Facile Intramolecular Nucleophilic Attack by Alkoxide Ions on Ethyl and *p*-Nitrophenyl Carbamates

J. E. C. Hutchins[1] and Thomas H. Fife*

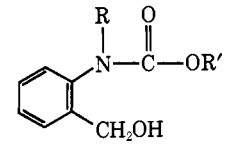
Contribution from the Department of Biochemistry, University of Southern California, Los Angeles, California 90033. *Received November 6, 1972*

Abstract: The rates of ring closure and phenoxide ion release from the ethyl and *p*-nitrophenyl esters of 2-hydroxymethyl-*N*-methylcarbanilic acid and 2-hydroxymethylcarbanilic acid have been measured in H_2O at 25°. The relatively stable benzoxazin-2-one is obtained as the product in each case. Plots of log k_{obsd} *vs.* pH are linear with slopes of 1.0. Release of *p*-nitrophenoxide ion from the ester of 2-hydroxymethylcarbanilic acid is approximately 10^4 times faster than from the corresponding N-methylated derivative, but occurs at nearly the same rate as from *p*-nitrophenyl carbanilate. It is likely therefore that reaction of the former compound involves an elimination with production of an isocyanate intermediate. The effectiveness of the neighboring hydroxymethyl group of *p*-nitrophenyl 2-hydroxymethyl-*N*-methylcarbanilate as an intramolecular nucleophile can be seen from the fact that the rate constant is 10^5 greater in comparison with pentaerythritol attack on *p*-nitrophenyl *N*-methylcarbanilate and 3×10^5 times greater in comparison with hydroxide ion. Ring closure in the case of the two ethyl esters proceeds at approximately the same rate and 1.3×10^6 times faster than reaction of hydroxide ion with ethyl *N*-methylcarbanilate. Thus, a neighboring alkoxide ion is an extremely powerful intramolecular nucleophile toward both nitrophenyl and ethyl esters.

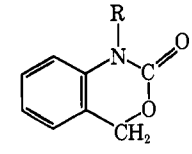
In the α-chymotrypsin-catalyzed hydrolysis of esters and amides it is the hydroxyl group of serine-195 that is initially acylated in the reaction.[2] Studies of intramolecular nucleophilic attack by alkoxide ions at ester carbonyl groups might then give useful information pertaining to the ability of the serine hydroxyl group to participate in intracomplex reactions. The study of intramolecular catalysis can lead to insight into analogous enzymatic reactions because of the striking analogy between an intramolecular reaction and an enzyme-catalyzed reaction proceeding through an enzyme–substrate complex.

We have observed that neighboring phenoxide ions will participate as nucleophiles in the hydrolysis of carbamate esters with phenolic leaving groups.[3] In these reactions the effective molarity of the phenoxide ion is $\sim 10^8$ *M* in comparison with bimolecular nucleophilic attack by a phenoxide ion of the same pK_a (sec^{-1}/M^{-1} sec^{-1}). This is the concentration of the bimolecular nucleophile required to give a pseudo-first-order rate constant of the magnitude observed in the intramolecular reaction. Neighboring phenoxide ions will also participate in the hydrolysis of *p*-nitrophenyl 5-nitrosalicylate,[4] catechol monobenzoate,[5] and ethyl 2-hydroxy-5-nitrophenyl carbonate[6] as intramolecular general bases.

Bruice and Marquardt[7] studied the hydrolysis of γ-hydroxybutyramide and found rate enhancements in comparison with hydrolysis of butyramide and acetamide in the hydroxide ion catalyzed reaction and in the pH region around neutrality. These reactions probably involve attack of the oxygen anion on the neutral and protonated amides, respectively. Intramolecular nucleophilic participation by alkoxide ions in ester hydrolysis has not been studied and therefore no estimates have been made of the effective molarity of such a species. Consequently, we have studied the ring-closure reactions of the carbamate esters, I–IV, which give as products



I, R = H; R′ = $C_6H_4NO_2$-*p*
II, R = CH_3; R′ = $C_6H_4NO_2$-*p*
III, R = H; R′ = Et
IV, R = CH_3; R′ = Et



V, R = H
VI, R = CH_3

the 1,3-benzoxazin-2-ones, V and VI. Hegarty and Frost[8] have studied reactions of *p*-nitrophenyl *N*-(2-aminophenyl)carbamate and have concluded that an isocyanate intermediate is formed. In the present study, however, that is the case only with I. Compounds II–IV cyclize with direct attack by the neighboring alkoxide ion at the ester carbonyl with expulsion of either *p*-nitrophenoxide or ethoxide.

Experimental Section

Materials. Ethyl 2-hydroxymethylcarbanilate (III) was prepared by slowly adding ethyl chloroformate dissolved in anhydrous ether to a stirred solution of 2 equiv of 2-aminobenzyl alcohol (Aldrich Chemical Co.) in the same solvent. After addition, stirring was continued for 2–3 hr at room temperature and the hydrochloride of the amino alcohol removed by filtration. Concentration of the filtrate yielded a light brown viscous oil. Crystallization was achieved by adding small aliquots of hexane over a period of days to a solution of the oil dissolved in dichloromethane kept in the freezer. Too much hexane resulted in separation of the oil. A second crystallization from hexane yielded white crystals, mp 60–61°. *Anal.* Calcd for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71; N, 7.18. Found: C, 61.68; H, 6.70; N, 7.30. Infrared analysis showed absorptions at 2.87, 2.95, and 5.83 μ, as expected for the required compound.

The other carbamates were prepared by similar methods using

(1) Postdoctoral Fellow, Department of Biochemistry, University of Southern California.
(2) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," W. A. Benjamin, New York, N. Y., 1966, Chapter 2.
(3) J. E. C. Hutchins and T. H. Fife, *J. Amer. Chem. Soc.*, **95**, 2282 (1973).
(4) M. L. Bender, F. J. Kezdy, and B. Zerner, *ibid.*, **85**, 3017 (1963).
(5) B. Capon and B. Ch. Ghosh, *J. Chem. Soc.*, 472 (1966).
(6) T. H. Fife and J. E. C. Hutchins, *J. Amer. Chem. Soc.*, **94**, 2837 (1972).
(7) T. C. Bruice and F. H. Marquardt, *ibid.*, **84**, 365 (1962).
(8) A. F. Hegarty and L. N. Frost, *J. Chem. Soc., Chem. Commun.*, 500 (1972).

the amine or amino alcohol and the appropriate chloroformate. Ethyl 2-hydroxymethyl-*N*-methylcarbanilate (IV) was prepared from 2-(*N*-methylamino)benzyl alcohol (see below) and was distilled as a pale yellow liquid, bp 157° (1.5 mm), $n^{26}D$ 1.5240. *Anal.* Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.06; H, 7.07; N, 6.72. *p*-Nitrophenyl 2-hydroxymethylcarbanilate (I) was recrystallized from anhydrous ethyl acetate, mp 103°, resolidifies at 105°. *Anal.* Calcd for $C_{14}H_{12}N_2O_5$: C, 58.33; H, 4.20; N, 9.72. Found: C, 58.70; H, 4.40; N, 9.60. *p*-Nitrophenyl 2-hydroxymethyl-*N*-methylcarbanilate (II) was crystallized from hexane–ethyl acetate (*ca.* 3:2), mp 114–116°. *Anal.* Calcd for $C_{15}H_{14}N_2O_5$: C, 59.60; H, 4.67; N, 9.27. Found: C, 59.92; H, 4.76; N, 9.11.

1,3-Benzoxazin-2-one (V) was prepared from 2-aminobenzyl alcohol and phosgene using the method reported for preparation of bis(4-nitrophenyl) carbonate.[9] The material was recrystallized from CH_2Cl_2–hexane (mp 123–126°). *Anal.* Calcd for $C_8H_7NO_2$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.42; H, 5.08; N, 8.94.

N-Methyl-1,3-benzoxazin-2-one (VI) was prepared in a similar manner. The material was distilled from the crude reaction product as a yellow oil, bp 119° (0.3 mm), $n^{25}D$ 1.5785. *Anal.* Calcd for $C_9H_9NO_2$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.19; H, 5.83; N, 8.56.

2-(*N*-Methylamino)benzyl alcohol was prepared by reduction of *N*-methylanthranilic acid (Aldrich Chemical Co.).[10] The product distilled as a yellow oil at 84–86° (0.3 mm) (lit.[10] 83–85° (0.3 mm)), $n^{25}D$ 1.5829.

p-Nitrophenyl *N*-methyl-*N*-phenylcarbamate was prepared by dissolving 4-nitrophenyl chloroformate in ether and stirring in a three-necked flask with silica gel guard tube and addition funnel. Equivalent amounts of *N*-methylaniline in ether, then pyridine in ether were added and the mixture stirred overnight. Pyridinium hydrochloride was removed by filtration. The solution was evaporated and the solid residue recrystallized from hexane, mp 59–60.5°. *Anal.* Calcd for $C_{14}H_{12}N_2O_4$: C, 61.76; H, 4.44; N, 10.29. Found: C, 61.92; H, 4.58; N, 10.46.

p-Nitrophenyl *N*-phenylcarbamate was prepared by heating together equivalent amounts of phenyl isocyanate and *p*-nitrophenol, plus a drop of pyridine at 100° for 30 min in a vessel fitted with drying tube. A solid mass formed which was heated under vacuum to remove excess isocyanate and twice recrystallized from ethyl acetate, mp 143–146° (lit.[11] 149–150°; also[12] 153°). *Anal.* Calcd for $C_{13}N_{10}N_2O_4$: C, 60.47; H, 3.90; N, 10.85. Found: C, 60.77; H, 4.12; N, 10.70. If the material is contaminated with the most likely side product, *N,N*-diphenylurea, the extent of contamination must be very small, but this may have a significant effect on the melting point.

Buffers were prepared using analytical grade materials and deionized water. Pentaerythritol was used without purification (Matheson Coleman and Bell reported mp 258–260°).

Kinetic Methods. All rate measurements were carried out spectrophotometrically using either a Gilford 2000 recording instrument or Durrum Gibson (Model D110) stopped-flow spectrophotometer. Operating techniques used were those previously described.[3,13] The cyclization reactions were monitored at the following wavelengths: I at 320 or 400 nm; II at 400 nm; III and IV at 245 nm. Temperature was controlled at 25 ± 0.1° for the ring-closure reaction of compound I and for the hydrolysis of 4-nitrophenyl *N*-phenylcarbamate. The remaining work was carried out at 30 ± 0.1°. Ionic strengths were 0.5 *M* throughout. Stock solutions of I were made in 50% dioxane–0.01 *M* HCl (v/v); acetonitrile was used for the remaining compounds. Reaction solution pH's were measured with a Radiometer pH meter Model 22 and GK2302C combined electrodes standardized with Mallinchrodt standard buffer solutions.

Product Determination. Compounds I and III were dissolved in methanol, and aqueous KOH was added. The solutions were extracted with ether, and the ether was evaporated. With both compounds the residual material was identified as compound V. Similar work was done to show that compounds II and IV react in basic solutions to yield VI. Experiments to show that the ring closures occur quantitatively are described in the following section.

Spectral Measurements. The data shown in Table I were obtained using a Cary 15 spectrophotometer and 1-cm quartz cells containing the appropriate buffer (μ = 0.5) in both sample and reference compartments. Compounds were introduced as solutions in 10–30 μl of acetonitrile, and spectra were taken immediately after mixing (Table I).

Additional matching of the spectra of reacted solutions and the appropriate cyclic carbamate and ROH were obtained for I in 0.03 *M* KOH and for III and IV in 1.0 *M* KOH. In the case of III and IV, subsequent spectral changes corresponded quantitatively to the changes observed for V and VI (footnotes *f* and *g*, Table I).

Table I. Data Obtained from the Spectra of Compounds I–VI in Aqueous Solution Immediately after Mixing

Compd	Buffer	λ_{max}, nm	Log ϵ
I	0.01 *M* HCl	275	3.98
	pH 5.0[a]	275	3.98
II	pH 8.97[b]	272	4.06
III	pH 10.46[c]	230	3.86
IV	pH 11.50[d]	240	3.91
V	pH 6.64[e]	240	3.98
	0.1 *M* KOH[e]	250–260	3.92
	1.0 *M* KOH[f]	260	4.10
VI	pH 6.64	242	3.98
	pH 11.50	242	3.98
	1.0 *M* KOH[g]	242	3.98

[a] Spectrum changed rapidly until it closely matched that of V and *p*-nitrophenol. Isosbestic points observed at 250 and 296 nm. [b] Spectrum changed to match that of VI and *p*-nitrophenol. Isosbestic points observed at 256 and 320 nm. [c] Spectrum changed to match that of V under identical conditions. [d] Spectrum changed to match that of VI under the same conditions. [e] Solutions of intermediate basicity between pH 6.64 and 1.0 *M* KOH showed progressive decline in OD_{240} and increase in OD_{260} as the pH was raised. In 0.1 *M* KOH the change in absorbance at both wavelengths was about half of the total change observed in each. [f] The absorbance at 260 nm declined and a new absorption (λ_{max} 235 nm (log ϵ 3.91)) developed. Isosbestic point, 243 nm. [g] A rapid loss in OD_{242} occurred, the maximum being replaced by a shoulder whose λ_{max} lies below 230 nm. The greatest change in OD occurred at 245 nm.

Results

The reactions of compounds I–IV in aqueous solution have been studied over a wide pH range. The products of reaction have been identified as the cyclic carbamates V and VI by (a) analysis of material extracted from suitable basic H_2O–CH_3OH mixtures, (b) through the identity of uv spectra taken of reaction solutions after reaction was complete, and those of solutions containing the same concentration of the appropriate cyclic carbamate (plus *p*-nitrophenol in the case of compounds I and II), and, finally, (c) by the finding in the case of compounds III and IV that solutions containing equal amounts of the open-chain and corresponding ring-closed material in 1 *M* KOH showed identical absorbance changes at 245 nm, the changes corresponding to first order processes whose rate constants were identical.

The pH–rate constant profiles of the cyclization reactions show a uniformly linear dependence upon [OH^-] concentration as shown in Figures 1 and 2, in which log k_{obsd} is plotted as a function of pH for each of the compounds. The straight lines were obtained by a computerized weighted linear least-squares fit.[14] Sec-

(9) T. H. Fife and D. M. McMahon, *J. Amer. Chem. Soc.*, **91**, 7481 (1969).

(10) M. Lora-Tamayo, R. Madronero, and G. G. Munoz, *Chem. Ber.*, **94**, 208 (1961); *cf. Chem. Abstr.*, **55**, 8410f (1961).

(11) M. Busch, G. Blume, and E. Pungs, *J. Prakt. Chem.*, [2] **79**, 533 (1909).

(12) G. Illari, I. Marenghi, and A. Stuani, *Ann. Chim. (Rome)*, **43**, 744 (1953).

(13) J. E. C. Hutchins and T. H. Fife, *J. Amer. Chem. Soc.*, **94**, 8848 (1972).

(14) Computer programs were provided by Dr. Edwin Anderson of this address.

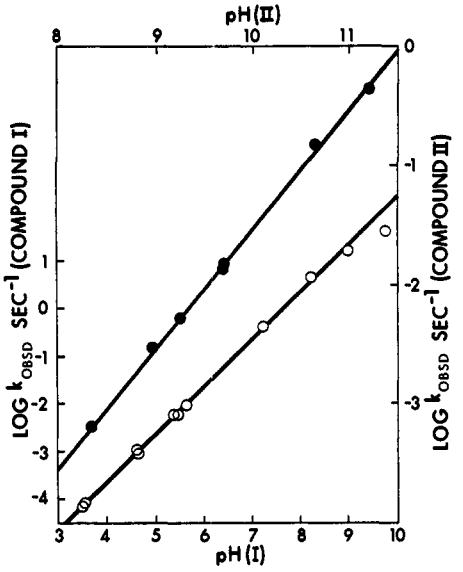


Figure 1. Plots of log k_{obsd} *vs.* pH for the ring closures of compound I (lower and left-hand scales, ○) and compound II (upper and right-hand scales, ●). I at 25°, 1.0% (v/v) CH_3CN, μ = 0.5 *M* (KCl). II at 30°, 0.83% (v/v) CH_3CN, μ = 0.5 *M* (KCl). Line drawn using computer-calculated values of *k*.

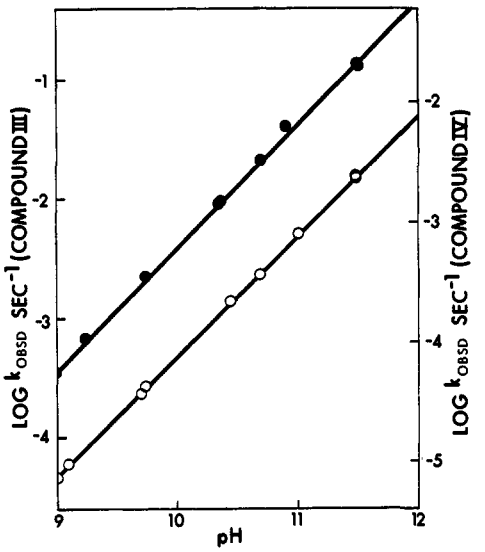


Figure 2. Plots of log k_{obsd} *vs.* pH for the ring closures of compound III (left-hand scales, ○) and compound IV (right-hand scales, ●). Reaction conditions for both: 30°, 0.7% (v/v) CH_3CN, μ = 0.5 *M* (KCl). Line drawn using computer-calculated values of *k*.

ond-order rate constants (k_{obsd} log^{-1} pH/K_w) are given in Table II along with other relevant data. Rate constants obtained from the hydrolysis of V and VI are given in Table III, together with data for the hydrolysis of the rapidly formed intermediates from III and IV in 1 *M* KOH.

Table II. Apparent Second-Order Rate Constants k_{OH} = k_{obsd} · log^{-1} pH/K_w M^{-1} sec^{-1} for the Cyclization Reactions of Compounds I–IV

Compd	k_{OH}, M^{-1} sec^{-1} [a]	Slope of log k_{comp} *vs.* pH
I[b]	(2.26 ± 0.13) × 10^6	1.003
II[c]	289 ± 14	0.996
III[d]	4.66 ± 0.08	1.003
IV[d]	6.69 ± 0.20	1.036

[a] Error limits indicated are standard deviations. [b] 25°, 1.0% v/v CH_3CN, μ = 0.5 *M*. [c] 30°, 0.83% v/v CH_3CN, μ = 0.5 *M*. [d] 30°, 0.70% v/v CH_3CN, μ = 0.5 *M*.

Table III. Rate Constants Obtained for the Hydrolysis of Compounds V and VI in Aqueous Hydroxide Solutions at 30°

Compd	[OH^-], *M*	k_{obsd}, sec^{-1} [a]
V	1.0	5.11 × 10^{-4}
	1.0[b]	5.12 × 10^{-4}
	1.0	4.84 × 10^{-4}
	0.5	4.90 × 10^{-4}
	0.1	3.09 × 10^{-4}
VI	1.0	8.84 × 10^{-3}
	1.0[c]	9.13 × 10^{-3}
	0.5	4.11 × 10^{-3}
	0.1	7.15 × 10^{-4}

[a] Acetonitrile concentration varied at most from 0.33% v/v to 0.80% v/v. [b] An equivalent concentration of III was used. [c] An equivalent concentration of IV was used.

A search was made for buffer catalysis in the reactions of I–IV, but none was found. The buffers investigated were: acetate, formate, imidazole, and pyridine (I); borate (III); phosphate and carbonate (II and IV). The lack of any significant deviations from the plots of k_{obsd} *vs.* pH, where a variety of buffers were employed additionally, rules out buffer catalysis in the following buffers: borate (I, II, and IV); carbonate (I and III); phosphate (I).

The susceptibility of *p*-nitrophenyl *N*-methyl-*N*-phenylcarbamate to attack by hydroxide ion and pentaerythritol monoanion was measured, and rate constants are given in Table IV. Plots of k_{obsd} *vs.* anion concentration were linear. The data were analyzed by a weighted least-squares computer technique[14] from which the following results were obtained at 30° ([CH_3CN] = 0.7–0.83% v/v, μ = 0.5 *M*): k_2 $(CH_2OH)_3CCH_2O^-$ = 4.9 ± 0.9 × 10^{-3} M^{-1} sec^{-1} (from four concentrations 0.06 to 0.3 *M* at pH 12.56); pK_a of pentaerythritol = 14.0;[15] k_{OH} = 1.09 ± 0.08 × 10^{-3} M^{-1} sec^{-1} (six concentrations from 0.1 to 1.0 *M*).

Discussion

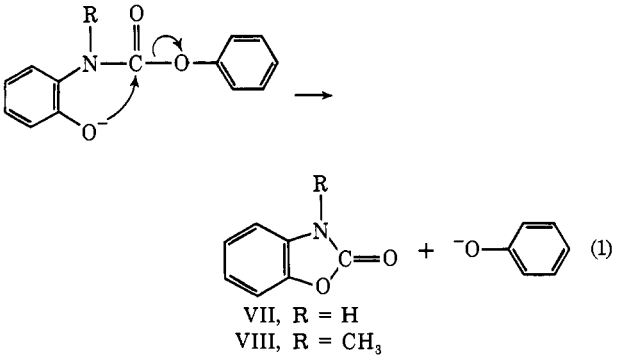
Neighboring phenoxide ion attack on phenyl carbamates takes place with great facility to release phenoxide ion and to form a benzoxazolinone (eq 1).[3] The effective molarity of the neighboring phenoxide ion is 10^8 *M* in comparison with reaction of phenyl *N*-methyl-*N*-phenylcarbamate with 1 *M* phenoxide ion of the same pK_a in an intermolecular reaction (sec^{-1}/M^{-1} sec^{-1}). At pH values up to 10, the rates of cyclization of the compounds where R = CH_3 or H were similar, showing that an isocyanate intermediate was not being formed from the compound where R = H. Phenolic carbamate esters can undergo such an elimination reaction with rates approximately 10^6 greater than for hydroxide ion catalyzed hydrolysis of N-methylated esters.[16] In the case of VIII, hydroxide ion catalysis was not observed, while with VII it was seen at pH values above 12.

(15) P. Ballinger and F. A. Long, *J. Amer. Chem. Soc.*, 82, 795 (1960).
(16) M. L. Bender and R. B. Homer, *J. Org. Chem.*, 30, 3975 (1965).

Table IV. Rate Constants for the Attack of Oxygen Anions on Carbamate Esters

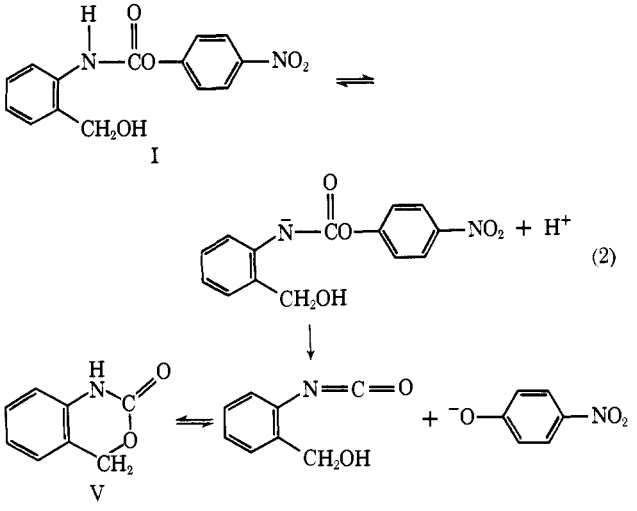
Compd	RO^-	k_2, M^{-1} sec^{-1}
4-Nitrophenyl *N*-methylcarbanilate	OH^-	$1.09 \pm 0.08 \times 10^{-3}$ [a,b]
	$(CH_2OH)_3CCH_2O^-$	$4.9 \pm 0.9 \times 10^{-3}$ [c]
4-Nitrophenyl carbanilate	OH^-	3.6×10^{5} [d]
Ethyl carbanilate	OH^-	3.25×10^{-5} [e]
Ethyl *N*-methylcarbanilate	OH^-	4.98×10^{-6} [e]

[a] Six concentrations of OH^- from 0.1 to 1.0 *M*. [b] $[CH_3CN]$ = 0.7–0.83% v/v, μ = 0.5, T = 30°. [c] Four concentrations from 0.06 to 0.3 *M*. [d] Six concentrations (pH 5.5–9.0), $[CH_3CN]$ = 0.25%, v/v, T = 25°. [e] Results at 25° from I. Christenson, *Acta Chem. Scand.*, **18**, 904 (1964).



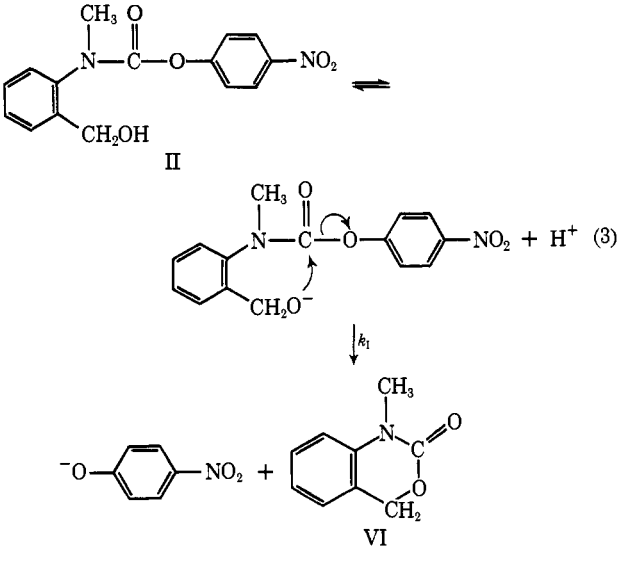
VII, R = H
VIII, R = CH_3

In the present study I releases nitrophenoxide ion 10[4]



times more rapidly than II where the *N*-methyl group precludes isocyanate formation. Therefore, it is likely that reaction of I does involve an isocyanate intermediate. That this type of reaction takes place readily with I but only at very high pH with VII is probably due to the better leaving group of I, which makes the elimination reaction easier, and to less efficient intramolecular participation with I due to formation of a six-membered ring transition state rather than five-membered with VII (the lower concentration of the attacking oxide ion in I would be partially compensated for by much greater basicity).

In the case of compound II, where an isocyanate intermediate cannot be formed, cyclization must occur with nucleophilic participation by the neighboring hydroxymethyl group. The rate constant for apparent hydroxide ion catalysis, k_{OH}, is 3×10^5 greater than that for the corresponding unsubstituted compound, *p*-nitrophenyl *N*-methylcarbanilate. The ionized species of pentaerythritol acts as a bimolecular nucleophile toward the latter compound, but with a second-order



rate constant 10^5 less than k_{OH} for II. Thus, the greatly enhanced reactivity of II, beyond what would be expected on the basis of inductive or steric effects for an ortho hydroxymethyl group, shows that intramolecular nucleophilic attack is taking place.

The apparent hydroxide ion catalysis seen in the cyclization of II–IV is due to preequilibrium ionization of the neighboring hydroxymethyl group. If the reaction proceeds as in eq 3 then the rate equation is

$$dP/dt = k_I[ECH_2O^-] \quad (4)$$

$$= k_I[ECH_2OH]_{tot}[K_a/(K_a + a_H)] \quad (5)$$

since $[H^+] \gg K_a$

$$\frac{dP}{dt} = \frac{k_I K_a[ECH_2OH]_{tot}}{[H^+]} \quad (6)$$

$$= \frac{k_I K_a}{K_w}[ECH_2OH]_{tot}[OH^-] \quad (7)$$

$$k_{obsd} = (k_I K_a[OH^-])/K_w \quad (8)$$

and

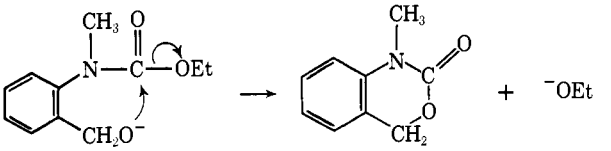
$$k_{OH} = k_I K_a/K_w \quad (9)$$

where K_w is the ion product of water, K_a is the dissociation constant of the hydroxymethyl group, and $[ECH_2O^-]$ and $[ECH_2OH]$ represent the concentrations of ionized and un-ionized ester, respectively.

Buffer catalysis is not observed in the cyclization reactions of compounds I–IV or with the analogous carbamate esters having a neighboring phenolic hydroxyl group. The apparent specific base catalysis that is observed shows that the reaction involves the

completely ionized species, as in eq 3. This is possibly a consequence of the fact that the carbonyl group of carbamate esters is deactivated by the adjoining nitrogen so that the transition state for formation of a tetrahedral intermediate will be difficult to attain, necessitating attack by a fully developed negative charge. It is possible that decomposition of a tetrahedral intermediate is rate determining with III and IV, but this is unlikely with II because of the excellent leaving group, *p*-nitrophenoxide ion.

A neighboring alkoxide ion is also an efficient intramolecular nucleophile when the leaving group is poor. The similarity in the rates of cyclization of III and IV



IV

indicates that the mechanism is the same for both compounds and must involve intramolecular nucleophilic attack. The pK_a of the hydroxymethyl group is undoubtedly comparable to that of ethanol. The ionized species is therefore sufficiently basic to displace ethoxide. Christenson has determined the rate constants for hydroxide ion catalyzed hydrolysis of ethyl carbanilate and ethyl *N*-methylcarbanilate at 25°. These values are given in Table IV. The k_{OH} value for IV is 1.3×10^6 greater than that for ethyl *N*-methylcarbanilate.

Calculation of the effective molarity of the neighboring hydroxymethyl groups in the present study depends upon an evaluation of k_I from eq 8. This rate constant can only be approximated since K_a cannot be directly measured. There is no significant negative deviation of points in the linear plots of log k_{obsd} *vs.* pH at pH values as high as 13. Therefore, it is likely that pK_a for compounds I–IV is no lower than 14. From the rate constants in Tables II and IV, a minimum value of the effective molarity of the neighboring alkoxide ion of II can then be estimated as 10^5 *M*. Thus, the efficiency of the intramolecular reaction involving an alkoxide ion is only slightly less than that for phenoxide ion (eq 1) even though a kinetically less favorable six-membered ring transition state is being formed. Bruice and Pandit[17] found that a neighboring carboxylate anion is more effective by a factor of 230 when the transition state is five membered rather than six. Taking this into account, the phenoxide and alkoxide intramolecular groups are about equal in catalytic efficiency. Thus, once again an extremely high effective molarity has been found for an oxygen anion nucleophile. Previously, a value of about 10^8 *M* had been estimated for a carboxylate anion nucleophile.[18] These values are much larger than have been found to date for neutral nitrogen nucleophiles, the largest being 5×10^3 *M* for the dimethylamino group of phenyl λ-dimethylaminobutyrates in comparison with trimethylamine attack on substituted phenyl acetates.[19] The neighboring pyridine in substituted phenyl β-pyridylethyl carbonate has effective molarities of from 30 to 50 *M*, depending on the substituent group, in comparison with bimolecular attack of pyridine on ethyl (substituted phenyl) carbonates.[20] A neighboring amide group, where a negatively charged nucleophile participates, increases the rate of hydrolysis of a methyl ester by 10^5.[21] While proper orientation of the nucleophile to the carbonyl group in these compounds is undoubtedly of importance in leading to the highly efficient intramolecular reactions, still it is probable that other factors are also involved. Correct orientation would not explain why anionic nucleophiles are relatively so superior to neutral nitrogen nucleophiles in intramolecular reactions. One possibility is that desolvation of anionic nucleophiles is not as energetically unfavorable in intramolecular reactions as in corresponding bimolecular cases.

That alkoxide ions are extremely powerful intramolecular nucleophiles is of interest in regard to the mechanism of action of α-chymotrypsin since it is the hydroxymethyl group of serine-195 that is acylated during the enzyme reaction with ester and amide substrates.[2] Acylation, proceeding through an enzyme–substrate complex, can be considered quite analogous to an intramolecular reaction. The mechanism generally considered to be most probable involves partial removal of the proton on the serine hydroxyl by histidine-57 acting as a general base. It is clear that the serine oxygen will be a powerful nucleophile in an intracomplex reaction.

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

(17) T. C. Bruice and U. K. Pandit, *J. Amer. Chem. Soc.*, **82**, 5858 (1960); see also E. Gaetjens and H. Morawetz, *ibid.*, **82**, 5328 (1960). They found that the ratio of the rates varies with the para substituent of phenyl esters from 125 with *p*-$COOCH_3$ to 200 for *p*-Cl in hydrolysis reactions assisted by a neighboring carboxylate when compounds forming five- and six-membered ring intermediates are studied.

(18) T. C. Bruice and A. Turner, *ibid.*, **92**, 3422 (1970).
(19) T. C. Bruice and S. J. Benkovic, *ibid.*, **85**, 1 (1963).
(20) J. E. C. Hutchins and T. H. Fife, unpublished data.
(21) R. Shafer and H. Morawetz, *J. Org. Chem.*, **28**, 1899 (1963).

Communications to the Editor

Binary Mixed Dinitrogen Dioxygen Complexes of Nickel. $(N_2)Ni(O_2)$ and $(N_2)_2Ni(O_2)$

Sir:

One of us (G. A. O.) has recently reported matrix isolation infrared and laser Raman spectroscopic evidence for the binary dinitrogen complexes $Ni(N_2)_n$ where $n = 1$–4, formed in the cocondensation reaction of monatomic nickel vapor with pure N_2 and dilute N_2/Ar matrices.[1] The mode of bonding of the di-

(1) H. Huber, E. P. Kündig, M. Moskovits, and G. A. Ozin, *J. Amer. Chem. Soc.*, **95**, 332 (1973).