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ARTICLE

Orthogonal switching of self-sorting processes in a stimuli-responsive library of cucurbit[8]uril complexes†

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The self-sorting processes in dynamic libraries of cucurbit[8]uril complexes can be switched in an orthogonal way by external stimuli. Protonated phenylpyridine guests form a 2:1 homo-ternary π-donor-π-acceptor complex, while deprotonation makes it a partner for ethylviologen in a 1:1:1 heteroternary complex. Reduction of the viologen instead generates 2:1 homoternary complexes of viologen radical-cation.

To construct functional (supra)molecular devices,[1] supramolecular chemistry adopted many concepts that also control the form and function of living systems such as molecular recognition,[2] templation,[3] self-assembly,[4] self-sorting,[5] and multivalency.[6] With these concepts of supramolecular synthesis, complex structures can be accomplished from simple programmed building blocks through a bottom-up design strategy.[7]

Cucurbit[8]uril **Q** as a macrocyclic host forms homo- and heteroternary complexes with various aromatic guests[8] – e.g. with two viologen cation-radicals[9] or with an electron-poor guest such as a viologen dication and an electron-rich guest like dihydroxynaphthalene,[10] respectively. It is thus a good example for a host capable to induce self-sorting in complex mixtures by selecting either two identical copies of the same guest or two different guests that match with respect to their electronic features.[9-11] Beyond the mere self-sorting itself, being able to switch the self-sorting processes with different external and reversible stimuli provides control over the self-sorting processes.[12] Tuning the stimuli-responsiveness of these supramolecular switches in aqueous environment attracted significant interest over the last decades[13] (including cascades with a series of sequentially added stimuli[14]). However, a major limitation is the combination of multiple stimuli to obtain orthogonal control and thus more complex behaviour of the chemical system. Kim and co-workers reported a three-way supramolecular switch composed of viologen and tetrathiafulvalene, based on the redox-controlled, highly selective interconversion between hetero- and homo-guest pairs.[15] Scherman et al. used redox-switchable viologen in combination with a photo-responsive azobenzene derivative as the second binding partner.[13c, 16] Reduction of the system results in a redox-driven homoternary complex and photoexcitation in a light-driven "uncomplexed" state.

Herein, we report a novel supramolecular system which includes ternary complexes in every state. The self-sorting network is based on cucurbit[8]uril, which complexes the pH-responsive phenylpyridine derivative **P**, redox-responsive viologen $\mathbf{V^{2+}}$ and a neutral, electron-rich naphthalene derivative **N** as the guests in water (Scheme 1).

The distinct feature of monocationic 4-phenylpyridinium derivatives is the formation of 2:1 homoternary complexes.[17] If this holds also true for protonated rather than methylated 4-phenylpyridinium, switching between a charged and a neutral state becomes possible by (de)protonation. Consequently, this guest becomes controllable by external stimuli. Scheme 1 summarizes the work presented here: All compounds used, the external stimuli, and the complexes formed in the present work including previously described complexes[9-11] and the orthogonal switching of self-sorting processes are shown.

Figure 1 shows ^{1}H NMR spectra of neutral **P** (a), protonated $\mathbf{PH^+}$ (b), and the 2:1 complex $\mathbf{(PH^+)_2@Q}$ (c) in D_2O (for detailed signal assignments, see Fig. S5; ESI†). The complex exhibits a well-defined, somewhat broadened set of signals with significant complexation-induced signal shifts in agreement with those reported for the methylated analogue.[18] Upon deprotonation, the signals of the free guest **P** are observed (Fig. 1d) suggesting the complete dissociation of $\mathbf{(PH^+)_2@Q}$.

The switching can also be observed by UV/Vis spectroscopy and is fully reversible over several cycles (Fig. S6; ESI†). Compound **P** is not fluorescent, but $\mathbf{PH^+}$ features a blue emission at 418 nm upon excitation at 366 nm. The corresponding cucurbituril complex $\mathbf{(PH^+)_2@Q}$ exhibits a

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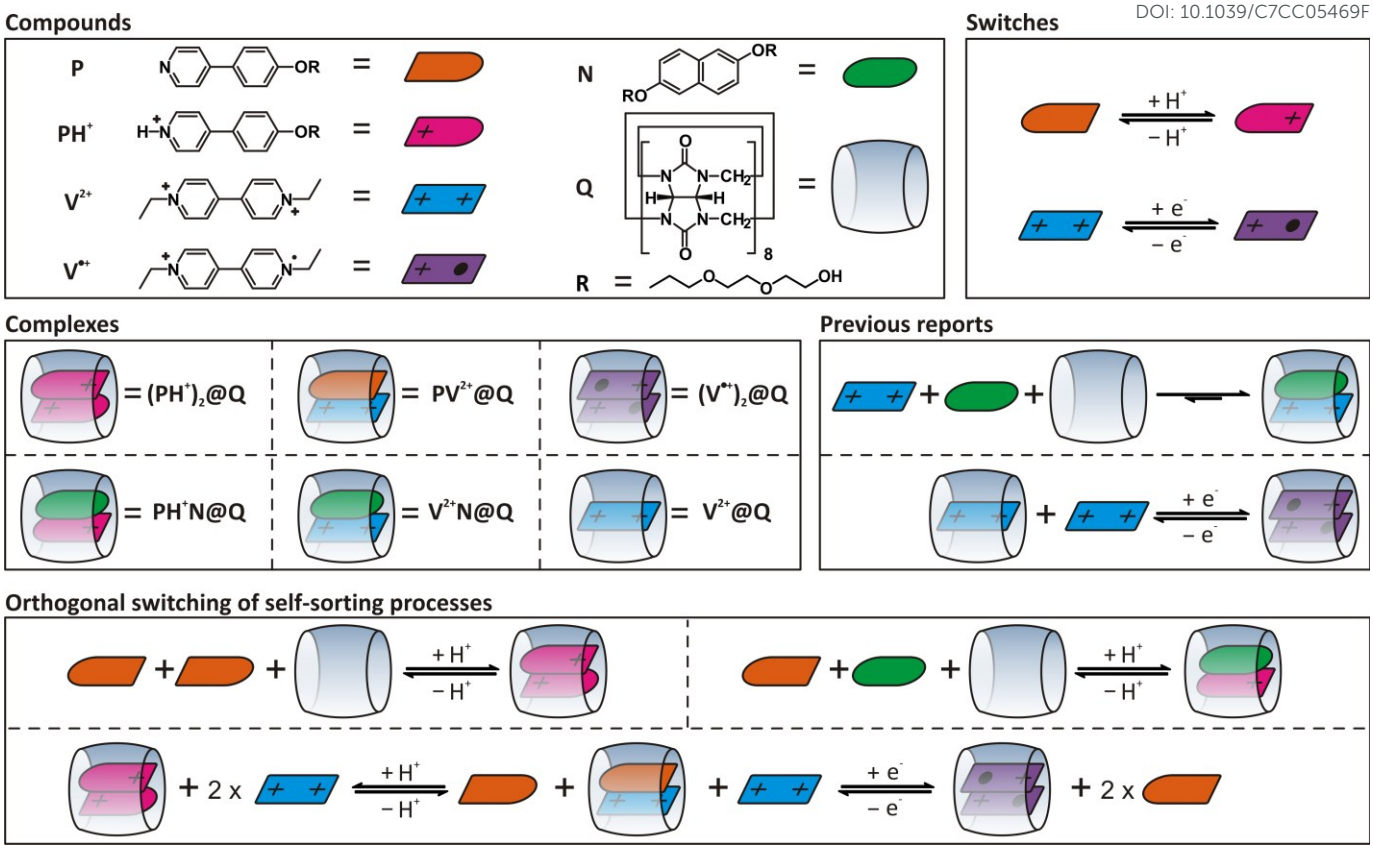

Scheme 1 Top left: Cucurbit[8]uril as the host and the guests used in this study together with the cartoons used to represent them; top right: (De)protonation of 4-phenylpyridine **P** and reduction/oxidation of ethyl viologen $\mathbf{V^{2+}}$ as the two orthogonal external stimuli. Middle left: Complexes that form; middle right: Previously reported complexes.[9-11] Bottom: Stimuli-responsive self-sorting processes.

fluorescence red shift to 439 nm with a remarkable increase in emission (Fig. S7 ESI†), which is in line with literature for similar phenylpyridinium derivatives.[18] The equilibrium association constants for the $\mathbf{(PH^+)_2@Q}$ complex as determined by isothermal titration calorimetry (ITC) are K_1 = 1.66 x 10^7 M^{-1}, K_2 = 0.97 x 10^5 M^{-1} and $K_1 \times K_2$ = 1.61 x 10^{12} M^{-2} (Fig. S8; ESI†) and agree well with those of the methylated analogue.[18] Complex $\mathbf{(PH^+)_2@Q}$ is also detected at *m/z* 969 (Fig. S9, ESI†) in the ESI mass spectra. However, this signal is not very intense as charge repulsion leads to quick fragmentation in the gas phase.

In analogy to the literature-known viologen-naphthalene dimer complex $\mathbf{V^{2+}N@Q}$,[10] a π-donor π-acceptor complex $\mathbf{PH^+}$-**N** forms in competition with $\mathbf{(PH^+)_2@Q}$. Figure 1 shows ^{1}H NMR spectra of the electron rich guest **N** (g) and the 3:1:2 mixture of $\mathbf{PH^+}$, **N** and **Q** in acidic medium (e) (for details, see Fig. S10, ESI†). Two sets of signals are observed, one for the $\mathbf{(PH^+)_2@Q}$ complex described above and a second one for $\mathbf{PH^+N@Q}$. The strong high-field shifts of the signals of **N** indicate its presence inside the cucurbituril cavity, where it experiences the anisotropy of the aromatic rings of **P** in close analogy to the known complex $\mathbf{V^{2+}N@Q}$ (Fig. S11, ESI†).

A confirmation of the formation of $\mathbf{PH^+N@Q}$ by ESI-MS is not possible because of the easy loss of the uncharged **N** during the ionization process. After deprotonation, the region of guest signals in the ^{1}H NMR spectrum (f) matches the superposition of the signals of the free guests (a,g), indicating the complete dissociation of $\mathbf{(PH^+)_2@Q}$ and $\mathbf{PH^+N@Q}$.

Figure 2 shows the ^{1}H NMR spectrum of a 2:1:1 mixture of $\mathbf{PH^+}$, $\mathbf{V^{2+}}$ and **Q** in acidic medium (c) (for details see Fig. S12, ESI†), which clearly is a superposition of the spectra of $\mathbf{V^{2+}}$ and

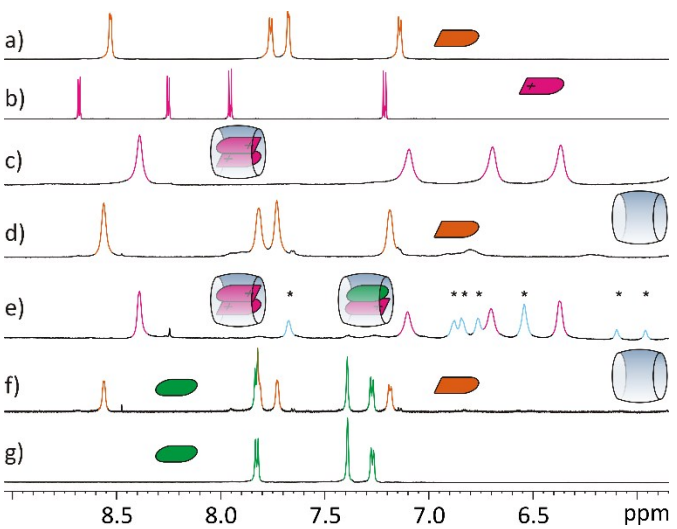

Fig. 1 Partial ^{1}H NMR spectra (700 MHz, 298 K, D_2O, 1.0 mM) of (a) **P**, (b) $\mathbf{PH^+}$, a 2:1 mixture of $\mathbf{PH^+}$ and **Q** (c) in acidic (pH 4) and (d) in basic (pH 10) medium, (e) a 3:1:2 mixture of $\mathbf{PH^+}$, **N** and **Q** in acidic medium (pH 4; asterisks mark the newly formed complex), (f) an equimolar mixture of $\mathbf{PH^+}$, **N** and **Q** in basic medium (pH 10), and (g) **N**; DCl (35% in D_2O) and K_2CO_3 were used to (de)protonate.

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$(PH^+)_2$@Q. This is in agreement with the binding constants determined for the possible complexes **$(PH^+)_2$@Q** and **V^{2+}@Q**, already the first binding constant of **PH^+** to **Q** (K_1 = 6.63 x 10^6 M^{-1}) is higher than that of **V^{2+}** to **Q** (K = 1.1 x 10^5 M^{-1})[9] by a factor of about 60. The ^{1}H NMR spectrum of the mixture after deprotonation of **PH^+** shows a new set of signals (d), indicating the formation of the 1:1:1 complex **PV^{2+}@Q**. The signal at 6.75 ppm can be attributed to two different protons of **P** and one set of signals of the viologen protons is broadened (see ^{1}H,^{1}H COSY NMR Fig. S13, ESI†). The formation of **PV^{2+}@Q** is also confirmed by its characteristic charge-transfer band at around 450 nm in the UV/Vis spectrum of the complex (Fig. S14, ESI†). Again, the switching is fully reversible upon protonation (Fig. S14, ESI†).

It is well known that viologen dications can be reduced to the corresponding radical cations, which tend to dimerize inside the cucurbituril cavity, yielding **$(V^{\bullet+})_2$@Q** (K_2 = 2.0 x 10^7 M^{-1}).[9] Formation of this complex is favoured over the charge-transfer complex **V^{2+}N@Q** (K_2 = 5.9 x 10^5 M^{-1}).[8, 11b] Consequently, it should be favoured over **PV^{2+}@Q** as well, considering the fact that **N** is more electron rich than **P.** This allows us to use redox chemistry as a stimulus in this system. The reduction potential of cucurbituril complex **V^{2+}@Q** ($E^1_{1/2}$ = -0.58 V) was determined by cyclic voltammetry (CV) (Fig. S15, ESI†). Neither the compounds **P** and **PH^+**, nor complex **$(PH^+)_2$@Q** are reduced under these conditions (Fig. S15, ESI†). When sodium dithionite is used for chemical reduction of viologen to its cation radical **$V^{\bullet+}$** the 2:1 complex **$(V^{\bullet+})_2$@Q** forms as clearly indicated by the typical absorption bands at 541 nm (Fig. 3a) and 982 nm (Fig. S16, ESI†). The same bands are observed when the literature-known charge-transfer complex **V^{2+}N@Q** and when independently prepared **PV^{2+}@Q** (Fig. 3b) are reduced. These results clearly indicate the formation of **$(V^{\bullet+})_2$@Q** in both cases together with the release of **N** or **P**, respectively.

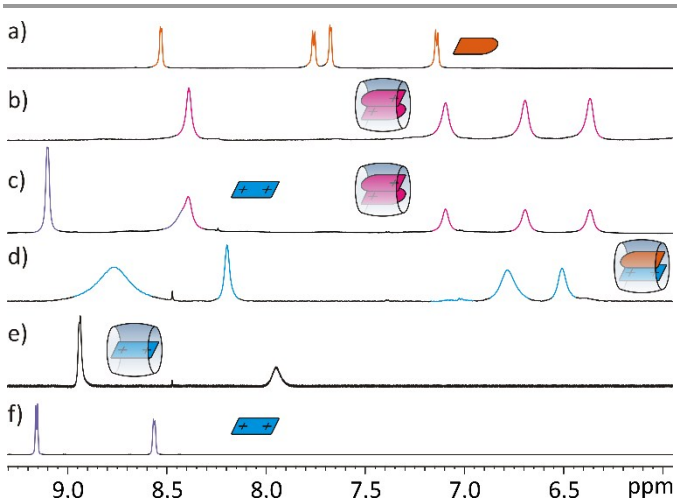


Fig. 2 Partial ^{1}H NMR Spectra (700 MHz, 298 K, D_2O, 1.0 mM) of (a) **P**, (b) a 2:1 mixture of **PH^+** and **Q** in acidic medium (pH 4), (c) a 2:1:1 mixture of **P**, **V^{2+}** and **Q** in acidic medium (pH 4), (d) an equimolar mixture of **P**, **V^{2+}** and **Q** in basic medium (pH 10), (e) an equimolar mixture of **V^{2+}** and **Q** forming **V^{2+}@Q**, and (f) **V^{2+}**; DCl (35% in D_2O) and K_2CO_3 were used to (de)protonate.

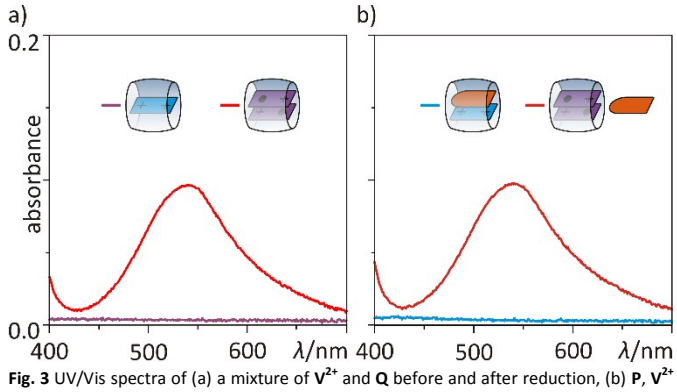
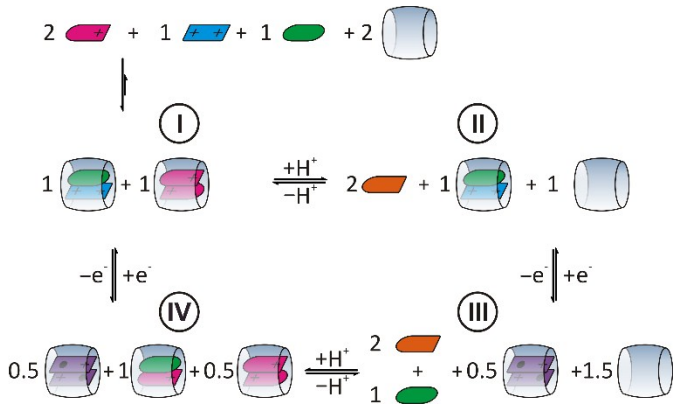


Fig. 3 UV/Vis spectra of (a) a mixture of **V^{2+}** and **Q** before and after reduction, (b) **P**, **V^{2+}** and **Q** before and after reduction with 10 equiv. $Na_2S_2O_4$ (24 μM **V^{2+}**); in both cases radical-cation dimer **$(V^{\bullet+})_2$@Q** forms after reduction.

Based on this simple library of complexes, a more complex four-step self-sorting network was designed (Scheme 2) which is responsive to redox and pH stimuli. The 2:1:1:2 mixture of **PH^+**, **V^{2+}**, **N** and **Q** contains the two complexes **$(PH^+)_2$@Q** and **V^{2+}N@Q** and corresponds to state **I**. The ^{1}H NMR spectrum is a superposition of the spectra of independently prepared complexes and is shown in figure 4(b) (for details see Fig. S17, ESI†). Deprotonation (d) gives state **II** with viologen-naphthalene complex **V^{2+}N@Q** still intact and the signals of free **P** indicate the complete dissociation of **$(PH^+)_2$@Q**. To avoid formation of **PV^{2+}@Q** a slight excess of **N** was used, thus resulting in a set of signals for free **N**. Subsequent reduction with $Na_2S_2O_4$ results in the distinct UV/Vis absorption spectrum (Fig. 4(g)) of complex **$(V^{\bullet+})_2$@Q** with the radical cation viologen dimer inside the cucurbituril cavity (blue line). **P** and **N** in the mixture are not affected by the reduction as shown by NMR experiments (Fig. S18, ESI†), so state **III** is obtained. The reduction of the viologen in acidic medium is possible, but subsequent reoxidation occurs rapidly. Hence, the solution of state **III** was prepared with just a slight excess of free protons (for procedure see Fig. S19, ESI†) and then reduced, giving the unique absorption maxima of **$(V^{\bullet+})_2$@Q** and therefore indicating state **IV** (red line). To demonstrate the pH switching of the system between the reduced states **III** and **IV**, the more oxidation stable state **III** was prepared and



Scheme 2 Four step self-sorting square with two switches based on pH and redox with state **I** to **IV**.

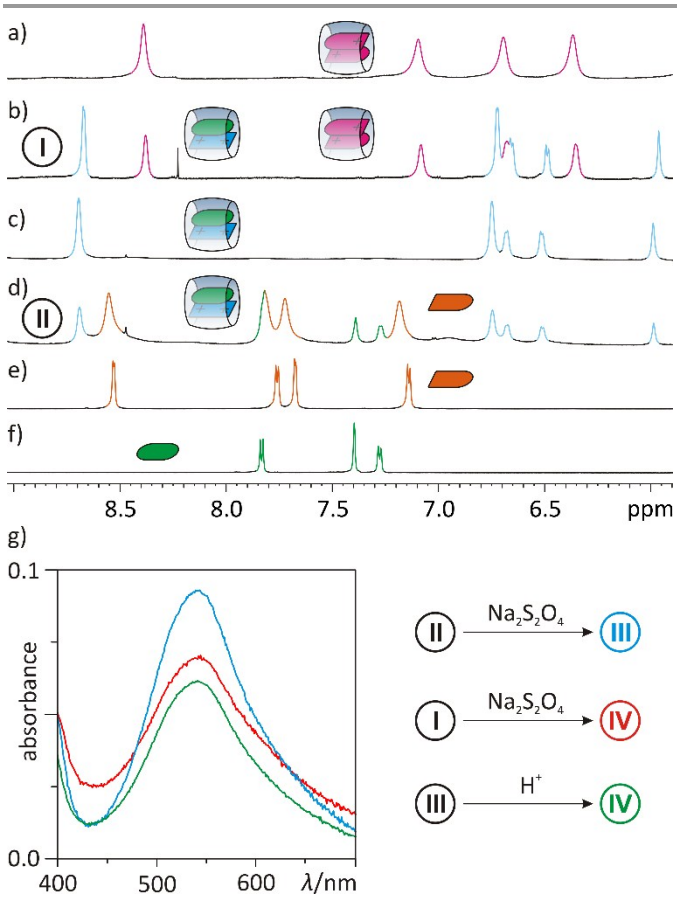


Fig. 4 Partial ^{1}H NMR spectra (700 MHz, 298 K, D_2O, 1.0 mM) of (a) **$(PH^+)_2$@Q**, (b) a 2:1:1:2 mixture of **PH^+**, **V^{2+}**, **N** and **Q**, (c) **PV^{2+}@Q**, (d) a 2:1:1:2 mixture of **P**, **V^{2+}**, **N** and **Q**, (e) **P**, (f) **N**; (a) and (b) pH 4, (d) and (e) pH 10; DCl (35% in D_2O) and K_2CO_3 were used to (de)protonate; and (g) UV/Vis spectra of state **III** derived from reduction of state **II** (blue), state **IV** derived from reduction of state **I** (red) and state **IV** derived from acidification of state **III** (green) (24 μM **V^{2+}**); reducing agent is $Na_2S_2O_4$.

acidified (green line). Complex **$(V^{\bullet+})_2$@Q** is still present under acidic conditions, but fast re-oxidation can be observed by consecutive measurements over the span of two minutes (Fig. S20, ESI†).

In conclusion, an orthogonally switchable self-sorting network consisting of **PH^+**, **V^{2+}**, **N** and **Q** was realized with pH and redox signals as the external stimuli. The new acid/base-sensitive guest **PH^+** can form the 2:1 complex **$(PH^+)_2$@Q**. In combination with the electron rich partner **N** it can form the π-donor-π-acceptor complex **PH^+N@Q**. In its deprotonated form, **P** can act as the electron rich counterpart to **V^{2+}**, forming π-donor-π-acceptor complex **PV^{2+}@Q**. Both compounds, **P** and **PH^+**, are electrochemical stable and, thus, allow an orthogonal redox-switching of **V^{2+}** generating **$(V^{\bullet+})_2$@Q**. This is the first example of a cucurbituril-based self-sorting system which is orthogonally switchable by pH and electrochemical inputs. The high tolerance of this system is shown with a simple fully controllable square network. This work is unique, as it is possible to switch its self-sorting behaviour between the three ternary cucurbituril complexes **$(PH^+)_2$@Q**, **PV^{2+}@Q** and **$(V^{\bullet+})_2$@Q**.

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