Switching a molecular shuttle on and off: simple, pH-controlled pseudorotaxanes based on cucurbit[7]uril†

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Cucurbit[7]uril, the wheel component in two new and structurally simple pseudorotaxanes, shuttles between the two axle termini at low pH, whereas the shuttling motion stops at higher pH, as the wheel is bound to the center of the axle.

The chemistry of interlocked molecules[1–6] has experienced a remarkable development in the last decade, as noncovalent forces have been utilized to effectively assemble rotaxanes, catenanes and other structures in which at least two molecular components are mechanically intertwined, without any covalent bonds between them. The relative positions of the two components may, in favorable instances, be controlled in reversible fashion through chemical (acid–base, ions), electrochemical or photochemical stimuli.[7] In particular, the use of bi-stable, switchable rotaxanes constitutes one of the more popular approaches in the long journey to develop molecule-based electronic devices.[8] Rotaxanes are interlocked molecules in which a macrocycle (the 'wheel') is threaded by a long 'axle' component. Wheel dissociation is prevented by bulky stopper groups at both ends of the axle. The mechanically locked wheel can thus move along the axle. In bi-stable, switchable rotaxanes, at least two different residues that can develop strong intermolecular interactions with the wheel are inserted on the axle, and the relative strength of their interactions with the wheel is controlled by external stimuli.[5–8] The resulting molecule exhibits at least two forms characterized by different positions of the wheel along the axle.

In this work, we show that two structurally simple dicationic compounds (see structures $\mathbf{1}^{2+}$ and $\mathbf{2}^{2+}$ in Fig. 1) form highly stable inclusion complexes with a macrocyclic host, giving rise to pseudorotaxanes that can be switched between two states with different shuttling properties. The axle component contains a central 4,4′-bipyridinium (viologen) aromatic subunit with two identical carboxylic acid-terminated, aliphatic N-substituents at both ends. The wheel is cucurbit[7]uril (CB7),[9,10] a macrocyclic host that can be readily prepared and isolated from the acid-catalyzed condensation of inexpensive starting materials (glycoluril and formaldehyde). The host–guest system reported here presents several innovations compared to the majority of reported rotaxanes. First, the structural simplicity of the axle component is remarkable. The bromide salts of dications $\mathbf{1}^{2+}$ and $\mathbf{2}^{2+}$ are easily prepared by reaction of commercially available 4,4′-bipyridine with the corresponding bromocarboxylic acid. Second, many viologens form very stable inclusion complexes with CB7, with association equilibrium constants (K) in the range 10^5–10^6 M^{-1} in aqueous solution.[11–14] The high stability of these complexes means that, if both components are present in solution concentrations above 0.5 mM, complexation is essentially quantitative, suggesting that bulky stoppers may not be required to keep the wheel around the axle. Third, the host–guest system is operational in aqueous media, a relatively rare feat for switchable rotaxanes, as most of them operate in organic solvents. Fourth, switching is anticipated to rely on the strong electrostatic repulsions between the cavity opening of CB7 (in which a rim of negative charge density accumulates due to the presence of seven carbonyl oxygens) and the anionic carboxylate at either end of the axle.[15,16] Thus, our expectation was that the main binding site for CB7 on the protonated axle will be one of the two aliphatic substituents,[17] while deprotonation will shift the CB7 to the viologen nucleus, in the geometric center of the molecule.

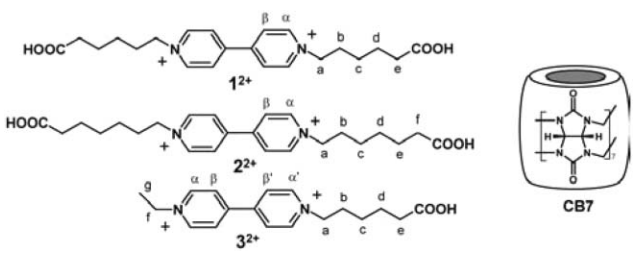

Fig. 1 Structures of the viologen guests (used as bromide salts) and the CB7 host.

We first investigated the host–guest interaction of $\mathbf{1}^{2+}$ with CB7 using ^{1}H NMR spectroscopy in 0.1 M NaCl–D_2O solution. Fig. 2 shows that the presence of 0.4 equiv. CB7 splits every aliphatic proton signal of the guest into two signals. This reveals that the chemical exchange rate between the free guest and the CB7-bound guest is slow in the NMR time scale. In the presence of 1.1 equiv. of CB7 this effect disappears, as only the complex resonances are observed. Further addition of host leads to the appearance of a new set of resonances, assigned to the 2 : 1 complex (containing two CB7 host molecules). The region of the spectrum corresponding to the aromatic protons (α and β protons on the viologen subunit) affords similar information. A very interesting aspect of the spectrum emerges in the presence of *ca.* 1 equiv. CB7 and relates to the observation of only two peaks for the aromatic viologen protons. This necessarily means that the CB7 host is undergoing fast exchange between all the available COOH-terminated aliphatic sidearms. Is this exchange predominantly intermolecular or intramolecular? In order to address this question

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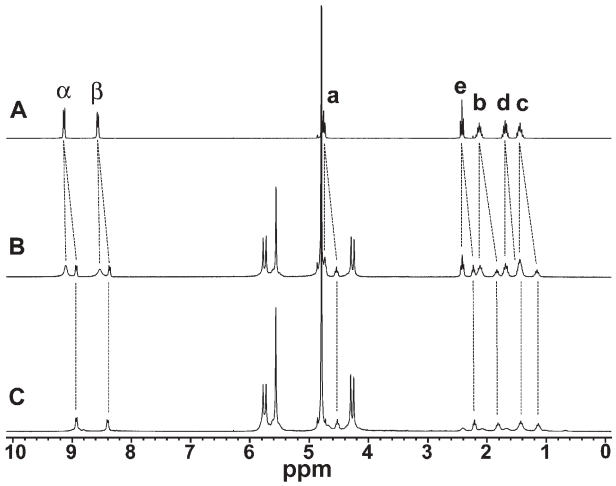


Fig. 2 ^{1}H NMR spectra (300 MHz, 0.1 M NaCl–D_2O, 23 °C) of $\mathbf{1}^{2+}$ (A) in the absence and in the presence of (B) 0.4 equiv. and (C) 1.1 equiv. CB7.

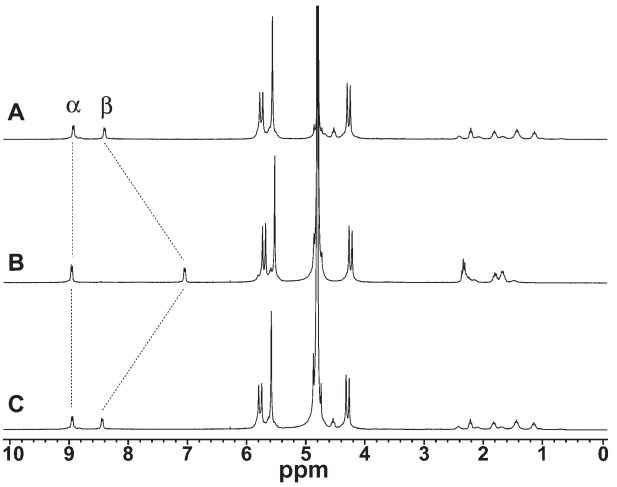


Fig. 3 ^{1}H NMR spectra (300 MHz, 0.1 M NaCl–D_2O, 23 °C) of the CB7·$\mathbf{1}^{2+}$ complex at (A) pH 2.6, (B) pH 7.6 and (C) pH 3.1. The solution pH was changed by addition of DCl or NaOD.

we performed a series of experiments varying the absolute concentrations of $\mathbf{1}^{2+}$ (0.92 to 5.52 mM) and CB7 and found no changes in the spectral patterns with samples containing a [CB7]/[$\mathbf{1}^{2+}$] ratio of 1.2 (see ESI†). These findings clearly suggest that the exchange is intramolecular, that is, the CB7 host is exchanging fast between the two sidearms of $\mathbf{1}^{2+}$, sliding over the viologen nucleus. This fast intramolecular exchange process averages out the differences between the two α aromatic protons, as well as those between the two β protons, leading to only two peaks for the aromatic protons of the viologen residue. This is an important finding regarding the dynamics of these host–guest complexes in aqueous solution. Once the CB7 is docked on one of the sidearm binding sites, it is kinetically easier for the macrocycle to jump through the viologen unit to the binding site on the other sidearm than it would be to undergo dissociation in order to find another binding site on the sidearm of a different dication. Indeed, this can be rationalized if one considers that the viologen unit offers considerable stability to the CB7 host,[11–14] whereas the negative charge density on the CB7 rim[15,16] works against the inclusion of the COOH groups by the host or even against the host sliding over them.

For comparison purposes we also investigated the binding interactions between the host CB7 and dication $\mathbf{3}^{2+}$, in which one of the COOH-terminated aliphatic sidearms is replaced by an ethyl group. In this case, fast intramolecular exchange of CB7 between the two sidearms is obviously impossible and this is reflected in the NMR spectrum (ESI†). In the presence of 0.5 equiv. of CB7 all the proton resonances of $\mathbf{3}^{2+}$ shift to higher field and this effect is even more pronounced upon addition of 1.1 equiv. CB7. This finding suggests that the intermolecular host exchange between the CB7·$\mathbf{3}^{2+}$ complex and the free guest is fast in the NMR time scale, a result that is due to the presence of the ethyl group at one of the guest ends, which affords a point for fast dissociation of the CB7 host. In contrast to this, the NMR spectroscopic data obtained with dication $\mathbf{2}^{2+}$ in the presence of CB7 are entirely similar to the spectral data obtained with $\mathbf{1}^{2+}$. These spectroscopic experiments, performed with the protonated dications reveal that (i) both $\mathbf{1}^{2+}$ and $\mathbf{2}^{2+}$ offer two identical aliphatic binding sites to CB7, (ii) their CB7 complexation leads to fast intramolecular host exchange between the two sites in the same guest molecule and much slower intermolecular host exchange between aliphatic binding sites on two guest molecules, and (iii) the terminal COOH groups act as 'pseudostoppers' by hindering the sliding of CB7 over them. In other words, the CB7·$\mathbf{1}^{2+}$ and CB7·$\mathbf{2}^{2+}$ complexes are pseudorotaxanes on the basis of steric considerations, but behave essentially as rotaxanes in the surveyed concentration range.

The complexation of all three viologen dications in Fig. 1 was also evidenced by MALDI-TOF mass spectrometric results (ESI†). We specifically investigated the binding between guest $\mathbf{3}^{2+}$ and CB7 by monitoring the absorbance of the viologen group at 262 nm as a function of the [CB7]/[$\mathbf{3}^{2+}$] concentration ratio.[11] The absorbance data fit perfectly a 1 : 1 binding isotherm with a K value of $(6.2 \pm 0.7) \times 10^5$ M^{-1}.

The influence of the solution pH on the location of CB7 within the CB7·$\mathbf{1}^{2+}$ and CB7·$\mathbf{2}^{2+}$ complexes was also investigated by NMR spectroscopy. Fig. 3 shows that raising the pH above the value required to ionize the terminal COOH groups has a pronounced effect on the β viologen protons. At pH 7.6 the signal for these protons appears at 7.1 ppm (from 8.45 ppm at pH 2.6),

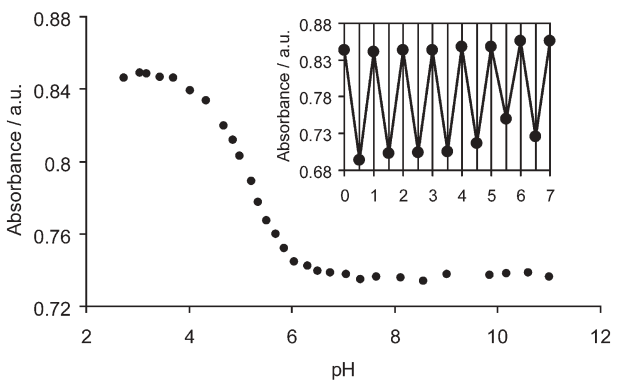
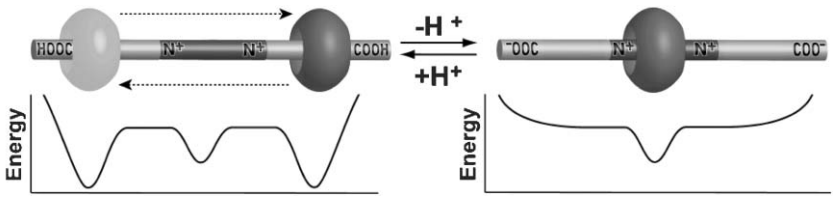


Fig. 4 Absorbance as a function of pH as recorded with a 34.1 μM solution of CB7·$\mathbf{2}^{2+}$ in 0.1 M NaCl at 23 °C. The inset records absorbance changes as the solution was cycled from pH ~ 2 to pH ~ 9.



Scheme 1 Pictorial representation of pH control on the location and movements of the CB7 wheel in the CB7·$\mathbf{1}^{2+}$ and CB7·$\mathbf{2}^{2+}$ pseudorotaxanes. The potential energy curves were estimated from the observed experimental behaviour.

while the sidearm aliphatic proton signals move downfield from their positions at lower pH. Our group[11] and Kim's[12] have demonstrated that the encapsulation of the viologen nucleus by CB7 leads to a considerable upfield shift of the bipyridinium β protons. In the absence of CB7, the proton NMR spectra of dications $\mathbf{1}^{2+}$ and $\mathbf{2}^{2+}$ are essentially invariant in the pH range 1–8, although the chemical shift of the methylene protons adjacent to the COOH groups is indeed pH sensitive. Therefore, the pronounced pH-driven changes in the NMR spectra of the CB7 complexes indicate that deprotonation of the COOH groups to their anionic carboxylate forms leads to the positioning of the CB7 on the viologen nucleus, stopping the fast intramolecular exchange between the two sidearm binding sites, which prevails at lower solution pH. As previously shown by us,[15,16] the negative charge on the carboxylate repels the carbonyl oxygen rims on the portals of the CB7, leading to the observed change on the range of movement of the host along the pseudorotaxane's molecular axle. The switching is completely reversible as shown by the spectrum in Fig. 3C.

Since inclusion of the viologen nucleus inside the cavity of CB7 is accompanied by a depression of the molar absorptivity coefficient of its electronic absorption band at 262 nm,[11] we also monitored these phenomena by UV-Vis spectroscopy. The results are in excellent agreement with the NMR data. Fig. 4 (inset) shows the reversible oscillations of absorbance (at 262 nm) measured in consecutive pH cycles with the CB7·$\mathbf{2}^{2+}$ complex. Notice that the absorbance goes from a high value at low (acidic) pH to a lower value at basic pH, reflecting the anticipated locations of the CB7 macrocycle. This figure also shows the progressive variation of the absorbance at 262 nm as the CB7·$\mathbf{2}^{2+}$ complex is titrated from pH 2 to pH 9. The inflection point of the sigmoidal titration curve corresponds to a pH of *ca.* 5, which is in good agreement with the pK_a of the terminal COOH groups on the complex. Similar data were recorded with the CB7·$\mathbf{1}^{2+}$ complex. In the absence of CB7 the absorption spectrum of the viologen guests was found to be pH independent. It must be noted that Kim and coworkers have reported on a CB6-based pseudorotaxane,[18] which also shows pH-dependent UV-Vis absorption changes. However, unlike in the system presented here, the observed spectral changes were not related to pH control on chromophore inclusion by the cucurbituril host.

Overall, we have presented evidence for a new type of pH-switchable, highly stable pseudorotaxane,[19] in which the wheel macrocycle exchanges rapidly (shuttles) between two identical sites at the extremes of the axle when the solution pH is low, while it is confined to bind the axle's central viologen residue at neutral pH. Scheme 1 depicts pictorially the switching mechanism, which can be thought of as chemical (proton transfer) control on the path length of the CB7 movements along the axle (long path at low pH and short path at high pH). In other words, the system behaves as a degenerate molecular shuttle at low pH, with the CB7 wheel oscillating back and forth between the two aliphatic binding sites, but the shuttling action is stopped at higher pH owing to the deactivation of the aliphatic binding sites, which limits the CB7 host to reside on the central viologen nucleus. Therefore, the system can be effectively considered as a molecular shuttle at low pH and as a highly stable pseudorotaxane complex in which the CB7 host is centered around the viologen residue at high pH. This system also illustrates nicely some of the most appealing binding properties of cucurbituril hosts.

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