

# Acylation of Phenol by Cyclic and Acyclic Anhydrides in Anhydrous Acetic Acid

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

**Abstract** □ Acylation of phenol with succinic, glutaric, *trans*-1,2-cyclohexanedicarboxylic, maleic, phthalic, and *cis*-1,2-cyclohexanedicarboxylic anhydrides in anhydrous acetic acid generally resulted in phenyl acetate as the major product. The formation of phenyl acetate as the major reaction product could be rationalized as being due to the reactivity of the cyclic anhydrides with acetic acid to form acetic anhydride as well as the greater reactivity of phenol with formed acetic anhydride than with the cyclic anhydride.

**Keyphrases** □ Phenol—acylation by cyclic and acyclic anhydrides in anhydrous acetic acid, rate constants, mechanisms □ Acylation—phenol by cyclic and acyclic anhydrides in anhydrous acetic acid, rate constants, mechanisms □ Perchloric acid—catalyst for acylation of phenol in anhydrous acetic acid, rate constants, mechanisms □ Anhydrides, cyclic and acyclic—acylation of phenol in anhydrous acetic acid, rate constants, mechanisms

Haddadin *et al.* (1) recently quantitated the equilibrium formation of acetic anhydride from the reaction of cyclic anhydrides with anhydrous acetic acid catalyzed by perchloric acid. Mechanistically, the rate-determining step for the forward reaction was postulated to be the breakdown of the tetrahedral intermediate formed by the attack of acetic acid on the protonated cyclic anhydride. The hydrolysis of cyclic and acyclic anhydrides has been extensively studied (2), and the results suggest that the rate-determining step usually is the formation of the tetrahedral intermediate adduct. The present study concerns the reactivity of a model nucleophile, phenol, with cyclic and acyclic anhydrides in anhydrous acetic acid. The main objective was to gain an understanding of the mechanisms involved in transacylation reactions taking place in nonaqueous media. This study provides a quantitative picture of the effects of molecular structure and the partitioning of tetrahedral intermediate formation and breakdown on leaving group tendencies, especially when cyclic and acyclic anhydrides are the substrates and phenol is the nucleophile. The reactivity of energy-rich tetrahedral intermediates as well as cyclic and acyclic anhydrides will be discussed as models for high energy acylators, as postulated in numerous pharmaceutically important reactions. The pharmaceutical implications of transacylation reactions have been well documented (3–8).

## EXPERIMENTAL

**Materials**—All materials were as described previously (1). Phenyl acetate was vacuum distilled at 211° and 0.7 mm Hg. The refractive index was 1.5008 [lit. (9) 1.5017] at 25°. Phenyl hemisuccinate was synthesized and purified according to the method of Baddar and Assal (10); phenol<sup>1</sup> was purified by sublimation, mp 42° [lit. (9) mp 43°].

*p*-Methylphenol<sup>2</sup> was sublimed and dried under vacuum, mp

36° [lit. (9) mp 34°]. *p*-Methoxyphenol<sup>3</sup>, mp 56–57° [lit. (9) mp 57°], *p*-iodophenol<sup>3</sup>, mp 93–94° [lit. (9) mp 93–94°], and *p*-fluorophenol, mp 46–47° [lit. (9) mp 48°], were recrystallized from benzene–petroleum ether.

**Apparatus**<sup>4</sup>—For the thermometric measurements, a simple dewar calorimeter was assembled from a wheatstone bridge circuit, a 1-mv recorder, a 2-K thermister probe, a dewar flask of convenient size, a thermometer<sup>5</sup>, two variable resistance boxes of 111.1 K, and a mercury cell of 1.35 v (11, 12). The recorder was calibrated to read a difference of 0.4° at ambient temperature per full-scale deflection.

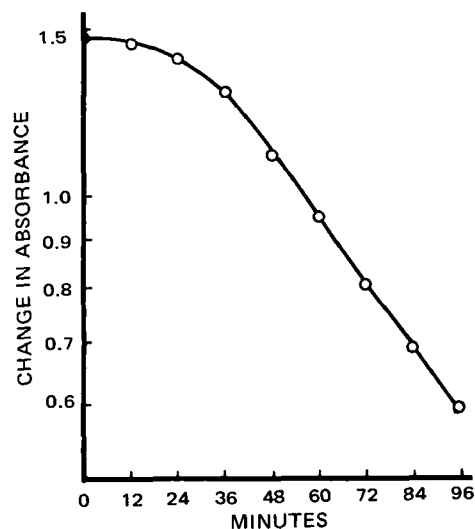
All spectroscopic measurements were carried out in the thermostated cell compartment of a UV spectrophotometer<sup>6</sup>.

**Procedures**—The reactions between acetic anhydride and phenol in anhydrous acetic acid, catalyzed by perchloric acid, were followed both spectrophotometrically and thermometrically.

For the spectrophotometric method, a few microliters of approximately  $1 \times 10^{-3}$  M phenol in anhydrous acetic acid was injected directly into a thermostated 1-cm cylindrical cell containing 0.1–0.5 M acetic anhydride and  $1 \times 10^{-3}$  M perchloric acid in anhydrous acetic acid. The disappearance of phenol was conveniently followed at 278 nm.

For the thermometric method, a few milliliters of  $1 \times 10^{-2}$  M phenol, dissolved in anhydrous acetic acid, was injected into an anhydrous acetic acid solution containing 0.1–0.5 M acetic anhydride and  $1 \times 10^{-4}$  M perchloric acid. All experiments were run at approximately 25°. The reaction was monitored by following the small change in the temperature of the solution. In all cases, this change was <0.09°.

The rate constants were obtained under pseudo-first-order conditions in which acetic anhydride was always in excess. The con-



**Figure 1**—Semilog plot of change in absorbance against time, demonstrating the lag time for the perchloric acid-catalyzed reaction of phenol with a fresh solution of succinic anhydride in acetic acid at 25°. The initial concentration of succinic anhydride was 0.30 M, and  $[HClO_4] = 1.244 \times 10^{-2}$  M.

<sup>3</sup> Aldrich Chemical Co., Milwaukee, Wis.

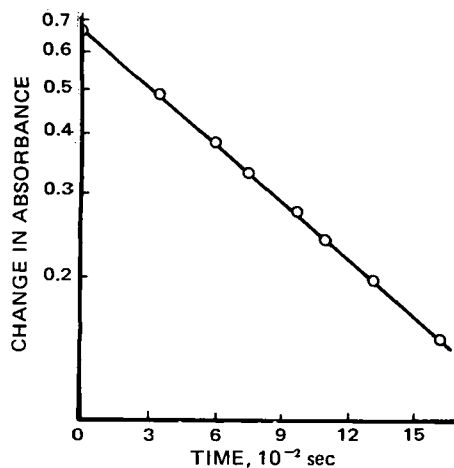
<sup>4</sup> NMR spectra were obtained on a Varian T60 NMR spectrometer.

<sup>5</sup> Beckman Instruments Inc., Fullerton, Calif.

<sup>6</sup> Cary model 14 with a thermostated cell compartment maintained at 25°.

<sup>1</sup> J. T. Baker Chemical Co., Phillipsburg, N.J.

<sup>2</sup> Unknown origin. Structure was confirmed by NMR and elemental analyses.

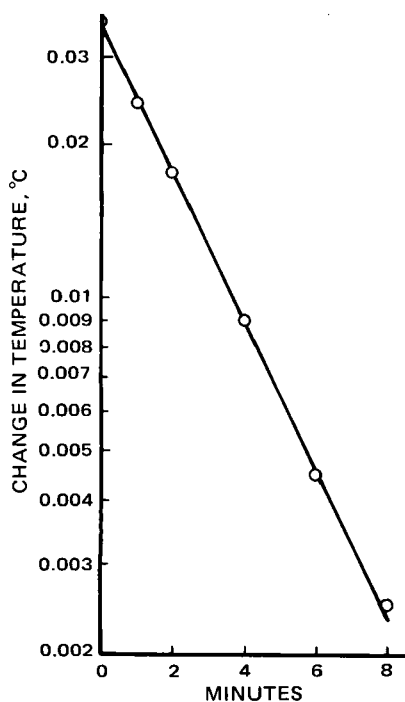


**Figure 2**—Semilog plot of change in absorbance against time, demonstrating first-order behavior in phenol when it was reacted with an equilibrated succinic anhydride solution, 0.51 M in acetic acid, in the presence of  $1.244 \times 10^{-3}$  M  $\text{HClO}_4$  at  $25^\circ$ .

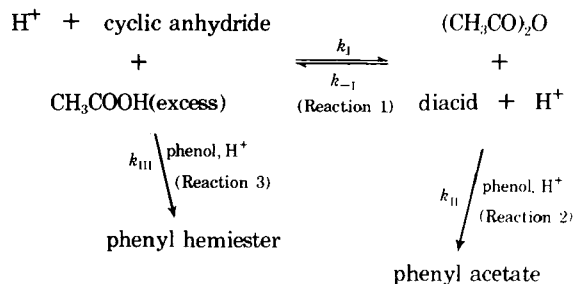
concentrations of acetic anhydride and the catalyst, perchloric acid, were varied independently. The slopes of the observed rate constant,  $k_{\text{obs}}$ , versus acetic anhydride concentrations and perchloric acid concentrations,  $[\text{HClO}_4]$ , were used to calculate the third-order rate constant for the reaction of phenol with acetic anhydride.

The reaction of *para*-substituted phenols was followed under the same conditions previously described, except that a convenient wavelength for following the disappearance of the phenol was used.

Reactions between phenol and succinic, glutaric, phthalic, maleic, *cis*-1,2-cyclohexanedicarboxylic, and *trans*-1,2-cyclohexanedicarboxylic anhydrides were studied by adding dilute solutions of phenol in anhydrous acetic acid to preequilibrated solutions of the cyclic anhydride in the anhydrous acetic acid in the presence of perchloric acid. The disappearance of phenol was followed at 278



**Figure 3**—Semilog plot of change in temperature against time, demonstrating first-order behavior with respect to phenol for the perchloric acid-catalyzed reaction of phenol with acetic anhydride in acetic acid at  $25^\circ$ ;  $[(\text{CH}_3\text{CO})_2\text{O}] = 0.21$  M, and  $[\text{HClO}_4] = 5.0 \times 10^{-3}$  M. The reaction was monitored thermometrically.



*Scheme I*

nm and  $25^\circ$ . The concentrations of the cyclic anhydrides ranged from 0.1 to 0.5 M, and the final concentrations of phenol and perchloric acid were  $1 \times 10^{-4}$  and  $1 \times 10^{-3}$  M, respectively.

To study the effects of added succinic acid on the reaction of phenol in the succinic anhydride-acetic acid system, succinic anhydride was maintained at 0.4 M while the succinic acid concentration was varied from 0.015 to 0.1 M. Similar studies with the corresponding acids of the other cyclic anhydrides were not attempted.

**Determination of Reaction Products**—The quantitative determination of the phenol ester products found in the phenol-cyclic anhydride-acetic acid reaction mixture was accomplished using the following procedure. Phenyl acetate was estimated by neutralizing a pipetted aliquot with ice-cold sodium carbonate solution to pH 9 and extracting with ether or carbon tetrachloride. The extracts were made up to a convenient volume. The UV absorbance of the solution at 266 and 278 nm was used to calculate the amount of phenyl acetate formed. The absence of phenol in the reaction mixture was verified by absorbance measurements at 278 nm. The shape of the absorbance versus wavelength scan corresponded to that of phenyl acetate. The concentration of phenyl acetate extracted was estimated by comparison with the absorbance of a standardized sample. The concentration of the phenol hemiester was calculated from the difference between the initial phenol concentration and the phenyl acetate concentration found.

To check if phenyl hemisuccinate underwent a reversible reaction in the perchloric acid-acetic acid solution, a standardized phenyl hemisuccinate solution was compared. Repetitive UV scanning and TLC showed that phenyl hemisuccinate was stable, *i.e.*, did not undergo a transacylation reaction.

TLC was employed to identify the phenol esters and to verify the spectrophotometric results. A few microliters of the reaction mixtures was spotted along with authentic samples of the various reactants and possible products on dry silica gel TLC plates (preheated at  $120^\circ$  for 30 min). The mobile phase was 3% butyl ether in pentane; the spots were developed in iodine vapor.

## RESULTS AND DISCUSSION

When phenol was added to a freshly prepared solution of succinic anhydride in acetic acid with perchloric acid present as a catalyst, the disappearance of the phenol showed a lag time of about 30 min followed by an apparent first-order disappearance (Fig. 1). If the reaction mixture of succinic anhydride and acetic acid was allowed to equilibrate before the addition of phenol, no lag time was observed and the disappearance of phenol followed first-order kinetics (Fig. 2). Similar results were obtained with glutaric anhydride and *trans*-1,2-cyclohexanedicarboxylic anhydride.

The presence of a lag time in the freshly prepared solution was postulated to be due to the formation of a more reactive intermediate, *i.e.*, acetic anhydride, which would then react with phenol as shown in Scheme I.

To test Scheme I, the reactivity of phenol with acetic anhydride in anhydrous acetic acid and in the presence of perchloric acid was studied. The products resulting from the reaction of phenol with the cyclic anhydride in acetic acid were determined as described under *Experimental*.

In the reaction of phenol with succinic anhydride in anhydrous acetic acid, for example, TLC revealed only one spot corresponding to phenyl acetate. When exogenous succinic acid was included in the system before adding phenol, both the rate of formation and the amount of phenyl acetate formed decreased. Furthermore, a

**Table I—Rate Constants of the Acetic Anhydride–Phenol Reactions at 25° in Acetic Acid with Perchloric Acid Present as a Catalyst**

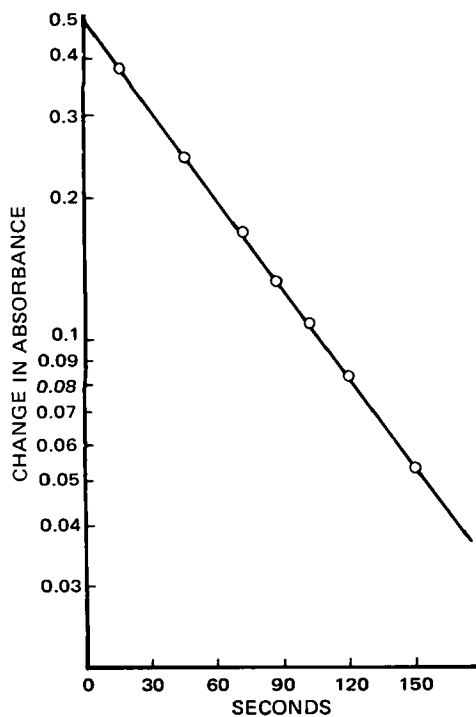
Phenol	$k_{II}, M^{-2} \text{ min}^{-1}$
<i>p</i> -Methoxyphenol	884
<i>p</i> -Methylphenol	482
Phenol	300 <sup>a</sup>
	287 <sup>b</sup>
<i>p</i> -Fluorophenol	271
<i>p</i> -Iodophenol	96

<sup>a</sup> From spectrophotometric method. <sup>b</sup> From thermometric method.

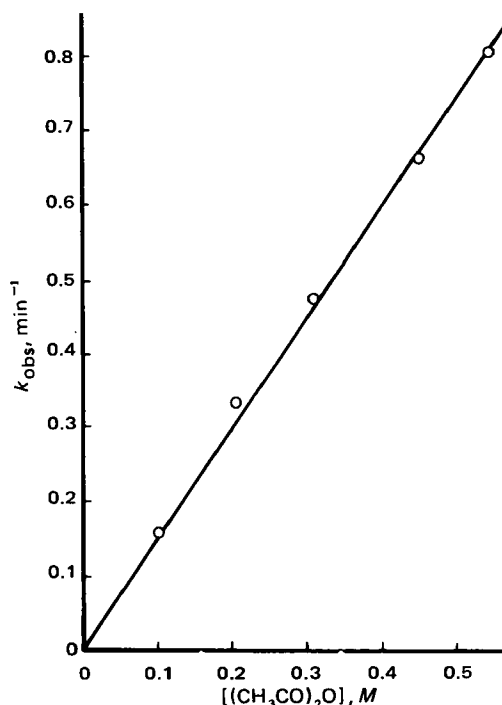
second spot corresponding to phenyl hemisuccinate was observed. This finding is consistent with Scheme I because exogenous succinic acid would be expected to force Reaction 1 to the left, thereby reducing the equilibrium concentration of acetic anhydride. Similar results were obtained for glutaric and *trans*-1,2-cyclohexanedicarboxylic anhydrides.

The third-order rate constant,  $k_{II}$ , for the reaction of phenol with acetic anhydride catalyzed by perchloric acid was determined independently, *i.e.*, in the absence of the cyclic anhydrides. Pseudo-first-order plots for the disappearance of phenol were obtained when perchloric acid was maintained constant and acetic anhydride was used in excess of the phenol. The disappearance of phenol monitored thermometrically and spectrophotometrically is shown in Figs. 3 and 4, respectively. The first-order dependency in acetic anhydride is shown in Fig. 5, and the first-order dependency on perchloric acid is shown in Fig. 6. The importance of perchloric acid can be seen in the near zero intercept.

The relative reactivity of various *para*-substituted phenols is shown in Table I. Included in this table are the values obtained for phenol. The objective of this study was to gain insight into the mechanism of acetylation of phenol under the reaction conditions. A Hammett plot of  $\log k_{II}$  for the various phenols *versus*  $\sigma$  *para* is shown in Fig. 7. These data support a mechanism involving nucleophilic attack of the phenol on the protonated acetic anhydride as the rate-determining step.



**Figure 4—Semilog plot of change in absorbance against time, demonstrating first-order behavior with respect to phenol for the perchloric acid-catalyzed reaction of acetic anhydride with phenol in acetic acid at 25°;  $[(CH_3CO)_2O] = 0.501 M$ , and  $[HClO_4] = 5.0 \times 10^{-3} M$ .**



**Figure 5—Plot of  $k_{obs}$  against  $[(CH_3CO)_2O]$ , showing first-order dependency with respect to acetic anhydride in its perchloric acid-catalyzed reaction with phenol;  $[HClO_4] = 5.0 \times 10^{-3} M$ . The reactions were monitored thermometrically.**

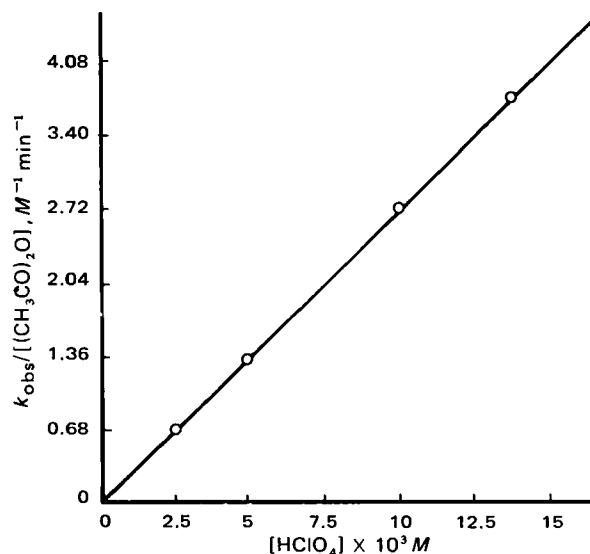
If a steady-state assumption is made for acetic anhydride in Scheme I, the following equation can be derived:

$$k_{obs} = k'_{III} [\text{cyclic anhydride}]_{eq} + k_{II} [(CH_3CO)_2O] \quad (\text{Eq. 1})$$

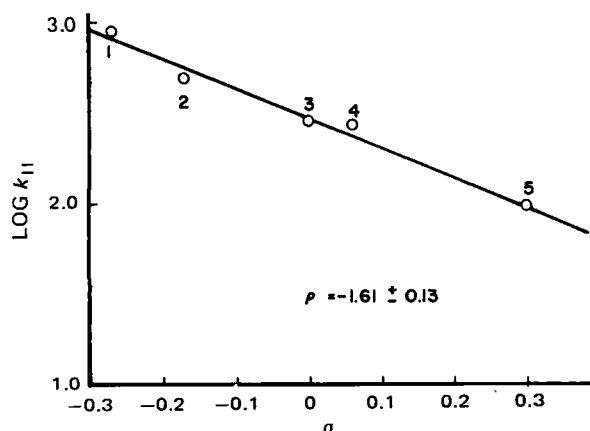
It follows that:

$$\frac{k_{obs}}{[\text{cyclic anhydride}]_{eq}} = k'_{III} + \frac{Kk_{II}}{[\text{diacid}]_{eq}} \quad (\text{Eq. 2})$$

where  $k_{obs}$  is the observed pseudo-first-order rate constant for the disappearance of phenol,  $k_{II}$  is equal to  $k_{II} [HClO_4]$ ,  $k'_{III}$  is equal to  $k_{III} [HClO_4]$ ,  $[\text{cyclic anhydride}]_{eq}$  is the concentration of the cyclic anhydride in the equilibrated solution,  $[\text{diacid}]_{eq}$  is the concentration of the diacid at equilibrium, and  $K = k_1/k_{-1}$ .



**Figure 6—Plot of  $k_{obs}/[(CH_3CO)_2O]$  against the perchloric acid concentration, demonstrating first-order behavior with respect to perchloric acid, the catalyst, in the reaction of acetic anhydride with phenol;  $[(CH_3CO)_2O] = 0.53 M$ .**



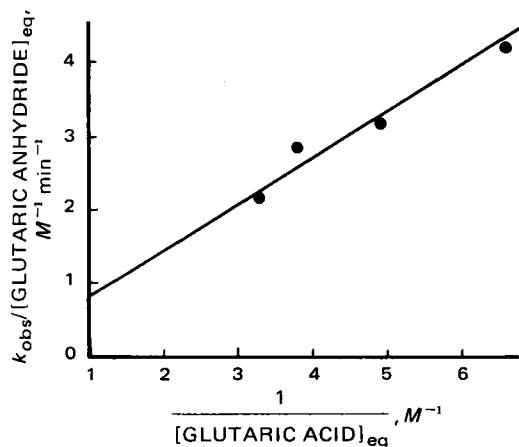
**Figure 7**—Semilog plot of  $k_{II}$  (a third-order rate constant) as a function of the Hammett  $\sigma$  para (23). Key: Compound 1, *p*-methoxyphenol; Compound 2, *p*-methylphenol; Compound 3, phenol; Compound 4, *p*-fluorophenol; and Compound 5, *p*-iodophenol.

The equilibrium concentration of the cyclic anhydride and the corresponding diacid under the experimental conditions described were previously determined (1). If the reaction shown in Scheme I and a steady state for acetic anhydride are assumed, then Eq. 2 predicts that a plot of  $k_{obs}/[\text{cyclic anhydride}]_{eq}$  versus  $1/[\text{diacid}]_{eq}$  should be linear with slopes equal to  $Kk_{II}$  and an intercept of  $k_{III}$ . Such plots were found to be linear, and a representative one is shown in Fig. 8. The third-order constant  $k_{III}$  was calculated to be 1.5, 37, and  $48 \text{ M}^{-2} \text{ min}^{-1}$  for succinic, glutaric, and *trans*-1,2-cyclohexanedicarboxylic anhydrides, respectively.

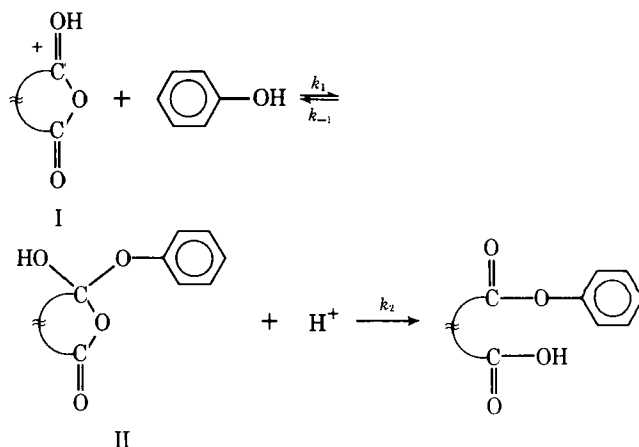
The validity of these intercepts was checked for succinic and *trans*-1,2-cyclohexanedicarboxylic anhydrides by comparing the expected ratios of the phenyl hemiester of the appropriate dicarboxylic acid to phenyl acetate from kinetic data to those found by the quantitative recovery of the products. With  $0.2 \text{ M}$  succinic anhydride in the presence of  $0.1 \text{ M}$  succinic acid and  $1 \times 10^{-3} \text{ M}$  perchloric acid, the ratio of phenyl hemisuccinate to phenyl acetate was expected to be 1:1 but experimentally the recovery was 0.8:1. With  $0.2 \text{ M}$  *trans*-1,2-cyclohexanedicarboxylic anhydride in the presence of  $1 \times 10^{-3} \text{ M}$  perchloric acid, the kinetically expected ratio of phenyl hemiester of *trans*-1,2-cyclohexanedicarboxylic acid to phenyl acetate was 1:8 whereas the experimental recovery was 1:8.6.

Both from the kinetic and TLC studies, no reaction between phenol and maleic, *cis*-1,2-cyclohexanedicarboxylic, and phthalic anhydrides to form the hemiesters could be detected.

The relative reactivity toward phenol of the various cyclic anhy-



**Figure 8**—Plot of  $k_{obs}/[\text{glutaric anhydride}]_{eq}$  versus  $1/[\text{glutaric acid}]_{eq}$  for the perchloric acid-catalyzed reaction of phenol with the glutaric anhydride-acetic acid system, varying the initial glutaric anhydride concentration. Slope =  $k_{III}[\text{HClO}_4]$ , where  $[\text{HClO}_4] = 5.6 \times 10^{-3} \text{ M}$ .



**Scheme II**

drides, when compared to the reaction of phenol with acetic anhydride, is not consistent with the relative hydrolytic behavior of these anhydrides (2). Eberson and Landström (2) showed that acetic, succinic, and glutaric anhydrides at  $20^\circ$  and pH 5.20 have almost identical hydrolysis rates, and they stated that there does not seem to be any mechanistic difference between the hydrolysis of open chain and cyclic anhydrides. Recent studies (13) with the slowly hydrolyzing tetramethylsuccinic anhydride suggest that the hydrolysis of this anhydride involves the breakdown of the tetrahedral intermediate whereas the spontaneous hydrolysis of other cyclic and acyclic anhydrides involves rate-determining formation of the tetrahedral intermediate adduct.

The relative reactivity of the *para*-substituted phenols toward acetic anhydride in anhydrous acetic acid in the presence of perchloric acid suggests that nucleophilicity of the phenol is important. This is consistent with the rate-determining step being the attack of the phenol on the protonated, positively charged, acetic anhydride. The relative reactivity of phenol toward succinic anhydride compared to acetic anhydride suggests that a change in the rate-determining step has occurred. Such a mechanism is shown in Scheme II, where I represents a cyclic or acyclic anhydride.

The ability of hemiesters and amides of cyclic acids to undergo a facile intramolecular reaction to form the corresponding anhydride has been well recognized (14–22). The relative reactivity of cyclic anhydrides to undergo solvolytic reactions with acetic acid was rationalized on the basis of the difficulty of expulsion of a carboxyl group from the tetrahedral intermediate formed by the attack of acetic acid on the protonated anhydride (reaction represented by  $k_1$  in Scheme I of Ref. 1). By the same argument, it appears that the rate-determining step in the reaction of phenol with succinic anhydride under the present conditions may be  $k_2$ , *i.e.*, the breakdown of the tetrahedral intermediate II, a conclusion based on the large difference between  $k_{II}$  and  $k_{III}$ .

The large negative entropy of activation changes and the large solvent isotope effects seen in the spontaneous hydrolytic reactions of various cyclic and acyclic anhydrides suggest that the transition state energy was lowered by hydrogen bonding with solvent molecules (2). The reduced ability to solvate a polar transition state by specific interaction in a lower dielectric medium like acetic acid will contribute to differences in the transition state for nucleophilic reactions in water *versus* those in acetic acid.

The relative reactivity of phenol with the cyclic anhydrides studied in the present case (including those anhydrides for which no measurable reactivity could be determined, *i.e.*,  $k_{III} \ll 1 \text{ M}^{-2} \text{ min}^{-1}$ ) is inverse to the ability of the hemiester and amides of the corresponding dicarboxylic acid to undergo intramolecular reactions (14–22). This finding suggests that the difficulty in expelling the neighboring carboxyl group, *i.e.*,  $k_2$  of Scheme II, is probably the rate-determining step.

## SUMMARY

The formation of phenyl hemiesters of dicarboxylic acids from the reaction of phenol with a dicarboxylic anhydride in anhydrous acetic acid catalyzed by perchloric acid is a function of two interre-

lated factors: (a) the reactivity of phenol toward the cyclic anhydride versus the reactivity of phenol toward the *in situ* formed acetic anhydride, and (b) the equilibrium concentration of acetic anhydride resulting from the solvolytic reaction of acetic acid with the cyclic anhydride. The more reactive the cyclic anhydride, the more readily it reacts with both phenol and acetic acid.

The present study provides a further quantitative picture of the effect of molecular structure on the partitioning between rate-determining formation and breakdown of the energy-rich tetrahedral intermediate for reaction at an acyl function. The poor leaving group tendency of the constrained neighboring carboxyl group in the reaction of phenol with cyclic anhydrides, due to the inclination of the neighboring carboxyl to undergo the reverse intramolecular reaction, resulted in tetrahedral intermediate breakdown being the rate-determining step. It is postulated that the good leaving group tendency of the unconstrained acetic acid in the reaction of phenol with the acyclic anhydride, acetic anhydride, results in tetrahedral intermediate formation being the rate-determining step. These differences in mechanism between the reactivity of cyclic and acyclic anhydrides in acetic acid compared to their hydrolytic reactivity must be due to the reduced ability of acetic acid, when compared to water, to solvate polar transition states.

#### REFERENCES

- (1) M. J. Haddadin, T. Higuchi, and V. Stella, *J. Pharm. Sci.*, **64**, 1759(1975).
- (2) L. Ebersson and L. Landström, *Acta Chem. Scand.*, **26**, 239(1972).
- (3) E. Shami, J. Dudzinski, L. Lachman, and J. Tingstad, *J. Pharm. Sci.*, **62**, 1283(1973).
- (4) A. E. Troup and H. Mitchner, *ibid.*, **53**, 375(1964).
- (5) A. L. Jacobs, A. E. Dilatush, S. Weinstein, and J. J. Windheuser, *ibid.*, **55**, 893(1966).
- (6) K. T. Koshy, A. E. Troup, R. N. Duvall, R. C. Conwell, and L. L. Shankle, *ibid.*, **56**, 1117(1967).
- (7) J. Halmekoski and K. Vesalainen, *Farm. Aikak.*, **78**, 249(1969).
- (8) J. Halmekoski and R. Mustonen, *ibid.*, **75**, 357(1966).
- (9) "Dictionary of Organic Compounds," 4th ed., Oxford Uni-

versity Press, New York, N.Y., 1965.

- (10) F. G. Baddar and L. S. Assal, *J. Chem. Soc.*, **1950**, 3606.
- (11) S. Sunner and I. Wadsö, *Acta Chem. Scand.*, **13**, 97(1959).
- (12) M. J. Haddadin, Ph.D. dissertation, University of Kansas, Lawrence, Kan., 1972, p. 8.
- (13) R. Gandour, V. Stella, M. Coyne, and R. Schowen, Abstract 563 presented at the 10th Midwest Regional ACS Meeting, Iowa City, Iowa, 1974.
- (14) T. C. Bruice and U. K. Pandit, *J. Amer. Chem. Soc.*, **82**, 5858(1960).
- (15) M. L. Bender, U. L. Chow, and F. Chloupek, *ibid.*, **80**, 5380(1958).
- (16) T. Higuchi, T. Miki, A. C. Shah, and A. Herd, *ibid.*, **85**, 3655(1963).
- (17) T. Higuchi, L. Ebersson, and J. McRae, *ibid.*, **89**, 3001(1967).
- (18) T. C. Bruice and W. C. Bradbury, *ibid.*, **87**, 4838(1965).
- (19) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N.Y., 1969, pp. 8-15.
- (20) T. C. Bruice and W. C. Bradbury, *J. Amer. Chem. Soc.*, **87**, 4846(1965).
- (21) T. Higuchi, L. Ebersson, and J. D. McRae, *ibid.*, **88**, 3805(1966).
- (22) A. J. Kirby and P. W. Lancaster, *J. Chem. Soc., Perkins Trans.*, **1972**, 1206.
- (23) G. B. Barlin and D. D. Perrin, *Quart. Rev.*, **20**, 75(1966).

#### ACKNOWLEDGMENTS AND ADDRESSES

Received January 8, 1974, from the Department of Pharmaceutical Chemistry, University of Kansas, Lawrence, KS 66044

Accepted for publication February 26, 1975.

Abstracted from a dissertation submitted by M. J. Haddadin to the University of Kansas in partial fulfillment of the Doctor of Philosophy degree requirements.

Supported in part by Alza Corp., Palo Alto, Calif.

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## Dissolution Patterns of Polydisperse Powders: Oxalic Acid Dihydrate

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**Abstract** □ The dissolution of oxalic acid dihydrate crystals of log-normal particle-size distribution in 0.1 N HCl was studied. A biphasic cube root dependence was found; the slopes of the initial cube root plots were consistent with theory based on dissolution of isometric, isotropic particles where assumptions were made of: (a) sink conditions, (b) particle-size-independent solubility, and (c)

particle-size-independent film thickness of adsorbed liquid layers.

**Keyphrases** □ Dissolution of polydisperse powders (oxalic acid dihydrate)—dissolution patterns, equations □ Oxalic acid dihydrate (polydisperse powder)—dissolution patterns, equations □ Powders, polydisperse—dissolution, oxalic acid dihydrate, equations

The rates of dissolution and the mechanisms involved in the dissolution process have been the subjects of many publications in the last decade. However, most dissolution work done on powders has been restricted to monodisperse powders (1-4).

#### BACKGROUND

Hixson and Crowell (5), basing their derivation on the Noyes-

Whitney equation (6), arrived at the so-called cube root dissolution rate law:

$$\sqrt[3]{W_0} - \sqrt[3]{W} = Kt \quad (\text{Eq. 1})$$

where  $W_0$  is the initial weight of the powder,  $W$  is the weight of undissolved powder at time  $t$ , and  $K$  is an apparent dissolution rate constant having units of (weight)<sup>1/3</sup> per unit time. The assumptions made in the derivation of Eq. 1 are: (a) all particles dissolve isotropically, (b) the particles are isometric, (c) the thickness of the diffusion barrier around each particle (the "film thickness,"