

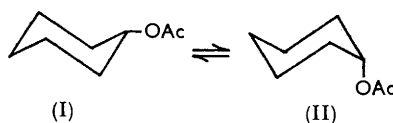
724. *Conformation and Reactivity. Part II.*¹ *Kinetics of the Alkaline Hydrolysis of the Acetates of the Methylcyclohexanols and of Related Alcohols.*

By N. B. CHAPMAN, R. E. PARKER, and P. J. A. SMITH.

The rates of alkaline hydrolysis in aqueous dioxan have been measured at three temperatures for cyclohexyl acetate, *cis*- and *trans*-2-, *cis*- and *trans*-3-, and *cis*- and *trans*-4-methylcyclohexyl acetates, *cis*- and *trans*-4-*t*-butylcyclohexyl acetates, bornyl and isobornyl acetates, and menthyl acetate, and at one temperature for neomenthyl acetate. By assuming that *cis*- and *trans*-4-*t*-butylcyclohexyl acetate exist entirely in conformations with their acetoxy-groups axial and equatorial, respectively, it is possible to derive the conformations of the remaining acetates from the kinetic results. The conformations so derived are confirmed by an infrared spectroscopic investigation of the acetates.

The hydrolysis of cyclohexyl acetate has been studied in two different aqueous dioxan solvents and the greater rate in the more aqueous solvent is discussed.

It is well known that esters of steroidal alcohols with equatorial hydroxyl groups undergo alkaline hydrolysis more rapidly than esters of axial steroidal alcohols,^{2,3} and effects of this kind on rates are often used to determine the conformations of reactive groupings. The present work is an application of this method to the determination of the conformations of the acetoxy-group in various acetoxy-cyclohexanes, and rates of alkaline hydrolysis in aqueous dioxan have been measured at three temperatures for the 12 acetates detailed above and (at one temperature only) for neomenthyl acetate. Since these compounds (except for the bornyl acetates) do not have their conformations stabilised by ring-fusion, they will each exist as an equilibrium mixture of two forms, *e.g.*, (I) and (II) for cyclohexyl acetate:



By assuming that *cis*- and *trans*-4-*t*-butylcyclohexyl acetate exist entirely in conformations with their *t*-butyl groups equatorial and that these groups have no effect on the reactivity of the acetoxy-group, other than by stabilising a particular conformation,⁴ it is possible to equate the rates of hydrolysis of these compounds to those of the conformational isomers (II) and (I), respectively, and therefore to calculate the position of equilibrium for cyclohexyl acetate. Similar analyses have been carried out for the other acetates and the results are confirmed by the infrared spectra of the acetates.

EXPERIMENTAL

Materials.—The preparation of the methylcyclohexanols is based on the methods of Jackman, Macbeth, and Mills,^{5,6} and the preparation of the *t*-butylcyclohexanols on the methods of Winstein and Holness.⁴ In most cases, however, it was necessary to modify these experimental methods.

All the acetates, prepared from the geometrically pure alcohols, were shown to be chemically

¹ Part I, Cavell, Chapman, and Johnson, *J.*, 1960, 1413.

² Barton, *Experientia*, 1950, **6**, 316; *J.*, 1953, 1027.

³ Fürst and Plattner, *Helv. Chim. Acta*, 1949, **32**, 275.

⁴ Winstein and Holness, *J. Amer. Chem. Soc.*, 1955, **77**, 5562.

⁵ Jackman, Macbeth, and Mills, *J.*, 1949, 1717.

⁶ Macbeth and Mills, *J.*, 1945, 709.

pure by gas-chromatographic analysis on a column of Silicone resin supported on Celite. This analysis did not, however, distinguish between geometrical isomers.

(±)-*trans*-2-Methylcyclohexyl acetate. (±)-2-Methylcyclohexanol (from British Drug Houses, Ltd.) was dried (Na_2SO_4) and distilled *in vacuo*. It had b. p. 65°/20 mm. The alcohol (50 g.) was esterified with 3,5-dinitrobenzoyl chloride (102 g.), giving a crude ester, m. p. 105—108° (138 g., 91%). Five crystallisations from ethanol gave pure (±)-*trans*-2-methylcyclohexyl 3,5-dinitrobenzoate (45 g.), m. p. 117—118° (lit.,⁵ 117°), which was hydrolysed with 5% methanolic potassium hydroxide to (±)-*trans*-2-methylcyclohexanol, b. p. 165—166°/772 mm., n_D^{25} 1.4562 (8.7 g., 58%). Acetylation with acetic anhydride gave (±)-*trans*-2-methylcyclohexyl acetate, b. p. 182—183°/770 mm., n_D^{25} 1.4355 (5.5 g., 44%).

(±)-*cis*-2-Methylcyclohexyl acetate. The mother liquors from the fractional crystallisation of the foregoing 3,5-dinitrobenzoate were evaporated to dryness. The residue, after 19 crystallisations from ethanol, gave pure (±)-*cis*-2-methylcyclohexyl 3,5-dinitrobenzoate (37 g.), m. p. 101° (lit.,⁵ 100—101°), which was hydrolysed as above to (±)-*cis*-2-methylcyclohexanol, b. p. 163°/765 mm., n_D^{25} 1.4596 (5.0 g., 57%). Acetylation gave (±)-*cis*-2-methylcyclohexyl acetate, b. p. 180°/763 mm., n_D^{25} 1.4368 (4.9 g., 71%).

(±)-*cis*-3-Methylcyclohexyl acetate. (±)-3-Methylcyclohexanol (from Eastman Organic Chemicals) was dried (Na_2SO_4) and distilled *in vacuo*. It had b. p. 69°/16 mm. The alcohol (50 g.) was esterified with 3,5-dinitrobenzoyl chloride (102 g.), giving a crude ester, m. p. 75—90° (116 g., 73%). Nine crystallisations from ethanol gave pure (±)-*cis*-3-methylcyclohexyl 3,5-dinitrobenzoate (49 g.), m. p. 99—100° (lit.,⁶ 99°), which was hydrolysed as above to (±)-*cis*-3-methylcyclohexanol, b. p. 170°/765 mm., n_D^{20} 1.4579 (13 g., 55%). Acetylation gave (±)-*cis*-3-methylcyclohexyl acetate, b. p. 185°/763 mm., n_D^{25} 1.4530 (13.5 g., 76%).

(±)-*trans*-3-Methylcyclohexyl acetate. (±)-3-Methylcyclohexanol (150 g.) was oxidised with chromic acid to 3-methylcyclohexanone, b. p. 60°/25 mm. (102 g., 69%). The ketone (75 g.) in ethanol (100 ml.) was shaken with hydrogen at 7 atm. for 12 hr. with Raney nickel (5 g.),⁷ giving (±)-3-methylcyclohexanol, b. p. 72°/23 mm. (58 g., 75%). The alcohol (50 g.) with 3,5-dinitrobenzoyl chloride (102 g.) gave a crude ester, m. p. 60—80° (114 g., 74%). Five crystallisations from light petroleum (b. p. 60—80°) gave pure (±)-*trans*-3-methylcyclohexyl 3,5-dinitrobenzoate (32 g.), m. p. 111° (lit.,⁶ 111°), which was hydrolysed as above to (±)-*trans*-3-methylcyclohexanol, b. p. 168°/766 mm., n_D^{25} 1.4545 (9.0 g., 67%). Acetylation gave (±)-*trans*-3-methylcyclohexyl acetate, b. p. 185°/765 mm., n_D^{25} 1.4369 (6.5 g., 53%).

trans-4-Methylcyclohexyl acetate. 4-Methylcyclohexanol (from Eastman Kodak Ltd.) was converted into *trans*-4-methylcyclohexyl 3,5-dinitrobenzoate by Jackman, Macbeth, and Mills's method.⁵ The pure ester had m. p. 142° (lit.,⁵ 142°) and was hydrolysed as above to *trans*-4-methylcyclohexanol, b. p. 173—174°/772 mm., n_D^{20} 1.4365. Acetylation gave *trans*-4-methylcyclohexyl acetate, b. p. 186°/767 mm., n_D^{25} 1.4352.

cis-4-Methylcyclohexyl acetate. *cis*-4-Methylcyclohexyl *p*-nitrobenzoate, prepared from 4-methylcyclohexanol according to Jackman, Macbeth, and Mills's method,⁵ had m. p. 95—96° (lit.,⁵ 96°). It was hydrolysed as above to *cis*-4-methylcyclohexanol, b. p. 167°/763 mm., n_D^{25} 1.4579. Acetylation gave *cis*-4-methylcyclohexyl acetate, b. p. 183—184°/756 mm., n_D^{25} 1.4365.

Cyclohexyl acetate. Cyclohexanol was purified by fractional freezing, followed by distillation through a 75 × 1.5 cm. column packed with Fenske helices, and had b. p. 161—162°/760 mm., m. p. 24°, n_D^{25} 1.4365. Acetylation gave cyclohexyl acetate, b. p. 176—177°/765 mm., n_D^{20} 1.4400.

(±)-*Bornyl* acetate. (±)-Borneol (from British Drug Houses Ltd.) was crystallised from light petroleum (b. p. 60—80°) to a constant m. p. of 208° [mixed m. p. with (±)-isoborneol, 190—200°]. Acetylation gave (±)-bornyl acetate, b. p. 104°/20 mm., n_D^{25} 1.4640.

(±)-*Isobornyl* acetate. (±)-Isoborneol (from L. Light & Co. Ltd.) was crystallised from light petroleum (b. p. 60—80°) to a constant m. p. of 211° [mixed m. p. with (±)-borneol, 190—200°]. Acetylation gave (±)-isobornyl acetate, b. p. 96°/15 mm., n_D^{25} 1.4640.

(±)-*Menthyl* acetate. (±)-Menthol (from British Drug Houses Ltd.) was fractionated through a 30 × 3 cm. Vigreux column and had b. p. 106°/20 mm. Acetylation gave (±)-menthyl acetate, b. p. 106°/20 mm., n_D^{25} 1.4440.

(±)-*Neomenthyl* acetate. (±)-Menthone, prepared by chromic acid oxidation of (±)-menthol, was converted into (±)-neomenthol, b. p. 178°/340 mm., by the method used by Grubb and

⁷ Wicker, personal communication.

Read⁸ for the preparation of the (+)-isomer. Acetylation gave (\pm)-neomenthyl acetate, b. p. 99°/25 mm., n_D^{25} 1.4472.

trans-4-t-Butylcyclohexyl acetate. *p-t*-Butylphenol (140 g., from British Drug Houses Ltd.), crystallised from light petroleum (b. p. 60—80°) to a constant m. p. 99°, was hydrogenated in ethanol (250 ml.) at 100 atm. at 125° for 9 hr. with Raney nickel (10 g.). The crude 4-*t*-butylcyclohexanol, m. p. 60—70°, was converted into *trans-4-t*-butylcyclohexanol by Winstein and Holness's method,⁴ light petroleum (b. p. 100—120°) being used to crystallise the hydrogen phthalate ester to constant m. p. The pure alcohol had m. p. 81—82° (lit.,⁴ 80—81°). Acetylation with acetic anhydride gave *trans-4-t-butylcyclohexyl acetate*,* b. p. 110°/16 mm., n_D^{25} 1.4500 (Found: C, 72.4; H, 10.7. C₁₂H₂₂O₂ requires C, 72.7; H, 11.2%).

cis-4-t-Butylcyclohexyl acetate. The mother liquors from the fractional crystallisation of the foregoing hydrogen phthalate were evaporated to dryness and the residue (38 g.) was hydrolysed with aqueous sodium hydroxide, giving crude 4-*t*-butylcyclohexanol, m. p. 65—75° (18 g., 95%). The *cis*-isomer was isolated by chromatography on alumina (500 g.), light petroleum (b. p. 40—60°) containing 20% of ether being used as eluant. The product had m. p. 79—81° (8 g.) and one crystallisation from aqueous ethanol gave pure *cis-4-t*-butylcyclohexanol (5 g.), m. p. 80—81° (lit.,⁴ 81—82°). Acetylation with acetic anhydride gave *cis-4-t-butylcyclohexyl acetate*,* b. p. 104°/15 mm., n_D^{25} 1.4480 (Found: C, 73.7; H, 11.6%).

Reagents.—Sodium hydroxide. The solutions were prepared from a standard solution, free from carbonate (from British Drug Houses Ltd.).

Potassium hydrogen phthalate. "AnalaR" salt was dried at 120° and stored in a desiccator.

Indicator.—The indicator used for all titrations was a mixture of Thymol Blue (6 parts of 0.1% solution) and Cresol Red (1 part of 0.1% solution).

Solvent.—Dioxan was purified as in Part I.¹ A Karl Fischer moisture determination⁹ showed less than 0.1% of water to be present. The dioxan was mixed with boiled-out, distilled water to give either 3 : 1 v/v water-dioxan or 1 : 1 v/v water-dioxan.

Kinetic Procedure.—The reactions were started by breaking a bulb containing a known weight of ester dissolved in dioxan above the hydrolysing solution of sodium hydroxide in a water-dioxan mixture. The reaction vessels were kept at temperatures constant to $\pm 0.02^\circ$ and an atmosphere of carbon dioxide-free nitrogen was maintained above the surface of the liquid. The reactions were followed by quenching aliquot parts in an excess of standard potassium hydrogen phthalate solution and titrating the excess of acid with standard carbonate-free sodium hydroxide solution. With bornyl, isobornyl, menthyl, neomenthyl, and the 4-*t*-butylcyclohexyl acetates it was necessary to add ethanol (5 ml.) before the back-titration, in order to keep the reaction products in solution. The end-points thus obtained were sharp.

The initial concentration of ester was 0.01M in every case, except for the 4-*t*-butylcyclohexyl acetates where, for reasons of solubility, an initial concentration of 0.005M was used. The initial concentration of alkali was also 0.01M in every case, except for neomenthyl acetate, where a concentration of 0.02M was used in order to increase the rate of the reaction.

Test for Elimination.—The products of a reaction of cyclohexyl acetate were extracted with toluene, and the extract dried (Na₂SO₄) and submitted to gas chromatography on a column of Silicone resin supported on Celite. A synthetic mixture containing added cyclohexene was submitted to gas chromatography under identical conditions. No cyclohexene (less than 5%) could be detected in the products from the reaction of cyclohexyl acetate.

Infrared Spectra.—Infrared spectra were measured in a Unicam S.P. 100 double-beam, infrared spectrophotometer, 1% v/v solutions of the esters in carbon tetrachloride being used.

RESULTS

The reaction between cyclohexyl acetate and hydroxide ion in 1 : 1 v/v water-dioxan at 21.10° was carried out at three different initial concentrations, and, by application of the differential method,¹⁰ was shown to be of the first order with respect both to the ester and to

* Since the completion of this work, *trans*- and *cis*-4-*t*-butylcyclohexyl acetate have been reported by Lemieux, Kulling, Bernstein, and Schneider,²¹ but no analyses are given. With allowance for the temperature differences, their refractive indices are in reasonable agreement with those measured by us.

⁸ Grubb and Read, *J. Soc. Chem. Ind.*, 1934, 53, 52r.

⁹ Smith, Bryant, and Mitchell, *J. Amer. Chem. Soc.*, 1939, 61, 2407.

¹⁰ Laidler, "Chemical Kinetics," McGraw-Hill, New York, 1950, p. 14.

hydroxide ion (orders 1.02 and 0.98 respectively). This was assumed to hold for the other cases also, as they all obeyed the second-order rate law (1) (for equal initial concentrations) or (2) (for unequal initial concentrations):

$$dx/dt = k_2(a-x)^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$dx/dt = k_2(a-x)(b-x) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

giving respectively

$$t = \frac{1}{k_2(a-x)} - \frac{1}{k_2 a}$$

or

$$t = \frac{2.303}{k_2(a-b)} \log_{10} \frac{b}{a} + \frac{2.303}{k_2(a-b)} \log_{10} \frac{a-x}{b-x}$$

where a is the initial concentration of hydroxide and b is that of ester. Values of the second-order rate coefficient, k_2 , were determined graphically from the slopes of plots of $1/(a-x)$ against t , or $\log_{10}(a-x)/(b-x)$ against t . The points all fell on good straight lines. A good proportion of the reaction was followed, usually 60–70%, and all the runs were done in duplicate, the values of k_2 generally agreeing to better than 2%.

TABLE 1. Measured rate constants in 1 : 1 water-dioxan, $10^3 k_2$ ($l. mole^{-1} sec^{-1}$).
(Figures in parentheses are temperatures in °c.)

Acetate			
Cyclohexyl *	9.67 (15.50°)	22.80 (29.60°)	55.50 (45.50°)
Cyclohexyl	11.70 (29.20)	29.50 (44.75)	69.50 (60.10)
<i>trans</i> -4-t-Butylcyclohexyl	17.50 (34.25)	35.00 (47.15)	61.00 (57.50)
<i>cis</i> -4-t-Butylcyclohexyl	3.45 (38.90)	6.13 (48.90)	11.60 (59.30)
<i>trans</i> -2-Methylcyclohexyl	3.09 (29.20)	8.15 (44.20)	20.60 (60.10)
<i>cis</i> -2-Methylcyclohexyl	2.06 (34.75)	4.80 (47.78)	10.40 (60.05)
<i>trans</i> -3-Methylcyclohexyl	5.00 (34.50)	11.20 (47.37)	23.20 (60.10)
<i>cis</i> -3-Methylcyclohexyl	18.20 (34.57)	38.00 (47.78)	72.00 (60.05)
<i>trans</i> -4-Methylcyclohexyl	5.27 (14.80)	14.00 (29.20)	37.00 (44.75)
<i>cis</i> -4-Methylcyclohexyl	7.07 (36.48)	13.77 (47.34)	29.14 (60.00)
Bornyl	4.40 (34.57)	7.80 (44.48)	19.20 (59.90)
Isobornyl	0.307 (29.20)	0.965 (44.20)	3.16 (59.90)
Menthyl	1.13 (36.48)	2.33 (47.70)	5.20 (60.30)
Neomenthyl	0.43 (57.50)		

* In 3 : 1 water-dioxan.

TABLE 2. Rate constants interpolated to 40°, and Arrhenius parameters in 1 : 1 water-dioxan.

$(k_2$ and A in $l. mole^{-1} sec^{-1}$; E in $kcal. mole^{-1}$)			
Acetate	$10^3 k_2 (40^\circ)$	E	$\log_{10} A$
Cyclohexyl *	40.5	10.50	5.94
Cyclohexyl	22.3	11.49	6.37
<i>trans</i> -4-t-Butylcyclohexyl	24.0	10.79	5.92
<i>cis</i> -4-t-Butylcyclohexyl	3.61	12.44	6.24
<i>trans</i> -2-Methylcyclohexyl	6.27	12.11	6.25
<i>cis</i> -2-Methylcyclohexyl	2.93	13.01	6.54
<i>trans</i> -3-Methylcyclohexyl	7.00	12.22	6.38
<i>cis</i> -3-Methylcyclohexyl	24.7	10.63	5.81
<i>trans</i> -4-Methylcyclohexyl	27.7	11.83	6.70
<i>cis</i> -4-Methylcyclohexyl	8.77	12.45	6.63
Bornyl	6.03	11.89	6.08
Isobornyl	0.716	15.25	7.50
Menthyl	1.41	13.15	6.33
Neomenthyl	0.43 †		

* In 3 : 1 water-dioxan. † $10^3 k_2$ at 57.50°.

The results are summarised in Table 1, and values of k_2 interpolated to 40°, together with the Arrhenius parameters, are collected in Table 2. The results of the infrared spectroscopic measurements are collected in Table 3.

TABLE 3. Infrared spectroscopic measurements (in carbon tetrachloride solution).

Acetate	Band at ca. 1250 cm. ⁻¹ (acyl-oxygen stretching)	Band in 1130— 1200 cm. ⁻¹ range	Bands in 1020—1060 cm. ⁻¹ range (alkyl-oxygen stretching)
<i>trans</i> -4-t-Butylcyclohexyl ...	Simple	—	1034, 1052
<i>cis</i> -4-t-Butylcyclohexyl	Complex	1183	1025
Cyclohexyl	Simple	1132	1030, 1052
<i>trans</i> -2-Methylcyclohexyl ...	Simple	—	1036
<i>cis</i> -2-Methylcyclohexyl	Complex	1139	1025
<i>trans</i> -3-Methylcyclohexyl ...	Complex	1139	1025, 1047
<i>cis</i> -3-Methylcyclohexyl	Simple	—	1033, 1048
<i>trans</i> -4-Methylcyclohexyl ...	Simple	—	1039
<i>cis</i> -4-Methylcyclohexyl	Complex	1139, 1168	1025, 1042
Menthyl	Simple	—	1032, 1044
Neomenthyl	Complex	1154	1027, 1033
Bornyl	Simple	—	1041, 1055
Isobornyl	Simple	1193	1028, 1060

DISCUSSION

The 4-t-Butylcyclohexyl Acetates.—It should be noted that these compounds do not obey the revised Auwers-Skita rule,^{11,12} which states, *inter alia*, that the isomer of least conformational stability has the higher refractive index. In fact, the conformationally more stable *trans*-4-t-butylcyclohexyl acetate has a higher refractive index than its *cis*-isomer. A similar exception to the rule has been noted for the melting points of the methyl 4-t-butylcyclohexanecarboxylates.¹

The *trans*- and *cis*-4-t-butylcyclohexyl acetate are assumed to exist entirely as conformations containing equatorial t-butyl groups.

The Conformations of the Remaining Acetates.—Table 2 contains a list of rates interpolated to 40°. It can be seen that the rate for cyclohexyl acetate (in 1 : 1 water-dioxan) falls between those for the 4-t-butylcyclohexyl acetates, *i.e.*, between the rate for a purely equatorial and for a purely axial acetoxy-group. Since its rate is nearer to that for *trans*-4-t-butylcyclohexyl acetate, cyclohexyl acetate must exist mainly in conformation (I), with its acetoxy-group equatorial. A quantitative assessment of the conformational equilibrium can be made by application of equation (3), due to Winstein and Holness:⁴

$$k_{\text{obs.}} = k_{\text{E}}N_{\text{E}} + k_{\text{A}}N_{\text{A}} \quad (3)$$

where $k_{\text{obs.}}$ is the observed rate coefficient, k_{E} and k_{A} are the rate coefficients corresponding to a purely equatorial conformation reacting through an equatorial-type transition state, and purely axial conformation reacting through an axial-type transition state, respectively, and N_{E} and N_{A} are the mole-fractions of equatorial and axial conformations, respectively. Putting k_{E} and k_{A} equal to the rate coefficients for *trans*- and *cis*-4-t-butylcyclohexyl acetate, respectively, we find the value of N_{E} for cyclohexyl acetate at 40° to be 0.92. Equations (4) and (5) give values for the conformational equilibrium constant, K , and the

$$K = N_{\text{E}}/N_{\text{A}} \quad (4)$$

$$\Delta G = RT \ln K \quad (5)$$

free-energy difference between the conformations, ΔG , of 11.1 and 1.5 kcal./mole, respectively. The values of N_{E} , K , and ΔG for cyclohexyl acetate, together with the corresponding values for the other acetates, are collected in Table 4. In every case, N_{E} refers to the conformation with an equatorial acetoxy-group and ΔG is positive when this conformation is the more stable one.

¹¹ Allinger, *Experientia*, 1954, **10**, 328.

¹² Kelly, *Canad. J. Chem.*, 1957, **35**, 149.

The results for *trans*-3-methylcyclohexyl acetate and *cis*-4-methylcyclohexyl acetate have been obtained in an exactly similar way to those for cyclohexyl acetate. The rates of hydrolysis of *trans*-4-methylcyclohexyl acetate and of *cis*-3-methylcyclohexyl acetate are slightly greater than that for *trans*-4-*t*-butylcyclohexyl acetate and N_E is, therefore, taken as unity for these compounds.

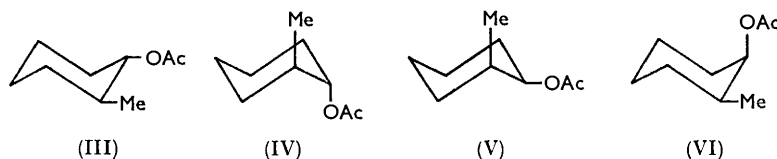
TABLE 4. Positions of conformational equilibria and free-energy differences in 1 : 1 water-dioxan at 40°.

Acetate	N_E	K	ΔG (kcal. mole ⁻¹)
Cyclohexyl	0.92	11.1	+1.5
<i>trans</i> -4- <i>t</i> -Butylcyclohexyl	1.00	—	—
<i>cis</i> -4- <i>t</i> -Butylcyclohexyl	0.00	—	—
<i>trans</i> -2-Methylcyclohexyl	1.00	—	—
<i>cis</i> -2-Methylcyclohexyl	0.37	0.60	-0.3
<i>trans</i> -3-Methylcyclohexyl	0.17	0.20	-1.0
<i>cis</i> -3-Methylcyclohexyl	1.00	—	—
<i>trans</i> -4-Methylcyclohexyl	1.00	—	—
<i>cis</i> -4-Methylcyclohexyl	0.25	0.34	-0.7
Menthyl	1.00 *	—	—
Neomenthyl	0.00 *	—	—

* At 57.50°.

N_E is the mole fraction of conformation containing an equatorial acetoxy-group. K and ΔG are calculated from equations (4) and (5), and a positive value for ΔG means that the conformation with the equatorial acetoxy-group is the more stable.

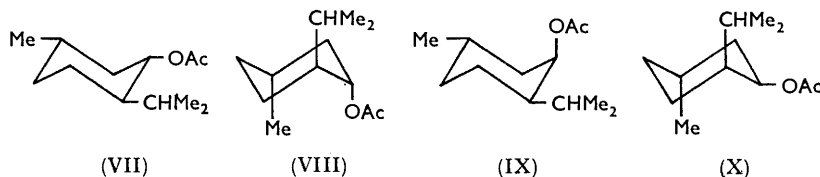
The rates for the 2-methylcyclohexyl acetates are considerably lower than those for the other methylcyclohexyl acetates, and it is evident that retardation due to the primary steric effect of the 2-methyl group is an added complication in the reactions of these compounds. The polar (inductive) effect of the 2-methyl group may also have a slight influence. The above method of analysis cannot, therefore, be applied to these cases. However, it can reasonably be assumed that *trans*-2-methylcyclohexyl acetate, like *trans*-4- and *cis*-3-methylcyclohexyl acetate, exists entirely in the conformation with its acetoxy-group equatorial (III). The alternative conformation (IV), with both groups in



axial positions, is likely to be considerably less stable. It is further assumed that the rate of hydrolysis of conformation (V) of *cis*-2-methylcyclohexyl acetate is the same as that of the *trans*-isomer [*i.e.*, conformation (III)]. This is again a reasonable assumption, since the equatorial acetoxy-group is the same distance from the 2-methyl group, whether the latter is equatorial or axial. Thus the primary steric effect of the methyl group can be expected to be identical for the hydrolysis of both (III) and (V). Any polar effect of the methyl group should also be identical in the two cases. A value for the rate coefficient for hydrolysis of conformation (VI) is arrived at by assuming that the rate ratio, (III) to (VI), is the same as that for *trans*- to *cis*-4-*t*-butylcyclohexyl acetate (6.64). In this way, application of equation (3) (with $k_E = 0.00627$, and $k_A = 0.00627/6.64$) to *cis*-2-methylcyclohexyl acetate gives a value for N_E of 0.37.

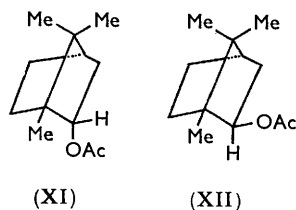
Since the rate of hydrolysis of neomenthyl acetate was only determined at one temperature (57.50°), the conformations of this compound and of menthyl acetate are con-

sidered at this temperature. It is safe to assume that menthyl acetate will exist entirely as conformation (VII) with all three groups equatorial, rather than as conformation (VIII) with all three groups axial. As the rate ratio for menthyl to neomenthyl acetate at



57-50° (10.1) is greater than that for *trans*- to *cis*-4-*t*-butylcyclohexyl acetate at the same temperature (5.93), neomenthyl acetate must exist entirely in conformation (IX) with an axial acetoxy-group, and not at all in conformation (X). The primary steric and polar effects of the 2-isopropyl group are no doubt responsible for the lower rates of the menthyl acetates than of those of the 4-*t*-butylcyclohexyl acetates, but these effects should be the same in (VII) as in (IX) and (X) and should not, therefore, influence the rate ratio.

In bornyl and isobornyl acetates the cyclohexane ring is fixed in the boat-conformation by the presence of the CMe_2 bridge. Bornyl acetate (XI) has its acetoxy-group in the "boat-axial" conformation, and the acetoxy-group and the methyl group on adjacent carbon atoms are *cis*. In spite of this *cis*-relation, models show that the relative positions of these two groups are very similar in bornyl acetate and in diequatorial *trans*-2-methylcyclohexyl acetate. This similarity is borne out by the kinetic results. Both compounds give very similar rates and Arrhenius parameters (cf. Table 2). This presumably means not only that the relative disposition of the methyl and acetoxy-groups is similar in the two compounds, but also that the "boat-axial" acetoxy-group in bornyl acetate is not appreciably more hindered than the equatorial acetoxy-group in *trans*-2-methylcyclohexyl acetate.



Hydrolysis of isobornyl acetate (XII) is characterised by an appreciably higher energy of activation (15.3 kcal. mole⁻¹) than the hydrolyses of the other compounds studied here (10.6—13.2 kcal. mole⁻¹), and this is undoubtedly due to the primary steric effect of the *gem*-dimethyl group.

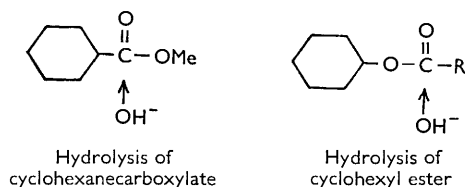
Spectroscopic Measurements.—In spite of the different solvent and temperature used for the infrared measurements (carbon tetrachloride at room temperature instead of 1 : 1 water-dioxan at 40°), the results in Table 3 provide striking support for the conformations deduced above from the kinetic data. It has previously been shown^{13,14} that, for certain acetoxy-steroids, a compound containing an equatorial acetoxy-group can be distinguished from one containing an axial acetoxy-group (*a*) by a simple, rather than a complex, peak at about 1250 cm.⁻¹ (acyl-oxygen stretching), and (*b*) by higher frequency absorption in the 1020—1060 cm.⁻¹ range (alkyl-oxygen stretching). This same pattern is shown by the 4-*t*-butylcyclohexyl acetates, the *trans*-isomer giving a simple peak at 1250 cm.⁻¹ and peaks at 1034 cm.⁻¹ and 1052 cm.⁻¹, and the *cis*-isomer giving a complex (triple) peak at 1250 cm.⁻¹ and a peak at 1025 cm.⁻¹. Also, the two isomers show different behaviour in the 1130—1200 cm.⁻¹ range. The *cis*-isomer gives a weak medium peak at 1183 cm.⁻¹, while the *trans*-isomer does not absorb in this region. The origin of the peak at 1183 cm.⁻¹ is not clear. It may be associated with one or other of the carbon-oxygen stretching vibrations or it may just conceivably be a grossly displaced carbon-hydrogen deformation band.

Comparisons with Results of Other Workers.—Winstein and Holness⁴ have measured the rates of alkaline hydrolysis in water of the hydrogen phthalates of cyclohexanol and

¹³ Jones, Humphries, Herling, and Dobriner, *J. Amer. Chem. Soc.*, 1951, **73**, 3215.

¹⁴ Page, *J.*, 1955, 2017.

cis- and *trans*-4-*t*-butylcyclohexanol. Their ratio of rates for *trans*- to *cis*-*t*-butyl compound (*i.e.*, rate of purely equatorial ester to purely axial ester) at 39° (10) is rather greater than our analogous ratio at 40° (6.6). Since cyclohexyl hydrogen phthalate is hydrolysed slightly more rapidly than its *trans*-4-*t*-butyl derivative, it must presumably be entirely in the conformation with the ionised hydrogen phthalate group equatorial. This is not surprising in view of the size of the ionised hydrogen phthalate group. A similar investigation by Hennion and O'Shea¹⁵ into the alkaline hydrolysis in aqueous acetone of the *p*-nitrobenzoates of the same three cyclohexanols gave an equatorial/axial ratio at 25° of 2.5. In this case the cyclohexyl ester reacted more slowly than its *trans*-4-*t*-butyl derivative and application of equation (3) showed 84% of equatorial cyclohexyl *p*-nitrobenzoate at 25°. Measurement of the hydrolysis rates of methyl cyclohexanecarboxylate and of its *cis*- and *trans*-4-*t*-butyl derivatives in 1:1 water-dioxan¹ gave an equatorial:axial ratio of 17 at 30°. The high ratio here is due to the attack of the hydroxide ion at a position one atom nearer to the cyclohexane ring than in the hydrolysis of cyclohexyl esters:



The increased proximity of the ring should not significantly affect the rate of hydrolysis of the equatorial isomer, but will increase the steric compression in the axial transition state, thereby reducing the rate of hydrolysis of the axial compound and increasing the equatorial:axial ratio. In this work methyl cyclohexanecarboxylate reacted faster than its *trans*-4-*t*-butyl derivative and presumably, therefore, exists entirely in the conformation with its methoxycarbonyl group equatorial.

Other related kinetic investigations include the acetylation with acetic anhydride in pyridine of cyclohexanol and its *cis*- and *trans*-4-butyl, *cis*- and *trans*-4-methyl, and *cis*- and *trans*-3-methyl derivatives;¹⁶ the alkaline hydrolysis in aqueous ethanol of the six methylcyclohexyl hydrogen phthalates;¹⁷ the alkaline hydrolysis in aqueous ethanol of bornyl and isobornyl acetates;¹⁸ and the esterification with *p*-nitrobenzoyl chloride in pyridine of menthol and neomenthol.¹⁹

The overall picture presented by the above investigations and the relative magnitudes of the rate coefficients conform closely with our results.

With regard to spectroscopic investigations, equatorial and axial cyclohexyl bromides have been distinguished by their infrared spectra²⁰ and equatorial and axial cyclohexyl acetates by their proton magnetic resonance spectra.²¹

Arrhenius Parameters.—For every pair of *cis-trans*-isomers studied, the compound with the greater proportion of equatorial acetoxy-conformation gives the lower energy and entropy of activation. This is probably because the type of closely packed transition state formed from an equatorial acetoxy-compound, such as *trans*-4-*t*-butylcyclohexyl acetate, cannot be formed from an axial acetoxy-compound, such as *cis*-4-*t*-butylcyclohexyl acetate, without appreciable steric compression from 1:3-diaxial interactions. In axial acetoxy-compounds, therefore, it may be supposed that the system prefers a more

¹⁵ Hennion and O'Shea, *J. Amer. Chem. Soc.*, 1958, **80**, 614.

¹⁶ Eliel and Lukach, *J. Amer. Chem. Soc.*, 1957, **79**, 5986.

¹⁷ Cornubert, *Bull. Soc. chim. France*, 1956, 996.

¹⁸ Lipp and Bund, *Ber.*, 1935, **68**, 249.

¹⁹ Read and Grubb, *J.*, 1934, 1779.

²⁰ Eliel and Haber, *J. Org. Chem.*, 1959, **24**, 143.

²¹ Lemieux, Kulling, Bernstein, and Schneider, *J. Amer. Chem. Soc.*, 1958, **80**, 6098.

loosely packed transition state (*i.e.*, one in which the hydroxide ion is further away from the carbonyl carbon atom), with the higher energy and entropy of activation which this implies. In the case of the bornyl acetates the position is reversed and it appears that, in this particular ring system, the transition state from a boat-axial acetoxy-group is subject to less steric compression than that from a boat-equatorial acetoxy-group.

Cyclohexyl acetate and *trans*-4-methylcyclohexyl acetate are exceptions to this generalisation. These two compounds, with their acetoxy-groups entirely or almost entirely in the equatorial conformation, might have been expected to give Arrhenius parameters similar to those for *trans*-4-*t*-butylcyclohexyl acetate (as does *cis*-3-methylcyclohexyl acetate). In fact, however, they give both higher energies and higher entropies of activation. There does not seem to be any obvious explanation for this behaviour.

TABLE 5. Rates of hydrolysis and positions of conformational equilibrium at 40° and at 100°.

Acetate	10 ³ <i>k</i> ₄₀	10 ³ <i>k</i> ₁₀₀	<i>N</i> _{E, 40}	<i>N</i> _{E, 100}
Cyclohexyl	22.3	434	0.92	1.00
<i>trans</i> -4- <i>t</i> -Butylcyclohexyl	24.0	395	1.00	1.00
<i>cis</i> -4- <i>t</i> -Butylcyclohexyl	3.61	89.5	0.00	0.00
<i>trans</i> -2-Methylcyclohexyl	6.27	143	1.00	1.00
<i>cis</i> -2-Methylcyclohexyl	2.93	83.2	0.37	0.46
<i>trans</i> -3-Methylcyclohexyl	7.00	166	0.17	0.25
<i>cis</i> -3-Methylcyclohexyl	24.7	383	1.00	0.96
<i>trans</i> -4-Methylcyclohexyl	27.5	588	1.00	1.00
<i>cis</i> -4-Methylcyclohexyl	8.77	216	0.25	0.41
Bornyl	6.03	130		
Isobornyl	0.716	37.0		
Menthyl	1.41	42.4	1.00	1.00

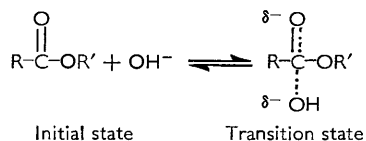
The Arrhenius parameters have been used to calculate the rates of hydrolysis at 100° and, from these rates, values of *N*_E have been determined as above. The results are compared with those for 40° in Table 5. For *cis*-2-, *trans*-3-, *cis*-3-, and *cis*-4-methylcyclohexyl acetate the variation of *N*_E with temperature is in the expected direction, a greater proportion of the higher-energy conformation being present at the higher temperature. Cyclohexyl acetate and *trans*-4-methylcyclohexyl acetate are again anomalous, however. Both compounds give greater rates of hydrolysis than does "purely equatorial" *trans*-4-*t*-butylcyclohexyl acetate, the rate for the *trans*-4-methyl compound being almost 50% greater. Furthermore, cyclohexyl acetate appears to contain more of the lower-energy equatorial form at 100° than it does at 40°.

In spite of these apparent anomalies, which may be due to our neglect of the small polar effect of the alkyl groups, the kinetic and spectroscopic evidence leaves little doubt that, at low temperatures, *trans*-2-, *cis*-3-, and *trans*-4-methylcyclohexyl acetates and menthyl acetate exist entirely in conformations with their acetoxy-groups equatorial, cyclohexyl acetate exists almost (but not quite) entirely in such a conformation, and *cis*-2-, *trans*-3-, and *cis*-4-methylcyclohexyl acetates and neomenthyl acetate exist mainly in conformations with their acetoxy-groups axial. The bornyl acetates have fixed conformations, and the conformations of the 4-*t*-butylcyclohexyl acetates are assumed to be fixed also. The accuracy of the kinetic results and the validity of the underlying assumptions is such that it is probably not justifiable to state the conclusions in a more quantitative way than this.

The Effect of Solvent.—One reaction, that of cyclohexyl acetate has been studied in both 1 : 1 water-dioxan and 3 : 1 water-dioxan, and the results are shown in Tables 1 and 2. Since bimolecular alkaline hydrolysis of esters with acyl-oxygen fission is known to involve an intermediate,²² the formation of which must be rate-determining (because of the well-known effects of polar substituents), it follows from the Hughes-Ingold theory

²² Bender, *J. Amer. Chem. Soc.*, 1951, **73**, 1626.

of solvent action²³ that such hydrolyses should be slower in a more strongly solvating solvent. This is because the charge is more dispersed in the transition state than in the initial state:



However, reference to Table 2 shows that, at 40°, cyclohexyl acetate is hydrolysed almost twice as fast in 3 : 1 water-dioxan as in 1 : 1 water-dioxan, in direct contradiction to the above prediction. The higher rate in the more aqueous solvent is due to a lower energy of activation, partially offset by a lower entropy of activation. Many similar effects of solvent in ester hydrolysis have been discovered,²⁴ but the fact that such cases provide exceptions to the otherwise very generally applicable rule of Hughes and Ingold does not seem to have been sufficiently emphasised.

One of us (P. J. A. S.) thanks the Ministry of Education for a State Scholarship.

THE UNIVERSITY, SOUTHAMPTON.

[Received, February 25th, 1960.]

²³ Ingold, "Structure and Mechanism in Organic Chemistry," G. Bell and Sons Ltd., London, 1953, p. 345.

²⁴ Tommila, *Suomen Kem.*, 1942, **15**, B, 9, and subsequent papers; Anantakrishnan, *Proc. Indian Acad. Sci.*, 1952, **36**, A, 201; Koivisto, *Acta Chem. Scand.*, 1955, **9**, 166.