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[2]Pseudorotaxane Composed of Heteroditopic Macrobicycle and Pyridine *N*-Oxide Based Axle: Recognition Site Dependent Axle Orientation

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Supporting Information

ABSTRACT: A strategy for threading an axle having a hydrogen bond acceptor unit in the cavity of a C_{3v} symmetric amido-amine macrobicycle is investigated. The macrobicycle acts as a wheel in its neutral as well as triprotonated states to form threaded architectures with a pyridine *N*-oxide derivative. The negative oxygen dipole of the axle is capable of [2]pseudorotaxane formation in two different orientations with the wheel in its neutral and triprotonated states.

Pseudorotaxanes are important building blocks for the syntheses of mechanically interlocked structures such as rotaxanes and catenanes for the construction of molecular level machines and switches.[1] Thus, the development of pseudorotaxanes/rotaxanes with new features is important to address novel mechanical and switching properties.[2] Literature reports show that most threaded molecules consist of macrocycles as wheels with various recognition elements in their backbones. Thus, crown ethers,[3] tetra-lactam wheels,[1c,4] 1,10-phenanthroline based macrocycles,[5] cyclobis(paraquat-*p*-phenylene) systems,[6] cyclodextrins,[7] cucurbiturils,[8] etc. are extensively utilized in this area. However, compared to macrocyclic wheels, macrobicyclic/cryptand based threaded molecules are less frequently reported. In this direction, Gibson, Huang and coworkers are successful in threading paraquat and diquat guests into crown ether-based cryptands which result in a variety of mechanically interlocked molecules with new properties.[9] Macro-polycyclic cryptands have evolved as receptors for various neutral/cation/anion guests and have revealed considerable information about guest encapsulation and recognition properties.[10] In general, cryptands are three-dimensional bicyclic hosts with preorganized cavities and usually offer higher binding affinities with the guest than the corresponding macrocycles due to preorganization of the hosts during the association process and the macrobicyclic effect in addition to the chelate effect.[10a] Threading of an axle through a polycyclic cage demands its preorganization, proper cavity dimension, and placement of recognition element in the bicyclic cage. Recently, we have reported a new hybrid macrobicylic host with two distinct cavities consisting of amine and amide as potential recognition elements for anionic guests.[11] Herein, we show the formation of [2]pseudorotaxanes on threading of a pyridine *N*-oxide (PNX) based axle into an amido-amine based heteroditopic macrobicyclic wheel in its neutral state (MBC) as well as triprotonated state (TMBC) (Figure 1) in two different binding orientations. To the best of our knowledge, this represents the first example of C_{3v} symmetric heteroditopic cryptand based [2]pseudorotaxanes having two distinct states of axle binding modes.

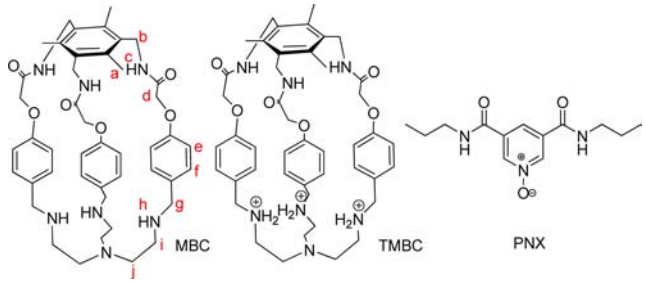

Figure 1. Chemical structure of wheels MBC, TMBC, and axle PNX.

The MBC consists of two clefts, triamide, and tetra-amine which are separated by *p*-phenylene spacers that provide rigidity to this cage and could also provide aromatic $\pi-\pi$ stacking interactions with aromatic guests. It has been found that the MBC is preorganized and the rigidity in the skeleton keeps the conformation nearly unchanged in triprotonated TMBC and unprotonated MBC states.[11] This result provides the opportunity to explore MBC in protonated as well as unprotonated states to develop a threading strategy. On the other hand, the triamide cleft of MBC and triammonium cleft of TMBC can separately interact with the incoming anionic moiety of the axle component to assist the threading process.

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Here our choice of axle is a pyridine *N*-oxide derivative, where a combination of hydrogen bonding, $\pi-\pi$ stacking, and hydrophobic interactions might play significant roles in threading. Importantly, pyridine *N*-oxide derivatives are interesting compounds for molecular recognition,[12] catalysis,[13] synthetic double helices,[14] and synthesis of macrocycle based threaded compounds.[15]

The axle, 3,5-bis[*N*-(*n*-propyl)carboxamido]pyridine-*N*-oxide (PNX), is synthesized in two steps from pyridine 3,5-dicarboxylic acid in good yield (Supporting Information). The amido-amine hybrid macrobicyclic MBC and triprotonated complex [TMBC$(PF_6)_3$] are synthesized by our previously reported procedures.[11]

Electrospray ionization mass spectrometry (ESI-MS) of an equimolar mixture of the axle PNX and wheel MBC shows a peak at m/z 1057.48 corresponding to [PNX@MBC + H]$^+$(Figure 2), indicating the formation of a [2]pseudorotaxane with 1:1 stoichiometry.

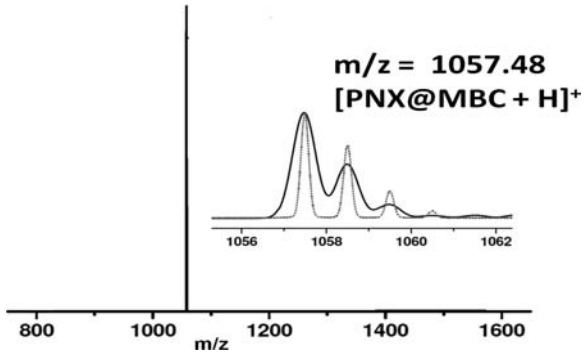

Figure 2. ESI-MS (+ve) mode of RTX. Inset shows similar isotopic distribution patterns for calculated (dotted) and experimental (bold) spectra of [PNX@MBC + H]$^+$.

Figure 3 represents ^{1}H NMR spectra of PNX, MBC, and a solution of PNX and MBC in $CDCl_3$. We observe significant

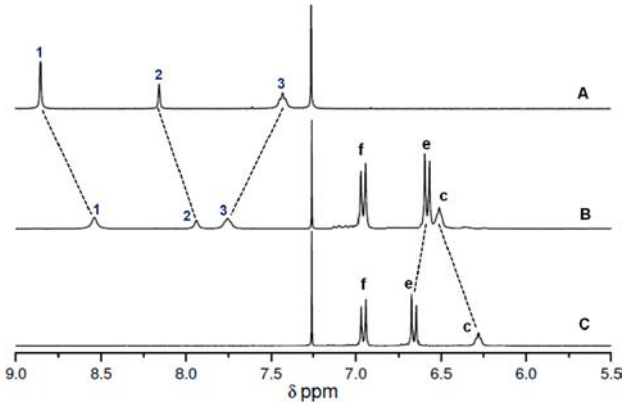

Figure 3. Partial ^{1}H NMR (300 MHz) spectra in $CDCl_3$ at 293 K of (A) axle PNX (7.5×10^{-3} M), (B) PNX + MBC (7.52×10^{-3} M), and (C) macrobicycle MBC (7.55×10^{-3} M).

shifts in the ^{1}H NMR spectrum of equimolar PNX and MBC in $CDCl_3$. The ^{1}H NMR spectrum of the solution provides evidence for the $\pi-\pi$ stacking interaction between electron-rich phenylene of the macrobicycle and the electron-deficient pyridine *N*-oxide aromatic moiety of the axle. This is signified by the upfield shifts of pyridine protons 1 and 2 and phenylene protons compared to their uncomplexed counterparts. This indicates host–guest interactions via interpenetration of PNX in MBC to form a [2]pseudorotaxane PNX@MBC. Importantly, the signals corresponding to macrobicycle amide c and axle 3 protons are significantly shifted downfield in the threaded complex, which could be due to the binding of the pyridine *N*-oxide oxygen dipole in the triamide cleft of MBC.

The DOSY NMR spectrum of equimolar PNX and MBC in $CDCl_3$ at 298 K provides further evidence for the formation of the threaded structure PNX@MBC (Figure 4b). The peaks

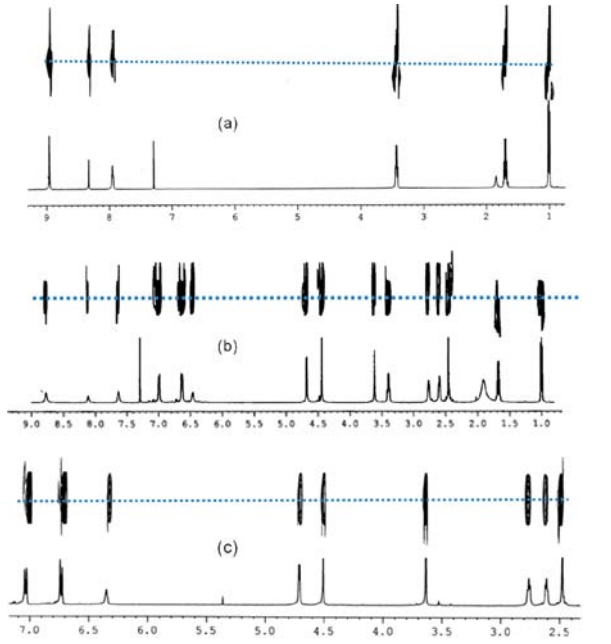

Figure 4. Partial DOSY spectra in $CDCl_3$ (7.52×10^{-3} M) of (a) PNX, (b) PNX@MBC, and (c) MBC.

which correlate to the signals in the chemical shift are in a horizontal line. Thus, all proton signals due to the wheel MBC and axle PNX display the same diffusion coefficient ($D = 5.5 \times 10^{-10}$ m^2 s^{-1}), supporting their participation in a common aggregate. The DOSY NMR spectra of individual components PNX and MBC having diffusion coefficient values 6.3×10^{-10} and 5.1×10^{-10} m^2 s^{-1} are shown in Figure 4a and 4c, respectively. Disassembly of PNX@MBC is observed in the presence of excess trifluoroacetic acid (Figure 11S in Supporting Information). It could be due to the protonation of the negative oxygen dipole of the PNX.

The weak acidic nature of MBC amide protons shows negligible chemical shifts in the NMR signals with the PNX guest. Thus, our effort toward the calculation of the association constant and stoichiometry by ^{1}H NMR titration is unsuccessful.

Further, formation of [2]pseudorotaxane is also achieved between triprotonated macrobicycle TMBC and PNX. The ^{1}H NMR spectrum of equimolar TMBC and PNX in 9:1 CD_3CN/$CDCl_3$ shows formation of [2]pseudorotaxane PNX@TMBC. Figure 5 shows comparison of ^{1}H NMR spectra of the threaded aggregate PNX@TMBC, the free axle PNX, and the free TMBC in 9:1 $CD_3CN/CDCl_3$. The upfield shifts of protons 1 and 2 of PNX and e proton of TMBC compared to that of free components indicate threading of PNX into the TMBC and supports the existence of $\pi-\pi$ stacking interaction between the

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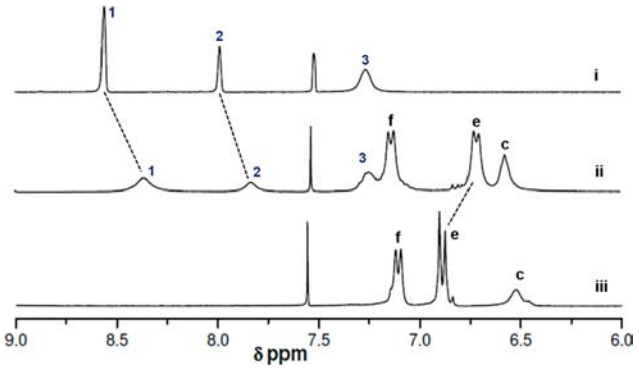

Figure 5. Partial ^{1}H NMR (300 MHz) spectra in 9:1 $CD_3CN/CDCl_3$ at 293 K of (i) component axle PNX (7.5×10^{-3} M), (ii) PNX + TMBC (7.58×10^{-3} M), and (c) triprotonated macrobicycle TMBC (7.26×10^{-3} M).

electron-deficient pyridine *N*-oxide aromatic surfaces of the axle and the phenylene moiety of TMBC.

Formation of [2]pseudorotaxanes PNX@MBC and PNX@TMBC are confirmed by single crystal X-ray diffraction studies. Slow evaporation of an equimolar mixture of PNX and the triiodide salt of TMBC in 9:1 CH_3OH/H_2O at room temperature results in crystals suitable for single crystal X-ray structural analysis. On the other hand, a solution of MBC and PNX in 9:1 $CHCl_3/CH_3OH$ results in very few crystals of poor quality at 4 °C. Single crystal X-ray structure analysis of **1**, PNX@MBC and **2**, and PNX@TMBC shows complete threading of the axle into the macrobicyclic wheel via formation of [2]pseudorotaxanes (Figure 6). The distances between the centroid of the bridge-

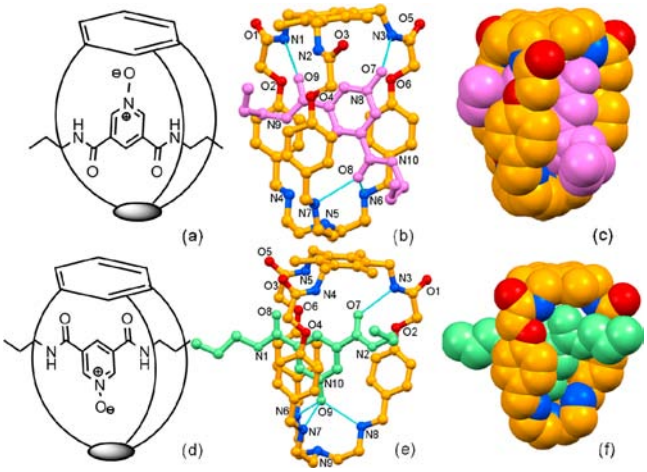

Figure 6. Cartoon presentations of [2]pseudorotaxanes (a) PNX@MBC and (d) PNX@TMBC. Single-crystal X-ray structures of [2]pseudorotaxanes 1,PNX@MBC and 2,PNX@TMBC (b and e); and space-filling models (c and f) respectively. H atoms, counteranions, and solvents are omitted for clarity.

head mesitylene and the apical nitrogen center are measured as 11.81 and 11.40 Å for protonated and unprotonated states of wheels, respectively, which are close to the values obtained in the case of MBC (12.19 Å).[11] This suggests the preorganization of the MBC which favors the formation of threaded complexes. In the case of TMBC, the pyridine *N*-oxide oxygen dipole is in the triammonium cleft of the wheel, and for the unprotonated macrobicycle MBC, the pyridine *N*-oxide oxygen dipole is in the triamide site of the wheel. This observation suggests the dual binding modes of the axle in the cage of the wheel in its protonated and unprotonated states. Three strong hydrogen bonding interactions are observed between the ammonium protons of TMBC and the pyridine *N*-oxide oxygen dipole for PNX@TMBC. On the other hand, in the case of the PNX@MBC complex, the oxygen dipole of the axle is hydrogen bonded with the amide protons of MBC. Since the single crystal data of PNX@MBC are poor, we further undertook theoretical investigation of PNX@MBC.

The DFT optimized structure (B3LYP, 6-31g) of the threaded host–guest assembly (PNX@MBC) shows a very similar pattern as that obtained from the crystal structure described above. The solid state structural analyses show that the cavity length of PNX@MBC is 11.42 Å (Figure 9S in Supporting Information) which is very close to that (11.20 Å) obtained from the optimized structure. Thus, the energetics of the interlocked assembly (M062X, 6-31+g(d)) encourages us to predict the threading behavior of the macrobicyclic host in the vacuum state. The computation is carried out by calculating the energy difference between 1 mol of macrobicyclic guest and 1 mol of axle with the same equivalent of the threaded assembly (PNX@MBC). According to the calculation, the threaded assembly formation is found to be 36.0 kcal/mol (M062X, 6-31+g(d)) more favorable than the summation of the individual energy of MBC and PNX.

In conclusion, a new strategy for self-assembly of [2]-pseudorotaxanes between a hybrid macrobicylic host with two distinct cavities consisting of an amine and amide as potential recognition elements and an anionic guest is demonstrated for the first time. We have established that a pyridine *N*-oxide derivative can form [2]pseudorotaxanes, which are stabilized by hydrogen bonding and $\pi-\pi$ stacking interactions with a triamide based heteroditopic macrobicycle, in solution and in solid states. We have also shown that the overall cavity dimension of this hybrid macrobicycle is relatively large and has two distinct compartments of different environments that have potential for dual binding orientation of the encapsulated guest. In particular, this type of C_{3v} symmetric heteroditopic host with the new guest recognition property may offer an alternative approach for the construction of a variety of interlocked architectures with new properties.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, synthesis, and crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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Monash University, Australia for his help to solve the structure of **1**.

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