Kinetics of the Acid and Alkaline Hydrolysis of Ethoxycarbonylmethyltriethylammonium Chloride.

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Kinetic measurements are reported on the acid and alkaline hydrolysis of ethoxycarbonylmethyltriethylammonium chloride $CO_2Et{\cdot}CH_2{\cdot}NEt_3\}Cl$, at 40° and 25° respectively. The former measurements involved titration and dilatometry, while the latter employed the thermal maximum method previously developed for the fast reactions. The observed velocities are compared with those for the hydrolysis of ethyl acetate, and it is concluded that the effect of the charge upon the reaction velocity and upon the parameters of the Arrhenius equation can be accounted for semi-quantitatively by a simple electrostatic treatment.

THE introduction of a quaternary ammonium group into an ester molecule represents the extreme case of an electron-attracting substituent. There is ample evidence that the effect of such a substituent is to retard acid hydrolysis, and to accelerate alkaline hydrolysis, but little quantitative work has been done. Nielsen (*J. Amer. Chem. Soc.*, 1936, **58**, 206) studied the alkaline hydrolysis of ethoxycarbonylmethyltriethylammonium iodide $EtO_2C{\cdot}CH_2{\cdot}NEt_3\}I$ at 20°, finding it to be very fast and to exhibit the expected negative salt effect. Bell and Waind (*J.*, 1950, 1979) made more accurate measurements on the same reaction at 0°, and in particular investigated the retarding effect of certain metallic cations. Walker and Owens (*J. Amer. Chem. Soc.*, 1952, **74**, 2547) report semi-quantitative measurements of the rate of hydrolysis of the *cyclo*hexyl compound $C_6H_{11}O{\cdot}CO{\cdot}CH_2{\cdot}NMe_3\}Cl$ by both acid and alkali, finding the former to be extremely slow. The present paper describes kinetic measurements on the hydrolysis of ethoxycarbonylmethyltriethylammonium chloride $CO_2Et{\cdot}CH_2{\cdot}NEt_3\}Cl$ by acid at 40° and by alkali at 25°. The latter measurements needed a special technique for studying fast reactions, and the results can be combined with those of Bell and Waind (*loc. cit.*) at 0° to obtain an energy of activation. While the work was in progress measurements were published by Butterworth, Eley, and Stone (*Biochem. J.*, 1953, **53**, 30) on the acid and alkaline hydrolysis of acetylcholine iodide $AcO{\cdot}CH_2{\cdot}CH_2{\cdot}NMe_3\}I$ (in which the quaternary group is in the alcohol rather than in the acid) over a range of temperatures, and also by Nilsson (*Svensk Kem. Tidskr.*, 1953, **65**, 213) on the same reaction at 20°. These measurements will be discussed, together with our own, in the final section of the paper.

EXPERIMENTAL

Ethoxycarbonylmethyltriethylammonium chloride (referred to subsequently as "ester") was prepared by refluxing equivalent quantities of ethyl chloroacetate and triethylamine, diluted with an equal volume of benzene, for 7 hr. The solid separating was washed with ether, dried over phosphoric oxide, and recrystallized from acetone, then having m. p. 126°. In an alternative preparation the ingredients, diluted with a little ether, were left for 3 weeks at room temperature and the washed solid was used without recrystallization. Analyses for chloride content and by hydroxyl ions used up in alkaline hydrolysis gave purities of 99—101% for three samples.

All the kinetic measurements on acid hydrolysis were carried out at 40°, and two methods were used for following the reaction. In the first, the acid produced by the reaction $^{+}NEt_3{\cdot}CH_2{\cdot}CO_2Et + H_2O \longrightarrow {}^{+}NEt_3{\cdot}CH_2{\cdot}CO_2H + EtOH$ was estimated by titration with aqueous ammonia, methyl-red being used as an indicator. The acid produced has a pK of about 2 (cf. Gustaffson, *Ber.*, 1944, **77**, 66) and is therefore titrated completely under these conditions, while the solution does not become sufficiently alkaline during titration to cause appreciable hydrolysis of the unchanged ester. However, this method of following the reaction is not very satisfactory since a high concentration of catalyst acid is needed to produce a reasonable reaction velocity, and the change of titre is therefore small unless very concentrated solutions of ester are used. Five experiments were carried out with an ester concentration of 1 mole per 1000 g. of solution, and hydrochloric acid in the range 1—5 molal. The results are shown in Table 1.

TABLE 1. *Acid hydrolysis at* 40°.

k = first-order velocity constant (sec.$^{-1}$).
Concentrations are in moles/1000 g. of solution.
Results obtained by the analytical method are marked with an asterisk.

[HCl]	0·946	0·972	1·48	2·08	2·08	2·44	2·79	2·94	3·35	3·72	3·79	4·56	4·81	4·86	4·91	5·10	5·38	5·69
[Ester]	0·100	0·982	0·101	0·095	0·968	0·101	0·092	0·986	0·100	0·091	1·046	0·096	0·094	0·929	0·982	0·195	0·094	0·096
10^7k	8·3	12·7*	13·5	17·7	29*	26	28	42*	40	43	60*	68	73	107*	126	76	86	100

More satisfactory results were obtained by a dilatometric method. The reaction is accompanied by a contraction of about 0·9 c.c. per mole of ester, and it was therefore possible to work with an ester concentration of 0·1M. In one experiment ten times this concentration was used for comparison with the titration experiments. The dilatometers used had a capacity of about 100 c.c. and capillaries of cross-sections between 0·1 and 0·3 sq. mm. Since the duration of the experiments was between 4 and 30 days, the dilatometers were sealed off and the solutions de-gassed before use. The reaction followed a first-order course and velocity constants were obtained graphically by Guggenheim's method (*Phil. Mag.*, 1926, **2**, 538). The results obtained by both methods are given in Table 1.

Table 1 shows that the value of k/[HCl] increases markedly with an increase of either [HCl] or [ester]. Since both of these concentrations contribute to the ionic strength, this is qualitatively what would be expected for a reaction between two positively charged ions. For comparison with other data it would be desirable to extrapolate to zero ionic strength, but the concentrations involved are of course much too high for any theoretical treatment of the salt effect to be valid: however, it is possible to make a rough graphical extrapolation by using the theoretical prediction that in very dilute solutions the plot of $\log_{10}\{k/[\text{HCl}]\}$ against $I^{\frac{1}{2}}$ (where I is the ionic strength) should have a slope of unity. This leads to a value of about $(1{\cdot}4 \pm 0{\cdot}7) \times 10^{-7}$ l. mole^{-1} sec.$^{-1}$ for the catalytic constant of the hydrogen ion at infinite dilution.

The kinetics of the alkaline hydrolysis were investigated at 25°. The half-times of the reactions studied ranged from 7 sec. (for a second-order reaction with each reactant 0·004M) down to 0·2 sec. for the reaction of ester with an excess of 0·2M-sodium hydroxide. These rapid reactions were studied by the thermal maximum method devised by Bell and Clunie (*Proc. Roy. Soc.*, 1952, *A*, **212**, 16), using a platinum vessel and a single thermocouple with amplifier as described by Bell, Gold, Hilton, and Rand (*Discuss. Faraday Soc.*, 1954, in the press). The reaction was started by breaking a bulb containing 0·2—0·7 g. of 1m-ester solution into 50 c.c. of sodium hydroxide solution of appropriate strength; separate experiments showed that the heat of dilution of the ester solution is negligible. The heat of reaction is about 15 kcal./mole, so that the temperature changes produced are ample for the purpose.

In one series of experiments sodium hydroxide was present in at least five-fold excess, so that the reaction followed approximately a first-order course. The results obtained are given in Table 2. These results were used to obtain T_0 (the temperature change under adiabatic conditions) by extrapolation, using the empirical equations given by Bell, Gold, Hilton, and Rand (*loc. cit.*). A slight modification is necessary for this reaction between two ions on account of the primary salt effect; although this is large, it can be predicted with reasonable certainty over the range of ionic strengths which we have used. In the experiments recorded in Table 2 the first-order velocity constant will be proportional to $[\text{OH}^-]f_+f_-$ rather than to $[\text{OH}^-]$, and f_+f_- can be estimated from the equation

$$-\log_{10} f_+f_- = I^{\frac{1}{2}}/(1 + I^{\frac{1}{2}}) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

The appropriate equations for extrapolation then become:

$$T_m/T_0 = 0{\cdot}875\{k_2/k^\circ f_+f_-[\text{OH}^-]\}^{\frac{1}{2}} + 1{\cdot}181 \quad . \quad . \quad . \quad . \quad . \quad (2a)$$

$$T_m/T_0 = \{k_2/k^\circ f_+f_-[\text{OH}^-]\}^{\frac{1}{2}} + 1{\cdot}337 \quad . \quad . \quad . \quad . \quad . \quad (2b)$$

where k° is the second-order velocity constant at zero ionic strength. With the exception of the value for $[\text{OH}^-] = 0{\cdot}2$, which lies outside the range of applicability of the empirical equations

(2*a* and *b*), the values of T_m in Table 2 give good straight lines when plotted against either $\{[OH^-]f_+f_-\}^{-\frac{1}{3}}$ or $\{[OH^-]f_+f_-\}^{-\frac{1}{2}}$. The values of T_0 derived from equations (2*a* and *b*) respectively were 113, 114 mm. of deflection per millimole of ester, and T_0 = 113·5 was used in subsequent calculations.

TABLE 2. *Reaction of ester with an excess of sodium hydroxide at 25°.*

[NaOH] = mean concentration during experiment in moles/l.
Values of T_m represent the mean of at least two experiments.
T_0 = 113·5 mm./millimole.
k_2 = 0·066$_1$ sec.$^{-1}$. *k* in l. mole^{-1} sec.$^{-1}$.

[NaOH]	T_m/T_0	*k*[NaOH]/k_2	*k*	*k*°	[NaOH]	T_m/T_0	*k*[NaOH]/k_2	*k*	*k*°
0·0090	0·613	3·6	27	34	0·031	0·780	10·2	22	31
0·0113	0·633	4·7	27	34	0·047	0·832	16	22	34
0·0150	0·700	6·0	27	35	0·200	0·920	48	16	33
0·022	0·699	6·0	18	25					

Mean *k*° = 33.

The value of *k*° can be determined from the slope of the extrapolation plots, and equations (2*a* and *b*) give respectively *k*° = 32 and 31 l. mole^{-1} sec.$^{-1}$. Alternatively we can apply the exact equation $T_m/T_0 = (k_1/k_2)^{k_2/(k_2 - k_1)}$ (cf. Bell and Clunie, *loc. cit.*) to the individual measurements, the first-order constant k_1 being equal to *k*[NaOH]. The second-order constants *k* thus obtained are given in the fourth and ninth columns of Table 2, and are converted into the values of *k*° in the fifth and last columns by the relation $k°f_+f_- = k$. It is noteworthy that the fastest reaction (0·20M-NaOH, half-time *ca.* 0·2 sec.), which lies outside the range of the empirical expressions (2*a* and *b*), nevertheless gives a value of *k*° in good agreement with the other experiments.

Another set of experiments (slower and therefore probably more accurate) employed equal concentrations of ester and sodium hydroxide. The results are given in Table 3, and the values of ka/k_2 were calculated from T_m/T_0 by the relation already derived (equation 9 of Bell and Clunie, *loc. cit.*). In obtaining *k*° from *k* by means of equation (1) it must be remembered that the ionic strength decreases during the reaction, and it is easily shown that when the temperature maximum is reached at time t_m this decrease is :

$$\Delta I = kt_m a^2/(1 + kt_m a) \qquad (3)$$

In applying equation (1) the mean ionic strength was taken as $I = a - \frac{1}{2}\Delta I$. The mean value of *k*° thus obtained is 31 l. mole^{-1} sec.$^{-1}$, compared with 32, 31, and 33 obtained above; the overall mean is *k* = 32 l. mole^{-1} sec.$^{-1}$.

TABLE 3. *Reaction between equal concentrations of ester and sodium hydroxide at 25°.*

a = initial concentration of either reactant in moles/l.
T_0 = 113·5 mm./millimole. k_2 = 0·066$_1$ sec.$^{-1}$.
k in l. mole^{-1} sec.$^{-1}$.
The values of T_m represent the mean of at least two experiments.

10^4a	T_m/T_0	ka/k_2	*k*	*k*°	10^4a	T_m/T_0	ka/k_2	*k*	*k*°
41	0·338	1·49	24	29	98	0·451	3·31	22	29
46	0·361	1·77	25	30	98	0·470	3·75	25	32
52	0·380	2·02	26	32	110	0·480	3·98	23	30
54	0·408	2·44	30	36	120	0·489	4·26	23	30
62	0·406	2·42	26	32	136	0·500	4·56	22	30
71	0·430	2·87	27	34	153	0·500	4·56	20	28
81	0·441	3·11	25	32					

Mean *k*° = 31.

DISCUSSION

By comparing the results obtained here for the hydrolysis of ethoxycarbonylmethyltriethylammonium chloride with those for ethyl acetate at the same temperature (as given in International Critical Tables) it is found that the introduction of the group $^+NEt_3$ increases the rate of alkaline hydrolysis 200-fold, and decreases that of acid hydrolysis 2000-fold. This is, of course, what would be expected qualitatively in view of the charge on the ions OH^- and H^+. On a simple electrostatic picture the effect of the charge would be to multiply the reaction velocity by a factor exp $(\pm e^2/DakT)$, where D is the dielectric constant and a the distance between the two charges in the transition state. If we take $D = 80$ our measured velocity ratios correspond to $a = 1{\cdot}3 \times 10^{-8}$ and $0{\cdot}9 \times 10^{-8}$ cm. for alkaline and acid hydrolysis respectively. These distances are rather small, but more plausible values can be obtained by using a smaller value of D, as is reasonable in this type of problem (cf. Ingold, " Structure and Mechanism in Organic Chemistry," Cornell Univ. Press, New York, 1953, p. 729). It is not worth while to refine this electrostatic treatment further, especially as the hydrolysis of esters can take place by a variety of mechanisms (cf. Day and Ingold, *Trans. Faraday Soc.*, 1941, **37**, 686). It has recently been suggested (Cohen and Corwin, *J. Amer. Chem. Soc.*, 1953, **75**, 5880) that the hydrolysis of betaine esters (unlike that of ordinary esters) involves alkyl-oxygen fission, but the evidence presented shows only that this type of fission can take place, and not that it is the dominant mechanism in ordinary hydrolysis. In any case the presence of a net charge on the ester will be the major factor in modifying the reaction velocity, and our results are not useful in deciding the finer points of mechanism.

By combining our velocity constant for alkaline hydrolysis at 25° with that of Bell and Waind (*loc. cit.*) at 0° (4·5 l. $mole^{-1}$ $sec.^{-1}$ at zero ionic strength) we find 12·7 kcal./mole for the activation energy. It is at first sight surprising that this energy is *greater* than the activation energy of the much slower hydrolysis of ethyl acetate (11·7 kcal./mole: cf. International Critical Tables). However, this in fact would be expected on a simple electrostatic picture. If the ratio of the rates for the charged and the uncharged ester is given by $k^*/k = \exp(e^2/DakT)$, then the difference in the measured activation energies will be:

$$E^* - E = \boldsymbol{R}T^2 \mathrm{d} \ln (k^*/k)/\mathrm{d}T = -\frac{\boldsymbol{N}e^2}{Da}\left\{1 + \frac{T}{D}\frac{\mathrm{d}D}{\mathrm{d}T}\right\} \quad . \quad . \quad . \quad (4)$$

The expression in parentheses has a negative value for aqueous solutions, and hence $E^* > E$, as observed. On inserting the numerical values in (4), with $a = 1{\cdot}3 \times 10^{-8}$, we find $E^* - E = 0{\cdot}9$ kcal./mole: the close agreement with experiment is probably fortuitous. Another way of stating the same thing is to say that the collision factor for the cationic ester is about $10^{2\cdot7}$ times as great as that for ethyl acetate. It has of course been pointed out many times (see, *e.g.*, Moelwyn-Hughes, *Proc. Roy. Soc.*, 1936, *A*, **155**, 308) that a reaction between oppositely charged ions will have an abnormally high collision factor, but this appears to be the first quantitative comparison for charged and uncharged reactants of similar structure.

Butterworth, Eley, and Stone (*loc. cit.*) have come to similar conclusions about the rates and the parameters of the Arrhenius equation for the hydrolysis of acetylcholine iodide, though the effect of the positive charge is much smaller than in the present work; this is reasonable, since the quaternary group in acetylcholine is further removed from the scene of reaction. However, it should be remarked that the data of Butterworth, Eley, and Stone show no signs of the large kinetic salt effect which would be expected for a reaction between two ions and has been observed in our own measurements on ethoxycarbonylmethyltriethylammonium chloride. Nilsson's measurements (*loc. cit.*) on the alkaline hydrolysis of acetylcholine at a single temperature do show such a salt effect, and his velocity constants differ by a factor of two from those of Butterworth, Eley, and Stone at the same temperature. It appears, therefore, that further investigation of this reaction is desirable.

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