[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TENNESSEE]

The Kinetics of the Base-catalyzed Hydrolysis of the Methyl Esters of Cyclohexanedicarboxylic Acids[1]

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The dimethyl and monomethyl esters of the isomeric 1,2-, 1,3- and 1,4-cyclohexanedicarboxylic acids have been prepared and their rates of base-catalyzed hydrolysis in 85% methanol solution have been studied. Rate constants at 25, 35, 45 and 55° have been calculated and tabulated, together with the heats and relative entropies of activation. It has been shown that the difference between the rate constants for hydrolysis of the first and second ester groups is much greater than differences in rate constants for acid-catalyzed esterification of the first and second carboxyl groups in the corresponding cyclohexanedicarboxylic acids. This is probably due to the fact that the negative charge on the ester-ion repels the approach of the hydroxyl group which is necessary for further hydrolysis. The results are explained on the basis of the forms which would be most probable in the various isomers.

The acid-catalyzed esterification of the cyclohexanedicarboxylic acids has been previously investigated.[2] It was shown that for esterification of both the di- and monoesters, the *cis*-1,3 and *trans*-1,4 configurations gave similar rate constants, which differed from those for the *trans*-1,3 and *cis*-1,4 forms. The results were explained on the assumption that the cyclohexane ring is almost entirely in the chair form and that whenever two tautomeric forms of the chair isomer are possible, the one yielding the greater separation of substituents is predominant. It was also shown that the rates of esterification of the 1,2-cyclohexanedicarboxylic acids were slower than for other forms. For the 1,2-cyclohexanedicarboxylic acids, the *cis* form was esterified more rapidly than the *trans*, while for the monomethyl esters, the reverse was true.

When one deals with saponification of esters of dicarboxylic acids, the ester-ion formed when only one ester group is hydrolyzed carries a negative charge and should repel the approach of the hydroxyl ion which is necessary to cause further hydrolysis. For this reason the difference between the rate constants for hydrolysis of the first and second ester groups should be much greater than corresponding differences found in esterifications, although the general relationships between the various *cis* and *trans* acids should remain the same. The research reported here was undertaken to test these ideas.

Experimental

cis- and *trans*-1,2-cyclohexanedicarboxylic acids were prepared as previously described.[2] The dimethyl ester of each of these acids was prepared by refluxing 30 g. of the acid with 190 ml. of methanol and 2.3 ml. of sulfuric acid. After 4 hr., excess methanol was removed by distillation and the remainder treated with dilute sodium carbonate solution. This solution was extracted three times with ether and the ether removed by evaporation. For the *cis*-dimethyl ester, purification was accomplished by careful fractionation in a 2-ft. Vigreux column. A middle fraction of 15 ml. which distilled at 136.2° at 18 mm. mercury was used for kinetic studies. The *trans*-dimethyl ester is a low-melting solid. After three recrystallizations from a 50% methanol–water solution, the crystals melted at 31.0–31.5°.[3]

The monomethyl ester of *cis*-1,2-cyclohexanedicarboxylic acid was prepared by reaction of *ortho*-phthalic anhydride with methanol to form the monomethyl ester and subsequent hydrogenation in glacial acetic acid over Adams platinum catalyst. After the reduction of the benzene ring was complete, the solvent was removed by evaporation, the solid washed and dried and finally recrystallized twice from Merck C.P. Benzin. The material used for kinetic studies melted at 67.5–68.0°.[4]

The monomethyl ester of *trans*-1,2-cyclohexanedicarboxylic acid was prepared by reaction of the pure acid with acetyl chloride to form the anhydride which was subsequently treated with methanol to yield the half ester. After two recrystallizations from petroleum ether, the product melted at 94.5 to 95.0°.

The mixed dimethyl esters of 1,3-cyclohexanedicarboxylic acid were prepared by hydrogenation of dimethyl isophthalate in acetic acid solution with platinum catalyst. The mixture of the esters was carefully fractionated at a 250:1 reflux ratio in a 15-ft. Vigreux column under reduced pressure. The pure *trans* ester was collected at 140° under 20 mm. pressure.

Another portion of the mixed 1,3-esters was hydrolyzed, the resulting acids dissolved in hot water and allowed to cool slowly to room temperature with occasional addition of crystals of pure *cis*-1,3 acid. The precipitate was filtered, dried and then recrystallized twice from water by the above method. The pure acid, m.p. 167.5–168°,[5] was just neutralized with potassium hydroxide and then treated with silver nitrate. The precipitated silver salt was dried, suspended in absolute ether and treated with an ethereal solution of methyl iodide. This solution was extracted three times with sodium carbonate solution, once with water and the solvent evaporated. The resulting oil was fractionated under reduced pressure in a 2-ft. Vigreux column. The material used for kinetic measurements distilled at 148° at 20 mm.

The monomethyl ester of *cis*-1,3-cyclohexanedicarboxylic acid was prepared by treatment of the acid with acetyl chloride and methanol. After two recrystallizations from petroleum ether, the pure monomethyl ester melted at 65.8–66.5°.[6] The monomethyl ester of *trans*-1,3-cyclohexanedicarboxylic acid was prepared by reaction of 20.0 g. (0.1 mole) of the dimethyl ester with 5.6 g. (0.1 mole) of potassium hydroxide in 600 ml. of 90% methanol for 48 hr. at room temperature. The excess methanol was evaporated, the residue dissolved in dilute sodium carbonate solution and extracted three times with ether. The aqueous layer was acidified with hydrochloric acid, extracted four times with ether and these extracts combined. The oil remaining after solvent evaporation was dried in a vacuum desiccator over Drierite. This procedure yielded a sample of almost pure monomethyl ester contaminated with a small percentage of *trans*-1,3-cyclohexanedicarboxylic acid. Titration with standard base indicated 95% of the monomethyl ester and 5% of the parent acid. This material was used in kinetic studies with allowance being made for the contaminating acid and the initial alkali necessary to neutralize it.

The dimethyl esters of *cis*- and of *trans*-1,4-cyclohexanedicarboxylic acids were prepared by esterification of the pure *cis* and pure *trans* acids with methanol. The *cis* acid used melted at 170.6–171.5°,[7] and the ester produced from it

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[1] Presented before the Southeastern Regional meeting of the American Chemical Society, November 4, 1955.

[2] H. A. Smith and F. P. Byrne, THIS JOURNAL, **72**, 4406 (1950).

[3] A. Baeyer, *Ann.*, **258**, 217 (1890).

[4] M. Vavon and P. Peignier, *Bull. soc. chim. France*, **45**, 297 (1929).

[5] A. Skita and R. Rossler, *Ber.*, **72B**, 265 (1939).

[6] F. Ramirez and J. W. Sargent, THIS JOURNAL, **74**, 5785 (1952).

[7] R. Malachowski and J. Jankiewicsowna, *Ber.*, **67B**, 1783 (1934).

was fractionated in a 2-ft. Vigreux column under reduced pressure. The sample used for kinetic studies distilled at 143° at 20 mm. The *trans* acid used melted at 312–313°[7] while the ester formed melted at 67.6–68°.[8]

The monomethyl esters of the 1,4-cyclohexanedicarboxylic acids were prepared by partial saponification of the dimethyl esters as described for the preparation of the *trans*-1,3-monomethyl ester. These esters were extracted from contaminating acid by treatment with several portions of cold, dry chloroform. After three subsequent recrystallizations from a mixture of one part chloroform to ten parts petroleum ether, the following melting points were obtained: *cis* form, 106.8–107.4°; *trans* form, 125.7–126.6°.

All kinetic experiments were carried out in thermostats at temperatures of 25.00 ± 0.04°, 35.00 ± 0.02°, 45.00 ± 0.02° and 55.00 ± 0.02°. The solvent was 85 weight per cent. methanol in water. Initial concentrations of carbonate-free alkali and dimethyl ester were 0.100 and 0.050 M, while with alkali and monomethyl ester they were 0.050 M for each at the temperature of the reaction, allowance having been made for neutralization of the free carboxyl group on the monomethyl ester ion. The rate of hydrolysis was followed by withdrawing 10-ml. samples at known times; these were added to flasks containing known amounts of hydrochloric acid. The excess acid was subsequently titrated to the end-point of a mixed phenolphthalein–thymol blue indicator.

Experimental Calculations and Results

Saponifications involving the monomethyl esters and alkali are strictly first order with respect to alkali and first order with respect to ester. Since the initial concentrations of alkali and ester were equal, the following rate equation should apply

$$\frac{1}{C} = k_2t + \frac{1}{C_0}$$

where C_0 is the initial molar concentration, C is the concentration at time t and k_2 is the specific reaction rate constant for saponification of the ester group in the half ester. According to this equation, a plot of the reciprocal of alkali concentration against time should give a straight line of slope k_2. Good straight lines were always obtained, and the values of k_2 given in Table I were calculated in this manner.

For the *cis*-1,2, *trans*-1,2, *trans*-1,3 and *cis*-1,4 forms of the dimethyl esters of the cyclohexanedicarboxylic acids, it was found that saponification of the first ester group was so much more rapid than for the second that, in the early stages of the reaction (up to some 20%), the kinetic behavior was second order. Since the initial concentrations were 0.100 M for alkali and 0.050 M for ester, the applicable rate equation for second order reactions is

$$\frac{1}{C_A^\circ - C_B^\circ}\ln\frac{C_A^\circ C_B}{C_B^\circ C_A} = k_1t$$

where C_A and C_B are the concentrations of alkali and ester, respectively, at any time t, C_A° and C_B° represent the corresponding initial concentrations, and k_1 is the specific reaction rate constant, in this case for saponification of the first ester group. According to this equation, a plot of the logarithm of the ratio of ester to alkali concentration at time t, *versus* t should give a straight line from the slope of which k_1 may be determined, provided the saponification of the second ester group is unimportant. Figure 1 shows such a plot for saponification of the dimethyl ester of *cis*-1,4-cyclohexanedicarboxylic acid, and the k_1 values for four of the esters listed in Table I were determined in this manner. The deviation from a straight line at the higher reaction times seen in Fig. 1 is due to the saponification of the half ester.

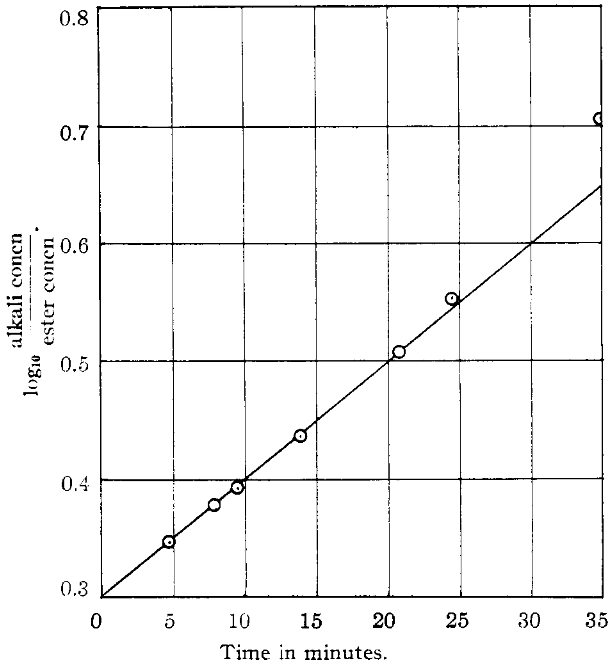

Fig. 1.—Second-order kinetics plot for the *cis*-1,4-dimethyl ester at 55°.

TABLE I

RATE CONSTANTS AND ACTIVATION ENERGIES FOR THE METHYL ESTERS OF THE CYCLOHEXANEDICARBOXYLIC ACIDS

Ester		Rate constants in l. mole⁻¹ hours⁻¹ 25°	35°	45°	55°	$E_A \times 10^{-4}$ (cal. mole⁻¹)
cis-1,2	(k_1)	0.204	0.533	1.66	4.21	1.98
	(k_2)	0.00195	0.00645	0.0176	0.0510	2.10
trans-1,2	(k_1)	0.547	1.32	3.56	8.43	1.79
	(k_2)	0.00835	0.0250	0.0680	0.200	2.05
cis-1,3	(k_1)	4.69	11.61		59.51	1.64
	(k_2)	0.521	1.35	3.20	7.02	1.69
trans-1,3	(k_1)	1.40	3.95	11.53	30.54	2.01
	(k_2)	0.0914	0.279	0.771	2.06	1.99
cis-1,4	(k_1)	1.62	4.33	11.60	26.4	1.82
	(k_2)	0.146	0.385	0.973	2.25	1.81
trans-1,4	(k_1)	4.19	10.1	25.1	55.5	1.65
	(k_2)	0.667	1.52	4.07	8.49	1.67

For the *cis*-1,3 and *trans*-1,4 forms, this method was not very satisfactory. The second ester group reacts at such a speed relative to the first one that data taken in the early stages of the reaction and substituted into a simple second-order equation did not give reliable rate constants. Accordingly the alkali concentration in reaction mixtures containing these acids was determined over about 90% of the range for hydrolysis of both ester groups, and plots of alkali concentration *versus* time were made. Graphical differentiation from this plot was applied by the method of Ritchie[9] to calculate the ratio $(k_1 - k_2)/k_1$. Since the value of k_2 was determined from experiments with the monomethyl esters, the value of k_1 could be calculated from this ratio.

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(8) F. Fichter and T. Holbro, *Helv. Chim. Acta*, **21**, 141 (1938). These authors report a melting point of 71°. Three separate preparations together with recrystallization from a variety of solvents failed to produce crystals melting above 68°.

(9) M. Ritchie, *J. Chem. Soc.*, 3112 (1931).

A plot of the logarithm of the rate constants *versus* the reciprocal of absolute temperature gave good straight lines for all the reactions studied. The heats of activation calculated from the slopes of these lines, together with the rate constants for each temperature, are included in Table I. All rate constants are thought to be correct to ±0.5% and all activation energies to ±100 cal. per mole.

Discussion

The results given in Table I show several interesting features. In correspondence with the results of Smith and Byrne[2] for the esterification of the cyclohexanedicarboxylic acids, the *cis*-1,3 esters behave similarly to the *trans*-1,4, while the kinetic behaviors of the *cis*-1,4 and *trans*-1,3 forms resemble each other. This is explained on the basis of similar spatial forms for those esters which show similar rate behavior.[2]

Table I also demonstrates the fact that for each ester there is a large decrease in the saponification rate of the second ester group as compared with the first. The difference is much greater than the factor of two which would be expected on a purely statistical basis and which was found to be approached for esterification of all of the cyclohexanedicarboxylic acids except the *cis*-1,2 configuration. For esterification of this acid it was suggested that the methyl group of the monoester hinders esterification of the second carboxyl group. The fundamental difference in the two processes lies in the fact that in the esterification process the monoester is in the form of an uncharged molecule and exerts no great electrical influence on the approach of the positively charged ion in the reaction

$$C_6H_{10}(COOCH_3)COOH + CH_3OH_2^+ \longrightarrow C_6H_{10}(COOCH_3)_2 + H_3O^+$$

while for base-catalyzed hydrolysis, the partially saponified ion is negatively charged and repels the attack of the negatively charged base

$$C_6H_{10}(COOCH_3)COO^- + OH^- \longrightarrow C_6H_{10}(COO^-)_2 + CH_3OH$$

The closer the charge on the ester-ion is to the point of attack of the base, the greater should be its repelling action. Thus, for the ester of *cis*-1,2-cyclohexanedicarboxylic acid the ratio k_1/k_2 is 104.6 at 25°, while for the *trans*-1,4 isomer, the corresponding ratio is only 6.3. On the basis of the ratios of the first and second rate constants for saponification of the esters studied, the separation of the two ester groups shows the following order: *trans*-1,4 > *cis*-1,3 > *cis*-1,4 > *trans*-1,3 > *trans*-1,2 > *cis*-1,2. This corresponds to the expected separation as shown by scale models.[10] It is interesting to note that the influence of steric hindrance in the *cis*-1,2 form is such as to decrease the expected ratio of k_1/k_2 for saponification of this isomer. This accounts for the fact that the velocity constants for hydrolysis of both the first and second ester groups are greater for the *trans*-1,2 than for the *cis*-1,2 forms, while for the corresponding esterification, $k_{1_{cis-1,2}} > k_{1_{trans-1,2}}$ but $k_{2_{trans-1,2}} > k_{2_{cis-1,2}}$.

The relative entropies of activation for the saponification reactions based on the monomethyl ester of *cis*-1,2-cyclohexanedicarboxylic acid are given in Table II. These should be correct to better than one entropy unit. This tabulation does not seem to be particularly helpful in the interpretation of the results obtained. However, if one calculates the differences in the relative entropies of activation and arranges them in increasing order, as given in Table III, the result is quite interesting. On the basis of the expected spatial forms of the cyclohexanedicarboxylic acids as previously discussed,[2] the first isomer, *trans*-1,2, has the two ester groups substituted on the cyclohexane ring in axial[11] positions. The next two isomers have relative entropy of activation differences very close to each other, and each of these has two equatorial substituents. Finally, the *cis*-1,2, *trans*-1,3 and *cis*-1,4 isomers form a group with similar values, and each of these has one axial and one equatorial substituent.

TABLE II

RELATIVE ENTROPIES OF ACTIVATION FOR SAPONIFICATION OF THE VARIOUS ESTERS STUDIED

Ester	$\Delta S^* - \Delta S_0^*$
cis-1,2-Monomethyl[a]	0.00
cis-1,2-Dimethyl	3.83
trans-1,2-Monomethyl	1.22
trans-1,2-Dimethyl	−0.58
cis-1,3-Monomethyl	−2.66
cis-1,3-Dimethyl	−1.36
trans-1,3-Monomethyl	4.30
trans-1,3-Dimethyl	8.32
cis-1,4-Monomethyl	−1.16
cis-1,4-Dimethyl	1.81
trans-1,4-Monomethyl	−2.84
trans-1,4-Dimethyl	−1.28

[a] This was taken as the reference reaction and arbitrarily assigned the value of zero.

TABLE III

DIFFERENCES IN RELATIVE ENTROPIES OF ACTIVATION (DI-ACID OR ESTER–MONO-ACID OR ESTER) FOR SAPONIFICATION AND ESTERIFICATION REACTIONS

	$\Delta(\Delta S^* - \Delta S_0^*)$	
Acid or ester	Saponification	Esterification
trans-1,2	−1.80	3.18
cis-1,3	1.30	0.81
trans-1,4	1.56	2.16
cis-1,4	2.97	3.29
cis-1,2	3.83	1.08
trans-1,3	4.02	3.78

Similar values for the esterification reactions are also included in Table III. Here one finds that there is reasonable agreement between the two processes for the 1,3 and 1,4 compounds. This is not true for processes involving either *cis*- or *trans*-1,2-cyclohexane-dicarboxylic acids and esters. This is probably not surprising, since the steric influence of one reactive group on the other is important in these isomers, particularly in the *cis* form, and the relative values of k_1 and k_2 for the esterification and saponification processes are affected in a different manner by this factor. Thus, steric hindrance of this type decreases the ratio of k_2/k_1 for esterification; however, it is the inverse ratio, k_1/k_2, which is decreased for hydrolysis. This influence should be reflected in the differences in relative entropies of activation as given in Table III.

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(10) Pictures of scale models of the cyclohexanedicarboxylic acids have already been published in reference 2.

(11) The term "axial" replaces "polar" used in earlier publications.