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High Affinity Crown Ether Complexes in Water: Thermodynamic Analysis, Evidence of Crystallography and Binding of NAD^+

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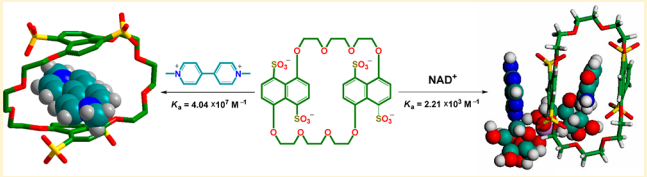
Supporting Information

ABSTRACT: Improving traditional crown ether to the water-soluble and high binding ability host molecule is critical to our efforts to model or mimic biological supramolecular systems. In this paper, we converted two traditional crown ethers, 1,5-dinaphtho-32-crown-8 and 1,5-dinaphtho-38-crown-10, into the water-soluble tetrasulfonated 1,5-dinaphtho-32-crown-8 and tetrasulfonated 1,5-dinaphtho-38-crown-10, evaluated their complexation with three dicationic bipyridiniums in aqueous solution by microcalorimetric titration, UV−vis, and NMR experiments, and then determined the crystal structures of three tetrasulfonatocrown ether-bipyridinium complexes. The equilibrium association constants of tetrasulfonated 1,5-dinaphtho-32-crown-8 with these bipyridiniums reach up to 10^7 M^{-1}, while those of tetrasulfonated 1,5-dinaphtho-38-crown-10 are just in the range of 10^5 M^{-1} order of magnitude. The thermodynamic data obtained show that the complexation of two tetrasulfonatocrown ethers with dicationic bipyridiniums is absolutely enthalpy-driven in water with an accompanying little entropic gain, and each monocationic pyridinium moiety in guest molecules can provide about −10 to −15 kJ·mol^{-1} enthalpy contribution irrespective of the size of ether crowns. Moreover, we also investigated the recognition capability of the two water-soluble crown ethers with NAD^+ and NADH by microcalorimetric titration and NMR experiments, indicating that tetrasulfonated 1,5-dinaphtho-32-crown-8 shows exclusive selectivity to NAD^+. The water-solubility and high affinity of this system as well as the flexible and non-preorganized characteristic of these crown ethers make it suitable to serve as a model for mimicking biological systems.



INTRODUCTION

Supramolecular chemistry has expanded significantly in recent years to model or mimic biological processes.[1] There are two critical factors for designing the artificial biologically supramolecular systems. One factor is that the supramolecular systems must be water-soluble,[2] the other is that there exists strong monovalent affinity between host and guest. The water-soluble cavitands adopting a rigidified and preorganized structure are well-known candidates. The representative cavitands include cyclodextrins,[3] calixarenes,[4] resorcin[4]-arenes,[5] cucurbituril,[6] coordination cage,[7] et al. However, no rigidified and preorganized cavitands were found in the biological systems. Thus, seeking the flexible and non-preorganized cavitands and acyclic hosts[8] with both water-solubility and high affinity will be significant for combining supramolecular chemistry with biology.

Crown ethers are the simplest and most widely used host molecules for both metallic and organic cations. Their investigations were mainly performed in the organic solutions rather than in aqueous solution due to the poor water solubility and the weak affinity with guests. Water-soluble crown ethers, such as 18-crown-6, [2.2.2]cryptand, display higher association constants in the organic solvent than in water. When the association constant of 18-crown-6 with potassium cation reaches up to 10^6 M^{-1} in methanol, this value in water is only 100 M^{-1}.[9] A similar case occurs on the macrobicyclic [2.2.2]cryptand: 10^{10} M^{-1} in methanol vs 10^5 M^{-1} in water.[10] Recently, several negative charged crown ethers were reported and show moderate affinity in water.[11] A comprehensive analysis indicates that water molecules not only strongly interfere the ion−dipole interaction between crown ethers and guest molecules, but also are unfavorable for entropy change due to the flexible and low preorganized polyethyleneoxy chain.[2a] Herein, we present unexpected high affinity crown ether complexation in water. Using UV−vis, NMR spectra, and X-ray crystallography, we will show that bipyridinium guests $\mathbf{3}\cdot Br_2$−$\mathbf{5}\cdot Br_2$ can interpenetrate both tetrasulfonated 1,5-dinaphtho-32-crown-8 ($Na_4\cdot\mathbf{1}$) and tetrasulfonated 1,5-dinaphtho-38-crown-10 ($Na_4\cdot\mathbf{2}$) (Chart 1) via electrostatic interaction and π-stacking interaction. Microcalorimetric titration experiments display that the association constants (K_a) of $Na_4\cdot\mathbf{1}$ with $\mathbf{3}^{2+}$−$\mathbf{5}^{2+}$ reach up to 10^7 M^{-1} in water and are 2 orders of magnitude higher than those of $Na_4\cdot\mathbf{2}$. This is the first example of the unrigidified and non-preorganized macrocyclic compounds binding guest molecules in water with high affinity. Considering that the onium nicotinamide group in NAD^+ is also a pyridinium derivative, we further investigated the binding capability of NAD^+/NADH with $Na_4\cdot\mathbf{1}$/$Na_4\cdot\mathbf{2}$ in water by

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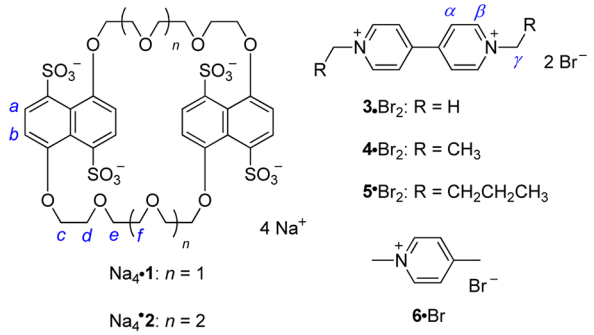
Chart 1. Structure of Crown Ethers Na_4·1, Na_4·2, Bipyridiniums 3·Br_2−5·Br_2, and Pyridinium 6·Br



means of NMR and microcalorimetric titration experiments. As expected, only Na_4·**1** can bind NAD^+ with a moderate K_a value.

RESULTS AND DISCUSSION

Synthesis. The chlorosulfonation reaction of 1,5-dinaphtho-32-crown-8 (**7**) or 1,5-dinaphtho-38-crown-10 (**8**) with excess chlorosulfonic acid in chloroform, and following neutralization by tetraethylammonium hydroxide (NEt_4OH), gave $(NEt_4)_4$·**1** and $(NEt_4)_4$·**2**, respectively. $(NEt_4)_4$·**1** and $(NEt_4)_4$·**2** were further changed into Na_4·**1** and Na_4·**2** with counterion exchange processes (Scheme 1). We even tried to synthesize the two compounds according to the method reported,[11a] but only products of two isomeric disulfonated crown ethers were obtained. Herein, the use of chlorosulfonic acid as a stronger sulfonating agent can obtain the tetrasulfonated crown ethers $(NEt_4)_4$·**1** and $(NEt_4)_4$·**2** with satisfactory yields. It is worth mentioning that the chlorosulfonation reaction just occurs at the 4- and 8-position of naphthyl groups despite the strong steric hindrance. The repulsion between sulfonate groups and polyethylene glycol chains even distorts the naphthalene rings (see below crystal sections). With such sterically disadvantaged sulfonation positions in naphthalene ring, one might assert that the chlorosulfonation should be a kinetic control process due to the activity of 4- and 8-position.

^{1}H NMR Spectra. The association between Na_4·**1**/Na_4·**2** and bipyridinium guests 3·Br_2−5·Br_2 were examined by ^{1}H NMR spectra in D_2O. The tetraethyl ammonium salts of $\mathbf{1}^{4-}$/$\mathbf{2}^{4-}$ were not chosen for the studies of solution experiments due to the slight affinity between counterion NEt_4^+ and $\mathbf{1}^{4-}$/$\mathbf{2}^{4-}$. As a result, we used the sodium salts of $\mathbf{1}^{4-}$/$\mathbf{2}^{4-}$ for all solution experiments in consideration of the negligible affinity of $\mathbf{1}^{4-}$/$\mathbf{2}^{4-}$ with counterion Na^+. As can be seen from Figure 1, upon complexation with $\mathbf{3}^{2+}$, both $\mathbf{1}^{4-}$ and $\mathbf{2}^{4-}$ have similar NMR signal change with a fast-exchange on their ^{1}H NMR time scale.

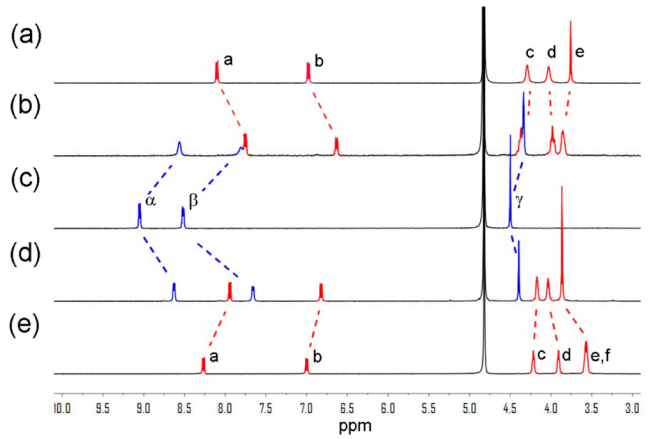


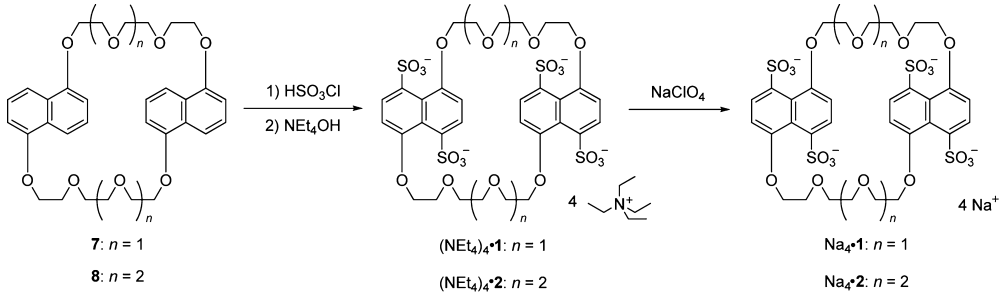
Figure 1. Partial ^{1}H NMR spectra (400 MHz, D_2O, 25 °C) of (a) free host Na_4·**1** ([Na_4·**1**] = 2 mM); (b) Na_4·**1** and equiv **3**·Br_2 ([**3**·Br_2] = [Na_4·**1**] = 2 mM); (c) free guest **3**·Br_2 ([**3**·Br_2] = 2 mM); (d) Na_4·**2** and equiv **3**·Br_2 ([**3**·Br_2] = [Na_4·**2**] = 2 mM); (e) free host Na_4·**2** ([Na_4·**2**] = 2 mM).

The chemical shifts of aromatic protons in $\mathbf{1}^{4-}$/$\mathbf{2}^{4-}$ and all protons in bipyridinium guests exhibit upfield shift, which are mainly attributed to mutual strong diamagnetic shielding between naphthalene and pyridinium rings. In contrast with these aromatic protons, the methylene protons (H_c) next to aromatic rings show obviously upfield shift upon complexation, while the others (H_d, H_e and H_f) do downfiled shift. These downfiled shifted should be contributed by weak C—H···O hydrogen bonds between $\mathbf{3}^{2+}$ protons and oxygen atoms on polyethylene chains. However, the remarkable chemical shift changes for H_e and H_f in $\mathbf{2}^{4-}$ ($\Delta\delta_{e,f}$ = 0.30 ppm) indicate significant contribution by C—H···O hydrogen bond, whereas the small $\Delta\delta_e$ values ($\Delta\delta_e$ = 0.09 ppm) of $\mathbf{1}^{4-}$ means a very slight contribution by C—H···O hydrogen bond.

On the other hand, there are also some notable differences between the two complexation processes. For $\mathbf{3}^{2+} \subset \mathbf{2}^{4-}$, the two protons ($H_a$ and H_b) on naphthalene rings have different chemical shift changes ($\Delta\delta_a$ = 0.33 ppm, and $\Delta\delta_b$ = 0.18 ppm, Figure 1d) upon complexation, while those in Na_4·**1** exhibit the same $\Delta\delta_a$ values ($\Delta\delta_a$ = $\Delta\delta_b$ = 0.35 ppm, Figure 1b). These observations suggest that there must be different π-stacking orientation in the two complexes.

Association Constants and Thermodynamics. We investigated the complexation stability and the thermodynamic origin of tetrasulfonated crown ethers Na_4·**1** and Na_4·**2** with pyridinium and bipyridinium guests in aqueous solution by isothermal titration calorimetry (ITC) (Figures 2 and 3). Because the bipyridinium complexes of Na_4·**1** show extremely

Scheme 1. Synthesis of Na_4·1 and Na_4·2



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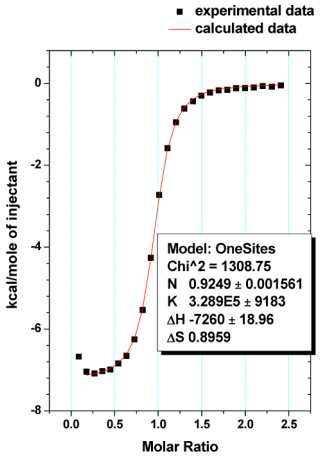

Figure 2. ITC experiments of Na_4·**2** with **3**·Br_2 in neat water at 25 °C.

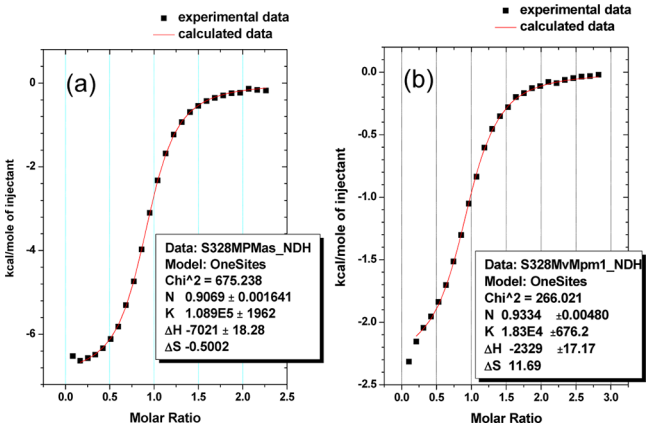

Figure 3. (a) ITC experiments on complexation of **6**·Br with Na_4·**1** in neat water at 25 °C; (b) competition ITC experiments on complexation of Na_4·**1** with **3**·Br_2 in 22.22 mM solution of **6**·Br used as competitor.

high stability, the K_a values cannot be measured by any direct methods. Correspondingly, a two-step competition method was employed.[12] We selected *N*-methylpicolinium bromine (**6**·Br), which has an association constant of 1.13 × 10^5 M^{-1}, as the competitor. A typical titration curve of the two step competition titrations for **6**·Br with Na_4·**1** is shown in Figure 3a. As expected, the obtained data were consistent with a 1:1 bonding model, and the thermodynamic parameters obtained were listed in Table 1.

As can be seen from Table 1, the K_a values obtained for the complexation of Na_4·**2** with three bipyridinium guests display the high affinity over 10^5 M^{-1}. Alkyl chain length of bipyridiniums can not change dramatically the K_a values. The observation that the K_a value of Na_4·**2** with $\mathbf{3}^{2+}$ is 1.7 times larger than those with $\mathbf{4}^{2+}$ or $\mathbf{5}^{2+}$ could be explained as the methyl protons of $\mathbf{3}^{2+}$ being a little more acidic than the ethyl or butyl protons of $\mathbf{4}^{2+}$ or $\mathbf{5}^{2+}$. For the complexation of Na_4·**1** with $\mathbf{3}^{2+}$–$\mathbf{5}^{2+}$, we surprisingly found that their K_a values reach up to 10^7 M^{-1} in water, which are 2 orders of magnitude higher than those of Na_4·**2**.

The obtained thermodynamic data clearly indicate that the complexation of Na_4·**1**/Na_4·**2** with $\mathbf{3}^{2+}$–$\mathbf{5}^{2+}$ in water is exclusively driven by the large negative enthalpy changes ($-\Delta H^\circ$ = 27.20–43.92 kJ·mol^{-1}) accompanied by a little entropic gain ($T\Delta S^\circ$ = −0.17–4.47 kJ·mol^{-1}), as shown in Table 1. In spite of the accordant contribution between the negative ΔH° and the positive $T\Delta S^\circ$, the K_a values in water are distinctly different. The complexation of $\mathbf{3}^{2+}$–$\mathbf{5}^{2+}$ with Na_4·**1** gives more favorable enthalpy gains ($\Delta H^\circ_1 - \Delta H^\circ_5$ = −8.80 kJ·mol^{-1}, $\Delta H^\circ_2 - \Delta H^\circ_6$ = −14.34 kJ·mol^{-1}, $\Delta H^\circ_3 - \Delta H^\circ_7$ = −16.65 kJ·mol^{-1}) as compared with those of $\mathbf{3}^{2+}$–$\mathbf{5}^{2+}$ with Na_4·**2**. It is known that the negative enthalpy contributions arise mainly from the electrostatic, hydrogen bonding, π-stacking and van der Waals interactions upon complexation of host with guest. The present two systems (one is the Na_4·**1** complexes, the other is the Na_4·**2** complexes) have the same charge number and charged functional groups for both host and guest, so the size of crown ether must play a crucial role in arousing the distinctly different enthalpy changes. There are two electron-rich sulfonato 4,8-disulfonato-1,5-dialkoxynaphthalene (SAN) groups in Na_4·**1**/Na_4·**2** and two electron-deficient bipyridinium (BPY) surfaces unit in $\mathbf{3}^{2+}$–$\mathbf{5}^{2+}$. The two kinds of specific groups would lead to a preference for electron-rich and electron-deficient aromatic stacking.[13] The smaller the cavity of crown ether, the closer and compacter aromatic stacking between SAN and BPY. In other words, there is the stronger aromatic donor–acceptor interaction between Na_4·**1** and $\mathbf{3}^{2+}$–$\mathbf{5}^{2+}$. The following crystal structures will confirm that there exists indeed the aromatic donor–acceptor interaction with the face-centered stacking in the solid.

On the other hand, the complexation of Na_4·**1**/Na_4·**2** with $\mathbf{3}^{2+}$–$\mathbf{5}^{2+}$ also exhibits the somewhat favorable entropy changes from −0.17 to 4.47 kJ/mol. Comparing the entropy gains of complexes $\mathbf{3}^{2+} \subset \mathbf{1}^{4-}$, $\mathbf{4}^{2+} \subset \mathbf{1}^{4-}$, $\mathbf{5}^{2+} \subset \mathbf{1}^{4-}$ with those of $\mathbf{3}^{2+} \subset \mathbf{2}^{4-}$, $\mathbf{4}^{2+} \subset \mathbf{2}^{4-}$, $\mathbf{5}^{2+} \subset \mathbf{2}^{4-}$, we found that the corresponding entropy gains change from the favorable positive value ($T\Delta S^\circ_1 - T\Delta S^\circ_5$ = 3.14 kJ·mol^{-1}) to the unfavorable negative values ($T\Delta S^\circ_2 - T\Delta S^\circ_6$ = −0.36 kJ·mol^{-1}, $T\Delta S^\circ_3 - T\Delta S^\circ_7$ = −3.00 kJ·mol^{-1}). These results completely cancel the increasing enthalpy gains with the alkyl chain length, leading to standard free energy (ΔG°) of the complexation of the three

Table 1. T Complex Associate Constants (K_a/M^{-1}), Enthalpy (ΔH°/kJ·mol^{-1}) and Entropy Changes ($T\Delta S^\circ$/kJ·mol^{-1}) for 1:1 Inclusion Complexation of Na_4·1 or Na_4·2 with Bipyridinium Guests $\mathbf{3}^{2+}$–$\mathbf{5}^{2+}$ and Pyridinium 6·Br in Water at 25 °C

entries	host	guest	K_a	$-\Delta G^\circ$	$-\Delta H^\circ$	$T\Delta S^\circ$
1	Na_4·**1**	$\mathbf{3}^{2+}$	(4.04 ± 0.35) × 10^7	43.40 ± 0.22	38.93 ± 0.27	4.47 ± 0.05
2		$\mathbf{4}^{2+}$	(5.25 ± 0.58) × 10^7	44.04 ± 0.28	41.54 ± 0.54	2.50 ± 0.26
3		$\mathbf{5}^{2+}$	(4.66 ± 0.48) × 10^7	43.75 ± 0.26	43.92 ± 1.05	−0.17 ± 0.79
4		$\mathbf{6}^{+}$	(1.13 ± 0.06) × 10^5	28.84 ± 0.04	29.23 ± 0.23	−0.39 ± 0.35
5	Na_4·**2**	$\mathbf{3}^{2+}$	(3.25 ± 0.04) × 10^5	31.46 ± 0.03	30.13 ± 0.24	1.33 ± 0.21
6		$\mathbf{4}^{2+}$	(1.85 ± 0.04) × 10^5	30.06 ± 0.05	27.20 ± 0.01	2.86 ± 0.07
7		$\mathbf{5}^{2+}$	(1.88 ± 0.02) × 10^5	30.10 ± 0.03	27.27 ± 0.01	2.83 ± 0.02
8		$\mathbf{6}^{+}$	(4.42 ± 0.26) × 10^2	15.03 ± 0.69	14.71 ± 1.29	0.38 ± 1.43

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bipyridinium guests with Na_4·**1** or Na_4·**2** changes in a very small range. These phenomena could be interpreted by the cavity sizes of $\mathbf{1}^{4-}/\mathbf{2}^{4-}$. The thermodynamic of $\mathbf{2}^{4-}$ with larger cavity is less affected by the bipyridinium guests with different N-aryl groups, whereas the thermodynamic of $\mathbf{1}^{4-}$ is easily affected due to the smaller cavity and closer host–guest contact.

It has been documented that there are the large positive enthalpy changes for complexation of tetrasulfonatocalixarenes with dicationic bipyridiniums,[14] and the favorable entropy changes for the rigidified and preorganized cavitands, such as cyclodextrins,[3a] cucurbituril.[12] The large enthalpy changes of the former are mainly contributed by the electrostatic interaction between the negative host and the positive guest, while the latter favorable entropy changes are afforded by the extensive desolvation upon complexation of the rigidified and preorganized cavitands with guest. However, the unfavorable entropy change in the tetrasulfonatocalixarenes-bipyridinium system cancels partly the former enthalpic contribution leading to the smaller association constants, and the absence of the electrostatic interaction decreases distinctly the enthalpy values for the cavitand systems. In the present tetrasulfonatocrown ether-bipyridinium system, there are both the electrostatic interaction of the negative host with the positive guest and the desolvation effect from the inclusion interaction, which cooperatively contribute to the high affinity.

To further understand the large negative enthalpy changes and the resulting high affinity for the complexation of Na_4·**1** with the three dicationic bipyridiniums, we also performed the ITC experiments of monocationic guest $\mathbf{6}^+$ with the two tetrasulfonated crown ethers in water. As shown in Table 1, the K_a values of both complex $\mathbf{6}^+ \subset \mathbf{1}^{4-}$ (1.13×10^5 M^{-1}) and $\mathbf{6}^+ \subset \mathbf{2}^{4-}$ (442 M^{-1}) decrease about 2 orders of magnitude as compared with the corresponding dicationic bipyridiniums. These are mainly caused by the half smaller aromatic surface and single positive charge of $\mathbf{6}^+$ compared to **3**–**5** being doubly positive charged. Inspection to the thermodynamic data finds that there are ignorable entropy changes for both dicationic bipyridiniums $\mathbf{3}^{2+}$–$\mathbf{5}^{2+}$ and monocationic $\mathbf{6}^+$, so the contribution to the K_a values mainly comes from enthalpy changes. For the two $\mathbf{6}^+$ complexes, there also are the same charge number and charged functional groups for both host and guest as well as the electron-rich SAN groups in host and the electron-deficient BPY unit in guest. However, the complexation of $\mathbf{6}^+$ with Na_4·**1** still gives considerable favorable enthalpy gain ($\Delta H^\circ_4 - \Delta H^\circ_8 = -14.52$ kJ·mol^{-1}) as compared with that of $\mathbf{6}^+$ with Na_4·**2**, which should come from the contribution of the aromatic donor–acceptor interaction between Na_4·**1** and $\mathbf{6}^+$. The above comprehensive analysis may draw a reasonable conclusion that the cavity of Na_4·**1** can provide an appropriate distance between two SAN groups for the formation of the aromatic donor–acceptor pairing, leading to the largest negative enthalpy changes and the resulting high affinity for the Na_4·**1** complexes.

It is worth noting that the complexation of Na_4·**1** with $\mathbf{3}^{2+}$–$\mathbf{5}^{2+}$ gives more favorable enthalpy gains (from −9.70 kJ·mol^{-1} to −14.69 kJ·mol^{-1}) than that with $\mathbf{6}^+$, while the corresponding enthalpy gains for the Na_4·**2** complexes are from −12.56 to −15.42 kJ·mol^{-1}. These results suggest that each monocationic pyridinium moiety could provide about −10 to −15 kJ·mol^{-1} enthalpy contribution irrespective of the size of ether crowns. The preliminary conclusion would be beneficial to our understanding of the assembly behavior and mode through alternating electron-rich and electron-deficient aromatic stacking.

UV Spectra. It has been documented that a face-centered stacked arrangement through alternating electron-rich and electron-deficient aromatics can result in varying degrees of π orbital mixing and resulting charge transfer (CT) absorbance band in a longer wavelength.[13,15] Our UV–vis absorption spectroscopy experiments confirm unambiguously that there is the aromatic donor–acceptor interaction upon complexation. As can be seen from Figure 4, a new absorption band centered

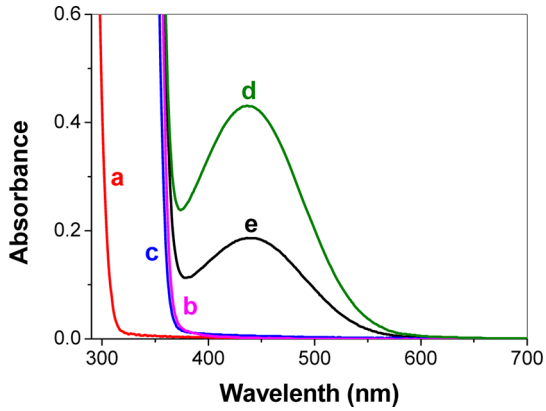

Figure 4. UV–vis absorption spectra of (a) **3**·Br_2 (1.0 mM), (b) Na_4·**2** (1.0 mM), (c) Na_4·**1** (1.0 mM) (d) Na_4·**2** (1.0 mM) + **3**·Br_2 (1.0 mM) (e) Na_4·**1** (1.0 mM) + **3**·Br_2 (1.0 mM) in H_2O, at 25 °C.

at 436 nm is observed upon addition of equimolar $\mathbf{3}^{2+}$ to the aqueous solution of Na_4·**2**, which indicates that there exists the CT interaction between $\mathbf{3}^{2+}$ and Na_4·**2**. Similarly, there is also a CT absorbance peak at 440 nm for the 1:1 mixture of $\mathbf{3}^{2+}$ with Na_4·**1**. These phenomena suggest a face-centered stacking between the tetrasulfonated crown ethers and the dicationic bipyridiniums in solution. Considering the much higher affinity for the complexation of Na_4·**1** with $\mathbf{3}^{2+}$ than that of Na_4·**2**, one could wonder why the absorbance of the former ($\varepsilon = 1.9 \times 10^2$ L·mol^{-1}·cm^{-1}) is smaller than that of the latter ($\varepsilon = 4.3 \times 10^2$ L·mol^{-1}·cm^{-1}), while bathochromic-shift is larger (440 vs 436 nm). We can explain reasonably these freak observations by means of the crystal structures of the two complexes. On one hand, the two pyridinium rings of $\mathbf{3}^{2+}$ in $\mathbf{3}^{2+} \subset \mathbf{2}^{4-}$ almost are coplanar, while the same groups in $\mathbf{3}^{2+} \subset \mathbf{1}^{4-}$ adopt a slight torsion arrangement. As a result, the electron transition from the HOMO π-orbital on the electron-rich SAN aromatic group in Na_4·**2** to the LUMO π-orbital on the coplanar electron-deficient BPY unit in $\mathbf{3}^{2+}$ is easier than that from the SAN aromatic in Na_4·**1** to the nonplanar BPY unit in $\mathbf{3}^{2+}$, leading to a stronger absorbance in complex $\mathbf{3}^{2+} \subset \mathbf{2}^{4-}$. On the other hand, the relative short distance between the SAN aromatic in Na_4·**1** and the BPY unit in $\mathbf{3}^{2+}$ implies smaller HOMO–LUMO energy gap, and resulting in a longer wavelength CT absorbance. The causal connection between structure in the solid state and properties in solution indicates that the binding modes of the tetrasulfonated crown ethers with the dicationic bipyridiniums in solution are consistent with those in the solid state.

Solid-State Structures. Three crystalline complexes $\mathbf{3}^{2+} \subset \mathbf{1}^{4-}$, $\mathbf{3}^{2+} \subset \mathbf{2}^{4-}$ and $\mathbf{4}^{2+} \subset \mathbf{2}^{4-}$ were obtained in their monocrystalline forms by slow diffusion of organic solvent into their electrostatic salts solution. As can be seen in Figure 5,

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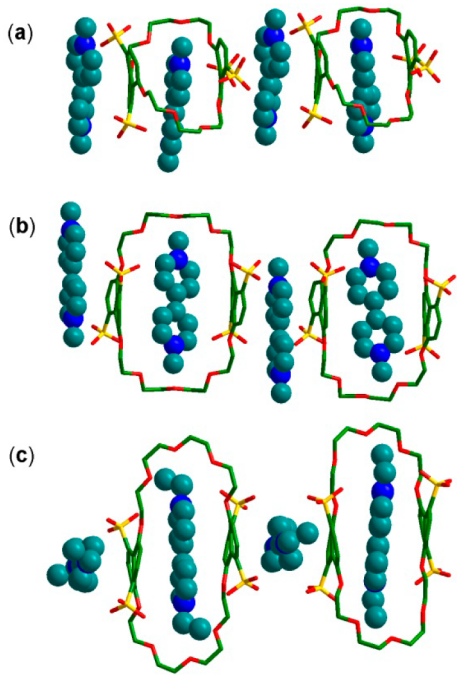

Figure 5. The packing representation of inclusion complexes of (a) $3^{2+} \subset 1^{4-}$, (b) $3^{2+} \subset 2^{4-}$ and (c) $4^{2+} \subset 2^{4-}$.

the sulfonated naphthalene rings are distorted due to repulsion between sulfonate and alkoxyl groups, and all three complexes consist of one host and two guest molecules. One of bipyridinium molecules is sandwiched between two distorted naphthalene rings, while the other acts as counterions in the crystal lattice.

As can be seen from Figure 6, in both crystalline complexes $3^{2+} \subset 2^{4-}$ and $4^{2+} \subset 2^{4-}$, four C—H···O hydrogen bonds are observed, compared to the only two C—H···O hydrogen bonds in $3^{2+} \subset 1^{4-}$.[17] This is well consistent with the chemical shift changes in Figure 1. On the other hand, careful examination of three crystal structures confirms differences of π-stacking. In $3^{2+} \subset 1^{4-}$, the distance between the centroid of the naphthalene ring and the average plane of the included bipyridinium unit is 3.44 Å. This is a reasonable distance of face-to-face π-stacking interaction, suggesting that there is the π-donor−acceptor interaction between naphthalene and bipydidinium.[16] In $4^{2+} \subset 2^{4-}$, the distance between π-donor−acceptor pairs is 3.54 Å, which is larger than that of $3^{2+} \subset 1^{4-}$. In addition, the centroid−centroid distances between SAN and BPY aromatic rings in $3^{2+} \subset 1^{4-}$ are 3.64 and 3.71 Å, respectively, and those in $4^{2+} \subset 2^{4-}$ are 3.85 and 4.00 Å. It is reasonable that the closer distance between π-donor−acceptor pairs is more favorable for aromatic interactions. An unexpected phenomenon is that the average plane of naphthalene ring is not parallel to the bipyridinium in $3^{2+} \subset 2^{4-}$. There are interplanar angles of 5.5° and 64.5°. The inclusion mode of this complex does not increase the distance between two positive charged centers in guest and four negative charged centers in host. Thus, the distinctive observation of π-stacking geometry can support our conclusion that there are stronger π-stacking interactions in bipyridinium complexes of 1^{4-} than that of 2^{4-}.

A notable detail of the crystalline complexes is that the four sulfonate groups in $1^{4-}/2^{4-}$ have different steric arrays. In both $3^{2+} \subset 2^{4-}$ and $4^{2+} \subset 2^{4-}$, the four sulfonate groups employ a *cis* conformation to interact with inclusion bipyridinium guests,

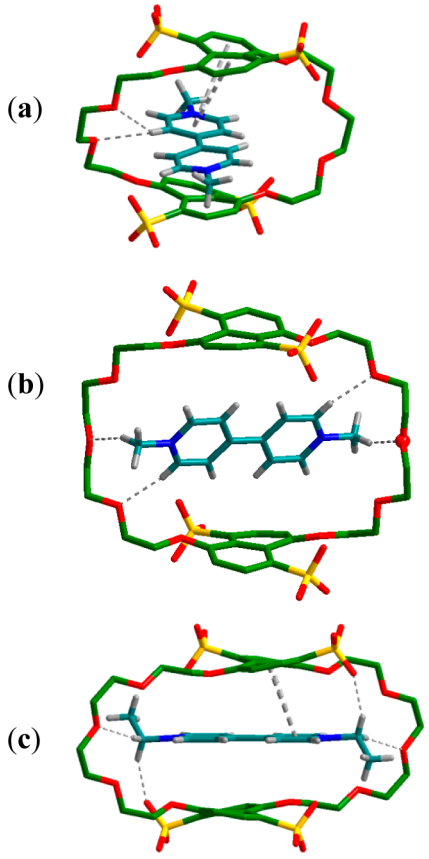

Figure 6. The molecule structures of inclusion complexes of (a) $3^{2+} \subset 1^{4-}$, (b) $3^{2+} \subset 2^{4-}$, and (c) $4^{2+} \subset 2^{4-}$.

while the four sulfonate groups in $3^{2+} \subset 1^{4-}$ take on a *trans* array. These phenomena should be attributed to the intermolecular charge repulsion between sulfonate groups. The *trans* array of sulfonate groups could distance sulfonate groups as far as possible and minimize charge repulsion. Because of the smaller cavity of 1^{4-}, the charge repulsion of 1^{4-} is stronger than that of 2^{4-}, which could be expected to prevent collapse of the cavity of 1^{4-}. The presence of four sulfonate groups in 1^{4-} would preorganize the flexible crown ethers in a certain degree to result in a better π-acceptant cavity. This should be an important reason for the higher affinity of 1^{4-}.

Recognition of NAD$^+$. NAD^+ and its reduced form (NADH) play a crucial role in biological systems as redox coenzymes.[18] Selective molecular recognition and detection of NAD^+ and NADH by artificial receptors is a challenging research subject for chemists.[19] To date, only rigid molecular clips[20] were demonstrated to be the efficient and selective synthetic receptor for NAD^+ and NADH. Differing from the rigid molecular clip receptors, Na_4·**1** is unrigidified and non-preorganized, and shows the high affinity for pyridinium and bipyridinium guests, which makes it possibly bind the onium nicotinamide group in NAD^+.

As can be seen form Figure 7, when NADH was added to the aqueous solution of Na_4·**1**, no interaction was observed. However, when NADH was replaced with NAD^+, the complexation between Na_4·**1** and NAD^+ can be monitored by ^{1}H NMR spectroscopy. H_1−H_5 of NAD^+ and H_a/H_b of Na_4·**1** shift upfield from 0.11 to 0.27 ppm. These observations indicate that the onium nicotinamide of NAD^+ is bound in the macrocycle of Na_4·**1**. In addition, we noticed that two protons

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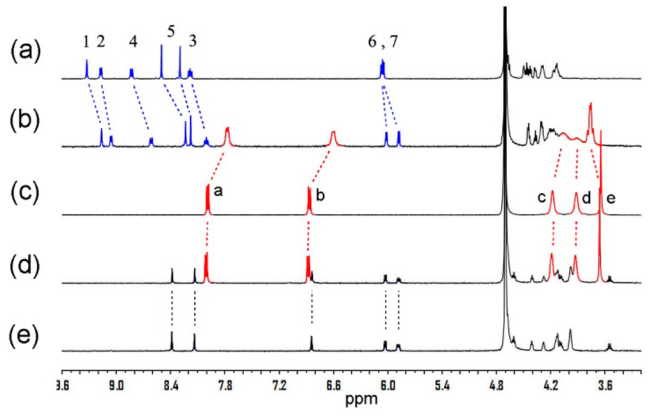

Figure 7. Partial ^{1}H NMR spectra (400 MHz, D_2O, 25 °C) of (a) free NAD^+ ([NAD^+ = 2 mM]); (b) NAD^+ and Na_4·**1** ([NAD^+] = [Na_4·**1**] = 2 mM); (c) free Na_4·**1** ([Na_4·**1**] = 2 mM); (d) NADH and Na_4·**1** ([NADH] = [Na_4·**1**] = 2 mM); (e) free NADH ([NADH] = 2 mM). All the solution is neutralized with minor quantity of HCl/NaOH to pH = 7.0 ± 0.2.

(H_6 and H_7) in the adenine group of NAD^+ also shift upfield in different degrees, which suggests that the adenine stacks with naphthalene externally to the cavity. The schematic representation of the presumed complexation model for the interaction of Na_4·**1** with NAD^+ is illustrated in Figure 8.

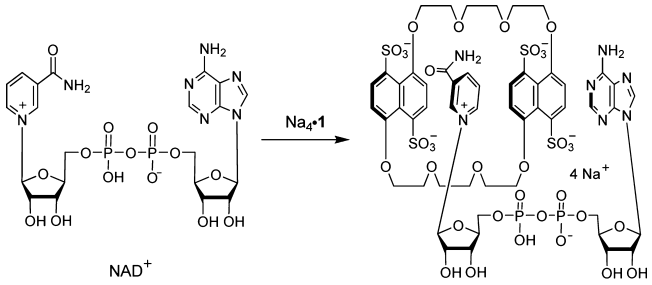

Figure 8. Possible structure of complex $NAD^+ \subset \mathbf{1}^{4-}$ in aqueous solution.

To quantitatively investigate the binding behavior of NAD^+/NADH with Na_4·**1**/Na_4·**2** in water, microcalorimetric titration has been performed at 25 °C in aqueous solution to give K_a and the thermodynamic parameters upon their complexation. As expected, the little net complexation heat was observed for interaction of Na_4·**1**/Na_4·**2** with the uncharged NADH, suggesting very weak binding. The K_a value for interaction of NAD^+ with Na_4·**1** is 2.21 × 10^3 M^{-1}, accompanying with favorable enthalpy gain ($-\Delta H^\circ$ = 67.9 kJ·mol^{-1}) and unfavorable entropy change ($T\Delta S^\circ$ = −48.87 kJ·mol^{-1}). The unfavorable entropy change might be attributed to the electrostatic repulsion, which has an inverse entropical effect with the electrostatic attraction. Unexpectedly, there is hardly net heat observed for complexation of NAD^+ with Na_4·**2**, indicative of very weak binding. These observations are consistent with those of NMR experiments.

CONCLUSION

Two water-soluble sulfonatocrown ethers Na_4·**1** and Na_4·**2** have been synthesized through the chlorosulfonation reaction of two 1,5-dinaphthocrown ethers rather than the sulfonation reaction. Their complexation with one pyridinium, three dicationic bipyridiniums, NAD^+ and NADH were evaluated by microcalorimetric titration and ^{1}H NMR experiments, indicating that the association constants of the smaller ring Na_4·**1** with these bipyridiniums reach up to 10^7 M^{-1} in water, while the corresponding values for the bigger Na_4·**2** are just in the order of magnitude of 10^5 M^{-1}. Combining with the crystallography evidence of three complexes as well as the thermodynamic data for their complexation with the monocationic pyridinium, we elucidated the mechanisms of the high affinity crown ether complexation in water. (a) Thermodynamically, their complexation with dicationic bipyridiniums is absolutely enthalpy-driven in water with little accompanying entropic gain. The electrostatic interaction of the negative host with the positive guest and the aromatic donor−acceptor interaction between SAN groups and BPY jointly contribute to the large positive enthalpy changes, while the extensive desolvation upon complexation do favorable entropy changes like the rigidified and preorganized cavitands. (b) Structurally, the interpenetration of the bipyridinium molecules into the cavity of Na_4·**1**/Na_4·**2** not only shortens the distance between two positive charged centers in guest and four negative charged centers in host, but also closes the planes of bipyridinium in guest with naphthalene ring in host, making both the electrostatic interaction and the aromatic donor−acceptor interaction become stronger.

From microcalorimetric titration and NMR experiments of interaction of NAD^+/NADH with Na_4·**1**/Na_4·**2**, we found that only Na_4·**1** can bind NAD^+ in water. So, the intrinsic water-solubility and the high monovalent affinity of the tetrasulfonated crown ethers as well as their flexible and non-preorganized characteristic make them suitable to serve for mimicking biological systems. The present investigation maybe open new doors for usage of crown ethers in the biological supramolecular systems.

EXPERIMENTAL SECTION

General Method. All chemicals were commercially available unless noted otherwise. Starting materials **7** and **8** were prepared according to literature procedures.[21] Guest molecules $\mathbf{3}^{2+}$, $\mathbf{4}^{2+}$, $\mathbf{5}^{2+}$ and $\mathbf{6}^{+}$ were used with bromine salts. All the solution of NAD^+ and NADH were neutralized with minute quantity of HCl/Na_2CO_3 to pH = 7.0 ± 0.2 before using. NMR data were recorded on 400 M spectrometer. All chemical shifts were referenced to the internal CH_3CN signal at 2.06 ppm.[22] Absorption spectra were recorded on a UV−vis spectrometer. Mass spectra were performed on Q-TOF LC−MS (ESI). All the X-ray intensity data were collected on a a rotating anode diffractometer equipped with a CCD Area Detector System, using monochromated Mo Ka (λ = 0.71073 Å) radiation at T = 113(2) K. CCDC-875323, -875325, and -875324 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

A thermostatted and fully computer-operated isothermal calorimetry (VP-ITC) instrument was used for all microcalorimetric experiments. The ITC experiments were performed at 25 °C in aqueous solution, giving the association constants (K_a) and the thermodynamic parameters of guests upon complexation. In each run, a solution of guest in a 0.250 mL syringe was sequentially injected with stirring at 300 rpm into a solution of host in the sample cell (1.4227 mL volume). A control experiment to determine the heat of dilution was carried out for each run by performing the same number of injections with the same concentration of guest compound as used in the titration experiments into the same solution without the host compound. The dilution enthalpies determined in control experiments were subtracted from the enthalpies measured in the titration experiments to obtain the net reaction heat. All thermodynamic

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parameters reported in this work were obtained by using the "one set of binding sites" model. Two independent titration experiments were performed to afford self-consistent parameters and to give the averaged values.

Preparation of $(NEt_4)_4$·1. A solution of chlorosulfonic acid (1.17 g, 10.01 mmol) in dry $CHCl_3$ (30 mL) was added dropwise over a period of 2 h to a stirred solution of bis(1,5-naphtho)-32-crown-8 (0.50 g, 0.91 mmol) in dry $CHCl_3$ (90 mL) at −5 °C. Then the mixture was stirred at −5 °C for an additional 4 h to give a white precipitate. The precipitate was carefully collected by filtration and washed with dry $CHCl_3$ (50 mL) at once. The reside was taken up into H_2O (80 mL), and NEt_4OH solution was added until pH = 7. The solvate was envapored and dried by vacuum. After recrystallization from acetonitrile−acetone for three times and drying by vacuum, $(NEt_4)_4$·1 was afforded as white solid that absorbs moisture in the air (0.86 g, 68.6%): ^{1}H NMR (400 MHz, D_2O) δ 8.16 (d, J = 8.2 Hz, 4H), 6.97 (d, J = 8.4 Hz, 4H), 4.25 (s, 8H), 4.00 (s, 8H), 3.72 (s, 8H), 3.22 (d, J = 7.2 Hz, 32H), 1.24 (s, 48H); ^{13}C NMR (100 MHz, D_2O) δ 156.5, 131.4, 130.4, 123.9, 106.9, 69.7, 68.6, 68.1, 51.6, 6.4; HRMS (ESI) m/z [M − 4NEt_4 + 3H]$^-$ cacld for $C_{32}H_{35}O_{20}S_4$ 867.0604, found 867.0598; [1/2 (M − 4NEt_4 + 3H)]$^-$ cacld for $C_{16}H_{17}O_{10}S_2$ 433.0263, found 433.0266.

Preparation of Na_4·1. $(NEt_4)_4$·1 (1.00 g, 0.72 mmol) was dissolved in CH_3CN (30 mL), and a solution of $NaClO_4$ (14.40 mmol, 1.76 g) in CH_3CN (60 mL) was added slowly with stirring. The precipitate was filtered off and washed with CH_3CN for three times. After drying by vacuum, Na_4·1 was afforded as a white solid (0.67 g, 97.1%): ^{1}H NMR (400 MHz, D_2O) δ 8.11 (d, J = 8.5 Hz, 4H), 6.99 (d, J = 8.6 Hz, 4H), 4.30 (s, 8H), 4.04 (s, 8H), 3.77 (s, 8H); ^{13}C NMR (100 MHz, D_2O) δ 156.4, 131.1, 130.4, 123.8, 107.3, 69.6, 68.5; HRMS (ESI) m/z [M − Na + 2H]$^+$ cacld for $C_{32}H_{34}O_{20}Na_3S_4$ 935.0220, found 935.0207; [M − 3Na + 4H]$^-$ cacld for $C_{32}H_{36}O_{20}NaS_4$ 891.0580, found 891.0573.

Preparation of $(NEt_4)_4$·2 and Na_4·2 is similar to the procedures of $(NEt_4)_4$·1 and Na_4·1.

$(NEt_4)_4$·2: Yield 71.3%; ^{1}H NMR (400 MHz, D_2O) δ 8.16 (d, J = 8.5 Hz, 4H), 6.93 (d, J = 8.6 Hz, 4H), 4.14 (s, 8H), 3.84 (d, J = 4.1 Hz, 8H), 3.58−3.40 (m, 16H), 2.91 (q, J = 7.3 Hz, 32H), 1.09−0.88 (m, 48H); ^{13}C NMR (100 MHz, D_2O) δ 156.7, 131.7, 130.6, 124.1, 107.2, 69.6, 68.5, 68.2, 51.6, 6.4; HRMS (ESI) m/z [M + 1]$^+$ calcd for $C_{68}H_{121}N_4O_{22}S_4$ 1473.7355, found 1473.7345; [M − NEt_4 + 2H]$^+$ calcd for $C_{60}H_{102}N_3O_{22}S_4$ 1344.5837, found 1344.5841.

Na_4·2: Yield 98.0%; ^{1}H NMR (400 MHz, D_2O) δ 8.15 (d, J = 8.5 Hz, 1H), 6.88 (d, J = 8.6 Hz, 1H), 4.10 (s, 2H), 3.80 (d, J = 4.5 Hz, 2H), 3.45 (d, J = 5.4 Hz, 4H); ^{13}C NMR (100 MHz, D_2O) δ 156.6, 131.3, 130.6, 124.0, 108.0, 69.5, 69.1, 68.8, 68.4; HRMS (ESI) m/z [M + H]$^+$ cacld for $C_{36}H_{41}O_{22}Na_4S_4$ 1045.0564, found 1045.0519; [M − 4Na + 3H]$^-$ cacld for $C_{36}H_{43}O_{22}S_4$ 955.1128, found 955.1130.

Preparation of electostatic salts of 3_2·1, 3_2·2, and 4_2·2: $(NEt_4)_4$·1 or (NEt4)$_4$·2 (0.8 mmol) was dissolved in CH_3CN (30 mL), and a solution of bipyridinium hexafluorophosphate 3·$(PF_6)_2$ or 4·$(PF_6)_2$ (4 mmol) in CH_3CN (60 mL) was added slowly with stirring. The precipitate was filtered off and washed with CH_3CN for three times. After drying by vacuum, the electrostatic salts were afforded as orange solid.

3_2·1: ^{1}H NMR (400 MHz, D_2O) δ 8.81−8.46 (s, 8H), 8.24−7.74 (s, 8H), 7.61 (d, J = 8.3 Hz, 4H), 6.50 (d, J = 8.5 Hz, 4H), 4.40−4.11 (m, 20H), 3.85 (t, J = 9.6 Hz, 8H), 3.74 (d, J = 7.4 Hz, 8H); ^{13}C NMR (100 MHz, D_2O) δ 155.7, 145.6, 131.6, 129.9, 125.3, 123.4, 106.2, 70.1, 68.7, 68.2, 48.2; HRMS (ESI) m/z [M − H]$^-$ cacld for $C_{56}H_{59}N_4O_{20}S_4$:1235.2605, found 1235.2602.

3_2·2: ^{1}H NMR (400 MHz, D_2O) δ 8.64 (d, J = 6.3 Hz, 8H), 7.81 (d, J = 8.5 Hz, 12H), 6.69 (d, J = 8.6 Hz, 4H), 4.30 (s, 12H), 4.05 (s, 8H), 3.92 (s, 8H), 3.75 (s, 16H); ^{13}C NMR (100 MHz, D_2O) δ 156.1, 145.8, 131.7, 130.2, 125.0, 123.6, 107.6, 69.8, 69.1, 68.6, 48.2; HRMS (ESI) m/z [M − 3 + H]$^-$ cacld for $C_{48}H_{55}N_2O_{22}S_4$ 1139.2128, found 1139.2121.

4_2·2: ^{1}H NMR (400 MHz, D_2O) δ 8.70 (d, J = 6.7 Hz, 8H), 7.89 (d, J = 6.4 Hz, 8H), 7.71 (d, J = 8.5 Hz, 4H), 6.60 (d, J = 8.6 Hz, 4H), 4.54 (q, J = 7.4 Hz, 8H), 4.03 (d, J = 4.4 Hz, 8H), 3.92 (s, 8H), 3.73 (s, 16H), 1.57 (t, J = 7.4 Hz, 12H); ^{13}C NMR (100 MHz, D_2O) δ 156.1, 147.2, 144.5, 131.8, 130.0, 125.5, 123.6, 107.2, 69.8, 68.8, 68.5, 57.4, 15.4; HRMS (ESI) m/z [M − 4 + 3H]$^+$ cacld for $C_{50}H_{61}N_2O_{22}S_4$ 1169.2598, found 1169.2595.

■ ASSOCIATED CONTENT

Supporting Information

Characterization of all materials, complexation ^{1}H NMR spectrum and UV−vis spectrum, calorimetric titration data for guests 3·Br_2, 4·Br_2, 5·Br_2, and 6·Br with Na_4·1 and Na_4·2, and X-ray diffraction data (CIF). 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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(17) Hydrogen-bond parameters are shown as follows: in $3^{2+} \subset 1^{4-}$, the H···O distance, C—H···O angle, and C···H distance values of two hydrogen bonds are 2.44 Å, 143°, 0.95 Å, and 2.82 Å, 126°, 0.95 Å, respectively. In $3^{2+} \subset 2^{4-}$ and $4^{2+} \subset 2^{4-}$, there are two set of the same hydrogen bonds in their four hydrogen bonds. In $3^{2+} \subset 2^{4-}$, the corresponding values are 2.24 Å, 157°, 0.95 Å, and 2.32 Å, 160°, 0.98 Å, respectively; in $4^{2+} \subset 2^{4-}$, the corresponding values are 2.38 Å, 153°, 0.99 Å, and 2.50 Å, 154°, 0.99 Å, respectively.

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