CCXCV.—*The Mechanism of, and Constitutional Factors controlling, the Hydrolysis of Carboxylic Esters. Part VI. Kinetics of the Hydrolysis of Some Paraffin αω-Dicarboxylic Esters in very Dilute Aqueous Solution; and the Derivation, with Corrections for Solvent Electrostriction, of their Molecular Dimensions. Remarks on the Spatial Form of Polymethylene Derivatives in Dilute Solution.*

By Christopher Kelk Ingold.

In Part III (J., 1930, 1375) it was shown that the catalytic coefficients for the hydrolysis of esters are connected with the spatial configuration of the esters in such a way as to permit the calculation of molecular dimensions in certain cases. The principle involved is the following: Two esters are compared which differ only in the circumstance that one contains a polar group not possessed by the other; this constitutional difference creates a difference between the potential energies of the same polar reagent at the moment of reaction; the electrical constants of the polar substituent and reagent being known, it is possible in simple cases to calculate the energy difference on an electrical basis; the energy difference can then be related in the usual way to a velocity ratio.

The matter was illustrated by reference to the simple case in which the polar substituent is an ionic centre such as $-CO_2'$ or $-NH_3^{\bullet}$ and the reagent is an ion; and the energy difference was calculated in the ordinary elementary way as qq'/r (for symbols, see this vol., p. 2179). It was realised that this was not a precise expression for the electrical energy difference, but then the data available for the application of the theory were on the whole of such a low order of accuracy that a more elaborate theoretical treatment would not have been justified; all that one could hope to show on the basis of published figures was that an aspect exists from which it is possible to envisage the effect of constitutional changes on reaction velocity in terms of electrical conceptions which in theory are quantitative although their exact numerical evaluation may present difficulties.

The situation has now been changed by the circumstance that a calculation has been given (this vol., p. 2179) by means of which the electrical energy difference can be evaluated to a second approximation for those cases in which the polar group is an ionic centre and the reagent is an ion, and the structure of the ester undergoing hydrolysis is such that we are justified in disregarding the effect of intramolecular polar transmission. It was therefore desirable to revise and extend the existing experimental data, and this has been done for the series of compounds which formed the principal illustration in Part III, *viz.*, that in which the neutral esters,

$$CO_2R\cdot[CH_2]_n\cdot CO_2R,$$

of the normal dibasic acids are compared with the corresponding anionic esters, $CO_2R\cdot[CH_2]_n\cdot CO_2{}'$.

The essential measurements are those of k_1 and k_2, the velocity coefficients for the first and second stages of hydrolysis of the dicarboxylic esters by alkali *hydroxide* (not alkaline buffers) in *very dilute*, *aqueous* solution. The recorded data for the normal dicarboxylic esters are deficient in the following respects. First, there are no data at all for certain intermediate members of the series, *viz.*, the esters of adipic and pimelic acids. Secondly, in some cases only measurements in buffers are available, and no data permitting correction for the contributory effect of the buffer constituents exist; this applies particularly to the esters of oxalic acid. Thirdly, in the cases in which the esters are sparingly soluble in water, a large proportion of alcohol has been added to facilitate solution; this applies to the esters of glutaric, suberic, azelaic, and sebacic acids. Fourthly, the theory of kinetics of the consecutive bimolecular reactions of which the saponification of a dicarboxylic ester consists have not been sufficiently carefully examined; very crude methods of computation have been used, and this introduces liability to an error of the order of 10% in *all* the recorded k_1's, and in those k_2's which are not based on measurements on isolated and purified acid-esters, *i.e.*, in the k_2's for all those esters which are higher in the series than the succinic esters.

The writer has not yet attempted to obtain precise values of k_1 and k_2 for esters of oxalic and malonic acids, because these are acids in which internally transmitted polar influences cannot be neglected; he has, however, endeavoured to produce some better and more complete data for esters of the normal acids from succinic acid to azelaic acid inclusive. The chief improvements in method relate to the use of dilute aqueous solutions with appropriately refined analytical technique, and to schemes for evaluating k_1 and k_2 from the velocity measurements.

Method and Results.

Preparation of Materials.—Succinic acid was purchased, and the remaining acids were prepared by known methods. All the acids were carefully purified by fractional crystallisation. They were esterified with Kahlbaum's pure methyl or ethyl alcohol.

Velocity Measurements.—The thermostat temperature was 20·30° ± 0·05°. The solutions of esters and of carbonate-free sodium hydroxide were brought to the temperature of the thermostat before mixing. The time of mixing was taken as the starting time even although a few more seconds were required to adjust the volume by the addition of water that had also acquired the temperature of the thermostat.

Analytical.—As the solutions were very dilute (never stronger than $N/500$) care had to be taken in regard to the conditions of the titrations. The samples (50—100 c.c.) were run into a known volume (10—20 c.c.) of 0·01N-hydrochloric acid, the mean time of mixing being taken as the time of arrest of the reaction. They were then titrated with carbonate-free 0·01N-sodium hydroxide to a predetermined p_H, a suitable indicator being used in conjunction with a colour standard prepared with the aid of an appropriate buffer. The p_H at the end-point was calculated from the dilution and dissociation constants of the acids present, only very rough values being required for this purpose; it usually amounted to about 8 units, and errors up to 0·5 p_H unit could be shown by calculation to be immaterial. An appropriate indicator was found in cresol-red, and Clark and Lubs's borate buffer (*J. Biol. Chem.*, 1916, **25**, 479) was employed for the preparation of a colour standard.

Determination of k_2.—The values of k_2 for methyl and ethyl succinate have been determined by other workers by the use of acid ester, but in the case of esters of the higher homologous acids the usual plan has been to employ the neutral ester, calculate the results by means of the ordinary equation for a *single*-stage bimolecular process, and then determine the value towards which the "constant" tends towards the end of the reaction. The difficulty about this is, of course, that the "tail" of the first stage of hydrolysis seriously affects the velocities right up to the time at which the whole reaction is so nearly finished that the measurements give differences which are too small to yield accurate velocity coefficients. It is, however, easy to evaluate k_2, even when the acid ester is difficult to isolate or purify, because it is not necessary to isolate it in order to use it without interference from the neutral compound.

The method adopted in the present work was as follows. The neutral ester was saponified with one molecule of sodium hydroxide and the solution was extracted first with chloroform, and then with pentane, to remove the unaltered dicarboxylic ester. The neutral solution was made up to a convenient volume. A portion of this was used in order to estimate the concentration of the monocarboxylic ester by determination of the saponification value, whilst another portion was taken for the velocity measurements. Owing to the presence of a certain amount of the disodium salt, the ionic strengths of solutions prepared in this way were a little greater than if the acid esters had been isolated, but this was immaterial on account of the high dilutions at which the velocities were measured.

Determination of k_1.—Previous workers have sought to evaluate k_1 by confining attention to the commencement of the reaction between the dicarboxylic ester and alkali, the disturbance due to the incursion of the second stage of hydrolysis being neglected. This procedure involves a difficulty analogous to that discussed at the beginning of the preceding section. The commencement of the reaction is the most difficult portion of its course to follow with accuracy owing to the effect of the initial temperature disturbance and of the uncertainty about the starting time; and, before the influence of these disturbances has died away, the second stage of hydrolysis has begun to affect the measurements.

The method by which this difficulty has been overcome in the present work will now be explained.

Let a be the initial concentration of the dicarboxylic ester and of the sodium hydroxide; and after a time t let the fall in concentration of the ester be x and the rise in concentration (initially zero) of the disodium salt of the acid be y. The differential equations for the two stages are:

$$\dot{x} = k_1(a - x)(a - x - y) \quad . \quad . \quad . \quad . \quad (1)$$

$$\dot{y} = k_2(x - y)(a - x - y) \quad . \quad . \quad . \quad . \quad (2)$$

The measured quantity is $x + y$, and we will call this u. The result of adding (1) and (2) may be expressed

$$\dot{u} = (a - u)\{k_1(a - u + y) + k_2(u - 2y)\} \quad . \quad . \quad (3)$$

It will now be shown that the integrated form of (3) can be expressed as a series, and that by taking a sufficient number of terms one obtains approximation formulæ which are applicable, with any desired degree of accuracy, to a predetermined proportion of the reaction.

The basis of the approximation is that if u is small compared with a, y will be small compared with u. This must be true provided that k_2 is not large in comparison with k_1; and, in real cases, k_2 is always smaller than $\frac{1}{2}k_1$. The orders of the concentration functions we shall require are here tabulated for convenience:

Order	0	1	2	3
Linear	a	u	y	—
Quadratic	a^2	au	ay, u^2	uy

The first approximation to (3) is, of course, $\dot{u} = k_1a^2$, and its integrated form is

$$t = u/k_1a^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

This is the mathematical equivalent of the method criticised at the commencement of this section; its degree of validity will be illustrated later.

The second approximation to (3) is obtained by neglecting the second- and third-order terms; it is

$$\dot{u} = k_1a^2 - (2k_1 - k_2)au$$

This on integration gives a logarithmic function which has to be expanded in ascending powers of u/a as far as the term in $(u/a)^2$. The resulting equation is

$$t = \frac{u}{k_1a^2}\left\{1 + \frac{u}{a}\left(1 - \frac{k_2}{2k_1}\right)\right\} \quad . \quad . \quad . \quad . \quad (5)$$

In order to obtain the third approximation to (3) in an integrable form we must first get rid of the third variable, y. Having regard to the order of y, all that is necessary for this purpose is that y should be expressed in terms of u to a first order of approximation; that is, if we write

$$y/a = A(u/a)^2 + B(u/a)^3 + \ldots\ldots$$

all that we need know at this stage is the first term of the series in powers of (u/a). The value of the coefficient of this term is readily deduced. The first approximation to equation (2) is $\dot{y} = k_2au$ and the right-hand side of this is equal to $k_1k_2a^3t$ by (4). Therefore, integration gives $y = \frac{1}{2}k_1k_2a^3t^2$, and, on again using (4), we see that the right-hand side of this is equal to $\frac{1}{2} \cdot \frac{k_2}{k_1} \cdot \frac{u^2}{a}$; thus the value of A in the assumed expansion is simply $\frac{1}{2}k_2/k_1$. The third approximation to (3) now takes the form

$$\dot{u} = k_1a^2 - (2k_1 - k_2)au + \frac{2k_1^2 - k_1k_2 - 2k_2^2}{2k_1}u^2.$$

On integration, we again obtain a logarithmic function, and this requires to be expanded as far as the third power of (u/a). The result of this calculation may be expressed in the form

$$t = \frac{u}{k_1a^2}\left\{1 + \frac{u}{a}\left(1 - \frac{1}{2}\frac{k^2}{k_1}\right) + \frac{u^2}{a^2}\left(1 - \frac{7}{6}\frac{k_2}{k_1} + \frac{2}{3}\frac{k_2^2}{k_1^2}\right)\right\} \cdot \quad (6)$$

It is obvious that this process can be continued. Thus in the fourth approximation, we have to evaluate y in terms of u to a second approximation, *i.e.*, we must evaluate B; and we can do this by using equation (5) in just the same manner as in the previous paragraph we employed equation (4). The method of generalisation is mentioned in view of its possible utility in other investigations, but in the present work equation (6) was found to contain a sufficient number of terms to give the accuracy required. It usually enabled the first 30—40% of the reaction to be used for the purpose of calculating its velocity coefficient.

Typical Experiment: Methyl Glutarate, First Stage.—In this experiment 10^3a was 1·999; the values of 10^3u are shown in col. 2 of Table I, col. 1 of which records the corresponding times in minutes. Col. 3 contains the values of $10^2u/a$, *i.e.*, it shows the progress of the reaction as a percentage. The value of k_2 for methyl glutarate having been determined, an inspection of these figures led to the guess that k_1 would be about 7·35, and this figure, when introduced along with $k_2 = 1·12$, into equations (4), (5), and (6 , gave the calculated times shown in cols. 4, 5, and 6 respectively. The ratios of these calculated times to the found times are in cols. 7, 8, and 9 respectively. It will be seen that formula (4) fails to express the course of the change after the first reading (3·5% of the reaction). Formula (5) holds up to the sixth reading (15% of the reaction) and then begins to fail. Formula (6), however, clearly holds up to the end of the series (35% of the reaction) because the figures in col. 9 do not exhibit the general downward drift characteristic of those in cols. 7 and 8. The mean value of the ratios in col. 9 is 0·985, and this shows that the original guess as to the value of k_1, was not quite accurate: that assumed figure, 7·35, must be multiplied by 0·985 to give the value, $k_1 = 7·24$, which best represents the result of the experiment.

TABLE I.

Methyl glutarate: first stage.

($10^3a = 1·999$; $k_2 = 1·12$; provisionally assumed $k_1 = 7·35$.)

t	Found.		*t* calc. by			*t* calc./*t* found.		
(mins.).	10^3u.	$10^2u/a$.	(4).	(5).	(6).	(7).	(8).	(9).
2·5	0·070	3·5	2·4	2·5	2·5	0·96	1·00	1·00
4·2	0·116	5·8	3·9	4·1	4·1	0·93	0·98	0·98
6·0	0·160	8·0	5·4	5·8	5·8	0·90	0·97	0·97
8·0	0·212	10·6	7·2	7·9	8·0	0·90	0·99	1·00
10·0	0·256	12·8	8·7	9·7	9·8	0·87	0·97	0·98
12·0	0·300	15·0	10·2	11·6	11·8	0·85	0·97	0·98
14·1	0·344	17·2	11·7	13·6	13·9	0·83	0·96	0·98
16·0	0·380	19·0	12·9	15·2	15·7	0·81	0·95	0·98
18·0	0·422	21·1	14·4	17·2	17·9	0·80	0·96	1·00
20·0	0·460	23·0	15·6	18·9	19·7	0·78	0·94	0·98
23·0	0·512	25·6	17·4	21·5	22·7	0·76	0·93	0·99
26·0	0·564	28·2	19·2	24·2	25·8	0·74	0·93	0·99
29·0	0·612	30·6	20·8	26·7	28·8	0·71	0·92	0·99
32·0	0·654	32·7	22·2	28·9	31·5	0·69	0·90	0·99
35·0	0·692	34·6	23·5	31·0	34·1	0·67	0·89	0·97
							Mean	0·985

(Corrected $k_1 = 7·35 \times 0·985 = 7·24$.)

Summary of Results.—In the head-line of Table II, a_1 represents the initial ester concentration in experiments to determine k_1, and

a_2 similarly denotes the initial acid-ester concentration in experiments to obtain k_2. The values of k_1/k_2 are given in the right-hand column. The agreement with results published by other workers is fair in the case of the succinic esters but poor for the methyl esters of glutaric, suberic, and azelaic acids. This is intelligible because the succinic esters have previously been examined in aqueous solution whereas aqueous-alcoholic solutions have hitherto been employed in the other examples. Full references to the previous literature are given in Part III (*loc. cit.*).

TABLE II.

Ester.	10^3a_1.	k_1.	Mean.	10^3a_2.	k_2.	Mean.	k_1/k_2.
Methyl succinate ...	2·002 1·987	14·71 14·78	14·74	1·762 1·854	1·531 1·522	1·526	9·66
Ethyl succinate ...	2·000 1·995	11·99 12·12	12·05	1·677 1·906	1·252 1·255	1·253	9·62
Methyl glutarate ...	1·999	7·24	7·24	1·760 1·841	1·130 1·116	1·123	6·45
Ethyl glutarate	1·963 1·984	5·75 5·79	5·77	1·847	0·902	0·902	6·40
Methyl adipate	2·026	4·18	4·18	1·932 1·869	0·840 0·847	0·844	4·95
Ethyl adipate	1·008 0·987	3·50 3·54	3·52	1·760 1·698	0·700 0·707	0·704	5·00
Methyl pimelate ...	2·002 1·970	2·09 2·10	2·09	1·730 1·691	0·480 0·483	0·481	4·34
Methyl suberate ...	1·000 1·010	1·24 1·24	1·24	1·343 1·462	0·316 0·319	0·317	3·91
Methyl azelate	0·497	0·82	0·82	1·072 0·945	0·230 0·225	0·227	3·61

Discussion of Results.

The ratio k_1/k_2 is the essential datum required for the calculation of the distance, r, between the carboxyl groups by the method already indicated, that is, by combining the formulæ of Part III with the process for evaluating the energy difference outlined in the accompanying paper (this vol., p. 2179). The values of the k-ratio contained in Table II have been treated in this way, and the derived distances are shown in Table III.

In order to make the series of values more complete for the purposes of the comparison which follows, the mean values of k_1/k_2, derived from the literature, for the esters of oxalic and malonic acids have been similarly computed and the results of the calculation have been included in Table III in parentheses. The sources of the values used will be found on reference to Part III. For reasons already given, these values can only be regarded as approximate, but the present state of the theory relating to the determination of intramolecular distances in these short molecules in the dissolved state is such that quantitative refinement is not required.

The distance r is, in theory, the distance between the mean ionic centre (compare this vol., p. 2153) in the carboxylate ion of the ionic ester $CO_2R\cdot[CH_2]_n\cdot CO_2'$ and the mean focus of the reaction with hydroxide ion in the carboxylic ester group. Since the hydroxide ion must attack the unsaturated carbonyl linking, and not the saturated ether linking, in the ester group, it is to be expected that the distance, r, would, to a first approximation, be independent of the nature of the alcoholic radical R. This is seen to be the case, and thus we have practical as well as theoretical justification for taking the mean value of the k-ratios for methyl and ethyl esters of the same acid and for regarding the corresponding mean r value as essentially characteristic of the acid component of the esters.

TABLE III.

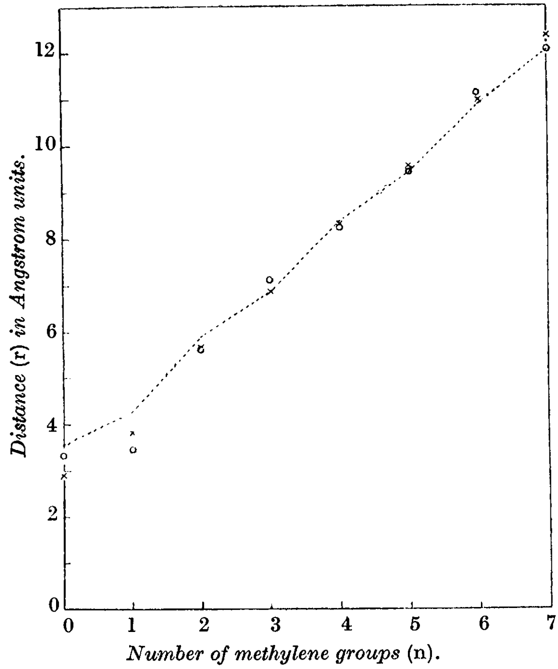
Ester.	k_1/k_2.	Mean.	r (Å.U.).	Mean r.
Methyl oxalate	(10^4)	(10^4)	(2·9)	(2·9)
Ethyl ,,	(10^4)		(2·9)	
Methyl malonate	(92)	(91)	(3·8)	(3·8)
Ethyl ,,	(90)		(3·8)	
Methyl succinate	9·66	9·64	5·61	5·62
Ethyl ,,	9·62		5·63	
Methyl glutarate	6·45	6·42	6·81	6·83
Ethyl ,,	6·40		6·85	
Methyl adipate	4·95	4·97	8·34	8·30
Ethyl ,,	5·00		8·26	
Methyl pimelate	4·34	4·34	9·57	9·57
Methyl suberate	3·91	3·91	10·97	10·97
Methyl azelate	3·61	3·61	12·38	12·38

The most remarkable feature of these results is that the r values all agree to within half an Ångstrom unit with the distances derived from the first and second dissociation constants of the corresponding free acids (this vol., p. 2160). The largest difference occurs with oxalic acid (0·47 Å.U.), but here, as in the case of malonic acid (difference 0·37 Å.U.), we hardly expect agreement. The comparison is exhibited in Fig. 1, in which the points of inflexion of the graph represent the distances required by the rigid, uniplanar, zig-zag model worked out in connexion with the study of the acids (*loc. cit.*, p. 2164). This model, it may be recalled, assumed an intervalency angle of 114° and a distance equal to 1·0 Å.U. between the centre of a carboxyl carbon atom and the point in the corresponding carboxyl group from which the distance, r, is measured. The figure shows that the same dimensions apply to the ester case to a close degree of approximation.

That data relating to thermodynamic stabilities, on the one hand, and the speeds of irreversible reactions, on the other, thus lead to quantitatively identical conclusions about molecular configuration, constitutes strong support for the logarithmic relation between velocity and energy (even for reactions in solution) which is the assumed basis for connecting reaction velocity with electropolar activation by substituents (compare Part V ; this vol., p. 2043).

Apart from this, however, it is noteworthy that the identity relates to structures which, except under the influence of "packing forces," are usually considered to be freely flexible owing to the absence of any marked resistance to the relative rotation of the atoms about the linkings joining them. Now, in the calculations based on the electrolytic dissociation constants of the acids, the distance considered, *r*, is that between the ionic centres in the bivalent anion; and in the paper dealing with that subject (*loc. cit.*), the hypothesis that the molecules are held in the extended zig-zag form by the mutual repulsion of the ionic centres was examined and discarded. On the other hand, in the calculations, the results of which are in Table III, the distance, *r*, is the distance between a point in the charged carboxylate group and a point in the neutral carbalkoxyl group in the ester-ion. The electrical forces between these terminal groups must be much weaker than those obtaining in the bivalent anion, and, such as they are, they should be attractive forces ; yet the zig-zag form is apparently maintained. We are therefore confirmed in our rejection of the electrostatic repulsion hypothesis, and in the adoption of what seems to be the only possible alternative, namely, that some *intrinsic* property of the methylene group enables a chain of such groups to exert a notable resistance to any mutual rotation of carbon atoms that would create a departure from the uniplanar zig-zag arrangement. Few methods are avail-

FIG. 1.



KEY { × *Speeds of saponification of esters.*
⊙ *Electrolytic dissociation equilibria of acids.* }

able for the determination of molecular dimensions in the absence of packing forces, but it would be interesting (and possible) to ascertain whether these conclusions, which relate to substances in dilute solution, also apply to the state of vapour.

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