loses a proton to give the uncharged amide in a reaction that makes the overall reaction strongly exergonic.

## References and Notes


(1) Supported by grants from the National Science Foundation (GB-31740) and the National Institute of General Medical Sciences of the National Institutes of Health (GM20888). M.J.G. was a Predoctoral Fellow of the National Institutes of Health (GM-212).
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# Ester Aminolysis. Partitioning of the Tetrahedral Addition Intermediate, $T^{\pm}$, and the Relative Leaving Ability of Nitrogen and Oxygen[1]


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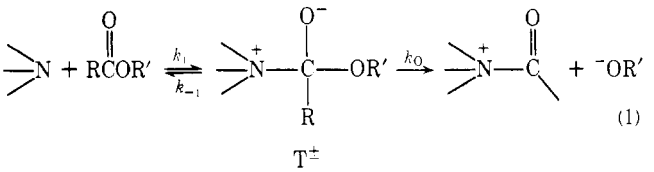
**Abstract.** The tetrahedral addition intermediate $T^{\pm}$ that is presumably formed in the aminolysis of unsymmetrical carbonate esters was generated from two different reactions: (a) reaction of an aryl chloroformate with a tertiary amine followed by addition of phenoxide ion and (b) reaction of a symmetrical bis(aryl) carbonate with amine followed by trapping with phenoxide ion. The partitioning between amine and aryl oxide expulsion is the same when $T^{\pm}$ is generated by these two paths. It also agrees with the partitioning estimated from kinetic data, confirming that the nonlinear Brønsted-type plot for aminolysis represents a change in rate-determining step from amine attack to aryl oxide expulsion. Equal partitioning with the 3,4-dinitrophenoxide leaving group occurs with amines that are 4.4 p$K$ units more basic. The results provide evidence that $T^{\pm}$ is a discrete intermediate with a lifetime that is adequate for equilibration of solvation and rotation around the central carbon atom; there is no evidence that stereoelectronic control affects the partitioning ratio. The $\Delta pK$ for equal partitioning increases with increasing p$K$ of the aryl oxide and aryl oxide expulsion is favored by increasing p$K$ of the "acyl" substituent that is not expelled. These results suggest that electron donation by resonance from oxygen contributes significantly to leaving group expulsion. Amine expulsion is favored by addition of aprotic solvent. *N*-Methylimidazole and 4-*N*,*N*-dimethylaminopyridine are less good leaving groups than aliphatic amines of the same p$K$. The results show that relative leaving group ability is controlled by the electron-donating ability of the remaining group, polar substituents on the "acyl" group, solvent, and probably electrostatic effects, as well as by the p$K$ of the leaving group.


The first problem in the analysis of the mechanism of acyl transfer reactions, such as ester aminolysis (eq 1), is to determine whether the rate-determining step is the attack of the nucleophilic reagent on the acyl compound ($k_1$) or the expulsion of the leaving group from a tetrahedral intermediate, $T^{\pm}$, that is formed in a rapid, equilibrium addition reaction ($k_O$,



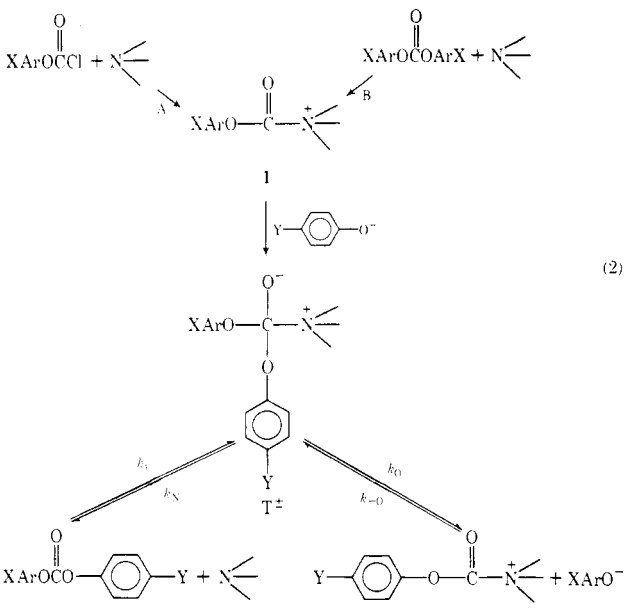
(1)

when $k_{-1} > k_O$); the possibility also exists that the reaction proceeds through a concerted path with no discrete addition intermediate. The rate-limiting step is determined by the relative rates of expulsion of the nucleophile and leaving group from a tetrahedral addition intermediate, $k_{-1}/k_O$: if one group leaves faster than the other, the step involving the poorer leaving group is rate determining. The relative leaving ability of the two groups is not determined only by their p$K$ (as is sometimes assumed) because different leaving atoms have different bond strengths to carbon, steric effects, and rate constants for bond cleavage. Furthermore, the relative rate of leaving group departure is determined by the *push* provided by the atoms that remain behind as well as the *pull* provided by the group that leaves.

The assignment of the rate-determining step may be made from structure–reactivity correlations of kinetic data,[2] but is more reliably made by generating the addition intermediate through some other reaction and determining directly which leaving group is expelled most rapidly, by analysis of the reaction products. However, this method has led to incorrect conclusions regarding the rate-determining step in ester aminolysis, based on an analysis of the reaction products from the breakdown of the tetrahedral addition intermediates that are formed in the hydrolysis of phenyl imidates, because these intermediates are not at equilibrium with respect to interconversion of different ionic forms. Proton transfer steps involving these intermediates are significant in determining the partitioning to products and the kinetics of these reactions, and, when these steps are taken into account, the kinetic and partitioning data are consistent with the conclusion that amines are expelled much faster than oxy anions from the addition intermediate $T^{\pm}$ unless the amine is much more basic than the oxy anion.[3-5]

The experiments reported here were carried out in order to determine the relative leaving ability of amines and aryl oxide anions in ester aminolysis directly in a system in which proton transfer is not significant, by generating the addition intermediates that are presumably formed in the reactions of tertiary amines with carbonate esters. Schowen and coworkers have used mixed carbonate esters to show that the leaving ability of aryl oxides is greater than that of methoxide ion from the addition intermediate that is presumably formed in the basic methanolysis of aryl methyl carbonates and more recently it has been shown that the less basic oxygen atom is expelled in the reactions of asymmetrically monosubstituted cyclic carbonate esters with nucleophiles.[6]

In the work reported here the addition intermediate of carbonate ester aminolysis was generated and its partitioning to products was determined in three different ways: (1) from the nonlinear structure–reactivity behavior of the aminolysis kinetics that results from a change in rate-determining step from amine attack ($k_1$, eq 2) to oxy anion leaving ($k_O$) with changing p$K$ of the nucleophile and leaving group,[2] (2) by reaction of phenoxide ion with **1**, which was in turn generated by the reaction of an aryl chloroformate with a tertiary amine (path A, eq 2) and determination of the product ratio from the breakdown of the intermediate $T^{\pm}$, and (3) by generating **1** from the reaction of a symmetrical carbonate ester with an amine (path B, eq 2), followed by the trapping of **1** with phenoxide ion and kinetic determination of the relative amounts of products formed from the breakdown of the tetrahedral intermediate $T^{\pm}$. The results of the three methods are consistent with each other and with the conclusions reached



(2)

previously for the aminolysis of acetate esters.[4,5] The results demonstrate that factors other than the intrinsic leaving ability of the two leaving groups are important in determining the partitioning of addition intermediates and the rate-determining step in these and other reactions. A preliminary report of this work has been presented.[1]

## Experimental Section

**Materials. 2,4-Dinitrophenyl chloroformate** was prepared by a modification of a published procedure for 2,4,5-trichlorophenyl chloroformate.[7] An excess of phosgene (*caution*) was bubbled through concentrated sulfuric acid and into a solution of 5 g of 2,4-dinitrophenol in 250 mL of dry toluene (distilled from calcium hydride). After the mixture was cooled in an ice bath, 3 mL of redistilled *N,N*-dimethylaniline in 20 mL of toluene was added over 30 min with protection from moisture and the solution was stirred overnight at room temperature. Dry nitrogen was bubbled through the mixture to remove excess phosgene and 100 g of ice was shaken with the mixture and filtered off. The organic layer was washed three times with cold 10% sodium chloride, dried over calcium sulfate, and reduced on a rotary evaporator to a yellow oil that subsequently crystallized (mp 59–60 °C after recrystallization from ether). Anal. Calcd for $C_7H_3O_6N_2Cl$: C, 34.10; H, 1.23; N, 11.35. Found: C, 34.32; H, 1.24; N, 11.41.

The bis(aryl) carbonates were prepared either by a procedure analogous to that for the chloroformates with chloroformate used in place of phosgene, except with only 1 equiv each of chloroformate, substituted phenol, and *N,N*-dimethylaniline, and with a 5% HCl wash in the workup to remove any excess aniline; or from 1 equiv of phosgene (12.5% solution in benzene) and 2 equiv each of substituted phenol and *N,N*-dimethylaniline, with the same workup as with the other method. **Bis(2,4-dinitrophenyl) carbonate** had mp 130–131 °C. Anal. Calcd for $C_{13}H_6O_{11}N_4$: C, 39.61; H, 1.53; N, 14.24. Found: C, 39.65; H, 1.39; N, 14.20. **Bis(3,4-dinitrophenyl) carbonate** had mp 188–189 °C. Anal. Calcd for $C_{13}H_6O_{11}N_4$: C, 39.61; H, 1.53; N, 14.24. Found: C, 39.59; H, 1.47; N, 13.99.

**1-(4-Nitrophenoxycarbonyl)-3-methylimidazolium chloride** was prepared from 4-nitrophenyl chloroformate and 1-methylimidazole under strictly anhydrous conditions, but was not isolated. Addition of 10 μL of 1-methylimidazole to 25 mg of 4-nitrophenyl chloroformate in 1 mL of acetonitrile followed by cooling in an ice bath and then a calcium chloride–water–Dry Ice bath to −40 °C gave a white crystalline product which was sedimented by brief centrifugation after addition of 1 mL of acetonitrile and washed quickly with two additional portions of acetonitrile. The solid was partly dissolved in 1 mL of acetonitrile and the clear solution was separated and diluted with an additional 1 mL of acetonitrile to ensure that no particles remained suspended. This sample was distributed into several dry tubes and used shortly afterward. All operations were carried out under a stream of dry nitrogen in tubes that were flushed with dry nitrogen; transfers were effected with syringe needles through no-air stoppers. **1-(Phe-**

**Table I.** Partitioning of $T^{\pm}$ Formed from an Aryl Chloroformate, ArOCOCl, a Substituted Quinuclidine, and a Nucleophile, B[a]

| Ar | % $ArO^-$ leaving | | | |
|---|---|---|---|---|
| | Quinuclidine | 3-Quinuclidinol | 3-Chloroquinuclidine | 3-Quinuclidone |
| | | B = Phenoxide, p$K$ 9.86[b] | | |
| *p*-Nitrophenyl | 10 | <5 | <5 | |
| 3,4-Dinitrophenyl | 84, 85[c] | 68, 63[c] | 36, 29[c] | |
| 2,4-Dinitrophenyl | >95 | >95 | >85 | 65, 58[c] |
| | | B = *p*-Acetophenoxide, p$K$ 8.05[b] | | |
| *p*-Nitrophenyl | <5 | <5 | <5 | |
| 3,4-Dinitrophenyl | 70 | 49, 30[d] | 27, 13[d] | 10 |
| 2,4-Dinitrophenyl | >95 | >95 | 81, 62[d] | 56 |
| | | B = Pentafluorophenoxide, p$K$ 5.33[b] | | |
| 3,4-Dinitrophenyl | 37 | 22 | 4 | |
| | | B = $HOPO_3^{2-}$ | | |
| *p*-Nitrophenyl | <5 | <5 | <5 | |
| 3,4-Dinitrophenyl | 50 | 25 | 10 | |
| 2,4-Dinitrophenyl | >95 | >95 | >71 | |

[a] At 25 °C in 4% tetrahydrofuran, unless otherwise indicated. The reaction mixtures were buffered with 0.01 M borate, 20% base. The ionic strength was not maintained constant. [b] The p$K_a$ values of aryl oxide nucleophiles are from measured pH values of half-neutralized solutions in 1.0 M potassium chloride. [c] 36% acetonitrile, 4% tetrahydrofuran. [d] 72% acetonitrile, 4% tetrahydrofuran.

**noxycarbonyl)-3-methylimidazolium chloride, 1-(3,4-dinitrophenoxycarbonyl)-3-methylimidazolium chloride,** and **1-(4-nitrophenoxycarbonyl)-4-*N*,*N*-dimethylaminopyridinium chloride** were prepared similarly except that the 3,4-dinitrophenyl compound was prepared by mixing solutions of the chloroformate and amine in acetonitrile at −40 °C and the pyridinium compound was prepared by mixing solutions of the chloroformate and amine in ether. Other materials[2] were commercial products.

**Partitioning and Kinetics.** Reactions were initiated by injecting 0.1 mL of a solution of aryl chloroformate or bis(aryl) carbonate in dry tetrahydrofuran from a Hamilton CR700-200 spring-loaded syringe into the reaction mixture[8,9] to give a final volume of 2.5 mL. The reaction mixture was in a round 1-cm cuvette in a thermostated cuvette holder in a Gilford spectrophotometer. Mixing was complete in 0.1 s as determined by injecting solutions of *p*-nitrophenol in tetrahydrofuran into aqueous buffer solutions. The ranges of experimental conditions used are indicated in the figure legends except for the experiments with phosphate as the anionic nucleophile; total phosphate concentrations of 0.05 and 0.1 M were used with 0.01 M borate buffer, 20% base, and the ranges of amine concentrations used were the same as those for the experiments with *p*-acetophenoxide ion as the anionic nucleophile.

Absorbance changes were recorded on a chart recorder or storage oscilloscope and $A_\infty - A_t$ values were plotted logarithmically against time. Such plots were linear for >3 half-lives and, in the case of the experiments using phenoxide as the anionic nucleophile, gave the same pseudo-first-order rate constants as did the appropriate aryl phenyl carbonates under similar conditions. Extrapolation of the plots to zero time gave the extent of the bursts. The chloroformate solutions sometimes contained a small amount, usually <5%, of substituted phenol as indicated by a small burst of optical density in the absence of amine that did not decrease when the concentration of anionic nucleophile was increased. The observed bursts were corrected for this impurity.

Experiments with the *N*-methylimidazole and 4-*N*,*N*-dimethylaminopyridine compounds were carried out similarly using solutions in acetonitrile and phenoxide or methoxide ion as the nucleophile. The release of phenoxide or nitrophenoxide from cleavage of the mixed carbonate ester product was followed at 290 or 400 nm, respectively, and followed first-order kinetics for 5 half-times. The initial burst was measured from extrapolation of the first order plots to zero time and comparison of the change in absorbance from ester cleavage to the total absorbance at $t_\infty$, in the range of 0.2 to 1.0. Aliquots of the acyl compound were withdrawn from the stock solutions (at −40 °C) using a Hamilton syringe fitted with a disposable glass micropipet attached to the needle with a piece of polyethylene tubing. This was inserted through a large syringe needle while dry nitrogen was blown over the solution through another needle inserted into the no-air stopper. The syringe was rinsed once with the adduct solution before each run and 10 times with dry acetonitrile after each run. These precautions were necessary to avoid the formation of bis(aryl) carbonate, which could be identified by its characteristic kinetic behavior. It was shown in all cases that the stock solutions contained <2% phenol or substituted phenol. This analysis was made spectrophotometrically by comparing the ultraviolet spectrum of a sample diluted to 10 mL in dry acetonitrile with the spectrum of the same sample after hydrolysis by the addition of a small volume of aqueous sodium hydroxide followed by acidification with a small volume of hydrochloric acid. For experiments in which methoxide ion was the nucleophile, the concentration of methanol was varied from 0 to 97%. The fractional yield of mixed ester product leveled off at intermediate methanol concentrations and remained essentially constant at higher concentrations.

## Results

**Generation of $T^{\pm}$ from the Reaction of Aryl Chloroformates with Amines and Phenoxide Ion.** The partitioning of the addition intermediate $T^{\pm}$ with aryl oxide and amine expulsion (eq 2, $k_O$ and $k_N$) was determined by generating the acylated tertiary amine cation **1** from the reaction of aryl chloroformate with a substituted quinuclidine (path A, eq 2) in the presence of sufficient phenoxide ion to trap **1** quantitatively. The reactions were initiated by injecting an aliquot of the chloroformate in tetrahydrofuran into a buffered aqueous solution containing amine and phenol. All of the reactions shown in eq 2 were complete within the mixing time of 0.1 s. The fraction of aryl oxide expulsion therefore appears as an initial burst of absorbance increase, which is followed by a slower increase due to the cleavage of the aryl phenyl carbonate product. Thus, the ratio of $k_O/k_N$ is equal to the ratio of aryl oxide and ester products and is measured from the ratio of the absorbance changes in the burst of aryl oxide formation and in the slower, first-order hydrolysis of the ester. It was shown in control experiments that the rate of hydrolysis under the conditions of the partitioning experiments is the same for the ester product and for authentic ester. In cases in which no ester formation was observed in partitioning experiments it was also shown by the use of authentic esters that it could have been observed if it had been formed.

In a typical experiment the concentration of amine was increased until the burst size became constant, indicating that all of the added chloroformate had reacted with amine to form **1** rather than undergoing hydrolysis or reaction with the phenoxide ion. As shown in Figure 1, the concentration of

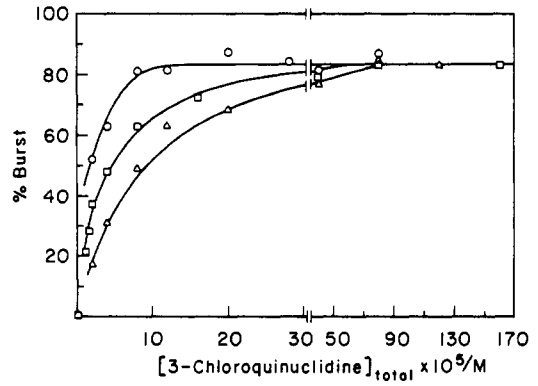



**Figure 1.** The burst of 2,4-dinitrophenoxide ion formation from the partitioning of $T^{\pm}$, formed from the reaction of dinitrophenyl chloroformate with increasing concentrations of 3-chloroquinuclidine in the presence of $5 \times 10^{-4}$ M (○), $1 \times 10^{-3}$ M (□), and $2 \times 10^{-3}$ M (△) *p*-acetophenol (total concentrations) in 4% tetrahydrofuran, buffered with 0.01 M borate at pH 8.7 ± 0.2.

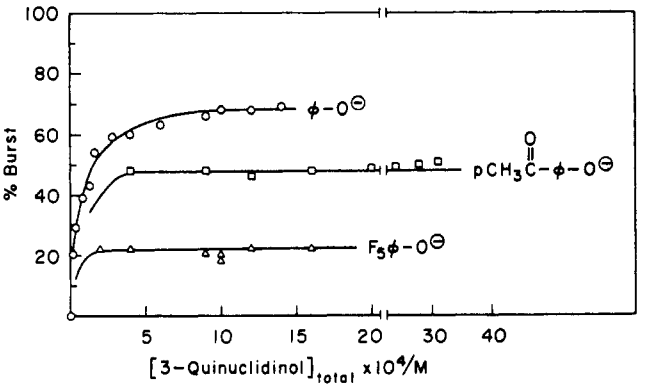



**Figure 3.** Effect of anionic nucleophile structure on the percent of 3,4-dinitrophenoxide ion release that appears as a burst when 3,4-dinitrophenyl chloroformate is reacted with 3-quinuclidinol in the presence of $4 \times 10^{-3}$ M phenol (○), $1 \times 10^{-3}$ M *p*-acetophenol (□), and $2 \times 10^{-3}$ M pentafluorophenol (△). The reactions were run in 4% tetrahydrofuran buffered with 0.01 M borate, pH 8.7 ± 0.2.

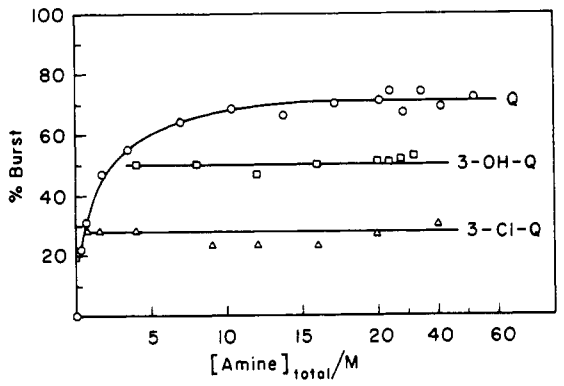



**Figure 2.** Effect of amine basicity on the percent of 3,4-dinitrophenoxide ion release that appears as a burst when 3,4-dinitrophenyl chloroformate is reacted with various concentrations of quinuclidine, 3-quinuclidinol, and 3-chloroquinuclidine in the presence of $10^{-3}$ M *p*-acetophenol (total concentration). The reactions were run in 4% tetrahydrofuran buffered with 0.01 M borate, pH 8.7 ± 0.2. Quinuclidine concentrations are times $5 \times 10^3$; 3-quinuclidinol and 3-chloroquinuclidine concentrations are times $10^4$.

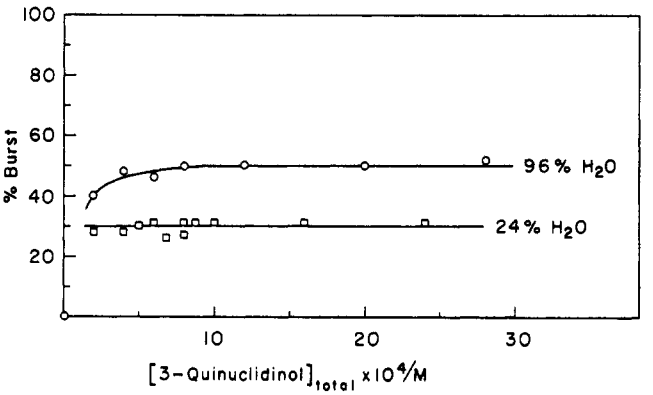



**Figure 4.** Effect of solvent on the percent of 3,4-dinitrophenoxide ion release that appears as a burst when 3,4-dinitrophenyl chloroformate is reacted with 3-quinuclidinol in the presence of $10^{-3}$ M *p*-acetophenol (total) in 4% tetrahydrofuran (○) and in 4% tetrahydrofuran plus 72% acetonitrile (by volume) (□). The solutions were buffered with 0.01 M borate, 20% base.

amine that is required to reach a constant burst size increases with increasing phenoxide ion concentration, as expected if the two nucleophiles compete for reaction with chloroformate. Figure 1 also shows that the same limiting burst size is reached at different phenoxide ion concentrations, demonstrating that **1** reacts quantitatively with the phenoxide to form $T^{\pm}$ which undergoes partitioning with a constant ratio of aryl oxide and amine expulsion.

The effects on the partitioning ratio of varying amine basicity, the basicity of the anionic nucleophile, and the solvent are illustrated in Figures 2–4. These results and others are summarized in Table I.

At amine concentrations higher than those used in these experiments a significant amount of the symmetrical bis(aryl) carbonate was formed and was identified by its kinetic behavior. This presumably results from the reaction of local high concentrations of aryl oxide ion with **1** under conditions of incomplete mixing. It was shown that, under the conditions of the experiments reported here, the partitioning ratio is constant over a fourfold range of chloroformate concentration. The p*K* of pentafluorophenoxide is the same as that of 3,4-dinitrophenoxide ion, so that the former compound will sometimes be expelled from $T^{\pm}$. However, this will only regenerate **1** and will not affect the measured ratio of partitioning of $T^{\pm}$ with respect to aryl oxide and amine expulsion.

**Generation of $T^{\pm}$ from the Reaction of Bis(aryl) Carbonates with Amines.** The reaction of bis(3,4-dinitrophenyl) carbonate with phenolate, in the absence of added amine, rapidly gives the mixed ester with the release of 1 mol of 3,4-dinitrophenoxide ion, followed by a much slower reaction with the mixed ester to release the second mole of 3,4-dinitrophenoxide ion (Figure 5, upper curve). When 3-quinuclidinol is added, the reaction with this amine gives **1**, the same intermediate that is formed from amine and chloroformate, which then reacts with phenolate ion to give $T^{\pm}$ and the products of breakdown of $T^{\pm}$ (eq 2, path B). The initial reaction to form **1** releases 1 mol of 3,4-dinitrophenoxide ion and any partitioning of $T^{\pm}$ with aryl oxide expulsion will result in an additional fast formation of aryl oxide. Thus, any formation of aryl oxide in the initial rapid phase of reaction that is >1.0 mol is a measure of the amount of partitioning of $T^{\pm}$ with aryl oxide expulsion, whereas the slow phase represents cleavage of the unsymmetrical ester that is formed by amine expulsion. As shown in the remaining curves of Figure 5, the addition of amine results in an increase in the *extent* of the fast phase of the reaction, which appears as a burst in most of the experiments, and a corresponding decrease in the amount of slowly reacting ester. As the amine concentration is increased further, the ratio of the fast and slow phases approaches a constant value, as shown more directly in Figure 6. This means that at high amine concentration all of the ester is reacting with the amine and the

**Table II.** Partitioning of $T^{\pm}$ Formed from Bis(aryl) Carbonates, ArOCOOAr, Substituted Quinuclidines, and Phenoxide Ion[a]

| | % ArO leaving | | | |
|---|---|---|---|---|
| Ar | Quinuclidine | 3-Quinuclidinol | 3-Chloroquinuclidine | 3-Quinuclidinone |
| 3,4-Dinitrophenyl | 82 | 60 | | |
| 2,4-Dinitrophenyl | >90 | >90 | 80 | 56 |

[a] At 25 °C in 36% acetonitrile, 4% tetrahydrofuran, buffered with 0.01 M borate, 20% base. The ionic strength was not maintained constant.

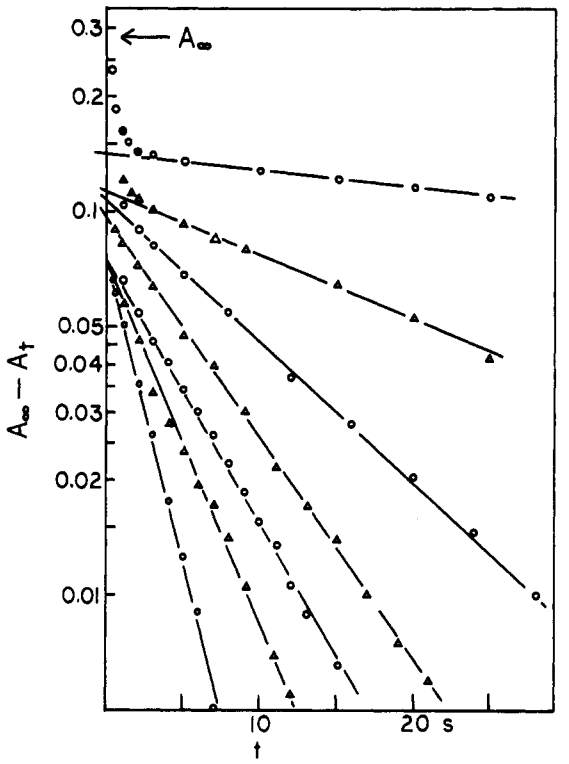



**Figure 5.** The effect of 3-quinuclidinol concentration on the kinetics of the reaction of bis(3,4-dinitrophenyl) carbonate with $4 \times 10^{-3}$ M phenol (total). The concentrations of 3-quinuclidinol (total) used, going from the slowest to the fastest rate, were 0.0, $1.6 \times 10^{-4}$ M, $4 \times 10^{-4}$ M, $6 \times 10^{-4}$ M, $1 \times 10^{-3}$ M, $1.4 \times 10^{-3}$ M, and $2 \times 10^{-3}$ M. The reactions were run in 36% acetonitrile and 4% tetrahydrofuran and were buffered with 0.01 M borate at pH 8.7 ± 0.2.

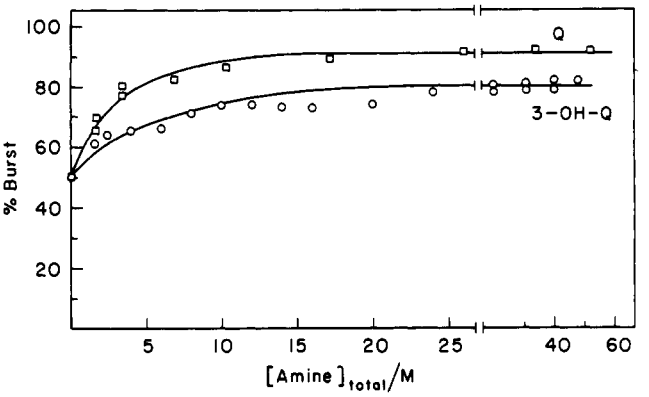


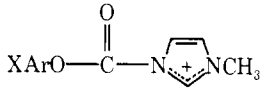

**Figure 6.** The fraction of 3,4-dinitrophenoxide ion that is released in the fast phase when bis(3,4-dinitrophenyl) carbonate reacts with various concentrations of quinuclidine (□) and 3-quinuclidinol (○) in the presence of $4 \times 10^{-3}$ M phenol (total concentration) in 36% acetonitrile and 4% tetrahydrofuran buffered with 0.01 M borate, pH 8.7 ± 0.2. The quinuclidine concentrations are times $5 \times 10^3$ and the 3-quinuclidinol concentrations are times $10^4$.

amount of 3,4-dinitrophenoxide ion in excess of 1.0 mol that is released in the fast phase and the amount of ester cleaved in the slow phase are measures of the partitioning of $T^{\pm}$ to expel aryl oxide and amine, respectively ($k_O/k_N$, eq 2). The increase in the *rate* of the second phase of the reaction with increasing amine concentration is caused by amine-catalyzed cleavage of the ester and is not relevant to our main concerns here. It was shown in a number of control experiments that the authentic mixed carbonate ester is cleaved with the same rate constant that is observed in the slow phase of the partitioning experiments under the same experimental conditions. It was also shown that at high amine concentrations the extents of the fast and slow phases do not change with an increase in phenoxide concentration, indicating that all of **1** is trapped by phenoxide ion.

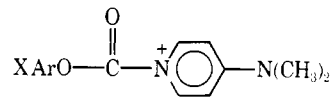
The results of the partitioning experiments with bis(aryl) carbonates are summarized in Table II.

Attempts to measure partitioning ratios with less reactive bis(aryl) carbonates and amines were unsuccessful. These reactions require higher amine concentrations in order to achieve satisfactory reaction rates and competition with phenoxide ion. A constant partitioning ratio was not reached at high amine concentrations; possible reasons for this include amine catalysis of the breakdown of **1** or trace impurities in the amine.

**Generation of $T^{\pm}$ Directly from Methylimidazole and Pyridine Derivatives.** It was possible to prepare the imidazole and pyridine compounds **2** and **3**, although they were not isolated,




**2**




**3**

so that the relative leaving of imidazole and pyridine compared with aryl oxide ion could be measured by the direct generation of $T^{\pm}$ from the reactions of **2** and **3** with phenolate or methoxide ion as nucleophiles. In each series of experiments a constant amount of **2** or **3** was injected into the reaction mixture and the concentration of nucleophile was increased until the product ratio from the partitioning of $T^{\pm}$ reached a constant value. The results of a typical experiment are shown in the form of a reciprocal plot in Figure 7; the ordinate intercept gives the ratio of aryl oxide to amine expulsion. Aryl oxide expulsion is observed as a rapid burst of aryl oxide release and amine expulsion is measured from the amount of the slower, first-order release of aryl oxide ion from the hydrolysis of the mixed ester. It was shown that the authentic mixed ester, generated from symmetrical ester and the nucleophile, was cleaved with the same rate constant as was observed in the partitioning experiments under the same experimental conditions. In cases in which no slowly reacting ester was generated from the partitioning of $T^{\pm}$, it was shown that the ester could have been detected if it had been formed.

The results are summarized in Table III. The last column of the table gives the percent ester formation, which is equal to the percent of amine expulsion from $T^{\pm}$. The partitioning to give 4-nitrophenolate ion and methylimidazole expulsion, with phenolate ion as the nucleophile, is the same at pH 8.5 and 10.5; it was also shown to be unchanged upon decreasing the

**Table III.** Products of the Reaction of XArOC(=O) $N^+<$ with the Anion of a Nucleophile, nuc[a]

| X | Amine | nuc[b] | Buffer[c] | pH | % XArOC(=O)-nuc |
|---|---|---|---|---|---|
| H | *N*-Methylimidazole | MeOH[d] | Carbonate, 17% base | | >95 |
| 4-Nitro | *N*-Methylimidazole | MeOH[d] | Carbonate, 17% base | | 84 |
| 4-Nitro | *N*-Methylimidazole | 0.2 M PhOH | Borate | 8.5 | 90 |
| 4-Nitro | *N*-Methylimidazole | 0.04 M PhOH | Carbonate | 10.5 | 90 |
| 3,4-Dinitro | *N*-Methylimidazole | 0.2 M PhOH | Carbonate | 10.5 | <5[e] |
| H | 4-*N,N*-Dimethylaminopyridine | MeOH[d] | Carbonate, 17% base | | >95 |
| 4-Nitro | 4-*N,N*-Dimethylaminopyridine | 0.04 M PhOH | Carbonate | 10.5 | 80 |

[a] At 25 °C, ionic strength not maintained constant. [b] The concentrations of phenol shown are the maximum of the range of concentrations used. [c] 0.0024–0.003 M. [d] Varied from 0 to 97%. [e] Result from a single experiment.

**Table IV.** Partitioning of the Addition Intermediate $T^{\pm}$ as Estimated from Product Analysis and Kinetic Data

| | % $ArO^-$ leaving | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Quinuclidine | | 3-Quinuclidinol | | 3-Chloroquinuclidine | | 3-Quinuclidinone | |
| Ester | Obsd | Calcd[a] | Obsd | Calcd[a] | Obsd | Calcd[a] | Obsd | Calcd[a] |
| *p*-Nitrophenyl | 10 | 16 | <5 | 2 | <5 | 0 | | |
| 3,4-Dinitrophenyl | 83 | 93 | 64 | 55 | 36 | 20 | | |
| 2,4-Dinitrophenyl | >95 | 100 | >95 | 98 | 83 | 92 | 60 | 51 |

[a] Calculated from 100 $k_{obsd}/k_1$, based on the kinetic data reported in the previous paper; the values of $k_1$ and $k_{obsd}$ were obtained from eq 5–7 and Table III.[2]

borate buffer concentration by a factor of 6 and the carbonate buffer concentration by a factor of 3.

## Discussion

**Comparison of the Results from Different Methods for Measuring the Partitioning of $T^{\pm}$.** The product ratios from the partitioning of the addition intermediate $T^{\pm}$ are the same when the intermediate is generated from aryl chloroformate and amine to form **1**, followed by trapping of **1** with phenolate ion (Table I, path A of eq 2), as when it is generated via **1** from the symmetrical carbonate ester and amine (Table II, path B of eq 2). These results are compared with the partitioning estimated from the kinetic results reported in the previous paper in Table IV. The rate constant for aminolysis (eq 2, lower part) is related to the partitioning of $T^{\pm}$ by the steady state-rate eq

$$k_{obsd} = k_1(k_O/(k_N + k_O)) \quad (3)$$

so that the percent aryl oxide expulsion from the kinetic data is equal to 100 $k_{obsd}/k_1$, as calculated from eq 5–7 and Table III of the previous paper.[2] The results agree well within the estimated experimental error of the calculation of partitioning ratios from the position of the change in rate-determining step in the structure–reactivity correlations; the directly measured partitioning ratios are more accurate than those calculated from the kinetic data. The points indicated with the symbol x in Figure 2 of the previous paper[2] were calculated from the experimental partitioning ratios reported in Tables I and II and the values of $k_1$ or $k_b$ that are obtained from eq 5 and 6 and the constants in Table III[2] for reactions in which both steps are partly rate determining. The directly measured partitioning ratios successfully predict the curvature of the structure–reactivity correlations in the region in which the change in rate-determining step occurs and there is satisfactory agreement of the calculated and observed rate constants.

The agreement of these results from three different methods establishes that the nonlinear structure–reactivity correlations in the aminolysis of carbonate esters are caused by a change in rate-determining step with changing structure of the nucleophile and leaving group, as was concluded previously for the aminolysis of acetate esters.[4,5] Structure–reactivity data

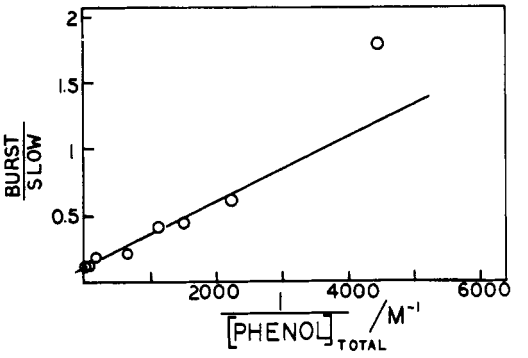



**Figure 7.** The ratio of burst to slow release of 4-nitrophenoxide ion as a function of the reciprocal of the phenol concentration, in the partitioning of the intermediate formed from 1-(4-nitrophenyloxycarbonyl)-3-methylimidazolium ion at 25 °C in 0.0024 M borate buffer, pH 8.5.

provide strong evidence for the same conclusion in the aminolysis of phenyl chloroformates[10] and other esters.[11]

The fact that the same partitioning is observed when $T^{\pm}$ is generated from three different routes suggests that $T^{\pm}$ is a true, solvent-equilibrated intermediate with a finite lifetime, i.e., that there is a significant activation energy for the breakdown of $T^{\pm}$ in any direction. If the expulsion of amine and aryl oxide from **1** by phenoxide ion occurred by displacement through two parallel transition states, rather than through an intermediate $T^{\pm}$ with a finite lifetime, the results require that the relative stabilities of these two transition states must be the same as those of the two sequential transition states in the ester aminolysis reactions, for a number of different reactions. In addition to differences in solvation and geometry, the transition states for displacement reactions from **1** differ from those for ester aminolysis in that there is only partial bond formation to the attacking phenoxide ion in the displacement reactions, whereas this bond is fully formed in the aminolysis reactions. It is unlikely that these two pairs of transition states would have the same relative energies for the reactions of all the different amines and leaving groups that give similar behavior in the kinetic and partitioning experiments. Results that will be discussed below demonstrate directly that the electron density on this phenolic group influences the relative rates of expulsion

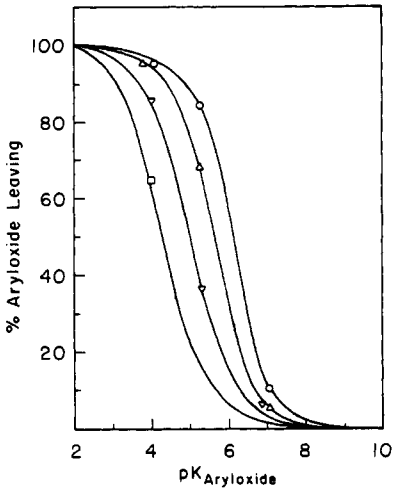



**Figure 8.** Dependence on the p$K$ of the leaving aryl oxide ion of the partitioning of tetrahedral intermediates, T±, containing a substituted quinuclidine and phenol. Quinuclidine, ○; 3-quinuclidinol, △; 3-chloroquinuclidine, ▽; and 3-quinuclidinone, □. The points at 95 and 5% aryl oxide leaving are limiting values.

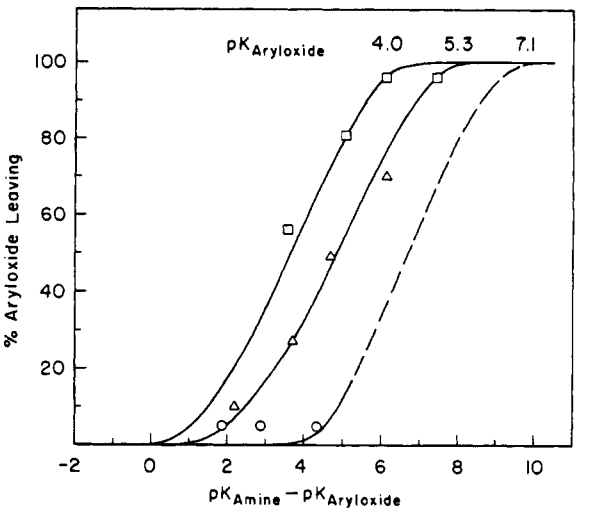
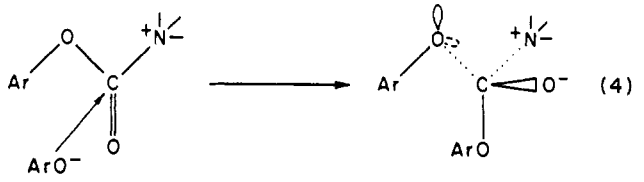



**Figure 9.** Partitioning of tetrahedral addition intermediates, T±, as a function of the difference in p$K$ of the amine and aryl oxide leaving groups. Each line represents a series of intermediates with a common aryl oxide leaving group of the indicated p$K$ and varying amine. The points at 95 and 5% aryloxide leaving are limiting values.

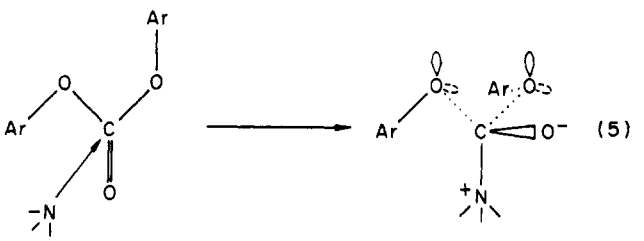
of amine and aryl oxide ion, so that a difference in partitioning would be expected if bonding to the phenol were partial or complete.

The agreement of the partitioning ratios from the different routes also suggests that there is rapid rotation of the aryl oxide groups in the tetrahedral intermediate, because it is difficult or impossible to generate the same product ratios from different routes without such rotation. For example, nucleophilic attack on the species **1** and **4** in eq 4 and 5 gives two different




(4)

**1** **5**




(5)

**4** **6**

intermediates, **5** and **6**, as the immediate products. In **5** the lone-pair electrons of the carbonate aryl oxide oxygen atom are not antiperiplanar to the amine and in **6** the lone-pair electrons of one aryl oxide oxygen atom are not antiperiplanar to the other aryl oxide group. Thus, **5** and **6** would give different ratios of amine to aryl oxide expulsion if, as has been suggested in the theory of "stereoelectronic control",[12] the direction of leaving group expulsion is determined by the location of electron pairs antiperiplanar to the leaving group and there is no rotation prior to leaving group expulsion. If nucleophilic attack occurs on the carbonate ester with both aryl oxide groups in an s-cis,s-cis conformation, for which there is some evidence for certain carbonate esters,[13] there will be no aryl oxide electron pairs antiperiplanar to the other aryl oxide group until rotation takes place. Therefore, it appears that in the carbonate system there is rapid equilibration of the intermediates by rotation so that electron pairs can achieve the optimal geometry to stabilize the transition state and product.

The kinetic results reported in the previous paper[2] also suggest that rotation of the aryl oxide group is not kinetically significant in the aminolysis reaction. The value of $\beta_{nuc} = 0.3$ that is observed with basic amines and good leaving groups is evidence for an early transition state for amine attack with incomplete bond formation to carbon and the value of $\beta_{lg} = -1.3$ for less basic amines and poor leaving groups is evidence for a late transition state with significant cleavage of the bond to the leaving aryl oxide ion. The transition state for rate-determining rotation should resemble T±, with complete formation of the C–N and C–O bonds. However, it is possible that a fraction of the T± intermediates could break down without aryl oxide rotation (i.e., those in which the leaving group is the left-hand aryl oxide group in **6**).

The results of the partitioning experiments provide direct evidence for the conclusions reached in the previous paper from kinetic evidence that the expulsion of amine and of aryl oxide from T± is favored by electron-withdrawing substituents in the leaving group and that the sensitivity to polar substituents is larger for substituents on oxygen than on nitrogen. The sharp decrease in aryl oxide expulsion with increasing aryl oxide basicity for the series of intermediates formed from each of the different quinuclidines as illustrated in Figure 8. The partitioning of a series of intermediates containing a constant aryl oxide group shows a somewhat smaller dependence on the basicity of the amine (Figure 9). Partitioning of the addition intermediates that contain the 3,4-dinitrophenyl group gives equal breakdown in both directions when the amine is 4.4 units more basic than the aryl oxide leaving group, in agreement with the Δp$K$ of 4.6 units obtained from the kinetic data.[2]

The partitioning in Figure 9 is plotted as a function of the *difference* in the p$K$ of the amine and aryl oxide leaving groups and the fact that this difference increases with increasing p$K$ of the aryl oxide confirms the conclusion[2] that amine expulsion becomes progressively more favorable for a given difference in p$K$ as the absolute basicity of the aryl oxide increases. The position of the midpoints of the curves in Figure 9, at which aryl oxide and amines expulsion are equal, shows that the Δp$K$ for equal partitioning of T± increases with increasing p$K$ of the aryl oxide. This can be interpreted as a consequence of electron

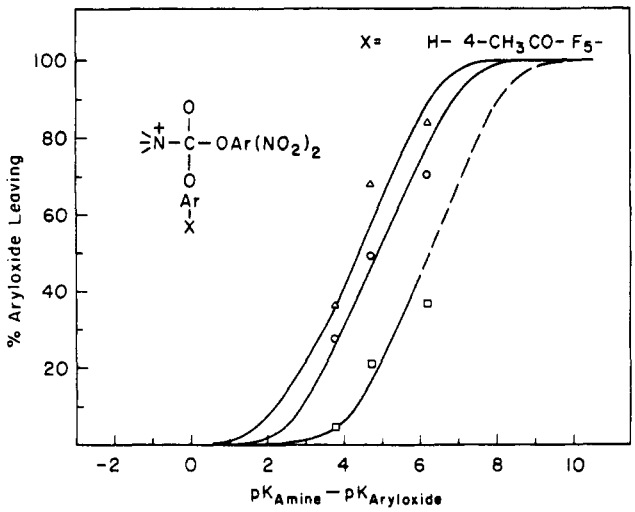



**Figure 10.** Effect of the "acyl" substituent, XArO-, on the partitioning between expulsion of 3,4-dinitrophenoxide and substituted quinuclidines from the tetrahedral addition intermediate T±.

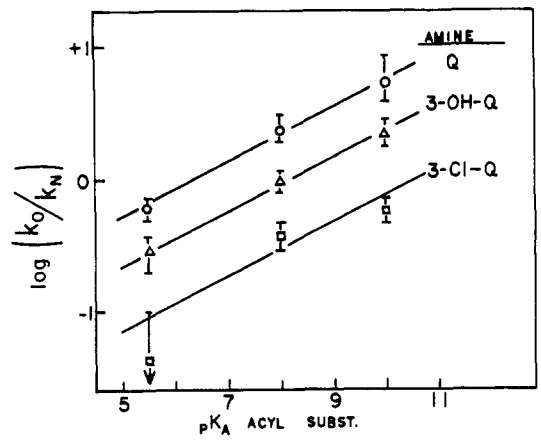
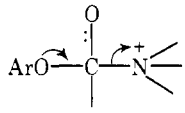



**Figure 11.** Logarithmic plot of the partitioning ratio for T± against the $pK_a$ of the conjugate acid of the "acyl" substituent. The aryl oxide leaving group is 3,4-dinitrophenoxide for all three correlations. The amine leaving groups are, as indicated, quinuclidine, 3-quinuclidinol, and 3-chloroquinuclidine. The slope of the lines is +0.2.

donation from oxygen that provides a *push* to help expel the levaing amine and stabilize the product ester (**7**) with little or



**7**

no such electron donation from nitrogen to expel the aryl oxide.

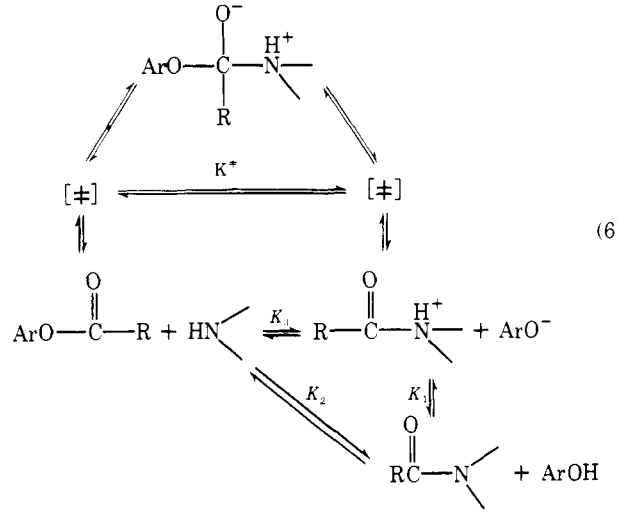
Although product analysis provides a more accurate measure of the partitioning of intermediates than does kinetic data in the region in which partitioning occurs to an easily measurable extent in both directions, this technique provides a less accurate quantitative measure of the effects of substituents on "effective charges" and partitioning because of the limited range of structural variation over which accurate product ratios can be determined. The slope of a plot of log ($k_N/k_O$) against $pK_{amine}$ from the partitioning data for intermediates containing 3,4-dinitrophenol and phenol has a slope of 0.45 ± 0.2 which is consistent, within the experimental error of the two methods, with the value of 0.7 from the kinetic data.[2] The corresponding slopes of plots against the p$K$ of the aryl oxide for each of the three more basic amines are −1.0 ± 0.1, which agree well with the slope of 1.1 from the kinetic data;[2] however, each of these slopes is based on only one-two points and one-two limiting values of the partitioning ratios.

**The Effect of Organic Cosolvents on the Partitioning Ratio.** The addition of acetonitrile to the aqueous solvent increases the fraction of amine expulsion to form ester (Figure 4 and Table I). This demonstrates the expected stabilization by an aprotic cosolvent of the transition state for the breakdown of T± to form uncharged products relative to that for the formation of aryl oxide anion and cationic amide. The effect of 36% acetonitrile is small (in one case absent) and 72% acetonitrile causes a 2.2–2.5-fold change in the partitioning ratio. It is likely that partitioning upon addition to the aqueous solution occurs before mixing of the tetrahydrofuran solution of aryl chloroformate with the reaction mixture is complete, so that the partitioning may occur in a partially organic environment even in the "aqueous" experiments. However, the results of the partitioning experiments with chloroformates agree with those obtained with bis(aryl) carbonates, for which there is no such mixing problem (Tables I and II).

**Effect of the "Acyl" Substituent on Partitioning.** The results obtained with different substituted phenoxide ions as trapping reagents to form T±, shown in Figures 3 and 10, demonstrate that electron-donating substituents in the group which does not leave favor the expulsion of aryl oxide anion relative to amine. This may be regarded as an effect of the nonreacting "aryl" group on partitioning that can be described by a $\beta_O$ value of 0.2, from the slope of the lines in Figure 11. Thus, electron-withdrawing substituents in the acyl portion of esters are expected to increase the $\Delta pK$ value at which amine and aryl oxide leave at equal rates and there is a change in the rate-determining step of aminolysis.

This result may be rationalized in two ways.

(1) A thermodynamic cycle for the breakdown of T± to amide and ester is shown in eq 6. It is probable that there is only



(6)

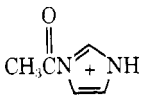
a small effect of polar substituents in the acyl group, R, on the equilibrium constant for acyl transfer between ester and uncharged amide, $K_2$. The values of $\beta_{eq}$ for the formation of esters and amides from alcohols and amines of varying p$K$ are in the range of 0.6 ± 0.1, indicating that the "effective charge" on the oxygen and nitrogen atoms of these acyl compounds is similar, and the equilibrium constants for the formation of esters and of thiol esters from carboxylic acids are both independent of the acyl substituent, indicating that the effective charge that is "seen" by substituents on the acyl group is the same for these two acyl compounds.[14-17] However, the dissociation constant, $K_1$, for conversion of cationic to neutral amide will certainly be increased by electron-withdrawing substituents on the acyl group. It follows that the equilibrium constant

$K_3$ will be decreased by electron-withdrawing substituents and, since the $\beta_N$ and $\beta_O$ values of $-0.7$ suggest a similar amount of bond breaking in the transition states for amine and aryl oxide expulsion,[2] it is expected that the equilibrium constant $K^{\pm}$ will be decreased by electron-withdrawing substituents on the acyl group. The transition state for amine expulsion will, therefore, be destabilized relative to that for aryl oxide expulsion, as observed.

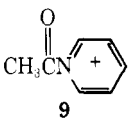
(2) The acyl group, R, provides the only possible source for resonance stabilization of the carbonyl group of the cationic amide, whereas the ester is stabilized by resonance from the ether oxygen atom so that any additional electron donation from the acyl substituent must compete with the electron donation from this oxygen atom. The same situation holds in the transition states for amine and aryl oxide expulsion. Consequently, electron-donating substituents in the acyl group may be expected to stabilize the transition state for aryl oxide expulsion and the cationic amide product more than the alternative transition state and product because of the greater electron demand in the former reaction.

Since electron-withdrawing substituents favor amine expulsion, it would be expected, if only inductive and field effects are important, that acetates would exhibit relatively more amine expulsion than phenyl carbonates because of the larger electron-withdrawing effect of the phenol than of the methyl group. The fact that the $\Delta pK$ for the change in rate-determining step is similar for the two classes of compounds therefore provides evidence that electron donation from the phenolic oxygen atom by resonance must be significant in favoring aryl oxide expulsion in the carbonate series.

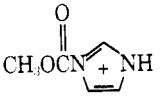
This difference in resonance stabilization is also evident in the rates of hydrolysis of the corresponding acyl compounds. The rates of hydrolysis of acetylimidazolium and acetylpyridinium compounds, **8** and **9**, are more than 100 times faster



**8**



**9**



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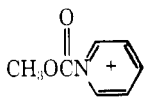
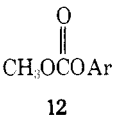


**11**



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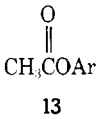


**13**

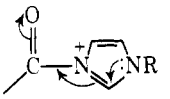
than those of the corresponding methoxycarbonyl compounds, **10** and **11**, in which the carbonyl group is stabilized by electron donation from oxygen; however, there is no significant difference in the rates of hydrolysis or aminolysis of the phenyl esters of methyl carbonic acid (**12**) and acetic acid (**13**), indicating that there is less stabilization from the additional oxygen atom if one oxygen atom is already present.[18,19]

**The Relative Leaving Group Abilities of Imidazole and Pyridine.** The results in Table III, although less extensive than those for the quinuclidine series, show that there is a significant amount of 4-nitrophenoxide ion expulsion that competes with *N*-methylimidazole expulsion from $T^{\pm}$ in spite of the fact that both of these leaving groups have essentially the same p$K$. With the more acidic 3,4-dinitrophenoxide ion leaving group there is no detectable expulsion of imidazole. These results are consistent with evidence from a nonlinear structure–reactivity correlation for the reaction of phenyl acetates with imidazole which indicates that there is a change from predominant imidazole to predominant aryl oxide expulsion, i.e., a change in rate-determining step, as the p$K$ of the leaving aryl oxide ion is varied; the change occurs at an aryl oxide p$K$ of roughly 8.5.[20]

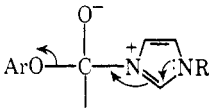
The results are similar to those for the quinuclidine series in that amine expulsion is favored over aryl oxide expulsion when both groups have equal basicity. The ratio of $k_N/k_O$ is ~9 for *N*-methylimidazole–4-nitrophenolate; it is >20 for 4-*N*,*N*-dimethylaminopyridine–phenolate, which have p$K$ values of 9.8 and 10.0, respectively. Significant aryl oxide expulsion occurs with the more acidic 4-nitrophenolate group (p$K$ = 7.1) and 4-*N*,*N*-dimethylaminopyridine, with a ratio $k_N/k_O$ of 4. The results differ from the quinuclidine series in that the pyridine compound is a poorer leaving group and the imidazole group is still poorer than an aliphatic tertiary amine of the same p$K$. Thus, for equal p$K$ values of 7, the ratio of $k_N/k_O$ is ~7800 in the quinuclidine system, and, for a quinuclidine of p$K$ = 9.8 and an aryl oxide of p$K$ = 7.1, $k_N/k_O$ is 110 instead of 4.[2] The relatively poor leaving ability of imidazole has been noted before in phthalimidium addition compounds, from which (protonated) imidazole is expelled ~$10^4$ more slowly than aliphatic amines of the same p$K$.[9]

A comparison between kinetic and thermodynamic partitioning in the imidazole series can be made if it is assumed that the behavior of acetates is similar to that of carbonates, as it appears to be in this and other reaction series. The equilibrium constant $K_3$ (see eq 6) for acetyl transfer from 4-nitrophenolate ion to imidazole or *N*-methylimidazole[16] is close to $10^{-3.6}$, whereas the equilibrium constant $K^{\pm}$ that describes the relative stabilities of the two transition states for the partitioning of $T^{\pm}$ in the carbonate compound is $10^{-0.95}$. This suggests that, as in the quinuclidine series, kinetic partitioning follows the relative thermodynamic stabilities of the products, but the differences are much smaller than in the quinuclidine series, for which the comparable values of $K_3$ and $K^{\pm}$ for acetates[2] are $10^{-7.5}$ and $10^{-3.8}$. A similar calculation[21] for acetyl transfer from 4-*N*,*N*-dimethylaminopyridine to phenolate anion gives an approximate value of $K_3 = 10^{-5.5}$ and a partitioning ratio corresponding to $K^{\pm} = 10^{-3.8}$; again kinetic follows thermodynamic partitioning and the differences are smaller than for the quinuclidine series,[2] for which $K_3 = 10^{-7.5}$ and $K^{\pm} = 10^{-4.5}$.

The relatively poor leaving ability of imidazole and pyridines and the enhanced stability of the acylated products are consistent[2,22] with a significant contribution of resonance stabilization by electron donation from the unsaturated amine to the carbonyl group of the acyl product and to the oxygen leaving group in the transition state for the breakdown of $T^{\pm}$. These are shown as **14** and **15**, respectively, for imidazoles;



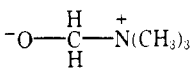
**14**



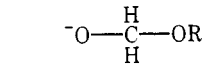
**15**

analogous structures can be drawn for the pyridine compounds. Delocalization of positive charge over the two nitrogen atoms and steric effects have also been suggested as possible contributory factors to the slow expulsion of imidazole from the phthalimidium addition compound and may also be significant in the ester series.[9]

**Comparison with Other Systems.** The rate constant for the expulsion of trimethylamine from **16** ($3.4 \times 10^3$ $s^{-1}$) is only slightly larger than the rate constant for the expulsion of methoxide ion from **17** ($3 \times 10^2$ $s^{-1}$).[23,24] Since the rate of



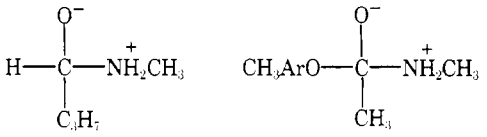
**16**



**17**

alkoxide expulsion is expected to increase with decreasing basicity[25] and methoxide ion is $10^5$ more basic than trimethylamine, it is virtually certain that an alkoxide ion of the same basicity would be expelled *faster* than trimethylamine. The driving force provided by the oxy anion is the same for the

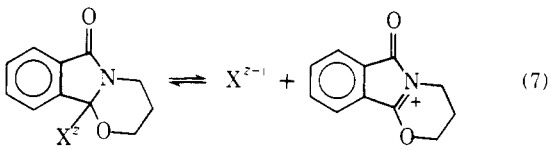
expulsion of both leaving groups in these compounds. The striking difference in behavior between these formaldehyde addition compounds and the addition compounds described here provides further evidence that a significant *push* by electron donation from the alcoholic oxygen atom facilitates the expulsion of amines from the tetrahedral addition intermediates that are formed in ester aminolysis (**7**), although steric effects may also be significant. Furthermore, the fact that the estimated rate constant for methylamine expulsion from **18** ($k = 5 \times 10^6\ s^{-1}$)[26] is nearly $10^3$ smaller than that for **19**



**18** **19**

($k = 3 \times 10^9\ s^{-1}$)[4] suggests that electron donation from the phenolic oxygen atom in **19** provides significant additional driving force for amine expulsion.

On the other hand, the rate of expulsion of leaving groups, X, from tetrahedral addition compounds of a phthalimidium ion (eq 7) is $\sim 10^5$ faster for (protonated) amines than for



(7)

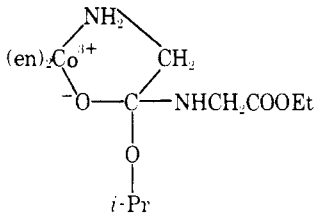
**20** **21**

alkoxide ions of comparable basicity.[9] Again, the driving force for leaving group expulsion is the same for both leaving groups in this system. Although steric, solvation, and other effects may also be significant, the different relative leaving group ability compared with the oxy anion systems **16–19** is probably in large part an electrostatic effect. The change in charge when a leaving group departs from **20** is the same as in the reference ionization reaction of the leaving group, so that electrostatic effects should not be important for reactions of **20** if leaving groups are compared at constant p$K$. Thus, the observed rate difference with **20** apparently reflects an intrinsically larger basicity toward carbon of oxy anions than of amines, for a given basicity toward the proton. This difference also appears in the $10^7$ more favorable equilibrium constants for the addition to the phthalimidium ion of oxy anions compared with amines.[9]

However, the equilibrium constant for the addition of trimethylamine to formaldehyde is almost the same as that for addition of the much more basic hydroxide ion.[27] The dipolar product of this reaction, **16,** is stabilized by the electrostatic interaction of the two charges, which does not exist in the reference protonation reaction of the amine; there is no such stabilization for the addition of hydroxide ion. The expulsion of oxy anions from **17** and **19** does not involve charge separation and the expulsion of amines requires the loss of the electrostatic stabilization from the charges in $T^{\pm}$, so that a relatively slower expulsion of amines is expected in this series, as observed. The electrostatic effect is also observed in the reverse, addition reaction: trifluoroethoxide ion reacts 100-fold faster than piperidine with the phthalimidium cation **21,** but adds slightly more slowly than piperidine to the neutral ester dinitrophenyl acetate,[3,9] and trimethylamine adds to formaldehyde faster than hydroxide ion.[27]

This electrostatic effect has been estimated[28] to represent a factor of $\sim 10^{4.8}$ for the ionization of tetrahedral addition intermediates; the dissociation of the -OH of T is increased and the dissociation of the NH of $T^-$ is decreased by this factor compared to the ionization in which there is no such electrostatic effect.

The breakdown of the tetrahedral addition compound **22**



**22**

in dilute acid occurs with alcohol expulsion to give the peptide; i.e., protonation and expulsion of oxygen is favored over protonation and expulsion of nitrogen in spite of the high basicity and leaving ability of amines.[29] This result suggests that, when the driving force provided by the electron pair on the oxy anion is reduced by coordination to $Co^{3+}$, the *push* provided by the electron pair on nitrogen becomes relatively much more important than in noncoordinated addition intermediates and is sufficient to favor oxygen expulsion over the alternative protonation and expulsion of nitrogen, which is aided only by the more weakly electron-donating oxygen atom on the alcohol.

The large differences in the behavior of these different classes of addition intermediates serve to emphasize that there is no single measure that will describe the relative leaving group ability of different groups in different systems. Electron donation by the group which does not leave and by other groups in the electrophilic reactant and electrostatic effects can be identified as important factors that govern the relative leaving ability of different groups. An understanding of these factors and data from appropriate model reactions should make possible semiquantitative predictions about relative leaving group ability in a given system.

## References and Notes


(1) Supported by grants from the National Science Foundation (GB-31740) and the National Institute of General Medical Sciences of the National Institutes of Health (GM20888). M.J.G. was a Predoctoral Fellow of the National Institutes of Health (GM-212). Some of these results have been previously reported (Abstracts, the 172nd National Meeting of the American Chemical Society, San Francisco, Calif., Aug 30–Sept 3, 1976, ORGN 191).
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# Restricted Rotation in Hexaarylbenzenes[1]

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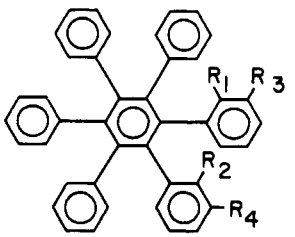
**Abstract:** Hexaarylbenzenes exist in a conformation in which the peripheral rings are perpendicular to the plane of the central ring on the nmr time scale. Hexaarylbenzenes substituted in ortho or meta positions of the peripheral rings display restricted rotation about the single bonds joining the central and peripheral rings, and complex stereoisomerism and stereoisomerization behavior results. The rotational barriers observed are relatively high (up to ~38 kcal/mol), and even rings bearing only a *m*-methyl substituent lead to barriers of ~16 kcal/mol.

Recent studies of torsional isomerism in triarylmethanes,[2] tetraarylethanes,[3] and related systems[2,4] suggested that suitably substituted hexaarylbenzenes might also demonstrate restricted rotation. If substituted hexaarylbenzenes having relatively high barriers to rotation about the bonds connecting the peripheral and central aromatic rings could be synthesized, a molecular system possessing a rich variety of interesting stereochemical features would result. Reported here are the results of an initial study demonstrating that this is indeed the case.

**Synthesis and Properties of Substituted Hexaarylbenzenes.** Previously synthesized hexaarylbenzenes have been unsubstituted, or have had substituents only in the para positions of some of the peripheral rings.[5] To investigate the possibility of restricted rotation in this class of compounds, molecules bearing substituents in the ortho or meta positions were desired. Hexaarylbenzene **1**, in which two adjacent phenyl rings each




1, $R_1 = OCH_3$; $R_2 = CH_3$; $R_3 = R_4 = H$

2, $R_1 = R_2 = CH_3$; $R_3 = R_4 = H$

3, $R_1 = R_2 = H$; $R_3 = R_4 = CH_3$

bear an ortho substituent, was prepared using a series of well-known reactions (see Experimental Section). The synthesis of *trans*-2-methoxy-2′-methylstilbene was accomplished by means of the Wittig reaction. Using the procedure of Fieser,[5c] this material was brominated with pyridinium hydrobromide perbromide, and the resulting dibromide was dehydrohalogenated with potassium hydroxide to yield 2-methoxy-2′-methyldiphenylacetylene. Refluxing a mixture of the acetylene and tetraphenylcyclopentadienone in benzophenone gave **1** in 66% yield. Column chromatography of **1** (silica gel, carbon tetrachloride) yielded two different substances, **1a** and **1b**, in roughly equal amounts. These two substances gave similar, but not identical, $^1H$ NMR spectra. The spectrum of **1a** featured a single aromatic methyl singlet at $\delta$ 2.02 ppm, and a single methoxy group resonance at 3.40, as well as the expected aromatic proton resonances, whereas the spectrum of **1b** featured the aromatic methyl resonance at $\delta$ 2.02 and the methoxy resonance at 3.47. Each compound gave carbon and hydrogen analyses and mass spectra consistent with the proposed structure, and each melted at 358–359 °C with some sublimation before melting.

Upon heating in 1-bromonaphthalene solution at 215 °C for 30 min, **1a** was converted cleanly to a mixture containing 46% **1a** and 54% **1b**. Under the same conditions, **1b** gave an identical mixture. Further heating did not change these percentages. Kinetic studies of the interconversion (see Experimental Section) yielded[6] $\Delta G^{\ddagger}_{419} = 32.7$ kcal/mol for the conversion of **1a** into **1b**, and $\Delta G^{\ddagger}_{419} = 32.8$ kcal/mol for the reverse reaction. As is shown in the following sections, all of the above data are consistent with the conclusion that **1a** and **1b** are stereoisomers which are interconverted at elevated temperatures by rotation about the single bonds joining the central and peripheral aryl rings.

**Conformation of Hexaarylbenzenes.** A perusal of molecular models suggests that the six peripheral rings of a substituted hexaarylbenzene cannot lie in the plane of the central ring because of steric hindrance. An x-ray structure determination of hexaphenylbenzene itself[7] showed a propeller conformation in which the peripheral aryl rings make angles of ~65° with the plane of the central ring. An electron diffraction study[8] found that, in the gas phase, the peripheral rings were approximately perpendicular to this plane, with oscillations of about ±10°. These data suggest that, in the ground-state conformation, hexaarylbenzenes assume either a propeller-like geometry or a conformation in which the peripheral rings are approximately perpendicular to the plane of the central rings.

The results reported above for **1** shed some light on the solution conformation of hexaarylbenzenes. In the event of restricted rotation of the peripheral rings, the various possible