Highly Efficient Intramolecular Nucleophilic Reactions. The Cyclization of *p*-Nitrophenyl *N*-(2-Mercaptophenyl)-*N*-methylcarbamate and Phenyl *N*-(2-Aminophenyl)-*N*-methylcarbamate

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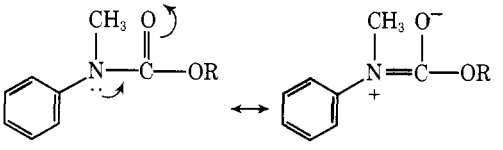
Abstract: *p*-Nitrophenyl *N*-(2-mercaptophenyl)-*N*-methylcarbamate cyclizes rapidly at 25° to *N*-methylbenzothiazolone with release of *p*-nitrophenol. The pH–rate constant profile is sigmoidal with pK_{app} = 8.7. The effective molarity of the neighboring sulfhydryl group is 1.4×10^5 *M* in comparison with bimolecular attack of thiols on *p*-nitrophenyl *N*-methyl-*N*-phenylcarbamate. The pH–rate constant profile for cyclization of phenyl *N*-(2-aminophenyl)-*N*-methylcarbamate to 1-methyl-2-benzimidazolone is sigmoidal at 50° with pK_{app} of 2.7. The solvent isotope effect k_{H_2O}/k_{D_2O} is 1.2 for the pH-independent reaction where participation by the neighboring group is maximal. Bimolecular reaction of cyclohexylamine (pK_a = 10.7) with phenyl *N*-(4-aminophenyl)-*N*-methylcarbamate was too slow to be accurately measured, but, employing the upper limit of a detectable second-order rate constant and a reasonable value for the Brønsted coefficient, the effective molarity of a neighboring amine group in reaction with carbamate esters was calculated to be at least 3×10^8 *M*. Thus, large effective molarities of 10^5–10^8 *M*, previously observed only with oxy anion nucleophiles, can also be obtained in intramolecular reactions of neutral amine nucleophiles. The ΔS^* for intramolecular nucleophilic amine attack is −23.8 eu which implies that part of the large rate enhancement is probably due to a relatively favorable ΔH^* value. Cyclohexylamine catalyzed release of *p*-nitrophenoxide ion from *p*-nitrophenyl *N*-methyl-*N*-phenylcarbamate at 50° is characterized by $\Delta S^* = -32.5$ eu.

An intramolecular reaction bears a striking resemblance to an enzymatic reaction proceeding through an enzyme–substrate complex.[2] The study of intramolecular reactions has therefore been of great importance in attempts to understand the mechanism of enzyme catalysis.[2,3]

Various intramolecular nucleophiles have been studied in the hydrolysis of carbamate esters.[4-6] These reactions occur with great facility. Neighboring hydroxymethyl and phenolic OH groups have effective molarities of 10^5–10^8 *M* in comparison with analogous bimolecular reactions.[4,5,7]

Carbamate esters are especially favorable compounds with which to study intramolecular nucleophilic processes since the acyl group is highly deactivated by resonance interaction with the adjoining nitrogen (eq 1) which reduces



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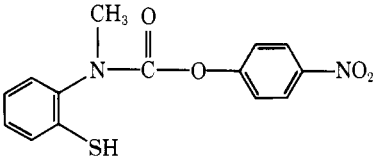
the partial positive charge on the carbonyl carbon. Thus, acyl group deactivation will greatly slow the bimolecular reactions. Carbamate esters are normally quite stable under hydrolytic conditions.[8] In a nucleophilic reaction at a carbamate carbonyl, considerable bond making with the incoming nucleophile will be required to attain the transition state. A tight transition state[9] will thereby result in which maximum translational and rotational entropy of the nucleophile will be lost in the bimolecular comparison. The maximum effectiveness of a properly positioned intramolecular nucleophile might therefore be determined.

The intramolecular nucleophiles that have been utilized previously in carbamate ester hydrolysis are all oxy anions.[4-6] To determine whether large effective molarities are general for negatively charged nucleophiles of various type, we have measured rates of cyclization for carbamate ester I having a neighboring thiol group. Reaction of I takes place through the thiol anion. The effect of a neutral amine neighboring group has been ascertained with carbamate ester II.



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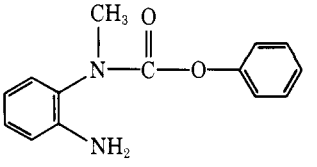


II

Experimental Section

Materials. 2-Aminothiophenol was obtained from Aldrich. *N*-Methyl-2-aminothiophenol was prepared by refluxing 2-aminothiophenol and iodomethane (Mallinckrodt) in ethanol (1500 ml) for 5 hr. The yellowish white solid remaining after removal of the solvent was dissolved in water and neutralized with aqueous Na_2CO_3. The *N*-methylaminothiophenol was extracted with chloroform, and the chloroform solution was dried over anhydrous Na_2SO_4. *p*-Nitrophenyl *N*-(2-mercaptophenyl)-*N*-methylcarbamate (I) was prepared by reacting the aminothiophenol with *p*-nitrophenyl chloroformate in anhydrous chloroform by methods analogous to those used with the corresponding phenolic compounds.[4] The infrared spectrum of compound I (mp 99–103°) showed strong carbonyl absorption at 1750 cm^{-1} and weak S–H absorption at 2550 cm^{-1}. Anal. Calcd for $C_{14}H_{12}N_2O_4S$: C, 55.25; H, 3.98. Found: C, 54.95; H, 4.20.

Benzothiazolone was prepared by heating urea and 2-aminothiophenol at 155–165° for 1 hr. The product was recrystallized twice from hot water [mp 129–133° (lit.[10] 128°)]. Anal. Calcd for C_7H_5ONS: C, 55.61; H, 3.33. Found: C, 55.59; H, 3.49. Benzothiazolone was dissolved in 1.5 *N* NaOH and shaken with dimethyl sulfate to yield *N*-methylbenzothiazolone. Recrystallization from hot water gave white crystals (mp 70–71°). Anal. Calcd for C_8H_7ONS: C, 58.16; H, 4.27. Found: C, 58.06; H, 4.36.

Phenyl *N*-(2-nitrophenyl)-*N*-methylcarbamate was prepared by stirring *N*-methyl-*o*-nitroaniline (12.7 g, 0.084 mol) and phenyl chloroformate (6.55 g, 0.042 mol) in anhydrous ether for 3 days at

room temperature. The hydrochloride precipitate was removed by filtration and the filtrate washed with 10% HCl. The ether layer was then evaporated to yield an oil. This material was reduced to phenyl *N*-(2-aminophenyl)-*N*-methylcarbamate hydrochloride using stannous chloride–concentrated HCl.[11] The solid hydrochloride was added to an aqueous buffer (pH 6.5) and the solution extracted twice with ether. The ether was evaporated and water removed by azeotropic distillation with methanol at 30°. The white solid obtained was recrystallized from cyclohexane containing a little benzene (rectangular plates, mp 95–96.5°). Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.82; N, 11.56. Found: C, 69.49; H, 5.78; N, 11.68.

1-Methyl-2-benzimidazolone (III) was prepared according to a published procedure,[12] by heating *N*-methyl-*o*-phenylenediamine (hydrochloride from Eastman) and urea 16 hr at 170–180° under a flow of nitrogen. The product was extracted with chloroform and recrystallized from methanol after treatment with charcoal [mp 175–185° (lit.[12] 188–190°)]. Purer material with an identical infrared spectrum was obtained by cyclization of phenyl *N*-(2-aminophenyl)-*N*-methylcarbamate in hot ethanol. This material melted at 187–190°.

Phenyl *N*-(4-aminophenyl)-*N*-methylcarbamate was prepared by room temperature hydrogenation of the nitro derivative dissolved in ethanol at 65 psi H_2. A pinch of 5% Pt on charcoal (Matheson Coleman and Bell) was used as a catalyst, and the reaction was allowed to proceed for 48 hr. The product was recrystallized from benzene containing a little hexane, yielding white needles (mp 103–104°). Phenyl *N*-(4-nitrophenyl)-*N*-methylcarbamate was prepared in an identical manner with the ortho derivative. It was recrystallized from ethyl acetate–hexane before reduction.

Phenyl *N*-methyl-*N*-phenylcarbamate and *p*-nitrophenyl *N*-methyl-*N*-phenylcarbamate were previously prepared samples.[4] 2-Aminoethanethiol was obtained from J. T. Baker Chemical Co. Buffers were prepared using AR grade materials and deionized water. Ionic strength was maintained at 0.5 *M* using KCl.

Kinetic Methods. The formation of *p*-nitrophenolate and *N*-methylbenzothiazolone from *p*-nitrophenyl *N*-(2-mercaptophenyl)-*N*-methylcarbamate was followed at 400 nm using a Durrum stopped-flow spectrophotometer (Model D-110). Stock solutions of substrate (10^{-2} *M*) were made up in anhydrous acetonitrile, and 40 μl was injected into 25 ml of 0.01 *M* HCl (μ = 0.5 *M*, KCl). This solution was then introduced into one of two drive syringes. The other contained a buffer such that, on mixing of equal volumes from the two syringes, a reaction solution at the required pH value was obtained. The temperature of the water in the water trough of the stopped-flow spectrophotometer was maintained at 25.0 ± 0.1°. Absorbance changes after mixing were recorded on a Hewlett-Packard storage oscilloscope (Model 1207 B). First-order rate constants at each pH were calculated as the average of four to six determinations. Rate constants were calculated using an Olivetti-Underwood Programma 101. Pseudo-first-order rate constants for attack of thiols on *p*-nitrophenyl *N*-methyl-*N*-phenylcarbamate were obtained by following the release of *p*-nitrophenolate ion at 400 nm using a Gilford 2000 recording spectrophotometer. All pH values were measured using a Radiometer pH meter with a GK 2302B combined electrode.

The cyclization reaction of II to give III and phenol was monitored spectrophotometrically at 277 nm. The substrate was introduced into 3 ml of the appropriate buffer as 15 μl of 0.03 *M* material dissolved in dry acetonitrile. A Gilford 2000 recording spectrophotometer with cell compartment thermostated at 50 ± 0.1° was employed. Absorbance changes were generally about 0.8 units, and the data were analyzed by a nonlinear least-squares regression technique.[13] Agreement between experimental and calculated data points was generally excellent.

Spectral Measurements. All spectra were measured using a Cary 15 spectrophotometer and 1-cm quartz cells containing the appropriate buffers in both sample and reference cells. The spectrum of *N*-methylbenzothiazolone showed the following absorptions: λ_{max} (pH 7.40) 245 nm (log ε 3.80), (pH 7.40) 279 (3.48), (pH 7.40) 287 (3.50), (pH 13.05) 245 (3.78), (pH 13.05) 279 (3.48), (pH 13.05) 287 (3.49). Benzothiazolone showed the following absorptions: λ_{max} (pH 7.40) 243 nm (log ε 3.84), (pH 7.40) 279 (3.46), (pH 7.40) 287 (3.48), (pH 13.05) 258 (3.98), (pH 13.05) 287 (3.37), (pH 13.05) 293 (3.38). Neither *N*-methylbenzothiazolone nor benzothiazolone showed spectral changes at pH 7.40 or 13.05 for over 1 hr. The spectrum of a solution containing 3.3×10^{-5} *M* *p*-nitrophenyl *N*-(2-mercaptophenyl)-*N*-methylcarbamate at pH 7.40 or 13.05 rapidly matched the spectrum of a solution containing 3.3×10^{-5} *M* *N*-methylbenzothiazolone and 3.3×10^{-5} *M* *p*-nitrophenol at the corresponding pH value.

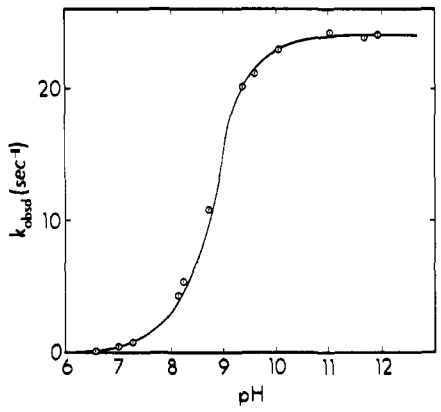


Figure 1. Plot of k_{obsd} for release of *p*-nitrophenolate from *p*-nitrophenyl *N*-(2-mercaptophenyl)-*N*-methylcarbamate (I) vs. pH at 25° in H_2O with μ = 0.5 *M* (KCl).

Phenyl *N*-(2-aminophenyl)-*N*-methylcarbamate (II) in aqueous solutions gave the following spectral data at 25° (μ = 0.5), λ_{max} (pH 7.64) 284 nm (log ε 3.38), λ_{min} (pH 7.64) 257 (2.86), λ_{max} (1.0 *M* KOH) 284 (3.40), λ_{min} (1.0 *M* KOH) 257 (2.92), λ_{max} (1.0 *M* HCl) 255 (2.73), showing that the same species is present in neutral solution and at 1.0 *M* KOH. λ_{max} and ε were unchanged at 50°. The pK_a of II at both 25 and 50° was determined spectrophotometrically by measuring A_{284} as a function of pH. The values obtained were: pK_a (25°) = 2.75 (ten buffers), pK_a (50°) = 2.65 (eight buffers) (μ = 0.5). In a reaction of II at 50° (pH 7.52, 0.1 *M* phosphate, μ = 0.5), samples were removed at different times and analyzed spectrophotometrically at 25°. A continuous increase in absorption at 277 nm (the final λ_{max}) was noted together with a continuous decrease at wavelengths less than 252 nm, the only isosbestic point. Spectra were taken of several reacted solutions both at neutral pH and at 1.0 *M* KOH and were found to be identical. The spectra obtained could be reproduced by making up solutions containing the appropriate concentrations of 1-methyl-2-benzimidazolone and phenol in the same buffers.

1-Methyl-2-benzimidazolone yielded the following spectral data: λ_{max} (pH 6.61) 278 nm (log ε 3.83), λ_{min} (pH 6.61) 248 (2.53), λ_{max} (1.0 *M* KOH) 287 (3.90), λ_{max} (1.0 *M* KOH) 244 (3.70), λ_{min} (1.0 *M* KOH) 262 (3.21), λ_{max} (pH 11.64) 282.5 (3.82). These data indicate that ionization of 1-methyl-2-benzimidazolone is occurring, the substrate having a pK_a of about 12. The spectrum in 1.0 *M* KOH showed no change after 16 hr at 50°. A solution of phenyl *N*-(4-aminophenyl)-*N*-methylcarbamate in phosphate buffer (pH 7.64) gave the following spectral data: λ_{max} 246 nm (log ε 4.15), λ_{max} 284 (3.14), λ_{min} 275 (3.11).

Results

The spectrum of *p*-nitrophenyl *N*-(2-mercaptophenyl)-*N*-methylcarbamate (I) changed rapidly to give a spectrum identical with that of identical concentrations of *N*-methylbenzothiazolone and *p*-nitrophenol, showing that rapid ring closure is occurring. In Figure 1, a plot is shown of k_{obsd} vs. pH for release of *p*-nitrophenol or *p*-nitrophenolate from I at 25°. A sigmoidal profile was obtained with pK_{app} = 8.7. The rate constant for the pH-independent reaction at high pH where participation by the neighboring group is maximal is 24 sec^{-1}. Hydroxide ion catalysis was not detected at pH values below 12. The second-order rate constants for reaction of three different thiols with *p*-nitrophenyl *N*-methyl-*N*-phenylcarbamate were determined at 25°. The values are reported in Table I. The rate constant for mercaptoethanol is nearly the same in H_2O and D_2O, indicating that the thiol is acting as a nucleophile.

The ring closure reaction of phenyl *N*-(2-aminophenyl)-

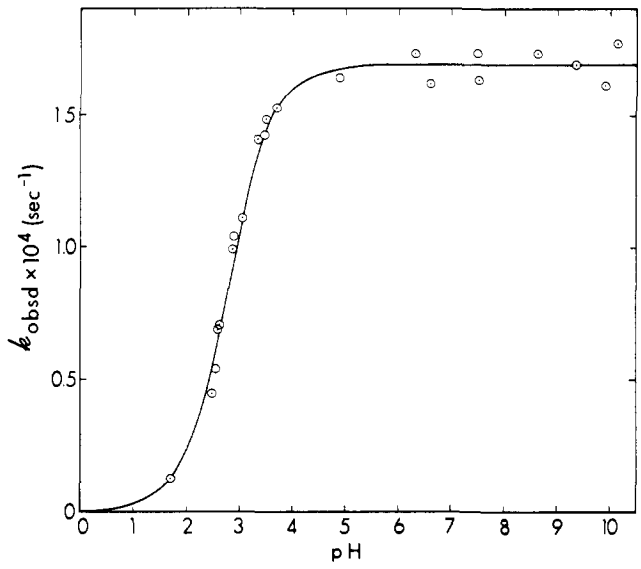


Figure 2. Plot of k_{obsd} for cyclization of phenyl *N*-(2-aminophenyl)-*N*-methylcarbamate (II) vs. pH at 50° in H_2O with μ = 0.5 *M* (KCl).

Table I. Values of the Second-Order Rate Constants (M^{-1} sec^{-1}) for Reaction of *p*-Nitrophenyl *N*-Methyl-*N*-phenylcarbamate at 25° and μ = 0.5 *M* with Thiols

Thiol	pK_a	$k_{RS^-} \times 10^4$
Mercaptoacetate	10.2	3.10
Mercaptoethanol (H_2O)	9.75	2.30
(D_2O)	10.1	2.46
2-Aminoethanethiol	8.3	1.5

carbamate on treatment with alkali has been reported.[14] In the present study, the ring closure of the *N*-methyl analog (II) has been shown to occur quantitatively, yielding 1-methyl-2-benzimidazolone (III) and phenol. Rate constants for this process were obtained by monitoring the rate of appearance of III and phenol spectrophotometrically. Rate measurements were made at 50° over the entire pH range (0.1 *M* HCl to 1.0 *M* KOH). Observed rate constants obey the relationship given in eq 2:

$$k_{obsd} = k_B K_a/(K_a + a_H) + k_{OH}(OH^-) \qquad (2)$$

The results are plotted in Figure 2 which also shows the calculated nonlinear least-squares fit to these data. The best values for the parameters in eq 2 are: $k_B = 1.70 \times 10^{-4}$ sec^{-1}, $k_{OH} = 1.02 \times 10^{-3}$ M^{-1} sec^{-1}, and pK_{app} = 2.70. The second-order rate constant for hydroxide ion catalysis k_{OH} was determined from the slope of a plot of k_{obsd} vs. hydroxide ion concentration with [$^-$OH] concentrations varying from 0.1 to 1.0 *M*. Measurement of k_B in D_2O gave a ratio $k_B^{H_2O}/k_B^{D_2O} = 1.2$. No systematic evidence for buffer catalysis was found, although there was some indication that rate constants increased slightly as the total buffer concentration was raised. An increase in phosphate buffer concentration from 0.025 to 0.25 *M* (pH 6.65) increased k_{obsd} by 16%, and an increase in acetate buffer from 0.1 to 0.5 *M* (pH 5) raised k_{obsd} by 14%. It was indeterminate whether the effect in phosphate buffers was greatest at high or low pH values. Thus, the observation may be simply that of a specific salt effect.

The rate constant k_B was determined as a function of temperature, and values are reported in Table II. The value of ΔH^* is 16.8 ± 0.5 kcal/mol and ΔS^* is −23.8 ± 1.5 eu calculated at 50° with the rate constant k_B having units sec^{-1}. Activation parameters were also obtained for reaction of cyclohexylamine with *p*-nitrophenyl *N*-methyl-*N*-phenylcarbamate; ΔH^* is 14.8 ± 0.5 kcal/mol and ΔS^* is −32.5 ± 1.5 eu at 50° (k_{RNH_2} has units M^{-1} sec^{-1}). Error limits were calculated from the standard error of the plot of log k vs. $1/T$. Values of k_{RNH_2} at different temperatures are reported in Table II. Cyclohexylamine acts as a nucleophile as shown by the ratio of rate constants in H_2O and D_2O $k_{RNH_2}^{D_2O}/k_{RNH_2}^{H_2O} = 1.4$.

Table II. Values of k_B (sec^{-1}) for Cyclization of Phenyl *N*-(2-Aminophenyl)-*N*-Methylcarbamate and k_{RNH_2} (M^{-1} sec^{-1}) for Reaction of Cyclohexylamine with *p*-Nitrophenyl *N*-Methyl-*N*-phenylcarbamate at Various Temperatures

Compd	*T*, °C	$k_B \times 10^5$, sec^{-1}	$k_{RNH_2} \times 10^5$, M^{-1} sec^{-1}
Phenyl *N*-(2-amino-phenyl)-*N*-methyl-carbamate	25 (H_2O)	1.73	
	25 (D_2O)	1.3	
	32.5	3.89	
	40	7.36	
	50	17.2	
	65	58.4	
p-Nitrophenyl *N*-methyl-*N*-phenyl-carbamate	30 (H_2O)		0.98
	30 (D_2O)		1.40
	50		5.1
	65		14.4

Table III. Values of the Second-Order Rate Constants (M^{-1} sec^{-1}) for Reaction of *p*-Nitrophenyl *N*-Methyl-*N*-phenylcarbamate at 30° and μ = 0.5 *M* with Amines

Amine	pK_a	$k_{RNH_2} \times 10^5$
n-Butylamine	11.0	10.33
Cyclohexylamine	10.7	0.98
Ethanolamine	9.7	1.8
Morpholine	8.8	0.25
Tris	8.3	<0.016[a]
Imidazole	7.1	0.004

[a] Upper limit.

In an attempt to estimate the effective concentration of the neighboring amine group of II, a solution of phenyl *N*-(4-aminophenyl)-*N*-methylcarbamate in a half-neutralized 0.5 *M* cyclohexylamine buffer was left 7 days at 50°. Only small spectral changes were observed over this period, accountable in part by hydroxide ion catalyzed hydrolysis, indicating that little or no reaction with amine had occurred. An upper limit for the second-order rate constant for cyclohexylamine catalysis was calculated to be 1.2×10^{-6} M^{-1} sec^{-1}. Second-order rate constants were also obtained for nucleophilic attack by various amines on *p*-nitrophenyl *N*-methyl-*N*-phenylcarbamate. These rate constants are reported in Table III.

The hydrolysis rate of phenyl *N*-methyl-*N*-phenylcarbamate was measured in hydroxide ion solutions at 50° (four different OH$^-$ concentrations), yielding a second-order rate constant 4.55×10^{-4} M^{-1} sec^{-1}, compared with the value 3.42×10^{-4} M^{-1} sec^{-1} obtained by Christenson.[8] The corresponding second-order rate constant for hydroxide ion catalyzed hydrolysis of phenyl *N*-(4-aminophenyl)-*N*-methylcarbamate at 50° was 1.2×10^{-4} M^{-1} sec^{-1}.

Discussion

The effectiveness of intramolecular catalysis is usually estimated by comparing the rate constant of the intramolecular reaction (sec^{-1}) with that of the analogous bimolecular reaction (M^{-1} sec^{-1}) proceeding by the same mechanism. The ratio of rate constants has units of molarity and is considered to be the effective concentration of the intramolecular catalyst (the concentration of the bimolecular catalyst that will give a pseudo-first-order rate constant equal in magnitude to that obtained in the intramolecular reaction).

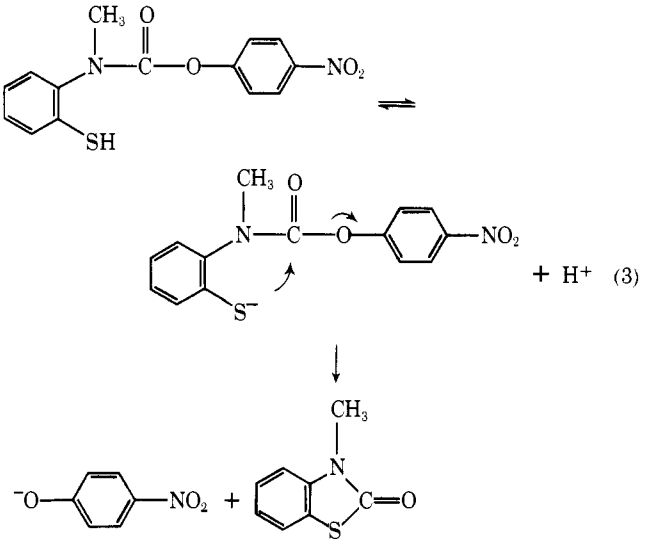
Large rate enhancements of 10^5–10^8 M in intramolecular nucleophile catalyzed ester hydrolysis reactions have previously been observed only with negatively charged nucleophiles.[4,5,15] Neighboring carboxylate accelerates phenyl ester hydrolysis and has an effective molarity of 10^7–10^8 M.[15] Likewise, a phenoxide ion has an effective concentration of 3×10^8 M in cyclization of phenyl carbamate esters,[4] and neighboring hydroxymethyl acts as a nucleophile toward both nitrophenyl and ethyl carbamates[5] with an effective molarity of 10^5 M. These effective concentrations are much larger than have been observed with neutral nucleophiles. The largest effective molarity for a neutral nitrogen nucleophile is 5×10^3 M in the case of dimethylamino group participation in hydrolysis of p-nitrophenyl γ,γ-dimethylaminobutyrate.[16]

The carbamate esters I and II both have the carbamate nitrogen substituted with a methyl group to prevent elimination of phenol to give an isocyanate. It was noted previously that aromatic carbamate esters can eliminate to an isocyanate with rate constants 10^4–10^6 greater than that for hydrolysis of N-methylated carbamates where elimination is precluded.[17] Such elimination has been observed with p-nitrophenyl N-(2-aminophenyl)carbamate[18] and p-nitrophenyl 2-hydroxymethylcarbanilate.[5]

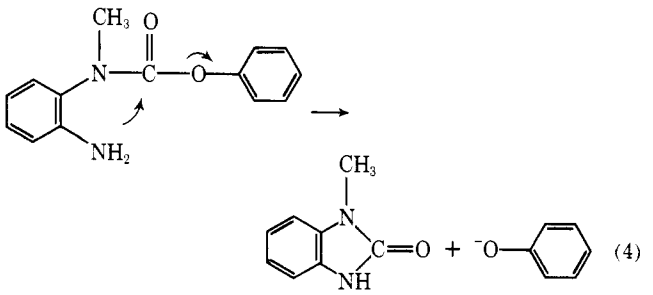
In the present work, the sulfhydryl group of p-nitrophenyl N-(2-mercaptophenyl)-N-methylcarbamate (I) gives rise to a sigmoidal pH–rate constant profile for cyclization to N-methylbenzothiazolone with pK_{app} of 8.7. The effective molarity of the neighboring group is 1.6×10^5 M in comparison with reaction of 2-aminoethanethiol (pK_a = 8.3) with the unsubstituted ester p-nitrophenyl N-methyl-N-phenylcarbamate. For a precise calculation of the effective molarity, the pK_a's of the intra- and intermolecular nucleophiles must, of course, be the same. The thiols employed were suitable bimolecular nucleophiles because their solubility allowed the necessary concentrations in the reaction solutions. The pK_a of 2-aminoethanethiol (8.3) deviates by 0.4 pK units from the pK_{app} of I, but this difference has little effect on the determination in view of the small influence of pK_a of thiol nucleophiles in attack at the carbamate ester carbonyl, as seen from the data in Table I. Low sensitivity of the rate constants to the pK_a of the nucleophile has also been noted[19] for thiol attack on p-nitrophenyl acetate (β = 0.38). Interpolation of a plot of log k_{RS^-} vs. pK_a to obtain the rate constant for attack of a thiol of pK_a 8.7 on p-nitrophenyl N-methyl-N-phenylcarbamate gave a value of 1.74×10^{-4} M^{-1} sec^{-1} and accordingly an effective molarity of 1.4×10^5 M for the thiol group of I.

There is no evidence from the kinetic data or from product analysis that the amine function of 2-aminoethanethiol is also acting as a nucleophile. If amine attack were occurring, the calculated effective molarity of the thiol would then be a lower limit. The second-order rate constant did not increase with increasing pH in the range 10.7–11.4, showing that the neutral amine species does not promote the rate of the reaction at pH values where the thiol is almost completely ionized. A 15% decrease in the second-order constant as pH is raised in that range may be due to a change in the thiol pK_a as protonation of the amine group is decreased.[19] Amines are relatively poor bimolecular nucleophiles for attack on carbamate esters. The rate constant for reaction of cyclohexylamine (pK_a = 10.7) with p-nitrophenyl N-methyl-N-phenylcarbamate is 9.8×10^{-6} M^{-1} sec^{-1} at 30°. Thus, the amine group of 2-aminoethanethiol (pK_2 = 10.5) should not compete significantly with the thiol nucleophile in giving rise to the observed rate constant (1.5×10^{-4} M^{-1} sec^{-1} at 25°).

The rate constant for thiophenoxide ion participation with I is approximately tenfold greater than that for attack of a neighboring phenoxide ion in the case of phenyl N-(2-hydroxyphenyl)-N-methylcarbamate.[4] The lower effective molarity of the neighboring group of I must then be due to a more favorable bimolecular reaction of the unsubstituted ester with a thiol than an alcohol anion. Nevertheless, once again a large rate enhancement has been obtained in an intramolecular reaction of a negatively charged nucleophile (eq 3).



The neighboring amino group of phenyl N-(2-aminophenyl)-N-methylcarbamate (II) also produces a facile ring closure reaction. The pH–rate constant profile is again sigmoidal with pK_{app} = 2.7 (the spectrophotometrically determined pK_a is 2.65). It will be noted in Figure 2 that hydroxide ion catalysis is not encountered below pH 12. No intermediate could be detected spectrophotometrically before the final products which were identified as 1-methyl-2-benzimidazolone and phenol (see Experimental Section). The D_2O solvent isotope effect for the intramolecular reaction of II is nearly unity (k_{H_2O}/k_{D_2O} = 1.2). Therefore, the reaction must involve intramolecular attack by the neutral amine group. General base catalysis by the amine substituent should give a sizable solvent isotope effect and would lead to products different from those observed.



Bimolecular reactions of amines with phenyl N-(4-aminophenyl)-N-methylcarbamate could not be detected. In the presence of 0.5 M cyclohexylamine, little spectral change was observed at 50° over a period of 7 days. Thus, an effective molarity for the amine substituent of II cannot be directly calculated; however, by calculation of an upper limit for the rate constant of a detectable bimolecular reaction (1.2×10^{-6} M^{-1} sec^{-1}), a lower limit of the effective molarity of the neighboring group of II was determined to be 1.4×10^2 M. This lower limit involves comparison of an intramolecular nucleophile of pK_a 2.7 with a bimolecular nucleophile of pK_a 10.7. Assuming a reasonable Brønsted coefficient of 0.8 for bimolecular aminolysis,[20] the second-order rate constant for reaction of an amine of pK_a 2.7 can

be obtained. Employing this rate constant, the effective concentration of the amine nucleophile of II is 3×10^8 M.

Attack of amines on p-nitrophenyl N-methyl-N-phenylcarbamate can be observed. From the second-order rate constants (Table III), it can be concluded that β must approximate 0.8. The rate constant for cyclohexylamine shows negative deviation from a plot of log k_{RNH_2} vs. pK_a with a slope of 0.8. If this were also the case when the leaving group is phenol, then the calculated effective molarity would have to be reduced by a factor of ~5. Extrapolation of the Bronsted plot for the p-nitro derivative to pK_a 2.7 gives a value of $k_{RNH_2} = 2.5 \times 10^{-11}$ M^{-1} sec^{-1} at 30°. Assuming a reasonable rate constant difference of 10^2 due to the different leaving groups[1,20c] (the ratio of k_{OH} values is 10^2) gives $k_{RNH_2} = 2.5 \times 10^{-13}$ M^{-1} sec^{-1} for attack of an amine of pK_a 2.7 on phenyl N-methyl-N-phenylcarbamate. From this rate constant, an effective molarity of 10^8 M can again be calculated for the amine function of II. It is clear that the neighboring amine group of II is a highly efficient intramolecular nucleophile.

The fact that very large rate enhancements (10^5–10^8) in intramolecular nucleophilic reactions have previously been observed only with anionic nucleophiles has led to suggestions that desolvation might be an important factor in giving rise to very efficient intramolecular reactions.[2,4,21] Before a nucleophile can attack, it must be desolvated, but an intramolecular nucleophile should be less highly solvated than a bimolecular nucleophile in dilute solution. If the intramolecular nucleophile and the reaction center are in close proximity, then water molecules might not be able to fit between and desolvation could be of little importance. Desolvation of anions is energetically difficult;[22] therefore, part of the great efficiency of anionic intramolecular nucleophiles could be due to this factor. Bruice and Turner[15b] have found that the effective molarity of an intramolecular carboxylate anion is the same in water and 1 M H_2O–Me_2SO, but hydroxide ion is still well solvated by water in such a solvent mixture.[23] The extremely efficient intramolecular reaction of the neutral amine group of II shows that anionic nucleophiles are not required for large rate facilitations. Neutral nucleophiles can give enhancements in the rates of intramolecular reactions comparable to those observed previously in reactions of negatively charged nucleophiles. The general importance of desolvation effects in intramolecular reactions cannot at present be directly assessed, but it is unlikely that such effects are of great significance in producing differences between anionic and neutral nucleophiles. The normal pK_{app} values of the neighboring thiol of I and the phenolic hydroxyl of phenyl N-(2-hydroxyphenyl)-N-methylcarbamate[4] argue against reduced solvation of the respective anions of those compounds.

It is generally held that much of the efficiency of intramolecular reactions results from relatively favorable ΔS^* values. Page and Jencks[24] have calculated that these favorable ΔS^* values in comparison with those of analogous bimolecular reactions could account for accelerations in rate of 10^8 M. Steric compressional effects may be manifested in ΔH^*; for example, tetramethylsuccinanilic acid cyclizes 1200 times more rapidly than succinanilic acid and this difference is due entirely to a more favorable ΔH^*, the value of ΔS^* actually being unfavorable in comparison with succinanilic acid.[25] The ΔS^* for cyclization of II is −23.8 eu. A rate difference of 10^8 in comparison with an analogous bimolecular reaction would require a $\Delta\Delta S^*$ of ~37 eu. It seems unlikely that bimolecular reaction of an amine with phenyl carbamate esters would have ΔS^* more negative than −60 eu as would be necessitated if the rate advantage of the intramolecular reaction were to be attributed entirely to a more favorable ΔS^*. The ΔS^* for cyclohexylamine catalyzed release of p-nitrophenoxide ion from p-nitrophenyl N-methyl-N-phenylcarbamate at 50° is −33 eu, and ΔS^* for alkaline hydrolysis of phenyl N-methyl-N-phenylcarbamate is −28 eu.[8] Thus, it is probable that part of the large rate advantage of intramolecular aminolysis in II is the result of a less positive ΔH^* in a system where steric compressional effects are presumably absent. Without values of the activation parameters for aminolysis of the reference ester phenyl N-(4-aminophenyl)-N-methylcarbamate, the above discussion can only be speculative, but it is clear that much more abundant data will be required before intramolecular reactions can be confidently considered to be understood. In particular, it is necessary that activation parameters be measured for an extensive series of intramolecular reactions and their bimolecular counterparts where large effective molarities (10^5–10^8 M) have been determined. Nucleophilic attack on carbamate esters appears to be particularly well suited for such an attempt to gain deeper insight into the nature of intramolecular catalysis.

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References and Notes

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