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Structure and Reactivity of Highly Twisted *N*-Acyl Imidazoles

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Abstract

A modular and efficient synthesis of highly twisted *N*-acyl imidazoles is reported. These twist amides were characterized *via* X-ray crystallography, NMR spectroscopy, IR spectroscopy, and DFT calculations. Modification of the substituent proximal to the amide revealed a maximum torsional angle of 88.6° in the solid state, which may be the most twisted amide reported for a non-bicyclic system to date. Reactivity and stability studies indicate that these twisted *N*-acyl imidazoles may be valuable, namely as acyl transfer reagents.

Graphical Abstract

Imidazoles are a prevalent and critical scaffold in a variety of biological molecules, such as histidine, histamine, and biotin; modified biomolecules, including peptidomimetics; as well as natural and synthetic products.¹ Many of these imidazole-containing compounds exhibit a vast array of bioactivities, treating inflammation, pain, diabetes, infections, viruses, and cancer (Figure 1). For example, L-779,450 has been identified as a potent and selective B-Raf kinase inhibitor with $K_d = 2.4$ nM for the treatment of strokes.² Imidazoles are also valuable in synthetic chemistry, serving as acyl transfer reagents,³ ionic liquids,⁴ organocatalysts,⁵ precursors to *N*-heterocyclic carbenes,⁶ and photochromic materials.⁷

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ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details, characterization data, crystallographic details, and DFT computational details for *N*-acyl imidazoles (PDF).

NOTES

Crystallographic data are deposited with the Cambridge Crystallographic Data Centre (CCDC) under the following accession numbers: **7a** (1897303), **7b** (1895220), **8a** (1895221), and **9** (1895222).

In the context of acyl transfer, *N*-acylation of imidazoles has been shown to generate reactive heterocyclic amides, or azolides.⁹ Unlike typical amides, *N*-acyl imidazoles are far more reactive towards nucleophilic attack (e.g., hydrolysis). This intriguing reactivity has spurred several studies of the stability and conformational features of *N*-acyl imidazoles.^{9–10} Although this class of imidazoles has been shown to exhibit conformational equilibria, significantly twisted *N*-acyl imidazoles have not been synthesized.

Although the majority of amides are planar due to the strong, stabilizing resonance between n_N and $\pi^*_{C=O}$ (Figure 2a);¹¹ deviations from this planarity have been observed in peptides¹² and small molecules.¹⁵ A resultant disruption of amide bond resonances, a fundamental characteristic of a twist amide, induces several changes in the properties of the amide: (i) longer *N*–C(O) bond, (ii) lower rotational barrier for *cis*–*trans* isomerization, (iii) higher C=O infrared stretching (IR) frequency, (iv) and more downfield C=O shift by ¹³C NMR spectroscopy, and (v) increased reactivity in nucleophilic addition and hydrolysis.¹⁶ To quantify the degree of distortion in the amide bond, Winkler and Dunitz developed several additional parameters (Figure 2b): twist angle (τ), pyramidalization at nitrogen (χ_N), and pyramidalization at carbon (χ_C).¹³ For fully planar bonds, $\tau = \chi_N = \chi_C = 0^\circ$. Accordingly, a fully orthogonal amide bond would correspond to a twist angle of 90° , and $\chi_N = \chi_C = 60^\circ$ for fully pyramidalized amide bonds. Yet, χ_C values are typically close to 0° regardless of the degree of distortion due to the contribution of the amino ketone resonance structures (Figure 2a, **A** and **B**). The Szostak Group has also identified the additive Winkler–Dunitz distortion parameter ($\Sigma\tau + \chi_N$) for better predicting structural and energetic properties of twist amides.¹⁷ In addition to the Winkler–Dunitz parameters, distortion of the amide bond can be quantified according to θ , the sum of the bond angles at nitrogen, which is 328.4° for sp^3 hybridized atoms and 360° for sp^2 atoms.¹⁸

The study of twist amides began with the proposal of Lukeš¹⁹ in 1938 in which the incorporation of an amide bond nitrogen atom at the bridgehead position in a bi-, or polycyclic molecule would result in amide bond distortion. Since then, several quintessential examples of twist amides have been synthesized and characterized (Figure 2c). Notably, twist angles of 89.5° and 89.2° have been achieved by Kirby (**1**)^{14d} and Stoltz (**2**),^{14e} respectively, in bridged lactams. Disrupting amide resonance in non-bicyclic systems has been more challenging. Yet, this feat has also been accomplished, with one early example of a twisted mercaptothiazoline reported by Yamada in 1993 (**3**, $\tau = 74.3^\circ$).^{14b} Remarkably, Szostak has very recently reported a seminal case of an acyclic twist amide with nearly ideal orthogonality of substituents using *N,N*-disubstituted benzamide **4**.^{14c}

Although the degree of twisting in *N*-acyl imidazoles has been examined,^{10e} the highest degree of torsional distortion previously reported crystallographically, to our knowledge, was the case of **5** ($\tau = 47.0^\circ$) for a tetrasubstituted *N*-acyl imidazole prepared by Hashmi.^{14a} While exploring the synthesis of highly substituted imidazoles in pursuit of compounds with multiple potential axes of chirality,²⁰ we made the serendipitous discovery of several new, highly twisted *N*-acyl imidazoles, including one that exhibits nearly ideal orthogonality. Thus, we report herein the synthesis, crystal structures, and reactivity of these compounds, including what may be the most twisted amide in a non-bicyclic system reported to date (**8a**, $\tau = 88.6^\circ$).

The synthesis of these highly twisted *N*-benzoyl imidazoles follows a similar strategy to that employed by Merck for the generation of potent tetrasubstituted-imidazole inhibitors of p38 mitogen-activated protein (MAP) kinase (Scheme 1).²¹ The imidazole core was readily constructed *via* condensation of 2-bromoacetophenone with benzamidine in DMF at 45 °C. Installation of the benzoyl group was accomplished by deprotonation of **6a** with sodium hydride followed by addition of benzoyl chloride. The crude product was carried forward without further purification; bromination with *N*-bromosuccinimide thus afforded **7a** in 74% yield over 2 steps. Lastly, Suzuki-Miyaura cross coupling was performed with subsequent TBS deprotection to produce **8a** (54% over 2 steps). To increase the solubility of the imidazole-containing compounds, this procedure was repeated starting with 2-bromo-4'-(trifluoromethyl)-acetophenone to afford **6b–8b**. The brevity and efficiency of this route should facilitate synthesis of numerous analogs of **8**.

Initially, crystallography was employed to confirm the regioisomer obtained following benzoylation. Strikingly, we observed a high degree of amide twisting in **7a**, which was even more pronounced in **8a** (Figure 3). Table 1 summarizes key geometric parameters of the crystal structures of **7a** and **8a**, including: bond lengths (entries 1–5), dihedral angles (entries 6–9), Winkler–Dunitz distortion parameters (entries 10–13), and θ (entry 14); carbonyl IR stretching frequencies (entry 15) and ¹³C NMR shifts (entry 16); as well as calculated N–C(O) rotational barriers (B3LYP/6–311++G(d,p); entry 17). While the bond lengths for **7a** and **8a** are similar, the dihedral angles are significantly different, revealing a greatly increased twist angle ($\tau = 52.5^\circ$ vs. 88.6° for **7a** and **8a**, respectively; entry 10). Further analysis of the Winkler–Dunitz distortion parameters reveals that while the pyramidalization at nitrogen in **8a** is greater than that of **7a**, there is also less pyramidalization at the carbonyl carbon (entries 11 and 12, respectively). The nature of the amide nitrogen is further described using the parameter θ , indicating that this nitrogen has less s-character in **8a** than in **7a** (entry 14). Lastly, the relative degrees of twisting are also described by their significantly different values for the additive Winkler–Dunitz distortion parameter (63.1° for **7a**, 110.5° for **8a**; entry 13).

In addition to examining the crystal structures of **7a** and **8a**, these compounds were characterized spectroscopically. While typical C=O stretching frequencies for amides are $1690\text{--}1630\text{ cm}^{-1}$, **7a** and **8a** show resonances at 1714 and 1713 cm^{-1} , respectively, which are in the range of typical aliphatic ketones. These resonances also allude to the highly electrophilic nature of these amide carbonyls (entry 13).¹⁷ The twists intrinsic to these amide bonds are also conveyed in the downfield shifts of the carbonyl carbons in ¹³C NMR, with a greater shift seen for **8a** (168.6 ppm for **7a** vs. 169.6 ppm for **8a**; entry 14).

Moreover, the N–C(O) rotational barriers were calculated (B3LYP/6–311++G(d,p)). Relative to typical amides, with rotational barrier for *cis–trans* isomerization between $15\text{--}20\text{ kcal/mol}$, these twist amides exhibit low rotational barriers (9.8 and 9.7 kcal/mol for **7a** and **8a**, respectively; entry 15), consistent with their elongated N–C bond (entry 1). In determining this rotational barrier, we noted an intriguing disparity in the degree of torsion between the crystal and calculated structures (Figure 3). While the optimized ground state of **7a** displayed an increased τ (60.5° vs. 52.5° , respectively) relative to the solid state, this

trend was reversed and amplified for **8a** (66.5° vs. 88.6°, respectively). A better understanding of these conformational discrepancies was realized by examining the crystal packing. In the crystal lattice of **7a**, relatively weak Br- π and CH- π intermolecular interactions appear to spur the slight deviation seen from the optimized ground state structure (Figure 3, top). Substitution of bromine for phenol, however, induced a more significant conformational change, as the aryl rings rotate to enable favorable CH- π , π - π , and H-bond interactions within the crystal lattice. The crystal packing can also be used to rationalize why **7a** and **8a** display significantly enhanced twist angles relative to a similar tetrasubstituted *N*-acetyl imidazole (**5**) synthesized by Hashmi (τ = 47.0°, Figure 2) that is incapable of engaging in π -interactions with the *C*-substituent of the amide.^{14a} While there are very few examples of highly distorted amides with twist angles near 90°—with most as bicyclic systems—the crystallographic and spectroscopic data for **8a** all reflect the nearly maximal twisting of the *N*-acyl imidazole moiety (τ = 88.6°) in the solid state.

With twist amides **7** and **8** in hand, their relative *N*-C(O) stability and reactivity were examined experimentally (Scheme 2). Specifically, **7b** and **8b** were studied, as these compounds were more soluble in various solvents. A crystal structure of **7b** was also obtained, affording a twist angle of 59.6° in the solid state, similar to that of **7a** (see Supporting Information). We also anticipate the twist angle of **8b** to be comparable to that exhibited in **8a**. Although twisted bridged lactams, such as aza-2-adamantanones and 2-quinuclidones (Figure 1) are prone to hydrolysis,^{14d, 14e} both **7b** and **8b** were found to be stable when stirred rapidly in aqueous acetonitrile (1:1 v/v) for 15 h (Scheme 2, Condition A). Moreover, **8** is synthesized *via* Suzuki–Miyaura cross coupling, involving prolonged exposure (16 h) to aqueous toluene (10:1 v/v) at an elevated temperature (110 °C), followed by TBS deprotection with TBAF (1 M in THF), further indicating that **8a** and **8b** are less prone to hydrolysis than twisted bridged lactams. Interestingly, when quenching this deprotection reaction with citric acid (10% m/v), *N*-to *O*-acyl transfer of **8b** was observed, isolating **9** in 8% yield over 3 steps, an outcome that was confirmed crystallographically (Scheme 2, Condition B). However, when twist amide **7b** was exposed to a biphasic citric acid solution, it proved stable (Scheme 2, Condition B').

Given the enhanced reactivity of both twist amides^{14c, 15b, 16a, 22} and *N*-acyl imidazoles^{3, 9} towards acyl transfer, we sought to examine the efficacy of **7b** and **8b** as acylation reagents (Scheme 2, Condition C). Under mild conditions, complete benzoyl transfer from **7b** to *N*-benzylamine, furnishing **10** (full conversion, 80% isolated yield) and *N*-benzylbenzamide, was accomplished in 15 h. Of note, the use of **8b**, presumably possessing a larger degree of amide twisting, led to a more sluggish reaction, affording **11** in 67% isolated yield (84% conversion) within the same time frame. Although **8b** should be significantly more twisted than **7b**, it may be that the increased steric bulk surrounding the benzoyl group in **8b** may impede the reaction, perhaps due to increased steric demand in the formation and breakdown of tetrahedral intermediates. Indeed, it has been shown that sterically hindered *N*-acyl imidazoles are more stable against nucleophiles than those that are unhindered.^{9, 10c} Accordingly, our results reinforce the notion that variation of the *C*³-amide moiety can tune the reactivity of these twisted *N*-acyl imidazoles.

In conclusion, we report an efficient, modular synthesis and full structural characterization of several new, twist amide *N*-acyl imidazoles. Crystallographic analysis of these twist amides revealed a maximum torsional angle of 88.6° in the solid state, which may be the most extreme case reported to date, slightly closer to ideal than the recently reported and seminal example of Szostak. IR spectroscopy, ¹³C NMR, and computational data all support the presence of highly twisted amides. Preliminary reactivity and stability studies indicate that **7b** and **8b** may be used as mild acylating reagents with tunable reactivity depending on the C^β-amide substituent, which can be easily modified using the synthetic route utilized herein. Furthermore, these twist amides withstand hydrolysis; therefore, twisted *N*-acyl imidazoles could be explored as potential pharmaceuticals given the diverse array of bioactivities exhibited by imidazole-containing compounds.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Examples of imidazole-containing compounds.^{2, 7b, 8}

a. Amide Bond Resonance

b. Winkler–Dunitz Distortion Parameters

$$\tau = 1/2(\omega^1 + \omega^2)$$

$$\omega^1 = \omega(\text{C}^1\text{--C--N--C}^2) \quad \omega^3 = \omega(\text{O--C--N--C}^2)$$

$$\omega^2 = \omega(\text{O--C--N--C}^3) \quad \omega^4 = \omega(\text{C}^1\text{--C--N--C}^3)$$

$$\chi_{\text{C}} = (\omega^1 - \omega^3 + 180^\circ) = (\omega^4 - \omega^2 - 180^\circ)$$

$$\chi_{\text{N}} = (\omega^2 - \omega^3 + 180^\circ) = (\omega^4 - \omega^1 - 180^\circ)$$

c. Select Examples of Twisted Amides

Figure 2.

Characteristics of amides. (a) Amide bond resonance, inducing a planar structure. (b) Winkler-Dunitz distortion parameters¹³ for describing twist amides, with (c) select examples.¹⁴

Figure 3.

An overlay of the crystal structure (maroon) and geometry optimized structure (navy) of **7a** (top) and **8a** (bottom) is shown on the left (B3LYP/6-311++G(d,p)). Select crystal packing motif of **7a** (top) and **8a** (bottom) with intermolecular interactions highlighted in turquoise and distances in Å indicated, 50% ellipsoids. A symmetry equivalent Br- π interaction in **7a** is omitted for clarity.

Scheme 1. Synthesis of Highly Twisted *N*-Benzoyl Imidazoles.

Scheme 2.

Amide Reactivity of *N*-Acyl Imidazoles **7b** and **8b**. Suzuki-Miyaura cross coupling and deprotection conditions are shown in Scheme 1. Crystal structure of *N*-to *O*-benzoyl migration product (**9**) shown on right with hydrogens omitted for clarity, 50% ellipsoids.

Table 1.

Select Geometric Parameters,^a Spectroscopic Data,^b and Computed N–C(O) Rotational Barriers^c of **7a** and **8a**.

entry	parameter	value for 7a	value for 8a
1	N–C	1.4520(18)	1.469(2)
2	C–O	1.2026(18)	1.201(2)
3	C–C ¹	1.484(2)	1.473(3)
4	N–C ²	1.3143(19)	1.376(2)
5	N–C ³	1.3998(18)	1.399(2)
6	C ¹ –C–N–C ²	–48.8(2)	–77.7(2)
7	C ¹ –C–N–C ³	120.59(15)	80.4(2)
8	O–C–N–C ²	134.54(15)	102.5(2)
9	O–C–N–C ³	–56.1(2)	–99.4(2)
10	τ	52.5	88.6
11	χ_N	10.6	21.6
12	χ_C	3.3	0.2
13	$\tau + \chi_N$	63.1	110.5
14	θ	359.35	357.06
15	$\tilde{\nu}(\text{C=O})$	1714	1713
16	$\delta(^{13}\text{C=O})$	168.6	169.6
17	$G^{\ddagger} \text{N–C(O)}$	9.8	9.7

^a Bond lengths and angles are reported in Å and degrees, respectively.

^b IR (neat) frequencies reported in cm^{–1}; ¹³C NMR (151 MHz, DMSO-*d*₆) resonances reported in ppm.