Mechanism of Cleavage of Carbamate Anions[1]

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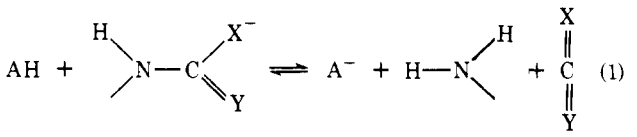
Abstract: Carbamates and monothiocarbamates of basic aliphatic amines undergo rate-determining C–N cleavage after a rapid equilibrium protonation step, as shown most directly by inverse solvent deuterium isotope effects of k_D/k_H = 3.6–4.8 for *O,O*- and *O,S*-*N*-*n*-butylcarbamates and by rapid acid-catalyzed exchange of the NH proton of *n*-BuNHCOS$^-$ with k_{exch} = 5×10^7 M^{-1} s^{-1}. The lifetimes of substituted N-protonated carbamates have been estimated to range down to $<10^{-10}$ s. It is concluded that general acid catalysis of the cleavage of carbamates of weakly basic anilines (α = 0.84) occurs through an enforced preassociation mechanism with hydrogen bonding to the leaving protonated nitrogen atom and C–N cleavage in the rate-determining step. There is more proton transfer in the transition state (larger α) and a smaller β_{lg} with more basic amines and upon substitution of sulfur for oxygen. The low pK_a values of N-protonated carbamates and monothiocarbamates illustrate the strong electron-accepting ability of –COO$^-$ and –COS$^-$.

Introduction

The mechanism of general acid catalysis of reactions involving the addition of nucleophilic reagents to the carbonyl group is frequently determined in a simple way by the lifetime and acid–base properties of the addition intermediate.[2] Catalysis of the addition of thiol anions to acetaldehyde, for example, follows a sequence of mechanisms with no catalysis or weak catalysis by hydrogen bonding for basic nucleophiles that form a stable intermediate, enforced catalysis by diffusion-controlled trapping of less stable intermediates formed from less basic nucleophiles, and enforced catalysis by a preassociation mechanism with weakly basic thiol anions, which form intermediates that revert to reactants faster than the catalyst can diffuse away from them.[3] The addition of weakly basic alcohols to formaldehyde gives a still less basic dipolar "intermediate", T$^{\pm}$, that is probably too unstable to exist, so that the reaction is forced toward a more-or-less fully concerted mechanism of catalysis.[4]

We describe here a series of experiments that were carried out in an attempt to determine the role of the lifetime of the addition intermediate in catalysis that involves proton transfer to or from the nucleophilic, rather than the electrophilic, reactant. We have examined the acid-catalyzed cleavage of a series of carbamates (eq 1) in which X and Y = O or S and



(1)

have made an estimation of the pK_a and lifetime of the N-protonated dipolar intermediate[5] by determining the rate of acid-catalyzed NH proton exchange. The principal mechanistic questions in this reaction are how the proton is transferred to and from the amine and how the transition state adjusts to the change of some 30 units in the pK_a of the amine as the C–N bond is formed or broken. Carbamate cleavage provides a convenient system in which to study the mechanism of catalysis of nitrogen expulsion and addition because the site of catalysis is unambiguous, it is possible to estimate the lifetime of intermediates, and the transition state can be characterized by structure–reactivity interactions. Addition reactions of amines are likely to occur through uncatalyzed or trapping mechanisms, in contrast to the concerted mechanism that is common for alcohols and water, because of the stability of the protonated amine in the addition compound. It is of interest to examine further how the mechanism of amine addition and expulsion changes as the intermediate becomes less stable.[6] We have examined mainly the cleavage of *O,S*-carbamates, because of their convenient spectrophotometric properties, but have also extended previous investigations of the cleavage of *O,O*- and *S,S*-carbamates.[5,7-16]

The most complete studies of carbamate cleavage have been carried out by Caplow and by Johnson and Morrison, who examined the effect of amine basicity on the reaction rate, demonstrated general acid catalysis of the expulsion of weakly basic amines, and suggested that the rate of protonation of the leaving nitrogen atom is kinetically significant in certain of these reactions.[7,8,15] Carbamates are of biochemical interest because of their spontaneous formation from free amino groups of hemoglobin and other proteins and the role of the weakly basic ureido nitrogen atom of biotin as the carrier for activated carbon dioxide.

Experimental Section

Materials. Reagent grade inorganic salts were used without further purification. Organic compounds were generally recrystallized or distilled before use and dioxane was freshly distilled from sodium. Carbamates were prepared from the corresponding isocyanates in dioxane or acetonitrile and sodium hydroxide or from the amines and carbon dioxide.[8] For example, the sodium salt of *N*-*p*-nitrophenylcarbamate was prepared by adding 1 mL of a saturated solution of *p*-nitrophenyl isocyanate in dioxane to 2 mL of 0.5 M aqueous sodium hydroxide. The precipitate was collected after 10 min. This compound was also isolated as a side product in the reaction of *p*-nitrophenyl isothiocyanate with sodium hydroxide and gave identical kinetic behavior. The decomposition of these carbamates in water (λ_{max} 349 nm) gave the expected *p*-nitroaniline (λ_{max} 381 nm). The triethylammonium salt of *N*-*n*-butylcarbamate was prepared by passing carbon dioxide through 5 mL of *n*-butylamine in 60 mL of triethylamine or by slowly adding a mixture of 10 mL of *n*-butylamine and 10 mL of triethylamine to 40 mL of triethylamine in 100 mL of benzene through which carbon dioxide was bubbled. The precipitate was collected after partial removal of the benzene by evaporation followed by freezing and thawing. Cyclohexylammonium *N*-cyclohexylcarbamate (Eastman) was recrystallized from chloroform.

Triethylammonium salts of monothiocarbamates were prepared by bubbling carbon oxysulfide through a solution of equimolar primary amine and triethylamine in dioxane.[16-18] Precipitates of the aniline and *n*-butylamine derivatives (except for the *p*-methoxyaniline compound) were collected; solutions of the other monothiocarbamates were used directly. Precipitation was sometimes facilitated by freezing and thawing the reaction mixture. The product was stored at −20 °C. A solution of N-*p*-nitrophenylmonothiocarbamate prepared from *p*-nitrophenyl isocyanate and aqueous NaHS gave poor kinetic data because of interference from yellow impurities. The UV spectra of the *N*-alkylmonothiocarbamates showed absorption maxima at 226–236 nm[17] and the infrared spectrum of triethylammonium *N*-*n*-butylmonothiocarbamate (KBr pellets) showed bands at 1210 and 1500 cm^{-1} (m); there were no bands at 1590 (COO$^-$) or 2000–2200 cm^{-1} (RNCS or RNCO).

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Dithiocarbamates were prepared by mixing solutions of isothiocyanate in dioxane and 1–3 M dipotassium sulfide in water or from equimolar amounts of carbon disulfide and amine in dioxane containing 2 equiv of potassium hydroxide.[11,13,19] Solutions of *N*-*p*-nitrophenyldithiocarbamate were prepared from 0.05 g of *p*-nitrophenyl isothiocyanate and 0.1 mL of purified[20] triethylamine in 2 mL of dioxane and 0.5 mL of aqueous 1 M Na_2S,[7] and from 0.1 M *p*-nitroaniline and 0.1 M carbon disulfide in 0.1 M aqueous sodium hydroxide containing tetramethylammonium chloride. The two preparations were found to give the same UV spectra and kinetic results. The solid products were collected, except for the *p*-nitroaniline, aniline, and *n*-butylamine derivatives, which were examined directly using aliquots of the reaction mixture.

Methods. Stock solutions of carbamates were prepared in 0.01–0.1 M sodium hydroxide, in water or 50% dioxane. All solutions were prepared using glass-distilled water. Kinetic measurements were usually initiated by the addition of 0.01–0.05 mL of the carbamate solution to 3 mL of temperature-equilibrated buffer in a cuvette; some experiments with aliphatic carbamates were initiated by addition of the solid salt. Reaction rates were followed spectrophotometrically using a thermostated cell compartment. The release of anilines was followed at 400–410 (*p*-NO_2), 261 (*m*-NO_2), 269 or 310 (H), 261 (*m*-Cl), 260 (*p*-CH_3O), and 261 nm (*p*-HO). The cleavage of *N*-alkylcarbamates was followed by measuring the small increase in absorbance at 220 nm upon release of the free amine ($\epsilon \sim 70\ M^{-1}$); a decrease in absorbance has been reported previously for this reaction.[8] A decrease in absorption was followed at 225–230 nm for *N*-alkylmonothiocarbamates and 280 nm for *N*-alkyldithiocarbamates. The ionic strength was maintained at 1.0 M with potassium or tetramethylammonium chloride. Pseudo-first-order rate constants were obtained from semilogarithmic plots of $(A_\infty - A_t)$ or $(A_t - A_\infty)$ against time and were usually found to be linear for over 4 half-times for carbamates and for over 3 half-times for monothiocarbamates and dithiocarbamates. Catalytic constants for general acid catalysis were typically obtained from four to eight rate constants that were determined at a series of buffer concentrations up to 0.8 M, except that dianions were examined up to 0.3 M and borate buffers up to 0.08 M. Corrections were made for small variations in pH with increasing buffer concentration at constant buffer ratio according to

$$k_{cor} = k_{obsd} + \Delta(\text{antilog } -\text{pH})k_H$$

where k_H is the apparent rate constant for hydronium ion catalysis based on the intercept at zero buffer concentration. Rate constants for catalysis by buffers, k_{cat}, were obtained from plots of the corrected pseudo-first-order rate constants against buffer concentration and catalytic constants for general acid catalysis, k_{HA}, were obtained by dividing k_{cat} by the fraction of acid in the buffer. Experiments at different buffer ratios gave no evidence for catalysis by the basic component of buffers. Catalytic constants for the proton were obtained by dividing the intercepts of the buffer plots by antilog −pH or antilog −pD. The pH was measured at the completion of each experiment using a Radiometer PHM-26 pH meter and a combined glass electrode. The pH meter was standardized at pH 12.54 at 25 °C for measurements in strongly alkaline solution.[21] Measurements of pD were made by adding 0.4 to the apparent pH of solutions in deuterium oxide.[22] Statistical corrections of rate and dissociation constants were made according to Bell and Evans.[23]

NMR spectra and measurements of chemical exchange were performed at 270 MHz essentially as described previously.[24] Selective saturation–recovery rates were measured by applying a selective 0.1-s preirradiation pulse at the NH resonance of the carbamate proton of triethylammonium *N*-*n*-butylmonothiocarbamate. This was followed by a 2-ms homospoil pulse, and a variable delay τ, before application of a roughly 60° observation pulse. The latter was a 214 pulse[25] which affects the resonance of interest without affecting water protons. The signal was digitized at a rate of 1280 complex points per second, and 512 complex points were Fourier transformed. The NH signal was 480 Hz downfield from water. Eight free-induction decays were obtained for each delay time and the spectrum for each delay time was recorded on tape. Seven delay times were used for each kinetic run and three consecutive runs were completed within 5 min. These spectra were transferred by a data link to a Nicolet BNC-12 computer and analyzed using a program written by J. D. Stoesz. Each spectrum was tilted, to flatten the base line, and then the central region of each peak was integrated. The recovery rate was determined by hand-fitting data to an exponential recovery. The degree of saturation for short τ was about 80%. Transfer of saturation was performed with a 2-s preirradiation at the water frequency and zero τ. It was verified by direct observation that this pulse saturated the water resonance at least 95%, and that its direct effect on the NH resonance was negligible. Water saturation transfer observations were interleaved with the saturation–recovery runs. The saturation transfer reported here is the difference between the intensity of the NH signal without water preirradiation and that with preirradiation, divided by the former. The chemical exchange rate constant is the product of this number times the observed saturation–recovery rate constant.[24]

Table I. General Acid Catalysis of $O_2NPhNHCOO^-$ Cleavage at 25 °C, Ionic Strength 1.0 M (KCl)

buffer or catalyst	pK_a	pH	k_{HA}, $M^{-1}\ s^{-1}$
H^+	−1.74	*a*	1.1×10^6
glycolic acid (Gly)[b]	3.62[c]	8.39	510
		8.01	410
		8.18	420
acetic acid (Ac)[b]	4.61[d]	8.00	65
		8.35	85
		8.42	63[e]
cacodylic acid (Ac)[b]	6.15[f]	8.06	7.8
β-glycerophosphate (GP)	6.00[g]	7.44	6.5
trifluoroethylamine (TFE)[b]	5.84[d]	8.11	0.35
		8.68	0.33
phosphate (P)	6.8[f]	7.82	1.32
		7.47	1.65
imidazole (Im)	7.21[d]	7.91	5.3×10^{-2}
		8.27	6.3×10^{-2}
ethyl phosphonate (EtP)	7.85[f]	8.94	7.6×10^{-2}
3-quinuclidone (QO)	7.3[h]	8.58	2.1×10^{-2}
		8.23	1.66×10^{-2}
cyanoethylamine (CEA)	8.08[f]	8.48	2.1×10^{-3}
		8.63	1.87×10^{-3}
borate (B)	9.4[f]	9.90	8.6×10^{-3}
morpholine (M)	8.82[i]	9.06	1.17×10^{-3}
		9.14	1.53×10^{-3}[j]
		9.24	1.47×10^{-3}
		9.47	1.31×10^{-4}
		9.79	1.01×10^{-4}
carbonate (C)	9.78[f]	10.68	1.32×10^{-3}
		10.67	1.36×10^{-3}
		10.60	1.31×10^{-3}
		11.27[k]	8.5×10^{-4}[k]
		10.74	1.79×10^{-3}[e]
ammonia (A)	9.48[f]	10.06	4.3×10^{-4}
		10.39	4.0×10^{-4}
3-hydroxyquinuclidine (HQ)	9.83[l]	10.47	8.8×10^{-5}
pyrrolidine (Py)	11.51[m]	11.78	9.5×10^{-6}
quinuclidine (Q)	11.45[h]	11.87	1.43×10^{-5}
water	15.74	*n*	2.16×10^{-8}[n]

[a] Based on 10^{-pH} and rate constants extrapolated to zero buffer concentration at pH 3.6–11.5. [b] In 0.1 M Tris buffer at the indicated pH. [c] Sayer, J. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1969**, *91*, 6353–6361. [d] Jencks, W. P.; Gilchrist, M. *Ibid.* **1968**, *90*, 2622–2637. [e] With carbamate prepared from the isocyanate and hydroxide ion. [f] Fox, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 1436–1449. [g] Sayer, J. M.; Jencks, W. P. *Ibid.* **1973**, *95*, 5637–5649. [h] Gresser, M. J.; Jencks, W. P. *Ibid.* **1977**, *99*, 6963–6970. [i] Page, M. I.; Jencks, W. P. *Ibid.* **1972**, *94*, 8828–8838. [j] Ionic strength maintained at 1.0 M with tetramethylammonium chloride. [k] In D_2O; pD = pH(obsd) + 0.40. [l] Jencks, W. P.; Salvesen, K. *J. Am. Chem. Soc.* **1971**, *93*, 1419–1427. [m] Based on the pH of buffer solutions. [n] From experiments in 0.001, 0.01, 0.1, and 1.0 M KOH, pH 10.78–13.76. $k_{H_2O} = 1.20 \times 10^{-6}\ s^{-1}/55.5\ M = 2.16 \times 10^{-8}\ M^{-1}\ s^{-1}$.

Results

Carbamates. Rate constants for the acid-catalyzed cleavage of a series of carbamate anions in water and deuterium oxide are given in Tables I and II. The reactions follow the rate law

$$v = k_H a_{H^+} + k_{HA}[HA] + k_w$$

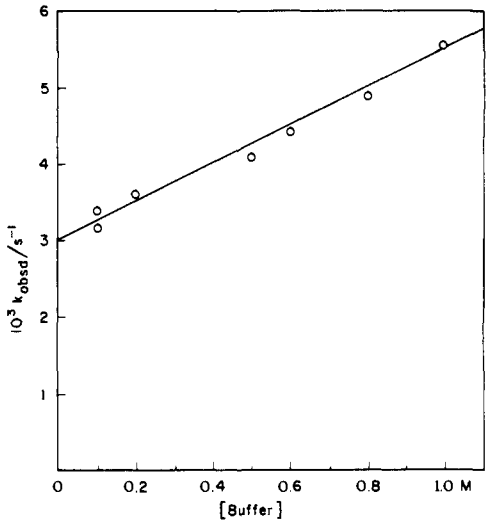


Figure 1. The effect of buffer concentration on the rate of decarboxylation of *N*-*p*-nitrophenylcarbamate in morpholine buffer (10% BH^+) at 25 °C, ionic strength 1.0 M (KCl).

Table II. Solvent Deuterium Isotope Effects for Carbamate Cleavage[a]

compd	buffer	k_H, M^{-1} s^{-1}	k_D, M^{-1} s^{-1}	k_D/k_H
n-BuNHCOO$^-$	phosphate[b]	4.7×10^7	1.7×10^8	3.6
cyclohexyl-NHCOO$^-$	phosphate[b]	1.5×10^8 [c]	5.4×10^8	3.6
p-NO_2PhNH-COO$^-$	carbonate, 90% CO_3^{2-}	1.0×10^6	1.49×10^6	1.5
n-BuNHCOS$^-$	imidazole, 90% base	3.94×10^4	1.97×10^5	5.0
	50% base	3.21×10^4	1.47×10^5	4.6
	phosphate[d]	3.73×10^4	1.42×10^5	3.8
PhNHCOS$^-$	phosphate[d]	6.68×10^5	1.16×10^6	1.7

[a] At 25 °C, ionic strength maintained at 1.0 extrapolated to zero buffer concentration from three to four runs in the range 0.1-0.7 (imidazole) or 0.05-0.35 M (phosphate and carbonate) buffers. [b] 0.28 M phosphate buffer, pH 10.78 in water. Buffer catalysis is not significant at this buffer ratio. [c] A value of $k_H = 2 \times 10^8$ M^{-1} s^{-1} has been reported previously.[8] [d] 10% $H_2PO_4^-$, 90% HOP_4^{2-}, pH 7.5 in water. Each rate constant is extrapolated to zero buffer concentration, based on four runs in 0.05-0.35 M buffer, in order to correct for a small effect of buffer on k_{obsd}.

although the terms for general acid catalysis, k_{HA}, and for the pH-independent "water" reaction, k_w, are not significant for all compounds. The rate constants for proton-catalyzed cleavage of *N*-*p*-nitrophenylcarbamate and *N*-cyclohexylcarbamate agree well with previous results and rate constants for general acid catalysis of the cleavage of *N*-*p*-nitrophenylcarbamate (Table I) confirm and extend the data obtained by Johnson and Morrison.[8] The amount of general acid catalysis by buffers is generally not large compared with the background proton-catalyzed reaction, especially for catalysis by protonated amines. Figure 1 shows typical results for one of the weaker catalysts, the conjugate acid of morpholine. Rate constants for general acid catalysis were measured in buffers containing mainly the basic component of the catalyst or in the presence of another buffer at a pH well above the p*K* of the catalyst being examined. This apparently paradoxical procedure provides the largest ratio of the catalyzed reaction to the proton-catalyzed background reaction because the ratio $[HA]/[H^+]$ is constant at pH values well above the pK_a of HA, but is smaller at pH values near or below this pK_a. The reliability of the measurements was checked for a number of the catalysts at several different pH values (Table I).

The solvent effect of dioxane on the rate of *N*-*p*-nitrophenylcarbamate cleavage was found to be small, with no significant effect of concentrations up to 1 M in 0.1 M imidazole buffer, 10% BH^+, and a 12% decrease in the rate in a similar experiment in 0.1 M morpholine buffer, 40% BH^+. The same catalytic constant was obtained with morpholine buffers when the ionic strength was maintained constant at 1.0 M with potassium chloride or with tetramethylammonium chloride (Table I). The same rate constants were found when the ionic strength was maintained at 1.0 M with potassium chloride or with potassium sulfate for eight experiments in 0.15-0.30 M phosphate buffers, 90% dianion.

A rate constant of $k_H = 1.1 \times 10^6$ M^{-1} s^{-1} was obtained for *N*-*p*-nitrophenylcarbamate from the intercepts at zero buffer concentration, which were in good agreement up to pH 11. A rate constant of $k_w = 55.5k_{HOH} = 1.20 \times 10^{-6}$ s^{-1} for the pH-independent "water" reaction was obtained from experiments in 0.001, 0.01, 0.10, and 1.0 M potassium hydroxide solutions with no indication of a further decrease in rate at high base concentrations, in agreement with earlier results.[8]

p-Nitrophenyl isocyanate is excluded as an intermediate in the decomposition reaction because it was found to react with a rate constant of 4×10^{-4} s^{-1} in 0.1 M imidazole buffer at pH 8.2, 17 times slower than *N*-*p*-nitrophenylcarbamate under the same conditions, and its reaction is inhibited rather than catalyzed at higher imidazole concentrations, consistent with previous results.[26] It was also found that 0.1-0.3 M NaHS, which would be expected to react with an isocyanate intermediate,[9] did not decrease the rate of cleavage of the carbamate at pH 8.0. These data gave an upper limit of $k_{HA} \geq 0.2$ M^{-1} s^{-1} for catalysis of carbamate cleavage by H_2S (pK_a = 7.0).

The acid-catalyzed cleavage of *N*-alkylcarbamates and monothiocarbamates exhibits large inverse solvent deuterium isotope effects in the range of k_D/k_H = 3.6-5.0 for *N*-*n*-butylcarbamate, *N*-cyclohexylcarbamate, and *N*-*n*-butylmonothiocarbamate (Table II). Much smaller inverse isotope effects of k_D/k_H = 1.5 and 1.7 are exhibited by *N*-*p*-nitrophenylcarbamate and *N*-phenylmonothiocarbamate, respectively. Catalysis by bicarbonate buffer shows a small normal isotope effect of k_{HA}/k_{DA} = 1.5 for *N*-*p*-nitrophenylcarbamate (Table I). Values of k_D/k_H = 1.0 for *N*-*p*-nitrophenylcarbamate and k_D/k_H = 1.0 and k_{DOD}/k_{HOH} = 0.25 for *N*-phenylcarbamate cleavage have been reported previously; the reported data also give a solvent isotope effect of $k_{HA}/k_{DA} \sim 1.4$ for bicarbonate catalysis of the cleavage of *N*-phenylcarbamate.[8]

Monothiocarbamates. Rate constants for the acid-catalyzed cleavage of monothiocarbamates are summarized in Table III. Cleavage of the monothiocarbamates of weakly basic anilines exhibits significant general acid catalysis, although less than the corresponding oxygen carbamates, but the catalysis becomes progressively less significant relative to the base line proton-catalyzed reaction as the aniline becomes more basic and there is no significant catalysis for monothiocarbamates of aliphatic amines. A series of experiments with monothiocarbamates of *n*-butylamine, ethylamine, cyanoethylamine, and glycine ethyl ester in 0.05-0.35 M phosphate buffers at pH values between 7.1 and 7.8 showed a decrease in rate of ~30% and an increase in pH with increasing buffer concentration; there was no significant change in rate after correction for the change in pH. Under the same conditions catalysis is easily observable with the *N*-*p*-nitrophenyl compounds. Cacodylate buffers gave no rate increase with the *n*-butylamine compound up to 0.9 M at 20% HA, but gave 20-30% increases in k_{obsd} with the cyclohexylamine and trifluoroethylamine compounds at 50% HA, conditions which are not favorable for observing general acid catalysis in this system. Rate increases of 40, 19, and 25% were observed with up to 0.7 M imidazole

Table III. Acid Catalysis of the Cleavage of Monothiocarbamates[a]

buffer or catalyst	pH	k_{HA}, M^{-1} s^{-1}	buffer or catalyst	pH	k_{HA}, M^{-1} s^{-1}
	p-NO_2PhNHCOS$^-$			*m*-ClPhCOS$^-$	
H^+		3.2×10^4 [b]	H^+		3.2×10^5 [b]
acetic acid[c]	7.41	0.74	phosphate	7.57	0.033
	8.40	0.85		7.98	0.029
			imidazole	7.26	*e*
cacodylic acid[c]	8.02	0.041		8.15	0.007
	8.38	0.035			
				PhNHCOS$^-$	
phosphate			H^+		8.5×10^5 [b]
	7.68	0.021	glycolic acid[c]	8.40	90
	7.70	0.020	acetic acid[c]	8.37	6.9
			cacodylic acid[c]	8.08	0.28
imidazole	8.48	0.0016[d]	phosphate	8.03	0.047
	m-NO_2PhNHCOS$^-$		imidazole	8.26	0.025
				8.56	0.028
H^+		1.03×10^5 [b]			
formic acid[c]	8.01	11.7		*p*-CH_3OPhNHCOS$^-$	
acetic acid[c]	7.83	1.53	H^+		1.1×10^6 [b]
	8.22	1.46	acetic acid[c]	7.75	5.8
phosphate	6.68	0.037		8.25	8.0
	7.10	0.020			
			phosphate	7.46	*e*
	7.45	0.019	imidazole	7.49	0.019
	7.77	0.016		8.55	0.029
imidazole	8.53	0.0027		8.55	0.032
				8.56	0.037

compd	k_H,[b] M^{-1} s^{-1}
p-HOPhNHCOS$^-$	1.03×10^6 [f]
$CF_3CH_2NHCOS^-$	1.9×10^4 [g]
$EtOOCCH_2NHCOS^-$	7.4×10^4 [h]
$NCCH_2CH_2NHCOS^-$	2.4×10^4 [h]
$MeOCH_2CH_2NHCOS^-$	7.1×10^4 [h]
cyclohexylNHCOS$^-$	6.0×10^4 [d,h,i]
EtNHCOS$^-$	4.5×10^4 [h]
n-BuNHCOS$^-$	3.6×10^4 [i,j]
	3.5×10^4 [d,h,i]

[a] At 25 °C, ionic strength 1.0 M (KCl). [b] Based on 10^{-pH} and rate constants extrapolated to zero buffer concentration. [c] In 0.1 M Tris buffer at the indicated pH. [d] The monothiocarbamate was prepared from the isocyanate and KSH or K_2S. [e] No catalysis was observed. [f] Determined in 0.01 M imidazole buffer, pH 8.22. [g] Determined from 26 runs in cacodylate and phosphate buffers, pH 6.16–6.36. [h] Determined in phosphate buffers. [i] Determined in cacodylate buffers. [j] Determined in imidazole buffers.

(10% HA), imidazole (50% HA), and triazole (at pH 7.2), respectively. However, these rate increases probably do not represent buffer catalysis because imidazole is a less effective catalyst than phosphate for carbamate decomposition (Tables I and III) and phosphate buffers give no rate increase. Furthermore, if imidazole-H^+ were giving true catalysis, triazole-H^+ (pK_a = 2.6) would not be expected to give detectable catalysis, assuming a linear Brønsted relation between the catalytic constants for imidazole-H^+ and the proton. Thus, there is no evidence for significant general acid catalysis of these reactions and we conclude that the small rate increases that are observed with cacodylate and imidazole buffers probably represent medium effects at high buffer concentrations.

The rate of exchange of solvent protons with the N-H group of *N*-*n*-butylmonothiocarbamate was determined in the presence of phosphate buffers in the pH range 7.7–8.5 by Fourier transform NMR measurements of saturation-recovery rates and transfer of saturation from water to the N-H proton,[24] as described in the Experimental Section. The pseudo-first-order rate constants for the exchange reaction (Table IV) increase linearly with 10^{-pH} and give a second-order rate constant of 5×10^7 M^{-1} s^{-1} for the acid-catalyzed exchange reaction; there is also an (uncertain) intercept of 0.12 s^{-1} at zero [H^+] that may respresent a pH-independent exchange reaction.

Carbon oxysulfide was shown to be the product of the acid-catalyzed cleavage of *N*-phenylmonothiocarbamate, *N*-*m*-nitrophenylmonothiocarbamate, and *N*-*n*-butylmonothiocarbamate by following its reaction with 0.5 M tris(hydroxymethyl)aminomethane (Tris) buffer at pH 7.7. Aliquots of solutions of the thiocarbamates that had been subjected to acid-catalyzed cleavage were found to give the same rate constants (0.016 s^{-1}) for reaction with Tris as an aliquot of saturated COS in dioxane, as shown for the product of *N*-*m*-nitrophenylthiocarbamate decomposition in curves A and B of Figure 2. The formation of the Tris monothiocarbamate was also followed during the decomposition of *N*-*m*-nitrophenylcarbamate in Tris buffer, which traps the COS as it is formed. As shown in curve C, Figure 2, the formation of the Tris monothiocarbamate proceeds with a lag phase followed by an approach to a limiting rate constant of 1.8×10^{-3} s^{-1},

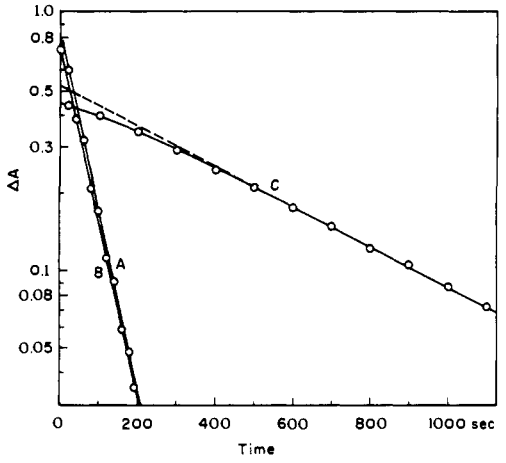


Figure 2. Change in absorbance at 228 nm from the reaction of carbon oxysulfide with 0.5 M Tris buffer, pH 7.7: (A) aliquot of a solution of *N*-*m*-nitrophenylmonothiocarbamate after cleavage in excess hydrochloric acid; (B) aliquot of carbon oxysulfide in dioxane; (C) cleavage of *N*-*m*-nitrophenylmonothiocarbamate in the Tris buffer.

Table IV. NMR Determination of the Rate of Exchange of the NH Proton of *N*-*n*-Butylmonothiocarbamate by Saturation-Recovery and Transfer of Saturation[a]

pH	$1/T$, s^{-1}	transfer of saturation, %	k_{exch}, s^{-1}
8.49	0.94	31	0.29
8.19	1.10	41	0.45
8.03	1.25	50	0.63
7.90	1.27	53	0.67
7.71	1.64	63	1.03

[a] In 0.05 M potassium phosphate buffers (Fisher Primary Standard) containing 0.10 M triethylammonium *N*-*n*-butylmonothiocarbamate and 10% deuterium oxide, at 25 °C. The data are the average of three determinations of the relaxation rate constant of the NH proton of the carbamate at 6.8 ppm from DSS after saturation ($1/T$) and the transfer of saturation to this peak after saturation of water, between 1.5 and 6 min after adding buffer to a stock solution of the carbamate. The pH was determined in parallel runs and was constant to ±0.02 pH during this period. The runs at pH 7.90 and 7.71 also contained 0.1 M *n*-butylammonium chloride.

which agrees with the expected rate constant of 2.0×10^{-3} s^{-1} for cleavage of the carbamate at this pH.

Dithiocarbamates. Rate constants for the proton-catalyzed cleavage of a selected group of dithiocarbamates are given in Table V. The rate constant for the piperidine compound shows fair agreement with previously reported rate constants that were obtained under slightly different conditions.[5,13,14] The results show that general acid catalysis is not significant for the cleavage of dithiocarbamates under conditions in which it is observed for analogous carbamates and monothiocarbamates. There is no increase in the observed rate constants with increasing buffer concentration. After correction of the observed rate constants for changes in the apparent pH with increasing buffer concentration, small increases of <25% were found with some buffers at concentrations of up to 0.8 M, but not with others. Previous publications have reported both the presence[9,13] and the absence[5,10,16] of general acid catalysis for this reaction, but no definite evidence for such catalysis has been published.

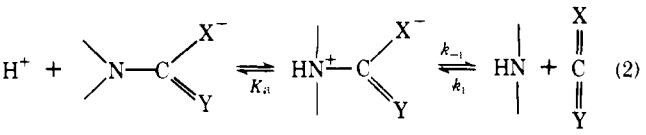
Discussion

Basic Conclusions. We conclude that *carbamates of basic aliphatic amines* are cleaved through specific acid catalysis (eq 2), i.e., by a mechanism involving protonation in a fast equilibrium step followed by amine expulsion in the rate-limiting step. In the addition direction, nucleophilic attack of the amine is rate limiting and is followed by rapid loss of a proton to water.

Table V. Acid Catalysis of the Cleavage of Dithiocarbamates[a]

buffer	pH	rate[b] change, %	k_H, M^{-1} s^{-1}
CyclohexylNCS$_2^-$			
acetate, 10% HA, 0.1-0.8 M	5.54	+21[c]	96[d]
glycolate, 10% HA, 0.1-0.8 M	4.62	−10	115
$CH_3CH_2CH_2CH_2NHCS_2^-$			
acetate, 50% HA, 0.05 M	4.58		0.35
$CF_3CH_2NHCS_2^-$			
acetate, 10% HA, 0.1 M	5.55		19
PhNHCS$_2^-$			
acetate, 50% HA, 0.05 M	4.57		560
acetate, 10% HA, 0.1-0.8 M	5.55	+23[c]	645
p-O_2NPhNHCS$_2^-$			
acetate, 50% HA, 0.05 M	4.57		400
acetate, 10% HA, 0.1-0.7 M	5.52	0	465
glycolate, 10% HA, 0.1-1.0 M	4.62	+9[c]	497

[a] At 25 °C, ionic strength 1.0 M (KCl). [b] From zero to the highest indicated concentration of buffer. [c] The observed rate constants were corrected for small changes in pH with increasing buffer concentration. No increase in k_{obsd} was observed without this pH correction. [d] Rate constants of k_H = 83, 45 (25 °C), and 86 (30 °C) M^{-1} s^{-1} have been reported previously.[5,13,14]



The large inverse solvent deuterium isotope effects, in the range k_H/k_D = 3.6-5.0 for aliphatic carbamates and monothiocarbamates (Table II), support this conclusion. Large inverse isotope effects are expected for specific acid catalysis, as a consequence of the more favorable equilibrium for substrate protonation in deuterium oxide, but are inconsistent with rate-determining diffusion-controlled protonation or a concerted mechanism.

It has been suggested that the rapid rate and small dependence on the pK of the leaving amine for the decomposition of aliphatic carbamates may be a consequence of rate-determining diffusion-controlled proton transfer.[7,8] but the much smaller rate constants for aliphatic monothio- and dithiocarbamates, which are not diffusion controlled, also show a very small dependence on amine pK (Tables III and V, Figures 3 and 4). Furthermore, if protonation is thermodynamically favorable and diffusion controlled, it should occur with buffer acids as well as the proton,[27] but general acid catalysis is not observed with aliphatic carbamates.[8] If proton transfer is thermodynamically unfavorable, there should be a very large dependence of the rate on amine basicity, with β_{lg} = 1.0,[27] which is not observed. Finally, the existence of a fast equilibrium protonation step is shown by the fact that the rate constant of 5×10^7 M^{-1} s^{-1} for protonation of the nitrogen atom of *N*-*n*-butylmonothiocarbamate, from measurements of the acid-catalyzed rate of exchange of the NH proton, is 1400 times faster than the rate constant for decomposition of this carbamate.

The small dependence of the rate on the pK of the aliphatic amine means that there is little positive charge on the amine in the transition state. Consequently, the transition state (**1**) is late in the direction of expulsion of protonated amine and early in the direction of amine attack. Chipperfield has found a value of β_{nuc} = 0.26 for the attack on carbon dioxide of a series of ten amino acid derivatives of pK 7.8-10.8.[28] Caplow has shown that there is no detectable dependence of the equi-

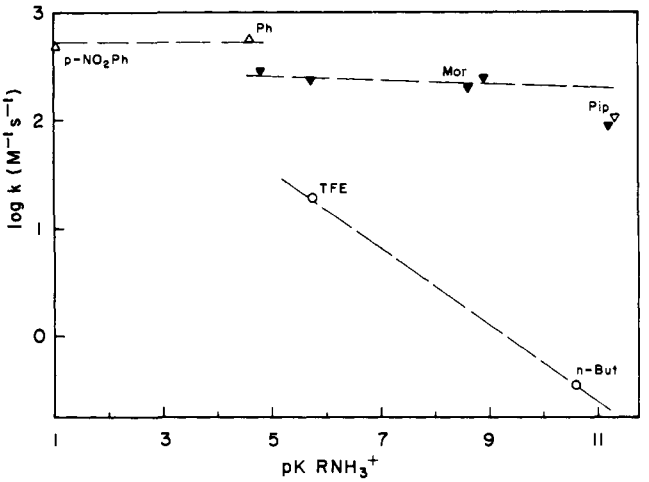
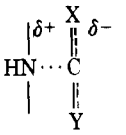


Figure 3. The dependence on amine structure of k_H for the cleavage of dithiocarbamates at 25 °C. *N*-Aryldithiocarbamates, △; *N*-trifluoroethyl- and *N*-*n*-butyldithiocarbamates, ○; piperidinedithiocarbamate, ▽; dithiocarbamates of cyclic secondary amines at 30 °C, ▼.[13,14]



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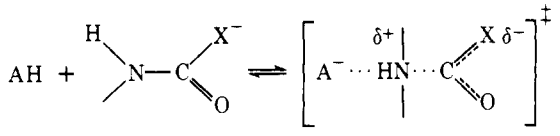
librium constant for carbamate formation on amine pK and from the equilibrium constants for structurally related amines it appears that $\beta_{eq} = 0 \pm 0.1$.[7] The value of β_{lg} for basic aliphatic amines should, therefore, also be close to 0.26, which is consistent with a reported value of $\beta_{lg} \sim 0.34$ for a series of cyclic secondary amines[14] and other published rate constants for carbamate cleavage.[7] The values of β_{lg} for mono- and dithiocarbamates are even smaller and also suggest transition states that are late for amine expulsion and early for amine attack. Lines of slope $\beta_{lg} = 0.04$ and 0.36 have been drawn through the points for *N*-alkyl- and *N*-arylmonothiocarbamates, respectively, in Figure 4, although it is possible that the data exhibit a slight curvature. Rate constants for the cleavage of dithiocarbamates from this and other studies show no significant increase with increasing amine basicity for either the alkyl or aryl derivatives; in particular, the rate constants for *N*-*p*-nitrophenyl- and *N*-phenyldithiocarbamates are almost the same and the *N*-trifluoroethyl compound reacts faster than the *N*-*n*-butyl compound (Table V, Figure 3).[5,9,11,13]

We conclude that *O,O- and O,S-carbamates of weakly basic anilines* are cleaved with general acid catalysis by a mechanism that involves hydrogen bonding of the conjugate base of the catalyst to the leaving protonated amine. In the addition di-



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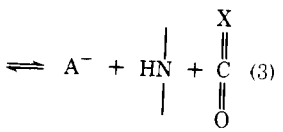


(3)

rection this corresponds to general base catalysis of amine attack. The Brønsted plot for the acid-catalyzed cleavage of *N*-*p*-nitrophenylcarbamate (Figure 5) extends the data obtained previously by Johnson and Morrison[8] and shows that the rate constants for cationic and for neutral or anionic cat-

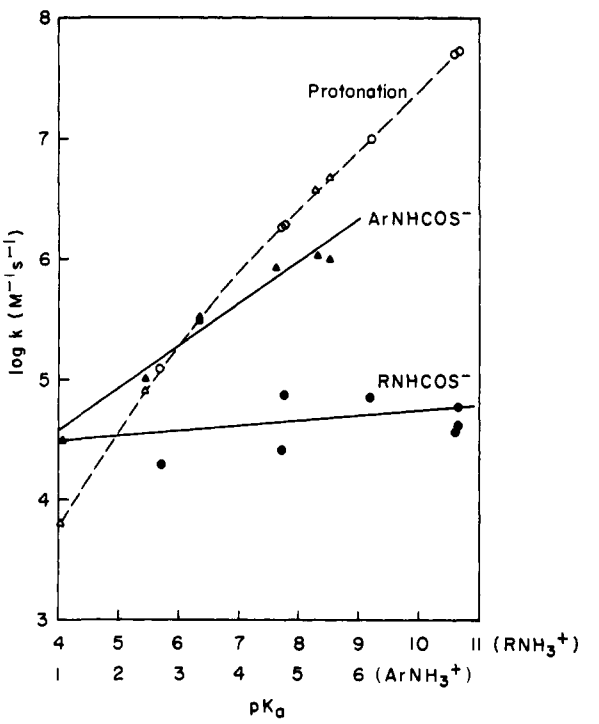


Figure 4. The dependence on the pK of the leaving amine of k_H for cleavage of *N*-arylmonothiocarbamates (▼) and *N*-alkylmonothiocarbamates (●) at 25 °C. Observed and calculated rate constants for protonation of the leaving nitrogen atom are shown by the dashed line (open symbols).

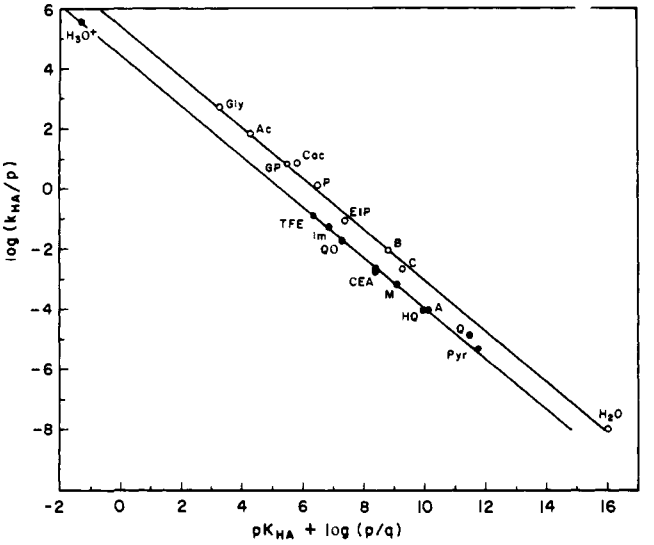


Figure 5. Brønsted plot for general acid catalysis of the cleavage of *N*-*p*-nitrophenylcarbamate at 25 °C, ionic strength 1.0 M (KCl). Uncharged and anionic acids, ○; cationic acids, ●. Abbreviations for the catalysts are listed in Table I.

alysts fall on separate lines of slope $\alpha = 0.84$. The proton and water do not deviate from the lines for other catalysts of the same charge. The constant value of α over a range of >17 pK units in acid strength and 5×10^{13} in k_{HA} makes this one of the longest linear Brønsted plots that has been reported. The eightfold larger rate constants for neutral and anionic catalysts are attributed to stabilization of the transition state by an electrostatic interaction of A^- with the protonated amine (**2**); this interaction is not present in the reference ionization reaction of the acid.[29] A similar difference has been reported for general acid catalysis of the decomposition of *N*-carboxy-2-imidazolidone.[15]

The less extensive data for general acid catalysis of the cleavage of *N*-arylmonothiocarbamates by oxygen acids are

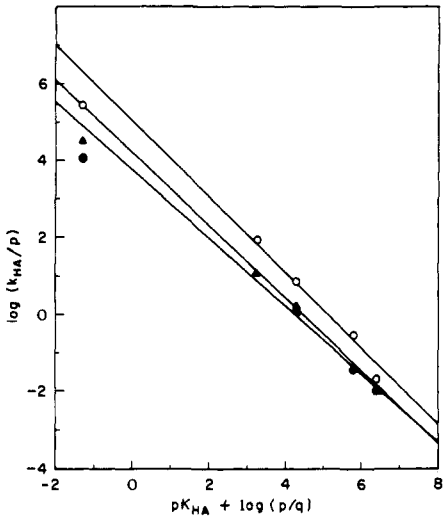


Figure 6. Brønsted plot for catalysis by oxygen acids of the cleavage of *N*-phenyl- (○), *N*-*m*-nitrophenyl- (▲), and *N*-*p*-nitrophenylmonothiocarbamate (●) at 25 °C, ionic strength 1.0 M (KCl).

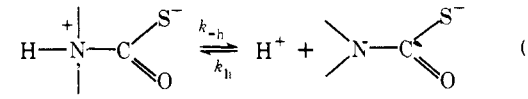
plotted in Figure 6. The solid lines are drawn assuming that the proton exhibits the same eightfold negative deviation from the Brønsted line for other oxygen acids that is found with *N*-*p*-nitrophenylcarbamate (Figure 5) and have slopes of α = 0.99, 0.95, and 0.89 for *N*-phenyl-, *N*-*m*-nitrophenyl-, and *N*-*p*-nitrophenylmonothiocarbamate, respectively. Catalysis becomes progressively more difficult to detect as the pK of the leaving amine increases and would not be detectable if the proton did not exhibit a negative deviation from the Brønsted lines.

A small normal solvent isotope effect of k_{HOH}/k_{DOD} = 1.5 for catalysis of *N*-*p*-nitrophenylcarbamate cleavage by bicarbonate (Table I) and the small inverse isotope effects in Table II of k_H/k_D = 0.67 and 0.57 for cleavage of *N*-*p*-nitrophenylcarbamate and *N*-phenylmonothiocarbamate, respectively, are consistent with the mechanism of eq 3. A similar isotope effect of k_{HOH}/k_{DOD} = 1.75 has been reported for catalysis by phosphate buffer of the cleavage of *N*-carboxy-2-imidazolidone.[15] The normal isotope effects for the buffer-catalyzed reactions are consistent with hydrogen bonding in the transition state and the small inverse isotope effects for the proton-catalyzed reactions suggest that the large inverse isotope effects that are expected for equilibrium proton transfer are partly compensated by a normal isotope effect for formation of the hydrogen-bonded transition state.

The linear Brønsted plots with α = 0.84 for *N*-*p*-nitrophenylcarbamate (Figure 5) are inconsistent with simple rate-determining protonation of the leaving aniline according to the three-step mechanism described by Eigen because the Brønsted plots for such proton-transfer reactions are curved, with a break at the pK_a of the protonated product and a positive deviation of the point for the proton.[27] If the pK_a of the protonated product is less than that of the solvated proton, so that proton transfer is always thermodynamically unfavorable, the values of α and β should be 1.0 and catalysis by acids other than the proton should not be detectable. This is inconsistent with the observed values of α = 0.84, the existence of general acid catalysis, and the values of $\beta_{lg} \ll 1.0$. Furthermore, if this proton transfer were extremely unfavorable, it is unlikely that C–N bond cleavage would be faster than the ultrafast transfer of the proton back to A^-, which would be required for rate-determining proton transfer. Finally, the rate constant for the thermodynamically unfavorable protonation of *N*-phenylcarbamate and *N*-*p*-nitrophenylcarbamate by bicarbonate ion should be proportional to the basicity of the nitrogen atoms of the two compounds.[27] However, the ratio of the observed rate constants for the bicarbonate-catalyzed cleavage of these two compounds[8] is ~10, whereas the ratio of the basicities of the parent anilines is 2500, so that both of these rate constants cannot represent rate-determining protonation. Catalysis of the cleavage reaction by rate-determining protonation corresponds to catalysis of the reverse, addition reaction by rate-determining deprotonation and, in general, such catalysis will not be significant for reactions involving the attack of weakly basic amines because proton transfer to water, when it is strongly favorable thermodynamically, will be faster than to added buffer bases. Consequently, if buffer catalysis of such reactions is observed, it must represent hydrogen bonding or a concerted mechanism of catalysis.

The fact that the proton and water fall on the same Brønsted lines as other monofunctional and bifunctional acids and bases (Figure 5) makes it unlikely that the reaction proceeds through a cyclic mechanism of proton transfer involving the $-COX^-$ group of the carbamate (the proton-catalyzed cleavage is equivalent to the water-catalyzed addition reaction, which might be thought to proceed with a cyclic proton transfer through water or a bifunctional catalyst to the developing negative charge of $-COX^-$).

Lifetimes and Dissociation Constants of the N-Protonated Carbamates. The rate constant for the acid-catalyzed exchange of the NH proton of *N*-*n*-butylmonothiocarbamate permits an estimation of the pK_a values of the N-protonated carbamates, as has been done previously for N-protonated amides,[30] and of the rate constants for their decomposition. Assuming a value of $k_{-h} = 10^9$ s^{-1} for the protonation of water by the N-protonated carbamate (eq 4) the observed value of k_h = 5


(4)

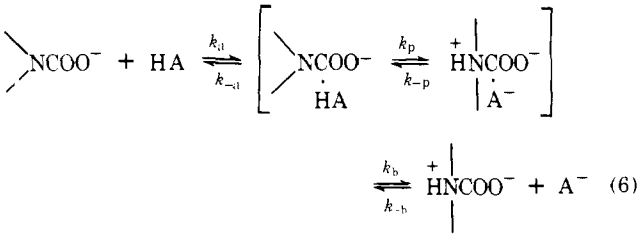
× 10^7 M^{-1} s^{-1} for acid-catalyzed NH exchange gives a value of pK_a = $-\log K_a$ = $-\log (k_{-h}/k_h) = -1.3$. This value of k_{-h} is uncertain and there is a corresponding uncertainty in the estimated pK_a value. The value $k_{-h} = 10^9$ s^{-1} represents a conservative estimate that was chosen because proton transfers near $\Delta pK = 0$ are slower than thermodynamically favorable proton transfers.[27] This value corresponds to $k_{-h} = 2 \times 10^9$ s^{-1} at $\Delta pK = 0$ from the Eigen curve for proton transfer from an acid of pK_a = −1.74, which is five times smaller than the commonly used value of $k_{-h} = 10^{10}$ s^{-1} for thermodynamically favorable proton transfers.[30] The same Eigen curve agrees well with the observed rate constants for the cleavage of *N*-phenylcarbamate,[8] as will be described below. Larger values of k_{-h} would give correspondingly lower pK_a values and larger rate constants for decomposition of the protonated carbamate.

The value of k_{-1} for the cleavage of N-protonated *N*-*n*-butylmonothiocarbamate (eq 2) is then $k_{-1} = k_H/K_a = 7 \times 10^5$ s^{-1}. Assuming that the effect of the $-COS^-$ substituent on the pK_a of the amine is constant, the values of pK_a for other aliphatic N-protonated monothiocarbamates are given by

$$pK_a = pK_N - 11.9 \quad (5)$$

in which pK_N is the pK of the parent amine. The pK_a of the N-protonated trifluoroethylamine compound is then −6.1 and the value of k_{-1} for its cleavage is 2×10^{10} s^{-1}.

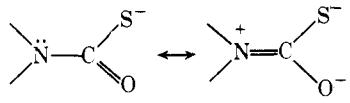
The rate constants for N-protonation of monothiocarbamates may be calculated from the observed value of $k_h = 5 \times 10^7$ M^{-1} s^{-1} for *N*-*n*-butylmonothiocarbamate and the equations for protonation according to the three-step Eigen mechanism to give solvent-equilibrated products,[3,27,31] with HA = H_3O^+ and assuming $k_a = k_{-b} = 10^{10}$ M^{-1} s^{-1}, $k_{-a} = k_b = 5.5 \times 10^{11}$ s^{-1}, $\log k_p = \log k_p^0 + 0.5\,\Delta pK$, $\log k_{-p} = \log k_p^0 - 0.5\Delta pK$ (in which k_p^0 is k_p when $\Delta pK = 0$; the value of k_p^0 is 2×10^9 s^{-1}, based on pK_a = −1.3 for N-protonated



$$k_h = \frac{k_a k_p k_b}{k_p k_b + k_{-a} k_b + k_{-a} k_{-p}} \quad (7)$$

N-*n*-butylmonothiocarbamate). The calculated values of k_h, which are shown as the dashed line in Figure 4, are larger than the rate constants for the acid-catalyzed cleavage of aliphatic monothiocarbamates, in agreement with the proposed mechanism of specific acid catalysis for these reactions.

The same procedure cannot be applied directly to *N*-arylmonothiocarbamates, because the pK_a values of the parent anilines are influenced by resonance as well as polar effects of the aryl group. The large decrease of 11.9 units in the pK_a of N-protonated monothiocarbamates, compared with the parent amines, means that there must be a large amount of delocalization of the electron pair of nitrogen into the thiocarbamate



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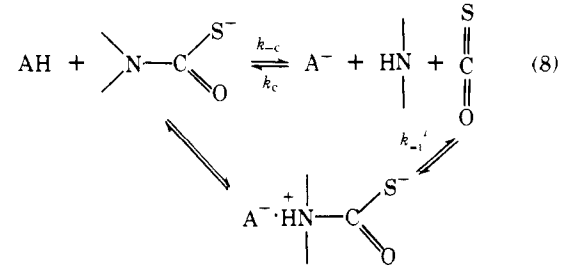
group, although less than for amides and thioamides.[32] Such delocalization becomes more significant upon substitution of sulfur for oxygen and there are indications from C–N bond lengths and infrared spectra that it is important in dithiocarbamates.[32,33] This strong delocalization is expected to inhibit delocalization of the electron pair into the benzene ring of the aniline. There is evidence for similar inhibition in acetanilides from the fact that the equilibrium constants for acetanilide formation from substituted anilines follow σ^- rather than σ.[34] It is also likely that such delocalization is inhibited by nonplanarity of the benzene ring and the carbamate group. The surprisingly low pK_a values of 14.7 and 17 for ionization of the NH protons of $PhNHCSS^-$ and $PhCH_2NHCSS^-$, respectively,[35] provide further evidence for electron delocalization as in **3**. The small difference of 2.3 units in the pK_a values for NH ionization of these compounds, compared with the difference of 4.8 units between the pK_a values of protonated aniline and benzylamine,[35] provides further evidence for inhibition of delocalization into the benzene ring of the aniline.

The pK_a values for the N-protonated aniline derivatives were calculated, therefore, after applying a correction of +3 units to the pK_a of the parent aniline, assuming that delocalization lowers the pK_a of anilines by 3 pK units[36] and that this delocalization is completely lost in the carbamate. The calculated values of pK_a for N-protonated monothiocarbamates of substituted anilines are then in the range −3.4 to −7.9 and the values of k_{-1} range up to 3×10^{11} and 2×10^{12} s^{-1} for the *m*-nitrophenyl and *p*-nitrophenyl compounds, respectively. A smaller correction would give correspondingly lower pK_a and larger k_{-1} values for the N-protonated carbamates.

These values of k_{-1} were calculated assuming that protonation occurs in a rapid equilibrium step and that the N-protonated carbamate exists as a free intermediate (eq 2). The very large values of k_{-1} suggest that this assumption may not be correct for the weakly basic aniline compounds because the protonated intermediate is likely to decompose before the proton donor molecule has diffused away, through a hydrogen-bonding "preassociation" mechanism (k_{-1}', eq 8),[2,3] or a concerted mechanism[7,8] (k_{-c}, eq 8). Such mechanisms are

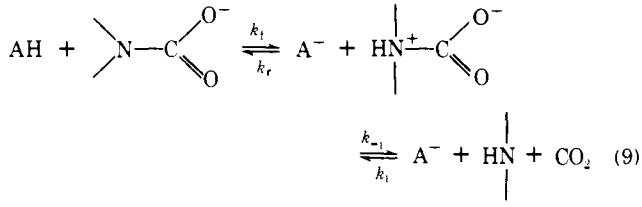


even more probable if the value of k_{-h} for N-protonated *N*-*n*-butylmonothiocarbamate is $>10^9$ s^{-1} or the resonance correction for aniline is less than 3 pK units.

The rate constants for N-protonation of monothiocarbamates of weakly basic anilines, calculated from eq 7 and shown as the dashed line in Figure 4, are comparable to or smaller than the observed rate constants for acid-catalyzed cleavage. This suggests that cleavage of these compounds cannot occur with specific acid catalysis through a rapid equilibrium protonation step, but is consistent with a concerted mechanism of protonation and C–N bond cleavage or breakdown of the N-protonated carbamate before the proton donor has diffused away. The rate constants for N-protonation in Figure 4 refer to the complete three-step proton-transfer process to give solvent-equilibrated products (eq 5). These rate constants follow a line of slope 0.5 for some distance on either side of $\Delta pK = 0$, in the region in which the k_p step is largely rate determining. Such behavior has been observed for other proton-transfer reactions.[37] If k_p decreases faster than predicted by this slope of 0.5 or if the pK_a of *N*-*n*-butylmonothiocarbamate is lower than −1.3, the rate constants for N-protonation will be correspondingly smaller.

Thus, the data suggest that general acid catalysis by buffers through a hydrogen-bonding mechanism becomes significant for carbamate cleavage only when the N-protonated intermediate becomes extremely unstable. Cleavage of the least basic carbamates probably proceeds through a preassociation mechanism that is enforced by the short lifetime of the N-protonated intermediate or through a concerted mechanism; both mechanisms involve hydrogen bonding to the catalyst in the transition state. The same conclusion probably applies to the expulsion of the still less basic ureido nitrogen leaving group in the cleavage of *N*-carboxybiotin and *N*-carboxyimidazolidinone,[7] although the possibility of oxygen protonation has not been excluded in these reactions. In general, reactions involving more basic amines or more stable intermediates proceed through stepwise mechanisms involving trapping of the intermediate by buffer or rapid proton transfer between the nitrogen atom and water.

Complex Conclusions. It has been shown in two laboratories that the cleavage of *N*-phenylcarbamate follows a sigmoid curve of log k against pH, with inhibition of the reaction at high concentrations of hydroxide ion.[8,38] This inhibition has been interpreted as evidence for a change in rate-determining step and, hence, a kinetically significant proton-transfer step in the reaction (eq 9).[8] This interpretation means that the



pH-independent and the proton-catalyzed reaction represent rate-limiting proton transfer from water and the solvated proton, respectively (k_f, eq 9), and the base-inhibited reaction represents rate-determining C–N cleavage (k_{-1}, eq 9).[8,39] A

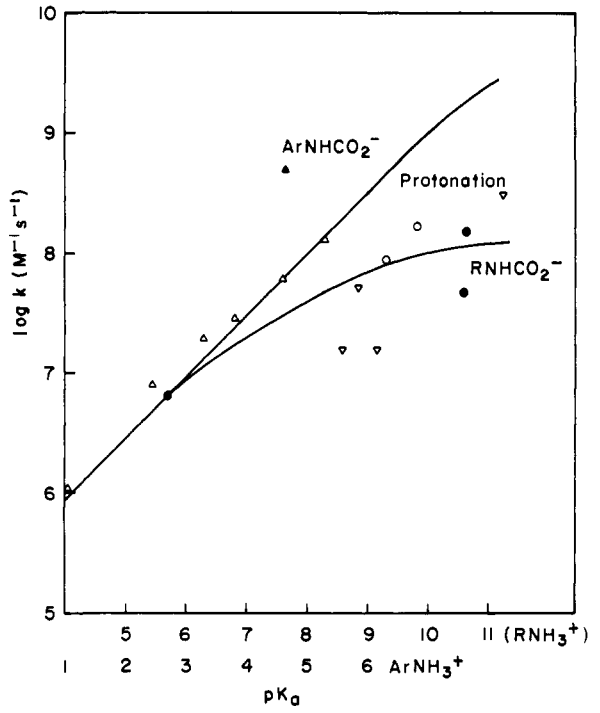


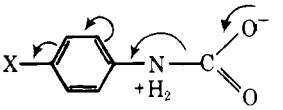
Figure 7. The dependence on the pK of the leaving amine of k_H for the cleavage of carbamates of anilines[8] (△), primary amines (○,●), and cyclic secondary amines[14] (▽). The calculated rate constants for protonation of the leaving nitrogen atom are shown by the upper line. The rate constant for the reaction of N-phenylcarbamate with rate-determining C–N cleavage at high pH[8] is shown as the solid triangle. The open circles are data at 10 °C corrected to 25 °C by the factor 1.9.[7]

similar result, and conclusion, has been obtained for N-(*p*-dimethylaminophenyl)carbamate.[40] The inhibition by hydroxide ion is almost certainly not a specific salt effect because there is no effect of comparable concentrations of potassium chloride and no such inhibition is observed for the N-*p*-nitrophenylcarbamate under similar conditions.[8]

We believe that this interpretation is probably correct, although it requires an unusual and fortuitous combination of circumstances for the N-phenyl compound. These include the following:

(1) Brønsted plots for rate-determining proton transfer are expected to follow nonlinear "Eigen curves" with $\alpha = \beta = 0$ when proton transfer is favorable and $\alpha = \beta = 1.0$ when it is unfavorable,[27] but the observed Brønsted plot is apparently linear with $\alpha = 0.76$ and the plot of β_{lg} for N-arylcarbamates is linear with $\beta_{lg} = 0.71$[8] (this plot does break for N-alkylcarbamates, but the evidence described above shows that proton transfer is not rate determining for these compounds). However, these results are explicable if (a) the pK_a of the N-protonated N-phenylcarbamate is slightly below zero; (b) the Brønsted line actually has a slope of $\alpha = 1.0$ for thermodynamically unfavorable proton transfer from weak acids and a negative deviation for the proton, because the proton transfer step itself (k_p, eq 6) becomes rate limiting; (c) the plot of β_{lg} reflects a different mechanism for less basic carbamates. In fact, the calculated pK_a of the N-protonated carbamate according to this mechanism is −0.77, based on $K_a = K_w k_f/k_r$, for A$^-$ = HO$^-$ (eq 9), the measured rate constant for the water reaction[8] of $k_{HOH} = k_f = 1.7 \times 10^{-5}$ s^{-1}, and the assumption that deprotonation by hydroxide ion is diffusion controlled with $k_r = 10^{10}$ M^{-1} s^{-1}, so that conditions (a) and (b) are reasonable. Evidence has been described above that weakly basic N-arylcarbamates cleave through a different mechanism (eq 3 and 8), which does not give rise to a change in rate-determining step with changing pH.

(2) The rate of C–N cleavage must be anomalously fast relative to the rate of proton transfer for N-phenylcarbamate. Starting with the carbamate of a basic amine, for which C–N cleavage is rate limiting, a decrease in amine basicity will decrease the rate of the observed reaction with rate-limiting C–N cleavage but is expected to have little or no effect on the rate of proton transfer to nitrogen (k_f) as long as the proton transfer remains thermodynamically favorable, so that the proton-transfer step should not become rate determining with decreasing amine basicity. However, it is reasonable that the k_{-1} step for C–N cleavage should be anomalously fast for anilines because the transition state is stabilized by resonance into the benzene ring[7] and, in fact, the observed rate constants for



aniline thiocarbamates are larger than for thiocarbamates of weakly basic aliphatic amines (Figures 3 and 4). The observed rate constant in strong base, which represents rate-determining C–N cleavage of N-phenylcarbamate according to the mechanism of eq 9, is shown as the solid triangle in Figure 7 and is still larger. Thus, the proton-transfer step can become rate determining for N-phenylcarbamate because C–N cleavage is fast and protonation becomes relatively slow when ΔpK is close to zero.

(3) The equilibrium solvent deuterium isotope effect for N-protonation of N-phenylcarbamate by solvent, $K = K_w/K_a$, is expected to be $K_{H_2O}/K_{D_2O} = 2.1$, from the isotope effects of 7.47 for K_w[41] and 3.6 for K_a, based on the observed inverse isotope effect for the acid-catalyzed cleavage of N-*n*-butylcarbamate (Table II). The solvent deuterium isotope effect on the rate constant for proton removal from the N-protonated carbamate by hydroxide ion, $k_r = k_f/K$ (eq 9, A$^-$ = HO$^-$), is then 4.0/2.1 = 1.9, based on the reported solvent isotope effect of 4.0 for the pH-independent cleavage of N-phenylcarbamate.[8] This value is larger than expected for a diffusion-controlled reaction. The mechanism of eq 9 would still be possible if the isotope effect on K_a were abnormally small for N-phenylcarbamate or if the isotope effect of 4.0 on the rate constant for the water reaction, which is not cleanly separated from the other kinetic terms, is in error. The absence of a solvent isotope effect for the pH-independent cleavage of N-carboxy-2-imidazolidone[15] supports the conclusion that cleavage of carbamates of weakly basic amines proceeds through a different mechanism.

(4) According to the mechanism of eq 9, the reverse of the "water" reaction with rate-determining proton transfer (k_f, AH = HOH) in the breakdown direction is the hydroxide ion catalyzed addition reaction with rate-determining proton transfer (k_r, A$^-$ = HO$^-$). The observed rate constants when this step is rate limiting (diffusion-controlled encounter of hydroxide ion with the N-protonated carbamate) should show a very large dependence on the basicity of the amine with $\beta_{nuc} = 1.0$, because the nitrogen atom carries a full positive charge in the transition state. However, Caplow has reported that there is essentially no dependence on amine basicity over a range of 7 pK units for the rate constant of the hydroxide ion catalyzed addition reaction.[7] Again, this result is consistent with a stepwise mechanism for N-phenylcarbamate cleavage only if this reaction is a special case and the reactions of carbamates of both more basic and less basic amines proceed through different mechanisms. This is not unreasonable.

If we accept the conclusion that the cleavage of N-phenylcarbamate is a stepwise process, with rate-determining proton transfer at most pH values, the available data are in good agreement with the mechanisms described above. The observed rate constant of 6×10^7 M^{-1} s^{-1} for the proton-catalyzed cleavage of N-phenylcarbamate[8] agrees well with the value

of $k_h = 9 \times 10^7\ M^{-1}\ s^{-1}$ calculated from eq 7 for rate-determining protonation, based on $pK_a = -0.77$ for the N-protonated carbamate and the same parameters as for the monothiocarbamates. Again, the proton transfer near $\Delta pK = 0$ is comparatively slow in both directions and is rate limiting; the rate constants for reprotonation of water and for cleavage[8] of the N-protonated carbamate are 5×10^8 and $2 \times 10^9\ s^{-1}$, respectively.

The pK_a values of other N-protonated carbamates were estimated from the pK_a of -0.77 and $k_h = 6 \times 10^7\ M^{-1}\ s^{-1}$ for the aniline compound and the equations

$$pK_a = pK_N - 5.4 \quad (10)$$

$$pK_a = pK_N - 8.4 \quad (11)$$

for *N*-arylcarbamates and *N*-alkylcarbamates, respectively, as described above for monothiocarbamates. The values of pK_a and k_{-1} for cleavage of the N-protonated carbamate (in parentheses) are 2.2 ($3 \times 10^5\ s^{-1}$) for *N*-*n*-butylcarbamate, −2.7 ($1 \times 10^9\ s^{-1}$) for *N*-trifluoroethylcarbamate, and −4.3 ($2.1 \times 10^{10}\ s^{-1}$) for *N*-*p*-nitrophenylcarbamate. The rate constants for N-protonation were calculated from eq 7 and are shown as the upper line in Figure 7. These rate constants are faster than the observed rate constants for cleavage of *N*-alkylcarbamates, consistent with a mechanism involving rapid protonation followed by rate-limiting C–N cleavage, i.e., specific acid catalysis. The rate constants for protonation are close to the observed rate constants (triangles) for acid-catalyzed cleavage of *N*-arylcarbamates, consistent with rate-determining protonation for at least some of these compounds.

These rate constants show that in this system amines are better leaving groups than alkoxides of the same p*K*. The rate constant of $k_{-1} = 3 \times 10^5\ s^{-1}$ for the expulsion of *n*-butylamine from $n\text{-}C_4H_9NH_2CO_2^{\pm}$ is 650 times larger than the rate constant of $440\ s^{-1}$ that is expected for expulsion of an alcohol of $pK = 10.6$ from $ROCO_2^-$.[42]

Although the calculated rate of N-protonation of *N*-*p*-nitrophenylcarbamate is the same as the observed rate of acid-catalyzed cleavage (Figure 7), there is no change in rate-determining step of the pH-independent reaction in alkaline solution at rate constants up to more than 100 times larger than that calculated for the proton-catalyzed reaction (Table I).[8] This is in contrast to the observed change in rate-determining step under the same conditions for the *N*-phenyl compound, which forms a more stable N-protonated species. The absence of a change in rate-determining step and the large rate constant of $k_{-1} = 2.1 \times 10^{10}\ s^{-1}$ for breakdown of the N-protonated intermediate provide further evidence for the proposed cleavage of the *N*-*p*-nitrophenyl compound through hydrogen-bonding catalysis in a preassociation or concerted mechanism (eq 8), which does not give a change in rate-determining step with changing catalyst concentration.

The change in rate-limiting step from C–N cleavage for *N*-alkylcarbamates to protonation for *N*-phenylcarbamate corresponds to a change from rate-limiting amine attack to deprotonation in the addition direction, as the amine becomes less basic. Similar behavior has been observed for the addition of amines to HNCO, for which the change in rate-determining step can also be demonstrated with increasing buffer concentration; the values of β_{nuc} and the absolute rate constants of the two reactions are also similar.[43] It is not known whether the cyanic acid reaction also shifts to a preassociation or concerted mechanism with a further decrease in the basicity of the attacking amine.

The cleavage of aryl- and alkylcarbamates occurs through a pH-independent "water" reaction at high pH values.[8,14] The point for catalysis by water of the cleavage of *N*-*p*-nitrophenylcarbamate falls on the Brønsted line of slope $\alpha = 0.84$ that is followed by other catalysts (Figure 5), so that this catalysis can be ascribed to catalysis by hydrogen bonding of hydroxide ion to the leaving N-protonated amine (eq 7, $A^- = HO^-$). Catalysis by hydroxide ion of the addition of weakly basic amines, which is the same reaction in the reverse direction, then represents stabilization of the transition state for amine attack by hydrogen bonding to hydroxide ion with $\beta = 1 - \alpha = 0.16$. It is probable that the same mechanism accounts for catalysis by hydroxide ion of the addition of basic amines and the pH-independent breakdown of carbamates of alkylamines, with values of $\beta \sim 0$ and $\alpha \sim 1.0$ so that catalysis by buffers is difficult to detect. The observed structure–reactivity parameters are not consistent with a fully concerted mechanism in which the proton is near the midpoint between the catalyst and the amine in the transition state. The "water" reaction has an early transition state for amine attack, with little charge development on nitrogen or C–N bond formation, and it is unlikely that the reaction catalyzed by hydroxide ion, a strong base, would have a later transition state. The observed independence of the hydroxide ion catalyzed reaction on amine basicity[7] then requires that there is little proton removal in the transition state, as expected for a hydrogen-bonding mechanism, because if there were much proton removal there would be a net negative charge on nitrogen in the transition state and the reaction would be faster for amines with electron-withdrawing substituents. Similarly, the increase in the rate of the water-catalyzed cleavage reaction with increasing basicity of secondary amines[14] suggests that the proton must be close to the nitrogen atom in the transition state.

The calculated pK_a of 2.2 for the zwitterion of *N*-*n*-butylcarbamate is consistent with the value of $H_0 = -3.3$ that has been reported for half-protonation of ethyl *N*,*N*-diisopropylcarbamate on nitrogen and an electrostatic effect of $+4.7 \pm 1.5$ units for the negative charge in the zwitterion.[44] The low pK_a values for the N-protonated carbamates and monothiocarbamates confirm the conclusion that the anions of carbamates are first protonated to give the neutral acid, with a much higher pK_a, rather than the dipolar, N-protonated species.[8]

Structure–Reactivity Relationships and the Nature of the Transition State. The properties of all of the reactions described here can be accounted for with essentially the same transition state and, except for basic *N*-arylcarbamates, by the same rate-determining step of C–N bond cleavage with hydrogen bonding to the solvent or to a buffer base. The transition state is characterized by three significant kinds of structure–reactivity behavior: (1) As the leaving amine becomes less basic (more acidic), hydrogen bonding to the transition state by acids exhibits a smaller Brønsted α coefficient (or β is larger for hydrogen bonding of the conjugate base of the acid to the protonated amine). For strongly basic amines there is hydrogen bonding only to HOH and HO^- with $\alpha \simeq 1.0$ and specific acid catalysis; the decrease in α for weakly basic amines gives significant general acid catalysis. (2) Although α changes with changing p*K* of the amine, it does not change with changing p*K* of the acid—α remains constant over more than 15 p*K* units for acids of a given charge type. (3) The dependence of the rate on the p*K* of the leaving amine (β_{lg}) becomes larger as the amine becomes less basic. For the purposes of this discussion we will assume that this represents a structure–reactivity effect and not some special property of aniline leaving groups; this assumption receives some support from the changes in β_{lg} with changing p*K* of leaving aliphatic amines.[7]

The nature of the transition state may be conveniently characterized with respect to these structure–reactivity effects by a near-vertical, slightly diagonal reaction coordinate on the three-dimensional reaction coordinate–energy diagram of Figure 8. In this diagram the amount of proton transfer is described by the horizontal axis, as defined by the experimental value of α, the amount of C–N bond formation or cleavage is

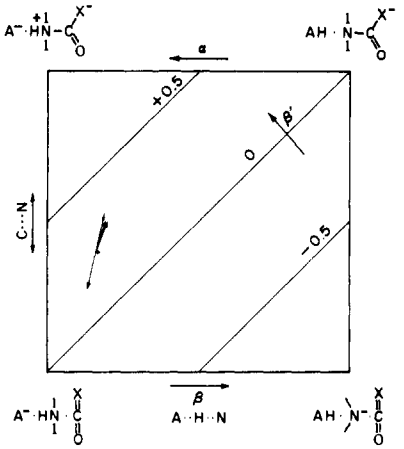


Figure 8. Reaction coordinate-energy diagram for the acid-catalyzed cleavage of carbamates. The horizontal axis for proton transfer is defined by the Brønsted α value and a diagonal axis is defined by $\beta' = \beta_{lg}$; the energy contour lines are omitted. A reaction coordinate is shown by the double-headed arrow.

indicated by the vertical axis (no direct experimental measure of this quantity is presently available), and the charge development on the central nitrogen atom, which is the resultant of these two processes, is measured by $\beta' = \beta_{lg} \simeq \beta_{nuc}$ along a diagonal axis. The energy contour lines are not shown and it is possible that there is a water molecule between AH and N. The large Brønsted α value places the transition state near the left edge and the small positive value of β_{lg} places it slightly above the diagonal line on the diagram. Cleavage of carbamates of basic amines proceeds through the metastable dipolar intermediate in the upper left corner ($A^- = HOH$), but this may not be possible for all carbamates because this "intermediate" may not have a significant barrier for breakdown or lifetime, with respect to C–N cleavage or proton transfer, when the amine is weakly basic.

An electron-withdrawing substituent that decreases the basicity of the leaving amine causes an increase in the energy of the upper left corner of the diagram of Figure 8. The transition state will then tend to slide downhill to the right, perpendicular to the reaction coordinate (an "anti-Hammond" effect) and to move uphill toward the top of the diagram, parallel to the reaction coordinate (a "Hammond effect"), as shown in the figure.[45,46] This shift corresponds to the structure-reactivity interactions (1) and (3) above. The shift to the right represents a decrease in the amount of proton transfer and the Brønsted α value and is consistent with the appearance of detectable general acid catalysis. The diagonal component of the shift corresponds to an increase on the diagonal $\beta' = \beta_{lg}$ scale and might be regarded as a "Hammond effect", with an earlier transition state for C–N cleavage in the breakdown direction and a later transition state in the attack direction for weakly basic amines. It is reasonable that the increased positive charge (β_{lg}) and acidity of the transition state with weakly basic amines should give a stronger hydrogen bond to the catalyst (increased β or smaller α).

The slightly diagonal direction of the reaction coordinate is consistent with the absence of a change in α with changing strength of the acid, interaction (2) above, in spite of the decrease in α with decreasing base strength of the amine. An increase in the strength of the acid raises the energy of the right side of the diagram and will tend to shift the transition state to the left, perpendicular to the reaction coordinate, and to the upper right, parallel to the reaction coordinate. The resulting cancellation of the shifts in the horizontal direction provides an attractive explanation for the constant value of α over a range of acid strength of 17 pK units (Figure 5). If the reaction coordinate were vertical, with the proton in a potential well of a hydrogen bond, the position of the well would be expected to shift to give a longer A–H distance with increasing acid strength if such a shift occurred with increasing base strength.[46,47]

A very similar reaction coordinate has been proposed previously for general acid catalysis of the addition of thiol anions to acetaldehyde, except that this reaction involves catalysis by hydrogen bonding to the carbonyl group (the electrophilic reagent, class e catalysis) rather than to the nucleophilic reagent (class n catalysis). This reaction exhibits an increase in $\beta' = \beta_{nuc}$ with decreasing basicity of the nucleophile (a Hammond effect) that presumably increases the electron density on the carbonyl oxygen atom and the strength of the hydrogen bond to the catalyzing acid, accounting for the observed increase in α; again, a slightly diagonal reaction coordinate can account for the absence of a change in α with changing acid strength.[3] A similar hydrogen-bonding mechanism, with the proton in a potential well, has been proposed for general acid catalysis of the addition of bisulfite to carbonyl compounds[48] and, by Eliason and Kreevoy, for other class n reactions with C–O cleavage.[49]

There are, however, two structure-reactivity effects which suggest that acid catalysis of C–O cleavage proceeds through a transition state that is significantly different from that for catalysis of C–N cleavage in carbamates. First, general acid catalysis of oxygen expulsion gives a decreased β_{lg} with decreasing basicity of the leaving alcohol (an "anti-Hammond" effect)[4] rather than the increase that is observed with carbamates. Second, the decrease in α with decreasing pK of the leaving group is larger for oxygen expulsion than for carbamate cleavage. Both of these differences are consistent with a predominantly diagonal reaction coordinate and a fully concerted mechanism for oxygen expulsion, and a nearly vertical reaction coordinate for nitrogen expulsion in carbamate cleavage. This suggests that the reaction coordinate for oxygen expulsion involves a large component of proton transfer in the transition state, whereas that for nitrogen expulsion involves primarily (but not entirely) cleavage of the C–N bond after most of the proton transfer has taken place. In terms of the diagram of Figure 8 the opposite signs of the changes in β_{lg} with pK_{lg} ($p_{y'}$ coefficient[46]) mean that one level line of constant energy passes vertically through the saddle point whereas the second level line is rotated clockwise by $\leqslant 45°$ for carbamate cleavage and by $>45°$ for oxygen expulsion; for a transformed diagram that is defined by perpendicular axes for α and β_{lg},[46] this corresponds to curvature in the horizontal direction through the saddle point that is zero or positive (uphill) for carbamate cleavage and negative (downhill) for oxygen expulsion.

These structure-reactivity interactions can be described more systematically and semiquantitatively by the coefficients[46]

$$p_{xy'} = \partial\alpha/\partial \mathrm{p}K_{lg}$$

which describes the decrease in α with decreasing pK_a of the leaving group,

$$p_{y'} = \partial\beta_{lg}/-\partial \mathrm{p}K_{lg}$$

which describes the increase in β_{lg} with decreasing pK of the leaving group, and

$$p_x = \partial\alpha/\partial \mathrm{p}K_{HA}$$

which describes the change in α with changing acidity of the catalyst and is zero for carbamate cleavage. A rough estimate of the $p_{xy'}$ coefficient can be obtained from the change in the ratios of the catalytic constants for the proton and phosphate monoanion, which decrease in the sequence $k_H/10^6k_{HA} = >20$, 18, 11, 8.7, and 1.6 for *p*-methoxy-, unsubstituted, *m*-chloro-, *m*-nitro-, and *p*-nitrophenylmonothiocarbamates, respectively. This corresponds to a change in α of 0.12 between

the unsubstituted and the *p*-nitro compounds and to a $p_{xy'}$ coefficient of 0.034. The smaller ratio of 0.7 for *N*-*p*-nitrophenylcarbamate reflects the smaller α value upon substitution of O for S in the carbamate. A similar comparison of the reported rate constant ratios for the proton and bicarbonate in the cleavage of substituted *N*-phenylcarbamates[8,50] shows a decrease in α of 0.06 from H to *p*-NO_2 and a $p_{xy'}$ coefficient of 0.016. An increase in β_{lg} from ~0.04 for an amine of pK = 9 to ~0.36 for an amine of pK = 3 corresponds to a positive coefficient of $p_{y'}$ = 0.053. A direct electrostatic effect, without changes in bond length, can contribute to the observed $p_{xy'}$ coefficient, but does not account for the positive $p_{y'}$ coefficient; an upper limit for this contribution is $\lesssim$0.024.[46,47,51]

These coefficients for monothiocarbamates and the constant value of α ($p_x = \partial\alpha/\partial pK_{HA} = 0$) correspond to horizontal, vertical, and diagonal curvatures of the energy surface of a = 39, b = 0, and c = −33, respectively, in the region of the saddle point of Figure 8.[46] These curvatures give coordinate ratios g_1/g_2 = 0 and 0.86 for the two lines of constant energy ("level lines") that pass through the saddle point and an angle of 41° between these lines (tan 40.7° = 0.86), so that a reaction coordinate that bisects these lines would be rotated about 20° clockwise from the vertical. The maximum contribution of 0.024 to $p_{xy'}$ from an electrostatic effect would reduce the angle between the level lines to 9°. The reaction coordinate in Figure 8 has been drawn with an intermediate angle of 12°. This treatment is crude, but nevertheless provides a description of a predominantly vertical reaction coordinate that will not be altered greatly by large errors in the structure-reactivity coefficients and is consistent with the experimental data.

Structure–Reactivity Behavior of *O*- and *S*-Carbamates. The acid-catalyzed cleavage of carbamates becomes progressively slower upon substitution of sulfur for oxygen, with rate constant ratios of ~10^5:$10^{2.5}$:1 for *O,O*-, *O,S*-, *S,S*-*N*-alkylcarbamates (Tables I, II, III, and V, ref 5, 7, 8, 11, and 14). The decreasing values of β_{lg} for the sulfur compounds might be interpreted as a "Hammond effect", with a later transition state for amine expulsion in the more difficult reaction. However, this interpretation is incorrect (as is often the case for such interpretations when the chemical nature of a reacting atom is changed) because there is a similar decrease in the rate constants for amine *addition*, with rate-constant ratios of 10^5:10^3:1 for CO_2:COS:CS_2.[11,18] Evidently, oxygen specifically stabilizes the transition state relative to *both* the reactants and the products, compared with sulfur. Nucleophilic attack on >C=S is slower than on >C=O in this system and an even larger difference in the same direction is seen in the 10^4 slower addition of amines to EtNCS compared with HNCO.[43a]

The relationship of the structure-reactivity behavior in the two directions is largely a consequence of resonance stabilization of the carbamate products, which is more important for sulfur than for oxygen carbonates. The absence of this resonance stabilization in the N-protonated intermediate and transition state is responsible for the slow rate of cleavage of the sulfur compounds. Thus, the estimated pK_a of N-protonated *N*-*n*-butylmonothiocarbamate of −1.3 is lower than the pK_a for N-protonated *N*-phenylcarbamate of −0.77, in spite of the much larger basicity of the aliphatic amine. It is this difference in basicity and the resulting decrease in the concentration of the N-protonated intermediate that is primarily responsible for the slower rate of acid-catalyzed cleavage of the sulfur compounds. There is a similar decrease in basicity of $10^{2.7}$ and an increase in acidity of 10^3 of the nitrogen atom of thioamides compared with oxygen amides that can be attributed to greater electron delocalization onto sulfur compared with oxygen.[32]

Summary

We conclude that carbamates of basic amines are protonated rapidly and expel the protonated amine slowly so that decomposition occurs through specific acid catalysis; the reverse, addition reaction is uncatalyzed. As the amine becomes less basic it is protonated more slowly and expelled more rapidly. The expulsion of aniline is also accelerated by resonance stabilization of the transition state, so that protonation becomes rate determining for *N*-phenylcarbamate; the addition of aniline to carbon dioxide occurs with rate-determining trapping of the initial N-protonated carbamate product by proton transfer to a base.[7,8] With still less basic amines the intermediate is even less stable and the transition state has a larger positive charge on nitrogen, so that decomposition occurs through a transition state that is stabilized by hydrogen bonding to A^-; the addition reaction occurs through the same transition state with hydrogen bonding to a base catalyst. With the least basic amines, cleavage of the C–N bond probably occurs through a preassociation or concerted mechanism before the proton donor can diffuse away from the reacting complex. The sequence of steps for acid catalysis is determined largely by the decrease, and possibly the disappearance, of the barriers for cleavage of the C–N and >N–H^+ bonds as the leaving group becomes less basic. Catalysis by trapping is significant for only a few amines of intermediate basicity; it is insignificant for less basic amines because the strongly acidic N-protonated intermediates formed from these amines transfer a proton to the solvent or A^- very rapidly.

After the submission of this manuscript we learned that Moodie and Sansom have independently proposed a somewhat similar sequence of reaction mechanisms.[52]

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References and Notes

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Kinetics and Mechanism of the Thiolytic Removal of the Dithiasuccinoyl (Dts) Amino Protecting Group[1,2]

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Abstract: The dithiasuccinoyl (Dts) amino protecting group is removed by thiols through the intermediacy of open-chain carbamoyl disulfides. The elucidation of practical and effective conditions for carrying out the reductive deprotection was facilitated by a rapid, convenient, and quantitative method to directly measure starting materials, intermediates, and products on a standard amino acid analyzer. The apparent pseudo-first-order rate constants were determined as a function of thiol, base, and solvent composition and concentration. Both steps of the mechanism were first order in thiol. In anhydrous solutions, the rate of the second step, k_2, varied directly with tertiary amine concentration, suggesting that the active species is an association complex of the thiol and the base. In contrast, a more complex explanation is required to account for the fact that plots of log k_1 against log [base] had a slope of only 0.7–0.8. The ratio of rates, $\kappa = k_2/k_1$, was generally between 0.1 and 5 for neutral monofunctional aliphatic thiols, but with bifunctional thiols, where the second step can proceed intramolecularly because a cyclic disulfide is formed, $\kappa \geq 100$ and consequently carbamoyl disulfide intermediates could not be observed. Intermediates were also never observed for thiophenol, the most acidic thiol tested, nor for 2-mercaptopyridine, a compound existing primarily as its thione tautomer. For these two cases, κ was estimated, by indirect means, as $\sim 10^5$ and $\geq 10^9$, respectively. The fastest overall rates were observed with thiols of intermediate acidity ($pK_a = 8.0$–9.5) in polar aprotic media of high dielectric constant. In aqueous solutions, the first step of the mechanism was rate limiting ($\kappa \sim 375$ based on an independent measurement). The observed rates k_1 were directly proportional to the thiol anion concentration and the data for monofunctional thiols fit a Brønsted correlation of thiol anion reactivity against pK_a with slope $\beta_{nuc} \simeq 0.9$. The two steps in the mechanism of thiolytic deprotection of dithiasuccinoyl amines have strikingly different electronic requirements, meaning that the transition states are different. The driving force for the first step appears to be relief of the ring strain of the Dts heterocycle, while the rate of the second step correlates with the ease of ionization of the thiocarbamate leaving group. Suitable conditions for the quantitative removal of the Dts protecting group from any amino acid residue at 25 °C include (1) β-mercaptoethanol (0.2 M)–triethylamine (0.5 M) in benzene for 5 min; (2) *N*-methylmercaptoacetamide or dithiothreitol (0.1 M) in neat pyridine for 5 min; (3) *N*-methylmercaptoacetamide or *N*-acetyl-β-mercaptoethylamine (0.1 M)–*N*-methylmorpholine (0.5 M) in acetonitrile for 1 min; (4) β-mercaptoethanol (0.1 M) and 2-mercaptopyridine or thiophenol (1.1 equiv over Dts amine) in *N*,*N*-dimethylformamide–pyridine (9:1) for 1 min; (5) *N*-methylmercaptoacetamide (0.2 M) in *N*,*N*-dimethylformamide–acetic acid (9:1) for 2 min; (6) dithiothreitol (10 mM) in pH 7.0 phosphate buffer for 2 min. The reductive deprotection of the Dts group and of carbamoyl disulfide intermediates is much more facile than the reduction of acyclic aliphatic disulfides.

The dithiasuccinoyl (Dts) amino protecting group[3-6] was developed for eventual application to *orthogonal* schemes[5,7,8] of peptide synthesis. On the one hand, the Dts group is stable under the acidolytic conditions used to remove *tert*-butyl and benzyl-based protecting groups, and it is also resistant to the photolytic conditions used to cleave the acid-stable *o*-nitrobenzyl and α-methylphenacyl esters. Conversely, the Dts function is rapidly and quantitatively removed in the presence of the other mentioned groups through application of mild and specific treatments[5,6] with thiols, borohydrides, and trialkylphosphines. The present paper provides practical details for effectively carrying out the reductive deprotection of dithiasuccinoyl amines with thiols; such information is a prerequisite for optimizing the conditions of solid-phase peptide

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