Michaelis–Menten Kinetics in the Catalyzed Solvolysis of Tetrachlorophthalic Anhydride

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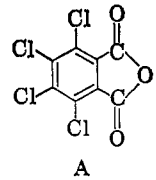
Abstract: The kinetics of methanolysis of tetrachlorophthalic anhydride (TCPA) in the presence of three additives (N,N-dimethylaniline, *p*-dimethoxybenzene, or pyridine) have been determined. N,N-Dimethylaniline accelerates the solvolysis; the rate constant *vs.* [catalyst] curve shows a pronounced saturation effect like that found in enzyme–substrate systems. The association constant for substrate–catalyst complexation (2.3 M^{-1}), obtained from the kinetic data by a Lineweaver–Burk-type plot, is in good agreement with a spectrophotometrically determined value. The nonnucleophilic π donor, *p*-dimethoxybenzene, inhibits solvolysis of the anhydride. The results with this additive are explained by formation of a complex (K = 1.1 M^{-1}) whose rate constant for methanolysis is within experimental error of zero. Pyridine (a nucleophile, but a poor π donor) catalyzes the solvolysis of TCPA by a simple bimolecular mechanism not involving a complex. The N,N-dimethylaniline-catalyzed reaction is best interpreted in terms of a "nonclassical" Michaelis–Menten mechanism, the first example of its kind.

We report here a study of the solvolysis of tetrachlorophthalic anhydride (TCPA) in methanol. TCPA is an excellent π acceptor;[1] treatment of the anhydride with a π-donating aromatic nucleophile would lead to charge-transfer complexation and, conceivably, to intramolecular-type catalysis. Thus, if N,N-dimethylaniline complexes with TCPA in methanol so that the nucleophilic dimethylamino group is positioned near the carbonyl carbon of the anhydride, then a rate enhancement might be observed which is greater than would be expected for ordinary bimolecular catalysis. Kinetically the reaction would resemble an enzyme-catalyzed transformation. If, on the other hand, the dimethylamino group within the complex were not situated near the carbonyl (*i.e.*, if the nitrogen were over one of the chlorines), then steric and electronic considerations[2] lead us to expect a retarded solvolysis as a result of complexation. In this paper we describe the effect of three additives (N,N-dimethylaniline, *p*-dimethoxybenzene, and pyridine) on the methanolysis of TCPA. N,N-Dimethylaniline is a good π donor and it possesses a nucleophilic group; *p*-dimethoxybenzene is a nonnucleophilic π donor; pyridine is a nucleophile but a poor π donor. As will be shown, these three additives affect the methanolysis of TCPA in remarkably different ways.



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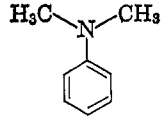

B

Experimental Section

Materials. Tetrachlorophthalic anhydride (Eastman) was crystallized three times from benzene, dried under reduced pressure, and stored in a desiccator. N,N-Dimethylaniline (Matheson Coleman and Bell "Free from Mono") was distilled through an efficient column three times, once from a solution of benzenesulfonyl chloride and twice over zinc dust. Vapor phase chromatographic analysis of the purified material showed no trace of either aniline or N-methylaniline. (A vpc column was selected for which the retention times of the two impurities were less than that of the tertiary amine.) *p*-Dimethoxybenzene (Eastman) was crystallized twice from methanol–water to give crystals of satisfactory melting point. Pyridine (Fisher Spectranalyzed) was distilled just prior to use, and methanol was distilled once over Mg. Acetonitrile (Eastman Spectro) was distilled once over P_2O_5 and once over anhydrous Na_2CO_3.

Kinetics. The procedure is given here for one particular additive, and it is typical of that which was used throughout. The solvolysis medium (0.00–0.95 M N,N-dimethylaniline in methanol) was equilibrated at 25.0 ± 0.1° in a stoppered cuvette placed within the thermostated chamber of a Cary 14 spectrophotometer. The wavelength was set at 335.0 mμ. A small amount (50 μl) of an acetonitrile solution of TCPA was added rapidly to the cuvette (with the aid of a stirring rod flattened at one end) such that the initial TCPA concentration was 3.3 × 10^{-4} M. The decrease in absorbance was then traced as a function of time. Reactions were always carried out to completion, and first-order plots were linear to greater than 80% reaction.

While the concentration of TCPA is too small to permit isolation of products under kinetic conditions, the observed decrease in absorbance is undoubtedly associated with simple methanolysis of the anhydride linkage to give an ester which has its absorbance maximum well below 335.0 mμ. Lawlor[3] has pointed out that nucleophilic reactions on TCPA are generally of high yield and free from side reactions. Nucleophilic aromatic substitution, the only conceivable side reaction, is very unlikely in view of the fact that it requires boiling aniline (184°) to replace a chlorine with a nitrogen.[4]

Spectrophotometric Determination of the Association Constant. The equilibrium constant for association of TCPA with N,N-dimethylaniline was obtained by measuring the increase in absorption at 400.0 mμ with increasing amine concentration, while keeping the substrate concentration constant. The substrate solvolyzes during the measurements, and it is necessary to extrapolate absorbance values to zero time. There is considerable error associated with this procedure. The absorbance data were treated in the usual manner[5] in order to obtain the equilibrium constant (K = 1.7 ± 0.5 M^{-1}).

Results

The three additives (N,N-dimethylaniline, *p*-dimethoxybenzene, and pyridine) affect the solvolysis of TCPA in quite different ways.

(1) N,N-Dimethylaniline accelerates the methanolysis of TCPA; the rate constant *vs.* [catalyst] curve (Figure

(1) L. J. Andrews and R. M. Keefer, "Molecular Complexes in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964.
(2) F. M. Menger and M. L. Bender, *J. Am. Chem. Soc.*, 88, 131 (1966).
(3) F. E. Lawlor, *Ind. Eng. Chem.*, 39, 1419 (1947).
(4) D. S. Pratt and G. A. Perkins, *J. Am. Chem. Soc.*, 40, 198 (1918).
(5) J. A. A. Ketelaar, C. van de Stolpe, A. G. Goundsmit, and W. Dzcubar, *Rec. Trav. Chim.*, 71, 1104 (1952).

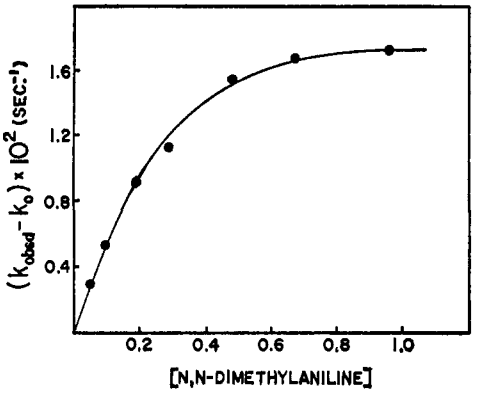

Figure 1. Plot of observed rate constants for methanolysis of tetrachlorophthalic anhydride in the presence of N,N-dimethylaniline minus k_0 (the rate constant for methanolysis in the absence of catalyst) *vs.* concentration of N,N-dimethylaniline, T = 25.0°; initial concentration of substrate = 3.3×10^{-4} M; $k_0 = 8.0 \times 10^{-3}$ sec^{-1}.

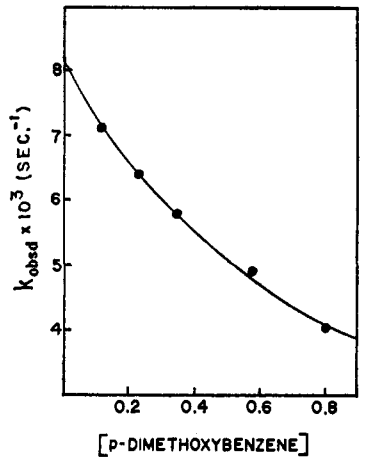

Figure 2. Plot of observed rate constants for methanolysis of tetrachlorophthalic anhydride *vs.* concentration of *p*-dimethoxybenzene, T = 25.0° and initial concentration of substrate = 3.3×10^{-4} M.

1) shows a pronounced saturation effect like that found in enzyme–substrate systems. The kinetic data are interpretable (see Discussion) in terms of an N,N-dimethylaniline–TCPA π donor–π acceptor complex having an association constant of 2.3 ± 0.2 M^{-1}. The substrate and catalyst in methanol form a yellow complex with a spectrophotometrically determined association constant of 1.7 ± 0.5 M^{-1}, in good agreement with the kinetically derived value.

(2) The nonnucleophilic π donor, *p*-dimethoxybenzene, inhibits the solvolysis of TCPA (Figure 2). The data are best explained by formation of a complex (K = 1.1 M^{-1}) whose rate constant for methanolysis is within experimental error of zero.[6]

(3) Pyridine (a poor π donor and, like N,N-dimethylaniline, a weakly basic tertiary amine) accelerates the solvolysis of TCPA (Figure 3). In contrast to the aniline case, the observed rate constant for catalyzed methanolysis is linearly related to the [catalyst] over the entire concentration range.[7] The pyridine reaction ex-

(6) See ref 2 and references cited therein for other examples of substrates becoming inert to nucleophilic attack when engaged in complexation.

(7) Above 0.1 M pyridine the reaction is too fast to measure with the available equipment.

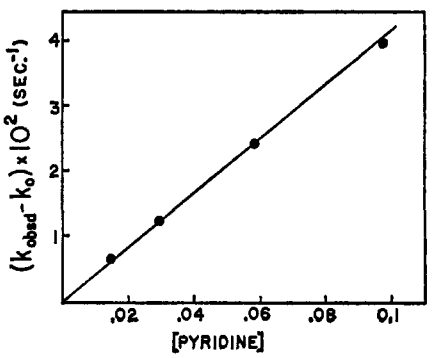

Figure 3. Plot of observed rate constants for methanolysis of tetrachlorophthalic anhydride in the presence of pyridine minus k_0 (the rate constant for methanolysis in the absence of catalyst) *vs.* concentration of pyridine, T = 25.0°; initial concentration of substrate = 3.3×10^{-4} M; $k_0 = 8.0 \times 10^{-3}$ sec^{-1}.

hibits simple nucleophilic or general base catalysis; there is no kinetic or spectrophotometric evidence for complexation between TCPA and pyridine below 0.1 M pyridine.

Discussion

The Michaelis–Menten behavior of N,N-dimethylaniline-catalyzed methanolysis (Figure 1) is consistent with two schemes (eq 1 and 2) in which A, B, AB, and

$$A + B \underset{}{\overset{K}{\rightleftharpoons}} AB \xrightarrow{k_1(MeOH)} P \qquad (1)$$

P represent TCPA, N,N-dimethylaniline, complex, and products respectively. Spontaneous solvolysis (A forming P directly with a rate constant, k_0) is an additional side reaction. Equation 1, which corresponds to the formulation usually presented for enzyme systems,[8] is kinetically indistinguishable from the second possibility (eq 2).

$$\begin{aligned} A + B &\overset{K}{\rightleftharpoons} AB \\ A + B &\xrightarrow{k_2(MeOH)} P \end{aligned} \qquad (2)$$

The complex AB in eq 1 may be visualized as a charge-transfer complex having the aromatic rings of the components parallel to one another for maximum orbital overlap.[1] In order for the complex to be reactive, the nitrogen of N,N-dimethylaniline must be located above the carbonyl carbon of TCPA. This would permit nucleophilic attack[9] at the carbonyl to form an unstable acylanilinium salt which would very rapidly solvolyze to the methyl ester. Formation and decomposition of the intermediate are conveniently included in a single k_1 step.

The parameters of eq 1 (K and k_1) were evaluated using eq 3, which was first derived by Colter and coworkers.[10] A plot of $1/(k_{obsd} - k_0)$ *vs.* 1/(B), using the

$$\frac{1}{(k_{obsd} - k_0)} = \frac{1}{(k_1 - k_0)} + \frac{1}{(k_1 - k_0)K(B)} \qquad (3)$$

data of Figure 1, shows excellent linearity. From it we obtain $K = 2.3$ M^{-1} and $k_1 = 3.8 \times 10^{-2}$ sec^{-1}. It may

(8) K. J. Laidler, "The Chemical Kinetics of Enzyme Action," Oxford University Press, London, 1958.

(9) Molecular models of the complex show that the possibility of general base catalysis is unlikely for steric reasons.

(10) A. K. Colter, S. S. Wang, G. H. Megerle, and P. S. Ossip, *J. Am. Chem. Soc.*, 86, 3106 (1964).

be noted that eq 3 is similar to the Lineweaver–Burk form of the Michaelis–Menten equation (eq 4). This

$$\frac{1}{v} = \frac{1}{V} + \frac{1}{VK_M^{-1}(S)} \quad (4)$$

is particularly evident if the rate constant for spontaneous solvolysis of TCPA (k_0) is imagined to be zero.

The complex AB of eq 2 differs from the one in eq 1 by being totally unreactive. This could result, for example, from positioning of the nitrogen of N,N-dimethylaniline over one of the chlorines of TCPA rather than over a carbonyl. Chemical reaction between substrate and catalyst is the result of a bimolecular collision; in other words, the k_2 step represents ordinary nucleophilic catalysis. The parameters of eq 2 may be calculated from the easily derived eq 5 and from the same plot used with eq 3. A plot of $1/(k_{obsd} - k_0)$ *vs.* 1/(B) is, of course, predicted to be linear by both mechanisms because the mechanisms are kinetically indistinguishable. Only the *meaning* of the slope and intercept of the plot varies with the particular mechanism. In the case of eq 2, K and k_2 are calculated to be 2.3 M^{-1} and 8.6×10^{-2} M^{-1} sec^{-1}, respectively.

$$\frac{1}{(k_{obsd} - k_0)} = \frac{K}{(k_2 - k_0K)} + \frac{1}{(k_2 - k_0K)(B)} \quad (5)$$

Although the two mechanisms (eq 1 and 2) yield rate laws consistent with Figure 1, our data support eq 2 for the following reasons. If eq 1 is correct, then k_1 is calculated to be only 4.6 times larger than k_0. Thus, placement of the nitrogen of the aniline near the anhydride carbonyl in the π complex results in only a small catalysis, which is in sharp contrast to the enormous rate enhancements often associated with intramolecular catalysis even in less rigid systems. (This argument against eq 1 is, unfortunately, weakened by the uncertainty regarding the reactivity of the species while engaged in complexation.) If on the other hand eq 2 is correct, then we obtain a value of 8.6×10^{-2} M^{-1} sec^{-1} for k_2. Approximately 60% of k_2 can be attributed to catalysis by traces of methoxide ion in equilibrium with the N,N-dimethylaniline, as shown by experiments in which the reaction solutions were buffered with N,N-dimethylaniline hydrochloride. Consequently, the value of the second-order rate constant for nucleophilic catalysis by N,N-dimethylaniline is roughly 3.4×10^{-2} M^{-1}, a reasonable number. The second-order rate constant for pyridine catalysis (Figure 3) is 12 times larger than this value, which is in accordance with the relative reactivity of pyridine and aniline toward another labile carbonyl compound, *p*-nitrophenyl acetate (6.7).[11] Equation 2 is also attractive because both of its steps have good analogies: the equilibrium step to form the complex is analogous to the formation of the unreactive *p*-dimethoxybenzene–TCPA complex (Figure 2); the rate step of eq 2 is similar to the pyridine catalysis (Figure 3).

Could it be that at least some enzyme systems are also better described by eq 2 than by the classical Michaelis–Menten formulation (eq 1)?[12] This is a possibility, particularly in multienzyme systems where the substrate is passed from one enzyme to another within a small molecular aggregate or on a membrane surface. The mechanism (eq 2) gives the biological system a means of "shutting off" the second-order enzyme–substrate reaction in the event that the cell is exposed to too much substrate. Thus, accumulation of products to a toxic level can be avoided. The specificity of the enzymes would, of course, be associated with a rate step rather than with an equilibrium process. Whatever the merit of these speculations, it seems clear that we have found the first simple model of such a "nonclassical" Michaelis–Menten mechanism.

Acknowledgment. I greatly appreciate a grant from the Research Corporation.

(11) M. L. Bender, *Chem. Rev.*, 60, 53 (1960).

(12) This question has been raised previously. See W. D. McElroy and B. Glass, Ed., "Mechanisms of Enzyme Action," Johns Hopkins Press, Baltimore, Md., 1954, p 215.