70. *The Influence of Alkyl Groups upon Reaction Velocities in Solution. Part IV. The Alkaline and Acid Hydrolyses of the Ethyl Esters of the Lower Saturated Aliphatic Acids in Aqueous Acetone.*

By GWYN DAVIES and DAVID P. EVANS.

A kinetic study of the acid and the alkaline hydrolysis of several aliphatic esters in aqueous acetone has yielded results which on analysis on the basis of the equation $k = PZe^{-E/RT}$ indicate that in alkaline hydrolysis the velocity varies mainly as a result of the changes in E. In the straight-chain esters there is a definite rise of the factor P with increase in E. On the other hand, in acid hydrolysis the activation energy is constant in straight-chain esters, although the velocity decreases as the series $R\cdot CO_2Et$ is ascended.

The mechanisms of alkaline and acid hydrolyses of esters are discussed.

IN Part III (J., 1938, 1439) the rates of saponification of the ethyl esters of a number of aliphatic acids in 85% alcohol were discussed. In order to confirm the conclusions there reached, we have studied the same reactions in aqueous acetone and also the acid hydrolyses in the same solvent. The differences between the activation energies for the alkaline hydrolyses of the normal esters in 85% alcohol were small, but in 70% acetone these differences are magnified considerably. We are thus able to amplify and confirm the conclusions recorded in Part III. The study of the acid hydrolyses in the same solvent has indicated that this reaction presents a marked contrast to the alkaline hydrolysis.

EXPERIMENTAL.

Esters.—The esters were obtained and purified by the methods described in Part III; they boiled within 0·1° of the temperatures there recorded.

Medium.—In all experiments the medium consisted of 70 c.c. of " A.R." acetone made up to 100 c.c. with water

Velocity Measurements.—(a) *Alkaline hydrolysis.* Except in the case of ethyl acetate, N/10-ester solutions were made at room temperature by weighing the necessary amount of ester into a glass-stoppered, graduated 100-c.c. flask, and adding 70 c.c. of acetone (from standard pipettes or burettes) and some water. After standing, with occasional shaking for 1 hour, the flask had attained room temperature and was filled to the mark with water. A similarly prepared 0·4M-aqueous solution of ethyl acetate was standardised by complete hydrolysis and back titration with standard acid, and the volume of this solution necessary to make 100 c.c. of 0·1M-ester solution was added to 70 c.c. of acetone contained in a 100-c.c. graduated flask, which was then filled to the mark with water at room temperature. The concentration of each ester solution was checked before use by complete hydrolysis and back titration with standard acid.

The alkaline hydrolysing agent was prepared by running the required volume of a standardised (approx. 0·35N) carbonate-free solution of sodium hydroxide into 70 c.c. of acetone and diluting it to 100 c.c. with water at room temperature. The concentration of this solution was made equal to that of the ester, and was checked by titration immediately before use.

Flasks containing the ester solution and the hydrolysing agent were placed in a thermostat (at 25°, 35°, or 45°) and allowed to attain temperature equilibrium. A determination of the concentration of the sodium hydroxide solution by titration then gave that of the ester. 25 C.c. of the ester solution were then transferred by means of a standardised pipette to a standard 50-c.c. graduated, glass-stoppered flask (also immersed in the bath), which was filled to the mark with sodium hydroxide solution by means of a rapid delivery pipette. The flask was stoppered, well shaken, and quickly returned to the bath. Zero time was taken at the instant of half delivery of the sodium hydroxide solution. The reaction was followed by withdrawing 5 or 10 c.c. of reaction mixture at suitable intervals (measured to the nearest second on a stop-watch), running it into 5 or 10 c.c. of 0·05N-hydrochloric acid, and finally titrating the excess of acid with 0·05N-barium hydroxide solution, with bromothymol-blue as indicator.

The velocity coefficients were calculated from the equation $k = x/at(a - x)$, and the values recorded in Table I are the mean of at least two, and occasionally three, concordant experiments.

TABLE I.

Alkaline Hydrolysis in 70% Acetone.

Ethyl ester.	$10^2k_{44\cdot7^\circ}$.	$10^2k_{35^\circ}$.	$10^2k_{24\cdot8^\circ}$.	$\log_{10} PZ$.
Acetate	13·5	8·22	4·65	5·9
Propionate	6·83	4·06	2·20	6·1
n-Butyrate	2·99	1·68	0·881	6·5
n-Valerate	2·45	1·33	0·659	6·9
n-Heptoate	2·21	1·19	0·608	6·9
*iso*Butyrate	1·80	1·03	0·550	6·0
*iso*Valerate	0·863	0·450	0·218	7·1
Trimethylacetate	0·0874	0·0456	0·0223	5·9
Diethylacetate	0·0371	0·0184	0·0083	6·4

(b) *Acid hydrolysis.* The ester solutions were prepared as described above. A solution of hydrochloric acid (approx. 0·6N) was standardised gravimetrically, and the volume necessary to give 100 c.c. of a 0·1M-solution was added to 70 c.c. of acetone, the mixture being made up to 100 c.c. with water at room temperature. Owing to the slow rate of reaction, the volatility of the solvent, and the possibility of side reactions at temperatures above 60°, the acid hydrolyses were carried out in sealed tubes at 25°, 35°, and 45°. 5 C.c. of N/10-ester solution and 5 c.c. of N/10-hydrochloric acid were mixed in test-tubes, which were sealed off and immersed in a thermostat, the moment of immersion being taken as zero time. At suitable intervals a tube was withdrawn, and the contents titrated against standard baryta solution (bromothymol-blue as indicator). Each end-point was matched against a colour standard consisting of 10 c.c. of N/10-barium chloride, 5 c.c. of N/10-barium acetate, and 10 c.c. of acetone containing the same amount of indicator as used in the velocity titrations.

In most cases the acid hydrolysis proceeded to about 90—95% change, and velocity coefficients were calculated from the simple expression $k_1 = 2{\cdot}303\ [\log_{10} a/(a - x)]/[\mathrm{H}]t$. Correction for solvent expansion was made in the usual manner. Over the range 10—40% change the above expression gave constant values of k_1 for most reactions. For ethyl trimethylacetate and diethylacetate, however, values of k_1 fell with time, and the following methods were employed to evaluate the true velocity coefficient. (1) Values of k_1 were plotted against percentage change or against time, and the curve was extrapolated to zero change or time (compare Timm and Hinshelwood, J., 1938, 864); (2) values of $\log_{10} 1/(a - x)$ were plotted against time, and k_1 was obtained from the slope of the tangent at zero time; (3) the fraction of ester hydrolysed (x) was plotted against time, and k_1 was computed from the slope of the tangent at the origin. The values of k_1 reported for these two esters are those obtained as means by the above methods. The results are summarised in Table II, which contains the velocity coefficients at three temperatures, the corresponding values of $\log_{10}PZ$, and the activation energies.

TABLE II.

Acid Hydrolysis in 70% Acetone.

Ethyl ester.	$10^5k_{44\cdot7^\circ}$.	$10^5k_{35\cdot0^\circ}$.	$10^5k_{24\cdot8^\circ}$.	$\log_{10} PZ$.	E (cals.).
Acetate	24·7	10·9	4·47	7·53	16,200
Propionate	20·7	9·24	3·70	7·46	16,200
n-Butyrate	10·8	4·83	1·96	7·11	16,100
n-Valerate	10·2	4·45	1·79	7·35	16,500
n-Hexoate	9·76	4·30	1·77	7·13	16,200
n-Heptoate	9·07	4·09	1·64	7·11	16,200
n-Octoate	8·70	3·85	1·55	7·16	16,300
*iso*Butyrate	7·46	3·43	1·46	6·40	15,300
*iso*Valerate	3·30	1·46	0·572	6·87	16,500
Trimethylacetate	1·10	0·363	0·128	—	—
Diethylacetate	0·869	0·333	0·117	8·08	19,100
Phenylacetate	8·84	3·84	1·58	7·08	16,200

DISCUSSION.

The trend of the velocity coefficients for the alkaline hydrolyses in acetone–water (Table I) is very similar to that found in 85% alcohol. In the straight-chain esters they decrease steadily to a constant value at ethyl *n*-valerate; the figure for this ester is probably near the average for the higher *n*-esters since the velocity coefficient for ethyl *n*-heptoate differs from it only slightly. Both ethyl *iso*butyrate and *iso*valerate are hydrolysed more slowly, and the velocity coefficients for the trimethylacetate and the diethylacetate are very low. The values of the energies of activation are all considerably smaller than the corresponding values for the reactions in 85% alcohol, as shown in Table III.

TABLE III.

Ethyl ester.	*E* (H_2O–$COMe_2$), cals.	*E* (H_2O–EtOH), cals.
Acetic	9,800	14,200 *
Propionic	10,600	14,500
n-Butyric	11,700	15,000
n-Valeric	12,400	14,700
n-Heptoic	12,400	15,000
*iso*Butyric	11,200	15,000 †
*iso*Valeric	13,300	15,700
Trimethylacetic	13,000	16,500
Diethylacetic	14,300	17,400

* Smith and Levenson (*J. Amer. Chem. Soc.*, 1939, **61**, 1172) claim that the *E* for ethyl acetate should be 14,700 cals., and that there is no difference between the activation energies of the *n*-esters. In view of the large differences found in aqueous acetone we believe that there is a trend towards a higher constant value as the *n*-series is ascended even in alcohol–water medium.

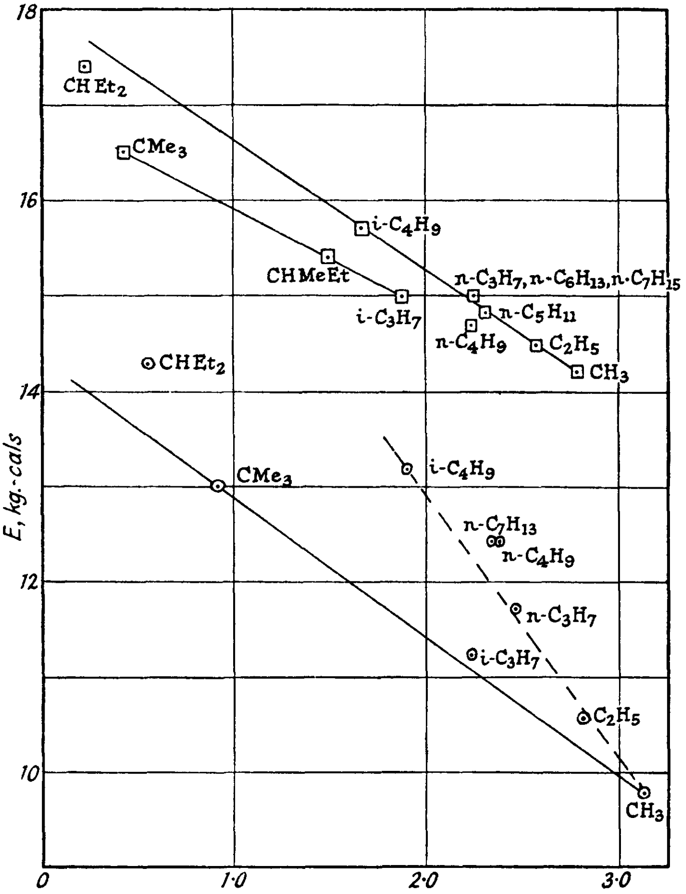
† Recalculated from the data of Part III.

It is noteworthy that, although Newling and Hinshelwood's (J., 1936, 1357) value of *E* for the alkaline hydrolysis of ethyl *iso*butyrate in 56% acetone (11,000 cals.) differs from the present value in 70% acetone by only 200 calories, yet the difference between the activation energies for methyl acetate in 56% acetone (11,500 cals.) and ethyl acetate in 70% acetone (9,800 cals.) is much greater.

Timm and Hinshelwood (*loc. cit.*) found that substituents had a greater effect upon *E* (*i.e.*, the differences were larger) for the alkaline hydrolysis of benzoic esters in alcohol–water than in acetone–water. The reverse is the case, however, with the aliphatic esters considered here. Solvent effects for a series of compounds having a variable substituent near the seat of reaction appear, therefore, to be different from those observed when the variable group is removed to some distance from the reactive centre. This may be connected with the usual constancy of *P* in the latter case but not in the former.

The general similarity of the results for the hydrolyses of the fatty acid esters $R{\cdot}CO_2Et$ in alcohol–water and in acetone–water is indicated by the plots of *E* against log *k* in the figure. In both media there is a definite rise in the activation energy to a constant value as the *n*-series is ascended, and the *iso*valerate has an even higher *E*. Also, the activation energies increase in the series $R = Me < Pr^{\beta} < Bu^{\gamma} < CHEt_2$. The conclusions of Evans, Gordon, and Watson regarding the influence of the inductive effect of *n*-alkyl groups upon the energy of activation for the alkaline hydrolysis of aliphatic esters are therefore confirmed (compare observations a, b, and c, Part III). In alcohol–water the activation energies for *n*- and *iso*-butyric esters are equal, but in acetone–water the value for the latter ester is smaller than for the straight-chain isomeride. On the basis of the inductive effects ($Pr^{\beta} > Pr^{\alpha}$) we should expect the activation energy for ethyl *iso*butyrate to be greater than that for the *n*-butyrate, and hence in both studies the larger inductive effect of the *iso*propyl group (in the *iso*butyrate) is counteracted by some other factor. This may be interpreted in the light of the postulates of Baker and Nathan (J., 1935, 1844), as already suggested in Part III.

All esters branched at the α-carbon have a *P* factor lower than that for the *n*-esters, and in both media the line through the points for $R = Pr^{\beta}$ and Bu^{γ} has almost theoretical slope ($- 2{\cdot}303\boldsymbol{R}T$). There is one notable difference between the two sets of results, however. Whereas in alcohol-water the *P* factor appears to be almost constant for the *n*-esters and ethyl *iso*valerate, yet in acetone–water this factor shows a perceptible increase as the series is ascended. This observation leads to the conclusion that a similar change in *P* probably occurs in the alcohol–water medium, but the results here are too close to permit of a definite decision. The main factor influencing the velocity coefficient in both cases, however, is the energy of activation. The regular increase in *P* for the *n*-esters in acetone–water is difficult to interpret. It appears possible that increasing the chain length of R in R·CO_2Et has some stabilising effect upon the transition complex which increases its life, and hence the factor *P* rises. This effect is evident in diethylacetic ester which, although branched at the α-carbon (which usually results in a low *P*; see above), has a higher *P* factor than either the *iso*butyric or the trimethylacetic ester. An alternative explanation for the increased *P* for diethylacetic ester has been given in Part III.



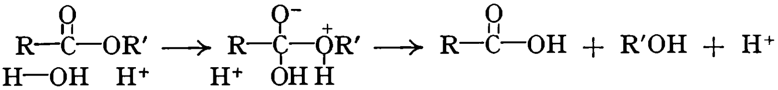
⊙ $\log_{10} 10^4 k_{44{\cdot}7^\circ}$: *Acetone–water.*
⊡ $\log_{10} 10^5 k_{25^\circ}$: *Alcohol–water.*

The acid hydrolysis of benzoic esters has recently been shown (Timm and Hinshelwood, *loc. cit.*) to be favoured by electron-attractive substituents. The acid hydrolyses of a series of aliphatic esters have now been examined, and the results recorded in Table II for acetone–water medium show that they differ distinctly from the alkaline hydrolyses. The activation energies for all esters not branched at the α-carbon are almost constant at 16,200 calories; *iso*butyric ester has a lower *E* by approximately 1000 cals., whilst the value for ethyl diethylacetate is very high, but the substitution of phenyl for α-hydrogen in ethyl acetate causes no change in the activation energy.

In agreement with Timm and Hinshelwood's results, the activation energies for the acid hydrolyses are all higher by a few thousand calories than the corresponding values for alkaline hydrolysis in the same medium. The *P* factors for the two reactions are very similar when consideration is given to the large range over which *P* can vary. The most notable difference between the results recorded for the acid and alkaline hydrolyses of aliphatic esters is as follows; whereas in alkaline hydrolysis there is a general tendency for the activation energy to follow the polar effect of the alkyl group, the E values in the acid-catalysed reactions of the *n*-esters are almost identical. In the former case there is a linear relation between E and $\log k$ (and between E and $\log PZ$) for esters not branched at the α-carbon, but in acid hydrolysis the variations of E and of $\log PZ$ are both small and irregular, and it would appear that both E and $\log PZ$ are approximately constant. It seems clear that in acid hydrolysis counteracting influences are at work.

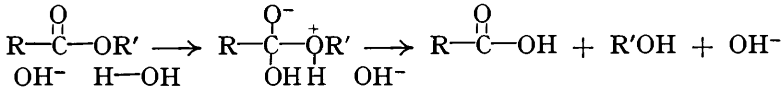
The Lowry mechanisms (J., 1927, 2558) for the reactions, which have met with widespread acceptance, are as follows :

Acid hydrolysis.



$$\begin{array}{l} \mathrm{R-\overset{\overset{O}{\|}}{C}-OR'} \\ \mathrm{H-OH\quad H^+} \end{array} \longrightarrow \begin{array}{l} \mathrm{R-\overset{O^-}{\underset{OH}{C}}-\overset{+}{\underset{H}{O}}R'} \\ \mathrm{H^+} \end{array} \longrightarrow \mathrm{R-\overset{\overset{O}{\|}}{C}-OH + R'OH + H^+}$$

Alkaline hydrolysis.



$$\begin{array}{l} \mathrm{R-\overset{\overset{O}{\|}}{C}-OR'} \\ \mathrm{OH^-\quad H-OH} \end{array} \longrightarrow \begin{array}{l} \mathrm{R-\overset{O^-}{\underset{OH}{C}}-\overset{+}{\underset{H}{O}}R'} \\ \mathrm{\qquad\qquad OH^-} \end{array} \longrightarrow \mathrm{R-\overset{\overset{O}{\|}}{C}-OH + R'OH + OH^-}$$

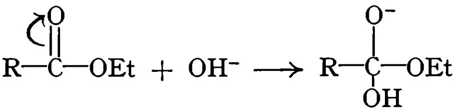
A complete proof of these mechanisms has not yet been put forward however. In particular, we do not know (i) whether in acid hydrolysis the proton adds to the carbonyl or to the ethereal oxygen, or (ii) whether in alkaline hydrolysis the hydrogen from water (if needed) similarly attacks the carbonyl or the ethereal oxygen. It has been definitely established, of course, that in both reactions the OEt^- group is withdrawn from the ester to form alcohol (Polanyi and Szabo, *Trans. Faraday Soc.*, 1934, **30**, 508; Datta, Day, and Ingold, J., 1939, 838).

The results can be interpreted on the basis of somewhat different mechanisms which appear on elementary grounds to be more probable. The initial and final states in alkaline and acid hydrolyses are as follows :

$$\mathrm{R{\cdot}CO_2Et + OH^- \longrightarrow R{\cdot}COO^- + EtOH} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (a)$$

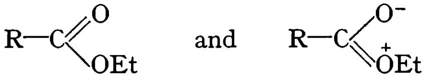
$$\mathrm{R{\cdot}CO_2Et + H^+ + HOH \longrightarrow R{\cdot}CO_2H + EtOH + H^+} \quad . \quad . \quad . \quad (b)$$

It is simplest, therefore, to suppose that in the former the activation energy represents the energy required for the formation of a transition complex containing ester and hydroxyl ion, whereas in the latter the complex contains ester, hydrogen ion, and a water molecule. In alkaline hydrolysis it may be assumed that the energy of activation is required for the process



$$\mathrm{R-\overset{\overset{O}{\|}}{C}-OEt + OH^- \longrightarrow R-\overset{\overset{O^-}{|}}{\underset{OH}{C}}-OEt}$$

i.e., E is actually the sum of the energies needed for the electromeric change $>\overset{\frown}{\mathrm{C{=}O}} \longrightarrow >\overset{+}{\mathrm{C}}-\overset{-}{\mathrm{O}}$ and the approach of the hydroxyl ion. The original ester, however, has considerable resonance energy (Pauling and Sherman, *J. Chem. Physics*, 1933, **1**, 606); it is a mesomeric state between the two structures

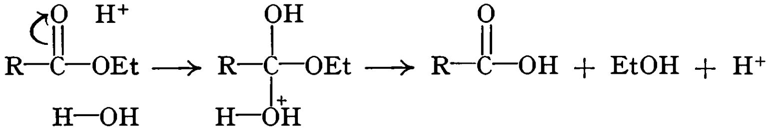


The transfer $\overset{\frown}{\mathrm{C{=}O}}$ has therefore occurred to some extent in the normal state of the molecule, and the energy required to complete this change may be relatively small; the main function of the activation energy is probably to overcome the repulsion between the ester molecule and the approaching ion. This accounts for the fact that the activation energy is reduced by electron-attractive groups in R (Evans, Gordon, and

Watson, J., 1937, 1430); the order would be reversed if the controlling factor were the energy required for the electromeric change $\overset{\curvearrowright}{\mathrm{C{=}O}}$. Jenkins (J., 1939, 1780) has recently shown that the plot of E for the alkaline hydrolysis of *p*-substituted benzoic esters against the electrostatic potential, ϕ, at the carbon to which the CO_2Et group is attached, is a straight line of slope Ne (1 Faraday). It follows that the difference in activation energy between the unsubstituted and the substituted esters, ΔE, is equal to $Ne(\phi_s - \phi_u)$, which confirms Hinshelwood, Laidler, and Timm's assumption (J., 1938, 848) that the differences in activation energy due to substituents are caused mainly by changes in classical electrostatic energy terms, and that the change in E is due almost entirely to the change in the repulsion of the hydroxyl ion.

In acid hydrolysis, which is also facilitated by electron-attractive substituents in R, the energy of activation is needed mainly for bringing up the water molecule to the carbonyl carbon (Hinshelwood, Laidler, and Timm, *loc. cit.*). This conclusion is inevitable, for both the electromeric change and the addition of a proton would be favoured by electron-repulsive groups. Since water is a much weaker base than hydroxyl ion, the energy of activation for the acid hydrolysis should be greater than for the alkaline reaction. These conclusions are similar to those of Hinshelwood and his collaborators and are in accord with their experiments.

Thus far the mechanisms are clear, but there are some reasons for supposing that in acid hydrolysis the hydrogen ion will co-ordinate with the carbonyl rather than the ethereal oxygen: the former is already fractionally negative owing to mesomerism, whereas for the same reason the latter is fractionally positive. Hinshelwood, Laidler, and Timm point out that, in compounds such as acyl chlorides and esters, the carbonyl carbon " bears through the influence of the oxygen a larger positive charge " than the central carbon in alkyl halides. In another system, association through hydrogen occurs in amides but not in the isomeric imino-ethers (Chaplin and Hunter, J., 1937, 1114) " due to the fact that the imino-ether, although it still possesses an imino-hydrogen, cannot utilise it to form a hydrogen bond because the oxygen, being ethereal and not ketonic, is available as a hydrogen acceptor only on becoming an oxonium ion." These considerations indicate the probability of the co-ordination of hydrogen ion at the negatively charged carbonyl oxygen rather than at ethereal oxygen; this process will need but little energy, and the requirements of experiment are met by a scheme of the following type:



$$\underset{\mathrm{H{-}OH}}{\mathrm{R{-}\overset{\overset{\curvearrowright O\quad H^{+}}{\|}}{C}{-}OEt}} \longrightarrow \mathrm{R{-}\overset{\overset{OH}{|}}{\underset{\underset{H{-}OH}{|+}}{C}}{-}OEt} \longrightarrow \mathrm{R{-}\overset{\overset{O}{\|}}{C}{-}OH} + \mathrm{EtOH} + \mathrm{H^{+}}$$

An electron-attractive substituent in R will here (1) facilitate the co-ordination of the water molecule and (2) operate unfavourably upon the electromeric change $\overset{\curvearrowright}{\mathrm{C{=}O}}$. It is therefore not surprising that the differences in the activation energies for a series of substituted ethyl benzoates are rather small, as found by Timm and Hinshelwood (*loc. cit.*). It might appear that a similar balancing of effects would be expected in alkaline hydrolysis, but here the change in the repulsion energy caused by a substituent is much greater than in acid hydrolysis because the attacking reagent is charged ($\Delta E = e_A \delta e_B / r$ is much larger; compare Hinshelwood, Laidler, and Timm, *loc. cit.*).

In the acid hydrolysis of the aliphatic esters the differences between the polar effects of the alkyl groups not branched at the α-carbon are much smaller than in the case of, *e.g.*, phenyl and *p*-nitrophenyl, and it is not surprising that the differences in activation energy are negligible. Incidentally, the constancy of the energy of activation for the *n*-esters and *iso*valeric ester in the acid hydrolyses appears to indicate that any geometric hindrance, if present, is very small, and following from this the rise in the activation energy as the *n*-series is ascended in the alkaline reaction cannot be attributed to increasing " steric hindrance." In the esters branched at the α-carbon the changes of inductive effect are more marked, and in the acid hydrolyses of trimethylacetic and diethylacetic esters the activation energies are as expected from the conclusions recorded in Part III. The low activation energy for ethyl *iso*butyrate (lower than the *n*-esters by 1000 cals.), however, was not anticipated. The mechanism suggested on p. 344 for acid hydrolysis bears some resemblance to both the acid- and the base-catalysed prototropy of phenyl alkyl ketones (Evans, J., 1936, 785; Evans, Gordon, and Watson, J., 1938, 1434). Thus the hydrolysis involves addition of proton at carbonyl oxygen and a base at the carbon. Of these additions, however, the work done in the latter contributes most to the activation energy, and therefore if a hydrogen bond is formed between β-carbon and carbonyl oxygen in esters branched at the α-carbon (as postulated in Part III for alkaline hydrolysis), it will have little effect upon the activation energy for acid hydrolysis; it may even cause a decrease in E owing to facilitation of the change $\overset{\curvearrowright}{\mathrm{C{=}O}}$ (compare J., 1937, 1423). The decrease in activation energy of 1000 cals. in ethyl *iso*butyrate, however, appears too large to be interpreted in this manner, and further experiments are needed before definite conclusions can be drawn.

According to the mechanism (*a*) for alkaline hydrolysis, no water molecule appears to be needed in the reaction. It is not intended, however, to preclude the possible intervention of a water molecule, which we believe is needed to stabilise or remove energy from the transition complex. If this is so, then alkaline hydrolysis may involve a ternary collision just as acid hydrolysis does, and the P factors for both reactions would be approximately equal. Newling and Hinshelwood (*loc. cit.*) have suggested that the energy of activation in acid hydrolysis is higher than for alkaline hydrolysis because in the former reaction extra energy is required to extract hydroxyl from a water molecule. It is difficult, however, to understand why this extra energy is not required to extract the proton from a water molecule in alkaline hydrolysis (Lowry mechanism), and it appears that the rôle of the water molecule in the latter reaction is probably different from that in acid hydrolysis.

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