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RESEARCH ARTICLES

Solvolytic Reactions of Cyclic Anhydrides in Anhydrous Acetic Acid

M. J. HADDADIN *, T. HIGUCHI †, and V. STELLA

Abstract □ The reversible reactions of several cyclic anhydrides with acetic acid to form acetic anhydride and the corresponding dicarboxylic acid, catalyzed by perchloric acid at 25°, were studied. The equilibrium constants, calculated from spectral data, were 4.85×10^{-4} , 1.08×10^{-1} , and 4.6×10^{-1} M for succinic, *trans*-1,2-cyclohexanedicarboxylic, and glutaric anhydrides, respectively. Maleic, phthalic, and *cis*-1,2-cyclohexanedicarboxylic anhydrides did not undergo any detectable reaction with acetic acid under these conditions, suggesting still higher stability. The reverse rate constants were found to be relatively independent of the structure of the attacking diacid, while the forward rate constants were found to parallel the equilibrium constants. The rate-determining

step for the forward reaction appears to be the breakdown of the tetrahedral intermediate formed by the attack of an acetic acid molecule on the protonated cyclic anhydride.

Keyphrases □ Anhydrides, cyclic—solvolytic reactions in anhydrous acetic acid, rate constants, mechanisms □ Solvolysis of cyclic anhydrides in anhydrous acetic acid—rate constants, mechanisms □ Perchloric acid—catalyst for solvolytic reactions of cyclic anhydrides in anhydrous acetic acid □ Acylation—reversible reactions of cyclic anhydrides in anhydrous acetic acid, rate constants, mechanisms

The chemistry of cyclic and linear anhydrides is of major interest to those concerned with transacylation reactions in both *in vitro* and *in vivo* systems. There is very little doubt that these active chemical species play significant roles in many acyl transfer reactions and in cleavage and formation of polycarboxylic acid derivatives. The present report is concerned with

some data obtained on the solvolytic behavior of a series of cyclic anhydrides of varying stability in anhydrous acetic acid. The results indicate relatively strong structural dependency on the ring opening and very little sensitivity to the reverse process.

Anhydrides of dicarboxylic acids have been used in the preparation of hemiesters of water-insoluble

Table I—Wavelengths and Species Monitored for All Reactions Studied

Reaction	Wave-length, nm	Species Monitored ^a
Succinic anhydride + acetic acid	252	Acetic anhydride (A)
Succinic acid + acetic anhydride	252	Acetic anhydride (D)
Glutaric anhydride + acetic acid	268	Acetic anhydride (A)
Glutaric acid + acetic anhydride	255	Acetic anhydride (D)
Phthalic acid + acetic anhydride	285	Phthalic acid (D)
Maleic acid + acetic anhydride	280	Maleic acid (D)
Phthalic anhydride + acetic acid	302	No change
Maleic anhydride + acetic acid	265	No change
<i>cis</i> -1,2-Cyclohexanedicarboxylic anhydride + acetic acid	265	No change
<i>cis</i> -1,2-Cyclohexanedicarboxylic acid + acetic anhydride	255	Acetic anhydride (D)
<i>trans</i> -1,2-Cyclohexanedicarboxylic anhydride + acetic acid	259	Acetic anhydride (A)

^a Disappearance and appearance are represented by D and A, respectively.

drugs such as hydrocortisone¹ (1), methylprednisolone¹ (1), and chloramphenicol (2). The popularity of these hemiesters as prodrugs stems from the enhanced aqueous solubility of their salt forms compared to the parent drugs. The ease with which they release the parent drug *in vivo* also has been noted.

The closure of these hemiesters and corresponding acids to their respective anhydrides is often taken as a simple model of intramolecular catalysis. The demonstration of participation of anhydrides in the hydrolysis and formation of amides (3, 4) and in the hydrolysis of hemiesters of dicarboxylic acids (5) strongly supports analogous mechanistic pathways for other related reactions. Transacylations in solid dosage forms, such as the reaction of amines and phenolic compounds with high energy acylators like acetylsalicylic acid, can be simulated by the reactivity of anhydrides (6, 7).

The solvolysis of cyclic anhydrides in aqueous solutions has been studied (8), and the equilibrium constants for the cyclic anhydride–diacid systems in water were largely determined by the formation of the cyclic anhydride.

The possible roles of anhydrides as high energy compounds in biological systems recently received some attention. For example, succinic (9) and acetic (10) anhydrides have been postulated in the biosynthesis of acetyl and succinyl coenzymes. Anhydrides also have been postulated as intermediates in model enzymatic reactions (11).

Attempts in these laboratories to react various drug molecules with succinic anhydride to form hemisuccinate esters using anhydrous acetic acid as a solvent resulted in the formation of acetate esters rather than the hemisuccinate. The results prompted a study of the reactions of several cyclic anhydrides in

Table II—Absorptivities^a of Anhydrides Used in Calculations

Anhydride	$\lambda_{\text{acetic acid}}^{25^\circ}$	ϵ
Succinic	252	3.4
Glutaric	268	1.6
<i>trans</i> -1,2-Cyclohexanedicarboxylic	272	0.36
Acetic	252	38.2
	268	5.6
	272	3.15

^a Absorptivities were obtained from Beer's law plots.

anhydrous acetic acid in an attempt to understand the quantitative aspects of acetic anhydride formation in anhydrous acetic acid in the presence of cyclic anhydrides and perchloric acid. The objectives were to relate this formation of acetic anhydride to the structure of the cyclic anhydride and to understand the mechanism of this transacylation reaction.

EXPERIMENTAL

Materials—All chemicals used were generally of reagent or analytical reagent grade and were purified before use.

Anhydrous acetic acid was prepared from analytical reagent grade acetic acid² by titration with freshly distilled acetic anhydride in the presence of catalytic quantities of perchloric acid. The reaction was monitored either thermometrically or spectrophotometrically. The thermometric technique involved the incremental addition of acetic anhydride until no further heat evolution could be detected. The spectrophotometric technique involved the addition of a slight excess of acetic anhydride. The excess amount of unreacted anhydride was determined at 252 nm and subsequently neutralized with an equivalent amount of water.

Acetic anhydride² was distilled over magnesium turnings; the middle fraction distilling at 137.5° was collected [lit. (12) bp 139°].

Acetous perchloric acid was prepared from 70% reagent grade perchloric acid³ by reaction in an ice bath with a calculated amount of distilled acetic anhydride added slowly to the perchloric acid. The last 2 ml of acetic anhydride was used to titrate the remaining water thermometrically. The acetous perchloric acid was standardized against NBS potassium acid phthalate, using gentian violet as an indicator (2% in nitrobenzene).

Succinic anhydride³, mp 118° [lit. (12) mp 119.6°], glutaric anhydride⁴, mp 55° [lit. (13) mp 56°], phthalic anhydride⁵, mp 130° [lit. (12) mp 130.8°], and maleic anhydride⁶, mp 52° [lit. (13) mp 52.8°], were purified by refluxing with excess acetic anhydride to remove any diacids. They then were precipitated and washed with petroleum ether and dried in a vacuum oven. *cis*-1,2-Cyclohexanedicarboxylic anhydride⁴ was dissolved in benzene, filtered, precipitated with petroleum ether, and dried in a vacuum oven, mp 33–34° [lit. (13) mp 32°]. *trans*-1,2-Cyclohexanedicarboxylic anhydride⁴ was used without further purification, mp 145–146° [lit. (13) mp 145–146°].

Succinic acid⁴ was recrystallized from benzene, mp 185° [lit. (12) mp 185–187°], while maleic acid, mp 130° [lit. (12) mp 130–131°], and glutaric acid, mp 97° [lit. (12) mp 97.5–98°], were recrystallized from chloroform. Both *cis*-1,2-cyclohexanedicarboxylic acid⁴, mp 190° [lit. (13) mp 192°], and *trans*-1,2-cyclohexanedicarboxylic acid³, mp 221° [lit. (13) mp 221°], were purified by dissolving in hot sodium hydroxide solution, decolorizing with charcoal, and precipitating by the dropwise addition of hydrochloric acid while still hot.

Kinetic and Equilibrium Measurements—The reactions between the various cyclic anhydrides and acetic acid were monitored spectrophotometrically⁷ at 25°. Table I gives the wave-

² Mallinckrodt Chemical Works, St. Louis, Mo.

³ J. T. Baker Chemical Co., Phillipsburg, N.J.

⁴ Aldrich Chemical Co., Milwaukee, Wis.

⁵ Matheson, Coleman and Bell, Norwood, Ohio.

⁶ Eastman Kodak Co., Rochester, N.Y.

⁷ Cary model 14 UV recording spectrophotometer with a thermostated cell compartment.

¹ Products marketed as Solu-Cortef and Solu-Medro by The Upjohn Co., Kalamazoo, Mich.

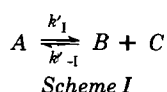
Table III—Conditions for Spectrophotometric Evaluation of k_{-1} for Scheme II

Acid	Excess Reactant	k_{-1} Evaluated from	Cell Path Length, cm
Succinic	Succinic acid	Slope of k_{obs} versus [acid]	5
Glutaric	Glutaric acid	$(k_1 + k'_{-1}) - k_1$; k_1 obtained from initial slopes or Scheme Ia	1
Phthalic	Acetic anhydride	Slope of k_{obs} versus $[(\text{CH}_3\text{CO})_2\text{O}]$	1
Maleic	Acetic anhydride	Slope of k_{obs} versus $[(\text{CH}_3\text{CO})_2\text{O}]$	1
<i>cis</i> -1,2-Cyclohexanedicarboxylic	<i>cis</i> -1,2-Cyclohexanedicarboxylic acid	Slope of k_{obs} versus [acid]	1
<i>trans</i> -1,2-Cyclohexanedicarboxylic	<i>trans</i> -1,2-Cyclohexanedicarboxylic acid	Slope of k_{obs} versus [acid]	1

$${}^a k'_{-1} = k_{-1}[\text{glutaric acid}].$$

lengths used and the species monitored. An accurately known quantity of the cyclic anhydride was quickly dissolved in a known volume of solution of perchloric acid (about $1 \times 10^{-3} M$) in anhydrous acetic acid in a 1-cm cylindrical cell.

The rate constant for the forward reaction, k'_1 , as shown in Scheme I:



where A is the cyclic anhydride, B is acetic anhydride, and C is the dicarboxylic acid, is obtained by plotting the integrated equation (14). For Scheme I, this equation is:

$$\ln \frac{a_0(x_e - x)}{a_0x_e + x(a_0 - x_e)} = -\frac{2a_0 - x_e}{x_e} k'_1 t \quad (\text{Eq. 1})$$

where a_0 is the initial concentration of the cyclic anhydride, x_e is the concentration of acetic anhydride at equilibrium, and x is the concentration of acetic anhydride at any time t . The rate constant k'_1 is equal to $k_1 [\text{HClO}_4]$. The acetic anhydride concentration x , at any time t , was calculated from known absorptivity constants (Table II) and measured absorbance readings using Eq. 2:

$$x = \frac{\Delta A}{\Delta \epsilon} \quad (\text{Eq. 2})$$

where ΔA is the change in absorbance from $t = 0$ to any time t , and $\Delta \epsilon$ is the difference in absorptivities of acetic and cyclic anhydrides at the wavelength used. Because the reaction between the cyclic anhydride and the solvent, acetic acid, proceeded slowly in the absence of the catalyst, perchloric acid, evaluation of the UV absorptivities of the various cyclic anhydrides could readily be accomplished.

Table III shows the conditions for the evaluation of the reverse rate constant k_{-1} . The unidirectional nature of the reactions was assured by the use of excess reactants, and the rate constant k_{obs} was obtained from normal semilogarithmic plotting procedures.

The equilibrium constant K , defined by Eq. 3, was evaluated spectrophotometrically. This was possible because the cyclic anhydride and the formed acetic anhydride were the only absorbing species at the selected wavelength:

$$K = \frac{[(\text{CH}_3\text{CO})_2\text{O}]_{\text{eq}}[\text{diacid}]_{\text{eq}}}{[\text{cyclic anhydride}]_{\text{eq}}} \quad (\text{Eq. 3})$$

$$K = \frac{(\Delta A/\Delta \epsilon)^2}{a_0 - (\Delta A/\Delta \epsilon)} \quad (\text{Eq. 4})$$

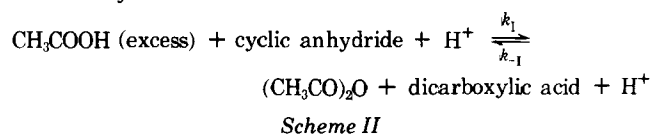
$$K = \frac{(\Delta A/\Delta \epsilon)(\Delta A/\Delta \epsilon + [\text{diacid}])}{[\text{cyclic anhydride}]_0 - \Delta A/\Delta \epsilon} \quad (\text{Eq. 5})$$

where [diacid] is the amount of dicarboxylic acid added to the system, $\Delta A/\Delta \epsilon$ (as defined earlier) is equal to the amount of acetic anhydride formed, and $[\text{cyclic anhydride}]_0$ is the initial concentration of the cyclic anhydride. The subscript eq refers to equilibrium concentration. Equation 4 could be used when no added diacid was needed to observe the equilibrium formation, whereas Eq. 5 was used for systems where free dicarboxylic acid was added along with

the cyclic anhydride. The value of K was also calculated from the ratio k_1/k_{-1} .

RESULTS

The course of the reaction between cyclic anhydrides with acetic acid in anhydrous acetic acid as a solvent, catalyzed by perchloric acid, to produce acetic anhydride and the corresponding dicarboxylic acid can be readily followed spectrophotometrically and can be described by Scheme II:



The spectral observations were possible because of differences in absorptivities between acetic anhydride and the cyclic anhydrides at given wavelengths (Tables I and II). The observed change in UV absorbance at 268 nm for a solution containing 0.25 M glutaric anhydride in acetic acid in the presence of $1 \times 10^{-3} M$ HClO_4 and a similar plot for 0.07 M *trans*-1,2-cyclohexanedicarboxylic anhydride in the presence of $3.73 \times 10^{-3} M$ HClO_4 at 259 nm as a function of time is shown in Fig. 1.

The reversibility of Scheme II was established spectrophotometrically. Also, when starting with the cyclic anhydride, the dicarboxylic acid could occasionally be isolated. Similarly, when starting with the dicarboxylic acid and an excess of acetic anhydride, the cyclic anhydride could be isolated. The change in UV absorbance of the reaction between succinic anhydride and acetic acid was shown to be a function of added succinic acid. Table IV shows the decrease in absorbance as the added concentration of succinic acid was increased for a constant initial concentration of succinic anhydride. The reverse reaction is applied commercially to prepare succinic anhydride (12). Succinic anhydride was isolated from a reaction mixture of succinic acid and acetic anhydride (in the presence of perchloric acid) in acetic acid and identified by its melting point of 118°.

The same trend in UV absorbance was observed for *trans*-1,2-cyclohexanedicarboxylic anhydride when acetic anhydride was added to the system. When more than 0.35 M of the anhydride was dissolved in acetic acid, *trans*-1,2-cyclohexanedicarboxylic acid precipitated out. It was identified by its melting point of 221°.

Table IV—Change in UV Absorbance as a Function of Added Succinic Acid for the Reaction Shown in Scheme II^a

Added Succinic Acid	Change in UV Absorbance ^b
0	0.45
0.0075	0.33
0.03	0.15
0.075	0.08

^a Succinic anhydride initial concentration was 0.40 M in all cases, and $[\text{HClO}_4]$ was of the order of $1 \times 10^{-3} M$. ^b Added succinic acid forced the equilibrium to the left in Scheme II, suppressing the formation of acetic anhydride, the major absorbing species, at 252 nm.

Table V—Equilibrium Constant in Acetic Acid at 25° and Equilibrium Concentrations of the Species in Scheme II

$\left[\text{Succinic Anhydride} \right]_0, M$	$\left[\text{Succinic Acid} \right]_0, M$	$\left[\text{Succinic Anhydride} \right]_{\text{eq}}, M$	$\left[\text{Acetic Anhydride} \right]_{\text{eq}}, M$	$\left[\text{Succinic Acid} \right]_{\text{eq}}, M$	K^a, M	Average, M
0.40	0	0.39	1.42×10^{-2}	1.42×10^{-2}	5.06×10^{-4}	
0.30	0	0.29	1.23	1.23	5.04	
0.40	0.03	0.4	0.50	3.5	4.90	4.85×10^{-4}
0.40	0.075	0.4	0.21	7.71	4.43	

$\left[\text{Glutaric Anhydride} \right]_0, M$	$\left[\text{Acetic Anhydride} \right]_{\text{eq}}, M$	$\left[\text{Glutaric Anhydride} \right]_{\text{eq}}, M$	$\left[\text{Glutaric Acid} \right]_{\text{eq}}, M$	K, M	Average, M
0.501	0.301	0.200	0.301	0.453	
0.402	0.261	0.139	0.261	0.489	
0.305	0.204	0.096	0.204	0.433	0.460
0.200	0.150	0.050	0.150	0.450	

$$\text{H}^+ + \text{trans-1,2-Cyclohexanedicarboxylic anhydride} + \text{CH}_3\text{COOH (excess)} \xrightleftharpoons{K} \text{H}^+ + (\text{CH}_3\text{CO})_2\text{O} + \text{trans-1,2-Cyclohexanedicarboxylic acid}$$

$\left[\text{Anhydride} \right]_0, M$	$\left[\text{Acetic Anhydride} \right]_{\text{eq}}, M$	$\left[\text{Anhydride} \right]_{\text{eq}}, M$	K, M	Average, M
0.3169	0.1392	0.1767	0.105	
0.2129	0.0978	0.1141	0.095	
0.1786	0.0911	0.875	0.083	0.108
0.1038	0.0712	0.0326	0.150	

^a $K = k_1/k_{-1}$.

Table V shows the equilibrium constants calculated from spectral data for succinic, *trans*-1,2-cyclohexanedicarboxylic, and glutaric anhydrides based on Eqs. 4 and 5. These were the only anhydrides of those studied that showed an observable reaction under the conditions employed. Spectra of phthalic, *cis*-1,2-cyclohexanedicarboxylic, and maleic anhydrides in acetic acid did not show any noticeable change. The concentrations of the cyclic anhydrides used in these measurements ranged from 0.1 to 0.5 *M*, except for phthalic anhydride which was about 1×10^{-4} *M*. The equilibrium constants reflect the relative stability of cyclic anhydrides which were 1000:5:1 for succinic, *trans*-1,2-cyclohexanedicarboxylic, and glutaric anhydrides, respectively.

The other anhydrides, maleic, *cis*-1,2-cyclohexanedicarboxylic, and phthalic, were much more stable, *i.e.*, $K < 1 \times 10^{-4}$ *M*.

The effect of moisture on the precision of the equilibrium constant determinations should be noted. Acetic acid is very hygroscopic; it has been estimated (15) that the water content of almost "dry" acetic acid, when exposed to the atmosphere for 0.5 hr, increased by 5×10^{-2} *M*. Although utmost care was taken to avoid moisture, errors of up to 10% were introduced into the equilibrium constant determinations by moisture. The relatively concentrated solutions of the anhydrides (not less than 0.1 *M*) used helped reduce the error due to moisture.

The forward rate constant k_1 at 25° for the system defined by Scheme II was evaluated from plots of Eq. 1. Figure 2 is a repre-

sentative plot for the loss of glutaric anhydride from solution. Although all cyclic anhydrides were studied, only k_1 values for succinic, glutaric, and *trans*-1,2-cyclohexanedicarboxylic anhydrides could be determined. The concentration range of cyclic anhydrides used in the rate evaluations was 0.1–0.5 *M*; as mentioned earlier, these relatively high concentrations were employed to help reduce the effect of extraneous moisture. The excellent fit of all data to Scheme I and Eq. 1 suggests that the reaction can be described by Scheme II.

Values of k_1 for the three cyclic anhydrides studied are shown in Table VI.

Table VII shows the third-order rate constant k_{-1} , *i.e.*, the rate constant of the reaction of the dicarboxylic acids with acetic anhydride catalyzed by perchloric acid. These rate constants were obtained under pseudo-first-order conditions, *i.e.*, where perchloric acid was maintained constant and an excess of one of the other reactants was used. For example, acetic anhydride was used in excess with acids having good chromophores such as phthalic and maleic acids. The disappearance of the acids followed pseudo-first-order kinetics. The third-order rate constant k_{-1} was then obtained from plots of k_{obs} versus the excess reagent. In the case of succinic and *cis*-1,2-cyclohexanedicarboxylic acids, the acids were used in excess and the disappearance of acetic anhydride was followed.

Two typical examples of these plotting techniques are shown in

Table VI—Forward Rate Constants, k_1 (Scheme II), at 25° in Acetic Acid

	Initial Cyclic Anhydride Concentration, M	$\left[\text{Acetic Anhydride} \right]_{\text{eq}}, M$	$\left[\text{Perchloric Acid} \right], M$	$k_1, M^{-1} \text{ min}^{-1}$
Succinic anhydride	0.4	0.0164	0.007	0.143
	0.3	0.0150	0.007	0.149
	0.2	0.0105	0.007	0.178
			Average	0.157
<i>trans</i> -1,2-Cyclohexanedicarboxylic anhydride	0.317	0.1392	0.007	21
	0.213	0.0978	0.007	20
	0.179	0.0911	0.007	20
	0.104	0.0712	0.007	18
			Average	19
Glutaric anhydride	0.2	0.15	0.0075	74
	0.3	0.204		78
	0.4	0.276		70
			Average	74 ^a

^a When using the initial slopes, a value of $81 M^{-1} \text{ min}^{-1}$ was obtained for this case.

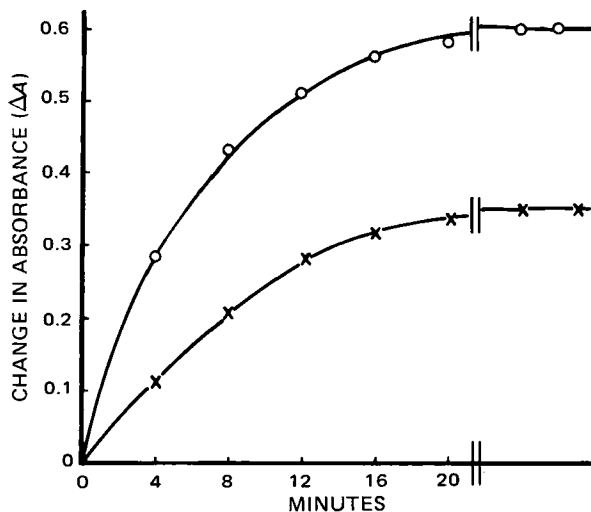


Figure 1—Increase in absorbance due to production of acetic anhydride as a function of time for the reaction of the cyclic anhydride with acetic acid catalyzed by perchloric acid in acetic acid. The plots show the change in absorbance versus time for: 0.25 M glutaric anhydride (O) in the presence of 1.0×10^{-3} M HClO_4 at 268 nm and 25° , and for 0.07 M trans-1,2-cyclohexanedicarboxylic anhydride (X) in the presence of 3.73×10^{-3} M HClO_4 at 259 nm and 25° .

Figs. 3 and 4. The rate constant k_{-1} for glutaric acid cyclization was obtained from the slope of the semilogarithmic plot of absorbance versus time where glutaric acid was in excess. The slope of such a line has the value of $k_1 + k_{-1}$ [glutaric acid]. Because k_1 was already estimated, k_{-1} could be calculated. The constant k_{-1} for trans-1,2-cyclohexanedicarboxylic acid was obtained from K/k_1 because of the insolubility problems with the dicarboxylic acid and its difficulty of purification.

Table VIII shows that the value of K as obtained from the k_1/k_{-1} ratio is in good agreement with the value of K determined independently by direct spectroscopic measurements.

DISCUSSION

A detailed scheme describing the interaction of the cyclic anhy-

Table VII—Values of k_{-1} at 25° for Scheme II

Dicarboxylic Acid	$k_{-1}, \text{M}^{-2} \text{min}^{-1}$
Glutaric	156
trans-1,2-Cyclohexane-dicarboxylic	220
Succinic	400
cis-1,2-Cyclohexane-dicarboxylic	445
Phthalic	585
Maleic	1000

Table VIII—Equilibrium Constants for Reactions (Scheme II) of Glutaric Anhydride and Succinic Anhydride with Acetic Acid

Anhydride	Constants Calculated from Equilibrium Data ^a , M	Constants Calculated from Rate Data ^b , M
Succinic	4.85×10^{-4}	4.5×10^{-4}
Glutaric	0.49	0.47

^a Determined from the UV absorbance of the reaction system at equilibrium and absorptivities of the species involved. ^b Determined from the rate constants $K = (k_1/k_{-1})$. It is recognized that the calculation of the k_1 values utilized equilibrium concentrations and were influenced to a degree by equilibrium data.

drides with acetic acid is shown in Scheme III. The part of the reaction scheme played by perchloric acid has not been included, Compound I is used to illustrate a general cyclic anhydride, and Compound V is used to illustrate its equivalent diacid.

Figure 5 shows the good log-log correlation between K and k_1 and the smaller inverse dependency of K on k_{-1} . As can be seen from Table VII, the rate of reaction of the diacids with acetic anhydride is relatively independent of structure, although subtle differences do appear to exist. When referring to Scheme III and, in particular, the reverse reaction pathways, reactions represented by the constants k_{-2} and k_{-1} would be expected to be rather fast relative to the steps represented by the rate constants k_{-3} and k_{-4} . The constant k_{-2} is expected to be quite large because it represents an intramolecular attack by a carboxyl group at an anhydride linkage. Intramolecular reactions are known to be many thousand times faster than their intermolecular equivalents (16).

The subtle differences in k_{-1} possibly suggest that the rate-determining step in the reaction of diacids with acetic anhydride is represented by the attack of the diacids on acetic anhydride. In the presence of perchloric acid, acetic anhydride is probably protonated. Maleic acid and phthalic acid [pKa 2.00 (17) and 2.95 (17), respectively], the two strongest acids in aqueous solution, have the fastest rates when reacting with acetic anhydride whereas the weakest acid, glutaric acid [pKa 4.34 (17)], has the slowest reaction rate. This finding does not imply that the same order of acidity exists in acetic acid; however, it may suggest that the nucleophilicity of the reactant dicarboxylic acids is important. This finding further supports the possibility that the rate-determining step in the

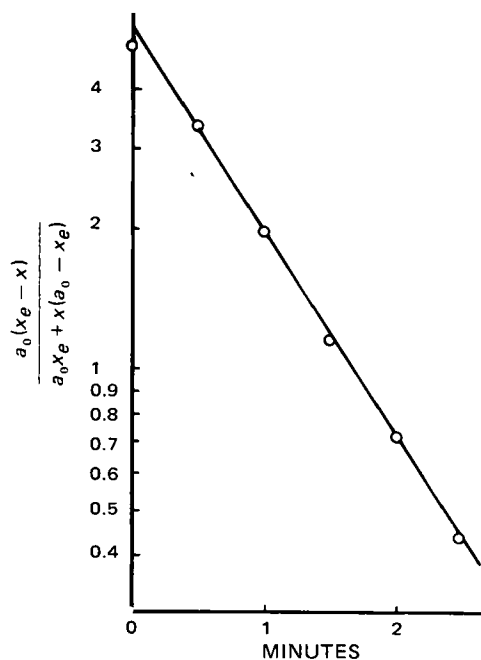


Figure 2—Perchloric acid-catalyzed reaction of glutaric anhydride with acetic acid. The figure shows a semilog plot of $a_0(x_e - x)/[a_0x_e + x(a_0 - x_e)]$ against time of the reaction of glutaric anhydride with acetic acid catalyzed by perchloric acid at 25° as described by:

$$\log \frac{a_0(x_e - x)}{a_0x_e + x(a_0 - x)} = - \frac{2a_0 - x_e[\text{HClO}_4]k_1t}{x_e 2.303}$$

and:

$$k_1 = \frac{-\text{slope} \times 2.303}{[(2a_0 - x_e)/x_e]} [\text{HClO}_4]$$

where a_0 is the initial glutaric anhydride concentration. The concentrations of acetic anhydride at any time and at equilibrium are represented by x and x_e , respectively; $a_0 = 0.40$ M; $[\text{HClO}_4] = 7.5 \times 10^{-3}$ M; $x_e = 0.242$ M; and k_1 is the pseudo-second-order rate constant.

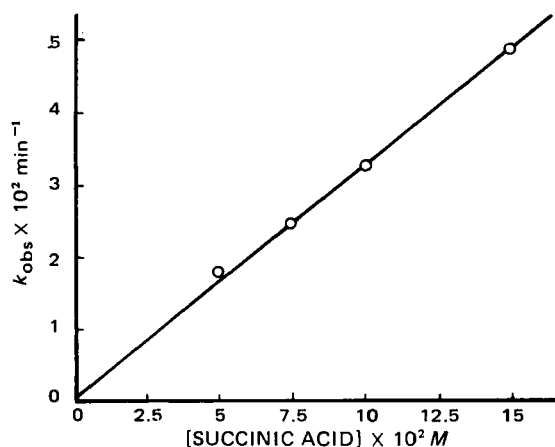


Figure 3—Perchloric acid-catalyzed reaction of succinic acid with acetic anhydride. The figure shows a plot of k_{obs} as a function of succinic acid for the perchloric acid-catalyzed reaction of acetic anhydride with succinic acid in acetic acid at 25°; $k_1 = slope/[HClO_4]$, and $[HClO_4] = 5.6 \times 10^{-3}$ M.

determination of k_{-1} is the formation of the tetrahedral intermediate IV.

As seen in Table VI, the values of k_1 appear to be a strong function of the molecular structure of the anhydrides. Since the steric and electrophilic factors of acetic anhydride and the mixed anhydride, III, would be considered to be similar, it seems reasonable to assume that the attack of acetic acid on the mixed anhydride and the subsequent breakdown of the intermediate IV would not be strongly influenced by the molecular structure of the diacid part of the mixed anhydride.

Similarly, because the hydrolytic behavior of all anhydrides, including acetic anhydride, is so similar (18) and the rate-determining step in the hydrolysis of the anhydrides is considered to be the formation of the tetrahedral intermediate, it follows that k_1 is probably not sufficiently perturbed by structure to result in the differences in reactivity seen with the various cyclic anhydrides. Therefore, the probable slow step in the reaction of the cyclic an-

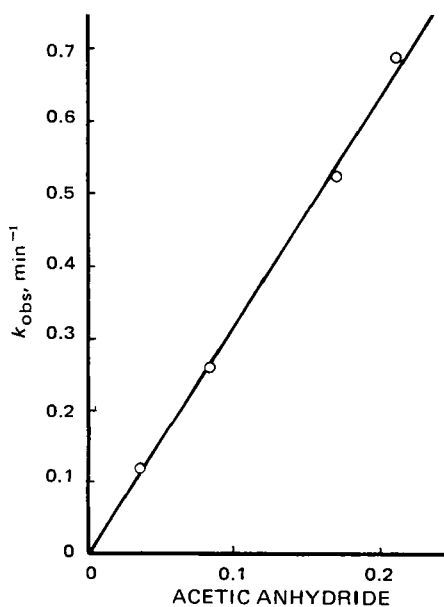


Figure 4—Perchloric acid-catalyzed reaction of phthalic acid with acetic anhydride as a function of acetic anhydride concentration, $[(CH_3CO)_2O]$. The figure shows a plot of k_{obs} against acetic anhydride for the perchloric acid-catalyzed reaction of phthalic acid and acetic anhydride in acetic acid at 25°; $k_{-1} = slope/[HClO_4]$, and $[HClO_4] = 1.0 \times 10^{-3}$ M.

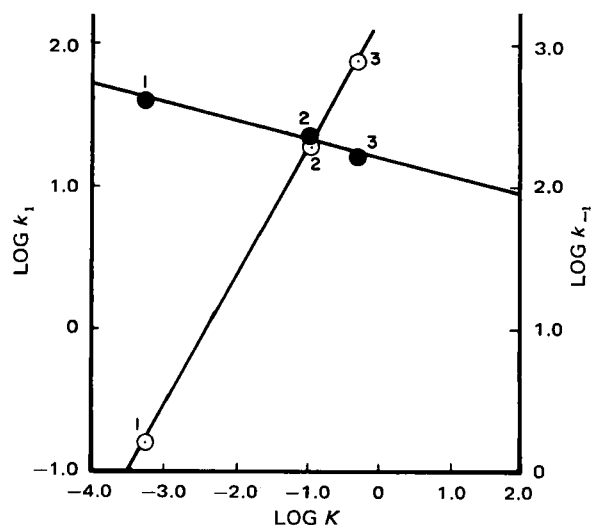


Figure 5—Plot showing the log-log correlation of k_1 and k_{-1} to K for Scheme II. The open circles represent the $\log k_1$ versus $\log K$ relationship, and the closed circles represent the $\log k_{-1}$ versus $\log K$ relationship. Compound 1 is succinic anhydride, Compound 2 is *trans*-1,2-cyclohexanedicarboxylic anhydride, and Compound 3 is glutaric anhydride.

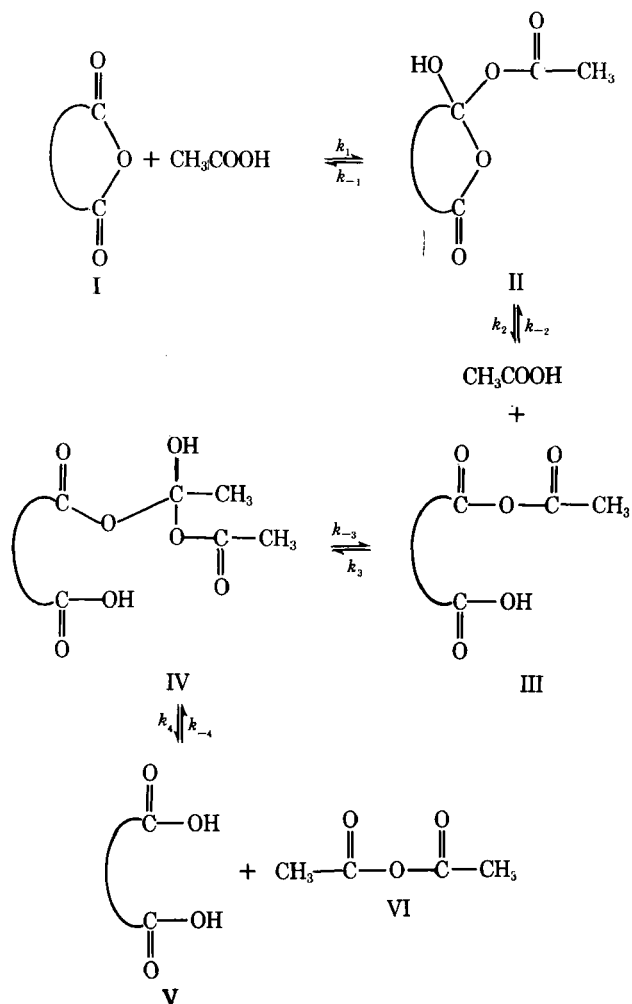
hydrides with acetic acid is the breakdown of the tetrahedral intermediate II.

The slowness of this step is rationalized on the basis that the transition state for the step requires the expulsion of the neighboring carboxyl group. The reverse of this step, represented by the constant k_{-2} , involves an intramolecular reaction. Increased rates of intramolecular reactions have been observed due to backbone alkyl substitution. Other means by which intramolecular reaction rates have been increased are by "locking" the reaction center "in line" with the nucleophile by constraining rotation within a ring system by: (a) decreasing ring size, *e.g.*, glutaric to succinic; (b) placement of a double bond in the ring system to prevent free rotation, *e.g.*, succinic to maleic and succinic to phthalic; or (c) placing the reaction centers near each other using favorable rigid analogs, *e.g.*, *cis*-1,2-cyclohexanedicarboxylic acid compared to *trans*-1,2-cyclohexanedicarboxylic acid. A complete argument on the subtleties of these various points can be found in Refs. 4, 5, 7, 8, and 19-28.

On the basis of the Hammond principle (29), the reverse of such an intramolecular reaction, or the ease with which the neighboring carboxyl group leaves, should be inverse to the ease with which the intramolecular reaction takes place. The order of reactivity of the cyclic anhydrides in the present study follows this pattern. The dependency of K on the constant k_1 and, subsequently, k_2 of Scheme III shows that the thermodynamic stability of the cyclic anhydrides is closely related to their molecular structure and can be rationalized on the basis of the known relative reactivity of intramolecular reactions compared to intermolecular reactions.

By the theory of microscopic reversibility, it follows that k_{-4} cannot be the rate-determining step for the reverse reaction and k_2 be the rate-determining step for the forward reaction. It was stated earlier that k_{-2} should be large relative to other rate constants for the reverse reaction because it involves an intramolecular reaction. Even though k_{-1} is not greatly perturbed by the structure of the cyclic anhydrides (Table VII), the order of reactivity of the dicarboxylic acids with acetic anhydride is consistent with those species most likely to undergo an intramolecular reaction, *i.e.*, maleic > phthalic > succinic > glutaric. It appears, therefore, that the transition state for the reaction of II in equilibrium with III probably represents the species of greatest free energy for the equilibrium formation of acetic anhydride from cyclic anhydrides dissolved in acetic acid.

In summary, the transacylation reaction presented in this study, *i.e.*, the equilibrium formation of acetic anhydride in anhydrous acetic acid in the presence of a high energy acylator such as a cyclic anhydride, could be rationalized on the basis of the known chemical reactivity of the anhydrides. These results provide additional insight into the chemistry of the energy-rich tetrahedral interme-



diates and cyclic anhydrides, which have been postulated in numerous pharmaceutically important reactions. The intermediacy of anhydrides in the hydrolysis of certain hemiesters has been established (5), and the acylating capacity of high energy pharmaceutical esters and amides such as aspirin and penicillin has been noted.

The present study provides a further quantitative picture of the effect of molecular structure on the partitioning of the tetrahedral intermediate between the open high energy configuration and the cyclic anhydride.

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