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Polyatomic Anion Assistance in the Assembly of [2]Pseudorotaxanes

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Supporting Information

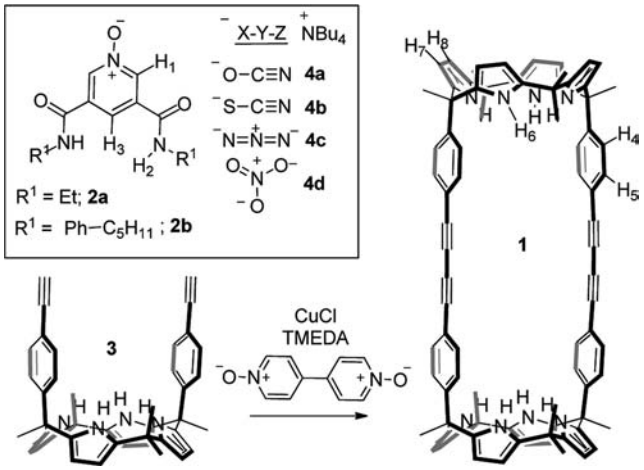
ABSTRACT: We describe the use of polyatomic anions for the quantitative assembly of ion-paired complexes displaying pseudorotaxane topology. Our approach exploits the unique ion-pair recognition properties exhibited by noncovalent neutral receptors assembled through hydrogen-bonding interactions between a bis-calix[4]-pyrrole macrocycle and linear bis-amidepyridyl-*N*-oxides. The complexation of bidentate polyatomic anions that are complementary in size and shape to the receptor's cavity, in which six NH hydrogen-bond donors converge, induces the exclusive formation of four particle-threaded assemblies.

Catenanes and rotaxanes are mechanically locked structures with potential application in molecular machinery.[1,2] Supramolecular assistance facilitates the preparation of these interpenetrated topologies.[3] A key intermediate for their construction is the noncovalent pseudorotaxane, where a linear molecule is threaded through the annulus of a macrocycle.[4] Thus, the development of new supramolecular strategies and interweaving motifs for the construction of pseudorotaxanes is a topic of current interest.[5,6] Specifically, examples of template assistance for the formation of rotaxanes, catenanes, and pseudorotaxanes using cations,[7−10] anions,[11−13] hydrogen bonds,[14−16] hydrophobic interactions,[17,18] and $\pi-\pi$ interactions[19,11,12] have all been reported. A general and versatile templating strategy for the construction of threaded assemblies that combines halide recognition by the macrocyclic component with strong ion-pairing of the linear component has been developed.[20] Here, we report the use of polyatomic anions for the quantitative construction of pseudorotaxane-like assemblies, which does not involve ion-pairing with the linear component. Rather, the approach described herein exploits the exceptional ion-pair recognition properties[21] of a self-assembled ditopic interwoven receptor.

The hydrogen-bonding complementarity that exists between homoditopic calix[4]pyrrole macrocyle **1** and ditopic linear *m*-bis-amide-pyridyl-*N*-oxides **2** induces the assembly of neutral interwoven receptors **1·2**.[22] The **1·2** complex has a pseudorotaxane topology,[23] and its components feature a binding site of six convergent hydrogen-bond NH donors: two from bound bis-amide and four from the opposing calix[4]-pyrrole cap of **1**. At millimolar concentrations, the complexation of bidentate polyatomic anions, complementary in size and shape to the cavity creates an ion-paired complex **4⊃1·2** displaying pseudorotaxane topology. The tetrabutylammonium counterion is bound opposite to the anion in the shallow aromatic cavity defined by the calix[4]pyrrole.

Hay coupling of calix[4]pyrrole **3** templated by one equivalent of 4,4′-bispyridine-1,1′-dioxide afforded macrocycle **1** in 60% yield (Scheme 1). The heteroditopic linear

Scheme 1. Synthetic Scheme for the Preparation of Macrocycle 1 and Structures of Bis-amidepyridyl-*N*-oxides 2 and the Tetrabutylammoniun Ion-Pairs of Polyatomic Anions 4



components, 3,5-pyridinecarboxamide-*N*-oxides **2**, were prepared following described procedures for similar compounds.[24,8]

The addition of 0.5 equiv of *N*-oxide **2a** to a millimolar $CDCl_3$ solution of **1** produced broadening of the pyrrole NH proton signal, preventing direct observation but suggesting hydrogen-bonding interactions (N−H···O) between the pyrrole NHs and the *N*-oxide oxygen. Likewise, the H_1, H_2, and H_3 proton signals for *N*-oxide **2a** are not detected due to broadening (Figure 1b). The doublet corresponding to the H_5 protons of the *meso*-phenyl residues in **1** also broadened beyond detection. Lowering the temperature to 233 K enabled the observation of two well-resolved downfield doublets corresponding to the *meso*-phenyl aromatic protons of free **1** (H_4, H_5) and two broad signals that were assigned to the same protons in the bound macrocycle (Figure S16, Supporting Information [SI]). The integral ratio of free and bound signals is 1:1. Taken together, these observations suggested the

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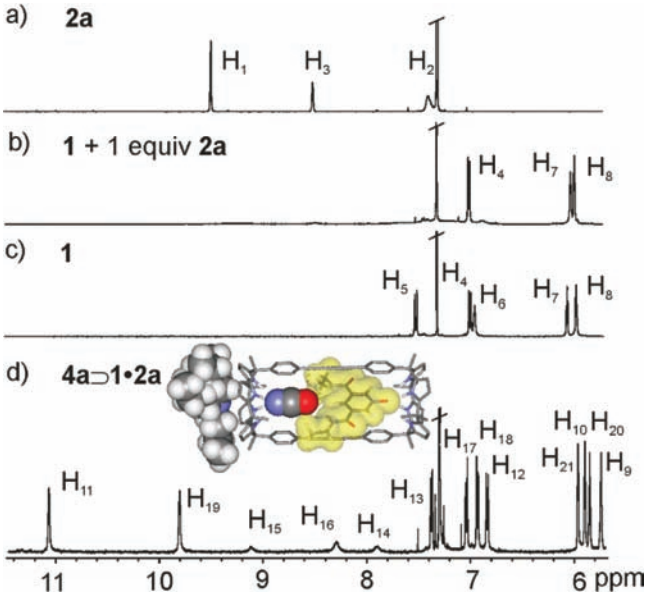


Figure 1. Downfield regions of the ^{1}H NMR spectra (500 MHz, $CDCl_3$, 298 K) of the free linear **2a** (a) and cyclic **1** (c) components of the pseudorotaxanes, its equimolar mixture (b) and the solution containing the three components **1**, **2a**, and **4a** in a 1:1:1 ratio (d). Inset: CAChe minimized structure of ion-paired [2]pseudorotaxane complex **4a⊃1•2a**. See Schemes 1 and 2 for proton assignments.

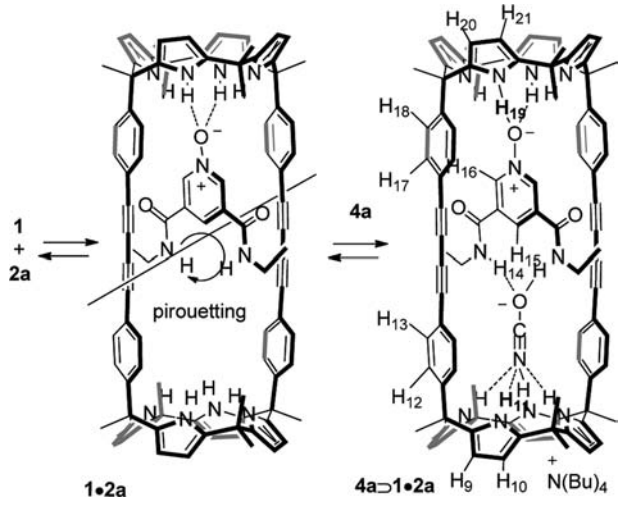
formation of a kinetically stable 1:1 complex between **1** and **2a** with a stability constant higher than 10^4 M^{-1} at 233 K.

We assigned a pseudorotaxane topology to the **1•2a** complex on the basis of the chemical shift changes observed at 233 K for the *meso*-phenyl protons in free and bound **1**. We interpreted the dissimilar exchange dynamics for the two sets of *meso*-phenyl protons as the result of the interweaving geometry assigned to the **1•2a** complex. At 233 K the threading/dethreading process becomes slow, producing separate signals for the aromatic protons of free and bound macrocycle **1**. However, the pirouetting process of the linear component **2a** occurring at an intermediate rate on the ^{1}H NMR time scale within the **1•2a** complex produced broadening of the aromatic protons of bound **1**.[25,26]

The addition of one equivalent of tetrabutylammonium cyanate **4a** to the equimolar $CDCl_3$ solution of **1** and **2a** produced a dramatic change in the ^{1}H NMR spectrum of the mixture (Figure 1d). All proton signals for **1** and **2a** became sharp and well-defined, and were easily assigned. Two different and highly downfield-shifted signals for the pyrrole NH protons (H_{11} and H_{19}) of **1** indicate participation in distinct hydrogen-bonding interactions. Four different sets of proton signals were observed for the aromatic and β-pyrrole protons. These findings point to an unsymmetrical assembly (Scheme 2 and Figure 1d). All the proton signals of the bis-amidepyridyl-*N*-oxide **2a** experienced significant chemical shift changes with respect to those observed for **2a** alone. In addition, the multiplet of the methylene protons alpha to the nitrogen atom of the tetrabutylammonium cation in **4a** was significantly downfield shifted.

Taken together, these observations give strong support for the quantitative formation of an unprecedented four-component pseudorotaxane-like complex between macrocycle **1**, linear component **2a**, and ion-pair **4a**. Accordingly, the ditopic linear component **2a** threads into **1** and hydrogen

Scheme 2. Two-Step Quantitative Self-Assembly of 4a⊃1•2a



bonds its *N*-oxide group to one of the calix[4]pyrrole caps of macrocycle **1** as described for the **1•2a** complex. Furthermore, the polyatomic anion guest hydrogen bonds simultaneously to the amide NHs of **2a** at one end and to the opposing calix[4]pyrrole unit of **1**.[27] The cyanate anion is included in the three-dimensional (3D) cavity defined by the macrocycle and the linear component of the pseudorotaxane, in which up to six hydrogen-bond donors converge, whereas the tetrabutylammonium counterion is located in the shallow external cavity defined by the pyrrole rings opposite to the included anion. Thus, pseudorotaxane-like complex **4a⊃1•2a** displays a separated ion-pair arrangement. In short, ion-pair **4a** acts as a template capable of driving the equilibria toward the quantitative assembly of a four-particle aggregate with pseudorotaxane topology. ROESY experiments were very useful in the assignment of the proton signals of **4a⊃1•2a** and revealed close intermolecular contacts as expected from the described pseudorotaxane topology. DOSY experiments also supported the formation of the pseudorotaxane-like complex **4a⊃1•2** in solution.[28] The values of the diffusion coefficients in $CDCl_3$ solutions of **2a** and **4a** are larger (7.5 and 8.2×10^{-10} m^2 s^{-1}, respectively) than for **1** (5.0×10^{-10} m^2 s^{-1}). This is expected on the basis of their relative molecular weights and sizes. A 2D DOSY experiment performed on an equimolar mixture of **1**, **2a**, and **4a** showed similar diffusion profiles for the three components, supporting their participation in a common aggregate. We also determined the diffusion coefficient value of the formed supramolecular entity **4a⊃1•2** as 4.5×10^{-10} m^2 s^{-1}. Not surprisingly, this value is only slightly lower than the one calculated for the free component **1**. This is because, although the change in molecular weight of **1** vs **4a⊃1•2a** is considerable, this is not the case for the values of the hydrodynamic radii.

Isothermal titration calorimetry (ITC) experiments were also performed to quantify the thermodynamic stability of the **4a⊃1•2a** pseudorotaxane-like complex. A $CHCl_3$ solution of *N*-oxide **2a** ([**2a**] = 0.6 mM) was added to an equimolar mixture of **1** and **4a** ([**1**] = [**4a**] = 0.06 M), and the resulting binding isotherm (normalized integrated heat vs molar ratio [**2a**]/[**1**]) was analyzed using a binding model that considered the formation of the following species: **4a⊃1•2a**, **1•4a**, and **1•(4a)$_2$**.[29] The fit of the titration data returned a stability

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constant value $K_{4a\supset 1\cdot 2a} = 9.1\times 10^{10}$ M^{-2} for the pseudorotaxane complex.[30]

The quantitative assembly of pseudorotaxane **4a⊃1·2** was also independent of the order of addition of its components. During the experimental investigations of the different addition strategies for the assembly of pseudorotaxane **4a⊃1·2a**, we also determined the stability constants of all the intermediate species.[26,29] We performed simulated speciations of the three possible addition alternatives for a two-step formation of **4a⊃1·2a** (SI). In complete agreement with experimental observations, the simulated profiles showed that working under strict stoichiometric conditions (1 equiv of each component) the pseudorotaxane **4a⊃1·2a** is quantitatively assembled independently of the order of addition of the components. However, the simulated speciation profiles indicated that when ion-pair component **4a** is added incrementally, pseudorotaxane **4a⊃1·2a** disassembles in favor of the formation of **1**·(**4a**)$_2$ in the presence of more than 1 equiv of the ion-pair. In contrast, self-assembled pseudorotaxane **4a⊃1·2a** remains stable in the presence of excess of either of the two other components: macrocycle **1** or *N*-oxide **2a**. The simulation results were also corroborated experimentally. In the presence of excess macrocycle **1** or *N*-oxide **2a**, pseudorotaxane **4a⊃1·2a** remained intact. We observed a slow chemical exchange on the ^{1}H NMR time scale between bound and free component added in excess. In contrast, the addition of excess of **4a** induced the emergence of proton signals assigned to **1**·(**4a**)$_2$ at the expense of those corresponding to **4a⊃1·2a**.

Other tetrabutylammonium salts of polyatomic anions were investigated as templates for the quantitative assembly of related pseudorotaxanes (i.e., azide **4c**, thiocyanate **4b**, and nitrate **4d**). In the case of the azide pair **4c**, the results paralleled those observed for **4a** (cyanate anion). Conversely, the addition of 1 equiv of thiocyanate **4b** or nitrate **4d** to an equimolar $CDCl_3$ solution of **1** and **2a** did not produce ^{1}H NMR spectra with sharp or well-resolved signals. Several proton signals in **1** and **2a** were not even observable due to broadening. However, lowering the temperature at 213 K for **4b** and 243 K for **4d** generated ^{1}H NMR spectra containing the diagnostic proton signals expected for the quantitative assembly of the pseudorotaxane-like complexes **4b⊃1·2a** and **4d⊃1·2a**. Most likely, hydrogen-bonding characteristics, and the shape and size of the polyatomic anions are key parameters for the quantitative assembly of the **4⊃1·2** aggregates at room temperature. Ion-pairs **4b** and **4d** did template the partial formation of the corresponding **4b,d⊃1·2** complexes. The exchange dynamics that exist between free and bound components resulted in broadening of the proton signals. At low temperature the thermodynamic and kinetic stability of the **4b,d⊃1·2a** complexes is increased, enabling their detection as the predominant species in solution. Interestingly, the interweaving structure of the **4b⊃1·2a** complex was confirmed in the solid-state from X-ray diffraction of a single crystal grown from an equimolar $CDCl_3$ solution of **1**, **2a**, and **4b** (Figure 2). The use of linear component **2b** in combination with **4a** was also effective in the quantitative assembly of **4a⊃1·2b** at 298 K. In combination, these results demonstrate the generality of the described assembly strategy in the preparation of pseudorotaxane-like motifs.

In conclusion, we have synthesized homoditopic calix[4]-pyrrole macrocycle **1** and used it in a general strategy for the quantitative self-assembly of pseudorotaxane-like complexes. At 298 K in $CDCl_3$ solution, an equimolar combination of tetrabutylammonium cyanate **4a** or azide **4c** with **1** and **2a** induces the quantitative formation of the ion-paired pseudorotaxane-like complex **4a,c⊃1·2a** independently of the addition order of the components. We are currently involved in exploiting this methodology of assembly of pseudorotaxanes in the synthesis of mechanically interlocked molecules (i.e., rotaxanes) through a capping approach.

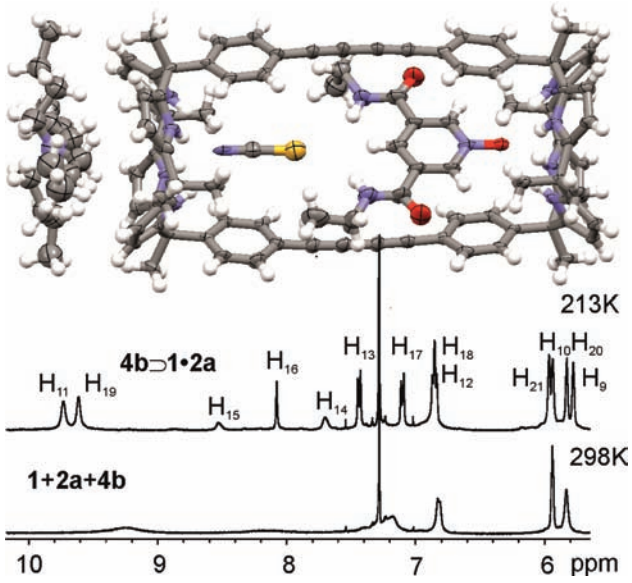

Figure 2. (Top) Single-crystal X-ray structure of **4b⊃1·2a**.[27] (Bottom) Downfield regions of the ^{1}H NMR spectra of the $CDCl_3$ solution containing an equimolar mixture of **1**, **2a**, and tetrabutylammonium thiocyanate **4b** recorded at 298 and 213 K. [**1**] = [**2a**] = [**4b**] = 4.6×10^{-3} M.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures for synthesis and binding studies, spectral data for new compounds, methods for the mathematical analysis of the titration curves, simulated speciation profiles, 2D ROESY and DOSY spectra of **4a⊃1·2a**, and X-ray crystallographic files of **1**, **1·2a** and **4b⊃1·2a**.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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(25) An interwoven structure for the **1·2a** complex was also observed in the solid-state. **2a** is threaded through **1**, showing disorder between two equivalent positions.
(26) Using ^{1}H NMR titrations we determined at 298 K the stability constant values for $K_{\mathbf{1\cdot 2a}}$ = 800 M^{-1}, $K_{\mathbf{2a\cdot 4}}$ = 3 × 10^3 M^{-1}, and a dimerization constant value K_d = 100 M^{-1} for **2a**.
(27) The cyanate and thiocyanate anions are ambidentate. Probably in solution, the sandwiched anion rotates freely within the complex.
(28) We attempted the characterization of the pseudorotaxane-like complex **4a**⊃**1·2a** in the gas phase using ESI-TOF-MS with negative mode detection. We could not detect the ion peak corresponding to [NCO⊃**1·2a**]$^-$ (1476.7 *m*/*z*). Instead, we observed a cluster of monocharged negative ions at 1479.7, 1496.7, 1529.9, 1546.9, and 1563.9 *m*/*z* (Figure S18 [SI]). These molecular masses and their corresponding isotopic distribution patterns coincide with those calculated for molecular formulas [NCO⊃**1·2a** + H_2 + H]$^{-\bullet}$, [NCO⊃**1·2a** + H_2 + H_2O]$^-$, [NCO⊃**1·2a** + 2H_2 + H_2O +CH_3O]$^{-\bullet}$, [NCO⊃**1·2a** + 2H_2 + H_2O +CH_3OH + HO]$^-$ and [NCO⊃**1·2a** + 2H_2 + H_2O +CH_3OH + 2HO]$^{-\bullet}$, respectively. Most likely, the anionic or anion−radical complex NCO⊃**1·2a** reacted with solvent molecules or ions/radicals derived from them in the ionization process.
(29) The values of the stability constants and enthalpies for formation for **1·4a** and **1**·(**4a**)$_2$ were fixed during the mathematical analysis of the titration data. $K_{\mathbf{1\cdot 4a}}$ = 1 × 10^{-5} M^{-1}, $\Delta H_{\mathbf{1\cdot 4a}}$ = −5 kcal/mol; $K_{\mathbf{1\cdot 4a}\leftrightarrow\mathbf{1\cdot(4a)_2}}$ = 1 × 10^{-6} M^{-1}, $\Delta H_{\mathbf{1\cdot 4a}\leftrightarrow\mathbf{1\cdot(4a)_2}}$ = −8 kcal/mol.
(30) The stability constants values of the complexes involving ion-pair **4a** should be considered as apparent because ion-pair dissociation and ion-paired complex formation equilibria are not taken into consideration in the mathematical analysis of the titration data.