# Hydrolysis of *N*-(1-Aminoalkyl)amides

By G. Marc Loudon* and James Jacob

(*Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, Indiana* 47907)

Summary   The hydrolysis of the title compounds involves the expulsion of an amide anion as a leaving group at basic pH, and probably an amide enol (imidoacid) as a leaving group at acidic pH.

$$R^1C(:O)NHCHR^2NR^3{}_2$$

(1)
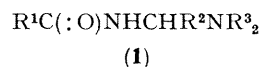
a; $R^1 = Me$, $R^2 = Pr^i$, $R^3 = H$
b; $R^1 = Bu^t$, $R^2 = Pr^i$; $R^3 = H$
c; $R^1 = Me$, $R^2 = Pr^i$, $R^3 = Me$

Compounds of type (1) are of interest because of their use as peptide protecting groups,[1] amino termini in retro-inverso peptides,[2] intermediates in carboxy-terminal peptide degradations,[3] and α-aminoalkyl cation synthons.[4]   Although their nature as masked aldehydes might lead one to expect that they would be hydrolytically unstable, the stability of such compounds is in fact such that many may be isolated from aqueous solution.   We here report the first study of the mechanism of hydrolysis of these compounds; the mechanism appears to involve the conjugate base anion of an amide as a leaving group in a solvolysis reaction.

The pH–rate profiles for the hydrolysis of both (**1a**) and (**1c**) (Figure)[5] indicate plateaus in both the acid and base pH regions; the profile is quantitatively fitted by equation (1) in which k_ψ is the observed rate constant, and $H = 10^{-pH}$.

$$k_\psi = k_A[H/(K+H)] + k_B[K/(K+H)] \qquad (1)$$

The hydrolytic mechanism is conveniently discussed in terms of the phenomena observed in the acidic and basic plateaus of the pH–rate profile, respectively.   The K in equation (1) for (**1a**), pK = 7.33 ± 0.14, may be identified with the K_a for the conjugate acid of (**1a**), p$K_a = 7.13$
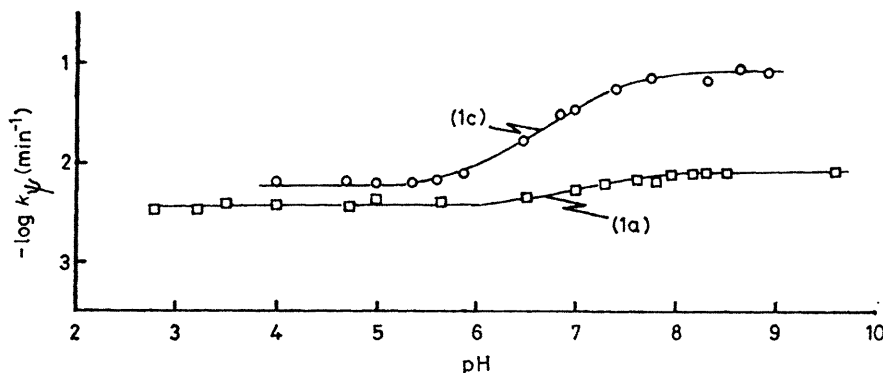

Figure.   The pH dependence for the hydrolysis of compounds (**1a**) (at 45 °C) and (**1c**) (at 60 °C).   The hydrolysis was followed in water, ionic strength 2·0 (KCl) mol dm⁻³, by observing the appearance of isobutyraldehyde spectrophotometrically at 286 nm.   The points are observed, and the lines are calculated, for a nonlinear least-squares fit to equation (1).

$\pm$ 0·07. The products in all regions of pH are isobutyraldehyde and acetamide [for (**1a**) and (**1c**)] or t-butyl carbamate [for (**1b**)]. If CN^- is included in the hydrolysis reaction mixture in basic solution, the product from (**1a**) is the cyanoamine $Pr^iCH(NH_2)-CN$, suggesting the intermediacy of isobutyraldehyde imine. At all pH values, the polarimetric rates for the hydrolysis of (**1a**) are essentially identical to the spectrophotometric rates, a point which rules out rapid reversible formation of trigonal proacyl carbon. In the basic region of pH, changing the leaving amide (**1a**)→(**1b**) results in a 248-fold rate enhancement; in the acidic region, the corresponding increase is a factor of 9·2. In the basic region, the change (**1a**)→(**1c**) results in a 92-fold rate enhancement; the corresponding change in the acidic region is a factor of 11. In the basic region, the activation entropies are $+16$ and $+34$ J K^{-1} mol^{-1} for (**1a**) and (**1c**), respectively, suggesting a dissociative process. In the acidic region, the corresponding activation entropies are $+1$ and $+3$ J K^{-1} mol^{-1}, respectively. Finally, no catalysis by added external buffers is observed at any pH for any compound.

The mechanism shown in equation (**2a**) fits all the facts. In particular, a cyclic proton transfer mechanism [equation (3)] appears to be ruled out by the more rapid reaction of (**1c**), for which such a mechanism is not available.

For hydrolysis in the acidic region, an equilibrium proton transfer followed by a mechanism [equation (**2b**)] analogous to that shown in equation (**2a**) is attractive, although a cyclic mechanism analogous to that shown in equation (3) (with an additional proton on the amino nitrogen) cannot be strictly ruled out.

An interpretation of the data in the basic region with reasonable estimates for the pK_a values of the leaving

amides[6] gives a β_{lg}† of about unity, a point which suggests that bond breaking is nearly complete in the transition state.

Several conclusions are immediately clear from the data. As the leaving amide anion is made less basic, compounds of type (**1**) will become less stable toward hydrolysis. One can estimate an approximate half-life for the retro-inverso peptides (R^3 = alkyl) of about 10—50 h at 25 °C on this basis. The stability of such compounds can be clearly attributed to the poor leaving group (an amide anion) in the basic region, and to the requirement for a highly unfavourable equilibrium prior to hydrolysis in the acidic region.

(Received, 30th November 1979; Com. 1248.)

† β_{lg} is equal to $(-\Delta\log k/\Delta pK$, where k denotes k_A or k_B, and K is the dissociation constant of the conjugate acid of the leaving group.

[1] P. M. Hardy and D. J. Samworth, *J.Chem. Soc. Perkin Trans. 1*, 1977, 1954.
[2] M. Goodman and M. Chorev, *Acc. Chem. Res.*, 1979, **12**, 1.
[3] M. E. Parham and G. M. Loudon, *Biochem. Biophys. Res. Commun.*, 1978, **80**, 1,7.
[4] H. E. Zaugg and W. B. Martin, *Org. React.*, 1965, **14**, 52.
[5] Synthesis of (**1a**), for example, can follow our methodology: A. S. Radhakrishna, M. E. Parham, R. M. Riggs, and G. M. Loudon, *J. Org. Chem.*, 1979, **44**, 1747.
[6] F. G. Bordwell, J. E. Bartmess, and J. A. Hautala, *J. Org. Chem.*, 1978, **43**, 3095.