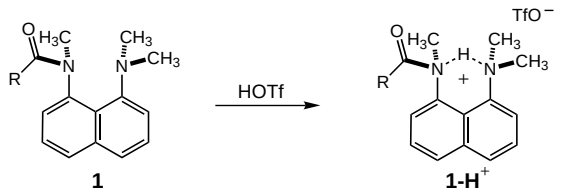
Strong Hydrogen Bonding to the Amide Nitrogen Atom in an "Amide Proton Sponge": Consequences for Structure and Reactivity**

Christopher Cox, Harald Wack, and Thomas Lectka*

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,[2] as well as in the related thiol-catalyzed amide hydrolysis reactions important in cysteine proteases,[5] 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.

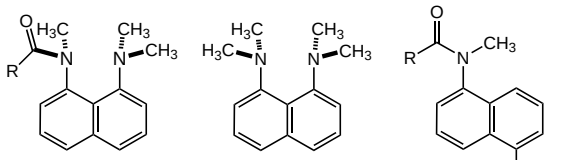
We designed system **1** in which a protonated amine group can act as a donor suitably positioned to engage in a strong intramolecular hydrogen bond with the amide nitrogen atom rather than with the carbonyl oxygen atom [Eq. (1)].[8] Compound **1** is based on the venerable "proton sponge" **2**



1 **1-H⁺** (1)

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 ^{1}H 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 $\delta = 11.0$, whereas the analogous signal in control **3a** under the same conditions appeared at $\delta = 9.4$, 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 ^{13}C NMR spectroscopy of **1a-H$^+$** in which the carbonyl carbon atom is ^{13}C-labeled. Before addition of acid, labeled **1a** shows amide carbonyl peaks at $\delta = 170.2$ and 171.3 corresponding to both the *cis* and *trans* forms of the amide; however, upon protonation the peaks coalesced and shifted downfield to $\delta = 175.0$,[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.[10]



1 **2** **3**

1a R = Ph
1b R = 2-FC$_6$H$_4$

3a R = Ph
3b R = 2-FC$_6$H$_4$

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 ^{13}C-labeled **1a** under identical conditions and found that the ^{13}C=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

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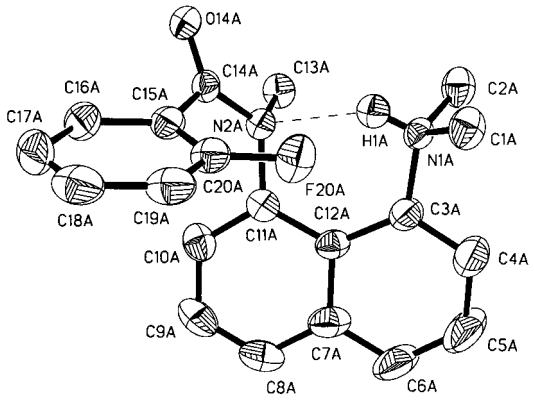
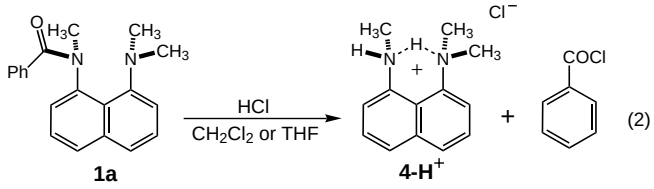


Figure 1. X-ray structure of the triflate salt of **1b-H**$^+$ (50% ellipsoids).[14] The unit cell consists of two molecules of **1b-H**$^+$, two triflate counterions, and one molecule of water. All hydrogen atoms, except for H1A, have been excluded for clarity. The dashed line indicates the proposed hydrogen bond between H1A and N2A. Selected bond lengths [Å] and angles [°]: N2A–H1A 2.17(4), N1A–N2A 2.869(5), C14A–N2A 1.369(5); N2A-H1A-N1A, 136(3)°.

valence angles around N2, $\Theta = 359.9°$ (perfectly planar = 360°), and the out-of-plane angle, $\alpha = 7.5°$ (perfectly planar = 0°).[17] On the other hand, **1b-H**$^+$ displays $\Theta = 349.4°$ and $\alpha = 36.0°$, 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.

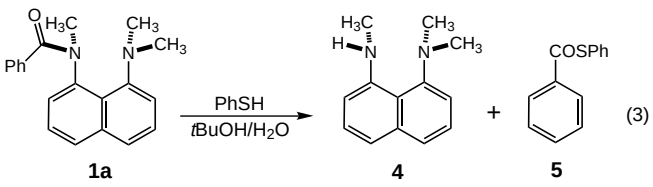
The first clue to the interesting reactivity of **1-H**$^+$ was discovered while we were attempting to obtain diffractable crystals of the hydrochloride salt of **1a**. After bubbling anhydrous HCl through a solution of **1a** in CH_2Cl_2 for one minute and storing the test tube in the dark for three days, we did not observe crystallization but instead noted the presence of benzoyl chloride [Eq. (2)]. The conversion in this process



(2)

was low, but when we performed the reaction in THF with gentle heating to 50 °C for 30 h, the reaction became quantitative based on recovery of 8-methylamino-1-dimethylaminonaphthalene hydrochloride **4-H**$^+$.[18] Under the same conditions control **3a** is inert, underscoring the importance of the strategically placed hydrogen bond in **1a-H**$^+$. 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 *t*BuOH/water under a nitrogen atmosphere in a pressure tube at 125 °C for 48 h, we observed 55% conversion of **1a** to **4**, as indicated by HPLC analysis of the crude reaction.



(3)

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 mimetic for the active site of cysteine proteases in which Cys 25 and His 159 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_2O, **1a** underwent no reaction, even when heated to 150 °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]

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[10] See the Supporting Information for details.

[11] The magnitude of the downfield shift of a hydrogen-bound proton is related to the strength of the bond; see: J. Emsley, *J. Chem. Soc. Rev.* **1980**, *9*, 91 – 125. No coupling was observed in **1a-H**$^+$ between the N-H proton and the methyl protons of the dimethylamino group, as is often noted for the protonated proton sponge **2**.[9]

[12] 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: a) C. Cox, T. Lectka, *J. Am. Chem. Soc.* **1998**, *120*, 10660 – 10668; b) C. Cox, V. G. Young, Jr., T. Lectka, *J. Am. Chem. Soc.* **1997**, *119*, 2307 – 2308; c) C. Cox, D. Ferraris, N. N. Murthy, T. Lectka, *J. Am. Chem. Soc.* **1996**, *118*, 5332 – 5333.

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[14] 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-H**$^+$, grown by slow diffusion of Et_2O into a solution of **1b-H**$^+$ in acetone: $C_{21}H_{21}F_4N_2O_{4.50}S$, $M_r = 481.46$, yellow block ($0.30 \times 0.26 \times 0.21$ mm), triclinic, $P\bar{1}$, $a = 12.5179(2)$, $b = 12.9868(1)$, $c = 14.3698(2)$ Å, $\alpha = 87.722(1)$, $\beta = 66.638(1)$, $\gamma = 89.306(1)^\circ$, $V = 2142.84(5)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.492$ Mg m^{-3}, $F(000) = 996$, Siemens SMART Platform CCD, $Mo_{K\alpha}$ radiation, $\lambda = 0.71073$ Å, $T = 173(2)$ K, 10567 reflections collected, 7152 independent reflections, structure solved by direct methods, difference Fourier synthesis, and full-matrix least-squares on F^2 (SHELXTL-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-104129 (**1b-H**$^+$) 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 inclusive of most biologically relevant interactions, such as the more common hydrogen bonding 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 Et_2O: $C_{20}H_{19}FN_2O$, $M_r = 322.37$, colorless block ($0.33 \times 0.24 \times 0.20$ mm), monoclinic, $P2_1/c$, $a = 8.1527(2)$, $b = 10.2495(3)$, $c = 19.5690(6)$ Å, $\beta = 90.305(1)^\circ$, $V = 1635.18(8)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.309$ Mg m^{-3}, $F(000) = 680$, Siemens SMART Platform CCD, $Mo_{K\alpha}$ radiation, $\lambda = 0.71073$ Å, $T = 173(2)$ K, 7755 reflections collected, 2819 independent reflections, structure solved by direct methods, difference Fourier synthesis, and full-matrix least-squares on F^2 (SHELXTL-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.[14b]

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

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

A Novel Phenylene Topology: Total Syntheses of Zigzag [4]- and [5]Phenylene**

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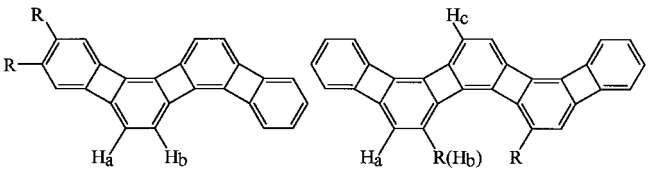
Missing from the phenylene topologies hitherto synthesized—linear, angular, and trigonal[1]—is the zigzag variant, exemplified by the title compounds **1a** and **2a**. These



1a, R = H
1b, R = $SiMe_3$

2a, R = H
2b, R = Ph
2c, R = Pr

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 O_h-C_{48}[4] and I_h-C_{120} (archimedene).[5] They are also interesting as members of a family of phenylene isomers with different topologies, in particular in comparison to their angular relatives in which

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