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Persistently Folded Circular Aromatic Amide Pentamers Containing Modularly Tunable Cation-Binding Cavities with High Ion Selectivity

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Abstract: In this work, we illustrated a novel design strategy that allows systematically tunable interior properties (effective cavity size, steric crowdedness, and hydrophobicity) contained within a novel class of shape-persistent aromatic pentamers to take place on a scale below 3 Å. Such finely tunable structural features are complimented by experimentally observable functional variations in ion-binding potential. Results of the selective, differential binding affinities of three circular pentamers for Li^+, Na^+, K^+, Rb^+, and Cs^+, substantiated by metal-containing crystal structures and computational modeling, are detailed.

Persistently folded aromatic macrocycles with rigid, noncollapsible backbones, such as porphyrin derivatives or analogues,[1a,b] arylene ethynylene macrocycles,[1c] macrocyclic Schiff bases,[1d] and hydrogen-bonded (H-bonded) macrocyclic foldamers,[1e−y] exhibit novel properties with potential for applications in chemistry, materials science, medicine, and biology. The shape persistency and rigidity of these macrocyclic frameworks are induced by covalent forces,[1c] built-in hydrogen bonds (H-bonds),[1a,e−y] and intrinsic conformational bias of the backbone[2a] or functional groups such as urea,[1p] amide,[2a,b] or sulfonamide,[2c,d] acting alone or in a cooperative manner. Owing to its robustness, predictability, and directionality, multiple-center H-bonding has become a top strategic choice for designing tailor-made macrocyclic aromatic foldamers.[1m−y] Such H-bonded aromatic macrocycles have been demonstrated to bind either neutral[1n,t] or cationic species,[1m,2e] act as ion transporters across cell membranes,[2f] and stabilize DNA G-quadruplex structures.[2g] However, few synthetic macrocyclic systems allow systematic fine-tuning of interior properties while maintaining overall topographic persistence;[1w,2h−j] even fewer have the proven propensity for selective metal ion recognition,[1m,2a] a feature that may enable important uses as imaging agents, disease-rectifying therapeutics, etc.[2l,m] To the best of our knowledge, among shape-persistent aromatic macrocycles,[1] currently there is no example that maintains a high degree of precisely tunable interior physical properties including effective cavity size, steric crowdedness, hydrophobicity, and *cation-binding capacity* on the scale below 3 Å.[3] Herein, we characterize, by an experimental-theoretical synergy, a new class of modular, H-bonded, shape-persistent, macrocyclic receptors, forming a cation-binding cavity in their anionic forms whose interior properties can be uniquely and selectively tailored to recognize specific alkali metal cations.

Recently, we reported a highly rigid and structurally well-defined circularly folded pentamer **1** containing five methoxy groups in its interior (Figure 1a).[1r] Its shape, a nearly planar, rigidified pentagonal aromatic amide backbone incorporating an inward-pointing, continuous H-bonding network, is quite unusual among unnatural foldamers.[1e−y] The single crystal X-ray structure[1r] reveals a cavity radius of ∼2.85 Å from the cavity center to the nucleus of the interior oxygen atom. Two steric caps comprised of three and two interior methoxy methyl groups, respectively, on either side of the foldamer backbone plane completely block the cavity and prevent any metal cation from entering it. Not surprisingly, our numerous attempts to effect the binding by all of the five alkaline metal cations were unsuccessful.

We envisioned that replacement of one or two interior methoxy groups in **1** with hydroxyl groups, giving rise to six pentamers **2**−**4** (Figure 1a−c), should increasingly open the cavity (Figure 1d−f), allowing selective binding to diverse metal cations to take place. This reasoning was based on the following premises: (1) the coordination distances between the oxygen atoms and the majority of metal cations fall below 2.85 Å; (2) pentamers **2**−**4** possess a cation-binding site displaying five oxygen donor atoms in a preorganized manner; (3) the binding site in **2**−**4** additionally incorporates at least one phenol moiety capable of ionic interaction with metal ions upon deprotonation under basic conditions; and (4) the methoxy methyl groups present in the interior are sterically bulky and hydrophobic in nature and may have subtly different orientations, possibly allowing the fine-tuning of cation-binding potential of **2**−**4**.

Toward characterizing our designs, we first constructed *ab initio* models using density functional theory (DFT) at the B3LYP/6-31G(d,p) level, on pentamers containing either one or two hydroxyl groups. The geometry-optimized circular conformer structures of pentamers **2a**−**4a** (see Figure S3a for **2a** and Figure 1e−f for **3a** and **4a**) in their anionic forms revealed that with incremental substitution of methyl groups with hydroxyl ones, going from **1** to **2a**−**4a**, the interior cavity gradually opens up, concomitant with a decrease in steric hindrance and hydrophobicity imparted by the interior methyl groups. Encouraged by these computational trends, we prepared all six hydroxyl-containing pentamers **2**−**4** by protecting the phenolic hydroxyl groups as benzyl ethers, followed by a stepwise elongation and subsequent debenzylation to generate one or two hydroxyl groups decorating the interior of **2**−**4**.[4,5]

Examining the single crystal structure of **2a** (slowly grown from methanol:dichloromethane =1:1, v/v) revealed pentamer **2a** folds into an almost planar disk arrangement of nearly perfect C_5 symmetry in the solid state (Figure 1d), remarkably similar to the B3LYP/6-31G(d,p) structure (Figure S3a). A continuously formed H-bonding network (5- and 6-membered NH...OMe = 2.09−2.33 and 1.70−1.99 Å, respec-

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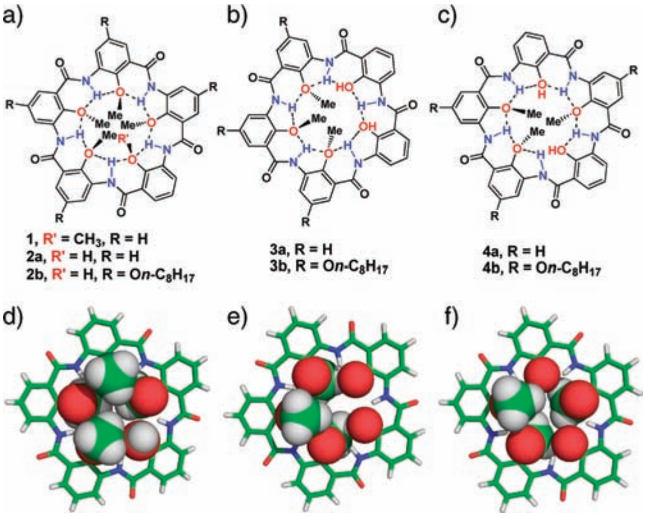

Figure 1. Chemical structures of **2** (a), **3** (b), and **4** (c) and top view of the determined crystal structure of **2a** in its neutral form (d), *ab initio*-optimized structure of **3a**$^{2-}$ (e) and **4a**$^{2-}$ (f), both in their anionic forms, showing one or two interior methyl groups form a hydrophobic cap above the pentamer plane; a second hydrophobic cap comprised of two methyl groups stays below the plane. CPK models of methoxy and hydroxyl groups were built based on the van der Waals radius (Gray: H = 1.20 Å; Green: C = 1.70 Å; Red: O = 1.52 Å, O$^-$ = 1.40 Å).

tively) brings the five aryl-bonded oxygens in a circular manner to enclose a cavity with a radius of ~2.88 Å, near-identical to that found in **1** (Figure 1a).[1r] Two hydrophobic caps comprising four methyl groups and one hydrogen atom are found below and above the plane (Figure 1d). Gratifyingly, the structural study demonstrated that replacing methoxy groups with hydroxyl groups does not interrupt the continuous H-bonding network nor does it adversely alter the cavity shape and size necessary for efficient cation interactions.

To facilitate evaluating the solution binding profiles of pentamers **2**−**4** toward metal cations, octyloxy side chains were introduced around the periphery of pentamers (**2b**−**4b**; Figure 1a−c) to enhance their solubilities in organic solvents. The circularly folded conformation of **2b**−**4b** in solution was supported by the amide protons resonating at the very low field ($\delta > 10.6$ ppm relative to TMS)[6] and by NOEs observed between interior methyl peaks and their adjacent amide protons in 2D NOESY spectra recorded in CDCl$_3$.[5] Upon deprotonation of phenolic hydroxyl groups in **4b** with tetrabutylammonium hydroxide, two amide protons significantly downfield shift to $\delta > 15$ ppm (Figure 3a−b; see Figure S2 for **3b**[5]), affirming the presence of exceptionally strong intramolecular H-bonds that are mediated by negatively charged oxygen atoms, rendering amide linkages more rigid and reinforcing the crescent-shaped aromatic backbone in anionic **3b**.

Next, we studied how the cation-binding function is related to subtle structural changes upon deprotonation by isothermal titration calorimetry (ITC) in acetonitrile at 25 °C for anionic **2b**−**4b** and in acetone at 25 °C for neutral **2b**−**4b** due to their insolubility in acetonitrile. Analysis of the resulting binding isotherms after subtraction of the heat of dilution gave the binding affinity, number of binding sites, and essential thermodynamic parameters (ΔG, ΔH, and ΔS).[5]

From results listed in Table 1, three general trends can be noted. First, none of neutral **2b**−**4b** binds any alkaline metal cation in acetone.[5] Second, a comparison in binding constants between **2b** and either **3b** or **4b** shows that the presence of more ionizable hydroxyl groups enhances the cation-binding potential of the resultant pentamers, as we designed. Third, separation of the two interior phenolic hydroxyl groups with one methoxy group (as in pentamer **4b**) significantly alters the binding profile toward all five alkaline metal cations, with respect to **3b** that carries two neighboring phenols. Moreover, tunability in interior properties indeed imparts experimentally measurable ion-binding selectivity to **3b** and **4b**. This can be supported by the following observations: (1) while the binding constants of anionic **3b**$^{2-}$ toward Na$^+$ and K$^+$ were determined to be 1.77×10^5 M^{-1} and 1.00×10^5 M^{-1}, respectively, no bindings were detected for either **2b**$^-$ or **4b**$^{2-}$ for both Na$^+$ and K$^+$, and (2) in the case of Rb$^+$ and Cs$^+$, only anionic **4b**$^{2-}$ displays appreciable binding constants of 0.12×10^5 M^{-1} and 0.55×10^5 M^{-1}, respectively. Such noteworthy differences in binding affinities between neutral and anionic forms of **2b**$^-$−**4b**$^{2-}$ and among anionic **2b**$^-$−**4b**$^{2-}$ fully ascertain the potential of our system, leading to precisely tunable interior chemical and physical properties. Notably, **2b**$^-$−**4b**$^{2-}$ display either comparably good or better selectivity against metal cations with respect to the two crown ethers.

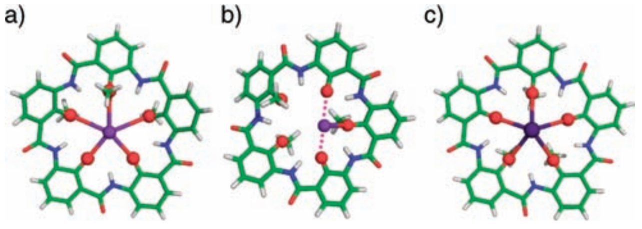

Figure 2. (a) X-ray crystal structure of the complex K$^+$@anionic **3a**$^{2-}$; (b) B3LYP/6-31G(d,p)(SCRF = PCM, solvent = CH$_3$CN) calculated structure of the complex K$^+$@anionic **4a**$^{2-}$;[5] (c) X-ray crystal structure of the complex Cs$^+$@anionic **4a**$^{2-}$. O = red sphere, K$^+$ = purple sphere, Cs$^+$ = deep blue sphere, weak coordination bonds = dotted pink lines, and intermediate and strong coordination bonds = solid sticks. For clarity of view, all the coordinated solvent molecules were removed in both (a) and (c).

Table 1. Association Constants ($K_a \times 10^{-5}$ M) for Complexation of Alkaline Metal Cations (Li$^+$, Na$^+$, K$^+$, Rb$^+$, and Cs$^+$) by Hosts of Anionic **2b**$^{2-}$−**4b**$^{2-a,b}$ as well as 15-Crown-5 and 18-Crown-6 Ethers Determined by Isothermal Titration Calorimetry (ITC) in Acetonitrile at 25 °C

	Li$^+$	Na$^+$	K$^+$	Rb$^+$	Cs$^+$
15-Crown-5	3.43 ± 1.33	0.95 ± 0.09	0.19 ± 0.05	0.04 ± 0.01[c]	—
18-Crown-6	—	0.51 ± 0.15	3.23 ± 0.24	0.76 ± 0.11	0.76 ± 0.19
2b$^-$	—	—	—	—	—
3b^{2-}	16.8/0.15[d]	1.77 ± 0.38	1.00 ± 0.18	—	—
4b^{2-}	0.85 ± 0.23	—	—	0.12 ± 0.03	0.55 ± 0.16

[a] Anionic **2b**$^{2-}$−**4b**$^{2-}$ were generated by deprotonating hydroxyl groups using tetrabutylammonium hydroxide; samples were fully dried using vacuum oven. [b] Either 1:1 binding stoichiometry or no binding was observed unless specified. [c] 1:2 Binding stoichiometry. [d] 2:1 Binding stoichiometry for two binding site mode (2Li$^+$@anionic **3b**$^{2-}$) is possible, but the uncertainties are greater than the binding constants.

As originally conceived, the above exhibited ion binding specificity by **3b**$^{2-}$ and **4b**$^{2-}$ can be interpreted on the basis of complementarity and preorganization, with emphasis on (1) the essentially nonmobile oxygen donor atoms in the interior, (2) the extent of coordination bond formation between metal ions and negatively charged oxygens, and (3) the subtly different orientations of hydrophobic methyl groups in the interior. As illustrated in Figure 2a by the crystal structure of the complex K$^+$@anionic **3a**$^{2-}$,[7] K$^+$ ions are stabilized in an off-center binding pocket in anionic **3a**$^{2-}$ formed by a hydrophobic methyl group (K$^+$---H−CH$_2$O distance = 3.21 Å), two strongly coordinating anionic phenolic oxygens (both K$^+$---O$^-$ distances = 2.68 and 2.73 Å), and three coordinating methoxy oxygens (K$^+$---O−CH$_3$ distances = 3.13, 2.23, and 3.24 Å). With respect to the position of K$^+$ in **3a**$^{2-}$, smaller cations such as Li$^+$ (VdW = 0.76 Å) and Na$^+$ (1.02 Å) remain in proximity to anionic oxygens while outlying the three methoxy oxygens and hydrophobic methyl group. This leads to two strong M$^+$---O$^-$ coordination bonds that stabilize the complexes formed between Li$^+$/

Na$^+$ and **3b**$^{2-}$. In contrast, larger cations, such as Rb$^+$ (1.52 Å) and Cs$^+$ (1.67 Å), are kept at bay from the two anionic oxygens while being forced into the vicinity of the hydrophobic methyl group. This apparently disallows concurrent binding of the two anionic oxygens, thus preventing Rb$^+$ and Cs$^+$ from favorably binding and subsequently entering the interior cavity of **3a**$^{2-}$ or **3b**$^{2-}$.

Compared to the strong interactions between K$^+$ and **3b**$^{2-}$ and no detectable binding between smaller Na$^+$ and **4b**$^{2-}$ (Table 1), the computationally determined very weak binding of ~5 M^{-1} (ΔG was computed to be −0.67 kcal/mol which is consistent with ITC result in Table 1) between K$^+$ and **4a**$^{2-}$ is effected through its larger VdW radius of 1.38 Å, allowing one strong K$^+$---O−CH$_3$ (2.77 Å), two relatively weak K$^+$---O$^-$ (2.86 and 2.96 Å), and two disfavored K$^+$---H−CH$_2$O (3.28 and 3.25 Å) interactions (Figure 2b). Conversely, as supported by two strong Cs$^+$---O$^-$ coordination bonds (3.00 and 3.05 Å) found in the complex Cs$^+$@**4a**$^{2-}$ (Figure 2c),[7] larger cations (Rb$^+$ and Cs$^+$) do allow two stronger M$^+$---O$^-$ interactions to take place simultaneously, thereby leading to their experimentally observable strong bindings toward **4b**$^{2-}$ (Table 1).

In the solid state of the complex Cs$^+$@**4a**$^{2-}$, the three methyl groups all stay on the same side (Figure 2c), which may be due to the crystal packing effect. Our surmise is that in solution anionic **4a**$^{2-}$ may adopt an alternative conformation where one or two methyl groups occupy either side of the pentamer plane (Figures 1f and 2b). The support of this comes from the fact that the comparative ^{1}H NMR studies do imply the existence of a difference in the orientation of methyl groups for anionic **4a**$^{2-}$ between its solution and solid state conformations (Figure 3b−d).

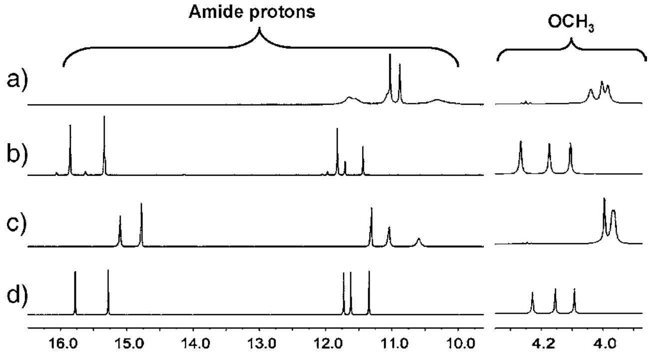

Figure 3. ^{1}H NMR spectra (5 mM, 500 MHz, 298 K, CDCl$_3$/DMSO-d$_6$ 4:1 v/v) of (a) neutral **4a**, (b) freshly prepared anionic **4a**$^{2-}$ of its tetrabutylammonium (TBA$^+$) salt containing two TBA$^+$, (c) a mixture containing 1:1 molar ratio of anionic **4a**$^{2-}$ of its TBA$^+$ salt and cesium tetraphenylborate (TPB$^-$), and (d) metal complex Cs$^+$@**4a**$^{2-}$ containing one **4a**$^{2-}$, one Cs$^+$, and one TBA$^+$ crystallized from the condition outlined in (c).

In conclusion, we have demonstrated a novel strategy for the modular construction of diverse macrocyclic pentamers. These function as modularly engineerable, scalable, cavity-forming systems, wherein precise pinpoint modifications, with variable functionalities in both the interior and exterior, can be readily attained. Their shape-consistent aromatic skeletons effectively preorganize and orient electronic (e.g., oxygen atoms) and steric/hydrophobic (e.g., methyl groups) features into a convergent arrangement that may eventually enable the circular pentamers to tightly, yet selectively, bind metal cations possessing a radius below ~1.5 Å. Along this line, further refinement in the binding profiles of circular pentamers is currently ongoing.

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Supporting Information Available: Synthetic procedures for six pentamers **2**−**4** along with a full set of characterization data including CIF files and crystal data (**2a**, K$^+$@**3a**$^{2-}$, and Cs$^+$@**4a**$^{2-}$), ^{1}H/^{13}C NMR, HRMS, NOESY, ITC, molecular modeling (anionic **1a**$^{2-}$−**3a**$^{2-}$ and K$^+$@**4a**$^{2-}$) and a full list of authors for ref 6b. This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) See Supporting Information.

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(7) Single crystals were obtained by slow diffusion of hexane (for K$^+$−**3a**$^{2-}$) or cyclohexane (for Cs$^+$−**4a**$^{2-}$) into a solution in acetone (for K$^+$−**3a**$^{2-}$) or THF (for Cs$^+$−**4a**$^{2-}$) containing 1:1 molar ratio of cesium tetraphenylborate and tetrabutylammonium salt of anionic **3a** or **4a**.

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