banions themselves. For example, although α-methyl substituents have been observed to decrease the rate of formation of a carbanion α to a carbonyl group,[2,14] they can increase the equilibrium constants,[15] just as with carbanions α to nitro groups.[16] Similarly, equilibrium measurements on acetophenone derivatives have shown that α-methoxy substituents stabilize carbanions substantially relative to α-methyl or α-hydrogen.[17] the comparison of α-methoxy with α-methyl is the same as seen in our rate data on ester; the comparison with α-hydrogen is not. Thus, carbanion stability must be an important factor in determining rates of carbanion formation, but it is not the only significant factor. Carbanion stability must be evaluated by equilibrium measurements, not rate measurements. The effect of α-amino substituents on equilibrium constants for carbanion formation by acetophenone derivatives in dimethyl sulfoxide solution has been studied by Bordwell and co-workers.[18]

Experimental Section

Minor modifications of literature procedures were used for the preparation of $Me_2NCH_2CO_2Me$ (1)[19] and methyl hygrate (2).[20] A general esterification procedure[21] was used to make $Me_2CHCH_2CO_2Me$ (3).[22]

Methyl *cis*-2-(Dichloromethyl)cyclopentanecarboxylate (6). A solution of 1.3 g (24 mmol) of NaOMe in 10 mL of MeOH was added dropwise to a mixture of 3.3 g (18 mmol) of 7,7-dichlorobicyclo[3.2.0]heptan-6-one[5] and 5 mL of MeOH at −5 to −20 °C. After removal of methanol, the residue was extracted with ether. After evaporation of the ether, distillation gave 2.4 g (62%) of 6: bp 73–74 °C (0.7 mm); NMR (CCl_4) δ 6.00 (d, 1, J = 9 Hz, $CHCl_2$), 3.65 (s, 3, OCH_3), 2.90 (m, 2, CHCH), 2.3–1.8 (m, 6, $CH_2CH_2CH_2$).

Anal. Calcd for $C_8H_{12}O_2Cl_2$: C, 45.52; H, 5.73; Cl, 33.59. Found: C, 45.76; H, 5.74; Cl, 33.09.

Methyl *cis*-2-Methylcyclopentanecarboxylate (4). Dropwise addition of 2.3 g (11 mol) of 6 to 9 g (26 mmol) of tri-*n*-butyltin hydride in 40 mL of *n*-hexane and a little 2-azobis(isobutyronitrile) at reflux was followed by 1 h of additional refluxing. Distillation gave 0.9 g (57%) of 4: bp 28–29 °C (1 mm): NMR (CCl_4) δ 3.60 (s, 3, OCH_3), 2.76 (m, 1, $CHCO_2$), 2.30 (m, 1, $CHCH_3$), 1.70 (m, 6, $CH_2CH_2CH_2$), 0.90 (d, 3, J = 6 Hz, $CHCH_3$). A small amount of 5 present as an impurity was removed by preparative VPC.

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.24; H, 9.91.

Methyl *trans*-2-Methylcyclopentanecarboxylate (5). Dropwise addition of 6.62 g (45 mmol) of 2-methylcyclopentanecarbonyl chloride[8] to 1.45 g (45 mmol) of methanol at 0 °C was followed by 1 h of stirring at room temperature. The mixture was poured into water and the organic layer was washed with sodium bicarbonate solution, dried over magnesium sulfate, and distilled to give 6 g (93%) of ester: bp 28–33 °C (0.5 mm); NMR (CCl_4) δ 3.60 (s, 3, OCH_3), 2.3–1.5 (m, 8, $CHCH_2CH_2CH_2CH$), 1.00 (d, 3, J = 6 Hz, $CHCH_3$) plus the peaks for 4, which VPC on a 6-ft 10% polyphenyl ether column showed to be present to the extent of about 12% as a more slowly eluted but partly overlapping peak. Preparative VPC gave a mixture of 93% 5 and 7% 4, which was used for the kinetic studies.

Kinetic Procedure. The reaction kinetics were followed, as described previously,[2,3] by IR measurements of the concentration of MeOH being formed. With the 0.05-mm Irtran-2 cell used the extinction coefficient was 107.4 M^{-1} cm^{-1}. The sodium methoxide concentration was determined at various times during each run. Although the concentration usually decreased slightly during the course of a run, in never deviated by more than 3% from the average value except in the run with 1 and 0.0298 M average [NaOMe], where deviations were as large as 8%. Initial ester concentrations were in the range 0.24–0.66 M. In the kinetic studies on 5 the presence of about 7% 4 was corrected for, using the rate constant obtained from studies on pure 4. All the other esters were at least 99% pure.

Equilibrium between 4 and 5. A solution of 0.4 g of a mixture of 12% 4 and 88% 5 in 6 mL of 1.4 M NaOMe was kept at 35.0 ± 0.1 °C for 34 days. After neutralization with 0.7 M HCl and extraction with ether, the ether was largely evaporated and the residue found by VPC analysis on a 6 ft-10% polyphenyl ether column at 85 °C to contain 9.4 times as much 5 as 4. The rate constant for approach to equilibrium (the sum of the forward and reverse rate constants for isomerization) may be shown to be between the rate constants for formation of the common carbanion by 4 and 5. If these rate constants are the same in CH_3OH as in CH_3OD, the half-time for equilibration under the present conditions will be between 8 and 29 h.

Registry No. 1, 7148-06-3; 2, 27957-91-1; 3, 556-24-1; 4, 80926-05-2; 5, 63649-24-1; 6, 80926-06-3.

(14) Hine, J.; Zeigler, J. P. *J. Am. Chem. Soc.* **1980**, *102*, 7524–9.
(15) Bordwell, F. G.; Matthews, W. S. *J. Am. Chem. Soc.* **1974**, *96*, 1214–6.
(16) Pearson, R. G.; Dillon, R. L. *J. Am. Chem. Soc.* **1953**, *75*, 2439–43.
(17) Bordwell, F. G.; Van Der Puy, M.; Vanier, N. *J. Org. Chem.* **1976**, *41*, 1885–6.
(18) Bordwell, F. G., Northwestern University, personal communication, 1981.
(19) Willstätter, R. *Ber. Dtsch. Chem. Ges.* **1902**, *35*, 584–620.
(20) King, H. *J. Chem. Soc.* **1941**, 337–9.
(21) Mičović, V. M. In "Organic Syntheses"; Gilman, H., Blatt, A. H., Ed.; Wiley: New York, 1943; Collect. Vol. II, pp 264–5.
(22) Petyunin, P. A. *J. Gen. Chem. U.S.S.R.* **1940**, *10*, 35–8; *Chem. Abstr.* **1940**, *34*, 4726[9].

Hydrolysis of Medium-Ring Phosphates. Mechanism of Rate Acceleration by an Amino Group

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Received September 21, 1981

A series of 2-oxo-2-(*p*-nitrophenoxy)-1,3-dioxa-2-phosphacyclooctane derivatives (1–5) having either a nitrogen or a sulfur atom placed transannularly in the ring were synthesized, and their rates of hydrolysis were examined. The pH–rate profile shows that while 1 undergoes hydrolysis over a wide pH range, others are hydrolyzed at a significant rate only in basic medium, thus implicating the amino function for rate enhancement. By comparison with rates obtained with 2 and 3 and the quarternary derivative 4, a mechanism involving rate-determining proton transfer from nitrogen to phosphoryl oxygen has been proposed for the hydrolysis of 1 at an acidic pH. The enhancement in the rate of spontaneous hydrolysis of the same compound, however, is explained by a combination of intramolecular general-base and nucleophilic catalysis.

The question of rate acceleration by neighboring carboxyl[1,2], hydroxyl[3], or amide[4] functions in phosphate ester hydrolysis has been the subject of several investigations. Of particular interest to our present problem are the

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Table I. Observed Pseudo-First-Order Rate Constants[a] at Different pH for Compounds 1-5 (in min^{-1})

condition	compd 1	2	3	4	5
0.055 N NaOH	7.95×10^{-3}	2.57×10^{-2}	4.80×10^{-3}	280[c]	4.41×10^{-4}
0.0055 N NaOH	9.30×10^{-4}	1.08×10^{-3}	1.75×10^{-4}		
10.6 carbonate buffer	4.46×10^{-4}	1.17×10^{-4}	3.17×10^{-7}[b]		
9.95 borate buffer	4.30×10^{-4}		3.07×10^{-7}[b]	1.75×10^{-2}	
8.00 phosphate buffer		1.00×10^{-5}[b]		1.0×10^{-3}	
7.60 phosphate buffer	3.33×10^{-4}			1.0×10^{-3}	
6.30 acetate buffer	8.85×10^{-4}				
5.65 acetate buffer	2.30×10^{-3}				
4.60 acetate buffer	1.46×10^{-2}				
2.16 HCl (KCl)	6.14×10^{-2}				
1.26 HCl (KCl)	5.87×10^{-2}				

[a] The rate constants are obtained in 45% (v/v) dioxane-water at 35 ± 0.1 °C at μ = 0.2 (KCl). For 2-4, values obtained at zero buffer concentration are presented. [b] Extrapolated rate from 55 and 75 °C. [c] Estimated from the rate constant obtained at pH 9.95 and K_w in 45% dioxane-water.

studies relating to rate acceleration by quinolinyl[5a] and pyridyl[5b] nitrogen. While nucleophilic catalysis has been implicated in the former system, the mechanism of the latter is decribed as general-base catalysis because of the strain involved in the formation of the three-membered ring. It was therefore thought that a suitably placed aliphatic amine could catalyze phosphoryl transfer more effectively in a physiological pH range, and from this viewpoint the kinetics of hydrolysis of medium-ring phosphates (1-5) capable of transannular interaction[6] were examined. Recently Lazarus and Benkovic[7] described the catalytic role of the amine function in the hydrolysis of acyclic phosphorylethanolamine derivatives. Our results show that amino group placed in a cyclic compound behaves quite differently from the acyclic analogues investigated by Lazarus et al. and demonstrate that a change in the mechanism of intramolecular participation can be brought about by structural modification.

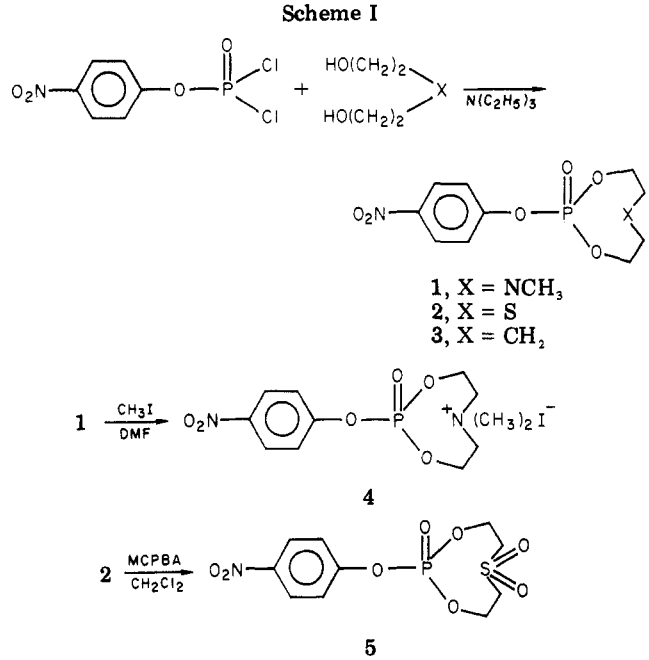
Synthesis

By the one-step procedure shown in Scheme I, cyclic phosphates 1-3 were synthesized and were characterized by standard methods (see Experimental Section). On quarternization with methyl iodide in DMF, 1 was converted to 4, and oxidation of 2 gave the corresponding sulfone derivative 5.

Results

The reactions followed pseudo-first-order kinetics in dioxane-water (45% v/v). For relatively fast reactions with $k > 5 \times 10^{-4}$ min^{-1}, they were monitored for 3 half-lives, and for others only initial rates were obtained. The rate constants obtained from the integrated first-order rate equation and a graphical representation of the same results

Scheme I



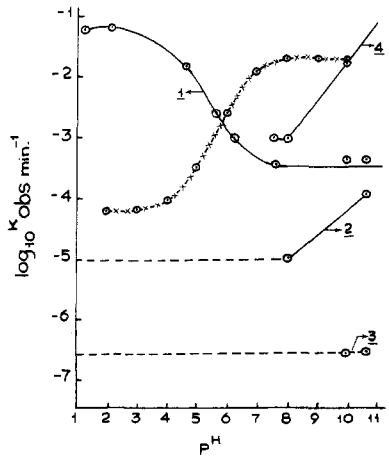


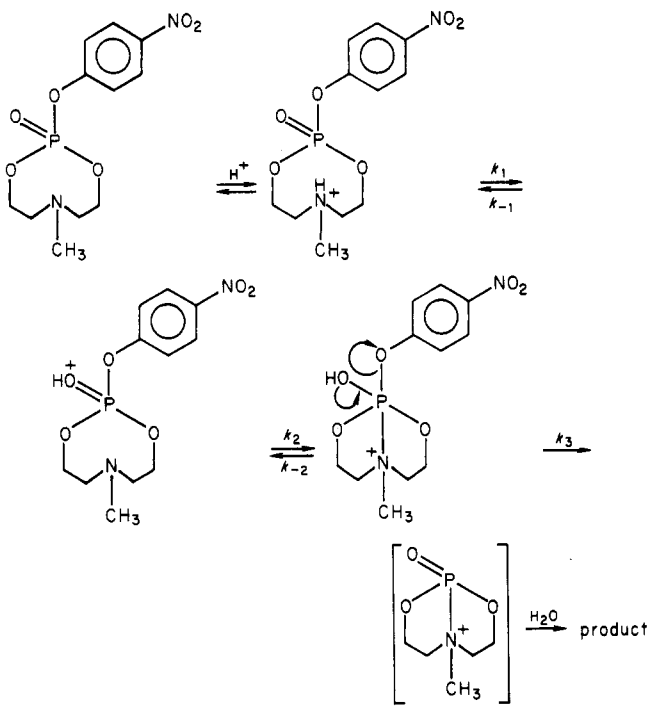
Figure 1. pH-log (rate) profile for 1-4 and the curve for compound **2a** of ref 7 (X-X-).

are given in Table I and Figure 1, respectively.

Spectral scanning experiments indicated that all esters hydrolyzed with 1:1 stoichiometry, and *p*-nitrophenol (ate) release was quantitative within experimental error. Therefore, the reaction under consideration is presumably *p*-nitrophenyl ester cleavage. This agrees with Kirby et al.[8], who hydrolyzed six-membered cyclic phosphates

(1) For a review see (a) S. J. Benkovic and K. J. Schray in "The Enzymes", P. D. Boyer, Ed., 3rd ed., Academic Press, New York, 1973, p. 201; (b) V. B. Bel'skii, *Russ. Chem. Rev. (Engl. Transl.)* **46**, 828 (1977).
(2) (a) M. L. Bender and J. M. Lawlor, *J. Am. Chem. Soc.*, **85**, 3010 (1963); (b) R. H. Bromilov, S. A. Khan, and A. J. Kirby, *J. Chem. Soc. B*, 1091 (1971); (c) S.S. Simons, Jr., *J. Am. Chem. Soc.*, **96**, 6492 (1974).
(3) J. I. G. Cadogen, J. A. Challis, and D. T. Eastlick, *J. Chem. Soc. B*, 1988 (1971).
(4) (a) R. Kluger and J. L. W. Chan, *J. Am. Chem. Soc.*, **98**, 4913 (1976); (b) R. A. Naylor and A. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1908 (1976).
(5) (a) J. S. Loran and A. Williams, *J. Chem. Soc., Perkin Trans. 2*, 64 (1977); (b) J. S. Loran, R. A. Naylor, and A. Williams, *ibid.*, 418 (1977).
(6) R. K. Sharma, K. Sampath, and R. Vaidyanathaswamy, *J. Chem. Res., Synop.*, 12 (1980); *J. Chem. Res., Miniprint*, 0217 (1980).
(7) (a) R. A. Lazarus and S. J. Benkovic, *J. Am. Chem. Soc.*, **101**, 4300 (1979); (b) R. A. Lazarus, P. A. Benkovic, and S. J. Benkovic, *J. Chem. Soc., Perkin Trans. 2*, 373 (1980).

Scheme II

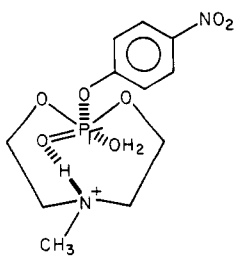


containing the same leaving group.

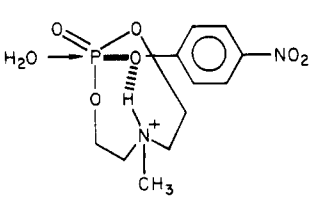
The following observations deserve special mention. (a) The hydrolysis of 1 is specific acid and base catalyzed whereas others are subject to buffer catalysis. For these compounds, therefore, rate constants extrapolated to zero buffer concentration are presented in Table I. (b) While 1 undergoes hydrolysis both under acidic and alkaline conditions, others show a significant hydrolysis rate only at higher pH. (c) pH–rate profiles for 1 and other phosphorylethanolamines studied by Lazarus et al.[7a] differ widely (clear from the curve in Figure 1 drawn from the rate constants and eq 1 provided by these authors for their compound **2a**). (d) In comparison to the rates for other cyclic derivatives, the rate of spontaneous hydrolysis of 1 is higher.

Discussion

Since *p*-nitrophenol was not detected during the hydrolysis of **2** and **3** at pH 4.6 and 2.16, it was assumed that the lowest rates expected are those of the pH-independent water reaction. The curves for these compounds in Figure 1 were accordingly extended to low pH. At the maximum rate observed for 1 (at pH 2.0) the rate enhancements over **2** and **3** are 6×10^3- and 2×10^5-fold, respectively. This rate acceleration is obviously due to participation of nitrogen atom which could be by any one of the following mechanisms: intramolecular general-acid catalysis through phosphoryl oxygen (I) or through *p*-nitrophenoxy oxygen



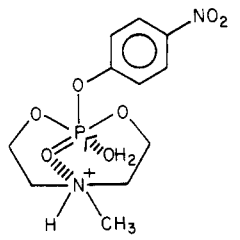
I



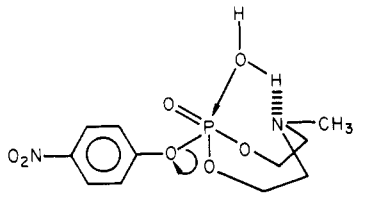
II

(8) S. A. Khan and A. J. Kirby, *J. Chem. Soc. B*, 1172 (1970).

(II), proton transfer from nitrogen to phosphoryl oxygen followed by nucleophilic attack by nitrogen (Scheme II) or electrostatic catalysis for water attack (III). The last



III



IV

mechanism (electrostatic catalysis) can be discarded for the following reasons. First, comparison to the quarternary derivative 4, the parent amine 1 hydrolyzes 60 times faster at pH 2.0, the pH at which it is expected to be completely protonated (apparent $pK_a = 4.21$).[9] Second, when 4 was hydrolyzed in 0.1 M HCl and in acetate buffer (pH 4.6), *p*-nitrophenol was not detected at all for much longer period than it takes to undergo complete hydrolysis at pH 7.6. Apparently compound 4 does not follow a mechanism similar to that for 1 in acid pH, and therefore it can be concluded that quarternary nitrogen per se cannot accelerate the reaction in the case of 1 also.

Intramolecular general-acid catalysis through phosphoryl oxygen as shown in I is also ruled out for the following reasons. First, in phosphorylethanolamine derivatives, the reactivity of the protonated form is entirely due to electrostatic interaction with quarternary nitrogen atom, though the same proximity and structural consideration warrant intramolecular general-acid catalysis also.[7a] Second, the estimated rate acceleration due to a neighboring NH group is only about 20-fold both in phosphono[4b] and carboxy ester hydrolysis.[10] General-acid catalysis through *p*-nitrophenoxy oxygen (II) can be discarded easily because this is the least basic of all oxygens. Therefore, the mechanism of hydrolysis of 1 presumably involves proton donation to phosphoryl oxygen, followed by formation of a pentacovalent intermediate having the *p*-nitrophenoxy groups and the quarternary nitrogen in apical positions (Scheme II). Since the solvent deuterium isotope effect at pD 4.92 is 2.0,[11] which is opposite that expected for a specific acid catalysed reaction, we believe that proton transfer (k_1) is rate determining. Whether or not the proton transfer and nucleophilic attack are concerted cannot be ascertained except that the large negative entropy of activation (−38 eu) at pH 4.6 points to a concerted process.

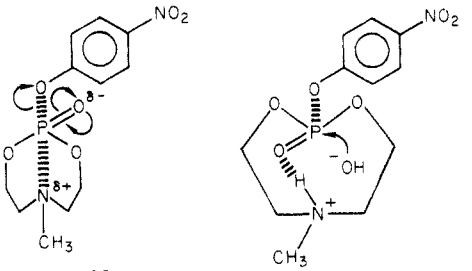
Spontaneous Hydrolysis. Comparison of the pH independent rates of hydrolysis of 1 and 3 indicates that the former is ca. 1000 times more reactive. A slow rate of spontaneous hydrolysis has been noted in six-membered cyclic system having the same leaving group (5.28×10^{-7} min^{-1}).[8] Since the latter reaction was done at 39 °C in about 96% water, the rate difference should have been greater. Several kinetically equivalent mechanisms are possible to explain the rate enhancement such as intra-

(9) The potentiometrically determined pK_a for 1 is 4.21 ± 0.05 and that for its *p*-methoxyphenoxy analogue is 4.67 ± 0.05 at 35 °C in 45% dioxane–water (v/v) with μ = 0.2 (KCl).

(10) A. Williams and G. Salvadori, *J. Chem. Soc., Perkin Trans. 2*, 883 (1972).

(11) The dissociation constant of 1 was corrected in D_2O by the equation $pK_a(D_2O) = 1.02pK_a(H_2O) + 0.41$.[7a] Therefore, the rate obtained at pD 4.92 in D_2O is compared with the rate obtained in H_2O at pH 4.43 by assuming that the concentration of protonated and deuterated forms will be equivalent at these pD (pH) values.

molecular general-base catalysis (IV), intramolecular nucleophilic catalysis (V) or hydroxide attack on the protonated form of 1 (VI). The rate of hydrolysis by the last mechanism when calculated[12] gives a value of ca. 5.6×10^7 M^{-1} min^{-1}, which is about 10^4 times faster than the rate of hydroxide attack on quarternary compound 6 and 10^8 times faster than the alkaline hydrolysis rate of 1, 2, or 3. It is quite unlikely that NH is such a powerful electrophile.[4b,10] Therefore, this mechanism can be rejected. Nucleophilic catalysis (V), is a possibility, but the rate acceleration is exceptionally low for such a mechanism. Further, the second-order rate constant for pyridine attack (having a similar pK_a) on 1,3,2-dioxaphosphorinane is 7.53×10^{-3} mol^{-1} min^{-1},[8] and therefore the effective molarity of intramolecular with respect to intermolecular nitrogen attack works out to be less than unity. However, it can be argued that the ground state is already stabilized by transannular interaction because IR spectral studies[6] on several phosphonates show positive evidence to this effect. Also, that the pK_a values of the amines studied are surprisingly low[9] further supports ground-state stabilization. The solvent deuterium isotope effect (1.4) at pH 9.6 substantiates this conclusion in that, in addition to intramolecular general-base catalysis, some other mechanistic pathway for rate acceleration should be available. Therefore, we feel that the spontaneous hydrolysis rate enhancement of 1 over 3 is due to both general-base and nucleophilic catalysis.



Alkaline Hydrolysis. Comparison of rates obtained with sodium hydroxide (at two different concentrations) with respect to 1–3 shows that they do not differ considerably. Further, the second-order rate constant for hydrolysis of 2 and 1,3,2-dioxaphosphorinane[8] (at 39 °C in 96% water) are within an order of magnitude, and therefore it is reasonable to assume that the reactions follow similar mechanisms [$S_N2(P)$]. In order to probe the catalytic effect of a transannularly placed sulfone group, we examined the hydrolysis rate of 5. The positively charged sulfur can withdraw the developing negative charge from either phosphorus or phosphoryl oxygen during an $S_N2(P)$ reaction so that the rate can be enhanced. However, this is not supported by the observed slow reaction rate. There is considerable rate acceleration in case of 4 due to the electrostatic effect of quarternary nitrogen. Similar effects have been observed by several groups,[5b,7a] and it is interesting that the magnitude of rate enhancement over the rate for the respective parent amine under the same condition is comparable in all these cases.

In conclusion, the studies on the hydrolysis of cyclic phosphates show the importance of both proximity and constraints necessary for rate acceleration and demonstrate the subtle difference in the mechanism of rate acceleration by an amine function when present in a cyclic ring in comparison to an acyclic analogue.[7a]

(12) $k'(OH) = k(H_2O)K_a/K_w$ (M^{-1} min^{-1}) where K_a is the dissociation constant of 1.

Experimental Section

All melting points were recorded in open capillaries and are uncorrected. IR spectra were taken with a Perkin-Elmer Model 577 and NMR spectra with a Perkin-Elmer R-32 instrument operating at 90 MHz with tetramethylsilane as an internal standard. Mass spectra were recorded on a JEOL-JMS-D 300 instrument. Thin-layer chromatography was performed on silica gel plates.

Deionized, doubly distilled water was used throughout. *p*-Dioxane was distilled over lithium aluminium hydride and kept frozen prior to use. All chemicals and solvents are commercial products and were distilled or recrystallized before use. Buffer salts were of analytical reagent grade and were used as such.

2-Oxo-2-(*p*-nitrophenoxy)-1,3-dioxa-2-phospha-6-methyl-6-azacyclooctane (1). *p*-Nitrophenyl phosphorodichloridate[13] (25.6 g, 0.1 mol) was added to a mixture of triethylamine (60.6 g, 0.6 mol), bis(2-hydroxyethyl)methanamine (11.9 g, 0.1 mol) and benzene (400 mL). After the mixture was stirred for 2 h without external cooling, the contents were filtered through a Büchner funnel, the precipitate was washed with benzene, and the filtrate was concentrated. After elution through a column of silica gel and recrystallization, 7.8 g (26%) of the required compound was obtained: mp 98 °C; IR (KBr) 1600, 1510, 1340, 1250, 1075, 1045, 920 cm^{-1}; ^1H NMR δ 2.58 (3 H, s), 2.90 (4 H, m), 4.12 (4 H, m), 7.35 (2 H, d, J = 9 Hz), 8.20 (2 H, d, J = 9 Hz); mass spectrum, m/e 302; UV max (water/dioxane, 55:45) 278 nm. Anal. Calcd for $C_{11}H_{15}N_2O_6P$: C, 43.71; H, 4.97; N, 9.27. Found: C, 43.92; H, 5.03; N, 9.48.

2-Oxo-2-(*p*-nitrophenoxy)-1,3-dioxa-2-phospha-6-thiacyclooctane (2). Thiodiglycol (12.2 g, 0.1 mol) and triethylamine (20.2 g, 0.2 mol) were dissolved in benzene (300 mL), and *p*-nitrophenoxy phosphoryldichloridate (25.6 g, 0.1 mol) in benzene (100 mL) was added dropwise without any external cooling. After the usual workup procedure and elution through silica gel with benzene/acetone (9:1), the desired product was obtained. This was recrystallized from benzene: 9.1 g (30%); mp 134–135 °C; IR (KBr) 1590, 1520, 1340, 1275, 1220, 1070, 1020, 935 cm^{-1}; ^1H NMR δ 3.02 (4 H, m), 4.44 (4 H, m), 7.40 (2 H, d, J = 9 Hz), 8.25 (2 H, d, J = 9 Hz); mass spectrum, m/e 305; UV (H_2O/dioxane, 55:45) λ_{max} 275 nm. Anal. Calcd for $C_{10}H_{12}O_6PSN$: C, 39.35; H, 3.94; N, 4.59. Found: C, 39.12; H, 3.76; N, 4.64.

2-Oxo-2-(*p*-nitrophenoxy)-1,3-dioxa-2-phosphacyclooctane (3). The above procedure was followed to prepare the title compound (7.4 g, 26%) from triethylamine (20.2 g, 0.2 mol), 1,5-pentanediol (10.4 g, 0.1 mol), and *p*-nitrophenyl phosphorodichloridate (25.6 g, 0.1 mol): mp 104 °C; IR (KBr) 1600, 1528, 1344, 1270, 1230, 1060, 1010, 950, 932 cm^{-1}; ^1H NMR δ 1.92 (6 H, m), 4.30 (4 H, m), 7.38 (2 H, d, J = 9 Hz), 8.25 (2 H, d, J = 9 Hz); mass spectrum, m/e 287; UV max (water/dioxan, 55:45) 272 nm. Anal. Calcd for $C_{11}H_{14}O_6NP$: C, 45.99; H, 4.88; N, 4.88. Found: C, 45.71; H, 4.49; N, 4.61.

2-Oxo-2-(*p*-nitrophenoxy)-1,3-dioxa-2-phospha-6,6-dimethyl-6-azacyclooctyl Iodide (4). A solution of 1 (303 mg, 0.001 mol) in dimethyl formamide (3 mL, dried over molecular sieves and distilled) was mixed with methyl iodide (1 g, 0.007 mol) in a flask and left for 0.5 h. The polarity of the medium was reduced by the addition of dry distilled ether, and a precipitate appeared. This was filtered, and the granular solid was washed several times with ether. The sample thus obtained in almost quantitative yield was analytically pure as elemental analysis proved later. The compound (mp 165 °C dec) gave a positive iodide test with silver nitrate and did not move from the origin on a TLC plate (acetone): IR (KBr) 1580, 1510, 1340, 1290, 1090, 940 cm^{-1}; ^1H NMR (D_2O) δ 3.38 (6 H, s), 4.00 (4 H, m), 4.78 (4 H, m), 7.32 (2 H, d, J = 9 Hz), 8.15 (2 H, d, J = 9 Hz); UV (2% DMF in MeOH) λ_{max} 265 nm (ϵ 8930). Anal. Calcd for $C_{12}H_{18}N_2O_6PI$: C, 32.45; H, 4.05; N, 6.30. Found: C, 32.33; H, 4.18; N, 6.02.

2-Oxo-2-(*p*-nitrophenoxy)-1,3-dioxa-2-phospha-6,6-dioxo-6-thiacyclooctane (5). *m*-Chloroperbenzoic acid (4.3 g, 0.025 mol) in dichloromethane (25 mL) was added to a solution of 2 (3.05 g, 0.01 mol) in dichloromethane (50 mL). The contents were

(13) G. M. Kosalapoff, "Organophosphorous Compounds", Wiley, London, 1950, p 211.

stirred at 25 °C for 1 h. The excess of peracid was then destroyed by addition of 10% sodium sulfite until a test starch iodide paper was negative. The reaction mixture was then transferred to a separatory funnel and washed with 5% sodium bicarbonate solution and then with water. After the mixture was dried, 2.5 g (74%) of the title compound (mp 182 °C) was obtained which was homogenous on TLC: IR (KBr) 1590, 1520, 1490, 1330, 1285, 1220, 1165, 1125, 1060, 1010 cm^{-1}; ^1H NMR δ 3.78 (4 H, m), 4.75 (4 H, m), 7.60 (2 H, d, J = 9 Hz), 8.38 (2 H, d, J = 9 Hz); mass spectrum, m/e 337. Anal. Calcd for $C_{10}H_{12}O_8PNS$: C, 35.60; H, 3.56; N, 4.15. Found: C, 35.32; H, 3.32; N, 4.28.

Dissociation Constants, pH Measurements, and Kinetic Methods. pK_a and pH measurements were performed on a Toshniwal pH meter preset and standardized with standard buffers by using a glass electrode at 35 °C at an ionic strength of 0.2 (KCl) in 45% dioxan/water medium. pH meter readings were corrected for medium effects by using Irving and Mankot's equation.[14] pK_a's were determined potentiometrically.[15] The dissociation constant of water at 35 °C in 45% water/dioxane is 3.63×10^{-16} M^2.[16] The pD was calculated as pD = pH meter reading + 0.29.[17]

A Pye Unicam 500 spectrophotometer with a thermostated cuvette holder was used for kinetic measurements. All kinetic experiments were performed in 45% (v/v) dioxane/water at 35 ± 0.1 °C at μ = 0.2 (KCl). Stock solutions were prepared in dioxane (1–3 and 5) or in dimethylformamide (4). The hydrolysis rate at pH 8.0 and above was conveniently followed at 405 nm. At low pH, the reaction was monitored by the decrease in absorption at 280 nm and the increase at 320 nm. The rates were calculated[18] by solving the following simultaneous equations (eq 1 and 2). The pHs of the solutions were measured before and

$$A(320) = C_1\epsilon_1 + C_2\epsilon_1 \quad (1)$$

$$A(280) = C_1\epsilon_2 + C_2\epsilon_2 \quad (2)$$

after each kinetic run. They were within ±0.03 pH unit. In order to find the buffer catalysis, we serially diluted buffers, and an appropriate quantity of KCl was added to bring the ionic strength constant.

Acknowledgment. We thank Drs. P. K. Ramachandran and D. K. Jaiswal and Professor M. V. Bhatt for constructive criticism.

Registry No. 1, 80765-36-2; 2, 80765-37-3; 3, 80765-38-4; 4, 80765-39-5; 5, 80765-40-8; *p*-nitrophenyl phosphorodichloridate, 777-52-6; bis(2-hydroxyethyl)methylamine, 105-59-9; thiodiglycol, 111-48-8; 1,5-pentanediol, 111-29-5.

(14) H. M. N. H. Irving and U. S. Mankot, *J. Inorg. Nucl. Chem.*, **30**, 1215 (1968).
(15) A. Albert and B. P. Seargent, "The Determination of Ionization Constants", Chapman and Hall, London, 1971.
(16) H. S. Harned and L. D. Fallon, *J. Am. Chem. Soc.*, **61**, 2374 (1939).
(17) T. H. Fife and T. C. Bruice, *J. Phys. Chem.*, **65**, 1079 (1961).
(18) K. J. Laidler, "Physical Chemistry with Biological Applications", Benjamin-Cummings Publ. Los Angeles, CA, 1978, p 80.

Carboxyl Group Participation in Sulfate and Sulfamate Group Transfer Reactions

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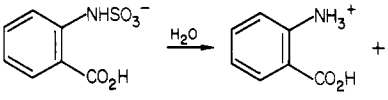
Received September 29, 1981

The pH dependence for the hydrolysis of *N*-(2-carboxyphenyl)sulfamic acid exhibits a plateau region corresponding to participation of the carboxyl function. A normal deuterium oxide solvent isotope effect indicates that proton transfer from the carboxylic acid is concerted with sulfamate group transfer to water. Hydrolysis of salicyl sulfate and *N*-(2-carboxyphenyl)sulfamate in ^{18}O-enriched water yields salicylic acid and anthranilic acids with no enrichment, excluding catalysis by neighboring nucleophilic attack on sulfur by the carboxylate group. Intermolecular catalysis by carboxylic acids is demonstrated in the hydrolysis of *N*-(1-naphthyl)sulfamic acid; the mechanism is shown to involve preequilibrium protonation of the nitrogen followed by nucleophilic attack on sulfur by the carboxylate anion. Fast decomposition of the acyl sulfate completes the hydrolysis; this mechanism is considered to be the most efficient but is excluded in the intramolecular case which is constrained by the electronic requirements of displacement at the sulfur atom (6-ENDO-tet).

We are interested in the acid catalysis of sulfamate group transfer from sulfamates to acceptor nucleophiles as a mild sulfonation method. There is strong evidence that transfer of sulfonate from sulfamates to aqueous or alcohol acceptors involves a preequilibrium protonation of the reagent followed by rate-limiting degradation to yield products (eq 1).[4] We considered the possibility of

$$RNHSO_3^- + H^+ \rightleftharpoons RN^+H_2SO_3^- \xrightarrow{R'OH} RNH_3^+ + R'OSO_3^- \quad (1)$$

intramolecular catalysis of the above sulfation reaction and looked at the kinetics of hydrolysis of *N*-(2-carboxyphenyl)sulfamic acid (eq 2). The effect of carboxyl group



(2)

interaction in analogous salicyl sulfate transfer reactions where sulfonate is transferred from phenolic oxygen is quite complicated although catalysis by the acid group has been demonstrated.[2]

The present study looks at both inter- and intramolecular catalysis of sulfonate group transfer from sulfamates. We demonstrate these mechanisms to be different.

Experimental Section

Materials. Sulfonation of amines was carried out by using the method of Audrieth and Sveda.[3] *N*-(1-Naphthyl)sulfamate was prepared by adding chlorosulfonic acid (4.6 mL) slowly to a stirred solution of 1-naphthylamine (10 g) in chloroform (100 mL) kept below 10 °C with an ice bath. When the addition was

(1) G. A. Benson and W. J. Spillane, *Chem. Rev.*, **80**, 151 (1980).
(2) S. J. Benkovic, *J. Am. Chem. Soc.*, **88**, 5511 (1966).
(3) (a) L. F. Audrieth and M. Sveda, *J. Org. Chem.*, **9**, 89 (1944). (b) G. N. Burkhardt and A. Lapworth, *J. Chem. Soc.*, 684 (1926); G. N. Burkhardt, C. Horrex, and D. T. Jenkins, *ibid.*, 1649 (1936).
(4) S. Thea and A. Williams, *J. Chem. Soc., Perkin Trans. 2*, 72 (1981).

0022-3263/82/1947-1745$01.25/0