The Most Twisted Acyclic Amides: Structures and Reactivity

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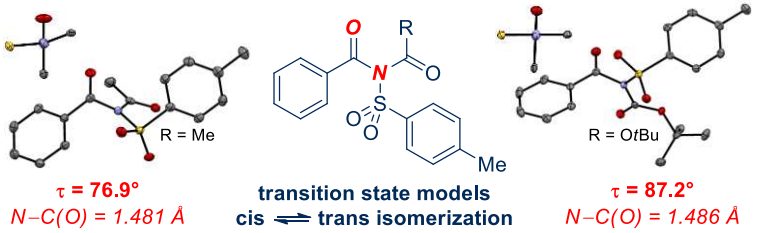
Supporting Information



ABSTRACT: The synthesis, the crystal structures and reactivity of the most twisted acyclic amides described to date are reported. Substitution at the nitrogen atom in simple benzamides with Ts and acyl or carbamate groups provides a unique way to achieve almost perpendicular twist in N-acyclic amides (τ = 77°, N = Ac; τ = 87°, N = Boc). The overlap between the Nlp and CO π* orbital is disrupted due to geometrical constraints around the N-substituents. The perpendicular acyclic twisted amides represent a transition state mimic of cis-trans peptide isomerization thus far only accessible by excessively twisted bridged lactams.

Chemists have long strived to prepare fully perpendicular amides.[1,2] However, disruption of amidic resonance ($n_N \rightarrow \pi^*_{C=O}$ conjugation, Figure 1A) is not trivial, despite it being proposed in numerous biological processes, including peptide hydrolysis, peptide folding and cis-trans isomerization of proteins.[3,4] Following the early proposal by Lukeš,[2] the first example of a substantially twisted amide was reported by Yamada in 1993 using a conformationally-constrained 1,3-thiazolidine-2-thione (Figure 1B, τ = 74°).[5] The structural characterization of 1-aza-2-adamantanone by Kirby in 1998 (Figure 1B, τ = 89.5°)[6] and 2-quinuclidonium tetrafluoroborate by Stoltz in 2006 (Figure 1B, τ = 89.2°)[7] represented a major breakthrough. Another intriguing example of a doubly-twisted amide was reported by Harrison (Figure 1B, τ = 66.4° and 54.3°) using a 2,5-dithioglycoluril scaffold,[8] wherein severe ring strain and nonbonding interactions forced the pivaloyl groups to heavily deviate from the amide bond planarity.

Our studies have focused on a family of non-planar N-acylglutarimides,[9] which, although severely twisted, have been limited to an N-cyclic substituent that cannot be rationally modulated and clearly represented a unique case in comparison with other related structures.[10] Furthermore, we recently demonstrated a reversible twisting of N,N-Boc_2 amides characterized by a twist angle of 72.5° in the parent compound.[11] Although the high lability of the N-Boc substituents enabled reversible deprotection of twisted amides, this instability limited the scope of valuable processes of the non-planar amide bond, and, furthermore, these amides could not reach perpendicularity characteristic to 1-aza-2-adamantanone[6] and 2-quinuclidonium tetrafluoroborate.[7]

Herein, we report the synthesis, the crystal structures and reactivity of the most twisted acyclic amides crystallized to date (Figure 1C). We demonstrate that substitution at the nitrogen atom in simple benzamides with Ts and acyl or carbamate groups provides a unique way to achieve almost perpendicular twist in N-acyclic amides (τ = 77°, N = Ac; τ = 87°, N = Boc), further emphasizing the utility of steric repulsion, as defined by Yamada,[10c] as a means to achieving full distortion of the amide bond.[12,13]

Amides **1** and **2** were prepared by the acylation route in 46% and 72% yields on gram scale, respectively (amine, benzoyl chloride, 1.0 equiv, DMAP, 0.50 mol%, Et_3N, 2.0 equiv, CH_2Cl_2, RT), and were conveniently purified by chromatography on silica gel. Crystals suitable for X-ray crystallography were obtained by slow evaporation from CH_2Cl_2 (**1**, Mp = 76-78 °C; **2**, Mp = 80-81 °C).[14] ORTEP drawings showing two orthogonal representations of **1** and **2** along with Newman projections along N–C(O) bonds are shown in Figure 2. Almost perfect perpendicular arrangement around the amide bond in **2** should be noted. Table 1 summarizes the key geometric parameters of amides **1** and **2**, including relevant bond lengths (entries 1-5), dihedral angles (entries 6-9), the Winkler-Dunitz distortion parameters (entries 10-11) and the sum of angles around the nitrogen atom (entry 12).

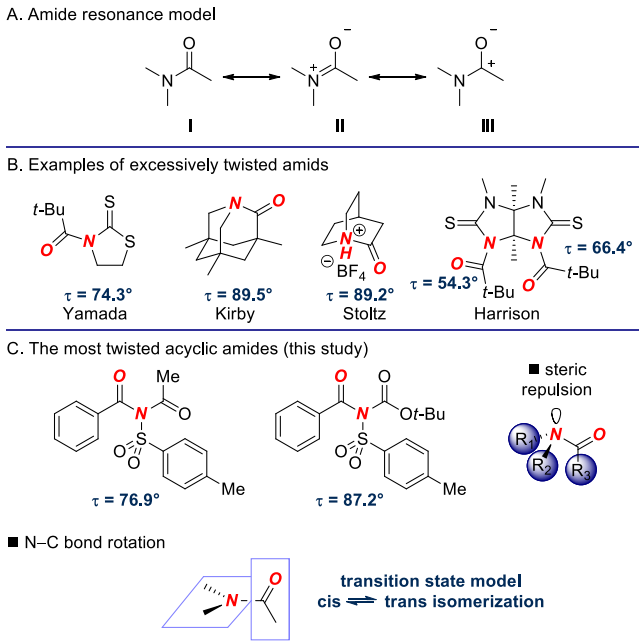


Figure 1. (a) Amide resonance model. (b) Examples of excessively twisted amides. (c) The most twisted acyclic amides (this study).

Notably, the structures of **1** (τ = 76.9°) and **2** (τ = 87.2°) show that the benzoyl amides are extremely twisted, while their twist angles represent the highest τ values reported to date for simple N-acyclic amides.[5–11] It is particularly noteworthy that the twist angle in **2** matches the perpendicularity thus far characteristic only to bridged and hypersensitive to hydrolysis 1-aza-2-adamantanone and 2-quinuclidonium tetrafluoroborate.[6,7]

It is further interesting to note that the N–CO amide bond lengths of 1.481 Å in **1** and 1.486 Å in **2** are the longest reported for acyclic amides.[5–11] These values can be compared with Yamada's amide (N–CO = 1.448 Å)[5] and Kirby's most twisted amide (N–CO = 1.475 Å)[6] in the neutral form.

Table 1. Selected Geometric Parameters of Amides 1-2[a]

entry	parameter	value for **1**	value for **2**
1	N1–C1	1.481(2)	1.486(2)
2	C1–O1	1.201(2)	1.193(2)
3	C1–C3	1.470(2)	1.483(2)
4	N1–C2	1.406(2)	1.404(2)
5	N1–S1	1.681(1)	1.679(1)
6	C3–C1–N1–C2	110.4(2)	91.4(1)
7	O1–C1–N1–S1	95.8(2)	94.2(1)
8	O1–C1–N1–C2	-68.3(2)	-87.2(2)
9	C3–C1–N1–S1	-85.5(1)	-87.2(1)
10	τ, χ_N, χ_C	76.9,15.9,1.3	87.2,1.4,1.4
11	τ+χ_N	92.8	88.6
12	θ	358.1	360.0

[a]This study. X-ray structures. Bond lengths and angles are given in Å/deg. For structural parameters of representative twisted amides, see ref. 13a,b and ref. 15.

Furthermore, the C=O bond lengths of 1.201 Å in **1** and 1.193 Å in **2** are in the same range as in Kirby's amide (C=O = 1.196 Å). Notably, the nitrogen atom in **1** and **2** is practically planar (**1**, χ_N = 15.9°, θ = 358.1°; **2**, χ_N = 1.4°, θ = 360.0°). As a consequence, amides **1** and **2** are best defined as classic twisted amides with the N–C(O) plane perpendicular to the N-substituents in an sp^2 arrangement.[5,10c] As expected, pyramidalization at the carbon atom (**1**, χ_C = 1.3°; **2**, χ_C = 1.4°) is not affected by the geometrical changes of the amide bond.[13]

The additive Winkler-Dunitz distortion parameter (τ+χ_N) provides a useful description of the properties of non-planar amides.[15] The (τ+χ_N) values of 92.8° and 88.6° in **1** and **2** respectively, further highlight that the overlap between the Nlp and CO π* orbital is disrupted due to steric interactions around the N-substituents. Furthermore, it should be noted that the N-

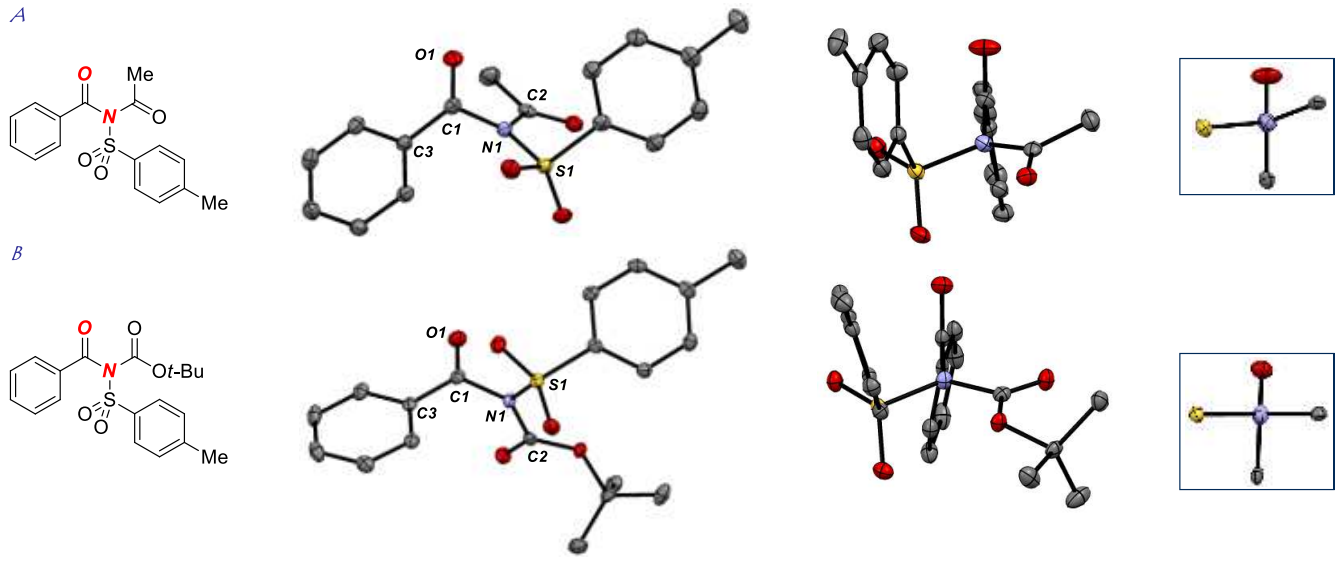


Figure 2. Two different views of the graphical representation of **1** and **2**. Inset shows Newman projection along N–C(O) bonds. Note almost perfect perpendicular arrangement around the amide bond in **2**. Hydrogen atoms have been omitted for clarity. 50% ellipsoids. (**1**, $C_{16}H_{15}NO_4S$, monoclinic, space group *P21/n* *a* = 7.6777(4), *b* = 15.0221(8), *c* = 13.1271(8) Å, *β* = 95.618(4)°, *T* = 100 K, *Z* = 4, R1 = 0.044; **2**, $C_{19}H_{21}NO_5S$, monoclinic, space group *C2/c* *a* =

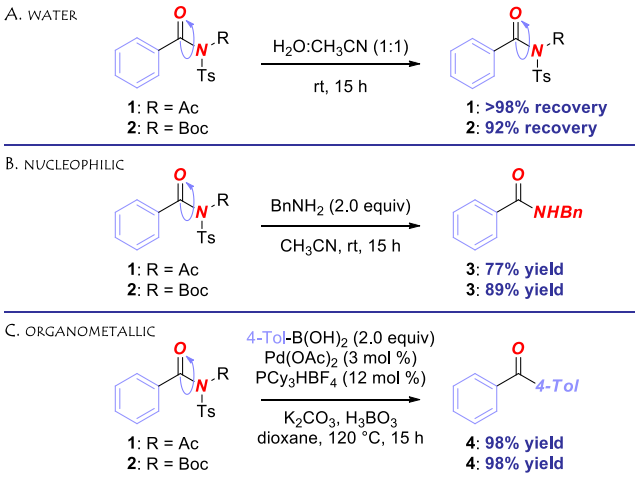
26.595(5), b = 9.089 (2), c = 16.938 (3) Å, β = 119.43 (3)°, T = 100 K, Z = 8, R1 = 0.036). Crystallographic data have been deposited with the Cambridge Crystallographic Data Center. CCDC 1870944 and CCDC 1870945. See SI for details and expanded tables.

acetyl group in **1** is practically planar (τ = 4.6°, χ_N = 16.4°, N–C(O) = 1.406 Å, C=O = 1.208 Å), indicating that the twist around the N-Ac group is relieved by rotation around the N-Bz bond.[16,17]

Significantly, the unique structures of **1** and **2** in conjunction with the literature data[9–11] permit us to arrange the effect of N-substitution on the twist of acyclic amides in the following order: Boc/Ts > Ac/Ts > Boc/Boc > R/Ac > R/Boc > R/Ts. The stability, ease of synthesis and flexibility in the preparation of analogues are additional positive factors that should be taken into account when considering using the steric repulsion method to attain amide bond distortion.[10c]

Given the unique structures of **1** and **2**, we performed preliminary reactivity studies to gain insight into the properties of the perpendicular amide bond (Scheme 1). While it is well-established that excessively twisted bridged lactams, such as 1-aza-2-adamantanones and 2-quinuclidones suffer from hyperreactivity of the amide bond towards hydrolysis,[6,7] we hypothesized that the special characteristics of twisted acyclic amides might enable convenient handling, thus making this class of compounds particularly attractive as models of a fully perpendicular amide bond. Indeed, although twisted lactams with similar amide distortion undergo rapid hydrolysis, we found that incubation of amides **1** and **2** in aqueous CH_3CN (1:1 v/vol) for 15 h afforded only recovered starting material (Scheme 1A). Furthermore, amides **1** and **2** serve as highly reactive acylating reagents, as expected from high twist and exemplified in the reactions with amines (Scheme 1B). Note that full selectivity in nucleophilic scission was observed in that only the twisted amide bond underwent the cleavage.[11] Finally, we demonstrated that both amides **1** and **2** behave as highly reactive acylating reagents in the transition-metal-catalyzed N–C(O) Suzuki cross-coupling (Scheme 1C).[18] These preliminary studies provide a solid foundation for the development of an array of reactions of twisted acyclic amides and bring about the key advantage of high stability over conventional bridged lactams.

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



The carbonyl stretching frequency in the IR data can reveal the presence of twisting in non-planar amides.[15b] However, in our experience the correlation between amide distortion and IR data is less straightforward. The benzoyl $\nu_{C=O}$ of 1698 cm^{-1} (**1**) and $\nu_{C=O}$ of 1697 cm^{-1} (**2**) indicate highly electrophilic amide carbonyls in these amides and are close to the range expected for saturated ketones. Ongoing studies are focused on determining the effect of twist on IR data in a broader range of acyclic amides. Likewise, it should be noted that in these amides twisting occurs as a consequence of both steric and electronic activation of the amide bond. Accordingly, these amides could also be referred to as N-sulfonyl imides. According to the IUPAC definition, amides are compounds in which "acidic hydroxy group has been replaced by an amino or substituted amino group." As such, it is critical that when referring to twisted amide bonds a correct N-C(O) bond is assigned as the twisted bond. In a broader sense, it is important to note that is possible that even more twisted amides than **1** and **2** have already been synthesized but their twist remains unknown. In general, there are very few examples of extremely twisted amides with twist values approaching 90°. Future work will focus on expanding the current understanding of amide bond twist in cyclic and acyclic amides.

In summary, we have reported the synthesis and full structural characterization of the most twisted acyclic amides described to date. Upon judicious N-substitution, the overlap between the lone pair at nitrogen and the carbonyl π system is disrupted, which results in full rotation around the N–C(O) axis. The twist angle of 87° for the first time matches perpendicular twist inherent thus far only to 1-aza-2-adamantanones and 2-quinuclidones. The method of amide bond twisting by geometric distortion in acyclic amides represents a powerful approach to unveil properties of the non-planar amide bond.[10a–c] Further work on mechanistic investigations of amide bond twisting and the preparation of new analogues of twisted acyclic amides is ongoing and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization data, crystallographic details, CIF files for amides **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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