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Control of the stoichiometry in host–guest complexation by redox chemistry of guests: Inclusion of methylviologen in cucurbit[8]uril†

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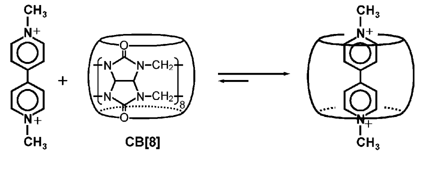
The binding stoichiometry of a host–guest complex can be effectively controlled by the redox chemistry of the guest: a 1 : 1 inclusion complex of methylviologen dication (MV^{2+}) in cucurbit[8]uril (CB[8]) converts completely and reversibly to a 2 : 1 inclusion complex of cation radical ($MV^{+\cdot}$) in CB[8] upon the reduction of the guest.

Unveiling the principles governing the interplay of redox and molecular recognition is important not only for understanding biological systems but also for designing molecular devices. A number of host–guest systems involving redox active guests have thus been studied to elucidate the interdependence of redox processes and molecular recognition.[1] Cucurbituril (CB[6]), a macrocyclic cavitand comprising six glycoluril units, has a hydrophobic cavity accessible through two identical carbonyl-fringed portals.[2] Because of its rigid structure and capability of forming complexes with molecules and ions CB[6] has been widely used as a synthetic receptor[1] and as a building block for supramolecular assemblies.[3] Our recent synthesis[4] of larger cucurbituril homologues, cucurbit[*n*]uril (CB[*n*], $n = 7$ and 8) containing seven and eight glycoluril units, respectively, has opened up new opportunities in supramolecular chemistry.[5,6] In terms of cavity size, CB[7] and CB[8] are similar to β- and γ-cyclodextrins (β- and γ-CDs), respectively, but their inclusion behavior is often quite different. For example, our recent investigation[7a] on inclusion behavior coupled with the redox chemistry of methylviologen (*N*,*N*-dimethyl-4,4-bipyridinium, MV) in CB[7] revealed that unlike β-CD, CB[7] prefers the charged species, methylviologen dication (MV^{2+}) and cation radical ($MV^{+\cdot}$) to the fully reduced neutral (MV^0) species as guests. Furthermore, dimerization of $MV^{+\cdot}$ is effectively suppressed by forming a stable complex with CB[7] in aqueous solution and the redox process ($MV^{2+}/MV^{+\cdot}$) of the MV^{2+}–CB[7] complex occurs predominantly *via* a direct electron transfer pathway. This interesting discovery led us to extend our study to the larger host CB[8]. Here we report the unusual redox-coupled inclusion behavior of MV in CB[8] demonstrating the binding stoichiometry of a host–guest complex can be effectively controlled by the redox chemistry of the guest.

We previously reported that CB[8] forms a 1 : 1 host–guest complex with MV^{2+} (Scheme 1) as evidenced by ^1H NMR and mass spectrometry, even though CB[8] has a cavity large enough to accommodate two MV^{2+} molecules.[5a] The exclusive formation of the 1 : 1 complex is also confirmed by UV–visible spectroscopy. The absorption spectrum of MV^{2+} changes gradually with a set of isosbestic points as the concentration of CB[8] increases up to 1 equivalent (see ESI†). The observation of the isosbestic points supports that the 1 : 1 complex is exclusively formed from MV^{2+} and CB[8]. The formation constant for the 1 : 1 complex MV^{2+}–CB[8] determined by the photometric titration is $(1.1 \pm 0.3) \times 10^5\ M^{-1}$ at 25 °C in water. The remarkably strong binding of MV^{2+} to CB[8] is in sharp contrast to the fact that γ-CD, which has a hydrophobic cavity with a comparable size, does not bind MV^{2+} appreciably.[8] As in CB[7],[7] the strong binding of MV^{2+} by CB[8] is presumably due to the favorable ion–dipole interaction between the positive charge of the guest and the portal oxygen atoms of CB[8] in addition to the hydrophobic effects.



Scheme 1 Schematic illustration for the inclusion of MV^{2+} in CB[8].

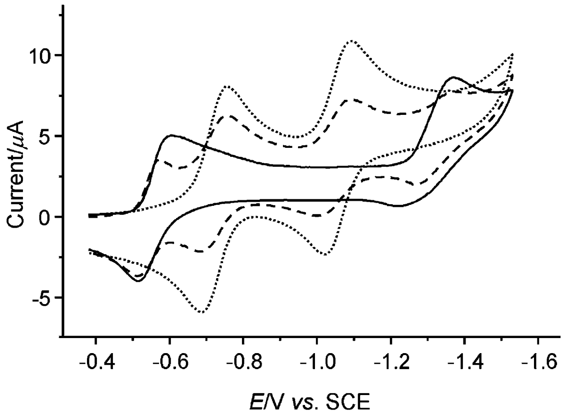


Fig. 1 Cyclic voltammograms at scan rate 0.1 V s^{-1} of a 0.5 mM solution of MV^{2+} in the absence (dotted line), in the presence of 0.25 equivalent (dashed line) and 1 equivalent (solid line) CB[8] in pH 7.0 phosphate buffer. SCE, saturated calomel electrode.

Having established the binding stoichiometry and constant of the complex between CB[8] and MV^{2+}, we investigated the interplay between the redox process of MV and its inclusion behavior in CB[8] by using cyclic voltammetry (Fig. 1). As well documented, MV^{2+} shows two reversible waves corresponding to the redox couples $MV^{2+}/MV^{+\cdot}$ and $MV^{+\cdot}/MV^0$ (dotted line).[7] In the presence of 0.25 equiv. CB[8] (dashed line), however, two additional redox waves are observed beside the ones for free MV: a reversible wave appears at a potential ~160 mV more *positive* than that for the first redox couple of free MV, and a quasi-reversible wave occurs at a potential ~280 mV more *negative* than that for the second redox couple of free MV (Table 1). In the presence of 1.0 equiv. of CB[8] (solid line), these new waves completely replace the ones for free MV, but they become less reversible, particularly the second one.

This cyclic voltammetric behavior of MV in the presence of CB[8] is quite different from that in the presence of other hosts.

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† Electronic supplementary information (ESI) available: details of electrochemical and spectroelectrochemical experiments. See http://www.rsc.org/suppdata/cc/b2/b202082c/

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Table 1 Comparison of voltammetric parameters for free MV^{2+}, MV^{2+}–CB[7] and MV^{2+}–CB[8]

	E^1_p $(\Delta E_p)^a$	$E^2_p(\Delta E_p)^b$	D^c/cm^2 s^{-1}	Ref.
MV^{2+}	−0.704 (64)	−1.014 (64)	6.6×10^{-6}	7*a*
MV^{2+}–CB[7]	−0.726 (66)	−1.164 (122)	1.8×10^{-6}	7*a*
MV^{2+}–CB[8]	−0.546 (65)	−1.290 (88)	1.7×10^{-6}	This work

[a] Half-wave potential for the first reduction process expressed in volts *vs.* SCE (saturated calomel electrode). The value in parenthesis represents the potential difference in mV between the cathodic and anodic peak potentials measured at 0.1 V s^{-1}. [b] For the second reduction process. [c] Diffusion coefficient determined from the plot of i_p *vs.* $v^{1/2}$.

For example, *β*- or *γ*-CD little affects the first reduction wave but causes a large *positive* shift of the second reduction wave because both CDs interact only with fully reduced neutral species MV^0.[8] Furthermore, CB[7] induces a small *negative* shift of the first reduction wave ($\Delta E^1{}_{1/2} \sim -20$ mV) and a large *negative* shift of the second reduction wave ($\Delta E^2{}_{1/2} \sim -110$ mV) since CB[7] has a high binding affinity to MV^{2+} ($K = 2.0 \times 10^5$ M^{-1}) but a slightly smaller affinity to $MV^{+\cdot}$ and a much smaller affinity to MV^0.[7]

For better understanding of this unusual behavior of MV in the presence of CB[8] we carried out a spectroelectrochemical study. Fig. 2 shows the absorption spectra of $MV^{+\cdot}$ generated by electrolysis of MV^{2+} in the absence (dashed line) and presence (solid line) of CB[8] (applied potential, −0.8 V *vs.* SCE). It is well known that $MV^{+\cdot}$ exists as an equilibrium mixture of the monomeric and dimeric forms in aqueous solution. When equimolar CB[8] is present, however, only the characteristic absorption of the dimeric species is observed even at a low concentration such as 0.5 mM. Therefore, we conclude that the first redox wave of MV^{2+} in the presence of CB[8] corresponds to one-electron reduction of MV^{2+}–CB[8] followed by rapid generation of the stable complex $(MV^{+\cdot})_2$–CB[8] as shown in Scheme 2.[9] The large positive shift of the first reduction peak is apparently related to facile formation of the stable complex $(MV^{+\cdot})_2$–CB[8]. From the spectroelectrochemical study the apparent dimerization constant of $MV^{+\cdot}$ in the presence of equimolar CB[8] is estimated[10] to be 2×10^7 M^{-1} (ESI†) which is about 10^5 times larger than that of $MV^{+\cdot}$ alone in aqueous media. Although CDs[10] and surfactants[11] are known to enhance the dimerization of $MV^{+\cdot}$, such a large enhancement has never been observed. The remarkable stability of the dimer within CB[8] may be attributed to the unique properties of CB[8] as a host providing the dimer not only with a hydrophobic cavity of a right size but also with polar oxygen atoms at the portals for ion–dipole interaction with the guest. Most importantly, our work demonstrates that the 1:1 inclusion complex MV^{2+}–CB[8] converts completely and reversibly to the 2:1 inclusion complex of $(MV^{+\cdot})_2$–CB[8] upon reduction of the guest, as illustrated in Scheme 2. To the best of our knowledge, this is the first example demonstrating that the binding stoichiometry of a host–guest complex can be effectively controlled by the redox chemistry of the guest. The large negatively shifted second redox wave of MV in the presence of CB[8] is apparently related to the reduction of $(MV^{+\cdot})_2$–CB[8], but at this moment we do not clearly understand this process. We are currently investigating these electrochemical processes in more detail in conjunction with the mechanism of the electron transfer coupled with inclusion process.

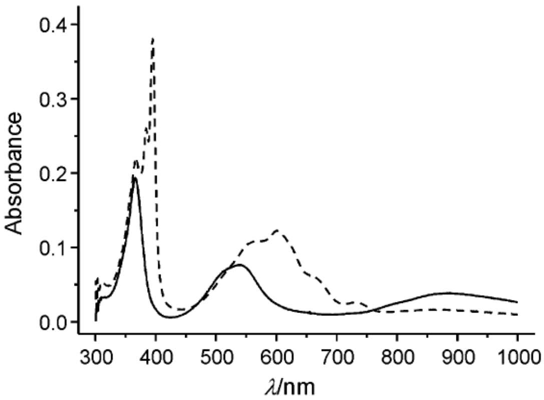
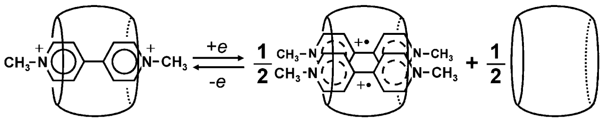


Fig. 2 Absorption spectra of $MV^{+\cdot}$ generated from a solution of MV^{2+} (0.5 mM) in phosphate buffer (pH = 7.0) using an indium tin oxide glass electrode (applied potential, –0.8 V *vs.* SCE). Solid and dashed lines represent spectra in the presence of 1 equiv. of CB[8] and in the absence of CB[8], respectively.



Scheme 2

In conclusion, we present a unique example demonstrating that the binding stoichiometry of a host–guest complex can be effectively controlled by the redox chemistry of the guest. This unprecedented redox control of the stoichiometry in host–guest complexation may provide a working principle for electrochemically controllable molecular machines.

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9 We have investigated the scan rate effect on the cyclic voltammograms to better understand the redox coupled inclusion process. As far as the first wave is concerned, the separation between cathodic and anodic peaks increases with increasing scan rate, but even at a high scan rate such as 3.0 V s^{-1} no other feature is observed (ESI†). We therefore tentatively conclude that the formation of complex $(MV^{+\cdot})_2$–CB[8] after one-electron reduction of MV^{2+}–CB[8] occurs rapidly on the cyclic voltammetry time scale. However, the second wave, apparently related to the reduction of $(MV^{+\cdot})_2$–CB[8], shows somewhat complicated features depending on scan rate. Further careful investigation including digital simulation of the cyclic voltammograms is in progress to elucidate the whole processes.

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