489. *Conformation and Reactivity. Part III.*[1] *Kinetics of the Acid-catalysed Hydrolysis of the Methyl Cyclohexane-mono- and -di-carboxylates and 4-t-Butylcyclohexanecarboxylates.*

By N. B. Chapman, J. Shorter, and K. J. Toyne.

The acid-catalysed hydrolysis of methyl cyclohexanecarboxylate (in 1 : 1 and 1 : 3 dioxan–water), of all the dimethyl and methyl hydrogen cyclohexanedicarboxylates (in 1 : 3 dioxan–water), and of methyl *cis*- and *trans*-4-t-butylcyclohexanecarboxylate (in 1 : 1 dioxan–water), has been studied and the Arrhenius activation energies and non-exponential factors have been determined. The rate coefficients for the first stage of hydrolysis of the diesters were obtained by using Widequist's method.[2] From the results for methyl *cis*- and *trans*-4-t-butylcyclohexanecarboxylate an equatorial methoxycarbonyl group is shown to react 4·8 times more rapidly than an axial methoxycarbonyl group at 90°. On this basis the results for the other esters are discussed in relation to their possible conformations. The methoxycarbonyl group is more stable in the equatorial than in the axial conformation, but the results for acid-catalysed hydrolysis of the *trans*-1,2-esters are best explained by assuming that the compound is diaxial. Polar effects in acid-catalysed hydrolysis of the esters are small. Some of the results obtained by Cavell, Chapman, and Johnson [3] for the alkaline hydrolysis of the esters are discussed in the light of the results for the acid-catalysed hydrolysis, and an attempt has been made to separate polar effects from steric effects in alkaline hydrolysis.

Previous papers [1,3] in this series have been concerned with the study of molecular conformation by determination of the kinetics of alkaline hydrolysis in aqueous dioxan of the isomeric dimethyl cyclohexanedicarboxylates, the methyl 4-t-butylcyclohexanecarboxylates, and the acetates of the isomeric methylcyclohexanols and related compounds. Other similar work includes the study of the kinetics of alkaline hydrolysis in aqueous methanol of the dimethyl cyclohexanedicarboxylates [4] and of the acid-catalysed esterification with methanol of cyclohexanedicarboxylic acids.[5]

The interpretation of the results for alkaline hydrolysis of diesters is not easy: the second stage of hydrolysis is subject to very large polar effects because the carboxylate group formed in the first stage of hydrolysis repels the attacking hydroxyl ion. Cavell, Chapman, and Johnson [3] showed that at 30° the *cis*-1,3- and the *trans*-1,4-ester had similar

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[1] Part II, Chapman, Parker, and Smith, *J.*, 1960, 3634.
[2] Widequist, *Acta Chem. Scand.*, 1950, **4**, 1216; *Arkiv Kemi*, 1955, **8**, 325, 545.
[3] Cavell, Chapman, and Johnson, *J.*, 1960, 1413.
[4] Smith and Fort, *J. Amer. Chem. Soc.*, 1956, **78**, 4000.
[5] Smith and Byrne, *J. Amer. Chem. Soc.*, 1950, **72**, 4407.

rates of hydrolysis and conformationally were diequatorial; the *cis*-1,4- and the *trans*-1,3-esters were also similar to each other, being necessarily axial-equatorial. With the *trans*-1,2-esters, they concluded that the diester was predominantly diequatorial but that " the monoester ion had characteristics of both conformations and was assumed to be an equilibrium mixture of diaxial and diequatorial conformations with probably a slightly greater proportion of diaxial." This conclusion concerning the *trans*-1,2-esters differs from Smith's view; [4,5] without a very detailed analysis, he concluded that the *trans*-1,2-diacid, diester, and monoester are diaxial.

The acid-catalysed hydrolysis in aqueous dioxan was therefore studied to shed further light on the conformations and also to study polar effects and steric effects separately as has been made possible, to a large extent, by the work of Taft.[6,7] The basic assumption in this treatment, made by Ingold [8] in a series of papers on constitutional factors controlling ester hydrolysis, is that in acid-catalysed hydrolysis, to a first approximation, steric effects alone determine the relative rate coefficient, while in alkaline hydrolysis polar and steric effects operate. Therefore from a study of the acid-catalysed and alkaline hydrolyses in the same solvents those two factors should be separable.

EXPERIMENTAL

Materials.—The esters were usually prepared and purified as described by Cavell, Chapman, and Johnson.[3] Methyl hydrogen *cis*-1,2- and *cis*-1,3-cyclohexanedicarboxylate, however, were also prepared by hydrogenating the corresponding monomethyl phthalates with a 5% rhodium–alumina catalyst (Baker Platinum Co. Ltd.) at room temperature and atmospheric pressure, until the calculated volume of hydrogen had been absorbed. The purity of methyl cyclohexanecarboxylate, the *cis*- and the *trans*-4-t-butyl esters, and all the diesters was tested by using vapour-phase chromatography with an alkali-washed Celite column with 12% of Apiezon L as stationary phase. In all cases single peaks were obtained with no minor peaks.

Dioxan was purified as described previously [3] and had b. p. 101·5°/760 mm., m. p. 11·8°, n_D^{22} 1·4212. Distilled water was passed through an Elgastat deioniser (Type B. 102); after this treatment it had a specific resistance greater than 4 megohm cm. This very high value indicates the removal of all dissolved carbon dioxide. Aqueous solutions of hydrochloric acid were made by diluting constant-boiling hydrochloric acid with the deionised water. Solutions of hydrochloric acid in 1 : 1 dioxan–water were prepared by mixing 1 vol. of pure dioxan (stored under nitrogen and with oxygen-free nitrogen bubbled through before use) with 1 vol. of ~0·02N-hydrochloric acid, and in 1 : 3 dioxan–water by mixing 1 vol. of pure dioxan and 3 vol. of ~0·013N-hydrochloric acid.* These solutions were always prepared immediately before the kinetic experiment and were not stored for any length of time. The resulting ~0·01N-hydrochloric acid was standardised against ~0·01N-sodium hydroxide (previously standardised against potassium hydrogen phthalate), a pH meter (E.I.L. model 23A) being used for the titrations.

Kinetic Measurements.—The ester was weighed accurately in a graduated flask, and the solution of hydrochloric acid in aqueous dioxan added to give 100 ml. of 0·01M-ester solution. Portions (10 ml.) of the solution were pipetted into Pyrex tubes which were placed in a bath of solid carbon dioxide and acetone. Air in the dead space above the frozen solution was blown out with nitrogen, and the tubes were sealed off and then suspended in the thermostat bath. It was found that, under the conditions used for the acid hydrolysis, dioxan may be decomposed slowly with the formation of acids. Exclusion of light retarded this decomposition to such an extent that it was negligible during an experiment.

At intervals a tube was removed and cooled rapidly in water. The contents of the tube were transferred completely to a 50 ml. beaker, deionised water (10 ml.) being used for washing.

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* As in the work of Cavell, Chapman, and Johnson [3] most of the esters were studied in the " 1 : 3 " solvent. Methyl *cis*- and *trans*-4-t-butylcyclohexanecarboxylate are insufficiently soluble in this solvent, so these were studied in the " 1 : 1 " solvent. Methyl cyclohexanecarboxylate was studied in both solvents to provide a link between them.

[6] Taft, *J. Amer. Chem. Soc.*, 1952, **74**, 3120.

[7] Taft, *J. Amer. Chem. Soc.*, 1953, **75**, 4231.

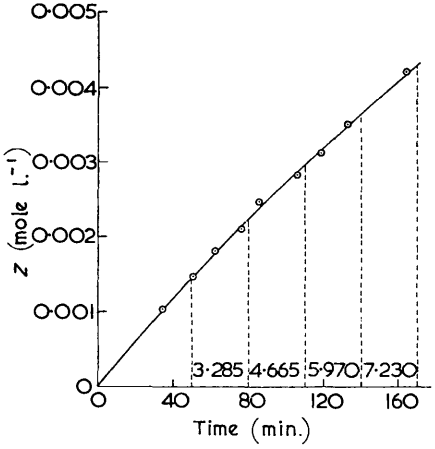
[8] Ingold and his co-workers, particularly, *J.*, 1930, 1032.

This solution was titrated with 0·01N-sodium hydroxide by using the pH meter, atmospheric carbon dioxide being excluded with a stream of nitrogen.

By using the first-order rate equation for monoesters ln $a/(a - x)$ may be plotted against time or, by using the titration volumes, ln $(T_\infty - T_0)/(T_\infty - T_t)$ against time; the best straight line was drawn through the points. The slope of the line gave the apparent first-order rate coefficient (k_2') for the concentration of hydrochloric acid used in the experiment. To allow for solvent expansion at high temperatures the density of the solvent was determined at several temperatures, and the increase in volume from room temperature to the thermostat temperature calculated. The concentration of hydrochloric acid at room temperature was corrected to give the concentration at the experimental temperature. Division of the apparent first-order rate coefficient by this acid concentration gave the second-order rate coefficient for the acid-catalysed hydrolysis of the monoester (k_2). (Throughout this paper second-order rate coefficients are expressed in l. mole^{-1} sec.$^{-1}$.)

The activation energy, E, and non-exponential factor, A, were determined graphically as usual by using the method of least squares and are accurate to about ±300 cal. per mole and ±0·2 unit (in log A), respectively.

For the diesters, analysis of the results in terms of the apparent first-order rate coefficients k_1' and k_2' (for the first and the second stage of the hydrolysis respectively) was required.



Plot of z, the concentration of acid produced in hydrolysis, against time. (The area of each of the four strips under the curve is given by the corresponding figure above the abscissa. These give values of A′, *cf. below and Table* 1.)

Frost and Schwemer's method[9] of calculating the rate coefficient for the first of two competitive consecutive second-order reactions, as used, for example, in the alkaline hydrolysis work, cannot be applied to competitive consecutive first-order reactions and so the rate coefficients were calculated by Widequist's method[2] which depends on changing the time variable. The concentration of acid produced by the hydrolysis was plotted against time, and the area under the curve was divided into four strips, with neglect of the initial part of the curve representing the part of the reaction before the tubes had fully reached the thermostat temperature (see Figure). Then the equation derived by Widequist for competitive consecutive first-order reactions was used, *viz.*,

$$k_1' = \frac{z}{2at - A' - (a/k_2')[1 - \exp(-k_2't)]}$$

where k_1' and k_2' are the apparent first-order rate coefficients for the first and the second stage of hydrolysis respectively (k_2' was previously determined from the hydrolysis of the monoester); z is the amount of product per l. formed at time t (measured by the normality of the acid produced in the hydrolysis); a is the initial concentration of diester; and A' is the area under the curve between $t = 0$ and $t = t$, *i.e.*, $A' = \int_0^t z\,.\,\mathrm{d}t$.

The equation was adapted for the area under the curve between t_1 and t_2. In this way the

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[9] Frost and Schwemer, *J. Amer. Chem. Soc.*, 1952, **74**, 1268.

values of k_1' were determined for four intervals of time and these usually agreed to within 3% (cf. Table 1).

TABLE 1. *Acid-catalysed hydrolysis of dimethyl* trans-1,4-*cyclohexanedicarboxylate at* 81·0° *in* " 1 : 3 " *solvent: an example of the Widequist method.*

$k_2' = 2{\cdot}258 \times 10^{-5}$ sec.$^{-1}$; $a = 0{\cdot}01081$M; Hydrochloric acid = 0·009822N.

t_1 (min.)	t_2 (min.)	$10^6 z_1$ (mole l.$^{-1}$)	$10^6 z_2$ (mole l.$^{-1}$)	A' (mole sec. l.$^{-1}$)	$10^5 k_1'$ (sec.$^{-1}$)
50	80	1435	2220	3·285	4·424
50	110	1435	2975	7·950	4·405
50	140	1435	3680	13·920	4·359
50	170	1435	4360	21·150	4·340

Mean $k_1' = 4{\cdot}38 \times 10^{-5}$ sec.$^{-1}$; $k_1 = 4{\cdot}63 \times 10^{-3}$ l. mole^{-1} sec.$^{-1}$ (when corrected for solvent expansion).

The second-order rate coefficient k_1 was then obtained by using the corrected concentration of acid catalyst as before. The Arrhenius parameters, E and log A, were calculated by the method of least squares and are accurate to ±500 cal. per mole and ±0·4 unit respectively. The second-order rate coefficients and Arrhenius parameters for the compounds studied are given in Tables 2 and 3.

TABLE 2. *Rate coefficients (l. mole^{-1} sec.$^{-1}$) for acid-catalysed hydrolysis.*

Ester	Temp. 70·4° 10^4k	81·0° 10^4k	90·3° 10^4k	96·1° 10^4k	100·0° 10^4k	109·4° 10^4k	E (kcal./mole)	log A
Me cyclohexanecarboxylate [a]	8·10	15·7	26·2	—	53·0 [d]	74·9	15·0	6·45
Me *trans*-4-Bu^t-cyclohexane-carboxylate [a]	7·94 7·91	15·7	25·1	—	—	74·7	15·0	6·41
Me *cis*-4-Bu^t-cyclohexane-carboxylate [a]	—	4·12 [b]	5·56	7·74	13·1 [f]	16·0	15·3	5·92
Dimethyl cyclohexanedicarboxylates (k_1)								
trans-1,4	23·9	46·3	80·2	—	137	—	15·1	6·97
cis-1,4	15·3	29·2	52·0	—	87·4	—	15·2	6·83
trans-1,3	13·8	26·9	47·3	—	84·2	—	15·6	7·08
cis-1,3	22·3	42·8	75·8	—	132	—	15·4	7·14
trans-1.2	—	—	4·80	7·04	10·4 [e]	17·4 [h]	17·7	7·35
cis-1,2	—	—	4·53	6·61	10·2 [e]	17·3 [g]	18·8	7·97
Me cyclohexanecarboxylate	12·2	25·0	43·2	—	77·0	79·8 76·5 } [c]	15·6	7·05
Methyl hydrogen cyclohexanedicarboxylates (k_2)								
trans-1,4	12·4	23·9	42·6	—	75·1 75·1	—	15·6	7·03
cis-1,4 †	8·22	16·2	27·9	—	48·5 48·2	—	15·3	6·63
trans-1,3 †	7·58	15·1	25·7	—	47·4	—	15·7	6·88
cis-1,3 †	12·0	24·3	41·5	—	73·7	—	15·6	7·00
trans-1,2	—	—	2·21	3·28	4·92 [e]	7·93 [h]	17·7	6·99
cis-1,2	—	—	7·46	10·9	16·4 [e]	24·9 [g]	17·0	7·11

[a] In 1 : 1 dioxan–water. All other results refer to 1 : 3 solvent. [b] At 85°. [c] At 100·2°. [d] At 102·2°. [e] At 102·6°. [f] At 105·5°. [g] At 110·0°. [h] At 110·3°.

Values of k are accurate to ±2%, of E to ±300 cal. per mole, and of log A to ±0·2 unit, except for those determined by Widequist's method (see above).

† The alkaline hydrolysis of these monoesters at 25° and 50° was studied to confirm the values obtained by Cavell, Chapman, and Johnson [3] who used the diesters and calculated the rate coefficients by Widequist's [2] and Frost and Schwemer's [9] methods. Mean direct results for " 1 : 3 " solvent are shown below with the indirect values (10^3k) in parentheses, showing that fair agreement is obtained.

	25°	50°
cis-1,4-Monoester	12·6 (12·3)	48·1 (50·5)
trans-1,3-Monoester	10·8 (9·94)	48·1 (44·3)
cis-1,3-Monoester	37·8 (38·7)	143·5 (148·9)

DISCUSSION

Acid-catalysed Hydrolysis of Methyl Cyclohexanecarboxylate and the Methyl 4-t-Butylcyclohexanecarboxylates.—Winstein and Holness,[10] arguing that a t-butyl group attached

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[10] Winstein and Holness, *J. Amer. Chem. Soc.*, 1955, **77**, 5562.

TABLE 3. *Summary of rate coefficients (l. mole^{-1} sec.$^{-1}$) at 90° for acid-catalysed and alkaline hydrolysis in* 1 : 3 *dioxan–water (calculated from Arrhenius parameters).*

Me_2 cyclohexane-dicarboxylates	Acid 10^4k	Alkaline * 10^2k	Me hydrogen cyclohexanedicarboxylates	Acid 10^4k	Alkaline * 10^2k
trans-1,4	79·1	319	*trans*-1,4	42·2	80·4
cis-1,4-	50·2	151	*cis*-1,4-	27·9	30·1
trans-1,3-	47·1	144	*trans*-1,3-	26·3	25·1
cis-1,3-	74·8	346	*cis*-1,3-	41·8	79·3
trans-1,2-	4·62	51·3	*trans*-1,2-	2·19	2·75
cis-1,2-	4·32	23·8	*cis*-1,2-	7·46	0·587
Me cyclohexanecarboxylate	43·1	67·3			
Me cyclohexanecarboxylate [a]	26·5	37·6			
Me *trans*-4-t-butylcyclohexanecarboxylate [a]	25·8	29·9			
Me *cis*-4-t-butylcyclohexanecarboxylate [a]	5·48	3·60			

[a] In 1 : 1 dioxan–water.
* Values obtained from Ref. 3.

to a cyclohexane ring was necessarily in the equatorial conformation, accordingly used the 4-t-butyl group to lock the conformation of substituents at the 1-position in *cis*- and *trans*-isomers, the 1-substituents being respectively axial and equatorial.

From a study of a model of methyl *trans*-4-t-butylcyclohexanecarboxylate, the t-butyl group appears to have no steric effect on the access of a hydrogen ion or a water molecule to the reaction centre, as the t-butyl group is almost entirely hidden from the ester group by the cyclohexane ring. Similarly, in methyl *cis*-4-t-butylcyclohexanecarboxylate the t-butyl group is almost entirely hidden from the ester group by the axial 3- and 5-hydrogen atoms, and no direct steric effect appears possible, although it is conceivable that a small steric effect might be relayed from t-butyl *via* axial hydrogen to the ester group.[11] Further, acid-catalysed hydrolysis is not very sensitive to polar effects,[12] and the t-butyl group in the 4-position is only slightly electron-repelling,[13] so it seems probable that there will be no appreciable polar effect of the 4-t-butyl group in this reaction.

On this basis it follows that the rate coefficients for these two esters give directly the rate coefficients for the axial methoxycarbonyl group as $5{\cdot}48 \times 10^{-4}$ and for the equatorial group as $25{\cdot}8 \times 10^{-4}$ l. mole^{-1} sec.$^{-1}$ at 90° in 1 : 1 dioxan–water (see Table 3). (All rate coefficients considered in this Section refer to 90°.) The rate coefficient for methyl cyclohexanecarboxylate is $26{\cdot}5 \times 10^{-4}$, *i.e.*, only 3% different from that for methyl *trans*-4-t-butylcyclohexanecarboxylate. This confirms that there is no steric or polar effect of the t-butyl group in methyl *trans*-4-t-butylcyclohexanecarboxylate and suggests also that methyl cyclohexanecarboxylate has its methoxycarbonyl group almost entirely in the equatorial conformation. Similarly, cyclohexyl acetate has its acetoxy-group 92% in the equatorial conformation.[1]

If methyl cyclohexanecarboxylate is assumed to be entirely in the equatorial conformation in " 1 : 3 " solvent, and if the ratio of rate coefficients for equatorial and axial ester group (k_e/k_a) is the same in each solvent, then the rate coefficient for an equatorial ester group in methyl cyclohexanecarboxylate at 90° in " 1 : 3 " solvent is $43{\cdot}1 \times 10^{-4}$ (Table 3) and for an axial ester group is $43{\cdot}1 \times 10^{-4} \times 5{\cdot}48/26{\cdot}1 = 9{\cdot}03 \times 10^{-4}$ l. mole^{-1} sec.$^{-1}$ ($26{\cdot}1 \times 10^{-4}$ is the average of the values for methyl cyclohexanecarboxylate and methyl *trans*-4-t-butylcyclohexanecarboxylate in 1 : 1 solvent). The ratio of rate coefficients for equatorial and axial groups is therefore ~4·8.

Acid-catalysed Hydrolysis of 1,4- *and* 1,3-*Dimethyl and Methyl Hydrogen Cyclohexanedicarboxylates*.—The *cis*-1,4- and the *trans*-1,3-diester have unambiguous conformations: they must have one group equatorial and one axial. If the ester groups react independently (*i.e.*, neither group exerts a steric or polar effect on the other) then the rate coefficient should be $(9{\cdot}03 + 43{\cdot}1) \times 10^{-4}$ l. mole^{-1} sec.$^{-1}$. The observed value is

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[11] Cornubert, *Bull. Soc. chim. France*, 1956, 996.
[12] Newman, " Steric Effects in Organic Chemistry," Wiley, New York, 1956, p. 587.
[13] Ref. 12, p. 571.

$50{\cdot}2 \times 10^{-4}$ for the *cis*-1,4-diester and $47{\cdot}1 \times 10^{-4}$ for the *trans*-1,3-diester, agreeing reasonably with the calculated value.

The monoesters, however, may exist with the ester group axial and the carboxyl group equatorial, or *vice versa.* To interpret the results an assumption concerning the properties of the two conformations must be made. The carboxyl and ester groups should differ only slightly in their tendencies to take up axial or equatorial conformations since these tendencies should be governed mainly by interaction of the oxygen atoms with the ring hydrogen atoms, and the presence of OH or OMe should not make much difference. If equilibration takes place after the first stage of hydrolysis to give a monoester with 50% equatorial ester group then the calculated rate coefficient is $(43{\cdot}1 + 9{\cdot}03) \times 10^{-4}/2 = 26{\cdot}1 \times 10^{-4}$ l. mole^{-1} sec.$^{-1}$. The observed value for the *cis*-1,4-monoester is $27{\cdot}9 \times 10^{-4}$, and for the *trans*-1,3-monoester $26{\cdot}3 \times 10^{-4}$. Any preference would be for the equatorial ester group (unless solvation of the carboxyl group makes it effectively larger than the ester group) which might account for the observed velocity's being slightly higher than that calculated on a 50% basis.

If no equilibration takes place after the first stage of hydrolysis then the monoester will have 17·4% equatorial ester group and 82·6% axial, because in the first stage of hydrolysis the equatorial group is preferentially hydrolysed with respect to the axial group in the ratio of 4·8 : 1. The calculated rate coefficient for a monoester of this composition would be $14{\cdot}9 \times 10^{-4}$ l. mole^{-1} sec.$^{-1}$. This value is only half the observed value and it is therefore necessary to assume that rapid equilibration takes place.

The *trans*-1,4- and the *cis*-1,3-diester can in principle have both ester groups equatorial or both axial. Inspection of a model suggests that the conformation with both groups equatorial will be that preferred if the interaction of ester group and ring hydrogen is the dominating factor. It being assumed that the esters are entirely in this conformation, then the calculated rate coefficient is $2 \times 43{\cdot}1 \times 10^{-4} = 86{\cdot}2 \times 10^{-4}$, the observed value being $79{\cdot}1 \times 10^{-4}$ for the *trans*-1,4-diester and $74{\cdot}8 \times 10^{-4}$ l. mole^{-1} sec.$^{-1}$ for the *cis*-1,3-diester. Similarly the *trans*-1,4- and the *cis*-1,3-monoester probably have carboxyl and ester groups both in the equatorial conformation. The calculated rate coefficient is $43{\cdot}1 \times 10^{-4}$, the observed values being $42{\cdot}2 \times 10^{-4}$ and $41{\cdot}8 \times 10^{-4}$ l. mole^{-1} sec.$^{-1}$, respectively.

It is doubtful whether the deviation of the observed values from those calculated as above is large enough to indicate polar or steric effects in any particular case, especially when the initial assumption is that the ratio of equatorial to axial rate in 1 : 1 dioxan–water is the same as in the 1 : 3 solvent. Another complicating factor is that the *trans*-1,4- and *cis*-1,3-di- and mono-esters may in fact contain a small amount of the diaxial conformation.

It is illogical to suggest a steric effect of the 4-methoxycarbonyl and 4-carboxyl groups when it is assumed that the 4-t-butyl group has no steric effect. Further, inspection of models suggests that steric effects of 3-methoxycarbonyl and 3-carboxyl groups should also be very small. However, the ester and acid groups are fairly powerful electron-attracting groups, and although polar effects in acid hydrolysis are small, such effects may account for differences of the order of 10% between the calculated and the observed rate coefficients. The chlorine atom, which is comparable in size and electron-attracting behaviour[14] to the acid and ester groups, has been shown to have an appreciable polar effect in the acid-catalysed hydrolysis of the straight-chain aliphatic esters,[15] even when separated from the reaction centre by several carbon atoms. For example, the rate coefficient for acid-catalysed hydrolysis in water at 25° for $CH_3{\cdot}[CH_2]_3{\cdot}CO_2Me$ is $7{\cdot}35 \times 10^{-5}$, and for $Cl{\cdot}[CH_2]_3{\cdot}CO_2Me$ is $5{\cdot}19 \times 10^{-5}$ l. mole^{-1} sec.$^{-1}$.

In view of the possibility of this polar effect, it may be that the *cis*-1,4- and *trans*-1,3-mono-esters exist with approximately 60% equatorial and 40% axial ester group, rather than with 50% of each. This would give a calculated rate coefficient of

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[14] Jaffé, *Chem. Rev.*, 1953, **53**, 191.

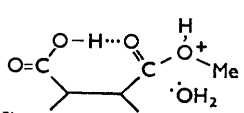
[15] Salmi, *Ber.*, 1939, **72**, 1767.

$29{\cdot}4 \times 10^{-4}$ l. mole^{-1} sec.$^{-1}$, which might be reduced to the observed values of $27{\cdot}9 \times 10^{-4}$ and $26{\cdot}3 \times 10^{-4}$ by polar effects.

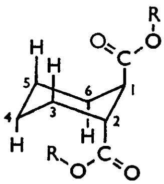
Acid-catalysed Hydrolysis of Dimethyl and Methyl Hydrogen Cyclohexane-1,2-*dicarboxylates.*—The results for the mono- and di-1,2-esters are more difficult to interpret than those for the 1,3- and 1,4-esters because in the 1,2-esters the groups do not react independently. With the *trans*-1,2-diester the rate coefficient is approximately twice that for the *trans*-1,2-monoester. This 2 : 1 ratio in rate coefficients is not a chance ratio arising from the temperature chosen, since the activation energies are the same within experimental error, and the ratio will therefore be the same over a considerable range of temperature. The ratio is predictable if the two compounds are conformationally similar and it corresponds to a simple statistical factor. The *trans*-1,2-esters can be either diaxial or diequatorial and since the *trans*-1,4- and *cis*-1,3-esters have been shown to exist largely in the diequatorial conformation it is reasonable to assume, in the first place, that the same is true of the *trans*-1,2-esters.[3] The rate coefficient for a diester with two equatorial groups reacting independently is $86{\cdot}1 \times 10^{-4}$ compared with the observed value of $4{\cdot}62 \times 10^{-4}$ l. mole^{-1} sec.$^{-1}$. Presumably this low value is chiefly due to a primary steric effect, although there will also be a small polar effect.

With the *cis*-1,2-esters the conformation is necessarily axial-equatorial and the distance between the two groups is the same as in the diequatorial conformation of the *trans*-1,2-esters. For the *cis*-1,2-diester the rate coefficient is $4{\cdot}32 \times 10^{-4}$ and the calculated value is $(43{\cdot}1 + 9{\cdot}03) \times 10^{-4} = 52{\cdot}1 \times 10^{-4}$ l. mole^{-1} sec.$^{-1}$; the observed value is about 8% of the calculated value, presumably because of a primary steric effect. For the *cis*-1,2-monoester the calculated rate coefficient is $(43{\cdot}1 + 9{\cdot}03) \times 10^{-4}/2 = 26{\cdot}1 \times 10^{-4}$ on the assumption that 50% of the molecules have the ester group equatorial (see interpretation of reactions of *cis*-1,4- and *trans*-1,3-monoesters, p. 2548); the actual value is $7{\cdot}46 \times 10^{-4}$ l. mole^{-1} sec.$^{-1}$, about 30% of the calculated value. If the *cis*-1,2-monoester had the ester group entirely in the equatorial conformation, then the observed rate coefficient would be 17% of the calculated value. The observed rate coefficient for the monoester is almost twice that for the diester. The reason for this, and for the ratio $k_{\text{obs.}}/k_{\text{calc.}}$ for the monoester being, even on an extreme assumption about the conformation of the monoester, much higher than that for the diester, may be that the steric effect of the carboxyl group, even when solvated, is less than the steric effect of the methoxycarbonyl group. In the crowded situation the loss of the methyl group in the first stage of hydrolysis might considerably reduce the steric hindrance for the reaction of the second ester group. However, this effect should also operate in the *trans*-1,2-compounds if they were diequatorial, since the distance between the two groups is then the same as in the *cis*-compound, but there is no sign of any such effect.

Another possible explanation for the increase in rate with the *cis*-1,2-monoester compared with the *cis*-1,2-diester is that internal hydrogen-bonding may occur in the monoester, producing a change in electron density at the carbonyl carbon atom of the ester group, so that the water molecule can attack more easily [see (I)]. This effect may also operate in the *trans*-1,2-monoester if diequatorial, but in this case no such effect is required to account for the results.



(I)



(axial H atoms only are shown)

(II)

It does not therefore seem possible to give an entirely satisfactory explanation of the rates for all four 1,2-esters on the assumption that the *trans*-1,2-esters are diequatorial, and the other extreme assumption may therefore be considered.[5]

If the *trans*-1,2-esters exist as diaxial compounds then the calculated rate coefficient for the diester is $18{\cdot}1 \times 10^{-4}$ l. mole^{-1} sec.$^{-1}$, so that the observed value is approximately 25% of the calculated value. However, the two ester groups are so separated that no primary steric effect can occur between the two groups to account for this reduction. It may, however, be accounted for in the following way. An ester group, undergoing acid hydrolysis, will increase in size on attaining the transition state because of the addition of the proton, the attacking water molecule, and other water molecules of solvation. With an isolated axial ester group the increase in size may cause pressure on the 3- and 5-axial hydrogen atoms and consequently buckle the cyclohexane ring to relieve the strain.[16] With another axial ester group (or acid group) present on the other side of the ring, in the 2-position for example, any displacement caused by the ester group undergoing hydrolysis would cause the axial 4- and 6-hydrogen atoms to interact with the ester group (or acid group) in the 2-position [see (II)]. This relayed steric effect may account for the observed reduction in rate.

If the *trans*-1,2-esters are diaxial then the *cis*-1,2-esters are much more crowded than the *trans*-1,2-esters because of the direct ester–ester or ester–acid interactions. If the steric effect of an acid group is less than that of an ester group in the *cis*-1,2-compounds, then this will increase the rate for the monoester as compared with the diester. The reactivity of *cis*-1,2-monoester may also be increased by the hydrogen-bonding effect. Neither of these influences will operate in the *trans*-1,2-monoester if this is diaxial, because the groups will be too far apart.

A peculiar relationship in rate of *cis*-1,2-compounds is also noticeable in the esterification of the *cis*-1,2-di- and mono-acids (monomethyl esters).[5] A preliminary abstract [17] seems to suggest that a similar effect is observed in the acid-catalysed hydrolysis in aqueous acetone. The rates of acid-catalysed hydrolysis of the 1,2-esters in " 1 : 3 " dioxan–water may thus be more satisfactorily explained on the basis of the *trans*-compounds' being diaxial than on the basis of their being diequatorial.

Activation Energies and Non-exponential Factors in Acid-catalysed Hydrolysis.—For the 1,3- and 1,4-positions, compounds with axial ester groups present appear to have a lower non-exponential factor than compounds with equatorial groups. The difference between the values for equatorial and axial ester groups in the same position and with the remaining part of the molecule fixed, is always small but is largest for methyl *trans*- and methyl *cis*-4-t-butylcyclohexanecarboxylate where the ester groups are entirely equatorial and axial respectively. In all other cases, *e.g.*, the *trans*-1,4-diester and *cis*-1,4-diester (and with the monoesters), there is a small difference, with the more axial compounds always having a lower non-exponential factor. This situation is possibly due to " classical steric hindrance " (see discussion of alkaline hydrolysis below). The variation in the value of the activation energy is not regular and is very small, almost covered by the estimated experimental error.

The 1,2-esters are quite different from the 1,3- and 1,4-esters in this respect. The *cis*-1,2-diester has a high activation energy and a high non-exponential factor due, probably, to steric hindrance, in the very crowded situation, decreasing solvation of the transition state. The *trans*-1,2-diester has a rather large activation energy and non-exponential factor. If the compound is diaxial this may be explained by the buckling effect (see above), raising E and decreasing solvation. If the compound is diequatorial the relation of the two groups to each other is the same as in the *cis*-1,2-diester; the values of E and log A are not raised to the same extent, however. The *trans*-1,2-monoester values are essentially similar to the diester values except that the log A factor is lower by 0·36. On

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[16] Cf. Newman, *op. cit.*, ref. 12, p. 31.

[17] Smith, Scrogham, and Stump, Amer. Chem. Soc. Meeting Abs., Sept. 1959, 36s.

a statistical basis the value might be expected to be 0·3 lower. With the *cis*-1,2-monoester, the activation energy and non-exponential factors are lower than for the diester. This may be due to less steric inhibition of solvation and possibly a special orientation of the transition state required for the hydrogen-bonding effect.

Alkaline Hydrolysis of Methyl Cyclohexanecarboxylate and the Methyl 4-t-Butylcyclohexanecarboxylates.—The work of Cavell, Chapman, and Johnson[3] may now be further discussed in relation to the acid-catalysed hydrolysis results and the conformations deduced therefrom. The rate coefficients for alkaline hydrolysis extrapolated to 90° are given in Table 3. In the absence of any steric effect of the 4-t-butyl group (see discussion of acid-catalysed hydrolysis, p. 2547) we can evaluate the polar effect (in log k units) of the equatorial 4-t-butyl group on the equatorial 1-ester group in the alkaline hydrolysis of methyl *trans*-4-t-butylcyclohexanecarboxylate. The value for " 1 : 1 " solvent at 90° is given by $\log (29{\cdot}9 \times 10^{-2}/37{\cdot}6 \times 10^{-2}) = -0{\cdot}10$.

With methyl *cis*-4-t-butylcyclohexanecarboxylate it is necessary to consider a possible change in the polar effect of the t-butyl group and also the change in the steric effect of ring hydrogen atoms, on changing the ester group from an equatorial to an axial conformation. The sum of the changes in polar and steric effects is $\log_{10} (3{\cdot}60 \times 10^{-2}/29{\cdot}9 \times 10^{-2}) = -0{\cdot}92$. It is reasonable to assume that changing the ester group from the equatorial to the axial conformation causes a reduction in rate because of steric influences which are chiefly due to 3- and 5-axial hydrogen atoms. The Taft–Ingold assumption is that steric influences are the same in acid-catalysed hydrolysis as in alkaline hydrolysis.[18] On the assumption of no polar effect of the 4-t-butyl group in acid hydrolysis, the steric effect of the axial hydrogen atoms in methyl *cis*-4-t-butylcyclohexanecarboxylate as compared with the *trans*-compound is obtained from the rate coefficients for acid-catalysed hydrolysis as $\log (5{\cdot}48 \times 10^{-4}/26{\cdot}1 \times 10^{-4}) = -0{\cdot}68$. Therefore the change in polar effect of the equatorial 4-t-butyl group in alkaline hydrolysis on changing the ester group to the axial conformation is $-0{\cdot}92 - (-0{\cdot}68) = -0{\cdot}24$, *i.e.*, the total polar effect is $-0{\cdot}34$. This value is 3·4 times the value found when the ester group is in the equatorial conformation.

It is doubtful whether so large an increase is reasonable. In principle, however, this change may result from one of two separate effects or a combination of them. Either it is caused by a change in the intrinsic polar influence of the 4-t-butyl group, *i.e.*, a change in the Hammett σ value,[19] or it is caused by the axial ester group's being more susceptible to polar influence than the equatorial ester group. This corresponds to a change in the Hammett ρ value. If this situation is accepted as reasonable, whatever factors are responsible, then it is desirable to see whether the behaviour of the other esters can be understood on the basis of (*a*) steric effects on axial ester groups being 4·8 times larger than for equatorial groups in both alkaline hydrolysis and acid hydrolysis, and (*b*) the changes in polar effect with conformation being similar to those observed with the 4-t-butyl ester.

Alkaline Hydrolysis of Dimethyl Cyclohexanedicarboxylates.—In the " 1 : 3 " solvent, the rate coefficient for an equatorial ester group in alkaline hydrolysis is $67{\cdot}3 \times 10^{-2}$, and for an axial group $67{\cdot}3 \times 10^{-2}/4{\cdot}80 = 14{\cdot}0 \times 10^{-2}$ l. mole^{-1} sec.$^{-1}$. Therefore the rate coefficient for the *trans*-1,4- and *cis*-1,3-diester with two equatorial groups reacting independently is $134{\cdot}6 \times 10^{-2}$, the average observed value being 332×10^{-2} l. mole^{-1} sec.$^{-1}$. This means that the polar effect of an ester group is responsible for an increase in rate by a factor of 2·6, or 0·42 in log units. For *trans*-1,3- and *cis*-1,4-compounds the calculated rate coefficient is $81{\cdot}4 \times 10^{-2}$ and the average observed value is $147{\cdot}5 \times 10^{-2}$ l. mole^{-1} sec.$^{-1}$, giving a factor of 1·81, or 0·26 in log units. These two factors are not very different and do not fit in with the supposed great differences in polar effect of the equatorial 4-t-butyl group as exerted on equatorial and axial ester groups.

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[18] Bender, *J. Amer. Chem. Soc.*, 1951, **73**, 1626.

[19] Hammett, " Physical Organic Chemistry," McGraw-Hill, New York, 1940, p. 184.

As an alternative the extreme view may be taken that there is negligible change in the polar effect of the 4-t-butyl group as between the equatorial and axial ester groups. The difference in rate coefficient for alkaline hydrolysis between methyl *trans*- and *cis*-4-t-butylcyclohexanecarboxylate would then be due entirely to the difference in steric effect of the ring hydrogen atoms on the equatorial and axial ester groups. This view involves rejecting, in this situation, the Taft–Ingold assumption concerning the similarity of transition states and steric effects in acid-catalysed and alkaline hydrolysis.

The Arrhenius parameters in alkaline and acid hydrolysis for the *cis*- and *trans*-4-t-butyl esters suggest that the Taft–Ingold assumption may indeed be incorrect in this case. For acid-catalysed hydrolysis a comparison of the *cis*- and *trans*-4-t-butyl esters shows that a change from *trans*- to *cis*- causes a small increase in activation energy and a *decrease* in the non-exponential term, and this appears to be due to " classical " steric hindrance. In alkaline hydrolysis,[3] however, the change from *trans*- to *cis*- causes a large increase in activation energy and an *increase* in the non-exponential term.* This may be caused by an increase in the steric hindrance to solvation of the transition state in the *cis*- as compared with the *trans*-compound. If this explanation is correct, then the change in solvation in going from the initial state to the transition state is evidently more important in alkaline than in acid hydrolysis.

If we take this view, the change in steric effect of ring hydrogen atoms when the ester group is changed from equatorial to axial conformations changes k by a factor of 8·3 in alkaline hydrolysis for the " 1 : 1 " solvent. If this factor is applied to the " 1 : 3 " solvent the rate coefficient for the equatorial ester group is $67{\cdot}3 \times 10^{-2}$ and that for the axial ester group is $8{\cdot}1 \times 10^{-2}$ l. mole^{-1} sec.$^{-1}$.†

For the dimethyl *trans*-1,4- and *cis*-1,3-esters in the absence of polar effects the rate coefficient would be $134{\cdot}6 \times 10^{-2}$. The average rate coefficient is 332×10^{-2} l. mole^{-1} sec.$^{-1}$ and this corresponds to the polar effect of ester group on ester group increasing the rate by a factor of 2·6 (the same value as if the Taft–Ingold view is accepted). For the dimethyl *cis*-1,4- and *trans*-1,3-esters the rate coefficients in the absence of polar effects should be $(67{\cdot}3 + 8{\cdot}1) \times 10^{-2} = 75{\cdot}4 \times 10^{-2}$ l. mole^{-1} sec.$^{-1}$ in each case. The observed average value is $147{\cdot}5 \times 10^{-2}$, and therefore polar effects increase the rates by a factor of $\sim 2{\cdot}0$. The difference between the factors of 2·6 and 2·0 may be explained if orientation of the dipoles in the ester groups gives slightly different polar effects. The logarithm of the mean of these factors, $+0{\cdot}36$, may be taken as an approximate measure of the polar effects of the ester group in the alkaline hydrolysis. Thus the polar effect of the t-butyl group in this reaction is $-0{\cdot}10$ (see above) and that of the ester group is $+0{\cdot}36$, *i.e.*, the relative polar effect of the two groups (ignoring the difference in sign) is $\sim 3{\cdot}5$. According to Jaffé [14] the σ_m values are $-0{\cdot}12$ for t-butyl and $+0{\cdot}32$ for the ester group. These are in the ratio of ~ 3 (σ_m values are approximate measures of inductive effects). The relative polar effect of the groups in the cyclohexane ring as derived above is thus approximately the same as their relative inductive effect in the benzene ring.

The alkaline hydrolysis of methyl cyclohexanecarboxylate, methyl *cis*- and *trans*-4-t-butylcyclohexanecarboxylate, and dimethyl 1,4- and 1,3-cyclohexanedicarboxylates can

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* For the *trans*-compound, $E = 11{\cdot}0$ kcal./mole and $\log A = 6{\cdot}1$; for the *cis*-compound, $E = 13{\cdot}6$ kcal./mole and $\log A = 6{\cdot}7$.

† The factor cannot be derived directly for the " 1 : 3 " solvent since the methyl 4-t-butylcyclohexanecarboxylates are too insoluble for kinetic study. The validity of assuming that the relative reactivity of equatorial and axial ester groups in alkaline hydrolysis is the same in the two solvents was tested by measuring the rate coefficients for dimethyl *trans*- and *cis*-1,4-cyclohexanedicarboxylates in the " 1 : 1 " solvent at 14·8°. The values are $3{\cdot}62 \times 10^{-2}$ and $1{\cdot}72 \times 10^{-2}$ l. mole^{-1} sec.$^{-1}$, respectively, the ratio of these being 2·1. Values calculated from Cavell, Chapman, and Johnson's work [3] for the " 1 : 3 " solvent are in the ratio of 2·3. The ratio of the rate coefficients for the *trans*- and *cis*-esters depends on (*a*) the relative reactivity of equatorial and axial ester groups in the absence of polar effects of substituents, and (*b*) the change in the mutual polar effects of the ester groups as between *eq-eq* and *eq-ax* conformations. The agreement (to within 8%) of the above values of the ratio suggests that (*a*) and (*b*) are about the same in the two solvents.

thus be explained fairly well in the following terms: (*a*) the conformations based on the results for acid-catalysed hydrolysis, (*b*) steric effects giving the equatorial and axial ester groups a relative reactivity of 8·3 at 90°, (*c*) polar effects of the t-butyl and methoxycarbonyl groups which are roughly independent of conformation and are related to the inductive effect of the groups in the benzene system.

The 1,2-*Diesters in Alkaline Hydrolysis.*—We consider first the *cis*-1,2-diester which has the unambiguous conformation of equatorial-axial ester groups. The rate coefficient in acid-catalysed hydrolysis for the compound with the groups reacting independently would be $52·1 \times 10^{-4}$, and the observed value is $4·32 \times 10^{-4}$, *i.e.*, there is a reduction in rate by a factor of 0·083 or −1·08 in log units. This is probably a measure of the mutual steric effect of the two ester groups in acid-catalysed hydrolysis and, if the Taft–Ingold view is accepted, it can be applied to the alkaline hydrolysis results. For alkaline hydrolysis the rate coefficient calculated for this compound with the groups reacting independently is either $81·4 \times 10^{-2}$ or $75·4 \times 10^{-2}$ (see discussion of *trans*-1,3- and *cis*-1,4-diesters, above and the observed value is $23·8 \times 10^{-2}$, giving a reduction factor of 0·29 or 0·32, *i.e.*, −0·53 or −0·50 in log units, depending on the value taken for the calculated rate; the polar effect derived by subtracting −1·08 is +0·55 or +0·58 respectively. These values are rather larger than the value of ~0·36 obtained for the polar effect in *trans*-1,3- or *cis*-1,4-diesters but are quite reasonable since the two groups are now much closer together.

If the *trans*-1,2-diester is diaxial (the conformation which gives the better explanation for the results of acid-catalysed hydrolysis) then the calculated rate coefficient for acid-catalysed hydrolysis is $18·06 \times 10^{-4}$; the observed value is $4·62 \times 10^{-4}$ l. mole^{-1} sec.$^{-1}$, giving a factor of 0·26 or −0·59 in log units. It is supposed that this value measures the steric effect produced by the buckling of the cyclohexane ring (see p. 2550). For alkaline hydrolysis the calculated rate coefficient is either $28·2 \times 10^{-2}$ or $16·2 \times 10^{-2}$ (see discussion of *trans*-1,3- and *cis*-1,4-diesters above, p. 2551) and the observed value is $51·3 \times 10^{-2}$ l. mole^{-1} sec.$^{-1}$; the factor is thus 1·82 or 3·16, *i.e.*, +0·26 or +0·50 in log units. If the measure of the steric effect based on the acid-catalysed hydrolysis may be applied, the polar effect in alkaline hydrolysis is either +0·85 or +1·09. If the *trans*-1,2-diester is supposed to have the diequatorial conformation (following Cavell, Chapman, and Johnson [3]) the polar effect in alkaline hydrolysis is +0·85.

Whatever assumption is made about the conformation of the *trans*-1,2-diester, the polar effect is thus calculated to be somewhat larger than that for the *cis*-1,2-diester (+0·55 or +0·58) and is considerably larger than the value for *trans*-1,3- and *cis*-1,4-diesters (+0·36). In the light of this discussion it does not seem possible to reach firm conclusions about the conformation of the *trans*-1,2-diester.

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