Article

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Naphthocage: A Flexible yet Extremely Strong Binder for Singly Charged Organic Cations

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ABSTRACT: We report a quite flexible naphthol-based cage (so-called "naphthocage") which adopts a self-inclusion conformation in its free state and is able to bind singly charged organic cations extremely strongly ($K_a > 10^7$ M^{-1}). Ion-selective electrodes prepared with this naphtocage show a super-Nernstian response to acetylcholine. In addition, the highly stable complex (10^{10} M^{-1}) between ferrocenium and the naphthocage can be switched electrochemically, which lays a basis for its application in stimuli-responsive materials.

INTRODUCTION

Preorganization[1] is a key principle in supramolecular chemistry that helped explaining many supramolecular phenomena and still guides the design of effective and selective molecular receptors. Highly preorganized molecular receptors are typically structurally rigid, therefore conformationally not responsive to environmental stimuli and often unable to accommodate even minor structural changes induced by a guest.[2] This is expressed in a relatively narrow binding scope and poor recognition ability of many rigid cage molecules in solutions.[3] Sanders[4] pointed out two decades ago that "the fear of entropy has taken supramolecular chemists too far in the direction of rigidity and preorganization, and … the future may lie in more flexible systems that rely on noncovalent interactions to impose order on three-dimensional structure." Flexible hosts are conformationally adaptive and can tolerate structural changes induced by the guests. Therefore, high selectivity may not be expected. However, by harnessing multiple noncovalent interactions cooperatively, high binding affinities would still be achieved despite of a high entropic penalty caused by large amplitude conformational changes upon binding.[5] Compared to many biological, protein-based receptors,[6] however, flexible synthetic hosts have only achieved low to moderate binding affinities.

Recently, we reported a new class of conformationally flexible macrocycles, the oxatub[n]arenes.[7] In particular, oxatub[4]arene shows decent binding affinities to many organic cations (10^2 – 10^5 M^{-1} in CD_2Cl_2 : CD_3CN (1:1)).[7b] Here, we report a new flexible naphthol-based cage (Figure 1a), which we – following the tradition of the naphthotubes[8] – coin "naphthocage". This cage is highly flexible and even adopts a self-inclusion conformation in solution when no cationic guest is present – in marked contrast to many other rigid cage structures.[3a,b] Despite the flexibility of naphthocage, it shows remarkably high binding affinities to many singly charged organic cations ($K_a > 10^7$ M^{-1}) in CD_2Cl_2 : CD_3CN (1:1). This naphthocage shows super-Nernstian electrochemical response to acetylcholine in water when incorporated in ion-selective electrodes. The binding between ferrocenium and the naphthocage can be electrochemically switched as the naphthocage exhibits an extremely high binding selectivity for ferrocenium over ferrocene.

RESULTS AND DISCUSSION

Synthesis and Characterization of NC. *Per*-butyl-substituted naphthocage (**NC**, Figure 1a) was synthesized by reacting (2,6-dibutoxynaphthalene-1,5-diyl)dimethanol with 1,3,5-tris(bromomethyl)-2,4,6-triethylbenzene[9] in the presence of NaH in dry THF under pseudo-high dilution conditions. Pure **NC** was then isolated through column chromatography as a white solid with a yield of 14%.

The structure of **NC** was characterized by NMR spectroscopy, mass spectrometry, and X-ray single crystallography (Figures S1-S13). Single crystals of **NC** were obtained by slow diffusion of diethyl ether into a saturated CH_3CN/CH_2Cl_2 (1:1) solution of **NC**. As shown in Figure 1b, a self-inclusion conformation is present in the crystal. This is in good agreement with (variable temperature) ^{1}H NMR data (Figures S12 and S13). The three signals for the $CH_2CH_2CH_3$ terminus of the butyl side chain included between the two outer naphthalenes appears in the spectra below 0 ppm as these protons experience the anisotropy of the surrounding aromatic rings. In the crystal, this conformation has C_1 symmetry. In solution, however, **NC** is highly flexible and relatively slow conformational changes lead to broad signals in the ^{1}H NMR spectra of unbound **NC** in different solvents (Figure S12). Upon cooling to 218 K, the averaged signals split into the number of signals expected for a non-interconverting self-inclusion complex (Figure S13).

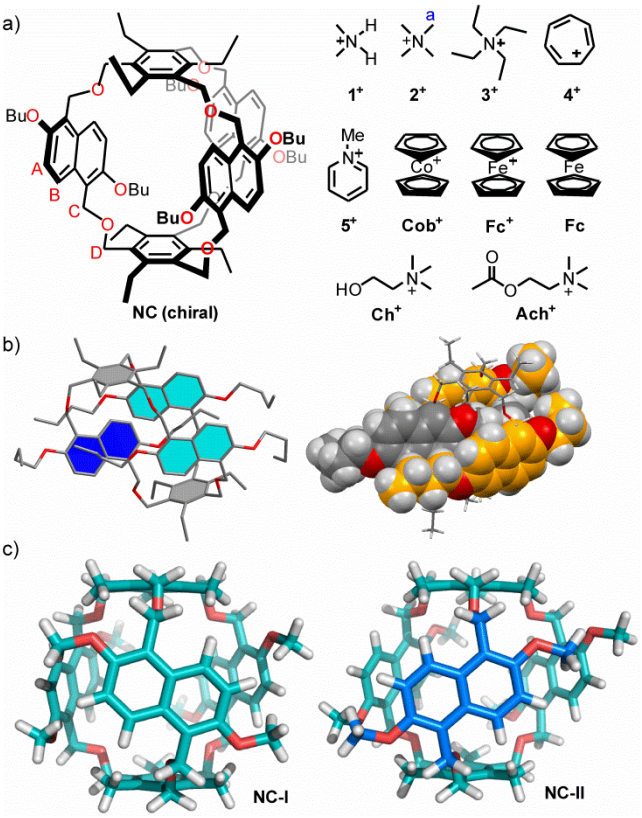

Figure 1. (a) Chemical structures of *per*-butyl naphthocage (**NC**) and the organic cations used as guests (used as PF_6^- salts). **NC** is chiral (only one enantiomer is shown). (b) X-ray single crystal structure of **NC** showing its self-inclusion conformation. CCDC number of **NC**: 1883700-1883701. (c) Conformers of **NC-I** and **NC-II** optimized at the TPSS-D_3(BJ) level of DFT are the structures of the **Cob**$^+$@**NC** complex in which **Cob**$^+$ has been omitted for viewing clarity (ethyl and butyl groups of **NC** are reduced to methyl groups for viewing clarity).

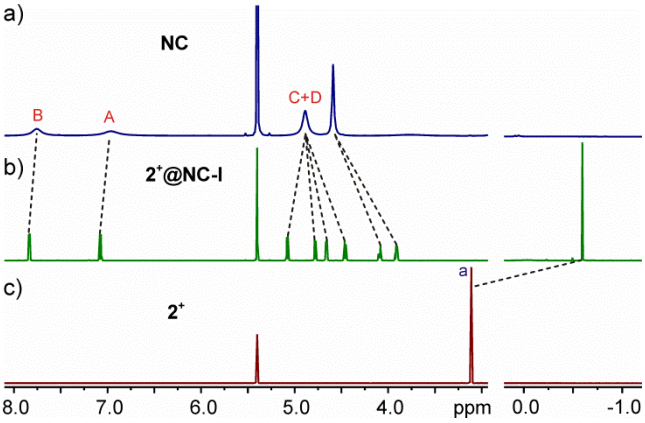

Figure 2. Partial ^{1}H NMR spectra (700 MHz, 2.0 mM, CD_2Cl_2 : CD_3CN = 1:1, 298 K) of (a) **NC**, (b) **2**$^+$@**NC-I**, and (c) **2**$^+$.

Guest-Binding Properties. Guests **1**$^+$ – **5**$^+$, **Cob**$^+$, **Ch**$^+$ and **Ach**$^+$ (Figure 1a) are encapsulated by **NC** in the mixture of CD_2Cl_2 and CD_3CN (1:1) with surprisingly high binding constants. Significant shifts of the signals for both host and guest in 1:1 binding are observed in their ^{1}H NMR spectra (Figures 2 and S14–S21). In particular, all guest signals undergo drastic upfield shifts of about $\Delta\delta$ = 3.0 – 3.7 ppm due to the anisotropy of the surrounding aromatic rings thus supporting the cations to be encapsulated in the cavity of the cage. The 1:1 stoichiometry is further confirmed by predominant peaks for 1:1 host-guest complexes in the corresponding ESI mass spectra (Figures S25–S32).

Additional evidence confirms these guests to be encapsulated inside the cavity of **NC**, and not to be merely attached to the exterior of the cage. Methylene protons *C* and *D* on the CH_2-O-CH_2 linkers (Figure 1a) are diastereotopic protons. But they constantly exchange positions through the conformational interconversion of free **NC**. When a guest is encapsulated inside the cavity of **NC**, this conformational interconversion is slowed down and its rate-determining step is guest exchange – a behavior similarly observed for oxatub[4]arenes.[7] This makes protons *C* and *D* split to four doublets (this analysis is only for conformer **NC-I**; 12 doublets would be expected for **NC-II**; see below for conformational analysis). This is observed for all the guests discussed above (Figures 2 and S14–S21). However, when a guest only binds to the exterior of **NC**, it would not cause the similar splitting of protons *C* and *D*. By using this characteristic feature, we can determine whether a guest is encapsulated inside the cavity of **NC** or not. Tetramethylammonium **2**$^+$ and tetraethylammonium **3**$^+$ are guests for the cavity of **NC**, but tetrapropylammonium and tetrabutylammonium are not (Figure S22). This indicates the size limit in the cavity of **NC**, which would not be expected for exterior binding. Furthermore, NOE signals between the guests and the host in 2D NMR spectra (Figures S42-S57) confirms the encapsulation of these guests inside the cavity. These pieces of evidence taken together clearly speak in favor of guest encapsulation.

Table 1. Association constants and thermodynamic parameters of NC binding to different organic cations (in form of the hexafluorophosphates) at 298 K as determined by ITC titrations.

	K_a (M^{-1})	ΔG^o (kJ/mol)	ΔH^o (kJ/mol)	$-T\Delta S^o$ (kJ/mol)
1$^{+\,a}$	(4.1 ± 0.4) ×10^5	-32.0 ± 0.3	-37.1 ± 1.4	5.1 ± 1.7
2$^{+\,a}$	(1.6 ± 0.3) ×10^7	-41.2 ± 0.3	-23.8 ± 0.5	-17.4 ± 0.8
3$^{+\,a}$	(3.7 ± 0.4) ×10^7	-43.2 ± 0.3	-52.8 ± 1.2	9.6 ± 1.5
4$^{+\,a}$	(8.9 ± 0.8) ×10^6	-39.7 ± 0.2	-34.6 ± 0.9	-5.1 ± 1.1
5$^{+\,b}$	(7.6 ± 2.4) ×10^8	-50.7 ± 0.7	-30.4^c ± 0.2	-20.3 ± 0.9
Ch$^{+\,a}$	(2.8 ± 0.2) ×10^7	-42.5 ± 0.2	-35.9 ± 0.8	-6.6 ±1.0
Ach$^{+\,b}$	(6.7 ± 2.1) ×10^9	-56.1 ± 0.7	-45.5^c ± 0.3	-10.6 ± 1.0
Cob$^{+\,b}$	(6.1 ± 1.9) ×10^9	-55.8 ± 0.7	-45.7^c ± 0.3	-10.1 ± 1.0

^{a} Determined by direct ITC titrations. ^{b} Determined by ITC competition experiments with **1**$^+$ as a reference. ^{c} ΔH^o is taken from direct ITC titrations.

Host-guest binding is remarkably strong and the binding constants exceed the limits of common spectroscopic titration experiments. Therefore, the binding constants in Table 1 were determined with isothermal titration calorimetry (ITC; Figures S34–S41). Except for those of **1**$^+$ and **4**$^+$, all association constants are larger than 10^7 M^{-1} and thus significantly larger than those of the same guest cations to oxatub[4]arene (10^2 – 10^5 M^{-1}).[7b] Even with guest **1**$^+$, which is not a guest for oxatub[4]arene in the same solvent, 10^5 M^{-1} was obtained in this study. Guests **5**$^+$, **Ach**$^+$ and **Cob**$^+$ exhibit binding constants even exceeding the limit of direct ITC titrations.[10] Therefore, we applied competition experiments[11] with **1**$^+$ as the reference

guest to determine the binding constants of these three cations (for details, see Table S2). The quite extreme binding constants are even more remarkable, when one considers (i) that **NC** is a highly flexible cage as expressed in the conformational dynamics discussed above and (ii) that it adopts a self-inclusion conformation in its free state so that guest binding does not benefit entropically from the liberation of solvent molecules from the cavity. In line with this argument, binding is dominated by enthalpy; presumably, cation-π interactions are the most important non-covalent forces involved.

Conformational Analysis. Two different orientations of the naphthalene moieties are possible, when a guest cation occupies the cavity: in conformer **NC-I** (Figure 1c) and its enantiomer, all three naphthalenes have the same helical sense, while in conformer **NC-II** and its enantiomer, one naphthalene has flipped into the opposite sense. They differ in symmetry[12] (**NC-I**: D_3 symmetry; **NC-II**: C_2 symmetry) and thus are expected to show different aromatic signals patterns in the ^{1}H NMR spectra.[7a] As shown in Figure 2, the broadened signals of free **NC** sharpen drastically when adding one equivalent of $\mathbf{2}^+$ into the solution of **NC**. Titration experiments (Figure S14) confirm this to be caused by slow guest exchange. Only two doublets for the aromatic peak signals are observed. Protons *C* and *D* are diastereotopic and split into four doublets. This is only consistent with the symmetry of conformer **NC-I** (Figures 1c).

Similar peak patterns are observed for the **NC** complexes of guests $\mathbf{1}^+$, $\mathbf{3}^+$ – $\mathbf{5}^+$, and $\mathbf{Ch}^+$, suggesting that **NC-I** is again the predominant conformer for these guests (Figures S42–S53, S56 and S57). As the symmetries of these guests differ from the D_3 symmetry of **NC-I**, a larger number of ^{1}H NMR signals would actually be expected. As this is not observed and as the guest exchange is slow on the NMR timescale, the guests must be small enough to tumble and rotate inside the **NC** cavity.[13]

For guests $\mathbf{1}^+$, $\mathbf{4}^+$, and $\mathbf{5}^+$, an additional set of six small doublets is observed in the aromatic region consistent with the C_2 symmetry of host conformer **NC-II**. The **NC-II** complexes represent a fraction of 18–22% of all **NC** complexes, while the **NC-I** complexes are still dominant. In contrast, **NC-II** is the predominant conformation for complexes of **NC** with $\mathbf{Ach}^+$ (Figures S54 and S55). Clearly, **NC** is conformationally flexible and can adapt to the size and shape requirements of its guests to maximize the non-covalent interactions.[7]

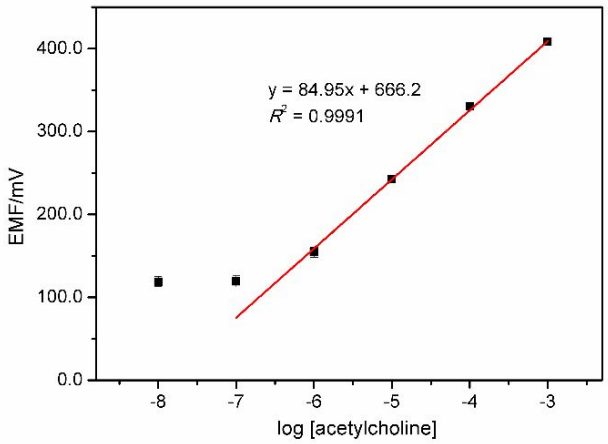

Figure 3. Super-Nernstian response curve of ISEs containing **NC** as the receptor for acetylcholine in water.

Ion-Selective Electrodes for Acetylcholine Chloride. Based on the strong binding of **NC** to $\mathbf{Ach}^+$, ion-selective electrodes (ISEs) for acetylcholine chloride in water were developed. ISEs normally require highly lipophilic receptors as the ionophore. This criterion is fully satisfied here, as **NC** exhibits very poor water solubility. The electrode membrane was prepared with plasticized poly(vinyl chloride) (PVC-DOS), cation-exchanger and **NC** according to established procedures (see supporting information for details).[14] As shown in Figure 3, a super-Nernstian response was observed with a slope of ca. 85 mV. Compared to conventional ISEs with Nernstian response, super-Nernstian electrodes can improve analytical sensitivity which is critical in real applications.[15] However, super-Nernstian ISEs are very rare and were so far only obtained for ionophores with extremely high binding affinities for metal ions (such as Ca^{2+}).[16] Therefore, this observation is fully in line with the above mentioned high association constant (10^9 M^{-1}) between $\mathbf{Ach}^+$ and **NC**. While further optimization is certainly possible, the lower detection limit for acetylcholine with the **NC**-based ISEs is currently in the micromolar concentration range. This is among the best detection limits known so far for ISEs developed for different analytes.[17]

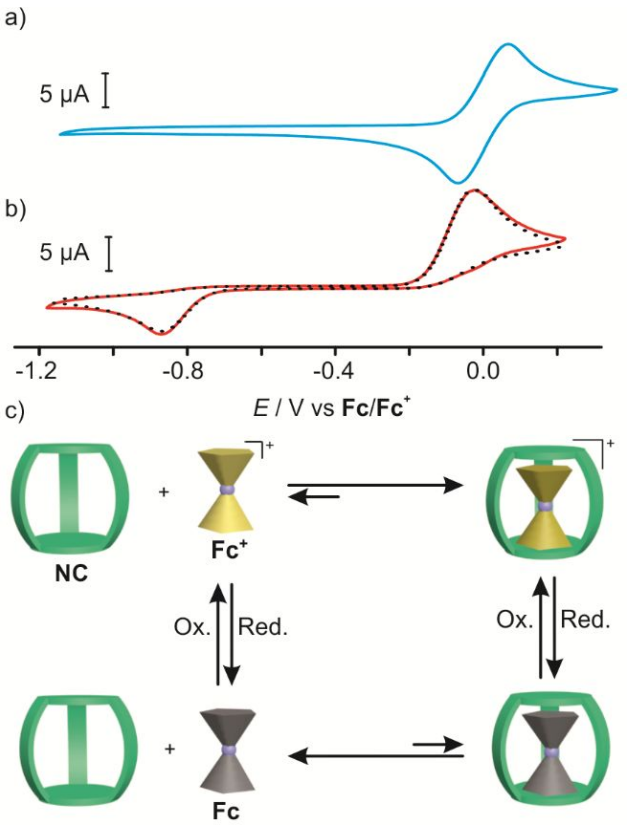

Figure 4. (a) Cyclic voltammogram of **Fc** (CH_2Cl_2, 1.0 mM, 298 K, 100 mV·s^{-1}) with *n*-Bu_4NPF_6 (0.1 M) as the electrolyte; (b) Cyclic voltammogram (solid red line) of **Fc** after addition of 1 equiv. **NC** and simulated cyclic voltammogram (dotted black line) by using thermodynamic and kinetic parameters in Table S3; (c) Cartoon representation of the redox-responsiveness of **Fc** and $\mathbf{Fc}^+$**@NC**.

Redox-Responsive Complex. Redox-switchable organic cations are expected to provide access to redox-responsive supramolecular complexes with **NC**. For example, **NC** shows no obvious binding to neutral ferrocene (**Fc**), but ferrocenium

(**Fc**$^+$) is a strong binder to **NC** (Figures S23 and S24). The association constant between **NC** and **Fc**$^+$ cannot be directly measured by ITC titration because of the intrinsic instability of **Fc**$^+$ in air.[18] However, the binding constant of the structurally very similar and more stable cobaltocenium analogue **Cob**$^+$ could be determined to amount to 10^9 M^{-1} (Table 1). The conversion between **Fc** and **Fc**$^+$ can be easily manipulated through redox chemistry.[18] Therefore, the binding events between **Fc**$^+$ and **NC** can be studied using cyclic voltammetry (CV). Addition of one equivalent of **NC** significantly alters the CV peaks of **Fc** (Figures 4a,b). The anodic peak potential is cathodically shifted by ca. 80 mV and the cathodic peak potential undergoes an enormous cathodic shift of 810 mV. The cathodic current associated with the reduction process of **Fc**$^+$ is slightly decreased owing to complexation with **NC**. The CV experiments are thus in excellent agreement with **Fc**$^+$ being highly stabilized in the presence of **NC**, whereas **Fc** displays no obvious affinity to the cage. Furthermore, the potential difference reveals an extremely large binding *selectivity* (ca. 10^{15} M^{-1}) of **Fc**$^+$ over **Fc** (Table S3). The CV experiments were repeated for a wide range of different scan rates (Figures S58–S60) and no significant change of the voltammograms was observed. This suggests that the chemical reversibility of the redox processes is stable.

To understand the binding behavior between **Fc**$^+$ and **NC** complex, CV titration experiments were performed (Figure S61). Due to the strong binding, both voltammetric traces of free and complexed **Fc**$^+$ are observed, when less than one equivalent **NC** is added. Addition of more than one equivalent of **NC** has no further effect on the cyclic voltammograms.

Digital simulations were employed to evaluate host-guest binding between **Fc**/**Fc**$^+$ and **NC**. In accordance with the square scheme depicted in Figure 4c, we simulated the cyclic voltammogram of complex **Fc**$^+$**@NC** at different scan rates and concentrations of **NC**. The computational model provides a set of self-consistent values which are a reasonable estimation of thermodynamic and kinetic parameters (Tables S3 and S4). As expected, **Fc**$^+$ is strongly complexed to **NC** with an association constant of $K = 1.4 \times 10^{10}$ M^{-1} (in dichloromethane) whereas **Fc** shows no obvious binding affinity with **NC**. The fitted rate constant of dissociation k_b = 5.6×10^{-4} s^{-1} is quite low in good agreement with a slow guest exchange as observed for the other guests as well in NMR experiments.

DFT calculations at the COSMO/B3LYP-D3(BJ) level were employed to evaluate binding energies and identify electronic interactions within **Cob**$^+$**@NC** (Figure 5). A free association enthalpy of -63.8 kJ/mol (Table S5) was computed which is in good agreement with the ITC data, when one takes into account that dichloromethane was assumed as the solvent in the calculations, while a more polar solvent mixture was used in the ITC experiments (due to its low polarity dichloromethane can be described more accurately in the calculations than, e.g., acetonitrile, see SI for detailed explanation). Analysis of the valence orbital structure and surface charge properties of **Cob**$^+$**@NC** illustrates the non-covalent interactions, mainly of electrostatic nature, responsible for the large gain in electronic energy (Figures S64 and S65).

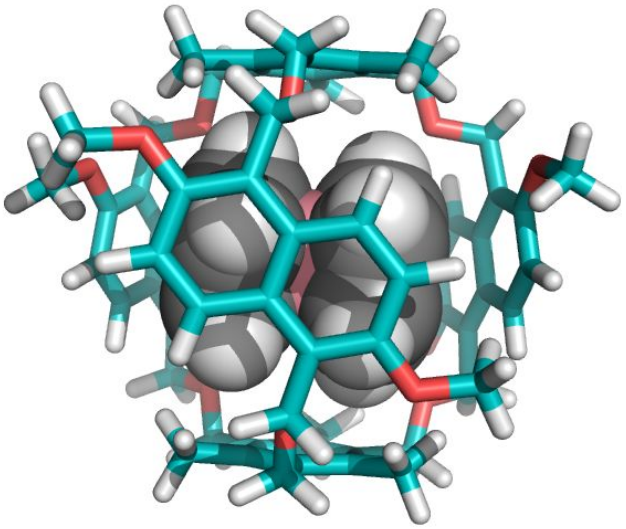

Figure 5. Conformer of complex **Cob**$^+$**@NC-I** optimized at the TPSS-D3(BJ) level of DFT. Butyl and ethyl groups of **NC** are shortened to methyl groups for viewing clarity.

Redox-switchable supramolecular complexes have been widely used to prepare stimuli-responsive materials.[19] Complex **Fc**$^+$**@NC** can also be switched reversibly by redox chemistry. I_2 and $NaBH_4$/hydrazine are used as oxidant and reductant, respectively. KPF_6 was also added to provide counterions for oxidized **Fc**$^+$. At the initial state, K^+ is bound in the cavity of **NC** (Figure S4) and K^+**@NC** predominates in the presence of neutral **Fc**. When adding one equivalent I_2, **Fc** is fully oxidized to **Fc**$^+$, which replaces the potassium cation in the cavity of **NC** giving rise to **Fc**$^+$**@NC**. Addition of $NaBH_4$ to the solution of **Fc**$^+$**@NC** reduces **Fc**$^+$ back to **Fc**, which leaves the cavity of **NC**. Now, one of the alkali metal ions binds to **NC** again. These processes can be monitored by ^{1}H NMR (Figures S66 and S67), UV-Vis spectroscopy (Figures S68 and S69) and ESI mass spectrometry (Figure S70). The redox switching cycle can be repeated by adding I_2 and hydrazine alternately (Figure S71). The ability to induce guest exchanges by electrochemical stimuli lays the basis for the application of **NC** in stimuli-responsive materials.[19]

CONCLUSION

In summary, we have reported the synthesis and recognition behavior of "naphthocage" **NC**, a very flexible naphthol-based cage receptor. In the free state, it adopts a self-inclusion conformation. Organic cations bind with surprisingly high affinities (>10^7 M^{-1}), even though quite substantial conformational changes are required to open the binding cavity for the guest. The cage can be used to prepare an ion-selective electrode with a super-Nernstian response to acetylcholine chloride in water. In addition, redox-switchable complexes were obtained from the naphthocage and ferrocenium, which paves the way for their application in stimuli-responsive materials. The present research also showcases flexibility is not necessarily the enemy of high-affinity binding. Harnessing multiple noncovalent interactions cooperatively would compensate the entropic penalty caused by large amplitude conformational changes upon binding.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: ……

Experimental and theoretical details, ^{1}H NMR spectra of the complexes, ITC titration data, control experiments, and single-crystal X-ray data (pdf). Crystallographic data for **NC** (cif). Authors.

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Notes

The authors declare no competing financial interests.

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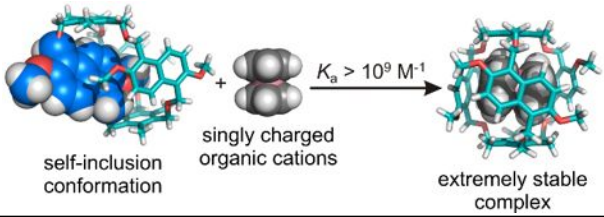
Table of Contents (TOC) Graphic


$K_a > 10^9\ M^{-1}$
self-inclusion conformation
singly charged organic cations
extremely stable complex