Synthesis of an Adamantane-based Tetralactam and its Association with Dicarboxamides

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Abstract: Tetralactam macrocycles are suitable candidates to be employed as synthetic receptors for charged or neutral guests. In the sensing of neutral molecules, non-polar solvents such as chloroform or dichloromethane are usually employed since the hydrogen-bonded interactions can be established. Thus, one of the main limitations of the studied macrocycles is their low solubility in those solvents. Herein we describe the synthesis of an adamantane-based tetralactam macrocycle which is soluble in chlorinated solvents. For this purpose, by following a clipping methodology, we firstly synthesized a kinetically stable pseudorotaxane, constituted by a removable tetraalkylfumaramide thread and the desired macrocycle. A subsequent thermal dethreading straightforwardly yielded the adamantane-based macrocycle. Afterwards the affinity of this receptor for a series of fumaramides and succinamides guests was studied, calculating the association constants when the corresponding [2]pseudorotaxanes are assembled.

Keywords: [2]pseudorotaxane, adamantane, amide, non-covalent interactions, molecular recognition

INTRODUCTION

Mechanically interlocked compounds[1] consist of two or more entangled components between which there is not any covalent linker. These components are connected by a so-called mechanical bond.[2] These systems are considered molecular compounds and thus a covalent bond must be broken in order to break apart their components.[3,4]

[2]Rotaxanes[5,6,7] are the most important category of mechanically interlocked molecules constituted by two components: a linear component, which has bulky groups at the ends, and a cyclic component, which surrounds the first. Although it has been more than four decades since the first [2]rotaxane was synthesized,[8] the most important advances in the research of this type of compounds have been produced in recent years.[1-7]

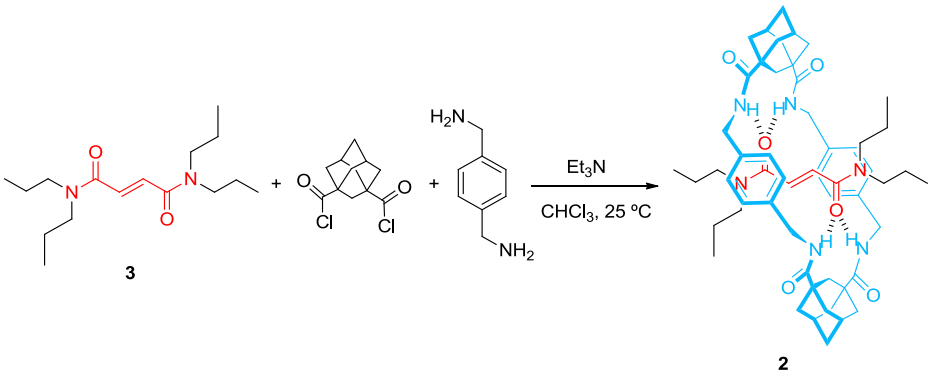
In one of our research programs focused to the development of novel hydrogen-bonded rotaxanes,[9,10,11,12,13,14,15,16] we described the preparation of kinetically stable pseudorotaxanes[12,15] bearing benzylic amide macrocycles and a dicarboxamide-based template such a fumaramides or succinamides. These studies settled the structural requirements of the interlocked systems to allow the dethreading reaction and their kinetic parameters under thermal and photochemical treatments.

Benzylic amide macrocycles have been employed as model compounds when investigating the effects of the mechanical bond in materials elaborated with hydrogen-bonded interlocked compounds.[1-7,17] These tetralactam rings are also able to bind to a variety of guest as squaraines[18,19] and acenes[19,20,21] guests, through molecular recognition processes. In less extension, these macrocycles have been used for sensing carbon dioxide[22] and to detect glucose.[23,24] Recently, Smith and coworkers reported that square planar precious metal halogen complexes such as $AuCl_4^-$, $AuBr_4^-$ and $PtCl_4^-$, are excellent guests.[25]

Herein we describe the preparation of a benzylic amide macrocycle bearing two adamantane units by the dethreading of the corresponding hydrogen bonded [2]rotaxane, which was previously prepared via a five-component clipping reaction. The association studies with different dicarboxamides in a non-competitive solvent is also reported.

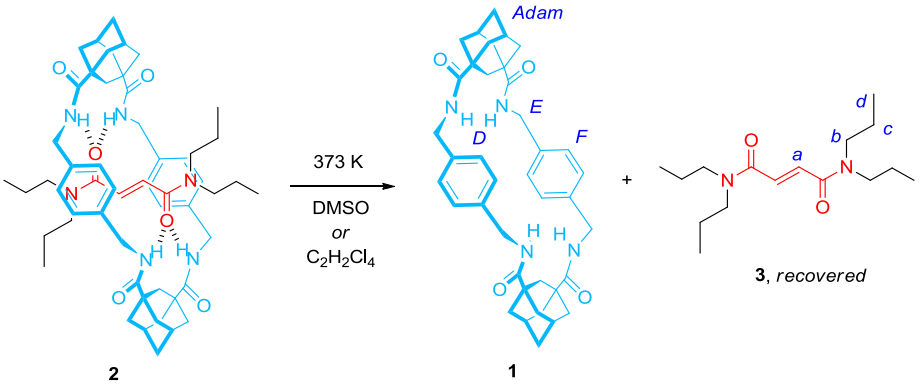
Result and discussion

For the synthesis of the desired adamante-based macrocycle **1** we followed a 2-step protocol. Firstly, we assembled the corresponding [2]rotaxane **2** bearing a removable tetrapropyl fumaramide thread **3** (Scheme 1). For this we carried out a five-component clipping reaction between *p*-xylylenediamine, 1,3-adamantanedicarbonyl dichloride and the thread **3**, providing the [2]rotaxane **2** in 5 % yield. The advantage of the initial synthsis of the rotaxane **2** resides in its easy isolation from other reaction byproducts. The obtained yield was lower than the reported ones for other tetraalkyl fumaramides analogs with an isophthaloyl-based macrocycle,[15] a consequence of the lesser acidity of the hydrogens of the amides for the macrocycle and thus, a lower stability of the different supramolecular intermediates.



Scheme 1. Synthesis of rotaxane **2**.

The next step consisted in a thermal dethreading of rotaxane **2** to afford the free macrocycle **1** (Scheme 2).[12] The reaction was conducted at 100 °C in two different solvents: tetrachloroethane and DMSO. In both solvents the reaction proceeded efficiently in short reaction times (84 % yield for DMSO and 80 % for $C_2H_2Cl_4$). When the more polar DMSO was employed the dethreading was faster (less than 1 h). In contrast, traces of DMSO were observed when the macrocycle **1** was isolated, even after exhaustive washings with various solvents, fact undesirable when is going to be tested as hydrogen-bonding receptor. Importantly the thread **3** could be totally recovered for future reutilizations. As expected, macrocycle **1** was soluble in CH_2Cl_2 or $CHCl_3$, preferred solvents for the NMR titrations experiments.



Scheme 2. Synthesis the macrocycle **1** following a thermal dethreading protocol.

Figure 1 displays the stacked ^{1}H NMR spectra of the thread **3**, its corresponding rotaxane **2** and the free targeted macrocycle **1** isolated after the dethreading protocol. The presence of the macrocycle over the fumaramide station in rotaxane **2** triggers the shifting to high field of its corresponding signals ($\Delta\delta H_a$: 1.4 ppm). After the dethreading reaction the signals referred to the methylene protons H_E in macrocycle **1**, which appeared as two signals due to the diastereotopic nature of these protons in rotaxane **2**, resonates as a only one signal at 4.43 ppm, due to the loss of the common chair-like conformation of this type of polyamide macrocycle in entwined structures. Moreover, the amide protons NH_D experienced an important movement to lower chemical shifts

when the rethreading takes place, revealing the disruption of the hydrogen-bonded interactions thread-macrocycle.

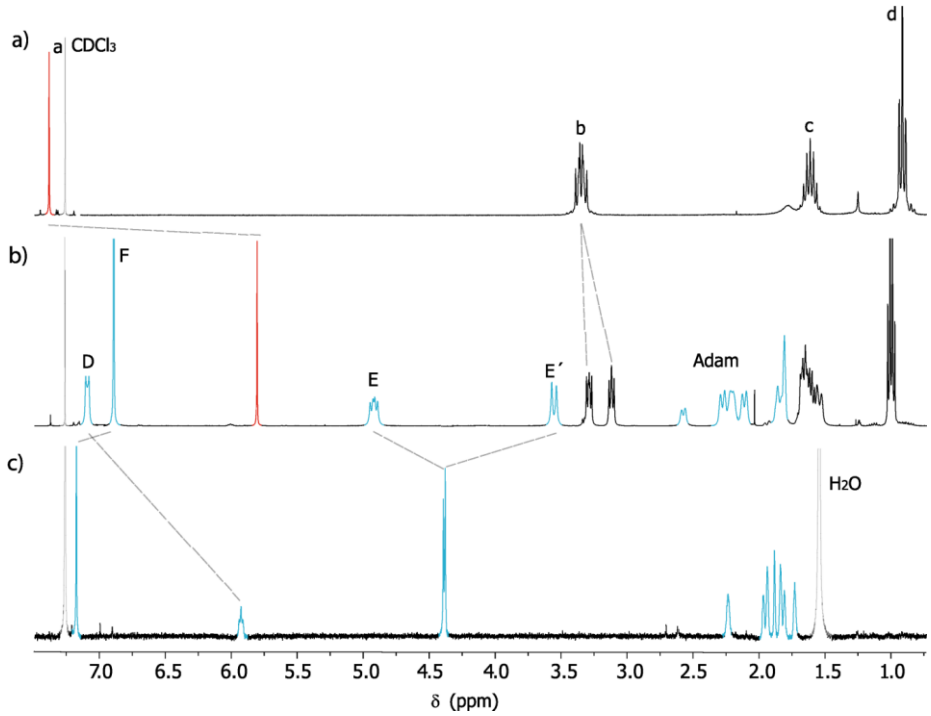
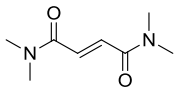


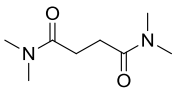
Figure 1. ^{1}H NMR spectra (400 MHz, $CDCl_3$, 298 K) of: a) thread **3**; b) [2]rotaxane **2**; c) macrocycle **1**. See lettering in Scheme 2.

Next, we tested the behavior of the macrocycle **1** as hydrogen-bonding receptor for the dicarboxamides *N,N,N′,N′*-tetramethylfumaramide (**4)** and *N,N,N′,N′*-tetramethylsuccinamide **(5)**, which were obtained using the reported synthetic protocols (Table 1).[26,27] The dynamic slipping process of guests **4** and **5** with macrocycle **1** was studied by carrying out titration experiments followed by ^{1}H NMR spectroscopy. For this goal a 40 mM solution of guest (**G**) was sequentially added to a 1 mM solution of macrocycle **1** in $CDCl_3$ and the corresponding association constants calculated. The displacement of the ^{1}H NMR signal of the amide NH_D was monitorized during the successive addition of the guests. The addition of increasing amounts of guest triggers the displacement of this signal to lower field due to the establishment of hydrogen-bonded interactions towards the dynamic formation of the pseudorotaxanes. The obtained constants for the formation of the 1:1 complex **G·1** were low if compared with the constants of other polyamide macrocycles with similar guests.[28] Probably, the low acidity of the hydrogen of the macrocyclic amides diminishes the ability of this ring as receptor. The structural similarity of the employed dicarboxamides, having linkers between the hydrogen bond acceptors in **4** and **5**, *-CH=CH-* and *-CH_2-CH_2-*, afford comparable association constants for these guests (Table 1). Note that the interaction is slightly stronger when the more rigid fumaramide **4** is used as guest.

Table 1. Calculated association constants between macrocycle **1** and guests **4**-**5**.



4



5

Guest	k_{assoc} (M^{-1})[a]
4	28.3
5	24.9

[a] Calculated by using the software HypNMR 2008.

CONCLUSIONS

In summary, we have described the assembly of an adamantane-based polyamide macrocycle, which resulted to be soluble in chlorinated solvents. This system was studied as receptor for succinamide and fumaramide guests. By carrying out titration experiments the association constants were calculated, revealing a limited capacity of this adamantane-based macrocycle for the establishment of hydrogen-bonded interaction with the selected threads. Currently, we are looking other suitable candidates for enhancing the interaction with this receptor.

EXPERIMENTAL SECTION

Preparation of [2]rotaxane 2

The thread **2** (1.00 g, 3.50 mmol) and Et_3N (6 mL, 42 mmol) in $CHCl_3$ (250 mL) were stirred whilst solutions of *p*-xylylenediamine (3.85 g, 28.32 mmol) in $CHCl_3$ (20 mL) and 1,3-adamantanedicarbonyl dichloride (7.40 g, 28.32 mmol) in $CHCl_3$ (20 mL) were simultaneously added over a period of 4 h using a motor-driven syringe pump. Afterwards the resulting suspension was filtered through a Celite® pad and the filtrate was washed with water (2 x 100 mL), $NaHCO_3$ (2 x 100 mL), HCl 1M (2 x 100 mL) and brine (2 x 100 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered and removed under reduced pressure. The resulting solid was subjected to column chromatography (silica gel) to yield unconsumed thread and [2]rotaxane **2** (141 mg, 5%). Rotaxane **2** showed identical spectroscopic data as those reported in ref. 15.

Preparation of macrocycle 1

A solution of rotaxane **2** (104 mg, 0,111 mmol) in tetrachloroethane (3 mL) was stirred at 100 °C for 2 days. After this time Et_2O (1 mL) and pentane (3 mL) were added, precipitating a white solid. The solid residue was filtered and washed with pentane, giving the title product as a white solid (58 mg, 80 %). Macrocycle **1** showed identical spectroscopic data as those reported in ref 15.

Titration experiments of macrocycle 1 with dicarboxamides 4 and 5

^{1}H NMR titration spectra were recorded on a Bruker Avance 400 MHz spectrometer, in $CDCl_3$ at 298 K.

General method for the titration experiments: A solution of guest (40 mM, and 1 mM in macrocycle **1**) was added to a solution of macrocycle **1** (0.5 mL, 1 mM). The chemical shift of a specific host proton was monitored for 14 titration points (for 0.0-34.0 equivalents of added guest). The signal referred to the amide proton NHD was used to determine the corresponding association constant k_{assoc} by using the software HypNMR 2008.

ACKNOWLEDGEMENTS

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