285. *Conformation and Reactivity. Part I. Kinetics of the Alkaline Hydrolysis of the Methyl Cyclohexane-mono- and -di-carboxylate and 4-t-Butylcyclohexanecarboxylates.*

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The preparation of pure *cis*- and *trans*-4-t-butylcyclohexanecarboxylic acid and their methyl esters is described. Heats and entropies of activation for the alkaline hydrolysis of these esters in dioxan–water (1 : 1), of methyl cyclohexanecarboxylate in dioxan–water (1 : 1 and 1 : 3), and of all the methyl hydrogen and dimethyl cyclohexanedicarboxylates in dioxan–water (1 : 3) have been determined by the methods of Frost and Schwemer [1] and of Widequist [2] where necessary. Since methyl *trans*-4-t-butylcyclohexanecarboxylate adopts the diequatorial conformation exclusively, the reactivity in hydrolysis of an equatorial methoxycarbonyl group has been characterised; also, with less certainty, that of an axial group, which is hydrolysed at least 17 times more slowly at 30°. The methoxycarbonyl group is apparently more stable in the equatorial than in the axial conformation. The conformations of the various methyl hydrogen and dimethyl cyclohexanedicarboxylates are discussed in the light of the kinetics of their hydrolyses; and conformational, electrostatic, and primary steric effects in the hydrolyses are elucidated.

The kinetics of alkaline hydrolysis of simple carboxylic esters have been extensively studied, but dicarboxylic esters have received much less attention because their hydrolysis usually involves competitive consecutive reactions. It is only recently through the work of Frost and Schwemer [1] and of Widequist [2] that explicit methods have been developed for determining the rate coefficients for the first and the second stage of the hydrolysis from measurements of the alkali consumed as a function of time. The object of the investigation now reported was to exploit these methods to study the hydrolysis of esters in which the conformation of the methoxycarbonyl group might be important in connexion with reactivity, and so to correlate conformation with the parameters of the Arrhenius equation and of transition-state theory. While the work was in progress Winstein and Holness [3] showed that the presence of a suitably placed t-butyl group in the cyclohexane structure rendered it conformationally homogeneous. Therefore, by including the methyl esters of *cis*- and *trans*-4-t-butylcyclohexanecarboxylic acid and of the unsubstituted acid the reactivity of axial and equatorial methoxycarbonyl groups could be determined. It was thus possible to elucidate more fully the structure and reactivity of the methyl hydrogen and the dimethyl esters of the cyclohexanedicarboxylic acids.

The medium used for most of our experiments was dioxan–water (1 : 3 by volume), containing ~15 g. per l. of potassium chloride to eliminate ionic strength effects; but because of the insolubility of the methyl 4-t-butylcyclohexanecarboxylates in this medium, their hydrolyses were carried out in less aqueous dioxan (1 : 1 by volume), containing potassium chloride as before, and an estimate of the influence of this change on the Arrhenius parameters was obtained by studying the hydrolysis of methyl cyclohexanecarboxylate in both media. The dioxan–water (1 : 3 by volume) medium was chosen originally because results on the hydrolysis of acyclic dicarboxylic esters in this solvent were available.[1] Smith and Fort [4] have independently studied the kinetics of alkaline hydrolysis of the methyl cyclohexanedicarboxylates in aqueous methanol, but their results, which are referred to below (p. 1421), were not available when this work was

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

[2] Widequist, *Acta Chem. Scand.*, 1950, **4**, 1216; *Arkiv Kemi*, 1955, **8**, 325, 545.

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

[4] Smith and Fort, *J. Amer. Chem. Soc.*, 1956, **78**, 4000.

begun and when a preliminary account of it was given.[5] As to the mechanism of ester hydrolysis operative in the examples we have studied there can be little doubt that this is, in the terminology of Day and Ingold,[6] base-catalysed bimolecular hydrolysis with acyl–oxygen fission.

The required esters were prepared by standard methods, details of which are given in the experimental section, and only methyl *cis*- and *trans*-4-t-butylcyclohexanecarboxylate call for comment. Morris and Buls [7a] described the preparation of two stereoisomeric 4-t-butylcyclohexanecarboxylic acids and we have confirmed their observation that hydrogenation of *p*-t-butylbenzoic acid in aqueous sodium hydroxide at 220°/100 atm. with a Raney nickel catalyst affords an acid of m. p. 174·5—175·5° (after recrystallisation from aqueous ethanol). Morris and Buls assigned the *trans*-configuration to this acid on the basis of method of preparation and m. p., and we believe this to be correct in view of the properties, discussed on p. 1419, of the methyl ester, which was obtained from the acid by the action of ethereal diazomethane. This ester, b. p. 245°/760 mm., 84°/0·9 mm., showed regular second-order kinetics in alkaline hydrolysis, analysed satisfactorily, and on partial or complete hydrolysis gave the acid of m. p. 174·5—175·5° without further purification. Morris and Buls obtained a second acid, of m. p. 89·5—90·5°, by hydrogenation of *p*-t-butylbenzoic acid in aqueous sodium hydroxide at 170°/70 atm. with a Raney nickel catalyst, and recrystallisation of the crude acid from aqueous ethanol. This method of purification is, however, unsatisfactory as the *cis*-acid is more soluble than the *trans*-acid in this solvent. We have separated the mixed *cis*- and *trans*-acids so produced by partial hydrolysis of the mixed methyl esters, the *trans*-ester being hydrolysed faster than the *cis* (cf. p. 1417), and thus obtained in the first place a specimen of methyl *cis*-4-t-butylcyclohexanecarboxylate of m. p. 26·1—26·7°, identical with the ester obtained by the action of ethereal diazomethane on an acid of m. p. 118° obtained as follows. *p*-t-Butylbenzoic acid was hydrogenated in acetic acid at 90° and 60 lb./sq. in. with Adams platinum catalyst, and the product was crystallised to constant m. p. from dry methanol at —80°. The *cis*-configuration was assigned on the basis of hydrogenation at low temperatures with a platinum catalyst, m. p., and rate of hydrolysis of the ester (p. 1417). Any specimen of the pure ester on partial or complete hydrolysis gave the acid having m. p. 118° without further purification. In our view Morris and Buls's acid of m. p. 89·5—90·5° is a mixture of the *cis*- and *trans*-isomers.

Since our work was completed, van Bekkum, Verkade, and Wepster [7b] have obtained the pure *cis*- and *trans*-4-t-butylcyclohexanecarboxylic acids, by an independent method. They record for the *cis*-acid, m. p. 118—118·5°, and for the *trans*-acid m. p. 175—176°, in close agreement with our observations.

EXPERIMENTAL

M. p.s and b. p.s of pure compounds are the same as those recorded in the literature, or very nearly so.

Materials.—Dimethyl esters of dicarboxylic acids. Dimethyl *cis*-cyclohexane-1,2-dicarboxylate was prepared by the method of Cope and Herrick [8] and had b. p. 70°/0·06 mm., 90°/1 mm., n_D^{20} 1·4565. Its purity is attested by the regular second-order kinetics observed in the first stage of hydrolysis. Dimethyl *trans*-cyclohexane-1,2-dicarboxylate was prepared by the esterification of the corresponding dicarboxylic acid (10 g.) by heating it with methanol (20 ml.), sulphuric acid (10 g.; *d* 1·18), and benzene (28 ml.) for 10 hr. The product was poured into water, and the benzene layer was separated, washed with 5% sodium carbonate solution and then with water, and dried ($MgSO_4$). The solvents were removed on the steam-bath, and the

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[5] Cavell, Chapman, and Johnson, *Chem. and Ind.*, 1956, 367.

[6] Day and Ingold, *Trans. Faraday Soc.*, 1941, **37**, 686.

[7a] Morris and Buls, U.S.P. 2,771,487; B.P. 703,516.

[7b] van Bekkum, Verkade, and Wepster, *Kgl. Akad. Wetensch., Proc., B*, 1959, **62**, 147.

[8] Cope and Herrick, *Org. Synth.*, **30**, 29, 93.

residue was distilled *in vacuo*, giving the pure *trans*-diester, b. p. 72°/0·01 mm. Recrystallisation to constant m. p. from benzene–light petroleum (b. p. 60—80°) gave material of m. p. 33—34° (yield 3 g., 26%). The *trans*-diacid was prepared in two ways. (*a*) The *cis*-diester was hydrolysed with methanolic potassium hydroxide, and the acid produced was rearranged by Smith and Byrne's method.[9a] (*b*) Dimethyl phthalate was hydrogenated at high temperature and high pressure with a Raney nickel catalyst, following Price and Schwarcz's directions,[9b] and the product was hydrolysed to the mixed acids, which were rearranged as in method (*a*). Dimethyl *trans*- and *cis*-cyclohexane-1,3-dicarboxylate were prepared by esterifying the corresponding pure dicarboxylic acids with an excess of ethereal diazomethane prepared by Boer and Becker's method.[10] Addition of the diazomethane was continued until its yellow colour persisted in the solution on shaking. The solution was gently warmed to decompose the excess of diazomethane, and dried (Na_2SO_4), and the ether was removed. The residue was in each case distilled *in vacuo*, to give the pure *trans*-, b. p. 91°/0·5 mm., n_D^{20} 1·4579, and *cis*-1,3-diester, b. p. 110°/1 mm., n_D^{20} 1·4569. The *trans*-1,3-diacid was prepared by hydrogenation of isophthalic acid (40 g., 0·24 mole) in 10% sodium hydroxide solution (300 ml.) at 150—200°/150—200 atm., with a Raney nickel catalyst (10 g.). The catalyst was removed and the solution was acidified with 6N-hydrochloric acid. After cooling, the precipitated acids were filtered off. The crude acids were separated by Skita and Rössler's method [11] to give the pure *trans*-1,3-diacid, m. p. 148—149°. The *cis*-1,3-acid was prepared by hydrogenation of dimethyl isophthalate by Ramirez and Sargent's method.[12] The mixed esters produced were hydrolysed with methanolic potassium hydroxide and the acids were separated, as in the preparation of the *trans*-acid, to give pure *cis*-1,3-diacid, m. p. 167°. Dimethyl *trans*-cyclohexane-1,4-dicarboxylate was prepared by Fichter and Holbro's method [13] and had m. p. 70—71°. Dimethyl *cis*-cyclohexane-1,4-dicarboxylate was prepared by esterification of the pure acid with ethereal diazomethane, as for the 1,3-esters, and had b. p. 70°/0·01 mm., n_D^{20} 1·4588. The *cis*-1,4-diacid was prepared by hydrogenation of terephthalic acid in sodium hydroxide solution at high temperature and pressure with a Raney nickel catalyst, as above. The mixed acids produced were separated by Smith and Byrne's method [9a] to give pure *cis*-1,4-diacid, m. p. 166·5—167·5°. The saponification equivalent of its dimethyl ester was 100·5 (required 100·1).

Monomethyl Esters of Dicarboxylic Acids.—Methyl hydrogen *cis*-cyclohexane-1,2-dicarboxylate, prepared by Smith and Byrne's method,[9a] had m. p. 69·5—70·5°. Its *trans*-isomer, prepared by Vavon and Peignier's method,[14] had m. p. 95·5—96·5°. Methyl hydrogen *trans*-cyclohexane-1,4-dicarboxylate was prepared by the partial hydrolysis of the dimethyl ester (4·7 g., 0·24 mole) with sodium hydroxide (2% in 1 : 4 v/v aqueous methanol, 47 ml.) for 4 hr. The methanol was removed and the solution shaken with ether to extract unchanged dimethyl ester. The monomethyl ester and the dicarboxylic acid were precipitated with 4N-hydrochloric acid and removed by filtration. The precipitate was recrystallised to constant m. p. from light petroleum (b. p. 60—80°), to give pure methyl hydrogen *trans*-cyclohexane-1,4-dicarboxylate, m. p. 126—126·5° (yield 1·68 g., 38%).

Methyl Esters of Monocarboxylic Acids.—Methyl cyclohexanecarboxylate was prepared by esterification of cyclohexanecarboxylic acid (from L. Light and Co.) with methanol and sulphuric acid as above. The product was fractionally distilled (18″ column) and had b. p. 74°/18 mm. *Methyl* cis- and trans-*4-t-butylcyclohexanecarboxylate* were prepared by the esterification of *cis*- and *trans*-4-t-butylcyclohexanecarboxylic acid respectively, with ethereal diazomethane as for the *trans*-1,3-diester. On recrystallisation to constant m. p. from pure methanol at −80°, the *cis*-ester had m. p. 26·1—26·7° (Found: C, 72·2; H, 11·1. $C_{12}H_{22}O_2$ requires C, 72·7; H, 11·2%). The *trans*-isomer had b. p. 84°/0·9 mm., 245°/760 mm. (Found: C, 72·9; H, 10·9%). The *cis*-acid was prepared by hydrogenation of *p*-t-butylbenzoic acid (10 g.) in glacial acetic acid (100 ml.) with Adams platinum catalyst (0·5 g.) at 90° and 60 lb./sq. in. The catalyst was filtered off and the acetic acid was removed *in vacuo*. The crude hydrogenated material was recrystallised to constant m. p. from pure methanol at −80°, to give pure cis-*4-t-butylcyclohexanecarboxylic acid*, m. p. 118° (Found: C, 72·2; H, 11·3. $C_{11}H_{20}O_2$ requires C, 71·6; H,

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[9a] Smith and Byrne, *J. Amer. Chem. Soc.*, 1950, **72**, 4406.
[9b] Price and Schwarcz, *ibid.*, 1940, **62**, 2894.
[10] Boer and Becker, *Rec. Trav. chim.*, 1954, **73**, 229.
[11] Skita and Rössler, *Ber.*, 1939, **72**, 265.
[12] Ramirez and Sargent, *J. Amer. Chem. Soc.*, 1952, **74**, 5785.
[13] Fichter and Holbro, *Helv. Chim. Acta*, 1938, **21**, 141.
[14] Vavon and Peignier, *Bull. Soc. chim. France*, 1929, **45**, 297.

10·9%). This acid was also prepared by the hydrogenation of *p*-t-butylbenzoic acid in sodium hydroxide solution with a Raney nickel catalyst at 170°/70 atm. The crude product was esterified with methanol and sulphuric acid, and the mixed esters (28 g., 0·14 mole) were partially hydrolysed with sodium hydroxide (4 g., 0·1 mole, in 1 : 1 v/v aqueous methanol, 300 ml.) for 24 hr. The methanol was removed by distillation and the aqueous solution was shaken with several portions of ether. The ethereal solution was washed with water and dried (Na_2SO_4). After removal of the ether, the crude ester was recrystallised to constant m. p. from pure methanol at −80°, and had m. p. 26·1—26·7° (yield 3·5 g., 9% overall). The *trans*-acid was prepared by Morris and Buls's method [7a] and had m. p. 174·5—175·5°.

Solvents.—Water. Carbon dioxide-free air was passed through freshly distilled water, contained in a tall aspirator, for about 10 days. After this time, no carbon dioxide could be detected in the water by titration.

Dioxan. Commercial " purified " dioxan (4 l.) was boiled with 12N-hydrochloric acid (56 ml.), stannous chloride (50 g.), and water (400 ml.) for 12 hr., with a continuous stream of nitrogen passing through the solution. The solution was cooled and sodium hydroxide (70 g.; commercial flake) was added. The mixture was shaken, set aside for several hours, and filtered. The filtrate was then left over further portions of sodium hydroxide, the solvent being decanted each time from the aqueous layer, until sodium hydroxide remained undissolved. The dioxan was then refluxed with freshly cut sodium for 12 hr., and finally distilled from sodium; then it had b. p. 101·5°/760 mm., m. p. 11·7°, n_D^{18} 1·4234. A Karl Fischer water determination [15] showed less than 0·1% of water to be present.

Procedure.—(a) *Hydrolysis of dimethyl cyclohexane*-1,3- *and* -1,4-*dicarboxylate*. The procedure was that of Schwemer [16] with a few minor alterations. A bulb containing a known weight of ester dissolved in 5·0 ml. of dioxan was broken in a flask containing an equivalent quantity of approximately 0·01N-sodium hydroxide, and the solutions were mixed by shaking in the thermostat-bath. The solvent composition after mixing was water : dioxan 3·03 : 1·00 (v/v). Carbon dioxide-free nitrogen, saturated with the solvent vapour, was passed through the reaction flask before the breaking of the bulb and during the reaction, in order to prevent access of air to the alkaline solution, and to prevent volume changes in the solution. Aliquot parts (10 ml.) were withdrawn at intervals and run into flasks containing 0·015N-potassium hydrogen phthalate (10 ml.) to arrest the reaction. The excess of potassium hydrogen phthalate was then titrated against 0·01N-sodium hydroxide.

(b) *Hydrolysis of methyl hydrogen dicarboxylates and methyl monocarboxylates.* The procedure was similar to that in (a), except that equivalent quantities of ester and alkali were unnecessary. For the methyl 4-t-butylcyclohexanecarboxylates, the solvent composition was 1 : 1 (v/v) dioxan–water. Methyl cyclohexanecarboxylate was studied in both solvents for comparison.

(c) *Hydrolysis of dimethyl cyclohexane*-1,2-*dicarboxylates.* The procedure was as in (b). The rate coefficient k_1 was sufficiently greater than k_2 to make the majority of the first stage of the hydrolysis into an apparently normal second-order reaction. The hydrolysis was therefore studied over about the first 35% of the total reaction to obtain k_1. The second stage of the hydrolysis was studied separately as in (b). (Subscripts 1 and 2 refer to the first and the second stage of hydrolysis respectively.)

(d) *Determination of order of reaction.* The reaction order was determined for the hydrolysis of methyl *cis*- and *trans*-4-t-butylcyclohexanecarboxylate by the differential method.[17] The reactions were found to be of the first order with respect to sodium hydroxide, first order with respect to ester, and second order overall.

(e) *Hydrolysis products.* The products of hydrolysis of methyl *cis*- and *trans*-4-t-butylcyclohexanecarboxylate were isolated at several stages of the reaction, and were found to be the corresponding *cis*- and *trans*-4-t-butylcyclohexanecarboxylic acid, thus indicating that no rearrangement took place during the hydrolysis, and that the esters were pure.

(f) All the hydrolyses were carried out in the presence of an excess of potassium chloride. The ionic strength was 0·200 ± 0·005 mole per kg. of solvent, except in the case of the methyl monocarboxylates when the ionic strength was 0·124 mole per kg. of solvent.

Calculation of Rate Coefficients.—The rate coefficients for the hydrolysis of the dimethyl

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[15] Smith, Bryant, and Mitchell, *J. Amer. Chem. Soc.*, 1939, **61**, 2407.

[16] Schwemer, Ph.D. thesis, North Western University, Evanston, Illinois, U.S.A., 1950.

[17] Laidler, " Chemical Kinetics," McGraw-Hill, New York, 1950, p. 14.

cyclohexane-1,3- and -1,4-dicarboxylates were calculated by Frost and Schwemer's method[1] and checked by that of Widequist.[2] Widequist obtained the equation:

$$k_1 = (z + k_2A)/\{k_2(a\theta^2 - B) + (a0 - A)\}$$

where z is the amount of alkali consumed at time t, a is the initial concentration of ester, θ is the "time variable" $\left[\theta = \int_0^t (a - z)\mathrm{d}t\right]$, $A = \int_0^\theta z.\mathrm{d}\theta$, $B = \int_0^\theta A.\mathrm{d}\theta = \iint_0^\theta z(\mathrm{d}\theta)^2$, and k_1 and k_2 are the rate coefficients for the two stages of the hydrolysis. Widequist used the equation to derive k_1, knowing k_2 already. However, k_1 can be calculated with fair accuracy by Frost and Schwemer's method, so this equation was used here to determine k_2 where k_1 is already known. The values of k_2 obtained by this method and by Frost and Schwemer's method had an accuracy of about $\pm 4\%$, and the values of k_1 obtained by Frost and Schwemer's method had an accuracy of about $\pm 2\%$.

The rate coefficients for the hydrolysis of the dimethyl cyclohexane-1,2-dicarboxylates, the monomethyl cyclohexanedicarboxylates and the methyl cyclohexanemonocarboxylates were calculated from the equation $\mathrm{d}x/\mathrm{d}t = k(A_0 - x)(B_0 - x)$ where A_0 is the initial alkali concentration, B_0 is the initial ester concentration (monocarboxylates and dimethyl dicarboxylates) or the initial ester salt concentration (monomethyl dicarboxylates), and x is the amount of alkali consumed at time t, by the use of appropriate linear plots.

The values of k_2 for the second stage of the hydrolysis depend on the ionic strength of the solution, according to the Brönsted equation $\log_e k_2 = \log_e k_2^0 + (2z_1z_2A'\sqrt{\mu})/(1 + \alpha B'\sqrt{\mu})$ where k_2 is the observed rate coefficient, k_2^0 is the rate coefficient at zero ionic strength, z_1 and z_2 are the valencies of the two ionic species 1 and 2, μ is the ionic strength of the solution, α is the mean distance between the reactive centre and the charged centre in the transition state, and A' and B' are the Debye–Hückel constants. Since the equation involves the distance α, the value of k_2 will depend on the conformation of the molecule. The values of k_2^0 have therefore been computed for each of the possible conformations of the compound in question. The corrections were made by using the equation $\log_{10} k_2 = \log_{10} k_2^0 + 3{\cdot}647 \times 10^6\sqrt{\mu}/\{(DT)^{3/2} + 5{\cdot}028 \times 10^6\alpha DT\sqrt{\mu}\}$, where D is the dielectric constant of the medium and T the absolute temperature (cf. Svirbely and Mador[18]). The values of D were obtained from the data of Åkerlöf and Short[19] and the values of α were determined by vector analysis as described by Corey and Sneen.[20] The rate coefficients evaluated as above were used to calculate Arrhenius parameters and heats and entropies of activation in the usual way. As the maximum error in most of the rate coefficients is about $\pm 2\%$, the energies of activation are accurate within about ± 300 cal. per mole, and the $\log_{10} A$ factors within about $\pm 0{\cdot}3$ unit. For those rate coefficients k_2 determined by Frost and Schwemer's method, where the accuracy is only about $\pm 4\%$, the energies of activation are accurate within ± 600 cal., and the $\log_{10} A$ factors within $\pm 0{\cdot}6$ unit.

RESULTS

The various results are assembled in Tables 1—4 and all the results are summarised in Table 5. Some of the values previously given[5] have been slightly revised and in one case (methyl hydrogen *trans*-cyclohexane-1,2-dicarboxylate) an error has been eliminated.

TABLE 1. *Rate coefficients * for the hydrolysis of methyl esters of monocarboxylic acids.*

Temperature	63·1°	45·8°	45·0°	29·4°	25·0°	18·2°
Compound	Rate coefficient (l. mole^{-1} sec.^{-1}) $\times 10^4$					
Me cyclohexanecarboxylate † ‡	—	—	827	—	266	179
	—	—	830	—	—	179
Me cyclohexanecarboxylate ¶	1080	426	—	163	—	—
	1050	—	—	162	—	—
Me 4-t-butylcyclohexanecarboxylate, *trans* ¶	895	358	—	142	—	—
	880	352	—	142	—	—
Me 4-t-butylcyclohexanecarboxylate, *cis* ¶	79·7	26·4	—	8·25	—	—
	79·3	25·9	—	8·33	—	—

* In this and succeeding Tables replicate values of k are given where available. † In 1 : 3 dioxan–water. ‡ $10^4k = 168$ at 17·5°. ¶ In 1 : 1 dioxan–water.

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[18] Svirbely and Mador, *J. Amer. Chem. Soc.*, 1950, **72**, 5699.
[19] Åkerlöf and Short, *J. Amer. Chem. Soc.*, 1936, **58**, 1241.
[20] Corey and Sneen, *J. Amer. Chem. Soc.*, 1955, **77**, 2505.

TABLE 2. *Rate coefficients for the individual hydrolyses of mono- and di-methyl cyclohexanedicarboxylates.*

Temperature	63·1°	59·9°	44·4°	34·8°	29·4°	25·5°	14·7°	0·0°
Compound	k_2, Rate coefficient (l. mole^{-1} sec.$^{-1}$) × 10^4							
trans-1,4	—	—	—	657	—	400	212	82·6
	—	—	—	—	—	—	—	82·7
trans-1,2	—	54·6	—	11·9	—	6·18 *	—	—
	—	55·2	—	—	—	6·23 *	—	—
cis-1,2	11·7	—	3·31	—	1·10	—	—	—
	11·8	—	3·29	—	1·08	—	—	—
Compound	k_1, Rate coefficient (l. mole^{-1} sec.$^{-1}$) × 10^3							
trans-1,2		140	—	39·6		23·6		
		140	—	—		23·1 *		
cis-1,2 ‡		54·5	20·2 †	—		—		

* At 25·3°. † At 42·4°. ‡ 10^3k_1 = 5·53, 4·50, and 4·32 at 21·5°, 19·1°, and 18·4° respectively.

TABLE 3. *Rate coefficients* k_1 *for the hydrolysis of dimethyl cyclohexanedicarboxylates calculated by Frost and Schwemer's method.*

Temperature	45·9°	44·9°	34·9°	29·5°	25·0°	18·4°	15·4°	0·0°
Compound	Rate coefficient (l. mole^{-1} sec.$^{-1}$) × 10^2							
cis-1,4	19·6	18·5	—	7·82	—	4·02	3·26 *	—
trans-1,4	—	—	24·3	—	—	—	—	2·77
	—	—	24·1	—	13·7	—	7·81	2·81
cis-1,3	—	—	26·3	—	14·9	—	8·54	3·01
	—	—	26·4	—	—	—	—	3·06
trans-1,3	17·5	16·7	—	6·06 †	—	3·49	—	—
	—	—	—	—	—	3·33 ‡	—	—

* At 15·0°. † At 27·4°. ‡ At 18·1°.

TABLE 4. *Rate coefficients for hydrolysis of methyl hydrogen cyclohexanedicarboxylates from the Widequist and Frost and Schwemer methods of calculation.*

Temperature		45·9°	44·9°	34·9°	29·5°	25·0°	18·4°	15·4°	0·00°
Compound		Rate coefficient (l. mole^{-1} sec.$^{-1}$) × 10^3							
cis-1,4	F & S	39·4	38·6	—	16·3	—	8·01	6·79	—
	W	—	38·5	—	16·1	—	8·41	6·75	—
trans-1,4	F & S	—	—	65·8	—	38·1	—	21·3	7·93
		—	—	64·4	—	—	—	—	—
	W	—	—	67·2	—	36·9	—	—	8·40
		—	—	—	—	—	—	—	8·00
cis-1,3	F & S	—	—	68·6	—	38·7	—	21·9	7·76
		—	—	65·9	—	—	—	—	7·93
	W	—	—	—	—	38·7	—	22·7	8·18
		—	—	—	—	—	—	—	8·07
trans-1,3	F & S	32·4	31·7	—	—	11·2 *	6·43 †	—	—
		—	—	—	—	—	6·20 †	—	—
	W	31·3	32·7	—	—	11·1 *	6·76 †	—	—
		—	—	—	—	—	6·54 †	—	—

* At 27·4°. † At 18·1°. Some of these values have been confirmed by Mr. K. J. Toyne, by direct measurements, using the pure monomethyl esters. That work will be reported later.

DISCUSSION

Conformation and Reactivity of the Methyl 4-t-Butylcyclohexanecarboxylates.—The possible conformations of these compounds are shown in Fig. 1. According to Winstein and Holness the t-butyl group has a marked preference for the equatorial conformation, the relevant free-energy difference being 5·6 kcal. per mole. Thus for any 4-substituted t-butylcyclohexane derivative where the second substituent is comparatively small, the t-butyl group will be in the equatorial conformation. Hence the methyl *trans*-4-t-butylcyclohexanecarboxylate will exist exclusively in the diequatorial conformation (d), provided that the methoxycarbonyl group is more stable in the equatorial than in the

TABLE 5.*

	10^4k_{30}	$4 + \log_{10} k_{30}$	E (kcal./mole)	$\log_{10} A$	$\Delta H^‡$ (kcal./mole)	$\Delta S^‡$ (e.u.)
Me cyclohexanecarboxylate †	169	2·228	11·3	6·4	10·7	−31·5
Me *trans*-4-t-butylcyclohexanecarboxylate †	147	2·167	11·0	6·1	10·4	−32·7
Me *cis*-4-t-butylcyclohexanecarboxylate †	8·63	0·936	13·6	6·7	13·0	−29·9
Me cyclohexanecarboxylate	357	2·553	10·5	6·1	9·9	−32·6
Me_2 *trans*-cyclohexane-1,4-dicarboxylate	1840	3·264	10·4	6·8	9·8	−29·4
Me_2 *cis*-cyclohexane-1,4-dicarboxylate	805	2·907	10·6	6·6	10·0	−30·5
Me_2 *trans*-cyclohexane-1,3-dicaroxylate	708	2·850	11·0	6·8	10·4	−29·4
Me_2 *cis*-cyclohexane-1,3-dicarboxylate	2010	3·303	10·4	6·8	9·8	−29·4
Me_2 *trans*-cyclohexane-1,2-dicarboxylate	304	2·483	10·3	5·9	9·7	−33·5
Me_2 *cis*-cyclohexane-1,2-dicarboxylate	97·0	1·987	11·7	6·4	11·1	−31·3
Me H *trans*-cyclohexane-1,4-dicarboxylate	512	2·709	10·0	5·9	9·4	−33·6
Me H *cis*-cyclohexane-1,4-dicarboxylate	167	2·223	10·5	5·8	9·9	−34·0
Me H *trans*-cyclohexane-1,3-dicarboxylate	135	2·130	10·6	5·8	10·0	−34·0
Me H *cis*-cyclohexane-1,3-dicarboxylate	501	2·700	10·0	5·9	9·4	−33·6
Me H *trans*-cyclohexane-1,2-dicarboxylate	8·67	0·938	12·4	5·9	11·8	−33·6
Me H *cis*-cyclohexane-1,2-dicarboxylate	1·14	0·058	14·2	6·3	13·6	−31·8

* The accuracy of the values given is stated on p. 1417. Units of k are l. mole^{-1} sec.$^{-1}$. † In 1 : 1 dioxan–water.

axial conformation. All the available evidence suggests that this is so. We may thus characterise the alkaline hydrolysis of an equatorial methoxycarbonyl group in 1 : 1 dioxan–water by $\Delta H^‡ = 10·4$ kcal./mole, $\Delta S^‡ = -32·7$ e.u., and $10^4k_{30} = 147$ (cf. above). Whether the *cis*-isomer exists exclusively in the conformation (a) (equatorial-axial) depends on the magnitude, X, of the free-energy difference between the equatorial and the axial conformation for the methoxycarbonyl group. Provided $X < 5·6$ kcal./mole, conformation (a) will predominate, the degree of predominance depending on the value of X, and the temperature, *e.g.*, for $X = 2·0$ kcal./mole, $N_a/N_b = K = 10^{2·6}$ for 27°C where N_a and N_b are the mole fractions of conformations (a) and (b). Winstein and Holness have developed the equation $k_{obs} = k_E N_E + k_A N_A$ (i), where subscripts E and A refer to compounds with the methoxycarbonyl group in the equatorial and axial conformation respectively. A necessary assumption was that equilibrium between the two conformations was rapidly and continuously established. It is readily shown that the strict second-order kinetics (cf. p. 1416) here observed also imply that this condition is fulfilled. The value of the coefficient k_A cannot be evaluated directly as N_A is not known, but the possible range of values for k_A may be obtained from equation (i) by putting $k_E = k_{trans}$ and $k_{obs} = k_{cis}$. These values for 30° are assembled in Table 6.

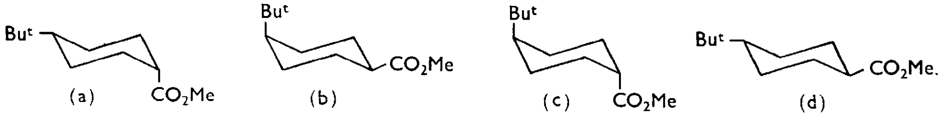

FIG. 1.

The maximum value of k_A is $8·64 \times 10^{-4}$ l. mole^{-1} sec.$^{-1}$ and hence $k_E/k_A \nless 17$, which is one of the highest values of this ratio so far observed for reactions the relative rates of which are controlled by conformational factors. Although it is improbable that the *cis*-ester, unlike the *trans*-ester, is conformationally homogeneous, it is clear that conformation (a) has a mole fraction not less than ~0·94, so that, noting the values of $\Delta H^{\ddagger} = 13{\cdot}0$ kcal./mole and $-\Delta S^{\ddagger} = 29{\cdot}9$ e.u. for the *cis*-ester, we may safely say that the slower hydrolysis of an axial than of an equatorial methoxycarbonyl group is due to an increment of ~2·6 kcal./mole in the heat of activation. The difference in $\Delta S^{\ddagger}$ is small, but is such as to favour the axial conformation as to rate of hydrolysis, but this factor is outweighed by the energy factor. From the results assembled in Table 5 for methyl cyclohexanecarboxylate it seems probable that the above values for $\Delta H^{\ddagger}$ would be reduced by ~0·8 kcal./mole if the reactions could be carried out in 1 : 3 dioxan–water, but the changes in $\Delta S^{\ddagger}$ would lie within experimental error. Relative values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ would be unchanged. The values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for methyl cyclohexanecarboxylate are very close to those for methyl *trans*-4-t-butylcyclohexanecarboxylate, indicating that in the former compound the methoxycarbonyl group occupies the equatorial position almost exclusively. However, the relative values of k_{30} indicate that the polar influence of the 4-t-butyl group is not entirely negligible in this case, since the value for methyl cyclohexanecarboxylate exceeds that for the *trans*-4-t-butyl compound, the value for which, on conformational grounds alone, should be greater. Winstein and Holness made similar observations with reference to cyclohexyl hydrogen phthalate. Eliel and Ro [21] postulated that for an axial hydroxyl group to be esterified it must first assume the equatorial conformation, and if this is true it is probable that it would apply to the hydrolysis of a methoxycarbonyl group. On this basis it is possible to derive a value of $\Delta G = 1{\cdot}6$ kcal./mole for the free-energy difference between the two possible conformations of the *cis*-ester studied by us, and hence for X a value of 4·0 kcal./mole. It is doubtful, however, whether the original postulate is strictly true.

TABLE 6.

N_a	0·9999	0·999	0·99	0·97	0·95	0·94
$10^4 k_A$ (l. mole^{-1} sec.$^{-1}$)	8·62	8·49	7·23	4·35	1·35	0

Conformation and Reactivity of the Dimethyl Cyclohexanedicarboxylates.—The possible conformations of the dimethyl cyclohexanedicarboxylates are as follows (*ax* = axial, *eq* = equatorial methoxycarbonyl group):

1,4-*trans* (I) 1 *eq*, 4 *eq* ⇌ 1 *ax*, 4 *ax*
1,4-*cis* (II) 1 *ax*, 4 *eq* ⇌ 1 *eq*, 4 *ax*
1,3-*trans* (III) 1 *eq*, 3 *ax* ⇌ 1 *ax*, 3 *eq*
1,3-*cis* (IV) 1 *ax*, 3 *ax* ⇌ 1 *eq*, 3 *eq*
1,2-*trans* (V) 1 *ax*, 2 *ax* ⇌ 1 *eq*, 2 *eq*
1,2-*cis* (VI) 1 *eq*, 2 *ax* ⇌ 1 *ax*, 2 *eq*

In cases (II) and (III) we have two identical conformations in equilibrium, in case (VI) two mirror-image conformations in equilibrium, and in cases (I), (IV), and (V) two different conformations in equilibrium. In calculating the rate coefficients for the hydrolysis of these esters it is necessary to assume that they are symmetrical with respect to reactivity. The esters (I), (IV), and (V) each comprise an equilibrated pair of geometrically symmetrical conformations and will therefore be symmetrical as to reactivity. The esters (II), (III), and (VI), although comprising geometrically unsymmetrical pairs of conformations, will in fact be symmetrical as to reactivity because the free-energy difference between the two conformations is zero. It is easily seen that for the first group of compounds, the rate coefficient for the first stage of hydrolysis, k'_1 is given by $k'_1 = 2k_E N_{EE} + 2k_A N_{AA}$ (ii) (the

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[21] Eliel and Ro, *Chem. and Ind.*, 1956, 251.

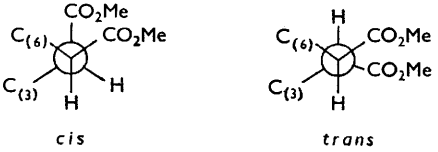
same notation being used as before). For the second group, $k_1 = N_{EA}(k_E + k_A) + N_{EA}(k_A + k_E) = k_E + k_A$ (iii), since $N_{AE} = N_{EA} = \frac{1}{2}$. Leaving aside the 1,2-esters, in which complications arise, we may apply equation (iii) to the results for compounds (II) and (III) (Table 3). The fact that the values of k_1 for these compounds are very nearly the same confirms the conformations proposed for compounds (II) and (III). Smith and Fort[4] made similar observations for hydrolysis in 85% methanol at 25° (*trans*-1,3-, $k_1 = 1{\cdot}40$; *cis*-1,4-, $k_1 = 1{\cdot}62$ l. mole hr.$^{-1}$).

If we set $k_A = mk_E$ $(0 < m < 1)$ it readily follows from (ii) and (iii) that $k'_1/2k_1 = (N_{EE} + mN_{AA})/(1 + m)$. From the results discussed on p. 1419 a reasonable value for m is 0·1. Since it is unlikely that $N_{AA} > N_{EE}$ the term mN_{AA} may be neglected, to a first approximation. This leads to a value of N_{EE} of $\sim$1·4 for the *trans*-1,4-ester and of $\sim$1·3 for the *cis*-1,3-ester: and, as the maximum value of N_{EE} is unity, this analysis strongly suggests that these esters exist exclusively in the diequatorial conformation. Moreover, these conclusions would be unaffected by taking the limiting (and absurd) value of unity for N_{AA}, providing $m \ngtr 0{\cdot}1$. These conclusions are also supported by using in a similar way the rate coefficients determined by Smith and Fort[4] for 85% methanolic solutions.

The hydrolysis of the 1,2-diesters is complicated by the proximity of the two methoxycarbonyl groups to each other, which introduces the following additional effects: (i) internally propagated polar effects; (ii) externally propagated polar effects, *i.e.*, the effect of the dipole of one ester group on the rate of hydrolysis of the other; (iii) the primary* steric effect of one ester group on the rate of hydrolysis of the other. Of these effects, the magnitude of the first will be the same for all conformations of the 1,2-diesters, and will be very small, but the magnitude of the second and the third effect will be different for each conformation of the 1,2-diesters.

The only possible conformation for the *cis*-1,2-diester is *eq,ax,* and the rate coefficient observed for the hydrolysis at 30° is $9{\cdot}70 \times 10^{-3}$ l. mole^{-1} sec.$^{-1}$. Comparison of this value with the corresponding values for the *cis*-1,4- and *trans*-1,3-diester shows that the proximity of the two methoxycarbonyl groups reduces the rate by a factor of about 8. The magnitude of the dipolar effect is difficult to estimate, because the orientation of the methoxycarbonyl groups in the two positions is uncertain, but it will certainly tend to reduce the rate of the reaction, as will the primary steric effect. The *trans*-1,2-diester can adopt two conformations, *eq,eq* and *ax,ax,* and the observed rate coefficient for the hydrolysis at 30° is $3{\cdot}04 \times 10^{-2}$ l. mole^{-1} sec.$^{-1}$.

If this ester adopts the diaxial conformation, then the two methoxycarbonyl groups will be well separated, and the main effect will be a " pure " conformational effect, *i.e.*, the rate coefficient will be approximately twice that for the hydrolysis of an axial methoxycarbonyl group, or less than about one seventeenth (cf. p. 1419) of that for the hydrolysis of the *trans*-1,4- or the *cis*-1,3-diester. If the ester adopts the diequatorial conformation, the two methoxycarbonyl groups will be close to each other, and the magnitudes of the dipolar and steric effects will be considerable. However, the two methoxycarbonyl groups in the *eq,ax-cis*-1,2- and in the *eq,eq-trans*-1,2-diesters are in the same relative positions, the only difference being that one of the groups which is in the equatorial conformation in the *trans*-ester is in the axial conformation in the *cis*-ester. This is shown in the projections in Fig. 2.



cis *trans*

FIG. 2.

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* The primary steric effect depends directly upon differences of non-bonding compressional energy.

The primary steric effect will therefore be almost the same in each case, and the dipolar effect should be approximately the same, the only difference being the possible variation in orientation of the second methoxycarbonyl group in the axial (in the *cis*-1,2) and the equatorial (in the *trans*-1,2) conformations with respect to the other methoxycarbonyl group. This effect, though noticeable, should not alter the order of magnitude of the rate coefficient, and therefore it would be expected that the rate coefficient for this conformation would be about twice that for the *cis*-1,2-ester,* or more, depending on the magnitude of the effect controlled by the orientation of the axial methoxycarbonyl group. The observed rate coefficient is about three times that for the *cis*-1,2-diester and about one fifth of that for the *cis*-1,3- or the *trans*-1,4-diester, and it is therefore concluded that the *trans*-1,2-diester is predominantly in the diequatorial conformation.

Smith and Fort,[4] who did not consider this type of argument, provide results which also support this conclusion. They claim that the *trans*-1,2-diester adopts the diaxial conformation, on the basis of a diaxial conformation for the corresponding acid, in favour of which only general arguments are provided.

The heats and entropies of activation for the hydrolysis of the truly symmetrical esters are:

trans-1,4-, $\Delta H^{\ddagger}$ = 9·8 kcal./mole, $\Delta S^{\ddagger}$ = −29·4 e.u.
cis-1,3-, „ = 9·8 „ „ „ −29·4 „
trans-1,2-, „ = 9·7 „ „ „ −33·5 „

The rate difference for the hydrolysis of *trans*-1,2-diester compared with the hydrolysis of the other esters is due solely to the large decrease in entropy of activation. We now revert to the hydrolysis of the 4-t-butylcyclohexanecarboxylates (p. 1420); it was seen that the faster hydrolysis of an equatorial than of an axial methoxycarbonyl group was due mainly to the greater heat of activation, offset by the greater entropy of activation of the latter, thus $\Delta H_{\mathrm{A}}^{\ddagger} - \Delta H_{\mathrm{E}}^{\ddagger} \approx 2{\cdot}6$ kcal./mole, $\Delta S_{\mathrm{A}}^{\ddagger} - \Delta S_{\mathrm{E}}^{\ddagger} \approx 2{\cdot}8$ e.u. Therefore the large positive difference of entropy of activation between the hydrolysis of the *trans*-1,4- and of the *trans*-1,2-diester is hardly likely to be due to a change from the diequatorial to the diaxial conformation, thus, $\Delta H_{1,4}^{\ddagger} - \Delta H_{1,2}^{\ddagger} \approx -0{\cdot}1$ kcal./mole, $\Delta S_{1,4}^{\ddagger} - \Delta S_{1,2}^{\ddagger} \approx +4{\cdot}1$ e.u. The *trans*-1,2-diester is therefore in the diequatorial conformation.

The entropies and heats of activation for the unsymmetrical diesters are:

cis-1,4-, $\Delta H^{\ddagger}$ = 10·0 kcal./mole, $\Delta S^{\ddagger}$ = −30·5 e.u.
trans-1,3-, „ 10·4 „ „ −29·4 „
cis-1,2-, „ 11·1 „ „ −31·3 „

The differences in this series are not so marked, but there is an apparent increase in heat and a decrease in entropy of activation for the *cis*-1,2-diester, no doubt caused by increased primary steric and dipolar effects. The increase in heat of activation that is observed here, but not in the hydrolysis of the *trans*-1,2-diester, may be due to increased dipolar effects as a result of the controlled orientation of the axial methoxycarbonyl group.

The smaller rates of hydrolysis of the 1,2-diesters may also be partly due to a decrease in the statistical factor of 2. This factor is introduced for those cases where the two possible sites of reaction are well separated; where the two groups are very close to each other, the probability of reaction is not doubled, as the approach of the attacking reagent must be from approximately the same direction for each. The value 2 must therefore be reduced slightly for these esters.

The Conformation and Reactivity of the Methyl Hydrogen Cyclohexanedicarboxylates.— The possible conformations of the methyl hydrogen cyclohexanedicarboxylates are the same as those described for the dimethyl esters (p. 1420), except that the conformations

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The *cis*-1,2-ester has only one equatorial group, and to a first approximation we neglect the reaction of the axial group.

eq,ax and *ax,eq* are not identical as there are now two different groups, the carboxyl group and the methoxycarbonyl group.

The hydrolysis of a monomethyl ester of a dicarboxylic acid in alkaline solution involves the reaction of two ions of like charge, the hydroxyl ion and the monocarboxylate ion, and it is therefore subject to a positive salt effect, and according to the Brönsted equation

$$\log_e k = \log_e k_0 + 2z_1z_2A'\sqrt{\mu}/(1 + \alpha B'\sqrt{\mu}) \quad . \quad . \quad . \quad . \quad \text{(iv)}$$

The hydrolysis of the monocarboxylate ion produces the dicarboxylate ion, and there is therefore an increase of valency from 1 to 2, with a corresponding increase in the ionic strength ($\mu = \frac{1}{2}\Sigma c_iz_i^2$) as the reaction proceeds. The observed rate coefficient should therefore also increase according to equation (iv) as the reaction proceeds. This was overcome by adding a large excess of a neutral salt so that any change in ionic strength during the reaction was negligible compared to the total ionic strength. This method suffers from the serious disadvantage that the effect of ionic strength depends upon the magnitude of α, the mean distance of closest approach of the two ionic centres, and this distance is different for each of the esters considered here. As the rate coefficients and entropies and heats of activation are to be used in the assignment of conformation, it is essential that they be compared under the same conditions; a correction has therefore to be made to each of the observed rate coefficients so that the comparison may be made for values referring to zero ionic strength. Equation (iv) was used for dioxan–water mixtures by Svirbely and Mador [18] in the form

$$\log_{10} k = \log_{10} k_0 + \frac{3{\cdot}647 \times 10^6\sqrt{\mu}}{(DT)^{3/2} + 5{\cdot}028 \times 10^6\,\alpha DT\sqrt{\mu}} \quad . \quad . \quad . \quad \text{(v)}$$

where D is the dielectric constant of the solvent, and T is the absolute temperature. The value of D was calculated from the equation $\log_{10} D = \log_{10} a - bT$ (vi) where a and b are constants, which was derived by Åkerlöf and Short.[19] For the solvent used in this work (25·3 wt.% dioxan), this equation becomes: $\log_{10} D = 1{\cdot}804 - 0{\cdot}00229T$. The main difficulty in the application of equation (v) lies in the estimation of α for the various esters. First, the exact locations of the charge of the carboxylate ion group and of the charge in the transition complex in the hydrolysis of a methoxycarbonyl group are not known and, secondly, the *trans*-1,4-, *cis*-1,3-, and *trans*-1,2-ester can each exist in two conformations with widely differing values of α. The first of these errors was minimised by taking the centre of the ionic charge of the two atoms to be about 0·5 Å out from the carbonyl carbon atom, as shown in Fig. 3. X is centre of charge, and C. . . . X = 0·5 Å. The second difficulty was partially overcome by correcting the rate coefficients in relation to each conformation separately.

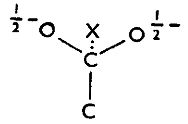

FIG. 3.

The distances α for each conformation were calculated by the method of vector analysis developed by Corey and Sneen,[20] using the following bond distances: C–C = 1·55 Å, C–H = 1·09 Å; ring angles 109° 28′. The values obtained for α, 10^5k_{30}, E, $\log_{10} A$, $\Delta H^‡$, and $\Delta S^‡$, are shown in Table 7.

Methyl hydrogen *cis*-cyclohexane-1,3-dicarboxylate can exist in the diequatorial and in the diaxial conformations. In the diequatorial conformation, the two groups are separated by a distance of about 5·9 Å, and the presence of the ionic charge of the carboxylate ion would therefore be expected to reduce the rate of hydrolysis of the methoxycarbonyl group by a factor $\bar{\theta}$, where $\bar{\theta}$ is given by the equation $\bar{\theta} = \exp \varepsilon^2/Dk\alpha T$, where ε is the electronic charge, D is the dielectric constant of the medium between the carboxylate ion and the transition complex in the hydrolysis of the methoxycarbonyl group, T is the absolute temperature, and k is the Boltzmann constant. The value of D is uncertain, because the medium between the two charged centres consists partly of solvent, and partly of the molecule itself. However, the order of magnitude of $\bar{\theta}$ may be estimated by assuming the value of D to be equal to the dielectric constant of the solvent, giving $\bar{\theta}$ a value of 5. Thus when the hydrolysis of the *cis*-1,3-monomethyl ester is compared with hydrolysis of the *cis*-1,3-dimethyl ester, the rate coefficient of the former reaction would be expected to be the smaller by a statistical factor of 2, to account for the presence of only one reacting group in the monoester, and by the factor 5 due to the electrostatic effect,* making a total factor of ~10.

TABLE 7. *Hydrolysis of the methyl hydrogen cyclohexanedicarboxylates at zero ionic strength.*

	Conformn.	10^5k_{30} (l. mole^{-1} sec.$^{-1}$)	E (kcal./mole)	$\log_{10} A$	$\Delta H\ddagger$ (kcal./mole)	$\Delta S\ddagger$ (e.u.)	α (Å)
cis-1,2-	*eq,ax*	3·80	13·7	5·4	13·1	−35·8	3·50
trans-1,2- ...	*ax,ax*	28·8	12·5	5·5	11·9	−35·3	4·85
	eq,eq	33·2	11·8	5·0	11·2	−37·8	3·50
cis-1,3-	*ax,ax*	2150	9·5	5·0	8·9	−37·6	2·53
	eq,eq	1460	9·8	5·4	9·2	−36·2	5·86
trans-1,3- ...	*ax,eq*	530	10·3	5·2	9·7	−36·8	5·11
cis-1,4-	*ax,eq*	661	10·1	5·1	9·5	−37·2	5·20
trans-1,4- ...	*ax,ax*	2070	9·7	5·3	9·1	−36·3	5·50
	eq,eq	2290	9·7	5·4	9·1	−35·9	6·88

In the diaxial conformation, the two groups are only 2·53 Å apart, and the reduction in rate, $\bar{\theta}$, due to the electrostatic effect, is ~50. The rate is also reduced, because of the primary steric effect of the carboxylate ion group on the rate of hydrolysis of the methoxycarbonyl group, by a factor of the order of 2; and because of the pure conformational effect of a methoxycarbonyl group in the axial conformation, by a factor of about 17 (p. 1419). Compared with the rate of hydrolysis of the diequatorial *cis*-1,3-dimethyl ester, the rate of hydrolysis of the monomethyl ester in the diaxial conformation should therefore be smaller by a factor of ~3400.

In view of the uncertainties in the ionic-strength correction applied to values of k_2, the values considered in what follows are average values of those obtained when the correction is made for each possible conformation separately (Table 7). Using these average values does not alter the conclusions reached as to conformations of the monoesters and simplifies the argument.

The rate coefficients for the hydrolysis of these esters at 30° are: monomethyl *cis*-1,3-, $k_2 = 1{\cdot}81 \times 10^{-2}$ l. mole^{-1} sec.$^{-1}$ (average value), and dimethyl *cis*-1,3-, $k_1 = 2{\cdot}01 \times 10^{-1}$ l. mole^{-1} sec.$^{-1}$. The rate reduction factor is therefore ~11 and it is obvious that the *cis*-1,3-monoester is in the diequatorial conformation.

A similar argument applies to the rates of hydrolysis of the conformations of the *trans*-1,4-monoester compared with the rates of hydrolysis of the *trans*-1,4-diester. The diaxial conformation will react more slowly by a factor of ~7 for the electrostatic effect, by a conformational factor of ~17, and by a statistical factor of 2, making a total factor of ~268. The diequatorial conformation will react more slowly by a factor of ~4 for the electrostatic effect, by a statistical factor of 2, making a total factor of ~8. The rate coefficients at 30° are: monomethyl *trans*-1,4-, $k_2 = 2{\cdot}18 \times 10^{-2}$ l. mole^{-1} sec.$^{-1}$ (average value), dimethyl *trans*-1,4-, $k_1 = 1{\cdot}84 \times 10^{-1}$ l. mole^{-1} sec.$^{-1}$. The rate-reduction ratio is therefor ~8·5 and it is clear that the monomethyl ester of *trans*-cyclohexane-1,4-dicarboxylate is in the diequatorial conformation.

The *cis*-1,4- and the *trans*-1,3-monoester can each exist in two conformations, (*a*) with the methoxycarbonyl group axial and the carboxylate ion group equatorial, and (*b*) with the methoxycarbonyl group equatorial and the carboxylate ion group axial. Since the methoxycarbonyl group is probably smaller than the solvated carboxylate ion group, it would be expected that the mole fraction of the conformation with the equatorial methoxycarbonyl group would be somewhat less than 0·5. The electrostatic effect will be approximately the same for the *cis*-1,4- and the *trans*-1,3-monoester, as the distances

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* The electrostatic effect is the effect of the charge of the carboxylate ion group on the rate of hydrolysis of the methoxycarbonyl group.

between the two groups are 5·1 and 5·2 Å respectively. This corresponds to a decrease in rate by a factor, $\bar{\theta} = 7$, and the observed rate coefficients should be rather more than $7 \times 2 = 14$ times smaller than those for the corresponding *cis*-1,4- and *trans*-1,3-diesters. The rate coefficients at 30° (l. mole^{-1} sec.$^{-1}$) are:

$$trans\text{-}1,3\text{-},\ k_2 = 5{\cdot}3 \times 10^{-3};\quad cis\text{-}1,4\text{-},\ k_2 = 6{\cdot}6 \times 10^{-3};$$
$$trans\text{-}1,3\text{-},\ k_1 = 7{\cdot}08 \times 10^{-2};\quad cis\text{-}1,4\text{-},\ k_1 = 8{\cdot}05 \times 10^{-2}$$

and the corresponding rate-reduction ratios are therefore, 13 for the 1,3-esters, and 12 for the 1,4-esters, values which are in accordance with those predicted.

The hydrolysis of the *cis*-1,2-monoester would be expected to be very slow, on account of the close proximity of the two groups. The electrostatic effect is therefore large for this conformation ($\bar{\theta} \gtrsim 20$); there is also a primary steric effect, and a small inductive effect, both tending to reduce the rate of hydrolysis. The rate coefficient for the hydrolysis at 30° is $k_2 = 3{\cdot}8 \times 10^{-5}$ l. mole^{-1} sec.$^{-1}$, which is about 174 times less than that for the hydrolysis of the *cis*-1,4-monoester. The reduction in rate due to the combined inductive and primary steric effects is therefore equivalent to a factor of about 9, which is in close agreement with the rate reduction factor (~8) due to steric and dipolar effects in the hydrolysis of the *cis*-1,2-diester (p. 1421), thus supporting the conformation proposed on p. 1421, assuming the *cis*-1,2- and *cis*-1,4-monoesters to have the same conformation.

The hydrolysis of the *trans*-1,2-monoester is best considered in terms of the two conformations separately. The diequatorial conformation is associated with approximately the same steric, inductive, and electrostatic effects as for the *cis*-1,2-monoester, because the two groups are similarly oriented with respect to each other (cf. Fig. 2). The diequatorial *trans*-1,2-monoester should therefore be hydrolysed about twice as fast as the *cis*-1,2-monoester, or a little more, depending on the value of the mole fraction of that conformation of the *cis*-1,2-monoester with the methoxycarbonyl group equatorial. The diaxial *trans*-1,2-monoester has the two groups about 4·9 Å apart, and hence the electrostatic effect is less than for the diequatorial conformation ($\bar{\theta} \sim 8$); the primary steric effect is absent from this conformation, and the inductive effect is small. There is, however, a conformational effect due to the presence of both groups in the axial conformations, and the rate of hydrolysis should therefore be reduced in comparison with the rate of hydrolysis of the *trans*-1,4-diester by a factor of $\sim 17 \times 2 \times 8 \sim 272$, where 2 is the statistical factor.

The rate coefficient for hydrolysis of the *trans*-1,2-monoester at 30° is $k_2 = 3{\cdot}10 \times 10^{-4}$ l. mole^{-1} sec.$^{-1}$ (average value). The observed reduction in rate coefficient compared with that for the hydrolysis of the *trans*-1,4-diester is ~590 and the observed increase compared with that for the *cis*-1,2-monoester is ~8·2. The value predicted for the diaxial conformation differs from that observed by a factor of ~2, and the value predicted for the diequatorial conformation by a factor of ~4. It therefore appears that methyl hydrogen *trans*-cyclohexane-1,2-dicarboxylate has characteristics of both conformations, and therefore it may be assumed to be an equilibrium mixture of diaxial and diequatorial conformations, with perhaps a slightly greater proportion of the diaxial conformation.

The heats and entropies of activation for the *trans*-1,4-, *cis*-1,3-, and *trans*-1,2-monoesters are given in Table 7. The smaller rate of hydrolysis of the *trans*-1,2-monoester is due mainly to the high heat of activation, and partly to a lower entropy of activation. These characteristics are mid-way between those shown for the axial methoxycarbonyl group, and for the diequatorial *trans*-1,2-dimethyl ester, and therefore support the theory that the two conformations are in equilibrium. The heats and entropies of activation for the hydrolysis of the *cis*-1,4-, *trans*-1,3-, and *cis*-1,2-monoester (Table 7) show that the smaller rate of hydrolysis of the *cis*-1,2-monoester is due to a higher heat of activation.

Barton and Cookson [22] suggest that the dianion of *trans*-cyclohexane-1,2-dicarboxylic

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[22] Barton and Cookson, *Quart. Rev.*, 1956, **10**, 44.

acid adopts the diaxial conformation, and that the dianion of *trans*-1,3-acid adopts the axial–equatorial conformation on the basis of pK_a values. In these cases the situation is dominated by electrostatic repulsion between charged groups, so that their conclusions are not necessarily in conflict with ours.

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