(2.98 mmol) of active *R*-(+)-**1a** in 10 mL of dry hydrocarbon-stabilized chloroform was added over 50 min (22 °C) to a solution of 820 mg (6.0 mmol) of phosphorus trichloride, with a vigorous stream of nitrogen to carry off the liberated HCl.[5] This was followed by the addition of 10 mL ml chloroform over 2 h (22 °C). The solution was heated to 46 °C for 19.3 h. Rotary evaporation left 791 mg (ca. 99%) of a mixture of 85% *R*-(−)-**3a** and 15% of the propargyl chloride. This mixture was dissolved in enough dioxane to make 5.00 mL; its rotation is given in the text. The dioxane solution was added dropwise over 3 min to 5 mL of 50% aqueous dioxane at 0 °C. This solution was stirred for 15 min at 0 °C, then 90 min at room temperature. Rotary evaporation (to 0.05 mm) left 570 mg (83%) of crude *R*-(−)-**4a** (melting point and rotation given in the text). This was recrystallized twice from 2 mL of 1:1 (v/v) acetone–acetonitrile to give optically pure material with melting point and rotation given in the text.

References and Notes

(1) This is part 5 in the series entitled "Phosphorus-Containing Products from Propargyl Alcohols and Phosphorus Trihalides".
(2) R. S. Macomber, *J. Org. Chem.*, **36**, 2713 (1971).
(3) R. C. Elder, L. R. Florian, E. R. Kennedy, and R. S. Macomber, *J. Org. Chem.*, **38**, 4177 (1973).
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(5) R. S. Macomber and E. R. Kennedy, *J. Org. Chem.*, **41**, 3191 (1976).
(6) See, for example, (a) W. L. Waters, W. S. Linn, and M. C. Caserio, *J. Am. Chem. Soc.*, **90**, 6741 (1968); **92**, 4018 (1970), and references cited therein; (b) R. D. Bach, *ibid.*, **91**, 1771 (1969).
(7) (a) T. L. Jacobs, R. Macomber, and D. Zunker, *J. Am. Chem. Soc.*, **89**, 7001 (1967); (b) K. Shingu, S. Hagishita, and M. Nakagawa, *Tetrahedron Lett.*, 4371 (1967).
(8) The excess OH integration is caused by the hygroscopic nature of these compounds.[2-5]
(9) W. L. Waters and E. F. Kiefer, *J. Am. Chem. Soc.*, **89**, 6261 (1967), and references cited therein.
(10) M. Karplus, *J. Am. Chem. Soc.*, **85**, 2870 (1963).
(11) (a) To prevent freezing the Me_2SO-d_6 solution was diluted with an equal volume of MeOH-d_4. (b) Temperature dependent ^1H NMR resonances for the *tert*-butyl groups in hindered compounds have been reported: J. E. Anderson and H. Pearson, *J. Chem. Soc. B*, 1209 (1971).
(12) (a) R. S. Macomber, *J. Org. Chem.*, **37**, 1205 (1972); (b) W. T. Borden and E. J. Corey, *Tetrahedron Lett.*, 313 (1969). Precision of specific rotations is ±1%.
(13) See footnote 14 of ref 12a.
(14) S. F. Mason et al., *Chem. Commun.*, 1261 (1971). For an excellent review on the subject of optically active allenes, see R. Rossi and P. Diversi, *Synthesis*, 25 (1973).
(15) H. L. Goering, J. N. Eikenberry, G. S. Koermer, and C. J. Lattimer, *J. Am. Chem. Soc.*, **96**, 1493 (1974).
(16) This reagent is marketed as Eu(tfac) by Norell Chemical Co. The solution consisted of 0.18 mmol of *R*-(−)-**4a** and 0.048 mmol of Eu(facam)$_3$ in 0.40 mL of acetone-d_6. The chemical shifts with (without[3]) shift reagent were δ 1.13, (1.04), 1.90 (1.19), 5.20 (5.31), 8.13 (6.31). Racemic **4a** gave an identical spectrum. Addition of more shift reagent broadens the peaks but does not resolve them.
(17) The heterocycle shown has the *R* configuration provided that E has a higher Prelog priority than carbon.
(18) (a) R. J. D. Evans, S. R. Landor, and R. Raylor Smith, *J. Chem. Soc.*, 1506 (1963); (b) E. R. H. Jones, J. D. Loder, and M. C. Whiting, *Proc. Chem. Soc., London*, 180 (1960).
(19) Like several of the other oxaphospholes encountered in this study,[2-5] **7a**-Br exhibited a stronger set of $(M + H)^+$ ions than molecular ions.
(20) Gentle warming required to dissolve the solute.
(21) The *specific* rotation of optically pure *R*-(+)-1a increases linearly with concentration: $[\alpha]^{25}_{578}$ +4.8° (*c* 1.00), +5.67° (*c* 5.00), +6.23° (*c* 7.71, chloroform).

Intramolecular Aminolysis of Amides. The Cyclization of 2-Aminomethylbenzamide to Phthalimidine

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Abstract: Rate constants for cyclization of 2-aminomethylbenzamide to phthalimidine have been determined in H_2O at 30 °C and $\mu = 0.5$. Hydroxide ion catalysis takes place at high pH with $k_{OH} = 0.16\ M^{-1}\ s^{-1}$, which is approximately the same as k_{OH} for cyclization of 2-hydroxymethylbenzamide to phthalide but 10^4-fold less than k_{OH} for cyclization of methyl 2-aminomethylbenzoate to phthalimidine. Thus, as in the case of aliphatic esters, the rate constants for intramolecular cyclization of amides are nearly independent of the nature of the nucleophilic group, but are highly dependent on the leaving group, i.e., whether the compound is an ester or an amide. The magnitude of k_{OH} is 10^4 greater than k_{OH} for hydroxide ion catalyzed hydrolysis of benzamide, illustrating the facility of the intramolecular reaction. Below pH 9 the cyclization reaction becomes nearly pH independent, but at approximately pH 7, k_{obsd} begins to decrease markedly, indicating a change in rate-determining step and, as a consequence, an intermediate in the reaction. Hydronium ion catalysis is observed from pH 2–5, but k_{obsd} is constant from pH 2 to 5 M HCl. Pronounced buffer catalysis occurs which is both general acid and general base catalysis or their kinetic equivalents. Bronsted plots of log k_B for general base catalyzed cyclization of the neutral species and log k_B^1 for general base catalyzed cyclization of the protonated species vs. the pK_a of the catalyst have slopes of 0.4, implying that in these reactions proton transfer and bond making or breaking are concerted processes.

Chemical intramolecular reactions bear a striking resemblance to enzymatic reactions proceeding through an enzyme–substrate complex.[1-3] An understanding of intramolecular catalysis is therefore of crucial importance in attempts to understand how enzymes function. Ester substrates acylate the enzyme α-chymotrypsin much more rapidly than do amides.[1,4] This dissimilarity could reside in alignment in the enzyme–substrate complex, or in mechanistic differences for the two types of substrates. Furthermore, it appears that the rate constants for acylation of the enzyme by amide substrates are completely explainable in terms of intracomplex nucleophilic attack by the hydroxyl group of serine-195 along with general base catalysis by histidine-57,[5,6] but this may not be the case for acylation by esters where other mechanistic factors may be involved.[5] Thus, it is important to determine how esters and amides differ quantitatively in susceptibility to intramolecular nucleophilic attack by various nucleophiles and whether significant mechanistic differences exist.

A neighboring hydroxymethyl group is an excellent nucleophile in cyclization of the ethyl ester[5] and amide[6,7] of 2-hydroxymethylbenzoic acid to phthalide. Rate constants for apparent hydroxide ion catalysis are 10^5 greater than for hydroxide ion catalyzed hydrolysis of ethyl benzoate and benzamide. We have recently investigated the intramolecular aminolysis of the sterically similar methyl 2-aminomethylbenzoate.[8] Important similarities were found with the cyclization reactions of ethyl 2-hydroxymethylbenzoate, but significant mechanistic differences were observed in comparison

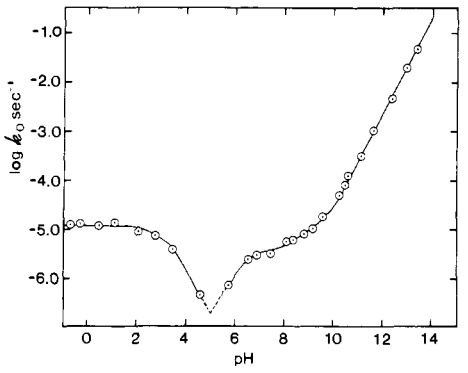


Figure 1. Plot of log k_o vs. pH for cyclization in H_2O of 2-aminomethylbenzamide to phthalimidine at 30 °C and μ = 0.5 M with KCl.

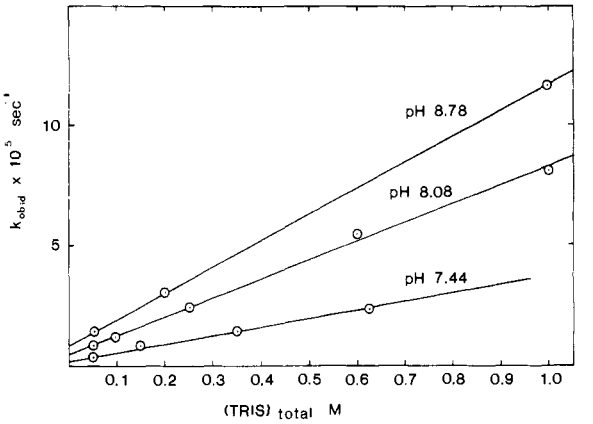
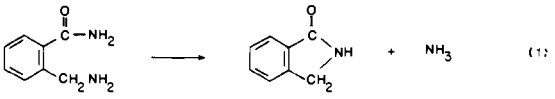


Figure 2. Plot of k_{obsd} vs. total Tris buffer concentration for cyclization of 2-aminomethylbenzamide to phthalimidine at 30 °C and μ = 0.5 M with KCl.

with previously studied bimolecular aminolysis reactions of aliphatic esters. The only previous reports of intramolecular aminolysis of an amide concerned cyclization of glutamine,[9] but with this amide the nucleophile is not rigidly held with respect to the carbonyl. In continuing a comparative study of various nucleophilic groups in sterically similar intramolecular reactions we have determined the rates of cyclization of 2-aminomethylbenzamide (I) to phthalimidine (eq 1).



(1)

Experimental Section

Materials. *o*-Cyanobenzamide was obtained from ICN. 2-Aminomethylbenzamide hydrochloride was prepared by catalytic reduction of the nitrile in ethanol-chloroform using platinum oxide as the catalyst by the method of Secrist and Logue.[10] Hydrogenation was carried out on a Parr apparatus for 15 h at 85 psi H_2. After filtration, the solvent was removed by rotary evaporation. The product was recrystallized from an ethanol-ethyl acetate mixture, yielding white crystals melting at 195–197 °C. Anal. Calcd for $C_8H_{11}N_2OCl$: C, 51.48; H, 5.94; N, 15.01. Found: C, 51.43; H, 6.24; N, 14.72.

Buffers were prepared from reagent grade materials. Amine buffer components were freshly distilled or recrystallized prior to use.

Kinetic Methods. The rates of cyclization of 2-aminomethylbenzamide to phthalimidine in H_2O were measured spectrophotometrically by following the increase in absorbance at 278 nm. The spectrum of the product was invariably identical with that of an equivalent concentration of synthetically prepared phthalimidine.[11,12] Temperature was maintained constant at 30 ± 0.1 °C by circulating water from a Precision Scientific Lo-Temptrol 154 circulating bath around the cell compartment. A Gilford 2000 or a Beckman 25 recording spectrophotometer was employed. A 45 μL sample of I in methanol (5×10^{-2} M) was injected into 3 mL of buffer (μ = 0.5 with KCl) to initiate the reactions. Phthalimidine is sufficiently stable to hydrolysis at all pH values that its breakdown does not interfere with the kinetic measurements.

Reaction solution pH values were measured with a Radiometer pH meter Model 22 and GK 2303C combined electrode standardized with Mallinckrodt standard buffer solutions. Pseudo-first-order rate constants were calculated with an Olivetti-Underwood Programma 101 or an IBM 360 computer.

Product Isolation. A 0.15-g sample of 2-aminomethylbenzamide in 35 mL of pH 12 solution was allowed to stand at room temperature until reaction was complete. The mixture was extracted with ether, and the ether extracts were dried over anhydrous sodium sulfate. Removal of the ether yielded material with an identical melting point (mp 148.5–150 °C) and UV spectrum as an authentic sample of phthalimidine.[11,12]

pK_a Determination. The pK_a of 2-aminomethylbenzamide at 30 °C and μ = 0.5 was determined spectrophotometrically, employing a Beckman 25 spectrophotometer. A series of 23 buffers in the pH range 7.6–11.1 was utilized. A plot of initial OD at 245 nm for identical concentrations of substrate vs. pH was sigmoidal. The pK_a thereby determined was 9.22.

Results

In Figure 1 is shown a plot of log k_o vs. pH for cyclization of 2-aminomethylbenzamide to phthalimidine at 30 °C and μ = 0.5 M, where k_o is k_{obsd} at zero buffer concentration. At pH values greater than 9 the slope of the plot is 1.0, indicating hydroxide ion catalysis (k_{OH} = 0.16 M^{-1} s^{-1}). At about pH 9 a change in slope occurs to approximately zero. The line in Figure 1 at pH values above 7.5 is generated by

$$k_o = [k_1 + k_{OH}(OH^-)]\left[\frac{K_a}{K_a + a_H}\right] + k_2\left[\frac{a_H}{K_a + a_H}\right] \quad (2)$$

where k_1 is the rate constant for uncatalyzed or water-catalyzed reaction of the neutral species ($k_1 = 2.0 \times 10^{-5}$ s^{-1}), k_2 is the rate constant for uncatalyzed or water-catalyzed reaction of the protonated species ($k_2 = 4.0 \times 10^{-6}$ s^{-1}), and K_a is the dissociation constant of the conjugate acid of 2-aminomethylbenzamide (pK_a = 9.2). The observed rate constants again begin to decline with decreasing pH at pH 7, which must signify a change in rate-determining step and, as a consequence, an intermediate in the reaction (see Discussion). Hydronium ion catalysis is observed from pH 2–5 ($k_H = 1.6 \times 10^{-2}$ M^{-1} s^{-1}). The values of k_{obsd} are independent of HCl concentration in the concentration range 0.01–5 M ($k_{obsd} = 1.22 \times 10^{-5}$ s^{-1}). This pH-independent reaction is slower in D_2O than in H_2O ($k_o^{H_2O}/k_o^{D_2O}$ = 1.55 ± 0.15).

Pronounced buffer catalysis is observed in the cyclization reaction. The slopes of plots of k_{obsd} vs. total buffer concentration increase as the pH increases as shown in Figure 2 for Tris catalysis. This may indicate that the base species of the buffer catalyzes the reaction. However, the slopes of plots of k_{obsd} vs. base concentration decrease as the pH increases, also indicating general acid catalysis or a kinetic equivalent. If the reaction is considered to involve general base catalysis of the cyclization of the neutral and protonated substrate, then the minimum equation for k_{obsd} would be given by the following equation:

$$k_{obsd} = k_o + k_B[B]\left[\frac{K_a}{K_a + a_H}\right] + k_B{}^I[B]\left[\frac{a_H}{K_a + a_H}\right] \quad (3)$$

Plotting the slopes (k_B total) of plots of k_{obsd} vs. buffer base concentration vs. $K_a/(K_a + a_H)$ gives straight lines. The intercept of such plots at $K_a/(K_a + a_H)$ = 1.0 is k_B, while $k_B{}^I$ is obtained as the intercept at $K_a/(K_a + a_H)$ = 0. The values of the rate constants are given in Table I. This procedure could not be applied below pH 7 to separate the rate constants be-

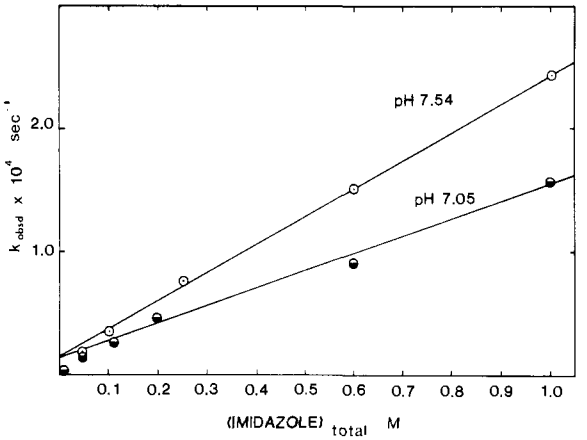


Figure 3. Plot of k_{obsd} vs. total imidazole concentration for cyclization of 2-aminomethylbenzamide to phthalimidine at 30 °C and μ = 0.5 M with KCl.

Table I. Values of the Rate Constants for Buffer-Catalyzed Cyclization of 2-Aminomethylbenzamide to Phthalimidine at 30 °C and μ = 0.5 M with KCl

Base	pK_a	$k_B \times 10^4$, M^{-1} s^{-1}	$k_B^1 \times 10^4$, M^{-1} s^{-1}
Piperidine	11.1	12.1	287.0
n-Butylamine	10.54	8.90	91.9
Ethanolamine	9.60	5.08	10.6
Morpholine	8.60	1.36	3.10
Tris	8.10	0.85	1.65
Imidazole	7.05		3.02[a]
Cacodylate	6.28		0.67[b]
Acetate	4.60		0.21[a]
Chloroacetate	2.80		0.054[b]
Water	−1.74		0.00072[c]

[a] Average value. [b] Determined at one pH value. [c] $k_2/55.5$ M.

cause of the extremely small percentage of unprotonated species. The rate constant k_B^1 was then obtained directly from the slope of a plot of k_{obsd} vs. buffer base concentration at high buffer concentration and at constant pH, or if determined at more than one pH, the values were averaged. Values of k_B total for imidazole and acetate are reasonably constant at two pH values. Due to the small magnitude of k_B at appropriate low pK_a values, negligible error will be introduced into k_B^1 by the above procedure. Downward curvature was detected in plots of k_{obsd} vs. imidazole, acetate, or chloroacetate concentration at total buffer concentrations less than 0.1 M. This curvature is illustrated in Figure 3 in which k_{obsd} is plotted vs. total imidazole concentration. In the cases where a curved plot was obtained, the value of k_B total was determined from the linear portion of the plot at buffer concentrations greater than 0.1 M. A detailed analysis of the curved plots at low buffer concentrations was not attempted.

In Figures 4 and 5 are presented Bronsted plots of log k_B and log k_B^1 vs. the pK_a of the conjugate acid of the general base catalyst. The slope, β, of Figure 4 is 0.39 (r = 0.986). A straight line through all of the points of Figure 5 has a least-squares slope of 0.40 with a correlation coefficient of 0.978. If the point for H_2O catalysis ($k_2/55.5$ M) is omitted from the correlation of Figure 5, the slope is 0.42 (r = 0.954). The plot shows a possible change of slope at about pK_a 8 with β = 0.75 (r = 0.991) at high pK_a and 0.39 (r = 0.995) at low pK_a.

Discussion

At high pH, 2-aminomethylbenzamide cyclizes to phthalimidine with apparent hydroxide ion catalysis (k_{OH} = 0.16 M^{-1} s^{-1}). This k_{OH} value is approximately 10^4 greater than the second-order rate constant for hydroxide ion catalyzed hydrolysis of benzamide (k_{OH} = 1.13 × 10^{-5} M^{-1} s^{-1} at 25 °C),[13] illustrating the great facility of the intramolecular reaction. Reasonable reaction schemes involve preequilibrium formation of the amine anion (eq 4), or initial attack of the

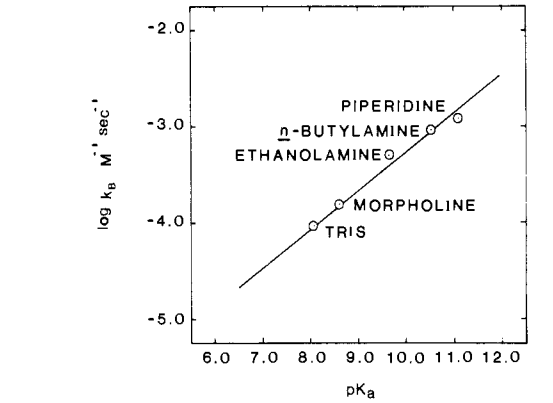


Figure 4. Plot of log k_B vs. pK_a of the conjugate acid of the catalyst for cyclization of 2-aminomethylbenzamide to phthalimidine at 30 °C and μ = 0.5 M with KCl.

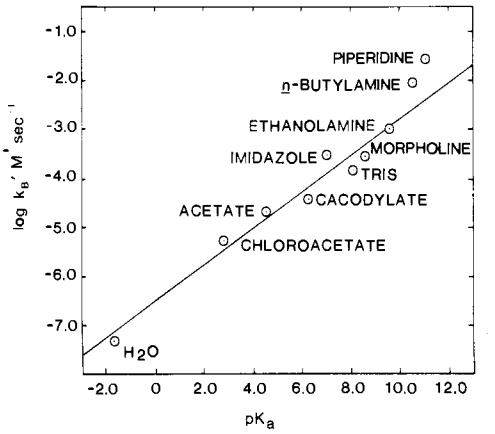
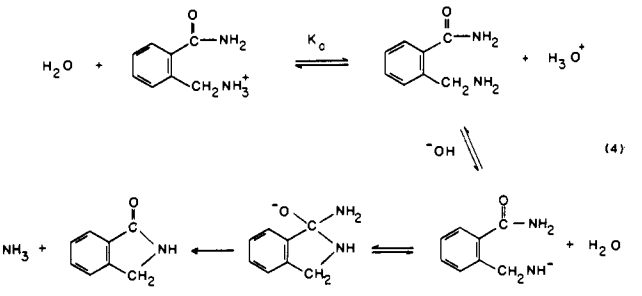
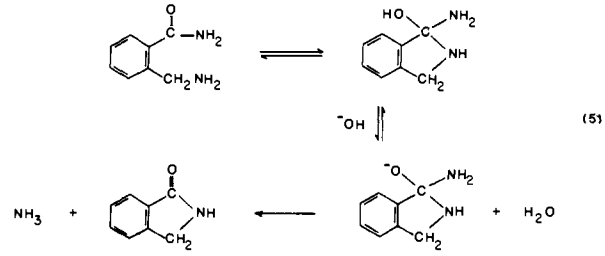


Figure 5. Plot of log k_B^1 vs. pK_a of the conjugate acid of the catalyst for cyclization of 2-aminomethylbenzamide to phthalimidine at 30 °C and μ = 0.5 M with KCl.

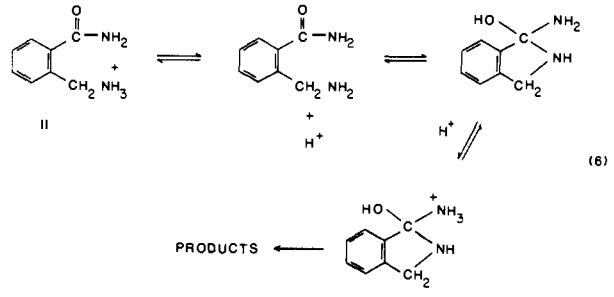


neutral amine group on the carbonyl, followed by rate-determining breakdown of an anionic tetrahedral intermediate to products (eq 5). The magnitude of k_{OH} is approximately the same for cyclization of I and 2-hydroxymethylbenzamide. Thus, as with aliphatic esters,[8] the rate constants are nearly independent of the nature of the nucleophilic group, even though the amine and hydroxyl group nucleophiles must differ greatly in basicity. There is, however, a large dependence of the rate constants on the leaving group. Cyclization of methyl 2-aminomethylbenzoate to phthalimidine has a k_{OH} of 7 × 10^3 M^{-1} s^{-1} at 30 °C, which is greater than that for cyclization of the amide I by a factor of 4 × 10^4.



(5)

The behavior of 2-aminomethylbenzamide at pH values below the pK_a of the amine is quite different than that of the corresponding methyl ester.[8] Hydroxide ion catalysis is observed at all pH values investigated in cyclization of the methyl ester. At pH values above its apparent pK_a, the slope of a plot of log k_o vs. pH is +1.0, but at pK_{app} (8.6) there is a change of slope to +2.0. Thus, the protonated species is unreactive, and cyclization occurs exclusively through the neutral species. On the other hand, the profile for amide cyclization at pH values below 9 becomes nearly pH independent, indicating the incidence of a reaction of the protonated compound or a kinetically equivalent acid-catalyzed reaction of the neutral species (eq 6). The break in the profile occurs close to the thermodynamic

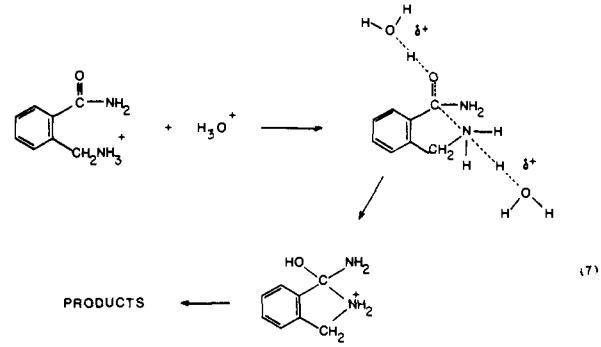


(6)

pK_a of I (9.2) and the near pH-independent reaction extends to pH 7. As seen in Figure 1, the rate constants k_o give a good fit above pH 7.5 to eq 2 in which uncatalyzed or water-catalyzed reactions of the neutral and protonated species are assumed. Nucleophilic attack at the carbonyl should not take place when the neighboring amino group is protonated; therefore, the reaction of the protonated species is best considered to be an acid-catalyzed cyclization of the neutral compound. Intramolecular attack by neighboring imidazole on γ-(4-imidazoyl)butyramide has a pH–rate constant profile showing dependence of the reaction on the protonated species.[14] This could also reflect attack of neutral imidazole on the protonated amide. Reasons for the difference in behavior of the amide I and the corresponding methyl ester below pH 9 must lie in the greater basicity of the amide function and in the very poor leaving group of the amide which will, as a consequence, have a requirement for protonation in decomposition of the tetrahedral intermediate to products. It is of interest that while the methyl ester cyclizes much more rapidly than the amide at high pH, because of the differently shaped pH–rate constant profiles, the rates are of comparable magnitude in the neutral pH range (6–7).

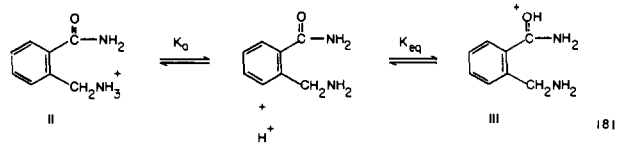
The downward bend in the pH–rate constant profile at approximately pH 7 can be considered evidence for a change in rate-determining step and, consequently, as evidence for the existence of an intermediate in the reaction. Hydroxide ion catalyzed reaction of the fully protonated compound or water-catalyzed reaction of the neutral species would give rise to the line of slope 1.0 in Figure 1 in the pH range 5–7, but assumption of such reactions in that pH range would not allow fit of a theoretical line to the experimental data above pH 7 if the rate-determining step is unchanged. Curvature was also detected in plots of k_{obsd} vs. imidazole, acetate, or chloroacetate concentration, showing that the rate-limiting step also changes with increasing buffer concentration. The identity of the rate-determining steps can be ascribed to formation of a tetrahedral intermediate at low pH (2–7) and decomposition of a tetrahedral intermediate to products at high pH (>7). It would reasonably be expected that formation of a tetrahedral intermediate would be retarded at low pH where the amino group is predominantly in the protonated form. At the same time, C–N bond breaking to give products should be favored at low pH because decomposition of a neutral or protonated tetrahedral intermediate should be facile in comparison with breakdown of the anionic intermediate required at high pH. Cyclization of 2-hydroxymethylbenzamide has been shown to proceed with rate-determining formation of a tetrahedral intermediate at low pH and rate-determining breakdown at high pH.[15]

Apparent hydronium ion catalysis is observed from pH 2–5. The second-order rate constant k_H is 1.6×10^{-2} M^{-1} s^{-1} at 30 °C which is much larger than the second-order rate constant reported for hydronium ion catalyzed hydrolysis of benzamide ($k_H = 7 \times 10^{-4}$ M^{-1} s^{-1} at 109 °C).[16,17] If the ground state at pH 5 is considered to be the fully protonated compound II, then acid catalysis would imply the presence of a second proton in the transition state. A reaction with concerted nucleophilic attack by the amine group and C–N bond breaking can be ruled out since the curved plots of k_{obsd} vs. acetate and chloroacetate concentration show that an intermediate is being formed in the pH range 2–5. If formation of a tetrahedral intermediate is rate determining, then a reasonable mechanism would be that of eq 7, where a proton is being transferred from



(7)

the amine group in the transition state. Considering the pK_a values of protonated amides,[18,19] a rate constant of 10^{-2} M^{-1} s^{-1} is less than might be expected for rate-determining protonation of the carbonyl of II by hydronium ion, but such protonation could, of course, be partially rate limiting in a concerted cyclization. The extremely small concentration of III (eq 8) at any pH value might prevent the cyclization re-



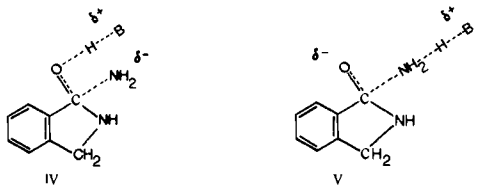
(8)

action from proceeding rapidly via a discrete stepwise pathway in which preequilibrium transfer of a proton from nitrogen to the carbonyl oxygen is followed by nucleophilic attack by the neutral amine. The ratio of (III/II) would be given by K_aK_{eq} from eq 8 and would have an approximate value of 10^{-12}.[17]

The rate of the reaction becomes constant from pH 2 to 5 M HCl. This pH-independent reaction is slower in D_2O than in H_2O ($k_o^{H_2O}/k_o^{D_2O} = 1.55 \pm 0.15$) which is consistent with a proton transfer reaction. The change in slope of the profile at pH 2 would occur if at that pH only one proton is present in the transition state as well as the ground state. Since formation of the tetrahedral intermediate is acid catalyzed and decomposition of the intermediate to products at low pH should

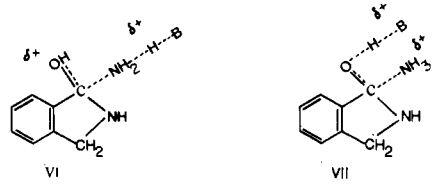
not be acid catalyzed, then an acid concentration must be reached where the rate-determining step undergoes a change back to tetrahedral intermediate breakdown. The rate constant for the pH-independent reaction is, in fact, slightly larger than the value of k_2 assumed to give the best fit to the experimental data at higher pH.[20] It may be noted in Figure 1, however, that extrapolation of the line for the pH-independent reaction to higher pH intersects the theoretical line obtained from eq 2 precisely at pH 9.2.

Pronounced buffer catalysis is observed in the cyclization of I to phthalimidine, which is general base catalyzed reaction of the neutral and protonated species or kinetically equivalent possibilities. Plots of the logarithms of k_B and k_B^I from eq 3 vs. the pK_a of the catalyst (Figures 4 and 5) have slopes, β, of 0.4. These values correspond to α values for the kinetically equivalent general acid catalyzed reactions of 0.6 ($\alpha = 1 - \beta$). If it is assumed that Bronsted coefficients of 0 and 1.0 are characteristic of rate-determining proton transfer reactions,[21] and Bronsted coefficients between 0 and 1.0 imply a reaction in which proton transfer is concerted with bond making or breaking, then buffer-catalyzed cyclization of I is best considered to be a concerted process. Concerted general base catalysis in decomposition of a tetrahedral intermediate could result from partial proton transfer from the neutral intermediate in eq 5 or the more likely kinetically equivalent proton donation to the leaving group. These possibilities are shown in IV and V. The apparent buffer-catalyzed reaction of the



IV V

protonated species could correspond to a general acid catalyzed reaction of the neutral substrate (VI) or general base catalyzed breakdown of a protonated tetrahedral intermediate (VII).



VI VII

Bronsted coefficients of 0.4 for general base catalyzed cyclization of 4- and 6-amino-2-hydroxymethylbenzamides[22] again suggest a concerted reaction in cases where a hydroxymethyl group acts as a nucleophile toward an amide.

Bimolecular aminolysis of simple amides has not been extensively studied because of the unreactivity of such compounds. Jencks and coworkers[23,24] have made a thorough investigation of the aminolysis reactions of the reactive amide *N*-acetylimidazole, and its conjugate acid where the pK's of the leaving groups are 14.2 and 7.0, respectively. Some of their pertinent conclusions can be summarized as follows: (1) nucleophilic attack on *N*-acetylimidazolium ion by strongly basic amines is unaided by general base catalysis; (2) attack of strongly basic amines on *N*-acetylimidazole is general acid catalyzed; (3) attack of weakly basic amines on *N*-acetylimidazole is assisted by general base catalysis in which a proton is partially removed from nitrogen in the transition state; and (4) the reactions appear to be characterized by the necessity to have the leaving group fully or partially protonated so as to avoid expulsion of an amine anion.

Rigorous mechanistic conclusions about intramolecular reactions cannot be drawn from a consideration of similar bimolecular reactions. For example, intramolecular aminolysis of the methyl ester, methyl 2-aminomethylbenzoate,[8] proceeds with significant mechanistic differences in comparison with bimolecular aminolysis of aliphatic esters.[25] However, it is chemically reasonable that certain important features of bimolecular aminolysis will also be important in the intramolecular reaction of I. Thus, it would not be expected that $^-NH_2$ would be an adequate leaving group, but would require complete or partial protonation. Consequently, transition state IV is less likely than V. The observed general base catalysis at high pH is best considered to be general acid catalyzed breakdown of an anionic tetrahedral intermediate. Likewise, transition state VII is more likely than VI since the microscopic reverse of VII would be general acid catalyzed attack of a highly basic amine whereas that of VI would be general base catalyzed attack of a strongly basic amine on a protonated carbonyl.

The curvature in plots of k_{obsd} vs. buffer concentration at pH values less than 7 in cyclization of I indicates that both steps in the reaction are catalyzed by buffer, but that catalysis is greatest for the step that is rate limiting at low buffer. If, as seems likely, the rate-limiting step for the spontaneous reaction (k_o) at pH values below 7 is formation of a tetrahedral intermediate, then the rate-determining step in imidazole, acetate, and chloroacetate buffers must change with increasing buffer concentration from formation to breakdown of the intermediate. The absence of a downward bend in the Bronsted plot of Figure 5 shows that the rate constants k_B^I, obtained at high buffer concentration, represent the same rate-determining step. A change in rate-limiting step with increasing buffer concentration was previously observed in the hydroxylaminolysis of formamide.[26]

In view of the Bronsted coefficient of 1.0 for general base catalyzed cyclization of methyl 2-aminomethylbenzoate,[8] implying rate-determining proton transfer, and the Bronsted coefficients much less than 1.0 for cyclization of 2-aminomethylbenzamide, implying a concerted reaction, it is clear that intramolecular nucleophilic attack by amines on esters and amides, assisted by general acid–base catalysis proceeds through different mechanistic pathways or with different rate-determining steps.

With the exception of reactive *N*-acylimidazoles, the only amides that serve as reasonably good substrates for α-chymotrypsin are those of the specific amino acids, tyrosine, phenylalanine, and tryptophan. In contrast, esterase activity is encountered with a variety of esters.[1,2] Thus, it is probable that precise alignment of substrate in the active site is of particular importance in the reactions of amide substrates. This could reflect the importance of protonation of the leaving group by a general acid in the enzymatic reactions of amides as in the analogous nonenzymatic reactions.

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Lithiation of Cyclopropyl and 2-Methylcyclopropyl Phenyl Sulfides. Addition to Carbonyl Partners

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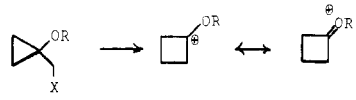
Abstract: Cyclopropyl phenyl sulfide undergoes complete metalation with *n*-butyllithium at 0 °C in about 1 h. The corresponding anion shows no inversion on the NMR time scale. It adds to the carbonyl group of saturated and α,β-unsaturated aldehydes and ketones. The stereochemistry, regiochemistry, and chemoselectivity of the addition is discussed. The effect of a β-methyl group on the metalation and carbonyl additions is examined. The question of nonclassical stabilization of the cyclopropyl anion is raised.

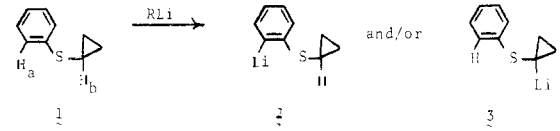
The generation of quaternary carbon atoms with stereochemical control is an important problem in organic synthesis. The replacement of the two carbon–oxygen bonds of a carbonyl group with two carbon–carbon bonds as a direct geminal alkylation has promise for organic synthesis.[1] The ability to incorporate these two bonds into a cyclobutyl ring has the virtue that the strain energy of the product can provide a driving force for further skeletal reorganization and the generation of a myriad of useful carbon frameworks.[2,3]

Wagner–Meerwein rearrangements of cyclopropyl systems offer a potential for accomplishment of such an overall process provided that the reaction can be made unidirectional for formation of the four-membered ring system.[4] Several reports in the literature suggested the ability to achieve this goal by placing an oxygen substituent on the cyclopropyl carbon atom.[5]

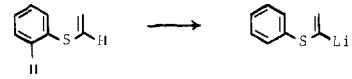


In ours[2,3] and other related work[6] this type of substitution was achieved by the formation of oxaspiropentane intermediates. Their accessibility directly from ketones via diphenylsulfonium cyclopropylide has offered a host of potential new approaches to the elaboration of organic molecules of theoretical and biological significance. Three limitations suggested the need for an alternative. (1) The ylide undergoes conjugate addition rather than carbonyl addition with α,β-unsaturated carbonyl compounds. (2) Very sterically hindered ketones react very sluggishly. (3) Silver salts are required in the preparation of the precursor sulfonium salt.

Cyclopropyl phenyl sulfides offered a potential for overcoming these limitations. Three questions that must be resolved are: (1) the ability to metalate directly; (2) the nucleophilicity of the resultant organometallic; and (3) the ability of sulfur



to direct the carbonium ion rearrangement. Metalation on carbon adjacent to sulfur had been reported for thioanisole[7] and allyl phenyl sulfide,[8] although rather drastic conditions had been employed for the latter case. On the other hand, thiophenetole had been reported not to metalate on the ethyl group.[9] In the case of thioanisole metalation occurs initially on the aromatic ring and subsequent rearrangements lead to the side chain metalation. The ability of oxygen to activate ortho positions in aryl ethers toward metalation further reinforced the idea that abstraction of Ha in **1** might be a very favorable process. On the other hand, it is reasonable to anticipate that the ability of sulfur to stabilize α-carbanions might overcome the unfavorable differences in hybridization of the C–Li bond between **2** and **3** to favor the formation of **3** at least in a thermodynamic, if not a kinetic, process. At the time this work was begun, the metalation of phenyl vinyl sulfide had not been reported. We found that metalation does proceed with



sec-butyllithium at the α-vinyl position.[10] Recently this metalation has also been accomplished with *n*-butyllithium–potassium *tert*-butoxide[11] and a related metalation of 1-ethoxy-2-phenylthioethene has been reported.[12] It is interesting to note that phenyl vinyl ether does metalate in the aromatic ring, which subsequently rearranges to the product of side