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2,3-Dialkoxynaphthalene-Based Naphthocage†

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**A 2,3-dialkoxynaphthalene-based naphthocage has been synthesized. This naphthocage prefers to bind small organic cations with its low-symmetry conformation, which is in contrast to those of 2,6-dialkoxynaphthalene-based naphthocages. Self-sorting of these two naphthocages with two structurally similar guests tetramethylammonium and tetraethylammonium was achieved as well.**

Preorganized and rigid molecular receptors often possess very high binding affinity and selectivity.[1] For example, Cram's spherands show remarkably high binding affinity and selectivity to Li^+ and Na^+ over other alkaline metal ions.[2] This is desirable for applications in sensing and separation. Nevertheless, the binding targets of rigid receptors are often difficult to predict because they cannot tolerate even minor structural changes induced by a guest. In contrast, flexible receptors[3] usually show low binding affinity and selectivity because of the entropic penalty upon binding caused by large amplitude conformational changes. One exception is the flexible triazacryptand reported by He and coworkers,[4] which shows high binding selectivity to K^+ over Na^+. Extensive binding sites arranged in three dimensions completely wrap around the targeted ion, leading to high binding affinity even in water; size and electronic complementarity results in high selectivity.

In the last years, we reported a series of dialkoxynaphthalene-based macrocycles with electron-rich cavities (oxatub[n]arenes and zorb[4]arenes).[5,6,7] These macrocycles are very flexible and possess multiple
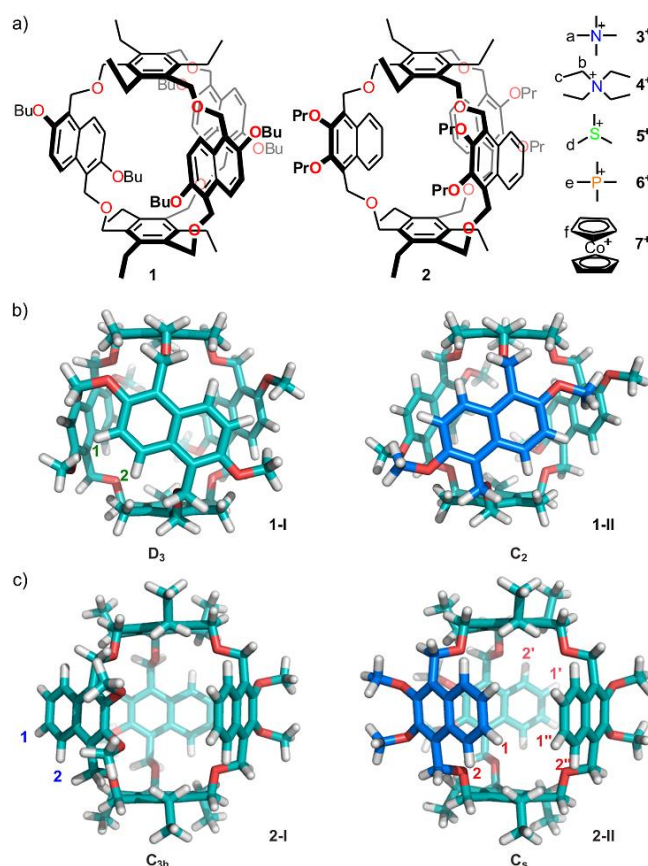
Fig. 1 (a) Chemical structures of two naphthocages **1** and **2** and the organic cations used as guests (used as PF_6^- salts); Optimized structures of two conformers (b) of naphthocage **1**[8a] and (c) of naphthocage **2** computed at the semi-empirical PM6 level of theory by Spartan'14 (Wavefunction, Inc.). All the peripheral feet were shortened to methyl groups for viewing clarity. Numbering on the structures corresponds to the assignment of NMR signals.

conformations. Therefore, they can conformationally adapt to the size and structural requirements of different guests, and thus have rather wide guest-binding scope. These macrocycles show decent binding affinities to common organic cations (10^2–10^5 M^{-1} in CD_2Cl_2/CD_3CN (1:1)). Recently, we extended these macrocycles to a three-dimensional cage structure with

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the 2,6-dibutoxynaphthalene-based naphthocage **1** (Fig. 1a).[8] Although the naphthocage **1** adopts a self-inclusion conformation in the free state, it shows remarkably high binding affinities to singly-charged organic cations, and the binding constants are generally over 10^7 M^{-1} (CH$_2$ClCH$_2$Cl/CH$_3$CN = 1:1). With the large guests such as colbaltocenium, the binding constant even reaches to 10^{10} M^{-1}. This high binding affinity is unexpected for such flexible receptors, and may originate from the similar reason as discussed above for the triazacrytand.

In this research, we report a 2,3-dipropoxynaphthanene-based naphthocage (**2**, Fig. 1a). This naphthocage shows similarly strong binding affinities to singly-charged organic cations but prefers to bind small ones. In addition, the low-symmetry conformation is predominantly selected by all the guests, which is in contrast to that of naphthocage **1**.

Naphthocage **2** was synthesized with 2,3-dipropoxynaphthalene as the starting materials instead of 2,6-diobutoxynaphthalene by using a similar procedure as that for **1** (see ESI†). The yield of the final macrocyclization for **2** (15%) is similar to that of **1** (14%). This new naphthocage has been characterized by ^{1}H, ^{13}C, 2D NMR spectroscopy and mass spectrometry (see ESI†).

Five singly-charged organic cations, which can well complex with naphthocage **1**,[8] were selected for the binding study with naphthocage **2**. These guests include quaternary ammoniums (**3$^+$** and **4$^+$**), sulfonium (**5$^+$**), phosphonium (**6$^+$**) and cobaltocenium (**7$^+$**). As shown in Fig. 2 and Fig. S1-S5 (ESI†), ^{1}H NMR spectra of both host and guest undergo obvious changes when mixing them together in 1:1 ratio. No signals for the free host and the free guests are detected, suggesting quite strong binding between them. In particular, the signals for all the guests undergo drastic upfield shifts ($\Delta\delta$ = - 2.5 – -3.7 ppm). This indicates that these guests are encapsulated in the cavity of **2** and experience the shielding effects of three naphthalenes and two triethylbenzenes. Quite clean electrospray ionization mass spectra were obtained on the
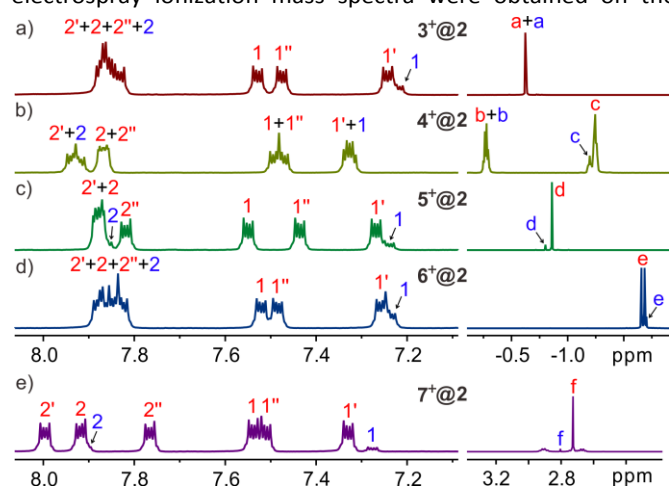

Fig. 2. Partial ^{1}H NMR spectra (500 MHz, CD$_2$Cl$_2$:CD$_3$CN =1:1, 25 $^\circ$C) of (a) **3$^+$@2**, (b) **4$^+$@2**, (c) **5$^+$@2**, (d) **6$^+$@2** and (e) **7$^+$@2**. The colour codes of the numberings on the NMR peaks are used to differentiate the two conformations (see Fig. 1). The NMR assignments were based on 2D NMR experiments (Fig. S17-S26)

Table 1. Binding constants (K_a, M^{-1}) of naphthocages **1** and **2** as determined by ITC titrations (CH$_2$ClCH$_2$Cl: CH$_3$CN = 1:1, 298 K)

Guests	**1**[a]	**2**[b]
3$^+$	$(1.6 \pm 0.3) \times 10^7$	$(1.1 \pm 0.1) \times 10^8$
4$^+$	$(3.7 \pm 0.4) \times 10^7$	$(3.5 \pm 0.2) \times 10^6$
5$^+$	$(1.8 \pm 0.1) \times 10^7$	$(7.5 \pm 0.9) \times 10^7$
6$^+$	$(5.1 \pm 0.2) \times 10^7$	$(1.5 \pm 0.1) \times 10^8$
7$^+$	$(6.1 \pm 1.9) \times 10^9$	$(8.9 \pm 0.3) \times 10^6$

[a] The binding constants of **1** were reported in the earlier publications[8]; [b] All the titration experiments were repeated thrice, and the averaged values with standard deviations are reported here.

equimolar mixtures of **2** with the guests, and the only peaks in the spectra can be assigned to the 1:1 complexes after losing PF$_6^-$ (Fig. S6-S10, ESI†). No peaks for free host and free guests can be found. This further supports the rather strong binding of **2** to these guests.

To quantify the binding affinities of naphthocage **2** to guests **3$^+$** - **7$^+$**, isothermal titration microcalorimetry (ITC) titrations (Fig. S11-S15) were performed. The binding constants are shown in Table 1. The binding constants of naphthocage **1** to these five guests, which were reported earlier,[8] are also included here for comparison.

Generally, **2** also shows very high binding affinity (10^6-10^8 M^{-1}) to these singly-charged organic cations. Tetramethyl ammonium (**3$^+$**) and phosphonium (**6$^+$**) are the best guests for **2**, with binding constants up to 10^8 M^{-1}. Guests with smaller or larger sizes lead to decreased binding constants. For example, guests **4$^+$** and **7$^+$** with a larger volume have the binding constants at the range of 10^6 – 10^7 M^{-1}; while sulfonium (**5$^+$**) with the smallest size also has a slightly weaker binding affinity when compared to **3$^+$**. Consequently, the binding preference of **2** is quite different from naphthocage **1.** As shown in Table 1, naphthocage **1** prefers the organic cations with larger volume among these five guests: cobaltocenium (**7$^+$**) is the best guest; tetraethyl ammonium (**4$^+$**) is better than tetramethyl ammonium (**3$^+$**). The different binding preferences of the two naphthocages may be due to the different size and shape in their cavities. The quite high binding constants of both naphthocages to these organic cations further demonstrate that with proper structural design, even highly flexible cages can achieve very strong guest binding.

Besides the different guest-binding preferences, the two naphthocages also have rather different conformational response to the same organic cation.

As shown in Fig. 1b, there are two representative conformations for naphthocage **1**, which can be interconvert through naphthalene flipping. It was reported earlier that the naphthalene flipping is quite fast at the NMR timescale at room temperature, and can only be slightly slowed down at − 20 $^\circ$C.[8] However, when a guest occupies the cavity, the interconversion kinetics of the two conformations would rely on the guest exchange kinetics. With a slowly-exchanged guest, the two conformations can be distinguished in the ^{1}H NMR spectra because they have different symmetry. For **1-I** with a D$_3$ symmetry, two aromatic signals are expected; while six

signals should be observed for the aromatic protons of **1-II** with a C_2 symmetry.

The same analysis also applies for naphthocage **2**. Two representative conformations due to naphthalene flipping are shown in Fig. 1c. In conformer **2-I**, three naphthalenes are arranged in a "head-to-tail" orientation, leading to a symmetry of C_{3h}; while one naphthalene is flipped for conformer **2-II**, resulting in a lower symmetry (C_s). Again, these two conformers have different patterns for the aromatic signals (two for **2-I** and six for **2-II**) in the ^{1}H NMR spectra if their interconversion is slow at the NMR timescale. The ^{1}H NMR spectrum of **2** is very simple (Fig. S16), and the CH_2-O-CH_2 methylene groups are not even split. This suggests that the naphthalene flipping and thus conformational interconversion of **2** are very fast at room temperature. Even at -80 ^{o}C, the NMR peaks of naphthocage **2** are only slightly broadened and no splitting was observed (Fig. S16).
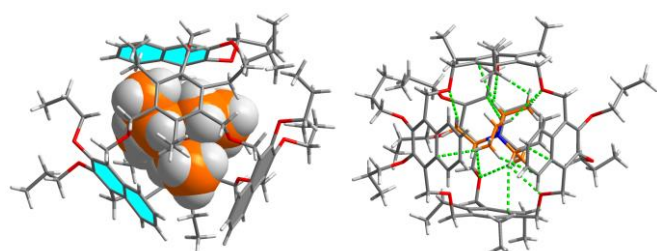

Fig. 3. X-ray single crystal structure of **4-PF$_6$@2-II.**

Table 2. The ratios of the two conformations of naphthocage **1** or **2** in the presence of guests **3$^+$** - **7$^+$** as determined from ^{1}H NMR spectra.

Guests	1-I : 1-II^a	2-I : 2-II
3$^+$	98:2	12:88
4$^+$	72:28	22:78
5$^+$	95:5	7:93
6$^+$	95:5	9:91
7$^+$	72:28	5:95

[a] these data are from the results published earlier. [8]

As shown in Fig. 2, the aromatic signals of naphthocage **2** are split into multiple peaks when adding a guest into its solution, and the diastereotopic methylene protons on the CH_2-O-CH_2 linkers are also split (Fig. S1-S5). This indicates that the conformational interconversion is slowed down when binding to these guests. According to the above analysis, the two conformations can be assigned based on the peak patterns. Six predominant aromatic signals exist for all the guests, suggesting that conformer **2-II** is predominantly selected. But minor aromatic signals, which should belong to **2-I**, are detected as well. Significant overlapping of these aromatic signals precludes accurate integration of the peaks and thus calculation of the ratios of the two conformers. However, the guest signals in the two conformations are clearly separated and can be used to calculate their ratios. The data are listed in Table 2. The ratios of the two conformations of naphthocage **1** in the presence of the same guest[8] are also included in Table 2 for comparison.

The predominant selection of conformer **2-II** by these guests is further supported by the X-ray single crystal structure of **4$^+$@2** (Fig. 3). Every neighbouring naphthalenes among these three are arranged in "head-to-head", "tail-to-tail" and "head-to-tail" patterns, respectively. The guest **4$^+$** is comfortably wrapped by the three naphthalenes and two triethylbenzenes. Multiple C-H···O and C-H···π interactions detected in the crystal structures (Fig. 3) should contribute to the high binding affinity.

As shown in Table 2, all these guests predominantly select the high-symmetry conformation (conformer **I**, D_3) of naphthocage **1**, but preferentially bind to the low-symmetry conformation (conformer **II**, C_s) of naphthocage **2**. This is counterintuitive at first glance! For self-assembly systems, quite often high-symmetry structures are predominantly formed to avoid strain and to maximize the cooperative interactions of all the non-covalent interactions or metal-coordinations. [9] However, for host-guest systems, guest template can sometimes bias this selection to the structure with a low symmetry and thus the host-guest interactions can be maximized.[10]

What is the reason for the conformational selection of naphthocages **1** and **2**? DFT calculations on four complexes **3$^+$@1-I**, **3$^+$@1-II**, **3$^+$@2-I**, and **3$^+$@2-II** were performed (Fig. 4). The results show that complexes **3$^+$@1-I** and **3$^+$@2-II** are more energetically stable than complexes **3$^+$@1-II** and **3$^+$@2-I**, respectively. This is in line with the conformational ratio in Table 2. The packing coefficients[11] of guest **3$^+$** in **1-I**, **1-II**, **2-I**, and **2-II** are 48%, 43%, 47% and 54% (for details, see Table S1 and Fig. S27-S32), respectively. This suggests the cavities of **1-I** and **2-II** are more suitable to the structure of **3$^+$** and thus better interactions can be achieved. Meanwhile, the packing
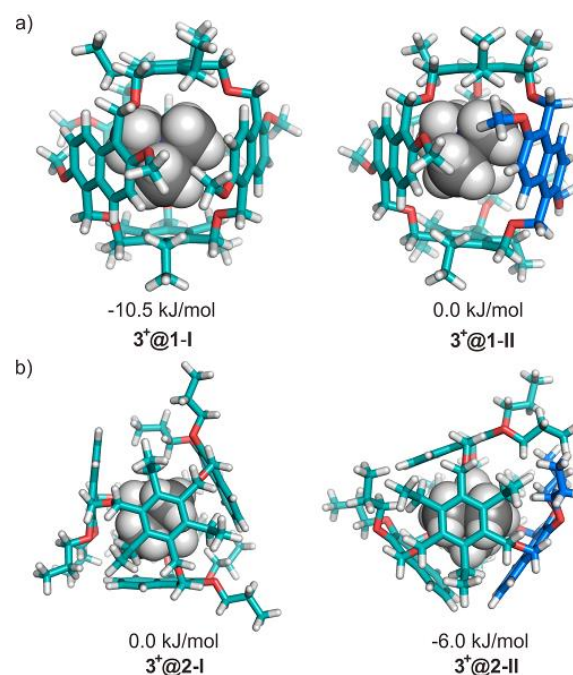

Fig. 4. Energy-minimized structures of complexes (a) **3$^+$@1-I** and **3$^+$@1-II**, (b) **3$^+$@2-I** and **3$^+$@2-II** calculated by DFT at the wB97XD/6-31G(d) level of theory in CH_2Cl_2. Butyl groups of **1** are shortened to methyl groups for viewing clarity.

coefficient of **3⁺@2-II** is closer to the ideal 55%,[11] supporting the better binding of **3⁺** in the cavity of **2**.

Lastly, naphthocages **1** and **2** show different binding preferences to guests **3⁺** and **4⁺** (Table 1). We are wondering whether these compounds can self-sort[12] when mixing them in an equimolar ratio. As shown in Fig. 5a-5c, the ¹H NMR spectrum of the mixture is exactly the superposition of the two ¹H NMR spectra of **4⁺@1** and **3⁺@2**. This suggests that self-sorting indeed occurs in this mixture. However, due to the coexistence of two conformations for both naphthocages, this evidence is not very clear. More clear-cut evidence is from mass spectrometry. Since naphthocages **1** and **2** have different side chains, they have different molecular weight and can thus be differentiated in mass spectra. Only two peaks at 1382.88 and 1523.04 *m/z* (which are assigned to [**3@2**]⁺ and [**4@1**]⁺, respectively) are detected (Fig. 5d). This unambiguously indicates that high-fidelity social self-sorting occurs in the equimolar mixture of these four compounds. This result is a bit surprising. Naphthocages **1** and **2** are very flexible and structurally similar, and the two guests (**3⁺** and **4⁺**) are also
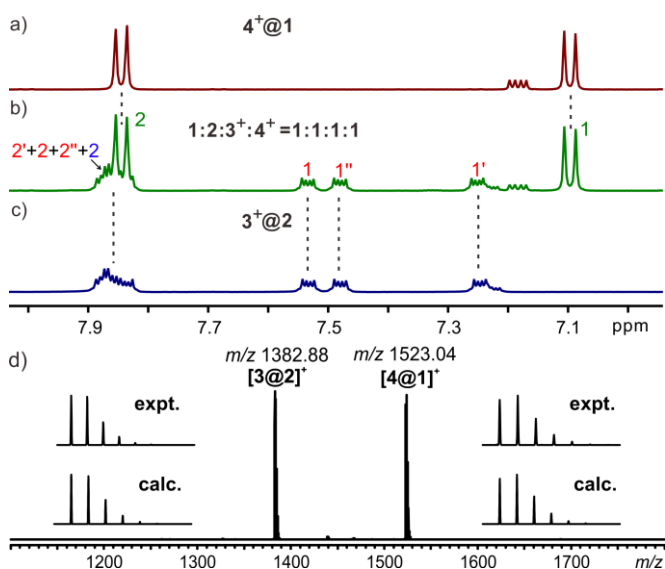
Fig. 5. Partial ¹H NMR spectra (500 MHz, CD₂Cl₂:CD₃CN = 1 : 1, 2.0 mM, 298 K) of (a) **4⁺@1**, (b) the equimolar mixture of **3⁺**, **4⁺**, **1** and **2**, and (c) **3⁺@2**; d) ESI mass spectrum of the equimolar mixture of **1**, **2**, **3**-PF₆ and **4**-PF₆ in the 1:1 mixture of CH₂Cl₂ and CH₃CN.

structurally similar. Self-sorting is usually difficult for such flexible and similar hosts with very similar guests.

In summary, we report the synthesis and host-guest chemistry of a 2,3-dialkoxynaphthalene-based naphthocage. Although structurally similar, this naphthocage shows a rather different guest-binding preference and conformational preference from those of the 2,6-dialkoxynaphthalene-based naphthocage. A high-fidelity self-sorting system is even constructed with these two naphthocages and two structurally-similar guests. However, both naphthocages show rather strong binding affinities to singly-charged organic cations. This research further demonstrates that high binding affinities can be achieved even with flexible receptors when the structure is appropriately designed.

Conflicts of interest

There are no conflicts to declare.

Acknowledgment

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