Specific Solvation Effects on Acylation of Amines in Solvents with Low Dielectric Constants

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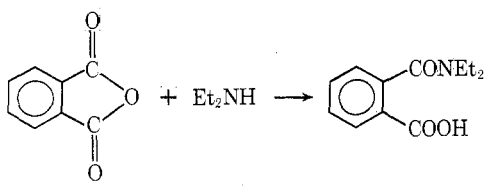
Kinetic solvent effects in solvents of relatively low dielectric constants are generally treated in a nonspecific manner. Differences in rate are usually reconciled using either an electrostatic approach[1] or the regular solution theory.[2] Certain solvents in this category, *e.g.*, chloroform and ether, in spite of similar dielectric constant and solubility parameter, may, however, exert tremendously different, and sometimes opposite, kinetic solvent effects because of their different ability to either accept or donate electrons to the reactants and/or transition state. In these cases, the kinetic solvent effects have to be viewed through specific solute–solvent interactions. In this communication, we present kinetic data of the aminolysis of phthalic anhydride in solvents of relatively low dielectric constants, *viz.*, cyclohexane, chloroform, diethyl ether and tetrahydrofuran (THF). It is shown that the apparent reaction rate and mechanism in these solvents are vastly different. The effect of added acid on the apparent aminolysis rate is shown to be dramatically solvent dependent, being catalytic in some solvents and inhibitory in others. Opposing solvent kinetic effects were also observed when acylation rates of phthalic anhydride by diethylamine and morpholine in mixed chloroform–cyclohexane solvents were compared. In the reaction with diethylamine, the rate increased with the chloroform content of the solvent, whereas the opposite was observed for the acylation reaction with morpholine. The collective data, however, can be interpreted in terms of a generalized reaction scheme which takes into account the role of each individual solvent on the reaction steps.

Results and Discussion

The stoichiometry of the reactions between phthalic anhydride and diethylamine (Et_2NH) in all the solvents studied is as given in eq 1.



(1)

In all the solvent systems studied, it was impossible to use one single rate expression to describe the entire course of the reaction. Therefore, initial and terminal rate expressions were separately determined. Initial rate plots as a function of diethylamine concentration are presented in Figure 1, and it can be observed, in the amine concentrations studied, that the reaction rate was about 10–120 times faster in chloroform and tetrahydrofuran than in

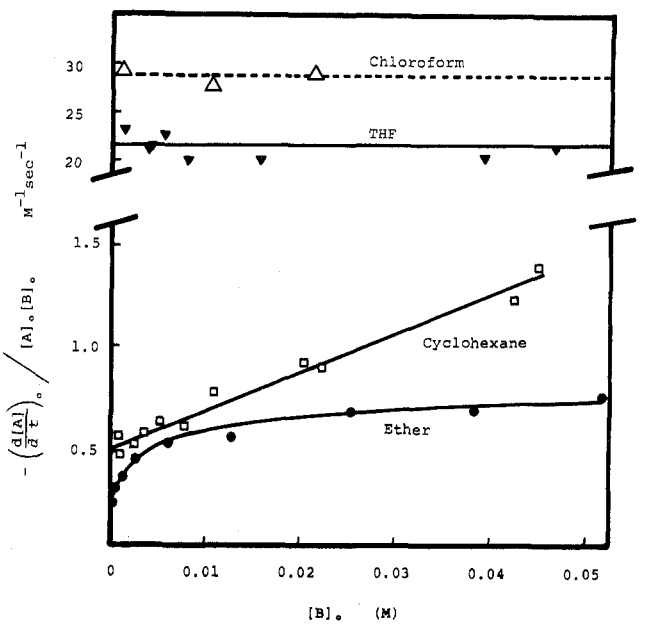


Figure 1. Initial rate plots of $-(d[A]/dt)_0/[A]_0[B]_0$ *vs.* $[B]_0$ for the reaction between phthalic anhydride and diethylamine in chloroform (△), tetrahydrofuran (▼), cyclohexane (□), and diethyl ether (●) at 25°.

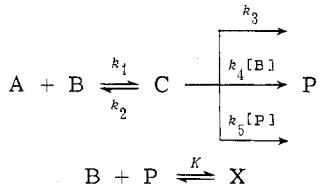
ether and cyclohexane. It is also evident that even among the initial rates measured, the rate dependence on amine concentration was influenced by solvent. The apparent rate expressions are presented in Table I.

The terminal rate expressions are even more complex than the initial rates because of the participation of the reaction product, *N,N*-diethylphthalamic acid, in the reaction. For example, in chloroform, the terminal rate was found to be slower than the initial rate, whereas in tetrahydrofuran, the reverse was true (Table I). It was also found that in any particular solvent, added acetic acid affected the acylation rate in a manner similar to that of added phthalamic acid, whereas added acetamide had no effect. Apparently, the carboxylic acid group, rather than the amide function, in the reaction product caused the effects on the observed rate changes.

In the presence of excess acetic acid the rate of disappearance of phthalic anhydride was first order in each solvent. The kinetic effects of added acetic acid on the ratio of observed pseudo-first-order rate constant over $[B]_0$ are shown in Figure 2. It appears that acetic acid catalyzed the reaction in both ether and THF. In ether, at the higher concentration of acetic acid, catalysis appeared to level off. In cyclohexane, the reaction between phthalic anhydride and diethylamine was accelerated at low acetic acid concentrations but inhibited at high acetic acid concentrations. In chloroform, the overall effect was inhibition. No simple relationship between the observed rate and acetic acid concentration could be formulated in ether and cyclohexane. Empirical rate expressions could be written for the reaction occurring in chloroform and THF; these are presented in Table I.

Scheme I depicts a series of reactions which can account for the kinetic results obtained for the acylation of diethylamine by phthalic anhydride in all the solvents studied.

Scheme I



In this scheme A is the anhydride, B the dialkylamine, and P the phthalamic acid. C is the reactive intermediate which can decompose to re-form the reactants (reaction 2) or to yield the phthalamic acid either in a spontaneous reaction (reaction 3), in a reaction catalyzed by a molecule of the dialkylamine (reaction 4), or in a reaction catalyzed by a molecule of the phthalamic acid (reaction 5). X is an unreactive complex formed by association of a molecule of amine with one or more phthalamic acid molecules. If a carboxylic acid is added to the reaction system, it is believed to participate in reactions similar to those of the phthalamic acid, since catalysis by the amide function appeared to be negligible.

In the absence of any evidence for an accumulation of C during the course of the acylation, the rate laws which describe Scheme I can be developed by using a steady-state approximation. Thus, in the absence of any added acid and when $[B]_0 \gg [A]_0$ and $[P]_0 = 0$, the initial rate of disappearance of anhydride is given by

$$-\left(\frac{d[A]}{dt}\right)_0 = \frac{k_1(k_3 + k_4[B]_0)}{k_2 + k_3 + k_4[B]_0}[A]_0[B]_0 \qquad (2)$$

The observed initial rate expressions in the solvents studied (Table I) can all be derived from eq 2. The differences arise because the relative magnitudes of the rate constants differ in the solvents. Thus, in Scheme I, it can be assumed that $k_3 \ll k_4[B]_0$ in ether, $(k_2 + k_3) \gg k_4[B]_0$ in cyclohexane, and $k_3 \gg k_4[B]_0$ in chloroform and THF.

From Scheme I, the rate of disappearance of anhydride when $[P] \neq 0$ is given by

$$\frac{-d[A]}{dt} = \frac{k_1 f(k_3 + fk_4[B]_0 + k_5[P])}{k_2 + k_3 + fk_4[B]_0 + k_5[P]}[A]_0[B]_0 \qquad (3)$$

where

$$f = (1 + K[P])^{-1} \qquad (4)$$

Again, the observed data in all solvents for the terminal rates or in those cases when acid is added can be derived from eq 3; the solvent plays its role in determining again the relative magnitudes of the rate constants as well as the contribution of the inhibiting equilibrium to the overall scheme. Thus, in ether and THF, the catalytic effects noted in the presence of small concentrations of P or of added acid (which appears in equivalent terms to those of P) would be expected when $K[P] \ll 1$ and $k_5[P]$ as well as $(k_3 + k_4[B]_0)$ was smaller than or comparable in size to k_2.

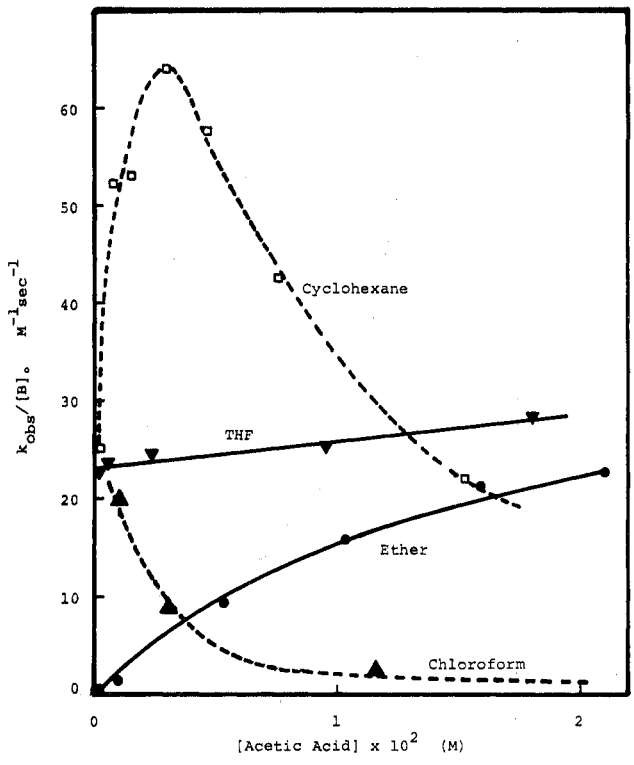


Figure 2. Effects of added acetic acid on $k_{obsd}/[B]_0$ of reaction between phthalic anhydride and diethylamine in chloroform (▲), tetrahydrofuran (▼), cyclohexane (□), and diethyl ether (●) at 25°. $[A]_0 \approx 1.3 \times 10^{-4}$ *M* in all solvents.

Since the complexation constant between acetic acid and diethylamine in ether is low ($K \simeq 50\ M^{-1}$),[3] the assumption of $K[P] \ll 1$ is valid at low [P]. The same situation will hold in the case of THF in which the complexation constant is expected to be even lower. When [P] or acetic acid concentration is high, the inhibitory effect will begin to become significant, and the catalytic contribution of [P] or added acid will be diminished (Figure 2). In cyclohexane, when high [P] is present, the overall effect is that of inhibition because the equilibrium constant, *K*, is much larger.[4] In chloroform, the term $k_5[P]$ is presumably small and no catalysis is ooserved, even at very low acid concentrations.

The formation of nonreactive complexes can also be invoked in viewing the solvent effects when the acylation rates of phthalic anhydride by diethylamine and morpholine in mixed chloroform–cyclohexane solvents were compared (Figure 3). In the reaction involving diethylamine, acylation was catalyzed by chloroform. However, in the acylation of phthalic anhydride by morpholine, an opposite solvent effect was observed in that the reaction was drastically inhibited in the presence of chloroform. We have determined that morpholine forms both 1:1 and 1:2 complexes with chloroform, with equilibrium constants at 25°

Table I
Summary of Observed Rate Expressions for Both Initial and "Terminal" Rates for Reaction between Phthalic Anhydride (A) and Diethylamine (B) in Various Solvents at 25°[a]

Solvent	Initial rate expression	"Terminal" rate expression
Cyclohexane	$0.49[A]_0[B]_0 + 18.7[A]_0[B]_0^2$	See text
Ether	$565[A]_0[B]_0^2/(1 + 1.02 \times 10^3[B]_0)$	See text
Chloroform	$28.2[A]_0[B]_0$	$25[A]_0[B]_0/(1 + 1000[P])$
THF	$21.2[A]_0[B]_0$	$22.8[A]_0[B]_0 + 280[A]_0[P][B]_0$

[a] [P] = [acetic acid]. Concentrations are in molar units and time is in seconds.

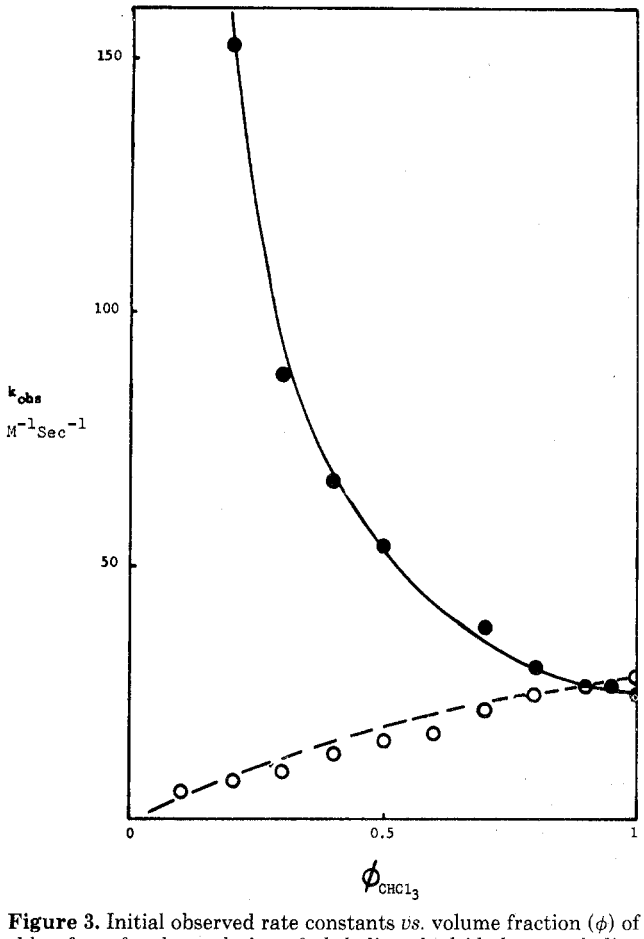


Figure 3. Initial observed rate constants *vs.* volume fraction (ϕ) of chloroform for the acylation of phthalic anhydride by morpholine (●) and diethylamine (○) in mixed chloroform–cyclohexane solvent systems.

of 1.05 M^{-1} and 0.29 M^{-2}, respectively. The stability constant for complexation between an aliphatic amine such as diethylamine with chloroform is likely to have a value of about 0.2 M^{-1} at 25°.[5] In the presence of excess chloroform relative to the amine concentration, as in the present case, the activity of morpholine may be drastically lowered through complexation without compensatory solvation of the transition state. Thus, the reaction rate is reduced with increasing content of chloroform in the reaction medium. In the case of the reaction involving diethylamine, the comparatively weaker solvation of the amine reactant by chloroform may be adequately counterbalanced by solvation of the transition state involved. Thus, inhibition by chloroform is not observed.

Experimental Section

Reagents. Unless otherwise specified, all reagents were of reagent grade. Diethyl ether (ACS) was dried over $LiAlH_4$ and distilled. Chloroform (AR) was washed with distilled water five to six times, dried over $CaCl_2$ overnight, then distilled over phosphorus pentoxide, and used immediately. Cyclohexane (AR) was distilled over phosphorus pentoxide. Tetrahydrofuran (AR) was dried by $LiAlH_4$ and distilled. All purified solvents were stored over molecular sieve (Linde 4A). Morpholine was refluxed with KOH pellets for 1 hr, fractionally distilled, and then again fractionally distilled over sodium. Diethylamine was refluxed with KOH pellets for 1 hr and then distilled. The middle fractions were collected and stored over KOH pellets. Piperidine was fractionally distilled over KOH pellets under nitrogen. The amines were stored under nitrogen in closed containers in a refrigerator. Their purity was checked by titration with standard acid. Phthalic anhydride was recrystallized from a chloroform–cyclohexane mixture; mp 129–130° (lit. mp 131.5°). *N,N*-Diethylphthalamic acid was prepared according to Maxim;[6] mp 151–152° (lit. mp 153°). Glacial acetic acid was used without purification.

Kinetic Procedure. Rates and rate constants for the acylation reactions were calculated from changes in ultraviolet absorbance at a wavelength where phthalic anhydride was the main absorbing species. Measurements were made using Cary 14, Cary 16, and Durrum stop-flow spectrophotometers. In the cases when the reactions were first order or pseudo first order (in the presence of excess amine), rate constants were calcualted from plots of log ($A - A_\infty$) against time. Initial rates were calculated from the spe of the ae to an absorbance against time plot at a point as close to zero time as possible. In these studies an accurate amount (0.01–0.1 ml) of a concentrated solution of the amine in the solvent to be studied was placed in a 1 cm absorption cell. Three milliliters of phthalic anhydride solution in the same solvent was injected into the cell through a hypodermic syringe. The instrument recorder was turned on after insertion of the needle through the cell compartment cover but before injection of the anhydride solution. For the studies of effects of acetic acid on the reaction, the proper amount of acetic acid was added to the amine before mixing with anhydride. The uv spectra of the products of the reaction, when different acids were used as catalysts, were identical. All kinetic studies were done at 25°.

Acknowledgment. This work was supported in part by Basic Research in Life Sciences, Department of the Army and a Kansas Research Grant.

Registry No.—Phthalic anhydride, 85-44-9; diethylamine, 109-89-7; cyclohexane, 110-82-7; diethyl ether, 60-29-7; chloroform, 67-66-3; THF, 109-99-9; morpholine, 110-91-8; *N,N*-diethylphthalamide, 53336-79-1; succinic acid, 110-15-6; benzoic acid, 65-85-0; trifluoroacetic acid, 76-05-1; acetic acid, 64-19-7.

Supplementary Material Available. Fuller kinetic details will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $5.00 for photocopy or $2.00 for microfiche, referring to code number JOC-75-378.

References and Notes

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Solvolysis Problems in Chlorinations in Sulfuric Acid

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Recently several papers have reported chlorinations in 50–96% sulfuric acid. Kollonitsch and coworkers used Cl_2 to chlorinate α-amino acids in 100% H_2SO_4[1] and 50% H_2SO_4,[2] amines in 100% H_2SO_4,[3] and carboxylic acids in H_2SO_4–HF.[3] Minisci and coworkers published a number of papers on chlorination of esters, amines, and 1-chloroalkanes using *N*-chloro- and *N*-bromoammonium ions in 85–96% H_2SO_4.[4] Our own group has studied Cl_2 and R_2NHCl^+ chlorinations of carboxylic acids in 85–96%