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Nonaggregational Shape-Persistent Cyclo[6]aramide and Its Macrocyclic Effect toward Binding Secondary Ammonium Salts in Moderately Polar Media

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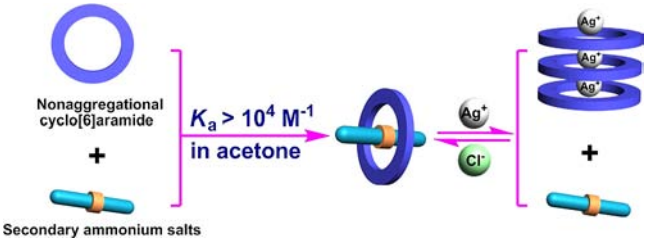
ABSTRACT



Simply by introducing steric side chains, the shape-persistent cyclo[6]aramides were found to exhibit nonaggregational behavior and strong association (3×10^4 M^{-1}) ability in acetone for binding secondary ammonium salt. The complexation can be switched in an on-and-off fashion using $AgPF_6$ and TBACl, contrasting sharply with their corresponding acyclic pentamer and demonstrating the macrocyclic effect.

With a noncollapsible framework and cavity that are distinguishable from less conformationally rigid cyclic molecules such as crown ethers and calixarenes, shape-persistent macrocycles of different size, shape, and topology have aroused great interest in the past years.[1] Among them, macrocyclic aromatic oligoamides with full amide linkage[2,3] have seen a fast increase concomitant with the development of hydrogen bonding-directed reactions. Shape-persistent aromatic oligoamide macrocycles developed by Gong and co-workers[3] represent an interesting class of cyclic compounds that structurally differ from most of the other oligoamide cycles[2,4] in the interior where

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amide carbonyl atoms are predisposed introvertively. These macrocyclic oligoamides with six residues and their derivatives serve as highly selective receptors for accommodating the guanidinium ion[5] and conducting transmembrane pores in ion-channel study.[6]

We recently revealed the unusually high efficient kinetic macrocyclization that is rare for macrocycle formation involving a large number of reacting units.[3b] Furthermore, these macrocycles carrying linear alkyl side chains exhibit a strong preference for directional self-assembly in both polar and nonpolar solvents.[3e] With the hydrophilic internal pores or channel, these macrocycles are also expected to interact with metal ions or hydrogen bond donors. This has been demonstrated by our finding that cyclo[6]aramides, as we named it for brevity, function as an excellent extractant in the separation of lanthanide and thorium elements.[7]

Despite much progress made in using secondary ammonium salts for the preparation of host–guest complexes with many 3D macrocycles including crown ethers,[8] cucurbiturils,[9] calixarenes,[10] and pillararenes,[11] as well as pore-containing aromatic oligoamides,[12] the complexation between shape-persistent 2D macrocycles and secondary ammonium salts is rare.[13] To construct supramolecular architecture such as rotaxane, the binding affinity between host and secondary ammonium salts is among one of the most important parameters for evaluating the complexing ability of macrocyclic hosts. The earliest report using benzo-24-crown-8 only afforded a binding constant of 135–261 M^{-1} in acetone.[14] Recently, use of a smaller crown analog, benzo-21-crown-7, led to the increased value of 527–1062 M^{-1} in the same solvent.[8b] In chloroform, the calix[6]arene[10] derivative and pillar[5]arene[11a] only provided the association affinity corresponding to binding constants of 3.5×10^4 and 1.09×10^3 M^{-1}, respectively. Further enhancement of the binding ability in solvents, particularly in polar surroundings, is still highly demanding. In addition, severe aggregation often leads to issues concerning low solubility and difficulty in structural characterization. This impedes greatly applications of aromatic oligoamide macrocyles with six residues, where nonaggregational ability is important for host–guest chemistry.[5b]

Herein we report on nonaggregational, soluble macrocycle **1a** which is realized simply by replacing linear alkyl groups with branched side chains and its binding toward various secondary ammonium hexafluorophosphates **2a**–**e** in moderately polar solvent, acetone (Figure 1). The binding process is switchable in an on-and-off manner by adding a silver ion and chloride anion. Besides tunable complexation, a macrocyclic effect was observed by comparing its corresponding open-chain anologes, i.e., pentamer **3a** and **3b**. We are not aware of the examples of binding secondary ammonium salts with aromatic oligoamide macrocycles with full amide linkage. A high binding constant has been achieved in this study, which is surpassing the known values recorded to date.

Instead of modifying the backbone via introducing substituents,[5b] it was reasoned that introducing steric hindrance around the macrocyclic periphery should lead to altered association ability and thus decreased aggregation. Such a possibility was first explored by macrocycle **1a** that contains hindered groups.[15] Much greater solubility was found for **1a** (> 100 mM) compared to **1b** (25 mM) in chloroform. Surprisingly, sharp signals for **1a** were observed in the ^{1}H NMR spectra in $CDCl_3$ or CD_3COCD_3.[15] Previous results for cyclo[6]aramides, e.g., **1b**, bearing linear alkyl side chains revealed the severely broadened ^{1}H NMR signals due to strong aggregation.[3e] In addition, the concentration-dependent ^{1}H NMR experiments disclosed no shifts of all protons of **1a** from 10 to 0.3 mM,[15] indicating that no aggregation occurred. Macrocycle **1c**, with shorter branched side chains, gave signals that are not so sharp compared to those of **1a**.[15] In stark constrast, **1d** bearing linear *n*-octyl groups was actually insoluble in the same solvent.[3a] The nonaggregational behavior of **1a** was further confirmed by UV–vis spectra and dynamic light scattering (DLS) techniques.[15] As expected, no blue or red shift was found in the concentration-dependent UV–vis

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spectra in $CHCl_3$. The results from DLS experiments showed that the average size of **1a** was 2.1 nm (1.0 mM) and 1.3 nm (5.0 mM) in $CHCl_3$. These data were close to the calculated value of the backbone size (ca. 1.5 nm) of macrocycle **1a**.[3f] These results demonstrate that, compared to the strongly aggregating **1b** and **1d**, macrocycles **1a** and **1c** have a very low propensity for aggregation in solution.

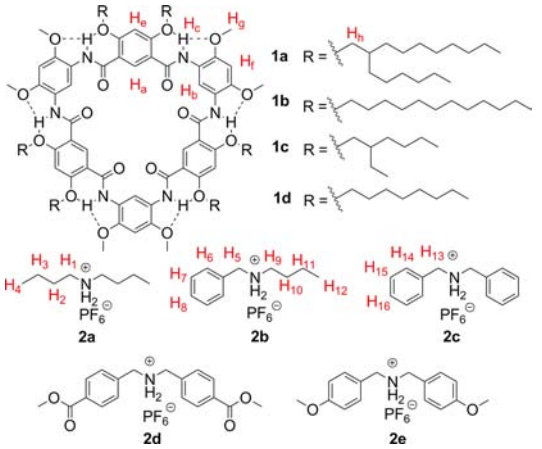

Figure 1. Chemical structures and proton designations of cyclo[6]aramides **1a**–**d** and secondary ammonium salts **2a**–**e**.

The first encouraging evidence for the interaction of **1a** with an equimolar dibutylammonium salt **2a** was from ^{1}H NMR spectra in acetone-d_6 (Figure 2).

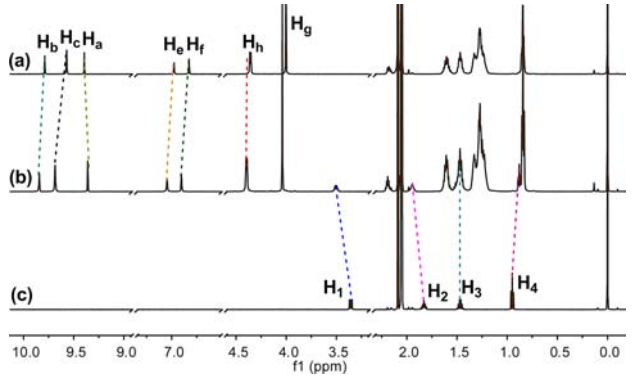

Figure 2. ^{1}H NMR spectra (600 MHz, acetone-d_6, 298 K) of (a) 1.0 mM cyclo[6]aramide **1a**, (b) 1.0 mM cyclo[6]aramide **1a** and **2a**, and (c) 1.0 mM **2a**.

All signals of protons H_a, H_b–H_f from amide and aromatic regions in **1a** shifted downfield except for H_a, and the signals of protons H_1 and H_2 in **2a** also followed the same trend by a downfield shift of 0.15 and 0.12 ppm, respectively. Only one set of signals were found for an equimolar solution of **1a** and **2a**, showing fast-exchange complexation between **1a** and **2a** on the ^{1}H NMR time scale. More direct evidence for the complexation came from a high resolution electrospray ionization mass spectra (HRESI-MS) study.[15] A highly intense fragment ion of $[M-PF_6]^+$ was found at m/z 2480.7222 for **1a**·**2a**, indicating the presence of the host–guest species in 1:1 stoichiometry.

The formation of the complex **1a**·**2a** was further evidenced by 2D ROESY (10 mM in acetone-d_6).[15] ROE correlations were observed between the methylene proton H_1 of **2a** and protons H_a and H_b of **1a**, suggesting that the positively charged moiety $-NH_2^+-$ resides in the cavity of **1a**. The optimized geometry of complex **1a**·**2a** which was obtained using the density functional theory (DFT) calculation indicated that cyclo[6]aramide **1a** was pierced by **2a**.[15] In other words, this implies the threading of an alkyl group through the cavity of the macrocycle to form a pseudorotaxane.

Then, a series of secondary ammonium salts **2b**–**e** were examined for their interactions with **1a**. A 1:1 stoichiometry was obtained for all salts by a molar ratio method using a ^{1}H NMR technique.[15] The HRESI-MS confirmed the 1:1 complexation of **1a**·**2b** and **1a**·**2c**. A common fragment ion of $[M-PF_6]^+$ was found at m/z 2500.9089 for **1a**·**2b** and at 2534.8940 for **1a**·**2c**.[15]

The ^{1}H NMR titration experiment of **1a** with **2a** from 0 to 1.8 equiv revealed a substantial downfield change for methylene protons **2a**-H_1 ($\Delta\delta$ = 0.15 ppm) and **2a**-H_2 ($\Delta\delta$ = 0.13 ppm),[15] indicating that ammonium hydrogens are involved in intermolecular H-bonding. By fitting the concentration-dependent change of the chemical shifts of proton **2a**-H_2 to a 1:1 binding motif,[15] an association constant of 2.54×10^4 M^{-1} (ΔG = −25.1 kJ/mol) was obtained (Table 1). Replacing one of two butyl groups of **2a** led to **2b**, which offered a K_a value of 3.38×10^4 M^{-1} (ΔG = −25.8 kJ/mol), indicative of only a marginal change upon threading. However, **2c** with two larger benzyl groups via substituting two butyl groups of **2a** provided a K_a of 7.50×10^3 M^{-1} (ΔG = −22.1 kJ/mol), a ca. 3-fold decrease with respect to **2a** in association affinity. It indicates that secondary dialkylammonium salt **2a** or **2b** fits the cavity of **1a** better than **2c**. These K_a values are higher in moderately polar solvent, indicating that the macrocycle **1a** is able to bind strongly secondary dialkylammonium salts in acetone. To the best of our knowledge, the K_a values ($> 10^4$ M^{-1}) represent the highest binding constants reported to date for shape-persistent macrocyles and secondary ammonium salts.

The chemically driven uncomplexing and recomplexing processes were further investigated (Figure 3). When 1 equiv of $AgPF_6$ was added to the solution of **1a** and **2c** (1:1 in molar ratio) in acetone-d_6, the interior aromatic protons H_a and H_b showed a significant upfield shift (0.41 ppm and 0.25 ppm) along with a concomitant downfield shift of amide H_c (0.16 ppm) and exterior protons H_e/H_f, indicating the strong interaction of the silver ion and **1a** to form a stable complex **1a**·Ag^+. This suggests disruption of the complexation of **1a**·**2c** due to the more competitive complexing ability of the silver ion with respect to $-NH_2^+-$ species. At the same time, the signals of

methylene protons of **2c** remained almost unchanged compared to those of free salt, strongly indicating dethreading of **2c** from the cavity of **1a**. Upon addition of 1 equiv of tetrabutylammonium chloride (TBACl), the spectral pattern obtained was almost identical to the one from the solution of **1a** and **2c**. This suggests the reformation of threaded structures. The reversible change upon the addition of Ag^+ and Cl^- demonstrates the possibility for manipulating the complexation behavior of **1a** and **2c** by external chemical stimulus. As expected, the complexing process of **1a** and **2a** could also be manipulated using this method.[15] In addition, the cesium ion driven uncomplexing process was similar to that observed with presence of the silver ion.[15]

Table 1. Stoichiometries and Association Constants of Complexes in Acetone-d_6 at 298 K

complex	molar ratio[a]	K_a (M^{-1})[b]	ΔG (kJ/mol)[c]
1a·2a	1:1	$(2.54 \pm 1.18) \times 10^4$	−25.1
1a·2b	1:1	$(3.38 \pm 1.64) \times 10^4$	−25.8
1a·2c	1:1	$(7.50 \pm 1.44) \times 10^3$	−22.1
1a·2d	1:1	$(8.03 \pm 1.67) \times 10^3$	−22.3
1a·2e	1:1	$(4.60 \pm 0.62) \times 10^2$	−15.2

[a] The 1:1 stoichiometry of each complex was established by the molar ratio method. [b] The association constant K_a values were obtained by proton NMR titration. [c] The Gibbs free energies (ΔG) of complexation were calculated from the K_a values, using the equation $\Delta G = -RT \ln K_a$.

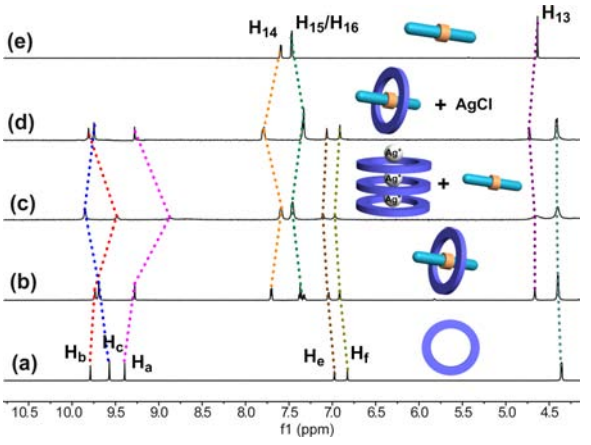

Figure 3. Partial ^{1}H NMR spectra (400 MHz, acetone-d_6, 298 K) of (a) 2.0 mM **1a**, (b) 2.0 mM **1a** and **2c**, (c) 2.0 mM **1a** and **2c** + 2.0 mM $AgPF_6$, (d) 2.0 mM **1a** and **2c** + 2.0 mM $AgPF_6$ + 2.0 mM TBACl, and (e) 2.0 mM **2c**.

Interestingly, a remarkable macrocyclic effect was observed when pentamer **3a** with a backbone rigidified by full three-center H-bonds or **3b** containing partial intramolecular H-bonds in a more flexible conformation was empolyed as a host for complexing **2a** (Figure 4). Both compounds have the same number of introverted amide oxygens as **1a**. ^{1}H NMR spectra of a solution of **3a** or **3b** and **2a** exhibited actually the presence of each component that corresponds to its free species.[15] This clearly shows a lack of interaction with secondary dialkylammonium salt with the acyclic analogs, reflecting the essential role the cycle played in facilitating the binding process.

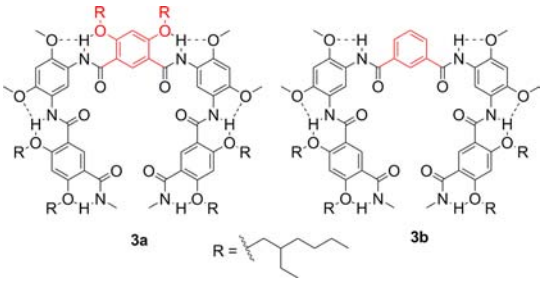

Figure 4. Chemical structures of pentamers **3a** (fully hydrogen bonded) and **3b** (partially hydrogen bonded).

In conclusion, we have demonstrated that the presence of steric side groups dramatically decreased the strong aggregation that typically accompanies macrocycles peripherally tethered with linear alkyl groups. The cyclo[6]aramide **1a** has shown capability in binding secondary ammonium salts in acetone with varying association affinity depending strongly on the molecular structure of the secondary ammonium salts. The binding constants ($> 10^4$ M^{-1}) achieved for **1a** with **2b** represents the largest value reported to date in moderately polar solvent for shape-persistent macrocycles. The complexation can be switched in an on-and-off fashion using $AgPF_6$ and TBACl. The macrocyclic effect has been shown to play a determined role in manipulating the association process. These cyclo[6]aramides containing hindered side chains are expected to hold potential as candidates of novel wheels for constructing mechanically interlocked architectures, such as molecular switches, molecular muscles, and other supramolecular machines.

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Supporting Information Available. Experimental procedures, analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.