22. *Kinetic Salt Effects and Mechanism in the Hydrolysis of Positively Charged Esters.*

By G. AKSNES and J. E. PRUE.

A kinetic study of the acid and alkaline hydrolysis of four esters containing a quaternary ammonium group is reported. Analysis of the dependence of the specific salt effects and the rate constants on the distance between the reaction centre and the positively-charged nitrogen atom gives information about the origin of the specific salt effects and the mechanism of ester hydrolysis. It is concluded that in acid-catalysed hydrolysis the proton is attached to the carbonyl oxygen atom of the ester group.

AN investigation[1] of the rates of alkaline hydrolysis of half-esters of dicarboxylic acids showed that with alkali-metal salts there is a negative specific salt effect whose magnitude depends on the separation of the charge of the ester ion from the reaction centre. It was therefore of interest to see whether a similar phenomenon exists in both the acid and alkaline hydrolysis of a series of esters carrying a positively-charged quaternary ammonium group. This was particularly so since Butterworth, Eley, and Stone's results[2] for the acid-catalysed hydrolysis of acetylcholine ($Me_3\overset{+}{N}{\cdot}[CH_2]_2{\cdot}O{\cdot}COMe$) bromide do not show the expected primary kinetic salt effect for a reaction between two positively charged ions; on the other hand, Bell and Lindars's results[3] for the ester-ion $Et_3\overset{+}{N}{\cdot}CH_2{\cdot}CO_2Et$ show normal salt effects for both acid and alkaline hydrolysis. Furthermore, we shall show that our results provide additional information on the detailed mechanism of hydrolysis of esters.

EXPERIMENTAL

2-*Methoxycarbonylethyltrimethylammonium Bromide*, $(Me_3\overset{+}{N}{\cdot}[CH_2]_2{\cdot}CO_2Me)Br^-$.—Ethylene chlorohydrin was converted into β-bromopropionic acid by successive treatment with sodium cyanide and 48% hydrobromic acid.[4] The acid was converted (70% yield) into the methyl ester (b. p. 62°/12 mm.) by treatment with methyl alcohol in carbon tetrachloride, toluene-*p*-sulphonic acid being used as catalyst. Excess of dry trimethylamine was added to a 30% solution of the ester in alcohol at 0°, and the mixture kept overnight; the yield of quaternary salt was almost quantitative. The *salt*, precipitated with ether and recrystallised from alcohol, had m. p. 182° (Found: Br, 35·27. $C_7H_{16}O_2NBr$ requires Br, 35·34%).

3-*Methoxycarbonylpropyltrimethylammonium Bromide*, $(Me_3\overset{+}{N}[CH_2]_3{\cdot}CO_2Me)Br^-$.—Propane-1 : 3-diol was converted into 3-chloropropan-1-ol by treatment with hydrogen chloride.[5]

---

[1] Hoppé and Prue, *J.*, 1957, 1775.

[2] Butterworth, Eley, and Stone, *Biochem. J.*, 1953, **53**, 30.

[3] Bell and Lindars, *J.*, 1954, 4601.

[4] " Organic Syntheses," John Wiley and Sons, New York, 1946, Vol. I, pp. 131, 256.

[5] *Op. cit.*, p. 533.

Potassium cyanide (34 g.) was added to a stirred solution of 3-chloropropan-1-ol (40 g.) in 200 ml. of ethanol–water (3 : 1 v/v). The solution was then boiled for 1½ hr., cooled, and filtered, and the alcohol and water were distilled off under reduced pressure to obtain 3-cyanopropan-1-ol (30 g., b. p. 122°/15 mm.). This was converted into γ-bromobutyric acid (m. p. 32°) by treatment with hydrobromic acid, and the methyl ester (b. p. 79°/20 mm.) prepared by treatment of the acid with excess of methyl alcohol, sulphuric acid being used as catalyst. A 20% yield of the quaternary salt was obtained by heating the ester with excess of alcoholic trimethylamine (33%) in a sealed tube at 70° for 20 hr. After the solution had cooled, the *salt* was precipitated with dry ether and recrystallised from acetone. It had m. p. 82° (Found: Br, 33·15; OMe, 12·88. $C_8H_{18}O_2NBr$ requires Br, 33·28; OMe, 12·92%).

2-Acetoxyethyltrimethylammonium Bromide (*Acetylcholine Bromide*), $(Me_3\overset{+}{N}\cdot[CH_2]_2\cdot O\cdot COMe)Br$.—A commercial sample (B.D.H. Ltd.), recrystallised from alcohol, had m. p. 146° (Found: Br, 35·25; $MeCO_2^-$, 26·08. Calc. for $C_7H_{16}O_2NBr$: Br, 35·34; $MeCO_2^-$, 26·11%).

3-Acetoxypropyltrimethylammonium Iodide, $(Me_3\overset{+}{N}\cdot[CH_2]_3\cdot O\cdot COMe)I^-$.—Excess of alcoholic trimethylamine (10 g., 33%) was added to 3-chloropropyl acetate (7 g.) and the mixture kept in a sealed tube at 110° for 16 hr. The chloride, obtained by precipitation with ether after cooling the alcoholic solution to −50°, was extremely hygroscopic. It was therefore converted into the less hygroscopic iodide by dissolving it in acetone, adding excess of sodium iodide to precipitate sodium chloride which was filtered off, and then distilling off the acetone. The *iodide*, recrystallised three times from alcohol–ether, had m. p. 80° (Found: $MeCO_2^-$, 20·46. $C_8H_{18}O_2NI$ requires $MeCO_2^-$, 20·56%).

Kinetic Measurements.—The rates of hydrolysis of the quaternary esters were studied in solutions of hydrochloric acid and sodium hydroxide at 25° ± 0·01°. Carbonate-free sodium hydroxide solution was prepared by dilution of a concentrated stock solution. All solutions were standardised against " AnalaR " potassium hydrogen phthalate.

TABLE 1.

(k_H in sec.$^{-1}$ l. mole^{-1} and concentrations in mole l.$^{-1}$.)

	2-Acetoxyethyltrimethylammonium bromide				3-Acetoxypropyltrimethylammonium bromide			
10^3[HCl]	96·71	70·85	51·59	25·80	78·54	58·89	46·37	27·45
10^3[ester] ...	33·79	23·05	26·61	28·94	25·06	25·21	24·83	23·55
10^5k_H(exp.) ...	2·82	2·68	2·62	2·47	5·10	5·03	5·00	4·83
10^5k_H(calc.) ...	2·82	2·68	2·60	2·47	5·08	5·05	4·98	4·85

	3-Methoxycarbonylpropyltrimethylammonium bromide		
10^3[HCl]	78·54	58·34	46·37
10^3[ester]	28·56	41·36	26·23
10^5k_H(exp.) ...	2·08	2·05	1·95
10^5k_H(calc.) ...	2·07	2·05	1·95

	2-Methoxycarbonylethyltrimethylammonium bromide	
10^3[HCl]	74·76	27·45
10^3[ester]	33·04	27·15
10^6k_H(exp.) ...	7·33	6·65
10^6k_H(calc.)......	7·33	6·65

The reactions in acid were slow ($t_{\frac{1}{2}}$ = 70—500 hr.) and for each concentration of acid several solutions were made up in 100 ml. standard flasks, each containing an accurately weighed amount of ester. The solutions were left for varying times corresponding to 20—60% hydrolysis, and the contents then weight-titrated against standard barium hydroxide solution. The solutions were well shaken during titration to avoid local temporary excesses of hydroxyl ions which would cause further ester hydrolysis. The first-order rate constants obtained did not deviate by more than 1% from their mean value. The mean values of the corresponding second-order rate constants k_H for reaction between the ester and hydrogen ion are given in Table 1.

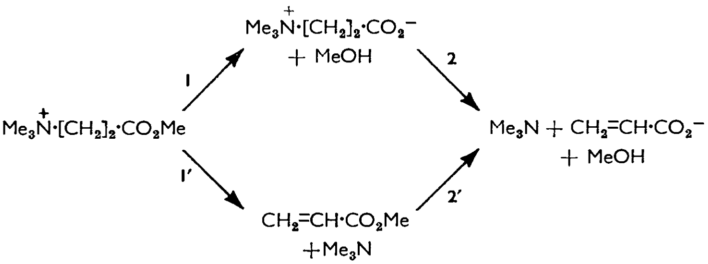
The reactions in alkali were much faster ($t_{\frac{1}{2}}$ = 1—6 min.). A weighed amount of ester was dissolved in an equivalent amount of standard sodium hydroxide solution in a conical flask previously placed in the thermostat; the esters dissolved almost instantaneously. After a suitable time excess of hydrochloric acid was added and the solution back-titrated against barium hydroxide solution. The individual values of the second-order rate constants k_{OH} did not deviate by more than 2% from the mean values recorded in Table 2. The ionic strength decreases during the alkaline hydrolysis of 3-methoxycarbonylpropyltrimethylammonium bromide, and the results in Table 2 for this ester are the average of several determinations at each concentration in which the reaction was stopped at approximately 50% hydrolysis; in analysing the results the ionic strength was taken as the value at 25% hydrolysis.

TABLE 2.

(k_{OH} in sec.$^{-1}$ l. mole^{-1} and concentrations in mole l.$^{-1}$.)

	3·Acetoxytrimethylammonium iodide				3-Methoxycarbonylpropyltrimethylammonium bromide				
10^3[NaOH]	34·68	23·12	17·34	11·56	34·68	23·12	19·87	17·34	11·56
$10k_{OH}$(exp.)	4·35	4·60	4·70	5·05	4·90	5·15	5·40	5·46	5·70
$10k_{OH}$(calc.)	4·35	4·60	4·76	5·01	4·90	5·21	5·33	5·43	5·71

The alkaline hydrolysis of the acetylcholine ion was too fast for accurate study, whilst that of the 2-methoxycarbonylethyltrimethylammonium ion is not a simple reaction. Willstätter [6] found previously that in addition to propylbetaine, trimethylamine and the acrylate ion are also produced. These could result from the attack of the hydroxyl ion on propylbetaine, and we find that on complete hydrolysis a quantitative yield is obtained of trimethylamine and acrylate ion. However, a considerable amount of methyl acrylate is formed as an intermediate, and can be extracted with carbon tetrachloride. The formation of methyl acrylate shows that there are two alternative reaction paths, a hydroxyl ion being consumed at each stage:



Semiquantitative studies show that the rate constants of 1 and 1′ are comparable and about 2—10 sec.$^{-1}$ l. mol.$^{-1}$ at 25°. Reaction 2 is approximately 1000 times slower than 1′, which is reasonable, because the negative charge on the carboxylate ion will strongly reduce the readiness of the β-hydrogen atom to be removed as a proton.

DISCUSSION

Salt effects due to the addition of alkali-metal salts can be adequately described [1] by the equation

$$\log k = \log k^\circ + \frac{2z_A z_B A I^{\frac{1}{2}}}{1 + I^{\frac{1}{2}}} + BI \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where z_A and z_B are the charges on the reacting ions, I is the ionic strength, A is a constant of the Debye–Hückel theory with the value 0·509 (l. mole^{-1})$^{\frac{1}{2}}$ for water at 25°, and B is an empirical parameter which takes account of any specific salt effects. We use this equation in this work. The values of k° and B can be found by plotting $\log k - 2z_A z_B A I^{\frac{1}{2}}/(1 + I^{\frac{1}{2}})$ against I, and are given in Table 3. The values of k (calc.) in Tables 1 and 2 are obtained by inserting these values of k° and B in eqn. (1), and we see that the calculated and observed values of k agree closely. This method of analysing the data is especially suitable if accurate values of k° are required. We now consider what further conclusions we can draw from the values of B and k°; we have numbered the esters in Table 3 for ease of reference.

The acid hydrolysis of ester 3 shows the expected positive salt effect, the rate constant increasing from $k_H = 1{\cdot}64 \times 10^{-5}$ sec.$^{-1}$ l. mole^{-1} at $I = 0$ (Table 3) to $2{\cdot}82 \times 10^{-5}$ at $I = 0{\cdot}13$ in contrast to Butterworth, Eley, and Stone's result,[2] $k_H = 3 \times 10^{-5}$. The specific salt effects are negative for acid hydrolysis, positive for alkaline hydrolysis, and tend to increase as the distance increases between the positively-charged quaternary nitrogen atom and the reaction centre. This is in agreement with the explanation previously advanced for such specific effects.[1] As the distance between the charges in the activated complex increases, the more each charge tends to build up its own ion atmosphere. This leads to a reduction in the normal positive salt effect for a reaction between two ions of the same charge, and in the normal negative salt effect for a reaction between two oppositely charged ions. The values of B and their dependence on the charge separation in the activated complex are comparable with those observed [1] in the alkaline hydrolysis of half-esters.

TABLE 3.

($k°$ in sec.$^{-1}$ l. mole^{-1}, B in l. mole^{-1}, r in Å.)

	Acid hydrolysis				Alkaline hydrolysis			
	$-B$	$10^5 k_H°$	α	r	B	$k_{OH}°$	α	r
1. $Me_3\overset{+}{N}{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2Me$	$0{\cdot}3_2$	0·44	27·2	2·2	—	—	—	—
2. $Me_3\overset{+}{N}{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2Me$...	$0{\cdot}2_6$	1·24	5·7	4·1	$0{\cdot}1_8$	0·76	0·133	3·5
3. $Me_3\overset{+}{N}{\cdot}CH_2{\cdot}CH_2{\cdot}O{\cdot}COMe$	$0{\cdot}2_6$	1·64	6·7	3·8	—	~1·8	0·061	2·5
4. $Me_3\overset{+}{N}{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}O{\cdot}COMe$	$0{\cdot}7_5$	3·43	3·3	6·0	$0{\cdot}3_8$	0·67	0·130	3·5

The values of $k_H°$ increase as the distance between the positive charge and the reaction centre increases. This we expect on electrostatic grounds. A more quantitative analysis can be made as follows. We compare the $k°$ values of the esters studied with those of the corresponding uncharged esters in which the group Me_3N^+– is replaced by hydrogen. We use values of $k_H°$ and $k_{OH}°$ given by Palomaa [7] and by Salmi and Leimu [8] respectively. They are (units sec.$^{-1}$ l. mole^{-1}): methyl propionate, $1{\cdot}21 \times 10^{-4}$, 0·164; methyl butyrate, $7{\cdot}05 \times 10^{-5}$, 0·101; ethyl acetate, $1{\cdot}10 \times 10^{-4}$, 0·110; propyl acetate, $1{\cdot}13 \times 10^{-4}$, 0·087. These values are unlikely to be seriously in error because of neglected salt effects, as the reactions are between an ion and a neutral molecule. The values of α in Table 3 are the quotient $k°$(neutral)/$k°$(charged). If we ascribe the differences of α from unity entirely to the electrostatic interaction between the charges in the activated complex, α is given by [9,10,11] $\ln \alpha = z_A z_B e^2/DkTr$ where e is the electronic charge, D the dielectric constant of the medium, k Boltzmann's constant, T the absolute temperature, and r the distance between the charges. Setting $D = 78{\cdot}5$, we obtain the values of r recorded in Table 3. The absolute values of r are too small, and in the acid hydrolysis the increments of r as the chain is lengthened are rather large. This is probably due to using the dielectric constant of the solvent rather than some smaller value; a similar effect is found in interpreting the dependence on chain length of the ratio of the acidity constants of dicarboxylic acids.[11]

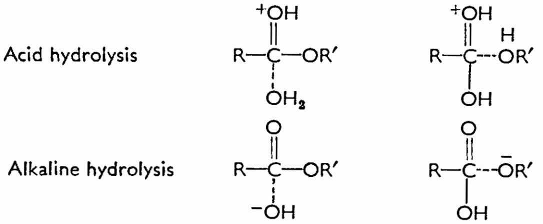
The values of r fall into three groups, *viz.*, 1(H^+), 3(OH^-); 2(H^+), 3(H^+), 2(OH^-), 4(OH^-); 4(H^+). We can only explain the similar values of r for acid hydrolysis of esters 2 and 3 if in the activated complex for acid hydrolysis the proton and positive charge are on the carbonyl oxygen and not on the ether oxygen atom. Furthermore, if in alkaline hydrolysis the negative charge in the activated complex is shared between the attacking hydroxyl ion and the ether oxygen, we see why the r values for alkaline hydrolysis of esters 2 and 4 are the same and similar to those for acid hydrolysis of esters 2 and 3, for the distance between the charge on the quaternary nitrogen atom and the centroid of charge on the ester end of the molecule will be similar in all four cases. That the values of r for alkaline hydrolysis are slightly less may be due to some coiling of the chain when it has oppositely-charged ends. Just as the r values for acid hydrolysis of 2 [2(H^+)] and

---

[6] Willstätter, *Ber.*, 1902, **35**, 584.
[7] Palomaa, *Ber.*, 1938, **71**, *B*, 480.
[8] Salmi and Leimu, *Suomen Kem.*, 1947, **20**, *B*, 43.
[9] Bjerrum, *Z. phys. Chem.*, 1923, **106**, 219.
[10] Ingold, *J.*, 1931, 2170.
[11] Wheland, " Advanced Organic Chemistry," John Wiley and Sons, New York, 1949, p. 434.

alkaline hydrolysis of 4 [4(OH$^-$)] are similar so are those for acid hydrolysis of 1 and alkaline hydrolysis of 3.

The most recent work [12] on the mechanism of ester hydrolysis, including the study of isotopic oxygen exchange, suggests that a symmetrical intermediate complex is formed in a reaction involving the solvent. This is probably the monoester of the ortho-acid $R{\cdot}C(OH)_2{\cdot}OR'$. The existence of catalysis by hydrogen or hydroxyl ions indicates that formation of the monoester, and conversion into the acid or reversion into the ester, takes place most readily through activated complexes having the composition of the protonated or deprotonated ortho-ester. Our observations are consistent with the two activated complexes' in each case having the following approximate charge distributions:



One of us (G. A.) thanks the Norwegian Technical and Scientific Research Council for a grant and the Norwegian Defence Research Establishment for leave of absence.

The University, Reading. [*Received, July 2nd*, 1958.]

---

[12] Bender, Ginger, and Unik, *J. Amer. Chem. Soc.*, 1958, **80**, 1044.