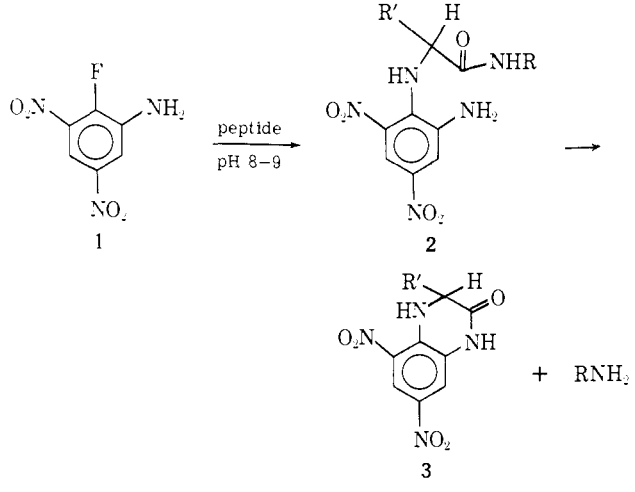
Intramolecular Aminolysis of Amides. Effects of Electronic Variation in the Attacking and Leaving Groups

Kenneth L. Kirk and Louis A. Cohen*

Contribution from the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Maryland 20014.
Received March 8, 1972

Abstract: The kinetics of lactam formation from a series of *o*-aminophenoxyacetamides has been studied at 52°. The rate of reaction increases with the acidity of the medium, reaching an essentially constant value below pH 3. The cyclization is catalyzed by formate and acetate buffer species; above pH 5, the rate decreases rapidly, no reaction being observed in alkaline media. A variety of kinetically equivalent mechanisms are considered, the favored mechanism being one in which the aniline base and an external proton source (general acid) attack the amide bond in concert. The observations of buffer catalysis and a Brønsted slope of 0.6 exclude consideration of a four-center electrophilic–nucleophilic mechanism or of one involving a preequilibrium protonation of the amide bond. Variation in the pK_a of the attacking aniline group provides ρ values of *ca.* −2.3 for catalysis by acetic acid and −2.0 for catalysis by hydronium ion. Variation in the pK_a of the leaving amine provides ρ values of +0.60 (for acetic acid catalysis) and +0.25 (for hydronium ion catalysis). Nominal solvent deuterium-isotope effects (1.3–1.9) are observed. While isotope incorporation from $H_2{}^{18}O$ is not observed in lactam formed at pH 3.7, incorporation (or exchange) does occur in 1 *N* hydrochloric acid. Values of the activation entropy (−14 to −18 eu) are consistent with the mechanisms proposed.

Several years ago we reported some studies on the application of intramolecular aminolysis to the sequential cleavage of peptide bonds (**1** → **2** → **3**).[1] The practical utilization of **1** for the intended purpose was, in part, restricted by the fact that the reaction sequence could not be interrupted after the coupling step; *i.e.*, the intramolecular aminolysis (**2** → **3**) could

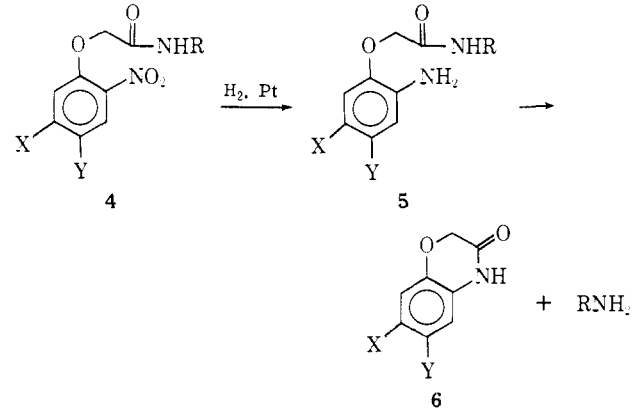


1

not be prevented (or effectively retarded) at any pH from −2 to 13. Since the state of ionization of the aniline nucleophile must change considerably over this pH range, it is apparent either that both the protonated and neutral forms of the base (and possibly the NH^- form) are kinetically effective participants or that a single form is effective, even in vanishingly small concentration.

The latter interpretation is particularly attractive since **2** may be subject to stereopopulation control,[2] a factor which could serve to increase considerably the ground-state population of its most productive conformation (see Discussion). Stereopopulation control of intramolecular processes can be responsible for quite sizable rates of reaction under conditions in which the fraction of an ionizable, kinetically active species is almost negligible.[3] Unfortunately, efforts to acquire kinetic and mechanistic data for the conversion of **2** to **3** have been thwarted by our inability to isolate **2**, its conversion to **3** apparently being faster than its formation from **1**.

As a first step toward providing comprehensive and detailed data on this reaction and on intramolecular aminolysis of amides in general, we have investigated the kinetics of lactam formation (in aqueous buffer media) for the series **5**. This type of compound,[4] in which an oxygen atom replaces the nonparticipating anilino nitrogen atom of **2**, was selected to eliminate any uncertainty regarding the site of base protonation.



Experimental Section[5]

N-(*o*-**Aminophenoxyacetyl)glycylglycines (5a–d).** Ring-substituted *o*-nitrophenoxyacetic acids were prepared by condensation

(1) K. L. Kirk and L. A. Cohen, *J. Org. Chem.*, **34**, 395 (1969).
(2) S. Milstien and L. A. Cohen, *Proc. Nat. Acad. Sci. U. S.*, **67**, 1143 (1970).
(3) (a) S. Milstien and L. A. Cohen, *J. Amer. Chem. Soc.*, in press; (b) R. T. Borchardt and L. A. Cohen, *ibid.*, in press.
(4) R. W. Holley and A. D. Holley, *J. Amer. Chem. Soc.*, **74**, 3069 (1952).
(5) Melting points are uncorrected. All analyses were performed by the Analytical Services Section of this laboratory, under the direction of Dr. W. C. Alford. For all crystalline compounds, the results of combustion analysis were well within the limits of acceptable error. All compounds were checked for homogeneity by tlc and their mass numbers verified by mass spectrometry.

of the appropriate sodium phenoxide with sodium chloroacetate.[6] Since this method failed in the case of 4-fluoro-2-nitrophenol, the desired compound was obtained by nitration of *p*-fluorophenoxyacetic acid.[7] The corresponding phenoxyacetyl chlorides[6] were coupled with glycylglycine to provide the *N*-(*o*-nitrophenoxyacetyl) dipeptides (**4a–d**).[4] Hydrogenation of the nitro group, in each case, was effected by use of platinum oxide and a solution of the substrate in aqueous sodium bicarbonate.[8] The solution of the resulting aniline was adjusted to pH 5, and the precipitate was collected and purified by a second precipitation from an acidified sodium bicarbonate solution. Melting points for both the nitro and aniline derivatives, which were obtained in 60–90% yield, are given in Table I.

Table I. Amides and Lactams

Compd	X	Y	R	Mp, °C 4	Mp, °C 5	Mp, °C 6
a	H	H	G[a]	210–212[b]	171–173[c]	135–138[d]
b	CH_3	H	G	218–222	179–181	194–196
c	H	CH_3	G	199–200	183–188	207–208
d	H	F	G	173–176	175–177	204–205
e	H	H	Ph	122–124	133–137	
f	CH_3	H	Ph	210–211	138–142	
g	H	CH_3	Ph	133–134	159–161	
h	H	F	Ph	151–152	137–139	
i	H	H	*p*-Tolyl	138–140	166–170	
j	H	H	*p*-Anisyl	133–134	177–181	
k	H	H	*p*-ClPh	169–171	129–131	

[a] G = $CH_2CONHCH_2COOH$. [b] Lit. mp 210–214° (ref 4). [c] Prepared by Holley and Holley (ref 4) but not isolated. [d] Lit. mp 133–138° (ref 4).

2-(*o*-Aminophenoxy)acetanilides (5e–k). A suspension of the appropriate aniline in cold 1 *N* sodium hydroxide was added to 1 molar equiv of the powdered phenoxyacetyl chloride. The mixture was stirred rapidly at ice temperature for 0.5 hr and was then stored overnight at ambient temperature. The reaction mixture was chilled and the anilide was collected by filtration. Following its recrystallization (ethanol or aqueous ethanol), the 2-(*o*-nitrophenoxy)acetanilide (**4e–k**) was subjected to hydrogenation over platinum oxide in ethanol;[8] the resulting 2-(*o*-aminophenoxy)-acetanilide (**5e–k**) was recrystallized from ethanol. Melting points for both series of compounds are given in Table I.

Lactams 6a–d. Authentic samples of the four lactams were obtained by catalytic hydrogenation of the respective *o*-nitrophenoxyacetic acids. The resulting *o*-aminophenoxyacetic acids cyclized spontaneously;[4] melting points of the lactams are given in Table I.

2-(*o*-*N*,*N*-Dimethylaminophenoxy)acetanilide (7). To a suspension of 248 mg (1 mmol) of *o*-nitrophenoxyacetanilide (**4e**) in 10 ml of ethanol was added 0.23 ml of aqueous formaldehyde (35%). Hydrogenation of the mixture over platinum oxide was complete in 24 hr, providing the *N*,*N*-dimethylaniline **7**. This compound could not be crystallized; however, identity and homogeneity were demonstrated by nmr and mass spectroscopy and by tlc.

Lactam Formation and Exchange in the Presence of $H_2{}^{18}O$. A solution of 7.8 mg of **5a** in 300 μl of formate buffer (pH 3.73, 0.5 *M*) was diluted with 300 μl of $H_2{}^{18}O$ (90% enriched) and the mixture maintained at 50° for 24 hr. The lactam **6a**, isolated by filtration of the chilled reaction mixture, showed a mass spectrum identical with that of the normal compound, no evidence for ^{18}O incorporation being observed. When lactam formation and exchange were studied in 1 *N* hydrochloric acid containing 45% $H_2{}^{18}O$, complete isotope exchange was observed in both reactions.

Kinetic Measurements. Acetate and formate buffers were prepared from commercial reagent-grade materials, using deionized, distilled water. The pH of each solution was measured on a Model TTT-1c Radiometer pH meter equipped with a scale expander and temperature compensator. pH values were measured at the temperature of the kinetic run, usually 52°. In selected cases, the pH was measured before and after a run; in no case was a pH change of greater than 0.02 unit detected. In work utilizing 99.8% deuterium oxide as solvent, the glass-electrode correction formula of Fife and Bruice[9] was employed in the determination of pD.

Reaction rates were followed spectrophotometrically, using a Model 15 Cary recording spectrophotometer, equipped with an automatic sample-changing accessory. Changes in optical density were recorded at wavelengths between 255 and 285 nm, the wavelength for maximum change having been determined for each compound in preliminary runs. Constant temperature was maintained by circulation of water from a Haake KT 41 constant temperature bath through the sample holder and walls of the spectrophotometer cell compartment. The temperature in the cell compartment was monitored continuously with a Yellow Springs Tele-thermometer, whose output was displayed on a 6-in. recorder. Except for those runs used in obtaining activation parameters, all kinetic data were obtained at 52 ± 0.05°.

To 3 ml of a previously equilibrated solution of buffer in the cuvette was added 20 μl of *ca.* 0.05 *M* substrate in dimethylformamide. The ionic strength of each solution was maintained 1 *M* with KCl. Reactions were followed in duplicate or triplicate to at least 85% completion, utilizing 3–6 different pH values for each buffer. Pseudo-first-order rate constants were calculated on a General Electric 265 computer, using a program designed to calculate a least-squares evaluation of $\ln (OD_\infty - OD_0)/(OD_\infty - OD_t)$ *vs.* time. The correlation coefficient was usually greater than 0.999. The second-order catalytic rate constants were obtained by a least-squares calculation of k'_{obsd} *vs.* concentration of buffer acid.[10] Activation parameters were obtained by least-squares analysis of plots of log k_{cat} *vs.* $1/T$ (°K) and were calculated at 52°. In all such calculations, standard deviations were within 3%.

pK_a Determinations. pK_a values for the several anilino groups were determined spectrophotometrically at 52°, using, in each case, the wavelength which showed the largest difference in optical density between the aniline and the anilinium ion. A 20-μl sample of the aniline (*ca.* 0.05 *M* in dimethylformamide) was added to 3 ml of previously equilibrated buffer or 1 *N* hydrochloric acid (μ = 1.0 *M*, KCl). Optical density was recorded as a function of time (since cyclization and the accompanying spectral change occurred slowly at 52°), and the values obtained by extrapolation to zero time were used for calculation. Duplicate measurements were made at 4–6 pH values. Deviations from the mean value were generally within 0.02 pK unit: **5a**, 3.97; **5b**, 4.54; **5c**, 4.04; **5d**, 2.91; **5a** (D_2O), 4.38. Variation in the nature of the amine component (R) of the amide had no detectable effect on aniline pK_a. For the four variants (**5a–d**), a ρ value of *ca.* −3.1 (at 52°) was obtained, close to that found for monosubstituted anilines at 25° (ρ = −2.9).[11] The pK_a of **5a** was also measured at other temperatures: 25°, 4.36; 40°, 4.11; 47.2°, 4.02; 60°, 3.88. A plot of pK_a *vs.* $1/T$ was linear, providing a ΔH_{ioniz} = +5.5 kcal per mol.[12] The pK_a of **5a** at 25°, 4.36, may be compared with that of *o*-ethoxyaniline, 4.47. To permit calculation of buffer ratios at 52°, pK_a values for the buffer acids were measured by half neutralization (μ = 1.0 *M*, KCl): acetic acid, 4.65; formic acid, 3.64; acetic acid (D_2O), 5.15.

Results

Kinetics of Cyclization in Buffer Media. Preliminary studies of cyclization in acetate and formate buffers revealed a dependence of rate on buffer concentration at constant pH. The cyclization reaction was followed in acetate buffer from pH 4 to 5 and, in formate buffer, from pH 3.1 to 3.7. General-acid catalysis of the cyclization reaction with participation of the aniline base ($ArNH_2$) is kinetically indistinguishable from general-base catalysis of the reaction with participation of the

(6) T. H. Minton and H. Stephen, *J. Chem. Soc.*, **121**, 1591 (1922).
(7) G. C. Finger, M. J. Gortatowski, R. H. Shiley, and R. H. White, *J. Amer. Chem. Soc.*, **81**, 94 (1959).
(8) An aqueous medium was necessary to effect solution of the substrate; in this medium slow cyclization occurred, which process could be inhibited by addition of sodium bicarbonate. Compounds **4e–k** were hydrogenated in ethanolic solution without occurrence of cyclization. This difference may be due to a significantly greater rate of reduction in the latter solvent.
(9) T. H. Fife and T. C. Bruice, *J. Phys. Chem.*, **65**, 1079 (1961).
(10) The symbol k' refers to values of k which have been adjusted to the fraction of aniline free base present at each pH value.
(11) A. I. Biggs and R. A. Robinson, *J. Chem. Soc.*, 388 (1961).
(12) For monosubstituted anilines, a ΔH_{ioniz} = +6.5 kcal per mol has been obtained: A. I. Biggs, *ibid.*, 2572 (1961).

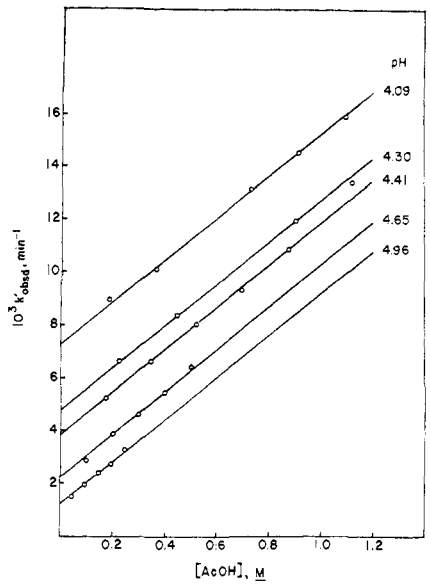


Figure 1. Typical plots of k'_{obsd} *vs.* concentration of buffer acid for **5a** in acetate buffer (52°), μ = 1.0 *M* (KCl).

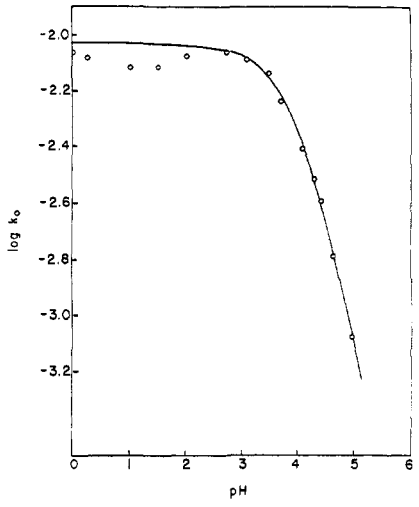


Figure 2. Plot of log k_0 (not adjusted for f_{ArNH_2}) *vs.* pH for **5a**. The solid line represents the theoretical curve calculated from log k_0 = log $[(k'_{H^+})(f_{ArNH_2})]$ − pH. Contributions to k_0 due to k_{H_2O} have been neglected.

anilinium ion ($ArNH_3^+$). For analysis of the kinetic data, the former combination was chosen arbitrarily. Values of k_{obsd} were divided by f_{ArNH_2}, the fraction of aniline base present at each pH, to provide the adjusted values, k'_{obsd}. For each compound, plots of k'_{obsd} *vs.* [BH], the concentration of buffer acid, were linear (in the concentration range examined) and gave reasonably constant slopes, as required for a reaction obeying eq 1. A representative series of plots is shown in Figure

$$k'_{obsd} = k'_{BH}[BH] + k'_0 \quad (1)$$

1 for **5a** in acetate buffer. Mean values of k'_{BH} for each compound are given in Table II; deviation from the mean rarely exceeded 3%. Plots of the intercept values (k'_0) *vs.* [H^+] were linear (eq 2), providing values

$$k'_0 = k'_{H^+}[H^+] + k'_{H_2O} \quad (2)$$

of k'_{H^+} (Table II) and of k'_{H_2O}. The contribution of

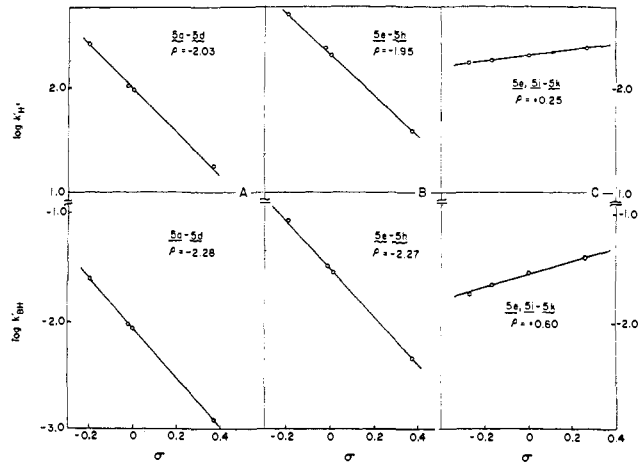


Figure 3. Hammett plots of log k'_{BH} (acetate buffer) and log k'_{H^+} *vs.* σ for the aniline nucleophile: (A) glycylglycine as leaving group (**5a–d**); (B) aniline as leaving group (**5e–h**); (C) abscissa = σ for the leaving group (**5e,i–k**).

Table II. Specific Rate Constants for Cyclization[a]

Compd	$10^3 k'_{BH}$[b]	k'_{H^+}
5a	8.44	92.9
5b	25.3	257
5c	8.92	99.1
5d	1.17	17.0
5e	29.0	188
5f	89.0	465
5g	33.9	226
5h	4.72	39.0
5i	22.1	174
5j	17.8	226
5k	37.0	164
5a	23.1[c]	90.0
5b	65.1[c]	257
5a	4.49[d]	72.0
5e	15.5[d]	142

[a] At 52°, μ = 1.0 *M* (KCl); rate constants = M^{-1} min^{-1}. [b] In acetate buffer, unless specified otherwise. [c] In formate buffer. [d] Acetate buffer in D_2O.

solvent catalysis to k'_{obsd} was found to be relatively small, values of k'_{H_2O} ranging from 2 to 4 × 10^{-4} min^{-1}.

Rates of cyclization decreased rapidly above pH 5; values of k_{obsd} in phosphate buffer (pH 7–8) were too low, at 52°, to warrant kinetic analysis. No significant reaction could be detected (for **5a** or **5e**) in 0.1 *N* sodium hydroxide at the same temperature. Under the conditions used for buffer-catalyzed cyclization of **5e** (pH 3–5), its *N,N*-dimethyl analog **7** showed no evidence for aniline release.

As the acidity of the medium increases, k_0 (or log k_0) approaches a limiting value, due to the cancellation of proportional changes in f_{ArNH_2} and in [H^+] (solid line in Figure 2).[13] Rate constants in acidic media (0.01–1 *N* hydrochloric acid), however, were consistently a little lower than the calculated value, the deficit showing no obvious relationship to the acid strength of the medium (Figure 2). The basis for these small discrepancies is not clear, nor was any effort made to resolve the matter experimentally.

Hammett plots for the three series of compounds are linear both for k'_{BH} and for k'_{H^+} (Figure 3); values of ρ

(13) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969, p 185.

accompany the plots. The σ values used are based on the pK_a values of the respective anilines and on the regression line for monosubstituted anilines given by Biggs and Robinson.[11]

For compounds **5a** and **5e**, rates of cyclization were also measured in acetate buffer in D_2O (Table II). The pK_a of the anilinium ion was raised from 3.97 (in water) to 4.38 (in D_2O). For both compounds, values of k_H/k_D for buffer-acid catalysis of *ca.* 1.9 were obtained, and for hydronium ion catalysis, *ca.* 1.3. Based on the values (for **5a**) of k'_{BH} in acetate, formate, and acetate–D_2O buffers and on that of k'_{H^+}, a Brønsted slope (α) of *ca.* 0.6 was obtained. A sample of **5a** was cyclized at pH 3.73 in 45%-enriched $H_2{}^{18}O$. On the basis of mass spectral data, the isolated lactam showed no evidence for ^{18}O incorporation. Exchange of the lactam oxygen with $H_2{}^{18}O$ was observed to occur readily in 1 *N* hydrochloric acid at 52°.

Activation parameters were calculated (at 52°) for **5a** from rate data in the temperature range 40–60°. Plots of log k'_{BH} and of log k'_{H^+} *vs.* $1/T$ were linear (Figure 4). For general-acid catalysis by acetic acid, $\Delta H^{\ddagger}$ = 19.1 kcal per mol, $\Delta F^{\ddagger}$ = 24.9 kcal per mol, and $\Delta S^{\ddagger}$ = −17.7 eu. For hydronium ion catalysis, $\Delta H^{\ddagger}$ = 14.2 kcal per mol, $\Delta F^{\ddagger}$ = 18.9 kcal per mol, and $\Delta S^{\ddagger}$ = −14.1 eu.

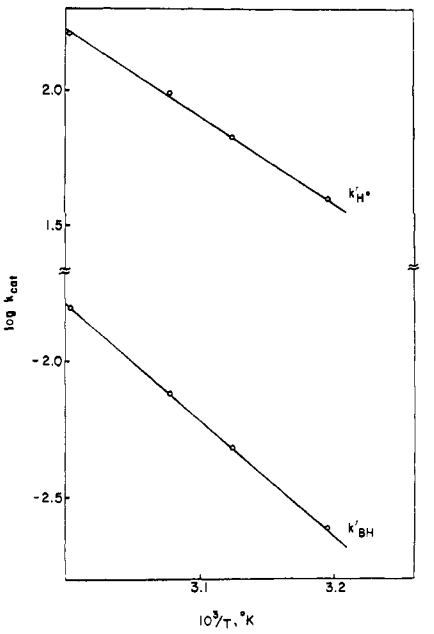
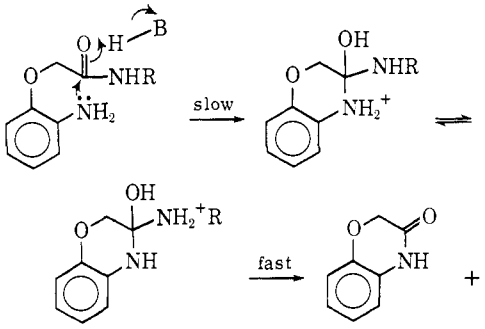


Figure 4. Variation of log k'_{BH} (acetate buffer) and of log k'_{H^+} *vs.* temperature (40–60°) for **5a**.

Discussion

In a variety of studies on the intramolecular (and bimolecular) aminolysis of esters,[14] the neutral form of the amine has been consistently considered the active participant. Far less information is available on the mechanisms for intramolecular attack of amines on amides, such reactions leading either to stable lactams or to transient N-acylated intermediates. On the basis of kinetic analysis, the ammonium,[15] alkylammonium,[14a] imidazolium,[14b] benzimidazolium,[16] pyridinium,[17] or anilinium[1] ion has been considered the active participant; however, the kinetically equivalent concerted attack of a neutral amine and an external proton on the amide has never been ruled out. Furthermore, it is entirely reasonable that the reaction mechanism may vary with the basicity either of the attacking amine or of the leaving amine.[18]

For the conversion of phthalamic acid to phthalic anhydride, Bender has considered two kinetically equivalent pathways:[19] (1) direct participation of the carboxyl group in an electrophilic–nucleophilic four-center process, in effect bypassing a tetrahedral intermediate; (2) nucleophilic attack by a carboxylate ion on a preequilibrium protonated amide. While Bender favored the four-center mechanism, Bruylants and Kezdy[20] have advanced arguments in support of the latter. Formation of a transient cyclic acylimidazole from the protonated imidazole-4-butyramide,[14b] and of cyclic acylpyridinium species from protonated acyclic precursors,[17] has also been viewed as a four-center process. The formation of stable lactams from aniline precursors may be considered analogous, in principle, to the formation of the transient phthalic anhydride or acylated heterocycle. Our observation of buffer catalysis in lactam formation, however, excludes the possibility of a four-center mechanism, since a buffer species can play no obvious role in such a pathway. Nor does the buffer acid seem a likely candidate for effecting any significant preequilibrium protonation of the amide, in view of the very large difference in pK_a values between buffer acid and substrate amide. We favor, therefore, a third kinetically equivalent mechanism: a concerted process in which intramolecular attack by the aniline base is coupled to proton transfer from the general acid (eq 3). This mechanism has also been advanced for the borate-catalyzed cyclization of glutamine[14a] and has been considered for the ammoniom-ion dependent ^{15}N exchange in benzamides.[15]



(3)

Since proton transfer from general acid to amide oxygen is not kinetically (or thermodynamically[21]) obligatory, bypass of a tetrahedral intermediate (eq 4) is yet a plausible alternative.

Rate-limiting formation of a tetrahedral intermediate *via* simultaneous association of the substrate, gen-

(14) (a) R. B. Martin, A. Parcell, and R. I. Hedrick, *J. Amer. Chem. Soc.*, **86**, 2406 (1964); (b) T. C. Bruice and J. M. Sturtevant, *ibid.*, **81**, 2866 (1959); (c) for a comprehensive review, see T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. I, W. A. Benjamin, New York, N. Y., 1966, Chapter 1.

(15) C. R. Everly and A. Fry, *J. Org. Chem.*, **36**, 3587 (1971).

(16) K. L. Kirk and L. A. Cohen, *ibid.*, **34**, 390 (1969).

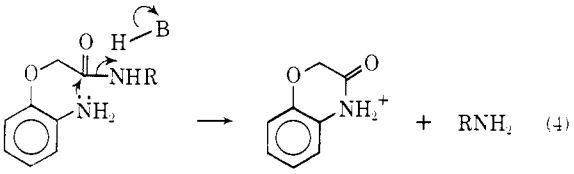
(17) A. Signor and E. Bordignon, *ibid.*, **32**, 1135 (1967).

(18) *Cf.* J. W. Thanassi and T. C. Bruice, *J. Amer. Chem. Soc.*, **88**, 747 (1966).

(19) M. L. Bender, Y.-L. Chow, and F. Chloupek, *ibid.*, **80**, 5380 (1958).

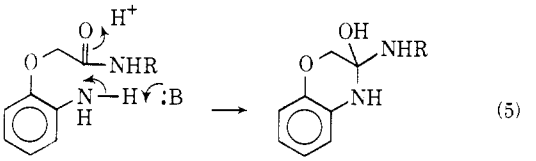
(20) A. Bruylants and F. Kezdy, *Rec. Chem. Progr.*, **21**, 213 (1960).

(21) M. Liler, *Chem. Commun.*, 115 (1971).



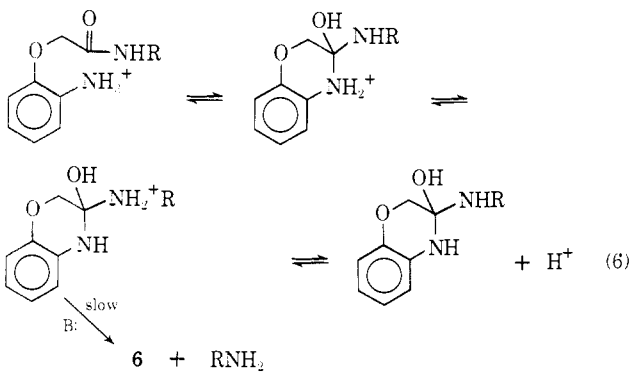
(4)

eral base, and proton (eq 5) might show an activation entropy somewhat more negative than the −14 to −18



(5)

eu observed.[22] If general base catalyzed collapse of a protonated tetrahedral intermediate were rate limiting (eq 6), such an intermediate should be in equilibrium with its conjugate base, and a discrepancy between

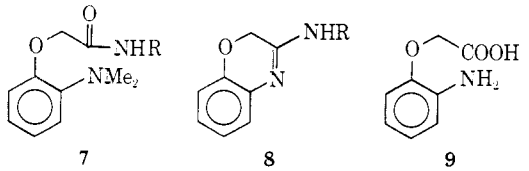


(6)

kinetically[23] and spectroscopically derived pK_a values would be anticipated;[24] however, aniline pK_a values obtained by the two methods are in excellent agreement, as seen in the close fit of observed and calculated points in plots of log k_0 *vs.* pH (Figure 2). Accordingly, we consider mechanisms involving general-base catalysis to be less attractive than those involving general acid.

Under the conditions used to effect cyclization of **5e**, the dimethylaniline group in **7** fails to promote amide hydrolysis. In principle, the tertiary amine could catalyze the addition of water to the carbonyl group by serving either as a general base (as $-NMe_2$) or as a general acid (as $-NMe_2H^+$), or, acting as a nucleophile, would first have to generate a quaternary acylium species. Although these alternative pathways differ markedly from that shown in eq 3, the result is surprising, in view of the fact that another tertiary amine, an *N*-methylbenzimidazole, has been found five times as effective as the corresponding benzimidazole in promoting a similar hydrolysis.[16]

The absence of ^{18}O incorporation from the solvent into lactam formed at pH 3.7 permits exclusion of



7 8 9

(22) *Cf.* S. Milstien and L. A. Cohen, *J. Amer. Chem. Soc.*, **92**, 4377 (1970), and ref 16.

(23) Calculated from reciprocal plots; see ref 16 for method.

(24) T. C. Bruice and G. L. Schmir, *J. Amer. Chem. Soc.*, **81**, 4552 (1959).

species such as **8** or **9** from consideration as intermediates. Since the isotope *is* found in the lactam formed in 1 *N* hydrochloric acid, species **8** or **9** may exist in the latter medium. Solutions of lactams in 0.1 or 1 *N* hydrochloric acid show ultraviolet absorption intensities 3–10% lower than those in buffer (at 52°). These differences suggest that the anilino acid **9** may be in equilibrium with lactam in the more acidic media. The magnitudes of the solvent deuterium-isotope effect (1.3–1.9) and of the Brønsted slope (0.6) are consistent with at least partial proton transfer in the rate-limiting step, rather than with preequilibrium protonation of the amide group.

The similarity in ρ values for k'_{BH} and for k'_{H} (Figure 3) suggests that the cyclization reactions proceed by the same (or closely similar) mechanisms for a range of general acid catalysts; in each case, the specific rate constant for cyclization increases with increasing basicity of the aniline group.[25] The parallelism in Hammett slopes for glycylglycine (**5a–d**) and for aniline (**5e–h**) as leaving groups implies further that there is little change in mechanism as the pK_a of the conjugate acid of the leaving group is varied over 5 units.

Aniline is *ca.* fourfold as effective a leaving group as is glycylglycine. This difference is entirely attributable to variation in basicity, since **5a,e,i–k** fit the same regression line in a plot of log k'_{BH} or log k'_{H} *vs.* pK_a of the leaving group. While the positive direction of ρ (Figure 3C) shows the weaker base to be the more effective leaving group, the small magnitude of the slope reveals a rather low sensitivity to variation in the pK_a of the leaving group. This lack of sensitivity may be indicative of compensatory electronic effects in the amide; progressive electron withdrawal by the aromatic system (R) should decrease the basicities of both the amide oxygen and nitrogen while it enhances the electrophilicity of the carbonyl carbon. In terms of mechanism 3 or 4, the small positive value of ρ for the leaving group suggests that the overall kinetics are somewhat more sensitive to nucleophilic attack by the aniline than to proton transfer by general acid.

Kinetic data on the acid hydrolysis of anilides[26] provide a ρ value of +0.19, close to our value of +0.25. In the acylation of the active serine of chymotrypsin by anilides of *N*-acetyl-L-tyrosine, preequilibrium[27] or transition-state[28] protonation of the anilide has been invoked; the ρ value of −2.0 for the enzymatic reaction stands in sharp contrast to that obtained for intramolecular aminolysis (+0.25) or for acid hydrolysis (+0.19).

The results obtained with series **5** fail to clarify the mechanism of the much faster and seemingly pH-independent cyclization of **2**. Although the mechanism of the latter reaction may vary with pH and with the principal ionic species present, we prefer the view that **2** and **5** utilize similar mechanisms. Maximization of resonance overlap with the benzene ring of the aryl-oxygen atom of **5**, and of the aryl-nitrogen atom of **2**, imposes a

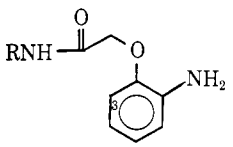
(25) For any mechanism involving the anilinium ion, the ρ values would be positive in slope, implying the weaker base or stronger conjugate acid to be the more effective participant. The same indeterminacy is encountered in the analysis of Brønsted slopes.

(26) V. F. Mandyuk and N. P. Lushina, *Ukr. Khim. Zh.*, 32, 607 (1966); *Chem. Abstr.*, **65**, 15175 (1966).

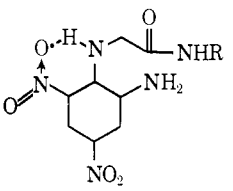
(27) L. Parker and J. H. Wang, *J. Biol. Chem.*, 243, 3729 (1968).

(28) T. Inagami, S. S. York, and A. Patchornik, *J. Amer. Chem. Soc.*, **87**, 126 (1965).

conformational restriction on the side chain. In the absence of a sizable ortho substituent (at C-3 in **10**), the nonproductive, planar transoid conformation **10** is the more likely, since it avoids steric interference with the solvated aniline (or anilinium ion). Hydrogen bonding

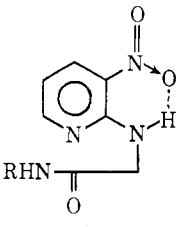


10

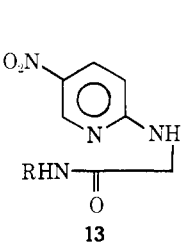


11

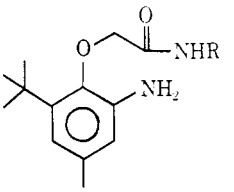
between the *o*-nitro group and NH (**11**) would serve to increase the population of molecules in the productive cisoid form. This factor has been found to increase the rate constant for amide hydrolysis in **12** over that in **13** *ca.* 100-fold.[17b] Furthermore, the introduction of a bulky substituent (such as nitro in **11**) should also have



12



13



14

the effect of increasing considerably the population of the productive cisoid conformer. This is, indeed, the case; the rate constant for general acid catalyzed lactamization of **14** has been found to exceed that of **5c** by a factor of *ca.* 3000.[29] The assumption that the rapid conversion of **2** to **3** is strongly assisted by stereopopulation control is, therefore, entirely reasonable.

(29) To be published separately.

Aminolysis of Acid Anhydrides in Water. I. Rate Acceleration by Hydrophobic Bonding in Reactions between Small Molecules

Ian H. Pitman,* K. Uekama, T. Higuchi, and W. E. Hall

Contribution from the Department of Analytical Pharmaceutical Chemistry and Pharmaceutics, University of Kansas, Lawrence, Kansas 66044.
Received February 17, 1972

Abstract: The aminolyses of phthalic anhydride in water by 14 aliphatic and alicyclic secondary amines were examined. The reactions were first order in both anhydride and amine neutral molecule concentrations when the total amine concentration (cation plus neutral molecule) did not exceed 5×10^{-3} *M*. At higher amine concentrations the reactions of amines containing six or more carbon atoms became zero order in amine concentration. Product analysis indicated that the amine neutral molecules participated primarily in the aminolysis reactions and did not significantly catalyze the parallel reaction in which the anhydride was being hydrolyzed. Linear correlations were observed between the logarithms of the aminolysis rate constants for amines that were structurally related and the logarithms of the partition coefficients of the amines between cyclohexane and 1.0 *M* NaOH but not between the logarithms of the rate constants and the acid dissociation constants of the amine cations. These results are suggested to be consistent with mechanisms in which either the reactants are approximated by intermolecular hydrophobic bonds prior to the rate-determining step in which a N–C bond is partially formed or in which the transition states are stabilized by hydrophobic forces.

Several reports have recently appeared about the accelerating effects on chemical reactions that result from approximation of the reactants by intermolecular hydrophobic bond formation. For example, pre-rate-determining step hydrophobic bond formation between reactants has been postulated to occur during the aminolyses of *o*-acylhydroxyquinolines[1] and of *p*-nitrophenyl esters[2] by aliphatic amines. In both of these studies the acceleration effects were only significant when molecules with large hydrophobic moieties were allowed to react. The present study was undertaken to ascertain whether similar effects could be observed during the aminolysis of phthalic anhydride by secondary amines with relatively short carbon chains.

(1) T. Maugh and T. C. Bruice, *J. Amer. Chem. Soc.*, **93**, 6584 (1971).
(2) J. R. Knowles and C. A. Parson, *Chem. Commun.*, 755 (1967).

Previous mechanistic studies on the aminolysis of anhydrides have been largely confined to the reactions occurring in nonaqueous solvents.[3–8] Under these conditions the reactions are very complex and, in many cases (*e.g.*, ref 3 and 4), probably involve rate-determining rearrangement or decomposition of a tetrahedral intermediate. The presence or absence of intermolecular hydrophobic bonding between reactants would,

(3) T. Higuchi, I. H. Pitman, and H. L. Fung, *J. Chem. Soc.*, in press.
(4) D. B. Denney and M. A. Greenboum, *J. Amer. Chem. Soc.*, **78**, 877 (1965).
(5) M. H. Loucheux and A. Banderet, *Bull. Soc. Chim. Fr.*, 2242 (1961).
(6) L. M. Livinenko, D. M. Aleksandrova, and A. A. Zhilinskaya, *Ukr. Khim. Zh.*, **26**, 476 (1960); *Chem. Abstr.*, **55**, 10022*h* (1961).
(7) S. Bruckenstein and A. Saito, *J. Amer. Chem. Soc.*, **87**, 698 (1965).
(8) J. Hipkin and D. P. N. Satchell, *J. Chem. Soc.*, 345 (1966).