Strong Hydrogen Bonding to the Amide Nitrogen Atom in an “Amide Proton Sponge”: Consequences for Structure and Reactivity**

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The carbonyl oxygen atom of the amide functional group is universally believed to be the thermodynamically preferred site of protonation in amides,[1] however, N protonation has been proposed to play a key role in biologically important reactions of peptides and proteins such as acid-catalyzed peptide hydrolysis[2] and cis–trans isomerization about the C–N bond.[3] Extensive research into the mechanism of acid-catalyzed amide hydrolysis has led to the belief that the O-protonated form is generally the important intermediate on the pathway to hydrolysis.[4] Still, evidence supporting N protonation in certain cases,[5] as well as in the related thiol-catalyzed amide hydrolysis reactions important in cysteine proteases,[6] has also been reported. N-Protonated amides have thus far eluded characterization, probably because they are disfavored thermodynamically relative to the O-protonated form by about 7 pK_a units in aqueous solution.[6] Even species showing strong hydrogen bonding between a donor and the amide N atom are unknown.[7] Herein we present the first spectroscopic and crystallographic characterization of a strong hydrogen bond between a charged donor (a protonated amine) and an amide nitrogen atom in a model system, and also disclose unusual reactivity of the amide functionality that stems from this interaction.

We designed system 1 in which a protonated amine group can act as a donor suitably positioned to engage in a strong intramolecular hydrogen bond with the amide nitrogen atom rather than with the carbonyl oxygen atom [Eq. (1)].[8] Compound 1 is based on the venerable “proton sponge” 2 whose exceptional basicity arises from destabilization in the free base due to electron–electron repulsion and also from formation of a strong intramolecular hydrogen bond upon protonation.[9] “Amide proton sponge” 1 is available in two steps from 1,8-diaminonaphthalene,[10] and we propose the isomeric 1,5-naphthalene 3 as a control compound to factor out through-bond inductive effects of the electron-withdrawing protonated amine.

The 1H NMR spectrum of 1a in [D_3]acetonitrile in the presence of one equivalent of trifluoromethanesulfonic acid (HOTf) displayed a broad signal due to one proton at δ = 11.0, whereas the analogous signal in control 3a under the same conditions appeared at δ = 9.4, a difference that hints at the presence of an intramolecular hydrogen bond between the protonated amine group and the amide N atom in 1a-H^+ [Eq. (1)].[11] Additional support for N coordination of a proton is provided by 13C NMR spectroscopy of 1a-H^+ in which the carbonyl carbon atom is 13C-labeled. Before addition of acid, labeled 1a shows amide carbonyl peaks at δ = 170.2 and 171.3 corresponding to both the cis and trans forms of the amide; however, upon protonation the peaks coalesced and shifted downfield to δ = 175.0,[12] consistent with the formation of a more ketone-like carbonyl group. The fact that both 1a and 3a are fully protonated by one equivalent of HOTf in acetonitrile is confirmed by UV/Vis spectroscopy.[13]

Evidence supporting hydrogen bonding to the amide N atom under these conditions was also obtained by means of IR spectroscopy. Upon protonation of 1a in [D_3]acetonitrile, the amide C=O stretch shifts + 47 cm^{-1} from 1637 to 1684 cm^{-1}. It has been previously proposed that a shift of this so-called amide I stretch to higher wavenumber is strong evidence for N coordination, if it could be validated that the peaks are correctly assigned.[13] To support our interpretation, we investigated 13C-labeled 1a under identical conditions and found that the 13C=O peak moves from 1597 to 1644 cm^{-1}, again a difference of + 47 cm^{-1}, confirming our assignment. Upon protonation of 3a, the C=O stretch undergoes a small shift of < 5 cm^{-1}, indicating that the + 47 cm^{-1} shift observed for 1a-H^+ is not due to inductive effects.

We also obtained the single-crystal X-ray structure of 1b-H^+(Figure 1) that clearly shows the hydrogen atom (H1A) placed between the amine nitrogen atom (N1A) and the amide nitrogen atom (N2A).[14] The N2A–H1A distance of 2.17 Å and the N2A–H1A–N1A angle of 136° in 1b-H^+ (as determined by isotropic refinement of H1A’s position) classifies the interaction as a moderately strong hydrogen bond by Jeffrey’s criteria.[15] Further evidence supporting the strong hydrogen bond was obtained by examination of the pyramidalization of the amide nitrogen atom (N2A) upon protonation and comparison to that of the free base 1b, whose X-ray structure was also solved.[16] As expected, 1b contains a planar amide unit, as characterized by summation of the three
valence angles around N2, $\Theta = 359.9^\circ$ (perfectly planar = 360\(^\circ\)), and the out-of-plane angle, $\alpha = 7.5^\circ$ (perfectly planar = 0\(^\circ\)).[13] On the other hand, 1b-H\(^+\) displays $\Theta = 349.4^\circ$ and $\alpha = 36.0^\circ$, values that correspond very closely to pyramidalized amides based on strained bicyclic systems.[17]

Thus, 1b-H\(^+\) is a rare case of a highly distorted amide whose pyramidalization is not the result of a strained backbone.

The first clue to the interesting reactivity of 1-H\(^+\) was discovered while we were attempting to obtain diffractable crystals of the hydrochloride salt of 1a. After bubbling anhydrous HCl through a solution of 1a in CH\(_2\)Cl\(_2\) for one minute and storing the test tube in the dark for three days, we did not observe crystallization but instead noted the presence of benzoyl chloride [Eq. (2)]. The conversion in this process was low, but when we performed the reaction in THF with gentle heating to 50\(^\circ\)C for 30 h, the reaction became quantitative based on recovery of 8-methylamino-1-dimethylaminonaphthalene hydrochloride 4-H\(^+\).[14] Under the same conditions control 3a is inert, underscoring the importance of the strategically placed hydrogen bond in 1a-H\(^+\).[15] To our knowledge, this is the only case where HCl reverts an amide to an acid chloride and amine salt, a transformation that can be thought of as the "reverse" of normal peptide bond formation.

A second novel reaction of 1 is the PhSH-mediated conversion to 4 and thioester 5 [Eq. (3)]. Upon heating 1a with 10 equivalents of PhSH in a thoroughly degassed 50/50 mixture of tBuOH/water under a nitrogen atmosphere in a pressure tube at 125\(^\circ\)C for 48 h, we observed 55\% conversion of 1a to 4, as indicated by HPLC analysis of the crude reaction.

The following control reactions were also run under identical conditions: 1) one equivalent of HOTf was added along with 1a and PhSH; and 2) control 3a was used instead as the substrate, both with 10 mol\% triethylamine and without. In each control there was no indication of any reaction, which suggests a mechanism in which a small amount of PhSH is deprotonated by 1a and the PhS\(^-\) subsequently attacks the amide carbonyl group to yield products. To our knowledge, this is the first example of the thiolysis of an unstrained, nonactivated amide under neutral conditions by a monofunctional thiol, and supports Brown’s mechanistic hypothesis that the thiol-mediated cleavage of amides is subject to rate-limiting proton transfer to a tetrahedral intermediate from a properly aligned general base.[19] The 1-PhSH system therefore appears to be a mimic for the active site of cysteine proteases in which Cys25 and His159 form a highly nucleophilic thiolate/imidazolium ion pair that is proposed to be the active species in these enzymes.[20]

In contrast to the results with HCl in organic solvents, the triflate salt of protonated amide 1a-H\(^+\) in aqueous solution showed a surprising lack of reactivity. In the presence of one equivalent of HOTf in a 50/50 mixture of EtOH/H\(_2\)O, 1a underwent no reaction, even when heated to 150\(^\circ\)C for 24 h in a pressure tube. The lack of reactivity in this case supports the hypothesis that the O-protonated form is the intermediate on the pathway to acid-catalyzed amide hydrolysis.[4] Further studies on the protonation of amide nitrogen atoms and the novel reactivity of amide sponges 1 are currently underway.[21]

Keywords: amides · hydrogen bonding · naphthalenes · proton sponges
The magnitude of the downfield shift of a hydrogen-bound proton is
See the Supporting Information for details.

[10] The observation that the resonances for the cis and trans isomers coalesce to one upon protonation is consistent with previous reports that predict a lower barrier to rotation about the C–N bond when an amide is N-coordinated to a Lewis acid. See, for example:

1988
Engl.
W. R. S. Steele, D. R. Winterman,
Saupe,
J. Am. Chem. Soc.
1997
19
112


[13] a) The unit cell consists of two molecules of 1b-H, two triflate counterions, and one molecule of water. X-ray crystal data for compound 1b-H1, grown by slow diffusion of Et2O into a solution of 1b-H1 in acetone: C8H7F2NO10s,a,b; M1 = 481.46; yellow block (0.30 × 0.26 × 0.21 mm), triclinic, P1, a = 12.5179(2); b = 12.9868(1); c = 14.3698(2) Å, α = 87.7221(1), β = 66.638(1), γ = 89.306(1), V = 2142.84(5) Å3, Z = 2, ρcosh = 1.492 Mg m−3, F(000) = 996, Siemens SMART Platform CCD, MoKα radiation, λ = 0.71073 Å, θ = 173.2° K, 10567 reflections collected, 715 independent reflections, structure solved by direct methods, difference Fourier synthesis, and full-matrix least-squares on F2 (SHELXL-V5.0). R1 = 0.0704, wR2 = 0.1688 for 4744 reflections; the hydrogen atoms on N1A and N1B were located in the Fourier difference map and refined isotropically, all other hydrogens were placed in ideal positions and refined as riding atoms: one of the triflate anions has significant disorder caused by a rocking motion. b) Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-1041229 (1b-H1) and CCDC-104130 (1b). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

[15] Jeffrey’s definition of a “moderately strong hydrogen bond” is insensitive of most biologically relevant interactions, such as the more common hydrogen bond mode available to amides wherein the oxygen atom is the acceptor; see: G. A. Jeffrey, An Introduction to Hydrogen Bonding, Oxford, New York, 1997, chap. 2.

[16] X-ray crystal data for compound 1b, grown by slow evaporation of Et2O: C12H16F3NO, M1 = 322.37; colorless block (0.25 × 0.20 × 0.20 mm), monoclinic, P21; a = 8.1257(2); b = 10.2495(3); c = 19.5690(6) Å, β = 90.305(1)°; V = 1635.18(8) Å3, Z = 4, ρcosh = 1.309 Mg m−3, F(000) = 680, Siemens SMART Platform CCD, MoKα radiation, λ = 0.71073 Å, θ = 173.2° K, 7755 reflections collected, 2819 independent reflections, structure solved by direct methods, difference Fourier synthesis, and full-matrix least-squares on F2 (SHELXL-V5.0). R1 = 0.0554, wR2 = 0.1196 for 2063 reflections; all hydrogen atoms were placed in ideal positions and refined as riding atoms; disorder was found in the position of the fluorine atom.[20]


[18] No transesterification products attributable to ring-opened THF were detected.


[21] We have recently demonstrated that sponge 1b-H1 undergoes dramatic intramolecular catalysis of amide isomerization in aqueous solution: C. Cox, H. Wack, T. Lectka, unpublished results.

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Mising from the phenylene topologies hitherto synthesized—linear, angular, and trigonal[12]—is the zigzag variant, exemplified by the title compounds 1a and 2a. These molecules are important as substructure models for the one-dimensional, zigzag phenylene polymer,[2] the two-dimensional all-carbon net based on the anti-kekulene motif,[1c, 2a, 3] and the three-dimensional carbon allotropes O4C8(C8)[4] and I2C120(archimedene).[3] They are also interesting as members of a family of phenylene isomers with different angularities, in particular in comparison to their angular relatives in which

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