J. Am. Chem. Soc. **1998,** *120,* 7101−7102

Communications to the Editor

Spontaneous, Millisecond Formation of a Twisted Amide from the Amino Acid, and the Crystal Structure of a Tetrahedral Intermediate

Anthony J. Kirby,* Igor V. Komarov,[†] and Neil Feeder

University Chemical Laboratory
Cambridge University
Cambridge CB2 1EW, UK

Received March 3, 1998

We recently reported the preparation of the 1-aza-2-adamantanone **1** and the unsurprising observation that when dissolved in water it is rapidly hydrolyzed to the ring-opened amino acid **2** (Scheme 1).[1] More remarkably, at pD 3.30 the solution in D_2O showed a ^{13}C NMR peak at 106.3 ppm, assigned "with some confidence" to the orthoamide carbon of the protonated hydrate **3**. Such structures are presumed short-lived, high-energy intermediates in the acid-catalyzed hydrolysis of normal amides.[2] We now report confirmation of the structure of **3**, in the shape of a crystal structure, and the extraordinary reactivity of the amino acid $\mathbf{2}^{\pm}$; which is converted to **3** at NMR rates at acidic pH in water and back to **1** in neutral methanol. In this system, proximity makes carboxylate an effective intramolecular acylating agent.

Compound **3** is indeed stable in aqueous solution at low pH: it could be isolated, simply by dissolving the twisted amide **1** in 0.1 M HCl and evaporating to dryness. The crystal structure[3] (Figure 1) shows the significant lengthening of the $C-N^+$ bond (1.552(4) Å), the related shortening of the two C−O bonds (1.382(4) Å) at the anomeric center, and the conformation about these C−O bonds expected for a normal anomeric effect.[4] The structural parameters are otherwise unremarkable.

When the solution of the amino acid $\mathbf{2}^{\pm}$ (formed over a few minutes by dissolving **1** in water) is acidified, it is completely converted into **3**, faster than we can record the high-field NMR spectrum (<30 s). In D_2O at pD 4.28 and 25 °C, $\mathbf{2}^{\pm}$ and **3** are both present, as shown by their characteristic ^{13}C and ^{1}H NMR spectra. On warming this solution, corresponding proton peaks broaden and then coalesce. The rate constant calculated for the equilibration at the coalescence point (60−63 °C, N^+-CH_2 signals) is 280 s^{-1}. This is quite extraordinarily fast for the formation of such a species from the zwitterionic form of an amino acid. It is not possible to derive an accurate effective molarity (EM),[5] because the corresponding intermolecular reaction is too slow to be observed. However, the mechanism should be relatively straightforward (Scheme 2), and we can make a rough estimate,[6] of 10^{11} to 10^{12} M, based on the intermolecular reaction of a secondary amine with a methyl ester.

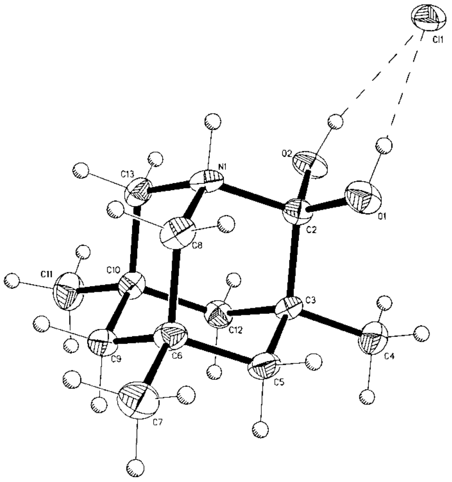
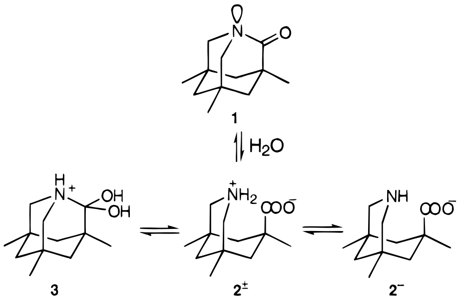
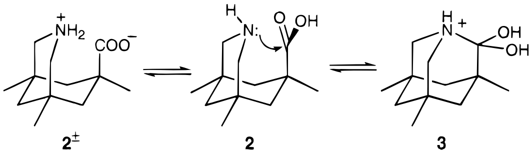


Figure 1. Molecular structure of **3** (ORTEP, ellipsoids are drawn at the 30% probability level).

Scheme 1



Scheme 2



At pHs where **2** is present as the zwitterion, $\mathbf{3}/\mathbf{2}^{\pm}$ will be in equilibrium also with small amounts of the twisted amide **1** itself. Not surprisingly, **1** cannot be observed in water, except during the few minutes it takes to disappear when dissolved in neutral

---

[†] Permanent address: Chemistry Department, Organic Chemistry Chair, Taras Shevchenko University, Kiev 252033 Ukraine.

(1) Kirby, A. J.; Komarov, I. V.; Wothers, P. D.; Feeder, N. *Angew. Chem., Intl. Ed. Engl.* **1998**, *37*, 785−786.

(2) Brown, R. S. *Acc. Chem. Res.* **1992**, *25*, 481−488. Protonated hydrates such as **3** are particularly readily formed from twisted amides. See, for example: Werstiuk, N. H.; Brown, R. S.; Wang, Q. *Can. J. Chem.* **1996**, *74*, 524−532.

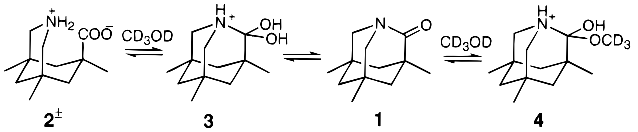
(3) For **3**: colorless crystal, monoclinic, space group $P2_1/n$, $a = 7.800(7)$ Å, $b = 13.441(8)$ Å, $c = 12.494(8)$ Å, $\beta = 100.00(6)°$, $V = 1290(2)$ Å^3, $Z = 4$, $R = 0.08$, goodness of fit on F^2 1.320. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre (CCDC Registry no. 101155). Copies of the data can be obtained free of charge on application to The Director, CCDC, 12, Union Road, Cambridge CB2 1EZ, UK (GFax: int. code + (1223) 336-033).

(4) Jones, P. G.; Kirby, A. J.; Komarov, I. V.; Wothers, P. D. Work to be published. These authors will discuss the relevance of a closely related system to the existence or nonexistence of the reverse anomeric effect. The normal anomeric effect conformation observed with **3** is reinforced by the steric effect of the C−Me group adjacent to the orthoamide but not imposed by hydrogen bonding: though the two OH protons are H-bonded to the chloride counterion, the ^+N-H proton forms a hydrogen bond to a second chloride anion.

(5) Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 183−278.

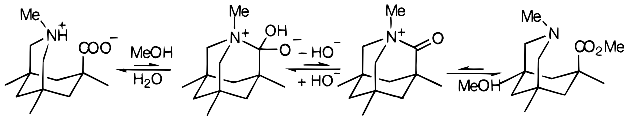
(6) The EM calculation is based on the intermolecular reaction of methyl formate with a six-membered cyclic secondary amine of pK_a 10.6, extrapolated from the measured rate constant for morpholine and an acceptable linear free energy relationship.[7] The estimated second-order rate constant of 0.1 $M^{-1}\,s^{-1}$ is compared with the observed rate constant for the formation of **3** of 280 s^{-1} at 63 °C, corresponding to, at most, 5 s^{-1} at 25 °C (using $E_a = 20$ kcal mol^{-1}). The ratio (50) has then to be corrected by factors of 10^6 for the preequilibrium formation of neutral **2** (Scheme 2), a conservative 10^3 for the lower intrinsic reactivity of a cyclohexane carboxylate compared with a formate ester [8] and a further order of magnitude to allow for the higher intrinsic reactivity of COOH compared with an ester group (figure[9] based on acid-catalyzed ^{18}O-exchange): a factor of 10^{10} in total, giving an estimated EM of $>5 \times 10^{11}$M.

D_2O. But it is present, in substantial amounts at equilibrium, in methanol. When the amino acid zwitterion **2**$^{\pm}$ is dissolved[10] in methanol-d_4, its NMR signals disappear with a half-time of ∼30 min at the probe temperature of 23 °C. NMR spectra show the appearance of two products, in a 4:1 ratio: the twisted amide **1** (20%) and a second, major product corresponding to **3**. We presume that this is the protonated hemiacetal **4** (though the NMR data do not exclude the possibility that it is the corresponding dimethyl acetal).



2$^{\pm}$ **3** **1** **4**

Much more reactive than **1** is its *N*-methyl derivative ($^{+}$**NMe-1**), made by reacting **1** with Meerwein's reagent.[1] Nevertheless, even this *N*-methylated amide is formed, as an intermediate, from the ring-opened *N*-methyl amino acid. Thus, when the zwitterion **NMe-2**$^{\pm}$ is dissolved[10] in methanol, it is converted, slowly (half-life 31 h), into the methyl ester **6**. The first step corresponds no doubt to that of Scheme 2, but the *N*-methylated intermediate **5**, unable to lose a proton from N, reverts almost exclusively to **NMe-2**$^{\pm}$. The much slower loss of hydroxide generates $^{+}$**NMe-1**,[11] which is rapidly solvolysed to the ester **6**.



NMe-2$^{\pm}$ **5** $^{+}$**NMe-1** **6**

The thermodynamic driving force which brings **2**$^{\pm}$ into close equilibrium with such normally high-energy species as **1**, **3**, and **4** is derived from steric strain in the bicyclic system, relieved when the third axial substituent is incorporated into the azaadamantane structure. It seems that the three C-methyl groups make a significant contribution to this driving force: the twisted amide is formed much less readily when only one CH_3 (α to the C=O group) is present.[12] Significantly, when the thermodynamics are favorable for the formation of the C−N bond, the kinetic barriers to amide formation and hydrolysis are seen to be very small.

Acknowledgment. I.V.K. gratefully acknowledges the award of a Royal Society-NATO Postdoctoral Fellowship for 1997.

Supporting Information Available: Experimental instructions for the synthesis and characterization of **3** and tables of crystal data, structure solution and refinement, atomic coordinates, bond lengths and angles, and anisotropic thermal parameters for **3** (9 pages print/PDF). An X-ray crystallographic file, in CIF format, is available via the Web only. See any current masthead page for ordering information and Web access instructions.

JA980700S

---

(7) Blackburn, G. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1968**, *90*, 2638−2645.

(8) Based on second-order rate constants for alkaline hydrolysis taken from Siegel (Siegel, S.; Komarmy, J. M. *J. Am. Chem. Soc.* **1960**, *82*, 2547−2551) and Kirby (Kirby, A. J. In *Comprehensive Chemical Kinetics*; Bamford, C. H., Tipper, C. F. H., Eds.; Elsevier: Amsterdam, 1972; Vol. 10, pp 57−208.

(9) McClelland, R. A.; Somani, R.; Kresge, A. J. *Can. J. Chem.* **1979**, *57,* 2260−2267.

(10) The zwitterion **2**$^{\pm}$ was isolated by careful evaporation to dryness of the aqueous solution under reduced pressure (rotary evaporator then over P_2O_5 in a vacuum desiccator). **NMe-2**$^{\pm}$ was prepared in the same way. ^1H and ^{13}C NMR spectra in $CDCl_3$ showed no detectable amounts of recyclization. (**1** is formed from **2**$^{\pm}$ only on prolonged heating at 100 °C in vacuo[1]).

(11) Tertiary amines react with esters with poor (alkoxide) leaving groups over 10^5 times less readily than secondary, for the same reason (Fersht, A. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1970**, *92*, 5442−5452).

(12) A. J. Kirby and I. V. Komarov, unpublished work.