Mechanism of Amine-Catalyzed Ester Formation from an Acid Chloride and Alcohol

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Stopped-flow FT-IR spectroscopy has been used to study the amine-catalyzed reactions of benzoyl chloride with either butanol or phenol in dichloromethane at 0 °C. There is a paucity of detailed rate information available in the literature for this process. Our goal was to determine whether amine catalysis operated by a nucleophilic-, specific-base-, or general-base-catalyzed mechanism. A large isotope effect was observed for butanol versus butanol-*O*-*d* which is consistent with a general-base-catalyzed mechanism. Some anomalous rate dependencies on reactant concentration and the relative rate of benzoyl chloride loss versus butyl benzoate formation were observed. The analogous reaction of phenol was studied in more detailed. An overall reaction order of three, and a negligible isotope effect for phenol versus phenol-d_6 are consistent with either a base- or nucleophilic-catalyzed mechanism. The most interesting result with phenol was a large sensitivity of the rate of phenyl benzoate formation on small structural changes in the amine (e.g., diethylmethylamine versus triethylamine). We observed the key intermediate (acylammonium salt) in the nucleophilic process via NMR for solutions of benzoyl chloride and amine in the absence of alcohol; however, we did not observe this intermediate in the IR during ester formation [with the exception of 4-(dimethylamino)-pyridine]. While we can rule out specific-base catalysis (no evidence for phenoxide intermediates), it is difficult to completely eliminate nucleophilic catalysis.

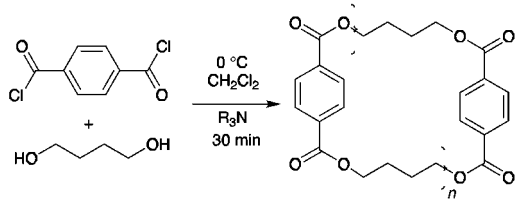
Introduction

Cyclic oligomers of engineering thermoplastics are promising precursor materials for reactive processing because of their low melt viscosity and their ability to undergo facile ring-opening polymerization. Brunelle and co-workers have developed high-yield processes for the synthesis of macrocyclic oligocarbonates.[1] Brunelle's methodology uses a Ziegler−Ruggli dilution method (sometimes called pseudo-high-dilution) that allows high product concentrations. In addition, the synthetic approach minimizes linear oligomers and produces a distribution of cyclic oligomers (as opposed to a preponderance of a single oligomer) which is advantageous for lower melt polymerization temperatures.

Recently, Brunelle and co-workers have published results on alkylene phthalate cyclic oligomers. Two methods have been described for the preparation of these macrocyclic oligoesters. One is the ring-chain equilibration from linear polymers.[2] Bryant and Semlyen[3] have also described the preparation and characterization of cyclic oligomers of poly(ethylene terephthalate) (PET) using the ring-chain process.

A second method (Scheme 1) is based on the amine-catalyzed reaction of acid chlorides with diols.[4,5] The yield of the cyclic oligomers is strongly dependent on the structure of the amine catalyst, with the highest yields

Scheme 1



obtained with sterically unhindered amines such as quinuclidine. Triethylamine, pyridine, and 4-(dimethylamino)pyridine led to small amounts (<5%) of cyclic oligomers. Higher yields of cyclics were obtained with quinuclidine and l,4-diazabicyclo[2.2.2]octane (DABCO). Optimization of cyclization conditions eventually led to a process which uses catalytic amounts of DABCO in conjunction with stoichiometric quantities of triethylamine; this process produces up to 85% yields of poly(butylene terephthalate) (PBT) cyclic oligomers.

Our interest in the utility of these macrocyclization reactions prompted us to investigate the mechanism of ester formation. It was felt that rational control of yields and ring-size distribution would be best achieved through an understanding of the mechanism of amine catalysis. The fundamental reaction involved in the oligoester macrocyclization is the amine-catalyzed formation of an ester from an acid chloride and an alcohol. The balance of intramolecular vs intermolecular ester bond formation controls the amount of cyclization versus chain extension.

We have found scant kinetic information in the literature on amine-catalyzed reactions of acid chlorides in aprotic, nonpolar solvents. It is generally recognized that these reactions are extremely rapid and, thus, difficult

(1) Brunelle, D. J. In *Macromolecular Design of Polymeric Materials*; Hatada, K., Kitayama, T., Vogl, O., Eds.; Marcel Decker: New York, Chapter 16, 1997.
(2) Brunelle, D. J.; Takekoshi, T. U. S. Patent 5 407 984, 1995.
(3) Bryant, J. J. L.; Semlyen, J. A. *Polymer* **1997**, *38*, 2475.
(4) (a) Brunelle, D. J.; Bradt, J. E. U.S. Patent 5 039 783, 1991. (b) Brunelle, D. J.; Bradt, J. E.; Serth-Guzzo, J.; Takekoshi, T.; Evans, T. L.; Pearce, E. J. *Polym. Prepr.* **1997**, *38*, 0000.
(5) Hubbard, P. A.; Brittain, W. J.; Simonsick, W. J., Jr.; Ross, C. W., III *Macromolecules* **1996**, *29*, 8304.
(6) Kivinen, A. In *The Chemistry of Acid Halides*; Patai, S., Ed.; Interscience: New York, Chapter 6, 1972.

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to study.[6] There have been some reports on the alcoholysis of acid chlorides in aprotic solvents without amine catalysis.[7,8] However, most literature work on the amine-catalyzed reactions of carbonyl compounds has been performed in protic solvents. A number of putative mechanisms have been proposed on the basis of these reports. Examples of general-base catalysis include the acetate-catalyzed hydrolysis of acetic anhydride[9] and several imidazole-catalyzed reactions of acetates.[10,11] In the hydrolysis of acetic anhydride, acetate ion acts as a base in the proton abstraction from a water molecule which is attacking the ester. The majority of the literature on amine-catalyzed reactions proposes a nucleophilic catalysis mechanism where the amine attacks the carbonyl bond, forming a transient tetrahedral intermediate; on displacement of the leaving group, a quaternary acylammonium salt (AAS) is formed. The AAS is then susceptible to attack by water, alcohol, or other nucleophile to form product. One fundamental study in this area was done by Fersht and Jencks.[12] They studied the pyridine-catalyzed hydrolysis of acetic anhydride; a nucleophilic mechanism was supported by several pieces of experimental evidence, including a slower rate of hydrolysis for 2-substituted pyridines. However, no direct observation of the acylammonium salt was reported.

Other proposed mechanisms for amine-catalyzed reactions of carbonyl compounds have involved acylium ion[9] and ketene intermediates (the latter can only occur for acid halides containing α-hydrogens).[10]

The mechanism of amine-catalyzed reactions of carbonyl compounds is determined by the reacting species as well as the reaction conditions. Johnson[13] reviewed the factors which determine whether a reaction follows a nucleophilic versus a base-catalyzed pathway. Nucleophilic catalysis mechanisms are indicated to be favored by good leaving groups, electronegative acyl groups, unhindered bases, and strongly basic nucleophiles.

Perhaps for the present study, previous work in our laboratories on the amine-catalyzed reaction of bisphenol A (4,4′-isopropylidenediphenol) bischloroformates is more relevant.[14] Similar to ester macrocyclization, the yield of cyclic carbonate oligomers is strongly dependent on the amine structure. In the cyclic carbonate case, the formation of AAS is directly observable via IR. The rate of AAS formation was found to be strongly dependent on amine structure. This dependence is in contrast to other reactions in the macrocyclization process (e.g., carbonate and carbamate formation) which were insensitive to the amine structure. This earlier work provides strong evidence in support of an active nucleophilic catalysis mechanism for amine-catalyzed macrocyclization reactions.

To shed further light on the mechanism of amine-catalyzed ester bond formation from the reaction of an acid chloride with an alcohol, we have studied the model reactions of benzoyl chloride with either phenol and butanol in dichloromethane. We have used stopped-flow techniques to facilitate the observation of these fast reactions.

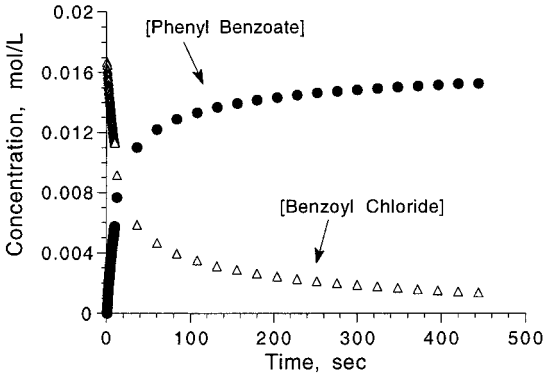


Figure 1. Representative data for the loss of benzoyl chloride, BC (●), and formation of phenyl benzoate, PB (∗), as a function of time using triethylamine (dichloromethane, 0 °C); $[BC]_0 = [phenol]_0 = [Et_3N]_0 = 0.0167$ M.

Results

The model reaction between benzoyl chloride and an alcohol to form a benzoate ester can be monitored by stopped-flow FT-IR spectroscopy. This technique was used previously to study the mechanism of carbonate macrocyclization.[15] Both the acid chloride and ester could be quantitatively monitored via their carbonyl absorptions in the IR spectrum. Benzoyl chloride displays two carbonyl bands, at 1775 and 1734 cm^{-1}; the splitting is a consequence of a Fermi interaction.[16] The carbonyl absorption of phenyl benzoate (1734 cm^{-1}) is coincident with one band of benzoyl chloride while butyl benzoate displays a carbonyl absorption at 1712 cm^{-1}. Molar absorptivities were determined and used to calculate concentrations from the spectra. The formation of phenyl benzoate was monitored by changes in the 1734 cm^{-1} peak after correction for the amount of benzoyl chloride (estimated from the area of the peak at 1775 cm^{-1}). Ester formation was relatively fast (several seconds to 1 h) with few side reactions. If anhydrous conditions were not maintained, anhydride formation was observed due to the rapid hydrolysis of the acid chloride to the carboxylic acid.

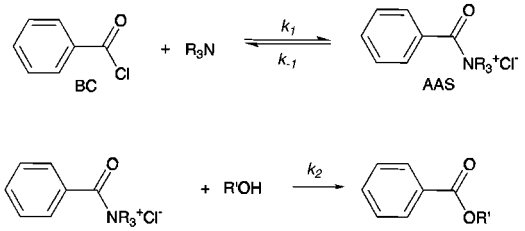
In determining the rate of reaction, both the decrease of benzoyl chloride ($-d[BC]/dt$) and the increase in either phenyl benzoate or butyl benzoate ($d[PB]/dt$, $d[BB]/dt$) with time were measured. The decrease in benzoyl chloride concentration was determined using the eq 1.

$$-\frac{d[BC]}{dt} = \frac{[BC]_0 - [BC]_t}{t} \qquad (1)$$

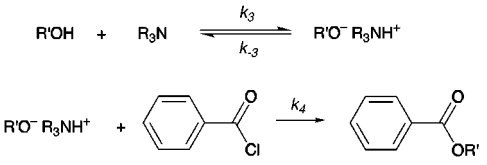
The rates of formation of the phenyl benzoate and butyl benzoate were similarly calculated. In experiments where no intermediate was observed in the IR, the rates of starting material loss and product formation are expected to be similar. The rate of the reaction was calculated from the initial slope of the concentration

(7) Kevill, D. N.; Foss, F. D. *J. Am. Chem. Soc.* **1969**, *91*, 5054.
(8) Bayliss, M. A. J.; Homer, R. B.; Shepard, M. J. *J. Chem. Soc., Chem. Commun.* **1990**, 305.
(9) Kilpatrick, M. *J. Am. Chem. Soc.* **1928**, *50*, 2981.
(10) Jencks, W. P.; Cariuolo, J. *J. Am. Chem. Soc.* **1961**, *83*, 1743.
(11) Kirsch, J. F.; Jencks, W. P. J. *J. Am. Chem. Soc.* **1964**, *86*, 837.
(12) Fersht, A. R.; Jencks, W. P. J. *J. Am. Chem. Soc.* **1970**, *92*, 5432.
(13) Johnson, S. L. In *Advances in Physical Organic Chemistry*; Gold, V., Ed.; Academic Press: London, 1967; Vol. 5, pp 271−317.
(14) Aquino, E. C.; Brittain, W. J.; Brunelle, D. J. *Macromolecules* **1992**, *25*, 3827.
(15) Brittain, W. J.; Aquino, E. C.; Dicker, I. B.; Brunelle, D. J. *Makromol. Chem.* **1993**, *194*, 1249.
(16) Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectrometric Identification of Organic Compounds*; John Wiley & Sons: New York, 1991; p 120.

Scheme 2



Scheme 3



versus time data. In this region, the slope was nearly linear. A typical concentration−time plot is shown in Figure 1.

Kinetic Model. We discounted ketene formation (because benzoyl chloride has no α-hydrogens) and acylium ions (because dichloromethane is a relatively nonpolar medium) as viable reactions.[17] Our mechanistic study focused on distinguishing between nucleophilic versus base catalysis. Scheme 2 depicts the nucleophilic mechanism for benzoate ester formation where the first step produces an AAS. The AAS reacts with an alcohol in the second step to form ester. Both steps 1 and 2 are assumed to proceed via a tetrahedral intermediate in accordance with the normal addition−elimination sequence of carbonyl addition reactions. Therefore, Scheme 2 depicts a simplified mechanism. If the first step is rate determining, then k_{-1} is much smaller than k_2[R′OH] and is assumed to be negligible, leading to eq 2.

$$-\frac{\mathrm{d[BC]}}{\mathrm{d}t} = k_1[\mathrm{BC}][\mathrm{NR_3}] \qquad (2)$$

If the second step is rate determining, the rate expression is third-order overall, being first order in each of the reactants as shown in eq 3.

$$-\frac{\mathrm{d[BC]}}{\mathrm{d}t} = \frac{k_1 k_2}{k_{-1}}[\mathrm{BC}][\mathrm{NR_3}][\mathrm{R'OH}] \qquad (3)$$

A simplified mechanism for specific-base catalysis is shown in Scheme 3. Specific-base catalysis requires that the amine remove a proton from the alcohol to form an alkoxide which can then attack benzoyl chloride. If the acid−base reaction in step 1 is rate-determining, the rate expression is second-order, eq 4.

$$-\frac{\mathrm{d[BC]}}{\mathrm{d}t} = k_3[\mathrm{R'OH}][\mathrm{NR_3}] \qquad (4)$$

If the second step is rate-determining, the reaction is third-order overall as shown in eq 5.

$$-\frac{\mathrm{d[BC]}}{\mathrm{d}t} = \frac{k_3 k_4}{k_{-3}}[\mathrm{BC}][\mathrm{NR_3}][\mathrm{R'OH}] \qquad (5)$$

General-base catalysis is similar to specific-base catalysis except the discrete formation of phenoxide ion is not required. Instead, the alcohol coordinates with the base to give a partial negative charge on oxygen; this alcohol−amine complex would then react with benzoyl chloride to form product. General-base catalysis would be a third-order reaction. Isotope effects have been useful in the diagnosis of general-base catalysis.[18] A comparison of isotope effects in substitution reactions at carbonyl carbons shows values greater than 2 for general-base catalysis and values near 1 (no isotope effect) for reactions following nucleophilic catalysis. An isotope effect would also be possible if the first step in specific-base catalysis is rate determining.

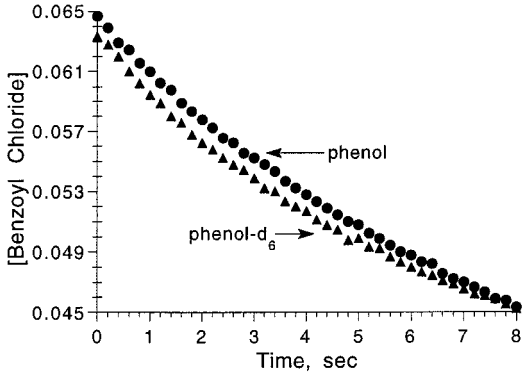


Figure 2. Isotope effect for the reaction of benzoyl chloride (BC) with phenol versus phenol-d_6 in the presence of triethylamine in dichloromethane at 0 °C; $[\mathrm{BC}]_0 = [\mathrm{phenol}]_0 = [\mathrm{Et_3N}]_0 = 0.067$ M.

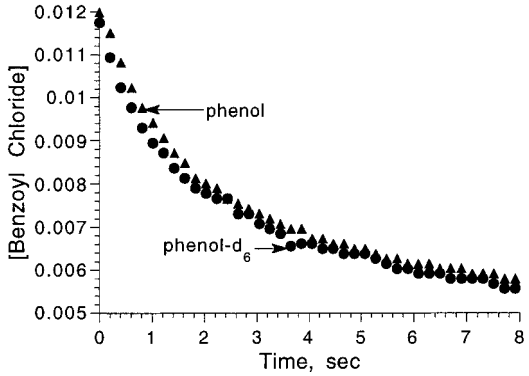


Figure 3. Isotope effect for the reaction of benzoyl chloride (BC) with phenol versus phenol-d_6 in the presence of DABCO in dichloromethane at 0 °C; $[\mathrm{BC}]_0 = [\mathrm{phenol}]_0 = [\mathrm{DABCO}]_0 = 0.0167$ M.

Phenyl Benzoate Formation. Isotope Effect. Experiments were run to determine if a primary isotope effect exists in the reaction of phenol with benzoyl chloride when catalyzed by either triethylamine or DABCO. A decrease in reaction rate with phenol-d_6 relative to phenol would indicate O−H (O−D) bond cleavage in the rate-determining step, as predicted for base catalysis. Results are shown in Figures 2 and 3. In both cases, reaction rates for phenol and phenol-d_6 were nearly identical, indicating a small or negligible isotope effect. The apparent lack of an isotope effect does not rule out any of the mechanisms.

Rate Order. The rate order of each species in the triethylamine-catalyzed reaction of benzoyl chloride with

(17) Bentley, T. W.; Carter, G. E.; Harris, H. C. *J. Chem. Soc., Perkin Trans. 2* **1985**, 983.

(18) Johnson, S. L. In *Advances in Physical Organic Chemistry*; Gold, V., Ed.; Academic Press: London, 1967; Vol. 5, p 281.

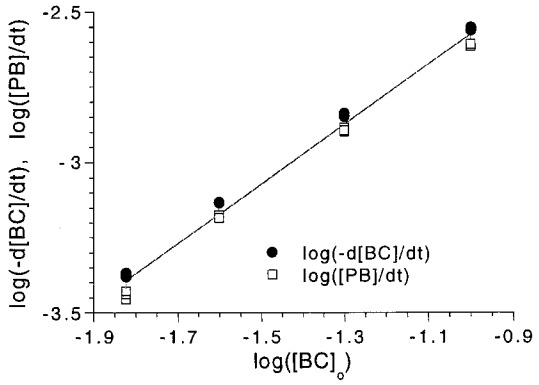


Figure 4. Rate-order plot for benzoyl chloride (BC) reaction with phenol in the presence of triethylamine (dichloromethane, 0 °C).

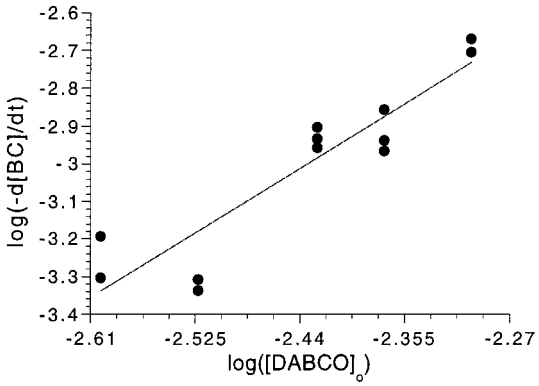


Figure 5. Rate-order plot for benzoyl chloride (BC) reaction with phenol in the presence of DABCO (dichloromethane, 0 °C).

Table 1. Rate Orders for Phenyl Benzoate Formation[a,b]

component	−d[BC]/dt	−d[PB]/dt
Et_3N	1.0	0.8
benzoyl chloride	1.0	1.0
phenol	1.3	1.2

[a] Triethylamine-catalyzed reaction of benzoyl chloride and phenol; −d[BC]/dt = rate of benzoyl chloride loss, [PB]/dt = rate of phenyl benzoate formation. [b] Experimental error in rate order values is ±0.1.

phenol was measured to help distinguish between specific-base catalysis and nucleophilic catalysis. For rate order data to distinguish between these two mechanisms, the first step of either reaction would need to be rate-determining. Otherwise, the reaction will be third-order overall for both mechanisms.

To determine reaction orders, reactions were run under pseudo-first-order conditions (see Experimental Section) where the starting concentration of the component of interest was 5-fold lower relative to other reactants. The log plot of the initial rate against the log of the initial concentration gives a line whose slope equals the reaction order.[19] Figure 4 shows the rate-order plot for benzoyl chloride.

The results for three reactants are summarized in Table 1. The reaction was found to be third-order overall and first-order in each reactant. This result is consistent with either base catalysis or nucleophilic catalysis. Therefore, under our conditions, the mechanisms are indistinguishable on the basis of rate-order analysis.

Triethylamine was chosen as the catalyst in this study because its reaction times were slow enough that small variations in reaction rates could be monitored accurately. Concerned that the rate-order results might vary for different amine catalysts, we also studied the rate order of DABCO. Figure 5 shows the rate-order plot for DABCO. We observed a second-order dependence (2.0 when determined by benzoyl chloride loss and 1.7 when determined by phenyl benzoate formation). A second-order dependence for DABCO may indicate a dual role for DABCO, where it simultaneously operates by both mechanisms.

Reaction Intermediates. Each of the proposed mechanisms is associated with a key intermediate; the AAS in the nucleophilic process and an ammonium phenoxide in the specific-base-catalyzed process. This section describes experiments aimed at detection of these putative intermediates. UV−vis spectroscopy can be used to distinguish between phenol and phenoxide. Tetraethylammonium phenoxide displayed an absorption maximum at 250 nm in dichloromethane and under the same conditions, phenol displayed a small peak at 228 nm and a stronger absorption at 275 nm. However, when a solution of phenol and triethylamine was prepared in dichloromethane and the UV−vis spectrum recorded, no evidence of phenoxide was observed. Therefore, under the experimental conditions used for ester formation, we did not observe a discrete phenoxide ion (detection level of phenoxide ≈5%). This result argues against a specific-base-catalyzed mechanism.

In previous work, we observed AAS formation during the reaction of phenylchloroformate with tertiary amines.[14] The AAS is characterized by its unique carbonyl absorption in the IR. In the present study, reaction of benzoyl chloride with different amines at 0 °C in the absence of phenol gave mixed results. Only 4-(dimethylamino)-pyridine (DMAP) led to AAS formation, as evidenced by a new absorption at 1739 cm^{-1}. Triethylamine, quinuclidine, and DABCO did not form AAS in the IR experiments. The undetectable level of AAS may be the result of the electrostrictive effect[20] in which a large charge dipole destabilizes species such as the AAS in aprotic, nonpolar solvents.

Because of the −10 °C lower temperature limit in the IR experiments, we chose to extend the temperature range for observations by using NMR to further investigate AAS formation.[21,22] Equimolar amounts of amine and benzoyl chloride in dichloromethane-d_2 were studied over the temperature range of −60 to −90 °C. The amines studied included triethylamine, DABCO, and DMAP. DMAP reacted completely to form AAS with the aromatic nitrogen of DMAP attacking the benzoyl chloride. The NMR shifts were consistent with the results of King and Bryant[22] for the AAS of benzoyl chloride and DMAP that was prepared using nonnucleophilic counterions. DABCO was partially converted to AAS over the temperature range studied; the most diagnostic resonance was that for the ortho hydrogens of benzoyl chloride which shifted from a doublet at 8.21 ppm to a broad peak at 8.31 ppm at −90 °C. On the basis of the

(19) Schmid, R.; Sapunov, V. N. *Non-Formal Kinetics*; Verlag Chemie: Weinheim, 1982.

(20) King, J. A., Jr. *J. Am. Chem. Soc.* **1988**, *110*, 5764.
(21) Brunelle, D. J.; Boden, E. P. *Makromol. Chem., Macromol. Symp.* **1992**, *54/55*, 397.
(22) King, J. A., Jr.; Bryant, G. L. *J. Org. Chem.* **1992**, *57*, 5136.

Table 2. Acyl Ammonium Salt Formation from Benzoyl Chloride[a]

	% acyl ammonium salt		
temp (°C)	DMAP	DABCO	Et_3N
0[b]	100	0	0
−60[c]	100	62	0
−90[c]	100	76	24

[a] Experimental error = 3%. [b] IR result. [c] NMR result.

Table 3. Phenyl Benzoate Formation: Rate vs Amine[a]

amine[b]	pK_a	−d[BC]/dt,[c] M/s	d[PB]/dt,[c] M/s
DMAP	9.45[d]	>0.3	>0.3
quinuclidine	10.95[e]	>0.1	>0.05
DABCO	8.77[f]	0.00373	0.00277
Et_2MeN	10.43[g]	0.00215	0.00223
N-MeP	10.19[g]	0.00128	0.00135
Et_3N	10.75[e]	0.00028	0.00025
Pr_3N	10.66[g]	0.00011	0.0001
pyridine	5.21[e]	2.1×10^{-6}	1.7×10^{-6}

[a] $[BC]_0 = [phenol]_0 = [amine]_0 = 0.0167$ M, dichloromethane, 0 °C; all rate values are the average of at least two separate runs; experimental error never exceeded 5% of reported value. [b] *N*-MeP = *N*-methylpiperidine. [c] −d[BC]/dt = rate of benzoyl chloride loss, d[PB]/dt = rate of phenyl benzoate formation. [d] Reference 23. [e] Reference 24. [f] Reference 25. [g] Reference 26.

integrated areas of these two peaks, we observed 62% AAS at −60 °C and 76% at −90 °C. Triethylamine also formed AAS but to a lesser extent. The amine α-hydrogens shifted from 2.47 to 3.10 ppm at −90 °C, where 24% conversion to AAS was observed. The most important result from these IR and NMR studies is the observation of AAS under conditions used for ester formation. This indicates the possibility of a nucleophilic catalysis mechanism.

To help interpret our AAS studies, we estimated the relative AAS stabilities using SYBYL 6.0. The structure of the AAS was drawn for a series of amines, and the software determined the most stable conformation and produced a minimized energy value for that conformation. Structures with lower minimized energy values should form the AAS more readily. We obtained the following ordering of calculated AAS stabilities, ranked from most to least stable (SYBYL values given in parentheses, kcal/mol): DMAP (15) > quinuclidine (25), DABCO (25) > *N*-methylpiperidine (27) > Et_2MeN (33) > Et_3N (36) > Pr_3N (50). The calculated AAS stabilities correlate with experimental data in Table 2.

Effect of Amine Structure on Rate of Phenyl Benzoate Formation. Model reactions between benzoyl chloride and phenol in the presence of various tertiary amines were carried out to determine the effect of amine basicity and structure on the reaction rate. The results are given in Table 3. Table 3 is ordered with the most effective catalysts at the top and the poorest catalysts at the bottom. The rates listed are taken as the initial slope of the concentration−time curves. The two rate determination methods (−d[BC]/dt versus d[PB]/dt) agree, which is consistent with the absence of intermediates in the IR spectrum during the experiment. The amines chosen for this study represent a range of basicity and nucleophilicity and include amines which gave high yields of cyclic esters (quinuclidine and DABCO), moderate yields (*N*-methylpiperidine), and low yields (triethylamine). The reaction of DMAP with benzoyl chloride was complete within the first IR scan, so only a lower limit for the rate can be calculated. The reaction with quinuclidine was fast enough that the early part of the reaction could not be monitored, so the ester formation rate is greater than 0.1 M/s.

It is recognized that using aqueous pK_a values for reactions in aprotic, nonpolar media can be misleading. However, we perform this exercise to search for trends that might shed light on the mechanism. Comparing rates with pK_a values does not reveal a strong correlation with amine basicity. Quinuclidine and triethylamine were the two most basic amines, and the their rates differed by at least 3 orders of magnitude. These facts are inconsistent with a base-catalyzed mechanism which should show a rate increase with increased basicity. This conclusion assumes that the relative amine basicity values measured in water are a reasonable measure of basicity trends in dichloromethane.

There is a correlation between rates and AAS stability as predicted by SYBYL. Except for diethylmethylamine, the rates followed the same ranking as the AAS stabilities. This correlation supports a nucleophilic mechanism which requires AAS formation in the first step.

Summary of Phenyl Benzoate Study. The results of our investigation into the reaction between benzoyl chloride and phenol may be consistent with a nucleophilic mechanism for amine catalysis. The lack of phenoxide in the UV−vis work rules out specific-base catalysis. The AAS intermediate in the nucleophilic mechanism was observed in low-temperature NMR experiments. The rate of ester formation as a function of amine structure showed a correlation between AAS stability (as deduced from molecular modeling) and rate. Of course, the NMR observation of AAS may be unrelated to the reaction pathway for ester formation. Also, we recognize that the molecular modeling was performed at an unsophisticated level. What cannot be disputed is the rate data we report which shows a subtle sensitivity to modest changes in amine structure.

The ramification of a nucleophilic-catalysis mechanism for ester macrocyclization is obvious. There is a strong correlation between reaction rate and yield of cyclics formed, with faster reactions leading to higher yields of cyclics (DMAP was the only exception). As might be expected, faster reactions would minimize the concentration of end groups and thus favor cyclization. Slow ester-forming reactions would lead to a build-up of reactants during the addition process used in the cyclization methodology; the occurrence of intermolecular reactions would increase relative to the intramolecular reactions, and thus decrease the yields of cyclics.

Butyl Benzoate Formation. A better model reaction for PET and PBT cyclic ester formation is the reaction between benzoyl chloride and butanol. This reaction was not studied initially due to technical difficulties which produced side reactions (hydrolysis). The mechanistic study of butyl benzoate formation produced substantially different results. We view butyl benzoate formation to be analogous to phenyl benzoate formation in terms of proposed mechanisms (nucleophilic versus base catalyzed) and mechanistic strategy. The primary difference between these two reactions is the reactivity of butanol versus phenol; phenol is more acidic than butanol.

Effect of Amine Structure on Rate of Butyl Benzoate Formation. Four amines were studied to see if the rate trends for butanol were the same as for phenol. Table 4 shows that the four amines studied fall in the same order with respect to their effect on benzoyl chloride

Table 4. Butyl Benzoate Formation: Rate vs Amine[a]

amine[b]	pK_a	−d[BC]/dt,[c] M/s	d[BB]/dt,[c] M/s
DMAP	9.45[d]	>0.3	$>1.5 \times 10^{-6}$
quinuclidine	10.95[e]	≈0.1	≈0.1
N-MeP	10.19[f]	6.3×10^{-5}	1.5×10^{-5}
Et_3N	10.75[e]	1.3×10^{-5}	3.7×10^{-6}

[a] $[BC]_0 = [butanol]_0 = [amine]_0 = 0.03$ M, dichloromethane, 0 °C; all rate values are the average of at least two separate runs, experimental error never exceeded 5% of reported value. [b] *N*-MeP = *N*-methylpiperidine. [c] −d[BC]/dt = rate of benzoyl chloride loss, d[BB]/dt = rate of butyl benzoate formation. [d] Reference 23. [e] Reference 24. [f] Reference 26.

loss, −d[BC]/dt. The experiments in Table 4 were not carried out at the same concentrations as phenol, so the rates are not directly comparable. In general, butyl benzoate formation was slower than phenyl benzoate formation. In quinuclidine-catalyzed butyl benzoate formation, the reaction was sufficiently fast that we can only estimate the rate of reaction.

The first conclusion from the data in Table 4 is the disparity between −d[BC]/dt and d[BB]/dt for DMAP. The loss of benzoyl chloride was the most rapid among the amines studied; however, the formation of butyl benzoate occurred at a rate that was 5 orders of magnitude slower than benzoyl chloride loss! The large disparity between acid chloride loss and ester formation can be explained by a nucleophilic-catalysis mechanism in which the rate-determining process is the second step ($k_{-1} \gg k_2$, Scheme 2). Another possibility is that the AAS formation is a competing process with a base-catalyzed process. If we ignore quinuclidine since we could not precisely measure its rates, there was also a difference in the rate of benzoyl chloride loss and ester formation for the other amines. For both *N*-methylpiperidine and triethylamine, ester formation was slower. These results contrast those obtained with phenyl benzoate formation where the rates of benzoyl chloride loss and ester formation were comparable. However, we did not observe AAS formation in the IR spectrum during the kinetic runs for these two amines.

Given the unusual nature of the kinetics in the butyl benzoate study, it is difficult to draw definitive conclusions concerning correlations with amine basicity or nucleophilicity (as deduced by calculated AAS stability).

Rate Order. We attempted to study the rate order of quinuclidine in butyl benzoate formation and obtained surprising results. The reaction rate *decreased* as the concentrations of butanol and benzoyl chloride were *increased*. Figure 6 shows data for two experiments in which the quinuclidine concentration was maintained at 0.0167 M. In one experiment, stoichiometric concentrations (0.0165 M) of benzoyl chloride and butanol were used; in the other run, a 5-fold higher concentration (0.0825 M) of benzoyl chloride and butanol was used. If the concentration of quinuclidine was kept constant and the reaction orders a, b, and c were nonnegative in accord with eq 6, then the reaction rate would be expected to increase as the concentrations of benzoyl chloride and butanol were increased.

$$-\frac{d[BC]}{dt} = k_{obs}[BC]^a[quinuclidine]^b[butanol]^c \quad (6)$$

One possible explanation is a mechanism involving both AAS formation and a base-catalyzed mechanism. Facile ester formation will only occur once the amine concentration is high enough to assist the base-catalyzed reaction of butanol. If the amine concentration is substantially lower than that of benzoyl chloride, then the amine is consumed in the form of the AAS. Even though the benzoyl chloride and butanol concentrations are higher, the relatively lower amount of amine is insufficient to promote base-catalyzed reaction.

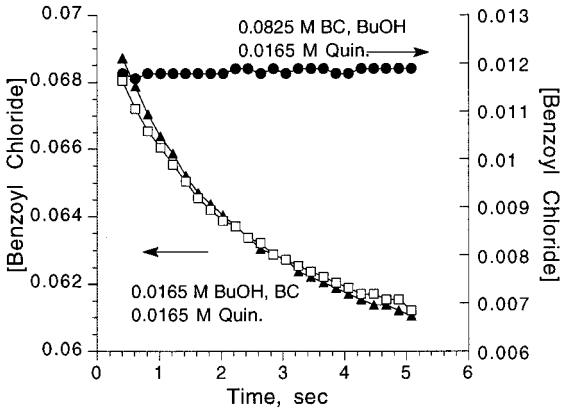


Figure 6. Reaction order experiment for quinuclidine-catalyzed reaction of benzoyl chloride with butanol in dichloromethane at 0 °C (concentrations given in the figure). The left *y*-axis is the benzoyl chloride concentration for the equimolar reaction and right *y*-axis is for the reaction with higher benzoyl chloride and butanol concentrations.

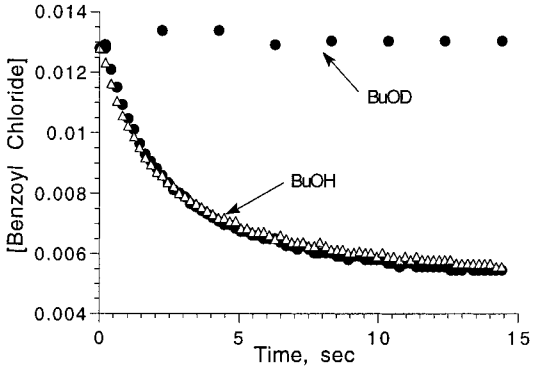


Figure 7. Isotope effect for the reaction of benzoyl chloride (BC) with butanol in the presence of quinuclidine in dichloromethane at 0 °C; $[BC]_0 = [butanol]_0 = [quinuclidine]_0 = 0.0167$ M.

Isotope Effect. The isotope effects during butyl benzoate formation are shown in Figure 7 for the quinuclidine-catalyzed reaction of benzoyl chloride with butanol. The reactions using butanol (BuOH) displayed a typical exponential decrease in benzoyl chloride concentration with time, but the results with butanol-*O*-*d* (BuOD) were quite unusual. Only the first 20 s of the reaction are shown in Figure 7, but the BuOD was essentially unreactive over a period of about 2−3 h. A primary isotope effect for a simple linear abstraction should show a difference in rate between BuOH and BuOD of a factor of 2−7, but the observed effect was much larger; we estimate $k_H/k_D > 100$. This large isotope effect was reproducible and provides evidence supporting a general-base-catalyzed mechanism.

Discussion

We interpreted the experimental evidence for the amine-catalyzed formation of phenyl benzoate from ben-

zoyl chloride and phenol in terms of a nucleophilic mechanism. The analogous mechanistic study of butyl benzoate produced interesting results. First and foremost, a large isotope effect is observed which is consistent with a general-base-catalyzed process. But, at this time we cannot fully reconcile the observed disparity in $-d[BC]/dt$ and $d[BB]/dt$ nor the unusual rate-concentration dependence in the butyl benzoate rate studies. The conclusion that the amine operates via a general-base-catalysis mechanism in the butanol reaction makes it difficult to accept the nucleophilic catalysis mechanism for phenol. Relative to butanol, phenol would be more likely to participate in a base-catalyzed process because it is more acidic. Consequently, we cannot completely resolve the mechanistic questions that motivated this study.

What remains is heretofore unavailable rate information for the amine-catalyzed reactions of benzoyl chloride with alcohols. Furthermore, the sensitivity of the rate of ester formation on small structural changes in the tertiary amine is consistent with observed trends in the yields of macrocyclic esters produced via similar chemistry. The amine structure exerts a powerful influence over ester formation rates and, combined with control over end-group concentration (by addition rates of reactants to the reaction mixture), can be used to control the yields of macrocyclic esters.

Experimental Section

Reagents. All reagents were purchased. Dichloromethane was distilled from P_2O_5 under nitrogen. Benzoyl chloride was refluxed with thionyl chloride overnight; the thionyl chloride was removed in vacuo, and the benzoyl chloride was fractionally distilled under vacuum. Triethylamine was fractionally distilled twice from CaH_2 under N_2. DABCO was recrystallized from diethyl ether. Quinuclidine was purified by sublimation. 4-(Dimethylamino)pyridine was purified by recrystallization from toluene. Diethylmethylamine, tripropylamine, pyridine, and *N*-methylpiperidine were refluxed over KOH for 16 h and then fractionally distilled under N_2. Phenol, phenol-d_6, and butanol-*O*-*d* were used as received. Butanol was fractionally distilled from Na. Dichloromethane-d_2 was dried over CaH_2 and distilled using a bulb-to-bulb technique. Tetraethylammonium phenoxide was prepared by the reaction of phenol with tetraethylammonium hydroxide; the product was recrystallized in acetonitrile. All materials used for kinetics experiments were stored and handled in an argon-filled glovebox.

NMR Studies. Variable-temperature NMR experiments were carried out using a 400 MHz spectrometer. Amine solutions (0.07 M) in 0.7 mL of dichloromethane-d_2 were prepared in the glovebox and transferred to NMR tubes with screw-caps and rubber septa. The sample was cooled in the NMR magnet (−60 to −90 °C) and the amine spectrum recorded. Benzoyl chloride (0.07 mol, 8.13 μL) was added and the spectrum recorded after reequilibration of temperature.

Stopped-Flow Kinetics. Kinetic experiments were performed using a stopped-flow FT-IR apparatus. Details of the technique have been published before.[27] An FTIR spectrometer was used which is capable of taking a full spectrum in 50 ms at 16 cm^{-1} resolution or 200 ms at 4 cm^{-1} resolution. Reagent solutions were prepared in the drybox. The stopped-flow syringes were assembled and filled in the drybox. Under positive argon flow, the syringe setup connected to the flow-through IR cell equipped with a temperature-controlled jacket. The IR cell contained CaF_2 optical windows separated by 0.025 cm PTFE spacers. The output of the IR cell was connected to a syringe. The stopped-flow syringes were immersed in an ice bath, and the IR cell was cooled by a refrigerated circulating bath set at 0 °C with 2-propanol as the cooling fluid. The temperature of the experimental setup was allowed to equilibrate for 30 min prior to beginning the experiment.

All rates were the average of at least two separate runs. Run-to-run variation in the rates never exceeded 5%.

For two-component reactions, a two-syringe setup was used with a component in each syringe. The three-component reactions (benzoyl chloride, alcohol, and amine) were carried out in one of two ways. In early experiments, reactions were done using three syringes and two mixers. Each syringe contained a separate component solution. The benzoyl chloride solution syringe and the alcohol solution syringe were connected to the mixer, and the output of that mixer was fed into the second mixer, as was the output of the amine solution syringe. In later reactions, a two-syringe setup was used with a premixed solution of benzoyl chloride and alcohol in one syringe. Results were the same for the two-syringe vs three-syringe experiments. The advantage of the two-syringe setup is the reduction in back pressure.

Molar absorptivities were determined by measuring the absorbances of solutions of known concentration. Absorbances were kept below 1 so Beer's law would be obeyed.

Phenyl Benzoate Kinetics. The three-syringe technique was used for tripropylamine, DABCO, DMAP, and triethylamine. The two-syringe technique was used for diethylmethylamine, *N*-methylpiperidine, quinuclidine, and pyridine. All experiments were run to produce an initial concentration of 0.0167 M for each reactant.

To determine the reaction order of benzoyl chloride, phenol and triethylamine concentrations were 0.167 M each and the concentration of benzoyl chloride solution was varied from 0.005 to 0.033 M. For determination of the reaction order of triethylamine, benzoyl chloride and phenol concentrations were 0.1 M and triethylamine concentration varied from 0.0067 to 0.02 M. To determine the reaction order of phenol, the concentrations of benzoyl chloride and triethylamine were 0.067 M and the phenol concentrations varied from 0.003 to 0.013 M.

For DABCO reaction order experiments, the concentrations of benzoyl chloride and phenol were 0.025 M and the DABCO concentration varied from 0.0025 to 0.005 M.

For isotope effect experiments in phenyl benzoate formation, three-syringe experiments were used. When triethylamine was the catalyst, the concentration of the reactants was 0.067 M each. This run was then compared with a similar one in which the phenol was replaced with phenol-d_6. When DABCO was the catalyst, the concentration of reactions was 0.0167 M.

Butyl Benzoate Kinetics. Runs were carried out under equimolar conditions using a two-syringe setup; the concentration of the reactants was 0.03 M. The isotope effect experiments were run with 0.0167 M concentrations.

Modeling. Predictions of relative acylammonium salt stability were carried out using SYBYL 6.0 on a Silicon Graphics workstation. Structures were drawn in several different conformations and each was energy-minimized to verify that values obtained did not represent local energy minima. Predictions of most favorable geometry were made using a force-field method. The energy minimization routine, MAXMIN2, used a conjugate gradient minimization method.

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(23) Aue, D. H.; Webb, H. M.; Davidson, W. R.; Toure, P.; Hopkins, H. P., Jr.; Moulik, S. P.; Jahagirdar, D. V. *J. Am. Chem. Soc.* **1991**, *113*, 1770.

(24) Arnett, E. M.; Mitchell, E. J.; Murty, T. S. S. R. *J. Am. Chem. Soc.* **1974**, *96*, 3875.

(25) Hine, J.; Kaufmann, J. C.; Cholod, M. S. *J. Am. Chem. Soc.* **1972**, *94*, 4590.

(26) Dean, J. A. *Handbook of Organic Chemistry*; McGraw-Hill: New York, 1987. Hine, J.; Chen, Y.-J. *J. Org. Chem.* **1987**, *52*, 2091.

(27) Brittain, W. J. *J. Am. Chem. Soc.* **1988**, *110*, 7440.