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Synthesis of a Rotaxane Cu^{I} Triazolide under Aqueous Conditions

Joby Winn, Aleksandra Pinczewska, and Stephen M. Goldup*

School of Biological Sciences, Queen Mary University of London, Joseph Priestly Building, Mile End Road, London E1 4NS, U.K.

Supporting Information

ABSTRACT: We describe the serendipitous isolation of a stable, neutral, monomeric mechanically interlocked Cu^{I} triazolide under aqueous conditions. This "trapped" intermediate of the CuAAC catalytic cycle is sterically protected from reprotonation by the rotaxane architecture, which renders the Cu^{I}–C bond stable toward moisture and air—even carboxylic acids protonate the Cu^{I}–C bond only slowly. The isolation of this remarkably stable Cu^{I} organometallic points toward potential applications of mechanical bonding in the study of reactive intermediates.

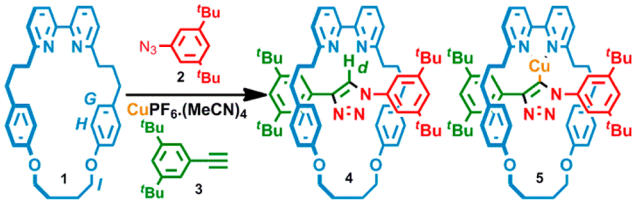
The kinetic stabilization of reactive species through steric isolation is a well-established technique in synthetic chemistry. The most commonly employed approach, covalent modification of the region around the reactive site with bulky substituents, has greatly facilitated the isolation, characterization, and application of otherwise short-lived species such as carbenes,[1] radicals,[2] and reactive organometallic catalysts.[3]

Here we demonstrate for the first time that a sterically hindered rotaxane environment can be used to stabilize a reactive organometallic species: a sterically congested mechanical bond renders the otherwise elusive Cu^{I} triazolide intermediate of the copper-catalyzed alkyne–azide cycloaddition (CuAAC) catalytic cycle remarkably stable—even carboxylic acids cleave the Cu^{I}–C bond slowly. These results point the way to the use of mechanical bonding in intercepting hitherto elusive reactive intermediates.

We recently extended the active template (AT) CuAAC reaction, originally developed by Leigh and co-workers,[4] to macrocycles with smaller cavities.[5] This simple modification dramatically increases the synthetic generality and yield of the reaction but necessitates long reaction times and elevated temperatures. We thus attempted to optimize the reaction conditions further. The reaction of novel macrocycle **1**, azide **2**, and acetylene **3** to give rotaxane **4** required 72 h under our previously reported conditions (Table 1, entry 1).[5] Encouragingly, when the reaction was carried out at room temperature (rt), addition of ^{i}PrEt$_2$N led to consumption of **1** within 18 h (entry 2). However, the isolated product after chromatography was not rotaxane **4** but an unknown compound that we had not previously observed in the AT-CuAAC reaction.

^{1}H NMR analysis of the unidentified product (Figure 1c) implied that it was mechanically interlocked, as evidenced by the characteristic shielding of protons H$_G$ and H$_H$ relative to the parent macrocycle (Figure 1a) and the splitting of H$_I$ into diastereotopic signals. Mass spectrometry indicated a peak at m/z 987, corresponding to [**4**·Cu^{I}]$^{+}$, but comparison with the product formed by combining **4** and CuPF$_6$·(MeCN)$_4$ in CDCl$_3$ ruled out [**4**·CuPF$_6$] (Figure 1d). Furthermore, the signal corresponding to the triazole proton, H$_d$, which was observed at 10.56 and 7.07 ppm in **4** (Figure 1b) and [**4**·CuPF$_6$] (Figure 1d), respectively, was absent from the spectrum of the unknown product.

Table 1. Synthesis of a Stable Interlocked Cu^{I} Triazolide[a]



Entry	Conditions	Product (%)
1	CH_2Cl_2, 80 °C, 72 h	**4** (96%[b])
2	CH_2Cl_2, ^{i}PrEt$_2$N, rt, 18 h	**5** (86%[c])
3	THF, ^{i}PrEt$_2$N, rt, 48 h	**5** (68%[c])
4	MeCN, ^{i}PrEt$_2$N, rt, 48 h	**5** (50%[c])
5	EtOH, ^{i}PrEt$_2$N, rt, 18 h	**5** (91%[c])
6	**1:1 THF-H$_2$O, ^{i}PrEt$_2$N, rt, 18 h**	**5 (82%[c])**

[a]1 equiv each of **1**, **2**, **3**, and ^{i}PrEt$_2$N (where indicated) with 0.95 equiv of CuPF$_6$·(MeCN)$_4$. For full details, see the Supporting Information. [b]Isolated yield of pure material after chromatography. [c]Isolated yield of pure material after recrystallization.

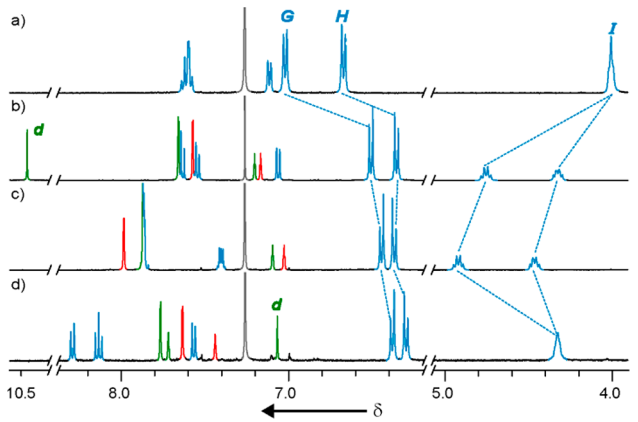


Figure 1. Partial 400 MHz ^{1}H NMR spectra of (a) macrocycle **1**, (b) rotaxane **4**, (c) triazolide **5**, and (d) [**4**·CuPF$_6$] in CDCl$_3$ at 300 K. Assignments as shown in Table 1.

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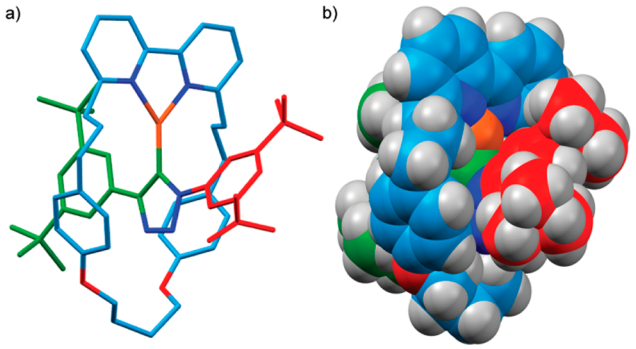
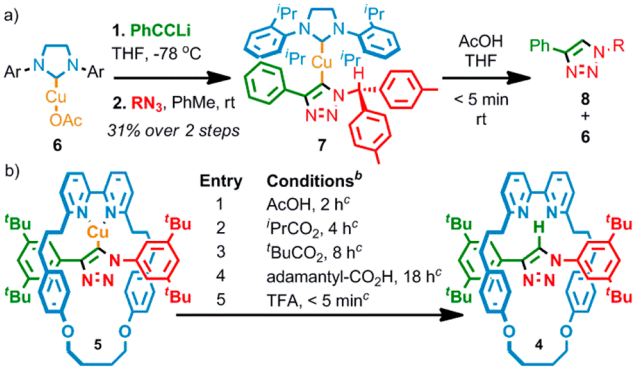


Figure 2. Structure of triazolide **5** determined by X-ray diffraction: (a) stick representation (H atoms omitted); (b) space-filling representation demonstrating the sterically shielded Cu−C bond.

Scheme 1. (a) Straub's Synthesis of Cu^{I} Triazolide 7 under Aprotic Conditions; (b) Protonation of Triazolide 5[a]



[a]Ar = 2,6-^{i}Pr$_2$Ph, R = (*p*-tolyl)$_2$HC. [b]Reactions were carried out at rt in $CDCl_3$ with 2 equiv of the acid and monitored by ^{1}H NMR spectroscopy at 30 min intervals. [c]Time for >95% consumption of triazolide **5**.

Slow evaporation of a saturated solution of the mystery product in Et_2O produced crystals suitable for single-crystal X-ray diffraction analysis, which revealed the mystery product to be mechanically interlocked Cu^{I} triazolide **5** (Figure 2). Triazolide **5** was also the major product when the reaction was carried out in other aprotic organic solvents (Table 1, entries 3 and 4), albeit in lower yield. Unexpectedly, triazolide **5** was the major product when the reaction was carried out in EtOH (entry 5) or even under aqueous conditions: **5** was isolated in excellent yield from 1:1 THF/H_2O (entry 6).[6]

The only previously reported Cu^{I} triazolide was isolated by Straub and co-workers by sequential reaction of sterically hindered SIPr−CuOAc (**6**) with a Li acetylide and a bulky azide under strictly anhydrous conditions (Scheme 1a).[7a] Conversely, in our study triazolide **5** was formed in high yield through the direct reaction of azide **2** and acetylene **3** under protic conditions in the presence of a full equivalent of ^{i}PrEt$_2$N·HPF$_6$, a remarkable result given that Cu^{I} organometallic species bearing anionic C-ligands[8] are typically air- and moisture-sensitive, requiring careful handling under an inert atmosphere and formation under aprotic conditions when employed in synthesis.[9,10]

Furthermore, although the steric isolation provided by the NHC ligand and the bulky substituents on the triazole itself allowed reactive Cu^{I} organometallic complex **7** to be isolated, Straub and co-workers reported that triazolide **7** was rapidly

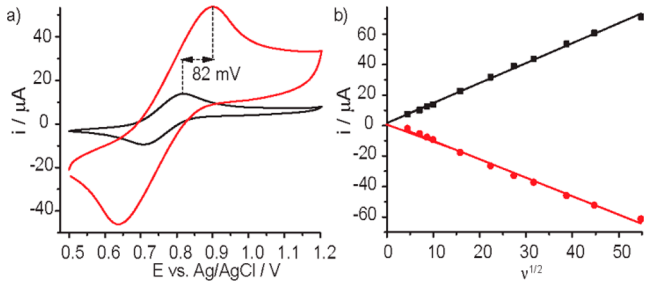


Figure 3. (a) Cyclic voltammograms at scan rates (υ) of (black) 0.1 and (red) 2.0 V s^{-1} recorded in a 2 mM solution of triazolide **5** in CH_2Cl_2 with 0.1 M ^{n}Bu$_4$N·BF$_4$ salt as the supporting electrolyte. (b) Plots of i_a (black) and i_c (red) as functions of $\upsilon^{1/2}$.

decomposed by AcOH (Scheme 1a).[7] In stark contrast, triazolide **5** reacted only slowly with AcOH (Scheme 1b, entry 1), requiring 2 h to reach >95% conversion to rotaxane **4**. Moreover, sterically hindered proton donors (entries 2−4) reacted even more slowly, with adamantylcarboxylic acid (entry 4) requiring a remarkable 18 h to completely consume the triazolide, demonstrating the sterically restricted nature of the mechanical bond. Stronger acids such as TFA (entry 5) and CCl_3CO_2H degraded **5** rapidly (<5 min). A brief study of the reactivity of isolated **5** revealed that it was also stable over 24 h in solution at 80 °C in both noncoordinating (CD_2Cl_2)[11] and strongly coordinating (dimethyl sulfoxide-d_6) solvents, when stirred vigorously in a mixture of CH_2Cl_2 and NH_3/EDTA(aq), or when dissolved in a mixture of CD_2Cl_2/MeOH-d_4.

The electrochemical stability of triazolide **5** was probed using cyclic voltammetry (Figure 3). A couple assigned to a Cu$^{I/II}$ process was observed with a middle peak potential (E_{mp}) of 0.84 ± 0.04 V vs Ag/AgCl. The peak separation (ΔE_p) varied with scan rate (υ) with $\Delta E_p \geq 59$ mV for all scan rates, which is consistent with an electrochemically quasi-reversible reaction.[12] Plots of peak current against $\upsilon^{1/2}$ were linear with gradients of unity for both anodic (i_a) and cathodic (i_c) currents, clearly demonstrating that the process is chemically reversible. Thus, triazolide **5** appears to be stable upon electrochemically induced electron transfer during the Cu$^{I/II}$ redox process, and the oxidized product is stable on the time scale of the cyclic voltammetry experiment.

To our knowledge, triazolide **5** is the first example of a mononuclear Cu^{I} organometallic species bearing an anionic C-ligand that is stable under aqueous conditions.[13] However, a small number of analogous thermodynamically stable mononuclear C−Cu^{II} and C−Cu^{III} complexes have previously been produced via C−H activation of highly preorganized substrates,[14] so we considered that this may be a possible route for the formation of **5**. However, when rotaxane **4** was subjected to the reaction conditions employed in the synthesis of **5** [$CuPF_6$·(MeCN)$_4$, ^{i}PrEt$_2$N, CH_2Cl_2, rt, 18 h], no trace of **5** was observed. Thus, triazolide **5** appears to be a true "trapped" CuAAC intermediate in which the steric hindrance provided by the mechanical bond prevents reprotonation of the Cu^{I}−C bond by ^{i}PrEt$_2$N·HPF$_6$.[15]

To probe the role of the rotaxane architecture in stabilizing the Cu^{I}−C bond, we investigated the reaction of phenylacetylene and phenyl azide mediated by $CuPF_6$·(MeCN)$_4$ in the presence of macrocycle **1**. Examination of the crude reaction mixture prior to aqueous workup revealed only the corresponding triazole product and recovered macrocycle, demonstrating the importance of the interlocked structure in

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stabilizing the reactive Cu^I organometallic species. Conversely, when aryl azide **2** was replaced with its benzylic homologue, 3,5-di-*tert*-butylbenzyl azide, under otherwise identical reaction conditions (Table 1, entry 2), ^1H NMR analysis indicated that the corresponding triazolide product was cleanly produced. However, aqueous workup led to quantitative protonation of the Cu^I–C bond to give the corresponding rotaxane (see the Supporting Information for full details). Thus, although the mechanical bond significantly enhances the stability of the Cu^I triazolide, it is not a sufficient precondition to render the Cu^I–C bond stable to water; the detailed structure of the thread also plays an important role.

In conclusion, for the first time the triazolide intermediate of the CuAAC reaction has been observed in the direct reaction of an azide and acetylene. The mechanical bond of triazolide **5** renders the normally reactive Cu^I–C bond kinetically stable to the point where **5** can even be synthesized under aqueous conditions in excellent yield. Indeed, the steric stabilization of the rotaxane architecture appears to be superior even to more commonly employed bulky ligands such as SIPr. Although it has previously been shown that mechanical bonding can be used to stabilize organic radicals,[16] protect dyes and conjugated polymers from environmental degradation,[17,18] and stabilize peptides to protease degradation,[19] this is the first time that mechanical bonding has been used to stabilize a reactive organometallic species. In view of the generality of the active template approach[20] and the relative ease with which such experiments can be designed and adapted,[21] we propose that the trapping of otherwise unstable species in mechanically bonded structures may prove to be a useful approach for the isolation and characterization of reactive intermediates in the future.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental details, including full characterization of all novel compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

s.m.goldup@qmul.ac.uk

Notes

The authors declare no competing financial interest.

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(6) When Et_3N was employed as the base in place of $^iPrEt_2N$ under the conditions reported in Table 1, entry 2, triazolide **5** remained the product but the reaction reached only 62% conversion after 18 h, while $BnNH_2$ led to only 8% conversion in the same time. In both cases, rotaxane **4** was not observed. Thus, it appears that the nature of the base affects the rate but not the outcome of the reaction.

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(8) In contrast, organometallic Cu^I complexes of neutral C-ligands such as N-heterocyclic carbenes and mesoionic carbenes, are often stable toward air and moisture and can be employed as catalysts in the CuAAC reaction. See respectively: (a) Díez-González, S.; Correa, A.; Cavallo, L.; Nolan, S. P. *Chem.—Eur. J.* **2006**, *12*, 7558–7564. (b) Nakamura, T.; Terashima, T.; Ogata, K.; Fukuzawa, S.-i. *Org. Lett.* **2011**, *13*, 620–623.

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(11) However, heating the reaction mixture (Table 1, entry 2) to 80 °C once the reaction was complete led to conversion of triazolide **5** to rotaxane **4** over 72 h, indicating that the $^iPrEt_2N{\cdot}HPF_6$ byproduct is acidic enough at elevated temperatures to slowly protonate the Cu^I–C bond. Similarly, conducting the same reaction at 80 °C led to the formation of rotaxane **4**. The instability of triazolide **5** at elevated temperatures under the reaction conditions contrasts with its stability once isolated and accounts for its absence under the conditions previously reported.[5]

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(15) During review, the question of the presence of a second Cu^I center in the key bond-forming step was raised. Although the AT-CuAAC reaction with larger macrocycles has been shown to involve at least two Cu^I ions,[4b] it is not clear that this is the case for smaller macrocycles given the sterically crowded nature of the cavity. Studies to elucidate this mechanistic detail are ongoing. We thank the reviewers for their comment.

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