Naphthocage:

A Flexible yet Extremely Strong Binder to Organic Cations with Naphthalene Walls

Dissertation to obtain the academic degree

Doctor rerum naturalium (Dr. rer. nat.)

Submitted to the Department of Biology, Chemistry and Pharmacy of

Freie Universität Berlin

By

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Berlin 2020

The work reported in this thesis was performed from September 2016 to February 2020 at the Institut für Chemie und Biochemie of Freie Universität Berlin under the supervision of Prof. Dr. Christoph A. Schalley.

1st reviewer: Prof. Dr. Christoph A. Schalley
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Date of defense: 01.07.2020

Abstract

Macrocyclic receptors are key elements in the foundation and development of supramolecular chemistry, because they not only provide binding cavities that are capable of trapping guest molecules and can be chemically modified to bear functional groups for their novel binding properties, but also reveal their nature of intermolecular interactions to know how to instruct supramolecular self-assembly and the applications of functional materials. Since 1967, either the old or the emergence of new ones, a wide range of applications (such as supramolecular assemblies, supramolecular polymers, supramolecular gelators, supramolecular catalysis, molecular machines and devices, and other kinds of novel materials) were intensively explored. Therefore, the design and synthesis of novel macrocyclic molecules and the investigation of their molecular recognition properties play a vital role in supramolecular chemistry.

There are many supramolecular macrocycles in the literature, but no particular one with an adaptable cavity and a broader guest binding scope. In 2015, we reported a flexible naphthalene-based macrocyclic receptor, namely oxatub[4]arene. Oxatub[4]arene is a highly flexible macrocycle in solution. It has four representative conformations resulting from the naphthalene rings flipping, each conformer with a deep and well-defined cavity. Thus, oxatubarene is expected to result in different guest binding preference due to the size and shape of the cavities. Regarding their interconvertible and deep cavities of four different conformers, oxatub[4]arene can be viewed as a molecular "transformer" being capable of encapsulating a wide range of organic cationic guests.

On the basis of the oxatub[4]arene, we designed a naphthalene-based organic covalent cage, so-called "naphthocage". Naphthocage is conformationally flexible and adopts a self-inclusion conformation in the absence of cationic guests, in which one of the naphthalene rings is intercalated between the other two. Owing to the rapid flipping of the naphthalene rings, the self-inclusion conformation interconverts with two other open host conformations **I** and **II**, which differ by the orientation of one of the three naphthalene walls. Despite of the high flexibility of naphthocage, the cage shows extremely strong binding affinities up to 10^9 M^{-1} to singly charged organic cation guests, such as tetramethylammonium, methylpyridinium, ferrocenium, cobaltocenium, choline or acetylcholine. An astonishingly high binding *selectivity* (ca. 10^{15}) was observed for ferrocenium over ferrocene. The naphthocage shows a super-Nernstian electrochemical response to acetylcholine in water when incorporated in ion-selective electrodes. Naphthocage also reveals

very strong binding (up to 10^{10} M^{-1}) to aromatic (di)cationic guest molecules, i.e., the tetrathiafulvalene mono- and dication and methyl viologen. The aromatic guest molecules can be switched into and out of the cage by redox processes with high binding *selectivity* (10^{12} to 10^{15}). The oxidation of the flexible cage itself in the absence of a guest leads to a stable radical cation with the oxidized naphthalene ring intercalated between and stabilized by the other two. The oxidation of the cage can be applied for controlled guest release from the cage cavity, which paves the way for novel applications in redox-controlled guest molecule release or in stimuli-responsive materials.

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1. Introduction

Supramolecular chemistry has greatly developed in the past two decades. Synthetic macrocycles have been recognized as powerful tools for supramolecular chemistry. Here, I briefly introduce the classic and novel macrocycles, which exhibit their features of binding cavities from the host structural models. In view of these known macrocycles with a wide range of applications in supramolecular chemistry fields, we envisioned an extension of the known macrocycles into tube-like or cage-like with an electron-rich scaffold, which would possess a deep and well-defined cavity and bind ammonium cationic guests in their cavities.

1.1 Supramolecular Chemistry

Supramolecular chemistry is usually taken as the intermolecular interactions of a number of molecules assembled together. The classic description of supramolecular chemistry in the textbook is "chemistry beyond the molecule," "the chemistry of the noncovalent bond," and even "Lego chemistry."[1] In the 1960s, the findings and investigations of crown ethers,[2] spherands[3] and cryptands[4] (Figure 1) laid a solid foundation for supramolecular chemistry, which helped establish the basic concepts and principles of supramolecular chemistry. Therefore, Charles J. Pedersen, Donald J. Cram and Jean-Marie Lehn were awarded the first Nobel Prize for supramolecular chemistry in 1987 for their development and use of their macrocycles with high selectivity. Again, Jean-Pierre Sauvage, Fraser Stoddart and Ben Feringa were awarded Nobel Prize in 2016 for their excellent contributions in the design and synthesis of molecular machines – thus putting function into the focus. Supramolecular chemistry is a new interdiscipline of organic chemistry, inorganic chemistry, biochemistry, medicinal chemistry, physical chemistry, electrochemistry, materials chemistry and analytical chemistry, and thus it can explore something unknown in nature with intermolecular and intramolecular interactions between receptors and substrates, which are inspiring and driving supramolecular chemists towards tomorrow.

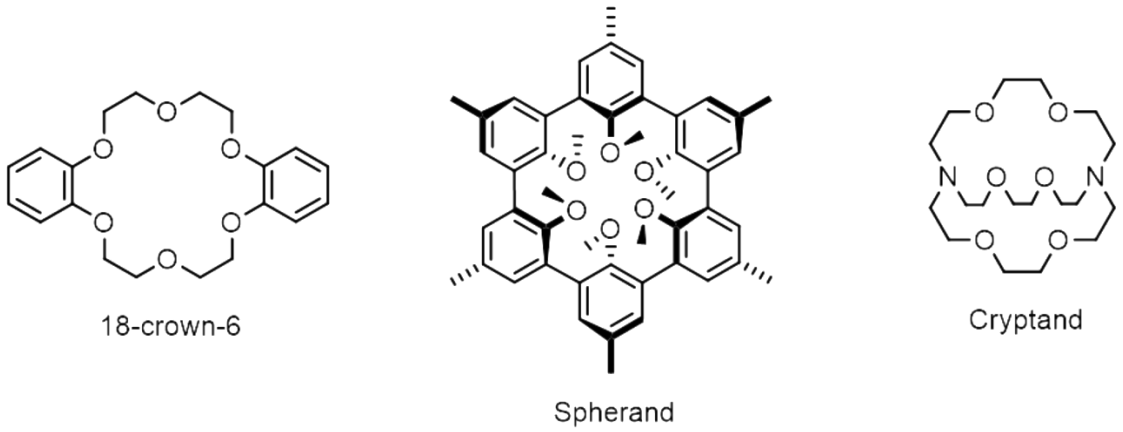

Figure 1. Chemical structures of the macrocycles of crown ether, spherand and cryptand.

1.2 Classic Macrocycles

In the earlier times, the intensive studies on crown ethers, spherands and cryptands paved the way for supramolecular chemistry. The first generation of a macrocyclic receptor, crown ether is still a hot topic for supramolecular chemists.[5] Cyclodextrins (α, β, γ, Figure 2)[6] are natural cyclic oligosaccharides with a hydrophobic basket-shaped cavity that can capture less polar or nonpolar molecules, such as *p*-xylene or benzoic acid in their hydrophobic cavities in water. Even though it was discovered in 1891, their molecular recognition abilities and the encapsulation of guest molecules were explored and found broad applications only after the pioneering study work of crown ethers, spherands and cryptands. The studies of cyclodextrins helped supramolecular chemists understand the hydrophobic effect in natural systems and push molecular recognition to a high level of chemical self-assembly. As the third generation of macrocyclic molecules, calix[n]arenes (n = 4, 5, 6 and 8)[7] were first found by Baeyer in 1872, but they were intensively investigated by Gutsche and coworkers only starting from the late of 1970s.[8] Calix[4]arene (Figure 2) is composed of substituted phenols bridged by methylene linkers at the positions of *2* and *6*. Calixarenes are considered as macrocycles with (almost) unlimited possibilities,[9] owing to their conformational features and easily functionalized scaffolds. Since the wide upper hydrophobic cavity and lower hydrophilic properties of calixarenes, which are capable of binding neutral guest molecules and ions through noncovalent interactions including the hydrophobic effect, cation-π, π-π stacking and hydrogen-bonding interactions.

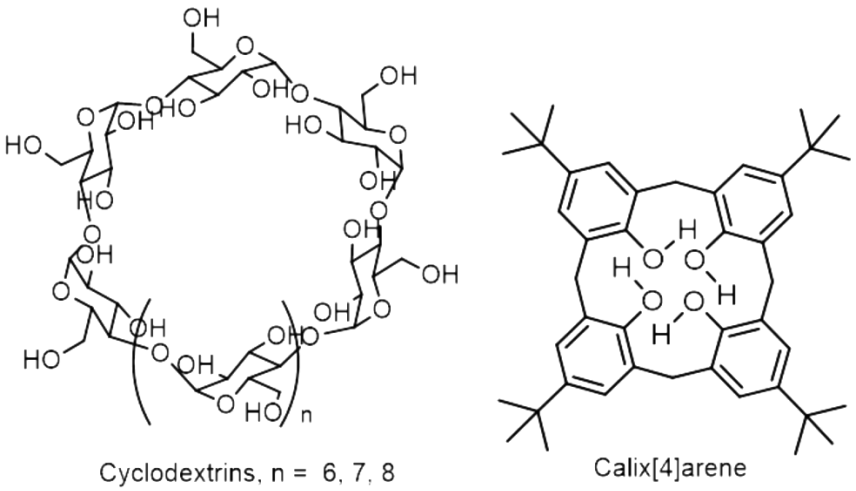

Figure 2. Chemical structures of classic macrocycles.

Considering the development of macrocyclic receptors from the first generation to the third generation, a large number of calix-like macrocyclic molecules were designed and synthesized, for example, calixarenes,[10] calixpyrroles,[11] calixpyridines,[12] oxacalixarenes,[13] thiacalixarenes,[14] heterocalixaromatics,[15] calixcarbazoles,[16] calixnaphthalenes,[17] resorcinarenes,[18] and cyclotriveratrylenes (CTV).[19] These synthetic macrocycles provide good examples to understand the concepts and principles of supramolecular chemistry and enrich the diversity of supramolecular chemistry as an interdisciplinary field, which developed into sophisticated molecular recognition, self-assembly, detection and sensor of cations, anions and neutral molecules, and the construction of advanced functional materials and molecular machines and devices. Thus, macrocycles play an important role in the development of supramolecular chemistry. Among other reasons, the preorganization of these macrocyclic molecules and guest molecules can – in form of the so-called macrocyclic or biomacrocyclic effect – overcome unfavorable entropy losses in molecular recognition and self-assembly processes.

1.3 Novel Macrocycles

The emergence of novel macrocycles (Figure 3) broadens the available features in molecular recognition and allows the supramolecular chemists to fine-tune and optimize their functional applications. These known macrocycles not only contribute to a profound conceptional understanding of molecular recognition,[20] but also further find a large number of extensive applications in many fields of molecular recognition, self-assembly,[21] molecular machines and devices,[22] gas absorption,[23] supramolecular polymers,[24] supramolecular sensors,[25] supramolecular catalysis,[26] drug discovery,[27] drug delivery,[28] ion channels and transmembrane transport of ions and molecules[29] supramolecular amphiphiles,[30] and functional materials.[31]

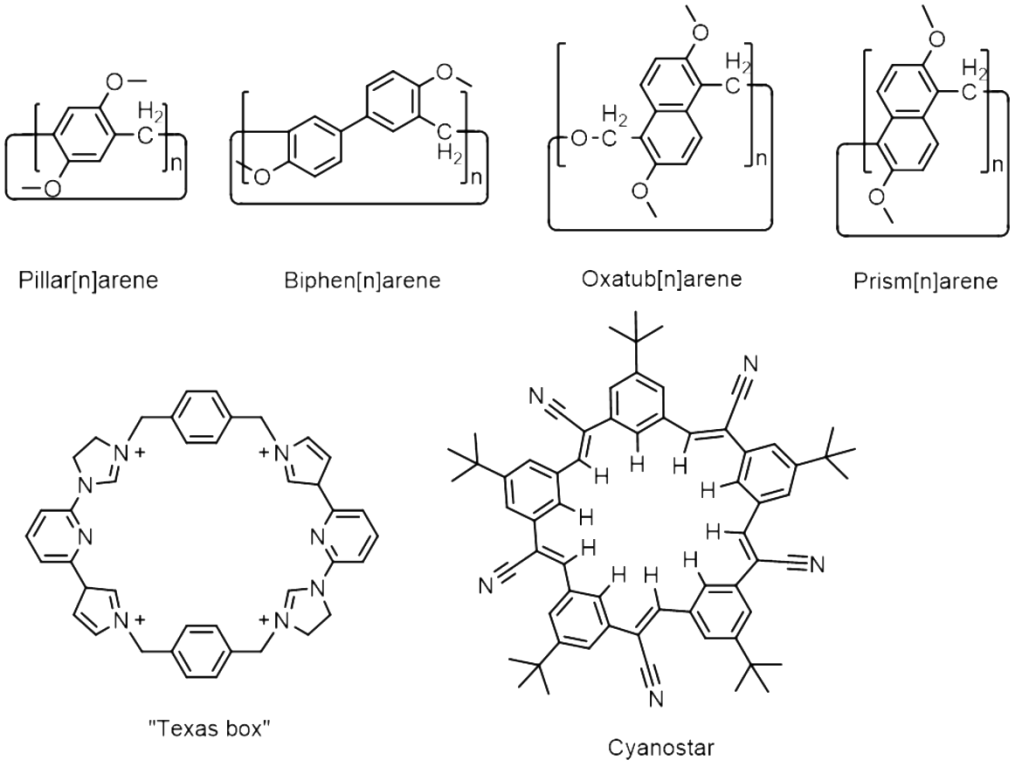

Figure 3. Chemical structures of representative examples of novel macrocycles.

In view of the wide application prospects of macrocyclic host molecules, supramolecular chemists have never stopped to develop and explore novel macrocycles.[32] In the past two decades, a number of novel macrocyclic receptors with given properties have been reported (Figure 3), for examples, pillar[n]arenes,[33] biphen[n]arene,[34] oxatub[n]arenes,[35] prism[n]arenes,[36] "Texas-sized box",[37] and "cyanostar".[38] These novel macrocycles present unique host–guest features with their

different binding affinities towards a well-defined set of guest molecules and enrich the research toolbox of supramolecular chemistry. In a word, the emergence of each novel macrocyclic molecule will bring new host-guest complexation properties and potentially functional applications.

Among these synthetic receptors, pillar[n]arenes are one of the most used players in supramolecular chemistry, which can be applied to many kinds of supramolecular assemblies.[39] Pillar[n]arene is facilely synthesized and modified, and well binding properties with cationic and neutral guests in versatile applications, including ion channel and transmembrane channels,[29] stimuli-responsive materials, [40] gas absorption and porous materials,[23] supramolecular amphiphiles,[30] supramolecular polymers[24] and other functional materials.[41] For example, Hou and coworkers developed a water transportation channel by inserting water-soluble pillar[5]arene dimers into the lipid bilayer, which showed an artificial channel to control the transport of water, amino acids and ions.[42] Single crystal structures of pillar[5]arene often contain solvent molecules in a cell, which can be applied to make porous crystal via an activation process. Yang and coworkers reported the crystal structure of pillar[5]arene with all naked hydroxy groups can selectively adsorb CO_2 over that of N_2 and CH_4, because of the phenolic groups formed inter/intramolecular hydrogen-bond interactions to stabilize the crystal structures.[43] Also, when all the hydroxy groups of pillar[5]arene replaced by ethoxy groups, the crystals did not adsorb CO_2 and N_2 after the activation process, suggesting the activated crystals are non-porous. However, the non-porous crystals can adsorb guest vapors only by exposing the crystals to alkane vapors, which can be used to the crystal transformation induced by guest vapors. The vapor uptake of alkane shape (linear, branched and cyclic) depends on the cavity size of pillar[n]arenes. In contrast to pillar[6]arene, the uptake behavior of pillar[5]arene activated crystal selectively uptake linear alkane.[44]

Another two obviously characteristic macrocycles are "Texas-sized box" and cyanostar. Sessler and coworkers[37] reported anion-induced pseudorotaxane monomers between a flexible tetracationic imidazolium-based macrocycle and mono-terephthalate, and further aggregate to form pseudo-oligorotaxanes at higher concentrations that are regarded as a supramolecular necklace. Flood and coworkers[38] developed a C_5-symmetric cyanostar macrocycle that the cyanostilbene-based CH groups provided hydrogen-bonding with anions inside the cyanostar cavities with high binding affinity (PF_6^-, 10^{12} M^{-1}). In the solid state, cyanostar forms π-stacked dimers composed of chiral *P* and *M* enantiomers. The cavity size of cyanostar can form an unprecedented [3]rotaxane

templated around a dialkylphosphate.

Besides the classic and novel macrocycles above, a large number of other macrocycles have been reported. For examples, cucurbit[n]urils,[45] "blue box",[46] "ExCage",[47] asararenes,[48] molecular triangular prisms,[49] lactam macrocycles,[50] bambus[n]uril,[51] tetrakisimidazolium macrocycles,[52] corona[n]arenes,[53] helical chiral arenes,[54] Janusarene,[55] tiara[5]arenes,[56] geminiarene,[57] Hybrid[3]arene,[58] Belt[n]arene[n]tropilidenes,[59] and others.[60] Among these macrocycles, kinds of the functional applications on their host-guest complexations have been well developed, which directly trace back to the basic structure of each macrocycle with a significantly repetitive scaffold. These repetitive building blocks of each macrocycle are connected by some functional linkers that shapes a well-defined binding cavity to accommodate a guest molecule.

2. Research Objectives

In this dissertation, I attempt to develop an organic cage and to explore their host-guest chemistry on functional properties. The basic idea is to extend the phenol-based macrocycles of calixarene and related types into an electron-rich scaffold of naphthalene-based receptor. As demonstrated earlier,[61] calixnaphthalenes are an ill-defined and shallow cavity. Thus, Adoption of a long linker CH_2OCH_2 to replace a short linker methylene group may avoid the unfavorably steric hindrance between two adjacent naphthalene rings. This measure indeed worked in two cases of oxacalixnaphthalene[62] and oxatubarene.[35]

Based on these investigations, we envisioned a naphthalene-based organic covalent cage (so-called "naphthocage") by employing two building blocks: 1,3,5-tri(bromomethyl)-2,4,6-triethylbenzene and 2,6-dihydroxynaphthalene. They are linked by sufficiently long linkers. The 1,3,5-triethylbenzene unit is a special motif in which the three ethyl groups in the 1,3,5-positions can instruct the substituents in the 2,4,6-positions to point to the same side of the benzene ring, thus favoring the synthesis of the cage by preorganization. The naphthalene rings are flat, electron-rich panels and thus are suitable walls of an electron-rich cavity suited for the formation of host-guest complexes with cationic guests. The length of the CH_2OCH_2 linkers on one hand allows the implementation of the needed curvature and avoids steric congestion between naphthalene rings, but is on the other hand sufficiently short to allow ring closure to occur. This cage is expected to offer a small cavity to accommodate cationic guest molecules inside the cage cavity with size selectivity. Therefore, this cage combines three important characteristics: flexibility, and thus interesting conformational dynamics and adaptability, an electron-rich cavity providing strong binding environments to cationic guests, and selectivity for guest size and charge. These three elements of this cage are quite different from that of structurally rigid covalent cage in the literature.

3. Naphthalene-Based Macrocycles

3.1. Historical Background

The design, synthesis of macrocycles with functional applications has been rapidly developed after the year 2000. For instance, functional calixarenes can be applied to biomedical therapy (drug delivery and release), biomedical sensing, biomedical imaging and other potential biomedical applications.[63] These inspiring studies of macrocycles in biomedical applications greatly encourage supramolecular chemists, which are particularly keen to design novel macrocycles to obtain new molecular recognition and functional applications. So far, the polyfunctionalized phenols have been applied to construct most of the known macrocycles (Figure 4a), such as, calix[4]arenes, cyclotriveratrylenes (CTV), resorcin[4]arenes, and pillar[5]arenes, which are linked by methylene groups. The starting materials of these macrocycles are commercially available. The conversion of the starting materials into the macrocycles undergoes a one-pot reaction catalyzed by acid in the presence of paraformaldehyde.

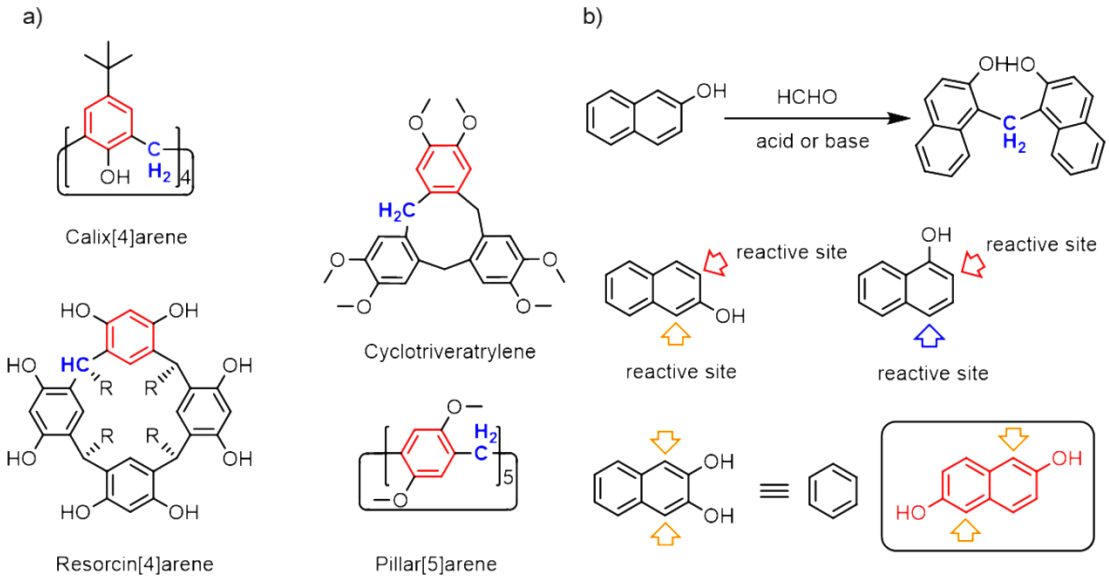

Figure 4. a) Chemical structures of four representative macrocycles, the repetitive unit is the substituted phenol in red color linked by methylene groups in blue color; b) The dimer product of 2-naphthol with paraformaldehyde (or formaldehyde) catalyzed by acid (or base) and the reactivities of naphthols, respectively; 2,6-dihydroxynaphthalene (red color) is a potential building block.

As shown in Figure 5 top, the calculated models of calix[4]arene, cyclotriveratrylene and resorcinarene possess clearly visible bowl-shaped cavities, which are capable of trapping guests in their cavities. The bowl-shaped cavities are quite different from the tube-like cavities of pillar[5]arene, oxatub[4]arene and prism[5]arene (Figure 5, bottom).The pioneering work of studying these phenyl-based macrocycles recently stimulated supramolecular chemists to develop and investigate naphthol as a replacement for the phenol in calix-like or pillar-like macrocycles. The extension of phenol to naphthol enlarges the range of cavities with more electron-rich building blocks and further reflects a wide range of functional applications.

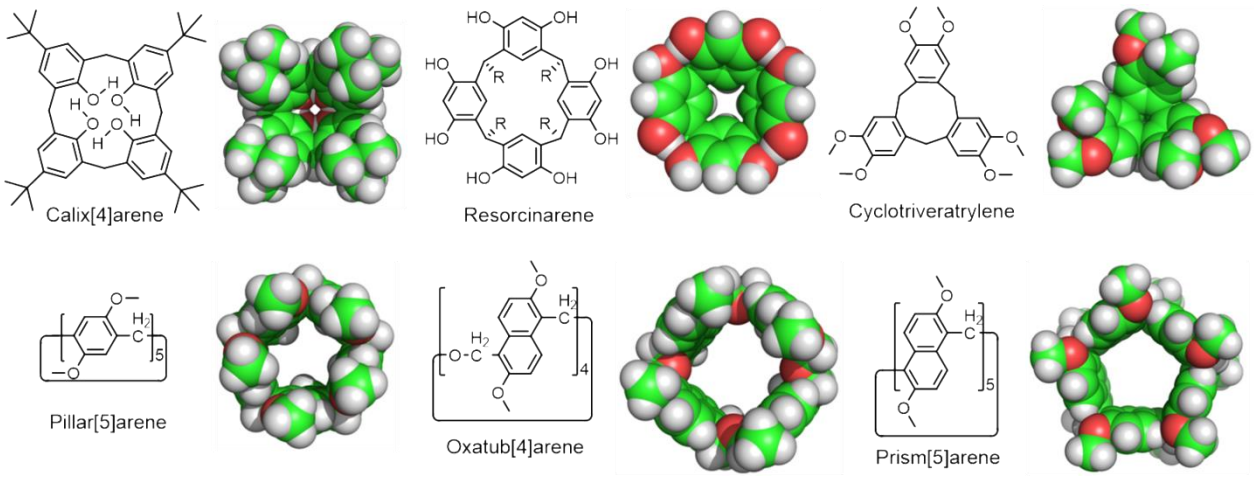

Figure 5. Chemical structures and corresponding energy-minimized models (MMFF94s) of macrocycles. Calix[4]arene, resorcinarene and cyclotriveratrylene present the bowl-shaped cavities. However, pillar[5]arene, oxatub[4]arene and prism[5]arene show the tube-like cavities.

In the 1890s, Hosaeus and Manasse [64] reported the reaction of 2-naphthol with paraformaldehyde (or formaldehyde) under acidic (or basic) conditions to obtain a dimer product (Figure 4b), however, the reaction of 1-naphthol and paraformaldehyde was catalyzed by acid to give cross-linked polymers.[65] In 1993, Georghiou and co-workers[17,66] reported that three of four regioisomers of *exo*-calixnaphthalenes (Figure 6a) were obtained by a one-pot reaction of 1-naphthol and formaldehyde in the presence of base; and the fourth isomer (Figure 6a, right bottom) was obtained by a stepwise procedure. In 1993, Böhmer and coworkers[67] reported an example of *endo*-calixnaphthalene (Figure 6b, right) in a one-pot reaction of 2-naphthol with paraformaldehyde under acid catalysis, the isomer of the *endo*-calixnaphthalene shown in Figure 6b (left) was reported by Georghiou and coworkers in 2002.[68] In comparison with calix[4]arene,

the cavities of *exo*-calixnaphthalenes and *endo*-calixnaphthalenes are ill-defined and shallow because two adjacent naphthalene rings connected by methylene groups result in steric hindrance. As shown in Figure 6a, two counter naphthalene rings of *exo*-calixnaphthalenes incline outward and the other two ones stand vertically, which leave the cavities narrow and further indicate poor host-guest complexation.

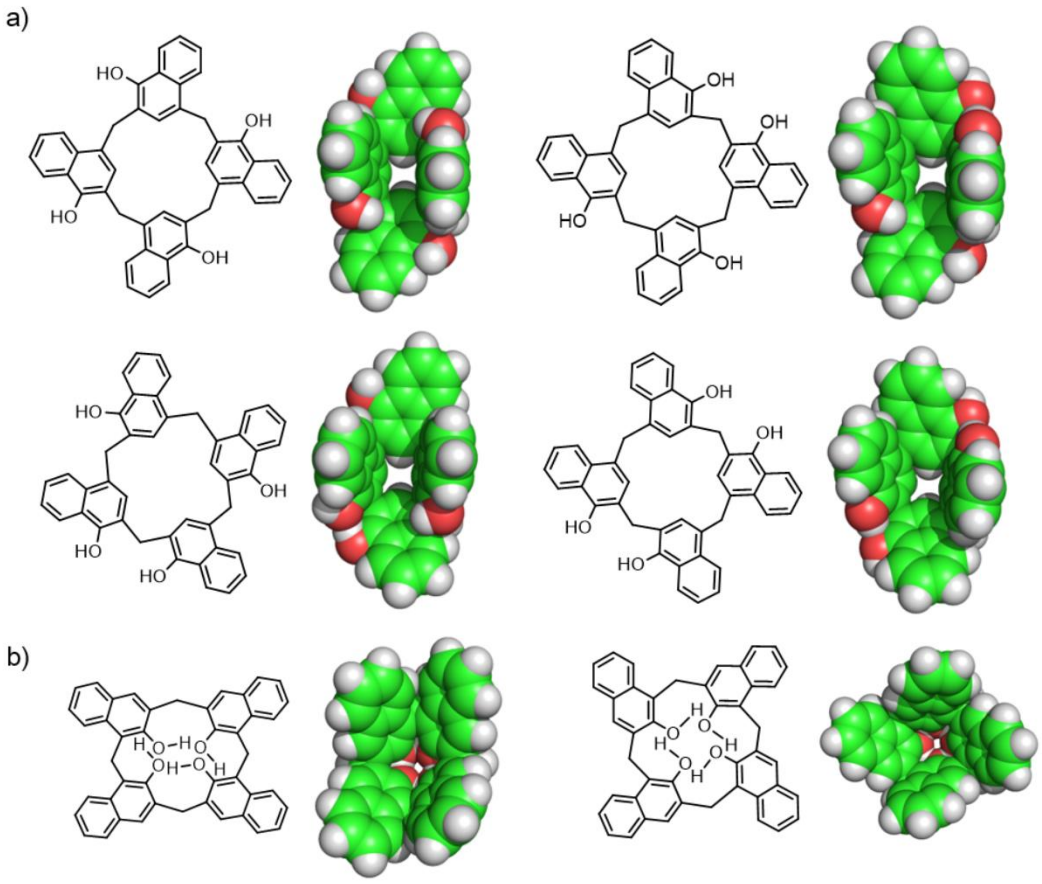

Figure 6. a) Chemical structures of four regioisomers of *exo*-calixnaphthalenes based on 1-naphthol and the corresponding energy-minimized models of regioisomers (MMFF94s); b) Chemical structures of two isomers of *endo*-calixnaphthalenes based on 2-naphthol and the corresponding energy-minimized models (MMFF94s).

The extension of the substituted phenolic scaffolds to naphthols enlarges the macrocyclic cavity leading to a cyclic tetramer to bind fullerene (C_{60}), for example, the *endo*-calixnaphthalene in Figure 7a, which adopts a "pinched cone" conformation.[69] On the contrary, only calix[6]arene

(Figure 7b) and calix[8]arene can satisfy the requirement of binding of fullerene (C_{60}) that adopt a preorganized cone conformation with a suitable inclination of the benzene rings.[70]

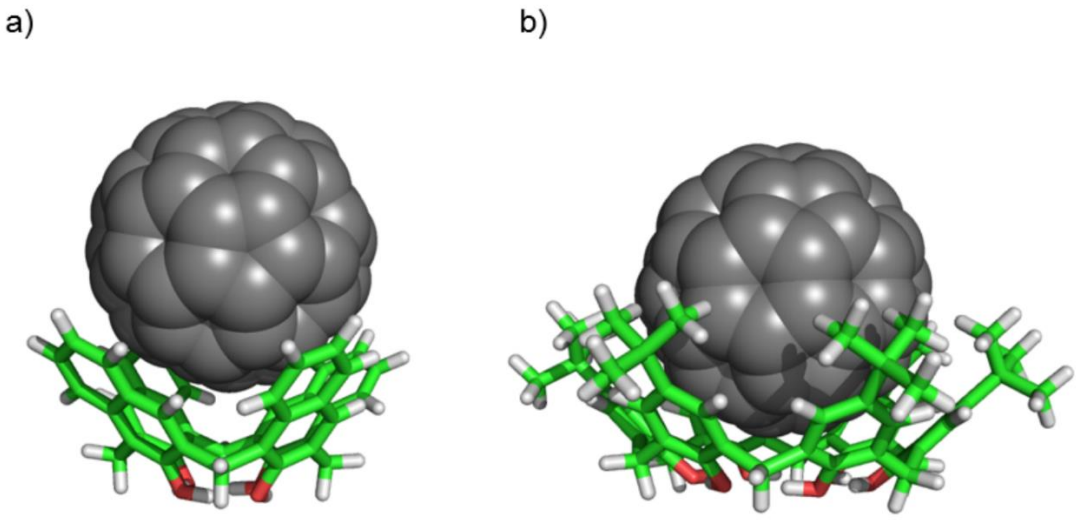

Figure 7. a) Energy-minimized model of C_{60}@*endo*-calixnaphthalene (MMFF94s); b) Energy-minimized model of C_{60}@calix[6]arene (MMFF94s).

Synthetic water-soluble macrocyclic receptors have been of great interest for supramolecular chemists, because molecular recognition processes are then similar to those in biological systems. Such macrocycles thus represent a model for hydrophobic cavities of enzymes.[71] In 1989, Poh and co-workers [72] reported a water-soluble cyclic tetrameric molecule, cyclotetrachromotropylene (CTCT, Figure 8), which is composed of four naphthalene rings linked by methylene groups. It was synthesized by reacting the disodium chromotropic acid salt with excess paraformaldehyde in water for one week. Because of the conformational flexibility of the macrocyclic structures, there are two possible conformers, a boat and a chair (Figure 8). While the chair conformation is expected to be a poor host for guests binding, the boat conformation is expected to be a better host for capturing guests.[73] CTCT can complex diverse kinds of guests in the hydrophobic cavity in water by the hydrophobic effect, hydrogen bonding, cation-π, and π-π interactions, for example, tetraalkylammonium cations, aromatic hydrocarbons (chrysene, pyrene, anthracene, phenanthrene, fluorene, acenaphthene, naphthalene and durene), and phenols.[74] Moreover, CTCT increases the solubility of aromatic hydrocarbons by factors of up to 100 in water and is able to disperse of single-walled carbon nanotubes in water.[75]

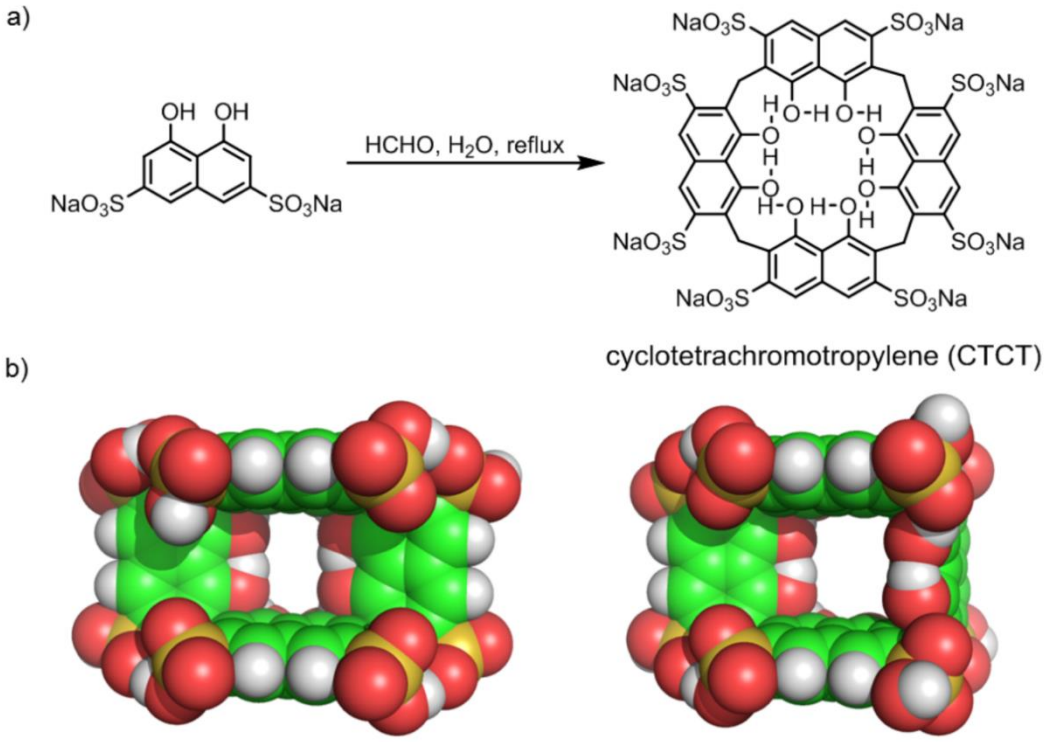

Figure 8. a) Synthesis of the water-soluble cyclic tetramer cyclotetrachromotropylene (CTCT); b) Energy-minimized models (top view, MMFF94s) of the boat (left) and chair (right) conformations of CTCT. The cavities of two conformations are expected to be expanded forms.

Due to the great contributions of calix[n]arenes and pillar[n]arenes, we envisioned a novel naphthalene-based macrocycle linked by methylene groups, named prism[n]arene, which possesses a well-defined and deep cavity that would possible trap ammonium guests in the host cavity because of the electron-rich naphthalene walls enclosing the host cavity (Figure 9). In 2014, the *n*-butyl-substituted of 2,6-dihydroxynaphthalene was used as a starting material and performed this reaction (Figure 9a) using *p*-toluenesulfonic acid as a catalyst in 1,2-dichloroethane (DCE). Consequently, we obtained oligomers including dimer, trimer, tetramer, pentamer and hexamer shown in Figure 9, where the naphthalene rings are only linked at the 1,1'-positions of naphthalene rings.[76] There are no ring-closing products obtained in the mixture. Recently, however, Gaeta and coworkers reported that prism[n]arenes were obtained by a templated approach of a thermodynamically controlled synthesis. Prism[n]arenes are capable of trapping ammonium guests (for example, tetramethylammonium and alkyl disubstituted of 1,4-diazabicyclo[2.2.2]octane (DABCO)) inside the host cavity.[36]

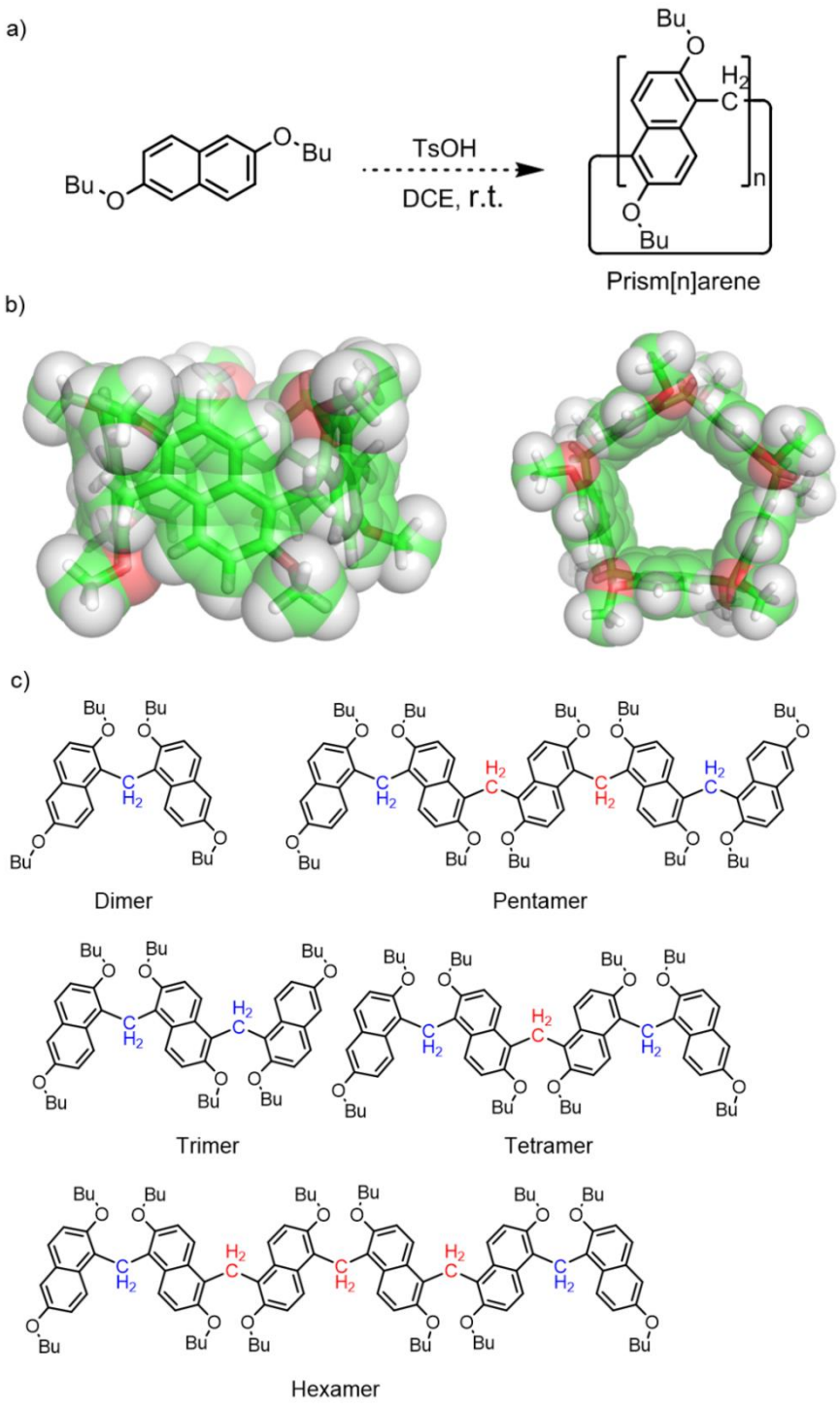

Figure 9. a) Intended procedure of prism[n]arene in a one-pot reaction catalyzed by acid; b) Energy-minimized models of the prism[5]arene@tetramethylammonium complex in which tetramethylammonium has been omitted for viewing clarity (top and side view, MMFF94s). c) Oligomers (dimer, trimer, tetramer, pentamer, hexamer).

Calix[4]arene is a classic macrocycle in supramolecular chemistry. In 1994, Brodesser and Vögtle[77] developed a series of expanded calixarenes that the linker methylene group are replaced by $(CH_2)_n$ (n = 2, 3, 4) or CH_2OCH_2. As shown in Figure 10a, oxacalixarene[78] presents an expanded cavity form of calixarene with different conformational preferences and host-guest complexation properties towards guest molecules. In 2001, Georghiou and coworkers reported the hexahomotrioxacalix[3]naphthalene [79] based on 2-naphthol, which showed host-guest complexation to alkali metal cations and can complex with C_{60} to form a dimeric capsule[80] shown in Figure 10b. In comparison with calixnaphthalenes, these achievements obtained from oxacalixnaphthalene and its derivatives have further helped to expand the cavity of macrocycles and have improved the ability of host-guest complexation with loss of steric hindrance of adjacent naphthalene rings. The long linker CH_2OCH_2 not only increase the host cavity size but also provide additional conformational flexibility to the macrocycles.

Other examples are the zorb[4]arenes (Figure 10c) reported by Georghiou and coworkers in 2005.[81] Zorb[4]arene is highly symmetrical and conformationally flexible in solution. In the solid state, zorb[4]arene (Figure 10c) adopts a flattened partial cone conformation that one naphthalene ring self-included in the cavity and two acetonitrile molecules involved within the cavity surrounding of other three naphthalene rings. Zorb[4]arene binds tetramethylammonium with a relatively weak binding constant (K_a = 1274 M^{-1}) when compared with oxatub[4]arene used the same guest (K_a = 6388 M^{-1}).[82] Last but not the least, it was oxatub[4]arene, which will be discussed in detail in the next chapter on conformational analysis.

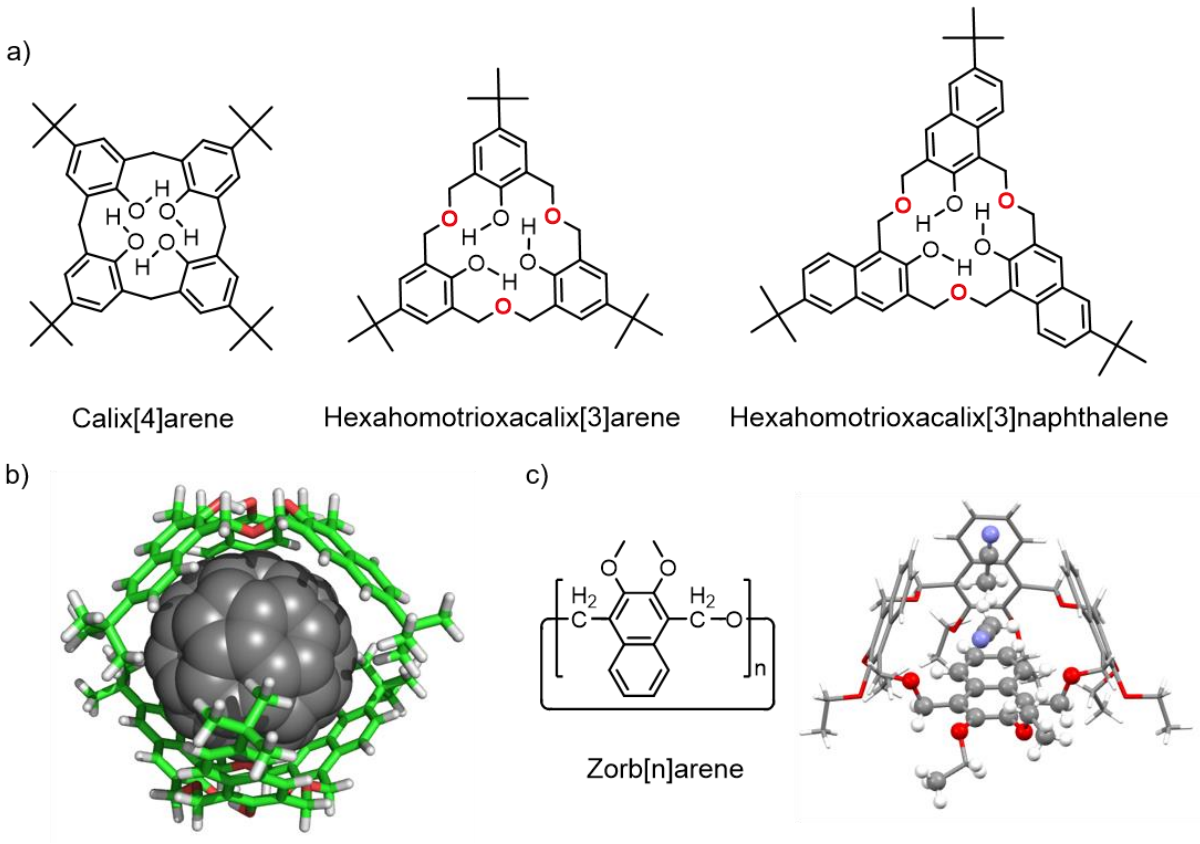

Figure 10. a) Calix[4]arene and expanded calixarene of hexahomotrioxacalix[3]arene, and expanded calixnaphthalene of hexahomotrioxacalix[3]naphthalene (only one isomer is shown here); b) Crystal structures of C_{60}@hexahomotrioxacalix[3]naphthalene, Copyright © 2001, the Royal Society of Chemistry; c) Zorb[n]arene and its crystal structure, Copyright © 2005, American Chemical Society.

3.2. Conformational Analysis

Molecular recognition is the basic topic in supramolecular chemistry, which is similarly related to the phenomenon in biological systems. The two models of lock-and-key[83] (the structural complementarity between enzyme and substrate) and induced fit[84] (conformational change during the binding) are responsible for the explanation of biological functions. Generally, proteins experience reversible structural changes to accomplish their functions. For example, the tetrameric hemoglobin binds O_2 in allosteric transition state.[85]

An example of synthetic conformation is calix[4]arene, which has "*cone*", "*partial cone*", "*1,2-alternate*" and "*1,3-alternate*" conformations,[86] as shown in Figure 11. These interconvertible conformers of calix[4]arene have been demonstrated by temperature-dependent ^{1}H NMR experiments. The unequivocal ^{1}H NMR signal of the linker methylene groups appears as a singlet above room temperature and as a pair of doublets below room temperature. It was inferred that calix[4]arene prefers the cone conformation but the interconversion of the cone conformation into the others occurs rapidly at room temperature on the NMR timescale. X-ray crystallographic studies provide evidence that calix[4]arene adopts cone conformation in the solid state with strong intramolecular hydrogen bonding interactions. Another example is calix[4]pyrrole that adopts a cone conformation in the presence of anions (F^- or Cl^-) with a significant change in the ^{1}H NMR spectrum. The preference of the cone conformation is also supported by single crystal structures.[11]

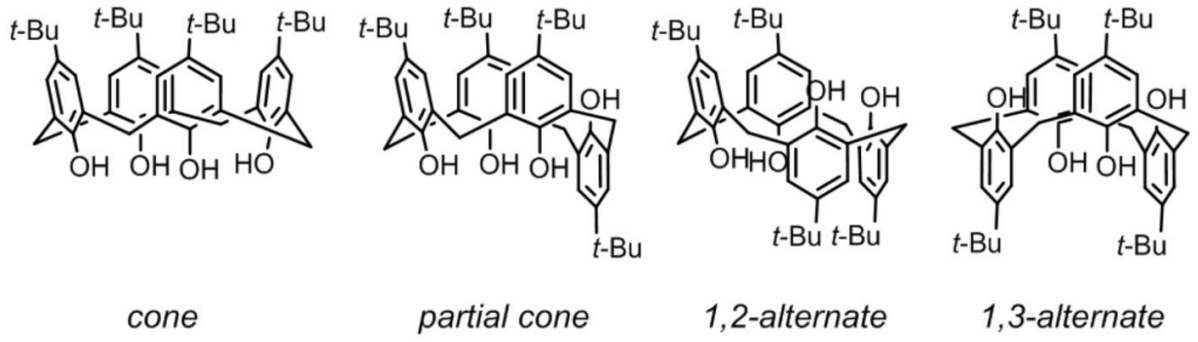

Figure 11. Chemical structures of four typical conformers of the calix[4]arene.

In 2015, we reported a naphthalene-based macrocyclic receptor with an adaptable cavity, named oxatub[4]arene[35] (Figure 12) – a name derived from the tube-like cavity and the oxygen atoms in the linkers. In comparison with calixnaphthalenes, the cavity of oxatub[4]arene is largely

expanded due to the long CH_2OCH_2 linker between neighboring naphthalene rings to avoid the steric hindrance in the structure of calixnaphthalenes with its shallow cavity.

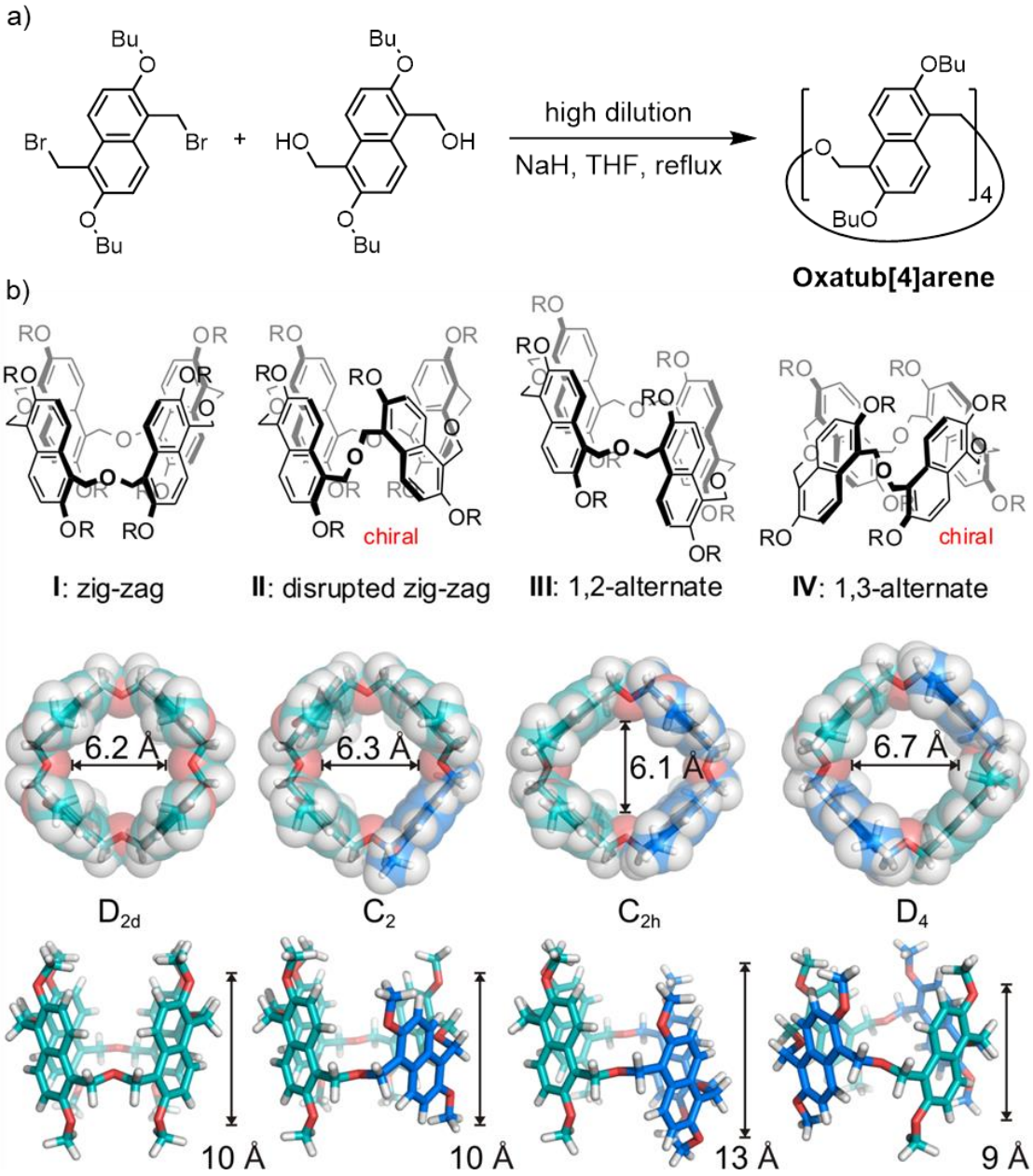

Figure 12.[35] a) Synthesis of oxatub[4]arene; b) Chemical structures of four typical conformers of oxatub[4]arene that result from naphthalene rings flipping (R = *n*-butyl), and the top and side views of the corresponding models. Butyl groups are shorted to methyl groups for viewing clarity. Copyright © 2015, the Royal Society of Chemistry.

Because of the precise linking positions on 1,5-position of the alkyl substituent of 2,6-dihydroxynaphthalene minimize potential isomerism and avoid self-occupation of the cavity as observed in zorb[4]arene, in favor of maintaining a deep cavity and good host-guest complexation properties with cationic guest molecules. Oxatub[6]arene[87] is even stronger to bind C_{60} than hexahomotrioxacalixnaphthalene does.

Oxatub[4]arene is a flexible macrocycle and thus possesses numerous conformations in solution. As shown in Figure 12b, oxatub[4]arene has four typical conformations resulting from naphthalene rings flipping. Each conformer creates a cavity of sizes different from those of the other conformers and thus is expected to result in different guest binding preferences.[35] According to their interconvertible and deep cavities of the four conformers, oxatub[4]arene is viewed as a molecular "transformer" capable of encapsulating a wide range of cationic guests, such as quaternary ammoniums, ferrocenium, cobaltocenium, sulfonium, tropylium, phosphonium, pyridinium and other appropriate cationic guests.[82]

The ^{1}H NMR data of free oxatub[4]arene show that these conformers rapidly interconvert in solution at room temperature. We could not distinguish the four typical conformers by using low-temperature ^{1}H NMR experiments, even though the four conformers have different symmetries. Fortunately, when adding guest molecules to a solution of free oxatub[4]arene, the conformational interconversion slows down and thus one conformer, or a combination of conformers is selected. All four conformers have been assigned when different guest molecules are used and characterized by ^{1}H NMR, 2D NMR and X-ray single crystallography. As shown in Figure 13, only conformer **II** with lowest symmetry shows a combination of conformations with conformer **I**, and the conformers **I**, **III**, and **IV** can be dominated by different size and shape guest molecules over 95% in solution, respectively.

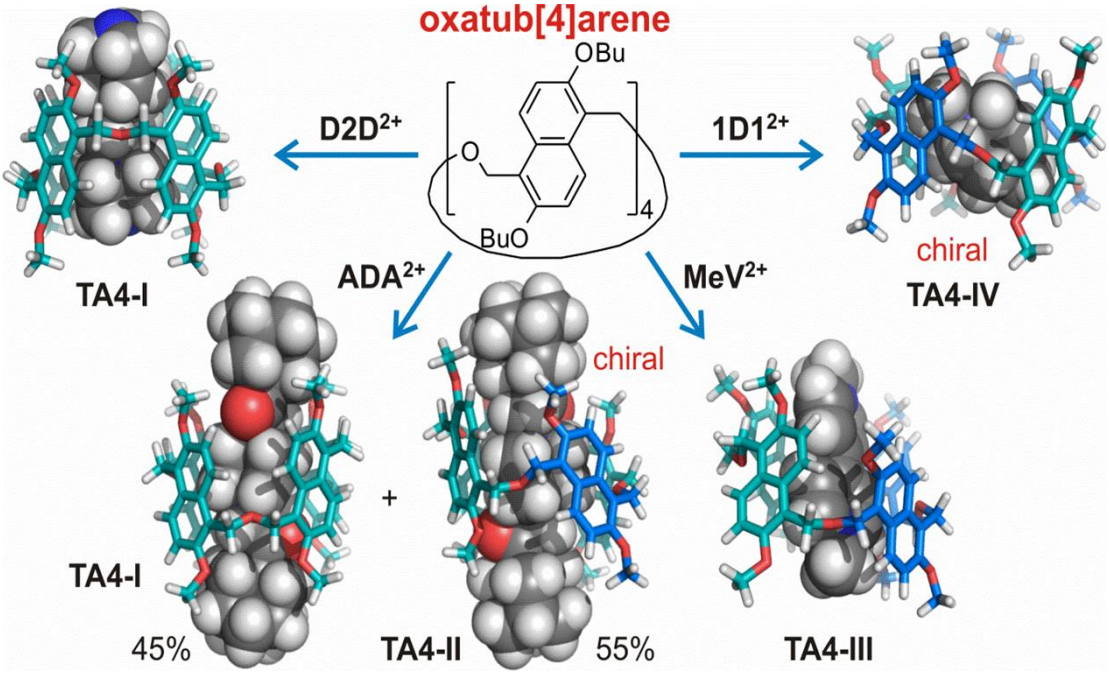

Figure 13.[35] Summary of the guests binding preference of four typical conformers of oxatub[4]arene. Copyright © 2015, the Royal Society of Chemistry.

3.3. The Design of Naphthocage

The 2,4,6-substituents of 1,3,5-triethylbenzene has been widely used as a scaffold in supramolecular chemistry. This building block is able to preorganize binding elements together to form host-guest complexes, of which present a steric-gearing conformation (for example, 1,3,5-tri(bromomethyl)-2,4,6-triethylbenzene, Figure 14a) to direct the complexation sites toward the same face of the central ring.[88] These studies of this scaffold have been reported by Anslyn,[89] Mislow,[90] Wilson,[91] Raymond[92] Rissanen[93] and others[94] to express the particularities.

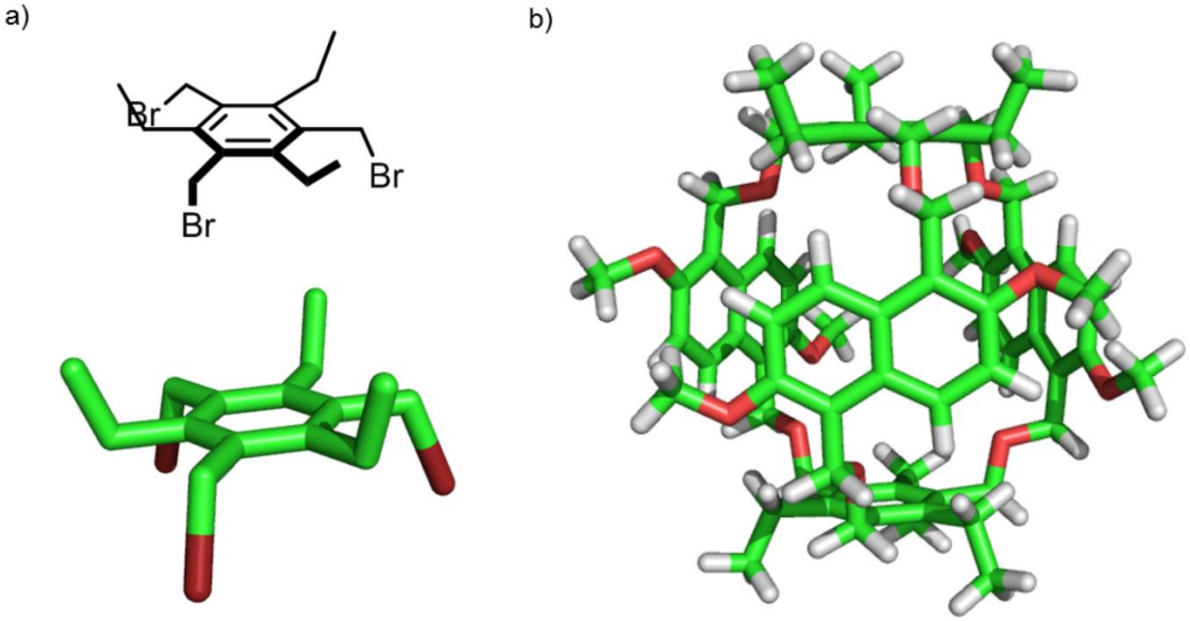

Figure 14. a) Chemical structure of 1,3,5-tri(bromomethyl)-2,4,6-triethylbenzene and corresponding model in steric-gearing forms (most favorable conformation (MMFF94), hydrogens are omitted for viewing clarity); b) Energy-minimized model (MMFF94s) for one of the conformers of naphthocage (**NC**, chiral, only one enantiomer is shown here). Butyl groups are shortened to methyl groups for viewing clarity.

Preorganization[95] is a key principle in the development of supramolecular chemistry that highly governs the orientation of host and guest for the complexation. Highly preorganized organic covalent cages[96] are typically structurally rigid and, therefore, offer less conformational response to environmental stimuli. Conformationally flexible molecular cages, in contrast, can respond to different shapes of organic guest molecules as well as environmental stimuli.

Here, we designed a naphthalene-based cage (Figure 14b), named "naphthocage" by using 1,3,5-tri(bromomethyl)-2,4,6-triethylbenzene as one of the scaffolds and combined with 2,6-dibutoxynaphthalene rings together. We envisioned the naphthocage and performed the synthesis of naphthocage (**NC**, Figure 15) by reacting (2,6-dibutoxynaphthalene-1,5-diyl)dimethanol with 1,3,5-tris(bromomethyl)-2,4,6-triethylbenzene in the presence of sodium hydride in dry THF under pseudo-high-dilution conditions. Pure **NC** was then isolated through flash column chromatography as a white solid with a reasonable yield of 14%. Naphthocage is expected to be a flexible cage with an electron-rich cavity, providing a good binding pocket for trapping cationic guests. Naphthocage possesses numerous conformations resulting from the dynamics of the naphthalene rings. There are two typical conformations, owing to the orientation of the naphthalene rings when a guest occupies the cage cavity. Therefore, this cage is well endowed with three important characters of flexibility, conformational dynamics and the ability to adapt, and an electron-rich cavity, which will probably present excellent host-guest complexation properties for functional applications.

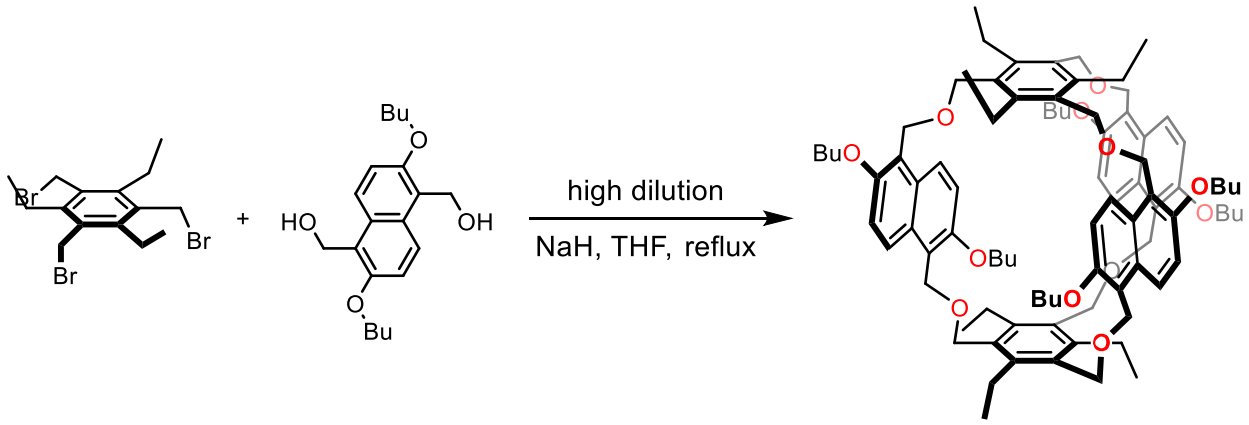

Figure 15. a) Synthesis of naphthocage (**NC**).

4. Experimental Methods

Isothermal Titration Calorimetry (ITC)

ITC is a widely used physical technique to directly determine the thermodynamic association and dissociation parameters of intermolecular complexes in supramolecular chemistry and biochemistry. This technique is based on the measurement of heat evolving and absorbed, when host-guest complexes are formed. An ITC instrument consists of two cells, one reference and one sample cell, which are enclosed in an adiabatic jacket (Figure 16). A heater is attached to the sample and reference cells and is automatically regulated by a feedback event to maintain the temperature difference at zero between the two cells.

In a typical titration experiment, the reference cell contains pure solvent and the sample cell usually contains a solution of one binding partner (for example the host molecule). A small amount of typically more concentrated solution of another binding partner (the guest molecule) is titrated into the sample cell. After each titration step, the association of the host-guest complex produces or consumes heat that raises or lowers the temperature in the sample cell. The temperature difference triggers the feedback to the heater to adjust the differential power (DP) to maintain the temperature difference at zero in both cells. If the guest solution is titrated aliquots to the sample cell, the host and guest are increasingly converted to the complex, leading to diminishing the heat. A typical example showing the exothermic encapsulation of **D2D**$^{2+}$ within oxatub[4]arene (**TA4**) in a 1:1 mixture of 1,2-dichloroethane and acetonitrile is depicted in Figure 16.

ITC is a quantitative method to directly determine the association stoichiometry n as the molar ratio of host and guest at the inflection point of the titration curve. Furthermore, the association constant K_a (or the dissociation constant K_d) can be obtained from the slope at the inflection point and the association enthalpy ΔH from the step height of the curve. The association free energy ΔG and the association entropy ΔS can be calculated by the Gibbs equation ($\Delta G = - R \cdot T \cdot \ln K_a = \Delta H - T \cdot \Delta S$). All these parameters can thus be obtained in a single experiment with a quite large dynamic range for the K_a values of 10^2-10^8 M^{-1}.[97] For an accurate titration experiment, the fitting curve should ideally be sigmoidal, which can be evaluated by the Wiseman c value ($c = n \times K_a \times [M]$, [M] is the concentration of titrate) that should range from 10 to 1000.[98] Most cases of the association constants are in the dynamic range of the method, but a number of cases exceed the upper limit and are significantly larger than 10^9 M^{-1}. The direct measurement of such large binding

affinity would require very low concentrations of host and guest, respectively, that however result in small heat signals unless the binding enthalpy changes are large. Normally, these difficulties can be relieved by raising the temperature or altering the solvent with more polar solvents instead, which however comes at the price of non-comparability with many other values that have been obtained at different temperatures or solvents. Another effective way to solve this problem is to use a competition experiment, in which a guest with medium affinity is replaced by a more strongly binding guest and the binding affinity difference is determined. With the knowledge of the binding parameters of the weaker guest, one can thus determine also the parameters for the stronger guest.

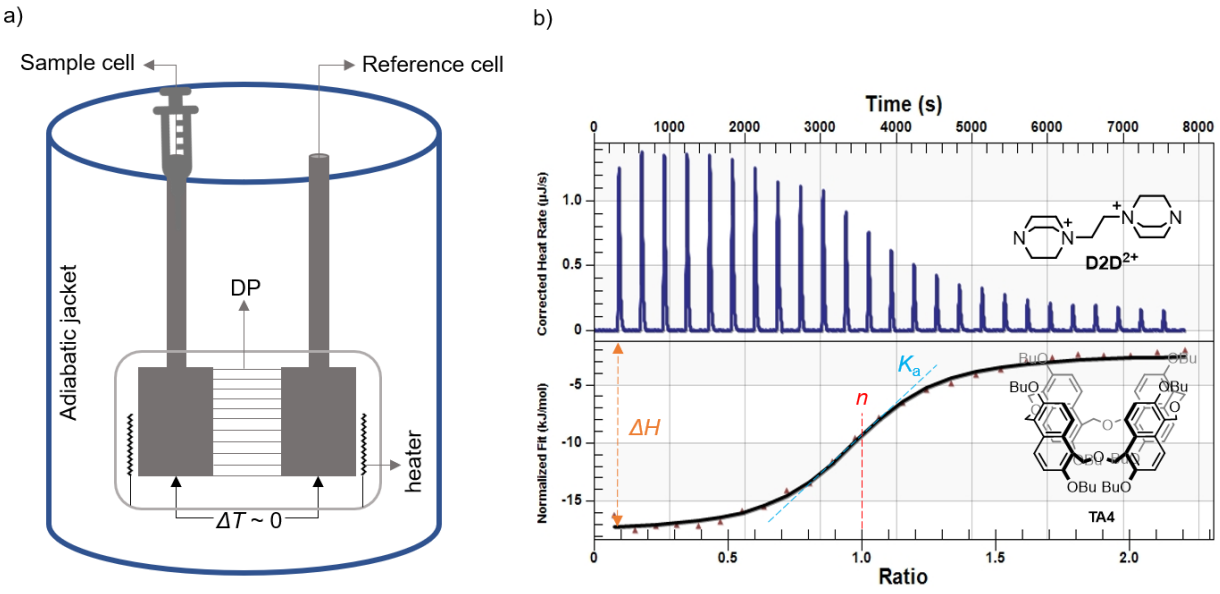

Figure 16. a) Schematic of an isothermal titration calorimetry instrument, the differential power (DP) is a measured power differential between the reference and sample cells to maintain the temperature difference at zero ($\Delta T = 0$); b) ITC titration of 0.16 mM oxatub[4]arene (**TA4**) in 1:1 mixture of 1,2-dichloroethane and acetonitrile with 1.0 mM D2D-2PF_6 in the same solvents (K_a = 2.3 × 10^5 M^{-1}, n = 1).[35] Color marks indicate the thermodynamic parameters n, K_a and ΔH in the plot, Copyright © 2015, the Royal Society of Chemistry.

Electrochemistry

Electrochemistry is a powerful physical tool to investigate chemical reactions involving electron transfers to chemical changes. In a chemical reaction, the homogeneous electron transfers between two molecules. For example, Ferrocenium (**Fc**$^+$) is reduced by cobaltocene (**Co**). In an electrochemical reaction, the heterogeneous electron transfers from an electrode to a molecule, for example, **Fc**$^+$ gains one electron from an electrode, which is reduced to ferrocene (**Fc**). **Fc** is oxidized to **Fc**$^+$ again in solution. Cyclic voltammetry (CV)[99] is a popular electrochemical technique used to study both the reduction and oxidation processes of chemical species. The thermodynamic equilibrium constant (K_{eq}) and the kinetic parameters of forward (k_f) and backward (k_b) rate constants of these processes can be determined.

In an electrochemical measurement, an electrolyte solution of analyte and salt (supporting electrolyte) with three electrodes (e.g. a freshly polished glassy carbon working electrode, a platinum-wire counter-electrode and a silver-wire reference electrode) are placed in an electrochemical cell. Cyclic voltammograms (Figure 17, here we take **Fc** as an example because it undergoes one-electron transfer reactions) are recorded with a certain scan rate. The scan rate describes the rate with which the potential is varied and is a crucial parameter for the experiment. From the voltammograms, the parameters of half wave potential ($E_{1/2}$), peak cathode potential (E_{pc}), peak anode potential (E_{pa}), peak cathode current (i_{pc}), peak anode current (i_{pa}) can be determined. The Nernst equation (1) describes the redox potential (E) (one-electron transfer reaction) of an electrochemical reaction relative to the standard potential (E^0) of the chemical species experiencing reduction (Red) and oxidation (Ox) in an equilibrium system.

$$E = E^0 + \frac{RT}{F} ln \frac{[Fc^+]}{[Fc]} \qquad (1)$$

where F is Faraday's constant, R is the gas constant and T is the temperature.

As the redox species sometimes deposit on the surface of electrode, it is essential to evaluate whether the redox species freely diffuse to the bulk solution that the redox processes are chemically and electrochemically reversible. Chemical reversibility depends on whether the analyte is stable upon reduction and can be oxidized again. Electrochemical reversibility depends on the kinetics of electron transfer from the electrode to the analyte. The peak current (i_p, A) against the square root of the scan rate (v, $V \cdot s^{-1}$) can be determined from the Randles-Sevcik equation (2). If the peak

current (i_{pc} and i_{pa}) increases linearly with the square root of the scan rate, the electrochemical processes are reversible.

$$i_p = 0.446nFAC^0(\frac{nFvD_o}{RT})^{1/2} \qquad (2)$$

where n is the number of electrons, A (cm^2) is the electrode surface area, D_o ($cm^2 \cdot s^{-1}$) is the diffusion coefficient of the oxidized analyte and C^0 ($mol \cdot cm^{-3}$) is the bulk concentration of the analyte.

Cyclic voltammograms are simulated with the DigiElch Professional software (ElchSoft GbR, Kleinromstedt, Germany) using the Butler-Volmer equation.[100] The charge-transfer coefficients α are set to an initial value of 0.5 and the heterogeneous rate constants k_s are estimated by the peak-to-peak separation and set to 0.05-0.1 $cm \cdot s^{-1}$. The diffusion coefficients are set to an initial value 1.0×10^{-5} $cm^2 \cdot s^{-1}$. The fitting and simulation processes should be repeated with cyclic voltammograms at different scan rates and/or at a different host concentration to ensure the reliability of thermodynamic and kinetic parameters.

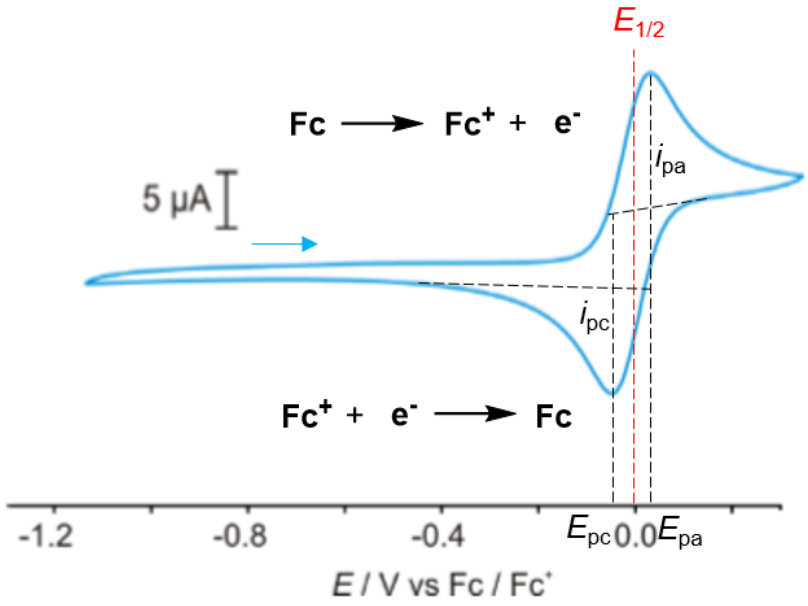

Figure 17. Cyclic voltammogram of **Fc** (CH_2Cl_2, 1.0 mM, 298 K, 100 $mV \cdot s^{-1}$) with n-Bu_4NPF_6 (0.1 M) as the electrolyte. Copyright © 2019, American Chemical Society.

5. Published Articles

5.1. Naphthocage

This article was published in the following journal:

F. Jia, H. Hupatz, L.-P. Yang, H. V. Schröder, D.-H. Li, S. Xin, D. Lentz, F. Witte, X. Xie, B. Paulus, C. A. Schalley* and W. Jiang*. Naphthocage: A Flexible yet Extremely Strong Binder for Singly Charged Organic Cations. *J. Am. Chem. Soc.*, **2019**, *141*, 4468-4473.

https://doi.org/10.1021/jacs.9b00445.

Declaration on the personal contribution in this work:

F. Jia designed, synthesized, purified and characterized the naphthocage by ^{1}H NMR, ^{13}C NMR, variable temperature ^{1}H NMR, and mass spectrometry. F. Jia performed the host-guest complexation experiments including complex characterization by ^{1}H NMR, 2D NMR and mass spectrometry. F. Jia performed the redox-switching experiments. F. Jia grew the crystals of naphthocage. D.-H. Li and L.-P. Yang repeated the synthesis of naphthocage. L.-P. Yang and H. Hupatz performed the ITC and the competition experiments, respectively. H. V. Schröder performed the electrochemical experiments. S. Xin and X. Xie performed the ion-selective electrode experiments. D. Lentz measured and refined the crystal structures of the naphthocage. F. Witte and B. Paulus performed the DFT calculations. C. A. Schalley supervised the project. F. Jia and W. Jiang analyzed the data and wrote the manuscript and all authors commented on it.

Summary of this work:

We have reported the synthesis and recognition behavior of "naphthocage", 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 not to be 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.

5.2. Redox-Responsive Host-Guest Chemistry

This article was published in the following journal:

F. Jia, H. V. Schröder, L.-P. Yang, C. Essen, S. Sobottka, B. Sarkar, K. Rissanen, W. Jiang* and C. A. Schalley*. Redox-Responsive Host-Guest Chemistry of a Flexible Cage with Naphthalene Walls. *J. Am. Chem. Soc.*, **2020**, *142*, 3306-3310.

https://doi.org/10.1021/jacs.9b11685.

Declaration on the personal contribution in this work:

F. Jia and C. A. Schalley developed the idea of this project. F. Jia synthesized, purified and characterized the naphthocage and control compound. F. Jia performed the experiments of host-guest complexation characterized by ^{1}H NMR, 2D NMR, EXSY, mass spectrometry and UV-vis spectroscopy. F. Jia performed the control experiments of guest release mediated by cage oxidation. F. Jia grew the crystals of the host-guest complex. L.-P. Yang and W. Jiang performed ITC experiments. H. V. Schröder and F. Jia performed the electrochemical experiments and simulations. H. V. Schröder performed the DFT calculations. S. Sobottka and B. Sarkar performed the CW-EPR sepectroelectrochemistry and UV/vis-NIR sepectroelectrochemistry experiments. C. Essen and K. Rissanen measured and refined the crystal structure of the host-guest complex. F. Jia and C. A. Schalley analyzed the data and wrote the manuscript and all authors commented on it.

Summary of this work:

We report the extremely strong complexations of the aromatic cations and dications of tetrathiafulvalene (**TTF**$^{2+}$) and methyl viologen (**MV**$^{2+}$) inside the naphthocage with affinities up to 3.1×10^{10} M^{-1}. The strong binding occurs through intercalation with the aromatic guests located inside the cage cavity between two naphthalene walls. Additionally, both guests and the free cage are redox-active. The guests can be switched into (**TTF** → **TTF**$^{2+}$) and out of (**MV**$^{2+}$ → **MV**) the cage with high selectivity by oxidation and reduction, respectively. The cage can be reversibly oxidized to its radical cation, which is stabilized by the self-inclusion of the oxidized naphthalene. The oxidation of the cage can be applied for controlled guest release from the cage cavity, which

paves the way for novel applications in the redox-controlled guest release or stimuli-responsive materials.

5.3. The Influence of Substituent Effects of Guests on the Binding of Oxatub[4]arene

This article was published in the following journal:

F. Jia, L.-P. Yang, D.-H. Li and W. Jiang*. Electronic Substituent Effects of Guests on the Conformational Network and Binding Behaviors of Oxatub[4]arene. *J. Org. Chem.* **2017**, *82*, 10444-10449.

https://doi.org/10.1021/acs.joc.7b01914.

Declaration on the personal contribution in this work:

F. Jia and W. Jiang developed the idea of this project. F. Jia synthesized, purified and characterized the oxatub[4]arene. F. Jia and D.-H. Li synthesized and characterized the quaternary ammonium guests. F. Jia performed the experiments of host-guest complexation characterized by ^{1}H NMR, 2D NMR. L.-P. Yang performed ITC experiments. F. Jia performed ^{1}H NMR titration experiments. F. Jia and W. Jiang analyzed the data and wrote the manuscript and all authors commented on it.

Summary of this work:

In summary, we synthesized a series of quaternary ammonium ion guests with different substituent groups and studied the influence of substituent groups of the guests on the binding behavior and conformational networks of oxatub[4]arene. The para-substitution can affect the binding affinities through a field/inductive effect by following a linear free energy relationship. Surprisingly, oxatub[4]arene undergoes a large amplitude of conformational changes in response to the remote substituents. To the best of our knowledge, this is the first time that such an effect was observed in synthetic molecular recognition. We believe this novel mode of synthetic molecular recognition may also have biological relevance.

6. Summary and outlook

In summary, this thesis has reported the synthesis of a naphthalene-based cage, the so-called "naphthocage", which is highly flexible and adopts a self-inclusion conformation in the solid state. Due to the helical arrangements of the three naphthalene walls, naphthocage is chiral. Through a naphthalene ring flip of one of the naphthalene rings, a D_3-symmetric conformer **I** can interconvert into a C_2-symmetric conformer **II**. Conformer **I** and its enantiomer have the opposite helical sense of the three naphthalene walls, while for conformer **II** and its enantiomer, one naphthalene ring rapidly flips into the opposite sense. They differ in symmetry and thus are expected to show different aromatic signals in the ^{1}H NMR spectra. When an achiral guest is encapsulated inside the cage cavity, the racemization of the two enantiomers will be slow down.

Naphthocage has an electron-rich cavity because of the three naphthalene walls and two phenyl rings surrounding the cage cavity. In solution, free naphthocage adopts a self-inclusion conformation, but owing to the rapid flipping of the naphthalene walls, the self-inclusion conformation interconverts with two other cage conformations **I** and **II**. Despite the remarkable flexibility of naphthocage, the cage expresses extremely strong binding affinities up to 10^9 M^{-1} to singly charged organic cations, such as Me_4N^+, ferrocenium (Fc^+) or acetylcholine. An astonishingly high binding *selectivity* (ca. 10^{15}) was observed for ferrocenium (Fc^+) over ferrocene (Fc). Naphthocage shows a super-Nernstain electrochemical response to acetylcholine in water when incorporated in ion-selective electrodes. Thus, these binding characters are quite adding colors to naphthocage, which are in marked contrast to many other rigid cage structures.

Naphthocage also reveals very strong binding affinities (up to 10^{10} M^{-1}) to aromatic (di)cationic guests, i.e., the tetrathiafulvalene mono- and dication and methyl viologen. The strong encapsulation occurs through the intercalation of the aromatic guest molecules inside the cage cavity between two naphthalene walls. In addition, when the guest is redox-active, the guest can be switched into and out of the cage with high binding selectivity by oxidation and reduction processes, respectively. Furthermore, the cage itself is also redox-active and cationic guest can be released from the cage cavity. The reversible oxidation of the flexible cage itself in the absence of a guest leads to a stable radical cation with the oxidized naphthalene intercalated between and stabilized by the other two. The oxidation of the cage can be applied for controlled guest release

from the cage cavity, which paves the way for novel applications in the redox-controlled guest release or stimuli-responsive materials.

Normally, the improvements of binding affinity and selectivity of synthetic receptors resorted to the development of preorganized rigid structures, since preorganization is believed by many supramolecular chemists to be a key principle to guide the design and synthesis of effective molecular receptors. However, rigid receptors suffer from limited adaptability of the scaffolds with a relatively less narrow binding scope and thus frequently limited functional applications. Sanders[101] pointed out two decades ago that "the fear of entropy has taken supramolecular chemists too far in the direction of rigidity and preorganization, and that the future may lie in more flexible systems that rely on noncovalent interactions to impose order on three-dimensional structures." Here, naphthocage is a good example of a conformationally flexible system that despite of its flexibility expresses high binding affinity and selectivity. This is reminiscent of natural systems, such as protein folding, the selective recognition between enzymes and substrates and DNA intercalation of flat aromatic molecules. Therefore, the investigations of naphthocage imply that supramolecular chemists may need to pay much more attention to the flexible systems that possess unlimited flexibility, conformational dynamics and adaptability to improve the binding affinity and selectivity.

7. Appendix

7.1. References

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7.2. List of Publications

3. F. Jia, H. V. Schröder, L.-P. Yang, C. Essen, S. Sobottka, B. Sarkar, K. Rissanen, W. Jiang* and C. A. Schalley*. Redox-Responsive Host-Guest Chemistry of a Flexible Cage with Naphthalene Walls. *J. Am. Chem. Soc.*, **2020**, *142*, 3306-3310.

2. F. Jia, H. Hupatz, L.-P. Yang, H. V. Schröder, D.-H. Li, S. Xin, D. Lentz, F. Witte, X. Xie, B. Paulus, C. A. Schalley* and W. Jiang*. Naphthocage: A Flexible yet Extremely Strong Binder for Singly Charged Organic Cations. *J. Am. Chem. Soc.*, **2019**, *141*, 4468-4473.

1. F. Jia L.-P. Yang, D.-H. Li and W. Jiang*. Electronic Substituent Effects of Guests on the Conformational Network and Binding Behaviors of Oxatub[4]arene. *J. Org. Chem.* **2017**, *82*, 10444-10449.

7.3. Poster Presentations

2. F. Jia, W. Jiang and C. A. Schalley. Redox-Responsive Host-Guest Chemistry of a Flexible Cage with Naphthalene Walls. *The 5th International Symposium of the Collaborative Research Center 765 "Multivalency in Chemistry and Biology"*, Freie Universität Berlin, Sep. 30-Oct. 2, **2019**.

1. F. Jia, H, Hupatz, H. V. Schröder, W. Jiang and C. A. Schalley. Naphthocage: A Flexible yet Extremely Strong Binder for Singly Charged Organic Cations. *The 14th International Symposium on Macrocyclic and Supramolecular Chemistry*, Lecce, Italy, Jun. 2-6, **2019**.

7.4. Curriculum Vitae

For the reasons of data protection, the curriculum vitae is not included in the online version.

7.5. Acknowledgements

Firstly, I would like to thank Prof. Dr. Christoph A. Schalley for giving me the opportunity to do my Ph.D. work in his research group. His research group expresses a friendly open environment that we nicely worked together and passionately discussed and exchanged ideas in the group seminar, which brought new ideas to me and I was benefited from this strong research culture and understood supramolecular chemistry work studies better. I really enjoyed the working experiences in Schalley group, when he gave me maximum freedom to explore and investigate the supramolecular chemistry fields what I am interested in. When I was in trouble or had any scientific questions during the study periods, he was nicely modest to teach me with his comprehensive chemical knowledge and rich experience, I learned a lot! I would really appreciate what you have done for me in the past four years, which will deeply affect my study life in the near future.

I would like to express many thanks to Prof. Dr. Beate Paulus for accepting my invitation to act as the second reviewer and spending her precious time in reviewing my thesis. I am so grateful to thank her good suggestions and comments for my PhD thesis, as well as good suggestions for cooperation projects before.

Also, I would be grateful to Prof. Dr. Wei Jiang (SUStech, Shenzhen) that we nicely worked together for three years as a result of over 10 publications contributed. Since 2013, Dr. Zhenfeng He (North University of China, Taiyuan), Dr. Gang Ye (University of Groningen, Netherlands), Dr. Dapan Li (Shenzhen) and I constituted a supramolecular research group of naphthols. Dr. Wei Jiang was a shepherd of me to enter in supramolecular chemistry fields. I really appreciate that he helped me a lot in understanding the concepts of supramolecular chemistry and how to start to study the content of supramolecular chemistry.

I would thank all my current and former co-workers in the Schalley group for their very good help during my research life and very helpful suggestions and comments to promote my study and innovation skills. They are Frau Carin Kietzmann (former secretary), Frau Silke Benndorf (current secretary), Dr. Andreas Springer, Dr. Dominik Weimann, Dr. Sebastian Richter, Dr. Thomas Heinrich, Dr. Larissa von Krbek, Dr. Ulrike Warzok, Dr. Hendrik Schröder, Dr. Stefan Schoder, Dr. Bo Zhen, Dr. Jan Wollschläger, Dr. Anneli Kruve-Viil, Dr. Chih-Wei (Wilber) Chu, Philip Barkawitz, Marius Gaedke, Tomas Feliksas Gutorovas, Henrik Hupatz, Tugrul Kaynak, Bo Li,

Longshang (Hubert) Liu, Daniel L. Stares, Qiangqiang Xu, Janos Wasternack, Konstantin Simon, Fabian Klautzsch, Sebastian Müller and Andrea Schulz.

I thank all my collaborators, Dong-Hao Li (PhD student, University of Notre Dame, America) Dr. Liu-Pan Yang (SUStech, Shenzhen), Shan Xin (SUStech, Shenzhen), Prof. Dr. Xiaojiang Xie (SUStech, Shenzhen), Prof. Dr. Dieter Lentz (Freie Universität Berlin, Berlin), Dr. Carolina von Essen (University of Jyvaskyla, Jyväskylä), Prof. Dr. Kari Rissanen (University of Jyvaskyla, Jyväskylä), Felix Witte (Freie Universität Berlin, Berlin), Prof. Dr. Beate Paulus (Freie Universität Berlin, Berlin), Sebastian Sobottka (Freie Universität Berlin, Berlin), Prof. Dr. Biprajit Sarkar (Freie Universität Berlin, Berlin).

I would like to thank Fabian Klautzsch, Dr. Jan Wollschläger, Dr. Ulrike Warzok and Dr. Andreas Springer in the Mass Spectrometry of Core Facility Biosupramol Department (Freie Universität Berlin, Berlin) for their professional guidance to using FTICR and IMS instruments, and experiments, respectively.

I thank Dr. Andreas Schäfer and his colleagues in the Core Facility Biosupramol for the help with NMR measurements.

I would thank Dr. Carlo Fasting (Freie Universität Berlin, Berlin) for the help with HPLC analysis.

I would like to thank all the members who work in the Institut für Chemie and Biochemie providing any convenient help in administration, materials store, transporting chemical waste and borrowing chemicals.

I am grateful to the members of Freie Universität Berlin who is responsible for the orientation week for Chinese people and the Pass Service for the help of visa application.

I thank the China Scholarship Council (CSC) for a PhD fellowship and the Deutsche Forschungsgemeinschaft (CRC 765) for funding.

I would thank all my friends for providing any help during the last four years in Berlin.

Finally, I would like to thank my family to support me to work here. And especially thank to my wife for her great support to my family and thank to my daughter and my son for bringing joy to my family. Thanks also go to my wife for her companionship in the last fifteen years (Wuhan, Guangzhou, Shanghai, Shenzhen and Berlin).