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Structural Characterization of N-Protonated Amides: Regioselective N-Activation of Medium-Bridged Twisted Lactams

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Although most amides are usually protonated on oxygen, amide N-protonation has nonetheless been proposed in a number of biologically relevant mechanisms,[1] including cis−trans peptide bond isomerization,[2] amide bond hydrolysis,[3] and protein splicing.[4] Although fundamentally different reactivity patterns are expected (and observed) to result from amide substitution,[5] the study of N-protonated amides has been hampered by the unavailability of molecules that contain them.

The characterization of N-protonated amides is challenging because such species are thermodynamically disfavored relative to their O-protonated isomers by ∼40 kcal/mol.[1] To date, examples of isolated and otherwise unadorned N-protonated amides are severely limited to perpendicularly twisted 2-quinuclidone derivatives (Figure 1a).[6a−f] In addition, Lectka reported an elegantly designed N-protonated amide stabilized by the proximity of an additional tertiary amine (Figure 1b).[6g] To date, only two N-protonated amides have been characterized by X-ray crystallography.[7] Herein, we demonstrate that a series of medium-bridged N-protonated lactams can be readily prepared by acid treatment. This streamlined access to multiple lactam conjugate acids has permitted the full structural characterization of three N-protonated amides and provided the first experimental evidence showing that N-protonation of amide bonds results in a dramatic increase in pyramidalization around the C−N amide bond.[8] Our data also suggest that ∼50° distortion of amide bonds (where 0° corresponds to a planar amide and 90° to a fully orthogonal amide bond) is sufficient for effective N-protonation or -alkylation of lactams.

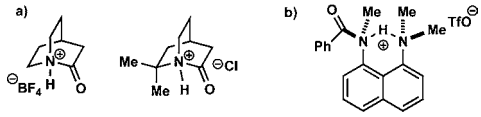
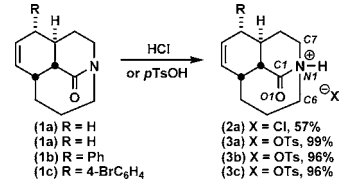


Figure 1. Previously reported examples of isolated N-protonated amides.

Recent efforts in this laboratory have provided ready access to a family of bridged lactams that are characterized by moderate amide bond distortion (twist values of 40−50°).[9] Such compounds display decidedly nontraditional amide bond reactivity patterns, including unusual cleavage reactions of a C−N σ bond adjacent to the amide bond.[9d−f] We hypothesized that these reactions take place via initial N-alkylation made possible by the increased basicity of the nonplanar amide nitrogen. The facility of these reactions suggested that it might be possible to isolate the responsible species by straightforward protonation or alkylation. Indeed, when tricyclic amides **1a**−**c** were exposed to mild acids, protonation took place at nitrogen to afford the corresponding stable salts in excellent yields (Scheme 1). The tosylates **3a**−**c** were crystalline, and their structures could be confirmed by X-ray crystallography (Figure 2). Table 1 summarizes the Winkler−Dunitz distortion parameters τ, χ_C, and χ_N (describing the magnitude of rotation around the N−C(O) bond, pyramidalization at carbon, and pyramidalization at nitrogen, respectively)[10] and bond lengths in the N-protonated lactams.

Scheme 1



Notably, the availability of the crystal structures of both **1c** and **3c** allowed the neutral amide and its conjugate acid to be easily compared. As expected, N-protonation of amide bonds enhances the pyramidal character at nitrogen (χ_N). The resulting change is substantial: from a moderately pyramidal to practically sp^3-hybridized nitrogen (in series **c**, χ_N increases from 36.1 to 52.1°). This is accompanied by flattening of the C═O carbon (in series **c**, χ_C drops from 12.8 to 1.4°) and a dramatic decrease in C−N bond planarity (τ is 81.9° in **2c** vs 51.5° in **1c**). The bond lengths were also influenced by N-protonation. The N−C(O) bond experiences significant lengthening (by 0.115 Å in **1c**), while the C═O bond is moderately shortened (by 0.026 Å in **1c**). Overall, these structural changes indicate substantial rehybridization upon N-protonation and C−N bond rotation, even in the fairly rigid tricyclic ring system of **1**.[8a,b]

Furthermore, the X-ray structures reveal that the N-protons are stabilized by hydrogen bonding to tosylate oxygens (Figure 2). The O1A−H1 (O3A−H1) distances of 1.79−1.82 Å and the N1−H1−O1A (N1−H1−O3A) angles of 163−177° are consistent with the presence of moderately strong hydrogen bonds. The bond distances

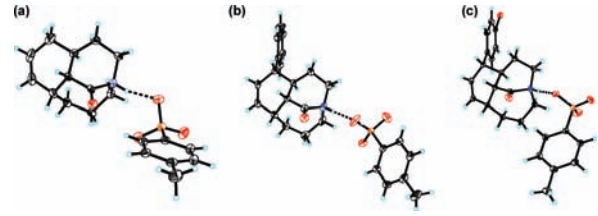


Figure 2. Crystal structures of (a) **3a**, (b) **3b**, and (c) **3c**. Selected bond lengths (Å) and angles (deg) in **3a**: N1−C1, 1.492(3); C1−O1, 1.202(4); C1−C2, 1.489(4); N1−H1, 0.93; C7−N1−C1−O1, −121.5(5); C6−N1−C1−O1, 111.1(5); C7−N1−C1−C2, 59.3(3); C6−N1−C1−C2, −68.2(3). In **3b**: N1−C1, 1.491(3); C1−O1, 1.197(3); C1−C2, 1.487(4); N1−H1, 0.86(4); C7−N1−C1−O1, −126.3(3); C6−N1−C1−O1, 106.2(3); C7−N1−C1−C2, 56.1(3); C6−N1−C1−C2, −71.5(3). In **3c**: N1−C1, 1.502(2); C1−O1, 1.192(2); C1−C2, 1.488(3); N1−H1, 0.89(3); C7−N1−C1−O1, −124.84(18); C6−N1−C1−O1, 107.21(19); C7−N1−C1−C2, 56.58(19); C6−N1−C1−C2, −71.38(19).

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Table 1. Summary of Structural Parameters of Amides and N-Protonated Amides

entry	amide (notes)	N−C(O) (Å)	C═O (Å)	χ_N (deg)	χ_C (deg)	τ (deg)
1[a]	**1c** (tricyclic)	1.387	1.218	36.1	12.8	51.5
2[b]	**1d** (bicyclic)	1.367	1.227	34.1	16.5	42.8
3	**3a** (N-protonated)	1.492	1.202	52.6	0.7	85.2
4	**3b** (N-protonated)	1.491	1.197	52.5	2.4	81.2
5	**3c** (N-protonated)	1.502	1.192	52.1	1.4	81.9
6[c]	**3d** (N-protonated)	1.526	1.192	59.5	0.2	90.9
7[d,e]	**1e** (formamide)	1.349	1.193	0.0	0.0	0.0

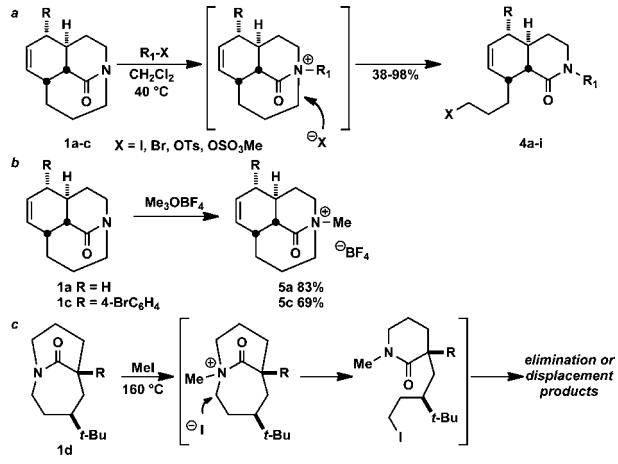
[a] Reference 9c. [b] Scheme 2c, R = 4-(MeO)C_6H_4. [c] **3d** = 2-quinuclidonium tetrafluoroborate, ref 6f. [d] Reference 8a. [e] Calculated.

between the amide nitrogens and tosylate oxygens in salts **3a**−**c** (2.68−2.72 Å) also support the formation of medium-strength hydrogen bonds engaging the amide nitrogen atoms.[11]

We previously reported that tricyclic lactams react with MeI to form the corresponding amidinium salts, which then undergo regioselective S_N2 displacement with iodide.[9e] As expected, similar chemistry was observed upon exposure of tricyclic amides to related electrophiles under mild conditions [Scheme 2a; see the Supporting Information (SI) for details]. In contrast, treatment with Meerwein's reagent, which lacks a nucleophilic counterion, permitted the isolation of two rare examples of N-alkylated amides (Scheme 2b).[12] Unfortunately, we were not able to obtain high-resolution crystal structures of these compounds.

Our attempts to similarly protonate or alkylate [4.3.1] bicyclic lactams such as **1d** revealed differences in reactivity between these species and their tricyclic cousins **3a**−**c** (Scheme 2c). For example, **1d** did not readily form a salt upon room-temperature treatment with acid or MeI. However, under forcing conditions, **1d** did afford products resulting from N-methylation followed by I^- displacement (Scheme 2c, R = Ph; see the SI for details). Control reactions confirmed that both the bridged structure and the alkylating agent were necessary for this reaction. Comparison of the twist parameters for the bicyclic and tricyclic lactams suggests that a twist angle of ≥50° is required for efficient N-protonation and N-alkylation of amide bonds,[8a,b] although a twist angle of ∼40° may be sufficient to result in N-alkylation under suitably vigorous conditions.

Scheme 2



In summary, this work has demonstrated that N-protonation of amide bonds results in a dramatic increase in distortion around the N−C(O) bond. Furthermore, even moderately distorted amide bonds participate in electrophilic N-activation of amides. Studies of general activation of amide bonds are underway.

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Supporting Information Available: Experimental details, characterization data for new compounds, and CIF files for **1d** and **3a**−**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Formation of the N-protonated amides was also evident from changes in the ^{13}C NMR and IR spectra (see Table B in the SI for details).

(12) To the best of our knowledge, only three examples of isolated N-alkylated amides have been reported to date (see refs 6a, 6e, and 7b). In contrast to the current study, all of these lactams contained perfectly perpendicular amide bonds. For an elegant study of the methylation of quinuclidone derivatives, see: Werstiuk, N. H.; Brown, R. S.; Wang, Q. *Can. J. Chem.* **1996**, *74*, 524.

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