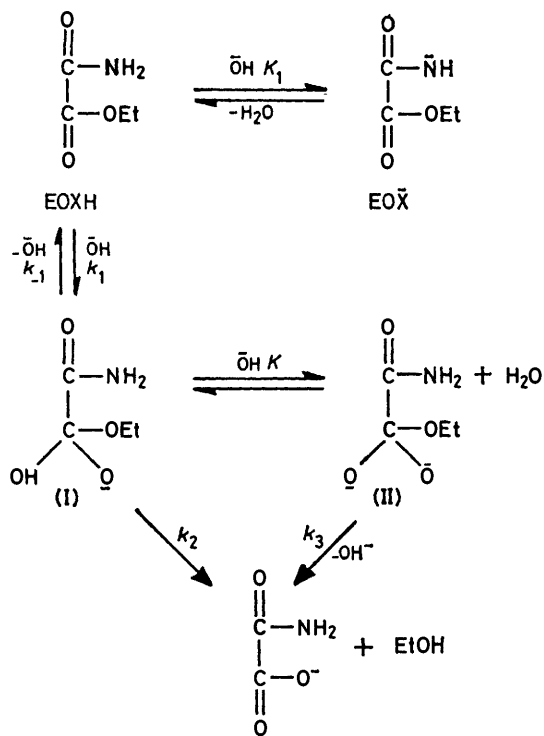[21] S. O. Eriksson and L. Bratt, *Acta Chem. Scand.*, 1967, **21**, 1812.
[22] I. Blagoeva, B. J. Kurtev, and J. G. Pojarlieff, *J. Chem. Soc. (B)*, 1970, 232.
[23] (a) R. L. Schowen and G. W. Zuorick, *J. Amer. Chem. Soc.*, 1966, **88**, 1223; (b) R. L. Schowen, H. Jayaraman, L. Kershner, and G. W. Zuorick, *ibid.*, p. 4008.
[24] P. D. Bolton and G. L. Jackson, *Austral. J. Chem.*, 1971, **24**, 969.
[25] J. G. Tillett and D. E. Wiggins, *Tetrahedron Letters*, 1971, 911.

In the lower region of hydroxide ion concentration it was assumed that k_2 and $(k_{-1} + k_2)$ are greater than

O
‖
C—NH₂   ŌH K_1 C—N̄H
| ⇌ |
C—OEt -H₂O   C—OEt
‖   ‖
O   O

EOXH   EOX̄

-ŌH ↑↓ ŌH
k_{-1} k_1

O   O
‖   ‖
C—NH₂   ŌH K C—NH₂ + H₂O
| ⇌ |
C—OEt   C—OEt
/\   /\
OH   O⁻   O⁻   Ō
(I)   (II)

k_2 k_3 _OH⁻

O
‖
C—NH₂   + EtOH
|
C—O⁻
‖
O

SCHEME 1

$k_3K[^-OH]$ and k'_2 and $(k'_{-1} + k'_2)$ are greater than $k'_3K'[^-OH]$. This is acceptable because previous

$$k_{1,\text{obs}} = \frac{k_1[^-OH]}{1 + K_1[^-OH]} \frac{k_2 + k_3K[^-OH]}{k_{-1} + k_2 + k_3K[^-OH]} \quad (7)$$

$$k_{2,\text{obs}} = \frac{k'_1[^-OH]}{1 + K'_1[^-OH]} \frac{k'_2 + k'_3K'[^-OH]}{k'_{-1} + k'_2 + k'_3K'[^-OH]} \quad (8)$$

studies [3,9-12,26] on related compounds revealed that an additional oxydianionic tetrahedral intermediate intervened only at considerably higher pH. This assumption simplifies equations (7) and (8) to (9) and (10), respectively. Equations (9) and (10) are similar to the

$$k_{1,\text{obs}} = k_1k_2[^-OH]/(1 + K_1[^-OH])(k_{-1} + k_2) \quad (9)$$

$$k_{2,\text{obs}} = k'_1k'_2[^-OH]/(1 + K'_1[^-OH])(k'_{-1} + k_2) \quad (10)$$

empirical equations (4) and (5), respectively, with $B_1 = K_1(k_{-1} + k_2)/k_1k_2$, $B_2 = (k_1 + k_2)/k_1k_2$ and $C_1 = K'_1(k'_{-1} + k'_2)/k'_1k'_2$, $C_2 = (k'_1 + k'_2)/k'_1k'_2$. The ratios $B_1 : B_2$ and $C_1 : C_2$ give the values of K_a/K_w and K'_a/K_w (Tables 2 and 3).

These results indicate that K_a and K'_a are the acidity constants of extremely weak acids; this order of acidity constants were previously reported by many workers [1,3,9-12,27] for the ionization of amides under strongly alkaline conditions.

A further increase in hydroxide ion concentration

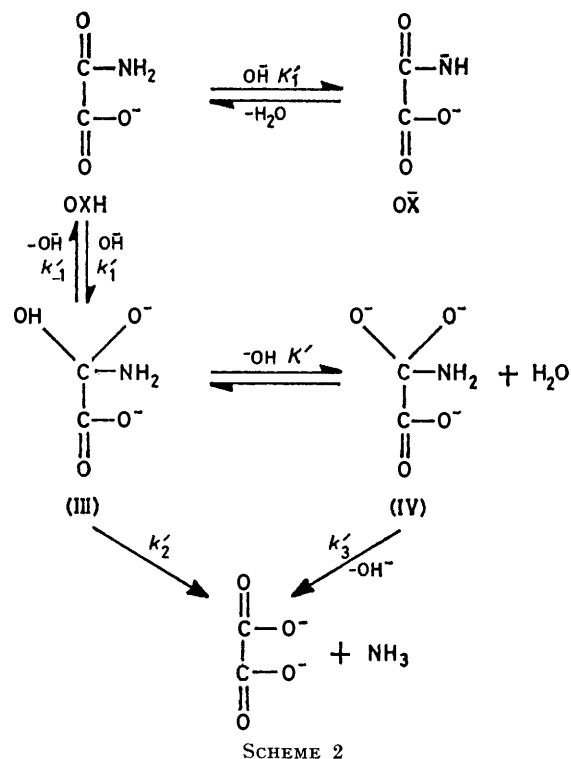[26] P. Y. Bruice and H. G. Mautner, *J. Amer. Chem. Soc.*, 1973, **95**, 1582.

implies that the conditions $1 < K_1[^-OH]$ and $1 < K'_1[^-OH]$ become more pronounced and equations (9) and (10) are reduced to (11) and (12), respectively,

$$k_{1,\text{obs}} = k_1k_2/K_1(k_{-1} + k_2) \quad (11)$$

$$k_{2,\text{obs}} = k'_1k'_2/K'_1(k'_{-1} + k'_2) \quad (12)$$

which asserts the independence of the rate from hydroxide ion concentration. The rate profiles shown in Figures 3 and 4 indicate this, and it is clearer in the second step than in the first. This may be due to the fact that the condition $k_3K[^-OH] < k_2$ is not valid for the first step. Because of this $k_{1,\text{obs}}$ increases slightly with an increase in hydroxide ion concentration in the region of the rate profile where equation (11) is thought to hold good. At 85°, the rate profile (Figure 3) indicates that equation (11) is no longer valid. This difference in reactivity can be attributed to the relative stability of the oxydianionic tetrahedral intermediates (II) and (IV) (Schemes 1 and 2). The doubly charged intermediate (II) with the electron-withdrawing stabilizing group $CONH_2$ is more stable than the triply charged intermediate (IV) with a destabilizing carboxy group.

At considerably higher concentrations of sodium hydroxide the rate profiles indicate that the two consecutive steps have different dependences on hydroxide ion concentration. Thus, the linear dependence of $k_{1,\text{obs}}$ on $[^-OH]$ entails that the condition $k_2 > k_3K[^-OH]$

O   O
‖   ‖
C—NH₂   ŌH K'_1 C—N̄H
| ⇌ |
C—O⁻   -H₂O   C—O⁻
‖   ‖
O   O

OXH   OX̄

-ŌH ↑↓ ōH
k'_{-1} k'_1

OH   O⁻   O⁻   O⁻
\ /   \ /
C—NH₂   -OH K' C—NH₂ + H₂O
| ⇌ |
C—O⁻   C—O⁻
‖   ‖
O   O

(III)   (IV)

k'_2 k'_3 _OH⁻

O
‖
C—O⁻
| + NH₃
C—O⁻
‖
O

SCHEME 2

no longer exists but $(k_{-1} + k_2) > K[^-OH]$ holds good. Applying these conditions equation (7) becomes (13)

[27] A. Bruylants and F. Kezdy, *Records Chem. Progr.*, 1960, **21**, 213.

which is comparable to equation (6) with $\alpha = k_1 k_2/K_1(k_{-1} + k_2)$ and $\beta = k_1 k_3 K/K_1(k_{-1} + k_2)$. It is evident

$$k_{1,\text{obs}} = \frac{k_1}{K_1(k_1 + k_2)} (k_2 + k_3 K[^-\text{OH}]) \quad (13)$$

from Figure 4 that $k_{2,\text{obs}}$ is almost independent of [$^-$OH] in the region where $k_{1,\text{obs}}$ varies linearly with [$^-$OH] and even shows negative deviations as the temperature is increased. Negative deviations of this nature were previously observed by Eriksson and his co-workers [28] for the alkaline hydrolysis of anilides.

Though Schemes 1 and 2 are sufficient to account for the observed data, the kinetically indistinguishable elementary steps in Scheme 3 cannot be completely ruled out.

The ionized forms of acyl substrates have been regarded as unreactive by many workers.[15,23] For the alkaline hydrolysis of trifluoroacetanilides, Mader [29] suggested that the ionized forms of anilides were also reactive towards product formation. Brooke *et al.*[30] suggested that the ionized form of N^1-methylnicotin-amide cation reacts with water to give a tetrahedral intermediate which breaks down to product. We have also made similar proposals in our previous studies.[3,11] The intermediates (V) and (VI) are the same as (II) and (IV) so that the kinetic equations derived by taking into

consideration these additional steps would have the same relationships with [$^-$OH] as equations (7)—(13).
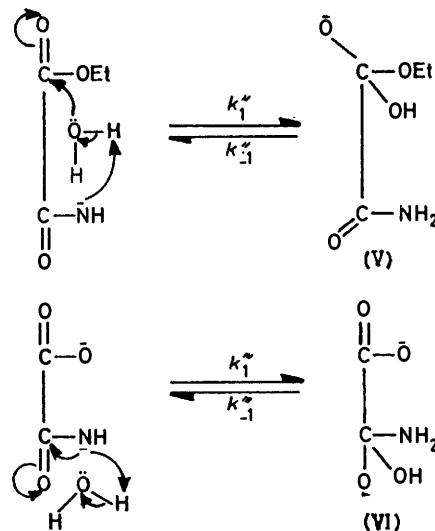
SCHEME 3

[28] S. O. Eriksson, *Acta Pharm. Suecica*, 1969, **6**, 139.
[29] P. M. Mader, *J. Amer. Chem. Soc.*, 1965, **87**, 3191.

[30] D. Brooke and D. E. Guttman, *J. Amer. Chem. Soc.*, 1968, **90**, 4964.