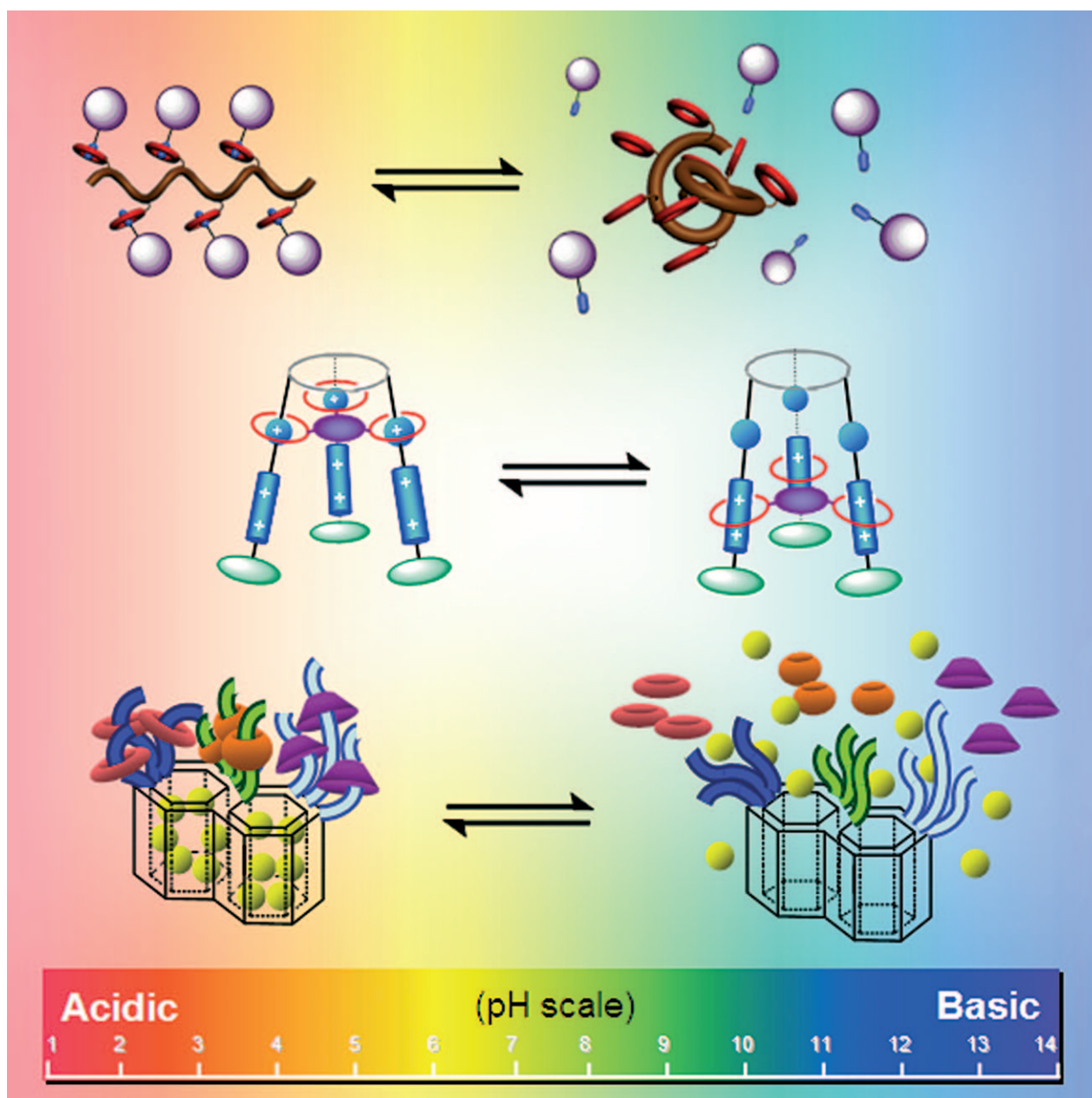


pH-Controllable Supramolecular Systems

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Abstract: This Focus Review surveys representative examples of pH-controllable supramolecular systems with interesting features and state-of-the-art applications such as 1) conformational changes within individual molecules; 2) folding/unfolding of polymers; 3) simultaneous binding of cations and anions; 4) logic function; 5) ON–OFF switchable colorimetric sensing; 6) translocation of macrocycle-in-rotaxane molecules; 7) large-scale movement within molecules; and 8) regulation of the substrate flow in nanocontainers. In particular, systems will be discussed that involve: pH-induced conformational changes of a resorcinarene cavitand and a bis(iron porphyrin) complex; pH control in assembly and disassembly of supramolecular systems stabilized with different major noncovalent

interactions; pH-driven movements of interlocked molecules involving rotaxanes, molecular elevators, and molecular muscles; and, finally, multicomponent supramolecular systems immobilized on solid supports as pH-responsive nanovalves for the controlled release of specific substrates. Recent advances in the understanding of pH-controllable supramolecular systems have led to the construction of meaningful molecular machines for electronic and biological applications that are amenable to control by simple perturbation with acids and bases.

Keywords: catenanes • protonation • rotaxanes • self-assembly • supramolecular chemistry

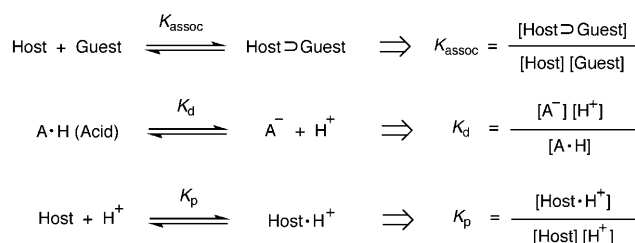
Introduction

Recently, supramolecular chemistry^[1] has been widely employed in self-assembling large and complex components for practical applications both in electronics^[2] and biological systems.^[3] For fabrication processes by self-assembly via “bottom-up”^[4] or “template-directed”^[5] approaches, the specific association and dissociation of different components in these processes are required to be controlled by external stimuli such as pH, electrical potential, redox agents,^[6] and light.^[7] Among these external stimuli, pH stimulation represents a convenient method to offer specific control with perturbation of protons by readily available acids and bases. Measurement of pH in solution is simple and acid–base titration can be quantitative.

In pH-switchable host–guest supramolecular binding, reactive donor atoms or groups must be present in either the host or guest, in which these donor groups usually involve

nitrogen or oxygen atoms commonly existing in amine/ammonium, pyridine/pyridinium, or phenolate/phenol forms. Small perturbations of these sensitive donor groups may have drastic effects on their supramolecular entities bonded through noncovalent interactions such as metal–ligand interactions,^[8] electrostatic interactions, hydrogen bonding,^[9] aromatic π – π interactions,^[10] hydrophobic effect,^[11] and so on. Because of the bases (e.g. amine, pyridine, or phenolate), competition with protons may add complexity to the systems such that the protonated or nonprotonated species exists at a specific pH value. This may allow pH control of the formation of one species among many others or, alternatively, to have one species self-assembled upon variation of the pH value. To control the dissociation or to trigger a motion (flipping, bending, rotation, or translocation) of a supramolecular system by pH change, the simplest way is by virtue of Coulombic or electrostatic repulsive force between protonated or deprotonated hosts and guests having the same electrostatic charges. Association and dissociation constants are defined in Scheme 1, where K_{assoc} is the associa-

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Scheme 1.

tion constant of the binding between a host and a guest, K_d is the proton dissociation constant in an acid, and K_p is the binding constant between a host and a proton.

For potential applications in biological systems, significant changes in pH value can be observed in many parts of the human body, for example, the dramatic difference in pH levels in the stomach and intestine as well as the higher acidity in tumors (pH $\approx$ 6.8), endosomes (pH $\approx$ 6.0), and lysosomes (pH $\approx$ 5.0) than in normal tissues.^[12] By proper design of pH-sensitive regulator systems, construction of pH-modulated or self-regulated drug delivery devices can be realized as an improved protocol for disease treatment.^[13] Furthermore, for biomolecular motors such as F_0F_1 ATPase and bacterial flagella motors, their rotary motions can be switched ON and OFF by successive protonation and deprotonation.^[14] As a consequence, underpinning the fundamental requirements for pH-responsive supramolecular materials would shed light on how to mimic these biomolecular motors on applications in both the biological and materials sciences.

1. Molecular Motion by pH-Induced Conformational Change

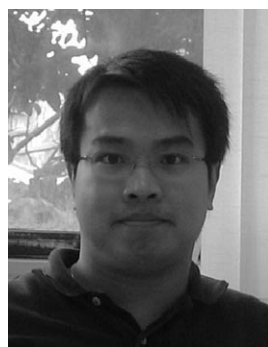
Recently, controlled conformational changes within molecules in response to various external stimuli have gained much attention with the purpose in designing functional materials such as molecular actuators.^[15] Conformational changes within molecules include rotation, bending, and flipping as well as the change of orientation in liquid crystals. In this context, Diederich et al.^[16] have developed a series of resorcin[4]arene cavitand-based^[17] molecular switches that are responsive to pH changes with flipping motion. Quinoxaline-bridged resorcin[4]arene cavitand **1** can be completely converted (Figure 1) into the vase conformation (C_{4v}

symmetry, quinoxaline groups pointing upward) at high pH value with tertiary amine bases or potassium carbonate and, conversely, the kite conformation (C_{2v} symmetry, quinoxaline groups pointing outward) at low pH value with trifluoroacetic acid (TFA). The vase–kite interconversion is quantitative at room temperature, monitored by the characteristic changes using UV/Vis and ^1H NMR (CD_2Cl_2 , methane proton on the resorcin[4]arene, $\delta \approx 5.5$ ppm for vase and $\delta \approx 3.7$ ppm for kite) spectroscopies.^[18,19] The driving force for the vase–kite interconversion in the quinoxaline-bridged resorcin[4]arene cavitand at low pH value is attributed to the protonation of the mildly basic quinoxaline nitrogen atoms, resulting in the Coulombic repulsion of the quinoxaline arms to afford the kite conformation.

The *syn*–*anti* conformational change in bis(iron(III) porphyrin)s has been evaluated recently^[20] upon acid–base-controlled switching. The facile switching from *anti* to *syn* requires an oxygen atom to bridge between the two porphyrins possessing a μ -oxo Fe–O–Fe moiety in the presence of aqueous sodium hydroxide (Figure 2). Conversely, the switching from *syn* μ -oxo bis(iron(III) porphyrin) **2** to the *anti* form **3** can be achieved by the addition of excess aqueous hydrochloric acid to regenerate the Fe–Cl moieties. The

Abstract in Chinese:

本文综述了几种具有特殊结构和应用前景的pH可控超分子体系。主要内容包括几个方面：(1) 单分子内部的构象变化；(2) 聚合物的折叠/去折叠；(3) 阴离子和阳离子的同步组装；(4) 逻辑功能；(5) 色度传感开关；(6) 轮烷分子中的大环移动；(7) 分子内部的大范围移动；和(8) 纳米容器中的底物流动。第二部分着重描述了pH变化对resorcinarene cavitand和bis(iron porphyrin)体系构象转变的影响。第三部分介绍的是pH可控的超分子体系的组装与分解，这些体系主要通过非价键如：金属配位键，静电引力，氢键，芳香族 π -电子堆叠作用和疏水作用稳定存在。pH变化同样可以驱动互锁分子的运动，因此在第四部分中主要讨论的是pH驱动在轮烷，分子升降机和分子肌肉等体系中的作用。最后，第五部分主要探讨多组分超分子体系在固相载体上的附载，这些pH响应的纳米管道可以控制性的释放特异的底物分子。这些简单的通过酸碱变化就可以控制的pH可控超分子体系的最新进展有助于我们理解并构建在分子电学和生物领域具有重要应用意义的分子器件。



Ken Cham-Fai Leung received his B.Sc. and Ph.D. degrees in chemistry from the Chinese University of Hong Kong in 1999 and 2003. Subsequently, worked as a Croucher postdoctoral fellow and then a CMISE scholar in the California Nano-Systems Institute and the Department of Chemistry and Biochemistry, the University of California Los Angeles with Professor Sir James Fraser Stoddart. In September 2006, he joined the Center of Novel Functional Molecules at the The Chinese University of Hong Kong as a Research Assistant Professor. His current

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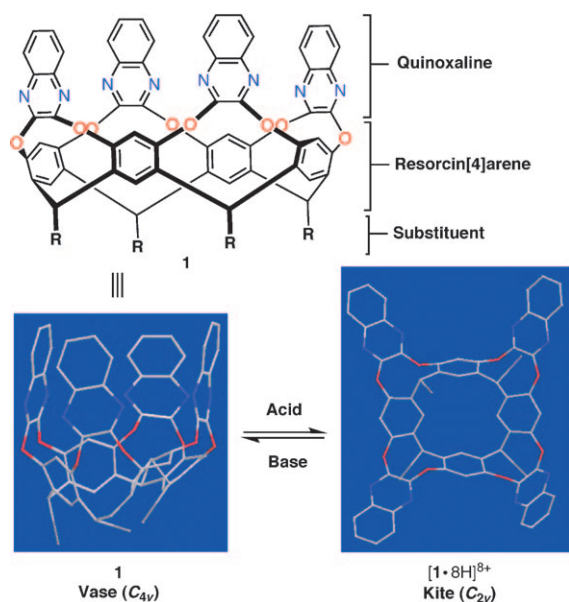


Figure 1. Molecular structure and models (gray: C; blue: N; red: O; dark gray: substituent R; all hydrogen atoms are omitted for clarity)^[2e] of the quinoxaline-bridged resorcin[4]arene cavitand (**1**) for which the complete vase–kite interconversion (flipping) can be activated by acid and base.

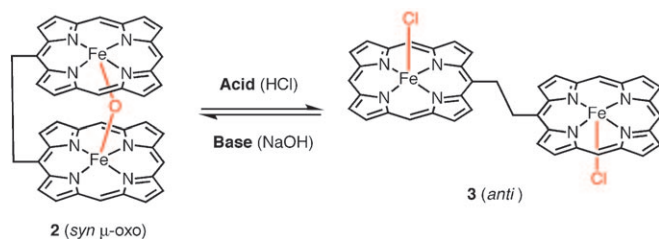


Figure 2. The acid (HCl)–base (NaOH)-controllable, *syn–anti* switching of a bis(iron(III)) porphyrin.

molecular weights of both *syn* and *anti* bis(iron(III)) porphyrins can be characterized successfully by electrospray ionization-mass spectrometry thanks to their difference in molecular weights. Moreover, UV/Vis spectroscopy is proven to be remarkably useful to characterize the significant changes before and after the conformational switching. The maximum of the Soret band at 407 nm in the *anti* form is red-shifted to 417 nm after the addition of base, leading to a conclusion for the formation of the *syn* form with a characteristic μ -oxo Fe–O–Fe moiety. Furthermore, in order to demonstrate the importance of the reversibility, the acid–base-controllable *syn–anti* switching of the bis(iron(III)) porphyrin is repeated for three times, showing that there is almost no loss in the absorbance signal, thus rendering this type of compound an inert, robust, and reversible pH-responsive molecular switch.

2. Self-Assembly and Disassembly Controlled by pH

In the previous section we described some selected examples of the pH-controllable conformational switchings (flipping and *syn–anti* switching) within individual molecules; in this section we will discuss several complex molecular or polymeric supramolecular systems for which the assembly and disassembly of the systems can be controlled by pH changes. Supramolecular systems are classified into five categories according to their major supramolecular interactions present in the complexes, and these include metal–ligand interaction, electrostatic interaction, hydrogen bonding, aromatic π – π interaction, and hydrophobic effect.

2.1. Metal–Ligand Interaction

Transition metals have been used conveniently to self-assemble supramolecular systems because of their ability to gather and coordinate organic electron-rich ligands in a geometrically precise fashion.^[21] Metal–ligand interaction can be classified as a particular kind of ion–dipole interaction. Recently, Lehn and Barboiu^[22] have reported a lead(II) pH-driven supramolecular system which possesses controllable and reversible extension (uncoiled linear chain)/contraction (coiled helix) molecular motion. The system features a pyridine–pyrimidine compound **4** with multiple N donor atoms and the macrobicyclic [2.2.2]cryptand **5** encapsulated lead(II) cations $[\text{Pb} \subset \mathbf{5}]^{2+}$ in one pot (Figure 3). The metal-free pyridine–pyrimidine compound **4** exists in a helical form with transoidal structure between each pyridine and pyrimidine group. To begin with, acidification of the mixture using 10 equivalents of triflic acid ($\text{CF}_3\text{SO}_3\text{H}$) results in the protonation of the macrobicyclic [2.2.2]cryptand **5** to give $[\mathbf{5} \cdot 2\text{H}]^{2+}$, which in turn displaces out the as-encapsulated Pb^{2+} cation by Coulombic repulsion. Subsequently, the displaced Pb^{2+} cations can be complexed to compound **4**, leading to the transformation of the coiled, helical compound **4** into the corresponding uncoiled linear complex $[\mathbf{4} \cdot 5\text{Pb}]^{10+}$ with a cisoidal structure between each pyridine–pyrimidine– Pb^{2+} moiety. This coiling (helix)/uncoiling (linear chain) process can be reversed by the addition of 10 equivalents of triethylamine base. Therefore, the macrobicyclic [2.2.2]cryptand **5** can be deprotonated and regains its higher competitive binding affinity^[23] towards the Pb^{2+} cation, leading to the demetalation of the uncoiled linear complex $[\mathbf{4} \cdot 5\text{Pb}]^{10+}$ to afford once again the original metal-free, coiled helix **4**. The linearity of the compound $[\mathbf{4} \cdot 5\text{Pb}]^{10+}$ is characterized by ^1H NMR spectroscopy with indication of high symmetry, which can be further confirmed by ROESY and the distinct NOE effect. The pH-driven switching between compounds **4** and $[\mathbf{4} \cdot 5\text{Pb}]^{10+}$ is quantitative, confirmed by ^1H NMR spectroscopy (in 2:1 $\text{CDCl}_3/\text{CD}_3\text{CN}$), with the disappearance/appearance of the signals of terminal pyridine protons ($\delta \approx 6.7$ and 7.1 ppm) in **4** as well as the appearance/disappearance of signals of the Pb^{2+} -complexed pyrimidine proton signals ($\delta \approx 10.3$ and 10.4 ppm) in

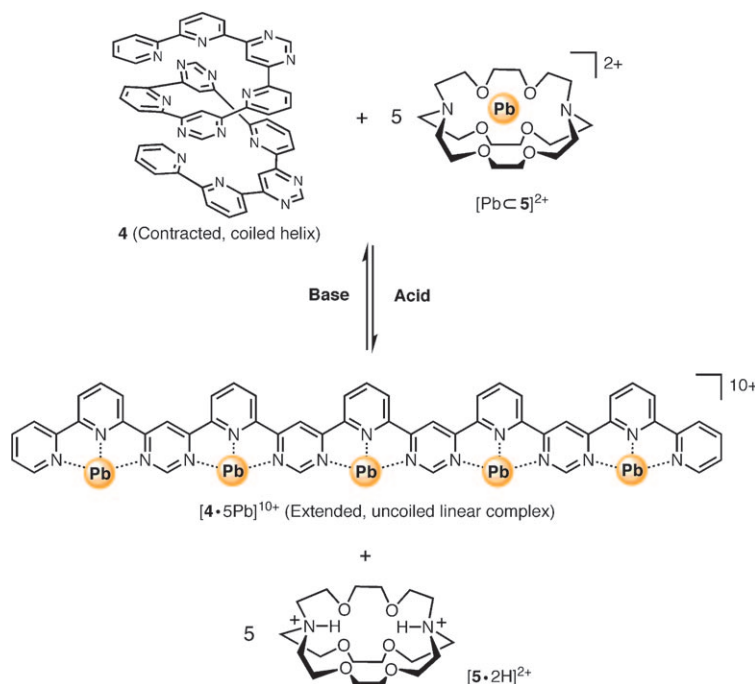


Figure 3. The pH-driven uncoiling of a contracted helix **4** to an extended linear complex $[4 \cdot 5Pb]^{10+}$ by competitive binding of Pb^{2+} cations with macrobicyclic [2.2.2]cryptands **5**.

$[4 \cdot 5Pb]^{10+}$. Additional NMR evidence is provided by observing the shift of the aliphatic proton signal between the Pb^{2+} -complexed and the noncomplexed macrobicyclic [2.2.2]cryptand **5**.

With controllable geometry between transition-metal ions and nitrogen-containing ligands, directed self-assembly of polydentate ligands with metal cations is feasible to produce exotic structures such as boxes,^[24] squares,^[25] racks,^[26] and grids.^[27] Other pH-driven, supramolecular assembly–disassembly of metal cations and ligand hosts can be the prototype of specific metal ion sensors.^[28,29]

2.2. Electrostatic Interaction

Electrostatic interaction involves the Coulombic attraction between charged (ions) or partially charged (dipoles) components and can be subdivided into three classes: ion–ion, ion–dipole, and dipole–dipole interactions. By far the simplest way to control the binding of different cations and anions is the interconversion of the N-containing, large macrobicyclic macrocycle **6** (Figure 4) by manipulating the pH.^[30] Initially, macrocycle **6** is suitable to bind cations such as ammonium or transition-metal cations, owing to the stabilization of the positive charge(s) of cations by electron-rich donor atoms (N and O). Lowering the pH value of **6** in solution results in the protonation of the bridgehead nitrogen atoms such that the protonated macrocycle $[6 \cdot 4H]^{4+}$ becomes a receptor for anions (e.g. Cl^-),^[31] thereby stabilized by the ion–ion interactions and hydrogen bonds with the N^+H moieties. Complete reversible switching from the anion receptor $[6 \cdot 4H]^{4+}$ to the cation receptor **6** is feasible upon

base addition. Noticeably, the binding affinity between the macrocycle and the ions requires mixing and matching in terms of the cavity volume, chain flexibility, and number of donor atoms of the macrocycle as well as the ionic radius of the ion. Therefore, the pH-controllable selectivity of a specific cation or anion towards a macrocyclic receptor can be fine-tuned by a proper structural design of the macrocycle.

This strategy has been employed (Figure 5) to construct a multifunctional receptor—tripodal amine-capped benzo crown *p*-*tert*-butylcalix[4]arene **7**^[32]—suitable for the transition-metal cation binding, and with its protonated form $[7 \cdot 4H]^{4+}$ (for simultaneous cation and anion binding).^[33] For compound **7**, it

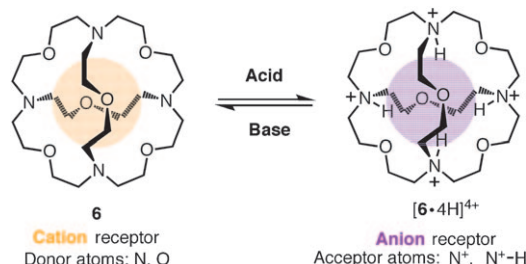


Figure 4. The interconversion of a cation receptor to an anion receptor in macrocycle **6** by acid and base.

is suitable to bind strongly to several first-row divalent transition-metal ions such as Co^{2+} , Ni^{2+} , Cu^{2+} , and Zn^{2+} , complementary to the receptor cavity volume with binding constants ($\log b$, 10 mM in MeOH, 298 K) 7.5, 7.0, 17.8, and 10.0, respectively. For $[7 \cdot 4H]^{4+}$, on the contrary, different types of anions such as spherical (F^- , Br^- , I^-), trigonal-planar (CO_3^{2-}), angular-planar (AsO_4^{3-}), and tetrahedral ($H_2PO_4^-$, HPO_4^{2-} , SO_4^{2-} , PO_4^{3-}) anions were tested for their binding affinities (with Na^+ or K^+ as the counteranion). However, only Br^- , I^- , and NO_3^- are screened out, without any precipitation or deprotonation when the anions are mixed with $[7 \cdot 4H]^{4+}$. The binding of these three anions towards $[7 \cdot 4H]^{4+}$ is observed by the upfield shift of the ammonium signal $RCH_2N^+H_2CH_2R$ at $\delta \approx 9.4$ to 9.8 ppm as well as slight peak shifts at the aromatic region at $\delta \approx 7.0$ –8.0 ppm from the 1H NMR spectra (in $CDCl_3/CD_3OD$). This observation indicates that the anion-encapsulated $[7 \cdot 4H]^{4+}$ is stabilized predominantly by the electrostatic interaction rather than hydrogen bonding. Moreover, a Job plot reveals

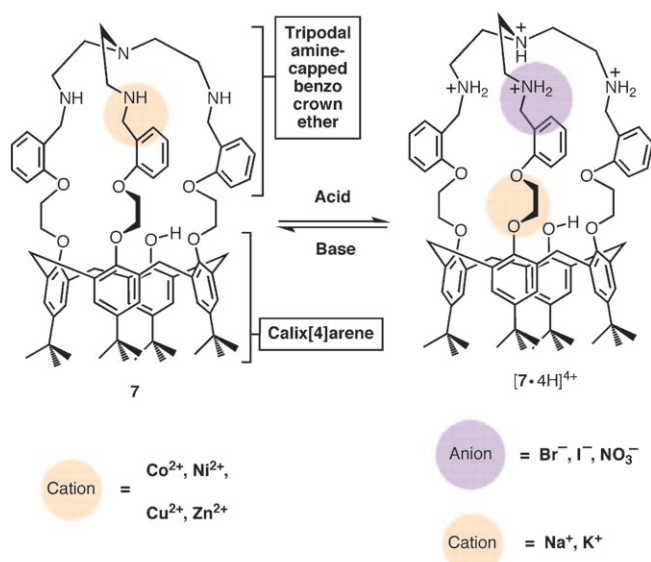


Figure 5. Tripodal amine-capped benzo crown *p*-*tert*-butylcalix[4]arene **7** suitable for transition-metal-cation binding and its protonated form $[7\cdot 4H]^{4+}$ for simultaneous cation and anion binding.

that the anion (Br^- , I^- , or NO_3^-) binds to $[7\cdot 4H]^{4+}$ in a 1:1 ratio with binding constants (K_{assoc}/M^{-1} , CD_3OD , 298 K) of 58.6, 77.2, and 190.2 respectively, with Na^+ as the counter-cation.

2.3. Hydrogen Bonding

As discussed earlier, ammonium ion has been widely used as a component to construct the pH-switchable supramolecular hosts. It is also well known that crown ethers such as [18]crown-6 and [24]crown-8 are ideal hosts for binding both with primary alkyl- and secondary alkyl-ammonium ions as a result of strong $[N^+-H\cdots O]$ and $[N^+C-H\cdots O]$ hydrogen-bonding interactions. These interactions can be destroyed simply by deprotonating the ammonium ion into an amine by various bases.^[34] Stoddart et al.^[35] have reported (Figure 6) an anthracene-containing amine **8** which can be self-assembled with the dibenzo[24]crown-8 (**DB24C8**, **9**) and the bis(*para*-phenylene)[34]crown-10 (**BPP34C10**, **10**) in 1:1 and 2:1 ratios, respectively, in the presence of acids such as TFA or TfOH. Both the solid-state crystal structures of $[8\cdot H\cdot DB24C8]^+$ and $[8_2\cdot 2H\cdot BPP34C10]^{2+}$ reveal that the ammonium protons and the α -methylene protons adjacent to the nitrogen atom

contribute to the hydrogen-bonding interactions with their corresponding crown ethers to give the [2]pseudorotaxane structures (see Section 3 for details on pseudorotaxane structures). For complex $[8_2\cdot 2H\cdot BPP34C10]^{2+}$, the two $[8\cdot H]^+$ threads are encircled by the ethylene glycol chains of the macrocycle **10**, where the anthracene groups of $[8\cdot H]^+$ are pointing in an opposite direction according to the solid-state crystal structure. The structural features after reversible switching are characterized by 1H NMR spectroscopy (in 6:1 $CDCl_3/CD_3CN$) by comparing the chemical shifts of the α -methylene protons adjacent to the nitrogen atom ($RCH_2N^+H_2CH_2R$) in compounds/complexes **8**, $[8\cdot H]^+$, $[8\cdot H\cdot DB24C8]^+$, and $[8_2\cdot 2H\cdot BPP34C10]^{2+}$. As an example, the chemical shifts (δ) of the α -methylene proton signals of $[8\cdot H\cdot DB24C8]^+$ are found at 5.4 and 5.2 ppm, while the proton signals of $[8\cdot H]^+$ are found at 5.1 and 4.3 ppm. After base treatment with quinuclidine, the proton signals of the resulting amine compound **8** shift to 4.5 and 4.0 ppm, indicating the dissociation between compounds **8** and **DB24C8**. Reprotonation of the system with TFA results in the observation of all original signals of the complex once again by 1H NMR spectroscopy, indicating the feasibility of the acid–base-controlled, reversible switching.

The $[8\cdot H\cdot DB24C8]^+$ system, moreover, exhibits photo-physical properties between the anthracene unit on the ammonium thread and the catechol unit on the **DB24C8** macrocycle. Upon excitation at 276 nm where most of the light is absorbed by the **DB24C8**, the **DB24C8** fluorescence ($\lambda_{\text{max}} = 312$ nm) is almost completely quenched while the fluorescence of $[8\cdot H]^+$ ($\lambda_{\text{max}} = 423$ nm) becomes much higher. This observation indicates that the fluorescent excited state of the **DB24C8** is deactivated by energy transfer to the lower-lying fluorescent excited state of the anthracene moiety of $[8\cdot H]^+$. As a consequence, this system can be regarded (Figure 6, the truth table) as a NOT logic gate^[36]

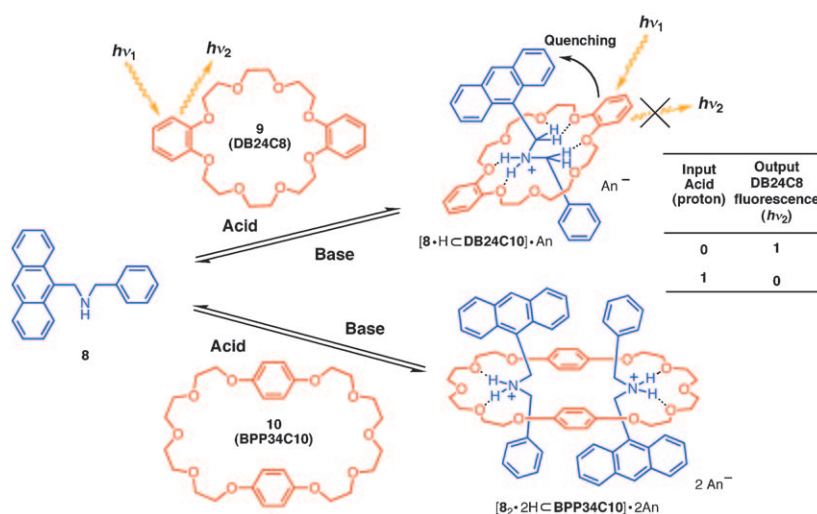


Figure 6. Acid–base reversible switching between macrocycles (**9** and **10**) and secondary dialkylamine **8** to form [2]pseudorotaxanes with photochemical properties and logic functions (note the truth table).

from which the acid (proton) serves as the input and the crown ether fluorescence serves as the output.

In addition, this type of pH-switchable, hydrogen-bonded supramolecular system based on ammonium and crown ether has been employed for the investigation of the assembling and disassembling properties in oligomers^[37] and polymers^[38,39] (Figure 7) by virtue of their strong binding affini-

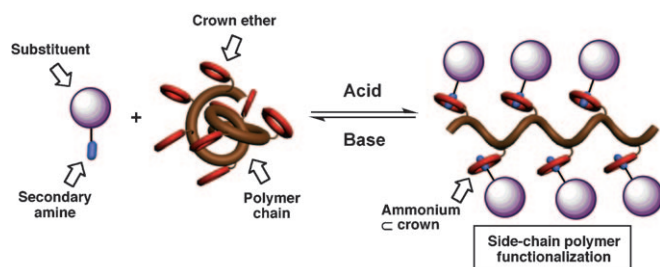


Figure 7. Graphical representation of acid–base-controllable side-chain polymer functionalization between a substituent bearing a secondary ammonium unit and a polymer chain bearing crown ether units.

ties. Depending on the substituents, the conformation (e.g. folding/unfolding, helix/linear chain) of the polymer chain can be switched simply by changing the pH in the solution.

In particular, Tang et al.^[40] have reported the feasibility of tuning the chain helicity^[41] and the organization morphology of an L-valine-containing polyacetylene **11** by pH changes (Figure 8). The pendant residue carboxylic acid and amide groups on the polyacetylene **11** possess multiple intra- or interchain hydrogen-bonding interactions to force the polyacetylene chains into helical strands, in which the polyacetylene helicity is monitored by circular dichroism spectroscopy. Obviously, the formation of the helical polymers is entropically unfavorable. However, this entropic cost can be

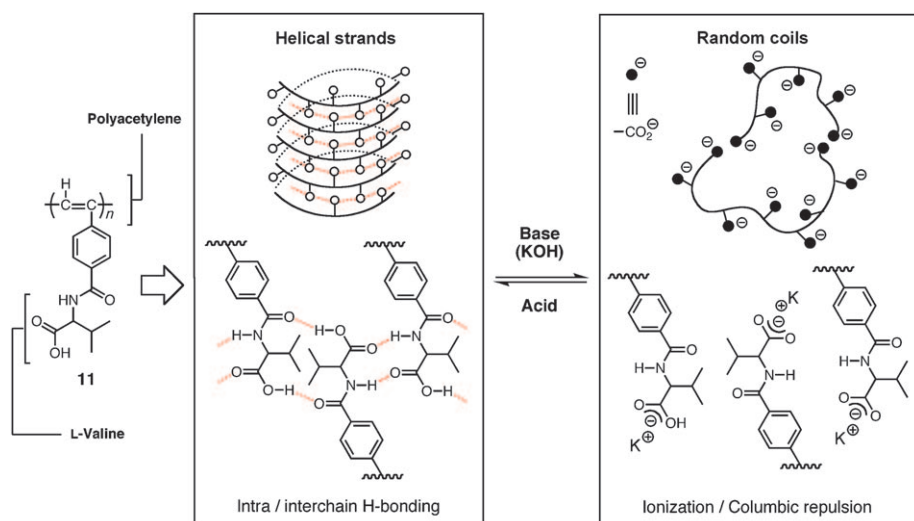


Figure 8. Helical-strand formation of L-valine-containing polyacetylene **11** with intra- or interchain hydrogen bonding. The switching of helical strands into random coils of polyacetylene **11** can be achieved by base (KOH) addition to disrupt the hydrogen bonding by ionization and charge–charge Coulombic repulsion.

compensated by the large enthalpic change from the multiple intra- or interchain hydrogen-bonding interactions. Upon the addition of KOH base (0 to 1.5 equivalents) to the helical polyacetylene **11** in methanol, the circular dichroism signals drop dramatically, indicating the collapse of the polyacetylene helicity with diminished hydrogen-bonding interactions by charge–charge Coulombic repulsion as well as the blocking effect of solvated methanol molecules on the resulting carboxylate ions. However, complete ionization/switching is not feasible because of the polymer effect in terms of the chain steric hindrance. Therefore, small fractions of carboxylic acid group may still remain intact and exist in un-ionized form in the polymer solution even in the presence of excess KOH. Additionally, atomic force microscopy (AFM) reveals that the polyacetylene **11** forms helical fiber bundles with average width of about 59 nm, while the base-treated polymers exist as single, randomly coiled polymer chains with an average width of about 2.4 nm.

Besides linear polymers, in addition, Meijer and Gibson et al.^[42] have reported (Figure 9) a pH-responsive dendrimer molecule decorated with crown ethers^[43] at the periphery. The skeleton of the system consists of a third-generation polypropylimine (PPI) dendrimer **12** and bis(*meta*-phenylene)[32]crown-10 (**BMP32C10**) at the periphery. Paraquat diol **13**·2PF₆ can be self-assembled to the **BMP32C10** to form supramolecular complex [**13**⊂**BMP32C10**]²⁺ with an association constant $K_{\text{assoc}} = 61 \pm 5 \text{ M}^{-1}$, which is stabilized crucially by [Ar–H⋯O] and [ArN⁺C–H⋯O] hydrogen bonds as well as ion–dipole and π – π stacking interactions. First, dendrimer **12** is titrated successively with paraquat diol **13**·2PF₆ to form polypseudorotaxane [**12**⊃**13**_{*n*}]²⁺ (*n* = 1–16). By analyzing the difference in chemical shifts during titration, the binding is determined to be negatively cooperative with an average binding constant $K_{\text{avg}} = 15 \pm 2 \text{ M}^{-1}$, which is less than that of [**13**⊂**BMP32C10**]²⁺. When imine-

containing dendrimer **12** is fully protonated with TFA to become [**12**·14H-TFA], the average binding constant (K_{avg}) between [**12**·14H-TFA] and **13**·2PF₆ to form polypseudorotaxane [**12**·14H-TFA⊃**13**_{*n*}]²⁺ (*n* = 1–16) is determined to be $70 \pm 8 \text{ M}^{-1}$, which is a 4.7-fold increase over that of [**12**⊃**13**_{*n*}]²⁺ ($K_{\text{avg}} = 15 \pm 2 \text{ M}^{-1}$). This pH-controllable switch may be due to the rigidification of the acidified iminium dendrimers [**12**·14H-TFA] for which the three-dimensional dendritic structure is forced electrostatically to adopt a near-spherical conformation that maximizes host binding with individual site isolation.

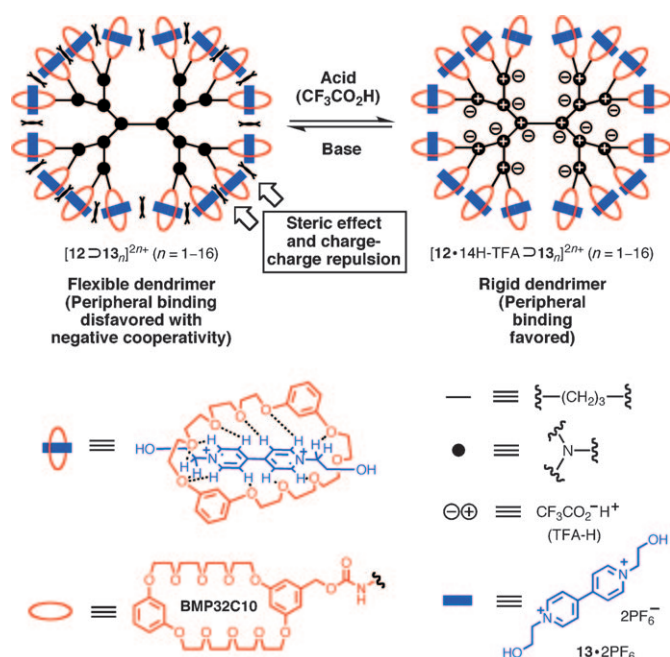


Figure 9. Graphical representation of pH-responsive dendrimer **12** self-assembling with paraquat derivative **13**²⁺ at the dendrimer's periphery with switchable cooperativity.

Last but not least, recognition between amides and phenoxy anions (Figure 10)^[44] is also a representative class of pH-switchable supramolecular system by forming the crucial

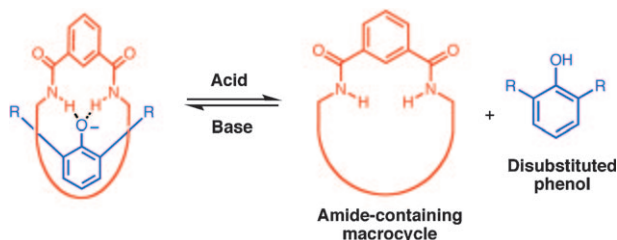


Figure 10. Graphical representation of a pH-responsive supramolecular system with amide-containing macrocycle and substituted phenolate (R = substituent) stabilized by [N-H...O[−]] hydrogen bonds.

[N-H...O[−]] hydrogen bonds. During the protonation of the phenoxy anion into phenol, the hydrogen-bonding interactions between the amide macrocycle and the phenol are diminished, leading to a reversible disassembly of the system. Other functional groups such as sulfoxide, nitron, phosphane oxide, and amide itself are excellent hydrogen-bond acceptors for the N-H bonds.

2.4. Aromatic π - π Interaction

Although π -electron-rich and π -electron-deficient donor-acceptor noncovalent bonding interactions have continued to play an important role in the synthesis of interlocked molecules (see Section 3) because of their high self-assembling

efficiencies, there are only a few examples^[45–47] of these donor-acceptor supramolecular systems that are responsive to pH changes. One example (Figure 11)^[45] involves the self-

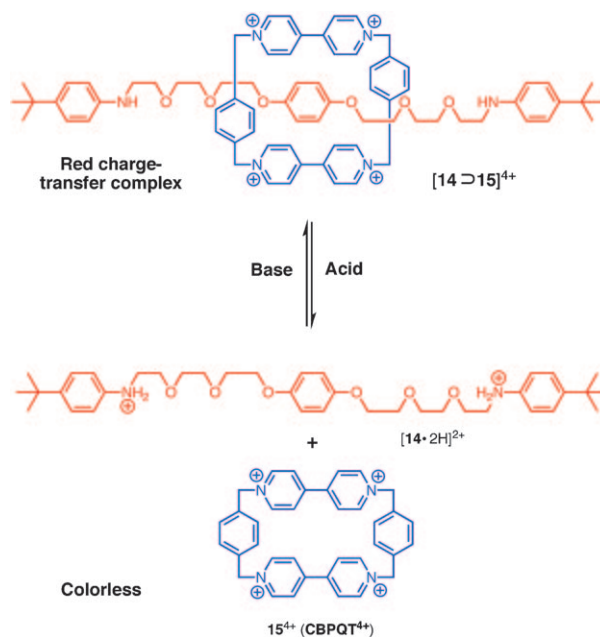


Figure 11. pH-Driven association and dissociation of π -electron-rich thread and π -electron-deficient macrocycle with color changes (red and colorless).

assembly between a π -electron-rich hydroquinone linked with triethylene glycol/4-*tert*-butylaniline units **14** as well as a π -electron-deficient macrocycle, namely cyclo(bis-paraquat-*para*-phenylene) tetracation (**15**⁴⁺, CBPQT⁴⁺). The 1:1 self-assembly of **14** and **15**⁴⁺ gives a red, charge-transferred complex of [2]pseudorotaxane [14 ⊃ 15]⁴⁺ with an association constant (K_{assoc}) of approximately 3000 M^{−1}, which is essentially stabilized by a combination of face-to-face π -stacking between the hydroquinone and the bipyridinium rings with an interplanar distance of about 3.4 Å. In fact, the flexible ethylene glycol units of **14** can be bent and wrapped around such that the aniline groups are also interacting with the pyridinium rings in **15**⁴⁺ with edge-to-face [C-H... π] interactions. In particular, the NMR signal of the hydroquinone protons shifts by $\delta = -3.80$ ppm on complexation and appears at $\delta \approx 3.0$ ppm in CD₃CN. When the red, charge-transferred complex [14 ⊃ 15]⁴⁺ is treated with 10 equivalents of TFA, the macrocycle **15**⁴⁺ is dissociated completely from the protonated thread [14 · 2H]²⁺ by electrostatic repulsion between the protonated anilines and **15**⁴⁺, yielding a colorless solution which is successfully characterized by ¹H NMR and UV/Vis spectroscopies. Detailed investigation by varying the amount of TFA indicates that the dissociation mechanism may involve the formation of intermediate complex [14 · H ⊃ 15]⁵⁺, which is partially stable in the presence of a certain amount of TFA. In addition, this type of donor-acceptor supramolecular system can act as an acid-base-controllable colorimetric switch.

Another example^[46] describes the formation of a donor–acceptor [2]pseudorotaxane complex with an electron-deficient dimethyldiazopyrenium and an electron-rich biphenyl-containing macrocycle. The assembly and disassembly of the complex can be controlled by competitive binding of the electron-deficient dimethyldiazopyrenium with an amine base (diethylamine), that is, addition of an amine base to the host–guest complex results in the formation of a new dimethyldiazopyrenium–amine complex, leading to the extraction of the free phenyl macrocyclic host.

Furthermore, the protonation and deprotonation of a pyridine moiety embedded in Pt-containing aromatic guests^[47] can also lead to the control of self-assembly and disassembly of neutral π -stacking molecular Pd tweezer by electrostatic interactions supplemented with weak metal–metal interactions.

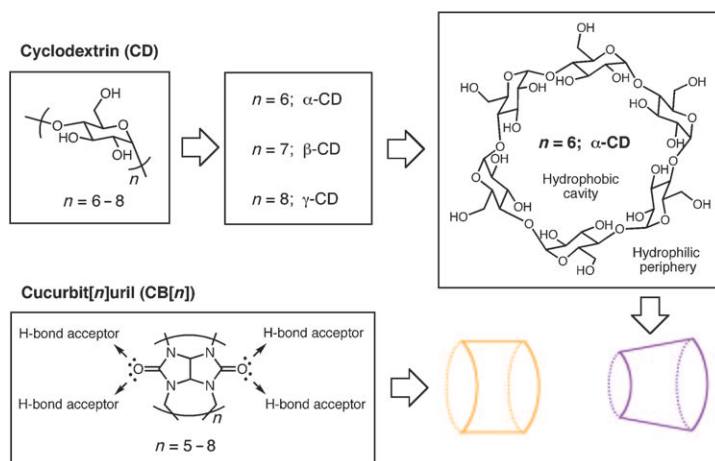


Figure 12. Structures and graphical representations of cyclodextrin (CD) and cucurbituril (CB).

2.5. Hydrophobic Effect

Rigid molecular hosts consist of a hydrophobic cavity and a hydrophilic periphery can facilitate the self-assembly with organic molecules to form inclusion complexes or pseudorotaxane structures in water, which are stabilized by van der Waals forces and π – π stacking interactions. This water-driven self-assembling process is governed by both enthalpic and entropic parameters. In particular, cyclodextrin (CD)^[11] and cucurbituril (CB)^[48] (Figure 12) are two representative macrocyclic hosts possessing excellent self-assembly with organic alkyl chains or aromatic compounds by hydrophobic effect in water.

It has been demonstrated^[11] that α -CDs ($n=6$) can be threaded efficiently with low-molecular-weight ($M_w=3000$ – $100\,000\text{ g mol}^{-1}$) polymers such as poly(ethylene glycol) (PEG), poly(dimethylsiloxane), poly(isobutylene), poly(ϵ -caprolactone), poly(lysine),^[49] poly(ethylenimine) (PEI),^[50] block copolymers PEI-*block*-PEG-*block*-PEI,^[51] and others. For amine-containing polymers poly(lysine) and PEI, the threading of CDs onto these polymer backbones can be controlled (Figure 13 A) by tuning the pH value ($8.5 < \text{pH} < 12.0$ for poly(lysine) and $9.0 < \text{pH} < 11.0$ for PEI) to afford the polypseudorotaxanes as precipitates in water. For $\text{pH} < 8.0$ and $\text{pH} > 12.0$, all the CDs are dethreaded from the polymer backbones by either the protonation of

amine groups on the polymer or the deprotonation of hydroxyl groups on the CDs, resulting in Coulombic repulsion. For the PEI-*block*-PEG-*block*-PEI copolymers threaded with CDs, acid treatment results (Figure 13 B) in the controllable dethreading of the CDs located at the exterior PEI blocks. However, the CDs threaded on the central PEG block remain self-assembled. The threading–dethreading processes of the CDs onto polymer backbones are character-

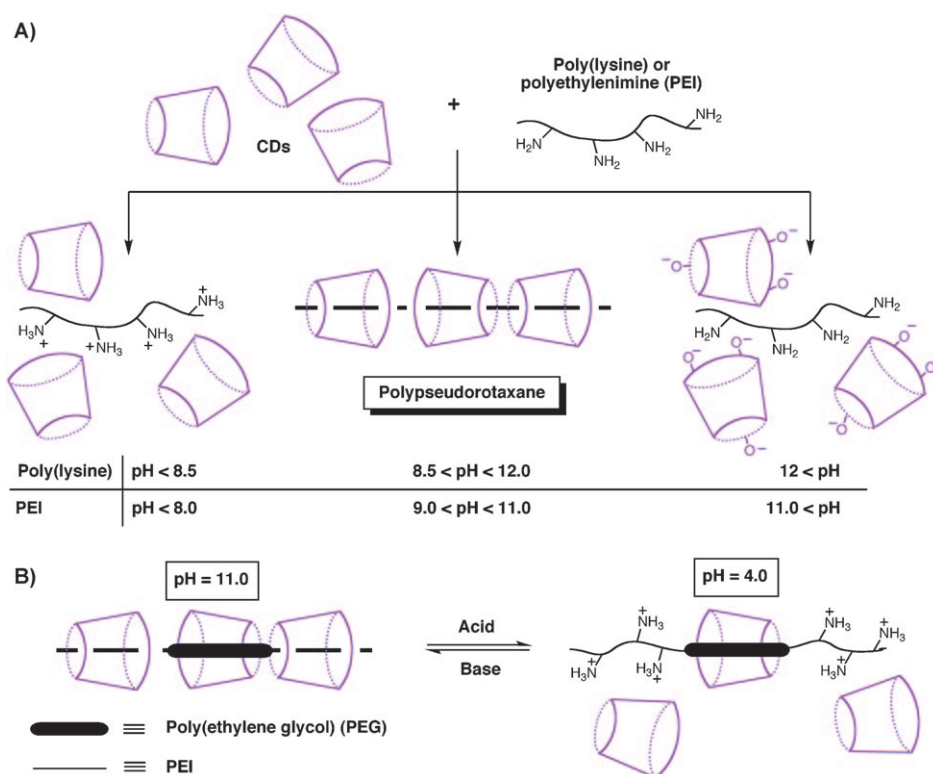


Figure 13. A) Controllable threading–dethreading of cyclodextrins (CDs) onto poly(lysine) and poly(ethylenimine) (PEI) at different pH values. B) Controllable threading–dethreading of CDs located at the exterior PEI blocks in the PEI-*block*-PEG-*block*-PEI copolymers.

ized by the significant changes from the shielding effect of protons, which can be observed by NMR and FTIR spectroscopies. X-ray diffraction (XRD) can also be employed for the characterization of any polypseudorotaxane crystalline structure. The threading–dethreading processes have been repeated for three times by alternating the pH of the system between 4.0 and 11.0. However, only about 85 % stoichiometric amount of the CDs can be threaded once again to the block copolymer backbone after the first deprotonation reaction starts from pH 4.0 to pH 11.0.

Recently, a pH-driven self-complexing switch has been constructed from a β -CD covalently conjugated with a pyridin-4-yl indolizine sidearm.^[52] At neutral state (pH 7), the pyridine-terminated sidearm self-complexes into the hydrophobic cavity of the β -CD. Subsequently, adjusting the pH of the complex to 3 with hydrochloric acid results in the protonation of the terminal pyridine group to become a pyridinium ion, leading to the dissociation of the sidearm from its β -CD cavity. Interestingly, the intrinsic fluorescent properties originating from the pyridin-4-yl indolizine sidearm can act as a probe to monitor the self-complexing and decomplexing processes.

On the other hand, pH-controllable threading–dethreading processes and the movement of macrocycles can also be observed in CBs threaded with organic alkyl chains bearing bis(ammonium)^[53] and amine^[54] moieties. In particular, CB[6]^[55] and CB[7] units^[56] can be threaded and assembled (Figure 14) onto a polymer bearing a bis(ammonium) triazole ring or 1,3-disubstituted phenyl ring, driven by hydrophobic effect as well as stabilized by $[C=O \cdots H-N^+]$ hydrogen bonds and ion–dipole interactions. Upon deprotonation of the bis(ammonium) unit by base, the noncovalent interactions are disrupted such that the CBs move to the neighboring alkyl or ethylene glycol chains. In another example involving a polymer threaded with both CB[7] and β -CD units (Figure 14B), the position of the β -CD remains unchanged and stays intact on the PEG block while the CB[7] can move along the polymer backbone upon acid–base reactions. Similarly, 1H NMR spectroscopy is employed to characterize the movement of CBs by monitoring the chemical shift of the prominent proton signal of the triazole ring in D_2O .

Recently, a one-pot guest swapping of β -CD and CB[6] hosts has been reported.^[57] The guests are adamantane-based hexyl secondary ammonium $[16-H]^+$ and adamantane-based hexyl dimethyl quaternary ammonium 17^+ . These guests are two-faced guests such that the hexyl ammonium favors the assembly with CB[6] while the adamantane group favors the assembly with β -CD (Figure 15). When a mixture containing the four components ($[16-H]^+$, 17^+ , β -CD, and

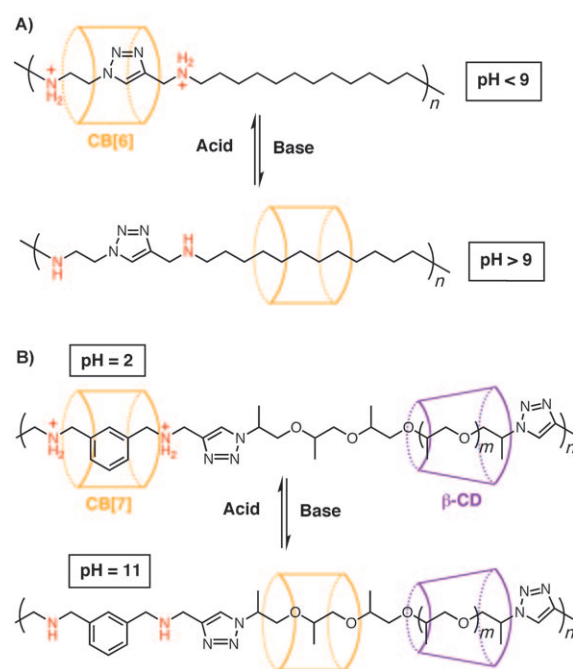


Figure 14. Acid–base-controlled movement of cucurbit[*n*]urils (CB[*n*]s) threaded on bis(ammonium)-containing polymer backbones.

CB[6]) in water at pH 7, supramolecular complexes $[CB[6] \supset 16-H]^+$ and $[\beta\text{-CD} \supset 17]^+$ coexist in the mixture. CB[6] favors $[16-H]^+$ over 17^+ in a 84:16 ratio. The CB unit^[6] binds more strongly with secondary ammonium $[16-H]^+$ than with 17^+ because of the complementary $[N^+ \cdots H \cdots O]$ hydrogen bonding and relatively stronger ion–dipole interaction. Upon adjusting the pH of the system to 13 with base, $[16-H]^+$ is deprotonated to **16**, thus reducing the binding affinity towards CB[6] and leading to the guest swapping with the existence of complexes $[CB[6] \supset 17]^+$ and $[\beta\text{-CD} \supset 16]$. NMR spectroscopy is used primarily to characterize the structural features after the swapping by monitoring the significant shift of the N^+CH_3 proton signals of 17^+ .

2.6. Miscellaneous Examples

Acid–base-controllable supramolecular self-assembly can furthermore lead to changes in microstructures, for example,

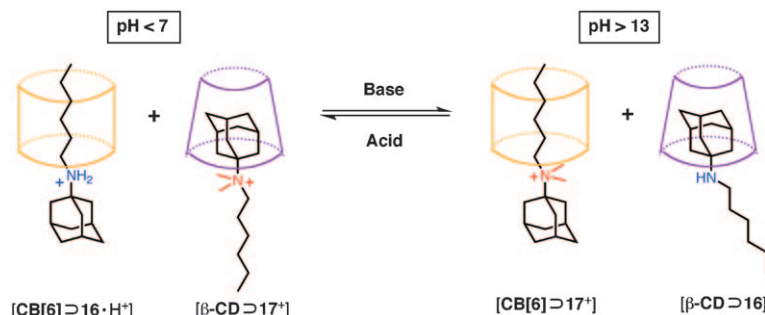


Figure 15. pH-Controlled guests ($[16-H]^+$, 17^+) swapping in CB[6] and β -CD hosts in one pot.

the reversible rodlike to tubular structural changes in phenylalanine-derived amphiphiles^[58] as well as the reversible soluble polymers to precipitate formation in calix[4]arene-based main-chain polymer capsules.^[59] Moreover, the crystal structures of molecules can be significantly altered by the treatment with acid or base.^[60] For applications in biological systems, pH-controllable supramolecular self-assembly can lead to the reversible anion and cation selectivity in rigid-rod β -barrel ion channels^[61] as well as the reversible operation of chiroptical switches between achiral molecules and DNA.^[62]

3. Interlocked Molecules

Interlocked molecules^[6a,63–67] consist of two or more components that are held together as a consequence of mechanical linking rather than by covalent bonds. Catenanes^[68–75] and rotaxanes^[76–87] are the archetypal examples of such mechanically interlocked compounds (Figure 16). Catenanes (from

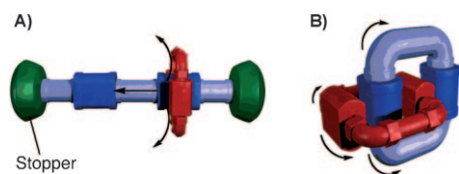


Figure 16. Graphical representation of a bistable A) rotaxane and B) catenane (blue: recognition site (station); red: macrocycle; green: bulky stopper). The arrows indicate the possible movement of the ring. In a rotaxane, end groups (stoppers) are used to prevent the ring from dethreading from the backbone.

the Latin *catena*, meaning “chain”) are composed of two or more mechanically interlocked macrocycles, whereas simple rotaxanes (from the Latin *rota* and *axis*, meaning “wheel” and “axle”, respectively) contain a linear dumbbell-shaped component—bearing bulky end groups or “stoppers”—around which one or more macrocycles are trapped. A pseudorotaxane is a supramolecular complex bound noncovalently between a macrocycle and a rodlike molecule without stoppers, such that the macrocycle can be dethreaded from the rodlike molecule by eliminating the noncovalent interactions. No longer esoteric curiosities, catenanes and rotaxanes are now being explored^[2b,d,f,i,88] as prototype molecular machines—an intriguing application that arises from the ability to control the relative translations of the interlocked compo-

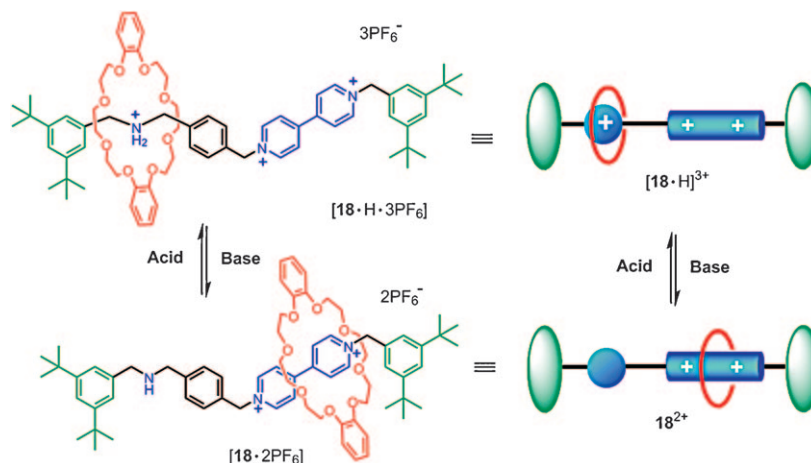


Figure 17. An acid–base-switchable shuttle $[18\cdot H\cdot 3PF_6]$. The **DB24C8** macrocycle (red) can be reversibly translocated between the secondary ammonium (N^+H_2) and 4,4'-bipyridinium ($bipy^{2+}$) stations (blue).

nents on different stations (recognition motifs) within any given molecular assembly.^[89] Molecular devices such as logic gates, switches, and shuttles are now a reality.

Figure 17 shows a representative example of acid–base-controllable molecular shuttle $[18\cdot H\cdot 3PF_6]$ based on a bistable [2]rotaxane structure.^[89b] It comprises a **DB24C8** ring mechanically interlocked with a dumbbell backbone bearing two different recognition sites—secondary dialkylammonium ($RCH_2N^+H_2CH_2R$) and 4,4'-bipyridinium ($bipy^{2+}$). Initially, the **DB24C8** ring resides exclusively on the dialkylammonium site by virtue of strong $[N^+H\cdots O]$ and $[C-H\cdots O]$ hydrogen bonds as well as π – π interactions. Addition of organic bases results in the deprotonation of the dialkylammonium unit of $[18\cdot H\cdot 3PF_6]$ into an amine and thereby expels the **DB24C8** ring to the $bipy^{2+}$ unit to obtain $[18\cdot 2PF_6]$, which is stabilized by ion–dipole interactions. To trigger the switching process, organic tertiary amines are ideal bases for the deprotonation of the dialkylammonium since they do not disrupt the chemical integrity of the $bipy^{2+}$ recognition site. The amine backbone can be reprotonated with TFA or triflic acid, leading to the ring movement from the $bipy^{2+}$ site to the reprotonated dialkylammonium site, owing to the difference in their binding affinities. However, the rate of **DB24C8** movement between the forward switching and the backward switching may be different because of the difference in their switching mechanisms. The structural features after acid–base-controllable switching can be characterized by 1H NMR spectroscopy (in CD_3COCD_3) with a significant downfield shift of NMR signal after the encirclement of the **DB24C8** toward a recognition site. Eventually, there is a significant change in chemical shifts of the methylene proton for $RCH_2N^+H_2CH_2R\subset DB24C8$ ($\delta \approx 4.8$ ppm), $RCH_2N^+H_2CH_2R$ ($\delta \approx 4.5$ ppm), and for RCH_2NHCH_2R ($\delta \approx 3.7$ ppm) after base deprotonation, which reveals the position of the **DB24C8** ring during the switching process. Recently, two types of acid–base-switchable [2]rotaxane have been developed based on this design by modifying 1) the $bipy^{2+}$ recognition site into 1,2-bis(pyridinium)ethane^[90] or

in the oligoethylene glycol,^[91] and 2) the **DB24C8** ring into an “oxygen-deficient” macrocycle.^[92]

Leigh and Keaveney^[93] have reported the pH-controllable shuttling of a hydrogen-bonded macrocycle on a rotaxane backbone through anion recognition. For the neutral rotaxane compound **19·H** (Figure 18), the rotaxane backbone

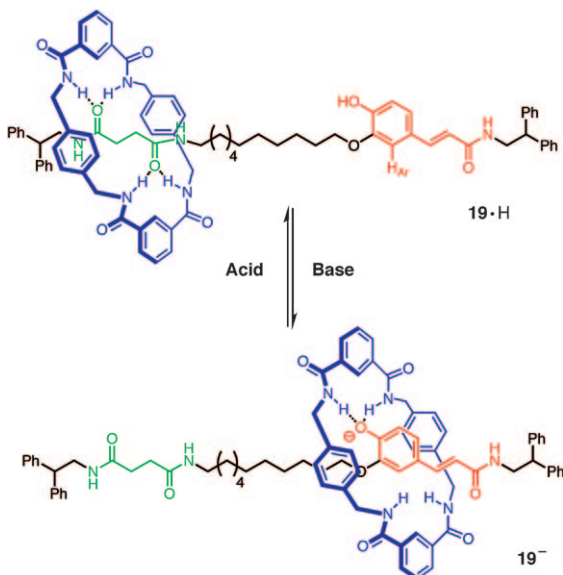


Figure 18. pH-Controllable shuttling of a hydrogen-bonded [2]rotaxane through anion recognition as a type of phenol–phenolate reversible formation.

consists of two molecular recognition units, namely the succinamide (green part) and the hydroxy cinnamamide (red part). Initially, the isophthalamide-containing macrocycle (blue part) resides preferentially on a succinamide unit rather than on a hydroxy cinnamamide unit, owing to the formation of more-stable amide–amide hydrogen bonds. Compared to the linear backbone (thread) without the macrocycle, the succinic methylene protons in **19·H** are shielded by $\delta > 1.2$ ppm, observed by ^1H NMR spectroscopy using a range of solvents (CDCl_3 , CD_2Cl_2 , CD_3CN , and N,N' -dimethylformamide ($[\text{D}_7]\text{DMF}$)). For the pH-controlled shuttling process of the macrocycle from succinamide to the hydroxy cinnamamide unit, various bases including LiOH , NaOH , KOH , CsOH , $n\text{Bu}_4\text{NOH}$, $t\text{BuOK}$, 1,8-diazabicycloundec-7-ene (DBU), and phosphazene P_1 can be used to deprotonate the phenolic proton present in the hydroxy cinnamamide unit to form anionic rotaxane **19[−]**. The signal of the proton H_{Ar} located over the phenolate anion is shifted by $\delta = -0.6$ ppm while the chemical shifts of the succinic methylene protons are unchanged compared to the deprotonated thread anion. This indicates that the macrocycle resides on the phenolate unit. The shuttling process was proven to be reversible by reprotonation of the phenolate using TFA, which again confirmed the original structure by ^1H NMR spectroscopy. Moreover, such a pH-controllable shuttling process is not influenced by counteranion (Li^+ , Na^+ , K^+ ,

Cs^+ , and $n\text{Bu}_4\text{N}^+$) and counteranion (F^- , Cl^- , Br^- , I^- , NO_3^- , and AcO^-) effects.

Furthermore, the authors have investigated the solvent effects upon the anion-induced shuttling process. Interestingly, they found out that the degree of discrimination of the macrocycle for the phenolate unit over the succinamide unit is excellent in polar solvents $[\text{D}_7]\text{DMF}$, CD_3CN , and CD_3OD but not in less polar solvents CDCl_3 or CD_2Cl_2 . Normally, polar solvents disfavor hydrogen-bond formation because the polar solvent molecules can be binded competitively to the hydrogen-bond donor–acceptor sites and diminished the hydrogen-bonding affinity. However, the observed result arises presumably because when all the amide groups (succinamide and isophthalamide) are adequately solvated by the polar solvents, the phenolate anion can still provide a hydrogen-bonding site for one of the isophthalamide units on the macrocycle.

The consequence of using Stoddart's type of the acid–base-switchable [2]rotaxane shuttles (**18·H·3PF₆**), see also Figure 17) leads to the design and construction of a “molecular elevator” **20·3H⁺** (Figure 19A).^[94] In the trifurcated molecular compound **20·3H⁺**, three rotaxane backbones similar to **18·H⁺** are augmented to a trisubstituted benzene ring, such that a platform bearing three **DB24C8** units is interlocked with each of the ammonium unit of the rotaxane backbone. The platform interlocked with the three rotaxane arms can be switched upon pH changes to give **20⁶⁺**, leading to a nanoscale movement (ca. 0.7 nm) of the platform with an estimated 200 pN force generated during each acid–base-controlled switching. The acid–base switching of the molecular elevator has been tested reversibly for 10 times with the successive addition of stoichiometric amount of phosphazene base and TFA. UV/Vis absorption spectrosc-

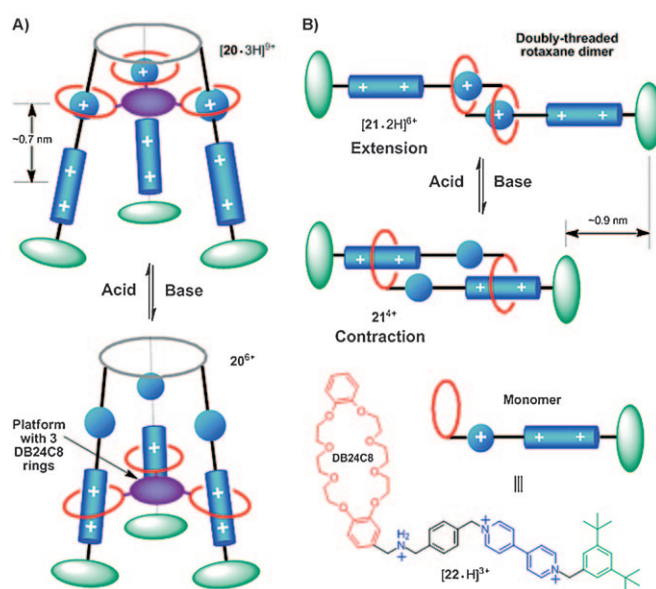


Figure 19. A) pH-driven molecular elevator containing a vertically movable platform. B) pH-Driven molecular muscle containing doubly threaded rotaxane dimer with extension/contraction movements.

copy was employed to monitor the change in absorbance at 310 nm during reversible switching, and there was only some loss of absorption signal observed in the first cycles, demonstrating the robustness and excellent reversibility of this class of molecular machine.

Furthermore, the acid–base-switchable [2]rotaxane shuttle bearing **DB24C8**, dialkylammonium, and bipy²⁺ ([**18**·H·3PF₆], see also Figure 17) can be used as a prototype to produce a “molecular muscle” [**21**·2H]⁶⁺ (Figure 19B)^[95] based on doubly threaded rotaxanes^[2f,96] using monomers [**22**·H]³⁺. The doubly threaded rotaxane or namely a [c2]daisy chain topology is identified wherein two mechanically interlocked filaments can glide along one another through the terminal **DB24C8** rings and in which the end of each filament is attached to a bulky stopper to prevent dethreading of the rings.^[97] In this Janus-type molecule [**21**·2H]⁶⁺, the two **DB24C8** rings move between the dialkylammonium and bipy²⁺ recognition sites under acid–base control, conferring upon the molecule’s overall expansion ([**21**·2H]⁶⁺)/contraction (**21**⁴⁺) behavior (difference in distance ca. 0.9 nm), reminiscent of the action of a muscle.^[95] Similarly, the structural features after the acid–base switching using TFA and phosphazene base were characterized using ¹H NMR and UV/Vis spectroscopies by observing the changes in the characteristic ammonium proton and methylene proton (RCH₂N⁺H₂CH₂R<**DB24C8**) signals and the absorbances.

It has been demonstrated that the pH-controllable switches are useful prototypes for the construction of complex supramolecular systems and functional molecular machines.^[2] However, molecular switches and operational molecular machines will be beneficial by immobilizing them on solid supports such as nanoparticles, flat metal surfaces, or microfluidic devices to overcome the Brownian motion in solution and to bring about order with specific patterns.

4. Multicomponent Supramolecular Systems

In the previous section, we discussed that mechanically interlocked molecules have been studied extensively for the ability of the interlocked ring to be switched on demand by pH changes with acid and base. Coupled with their ability to be customized and optimized for nanoscale functions, these interlocked molecules are excellent candidates as movable elements in the construction of a nanovalves^[98] based on a solid-phase support, for example, mesoporous silica—as a reservoir to incorporate molecules. Mesoporous silica MCM-41 consists of roughly spherical silica particles with an average diameter of 500 nm as verified by scanning electron microscope (SEM) which are templated by cetyltrimethylammonium bromide to produce pores with a diameter of 1.5–2.0 nm. Owing to its robust reactivity, the silanol group on mesoporous silica is effectively utilized to tether interlocked molecules and other nanovalve components, thus enabling the complete construction of a molecular valve. In the context of movable elements, the interlocked molecules

consist of two parts: ring and stalk (Figure 20). In its threaded form, the ring bonds noncovalently to the stalk at a recognition site. Using a proper stimulus to reduce or eliminate

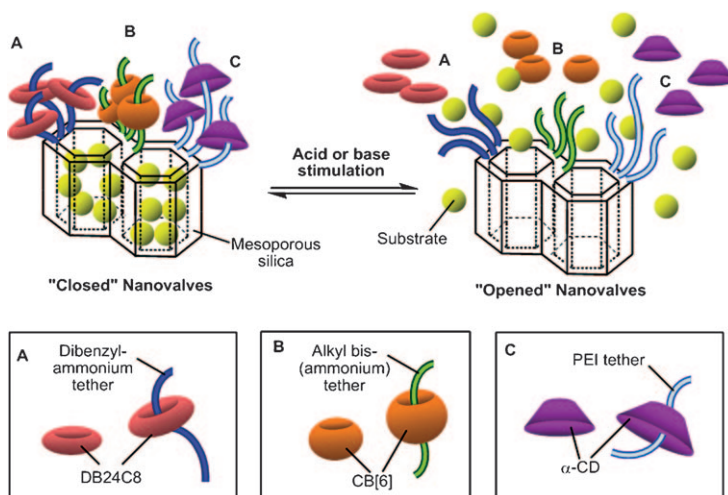


Figure 20. pH-Controlled substrate release in mesoporous silica with pseudorotaxane-based nanovalves: A) [**DB24C8** > dibenzylammonium]; B) [**CB[6]** > alkyl bis(ammonium)]; C) [α -CD > PEI]. The macrocycles threaded onto specific tethers are used to block the passageway, leading to the trapping of substrates. Acid or base stimulation can trigger the controlled release of trapped substrates by disrupting the noncovalent interactions between macrocycles and tethers.

the noncovalent binding, the ring dethreads from the stalk.^[99] The nanoscale passageways that contain trapped molecules and provide a platform for interlocked molecules are prepared by the surfactant-directed self-assembly to yield ordered hexagonal arrays of channels in sol–gel-derived silica.^[100]

A hydrogen-bonded supramolecular system based on the **DB24C8**/dialkylammonium ion pseudorotaxane (see also Figure 6) and functioning as the moving parts of nanovalves (Figure 20 A) meets the requirement of a pH-responsive nanovalve.^[101,102] Abstraction of protons from the dialkylammonium moieties by action of a base (such as triethylamine) switches off the hydrogen bonds between the dialkylammonium ions and the **DB24C8** rings, leading to dissociation of the rings and opening of the nanovalves. The functioning of the nanovalves depends on whether the moving parts can block the trapped molecules from leaking out when the nanovalves are closed and on the efficiency of their movement away from the pores to release the trapped molecules. A range of bases with different basicities and structural properties including hexamethylphosphorous triamide (HMPT), *N,N'*-diisopropylethylamine (DIPEA), and triethylamine is employed to effect the controlled release of coumarin 460. The half-life (*t*_{1/2}) is defined as the time the system takes to release half of the content characterized by the increase of coumarin’s fluorescent signal at 503 nm. For HMPT-triggered release, *t*_{1/2} is 450 ± 30 s. The *t*_{1/2} value for DIPEA-activated release is 300 ± 30 s. With triethylamine as base, the *t*_{1/2} value decreases further to 100 ± 20 s. Compar-

ing the three organic bases, the controlled release—according to the deprotonation mechanism—is governed by the basicity and the steric hindrance of the bases employed. DIPEA and triethylamine have similar basicities, as reflected by their pK_a values (9.0 and 8.5, respectively) in DMSO. The rate of release using DIPEA is lower than that when using triethylamine. This result indicates that the bulkier DIPEA—despite being the stronger base—deprotonates the complex tethered to the silica particles more slowly, thus affecting the rate of operation of the nanovalves. When a bulkier and weaker base (HMPT) is used, the rate of release is even slower. The variation of the bases having different steric properties and basicities is manifested in the three different release rates such that triethylamine > DIPEA > HMPT.^[101,102]

Moreover, supramolecular systems based on hydrophobic effect and ion–dipole interaction were employed to construct pH-responsive nanovalves on mesoporous silica for controlled substrate release. These systems, which can be operated under physiological conditions, utilize water-soluble, low-toxicity CD^[11] and CB[6]^[48] as the host molecules for trapping of a variety of linear hydrophobic compounds (see Section 2.5). By way of recent examples, [α -CD $\supset$ PEI] or [CB[6] $\supset$ alkyl bis(ammonium)] pseudorotaxanes (see also Figures 13 and 14) are linked successfully to the surface of mesoporous silica,^[103,104] affording biocompatible nanovalves for potential controlled drug release.

For the nanovalves utilizing [α -CD $\supset$ PEI] pseudopolyrotaxane as the stalks with loaded calcein substrates inside the orifice of mesoporous silica in a phosphate-buffered saline (PBS) solution, lowering the pH value from 11 to 5.5 in the system leads to the protonation of the PEI amines into the ammonium ions (Figure 20C). This process results in the dissociation of the α -CDs from the protonated PEI chains by Coulombic repulsion, leading to the release of calcein as detected by the increasing signal from fluorescence spectroscopy monitored at 520 nm (maximum fluorescent wavelength of calcein).^[103] On the other hand, for the nanovalves utilizing [CB[6] $\supset$ alkyl bis(ammonium)] pseudorotaxane as the stalks with loaded rhodamine B substrates inside the orifice of mesoporous silica in aqueous hydrochloric acid solution, increasing the pH to 10 by adding aqueous NaOH solution to the system leads to the deprotonation of the alkyl bis(ammonium) ions into the corresponding bis(amine) (Figure 20B). This process results in the dissociation of the CB[6] units from the deprotonated stalks by disrupting the ion–dipole interactions, leading to the release of rhodamine B as detected by the rapidly increased signal from real-time fluorescence spectroscopy monitored at 578 nm.^[104]

The pH-controlled release of trapped substrates in mesoporous silica^[105] is not only limited to the interlocked molecule-based nanovalves, but others involving polyamines^[106] or carboxylic acids^[107] can also act as the gate molecules to control the substrate release upon pH changes. For polyamines as the stalks in one nanovalve system,^[106] approximately 30 polyamine chains are attached to the nanopore orifice (Figure 21A). The protonated polyamines (polyam-

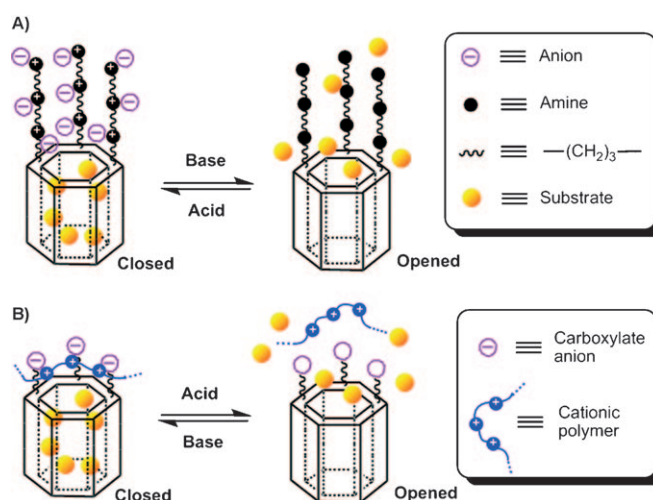


Figure 21. pH-Driven nanovalves on mesoporous silica. The bulky anion-polyammonium tethers (A) and the cationic polymer-carboxylate tether (B) are reversibly functionalizable to trap the substrates by steric hindrance. Addition of acid or base disrupts the electrostatic interactions of the stalks, thus inducing a controlled release of substrates.

monium) at pH 3 with sulfate or other anions (Cl^- , PO_4^- , ClO_4^- , or adenosine-5'-triphosphate (ATP^{2-})) result in shielding of the nanopores with trapped squaraine substrates or ruthenium complexes to obtain “closed” nanovalves. Increasing the pH value of the closed nanovalves to 6 leads to the deprotonation of polyammonium and thus the detachment of bulky anions from the stalks, thereby leading to the release of substrates. The rate of release can be controlled at different pH values. The bulkiness of different anions has drastic effects on the nanopore’s shielding efficacy in obtaining tightly “closed” nanovalves as well as the rate of controlled substrate release.

On the other hand, another nanovalve system^[107] involves multiple electrostatic interactions between carboxylate stalks and cationic polymers (poly(dimethyldiallylammonium chloride), PDDA) at pH 6.5 to block the nanoscale passageway, forming a “closed” nanovalve (Figure 21B). Upon addition of acid, the carboxylate stalks are protonated into carboxylic acid, which lowers the binding affinity of PDDA to the stalks and thus induces a controlled substrate (vancomycin) release. At pH 2.0, the release rate is fast with 90 wt % substrate released within 30 min. Noticeably, the employed mesoporous silica material is SBA-15 silica rod with a narrow pore size distribution (7.2 nm), which is large enough to contain ample functional molecules within the nanopores.

Conclusions and Perspectives

In conclusion, selected pH-responsive supramolecular systems can be switched by a variety of acids (trifluoroacetic acid, triflic acid, or hydrochloric acid) and bases (tertiary amine, secondary amine, hydroxide, butoxide, amidine, or phosphazene) on demand. These recent examples demon-

strate the ability of acid–base changes to facilitate the control of molecular and polymeric structural conformations (motion, movement) as well as the flow regulation in nanovalves—and these represent only the tip of the iceberg. Thus far, an increasing number of fascinating supramolecular molecular systems have been designed and synthesized^[108] for potential or practical use in molecular electronics, sensors, and drug delivery applications. However, one concern is the waste salts generated after each acid–base neutralization reaction. The accumulation of the salts after several switching processes in solution will eventually affect the supramolecular complexation and the characterization of resulting superstructures. To this end, the drawback can be solved by immobilizing the desired supramolecular systems onto solid-phase supports, flat metal surfaces, or fluidic devices, featuring washing processes with clean solvents for waste salt disposal, thus for continuous reversible switching. In one significant instance, the organization of desired pH-responsive supramolecular systems has emerged in the fabrication of useful devices for both electronic and biological applications.

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