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Preview

Hydrolysis of Twisted Amides inside a Self-Assembled Coordination Cage

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Mechanical twisting of amides is anticipated to enhance their reactivity considerably. Recent work published in *Nature Chemistry* by Fujita and co-workers demonstrates that reactive non-planar amide conformers can be bound inside a self-assembled coordination cage. The twisted amides are stabilized by the rigid cavity of the cage, and are thus up to 14 times more reactive towards hydrolysis under basic conditions.

Amide functional groups are prevalent in many natural products, proteins, agrochemicals, and pharmaceuticals. They also serve as versatile building blocks in synthetic chemistry.[1] The planar conformation of amides is preferred energetically because conjugation between the nitrogen lone pair and the carbonyl π^* orbital renders amides less reactive than other carbonyl compounds. Distortion of this planar structure disrupts conjugation, lending enhanced reactivity to twisted amides. Given the biological and technological relevance of amides, great effort has recently been devoted towards the synthesis and applications of their twisted congeners.[2] However, generating twisted amides has been a major challenge, due to their instability and tendency to adopt a planar conformation whenever possible.

Self-assembled supramolecular containers have fascinated chemists for many years due to their well-defined interior spaces and diverse functions.[3] Metal-coordination containers, in particular, are readily generated through coordination-driven self-assembly and have found broad applications in molecular recognition, guest separation, chirality sensing, catalysis, and the stabilization of reactive species.[4-6] In breakthrough work recently published in *Nature Chemistry*, Fujita and co-workers showed that such cages may also enable the stabilization of amides in a mechanically-twisted form.[7]

This work is built upon the Fujita group's octahedral metal-organic cage **1**, which self-assembles from four (2,4,6-tris(4-pyridyl)-1,3,5-triazine) ligand panels and six palladium(II) or platinum(II) metal corner complexes (Figure 1A). This class of cages features a hydrophobic cavity of ~460 Å^3, high symmetry (T_d), and V-shaped regions sandwiched between each pair of two panel ligands. Their earlier work indicated that cage **1** binds organic molecules strongly and in well-defined configurations, leading to the orthogonal packing of two linear molecules,[8] the twisting of an overcrowded alkene,[9] and the binding of specific open/closed configurations of phthalein dyes.[10] Based upon these previous findings, the Fujita group has recently provided a new solution to the challenge of amide twisting.[7] They demonstrated that *trans*-planar secondary aromatic amides are non-covalently encapsulated by coordination cage **1**, and thus twist by up to 34° to form *cis*-twisted amides. These twisted amides are stabilized in this reactive conformation by the rigid cavity of **1**.

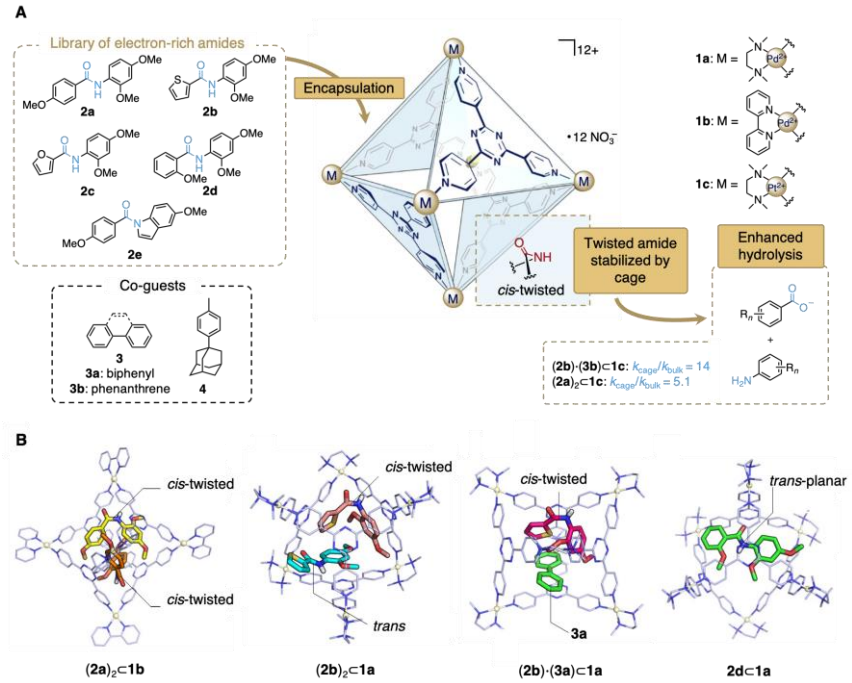


Figure 1. Mechanically twisting amides inside a self-assembled coordination cage enhanced their reactivity
(A) Structures of metal-coordination cages, amide guests and results of hydrolysis.
(B) X-ray single crystal structures of the host-guest complexes of these different amides.
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The authors began their investigation with palladium-based cage **1a** as the host and *N*-(2,4-dimethoxyphenyl)-4-methoxybenzamide (**2a**) as the guest. Interestingly, upon heating an aqueous solution of **1a** and **2a** at 100 °C for one hour, the faint yellow solution of **1a** changed to a reddish-orange solution. After workup, two sets of guest signals were observed in the ^{1}H NMR, consistent with the formation of inclusion complex (**2a**)$_2$⊂**1a**. Further single-crystal X-ray diffraction analysis revealed that two *cis*-twisted amides **2a** were non-covalently encapsulated inside host **1b**. As shown in Figure 1B, the two *cis*-twisted amides formed an asymmetric dimer in the cavity of **1b**, with dihedral angles (ω) around the amide bond of 34° and 30°, respectively. The color change that occurred during guest encapsulation was attributed to $\pi - \pi$ stacking (< 3.5 Å) between the triazine ligands on the cage of **1b** and the aromatic rings of amide **2a**.

Encouraged by this exciting result, the authors examined other electron-rich amide guests. In contrast to **2a**, thiophenyl- and furyl-amides **2b** and **2c** formed *cis-trans* 1:1 amide dimers in the cavity of cage **1b**. The structures of complexes (**2b**)$_2$⊂**1a** and (**2c**)$_2$⊂**1a** were also confirmed by X-ray crystal analysis. In contrast, *N*-(2,4-dimethoxyphenyl)-2-methoxybenzamide (**2d**) only afforded a 1:1 host-guest complex, and a *trans*-planar conformation was observed in the crystal structure of (**2d**)⊂**1a** (Figure 1B).

The formation of *cis-trans* 1:1 dimers of amides **2b** and **2c** inspired the authors to use a modulator guest, which mediated amide twisting *via* co-inclusion. Experimental results indicated that the degree of mechanical twisting could indeed be controlled using different modulators. For instance, using biphenyl **3a** as the modulator, a ternary complex (**2b**)·(**3a**)⊂**1a** was generated, where **2b** showed a *cis*-twist conformation with ω of 19° as indicated in the corresponding X-ray crystal structure (Figure 1B). However, switching to *p*-(1-adamantyl) toluene **4**, the *trans*-planar conformer of amide **2b** co-crystallized, with a ω value of 169° in the ternary complex (**2b**)·(**4**)⊂**1a**.

An impressive application of this mechanical twisting process was demonstrated in the acceleration of amide hydrolysis. Platinum cage **1c** was chosen for this study in light of its high stability under basic conditions. As noted in Figure 1A, hydrolysis of twisted amide **2b** in ternary complex (**2b**)·(**3b**)⊂**1c** proceeded more rapidly than hydrolysis without cage **1c**, with a rate enhancement (k_{cage}/k_{bulk} = 14). For the inclusion complex (**2a**)$_2$⊂**1c**, a rate enhancement of k_{cage}/k_{bulk} = 5.1 was recorded. In contrast, cage **1c** was found to suppress the hydrolysis of amide **2e** in complex (**2e**)$_2$⊂**1c** (k_{cage}/k_{bulk} = 0.11), due to the delocalization of the amide nitrogen lone pair into the indole ring.

By using a coordination cage, Fujita and co-workers provided a new method for the non-covalent mechanical twisting of amides, accelerating their hydrolysis in most cases. The ability of this cage to bind two peptides at once may open the door to the creation of a new 'protein splicing' molecular machine, where the *trans* peptides at a specific point in a protein backbone may be twisted and thus induced to hydrolyze, or possibly to exchange with other peptides held in close proximity. Future work on this topic is thus expected to be of great interest to practitioners across a wide array of fields.

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