Organic LETTERS

Letter

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Formation of a Hydrogen-Bonded Barbiturate [2]-Rotaxane

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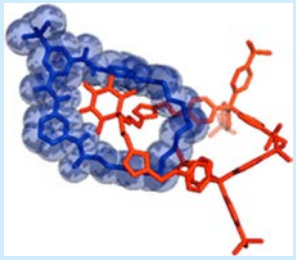
Supporting Information

ABSTRACT: Interlocked structures containing the classic Hamilton barbiturate binding motif comprising two 2,6-diamidopyridine units are reported for the first time. Stable [2]-rotaxanes can be accessed either through hydrogen-bonded preorganization by a barbiturate thread followed by a Cu^{+}-catalyzed "click" stoppering reaction or by a Cu^{2+}-mediated Glaser homocoupling reaction.



Interlocked structure synthesis generally relies on preorganization or templating using self-assembly, for example harnessing noncovalent interactions between a guest and a macrocyclic host, before covalent capture of the dynamic ensemble.[1] While a wealth of interlocked catenane and rotaxane structures have been reported, their synthesis often relies on the use of one of a limited number of popular motifs. Examples of directed synthesis of interlocked structures, where the necessary templates relies on hydrogen bonds, which afford intermolecular interactions between neutral molecules, have been reported.[2,3] Hydrogen bonds can offer both directionality and selectivity when multiple interactions are employed and have the advantage of being optically transparent and electrochemically stable. One of the most successful receptors for complexation of neutral molecules using hydrogen bonds is based on the highly selective barbiturate receptor developed by Hamilton and co-workers.[4] The complementarity between a bis-2,6-diamidopyridine group and the two imide sites on barbiturates results in the formation of six hydrogen bonds with a high association constant in noncompetitive solvents.[5] Various supramolecular systems harnessing this motif,[6] in the context of catalysis,[6a] sensing,[6b,c] photochromism,[6d] photoinduced charge separation,[6e] and the generation of self-assembled superstructures,[6f] have been reported. However, despite the success of this receptor−guest motif in generating supramolecular functionality, its use in the formation of interlocked structures has not been reported to date. Here we report the synthesis of such interlocked structures via two distinct strategies (Scheme 1) including **5**, which comprises an optimized macrocyclic variant of the Hamilton receptor bead and a barbiturate thread motif. Both bead and thread components of this rotaxane are accessible in two steps from commercial products, which demonstrates the potential for implementing this well-known H-bonding motif in various functional interlocked systems.

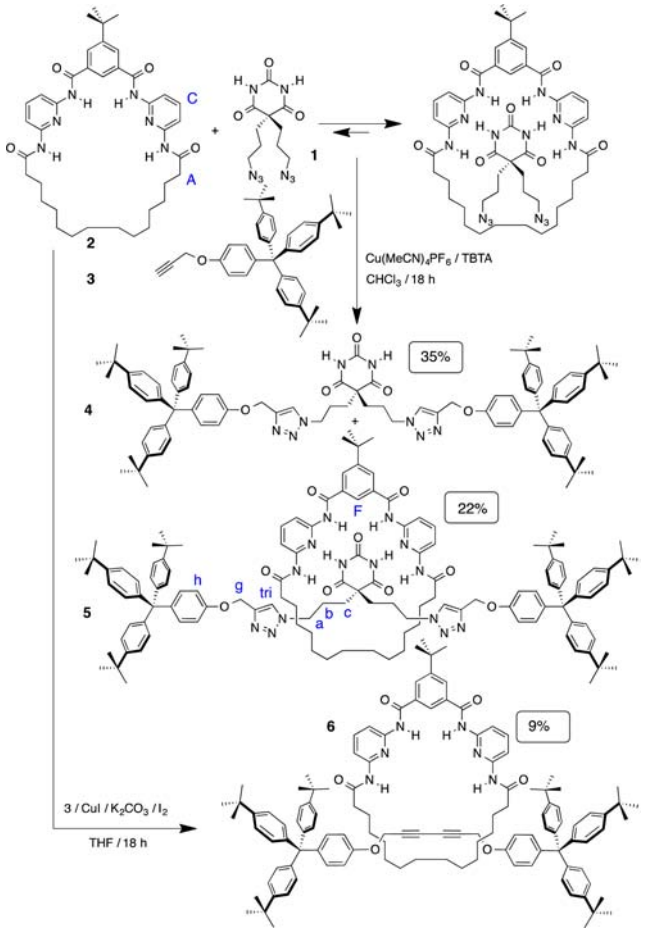
Bead component **2** was designed with the characteristic DADDAD H-bonding pattern suitable for binding a barbiturate guest, where D represents an H-bond donor group and A represents an H-bond acceptor group. Synthesis of **2** started with preparation of the central H-bonding unit through condensation of 3-*tert*-butylisophthalolyl chloride with 2,6-diaminopyridine.[7] Subsequent formation of a macrocycle of optimized size was achieved through condensation with the appropriate α,ω-diacyl chloride, giving **2** in 19% yield (see Supporting Information (SI) for synthetic details and characterization). Barbiturate thread synthon **1** offered the complementary ADAADA H-bonding pattern, while incorporation of only short alkyl chains was found to allow quantitative threading. Azide-terminated barbiturate **1** was synthesized in two steps (Scheme S1, SI).[8] Following dialkylation of diethyl malonate, condensation with urea in DMSO in the presence of NaH gave **1** in 35% yield. Formation of a 1:1 complex, fully satisfying the H-bonding motif, implies an interpenetrating pseudorotaxane structure, where the central barbiturate sp^3-carbon assures an orthogonality of the two chains in the barbiturate 5-position with respect to the plane of the receptor ring. Incorporation of reactive end groups on the thread, such as azides, would then allow further synthetic modification including stoppering.

Structural predisposition of this host/guest motif toward formation of complexes conducive with interlocked structure formation is supported by X-ray diffraction analysis of crystals of the molecular complex formed between **2** and barbital (5,5-

Received: January 11, 2014
Published: February 26, 2014

   dx.doi.org/10.1021/ol500099u | *Org. Lett.* 2014, 16, 1358−1361

Scheme 1. Synthesis of [2]-Rotaxane 5, Thread 4, and Glaser Coupling Product 6



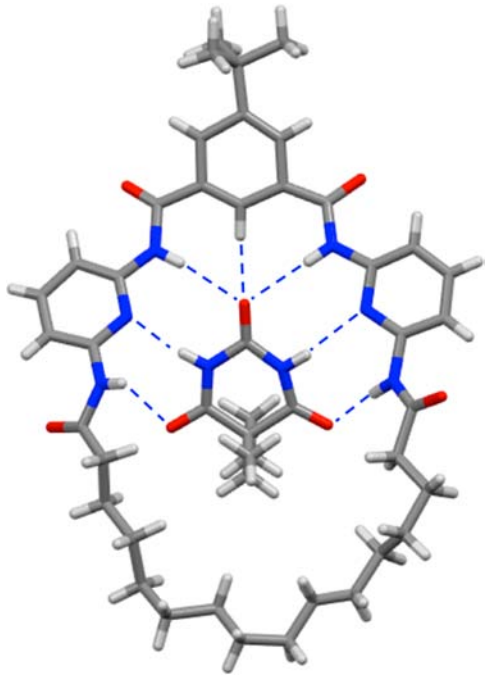


Figure 1. X-ray crystal diffraction structure of barbital ⊂ **2** (see SI for details). Dashed lines represent short contact distances of length (from left to right) 3.2, 2.0, 2.4, 2.2, 2.3, 2.1, and 1.9 Å.

diethylbarbituric acid); see Figure 1 and SI. Crystals were obtained via slow diffusion of pentane into a solution of the inclusion complex in dichloromethane, with a unit cell comprising two independent 1:1 complexes of similar geometry (see SI). The barbiturate guest is bound by six complementary H-bonds from the bisamidopyridine motif along with a central short contact [C−H---O═C] interaction and a length [N−H---O═C] of 1.9 to 3.2 Å with angles of 164° to 170°. In the complex, the medium annular plane of barbital formed an average tilt angle of ca. 26° with the medium plane of receptor **2** (see SI). Importantly, the two alkyl arms of the guest bonded to the sp^3 carbon protrude from both sides of the macrocycle cavity, a prerequisite for a stable threaded product.

Formation of complex **1** ⊂ **2** in chloroform could be followed by NMR, IR, and UV−vis spectroscopy. Indeed, analysis of the complexation-induced red-shifting of the pyridine absorption band of **2** at 315 nm allowed determination of an elevated binding constant (K_{ass} = 23 500 M^{-1}; see Figure S2). A 1:1 stoichiometry of the supramolecular inclusion complex **1** ⊂ **2** was confirmed via a Job plot (Figure S3), with the maximum absorbance change being obtained when the molar fraction ratio reached 0.5.

Binding in solution leading to complex **1** ⊂ **2** was also evidenced by ^{1}H NMR spectroscopy (Figure 2b). Addition of 1 equiv of guest to the macrocycle (10 mM, $CDCl_3$) resulted in strong downfield shifts of the N−H resonances of the barbiturate ($\Delta\delta$ = 3.8 ppm) and those of the amide protons of the receptor ($\Delta\delta$ = 1.5 and 1.6 ppm) compared to uncomplexed barbiturate **1** (Figure 2a) and receptor **2** (Figure 2c). A through-space correlation between amide protons of **1** and **2** (Figure S4) was observed by 2D NMR (NOESY) and confirmed their close proximity in the complex. Similarly, resonances corresponding to protons H_a, H_b, and H_c of the two alkyl arms of **1** correlated with the methylene protons (most clearly visible with H_A) of the alkyl chain of **2**. These observations are consistent with a symmetric interpenetrating pseudorotaxane structure. IR spectra of the 1:1 complex **1** ⊂ **2** (Figure S12, 10 mM) show intermolecular hydrogen bonding via a shift of characteristic N−H and C═O peaks, compared to uncomplexed **1** and **2**. In deuterated chloroform, free **2** shows an amide N−H stretching band at 3423 cm^{-1}, while guest **1** presents an N−H stretching band at 3378 cm^{-1} (see Figure S12). On mixing **1** and **2**, these bands shift to 3328 cm^{-1} for the N−H of **2** which is hydrogen bonded to the C═O of **1** and to 3100−2700 cm^{-1} (broad band) for the N−H of **1**. These results show complexation invoking all C═O and N−H groups consistent with formation of six hydrogen bonds.

Having the pseudorotaxane in hand, covalent capture of interlocked [2]-rotaxane **5** could be performed. Indeed, incorporation of the azide functions on **1** renders the pseudorotaxane **1** ⊂ **2** amenable to a mild stoppering reaction utilizing an efficient copper(I)-catalyzed alkyne−azide 1,3-cycloaddition (CuAAC) click reaction between an azide and an alkyne-containing stopper group,[9] which is an effective strategy for rotaxane and catenane formation.[10] The click reaction was performed between **1** ⊂ **2** (54 mM of each component in $CHCl_3$) and alkyne-terminated stopper **3** (Scheme 1), in the presence of a catalytic amount of $Cu(MeCN)_4PF_6$ and tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine (TBTA)[11] which resulted in the formation of [2]-rotaxane **5**, as well as free stoppered thread **4**. [2]-Rotaxane **5** and thread **4** were isolated by column chromatography (SiO_2: cyclohexane/ethyl acetate,

dx.doi.org/10.1021/ol500099u | *Org. Lett.* 2014, 16, 1358−1361

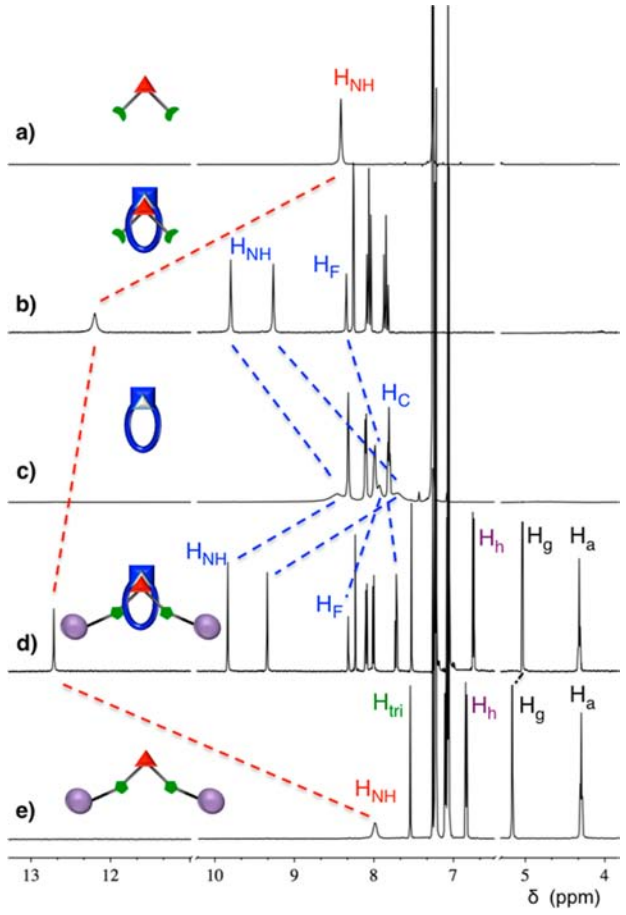


Figure 2. Partial ^{1}H NMR spectra (600 MHz) of barbiturate **1** (a), pseudorotaxane **1** ⊂ **2** (1:1, 10 mM) (b), macrocyclic receptor **2** (c), [2]-rotaxane **5** (d), and corresponding thread **4** (e) recorded at room temperature in $CDCl_3$.

7:3, v/v) in 22% and 35% yields, respectively, under conditions where the initial proportion of bound pseudorotaxane was >97%. Thread **4** could also be obtained in a much higher yield (80%) by performing the reaction between **1** and stopper **3** in the absence of **2**. It is noteworthy that macrocylic receptors containing a pyridine chelator have previously been shown to participate in rotaxane formation through complexed metal-mediated coupling reactions with different transition metals, including copper.[12] However, in the current case no evidence of alkyne−alkyne coupling was evidenced under reaction conditions used in the presence of barbiturate **1**. Optimized conditions for the Glaser homocoupling reaction in the absence of barbiturate **1** (bottom, Scheme 1), which is catalyzed by copper(II) rather than copper(I), showed only a modest yield of rotaxane **6** (9%). This result allows us to conclude that the click reaction is both compatible and orthogonal with H-bonded barbiturate templating.

Rotaxane **5** was fully characterized by 1D- and 2D-NMR, mass spectrometry, and IR measurements (Figures S1, S21, S27, S32, S37, S42, and S44). The ^{1}H NMR spectrum of **5** (Figure 2d) shows downfield shifts of several signals with respect to noninterlocked **2** and **4** (Figure 2c and 2e, respectively). In particular, downfield shifts of the amide proton signals of the macrocycle ($\Delta\delta$ = 1.7 ppm and 1.9 ppm) and those of the barbiturate protons in the thread ($\Delta\delta$ = 4.8 ppm) indicate H-bonding interactions. Stronger H-bonding in **5** compared with pseudorotaxane **1** ⊂ **2** is shown through further downfield shifting and narrowing of the barbiturate amide H_{NH} resonance ($\Delta\delta$ = 0.6 ppm; Figure 2d vs Figure 2b). NOESY experiments on pure **5** (Figure S44) show similar through-space barbiturate−receptor interactions as the pseudorotaxane **1** ⊂ **2** (see description above). IR spectroscopy was used to monitor the progression of the stoppering reaction between complex **1** ⊂ **2** and **3** (Figure S13). A decreasing intensity of alkyne (3308 cm^{-1}) and azide bands (2101 cm^{-1}), concomitant with the increase of the 1,2,3-triazole product absorption (3100−3150 cm^{-1}), was observed. Tracking absorbance changes with time (Figure S14) showed that the concentration of the two reactants diminished at a similar rate, typical of the click reaction, which corresponds to formation of thread **4** within the rotaxane. There was also evidence for the emergence of some free receptor with respect to the initial mixture of **1** and **2**, represented by an increase in a band associated with uncomplexed N−H (3423 cm^{-1}). This implies some dethreading on adding the first stopper group. A lower binding constant would contribute to, and explain, the formation of free **4** in addition to [2]-rotaxane **5**.

Further evidence for the formation of the [2]-rotaxane comes from comparison of ^{1}H NMR data of **5** with the non-interpenetrating perched complex **4**·**2**, formed by mixing the two preformed components in $CDCl_3$ (Figure S7, 10 mM). Compared to the signals for [2]-rotaxane **5** under the same conditions, these give small upfield shifts in the two signals of the amide protons of **2** ($\Delta\delta$ = 0.1 ppm), and a strong upfield shift in the barbiturate amide proton resonances ($\Delta\delta$ = 4.2 ppm). The **4**·**2** perched complex binding constant of 4000 M^{-1} in $CHCl_3$ (measured by fitting spectrophotometric data, Figure S8) is significantly weaker than that for the **1** ⊂ **2** complex, presumably for steric reasons. In addition, while the NMR spectrum for the **4**·**2** system in DMSO indicates a predominantly dissociated complex (Figure S6), the signals for **5** in DMSO (Figure S5) are remarkably similar to those in $CDCl_3$, denoting that the H-bonding motif remains intact in this competitive solvent. The kinetically-inert nature of interlocked compound **5** was verified via slippage experiments (Figure S5). No evidence for dethreading was obtained, as judged by ^{1}H NMR spectroscopy, even upon heating **5** (10 mM) for several days at 120 °C in DMSO. Similarly, heating equimolar quantities of **4** and **2** together for several days under similar conditions showed no evidence of threading (Figure S6).

In summary, unprecedented barbiturate-templated rotaxane formation is shown, thus adding to the relatively small library of motifs responsible for formation of mechanically interlocked structures. Rotaxane capture was achieved by an orthogonal stoppering reaction using a 1,3-cycloaddition click reaction on a readily accessible hydrogen-bonded pseudorotaxane. This versatile information-rich H-bonding templating motif holds promise for the development of multistation molecular machines and devices and is compatible with photoactive and electroactive variants.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, synthesis and characterization data of **1**−**7** (^{1}H, ^{13}C, COSY, HMBC, HSQC, NOESY NMR, HRMS, IR), single crystal X-ray data, and FTIR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

dx.doi.org/10.1021/ol500099u | *Org. Lett.* 2014, 16, 1358−1361

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Financial support from the School of Chemistry at the University of Birmingham (Ph.D. studentships to M.R. and P.J.T.); Advantage West Midlands for equipment; the EPSRC for the award of a Leadership Fellowship (EP/G007578/1); Région Aquitaine; University of Bordeaux; CNRS; and Ministère de la Recherche et de l'Enseignement Supérieur (A.T.) is gratefully acknowledged.

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