Fast Intramolecular Nucleophilic Attack by Phenoxide Ion on Carbamate Ester Groups

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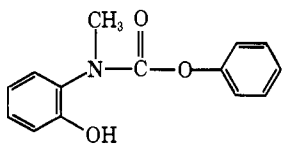
Abstract: The cyclization reactions of phenyl *N*-(2-hydroxyphenyl)-*N*-methylcarbamate (I) and phenyl *N*-(2-hydroxyphenyl)carbamate (II) to yield *N*-methyl-2-benzoxazolinone and 2-benzoxazolinone, respectively, occur with such facility in aqueous solution as to require stopped-flow rate measurements. The sigmoidal pH–rate profile for I shows $pK_{app} = 9.0$, corresponding to ionization of the neighboring phenol group, and exhibits a well-defined plateau rate at high pH. The profile for II is similar up to pH 11, but at higher pH's an additional term first-order in OH^- is required to fit the observed kinetic data. Buffer catalysis was not observed; hence, reaction proceeds through preequilibrium ionization of the phenol group. With I, attack by the neighboring phenolate ion occurs 5×10^4 times more rapidly than the reaction of phenyl *N*-methyl-*N*-phenylcarbamate (III) in 1 *M* potassium hydroxide. The susceptibility of III to attack by oxygen anions derived from trifluoroethanol and pentaerythritol has been measured, and an estimate has been made of the rate constant for the bimolecular reaction between III and phenoxide ion. The effective molarity of the adjacent phenoxide ion in I is thus $\sim 10^8$ *M*, demonstrating that such a species can be extremely effective as an intramolecular nucleophile.

The study of intramolecular reactions has been of great importance in attempts to understand the mechanism of enzyme catalysis. This is because of the striking analogy between an intramolecular reaction and an enzyme-catalyzed reaction proceeding through an enzyme–substrate complex.[2]

Various bases have been studied as intramolecular nucleophiles in the hydrolysis of esters. The effective molarity of the neighboring imidazole in *p*-nitrophenyl γ-(4′-imidazolyl)butyrate is 9.4 *M*.[3,4] This is the concentration of imidazole in the hydrolysis of *p*-nitrophenyl acetate required to give a pseudo-first-order rate constant of the magnitude observed in the intramolecular reaction. Effective molarities of 1000–5000 *M* are observed in hydrolysis of substituted phenyl *N*-dimethylaminobutyrates for the dimethylamino group catalyst in comparison with trimethylamine catalysis of the hydrolysis of phenyl acetates.[4] Carboxylate ions have been studied as intramolecular nucleophiles,[2,5] and although the corresponding intermolecular reactions (acetate ion catalyzed hydrolysis of phenyl acetates) proceed in part by a general base mechanism,[6] it has been found that the effective molarities must range up to 10^8 *M*.[7]

Neighboring phenoxide ions participate in the hydrolysis of *p*-nitrophenyl 4-nitrosalicylate,[8] catechol monobenzoate,[9] and ethyl 2-hydroxy-5-nitrophenyl-carbonate[10] as intramolecular general bases. Intramolecular alkoxide ion participation has been observed in amide hydrolysis. Bruice and Marquardt[11] studied the hydrolysis of γ-hydroxybutyramide and found enhancements of the rate 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.

Studies of intramolecular nucleophilic oxide ion attack with esters have not been carried out and no estimates have been made of the effective molarity of such a species in an intramolecular reaction. Likewise, there have not as yet been any thorough kinetic studies of intramolecular nucleophilic reactions involving phenoxide ions. Such reactions could be of considerable interest in regard to the mechanism of action of esteratic enzymes with which a serine hydroxyl is acylated in the initial reaction.[2] The study of oxygen anion nucleophiles in simple intramolecular chemical reactions could be useful in elucidating the factors influencing intracomplex nucleophilic attack by serine in the enzyme–substrate complex. We have studied in the present work the cyclization reactions of phenyl *N*-(2-hydroxyphenyl)-*N*-methylcarbamate (I) and phenyl *N*-(2-hydroxyphenyl)carbamate (II). In these reactions phenoxide ion is released and a cyclic carbamate ester is formed.



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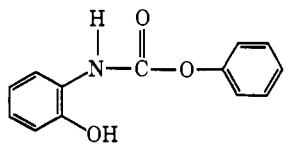


II

Experimental Section

Materials. *N*-Methyl-*o*-aminophenol was prepared in low yield by refluxing *o*-aminophenol (J. T. Baker, 55 g, 0.5 mol) and iodomethane (31.4 ml, 0.5 mol) in ethanol (1300 ml) for 5 hr. The dark oil obtained on removal of the solvent was neutralized with aqueous Na_2CO_3 and extracted with ether. The ethereal solution

(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 1.
(3) T. C. Bruice and J. M. Sturtevant, *J. Amer. Chem. Soc.*, **81**, 2860 (1959).
(4) T. C. Bruice and S. J. Benkovic, *ibid.*, **85**, 1 (1963).
(5) T. C. Bruice and U. K. Pandit, *ibid.*, **82**, 5858 (1960); E. Gaetjens and H. Morawetz, *ibid.*, **82**, 5328 (1960); J. W. Thanassi and T. C. Bruice, *ibid.*, **88**, 747 (1966).
(6) V. Gold, D. G. Oakenfull, and T. Riley, *J. Chem. Soc.*, 515 (1968).
(7) T. C. Bruice and A. Turner, *J. Amer. Chem. Soc.*, **92**, 3422 (1970).
(8) M. L. Bender, F. J. Kezdy, and B. Zerner, *ibid.*, **85**, 3017 (1963).
(9) B. Capon and B. Ch. Ghosh, *J. Chem. Soc. B*, 472 (1966).
(10) T. H. Fife and J. E. C. Hutchins, *J. Amer. Chem. Soc.*, **94**, 2837 (1972).
(11) T. C. Bruice and F. H. Marquardt, *ibid.*, **84**, 365 (1962).

was evaporated and extracted with boiling hexane. The hexane extract was treated with activated charcoal. On cooling, light brown crystals deposited (mp 83–86°, lit.[12] 92–95°) which darkened rapidly in air. Phenyl *N*-(2-hydroxyphenyl)-*N*-methylcarbamate (I) and phenyl *N*-(2-hydroxyphenyl)carbamate (II) were prepared according to a published procedure.[13] The former material was recrystallized from ethyl acetate–benzene (mp 110–113°, lit.[13] 146°). *Anal.* Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.07; H, 5.29; N, 5.78. The infrared spectrum showed strong absorptions at 3280 and 1680 cm^{-1} corresponding to OH and C=O (carbamate) stretching frequencies. After two crystallizations from $CHCl_3$, phenyl *N*-(2-hydroxyphenyl)carbamate melted at 144–147°, lit.[13] 150°. Some darkening occurred at 130°.

2-Benzoxazolinone was prepared by a published method[14] and recrystallized from ethanol (mp 140–141°, lit. 141–142°).[15a] Treatment of this compound with 1.5 *M* NaOH and dimethyl sulfate yielded *N*-methyl-2-benzoxazolinone.[12] Recrystallization from ethanol gave white crystals (mp 83–84°, lit.[15a] 87.5°).

Phenyl *N*-methyl-*N*-phenylcarbamate (III) was prepared by slowly adding *N*-methylaniline (2 equiv) to phenyl chloroformate (J. T. Baker, 1 equiv) dissolved in ether. The mixture was stirred for 2 hr, water was added to dissolve the hydrochloride, and the solution was extracted with ether. Evaporation of the solvent yielded the desired material which was recrystallized from hexane (mp 58.5–59°, lit.[15b] 58°).

Buffers were prepared using analytical grade materials and deionized water. 2,2,2-Trifluoroethanol was distilled (73°, 1 atm) before use; pentaerythritol was used without purification (Matheson Coleman and Bell reported mp 258–260°).

Kinetic Methods. The first-order process which resulted in formation of the benzoxazolinone and phenol (or phenolate) from both phenyl *N*-(2-hydroxyphenyl)carbamate and phenyl *N*-(2-hydroxyphenyl)-*N*-methylcarbamate was monitored at 270 nm using a Durrum–Gibson stopped-flow spectrophotometer (Model D 110). Stock solutions of substrate ($\sim 8 \times 10^{-2}$ *M*) were made up in anhydrous acetonitrile, and 33 μl was injected into 10 ml of 0.01 *M* HCl (μ = 0.5 *M*, KCl). This solution was introduced into one of two identical drive syringes. The other contained a high pH buffer, such that on rapid mixing of equal volumes from the two syringes a reaction solution at the required pH was obtained. The drive syringes, mixing chamber, and cuvette were suspended in a water trough whose temperature was maintained at 25 ± 0.1° by circulating the water through a heat exchanger immersed in a thermostat. Optical density changes after mixing were recorded on a Hewlett–Packard storage oscilloscope (Model 1207B). At each pH, four to six pairs of reactions whose oscilloscope traces overlapped were tabulated, and rate constants were calculated using an IBM 360 computer.[16] Several reactions at lower pH were followed using a conventional recording spectrophotometer (Gilford 2000). Acetonitrile concentration (0.1% v/v) and ionic strength (μ = 0.5 with KCl) were held constant. The base-catalyzed release of phenolate ion from phenyl *N*-methyl-*N*-phenylcarbamate was followed at 287 nm using a Zeiss PMQ II spectrophotometer with cell block thermostated at 25 ± 0.1°.

Spectral Measurements. Spectra were obtained using a Cary 15 spectrophotometer and 1-cm quartz cells containing the appropriate buffers in both sample and reference compartments. Aqueous solutions of *N*-methyl-2-benzoxazolinone exhibited the following ultraviolet absorptions: $\lambda_{max}^{pH\ 7.02}$ 270 nm (log ε 3.68); $\lambda_{max}^{1\ M\ KOH}$ 272 nm (log ε 3.65). The solution at pH 7.02 showed no spectral changes over 24 hr; that in 1 *M* KOH showed rapid changes leading to loss of the 272-nm peak and formation of a new absorption: λ_{max} 293 nm (log ε 3.70), isosbestic point 280 nm. 2-Benzoxazolinone solutions also showed strong ultraviolet absorptions: $\lambda_{max}^{pH\ 7.02}$ 271 nm (log ε 3.65); $\lambda_{max}^{1\ M\ KOH}$ 279 nm (log ε 3.76); $\lambda_{max}^{1\ M\ KOH}$ 239 (log ε 4.06). By measuring the absorbance at 239 nm as a function of pH in appropriate buffers (8 pH's, μ = 0.5) at 23°, the pK_a of 2-benzoxazolinone was found to be 8.9. A solution in 1 *M* KOH was observed to show no spectral changes in over 1 hr.

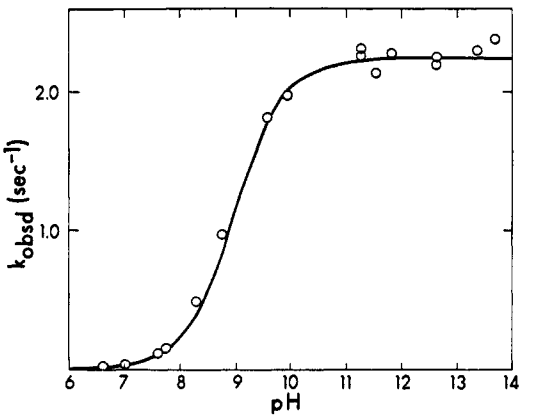


Figure 1. Plot of k_{obsd} for ring closure of phenyl *N*-(2-hydroxyphenyl)-*N*-methylcarbamate (I) to *N*-methyl-2-benzoxazolinone and phenoxide ion at 25° in H_2O with μ = 0.5 *M* (with KCl).

When phenyl *N*-(2-hydroxyphenyl)-*N*-methylcarbamate was introduced into buffer solution at pH 7.02 (0.1 *M* phosphate), an absorption at 270 nm rapidly developed, and the solution spectrum when this process had terminated very closely matched that obtained by mixing *N*-methyl-2-benzoxazolinone and phenol in identical and equal concentrations in the same buffer. Introduction of phenyl *N*-(2-hydroxyphenyl)-N-methylcarbamate (1.49×10^{-4} *M*) into 1 *M* KOH gave a solution whose absorbance at 270 nm was 0.83 unit. This rapidly fell by 0.39 unit. A solution containing phenol and *N*-methyl-2-benzoxazolinone in identical and equal concentrations behaved in the same manner; the reaction half-life in both cases was approximately 150 sec.

A solution of phenyl *N*-(2-hydroxyphenyl)carbamate at pH 6.61 (0.1 *M* phosphate) showed an absorbance maximum at 275 nm (log ε 3.49). The spectrum changed quite rapidly and was finally identical with that obtained by mixing phenol and 2-benzoxazolinone in identical and equal concentrations. A similar experiment in 1 *M* KOH yielded the same results.

Results

The ring closure reactions of phenyl *N*-(2-hydroxyphenyl)-*N*-methylcarbamate (I) and phenyl *N*-(2-hydroxyphenyl)carbamate (II) to yield *N*-methyl-2-benzoxazolinone and 2-benzoxazolinone, respectively, in aqueous base have already been documented.[13] Further evidence obtained from the ultraviolet absorption spectra of the appropriate reaction solutions has now confirmed that these processes occur quantitatively (see Experimental Section). In addition, rate constants at 25° have been obtained for both reactions over a wide pH range. A search was made for buffer catalysis of the ring closure of I, but none was found in acetate, pyridine, imidazole, or phosphate buffers. The pH–rate constant profile for I is shown in Figure 1. The curve was shown to be sigmoidal, and the best least-squares fit[16] to the curve generated by eq 1 was

$$k_{obsd} = k_I[K_I/(K_I + a_H)] \quad (1)$$

found. K_I corresponds to the apparent dissociation constant, pK_{app} = 9.0 and k_I = 2.23 sec^{-1}. There was no evidence for either a spontaneous water rate or for a hydroxide ion catalyzed reaction at high pH. A log rate constant–pH profile (not shown) was also drawn for the entire pH range. From pH 3.65 to 8, a straight line was obtained with slope = 0.99.

Rate constants for the ring closure of II are shown in Figure 2. The data have been shown to fit eq 2 by a

$$k_{obsd} = k_{II}[K_{II}/(K_{II} + a_H)] + k_{OH}[OH^-] \quad (2)$$

similar least-squares curve-fitting technique as em-

(12) G. de W. Anderson and F. Bell, *J. Chem. Soc.*, 2668 (1949).
(13) L. C. Raiford and G. O. Inman, *J. Amer. Chem. Soc.*, **56**, 1586 (1934).
(14) R. T. Williams, *Biochem. J.*, **41**, 1 (1947).
(15) I. M. Heilbron, *et al.*, Ed., "Dictionary of Organic Compounds," Oxford University Press, London, 1965: (a) p 355; (b) p 2295.
(16) Computer programs were devised by Dr. Edwin Anderson of this address.

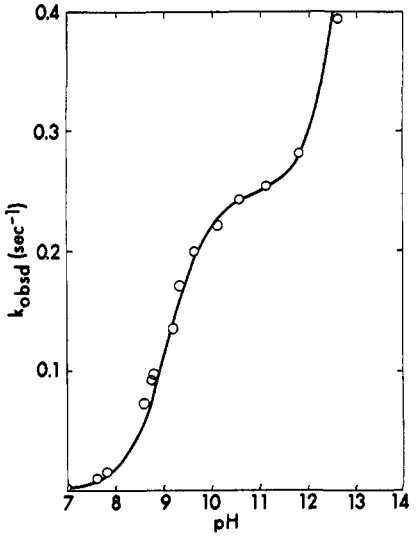


Figure 2. Plot of k_{obsd} for ring closure of phenyl *N*-(2-hydroxyphenyl)carbamate (II) to 2-benzoxazolinone and phenoxide ion at 25° in H_2O with $\mu = 0.5$ *M* (with KCl).

ployed with I.[16] The value obtained for pK_{II} is 9.1, and for k_{II}, 0.247 sec^{-1}. At high pH, in contrast with I, an apparent hydroxide ion catalyzed reaction is observed. The value of $k_{OH} = 5.14\ M^{-1}$ sec^{-1} was obtained from the slope of a linear plot of k_{obsd} *vs.* [OH$^-$]. Three concentrations of hydroxide ion were employed in the range 0.045 to 0.495 *M* ($\mu = 0.5$).

The susceptibility of phenyl *N*-methyl-*N*-phenylcarbamate (III) to attack by hydroxide ion, pentaerythritol monoanion, and trifluoroethoxide ion has been examined in order to be able to make an approximate estimate of the rate enhancement prevailing in the intramolecular ring closures of I and II, where attack at a similar carbonyl function occurs by a much weaker base. The slow hydroxide ion catalyzed hydrolysis of III has already been measured.[17] This work was repeated at 1 *M* KOH, and a rate constant of 4.27×10^{-5} sec^{-1} was obtained in excellent agreement with the corresponding previous result[17] (4.28×10^{-5} sec^{-1}). Christenson[17] also studied the reaction at 0.10 *M* KOH, thereby demonstrating a linear dependency of reaction velocity on hydroxide ion concentration. From the three rate constants, an average second-order rate constant of $4.27 \times 10^{-5}\ M^{-1}$ sec^{-1} can be obtained for the reaction between III and hydroxide ion. Bimolecular rate constants, k_2, for the reaction of III with anions from pentaerythritol and trifluoroethanol were obtained from the best computer fit[16] of the observed rate constants, k_{obsd}, to eq 3. The concentration of base in

$$k_{obsd} = k_2[RO^-] + k_{OH}\text{-}[OH^-] \qquad (3)$$

the ionized form was determined from the stoichiometry of the solutions with CF_3CH_2OH (half-neutralized buffers) and by assuming a p*K* of 14.0 (Table II, footnote *a*) in the case of pentaerythritol. In both cases [OH$^-$] was determined from measured pH's, assuming pH $= -\log [H^+]$. Computer calculated and observed values are given in Table I. Values of k_2 are shown in Table II. Because of the dominating effect of hydroxide ion catalysis at higher pH's and the extreme slowness of the reaction at lower pH's, it was impractical to make similar studies at widely varying pH values. However, initial rates for the release of phenolate ion from III in phosphate buffers at pH 10.35 showed that the presence of 0.3 *M* pentaerythritol or 1 *M* CF_3CH_2OH increased the reaction velocity by only about 60% from that in the buffer alone. Furthermore, the reactions with the added alcohols were at least 60-fold slower than under conditions where the hydroxide ion concentration was approximately 100 times greater. It is thus clear that the ionized alcohol or its kinetic equivalent is participating in the reactions with III.

The subsequent reaction of *N*-methyl-2-benzoxazolinone with hydroxide ion at 25° has been determined ($k_2(OH^-) = 4.8 \times 10^{-3}\ M^{-1}$ sec^{-1}) and thereby shown to be too slow to interfere with the stopped-flow experiments.

Table I. Computer Calculated and Observed Values (k_{obsd}) for First-Order Rate Constants for Release of Phenolate Ion from III in Solutions Containing Trifluoroethanol and Pentaerythritol

ROH	Total ROH concn, *M*	pH	k_{obsd}, sec^{-1}	k_{calcd}, sec^{-1}
CF_3CH_2OH	0.05	11.85	6.45×10^{-7}	6.50×10^{-7}
	0.50	12.25	3.18×10^{-6}	3.03×10^{-6}
	0.70	12.29	4.22×10^{-6}	3.88×10^{-6}
	1.00	12.40	5.01×10^{-6}	5.37×10^{-6}
	1.00	12.36	5.09×10^{-6}	5.22×10^{-6}
$(CH_2OH)_4C$	0.09	12.60	3.44×10^{-6}	3.48×10^{-6}
	0.174	12.65	4.86×10^{-6}	4.75×10^{-6}
	0.30	12.65	5.69×10^{-6}	6.01×10^{-6}

Table II. Second-Order Rate Constants for the Reaction between Oxygen Bases and III, Leading to Release of Phenolate Ion

Base	pK_a	k_2, M^{-1} sec^{-1}
OH^-	15.74	4.27×10^{-5}
$(CH_2OH)_3CCH_2O^-$	14.0[a]	$2.24 \pm 0.34 \times 10^{-4}$ [c]
$CF_3CH_2O^-$	12.36[b]	$7.41 \pm 0.64 \times 10^{-6}$ [c]

[a] P. Ballinger and F. A. Long, *J. Amer. Chem. Soc.*, **82**, 795 (1960). [b] **81**, 1050 (1959). [c] Standard deviations (fit to eq 3).

Discussion

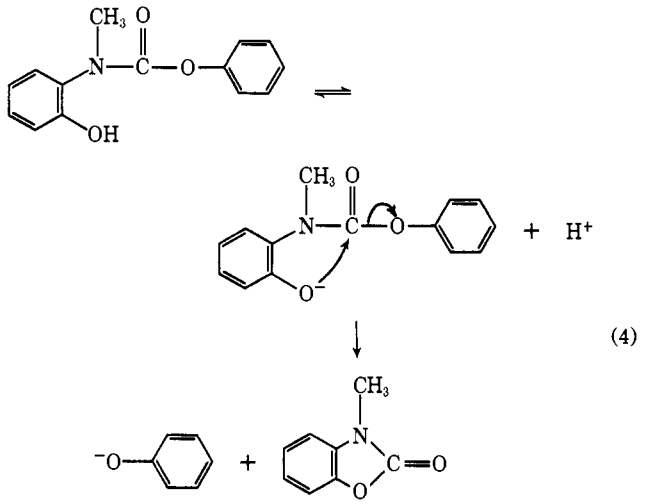
Stopped-flow rate measurements are necessary to follow the intramolecular reactions of I and II in contrast to the great stability normally exhibited by carbamate esters.[17-19] The sigmoidal pH–rate constant profile obtained for the ring closure reaction of I (Figure 1), together with the large rate enhancement obtained in comparison with the reaction of III with hydroxide ion, strongly suggests the participation of the ionized form of the phenol either prior to or during the rate-determining step. Lack of buffer catalysis in the cyclization of I (or II) indicates that both reactions proceed *via* preequilibrium ionization of the phenol group, as in eq 4.

The pH–rate constant profile for the ring closure reaction of II (Figure 2) is similar to that of I up to pH 11, and rate constants are less than those for I by a factor of only 9, suggesting a similar mechanism in both cases. Christensen[17] found the bimolecular rate constant for the attack of hydroxide ion on phenyl *N*-phenylcarbamate (IV) to be 47.2 M^{-1} sec^{-1} at 25°. Therefore, the ring closure of II at pH 10, with rate constant 0.22

(17) I. Christenson, *Acta Chem. Scand.*, 18, 904 (1964).

(18) L. W. Dittert and T. Higuchi, *J. Pharm. Sci.*, 52, 852 (1963).

(19) M. L. Bender and R. B. Homer, *J. Org. Chem.*, 30, 3975 (1965).



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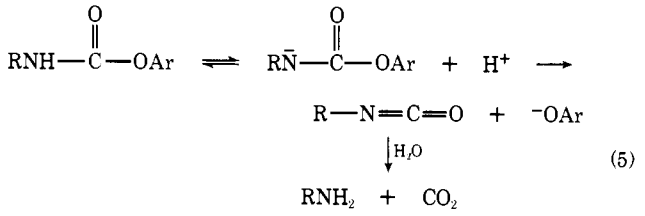
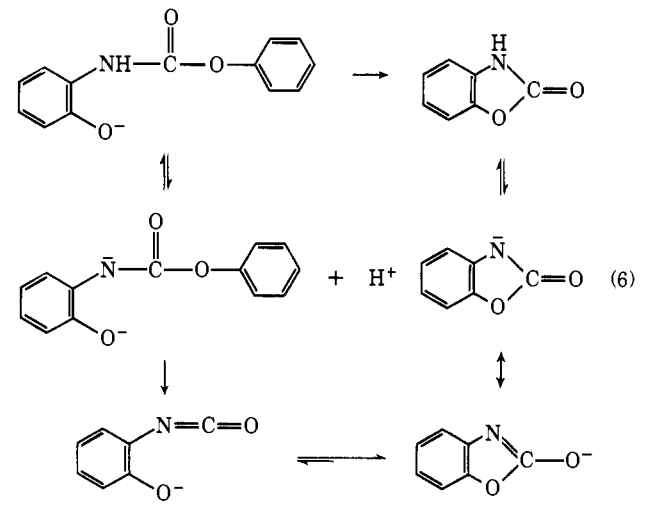
sec^{-1}, proceeds nearly 50 times more rapidly than the reaction of IV at the same pH, even though a highly favorable isocyanate mechanism (eq 5) exists for the



(5)

latter compound. Aromatic carbamate esters without nitrogen substitution hydrolyze *via* an isocyanate intermediate[17-19] with rate constants 10^6 greater than for the corresponding N-methylated compounds. The first-order dependence of the observed rate constants on hydroxide ion concentration for the ring closure of II at pH >11 (eq 2) indicates that the isocyanate mechanism can only intervene at pH's high enough to cause a second ionization in the substrate (eq 6). At pH

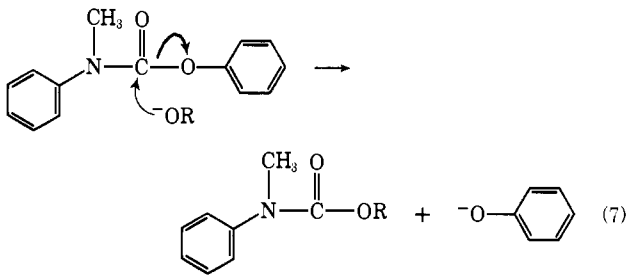


(6)

>12 the presence of a neighboring OH group in II is a hindrance to hydroxide ion catalyzed release of phenolate ion. (The bimolecular hydroxide ion rate constants for II and IV are 5.14 and 47.2 M^{-1} sec^{-1}, respectively.)

The cyclization product of I, *N*-methyl-2-benzoxazolinone, was found to hydrolyze slowly at high pH (see Results) whereas 2-benzoxazolinone formed from II is stable. Spectral changes observed for this latter compound (in particular, the appearance of a new absorption at 239 nm, as the pH is raised from 7 to 10) indicate that dissociation is occurring, with pK_a = 8.9. The ionized form of 2-benzoxazolinone accounts for the lack of hydrolytic reactivity toward hydroxide ion. That species is resonance stabilized, and while a rapid equilibrium doubtless exists between it and the open chain isocyanate (eq 6), it is probable that the equilibrium lies far to the right. This and the presence of a negative charge in the molecule makes reaction with hydroxide ion so slow that starting material can be recovered by acidification from solutions in 1 *M* KOH, even after more than 1 hr.[20]

Comparison of the unimolecular rate constant for the intramolecular reaction to the bimolecular rate constant for the corresponding intermolecular reaction proceeding by the same mechanism (sec^{-1}:M^{-1} sec^{-1}) gives a ratio with units of molarity which can be taken to be the concentration of catalyst in the bimolecular reaction necessary to give a pseudo-first-order rate constant of the magnitude obtained in the intramolecular reaction. The effective molarity of the neighboring phenoxide ion in I is 50,000 *M* in comparison with hydroxide ion catalyzed hydrolysis of the unsubstituted compound III. In the case of the reaction of oxygen anions as nucleophiles with *p*-nitrophenyl acetate,[21] it has been shown that there exists a fairly good linear relationship between log k_2 (k_2 is the bimolecular rate constant) and pK_a, and that points for both pentaerythritol and trifluoroethanol fall close to the line. Using the bimolecular rate constants for these two alcohols reacting with compound III (Table II) and assuming behavior similar to that observed with *p*-nitrophenyl acetate, a bimolecular rate constant for an oxygen anion of pK_a = 9 can be calculated (k_2 = 6.46 × 10^{-9} M^{-1} sec^{-1}, slope = 0.9). Thus, the effective molarity of the neighboring phenoxide ion of I can be determined by comparison with bimolecular transesterification of the unsubstituted compound by an oxide ion of the same pK_a (eq 7). A value of 3.5 × 10^8 *M* is obtained.



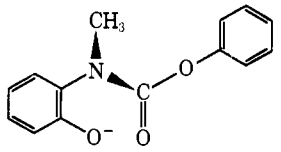
(7)

The large effective molarity (10^8 *M*) of the neighboring phenoxide ion in the reaction of I (eq 4) cannot be entirely due to an increase in local concentration of the nucleophilic group. A quantitative explanation cannot yet be given. However, it is likely that much of the efficiency of the neighboring oxide ion is due to a favorable steric situation. A Stuart–Briegleb model of compound I shows that in one of the conformations in which steric interactions are minimized, the phenoxide

(20) An analogous inhibition of reaction by a nonproductive ionization exists for the 5-nitrocoumaranone system: P. S. Tobias and F. J. Kezdy, *J. Amer. Chem. Soc.*, 91, 5171 (1969).

(21) T. C. Bruice, T. H. Fife, J. J. Bruno, and N. E. Brandon, *Biochemistry*, 1, 7 (1962); also ref 2, p 101.

ion lies immediately adjacent to the carbonyl so that perpendicular attack can readily occur.[22] Thus, the stereochemistry imposed on the molecule is such as to facilitate greatly the intramolecular nucleophilic reaction.



While other factors can also influence intramolecular catalysis, it appears reasonable that proper orientation is at least partly responsible for the efficient reaction in the present case.

Extremely large effective molarities in reactions of neighboring groups with ester functions have only been previously reported for carboxylate ions[5] (10^8 *M*), and so far, no comparable values have been found for neighboring nitrogen bases.[2-4] With neighboring pyridine in (para-substituted phenyl)ethylpyridine carbonate the effective molarity varies from 30 to 50 *M*, depending upon the substituent.[23] The largest effective molarity found to date for a nitrogen base is 5×10^3 *M* in the case of the dimethylamino group of *p*-nitrophenyl γ-dimethylaminobutyrate.[4] Therefore, it is possible that effective molarities of 10^8 *M* are characteristic of anionic nucleophiles. A possibility is that desolvation of highly solvated anionic nucleophiles is a requirement in intermolecular reactions, but not in intramolecular reactions where water molecules cannot fit between the nucleophilic group and the reaction center. The energy requirement for desolvation of an anion should be considerable.[24] Bruice and Turner[7] found that effective molarities of neighboring carboxyl did not vary greatly on changing the solvent from H_2O to 1 *M* H_2O–DMSO. However, it is not certain that a carboxyl group would be completely desolvated in 1 *M* H_2O–DMSO. Hydroxide ion is still highly solvated in that solvent.[25]

The fact that an oxide ion is an excellent intramolecular nucleophile when held adjacent to the carbonyl group is of interest in regard to the mechanism of action of esteratic enzymes having serine at the active site. The generally accepted mechanism for acylation of α-chymotrypsin involves histidine-57 general-base assisted acylation of serine-195.[2] In this mechanism a proton is partially removed from the serine hydroxyl group as it attacks the carbonyl group of the substrate. It is clear that a serine oxygen should be a powerful nucleophile in an intracomplex reaction towards an ester substrate where the carbonyl is bound in close proximity to the serine hydroxyl.

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

(22) M. L. Bender, *Chem. Rev.*, **60**, 63 (1960).
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Free-Radical Chemistry of Organophosphorus Compounds. III. α *vs.* β Scission in Reactions of Alkoxy and Thiyl Radicals with Trivalent Organophosphorus Derivatives

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Abstract: Reactions of a series of $X-P(OEt)_2$ (where X = Cl, alkyl, Ph, PhO, AcO, and n-Bu_2N) with alkoxy and thiyl radicals ($RA\cdot$, A = O or S) have been studied to attempt to understand more fully the factors which determine the relative amounts of oxidation [$APX(OEt)_2$] and displacement [$RAP(OEt)_2$] products which result in such systems. With A = O, both oxidation and displacement take place depending on the natures of R and X. Displacement as well as oxidation also is noted in a few instances with A = S when the P–X bond is relatively weak. Analysis of our findings along with those of other workers leads to the conclusion that to a first approximation the relative strengths of the R–A and P–X bonds in the probable phosphoranyl radical intermediates, $RAPX(OEt)_2$, determine the proportions of α-scission (displacement) and β-scission (oxidation) processes which occur. Inclusion of substituents in a five-membered ring [$MeOP(OCH_2)_2$] does not result in ring opening. Possible more subtle refinements of these ideas, which await experimental testing, are also presented.

Reactions of alkoxy or thiyl radicals with trivalent phosphorus compounds potentially may be divided into two distinct types, displacements (eq 1a) and oxidations (eq 1b). In terms of the phosphoranyl radical **1** which may be an intermediate in both pathways, the processes which lead to displacement or oxidation products may be classified respectively as α scission (eq 1a) and β scission (eq 1b). That both oxidations and displacements do in fact occur experimentally with A = O was noted in early studies of such systems; *e.g.*, reaction of n-Bu_3P with *tert*-butoxy radicals from di-*tert*-butyl peroxide decomposition at 130° gave[1] displace-

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