Direct Photoreaction of Indene with DCNB in Acetonitrile–Methanol. A 4:1 acetonitrile–methanol solution of indene (10 g, 86 mmol) and DCNB (2 g, 16 mmol) was irradiated for 60 h. After removal of the solvent, vacuum distillation gave unreacted indene (4.1 g) and 2-methoxyindan (2.4 g, 30% yield based on unrecovered indene). Column chromatography of the distillation residue on silica gel gave DCNB (1.0 g) and **14** (0.8 g, 40% yield based on unrecovered DCNB). Considerable amounts of heavy oils (~4 g) were eluted with benzene and then with 20% ethyl acetate in benzene. The oils were combined and then distilled in vacuo to give **15** (1.5 g, 20% yield based on unrecovered indene); bp 160–163 °C (0.1 mmHg).

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Mechanism of Hydrolysis of *N*-(1-Aminoalkyl) Amides[1]

G. Marc Loudon,* Merrick R. Almond, and James N. Jacob

Contribution from the Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, Indiana 47907.
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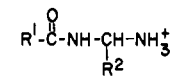
Abstract: Many of the title compounds (structure **1**) are remarkably stable to hydrolysis and can be isolated and characterized. The pH–rate profile for hydrolysis of the title compounds involves plateaus in the acid and base region, with the rates of hydrolysis in the basic region somewhat faster. The compounds hydrolyze to amides, aldehydes, and ammonia; the intermediacy of an imine in the basic region is demonstrated by its trapping with added CN^-. An optically active derivative of **1** hydrolyzes and loses optical activity at about the same rate in both the acidic and basic regions of pH. The reaction is characterized in basic solution by highly positive activation entropies, and alkylation of the amino nitrogen increases the rate significantly. The hydrolysis reaction shows no detectable buffer catalysis at any pH studied. The hydrolysis reaction is very sensitive to the amide leaving group; electron-withdrawing substituents on the amide portion of **1** substantially increase the rate of hydrolysis. The mechanism of hydrolysis in basic solution seems to be best described as a unimolecular solvolysis with an amide anion as a leaving group (Scheme I). In acidic solution the most likely mechanism of hydrolysis (Scheme II) appears to involve the expulsion of an amide enol (imidic acid). The implications of these findings are discussed for situations in which compounds of type **1** have found utility.

Compounds of type **1** have emerged as important entities in



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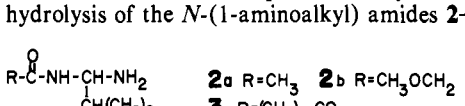
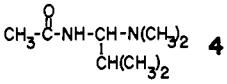
the peptide area in recent years. Goodman and his co-workers[2] have used such species as "mock" amino termini in the construction of several "retro-inverso" peptides. In such peptides, the N→C sequence of a normal peptide containing L amino acids has become the C→N sequence containing D amino acids. The result of this molecular "double-reverse" is that the retro-inverso peptide has in principle a side-chain topology similar to or identical with that of the natural peptide. The reversal of the amino and carboxyl terminus of such a peptide requires that groups be found which, simplistically stated, give the carboxyl terminus the appearance of the amino terminus, and vice versa. Despite the fact that peptides and their retro-enantiomers may not be rigorously correspondent,[3a] the concept appears to offer considerable pharmacological promise. A group closely related to **1** has been used as a new amino protecting group for introducing dipeptide synthons[3b] in peptide synthesis. The compound N^5, N^{10}-methylenetetrahydrofolate, which serves as a biochemical one-carbon shuttle from serine to methionine, features the N–C–N linkage, and a study of the breakdown of geminal diamines has been reported by several groups.[4] Finally, compounds of type **1** have proven to be stable intermediates in our carboxyl-terminal peptide degradation.[5]

Compounds of type **1** other than those derived from formaldehyde[6] were essentially unknown in the literature until Bergmann and Zervas[7] encountered them as isolable intermediates when they thermally rearranged acyl amino acid azides in benzyl alcohol and hydrogenolyzed the resulting carbamates. These authors noted that such compounds are sufficiently stable to be isolated in crystalline form, and further noted that the compounds were interesting and deserved additional investigation. Despite these comments, these derivatives have not reemerged in the literature until the recent past. One reason for this may be that these compounds are rather thinly veiled aldehydes; they are nitrogen analogs of "hemiacylals". One might naively have expected these compounds to be highly unstable but such is, in fact, not the case.

In order that the use of these compounds be optimized, a knowledge of their properties—in particular, their hydrolytic stability—is essential. In addition, the reasons for the hydrolytic stability are of interest. We here report our study on the mechanism of hydrolysis of the *N*-(1-aminoalkyl) amides **2–4**.



2a R=CH_3 **2b** R=CH_3OCH_2 **3** R=$(CH_3)_3$-CO



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(1) A preliminary account of this work has appeared: Loudon, G. M.; Jacob, J. *J. Chem. Soc., Chem. Commun.* **1980**, 377.
(2) (a) Goodman, M.; Chorev, M. *Acc. Chem. Res.* **1979**, *12*, 1. (b) Chorev, M.; Wilson, C. G.; Goodman, M. *J. Am. Chem. Soc.* **1977**, *99*, 8075.
(3) (a) Freidinger, R. M.; Veber, D. F. *J. Am. Chem. Soc.* **1979**, *101*, 6129. (b) Hardy, P. M.; Samworth, D. J. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1954.
(4) (a) Moad, G.; Benkovic, S. J. *J. Am. Chem. Soc.* **1978**, *100*, 5495. (b) Fife, T. H.; Hutchins, J. E. C.; Pellino, A. M. *Ibid.* **1978**, *100*, 6455. (c) Anderson, P. S.; Christy, M. E.; Colton, C. D.; Shepard, K. L. *J. Org. Chem.* **1978**, *43*, 3719.
(5) Parham, M. E.; Loudon, G. M. *Biochem. Biophys. Res. Commun.*, **1978**, *80*, 1, 7.
(6) (a) Einhorn, A.; Schupp, G. *Justus Liebigs Ann. Chem.* **1906**, *343*, 252. (b) Hellmann, H.; Opitz, G. "α-Aminoalkylierung"; Verlag Chemie: Weinheim, 1960; pp 64–47.
(7) Bergmann, M.; Zervas, L. *J. Biol. Chem.* **1936**, *113*, 341.

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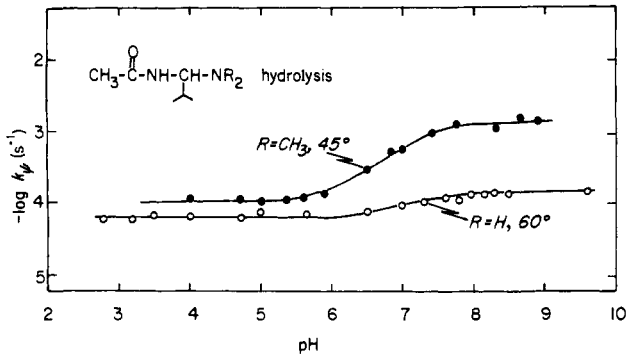
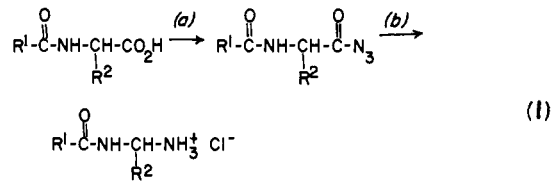


Figure 1. The log k_ψ vs. pH profiles for the hydrolysis reactions of **2a** (open circles) at 60 °C and **4** (filled circles) at 45 °C. The points are experimental, and the curves are calculated from eq 4 using the parameters in Table II.

Results

Synthesis of Compounds. Compounds of general type **1** were synthesized via the acyl azide, as shown in eq 1. The synthesis



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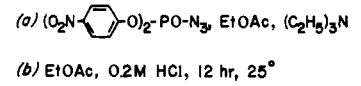
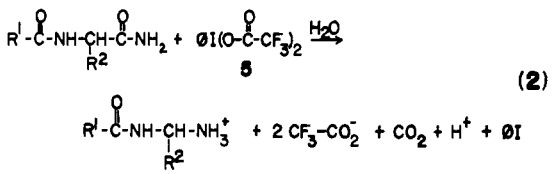


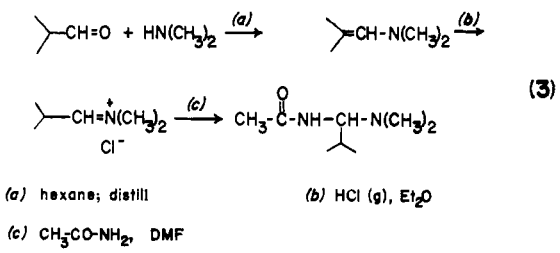
of the azide employed the bis(*p*-nitrophenyl)phosphoryl azide of Yamada.[8] Formation of urea in this reaction sequence is prevented by the extraction of the amine into the aqueous HCl layer as it is formed. For synthesis of compound **3**, the azide was converted to the benzyl carbamate by heating in benzyl alcohol/toluene, and the carbamate was then converted to **3** by hydrogenolysis in the presence of HCl.

Another synthesis of compounds of type **1** employed *I,I*-bis(trifluoroacetoxy)iodobenzene (**5**) using the procedure of Radhakrishna et al.,[9] as shown in eq 2. Compound **4** was synthesized



(2)

by the procedure shown in eq 3.



(3)

Kinetic Studies. The hydrolysis reactions of compounds **2**–**4** to isobutyraldehyde, acetamide (**2a**), or methoxyacetamide (**2b**), and ammonia (**2a** and **2b**) or dimethylamine (**4**) were followed by monitoring the appearance of isobutyraldehyde at 286 nm, a wavelength at which its apparent molar extinction coefficient was determined[10] to be 12.0. The ionic strength was maintained at 2.0 with KCl. The reason for the high ionic strength was the requirement for rather high buffer concentrations which, in turn, was necessitated by the high concentrations of the (ionic) substrate required in order to obtain reasonable changes in absorbance. The progress curves for the hydrolysis reactions were found to conform to a first-order rate law. Infinity points were, however, somewhat unstable in the basic region of pH, and this was established in

Table I. Kinetic Data for the Hydrolysis of Compounds **2**–**4**

buffer acid[a]	pH	$10^5 k_\psi$,[b] s^{-1}
Compound **2a** (60 °C unless noted)		
HCO_2H	3.20	5.23 ± 0.05
	3.50	6.28 ± 0.05
CH_3CO_2H	4.00	5.95 ± 0.05
	4.72	5.72 ± 0.05
	5.00	6.75 ± 0.05
CH_3CO_2H, 50°	4.64	1.60 ± 0.15
$H_2PO_4^-$	5.65	6.50 ± 0.08
	6.50	7.30 ± 0.06
	7.00	8.28 ± 0.15
	7.30	9.76 ± 0.09
	7.60	10.9 ± 0.10
	7.95	12.7 ± 0.18
$H_2PO_4^-$, 50°	7.95	2.91 ± 0.15
$(CH_3)_3CPO_3H^-$	7.84	10.1 ± 0.15
	8.16	12.4 ± 0.10
	8.52	13.4 ± 0.05
pH-stat[c]	8.30	12.5 ± 0.18
HCO_3^- [d]	9.60	13.9 ± 0.25
Compound **2b**, 60 °C		
HCl	2.58	4.25 ± 0.18
CH_3CO_2H	3.73	4.06 ± 0.26
	4.33	5.45 ± 0.46
	4.93	3.81 ± 0.37
$H_2PO_4^-$	5.74	13.2 ± 0.2
	6.45	41.1 ± 1.9
	7.10	71.7 ± 6.0
$(CH_3)_3CPO_3H^-$	8.15	123 ± 1.9
	8.50	155 ± 2.4
	9.34	124 ± 1.8
Compound **4**, 45 °C		
CH_3CO_2H	4.00	9.60 ± 0.15
	4.69	10.1 ± 0.05
	5.00	9.13 ± 0.05
	5.35	9.92 ± 0.09
$H_2PO_4^-$	5.60	10.9 ± 0.10
	5.90	11.9 ± 0.12
	6.50	28.3 ± 0.17
	6.85	49.7 ± 0.9
	7.00	52.7 ± 1.2
	7.40	95.5 ± 2.7
$(CH_3)_3CPO_3H^-$	7.75	115 ± 1.2
	8.30	98.8 ± 1.7
	8.65	146 ± 3.8
	8.90	131 ± 2.3
$(CH_3)_3CPO_3H^-$, 50°	8.33	232 ± 5.0
Compound **3**		
CH_3CO_2H, 50°	4.64	14.7 ± 0.6
$H_2PO_4^-$, 45°	6.45	144 ± 3.5
$H_2PO_4^-$, 40°	7.95	152 ± 1.8

[a] Buffer concentration (stoichiometric) = 0.5 M. [b] Errors are standard deviations in k_ψ. Precision is estimated at ±10–20% for reasons given in the text. [c] No buffer present; see text. [d] The rates showed a decrease with increasing HCO_3^- concentration. The number given here is extrapolated to zero buffer concentration.

(8) Shioiri, T.; Yamada, S. *Chem. Pharm. Bull.* **1974**, *22*, 855.
(9) Radhakrishna, A. S.; Parham, M. E.; Riggs, R. M.; Loudon, G. M. *J. Org. Chem.* **1979**, *44*, 1747.

(10) Because of the hydration of isobutyraldehyde (dissociation constant $K_d = 1.6$),[11] this is an apparent extinction coefficient based on the concentration [acetaldehyde] + [hydrate].
(11) Hine, J.; Houston, J. G.; Jensen, J. H. *J. Org. Chem.* **1965**, *30*, 1184.

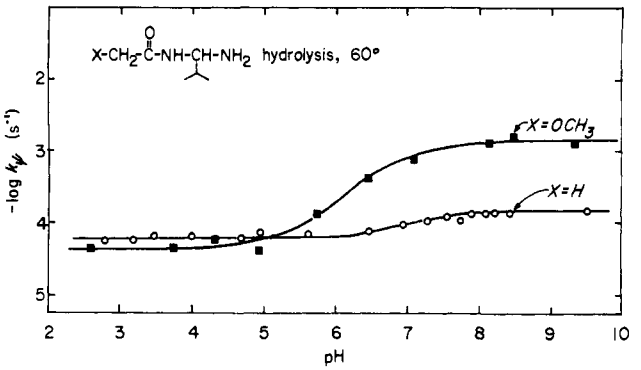


Figure 2. The log k_ψ vs. pH profiles for the hydrolysis reactions of **2a** (open circles) and **2b** (filled squares) at 60 °C. The points are experimental, and the curves are calculated from eq 4 using the parameters in Table II.

Table II. Kinetic Summary for the Hydrolysis of Compounds **2a**, 2b, and 4 According to Eq 4

	hydrolysis of compound		
	2a (60 °C)	**2b** (60 °C)	**4** (45 °C)
10^5k_A, s^{-1}	5.98 ± 0.18	4.06 ± 0.42	9.05 ± 0.55
10^5k_B, s^{-1}	13.4 ± 0.6	134 ± 14	138 ± 9
pK_a	7.33 ± 0.14	6.92 ± 0.11	7.27 ± 0.07

control experiments to be due to a further reaction of undetermined nature of the isobutyraldehyde. This instability, as well as the high and somewhat variable concentrations of substrates used, probably accounts for the fact that the precision of the rate data is not so high as one might ordinarily expect for spectrophotometric rate data. The logarithms of the rate constants for hydrolysis of **2a** and **2b** (at 60 °C) and **4** (at 45 °C) as a function of pH, shown in Figures 1 and 2, reveal two plateaus with a break in the pH 6 to pH 8 region. The data for hydrolysis of the various compounds studied are given in Table I.

Once it was established that the rates in both regions of the profile do not vary with buffer concentration (see below), 0.5 M concentrations of total buffer were used. One exception to this statement was a determination of the hydrolysis rate of **2a** made at pH 8.30 on the pH-stat. Over a limited pH range near this pH, the product NH_3 and the reactant have sufficiently different pK_a values that protons are consumed in the reaction. The rate determined on the pH-stat was identical within error to that determined by the spectrophotometric method. The data in Table I were fit, using a nonlinear least-squares procedure,[12] to the following equation.

$$k_\psi = k_A\left(\frac{H}{K_a + H}\right) + k_B\left(\frac{K_a}{K_a + H}\right) \qquad (4)$$

In this equation k_ψ, the observed pseudo-first-order rate constants, and values of H, taken as 10^{-pH}, were treated as the experimental variables and the remaining constants were calculated for optimum fit. A summary of the results of the calculation are given in Table II.

The hydrolysis rates of both compounds **2a** and **4** were considered as a function of buffer concentration at constant pH in various regions of the pH–rate profile. There were observed no systematic variations in rate with buffer concentration, as shown in Table III, although the precision of the data is such that weak buffer catalysis might not be detected. One exception to this statement is that there appeared to be a *downward* trend in the rate with increasing concentration of HCO_3^-/CO_3^{2-} buffers (not shown in the table), which may have resulted from covalent attack of the substrate on a form of CO_2. It is also worth noting that the data in the pH 8 to pH 9 region were conveniently accessible using the *tert*-butyl phosphonate buffers proposed by Kresge for this purpose.[13] The congruence of pH-stat rate data, taken in unbuffered solution, and spectrophotometric rate data, noted above, is further in accord with the absence of buffer catalysis.

A limited number of determinations of the rate of hydrolysis of the rather unstable compound **3** were made for the purpose of evaluating the effect of leaving group. The results are also reported in Table I.

The effects of temperature on the hydrolysis rates of **2a** and **4** were determined from data at two temperatures. The resulting activation parameters, shown in Table IV, are thus rather approximate, but allow the extrapolation of the data for these compounds to a common temperature.

(12) Wentworth, W. E. *J. Chem. Educ.* **1965**, *42*, 96.

Table III. Test for Buffer Catalysis in the Hydrolysis of **2a** and 4

buffer acid, pH	concn,[a] M	10^5k_ψ, s^{-1} [b]
Compound **2a**, 60 °C		
CH_3CO_2H, 4.73	0.5	5.71 ± 0.15
	0.3	6.52 ± 0.13
	0.2	6.13 ± 0.08
$H_2PO_4^-$, 6.50	0.5	7.30 ± 0.07
	0.4	7.30 ± 0.05
	0.3	7.32 ± 0.08
	0.2	7.27 ± 0.07
	0.1	7.12 ± 0.15
$(CH_3)_3CPO_3H^-$, 8.16	0.5	12.4 ± 0.1
	0.3	13.8 ± 0.3
	0.2	12.9 ± 0.15
Compound **4**, 60 °C		
CH_3CO_2H, 4.60	0.5	65.0 ± 0.8
	0.3	68.2 ± 0.5
	0.2	63.0 ± 1.3
	0.1	61.8 ± 0.5

[a] Stoichiometric buffer concentration; ionic strength held at 2.0 M with KCl. All buffers are potassium form. [b] See footnote *b*, Table I.

Table IV. Temperature Dependence for the Hydrolysis of **2a** and **4**

pH	$\Delta G^{\circ\ddagger}$, kcal/mol	$\Delta H^{\circ\ddagger}$, kcal/mol	$\Delta S^{\circ\ddagger}$, Gibbs/mol
Compound **2a**, 60 °C[a]			
4.72	25.9	27.4	+4.6
7.95	25.4	31.7	+19.0
Compound **4**, 60 °C[a]			
4.60	24.5	25.4	+2.7
8.30	22.8	20.3	−7.7

[a] Derived from a two-point temperature dependence of k_ψ (in s^{-1}) at the indicated pH using the data in Table II at 60 °C and the data in Table I at 50 °C (for **2a**); and the data in Table II at 45°, the average of the data in Table III at 60 °C, acidic region, and the data in Table I at 50 °C, basic region (for 4). From eq 4, the activation parameters can be associated with k_A and k_B, respectively. Because the temperature dependence is derived from two points, and because of the low precision of the rate data, no mechanistic significance is attached to the $\Delta S^{\circ\ddagger}$ values.

Table V. Comparison of Polarimetric (k_α) and Hydrolytic (k_ψ) Rates for Compound **2a** (60 °C, 0.5 M buffer, μ = 2.0 M (KCl))

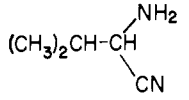
buffer, pH	10^5k_ψ, s^{-1}	10^5k_α, s^{-1}
CH_3CO_2H, 4.65	5.72 ± 0.15	5.45 ± 0.23
$(CH_3)_3CPO_3H^-$, 8.17[a]	13.4 ± 0.6	14.9 ± 0.1

[a] pH drift to 8.43 observed over the course of the polarimetric determination, attributed to the high substrate concentration required for reasonable values of optical rotation. The reaction rate as reflected by k_ψ shows neither pH nor buffer dependence over this range, and the polarimetric rate plot showed excellent first-order character.

(13) Chwang, W. K.; Eliason, R.; Kresge, A. J. *J. Am. Chem. Soc.* **1977**, *99*, 805.

Compound **2a** was synthesized in optically active form by the method of eq 1, and was found to have a specific rotation (see Experimental Section) at 365 nm sufficient for following its hydrolysis reaction polarimetrically.[14] A comparison of the polarimetric and spectrophotometric hydrolysis rates of compound **2a** in both the acidic and basic regions of the pH–rate profile are given in Table V.

Product Studies. A characterization of the products of the hydrolysis reaction of **2a** was carried out under acidic and basic conditions. In the basic region (pH 8), hydrolysis yields both isobutyraldehyde (isolated as the 2,4-dinitrophenylhydrazone, 41% yield) and acetamide (61% yield). Hydrolysis was also carried out in the presence of NaCN. Under these conditions, cyanoamine **6** was isolated in 60% yield from the reaction mixture. The identity



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of **6** was established both spectroscopically, by independent synthesis, and by conversion in 6 N HCl to valine. It is important to establish whether **6** arises from CN^- trapping of a reaction intermediate, or from the de novo Strecker synthesis from the NH_3 and isobutyraldehyde which might be formed as reaction products. Accordingly, the hydrolysis of **2a** was carried out at a given concentration at pH 11 (potassium phosphate buffers) in the presence of excess KCN (Table VI, Experimental Section). In a separate parallel control experiment, isobutyraldehyde and ammonia at the same concentration as **2a** in the first experiment were mixed in the presence of the same concentration of excess NaCN. Incubation of the reactions at 60 °C for 8 h was followed by isolation of **6** and hydrolysis to valine, which was quantitated by amino acid analysis and taken as a measure of the amount of **6** formed in the reaction. Indeed, a small amount of **6** was formed in the control experiment, but was found to be 19 ± 6% (three separate experiments) of that formed in the hydrolysis experiments. Thus, most if not all of **6** formed in the hydrolysis of **2a** in the presence of CN^- arises from a source other than resynthesis. The mechanistic implications of this observation will be considered in the next section.

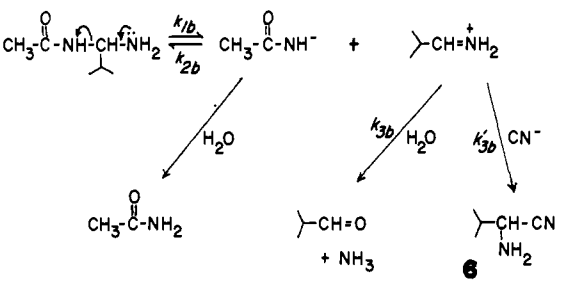
In the acidic region of pH (pH 4.5), the hydrolysis of **2a** was carried out in the presence of KCN (which exists essentially as HCN in this region of pH). Isobutyraldehyde cyanohydrin was isolated from this reaction in 87% yield, and was identified both spectroscopically and by comparison with a sample obtained by independent synthesis. Hydrolysis of **2a** was carried out in the presence of a known amount of benzoic acid as an internal standard at pH 2.21 (HCl) at 60 °C for 8 h. The solution was concentrated and the NMR spectrum of the residue indicated that a quantitative yield of acetamide was formed. A control demonstrated that acetamide and acetic acid give distinct NMR signals under these conditions, and that benzoic acid plus isobutyraldehyde, incubated for a similar period of time, give no NMR lines in the region of the methyl singlet used for quantitating acetamide. Further evidence that amides and not acids are the products of hydrolysis of compounds of the form **1** has already been obtained in our sequencing studies.[5]

Determination of pK_a. The pK_a values of **2a** were determined by direct titration at various temperatures (°C) (26°, 7.85; 32°, 7.75; 37°, 7.60) and ionic strength 2 N (KCl). These values were used to determine by extrapolation a pK_a value at 60 °C. The resulting value, 7.13, is in excellent agreement with the value determined directly at 60 °C, 7.10. The temperature study was considered necessary since some hydrolysis takes place during the pK_a determination at 60 °C.

Discussion

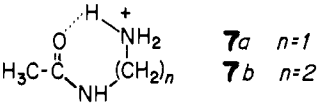
The pH–rate profiles (Figures 1 and 2) and the associated eq 4 suggest that there are two distinct mechanisms for the hydrolysis

Scheme I. The Mechanism of the Hydrolysis of 2a in Basic Solution



of compound **2a** and its analogs. In the acidic region of pH, the rate law suggests the involvement of the protonated form of **2a** or its kinetic equivalent. In the basic region, the rate law suggests the involvement of the free amine form of **2a** or its kinetic equivalent. The near identity of pK_a in eq 4 and Table II for compound **2a** with the independently measured pK_a value for the same compound supports the contention that the protonated state of the substrate is an important determinant of the hydrolysis mechanism.

Before considering mechanistic details, it is of interest to inquire whether the pK_a value of **2a** is unusual or whether it is the expected value for an acylaminoalkyl amine. the pK_a values for a series of amines $X–CH_2–CH_2–NH_3^+$ were used[15] to define substituent constants of X for the groups X = CH_3, CO_2R, C_6H_5, CH_3CO-NH, and CN. The resulting substituent effects were used to correlate the known pK_a values of amines $X–CH_2–NH_3^+$, except for the previously unknown X = CH_3CONH. An excellent linear correlation was obtained. Using the substituent constant derived above for X = CH_3CONH gave a predicted pK_a for $CH_3CONHCH_2NH_3^+$ of 7.8, in excellent agreement with the observed value for the pK_a of **2a** of 7.85 (26 °C). This result strongly suggests that there are no unusual effects operating in the pK_a of **2a** which do not equally operate in the model used for the determination of the substituent constant for the group CH_3CONH. In particular, this result provides no support for the possibility of an internally hydrogen-bonded structure such as **7a**, unless such a structure is equally important for **7b**, which was used to define the substituent constant for the CH_3CONH group.



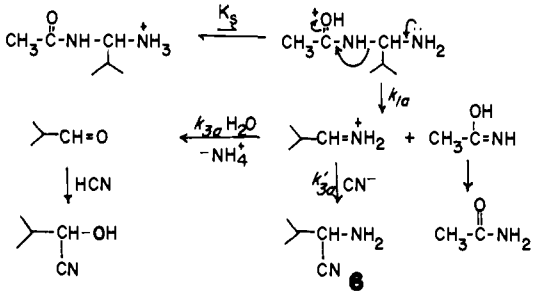
7a n=1 **7b** n=2

In the basic region of pH, the experimental facts can be accommodated by the mechanism shown in Scheme I. The product study establishes the predominant, if not exclusive, mode of bond cleavage to be that between the alkyl group and amide nitrogen. In particular, the trapping with CN^- strongly suggests the transient existence of isobutyraldehyde imine. Control experiments (Experimental Section) demonstrate that the cyanoamine **6** is a kinetic product, and not a product resulting from resynthesis utilizing isobutyraldehyde, acetamide, and NH_3 formed as the final products of the reaction. Since acetamide is the only acyl-derived product, the only reasonable source of imine is from the mode of bond cleavage shown in Scheme I. The observation that optical activity is lost at about the same rate as hydrolysis rules out any rapidly but reversibly formed intermediates which are trigonal at the carbon destined to become the carbonyl carbon of isobutyraldehyde. Actually, the loss of optical activity in this experiment may be somewhat faster than hydrolysis, a fact which could indicate a reversibly formed ion pair with a partially rate-determining diffusion apart of the amide anion and iminium cation. However, the precision of the rate data suggests that the significance of this difference is open to question.

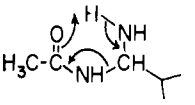
(14) Since racemization has been shown to accompany the use of bis(*p*-nitrophenyl)phosphoryl azide, the observed rotations may not be that of the pure enantiomer (see Experimental Section).

(15) Jencks, W. P.; Regenstein, J. In "Handbook of Biochemistry", 2nd ed.; Sober, H. A., Ed.; Chemical Rubber Co.: Cleveland, 1970; pp J-187–J-226.

Scheme II. The Mechanism of the Hydrolysis of 2a in Acidic Solution



The absence of general acid or general base catalysis rules out concerted proton transfers by solution components in the transition state. A formal possibility indicated by transition state **8** still



8

remains. The fact that compound **4**, for which such a proton transfer is not possible, hydrolyzes with a rate which is much faster than that of **2a**, seems to eliminate the transition state **8** as a possibility. The effect of methylation of the amino nitrogen (**2a** → **4**), which results in an increase in rate of 52-fold at 60 °C, is in the direction expected for alkyl group stabilization of an incipient double bond in the transition state, a point which is in further accord with the mechanistic picture presented in Scheme I.

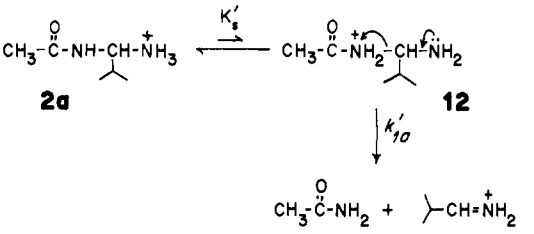
Finally, the effect of changing the structure of the leaving amide is substantial. In the basic region, the effect of changing the acyl group from acetyl to methoxyacetyl (**2a** → **2b**) results in an increase of tenfold (1 log unit) in rate. The difference in pK_a for N–H ionization of methoxyacetamide and acetamide is not known. However, this difference may be approximated as follows. The pK_a of methoxyacetic acid (3.53) is about the same as that of formic acid,[16] and the difference in pK_a between formamide and acetamide in Me_2SO solution[17] is about 2 units. If pK_a *differences* in Me_2SO solution carry over into water, then the "leaving group β", $(\Delta \log k_B)/(\Delta pK_a)$ is about −0.5. If, however, the difference in pK_a between two amides in water is about the same as that between the two parent carboxylic acids in water, then the leaving group β is about −0.8. A similar conclusion can be reached from the relative hydrolysis rates of **2a** and **3** although, for the latter compound, the leaving group is not a substituted acetamide and quantitative comparisons are perhaps less meaningful. In any event, there is a substantial effect of the amide leaving group on the rate, a fact which suggests a significant degree of bond cleavage in the transition state. The finding of an *amide anion* as a leaving group in a unimolecular solvolysis is a unique aspect of this work.

In the acidic region of pH, a number of candidate mechanisms are available. In Scheme II, it is assumed that protonation of the amide carbonyl group and deprotonation of the amine are required for the dissociation. If this mechanism is correct, then the failure of CN^- to trap a putative imine intermediate must be attributed to the fact that cyanoamine formation should be base catalyzed (as in cyanohydrin formation[18]), and at the lower pH values there is insufficient cyanide ion to compete with water for the iminium cation (i.e., $k_{3a}[H_2O] >> k'_{3a}[CN^-]$). Once the aldehyde product forms, of course, it is available indefinitely for cyanohydrin formation.

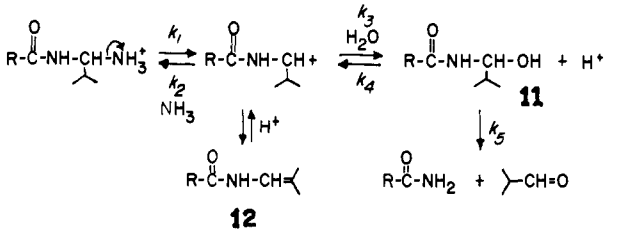
According to Scheme II, the observed first-order rate constant in the acid region, k_A (eq 4), is a composite constant:

$$k_A = K_s k_{1a} \quad (5)$$

Scheme III



Scheme IV



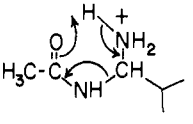
The constant K_s may be estimated from the known pK_a values of the amine (7.1) and a protonated acetamide[19] (−0.5) to be about 2.5×10^{-8}. This, together with the value of k_a from Table II, establishes k_{1a} to be about 2.4×10^3 s^{-1}. This calculation shows, not surprisingly, that compounds of type **1** are highly unstable when they are carbonyl protonated. However, the carbonyl-protonated species, despite their reactivity, are sufficiently stable to qualify as competent intermediates in the hydrolysis.

Another mechanism for the low-pH decomposition of **2a** is shown in Scheme III. In this scheme, the N-protonated amide acts as a leaving group. If this scheme is correct, then the observed rate constant k_A (eq 4) is a composite given by

$$k_A = K_s' k_{1a}' \quad (6)$$

The value of K_s' is the equilibrium constant for a proton switch from the amino to an amide nitrogen and is equal to the ratio of the ionization constants of the two protonated species **2a** and **9**. The pK_a of **9** is estimated to be −8.8 using σ_1 for the amino group[20] (0.12), ρ_1 for the acidity of simple ammonium ions[21] (8.4), and a pK_a of −7.7 for the N-protonation of *N*-methylacetamide.[22] Thus, pK_s' is about 16.6, which, with the observed k_A of 6×10^{-5} s^{-1}, leads to a value for k_{1a}' of 2.4×10^{12} s^{-1}. This number is unconfortably close to the maximum possible rate of a first-order decomposition at 60 °C (7×10^{12} s^{-1}), and it suggests that **9** borders on being too unstable to qualify as an intermediate.

Proton transfers from solution components are ruled out by the absence of buffer catalysis. However, the cyclic mechanism characterized by transition state **10** in the acidic region of pH is



10

in accord with the facts. It was noted previously that the pK_a of **2a** shows no evidence of hydrogen bonding (e.g., structure **7a**) of this sort in the *ground state*, although this fact obviously does not rule out such an interaction as a component of the transition state. The mechanism indicated by structure **10** bears close resemblance to the mechanism for the uncatalyzed hydrolysis of diphenylcarbinolamides, for which a similar cyclic mechanism of proton transfer was proposed.[23]

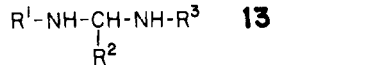
(16) Dippy, J. F. J.; Hughes, S. R. C.; Rozanski, A. J. *J. Chem. Soc.* **1959**, 2492.
(17) Bordwell, F. G.; Bartmess, J. E.; Hautala, J. A. *J. Org. Chem.* **1978**, *43*, 3095.
(18) Ching, W.-M.; Kallen, R. G. *J. Am. Chem. Soc.* **1978**, *100*, 6119.
(19) Huisgen, R.; Brade, H. *Chem. Ber.*, **1957**, *90*, 1432.
(20) Hine, J., "Structural Effects on Equilibria in Organic Chemistry", Wiley: New York, 1975; p 98.
(21) Fox, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 1436.
(22) It is assumed that pK_s, being a difference of pK_a values for two amines, will be relatively insensitive to temperature. See: Molday, R. S.; Kallen, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 6739.
(23) Sayer, J. M.; Conlon, P. *J. Am. Chem. Soc.* **1980**, *102*, 3592.

Another conceivable mechanism is shown in Scheme IV. The kinetic competency of carbinolamide **11** has not been tested. Although such compounds derived from formaldehyde are well known,[6,24] analgous open-chain compounds derived from other aldehydes or ketones are considerably less common.[23,25] Several facts, however, suggest that the mechanism in Scheme IV is not correct. If step k_5 in Scheme IV were rate limiting, then the polarimetric data are not in accord with this mechanism, because such a situation predicts that loss of optical activity should be considerably faster than hydrolysis. On the other hand, if step k_1 were rate-limiting, it is diffucult to understand the effect of changing the acyl group. Replacement of an acetyl group by the more electron-withdrawing *tert*-butoxycarbonyl group (**2a** → **3**) accelerates the reaction by a factor of 9.2 (50 °C, pH 4.64); a rate-retarding effect on carbonium ion formation would be predicted. Replacement of acetyl by methoxyacetyl does retard the rate by a factor of only 1.5. This is a smaller factor than the effect on the pK_a of the amine, one atom farther removed from the site of substitution.

Loss of a proton from the intermediate cation in Scheme IV to yield an *N*-acylenamine **12** is ruled out because (a) these compounds are known to be stable under the conditions used in this reaction (i.e., **12** is not a kinetically competent intermediate), and (b) protonation of *N*-acylenamines to yield this cation is the rate-limiting step in the hydrolysis of these compounds.[26] Thus, once formed, this cation should add a nucleophile more rapidly than it loses a proton. In summary, Scheme IV would appear to be ruled out by most of the data.

The mechanisms of Schemes I and II will be taken as the basis for further discussion with the proviso that Scheme II is somewhat less rigorously established. These mechanisms provide explanations for the (initially) rather surprising stability of compounds of type **1**. In the basic region of pH, the unpaired electrons of the free amino group can provide an electronic "push", but the amide anion leaving group is poor. In the acidic region, the amine electron pair is protonated, and a highly unfavorable equilibrium (K_s, Scheme II) must take place in order for the hydrolysis reaction to proceed.

The results of these studies fit a pattern established for the hydrolysis of geminal diamines.[4] For these compounds (**13**) it



13

was found that the more basic amine "pushes out" the protonated form of the less basic amine. To the extent that an amide can be considered an amine analog, the low pH mechanism for the hydrolysis of geminal amino amides **1** is identical. Similarly, no buffer catalysis was observed in the hydrolysis of geminal diamines. Finally, it has also been pointed out in the synthetic literature[24] that compounds of type **1** do not carry out *amido* alkylations, but rather cleave as we have shown to yield protonated imines (i.e., α-amino carbocations) which can act as *amino* alkylating agents. In fact, the structural requirements in compounds of type **1** for a different mode of breakdown are of some interest, and are the subject of continuing investigations.

Realizing that the mechanisms of Schemes I and II are really identical except for the state of protonation of the leaving group, one can also use these data to make separate estimates for the leaving group β in the hydrolysis reaction of **2a**. At basic pH values, the leaving group is the conjugate base of acetamide, pK_a = 15–17. At acidic pH values, the leaving group is the enol (imidic acid) form of acetamide, whose conjugate acid pK_a may be estimated[26] to be about 8. Corresponding to this difference in leaving group pK_a is a $\Delta(\log k)$ (i.e., $\log k_{1a} - \log k_B$) of about 7 units. Taken together, these results suggest a leaving group β for this reaction near −1.0, a value in close correspondence to that calculated earlier for two different leaving groups in the basic region only. Yet a third estimate for the leaving group β may be obtained solely from data in the acidic region by comparing the hydrolysis rates of **3** and **2a**. The hydrolysis of **3** is faster by a factor of 9.2 (50 °C). This rather small ratio conceals larger differences in k_{1a} for the two compounds, because a protonated carbamate carbonyl is considerably more acidic than a protonated amide.[27] Using the pK_a of protonated *tert*-butyl carbamate ($pK_a = -3$) as a model for the pK_a of protonated **3**, and that of acetamide ($pK_a = -0.5$) as a model for the pK_a of protonated **2a**, the k_{1a} values (eq 5) for **3** and **2a** are about 10^6 and 10^3 s^{-1}, respectively. These numbers, combined with the ΔpK_a values just calculated, suggest a substantial leaving group β near −1.0. The near-identity of the k_A values of **2a** and **2b** probably also reflects substantial but compensating differences in the K_s and k_{1a} values for the two compounds. Although all calculations have only semiquantitative significance, they are all mutually consistent in suggesting that bond cleavage in the transition states for the hydrolysis reactions of compounds of type **1** in both basic and acidic pH regions (Schemes I and II) is substantial.

These results have implications for the stability of "retro-inverso" peptides which employ the "mock amino terminus" of form **1**. First, there is not expected to be a great deal of difference in the stability of these compounds at mildly acidic vs. mildly basic pH. Although these studies at 60 °C suggest a somewhat enhanced stability of acidic pH, the two arms of the profile appear to have somewhat different temperature dependences which may "cross over" between 60 and 25 °C. Second, one can estimate the stability of such compounds at 25 °C at physiological pH. The known stability of **2a** extrapolated to 25 °C and the effect of leaving group suggest an aqueous solution half-life for compounds of type **1** (R^1CO- = acylaminoacyl) of about 10–50 h. Compounds of type **1** with R^2 = H should be more stable. Finally, the immediate product derived from the hydrolysis of these compounds is a protonated imine, which can in principle function as an alkylating agent.[24] This fact might have interesting pharmacological consequences.

Experimental Section

NMR spectra were recorded on either a Varian EM-360 or Varian FT-80 instrument. All chemical shifts are reported in ppm downfield from internal Me_4Si. Melting points were determined on a Buchi melting point apparatus and are uncorrected. Ethyl acetate (EtOAc) was dried by distillation from P_2O_5, and dimethylformamide (DMF) by distillation from CaH_2. Microanalyses were carried out by the Purdue University Chemistry Department.

Synthesis of *N*-(1-Aminoisobutyl)acetamide Hydrochloride (2a). Method A. To an ice-cold solution of racemic *N*-acetylvaline (3.0 g, 19 mmol) in 125 mL of EtOAc and 2.8 mL of triethylamine (19 mmol) was added a solution of bis(*p*-nitrophenyl)phosphoryl azide[8] (7.3 g, 20 mmol) in 125 mL of EtOAc. The mixture was stirred at 0 °C for 2.5 h. The precipitated triethylammonium salt of the phosphoric acid was filtered off, and the EtOAc solution was then stirred overnight with 100 mL of 0.2 N HCl solution at room temperature, with one change of the HCl layer. The combined aqueous layers were lyophilized to yield 2.65 g (84%) of **2a**, which was recrystallized from ethanol–ether (1.16 g, 37%).

NMR (Me_2SO-d_6): δ 0.95 (d, J = 7 Hz, 6 H), 1.6–2.4 (m superimposed on s at δ 1.93, 4 H), 4.70 (m, 1 H, collapses to d, J = 8 Hz, when D_2O is added), 8.55–8.90 (d, J = 9 Hz, overlapping a br s, 4 H, vanishes on addition of D_2O).

Anal. Calcd (C, H, N): 43.03, 8.71, 16.60. Found: 43.24, 9.07, 16.81.

The compound melts at 118–120 °C, then resolidifies and decomposes at 260–280 °C.

Method B. The second method used is very similar to that of Radhakrishna, et al.[9] A solution of *I,I*-bis(trifluoroacetoxy)iodobenzene (2.15 g, 5 mmol) and *N*-acetylvaline amide (0.79 g, 5 mmol) in 1:1 (v/v) acetonitrile:water (15 mL) was stirred at room temperature. The separation of iodobenzene was noted after 5 min. Stirring was nevertheless continued for 12 h, after which the mixture was diluted with 5 mL of concentrated HCl and extracted with 15 mL of ether. The water solution was lyophilized and ther residue was crystallized from ethanol–ether to

(24) Zaugg, H. E.; Martin, W. B. *Org. React.* **1965**, *14*, 52.
(25) Banfield, J. E.; Brown, G. M.; Davey, F. H.; Davies, W.; Ramsay, T. H. *Aust. J. Sci., Ser. A* **1948**, *1*, 330.
(26) This is the pK_a of the conjugate acid of an imidate ester. See: Pletcher, T. C.; Koehler, S.; Cordes, E. H. *J. Am. Chem. Soc.* **1968**, *90*, 7072.
(27) Armstrong, V. C.; Moodie, R. B. *J. Chem. Soc. B* **1968**, 275.
(28) Brannock, K. C.; Bell, A.; Burpitt, R. D.; Kelly, C. A. *J. Org. Chem.* **1961**, *26*, 625.

Table VI. Product Study and Control for Hydrolysis of 2a in the Presence of CN^- (see Experimental Section for Conditions)

expt no.	μmol used				valine, % of theory[a]	control, % of hydrolysis
	2a	isobutyraldehyde	NH_4Cl	NaCN		
H1	300		300	2040	61	28
C1		300	300	2040	17	
H2	100		100	2040	78	15
C2		100	100	2040	12	
H3	75		75	2040	43	14
C3		75	75	2040	6	
						19 ± 6

[a] Quantitated with glycine internal standard.

yield **2a** (82%), identical in all respects with the material obtained by method A.

Synthesis of (*S*)-(−)-*N*-(1-Aminoisobutyl)acetamide Hydrochloride (*S*(−)2a). Compound **2a** was synthesized from 2.0 g (13 mmol) of *N*-acetylvaline (Vega) using method A. When bis(*p*-nitrophenyl)-phosphoryl azide is used, some racemization is possible,[8] so that the optical rotations reported below may not be those of optically pure material. Nevertheless, the optical rotations of **2a** (as the hydrochloride in water, 1.91 g/mL, 25 °C) were determined at various wavelengths as follows (λ (nm) and observed rotation): 589, −1.515; 578, −1.616; 546, −1.845; 436, −3.198; 365, −5.098. The specific rotation at 365 nm is $[\alpha]^{25}_{365} = -266.7$ (*c* 1.91). The NMR spectrum of *S*(−)**2a** is identical in all respects with that of (±)**2a**.

Synthesis of *N*-(1-Aminoisobutyl)-2-methoxyacetamide Hydrochloride (2b). A solution of (±)-valine (3.51 g, 30 mmol) and 7.5 mL of 4 N NaOH was cooled to 5 °C in a 50-mL round-bottomed flask. To this solution were added alternately 9 mL of 4 N NaOH and 3.58 g (33 mmol) of methoxyacetyl chloride (prepared from methoxyacetic acid by the $SOCl_2$ procedure). The solution was extracted with ether and the aqueous phase was acidified (HCl) slowly to Congo Red. The solution was cooled an additional 15 min and extracted (4 × 20 mL) with EtOAc. The organic extracts were combined, dried ($MgSO_4$), and concentrated to yield N_α-(2-methoxyacetyl)valine (**14**), which was recrystallized from hexane–ether (67%, mp 72–4 °C).

The amide of **14** was synthesized by the mixed anhydride procedure. A mixture of **14** (946 mg, 5 mmol) and triethylamine (5 mmol) was disolved in 12 mL of CH_2Cl_2 and the resulting solution cooled to −10 °C. A solution of isobutyl chloroformate (0.67 mL, 5 mmol) in 10 mL of CH_2Cl_2 was added. After ca. 2 min, anhydrous NH_3 was passed through the solution for 1 h at room temperature. After stirring for an additional 4 h, the salt was filtered off and the CH_2Cl_2 removed in vacuo. The product, N_α-(2-methoxyacetyl)valinamine (**15**), a white solid, was recrystallized from CH_2Cl_2/hexanes (71%, mp 124–5 °C).

Compound **2b** was synthesized from amide **15** by method B on a 3-mmol scale using exactly the same procedure used for **2a**. The product, **2b**·HCl, was recrystallized from ethanol–ether (74%; mp 117–118°, product resolidified and decomposed at higher temperature).

Anal. Calcd (C, H, N): 42.48, 8.71, 14.24. Found: 42.88, 8.70, 14.39.

NMR (360 MHz, Me_2SO-d_6): δ 0.89, 0.95 (d + d, *J* = 8 Hz, 6 H), 2.15 (m, 1 H), 3.37 (s, 3.2 H, overlapping water peak), 3.91 (s, 2 H), 4.70 (t, 1 H, *J* = 10.6 Hz), 8.4 (br s, 3.3 H), 8.51 (d, *J* = 9.3 Hz, 1 H). [NMR spectrum determined at the Purdue Magnetic Resonance Center by John Kozlowski.]

Synthesis of *N*-(1-*N*,*N*-Dimethylaminoisobutyl)acetamide Hydrochloride (4). A mixture of isobutyraldehyde (0.26 mol) and dimethylamine (0.22 mol) was stirred overnight in 75 mL of hexane. The mixture was distilled and the fractions boiling between 70 and 82 °C were collected; these were found to contain the enamine contaminated with a small amount of hexane.[27]

The enamine was taken up in 50 mL of ether, cooled in an ice bath, and treated with dry HCl gas. The **isobutyraldehyde *N*,*N*-dimethylimine hydrochloride** was precipitated as a white solid which proved to be highly hygroscopic.

To a solution of the imine hydrochloride (1.1 g, 10 mmol) in 4.0 mL of DMF was added acetamide (0.92 g, 16 mmol) and the mixture was stirred at room temperature for 2 h. After ~3 mL of anhydrous ether was added, a crystalline material precipitated. The crystals were filtered, washed with 1:1 ethanol:ether, and dried in vacuo to give 285 mg (15%) of **4**. This material was too unstable on keeping for an elemental analysis.

NMR (Me_2SO-d_6): δ 1.0 (two overlapping d (apparent t), *J* = 7 Hz, 6 H), 2.05 (s, 3 H), 2.6 (br d; integral uncertain: overlapping with residual protons of solvent), 4.9 (overlapping br d of d, *J* = 10 Hz, 1 H; became doublet on adding D_2O), 9.2 (br d, *J* = 10 Hz, 1 H, exchanged with D_2O). The isopropyl methine, which may consist of up to 32 lines, was not directly observed and is probably buried in the δ 2–3 region.

Synthesis of *N*-(1-Aminoisobutyl)carbamic Acid *tert*-Butyl Ester Hydrochloride (3). To an ice-cold solution of *tert*-butoxycarbonylvaline (1.08 g, 5 mmol) and triethylamine (0.70 mL, 5 mmol) in 30 mL of anhydrous EtOAc was added in small amounts bis(*p*-nitrophenyl)-phosphoryl azide[8] (1.84 g, 5 mmol). The reaction mixture was stirred for about 2 h and the precipitated triethylammonium salt of the phosphoric acid byproduct was filtered off. The EtOAc solution was washed with ice water twice, dried over $MgSO_4$, and concentrated in vacuo to yield a semisolid residue which, by IR, was a mixture of both acyl azide and rearranged isocyanate. The residue was suspended in 5 mL of toluene and was added to a solution of benzyl alcohol in (0.7 mL) in toluene (10 mL) kept at 100–110 °C. Vigorous gas evolution was observed. The mixture was heated at the same temperature for 1.5 h and stirred overnight. The toluene was removed in vacuo and the residue heated in vacuo at 65 °C to remove the last traces of benzyl alcohol to yield 0.68 g (42%) of **1-benzyloxycarbonylamino-1-*tert*-butoxycarbonylamino-2-methylpropane.**

NMR (Me_2SO-d_6): δ 1.0 (d, *J* = 7 Hz, each peak doubled with Δδ = 1 Hz, 6 H), 1.5 (s), 1.9–2.2 (br, m; integral of previous two signals totals 10 H), 4.7–4.9 (br m, overlapping residual H_2O in Me_2SO), 5.20 (s, 2 H), 7.45 (s, 5 H).

A solution of this compound (0.5 mmol) in 10 mL of absolute ethanol containing 1 equiv of HCl and 20 mg of Pd on charcoal was stirred under H_2 atmosphere for 1 h. The reaction mixture was filtered, and the ethanol was removed in vacuo at low temperature. The residue was lyophilized and precipitated from ethanol with ether to yield **3** (16 mg, 14%).

NMR (Me_2SO-d_6): δ 0.95 (two doublets, *J* = 7 Hz, Δδ = 2 Hz, 6 H), 1.43 (s, 9 H), 2.1 (br m, 1 H), 4.5 (br, 1 H), 7.9 (br, 1 H), 8.5 (br, 3 H).

This material was quite unstable on storage, and the NMR spectrum showed increasing evidence of decomposition to *tert*-butyl carbamate and isobutyraldehyde (from reaction with residual water in the Me_2SO) with time.

Kinetic Procedures. Kinetic studies were carried out spectrophotometrically by following the appearance of isobutyraldehyde at 286 nm on a Cary Model 1605 spectrophotometer. The ionic strength was maintained at 2.0 using KCl, and the concentration of starting material was about 5×10^{-3} M. Reactions were initiated by adding the solid amine hydrochloride to the cuvette containing the preequilibrated buffer solution at the appropriate temperature. The pH values of the buffers were checked on a Radiometer Model 26 pH meter before and after the reaction, and the buffer solutions during the pH measurement were maintained at the temperature of the kinetic determination. Rate constants, absorbance values at time zero, and absorbance values at infinite time were estimated from a plot of the data using the method of Kézdy et al.,[29] and these numbers were used as initial estimates in a nonlinear least-squares analysis of the absorbance vs. time data carried out on a Hewlett-Packard 9810A calculator using the technique of Wentworth.[12]

Except in cases in which buffer catalysis was investigated, buffer concentrations were maintained at 0.5 M in total buffer species. The buffers used (pH ranges), all in K^+ form, were as follows: formate (2.8–3.5), acetate (4.0–5.0), phosphate (5.6–8), *tert*-butylphosphonate[13,30] (7.8–8.5), and phosphate (10.5–11.0).

Product Studies. Hydrolysis of 2a. A solution of **2a** (0.5 mmol) in 6 mL of water at pH 8.0 was heated at 60 °C overnight, cooled, and extracted with ether. The ether extract was washed with brine and dried over $MgSO_4$. To the ether solution was added 8 mL of 2,4-dinitrophenylhydrazine reagent and the solution was concentrated in vacuo. The

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(30) Preparation and physical properties of this material followed Crofts, P. C.; Kosolapoff, G. M. *J. Am. Chem. Soc.* **1953**, *75*, 3379.

residue was recrystallized from ethanol to yield the 2,4-dinitrophenylhydrazone of isobutyraldehyde (41%), mp 182–3 °C, (lit.[31] 179–86 °C).

The water layer from the ether extraction was concentrated to dryness and extracted with $CHCl_3$. Concentration of the $CHCl_3$ extracts yielded 61% of acetamide (mp 82 °C, lit.[32] 82.3 °C), whose NMR spectrum was identical with that of authentic material.

In another product study in the acidic pH region, compound **2a** (70 mg, 0.42 mmol) and benzoic acid (51 mg, 0.42 mmol, internal standard) were dissolved in 70 mL of dilute HCl to a final pH of 2.21. The final concentration of **2a** (6 mM) was comparable to that used in the kinetic studies. This solution was incubated at 60 °C for 8 h and then concentrated in vacuo. The residue was taken up in Me_2SO-d_6 and the acetamide singlet at δ 2.03 was integrated relative to the δ 8.0–8.3 part of the benzoic acid signal, which could be shown independently to be 36% of the total benzoic acid aromatic proton signal. (Other signals, probably due to the polymerization of the isobutyraldehyde during concentration, obscured the higher field portion of the benzoic acid signal.) The acetamide was found to be present in 106 ± 10% yield. Addition of acetic acid to the NMR tube served to show that acetamide and acetic acid singlets are clearly discernible, and therefore that the hydrolysis product is acetamide and not acetic acid. In a further control, isobutyraldehyde and benzoic acid were treated in the same manner and found not to give any interfering NMR signal in the δ 2 region.

It should be further noted that the absorbance developed in the reaction mixture as a function of time had a λ_{max} corresponding to that of authentic isobutyraldehyde.

Cyanide Trapping Experiments during the Hydrolysis of 2a. Compound **2a** (100 mg, 0.6 mmol) and NaCN (100 mg, 2.04 mmol) were heated together overnight in a phosphate buffer at 80–85 °C; the final pH of the solution was >9.0 because of the basic properties of CN^-. The reaction mixture was saturated with NaCl and extracted with $CHCl_3$. Concentration of the dried $CHCl_3$ extracts gave 35 mg of a liquid which was characterized as 2-amino-3-methylpropanenitrile (**6**). This identification was accomplished by spectral comparison with authentic material[33] and by hydrolysis in 6 N HCl (sealed tube, 110 °C, 21 h) to valine, which was identified by amino acid analysis. No valine was present unless the sample was first hydrolyzed. Preparations of the nitrile either during the hydrolysis of **2a** or de novo[33] always yielded material which was accompanied by a small amount of an impurity which was separated on preparative gas chromatography, and appears to be a dimer of the nitrile of as yet unidentified structure. This material does not hydrolyze to valine.

Control experiments were carried out to investigate whether the cyano amine **6** isolated from the hydrolysis of **2a** is a kinetic product of the reaction or a secondary product of de novo synthesis from isobutyraldehyde, ammonia, and cyanide. These experiments are summarized in Table VI. In a hydrolysis experiment (H1, H2, H3), 0.075–0.3 mmol (different concentrations in each experiment; an equal amount of NH_4Cl and 2.04 mmol of NaCN were added to 10 mL of a potassium phosphate buffer (pH 11, μ = 2.0 M (KCl)) in a serum-capped tube. The reaction tubes were incubated at 60 °C for 8 h and extracted with EtOAc (5 × 10 mL). The extracts were combined, dried (K_2CO_3), and concentrated in vacuo. An appropriate aliquot of the residue was subjected to 6 N HCl hydrolysis (110 °C, sealed tube, 22 h) and subjected to amino acid analysis. Control experiments (C1, C2, C3) were carried out in an identical manner except that isobutyraldehyde was substituted for **2a**. Valine was quantitated in an appropriate aliquot of the hydrolysate and taken as a measure of the cyanoamine **6** formed. Table VI shows that the valine found in the control is 19 ± 6% of that found in the hydrolysis.

For trapping under acidic conditions, a solution of KCN (195 mg, 3 mmol) in 5 mL of a 0.5 M acetate buffer (initially pH 4.69) was adjusted to pH 4.5 by addition of glacial acetic acid. Compound **2a** (100 mg, 0.6 mmol) was added and the reaction mixture was stirred at 60 °C for 24 h. The reaction mixture was taken to pH 10 with KOH and extracted with $CHCl_3$. The combined $CHCl_3$ extracts were washed with brine, dried, and concentrated in vacuo to yield a brown liquid (87%), identified as isobutyraldehyde cyanohydrin by comparison with an authentic sample.[34]

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Perchlorate Esters. 4. Kinetics and Mechanism of the Reactions of Alkyl Perchlorates with *N,N*-Dimethylanilines in Benzene[1,2]

Dennis N. Kevill* and Betty W. Shen

Contribution from the Department of Chemistry, Northern Illinois University, DeKalb, Illinois 60115. *Received December 29, 1980*

Abstract: The reactions in benzene of methyl, ethyl, and isopropyl perchlorates with *N,N*-dimethylanilines, to yield precipitates of the quaternary anilinium perchlorate, proceed with second-order kinetics and exhibit a large negative entropy of activation. At 25.0 °C, Hammett ρ values of −3.05, −2.86, and −2.78, respectively, indicate appreciable bonding to the nitrogen within the transition state. In reaction with methyl perchlorate, the *p*-cyano and *p*-nitro derivatives require values intermediate between σ^n and σ^- and a ρ' parameter (as defined by Young and Jencks) of −1.58 is indicated. The *p*-nitroso derivative reacts considerably faster than one would predict, and it is proposed that the nucleophilic center is the oxygen rather than the nitrogen. In reaction with *N,N*-dimethylaniline at 25.0 °C, comparison of methyl perchlorate with methyl-d_3 perchlorate leads to a k_H/k_D value of 0.94_2, and comparison with methyl iodide leads to a k_{MeOClO_3}/k_{MeI} ratio of 1170. The present results are considered together with earlier studies using methyl iodide, and mechanistic implications are discussed.

Studies of the kinetics of the Menschutkin reactions of alkyl iodides with *N,N*-dimethylanilines in a variety of organic solvents[3–11] have been important in the development of the Hammett equation. Because iodide is only a moderately good leaving group,[12,13] these reactions have usually been carried out at elevated

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