bath temperature); ^{1}H NMR ($CDCl_3$) δ 2.39-2.85 (8 H, m, NCH_2), 1.41-1.79 (12 H, br s, CCH_2C and NH_2); ^{13}C NMR ($CDCl_3$, Me_4Si) 27.12, 28.27, 31.62, 41.04, 55.75, 56.26 ppm; mass spectrum m/e 156.164 (calcd for $C_9H_{20}N_2$ 156.163).

***N,N'*-Dimethyl-1,5-diazacycloundecane.** The diamine **27** (780 mg, 5 mmol) in acetonitrile (30 mL) was treated successively with aqueous 37% formaldehyde (4.05 mL, 50 mmol) and sodium cyanoborohydride (754 g, 12.5 mmol) at 25 °C. The mixture was stirred at 25 °C for 1 h. Then glacial acetic acid (25 drops) was added dropwise at 25 °C to neutralize the reaction mixture. Further stirring was continued at 25 °C for 2 h. Evaporation of the solvents, followed by purification of the residue by column chromatography on silica gel (*i*-$PrNH_2$-$CHCl_3$, 1:20), gave *N,N'*-dimethyl-1,5-diazacycloundecane 825 mg, 90% yield) as a colorless oil: TLC R_f 0.40 (*i*-$PrNH_2$-$CHCl_3$, 1:9; IR (liquid film) 1471, 1460 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.21-2.57 (5 H, m, NCH_2), 2.12 (6 H, s, NCH_3), 1.30-1.69 (10 H, br s, CCH_2O); ^{13}C NMR ($CDCl_3$, Me_4Si) 24.39, 25.80, 25.98, 42.01, 53.19, 57.24; mass spectrum m/e 184.200 (calcd for $C_{11}H_{24}N_2$ 184.194).

Bis(*p*-toluenesulfonamide) of 27. Treatment of the diamine **27** with *p*-toluenesulfonyl chloride (2.5 equiv) and triethylamine (5 equiv) in dichloromethane at 0 °C for 1 h and then at 25 °C for 2 h, followed by purification of the resulting crude product by column chromatography on silica gel (ether-hexane, 1:1), gave the bis(*p*-toluenesulfonamide) as white crystals: TLC R_f 0.29 (ether-hexane, 1:1); IR (Nujol) 1340, 1159 cm^{-1} (SO_2); ^{1}H NMR ($CDCl_3$) δ 7.10-7.77 (5 H, m, aryl CH), 2.76-3.26 (8 H, br t, NCH_2), 2.42 (6 H, s, CH_3), 1.41-2.01 (10 H, br s, CCH_2C); mass spectrum, m/e 309 (M^+ - TsH).

General Methods for Preparation of Cyclic Amidines. Method A. The lactam (10 mmol) was added to a solution of triethyloxonium tetrafluoroborate[32] (11 mmol) in dichloromethane (25 mL) at 25 °C, and the resulting mixture was stirred at 25 °C for 17 h. Then the mixture was poured onto 5% potassium hydroxide solution (50 mL). The organic layer was separated and washed with cold water (3 × 50 mL). Each aqueous layer was washed with dichloromethane. The combined extracts were concentrated to give the imino ether in quantitative yield. Without purification this was dissolved in aziridine[33] (0.8 mL)-dichloromethane (3.3 mL) and treated with ammonium bromide (0.2 mmol) at 25 °C. Further stirring was continued at 25 °C for 30 h to ensure the formation of amidine, which was rearranged by exposure to iodine (0.5 mL) in benzene (15 mL) at 25 °C for 4 h and then reflux for 1 h to furnish the dihydroimidazole after purification by column chromatography on silica gel.

Method B. The lactam (10 mmol) was converted as described above into the imino ether in quantitative yield, which was treated with 3-bromopropylamine hydrobromide (11 mmol) in absolute ethanol (15 mL) at 25 °C. Stirring was continued at 25 °C for 40 h. Then powdered potassium carbonate (22 mmol) was added at 0 °C and the whole mixture was stirred at 0 °C for 150 min. Dilution with chloroform (300 mL), filtration, and washing of the residue with chloroform gave the tetrahydropyrimidine after purification by preparative TLC.

Method C. Sodium ethoxide was prepared by dissolving metallic sodium (10 mmol) in absolute ethanol (5 mL), followed by evaporation of excess ethanol. Toluene (30 mL) and the lactam (10 mmol) were added at 25 °C, and the resulting suspension was heated gently until a clear yellow solution was produced. Then acrylonitrile (100 mmol) was added slowly over 4 h at 25 °C with vigorous stirring. Further stirring was carried out at 25 °C for 3 h. The mixture was diluted with ethyl acetate to separate the polymer as yellow precipitates. The filtrate was concentrated and directly subjected to column chromatography on silica gel to give the *N*-cyanoethyl lactam. The *N*-cyanoethyl lactam (6.6 mmol) was dissolved in absolute ethanol (165 mL)-chloroform (3.3 mL) and hydrogenated over platinum oxide (50 mg) at 25 °C for 9 h. Filtration, washing of the residue with chloroform, and purification of the concentrated filtrate by column chromatography on silica gel gave the *N*-(3-aminopropyl) lactam. Titanium tetrachloride (1.5 mmol) was added dropwise to a solution of *N*-(3-aminopropyl) lactam (1 mmol) in xylene (5 mL) at 25 °C and the resulting mixture was refluxed for 9.5 h. The mixture was then cooled to 25 °C and treated with a methanolic solution (5 mL) of sodium hydroxide (6 mmol). Filtration, washing of the residue with chloroform, and purification by column chromatography on silica gel gave the tetrahydropyrimidine.

Physical properties and analytical data of the cyclic amidines are given in Table V.

(32) Meerwein, H. *Org. Synth.* **1966**, *46*, 113.
(33) Allen, C. F. H.; Spangler, F. W.; Webster, E. R. "Organic Syntheses"; Wiley: New York, 1963; Collect. Vol. 4, p 433.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society.

Effect of Nucleophile Basicity on Intramolecular Nucleophilic Aminolysis Reactions of Carbonate Diesters

Thomas H. Fife* and J. E. C. Hutchins

Contribution from the Department of Biochemistry, University of Southern California, Los Angeles, California 90033. *Received October 6, 1980*

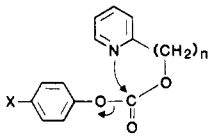
Abstract: The rates of phenol release from para-substituted phenyl 2-pyridylethyl carbonates have been measured in H_2O at 25 °C (μ 0.5 M). The pH-rate constant profiles are sigmoidal, showing participation by the pyridine neutral base species. The D_2O solvent isotope effect is nearly unity, indicating that participation is by a nucleophilic reaction. The Hammett ρ value for intramolecular pyridine assisted phenol release is +2.2, and the fit is better with σ^- than with σ, indicating considerable C-O bond breaking in the transition state. The effective molarity of the neighboring pyridine of *p*-nitrophenyl 2-pyridylethyl carbonate is 81 M in comparison with pyridine acting as a bimolecular catalyst in the hydrolysis of ethyl *p*-nitrophenyl carbonate. Intramolecular nucleophilic attack is 217 times more favorable when a five-membered ring is formed with phenyl 2-pyridylmethyl carbonate than in the case of phenyl 2-pyridylethyl carbonate where the reaction proceeds via a six-membered ring. The effective molarity of neighboring pyridine in the 2-pyridylmethyl series is 2×10^3 M. Sigmoidal pH-rate constant profiles were also obtained with neighboring imidazole, *N,N*-dimethylamino, and *N*-methylpiperidine nucleophiles. Values of the limiting rate constants (k_B) are similar in spite of pK_{app} values which vary from 3.9 to 10. The effective molarity of the dimethylamino group of *p*-nitrophenyl *N,N*-dimethylaminopropyl carbonate is only 32 M in comparison to reaction of trimethylamine with ethyl *p*-nitrophenyl carbonate. On the other hand, the effective molarity of the dimethylamino group of *p*-nitrophenyl *o*-(*N,N*-dimethylamino)phenyl carbonate (pK_{app} = 3.9) is >10^5 M. The most efficient intramolecular nucleophiles in reactions of *p*-nitrophenyl carbonate diesters are those of low pK_a. In contrast, with analogous carboxylate esters the converse is the case, even though the rate constants for bimolecular aminolysis of *p*-nitrophenyl acetate and ethyl *p*-nitrophenyl carbonate are closely similar. These results may indicate that C-N bond formation is not complete in the transition states of the intramolecular reactions.

Intramolecular nucleophilic attack on phenyl esters by amine bases has been extensively studied.[1-5] These reactions are considerably more efficient than corresponding bimolecular reactions proceeding by the same mechanism. The neighboring imidazole

0002-7863/81/1503-4194$01.25/0

group of phenyl esters of γ-(4-imidazolyl)butyric acid has an effective molarity of 9.4–32 M,[2,4] while the effective concentration of the dimethylamino group of *p*-nitrophenyl γ-(*N*,*N*-dimethylamino)butyrate is 5000 M in comparison with trimethylamine attack on *p*-nitrophenyl acetate.[4] The lower limit of the effective molarity of the amine group of phenyl *N*-(2-aminophenyl)-*N*-methylcarbamate is 10^8 M.[5] The effective molarity of a neighboring group is considered to be the ratio of the rate constants for the analogous intra- and intermolecular reactions. This ratio has units of molarity ($s^{-1}/M^{-1}\ s^{-1}$) and represents the concentration of the bimolecular nucleophile required to give a pseudo-first-order rate constant of the magnitude observed in the intramolecular reaction. Considerable effort has been devoted to investigations of the effect of amine basicity in bimolecular aminolysis reactions of phenyl esters.[6-8] Plots of log k_B vs. pK_a have slopes of ~0.8. In contrast, there have been no previous systematic attempts to determine the effect of amine basicity in intramolecular reactions.

Very large effective molarities are found in the intramolecular reactions of carbamate esters.[5,9,10] Intramolecular nucleophilic reactions of these compounds and related carbonate diesters may proceed with near maximum efficiency.[11] Thus, these esters are ideal compounds with which to study intramolecular processes. We have found that substituted nitrophenyl carbonate diesters can be obtained with relative ease. Furthermore, the rapid intramolecular reactions of such compounds are not complicated by competing hydroxide ion catalysis at pH values below 11–12. Thus, nucleophiles of widely varying basicity can be employed. In view of the importance of ascertaining the influence of pK_a of the nucleophile in attempts to gain increased understanding of intramolecular reactions, we have therefore studied the aminolysis reactions of a series of *p*-nitrophenyl carbonate diesters in which a six-membered ring transition state is formed in all cases and pK_{app} of the intramolecular nucleophile varies from 5.0 to 10.0. A detailed study of the reactions of esters having a neighboring pyridyl group, in which the leaving group and the ring size required for nucleophilic attack are varied, was also undertaken to de-



termine any mechanistic differences in the intramolecular reactions of carbonate and carboxylate esters. It might be expected that the presence of oxygen adjoining the carbonyl group of the carbonate diesters would lead to significant differences in transition state structure for the two types of compounds. There has been considerable recent interest in the bimolecular aminolysis of carbonate diesters.[12-16]

Experimental Section

Materials. ***p*-Nitrophenyl *o*-(*N*,*N*-dimethylamino)phenyl carbonate (I)** was prepared by adding *p*-nitrophenyl chloroformate in anhydrous ether dropwise to 2 equiv of *o*-dimethylaminophenol in ether. The mixture was stirred for 3 h. After filtration and removal of the ether by rotary evaporation, the residue was recrystallized from hexane, mp 93–94 °C. Anal. Calcd for $C_{15}H_{14}N_2O_5$: C, 59.60; H, 4.67; N, 9.27. Found: C, 59.41; H, 5.04; N, 9.67.

***p*-Nitrophenyl 2-Pyridylethyl Carbonate Hydrochloride (II).** 4-Nitrophenyl chloroformate (Pierce, 4.52 g, 0.022 mol) was stirred in a three-necked 250-mL flask with 50 mL of anhydrous ether until dissolved. Redistilled 2-pyridylethanol (Matheson Coleman and Bell Technical grade) (2.76 g, 0.022 mol) was dissolved in 20 mL of dry ether and introduced into the reaction flask over a period of 20 min via a dropping funnel. The mixture was stirred for 2 h after addition. The white precipitate was collected quickly on a Büchner funnel, washed with dry ether, and recrystallized from absolute ethanol. The ester hydrochloride melted at 168–170 °C. Anal. Calcd for $C_{14}H_{13}ClN_2O_5$: C, 51.78; H, 4.04; N, 8.63. Found: C, 51.62; H, 4.02; N, 8.43. Hydrolysis in basic aqueous solution gave a theoretical amount of *p*-nitrophenol.

***p*-Chlorophenyl 2-Pyridylethyl Carbonate Hydrochloride.** 4-Chlorophenyl chloroformate was prepared by adding 4-chlorophenol (12.9 g, 0.1 mol) slowly to a stirred, cooled suspension of NaH (4.1 g of 56% emulsion, 0.1 mol) in dried benzene. After hydrogen evolution ceased, the mixture was added, in portions, to a cooled solution of phosgene in benzene (100 mL, 12.5% phosgene). After stirring for 30 min the mixture was refluxed for 1 h and excess phosgene removed. Precipitated NaCl was filtered off, and the solution was evaporated. The crude chloroformate distilled at 91 °C (4.9 mm) yielding a clear product n^{23}_D 1.5360; lit.[17] bp 79–80 °C (5 mm). By stirring an ether solution of 2-pyridylethanol and 4-chlorophenyl chloroformate for 5 days at room temperature, a flocculent, hygroscopic white powder was obtained which was recrystallized from ethanol, melting at 145–148 °C. The infrared spectrum and the amount of phenol released in aqueous base were consistent with the required compound. Anal. Calcd for $C_{14}H_{13}Cl_2NO_3$: C, 53.52; H, 4.17; N, 4.46. Found: C, 53.59; H, 4.40; N, 4.19.

Phenyl 2-Pyridylethyl Carbonate. Phenyl chloroformate (J. T. Baker, 7.04 g, 0.045 mol) and 2-pyridylethanol (5.54 g, 0.045 mol) were separately dissolved in dried benzene and cautiously mixed together in a cooled flask. Stirring was continued overnight at room temperature, and the oil which separated was added to water. The solution was made basic to pH 8 and rapidly extracted with ether. After drying over Na_2SO_4, the ether was removed to yield an oil which solidified on addition of hexane followed by scratching the container wall with a glass rod. Recrystallization from cyclohexane gave white needles (mp 57–59 °C). Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.08; H, 5.41; N, 5.79.

***p*-Methoxyphenyl 2-Pyridylethyl Carbonate.** 4-Methoxyphenyl chloroformate was prepared in a manner similar to that described for 3-chlorophenyl chloroformate.[18] It was obtained as a clear liquid boiling at 68–69 °C (0.3 mm), n^{23}_D 1.5210. *p*-Methoxyphenyl 2-pyridylethyl carbonate was prepared in a manner identical with that described for the unsubstituted derivative. Stirring was continued for 48 h. The free base was obtained by basifying an ice-cold aqueous solution of the hydrochloride and rapidly extracting with ether. Recrystallization from hexane, following treatment with charcoal, yielded white crystals, mp 73–74.5 °C. Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13. Found: C, 66.04; H, 5.60; N, 5.06.

***p*-Nitrophenyl 2-Pyridylpropyl Carbonate.** 4-Nitrophenyl chloroformate (6.82 g) was dissolved in 100 mL of dry ether, and 2-pyridylpropanol (4.63 g, Matheson Coleman and Bell), dissolved in 30 mL of ether, was added dropwise over 30 min. After the mixture was stirred for 1 h at room temperature, 1 equiv of *N*-methylmorpholine (3.28 g) was added and stirring continued overnight. The precipitated material was removed, and the ether was evaporated to yield a yellow oil which soon crystallized. The solid was triturated with hexane at 40 °C and the liquid decanted (thus removing *p*-nitrophenol). Upon cooling, white needles appeared (mp 50.5–51.5 °C). Anal. Calcd for $C_{15}H_{14}N_2O_5$: C, 59.60; H, 4.67; N, 9.27. Found: C, 59.85; H, 5.02; N, 9.16.

Phenyl 2-Pyridylmethyl Carbonate Hydrochloride. Redistilled 2-pyridylcarbinol (Aldrich, 5.9 g, 0.054 mol) dissolved in anhydrous ether was slowly added to phenyl chloroformate (J. T. Baker, 8.5 g, 0.054 mol) in ether. A white precipitate formed immediately. The mixture was stirred overnight. After the solid was collected by filtration it was washed twice with dry ether and recrystallized as white crystals from ethyl acetate which had been dried over 4A molecular sieves. The hydrochloride melted at 115–117 °C. Anal. Calcd for $C_{13}H_{12}ClNO_3$: C, 58.77; H, 4.55; N, 5.27. Found: C, 58.79; H, 5.02; N, 5.28.

***p*-Nitrophenyl *N*,*N*'-dimethylaminopropyl carbonate hydrochloride (IV)** was prepared by adding *p*-nitrophenyl chloroformate in anhydrous ether to an equivalent quantity of *N*,*N*-dimethylaminopropanol in ether.

(1) Bruice, T. C.; Benkovic, S. J. "Bioorganic Mechanisms"; W. A. Benjamin: New York, 1966. Jencks, W. P. "Catalysis in Chemistry and Enzymology"; McGraw-Hill: New York, 1969.
(2) Bruice, T. C.; Sturtevant, J. M. *J. Am. Chem. Soc.* **1959**, *81*, 2860.
(3) Fife, T. H.; Bambery, R. J.; DeMark, B. R. *J. Am. Chem. Soc.* **1978**, *100*, 5500.
(4) Bruice, T. C.; Benkovic, S. J. *J. Am. Chem. Soc.* **1963**, *85*, 1.
(5) Fife, T. H.; Hutchins, J. E. C.; Wang, M. S. *J. Am. Chem. Soc.* **1975**, *97*, 5878.
(6) Bruice, T. C.; Lapinski, R. *J. Am. Chem. Soc.* **1958**, *80*, 2265.
(7) Jencks, W. P.; Carriuolo, J. *J. Am. Chem. Soc.* **1960**, *82*, 1778.
(8) Jencks, W. P.; Gilchrist, M. *J. Am. Chem. Soc.* **1968**, *90*, 2622.
(9) Hutchins, J. E. C.; Fife, T. H. *J. Am. Chem. Soc.* **1973**, *95*, 2282.
(10) Hutchins, J. E. C.; Fife, T. H. *J. Am. Chem. Soc.* **1973**, *95*, 3786.
(11) Fife, T. H. "Bioorganic Chemistry"; Van Tamelen, E. E., Ed.; Academic Press: New York, 1977; p 93.
(12) Fife, T. H.; McMahon, D. M. *J. Org. Chem.* **1970**, *35*, 3699.
(13) Bond, P. M.; Moodie, R. B. *J. Chem. Soc., Perkin Trans. 2* **1976**, 679.
(14) Gresser, M. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 6963.
(15) Gresser, M. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 6970.
(16) Castro, E. A.; Gil, F. J. *J. Am. Chem. Soc.* **1977**, *99*, 7611.
(17) Iwakura, Y.; Nabeya, A. *J. Org. Chem.* **1960**, *25*, 1118.
(18) Juenge, E. C.; Spangler, P. *J. Org. Chem.* **1964**, *29*, 226.

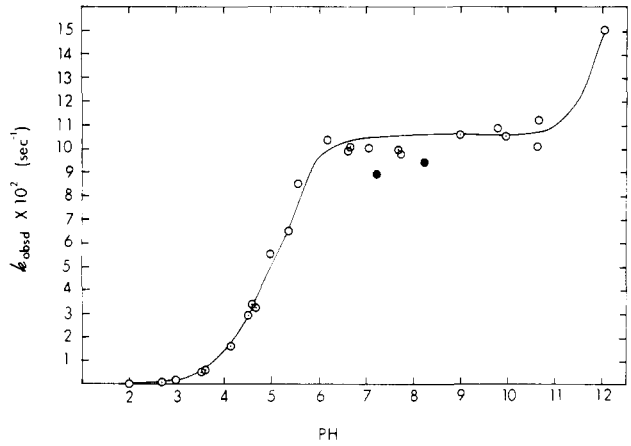


Figure 1. Plot of k_{obsd} vs. pH for *p*-nitrophenol release from *p*-nitrophenyl 2-pyridylethyl carbonate at 25 °C and μ 0.5 M (with KCl) in H_2O (○) and D_2O (●).

The mixture was stirred for 3 h. After filtering and washing with ether, the hydrochloride salt was recrystallized from ethanol, mp 138–140 °C (dec). Anal. Calcd for $C_{12}H_{17}ClN_2O_5$: C, 47.30; H, 5.62; N, 9.19. Found: C, 47.31; H, 6.07; N, 9.07.

Ethyl 4-(substituted phenyl) carbonates were made according to the following procedure: equimolar amounts of ethyl chloroformate and the appropriate substituted phenol were mixed in ether, and a further equimolar portion of pyridine in ether was slowly added. After addition, the reaction mixture was stirred overnight. The mixture was filtered, and the ether was evaporated. Ethyl *p*-chlorophenyl carbonate was purified by distillation [bp 151–152 °C (34 mm), n^{23}_D 1.5074; lit.[19] bp 149–151 °C (33 mm), n^{20}_D 1.5050]. Ethyl *p*-cyanophenyl carbonate was distilled (0.8 mm, 105–106 °C). Anal. Calcd for $C_{10}H_9NO_3$: C, 62.82; H, 4.74. Found: C, 63.47; H, 4.74. Ethyl *m*-nitrophenyl carbonate was recrystallized from cyclohexane, mp 50–51 °C, lit.[20] 52.5–53 °C. Ethyl 4-nitrophenyl carbonate was obtained by a previously described procedure.[21] Recrystallization from dry cyclohexane yielded white crystals, mp 66–67 °C, lit.[22] 67–68 °C.

Kinetic Measurements. The hydrolysis of para-substituted phenyl 2-pyridylethyl carbonates in aqueous buffers (μ 0.5 M) was measured at 25 and 50 °C. Substrates were introduced into the reaction cuvette in 10–15 μL of acetonitrile. The rate of appearance of the corresponding phenol or phenolate ion was monitored spectrophotometrically, using a Gilford 2000 recording spectrophotometer (1-cm quartz cells). Constant temperature was maintained by circulating water from a Precision Scientific Lo Temptrol Model-154 circulating bath around the cell compartment. Reactions that were too rapid to be monitored with a conventional spectrophotometer were followed using a Durrum–Gibson stopped-flow spectrophotometer (Model D-110). The substrate was dissolved at the desired concentration in an HCl solution where it is reasonably stable. This solution was introduced into one of two identical drive syringes. The other syringe contained the appropriate buffer. The drive syringes, mixing chamber, and cuvette were suspended in a water trough whose temperature was maintained at 25 °C. Optical density changes after mixing were recorded on a Hewlett-Packard storage oscilloscope (Model 1207B). Absorption changes corresponding to appearance of the appropriate phenol (or phenolate ion) were measured at the following wavelengths: *p*-NO_2, 330 or 400 nm; *p*-Cl, 280 nm; unsubst, 270 nm; *p*-OCH_3, 290 nm. The solution pH was determined after each run using a Radiometer pH Meter 22 equipped with GK 2302B combination electrode.

The pyridine-catalyzed hydrolysis of ethyl (substituted phenyl) carbonates was followed in 0–0.5 M pyridine solutions at pH 7.70 (phosphate buffer, μ 0.5, 25 °C) and at pH 5.38 in pyridine–pyridine hydrochloride buffers. Reactions were again monitored by following release of the corresponding phenol or phenolate ion, using wavelengths given above, and for *p*-CN, 285 nm, *m*-NO_2, 330 nm.

Results

The rates of phenol release from (substituted phenyl) 2-pyridylethyl carbonate esters were determined at 25 and 50 °C with μ 0.5 M. In Figure 1 is shown a plot of k_{obsd} vs. pH for the *p*-nitro-substituted ester. Sigmoidal pH–rate constant profiles were obtained in each case showing participation by the base species of the pyridyl group. Values of pK_{app} and k_{py}, the rate constant for maximum participation by the pyridine group, are reported in Table I. In D_2O, k_{py} is only slightly less than in H_2O ($k_{py}^{H_2O}/k_{py}^{D_2O}$ = 1.1). A plot of log k_{py} vs. σ^-, the Hammett conjugative substituent constant,[23] is given in Figure 2. The least-squares value of ρ is +2.2. Sigmoidal pH–rate constant profiles were also obtained for phenyl 2-pyridylmethyl and phenyl 2-pyridylpropyl carbonate; values of pK_{app} and k_{py} are reported in Table I.

Table I. Rate Constants for Release of Substituted Phenols from Para-Substituted Phenyl 2-Pyridylmethyl, -ethyl, and -propyl Carbonate Esters at 25 °C and μ 0.5 M (with KCl)

compound	para substituent	k_{py}, s^{-1}	pK_{app}
2-pyridylethyl	OCH_3	6.5×10^{-5}	
		5.5×10^{-4}[a]	4.75
	H	1.15×10^{-4}	
		1.13×10^{-3}[a]	4.75
		1.02×10^{-3}[a,b]	
	Cl	5.74×10^{-4}	
		5.90×10^{-3}[a]	4.80
	NO_2	1.05×10^{-1}	5.03
		9.07×10^{-2}[b]	
2-pyridylmethyl	H	2.5×10^{-2}	3.6
		2.33×10^{-2}[b]	
2-pyridylpropyl	NO_2	2.80×10^{-4}[a]	4.90
		2.68×10^{-4}[a,b]	

[a] At 50 °C. [b] In D_2O.

Table II. Second-Order Rate Constants for Pyridine-Catalyzed Hydrolysis of Ethyl (Substituted Phenyl) Carbonate Diesters at 25 °C, μ 0.5 M

substituent	$k_2 \times 10^3$ M^{-1} s^{-1}	σ^-
p-NO_2	1.29	1.27
p-CN	0.436	1.00
m-NO_2	0.254	0.71
p-Cl	0.024	0.227

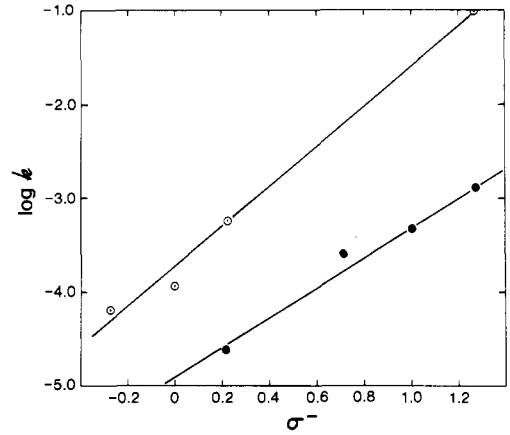


Figure 2. Plot of log k_{py} (s^{-1}) vs. σ^- for reactions of substituted phenyl 2-pyridylethyl carbonate (○) and a plot of log k_2 (M^{-1} s^{-1}) vs. σ^- for pyridine-catalyzed release of phenol from ethyl (para-substituted phenyl) carbonate esters (●) at 25 °C and μ 0.5 M (with KCl) in H_2O.

(19) Smith, G. G.; Kosters, B. *Chem. Ber.* **1960**, *93*, 2400.
(20) Smith, G. G.; Jones, D. A. K.; Taylor, R. *J. Org. Chem.* **1963**, *28*, 3547.
(21) Shah, A. A.; Connors, K. A. *J. Pharm. Sci.* **1968**, *57*, 282.
(22) Ransom, J. H. *Ber.* **1898**, *31*, 1055.
(23) Wells, P. R. *Chem. Rev.* **1963**, *63*, 171. Leffler, J. E.; Grunwald, E. "Rates and Equilibria of Organic Reactions"; Wiley: New York, 1963; Chapter 7.
(24) Fife, T. H.; Hutchins, J. E. C.; McMahon, D. M. *J. Am. Chem. Soc.* **1972**, *94*, 1316.
(25) Compound V was prepared by the same general procedure as IV. A sharp melting point was not obtained. However, in basic solution release of *p*-nitrophenol was quantitative.

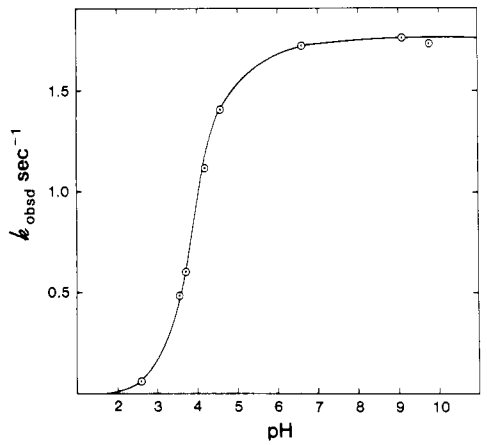


Figure 3. Plot of k_{obsd} vs. pH for *p*-nitrophenol release from *p*-nitrophenyl *o*-(*N*,*N*-dimethylamino)phenyl carbonate at 25 °C and μ 0.5 M (with KCl) in H_2O.

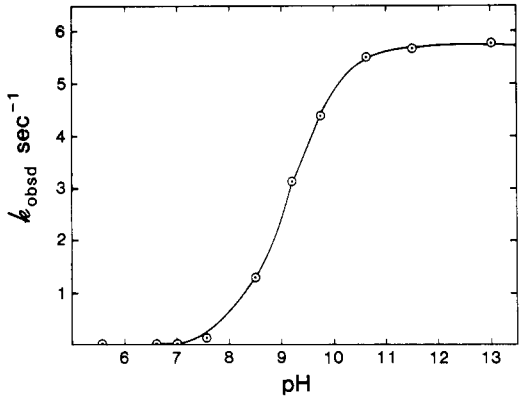


Figure 4. Plot of k_{obsd} vs. pH for *p*-nitrophenol release from *p*-nitrophenyl *N*,*N*-dimethylaminopropyl carbonate at 25 °C and μ 0.5 M (with KCl) in H_2O.

Second-order rate constants for pyridine-catalyzed release of phenol from ethyl para-substituted phenyl carbonate esters were determined at 25 °C, and values of k_2 are given in Table II. In Figure 2 is shown a plot of log k_2 vs. σ^-. The least-squares value of ρ is +1.6. The second-order rate constant for trimethylamine-catalyzed release of *p*-nitrophenoxide ion from ethyl *p*-nitrophenyl carbonate at 25 °C has the value of 0.18 M^{-1} s^{-1}.

The rates of *p*-nitrophenol release from *p*-nitrophenyl *o*-(*N*,*N*-dimethylamino)phenyl carbonate (I) and from *p*-nitrophenyl *N*,*N*-dimethylaminopropyl carbonate (IV) were also measured at 25 °C (μ 0.5 M with KCl). The pH–k_{obsd} profiles are presented in Figures 3 and 4. The sigmoidal profile for I gives pK_{app} = 3.9, and k_B, the limiting rate constant for neighboring group participation, is 1.76 s^{-1}. The profile for IV gives pK_{app} = 9.3 and k_B = 5.75 s^{-1}. Values of the rate constants and pK_{app} for a series of intramolecular nucleophilic reactions are given in Table III. In all cases values of k_{obsd} are given by eq 1.

$$k_{obsd} = [k_B + k_{OH}(OH^-)]\left[\frac{K_{app}}{K_{app} + a_H}\right] \quad (1)$$

Hydroxide ion catalysis, when observed, was, in general, only detected at pH values greater than 12 in hydrolysis of the carbonate diesters having a neighboring group. However, in the case of *p*-nitrophenyl 2-pyridylpropyl carbonate, hydroxide ion catalysis was found at 50 °C above pH 8 (k_{OH} = 34 M^{-1} s^{-1}). Pyridine catalysis was also found in the hydrolysis of *p*-nitrophenyl 2-pyridylpropyl carbonate (k_2 = 0.014 M^{-1} s^{-1}). Buffer catalysis was not observed in any of the intramolecular reactions. For example, in reactions of phenyl 2-pyridylethyl carbonate, buffer dilutions with formate, acetate, pyridine, and phosphate buffers had no effect on the rate constants.

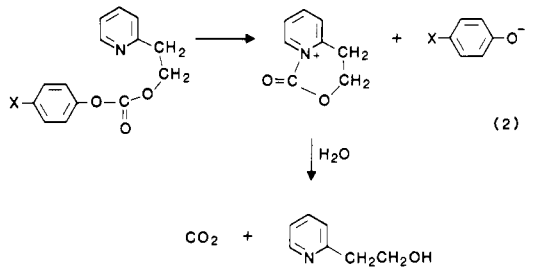
Table III. Rate Constants for Maximum Participation by Neighboring Amine Groups in Carbonate Diester Hydrolysis at 25 °C and μ 0.5 M (with KCl)

compound	k_B, s^{-1}	pK_{app}
p-nitrophenyl *o*-(*N*,*N*-dimethylamino)phenyl carbonate (I)	1.76	3.9
p-nitrophenyl 2-pyridylethyl carbonate (II)	0.10	5.0
p-nitrophenyl 2-(4,5-imidazolyl)ethyl carbonate (III)[a]	0.115 (15 °C)	6.5
p-nitrophenyl *N*,*N*-dimethylaminopropyl carbonate (IV)	5.75	9.3
p-nitrophenyl *N*-methylpiperidineethyl carbonate (V)[b]	4.7	10.0

[a] Reference 24. [b] Reference 25.

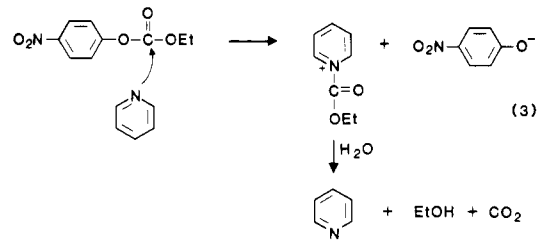
Discussion

The intramolecular pyridine-assisted release of para-substituted phenols from 2-pyridylethyl carbonate diesters undoubtedly proceeds with nucleophilic attack by the pyridine nitrogen (eq 2).



The pH–rate constant profiles are sigmoidal with apparent pK_a values similar to values expected for the pyridine nitrogen. Hydroxide ion catalysis is observed only at high pH. The D_2O solvent isotope effects ($k_{py}^{H_2O}/k_{py}^{D_2O}$) for the nitro and unsubstituted compounds are almost unity, indicating nucleophilic participation by pyridine. General base catalysis by pyridine would be considerably slower in D_2O than H_2O. The linear Hammett plot (Figure 2) also shows that the mechanism is the same for all compounds in the series. The large positive ρ value (+2.2) and the much better fit with σ^-, the conjugative substituent constant,[23] than with σ indicates considerable C–O bond breaking in the critical transition state.

Bimolecular pyridine-catalyzed release of *p*-nitrophenol from ethyl *p*-nitrophenyl carbonate must also take place through a nucleophilic mechanism, eq 3, although, with less reactive esters



having poorer leaving groups, it is possible that the reaction might occur in part via a general base mechanism. As in the case of intramolecular catalysis, the plot of log k_{py} vs. σ^- is linear with a slope of 1.6. The ρ values for the intra- and intermolecular reactions differ (2.2 compared to 1.6). Few comparisons exist of ρ for corresponding bimolecular and intramolecular reactions. Trimethylamine catalysis of phenyl ester hydrolysis is characterized by a ρ of +2.2, quite similar to that for intramolecular catalysis by a dimethylamino group in the hydrolysis of (substituted phenyl) *N*,*N*-dimethylaminobutyrate and valerate esters (+2.5).[4] However, ρ for intramolecular nucleophilic attack in phenyl esters of γ-(4-imidazolyl)butyric acid[2] is less (+1.3) than in bimolecular imidazole attack on phenyl acetates (+1.8). Substituent effects in intramolecular carboxylate ion attack on succinate and glutarate monoesters are much greater (ρ = 2.2)

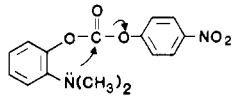
than for acetate ion catalyzed hydrolysis of substituted phenyl acetates (ρ = 1.1).[26] The mechanism of the latter reaction is, however, partly general base.[27] The Hammett ρ is dependent on transition-state structure which could change upon going from a bimolecular to an intramolecular reaction. Thus, there is no compelling reason for expecting ρ values to be similar in intra- and intermolecular reactions.

The ρ value for hydroxide ion catalyzed hydrolysis of substituted phenyl ethyl carbonates is 0.9.[28] Hydroxide ion catalyzed hydrolysis of substituted diaryl carbonates is characterized by a ρ of +2.7.[29] Assuming that substituent effects in the two rings are additive, the calculated ρ for monosubstitution would be +1.35. These values are consistent with a stepwise reaction in which the attack is rate limiting or a concerted reaction with little bond breaking in the transition state. The ρ for hydroxide ion catalyzed hydrolysis of substituted phenyl acetates is 1.1.[4]

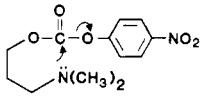
Formation of a five-membered ring transition state in the case of phenyl 2-pyridylmethyl carbonate is 217 times more favorable than with the analogous 2-pyridylethyl ester. Thus, the nucleophilic efficiency of the neighboring pyridine group increases greatly as degrees of rotational freedom of the nucleophile are removed. This was also observed with neighboring carboxylate in phenyl ester hydrolysis,[30] but the rates of intramolecular nucleophilic attack by the dimethylamino group of (substituted phenyl) γ-dimethylaminobutyrate and δ-dimethylaminovalerate esters differ by a factor of only 2.2.[4]

Neutral amine bases must be generally capable of providing large rate enhancements in intramolecular reactions.[5] In comparison with pyridine-catalyzed hydrolysis of ethyl *p*-nitrophenyl carbonate, the effective molarity of the pyridyl group of *p*-nitrophenyl 2-pyridylethyl carbonate is 81 M. Since phenol release from phenyl 2-pyridylmethyl carbonate occurs 217 times more rapidly than from phenyl 2-pyridylethyl carbonate, the effective molarity increases to 2×10^3 M, even though pK_{app} has dropped to 3.6. Assuming the same effect of ring size with the nitrophenyl esters, the effective molarity of the neighboring pyridyl group would be 2×10^4 M in a reaction via a five-membered ring. It is clear that the pyridyl group is an efficient nucleophile in intramolecular reactions despite a relatively low pK_a.

In these intramolecular reactions where pK_{app} values range from 5.0 to 10.0 (six-membered ring transition states), the results suggest that the magnitude of the rate constants for maximum participation by the neighboring group is not greatly influenced by amine basicity (47-fold difference). The *N*-methyl groups of IV and V will, of course, reduce the magnitude of the rate constants for intramolecular participation,[31] but it will be noted in Table III that the rate constants for *p*-nitrophenol release from these compounds are quite similar although pK_{app} differs by a pK_a unit. Likewise rate constants for II and III are nearly identical although pK_{app} differs by 1.5 pK_a units. It may also be noted in Table III that the dimethylamino group nucleophile of *p*-nitrophenyl *o*-(*N*,*N*-dimethylamino)phenyl carbonate (I) has a k_B only



I

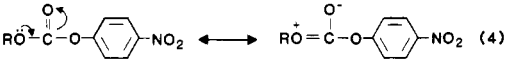


IV

three-fold less than that of *p*-nitrophenyl *N*,*N*-dimethylaminopropyl carbonate (IV), even though its pK_{app} is 5 pK_a units less. The large pK_a difference is almost totally compensated for by the sterically more favorable five-membered ring transition state of I.

The point for trimethylamine lies about 1 log unit below the Brønsted line for aminolysis of *p*-nitrophenyl acetate by primary and secondary amines,[8,32] undoubtedly in part because of increased steric hindrance. Bimolecular reaction of *p*-nitrophenyl acetate with trimethylamine is 186-fold faster than with pyridine,[32] whereas the ratio is 139 with ethyl *p*-nitrophenyl carbonate. It is clear that the bimolecular reactions of carbonate diesters display a similar sensitivity to methyl group substitution on the nitrogen nucleophile as the bimolecular aminolysis reactions of *p*-nitrophenyl acetate.

Bond and Moodie[13] found that the ratio of second-order rate constants for reaction of a series of eight amines, including pyridine and imidazole, with *p*-nitrophenyl acetate and methyl *p*-nitrophenyl carbonate varied only from 1.3 to 2.4, and this is also the case in reaction of trimethylamine with *p*-nitrophenyl acetate and ethyl *p*-nitrophenyl carbonate.[33] Thus, the correspondence between the two types of esters in their bimolecular reactions also extends to the absolute values of the rate constants for aminolysis. The alkoxy group adjoining the carbonyl of carbonate diesters will exert an electron-withdrawing inductive effect which will make attack of the nucleophile easier but which will retard departure of the leaving group. The alkoxy group will also donate electrons (eq 4) through a resonance effect, which will deactivate the



(4)

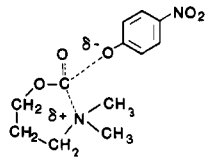
carbonyl, thereby hindering the attack step, but which will aid departure of the leaving group. The relative importance of these effects will depend upon the transition-state structure. The effects must almost exactly compensate in regard to their influence on the rate constants in the bimolecular reactions.

In spite of the very similar rate constants in the bimolecular comparison reactions for carboxylate and carbonate esters, the effective molarity of the dimethylamino group of IV is only 32 M, i.e., less than that of the pyridine group of II and much less than that of the dimethylamino group of *p*-nitrophenyl δ-(*N*,*N*-dimethylamino)valerate (2.3×10^3 M).[4,34] Extrapolation of a Brønsted plot for reaction of a series of sterically similar tertiary amines with *p*-nitrophenyl phenyl carbonate[14] to pK_a = 3.9 gives a rate constant of 5.0×10^{-6} M s^{-1}, from which an approximate effective molarity of 3×10^5 M can be calculated for the dimethylamino group of I. While this comparison is not exact, it does show the great efficiency of the intramolecular reaction of I. Thus, in contrast with carboxylate esters,[35] the most efficient intramolecular nucleophiles in reactions of carbonate diesters having phenolic leaving groups are those of low pK_a.[31]

Differences in effective molarities for groups in intramolecular reactions must be interpreted cautiously because such values depend upon the exactness of the bimolecular comparison. However, in considering the dimethylamino groups of IV and

(26) Gaetjens, E.; Morawetz, H. *J. Am. Chem. Soc.* **1960**, *82*, 5328.
(27) Gold, V.; Oakenfull, D. G.; Riley, T. *J. Chem. Soc. B* **1968**, 515.
(28) Calculated from the data of Cooper, G. D.; Williams, B. *J. Org. Chem.* **1962**, *27*, 3717. Dittert, L. W.; Higuchi, T. *J. Pharm. Sci.* **1963**, *52*, 852.
(29) Cooper, G. D.; Johnson, H. T.; Williams, B. *J. Org. Chem.* **1965**, *30*, 3989.
(30) Bruice, T. C.; Pandit, U. K. *J. Am. Chem. Soc.* **1960**, *82*, 5858.
(31) Attempts to prepare carbonate diesters containing amine nucleophiles of high pK_a having the nitrogen unblocked have to date been unsuccessful. *p*-Nitrophenyl *N*,*N*-dimethylaminoethyl carbonate has k_B = 100 s^{-1} and pK_{app} = 8.3 at 30 °C.
(32) At 26.2 °C (5% dioxane–H_2O). Bender, M. L.; Turnquest, B. W. *J. Am. Chem. Soc.* **1957**, *79*, 1656.
(33) Second-order rate constants are 0.071 M^{-1} s^{-1} for *p*-nitrophenyl acetate (20 °C)[4] (0.099 M^{-1} s^{-1} at 26.2 °C)[32] and 0.18 M^{-1} s^{-1} for ethyl *p*-nitrophenyl carbonate at 25 °C (this study).
(34) The pK_{app} of IV (9.3) is slightly lower than that of *p*-nitrophenyl δ-(*N*,*N*-dimethylamino)valerate (9.9). This is due to the difference in temperature (5 °C) and the inductive effect of the carbonate function. However, the pK_a of trimethylamine employed in the bimolecular comparisons (determined by half-neutralization) was found to be 9.80 in this study at 25 °C and μ 0.5 M, whereas the value found for the trimethylamine employed in the reactions with *p*-nitrophenyl acetate at 20 °C and μ 1.6 M was 10.27.[4] Thus, in both cases the pK_a of the bimolecular comparison amine is higher than pK_{app} by approximately the same amount. Therefore, any differences in rates of *p*-nitrophenol expulsion in the intramolecular reactions caused by differences in pK_{app} should cancel in the effective molarity ratios.
(35) The effective molarity of the imidazolyl group of *p*-nitrophenyl γ-(4-imidazolyl)butyrate is 9.4 M.[4] This ester appears to release *p*-nitrophenol slightly faster than the corresponding carbonate ester (III). It has a rate constant k_B of 3.3 s^{-1} (25 °C)[2] in comparison with k_B = 0.12 s^{-1} (15 °C) for III. However, direct comparison of these rate constants is difficult because of differences in temperature and solvent. The rate constants for the carboxylate ester were determined in 50% ethanol–H_2O (μ 0.04 M).

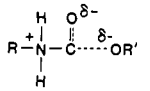
p-nitrophenyl δ-(*N*,*N*-dimethylamino)valerate, the difference in effective molarity of 80-fold clearly shows the greater efficiency of the nucleophilic reaction of the carboxylate ester. The effective molarity ratio is due to the greater rate of the intramolecular reaction of the carboxylate ester[36] than the carbonate diester. In this case the bimolecular comparisons are essentially the same, since the second-order rate constants for reaction of trimethylamine with ethyl *p*-nitrophenyl carbonate and *p*-nitrophenyl acetate are closely similar.[13,33] Thus, either the intramolecular aminolysis reactions of carboxylate esters are more affected by increases in amine basicity than are analogous reactions of carbonate esters, or their intramolecular reactions are less hindered by methyl group substitution on the nucleophilic nitrogen. Either possibility is difficult to reconcile with transition states for the intramolecular nucleophilic reactions in which C–N bond formation is complete. Differences in the effect of amine basicity or methyl substitution imply differences in the extent of bond making with the nucleophile. One or both of these reactions may more closely resemble a concerted reaction in which both C–N bond formation and C–O bond breaking are occurring; i.e., there is a large amount of C–O bond breaking, but C–N bond formation is not complete in the transition state VI.



VI

In the aminolysis of phenyl acetates, tertiary amines exhibit a sensitivity to amine basicity similar to that for primary and secondary amines, which implies that a proton is not necessarily dissociated from the primary and secondary amines upon formation of the transition states.[8] Thus, in the absence of proton transfers, if the reaction proceeds in discrete steps, the product must be formed by direct breakdown of a zwitterionic tetrahedral intermediate. With primary or secondary amine nucleophiles dissociation of a proton from the nucleophile would greatly stabilize an intermediate with respect to reactant. Concerted formation of a neutral tetrahedral intermediate would also avoid an unstable zwitterion, and this process could be of importance in intramolecular aminolysis reactions when the leaving group is poor.[3,37,38] The transition state in all cases will represent a compromise of effects so that the maximum rate will be achieved. The positively charged nitrogen of a zwitterionic tetrahedral intermediate would inhibit electron release by the remaining oxygen in leaving group departure in the intramolecular reactions of carbonate esters, and this inhibiting effect would increase as ring size was decreased. Furthermore, steric effects due to nitrogen substitution would be maximized in a tetrahedral intermediate. Thus, intramolecular nitrogen nucleophiles may react with carbonate esters having a very good leaving group via a transition state approaching that of a concerted reaction in which both bond breaking and formation are important. With carbonate esters, where the remaining group can enhance bond breaking, the tendency for a concerted reaction will be increased. It has been previously suggested that carbonate esters might hydrolyze with concerted bond breaking and bond formation with a nucleophile rather than formation of a tetrahedral intermediate.[39]

The Brønsted β for bimolecular attack of amines on carboxylate esters with phenolic leaving groups is 0.8, and there is no curvature at high amine pK_a except with exceptionally reactive esters.[6,8] In the transition states of bimolecular aminolysis reactions C–N bond formation must be nearly complete.[8,40] With *p*-nitrophenyl acetate the plot of log k_B vs. amine pK_a is linear. A linear plot ($\beta = 0.8$) is also obtained for bimolecular aminolysis of the carbamate ester *p*-nitrophenyl *N*-methyl-*N*-phenylcarbamate.[5] Gregory and Bruice[41] have presented evidence which indicates rate-determining attack of amine in the aminolysis of *p*-nitrophenyl acetate. Jencks and Gilchrist[8] suggested an asymmetrical transition state for aminolysis of phenyl acetates in which there is considerable bond breaking and bond formation with the attacking amine;[42] and it was later proposed[40] that the transition state appears as in VII;



VII

i.e., the rate-determining step is the breakdown of an addition intermediate. It was considered that the curved Brønsted relationship for aminolysis of diaryl carbonates with limiting slopes of 1.0 and 0.3 indicated formation of a tetrahedral intermediate with a change in the rate-limiting step from breakdown of the intermediate at low pK_a to formation at the break point 4–5 pK_a units above the leaving group pK_a.[14,15] A tetrahedral intermediate was also suggested in the reactions of 2,4-dinitrophenyl methyl carbonate with substituted pyridines on the basis of negative deviation of points for 4-amino- and 4-dimethylaminopyridine from the Brønsted line.[16] A concerted reaction might also give rise to a curved Brønsted plot over a wide range of pK_a, since the slope reflects charge development in the transition state, and from the Hammond principle[43] this should vary depending upon basicity of the nucleophile.

While bimolecular aminolysis of phenyl esters may proceed with formation of an addition intermediate, mechanistic differences in the intramolecular and bimolecular aminolysis reactions of *p*-nitrophenyl esters would not be surprising. Striking mechanistic differences have been found in the intramolecular aminolysis reactions of 2-substituted benzoate esters with poor leaving groups in comparison with bimolecular aminolysis of corresponding esters.[3,37,38] There is no reason to assume that intra- and intermolecular nucleophilic reactions will proceed by the same mechanism. Transition-state structure and/or the rate-determining step will very likely be found to vary in many cases.

Conclusions

Aside from the question of whether a tetrahedral intermediate is formed in the intramolecular aminolysis reactions of carbonate diesters, there are striking differences in the intramolecular reactions of nitrophenyl carbonate and carboxylate esters in comparison with corresponding bimolecular reactions. In summary: the efficiency of intramolecular aminolysis in carbonate ester reactions, as measured by the effective molarity, increases as the pK_a of the nucleophile decreases, in contrast to the large increase in efficiency in the case of carboxylate esters as pK_a of the nucleophile increases. Amines of low pK_a can be highly efficient intramolecular nucleophiles with large effective molarities in reactions of carbonate esters. This must also be the case in reactions of carbamate esters in view of the effective molarity of 10^8 M found for the neighboring amino group of phenyl *N*-(2-aminophenyl)-*N*-methylcarbamate[5] with which $pK_{app} = 2.7$. Also, neutral amine nucleophiles show a large increase of efficiency upon going from a six- to a five-membered ring transition state in reactions of carbonate esters (217-fold with pyridyl), comparable to that for COO^- in carboxylate ester reactions and in contrast to the small effect for nitrogen nucleophiles. These differences are undoubtedly due to differences in transition-state structure brought about by the presence of the neighboring alkoxy group in the carbonate diesters.

Acknowledgment. This work was supported by research grants from the National Institutes of Health.

(36) The rate constant k_B for *p*-nitrophenyl δ-(*N*,*N*-dimethylamino)valerate is 166 s^{-1} at 20 °C.[4]

(37) Fife, T. H.; DeMark, B. R. *J. Am. Chem. Soc.* **1976**, *98*, 6978.
(38) Fife, T. H.; DeMark, B. R. *J. Am. Chem. Soc.* **1979**, *101*, 7379.
(39) Johnson, S. L. *Adv. Phys. Org. Chem.* **1967**, *5*, 237.
(40) Satterthwait, A. C.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 7018.
(41) Gregory, M. J.; Bruice, T. C. *J. Am. Chem. Soc.* **1967**, *89*, 2121.
(42) See also Bruice, T. C.; Hegarty, A. F.; Felton, S. M.; Donzel, A.; Kundu, N. G. *J. Am. Chem. Soc.* **1970**, *92*, 1370.
(43) Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334.