A Cucurbit[8]uril 2:2 Complex with a Negative p K a Shift

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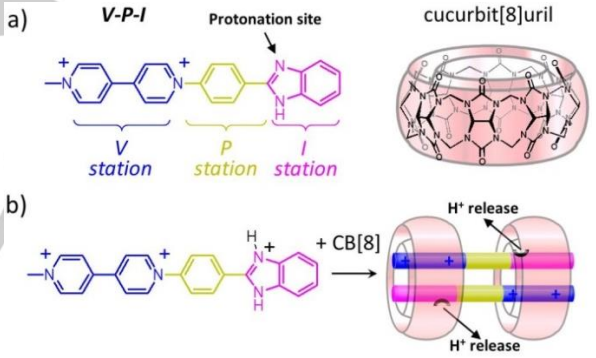
A cucurbit[8]uril 2:2 complex with a negative pK_a shift

Hang Yin,[a]† Qian Cheng,[a]† Roselyne Rosas,[b] Stéphane Viel,[c,d] Valérie Monnier,[b] Laurence Charles,[c] Didier Siri,[c] Didier Gigmes,[c] Olivier Ouari,[c] Ruibing Wang,*[a] Anthony Kermagoret,*[c] and David Bardelang.*[c]

Abstract: A viologen derivative carrying a benzimidazole group (***V-P-I***$^{2+}$) can be dimerized in water using cucurbit[8]uril (CB[8]) in the form of a 2:2 complex resulting in a negative shift of the guest pK_a, by more than 1 p*H* unit, contrasting with the positive pK_a shift usually observed for CB-based complexes. While 2:2 complex protonation is unclear by NMR, silver cations have been used for probing the accessibility of the imidazole groups of the 2:2 complexes. The protonation capacity of the buried imidazole groups is reduced, suggesting that CB[8] could trigger proton release upon 2:2 complex formation. The addition of CB[8] to a solution containing ***V-P-I***$^{3+}$ indeed released protons as monitored by p*H*-metry and visualized by a coloured indicator. This property was used to induce a host/guest swapping, accompanied by a proton transfer, between ***V-P-I***$^{3+}$•CB[7] and a CB[8] complex of 1-methyl-4-(4-pyridyl)pyridinium. The origin of this negative pK_a shift is proposed to stand in an ideal charge state, and in the position of the two p*H*-responsive fragments inside the two CB[8] which, alike residues engulfed in proteins, favour the deprotonated form of the guest molecules. Such proton release triggered by a recognition event is reminiscent of several biological processes and may open new avenues toward bioinspired enzyme mimics catalysing proton transfer or chemical reactions.

Introduction

In proteins, few amino acids are involved in catalysis and proton transport but Nature has found a highly tunable way to adapt the corresponding pK_a values to the functional needs of a given protein for its biological activity.[1] By sequestering p*H* responsive residues close to their active site, proteins have evolved toward dramatically shifting the pK_a of the buried fragments positively (ΔpK_a up to 8.0), and negatively (ΔpK_a up to 6.6) by several orders of magnitude,[2] ultimately to the right value enabling catalysis.[3] In a bioinspired approach, chemists have reported cage compounds that shifted the pK_a of size-complementary guest molecules[4] eventually enabling acid-catalyzed hydrolysis in basic solutions.[5] However, the tuning of pK_a values in the context of supramolecular catalysis remains highly challenging,[6] probably in part because water soluble molecules are needed, significantly restricting the palette of available systems. Among relevant macrocycles that would afford both a cavity for guest (substrate) binding and p*H* responsive functional groups (functionalization), cyclodextrins (CDs) have been studied regarding bioinspired catalysis[7] but only showed limited pK_a shifts.[8] Also relevant in this context, the supramolecular chemistry of cucurbiturils (CB[*n*]s) (Scheme 1) has dramatically expanded, in part after the discovery of larger macrocycles especially cucurbit[7]uril (CB[7]) and cucurbit[8]uril (CB[8]).[9]



Scheme 1. Structures of (a) the Viologen-Phenylene-Imidazole (***V-P-I***) guest with possible binding sites (stations) for cucurbit[8]uril (CB[8]) and (b) proton release upon 2:2 complex formation.

Cucurbit[*n*]urils have been shown to exhibit large positive pK_a shifts,[8, 10] mainly exploited toward enhancing drug stability[11] and bioavailability.[12] However, to the best of our knowledge negative pK_a shifts caused by CB[*n*] are rare and very weak.[8, 13] While CB[7] is more likely to bind guest molecules stoichiometrically,[14] CB[8] can bind two molecules, identical or not, and a growing subfield of cucurbituril chemistry concerns two donor-acceptor (DA) compounds, sequestered in CB[8],[15] and the use of this robust motif to assemble a large variety of structures (i. e. oligomers,[16] dendrimers,[17] polymers,[18] or proteins.[19]).[20] This double-recognition is highly favored mainly due to (i) favorable cation-dipole interactions[15a] leading to stabilized 1:1 complexes.[15a] and (ii) the release of "*high-energy*" water molecules from the hydrophobic cavity of CB[8].[21]
Recently, the combination of the donor and acceptor functions on the same molecule has opened new perspectives for the

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construction of dimeric structures including a pair of cucurbiturils and guest molecules (see example with ***V-P-I***, Scheme 1). This "*pairwise pattern*" presents the advantage of enhanced stabilities for the complexes compared to the corresponding monomeric structures, as exploited by Zhang et al.[22] and Zou et al.[23] to prepare strong supramolecular polymers via double DA linkage using CB[8]. Indeed, the frontier between well-defined 2:2 complexes and supramolecular polymers can be faint[24] as illustrated by thiazole orange DA compounds generating 2:2 complexes with CB[8] at low concentration (< 5 µM)[25] and evolving toward linear supramolecular polymers at higher concentration (> 50 µM).[26] The fluorescence properties of the included dyes are often impacted by the complexation mode and can be optimal in 2:2 complexes.[25, 27] The structure of Donor-Acceptor (DA) guest molecules has a strong impact on the final structure of CB[8] complexes, especially the flexibility of the DA linkers that can result in competitions between 1:1 complexes, 2:2 complexes,[24, 28] 3:2 complexes,[29] 5:5 complexes[30] or supramolecular polymers.[31] But pyridinium derivatives are also good candidates for the construction of 2:2 complexes[32] and to explore photo-responsive supramolecular systems.[33] Finally the introduction of a viologen group on a rigid structure could be a key design feature to favor the formation of well-defined 2:2 complexes.[34] Recently, we have described the controlled ring translocation of CB[7] over a rigid and linear conjugate of a viologen and a phenylene-benzimidazole fragment (***V-P-I***, Scheme 1) by Ag^+[35] or H^+.[12a] Here we show that, upon 2:2 complex formation with two molecules of CB[8], a functional guest (***V-P-I***) can unusually release protons (Scheme 1), instead of catching H^+ as a result of charge-stabilized ion-dipole interactions with a CB[*n*] rim.

Results and Discussion

2:2 complexes. The guest compound ***V-P-I*** was prepared according to a previously reported procedure as a dichloride salt.[35] ^{1}H NMR spectra in D_2O with increasing host/guest ratios (Figure 1) revealed an optimal complexation of ***V-P-I*** for ~1.25 equiv of CB[8]. The two intriguing features of the titration were (i) the signals of protons H_3, H_4, H_8 and H_9, all four largely upfield shifted in line with complex formation, and (ii) the signals of phenylene protons H_6 and H_7 appearing as a singlet reflecting formation of a symmetrical complex. The occurrence of 3:2 complexes appears unfavorable since the host:guest ratio above which there is no more change in NMR is < 1.5. Hence, we surmised formation of *n*:*n* supramolecular complexes, *n* > 1, because one CB[8] would normally not be enough to shield both viologen and benzimidazole regions. ^{1}H NMR signals are sharp (Figure 1a, 1.26 or 2.50 equiv CB[8]) suggesting formation of discrete species. We used DOSY NMR to get a quantitative estimation of the hydrodynamic radius of the complexes. We observed a significant decrease for the value of the diffusion coefficient after addition of 1.3 equiv of CB[8], from D_{VPI} = 4.68×10^{-10} $m^2.s^{-1}$ to $D_{VPI\cdot CB[8]}$ = 2.24×10^{-10} $m^2.s^{-1}$, the host and the guest diffusing at the same *D* value (Figure S3). Both this value and the ^{1}H NMR chemical shifts are in line with previous reports suggesting formation of host:guest 2:2 complexes.[28b, 32b] 2D-ROESY spectra support the formation of a 2:2 complex in which the two guests are head-to-tail positioned in the two CB[8] (e. g. see ROE cross-peaks between H_3-H_4 and H_8-H_9, Figure S5).

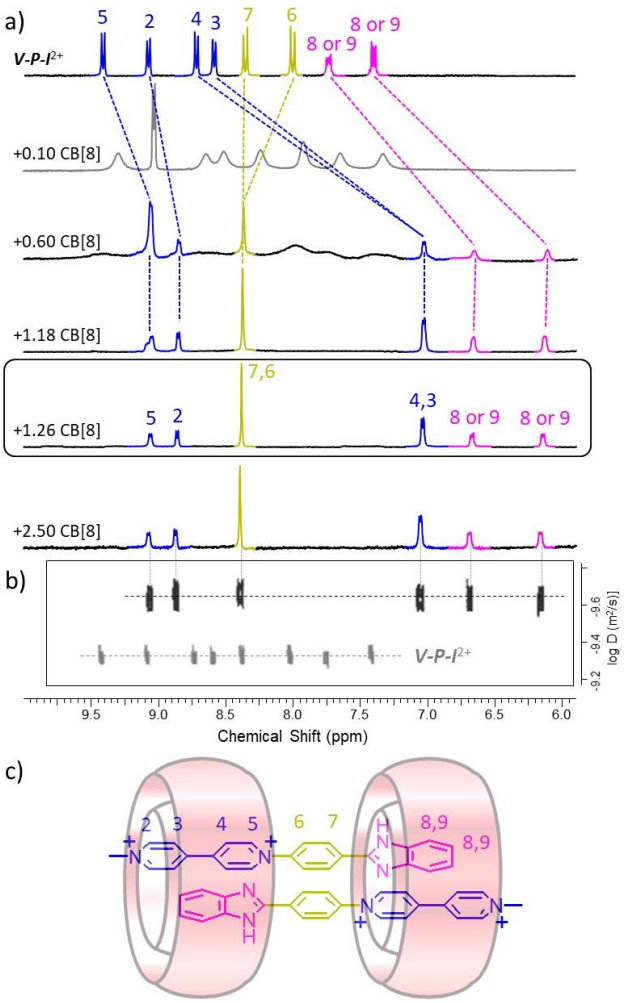

Figure 1. ^{1}H NMR titration (a) of ***V-P-I*** with CB[8] followed by (b) DOSY NMR of the ***V-P-I***•CB[8] complex (top) and of ***V-P-I*** (bottom) in D_2O. Proposed structure (c) of the quaternary 2:2 complex.

The CB[8] methylene signals, which reveal two non-equivalent CB[8] rims, also support a head-to-tail arrangement as four non-equivalent carbonyl rims would be expected in a head-to-head arrangement.[36] 2D NMRs did not allow to discriminate H_8 and H_9. Job plots[37] as determined by UV-vis titrations showed a maximum at 0.5 (Figure S6) confirming the favored 1:1 host :guest ratio. UV-vis titration of ***V-P-I*** with CB[8] showed a decrease of the band intensity at 355 nm with simultaneous intensity increase of the band at 395 nm up to approximately 1 equiv of CB[8] (Figure S7). Beside ***V-P-I***$^{2+}$ observed at *m/z* 182.1, the positive mode ESI mass spectrum showed the doubly charged 1:1 host:guest complex at *m/z* 846.3 as well as its protonated (*m/z* 564.5) and sodiated (*m/z* 571.9) forms (Figure S8). However, detailed inspection of the isotopic pattern at *m/z* 846.3 clearly evidenced the quadruply charged 2:2 complex, overlapping signals of the doubly charged 1:1 complex (Figure S8), as supported by accurate mass measurements (Table S1).
Several attempts to grow single crystals of the complexes suitable for X-ray diffraction were unsuccessful. We thus calculated the 2:2 complex structure by DFT (Figure S9) and found that the electron-donor character remains on the benzimidazole after complexation, as well as the electron-

acceptor feature, which remains on the viologen fragment (see HOMO and LUMO on Figure S9). Molecular dynamics simulations were then performed to (i) get information about the central phenylene zone and (ii) determine the mean inter-cucurbituril distance. For a simulation of 100 ns in a water-molecule box, the ***V-P-I***$_2$•CB[8]$_2$ complex was found to be stable (Figure 2), with a central zone characterized by two phenylene groups almost equally affected by the surrounding of the two nearby face-to-face CB[8] rims.

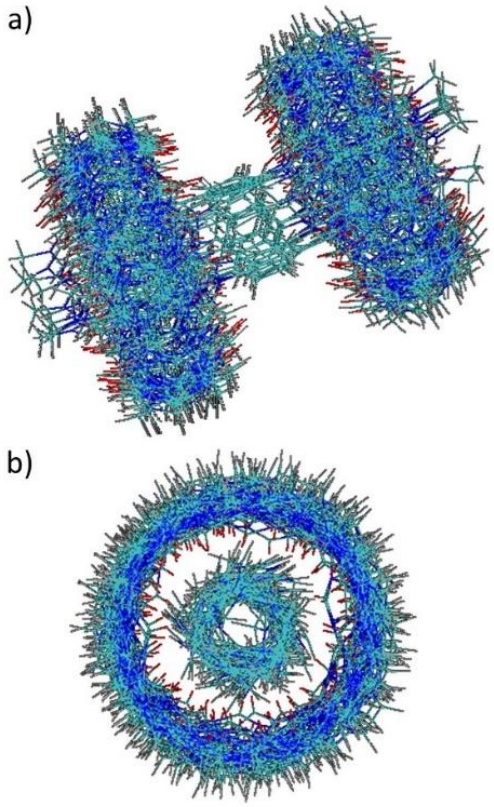

Figure 2. Side view (a) and top view (b) of superposed structures of the ***V-P-I***$^{2+}_2$•CB[8]$_2$ complex from the molecular dynamics trajectory.

This could explain the singlet observed by ^{1}H NMR for H_6 and H_7 (Figure 1). The inter-CB[8] distance (considering the center of each host) was found to be 11.9 ± 0.5 Å, in line with the proposed structure of Figure 1c. Subtracting the space toward each carbonyl rim and accounting for the van der Waals radii of oxygen atoms, the space left available between each carbonyl crown is ~2.9 ± 0.5 Å. Isothermal titration calorimetry (ITC) was performed and also supported a 1:1 host:guest ratio (Figure S10). Experiments to estimate the affinity between the hosts and the guests converged toward competition with amantadine, another guest known to bind relatively strongly to CB[8] (K_a = 8.19 10^8 M^{-1}).[38] ^{1}H NMR spectra of ***V-P-I*** with 1 equiv CB[8] and 1 equiv amantadine showed signals assigned to the 2:2 complex of ***V-P-I*** together with a small amount of included amantadine (Figure S11). Experiments were done in triplicate and an estimate for the global association constant for 2:2 complex formation is proposed to be $K_{a\ \mathbf{VPI2}\text{•}CB[8]2} \approx 8 \times 10^{19}$ M^{-3} (see SI for calculation details),[39] that is larger than that reported for another CB[8] 2:2 complex in the literature.[26]

Supramolecular pK_a shifts. Intrigued by the responsiveness of ***V-P-I***•CB[7] complexes toward p*H*,[12a] we recorded ^{1}H NMR spectra of the ***V-P-I***$_2$•CB[8]$_2$ complexes with increasing amounts of trifluoroacetic acid (TFA). The signals corresponding to guest protons hardly changed up to 2 equiv of TFA (Figure S12). This suggests that ***V-P-I*** has become harder to protonate as a result of 2:2 complex formation, which is opposite to the usual trend observed regarding cucurbituril binding (positive pK_a shift).[8] When more acid was added (up to 30 equiv of TFA, Figure S12), the singlet corresponding to protons H_6 and H_7 became broad and signals of protons H_3, H_4 and $H_{8,9}$ almost disappeared but still suggest similar guest inclusion. DOSY NMR showed signals aligned at a slightly different *D* value (*D* = 2.63×10^{-10} $m^2.s^{-1}$, Figure S13) showing that hosts and guests belong to the same hydrodynamic species, whose size is not largely different from that of the ***V-P-I***$_2$•CB[8]$_2$ complex (*D* = 2.24×10^{-10} $m^2.s^{-1}$). However, protonation of the complex could slightly affect its geometry, inducing a significant modification of its *D* value.[28b] While the addition of a large excess of TFA affected the 2:2 complex, these changes were reversible upon addition of $NaHCO_3$ (Figure S14). The addition of NaOH (5 equiv) only showed little changes by ^{1}H NMR (Figure S15, we assume that anion exchange has no effect of the 2:2 complex), suggesting that the 2:2 complexes are stable over a large p*H* range. Measurements of pK_a were done by UV-vis titrations affording two pK_a values at 2.8 ± 0.1, and ≈ 13 (Figure 3 and Figure S16).

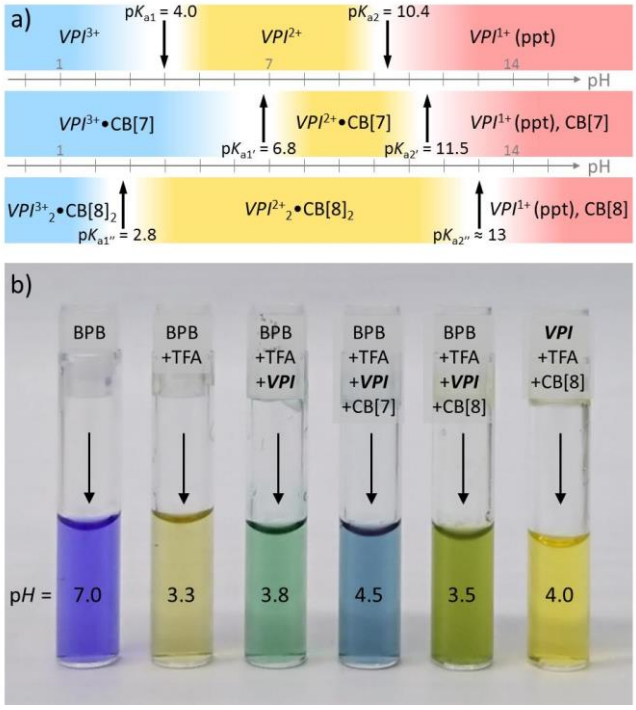

Figure 3. p*H* scales in a) illustrating the p*H* ranges where dominant species can be found regarding ***V-P-I*** and its complexes with CB[7] and CB[8] and solutions in b) illustrating positive and negative pK_a shifts upon CB[7] or CB[8] addition (BPB : bromophenol blue, p*H* indicated at the bottom, Figure S17).

Hence, the pK_a value corresponding to the ***V-P-I***$^{2+}$/***V-P-I***$^{3+}$ couple of 4.0[12a] without cucurbituril shifts to 2.8 after addition of CB[8]. However, cucurbiturils are known to shift guest pK_a values positively as a result of the protonation induced by cationic

charge stabilization provided by the CB[*n*] carbonyl rims. For instance, CB[7] shifts the pK_a of ***V-P-I*** positively by ~2.8 units (p$K_{a1'}$ = 6.8).[12a] We believe that the inclusion of a ***V-P-I*** pair by the two CB[8] shields the guest pair from its surrounding, impeding imidazole protonation to some extent. The estimation of the deepness of inclusion for the four imidazole nitrogen atoms was performed by molecular dynamics, calculating their distance to the mean plane of the relevant CB[8] (perpendicular to the C_8 axis and passing by all methine carbon atoms). The four distances are given hereafter: 2.58 Å (σ = 0.54 Å), 2.42 Å (σ = 0.34 Å), 2.12 Å (σ = 0.26 Å), and 1.80 Å (σ = 0.35 Å) revealing a shallow to significant inclusion in CB[8] (deepness of inclusion between ~0.47 and 1.25 Å, Figure 4).

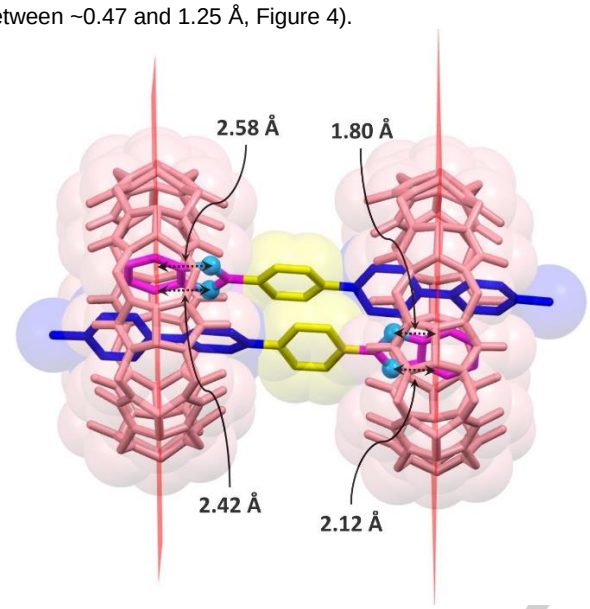

Figure 4. Schematic illustration of the deepness of inclusion of the imidazole nitrogen atoms in the ***V-P-I***$_2$:CB[8]$_2$ complex based on molecular dynamics calculations (see text).

Furthermore, the benzimidazole fragment is a good electron donor and can complement well the viologen fragment in the same CB[8], which would be no longer favorable upon protonation. Variations in the charge state of the complexes are so expected to play a strong role in the observed results. Usually, with two CB[8] in the complex, a maximum 4+ charge state can be expected with relevant guests. Recently, fluorescent 2:2 complexes of CB[8] have been reported to be p*H* responsive with a total charge state switching from 2+ to 4+, the p*H* impacting the fluorescence but not the complex integrity.[34b] For the ***V-P-I***$_2$•CB[8]$_2$ complex, protonation is unexpected because it would afford a 5+ or 6+ total charge complex. The unusual negative pK_a shift of the ***V-P-I***$^{2+}$/***V-P-I***$^{3+}$ couple after addition of CB[8] suggested that formation of the 2:2 ***V-P-I***•CB[8] complex could release a proton from ***V-P-I***$^{3+}$ in relevant conditions. Experiments were performed in this direction and the p*H* monitored both by a p*H*-meter and by bromophenol blue as a colored indicator (BPB, Figure 3b). In the presence of 1 equiv of TFA, ***V-P-I*** is protonated (***V-P-I***$^{3+}$) and induces a p*H* increase from 3.3 (p*H* of the TFA solution) to 3.8 affording a pale green solution (p*H* ≈ pK_a of BPB). The addition of 1 equiv of CB[7] turned the color to blue and illustrated well the positive pK_a shift of the complex with a p*H* value that was increased to 4.5. In contrast the addition of CB[8] in the ***V-P-I***$^{3+}$ solution afforded a yellow-green solution (p*H* = 3.5), reflecting proton release from the guest. As discussed before, below p*H* 2.8, the ***V-P-I***$_2$•CB[8]$_2$ complexes are supposed to be protonated but NMR data are unclear. We thus decided to use a metal ion as a local probe to determine whether an additional charge can be included in the complexes.

Silver binding. While metallic complexes have recently been reported to form 2:2 complexes with CB[8] with possible tuning of the head-to-head versus head-to-tail guest arrangement,[36] we wanted to determine whether a metal ion could include in the 2:2 complexes to support the previous findings regarding pK_a values, especially the restrained but possible guest imidazole accessibility (^{1}H NMR with high excess TFA, Figure S12). While NaCl or $CaCl_2$ have been reported to weaken CB[8] 2:2 complexes,[25, 40] we have tested a palette of metal ions by recording ^{1}H NMR spectra after addition of 16 equiv of metal ion to D_2O solutions of the 2:2 complexes. Na^+, K^+, Cs^+, Mg^{2+}, Ca^{2+}, Co^{2+}, Zn^{2+}, Ni^{2+}, Dy^{3+} and Yt^{3+} afforded ^{1}H NMR spectra with virtually no change (Figure S18) after metal salt addition. However, Ag^+ afforded new NMR spectra. Actually, silver cations interacting with CB[*n*] present a significant interest for catalytic applications.[41] ^{1}H NMR titration fixing the concentration of the 2:2 complex and gradually increasing that of $AgNO_3$ showed a significant split of the initial resonances of protons H_6 and H_7 as well as for protons H_3 and H_4 and a slight downfield shift for the signal of H_2 (Figure 5 and Figure S19).

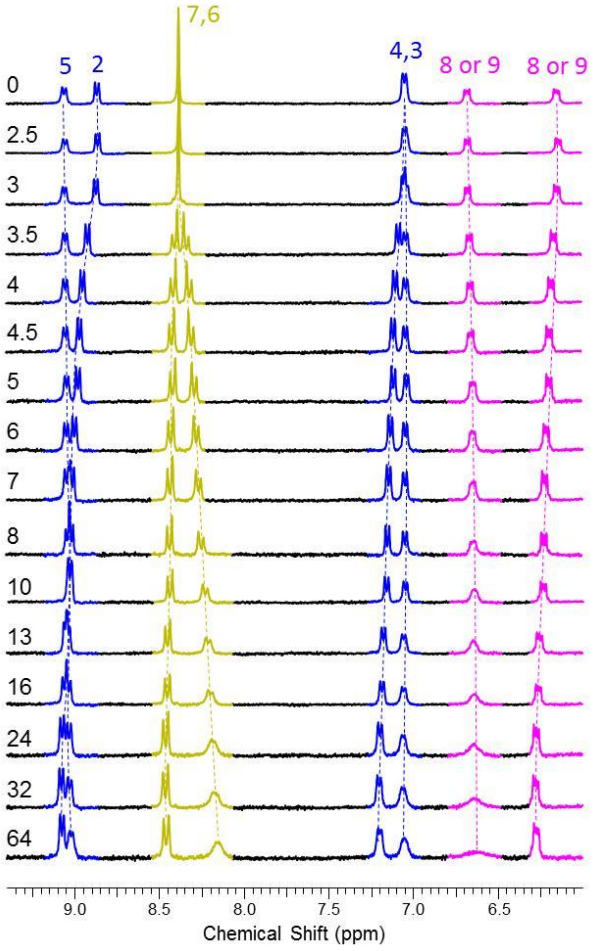

Figure 5. Excerpt of the aromatic region of the ^{1}H NMR spectra of a D_2O solution of ***V-P-I***$_2$•CB[8]$_2$ complexes upon gradual addition of $AgNO_3$ (0.41 mM ***V-P-I***, 1.22 equiv CB[8], number of equiv Ag^+ on the left).

The signals of guests protons generally remain in the initial regions suggesting that the structure of the ***V-P-I***$_2$•CB[8]$_2$ complexes remains similar. However, the observed splitting of some resonances and the unsymmetrical broadening of signals of H_6 and H_8 suggests Ag^+ binding possibly near an imidazole function (perturbing its immediate surrounding, i. e. the nearest, phenylene and benzimidazole protons).[35] DOSY NMR for a mixture containing the 2:2 complexes and 16 equiv Ag^+ afforded aligned resonances for the hosts and the guests (Figure S20) supporting again 2:2 complex formation and a diffusion coefficient value D = 2.19 × 10^{-10} $m^2.s^{-1}$ that is close to that of the 2:2 complexes ($D_{\mathbf{VPI2}\bullet CB[8]2}$ = 2.24 × 10^{-10} $m^2.s^{-1}$). In the majority of cases, CB[8] is known to prefer accepting two positive charges in its direct surrounding but exceptions are known.[42] Because the exchange is fast on the NMR timescale (splitting due to a symmetry break) and the amount of silver needed to reach saturation is high compared to the concentration of 2:2 complex, we propose that one silver cation transiently and weakly binds the 2:2 complexes affording 5+ charged 2:2:1 complexes. 2:2:2 complexes appear less likely due to the presence of 6 positive charges in a relatively small space. Assuming the 2:2 complex as a new stable entity (at least with respect to the NMR timescale), it is possible to fit the guest protons chemical shifts against the Ag^+ concentration according to a 1:1 (2:2 complex)$_1$:Ag^+_1 binding model. This method afforded binding constants $K_{a\ (2:2\ complex):Ag+}$ ranging from 224 ± 32 to 703 ± 180 M^{-1} (Figure S21) while considering binding two Ag^+ ions afforded inconsistent results. UV-vis titration showed a slight decrease in absorbance and a weak redshift of the band near 390 nm (Figure S22). Molecular dynamics simulations of the 2:2 complex in a water box including 64 equivalents of Ag^+ cations qualitatively reproduce the experimental trend with one cation transiently binding the complexes (radial distribution functions, Figure S23). Contraction of the 2:2 complex upon Ag^+ binding is very small, at the limit of significance with an inter-CB[8] distance of 11.1 ± 0.5 Å, but could explain why the ^{1}H NMR patterns are slightly affected (Figure 4). ESI mass spectrometry of a 1:1.25 mixture of ***V-P-I***:CB[8] with 16 equiv of Ag^+ showed a peak at *m/z* 600.5 corresponding to the triply charged species ***V-P-I***$_1$•CB[8]$_1$•Ag^+_1 (Figure S24) but no signal corresponding to a silver adduct of the 2:2 complex, presumably due to the high propensity to form ***V-P-I***$_1$•CB[8]$_1$ complexes in the gas phase (Figure S8).

Host-Guest swapping. Because of the good stability of the 2:2 complexes in various conditions (p*H*, presence of metal ions, competitive guests, i. e. amantadine), we surmised that a pre-complexed ***V-P-I*** in another host would be transferred to CB[8] while forming a stable 2:2 complex. Simultaneously, the guest initially present in CB[8] would be ejected and could further be trapped in the other host (guest-swapping). Previously, guest swapping was observed between CB[6] and β-cyclodextrin for guests of adamantyl-hexyl-amine type and triggered by p*H*.[43] To test the proposed hypothesis involving CB[7] and CB[8] with ***V-P-I***, we first assessed the CB[7]/CB[8] competition to complex ***V-P-I*** by transferring a ***V-P-I***$^{3+}$•CB[7] solution (containing 4 equiv. of TFA), onto solid CB[8]. The resulting solution turned orange and the ^{1}H NMR resonances corresponded to ***V-P-I***$^{2+}$ included in CB[8] (dimer) confirming the predominance of the 2:2 complex (Figure S25). Al^{3+} is also able to produce the ***V-P-I***$^{3+}$•CB[7] complex owing to its weak acidity,[35] and the addition of CB[8] (1.2 equiv.) again showed the occurrence of the ***VPI***$^{2+}_2$•CB[8]$_2$ complex (Figure S26). These results again support proton release after 2:2 complex formation.

To take advantage of the proton release, we decided to use a proton-responsive guest that is also a good guest for CB[7]: 1-methyl-4-(4-pyridyl)pyridinium, (***MPP***$^{1+}$). Simultaneous host/guest swapping was attempted after mixing two solutions, one containing the ***V-P-I***$^{3+}$•CB[7] complex, and the other the ***MPP***$^{1+}$•CB[8] complex. The ***VPI***$^{2+}_2$•CB[8]$_2$ complex should form, releasing a proton from ***V-P-I***$^{3+}$, ***MPP***$^{1+}$ trapping the released protons and being complexed by CB[7] in the form of ***MPPH***$^{2+}$•CB[7]. The ^{1}H NMR spectrum of the solution, resulting from the mixture of ***V-P-I***$^{3+}$•CB[7] and ***MPP***$^{1+}$•CB[8], showed the diagnostic resonances of the ***V-P-I***$^{2+}_2$•CB[8]$_2$ complex which formed almost quantitatively (Figure 6).

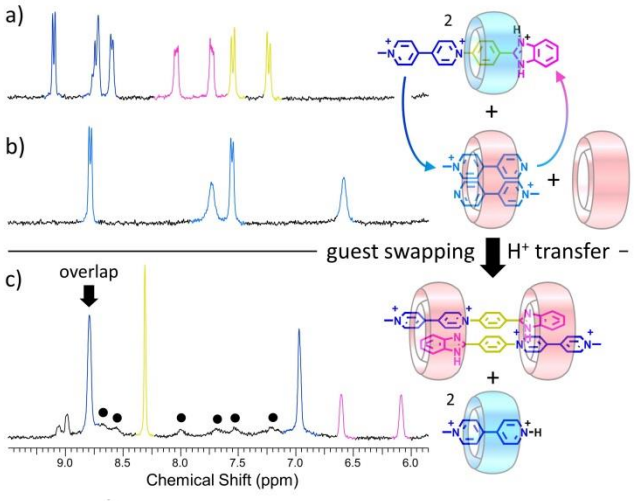

Figure 6. Excerpts of the aromatic region of ^{1}H NMR spectra for a) a mixture of ***V-P-I***$^{3+}$ and CB[7], b) ***MPP***$^{1+}$ and CB[8] and c) the mixture of solutions corresponding to a) and b) showing signals assigned to the formation of ***V-P-I***$^{2+}_2$•CB[8]$_2$ and of ***MPP***-H^{2+}•CB[7] (signal overlap, see text) and illustrating the simultaneous host/guest swapping and proton transfer (● stands for residual signals from ***V-P-I***$^{3+}$•CB[7]).

The broad signal at ≈ 8.8 ppm was assigned to ***MPPH***$^{2+}$•CB[7] (Figure S27), overlapped with protons H_2 of ***V-P-I***$^{2+}_2$•CB[8]$_2$ (integral: 6H, Figure S28). A CB[7]/CB[8] exchange has occurred between the two guests and was accompanied by a proton exchange between ***V-P-I***$^{3+}$ and ***MPP***$^{1+}$ to generate ***V-P-I***$^{2+}_2$•CB[8]$_2$ and a ***MPPH***$^{2+}$•CB[7] complex (Figure 6). The simultaneous and almost quantitative host/guest swapping was achieved since (i) ***V-P-I***$^{2+}_2$•CB[8]$_2$ favorably formed against ***V-P-I***$^{3+}$•CB[7] and (ii) the subsequent proton release helps to generate the ***MPPH***$^{2+}$ which is strongly complexed by CB[7].[44] These experiments show how 2:2 complex formation with CB[8] can be used to trigger cascade supramolecular events with redistribution of complexed species. More generally, pK_a-shifts are the attributes of numerous enzymes[2] that use prepositioned residues, engulfed near their active site for catalysis.[1a] In these cases, the key factor for them to operate lies in the protonation state of the relevant residue. In principle, new types of cucurbit[*n*]uril complexes can be developed as minimal enzyme mimics toward bioinspired catalysis[5, 9a, 45] and, in this context and owing to guest pK_a values that can be tuned either side, we believe that CB[*n*] can be key building-blocks toward bioinspired proton transfer systems.[46]

Conclusions

In this work, we showed that rigid ditopic guest compounds with one station designed to bind well CB[8] can trigger the formation of robust host:guest 2:2 complexes. Upon complex formation, the guest imidazole function is less accessible for protonation, resulting in a negative pK_a shift with respect to the free guest. Formation of the ***V-P-I***$_2$•CB[8]$_2$ complex can thus be accompanied by a release of protons and trigger host:guest rearrangements. Given their excellent binding properties in water and the increased possibilities to tune the pK_a of included fragments, cucurbiturils could become attractive hosts enabling both substrate binding and catalysis, adjusted by relevant pK_a shifts.

Experimental Section

Preparation and ^{1}H NMR spectrum of the *V-P-I*$^{2+}_2$•CB[8]$_2$ complex. A 0.66 mM solution of ***V-P-I***$^{2+}_2$•**CB[8]$_2$** was prepared from a mixture of 0.72 mg of solid CB[8] (5.2×10^{-7} mol), 108 µL of a 5 mM stock solution of of ***V-P-I***[35] in D_2O and 430 µL of D_2O. Acetone was used as internal reference (2.22 ppm). ^{1}H NMR (500 MHz, D_2O) δ 9.06 (d, *J* = 5.5 Hz, 2H), 8.86 (d, *J* = 6.4 Hz, 2H), 8.38 (s, 4H), 7.04 (d, *J* = 6.2 Hz, 4H), 6.67 (dd, *J* = 3.5, 3.5 Hz, 1.9H), 6.15 (dd, *J* = 3.5, 3.5 Hz, 2H), 5.87-5.71 (d, *J* = 14.9 Hz and d, *J* = 15.4 Hz, 20.6H), 5.53 (s, 19.9H), 4.27-4.19 (d, *J* = 16.0 and d, 16.0 Hz, 18.2H).

All experiments to support the conclusions of the present contribution, including NMR measurements, mass spectrometry, UV-vis spectroscopy, DFT calculations, molecular dynamics, p*H* measurements and isothermal titration calorimetry, are detailed in supporting Information.

Acknowledgements

CNRS and Aix Marseille Université are acknowledged for continuous support. This work was also partly funded by University of Macau (MYRG2016-00008-ICMS-QRCM, and MYRG2017-00010-ICMS) and National Science Foundation of China (21871301).

Keywords: 2:2 complexes • Host:Guest • Cucurbituril • Viologen • Imidazole

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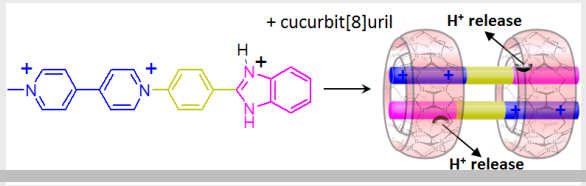

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A cucurbit[8]uril 2:2 complex with a negative pK_a shift