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J. Am. Chem. Soc., **Just Accepted Manuscript** • Publication Date (Web): 14 Dec 2017

Reversible Twisting of Primary Amides via Ground State N–C(O) Destabilization: Highly Twisted Rotationally-Inverted Acyclic Amides

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Supporting Information

ABSTRACT: Since the seminal studies by Pauling in 1930s, planarity has become the defining characteristic of the amide bond. Planarity of amides has central implications for the reactivity and chemical properties of amides of relevance to a range of chemical disciplines. While the vast majority of amides are planar, non-planarity has a profound effect on the properties of the amide bond, with the most common method to restrict the amide bond relying on the incorporation of the amide function into a rigid cyclic ring system. In a major departure from this concept, here, we report the first class of acyclic twisted amides that can be prepared, reversibly, from common primary amides in a single, operationally-trivial step. Di-*tert*-butoxycarbonylation of the amide nitrogen atom yields twisted amides in which the amide bond exhibits nearly perpendicular twist. Full structural characterization of a range of electronically-diverse compounds from this new class of twisted amides is reported. Through reactivity studies we demonstrate unusual properties of the amide bond, wherein selective cleavage of the amide bond can be achieved by a judicious choice of the reaction conditions. Through computational studies we evaluate structural and energetic details pertaining to the amide bond deformation. The ability to selectively twist common primary amides, in a reversible manner, has important implications for the design and application of the amide bond non-planarity in structural chemistry, biochemistry and organic synthesis.

Introduction

The amide bond represents one of the most vital functional groups in chemistry and biology.[1–3] As predicted by the Pauling's resonance theory,[4] the vast majority of amides are planar,[5] which has important implications for the reactivity (e.g. neutral hydrolysis of unactivated amides has a half-life of ca. 500 years),[6] structure (e.g. α-helix as a fundamental building block of proteins)[7] and chemical properties (e.g. vastly preferred O-protonation)[8] of amides. Extensive studies have shown that deviations of the amide bond from planarity greatly affect the stability and reactivity of amides.[9] Furthermore, amide bond twisting has been proposed as a central design element of enzymatic processes, including cis-trans isomerization,[10] amide hydrolysis[11] and protein splicing.[12] Recently, amide bond twisting has been demonstrated as a part of the mechanism in protein N-glycosylation involving primary carboxamide groups.[13] Moreover, recent work has implicated amide bond deformations as a controlling factor for selective amide bond activation/cross-coupling,[14] thereby emphasizing the role of amide bond twist as an enabling avenue in modern organic synthesis.[15]

The most common method to achieve amide bond twisting relies on the incorporation of the amide function into a rigid cyclic ring system (Figure 1A).[9a-c] These bicyclic bridgehead lactams feature extreme geometric properties of structurally-characterized amide bonds[16] (Winkler-Dunitz distortion parameters,[17] up to $\tau = 90°$, $\chi_N = 60°$). However, the synthesis of these lactams is notoriously challenging[1–3] due to severe diminution of amidic resonance (e.g. the landmark syntheses of the parent 2-quinuclidonium tetrafluoroborate[2] and 1-aza-2-adamantanone[16e] featured unique amide forming transforms), and typically this distortion method cannot be adapted to readily-available common acyclic amides.

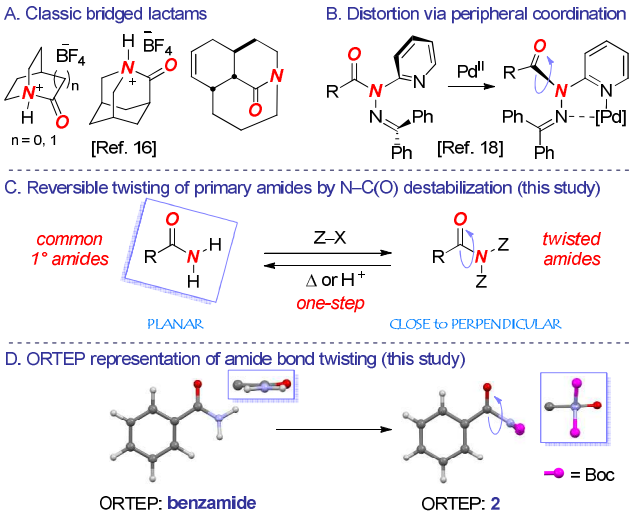


Figure 1. (a) Examples of highly distorted amides in cyclic frameworks (classic bridged lactams). (b) Amide distortion by peripheral coordination (Shibasaki et al.). (c-d) Reversible twisting of acyclic primary amides by ground-state N–C(O) destabilization (this study, insets show view along N–C(O) axis).

Recently, Kumagai, Shibaski et al. devised a new type of non-planar amides bearing predominantly pyramidalized amide bonds in which reversible deformation has been achieved by peripheral coordination of Pd(II) to Lewis basic nitrogen moieties (Figure 1B).[18] The method resulted in amides with remarkable deformations from planarity of up to χ_N = 56° and τ = 19°. However, the identification of peripheral coordination in these structurally intriguing amides renders the direct distortion of common acyclic amides more challenging. In addition, the emergence of specifically-tailored N-tetramethylpiperidine (TMP),[19] N-glutarimide[20] and N-1,3-thiazolidine-2-thione amides[21] has provided controlled access to non-planar amide bond geometries; however, these compounds are synthesized from the corresponding carboxylic acids and derivatives and often suffer from high susceptibility to hydrolysis as exemplified by TMP amides.[19]

With these considerations in mind, here, we report the first class of acyclic twisted amides that can be prepared, reversibly, from common primary amides[22] in a single, operationally-trivial step (Figure 1C-D). Amide bond distortion is triggered by selective di-*tert*-butoxycarbonylation of the amide nitrogen atom furnishing twisted amides in which the amide bond exhibits nearly perpendicular twist (up to τ = 82°). We report full structural characterization of a range of electronically-varied amides, and demonstrate through reactivity studies unusual properties of the amide bond in this new class of twisted amides, wherein selective cleavage of the N–C(O) or N–Boc bond can be achieved by a judicious choice of the reaction conditions. Through computational studies[23] we evaluate structural and energetic details pertaining to the amide bond distortion. We demonstrate that the amide bond deformation can be attributed to ground-state destabilization,[3] which results in the most twisted acyclic amide bonds reported to date.[1–3,9] Overall, our results demonstrate the ability to selectively induce twist of common primary amides, in a reversible manner, which may have broad implications for the design and application of non-planar amides in biochemistry, organic synthesis and molecular switching.[24]

Results and Discussion

Synthesis and Proof of Structure. Based on the experience in the chemistry of amides, we began our study by isolating N,N-di-Boc amides and growing single crystals of **2** (Figure 2). All amides **2** were prepared directly in one-step from the corresponding benzamides[25,26] by site-selective N,N-di-*tert*-butoxycarbonylation of the amide bond under mild conditions. It is worthwhile to point out that this widely-applicable process enables to directly engage common primary amides in amide bond twisting.[27] Since primary amides are among the most ubiquitous amide derivatives in organic synthesis and constitute widespread structural motifs in pharmaceutical industry,[22] the present study puts emphasis on the use of common acyclic amides[28] as models for amide bond distortion and establishes a distinguishing feature of this approach.

Amides **2a-e** (R = NMe_2, OMe, H, F, CN) were crystalline and their structures could be confirmed by X-ray crystallography (Tables 1-2, Figure 3). Table 1 summarizes the Winkler-Dunitz distortion parameters (τ, χ_N), the additive distortion parameter $\Sigma(\tau+\chi_N)$,[29] and selected bond lengths of the N,N-Boc_2-amides. The table also includes geometric parameters of the corresponding parent benzamide.[30] The structures of amides **2a-e** together with Newman projections along the N–C(O) axis are presented in Figure 3. The structure of the corresponding parent benzamide is shown in Figure 1D (see the SI, Supporting Information, for expanded ORTEP structures). Notably, the well-studied availability of the crystal structure of benzamide (**1c**, $PhCONH_2$) allows comparison of the parent amide and its N,N-Boc_2 twisted amide product.

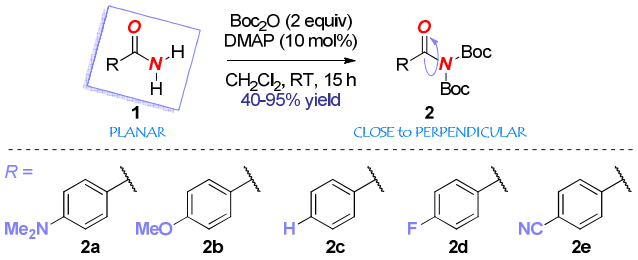


Figure 2. One-step synthesis of twisted amides.

Table 1. Summary of Structural Parameters for the X-ray Structures of 2a–e and Reference Benzamide[a]

Entry	2	N–C(O) (Å)	C=O (Å)	τ (deg)	χ_N (deg)	$\tau+\chi_N$ (deg)
1	**2a**	1.483	1.201	81.9	1.1	83.0
2	**2b**	1.458	1.205	59.2	0.2	59.4
3	**2c**	1.467	1.200	72.5	3.6	76.1
4	**2d**	1.433	1.206	38.3	4.7	43.0
5[b]	**2e**	1.418	1.205	28.9	19.5	48.4
6[b]	**2e'**	1.414	1.209	20.0	26.8	46.8
7[c]	**benzamide**	1.342	1.265	0.0	0.1	0.1

Crystallographic data have been deposited with the Cambridge Crystallographic Data Center. See SI for details and expanded tables. [b]Two independent molecules in the unit cell. [c]Benzamide, ref. 30.

Remarkably, the structure of **2a** (R = NMe_2) shows that this compound belongs to the most twisted amides isolated to date (τ = 81.9°).[1–3,9] Moreover, the N–CO amide bond length of 1.483 Å in **2a** is the longest recorded so far for an acyclic amide derivative. The observed length for the C=O bond is 1.201 Å. Interestingly, nitrogen in **2a** is basically sp^2 hybridized (χ_N = 1.1°), indicating that **2a** belongs to classic twisted amides as defined by Yamada et. al. The X-ray structures of **2b-e** (R = OMe, H, F, CN) reveal substantial twisting of the amide bond. The N–C(O) twisting is approximately aligned in the direction of the electron-density of the aromatic ring (vide infra), while the nitrogen becomes pyramidalized for more electron-withdrawing substituents. The amide **2e** (R = CN) was crystallized as two independent molecules in the unit cell. Analysis of the pyramidalization at nitrogen angle reveals significant pyramidalization in **2e** (up to χ_N = 26.8° in **2e'**). Pyramidalization at nitrogen has historically been one of the most valuable parameters to describe structural distortion of the amide bond.[1–9] More recent studies demonstrated that the additive amide bond distortion parameter, $\Sigma(\tau+\chi_N)$, provides a more accurate description of non-planarity of the amide linkage.[29] In the present case, it is likely that planarity around the nitrogen atom plays a role in the O-protonation of the amide oxygen despite high twist (vide infra).

It is instructive to compare structural parameters of the parent benzamide[30] (**1c**, R = H; τ = 0.0°; χ_N = 0.1°; N–C(O) = 1.342 Å; C=O = 1.265 Å, X-ray data) with the corresponding

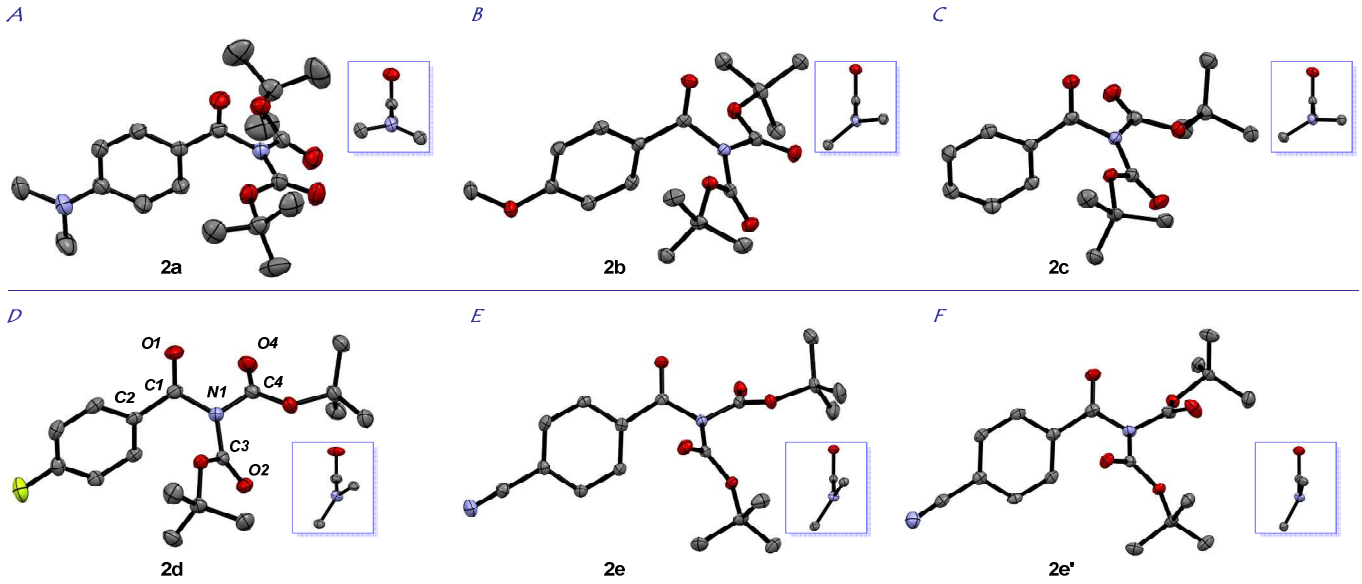


Figure 3. Crystal structures of amides **2a-e**. **2e**: two molecules in the unit cell. Insets show Newman projections along N–C(O) bonds.

Table 2. Summary of Additional Bond Lengths (Å) and Angles (deg) for the X-ray Structures of 2a–e[a]

Entry	2	C1–C2 (Å)	ω_1 (deg)	ω_2 (deg)	ω_3 (deg)	ω_4 (deg)
1	**2a**	1.452	-98.4	-97.9	81.0	82.7
2	**2b**	1.470	-58.8	-59.6	120.5	121.0
3	**2c**	1.479	71.6	73.4	-110.2	-104.8
4	**2d**	1.479	-41.7	-34.9	140.4	143.0
5	**2e**	1.493	39.7	18.1	-142.4	-159.9
6	**2e'**	1.495	-33.6	-6.4	146.8	173.2

[a] ω_1 = C2–C1–N1–C3; ω_2 = O1–C1–N1–C4; ω_3 = O1–C1–N1–C3; ω_4 = C2–C1–N1–C4. See SI for details and expanded tables.

N,N-Boc_2 twisted amide **2c** (R = H; τ = 72.5°; χ_N = 3.6°; N–C(O) = 1.467 Å; C=O = 1.200 Å). As shown in Table 1, N,N-di-*tert*-butoxycarbonylation dramatically enhances the twist angle (from 0° to 72.5°). This is accompanied by a significant increase of the N–C(O) bond length (by 0.125 Å) and a considerable shortening of the C=O bond (by 0.065 Å). Moreover, the observed N–C(O) bond length in **2e'** (1.414 Å) is shorter by 0.069 Å than the N–C(O) bond length in **2a** (1.483 Å), while the C=O bond lengths in **2a** (1.201 Å) and **2e'** (1.209 Å) differ by only 0.008 Å. Overall, these structural features in **2a-e** structures indicate substantial amide bond deviation from planarity upon N,N-di-*tert*-butoxycarbonylation. Furthermore, the observed changes in the N–C(O) and C=O bond lengths are consistent with classical amide resonance model.[1–3,23]

Detailed insight into the properties of **2a-e** can be gained from correlating structural and electronic parameters of the amide bond. The availability of five fully characterized compounds in one series allowed us for the first time to readily compare the effect of distortion on properties of the amide bond in twisted acyclic amides. The observed correlations are summarized as follows:

(1) Remarkably, a plot of N–C(O) bond length vs. τ gives an excellent linear correlation in the series (R^2 = 0.99) (Chart 1A). Thus, rotation around the N–C(O) bond disrupts $n_N \rightarrow \pi^*_{C=O}$ delocalization, increasing electrophilicity of the amide bond and lengthening the N–C(O) bond.

(2) Moreover, a closer analysis reveals an excellent inverse linear correlation between the N–C(O) amide bond length and the N–Boc bond length (R^2 = 0.99) (Chart 1B), and a good inverse linear correlation between the N–C(O) bond twist angle and the Ar–C(O) twist angle (R^2 = 0.86) (see the SI).

(3) Finally, an excellent linear correlation between the Ar–C(O) bond length and σ Hammett parameter is observed (R^2 = 0.99 (Chart 1C, see the SI for additional plots and discussion).

Collectively, the observed changes indicate that electron-donating groups promote an increase of rotation around the N–C(O) axis, which is accompanied by flattening of the Ar–C(O) twist angle to reinforce Ar to $\pi^*_{C=O}$ conjugation. Simultaneously, elongation of the N–C(O) bond is accompanied by a reinforced n_N to $\pi^*_{C=O(Boc)}$ conjugation as evidenced by a shortening of the N–Boc bond. Thus, on the basis of structural parameters, these amides can be regarded as electronically-tunable twisted amides, wherein electron-donor groups switch-off amidic resonance.[24e]

Bending Angle. We have also calculated ξ (ξ, C=O bending angle) in **2a-e**. This geometric parameter was recently introduced by Stoltz et al. to provide an additional measure of the stability of non-planar amides.[16b] We found positive ξ values of 4.4° and 2.6° for **2a** (R = NMe_2) and **2b** (R = OMe), respectively, indicating bending toward nitrogen, while **2c** (R = H), **2d** (R = F) and **2e**/**2e'** (R = CN) showed negative ξ values of–2.7°, –1.6° and –0.8°/–0.9°, respectively, indicating bending toward the aromatic ring. The observed values of ξ further support increased Ar to $\pi^*_{C=O}$ conjugation for electron-donating groups as a consequence of destabilizing n_O to σ_{C-C} /stabilizing n_O to σ^*_{C-N} interactions. Note that the observed ξ value of 4.4° for **2a** is in the range of the ξ value of 5.8° determined for the most twisted bridged lactam isolated to date, namely 7-hypoquinuclidone BF_3 complex,[16b] indicating an early stage of N–C(O) cleavage via oxocarbenium.

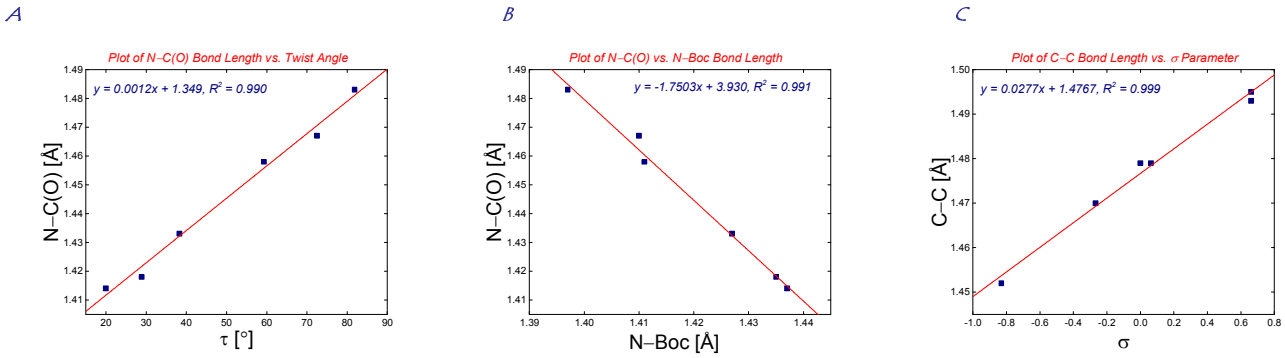
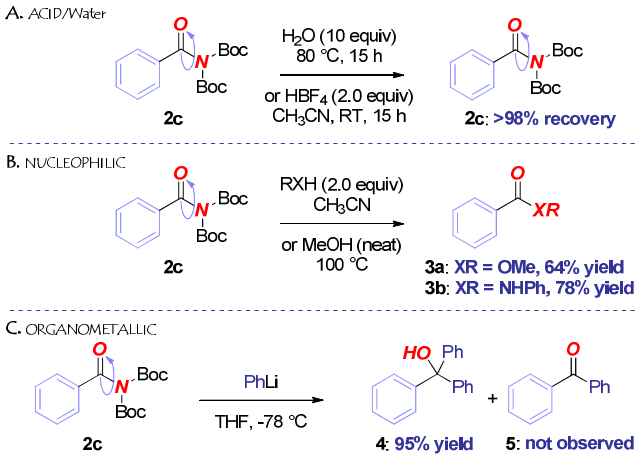
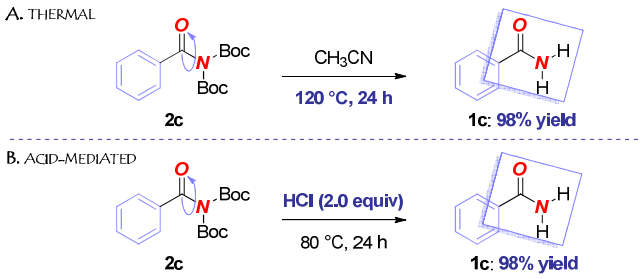


Chart 1. (a) Correlation of N–C(O) bond length [Å] to twist angle (τ) for amides **2a-e**. (b) Correlation of N–C(O) bond length [Å] to N–Boc bond length [Å] for amides **2a-e**. (c) Correlation of C–C bond length [Å] to Hammett σ parameter for amides **2a-e** (X-ray data).

Scheme 1. N–C(O) Cleavage Reactivity of Amides 2



Scheme 2. Thermal and Acid-Mediated Deconstruction of Amides 2: N–Boc Cleavage



Chemical Reactivity. It is well-established that deviations of the amide bond from planarity engender unusual reactivity of amides as a result of diminished resonance, including (1) hypersensitivity to hydrolysis, (2) N-protonation, and (3) high susceptibility to nucleophilic addition.[1–3,9] An interesting feature from the reactivity perspective, N–C(O) cleavage reactions substantially impact the overall applicability of non-planar amides.[2,9c] Having established a survey of structural properties of acyclic twisted amides **2**, next, we examined their chemical reactivity. The parent amide **2c** (R = H) was used as a model substrate.

As expected, the chemical reactivity of amides **2** is remarkable. Most notably, although twisted amides with a similar amide bond distortion are hypersensitive to hydrolysis,[9] we found that incubation of amide **2c** in aqueous CH_3CN (10 equiv of H_2O) at 80 °C for 15 h afforded only recovered starting material (Scheme 1A). Importantly, these acyclic twisted amides do not benefit from the thermodynamic stability afforded by a scaffolding effect of the medium-sized ring,[16f,g] which rules out reversibility of the amide bond hydrolysis. Furthermore, **2c** is remarkably stable to acidic conditions (Scheme 1A, see SI, page 14, for additional examples). For example, incubation of **2c** with HBF_4 (2 equiv) in CH_3CN at 23 °C for 15 h had no impact of the recovery of starting material (vide infra). In addition, amide **2c** is recovered unchanged from common nucleophilic solvents (e.g., DMSO, MeOH, 23 °C, 7 days, see SI). Amide **2c** is also very stable in aqueous solutions (e.g., D_2O:CH_3CN, 1:1, v/vol, 75% recovery, 23 °C, 7 days, vide infra). Collectively, these studies unambiguously demonstrate that acyclic twisted amides **2** show substantially higher stability to nucleophilic N–C(O) cleavage than classical bridged lactams. We note that the high stability of amides **2** bodes well for the development of synthetically-valuable reactivity governed by amide bond twist in easily accessible from 1° amides twisted acyclic amides.[27]

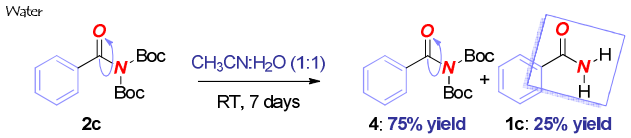
Despite high stability to nucleophilic cleavage relative to other classes of twisted amides, amides **2** react with nucleophiles under neutral conditions, i.e. in the absence of additional Lewis bases (Scheme 1B). For instance, the reaction of **2c** with MeOH (neat, 100 °C) or aniline (2.0 equiv, CH_3CN, 100 °C) cleanly affords the corresponding ester or amide by N–C(O) nucleophilic opening. Moreover, amides **2** react instantaneously with organometallic reagents, such as PhLi, at -78 °C resulting in exhaustive nucleophilic addition (Scheme 1C). The formation of acetophenone is not observed, even when limiting organometallic reagent is used. This is in sharp contrast to bridged lactams, which react by stable tetrahedral intermediates due to the lack of n_O to σ^*_{C-N} overlap,[31] but also differs from N,N-dialkylbenzamides (e.g. dimethylbenzamide), which give approx. 2:1 mixture of ketone:alcohol using the organometallic reagent in excess.[32] Collectively, these reactions demonstrate that while amides **2** show high stability, a property important from the practical standpoint, in the reactions with organometallic reagents these amides behave as acylating reagents with reactivity reminiscent of acyl halides.

The most remarkable feature of the reactivity of amides **2** is their capacity to revert to benzamides upon a judicious choice of the reaction conditions (Scheme 2).[33] We found that a simple exposure of amides **2** to thermal (120 °C, CH_3CN, 24 h) or acidic (HCl, 2 equiv, CH_3CN, 80 °C, 24 h) conditions results in fully chemo- and regioselective (vs. amide acyl N–C(O) bond) cleavage of the carbamate N–Boc

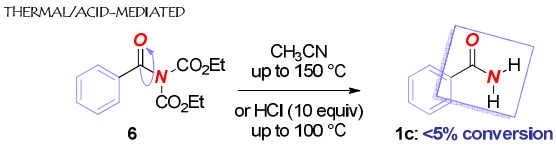
bonds likely via thermal/acid-mediated deprotection of the carbamate group (see SI, page 19, for additional discussion). Note that the reaction was completely regioselective with respect to the C–N bond that is less distorted from the C=O π system, in contrast to the previous examples of N–C cleavage of twisted amides.[16g,34]

Overall, these results unambiguously demonstrate novel reactivity of non-planar acyclic amides **2**. Importantly, in combination with the rapid access to N,N-Boc$_2$ twisted amides from common primary amides (Figure 2),[25] these studies illustrate the capacity to readily change molecular conformation around the amide bond in a highly efficient manner. To the best of our knowledge, this is the first example of a rapid formation/deconstruction of a twisted amide bond from the corresponding primary amide.[1–3,9] The abundance of primary amides[22] renders this process particularly attractive for a plethora of synthetic applications.

Scheme 3. Stability of Amides 2 in Aqueous Solutions



Scheme 4. Reactivity of N,N-(CO$_2$Et)$_2$-Benzamide (cf. N,N-Boc$_2$-Benzamide as in Scheme 2)



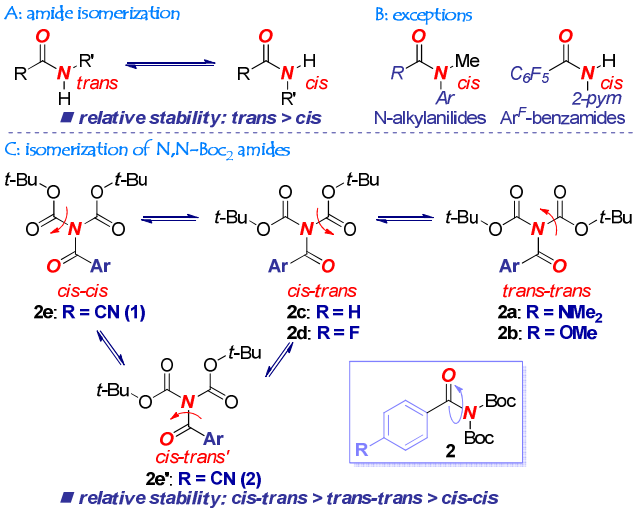
As noted earlier, amides **2** are very stable to aqueous conditions. We showed that the reaction of **2c** with D$_2$O:CH$_3$N (1:1, v/vol) at room temperature led to the recovery of **2c** and production of the parent benzamide **1c** in a 3:1 ratio after 7 days (Scheme 3). Thus, deconstruction of these twisted amides under mild, aqueous, thermodynamic conditions also appears to be synthetically accessible.

To gain insight into the factors that contribute to the rapid formation and deconstruction of acyclic twisted N,N-Boc$_2$-amides, synthesis of the corresponding N,N-(CO$_2$Et)$_2$-benzamide was studied (**6**, see SI). Under various conditions, only trace quantities of the product were formed with the majority of the mass balance corresponding to mono-acylation. Nevertheless, we were able to isolate the di- acylation product (**6**) and subject this amide to stability studies (Scheme 4). We found that (**6**) shows even higher stability than the corresponding N,N-Boc$_2$-benzamide.[26]

From the synthetic and stability studies of amides **2** and **6**, we conclude that (1) the observed reactivity in the synthesis of N,N-Boc$_2$-amides is consistent with sterically-induced O- to N-acyl transfer;[35] (2) the observed reactivity in the stability studies is consistent with N,N-Boc$_2$ cleavage reactivity pathway induced by thermal/acid-mediated deprotection of the carbamate.[36] (3) Computational studies (vide infra) demonstrate that *t*-Bu group is not critical to amide bond distortion (*t*-Bu vs. Et). High yields and stability of N,N-Boc$_2$ amides make the lack of success to rapidly prepare N,N-(CO$_2$Et)$_2$-benzamide inconsequential to the overall picture. Moreover, N,N-Boc$_2$ amides undergo reagent-controlled deconstruction to furnish primary amides, which appears to be more challenging with N,N-(CO$_2$Et)$_2$-benzamides.

Energetic Parameters. Computational studies were conducted to gain further insight into the structures of N,N-Boc$_2$-twisted amides.[23,29] Specifically, energetic parameters were analyzed to address the origin of amide bond deformation in these twisted amides.[37]

Scheme 5. Conformational Equillibria of Amides and Twisted Amides



Acyclic amides typically adopt a trans conformation around the amide bond; however, conformational preferences can be influenced by sterics and non-covalent interactions[38] (Scheme 5A-B). Principally, symmetrical acyclic imides may exist in three conformations: cis-cis, cis-trans, and trans-trans, while the presence of an additional N-acyl rotor yields further cis-trans' conformation (Scheme 5C).[39] Interestingly, we observed all four possible conformations in the solid state (Figure 3, cis-cis: R = CN-1, **2e**; cis-trans: R = H, **2c**; F, **2d**; trans-trans: R = NMe$_2$, **2a**; OMe, **2b**; cis-trans': R = CN-2, **2e'**). Geometry optimizations were performed using amides **2a-e**. Amides R = CF$_3$ (**2f**), Cl (**2g**), NO$_2$ (**2h**) were also included for comparison due to potential synthetic utility of these substrates. Calculations predict the following order of conformer stability: cis-trans' > trans-trans > cis-trans > cis-cis, in agreement with the repulsive 1,5-syn-pentane type interactions between imide oxygens (cis- cis) and electronic repulsion of the imide carbonyls (trans-trans).[40] The cis-trans' conformer is more stable than cis-trans due to avoidance of 1,5-nonbonding interactions between the carbonyl groups. However, the energy difference between the conformers is negligible and ranges between 0.0-1.5 kcal/mol (R = CN) to 0.0-2.1 kcal/mol (R = NMe$_2$).

Resonance energies of the amide bond in the parent amide (R = H) were calculated using the COSNAR method.[23a] Resonance energy in **2c** (RE = 6.3 kcal/mol) is much lower than in planar amides[5a,f] (approx. 65% decrease in amidicity compared with the planar N,N-dimethylacetamide, RE = 18.3 kcal/mol). Moreover, calculations predict the amide bond resonance energy in the corresponding N,N-Boc$_2$-acetamide (**2i**) as 7.6 kcal/mol, also dramatically lower than in N,N-dimethylacetamide (60% decrease in amidicity), and this is in line with the activating effect of N,N-Boc$_2$ substitution in both aromatic and aliphatic amides (eq. 1).

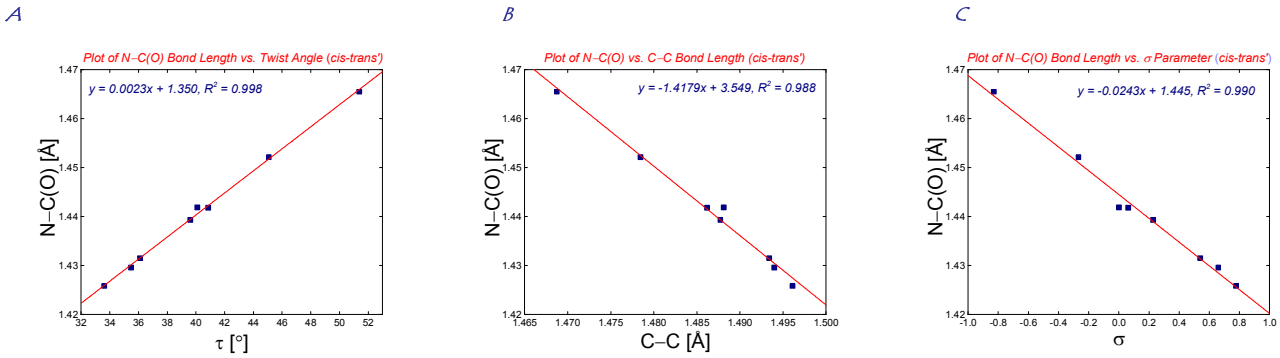


Chart 2. (a) Correlation of N–C(O) bond length [Å] to twist angle (τ) for amides **2a-h**. (b) Correlation of N–C(O) bond length [Å] to C–C bond length [Å] for amides **2a-h**. (c) Correlation of N–C(O) bond length [Å] to Hammett σ parameter for amides **2a-h** (cis-trans', B3LYP/6-311++G(d,p) data).

RE = 6.3 kcal/mol RE = 7.6 kcal/mol RE = 18.3 kcal/mol (1)

In contrast, resonance energies of the N-Boc carbamate groups in both the parent N,N-Boc_2-benzamide (**2c**) and N,N-Boc_2-acetamide (**2i**) are significantly lower: **2c**, 1.3 and 1.5 kcal/mol; **2i**, 2.4 and 0.0 kcal/mol, and indicate that RE of the N–Boc bonds are almost completely switched off as a result of electronic activation. The low energy difference between the conformers and the ability to freely-rotate the carbamate substituents accounts for the difference in conformers observed in the solid state. It is well-established that crystal packing can influence molecular conformation.[41]

As a further support of this notion, an excellent correlation between the N–C(O) bond length and twist angle for amides **2a-e** for the X-ray conformations has been found (R^2 = 0.99, see the SI). Furthermore, our analysis of the calculated structures for the most stable cis-trans' conformation reveals an excellent N–C(O) vs. τ correlation for amides **2a-h** (R^2 = 0.99, Chart 2A). Similarly, N–C(O) bond length correlates well with the Ar–C(O) bond length (R^2 = 0.99, Chart 2B) and with the Hammett σ parameter (R^2 = 0.99, Chart 2C) for the most stable cis-trans' conformation for the expanded set of N,N-Boc_2 activated amides **2a-h**. Moreover, separate analyses on the less stable but accessible cis-cis, cis-trans, and trans-trans conformations reveal similar relationship between structure and geometric properties in the series (see the SI for additional discussion).

The computational data closely parallel the experimental properties of the amide bond in **2**. As expected, computed data provide improved correlations vs. solid state structures.[23,29]

The viability of the proposed ground-state destabilization of amides **2** as the major contributor to amide deformation was further studied by obtaining a detailed rotational profile of the parent amide **2c** by systematic rotation along the O–C–N–C dihedral angle. The rotation was performed in both directions. We employed the X-ray structure of N,N-Boc_2 benzamide as the starting geometry and performed full optimization. Figure 4 shows rotational profile of **2c** (R = Ph) in comparison with **2i** (R = Me) and N,N-dimethylacetamide (DMAC). Rotational profile in **2c** confirms inverted rotation in **2c** (the energy maximum at ca. 0° O–C–N–C angle; the energy minimum at ca. 50° O–C–N–C angle) with significantly reduced barrier to rotation (cf. planar amides). *Generally speaking, the amide N–C(O) bond rotates from planarity to avoid steric interaction with the carbamate substituents.*[9b] *In contrast to typical cyclic twisted amides, the N–C(O) rotation occurs primarily as a consequence of N,N-Boc_2 substitution, which enables alternative n_N to $\pi^*_{C=O}$ delocalization.* This is further supported by a rotational profile of N,N-Boc_2-acetamide (**2i**), which shows energy minimum at ca. 0°, while the energy reaches maximum at ca. 90°, in a close analogy to dimethylacetamide, but at a dramatically lowered rotational barrier. During the O–C–N–C amide rotation, the N,N-Boc_2 linkage rotates along the N–C carbamate axes as measured by C–N–C=O and C–N–C–O carbamate dihedral angles. The rotational barrier was determined to be 3.33 kcal/mol (R = Ph, 0° O–C–N–C angle), and 5.63 kcal/mol (R = Me, 90° O–C–N–C angle).

Finally, the unique properties of twisted N,N-di-Boc amides are demonstrated by the protonation aptitude. As a consequence of $n_N \rightarrow \pi^*_{C=O}$ conjugation, there is a strong intrinsic bias for protonation of planar amides at the oxygen atom (e.g., 1-Me-pyrrolidinone, ΔPA = 14.8 kcal/mol).[23b] Twisted amides often undergo selective N-protonation with the N-/O-protonation switch proposed to occur around the amide bond geometry corresponding to $\Sigma(\tau+\chi_N)$ = 50-60°.[29a] In this context, Greenberg and co-workers reported an interesting O-to-N crossover in the protonation of bicyclic lactam 1-azabicyclo[3.3.1]nonan-2-one (τ = 20.8°; χ_N = 48.8°; $\Sigma(\tau+\chi_N)$ = 69.6°), wherein the presence of both protonated tautomers was observed by ^{1}H and ^{13}C NMR spectroscopy.[16h]

Remarkably, proton affinities (PA) in the parent amide **2c** (R = H) indicate that these N,N-Boc_2 twisted amides vastly favor protonation at the amide oxygen atom despite significant amide bond twist (ΔPA = 17.4 kcal/mol, vs. nitrogen).

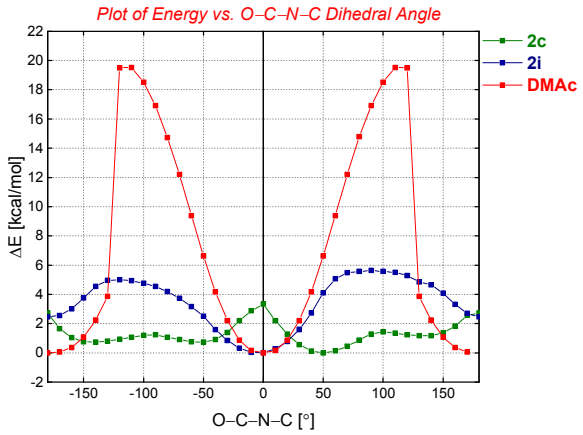


Figure 4. Correlation of ΔE [kcal/mol] to O–C–N–C [°] in **2c**, **2i** and DMAc (N,N-Dimethylacetamide).

Protonation of the carbamate carbonyls is energetically accessible in **2c** (ΔPA = 15.0 and 19.9 kcal/mol, vs. nitrogen), while N,N-Boc_2-acetamide (**2i**) favors protonation at the amide oxygen atom (ΔPA = 20.3 kcal/mol, vs. nitrogen; carbamates: ΔPA = 18.7 and 19.7 kcal/mol, vs. nitrogen). Note that while O-protonation at the amide oxygen leads to flattening of the amide bond (**2c**: τ = 40.1°; N–C(O) = 1.442 Å; **2c-OH**$^+$: τ = 8.0°; N–C(O) = 1.355 Å), the switchable O-/O-protonation of the carbamate oxygen leads to a very significant increase of twist (**2c**: τ = 40.1°; N–C(O) = 1.442 Å; **2c-OH**$^+$: τ = 87.3°; N–C(O) = 1.542 Å), activating the amide bond towards nucleophilic addition. Thus, these twisted amides present an exciting potential for switchable N–C(O) to N–Boc protonation at the oxygen atom to trigger the electrophilic reactivity of the amide bond.[42] As expected, protonation of the carbamate oxygen twists the acyl-amide bond, activating the N–C(O) bond towards nucleophilic addition.

Finally, it is worthwhile to point out that in the case of N,N-Boc_2 amides, the twisting occurs as a consequence of both steric and electronic activation of the acyclic amide bond. As such, these amides could also be referred to as N-acyl-imides rather than N,N-diacyl-amides. According to the IUPAC Gold Book, amides are denoted as compounds in which "acidic hydroxy group has been replaced by an amino or substituted amino group", while imides are denoted as "diacyl derivatives of ammonia or primary amides".[43] In the present case, N,N-Boc_2 amides may indeed be described as N-acylimides rather than N,N-diacylamides. However, the major difference originates from the synthetic disconnection by which the twisted amide bond is formed. In this regard, N,N-Boc_2 amides are unique from all other acyl- or acyl-type amide derivatives because these non-planar amides can be routinely prepared from the corresponding primary benzamides. This is distinct from N-acyl-glutarimides,[20] Yamada amides,[21] or related compounds[1–4,19] which are prepared by acylation of the imide component. The presented results demonstrate the first examples of reversible twisting of the amide bond, thereby providing novel handles on structure and reactivity of readily accessible acyclic benzamides.

Conclusions

In conclusion, we have reported the first class of acyclic twisted amides that can be prepared directly, in a reversible manner, from ubiquitous primary amides in a single operationally-trivial step. More importantly, our data demonstrate the propensity of common acyclic amides to participate in amide bond deformation pathways that can be attributed to ground-state destabilization of the amide bond, resulting in the most twisted acyclic amide bonds reported to date. Mechanistic and synthetic studies have provided insight into the structural and energetic properties of the amide bond and showed evidence for controlled generation/ deconstruction of acyclic twisted amides, wherein selective cleavage of the N–C(O) or N–Boc bond can be achieved by controlling the reaction conditions. On a fundamental level, our studies show that these structures are best represented as classic twisted amides as defined by Yamada et al., providing an alternative to generating substantial non-planarity of the amide bond without resorting to complex frameworks. Future work will focus on evaluating the generality of amide deformation modes that activate the amide linkage toward unusual reactivity. We fully expect that the results presented herein will contribute to a better understanding of the properties of the amide bond, including in structural chemistry and metal catalyzed reactions of amides. Further studies as well as the development of catalytic processes enabled by amide bond distortion of common primary amides are in progress.

ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization data, Cartesian coordinates, energies with zero-point energy and thermal corrections, CIF files for amides **2a-e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

Rutgers University and the NSF (CAREER CHE-1650766) are gratefully acknowledged for support. The Bruker 500 MHz spectrometer used in this study was supported by the NSF-MRI grant (CHE-1229030). We thank the Wroclaw Center for Networking and Supercomputing (grant number WCSS159).

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