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Modular construction of pyrido[24]crown-8-based templates in the self-assembly of cross-linked [n]catenanes

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ABSTRACT

Starting from the versatile 4-bromopyrido[24]crown-8 building block, novel ditopic and tritopic receptors have been synthesized and shown to be appropriate hosts for bis(4-formylbenzyl)ammonium hexafluorophosphate. Association constants (per binding site) for the corresponding [3]- and [4]pseudorotaxanes, assembled from these components, were determined to be 2753 M^{-1} and 723 M^{-1}, respectively. Mechanical bond formation was attempted utilizing dynamic imine bond formation between the formyl groups of the bound dibenzylammonium threads and *p*-phenylenediamine.

Introduction

For over 50 years, supramolecular chemistry has lent itself to the isolation of topologically-fascinating molecules[1–6] that are captivating in their own right.[7–12] The beginning of the synthesis of mechanically interlocked molecules (MIMs) is preserved in a 1960 publication by Wasserman[13] – the first reported synthesis of a [2]catenane by statistical threading. Since then, the protocols for the assembly of MIMs have evolved considerably,[14–16] utilizing highly efficient template-directed self-assembly protocols coupled with thermodynamically-governed post-assembly modifications to supramolecular complexes.[17–19] Over ten years ago, Chang et al.[20] proposed the existence of a new class of MIMs beyond the (by that time) well-established catenanes and rotaxanes. This class of compounds would later be named suitanes[21] which comprise a rigid cationic scaffold (with two or more protruding molecular arms) and a flexible net-like overlay consisting of at least two macrocycles. Williams et al.[21] later realized the synthesis of the first suitane by modification of the initially proposed design and, soon thereafter, Northrop et al.[22] reported two new members of the suitane family using a similar approach. The success of those that came before us[21–26] has proven that templation coupled with dynamic covalent chemistry[19,27] provides a highly efficient route towards the synthesis of MIMs of varying complexities.

We have therefore adopted this approach and demonstrated that it is possible to extrapolate suitane assembly to a reverse recognition system – a scaffold imparted with macrocyclic polyethers which can bind dibenzylammonium (DBA) threads. Subsequent linking of the bound threads (by covalent bond formation under thermodynamic control) affords the interlocked molecule whose topology is perhaps best described as a cross-linked [n]catenane or pseudocatenane.[28–37] Herein we report the synthesis of two novel bridged pyrido[24]crown-8-based receptors (pyridine-based crown compounds being previously shown[38] to better complex DBA ions than the commonly used dibenzo-24-crown-8 system) and demonstrate their ability to bind formyl-substituted dibenzylammonium threads affording precursors to interlocked molecules.

The synthesis of crown ethers is challenging in its own right. High dilution conditions are often used to promote ring closure (to form the macrocyclic monoadduct) but the process is still significantly limited by competition from step-growth polymerization. The synthesis of polytypic DBA receptors bearing several macrocyclic units is thus perhaps most aptly pursued via a modular approach in which preformed crown ethers can be covalently

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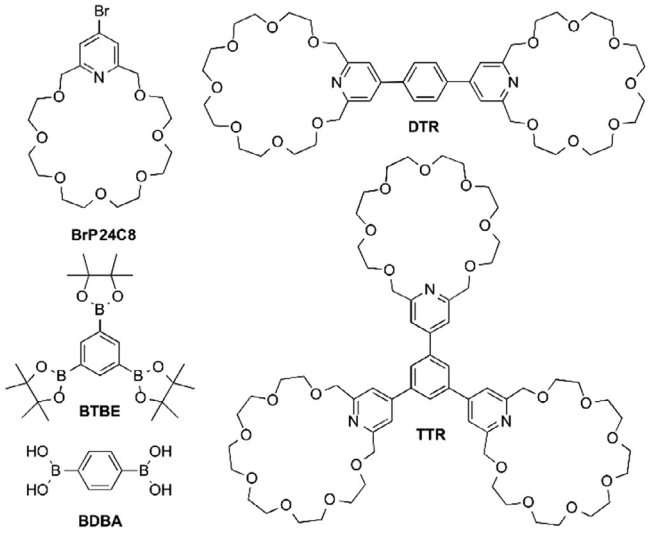

Fig. 1. Structures of the 4-bromopyrido[24]crown-8 building block, the boron reagents used in cross-coupling reactions and the two polytopic receptors synthesized.

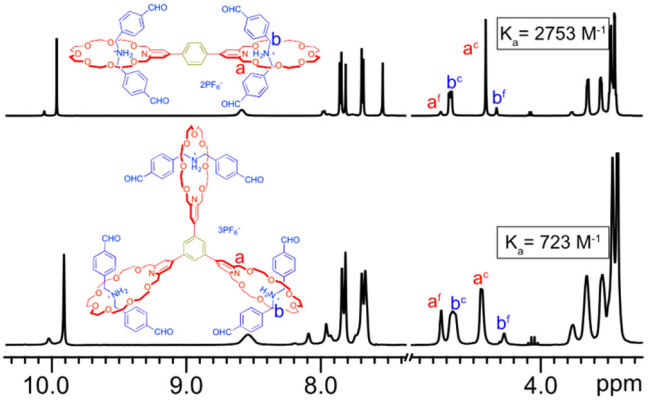

Fig. 2. Partial ^{1}H NMR spectra (CD_3CN) of the [3]pseudorotaxane (top) and the [4] pseudorotaxane (bottom) precursors where c and f correspond to protons associated with the complexed and free species, respectively. Binding constants reported are calculated per binding site.

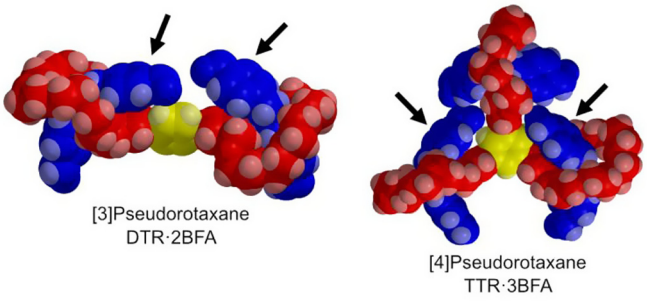

Fig. 3. The optimized equilibrium conformers of the pseudorotaxanes with arrows highlighting pi interactions between the BFA threads and the pyridines unit on the scaffolds.

attached at several points on a functionalised core molecule allowing a variety of geometries and complexities of macrocyclic hosts to be accessed. We have previously reported[39] the synthesis of 4-bromopyrido[24]crown-8 and demonstrated its ability to be coupled to aromatic boronic acids rendering it a versatile building block in synthesizing a variety of efficient receptors for DBA ions. In the same vein, we have coupled BrP24C8 to *p*-benzenediboronic acid (BDBA) and 1,3,5-benzenetriboronic acid tris(pinacol) ester (BTBE) to afford a ditopic (DTR) and a tritopic receptor (TTR), respectively (see Fig. 1). The formyl-substituted DBA thread, bis (4-formylbenzyl)ammonium hexafluorophosphate (BFA), is known[40] and was synthesized according to the literature procedure.[41]

Complexation occurs immediately upon mixing 2 equiv. of BFA and 1 equiv. of DTR and all peak shifts in the ^{1}H NMR spectrum associated with complex formation were as expected. The signal corresponding to the benzylic methylene protons of BFA shifted downfield from 4.35 ppm to 4.67 ppm appearing as a multiplet with a peak shape characteristic of hydrogen-bonded protons of this type[38] while the peak corresponding to the benzylic methylene protons of DTR shifted upfield from 4.81 ppm to 4.41 ppm (Fig. 2). Peaks corresponding to the free components were of minimal intensity indicating that the [3]pseudorotaxane exists as the dominant species. Indeed, we calculated the stability constant for the complex (K_a) to be 2753 M^{-1} per binding site via the single point method.[42,43] This is consistent with the association constant reported for the complex formed between the phenyl-substituted *p*-C_6H_5-P24C8 and BFA (2841 M^{-1})[39] supporting the notion that substitutions on the pyridine ring of P24C8 do not hinder the polyether unit's ability to strongly bind DBA ions. Similarly, we added 3 equiv. BFA to TTR and ^{1}H NMR spectroscopy indicated formation (Fig. 2) of a [4]pseudorotaxane with a stability constant of 723 M^{-1} per binding site.

The surprising difference in these stability constants was investigated computationally, utilizing molecular mechanics, owing to the large size of the complexes. Close inspections of the CPK models of the pseudorotaxanes (see Fig. 3) revealed pi-pi interactions between the phenyl groups on the BFA threads and the pyridine units on the macrocycle. In the case of TTR·3BFA however, only two of the three threads were capable of such interaction as a result of some negative cooperativity and therefore the binding affinity for the third complexation event was reduced due to apparent crowding of the center of the structure.[20] Indeed the experimental binding constants revealed a binding site occupancy of 70% for TTR·3BFA while DTR·2BFA yields ~90%, suggesting only partial occupancy of the third binding site in the former. While there is an important argument for considering the entropic cost of the final site, similar structures ([4]pseudorotaxanes), utilizing such benzylammonium threads and pyridine containing crowns, have been shown to successfully achieve >95% occupancy.[22] However, an observed reduction in the binding constant by a factor of more than three, with the addition of an electron withdrawing group on the pyridine unit, suggests that the enthalpy gain is also a crucial consideration.

With convincing evidence for the formation of the two threaded structures, we turned our attention to linking the formyl groups of the bound BFA threads via dynamic imine chemistry. Modeling our approach after Williams and co-workers,[21] we added 2 equiv. of *p*-phenylenediamine (PPD) to the DTR·2BFA and 3 equiv. PPD to the TTR·3BFA (Fig. 4).

We observed these mixtures via ^{1}H NMR spectroscopy immediately after mixing and noticed a total reorganization of the spectra with considerable disorder, particularly in the [4]pseudocatenane mixture. Nevertheless, the mixtures were monitored for 30 days to allow ample time for equilibration. During this time, we noted almost complete disappearance of the aldehyde peaks in each spectrum (see red traces in Fig. 4) and appearance of several new signals in the range 8 – 8.5 ppm indicative of successful imine bond formation (see Figs. S6 and S8 in the supporting information). For each mixture, however, the assortment of imine signals observed and unresolved disorder in the ^{1}H NMR spectra suggest a non-trivial mixture of products. This complexity of the NMR spectra