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

# The Kinetics of the Acid-Catalyzed Hydrolysis of the Methyl Esters of Cyclohexanedicarboxylic Acids<sup>1</sup>

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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 acid-catalyzed hydrolysis in 70% acetone-water solution have been studied. Rate constants at 25, 35, 45, and 55° have been calculated and tabulated, together with heats of activation. The rates of hydrolysis of the *cis*-1,3 esters are virtually identical with those for the *trans*-1,4 analogs; similarly, the reaction rates for hydrolysis of the *trans*-1,3 and *cis*-1,4 esters are found to be nearly the same. The 1,2-esters react at slower rates than do the 1,3- and 1,4-forms. For each 1,3- or 1,4-isomer, the monomethyl ester hydrolyzes about half as fast as the dimethyl ester. This is to be anticipated on a purely statistical basis. For the 1,2-isomers, the proximity of the two functional groups influences the rates of hydrolyzed less rapidly than the *cis*-1,2 monoester.

The acid catalyzed esterification of the cyclohexanedicarboxylic acids has been previously investigated.<sup>2</sup> It was shown that for esterification of both the di- and monoacids, 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 latter two also resembling each other. The results were explained on the assumption that the cyclohexane ring exists in the chair form,<sup>3</sup> and that when more than one conformation of the chair form is possible, the one yielding the greatest separation of the carboxyl groups is predominant. It was also demonstrated that the rates of esterification of the 1,2-cyclohexanedicarboxylic acids were slower than for other forms, with cis reacting more rapidly than the trans. However, for the monomethyl esters of the 1,2-acids, the trans form was esterified more rapidly than the *cis*.

The base-catalyzed hydrolysis of the methyl esters of the cyclohexanedicarboxylic acids has also been studied.<sup>4</sup> The ratios of the rates of hydrolysis of the first and second groups are much greater than predicted on a statistical basis, these ratios being around ten for the 1,3- and 1,4-forms and 100 for the 1,2-forms. This is caused by the fact that the product of hydrolysis of the first ester group is a negatively charged ester-ion, the charge on which repels the attacking negative hydroxyl ion, thus decreasing the rate. Similar results have been obtained by Carell, Chapman, and Johnson.<sup>5</sup>

The situation for acid hydrolysis should be somewhat different from that for the base-catalyzed reaction, in that the intermediate monoester resulting from the hydrolysis of one of the ester groups is uncharged; hence, one would expect the rate of hydrolysis of the dimethyl esters of the 1,3- and 1,4-cyclohexanedicarboxylic acids to be faster than for the corresponding monoesters by the statistical factor of two. For esters of the 1,2-acids, the proximity of the two ester groups would also influence the rates of their hydrolyses.

#### EXPERIMENTAL

Various isomeric cyclohexanedicarboxylic acids were prepared by catalytic reduction of the corresponding phthalic acids followed by separation and purification of the *cis* and *trans* isomers in the manner previously described.<sup>2,4</sup> The melting points of the purified acids were: *cis*-1,2, 194°; *trans*-1,2, 227.5-229.4°; *cis*-1,3, 167.2-168.2°; *cis*-1,4, 170-172°; *trans*-1,4, 312-313°.

The dimethyl esters of cis- and trans-1,2- and 1,4-cyclohexanedicarboxylic acids were prepared by acid catalyzed esterification of the corresponding pure acids with methanol. The cis-1,2 and cis-1,4 forms were further purified by careful fractionation under reduced pressure in a 2-ft. Vigreux column to give samples which distilled at  $124.4^{\circ}/12$  mm. and  $131.0^{\circ}/10$  mm., respectively. The trans-1,2 and trans-1,4 forms were purified by recrystallization from methanolwater solvent to give samples melting at  $30.2-30.8^{\circ}$  and  $69^{\circ}$ , respectively.

The dimethyl ester of cis-1,3-cyclohexanedicarboxylic acid was prepared from the purified acid by reaction of the silver salt with methyl iodide. The purified ester distilled at 130.6°/10 mm. The dimethyl ester of trans-1,3-cyclohexanedicarboxylic acid was prepared by low pressure hydrogenation of the dimethyl ester of isophthalic acid over Adams platinum catalyst, followed by fractionation under reduced pressure. The purified ester distilled at 140°/20 mm.

The monomethyl ester of cis-1,2-cyclohexanedicarboxylic acid was prepared by hydrogenation of the monomethyl ester of o-phthalic acid to give a product melting at 68.5-69°. That of trans-1,2-cyclohexanedicarboxylic acid was obtained by treatment of the acid with methanol. The desired product melted at 94.5-95.0°. The monomethyl ester of cis-1,3-cyclohexanedicarboxylic acid was also obtained by treatment of the acid chloride with methanol. The melting point of the product was 66.2-67°.

The monomethyl ester of *trans*-1,3-cyclohexanedicarboxylic acid was prepared as follows: The dimethyl ester was half-saponified by reaction at room temperature for 96 hr. in 90% methanol solution containing 1 equivalent of potassium hydroxide per mole of ester. The excess methanol

<sup>(1)</sup> Presented before the 136th Meeting of the American Chemical Society, Atlantic City, N. J., September 14-18, 1959.

<sup>(2)</sup> H. A. Smith and F. P. Byrne, J. Am. Chem. Soc., 72, 4406 (1950).

<sup>(3)</sup> R. S. Rasmussen, J. Chem. Phys., 11, 249 (1943).

<sup>(4)</sup> H. A. Smith and T. Fort, Jr., J. Am. Chem. Soc., 78, 4000 (1956).

<sup>(5)</sup> E. A. S. Carell, N. B. Chapman, and M. D. Johnson, Chem. & Ind. (London), 376 (1956).

	Rate Constants $\times$ 10 <sup>3</sup> in L. Mole <sup>-1</sup> min. <sup>-1</sup>				$\Delta H_a \times 10^4$ ,	
Ester	25°	35°	45°	55°	Cal. Mole <sup>-1</sup>	
		Dime	thyl Esters			
cis-1.2	0.0302	0.0962	0.288	0.746	2.09	
trans-1.2	0.0332	0.0990	0.350	0.786	2.10	
cis-1.3	1.37	3.36	8.22	17.9	1.68	
trans-1.3	0.695	1.80	4.40	10.4	1.76	
cis-1.4	0.820	1.94	5.34	12.8	1.81	
trans-1,4	1.64	3.71	8.67	18.8	1.59	
		Monor	nethyl Esters			
cis-1.2	0.0386	0.0836	0.175	0.524	1.66	
trans-1.2	0.0276	0.0628	0.136	0.306	1.55	
cis-1.3	0.688	1.76	4.08	9.06	1.70	
trans-1.3	0.398	1.02	2.50	6.06	1.76	
cis-1.4	0.412	1.03	2.58	5.26	1.67	
trans-1.4	0.686	1.75	4.18	9.22	1.68	

		TABLE I			
RATE CONSTANTS AN	D ACTIVATION	ENERGIES FOR ACID-CATALYZED	HYDROLYSIS OF THE	ESTERS OF THE	E CYCLOHEXANE-
		DICARBOXYLIC AC	IDS		

was removed, the residue treated with 0.1M sodium carbonate solution, which was then extracted three times with ether to remove any unsaponified diester. The aqueous solution was then acidified, extracted with ether, and the ether evaporated. The residue was carefully fractionated at 6 mm. pressure in a 3-ft. Vigreux column. Titration of the final product indicated 97.55% monoester and 2.45% diacid.

The monomethyl esters of *cis*- or *trans*-1,4-cyclohexanedicarboxylic acids were prepared by treatment of the corresponding dimethyl ester with 1 equivalent of potassium hydroxide per mole of ester, extraction of contaminating diacid with cold chloroform, and recrystallization from chloroform-ether. The *cis*-1,4-mono ester melted at 106.6-108.6°, while the *trans* form melted at 125.6-126.8°.

The reaction medium for the runs was 70 volume % acetone-water solution. The acetone was purified by fractionally distilling U.S.P. acetone from alkaline permanganate through an 8-ft. Vigreux column and collecting the fraction distilling at constant head temperature.

The procedure for starting a run was the same for all the esters. Approximately 1 g. of ester was weighed into the the reaction flask. To the ester in the flask were added the calculated amounts of acetone and water from burettee (with allowance made for solvent expansion), and the solution was thoroughly mixed. An equivalent amount of acid catalyst was added last, and the timing of the reaction was started with the addition of the acid catalyst. The reaction flask was then placed in the water bath and allowed to come to thermal equilibrium. Initial concentrations were 0.05M except for runs with the diester where the initial hydrochloric acid concentration was 0.10M.

The reactions were followed by pipetting 10-ml. samples from the reaction mixture and discharging them into 125-ml. Erlenmeyer flasks. Phenolphthalein indicator was added. The time of the sample was arbitrarily taken as the time when the pipetting of the sample was initiated. The amount of acid formed was determined by titration with standard carbonate-free alkali. The first sample was removed some 15 min. after the reaction flask was placed in the constant temperature bath.

The slow rate of the reactions (which required from 1 day to several months for satisfactory measurements) and the volatility of the solvent made necessary the use of a special reaction flask which consisted of a 3-in. length of 9-mm. Pyrex tubing attached to the rounded bottom of a 125-ml. Erlenmeyer flask, the mouth of which had been sealed in an oxygen-gas flame. A short piece of thick-walled rubber tubing was slipped over the narrow neck so that a glass plug could be inserted. In this manner, evaporation was reduced to a minimum; that is, the only solvent lost from a properly stoppered flask was that which escaped during the withdrawal of the samples. Checks of the volume of solution remaining in the flask after a number of samples had been withdrawn indicated no appreciable solvent loss.

A few reactions involving the slowest rates were also run by sealing 10-ml. samples of the reaction mixture in glass bulbs which were placed in the constant temperature bath. Individual bulbs were removed at appropriate times, broken, and the contents titrated. The two methods gave checking results.

#### EXPERIMENTAL CALCULATIONS AND RESULTS

Those reactions involving the monoester as starting material follow the simple expression for a first-order reaction. Very satisfactory lines were obtained when the logarithm of the concentration was plotted against time, and the rate constants were calculated by multiplying the slopes of these straight lines by 2.303. As the rate is proportional to the concentration of catalyzing acid, which remains constant during a run, the rate constants obtained from the linear plots have been divided by the concentration of hydrochloric acid. The results are given in Table I. Each value represents an average obtained from two or more individual runs, and has an estimated error of not more than 1%.

A similar procedure was followed in obtaining rate constants for the diesters. However, the plots were linear over only the initial portion of the hydrolyses. This method was completely satisfactory for reactions with the diesters of the 1,3- and 1,4acids (estimated error,  $\pm 2\%$ ) but must be considered to be approximate for diesters of the 1,2acids. The rate constants obtained for hydrolyses of the diesters are also given in Table I. This table includes values for the heats of activation of the individual reactions. These were calculated from slopes of the straight lines obtained by plotting the logarithms of the rate constants for an individual reaction against the reciprocal of the absolute temperature, and checked by the method of least squares.

#### DISCUSSION

The results as given in Table I show the following facts:

First, the rate constants for the 1,2-esters are somewhat slower than for the 1,3- and 1,4-isomers, thus probably indicating the importance of steric or electrical influences. This is also suggested by the fact that on a purely statistical basis the hydrolysis rates for the diesters should be twice that for the monoesters. This is not found. Actually, the trans-1,2-diester is hydrolyzed more rapidly than the cis-1,2-diester, while the trans-1,2-monoester is hydrolyzed less rapidly than the cis-1,2-monoester. This is in line with the rates of acid-catalyzed esterification of the cyclohexanedicarboxylic acids, since the trans-1,2-diacid is esterified less rapidly than the cis-1,2-diacid, while the trans-1,2-monoester is esterified to the diester more rapidly than is the cis-1,2-monoester. It should be noted that esterification of a cyclohexanedicarboxylic acid is the reverse of hydrolysis of a monomethyl ester of the acid.

Second, the rate constants for hydrolysis of the dimethyl esters of the 1,3- and 1,4-isomers are approximately twice as great as the rate constants for hydrolysis of the corresponding monomethyl esters. This is predicted on a purely statistical basis, and indicates no change in steric or electrical influences for hydrolysis of the first and second ester groups.

Third, one notes that for the 1,3- and 1,4-isomers, the corresponding *cis*-1,3 and *trans*-1,4 forms behave quite similarly to each other, while the *trans*-1,3 and *cis*-1,4 forms also resemble each other in reaction characteristics. This same result was found for other reactions of cyclohexanedicarboxylic acids and their esters,<sup>2,4,6</sup> and is readily explainable on the basis of the conformations of these compounds.

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(6) H. A. Smith and P. P. Hunt, J. Am. Chem. Soc., 81, 590 (1959).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVOF TENNESSEE]The Influence of Chelation on the Stabilf Enediols.II.<sup>1</sup> 1.2-Di-2-quinolyl-1.2-ethenediol NDioxide

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The attachment of an oxygen atom to the nitrogen atom in quinaldehyde does not prevent the formation of the corresponding enediol. At low concentrations of potassium cyanide it is formed as a red solid together with the isomeric quinaldoin. At higher concentrations of potassium cyanide the potassium salt of the enediol is formed either alone or with the quinaldoin. The enediol and quinaldoin are interconvertible and the potassium salt may be converted into the enediol or quinaldoin.

A trans-chelated, six- or seven-membered ring structure has been advanced for the enediol. In addition, an explanation has been proposed for the lack of color of its potassium salt.

It has been shown that quinaldehyde, in the benzoin condensation, forms a very stable enediol which has been assigned<sup>3</sup> the *trans*-chelated formula I. In this formula great importance has been



attached to the ability of the favorably located quinolyl nitrogen atoms to chelate. In the present

(3) C. A. Buehler and J. O. Harris, J. Am. Chem. Soc., 72, 5015 (1950).

investigation the reaction of potassium cyanide on quinaldehyde N-oxide has been studied to determine what effect, if any, the added oxygen atom would have on chelation and thus on enediol formation.

Quinaldehyde N-oxide was prepared by the selenium dioxide oxidation of quinaldine N-oxide. As is often the case in such oxidations, the results were not always reproducible<sup>4</sup> and led to yields from poor to moderate. The solvents used were either 95% ethanol or pyridine. Of the two, pyridine led to the more reproducible results. A portion of the difficulty in this oxidation results because the aldehyde first formed condenses with the starting material to produce the corresponding aldol and stilbazole, results similar to those obtained by Kaplan<sup>5</sup>

<sup>(1)</sup> Paper I of the series, C. A. Buehler, J. W. Addleburg, and D. M. Glenn, J. Org. Chem., 20, 1350 (1955).

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<sup>(4)</sup> H. S. Mosher, *Heterocyclic Compounds*, Vol. 1, Robert C. Elderfield, ed., Wiley, New York, 1950, p. 587.