

Studies on Cyclic Anhydrides

II.* Equilibrium Constants for the Equilibrium between Acid and Anhydride in Aqueous Solution of Some Alkylsubstituted Maleic Acids

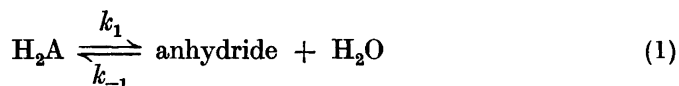
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The position of the equilibrium between acid and anhydride in aqueous solution has been determined for dimethyl-, methylethyl-, and diethylmaleic acid and 1-cyclohexene-1,2-dicarboxylic acid using a kinetic method. For the maleic acids the equilibrium constants ($c_{\text{anh}}/c_{\text{acid}}$) are about 5, whereas for the cyclohexene acid it is less than 0.1. The free diacid was found to be the kinetically active species in the cyclization reaction.

Apparent pK values, corrected for the presence of anhydride in equilibrium with the diacid, were also determined.

There is a lot of qualitative evidence¹ that certain dicarboxylic acids exist in equilibrium with detectable amounts of their anhydrides in aqueous solution:



On acidifying salt solutions of these acids the anhydride sometimes is the only species that can be isolated, whereas in other cases the diacid rapidly cyclizes upon recrystallization from organic solvents, melting, or merely upon standing at room temperature in the solid state.

In a few cases the position of the equilibrium is known. By using a titrimetric method Koskikallio² obtained a value of 3.2 at 20° for the equilibrium constant (defined as $c_{\text{anh}}/c_{\text{acid}}$) between dimethylmaleic acid and its anhydride in aqueous solution. Even for succinic acid Higuchi and co-workers³ have been able to show that the anhydride exists in aqueous solutions of the acid, the equilibrium constant being 2×10^{-7} at 20° and 3×10^{-5} at 95°. The existence of such minute amounts of succinic anhydride in aqueous solutions of succinic acid explains the facilitative role of the carboxylic grouping on for-

* Part I: see Ref.⁹

mation and hydrolysis of certain amido acids. In the cyclization of succinic acid the free diacid was shown to be the kinetically active species.

This paper is a report on the determination of equilibrium constants for dimethyl-, methylethyl-, and diethylmaleic acid, and 1-cyclohexene-1,2-dicarboxylic acid by a kinetic method. The results show that the position of the equilibrium for the substituted maleic acids is on the anhydride side, whereas "pinning" back the ethyl groups in diethylmaleic acid and uniting them by a carbon to carbon bond to give 1-cyclohexene-1,2-dicarboxylic acid shifts the equilibrium towards the side of the acid. In a forthcoming paper studies on similar equilibria for alkylsubstituted succinic acids will be reported.

METHOD AND RESULTS

The method used was to determine the variation of the observed rate constants (k_{exp}) for the solvolysis of the anhydride with the hydrogen ion concentration. Assuming that the free diacid is the kinetically active species in the forward reaction, k_{exp} is related to k_1 and k_{-1} by the expression:

$$k_{\text{exp}} = k_{-1} + \frac{k_1}{1 + K_1/[\text{H}^+]} \quad (2)$$

where K_1 is the first dissociation constant of the diacid (the second ionization can be neglected since in the cases studied the ratio between K_1 and K_2 is of the order of 10^3). Eqn. (2) is then rearranged to

$$\frac{1}{k_{\text{exp}} - k_{-1}} = \frac{1}{k_1} + \frac{K_1}{k_1} \cdot \frac{1}{[\text{H}^+]} \quad (3)$$

which means that plotting $1/(k_{\text{exp}} - k_{-1})$ against $1/[\text{H}^+]$ should give a straight line with an intercept on the ordinate of $1/k_1$ and a slope of K_1/k_1 . In order to use eqn. (3) it was necessary to have a preliminary value of k_{-1} . This was obtained by determining the solvolysis rate constant at pH 5.30, where the second term in (2) is very small as compared with k_{-1} . The preliminary value

Table 1. Observed rate constants for the solvolysis of dimethylmaleic anhydride in aqueous solution at 20.0° at different values of pH.

pH	k_{exp} in min^{-1}	pH	k_{exp} in min^{-1}
5.30	0.208 ^a	3.49	0.475
3.17	0.637	3.52	0.458
3.23	0.600	3.55	0.443
3.30	0.559	3.57	0.434
3.35	0.527	3.60	0.424
3.36	0.547	3.64	0.404
3.40	0.509	3.67	0.402
3.45	0.481	3.69	0.381
3.47	0.489	3.72	0.377

^a Preliminary value of k_{-1} ; mean value from four experiments.

was used for the computation of a first set of values of k_1 and K_1 from the straight line and then a corrected value of k_{-1} could be obtained from (2). This was used for a second calculation to give a new set of values, which did not change upon a third calculation.

Table 1 gives rate constants for the solvolysis of dimethylmaleic anhydride at different hydrogen ion concentrations, as determined by the pH-stat method. Fig. 1 shows a plot of $1/(k_{\text{exp}} - k_{-1})$ against $1/[\text{H}^+]$ (empty circles) and from

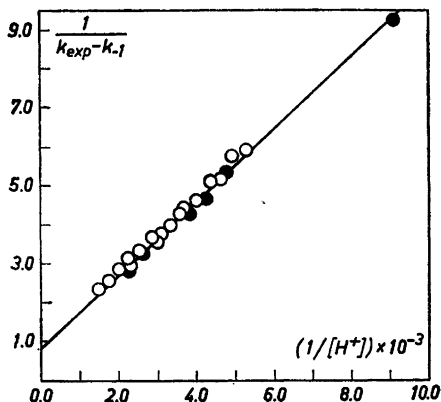


Fig. 1. Plot of $1/k_{\text{exp}} - k_{-1}$ against $1/[\text{H}^+]$. Empty circles: k_{exp} obtained by approaching equilibrium from the anhydride side; filled circles: k_{exp} obtained by approaching equilibrium from the diacid side.

this set of values the method of least squares gave $k_1 = 1.12 \text{ min}^{-1}$ and $K_1 = 1.1 \times 10^{-3}$. The second calculation with the corrected value of k_{-1} (0.204 min^{-1}) then gave $k_1 = 1.07 \text{ min}^{-1}$ and $K_1 = 1.0 \times 10^{-3}$. These values did not change k_{-1} so a third calculation was not necessary. The equilibrium constant was obtained as $k_1/k_{-1} = 5.3$.

Table 2. Observed rate constants for the solvolysis of methylethyl- and diethylmaleic anhydride and 1-cyclohexene-1,2-dicarboxylic anhydride in aqueous solution at 20.0° at different values of pH.

Methylethylmaleic anhydride		Diethylmaleic anhydride		1-Cyclohexene-1,2-dicarboxylic anhydride	
pH	k_{exp} in min^{-1}	pH	k_{exp} in min^{-1}	pH	k_{exp} in min^{-1}
5.30	0.165 ^a	5.30	0.111 ^a	5.30	0.381 ^b
3.38	0.416	3.50	0.279	3.38	0.379
3.44	0.372	3.55	0.268	3.48	0.383
3.50	0.366	3.62	0.246	3.60	0.385
3.53	0.350	3.68	0.230	3.70	0.377
3.58	0.332	3.72	0.221	3.82	0.379
3.61	0.325	3.79	0.207	3.99	0.380
3.69	0.308	3.90	0.193		

^a Preliminary value of k_{-1} ; mean value from four determinations.

^b This value of k_{-1} is the same as the mean value of the rate constants in the pH region 3.38–3.99.

Table 2 gives the observed rate constants for solvolysis of methylethyl- and diethylmaleic anhydride and 1-cyclohexene-1,2-dicarboxylic anhydride. The constants obtained from these data are summarized in Table 3.

Table 3. Final values of k_1 , k_{-1} , pK_1 and equilibrium constants K for (1) as calculated from the data in Tables 1 and 2.

Anhydride	k_1 min ⁻¹	k_{-1} min ⁻¹	pK_1	K	$k_1 + k_{-1}^d$
Dimethylmaleic	1.07	0.204	3.0 ^a	5.3	1.25 ± 0.06
Methylethylmaleic	0.70	0.162	3.1 ^b	4.3	0.91 ± 0.05
Diethylmaleic	0.50	0.108	3.2 ^c	4.7	0.65 ± 0.03
1-Cyclohexene-1,2-dicarboxylic		0.381		<0.1	

^a Value from potentiometric titration 3.1.

^b Value from potentiometric titration 3.2.

^c Value from potentiometric titration 3.3.

^d Determined spectrophotometrically.

Table 4. Observed rate constants for the cyclization of dimethylmaleic acid at different hydrogen ion concentrations as determined by the pH-stat method.

pH	k_{exp} in min ⁻¹
3.35	0.558
3.41	0.521
3.59	0.437
3.63	0.422
3.68	0.396
3.96	0.316

Table 5. Observed rate constants for the cyclization of dimethylmaleic acid at different [HCl], as determined spectrophotometrically (at 256 m μ).

[HCl]	k_{exp} in min ⁻¹
0.01	1.14
0.025	1.16
0.05	1.25
0.10	1.25
0.20	1.25

The results could be checked by measuring the specific rate for approaching equilibrium from the side of the acid by a spectrophotometric method at hydrogen concentrations where the ionization is totally suppressed. This method

gave a value of $k_1 + k_{-1}$, which is shown in the last column of Table 3. By carrying out measurements at different hydrogen ion concentrations it was established that the influence of $[H^+]$ was negligible (Table 5).

The constancy of the solvolysis rate of 1-cyclohexene-1,2-dicarboxylic anhydride shows that k_1 has so small a value that any contribution from the second term in (2) cannot be detected by this method. This was also found by the spectrophotometric method, since there was no change in optical density in a freshly prepared solution of the acid in hydrochloric acid at 256 $m\mu$, where the anhydride has an absorption maximum (as could be seen from spectra of the anhydride in the same solvent taken about 20 sec after mixing the reactants).

It is estimated that the pH-stat method described above cannot be used when the equilibrium constant is less than 0.1 and that experimental errors anyway will influence it appreciably in the region 0.1–1.0.

It was also possible to determine k_{exp} by approaching the equilibrium from the left side in eqn. (1) by using the pH-stat method. In these experiments a known amount of a stock solution of the monosodium salt was added to a known amount of hydrochloric acid in the pH-stat vessel. Thereby the diacid was liberated and the kinetics were followed by recording against time the amount of standard acid required to keep the pH constant. The results from a series of measurements on dimethylmaleic acid at different hydrogen ion concentrations are shown in Table 4. By using eqns. (2) and (3) the following values were obtained: $k_1 = 0.97 \text{ min}^{-1}$, $k_{-1} = 0.204 \text{ min}^{-1}$, $K_1 = 8.3 \times 10^{-4}$ and $K = 4.8$ in fair agreement with the values given above from measurements of the solvolysis reaction. The filled circles in Fig. 1 correspond to values obtained by approaching equilibrium from the left side. This procedure is however less satisfactory and was not used further, since the rate constants are subjected to larger experimental errors than in the solvolysis experiments.

Table 6 gives apparent pK_1 and pK_2 as determined potentiometrically for the acids investigated; methylmaleic and maleic acid are included for comparison. For dimethyl-, methylethyl-, and diethylmaleic acid pK_1 was correc-

Table 6. Apparent pK values for substituted maleic acids in aqueous solution.

Acid	pK_1^a	pK_2^a	ΔpK
Dimethylmaleic	3.1 ^b	6.1	3.0
Methylethylmaleic	3.2	6.1	2.9
Diethylmaleic	3.3	6.2	2.9
1-Cyclohexene-1,2-dicarboxylic	3.3 ^c	6.2	2.9
Methylmaleic	2.8 ^d	6.1 ^d	3.3
Maleic	1.91 ^e	6.33 ^e	4.42

^a Accuracy estimated at ± 0.1 pK unit.

^b Lit. value 3.2.³

^c Lit. values: pK_1 3.01,¹⁰ 3.2,¹¹ pK_2 5.34.¹⁰

^d Lit. values: pK_1 2.29,¹² 2.95;¹³ pK_2 5.98,¹³ 6.15.¹²

^e Ref.¹⁴

ted by the term $-\log(1 + K)$ due to the acid-anhydride equilibrium. The values are in good agreement with those obtained by the kinetic method (Table 3).

DISCUSSION

The accuracy of the equilibrium constants given in Table 3 is estimated at about $\pm 10\%$, which means that the value for dimethylmaleic acid, 5.3 ± 0.5 , is definitely not in agreement with that determined by Koskikallio,⁴ 3.2. It is, however, not quite clear from his experimental description how the analyses were carried out; especially it seems as if calibration experiments and determinations of the composition of the equilibrated mixtures were not conducted under exactly the same conditions. The good agreement between the $k_1 + k_{-1}$ value obtained by the pH-stat method and the spectrophotometric method indicates that the equilibrium constant reported here for dimethylmaleic acid is the correct one.

A discussion of the equilibrium data will be postponed until data for different types of dicarboxylic acid have accumulated.

It is interesting to note that the ΔpK values in Table 6 show the same trend as found by McCoy and Nachtigall⁴ for a series of alkylsubstituted *cis*-1,2-cyclopropanedicarboxylic acids, *i.e.* ΔpK decreases with increasing alkyl group substitution, which is contrary to the behavior of alkylsubstituted succinic acids.⁵ McCoy and Nachtigall explained this decrease as being due to an unfavorable geometry for the formation of an intramolecular hydrogen bond in the monoanion, as a result of increased steric crowding in the molecule. Since the steric situation in the cyclopropane acids is similar to that in alkylsubstituted maleic acids, the same explanation seems reasonable here. For substituted succinic acids the conformation with *gauche* carboxyl groups has a favorable geometry for hydrogen bond formation (linear hydrogen bond with an O...O distance of 2.4–2.6 Å) and this geometry is not influenced very much by introduction of alkyl groups with greater steric demands.

EXPERIMENTAL

Materials. Dimethylmaleic anhydride was purchased from Fluka AG, Buchs SG, Switzerland, and recrystallized and sublimed before use. Methylmaleic anhydride was prepared and purified over the barium salt as described by Küster.⁶ The final purification was achieved by fractional distillation, a fraction with n_D^{20} 1.4680 being used with a purity of $> 99.2\%$ as determined by v.p.c. analysis.

Diethylmaleic anhydride was prepared by treating diethylsuccinic anhydride (18.0 g) with bromine (7.0 ml) at 110–120°. Hydrogen bromide was evolved and the mixture kept at this temperature until the bromine color had faded. The reaction mixture was then dissolved in aqueous sodium hydroxide and the diethylmaleic anhydride was set free by acidification with concentrated hydrochloric acid. The crude anhydride was distilled and finally purified over the barium salt as described by Küster.⁷ A fraction boiling at 63–65°/0.6 mm was used in the kinetic experiments with a purity better than 99.5%, as determined by v.p.c. analysis.

1-Cyclohexene-1,2-dicarboxylic anhydride was prepared from the 4-isomer according to the method given by Ficken, France, and Linstead.⁸ The yield was very small (5%) in contrast to that (75%) obtained by the authors mentioned above. The anhydride was recrystallized from ethyl acetate-light petroleum (1:20) and then sublimed, m.p. 70–72°, reported m.p. 70°, purity better than 99.5% according to v.p.c. analysis.

Kinetic experiments. Rate constants k_{exp} were determined by the pH-stat method according to the procedure described in Part 1.⁹ The pH value was read directly from the pH-meter and a mean value from 10–12 readings during the run was taken as the final pH value. After each run the pH scale was checked against a standard buffer of pH 6.50.

In the determination of $(k_1 + k_{-1})$ 10 μ l of a 0.05 M solution of the disodium salt was added by means of a micropipette to 3.0 ml of hydrochloric acid, pre-thermostated to $20.0 \pm 0.1^\circ$ in the cell compartment of a Beckman DK-2 spectrophotometer, equipped with a time-drive attachment. The cell contents were mixed by blowing air bubbles through it for a few seconds and the kinetics were followed at 256 $m\mu$, where the anhydride has its absorption maximum.

Table 5 shows the effect of changing [HCl] in the case of dimethylmaleic acid. Each rate constant is the mean value of three runs and the error is estimated at $\pm 5\%$. For methylethyl- and diethylmaleic anhydride the results were similar and the $k_1 + k_{-1}$ values were taken as the value of k_{exp} in 0.05 M HCl, where the ionization of the diacid is almost totally suppressed.

All rate constants were evaluated by the Guggenheim method and in all cases excellent first-order plots were obtained.

Ionization constants were determined as described previously.⁵ The values given in Table 6 are not corrected to the thermodynamic scale.

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