N–C Bond Activation

International Edition: DOI: 10.1002/anie.201600919
German Edition: DOI: 10.1002/ange.201600919

Structural Characterization of N-Alkylated Twisted Amides: Consequences for Amide Bond Resonance and N–C Cleavage

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Abstract: *Herein, we describe the first structural characterization of N-alkylated twisted amides prepared directly by N-alkylation of the corresponding non-planar lactams. This study provides the first experimental evidence that N-alkylation results in a dramatic increase of non-planarity around the amide N–C(O) bond. Moreover, we report a rare example of a molecular wire supported by the same amide C=O-Ag bonds. Reactivity studies demonstrate rapid nucleophilic addition to the N–C(O) moiety of N-alkylated amides, indicating the lack of n_N to $\pi^*_{C=O}$ conjugation. Most crucially, we demonstrate that N-alkylation activates the otherwise unreactive amide bond towards σ N–C cleavage by switchable coordination.*

Over the last three decades, twisted amides have emerged as valuable transition state mimics of numerous biologically relevant enzymatic reactions.[1–4] Studies have implicated N-coordination as a method to disrupt the amide bond resonance, where a suitable ligand activates the amide bond towards isomerization[5] or σ N–C bond cleavage.[6] The characterization of N-protonated amides represents a significant challenge because the O-protonated structure is more thermodynamically stable than the N-protonated one (e.g. formamide, 13.9 kcal mol^{-1});[7] to date only few structural examples of N-protonated amides have been reported (Figure 1 A).[8] There is an intrinsic bias favoring N-alkylation vs. O-alkylation by ca. 2.5 kcal mol^{-1} compared with N-/O-protonation affinities.[9] O-methylation of dimethylacetamide is favored over N-alkylation by ca. 3 kcal mol^{-1}.[9] N-alkylation of amides plays a crucial role in a vast range of biologically relevant mechanisms,[10a–g] including enzymatic N-methylation of carboxamido groups,[10a] enzymatic N-alkylation of toxins,[10b] and N-alkylation of polypeptides;[10c] however, the study of N-alkylation of non-planar amides has been severely limited.[11] Alkyl groups exert a more stabilizing effect on the N–C(O) bond than H due to $\sigma_{C\text{-}H}$ to $\sigma^*_{N\text{-}C}$ hyperconjugation;[12] however, alkyl functions are also more sterically-demanding, which contributed to the formidable challenge in straightforward isolation of N-alkylated species.[11]

Recently, there has been a significant interest in the activation of N–C(O) amide bonds by selective metal insertion into the N–C(O) bond.[13] To date, the vast majority of these transformations involve a ground-state amide distortion[14] such as twisted cyclic imides reported by our group[14a,b,g,h] and acyclic twisted imides reported independently by Zou[14c] and Garg,[14d,e] where N-coordination[7f,g] is believed to activate the amide bond towards metal insertion (Figure 1 B). Moreover, while deuterium labeling has been used to investigate mechanisms of amide bond activation,[6a] the NH proton undergoes exchange. Thus, a straightforward access to N-alkylated amides would shed light on the mechanistic details of the N–C bond activation reactions.

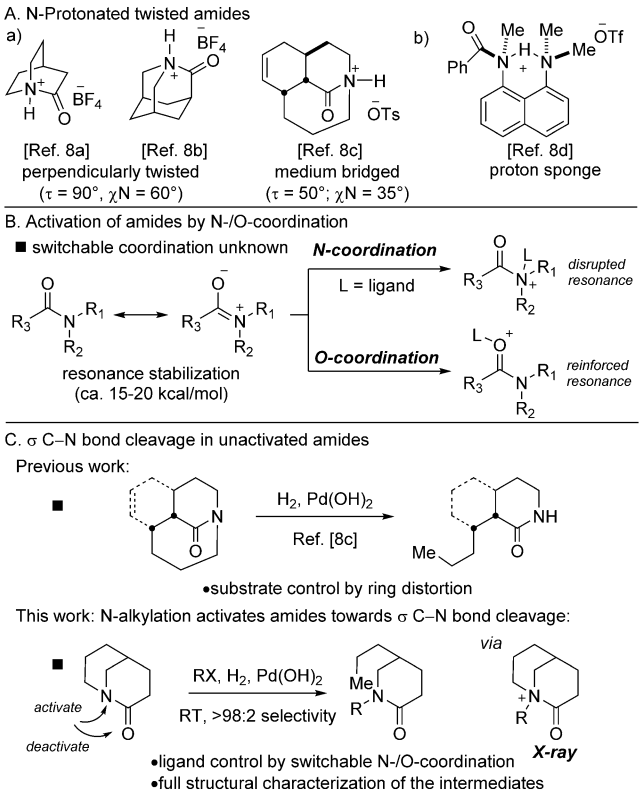

Figure 1. A) Previously reported examples of structurally-characterized N-protonated amides. B) Activation of amides by N-/O-coordination. C) This work: the first structural characterization and N–C cleavage of N-alkylated twisted amides.

Herein, we demonstrate the first structural characterization of N-alkylated twisted amides prepared directly by N-alkylation of the corresponding non-planar lactams. Most crucially, we demonstrate that N-alkylation activates the otherwise unreactive amide bond adjacent to N–C(O) towards amide σ C–N bond cleavage (Figure 1 C). This study provides the first experimental evidence that N-

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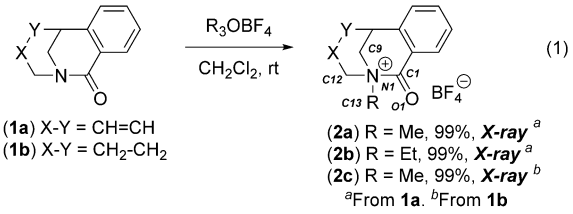
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under http://dx.doi.org/10.1002/anie.201600919.

alkylation results in a dramatic increase of non-planarity around the twisted N–C(O) amide bond. A direct comparison of neutral, N-protonated and N-alkylated amides in the same series of compounds is provided. We present a unique example of a molecular wire supported by the amide C=O–Ag bonds in the same amide scaffold. Reactivity studies demonstrate rapid nucleophilic addition to the N–C(O) moiety of N-alkylated amides, indicating the lack of n_N to $\pi^*_{C=O}$ conjugation. The mechanistic details have important implications for the amide bond resonance and the design of catalytic processes involving σ N–C bond activation.

The challenge of isolating N-alkylated non-planar amides is readily evident from the elegant studies by Brown[11] and Aubé[8c] on the reactivity of medium bridged lactams with alkylating reagents, in which susceptibility of the formed ammonium salts towards hydrolysis prevented the successful isolation and/or structural characterization. To begin to understand the role of amide bond twist and structural changes, we screened a series of non-planar amides using various alkylating reagents.[15] We were delighted to discover that twisted amide **1a** readily prepared via the intramolecular Heck reaction,[16] undergoes completely selective (N- vs. O-) alkylation at the nitrogen atom upon treatment with Meerwein's reagent containing a non-nucleophilic counterion, to afford the corresponding salt **2a** in quantitative yield [Eq. (1)].



(1)

The corresponding ethyl salt **2b** was also obtained in excellent yield, while the reaction of the fully saturated analogue **1b** (see below) demonstrated that the internal olefin is not required for the alkylation and stability. The N-alkylated products **2a**–**2c** were crystalline, and their structures could be unambiguously confirmed by X-ray crystallography (Figure 2). Table 1 summarizes the Winkler–Dunitz distortion parameters τ, χ_N and χ_C, and bond lengths of the N-alkylated lactams.[17] Notably, we also solved the crystal structure of the neutral amide **1a** (see Supporting Information (SI)). The availability of this structure allows ready comparison between the neutral amide and its N-alkylated salts. Furthermore, we have succeeded in the synthesis of N-protonated salts of **1a** using HBF_4 and $HSbF_6$. Both of these salts are thermally stable and give crystals suitable for structure determination (**3a**, **3b**, Figure 3, see SI and Table 1).

The structure of **2a** (N-Me salt) shows that N-methylation significantly enhances the pyramidal character of nitrogen (χ_N). The resulting change is substantial giving practically pyramidalized nitrogen of $sp^{2.97}$ (**2a**, χ_N increases from 49.7 to 58.3°). This is accompanied by a dramatic increase of N–C bond twist (**2a**, τ changes from 30.7 to 44.0°) and flattening of

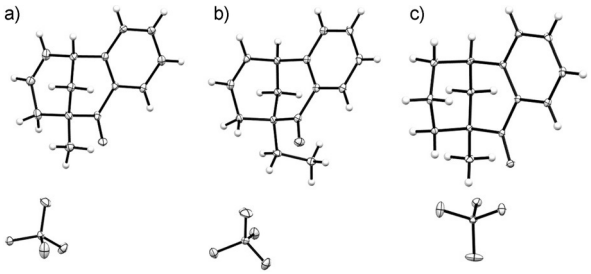


Figure 2. Crystal structures of a) **2a**, b) **2b**, and c) **2c**. Selected bond lengths (Å) and angles (deg) in **2a**: N1–C1 1.554(3), C1–O1 1.192(3), C1–C2 1.466(3), N1–C13 1.503(3); C9-N1-C1-O1 165.7(2), C12-N1-C1-O1 −72.6(3), C9-N1-C1-C2 −15.3(3), C12-N1-C1-C2 106.4(2). **2b**: N1–C1 1.546(2), C1–O1 1.192(2), C1–C2 1.467(2), N1–C13 1.521(2); C9-N1-C1-O1 168.6(1), C12-N1-C1-O1 −71.8(1), C9-N1-C1-C2 −11.6(2), C12-N1-C1-C2 108.0(1). **2c**: N1–C1 1.536(1), C1–O1 1.196(1), C1–C2 1.466(2), N1–C13 1.505(2); C9-N1-C1-O1 156.3(1), C12-N1-C1-O1 −83.0(1), C9-N1-C1-C2 −27.3(1), C12-N1-C1-C2 93.4(1).

Table 1: Summary of structural parameters.[a]

Entry	Amide	N–C(O) [Å]	C=O [Å]	χ_N [deg]	χ_C [deg]	τ [deg]
1	**1a**	1.386	1.226	49.7	7.1	30.7
2	**2a**	1.554	1.192	58.3	1.0	44.0
3	**2b**	1.546	1.192	60.4	0.2	41.7
4	**2c**	1.536	1.196	59.3	3.6	55.2
5	**3a**	1.522	1.201	55.2	0.9	42.8
6	**3b**	1.539	1.196	55.0	0.7	42.0
7	**4**	1.355	1.262	47.7	5.8	33.3
8	**1c**	1.349	1.193	0.0	0.0	0.0

[a] **1c**: Formamide, calculated values (Ref. [7a]).

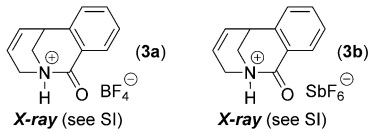


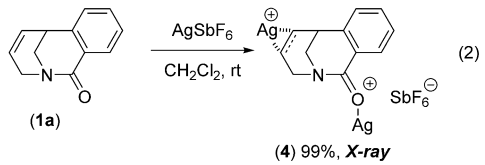
Figure 3. Structures of N-alkylated amides prepared by selective N-protonation of neutral amide **1a**.

the carbon atom (**2a**, χ_C decreases from 7.1 to 1.0°). The observed bond lengths in **2a** are N–CO bond length of 1.554 Å, and C=O bond length of 1.192 Å. This corresponds to a significant N–CO lengthening (by 0.168 Å) and a moderate shortening of the C=O bond (by 0.034 Å). Notably the N–CO amide bond length of 1.554 Å in **2a** is the longest recorded so far for an amide derivative.[18] Overall, the structural changes indicate that the amide bond in **1a** undergoes nitrogen rehybridization and bond rotation upon N-methylation.[8i]

The X-ray structure of N-protonated **1a** (**3a**, HBF_4 salt, see SI) reveals a N–C(O) bond distance of 1.522 Å and a C=O bond distance of 1.201 Å, which while still exceptional, clearly indicate that the amide bond in **1a** undergoes a smaller amide bond distortion upon N-protonation (cf. N-alkylation, **2a** and **2b**).[8a–d] Other distortion parameters in **3a** ($\tau = 42.8$; $\chi_N =$

55.2; $\chi_C = 0.9$) are in agreement with a less substantial amide bond rehybridization upon N-protonation.

We have also succeeded in the synthesis and full characterization of a rare O-coordinated silver salt of an amide bearing a single coordination site [Eq. (2)].[19]



(2)

Ligand coordination increases the rotational barrier (O-coordination) or disrupts the amide bond resonance (N-coordination).[20] Lectka[5a,b] and Bannwarth[5c,d] have reported studies on the role of Cu^{II} on the amide bond resonance with multiple binding sites. To date, the effect of N-/O-switchable metal coordination on the properties of amides has not been documented. The observed lengths of the N–C(O) bond in **4** are 1.355 Å, while the length of the C=O bond is 1.262 Å (Figure 4). Thus, N–C(O) experiences moderate shortening

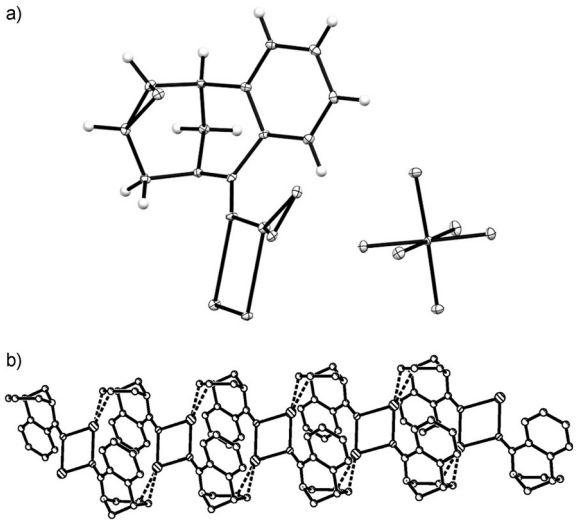
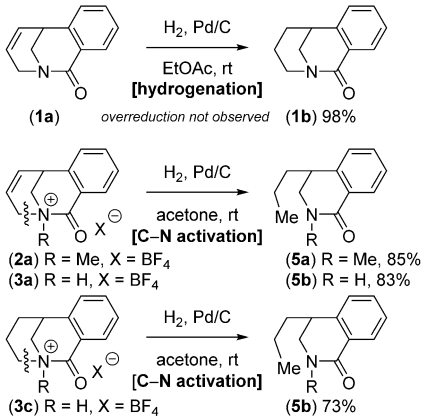


Figure 4. Crystal structure of **4**. a) Single molecule. b) Part of an infinite chain. SbF_6 counterions are not shown. Selected bond lengths (Å) and angles (deg) in **4**: N1–C1 1.355(5), C1–O1 1.262(4), C1–C2 1.475(5), O1–Ag1 2.224(2), C10–Ag2 2.292(3), C11–Ag2 2.463(3), Ag1–F 2.785; C9-N1-C1-O1 173.5(3), C12-N1-C1-O1 −54.3(4), C9-N1-C1-C2 −12.4(5), C12-N1-C1-C2 119.9(3), N1-C1-O1-Ag1 −160.0(2), C2-C1-O1-Ag1 13.8(5), C9-C8-C10-Ag2 116.2(3), N1-C12-C11-Ag2 −68.6(3).

(by 0.031 Å), while C=O is significantly lengthened (by 0.036 Å) upon Ag-coordination in **1a**. These structural changes indicate substantial increase in the double bond character in **1a** upon O-coordination. Strikingly, **4** crystallizes as a one-dimensional wire, displaying infinite chain structure.[21] Ag^I bonds to two carbonyl oxygens from two molecules across a center of symmetry forming a planar parallelogram (104.29° (Ag-O-Ag), 75.71° (O-Ag-O)) with the silver atom stabilized by π-donation from the endocyclic olefin.[22] The O–Ag bond distance is 2.571 Å, which is in a good agreement with the previously reported bond distance for Ag–O bond in glycylglycine of 2.494 Å.[23] The C10–Ag and C11–Ag distances are 2.292 Å and 2.463 Å, which corresponds to olefin–Ag complexes (e.g. $[Ag(\eta^2\text{-}C_2H_4)_3]^+$ of 2.396 Å).[24,25] The propensity of amide **1a** to undergo quantitative N- or O-coordination with different ligands suggests that selective modification of the amide bond rotational barrier may be possible by using appropriate ligands.[5]

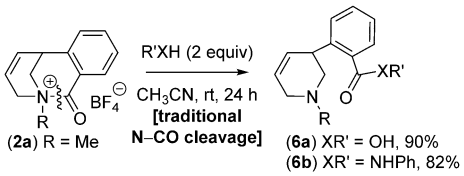
As expected, the chemical reactivity of N-alkylated amides is remarkable. Most notably, although the unactivated neutral precursor **1a** underwent clean hydrogenation under standard catalytic hydrogenation conditions (H_2, Pd/C, EtOAc), subjecting the N-methylated lactam **2a** to identical hydrogenation conditions afforded the sole product resulting from the cleavage of an otherwise unactivated σ C–N bond (Scheme 1).[6a] The reaction was completely regioselective



Scheme 1.

with respect to the C–N bond that is more distorted from the C=O π system. Moreover, the N-protonated lactam **3a** underwent the successful N–C hydrogenolysis, demonstrating that simple protonation is sufficient to trigger the N–C cleavage.[13b] The successful N–C hydrogenolysis of **5a** lacking an olefin, demonstrates that the internal olefin is not required for the reaction. Overall, these results unambiguously demonstrate that activation of the amide bond by N-coordination triggers novel reactivity of amides.

The N-methylated lactams react instantaneously at room temperature with standard nucleophiles resulting in fully regioselective cleavage of the amidic N–CO bond (structure unambiguously confirmed by X-ray crystallography of a derivative, see SI) (Scheme 2). For instance, the reaction of **2a** with 5 equiv of D_2O in CD_3CN gives a $t_{1/2}$ of 15.6 min, while the reaction of **2a** with 2 equiv of $PhNH_2$ in CD_3CN gives a $t_{1/2}$ of 12.5 min. The N-methylated **2a** is unstable to manipulations in common nucleophilic solvents such as DMSO or MeOH. By contrast, boiling of the neutral lactam **1a** in CH_3CN with H_2O (5 equiv, 100 °C, 24 h) or with $PhNH_2$ (2 equiv, 100 °C) affords only recovered starting material. These reactions



Scheme 2.

unambiguously demonstrate that N-coordination activates the amide linkage towards the nucleophilic opening.

In conclusion, the first structural characterization of N-alkylated twisted amides demonstrates that N-alkylation results in a dramatic increase of the amide bond distortion. A unique O-coordinated amide within the same amide provides insights into the effect of switchable N-/O-coordination. N-coordination triggers the amide bond towards catalytic cleavage of unactivated σ N–C bonds, which may find applications in biological contexts and metal catalyzed reactions of amides.

Acknowledgements

We acknowledge Rutgers University for financial support. The Bruker 500 MHz spectrometer used in this study was supported by the NSF-MRI grant (CHE-1229030). We also thank the Rutgers Research Council for financial support.

Keywords: amide bonds · N–C activation · N–C cleavage · N-coordination · twisted amides

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 5062–5066
Angew. Chem. **2016**, *128*, 5146–5150

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Received: January 27, 2016
Published online: March 8, 2016

