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Host–Guest Chemistry

Molecular Loop Lock: A Redox-Driven Molecular Machine Based on a Host-Stabilized Charge-Transfer Complex**

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Dedicated to Professor Dong H. Kim

Artificial molecular machines have received much attention in recent years because of their potential application in the creation of nanometer-scale molecular devices.[1,2] A wide variety of molecular machines such as shuttles,[3a] rotors,[3b] muscles,[3c] ratchets,[3d] pistons and cylinders,[3e] scissors,[3f] and elevators[3g] have been reported. Nevertheless, the design and synthesis of new molecular machines that are reminiscent of macroscopic machines would further widen the scope of this area of chemistry.

Cucurbit[8]uril (CB[8]),[4] a member of the host family cucurbit[*n*]uril, which has a cavity that is similar to that of γ-cyclodextrin, exhibits remarkable host–guest properties including the encapsulation of a hetero-guest-pair inside the cavity.[5] For example, it encapsulates methyl viologen (MV^{2+}) and 2,6-dihydroxynaphthalene ($Np(OH)_2$) inside the cavity to form the stable 1:1:1 complex $\mathbf{1}^{2+}$. Formation of the complex is driven by the markedly enhanced charge-transfer (CT) interaction between the electron-deficient and electron-rich guest molecules inside the hydrophobic cavity of CB[8].[5a] This discovery led us to build several novel supramolecular assemblies such as supramolecular amphiphiles that led to

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vesicles,[5b] molecular loops,[5c] supramolecular polymers on surfaces,[5d] and molecular necklaces[5e] by exploiting the host-stabilized CT interactions. Despite the progress in the construction of self-assembly systems, the redox properties of the host-stabilized CT complexes, in particular, the interplay between the redox process and the exchange of the guest within the host-stabilized CT complexes have not been reported. These properties may provide a novel operating principle of molecular machines or stimuli-responsive materials. Herein we report the redox-coupled guest-exchange properties of CB[8]-stabilized CT complexes which demonstrate the interconversion of hetero- and homo-guest-pair inclusion in a molecular host triggered by an external stimulus (Scheme 1). We also report a molecular loop lock, a novel redox-driven molecular machine based on this phenomenon.

Treatment of a mixture of methyl viologen (MV^{2+}) and the ternary complex $\mathbf{1}^{2+}$ (1:1) with a reducing agent such as sodium dithionite ($Na_2S_2O_4$) results in a drastic change in the UV/Vis spectrum. The appearance of new absorption bands at $\lambda = 365$, 540, and 884 nm (see Supporting Information) supports the near-quantitative formation of the 2:1 inclusion complex $(MV^{+\bullet})_2\subset CB[8]$ ($\mathbf{2}^{2+}$)[6] and free $Np(OH)_2$ (Scheme 1). Introduction of O_2 into the solution regenerates $\mathbf{1}^{2+}$ and MV^{2+}. This behavior is confirmed by UV/Vis and NMR spectroscopy, and this result demonstrates the reversible conversion of hetero- and homo-guest-pair inclusion inside CB[8] triggered by a redox stimulus.

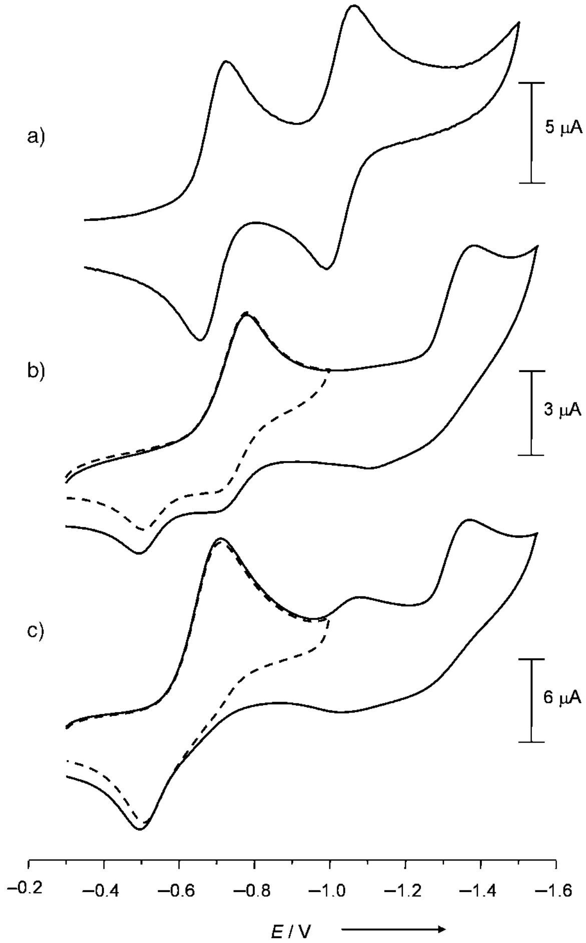
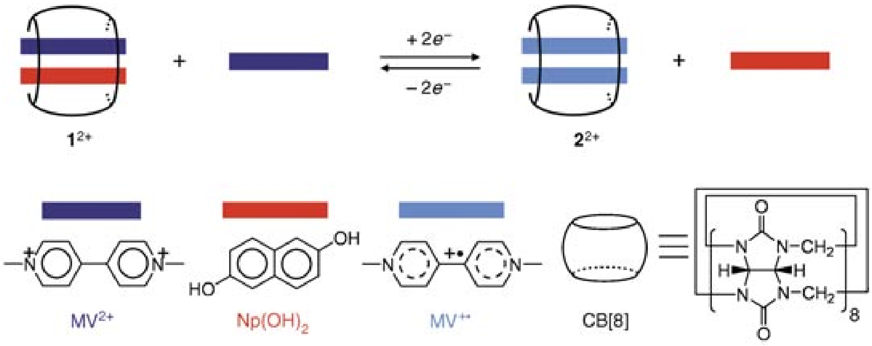


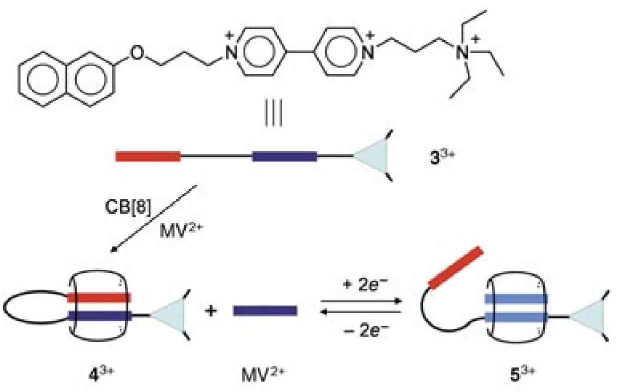
Figure 1. Cyclic voltammograms of a) MV^{2+} (0.5 mM) and b) $\mathbf{1}^{2+}$ (0.5 mM) in the absence of free MV^{2+}, and c) $\mathbf{1}^{2+}$ (0.5 mM) in the presence of free MV^{2+} (1 equiv) in phosphate buffer solution (0.1 M, pH 7.0). Scan rate = 100 mV s^{-1}; – – – different scan rate.



Scheme 1. Interconversion of hetero- and homo-guest-pair inclusion in CB[8] triggered by a redox stimulus. MV = methyl viologen, $Np(OH)_2$ = 2,6-dihydroxynaphthalene, CB[8] = cucurbit[8]uril.

The redox-coupled guest-exchange process was further investigated by cyclic voltammetry (Figure 1). Methyl viologen (MV^{2+}) shows two reversible waves that correspond to the redox couples $MV^{2+}/MV^{+\bullet}$ and $MV^{+\bullet}/MV^0$ (Figure 1 a). Compared to MV^{2+}, $\mathbf{1}^{2+}$ exhibits a moderate negative shift of the first reduction peak and a large negative shift of the second reduction peak (Figure 1 b). Furthermore, the oxidation process that corresponds to the first reduction process of $\mathbf{1}^{2+}$ shows two peaks at −0.71 V and −0.50 V (vs SCE—saturated calomel electrode), the latter of which is almost the same as that for the oxidation of $\mathbf{2}^{2+}$.[6] With increasing scan rates the oxidation peak at −0.71 V increases, whereas the peak at −0.50 V decreases (see Supporting Information), as often seen in processes that involve electron transfer followed by a chemical reaction. The addition of MV^{2+} (1 equiv) results in a small positive shift of the first reduction wave, disappearance of the oxidation peak at −0.71 V, and concomitant increase of the peak at −0.50 V (Figure 1 c).[7] A spectroelectrochemical study shows that the absorption spectrum of the species generated by the electrolysis of $\mathbf{1}^{2+}$ (applied potential, −0.85 V vs SCE, in the presence or absence of MV^{2+} (1 equiv)) is essentially identical to that of $\mathbf{2}^{2+}$ (see Supporting Information). Taken together, these results suggest that the reduction of $\mathbf{1}^{2+}$ initially generates the one-electron-reduced species $\mathbf{1}^{+\bullet}$, which contains $MV^{+\bullet}$ and $Np(OH)_2$ encapsulated in CB[8], and then reacts with free $MV^{+\bullet}$ to undergo the rapid guest exchange that leads to $\mathbf{2}^{2+}$ and free $Np(OH)_2$ (see Supporting Information). Note that the regeneration of $\mathbf{1}^{2+}$ and MV^{2+} by the oxidation of $\mathbf{2}^{2+}$ and $Np(OH)_2$ probably does not follow the reverse pathway because the 1:1 mixture of $\mathbf{2}^{2+}$ and $Np(OH)_2$ is thermodynamically far more stable than the 1:1 mixture of $\mathbf{1}^{+\bullet}$ and $MV^{+\bullet}$. Instead, it is more likely to occur through another pathway that involves the initial generation of the 1:1 complex $MV^{2+}\subset CB[8]$ by the oxidation of $\mathbf{2}^{2+}$, as we demonstrated previously,[6] which then reacts with free $Np(OH)_2$ to produce $\mathbf{1}^{2+}$ (see Supporting Information).

The discovery of the redox-coupled guest-exchange process prompted us to design and synthesize a redox-driven molecular machine that behaves as a molecular loop lock, which can be switched on and off (locked and unlocked) by means of a key and a redox stimulus (Schemes 2 and 3). The guest molecule $\mathbf{3}^{3+}$, which contains a naphthalen-2-yloxy (Np) unit and a viologen unit linked to each other by a flexible tether as well as a bulky cationic unit at the terminal,[8] was synthesized in four steps (see Supporting Information). Treatment of $\mathbf{3}^{3+}$ with CB[8] (1 equiv) in water resulted in the exclusive formation of the stable 1:1 complex $\mathbf{4}^{3+}$ through the formation of the intramolecular CT complex between the Np and viologen units inside CB[8], as confirmed by ESI-MS and UV/Vis and NMR spectroscopy analyses (see Supporting Information). In particular, the upfield-shifted signals for the protons of the Np and viologen units and the downfield-shifted signals for the protons of the linker and cationic terminal in the ^{1}H NMR spectrum of $\mathbf{4}^{3+}$ (see Supporting Information) are consistent with the formation of a molecular loop[5c] with a "closed" or "locked" conformation as illustrated in Scheme 2.



Scheme 2. Formation of the molecular loop lock $\mathbf{4}^{3+}$ (folded "locked" state) through the formation of an intramolecular CT complex inside CB[8], and the redox-induced formation of ternary complex $\mathbf{5}^{3+}$ (open "unlocked" state).

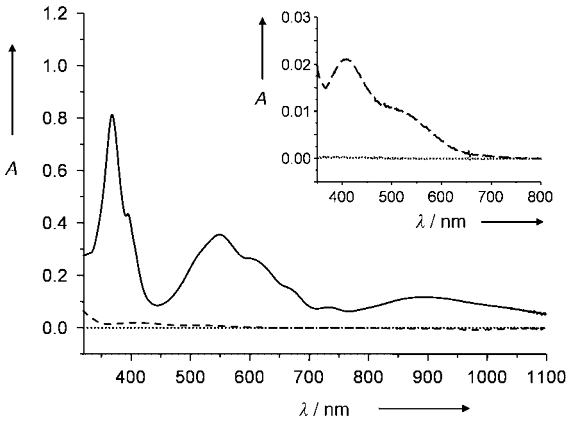


Figure 2. Absorption spectra of $\mathbf{4}^{3+}$ (0.25 mM) before (----- and inset) and after (——) reduction with $Na_2S_2O_4$ in the presence of MV^{2+} (1 equiv) in carbonate buffer (pH 10.0). Optical path = 1 mm; ••••• zero absorption.

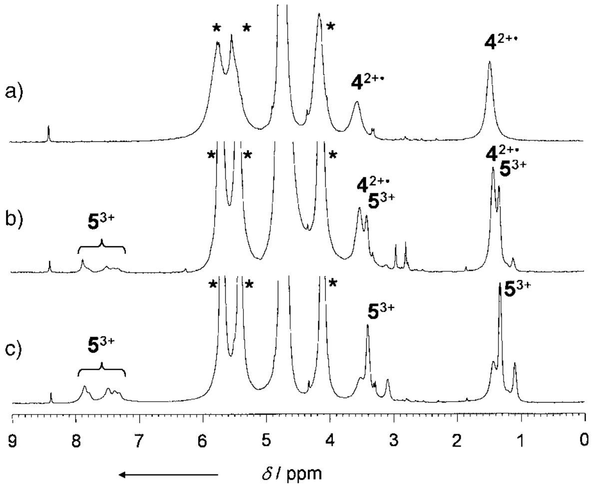
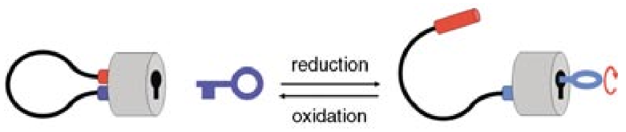


Figure 3. ^{1}H NMR spectra obtained after reduction of $\mathbf{4}^{3+}$ with $Na_2S_2O_4$ in carbonate buffer (pH 10.0) a) in the absence of MV^{2+}, b) in the presence of MV^{2+} (0.5 equiv), and c) in the presence of MV^{2+} (1.0 equiv). The signals labeled with * correspond to the CB[8] host.

The ^{1}H NMR spectrum of $\mathbf{4}^{3+}$ is not affected by the addition of MV^{2+} (1 equiv) which indicates that the 1:1 host–guest complex formed by the intramolecular CT interaction is much more stable than the ternary complex formed by the intermolecular CT interaction between the Np unit of $\mathbf{4}^{3+}$ and MV^{2+} inside CB[8]. However, treatment of a solution containing $\mathbf{4}^{3+}$ and MV^{2+} (1 equiv) with $Na_2S_2O_4$ results in the formation of the ternary complex $\mathbf{5}^{3+}$ (Scheme 2) in which the one-electron-reduced viologen unit of $\mathbf{3}^{2+\bullet}$ interacts with $MV^{+\bullet}$ inside CB[8]. The formation of this complex was confirmed by the appearance of new absorption bands at λ = 368, 550, and 890 nm, which are characteristic of a CB[8]-stabilized viologen radical-cation dimer (Figure 2).[9,10] Owing to the paramagnetic nature of $\mathbf{5}^{3+}$, the signals for the Np unit are broad, but are clearly observed by NMR spectroscopy (Figure 3).[10] Furthermore, the chemical shift values ($\delta \approx 7$–8 ppm) for the protons of $\mathbf{5}^{3+}$ are close to those for free $\mathbf{3}^{3+}$ which indicates that the Np unit is now located outside CB[8] and that $\mathbf{5}^{3+}$ has an open or "unlocked" conformation as schematically shown in Scheme 2. Introduction of O_2 into the solution of $\mathbf{5}^{3+}$ regenerates $\mathbf{4}^{3+}$ and MV^{2+} as confirmed by UV/Vis and NMR spectroscopy. Thus, $\mathbf{4}^{3+}$ with a "closed" conformation is converted into $\mathbf{5}^{3+}$ with an "open" conformation upon reduction in the presence of MV^{2+}, and the process can be reversed by oxidation.[11] This system thus behaves as a molecular loop lock that can be locked and unlocked with a key and a redox stimulus (Scheme 3): The two species $\mathbf{4}^{3+}$ and $\mathbf{5}^{3+}$ represent the locked and unlocked states, respectively, and MV^{2+}, which is activated by reduction, plays the role of the key. It may be regarded as a "safeguarded" lock that requires not only a key but also an activation process to open.[10,12,13]

In summary, we have demonstrated the redox-coupled guest-exchange of CB[8]-stabilized CT complexes which illustrates unprecendented interconversion, triggered by an



Scheme 3. Illustration of the working mode of a molecular loop lock with a key.

external stimulus, of hetero- and homo-guest-pair inclusion in a molecular host. Furthermore, we have synthesized a redox-driven molecular machine based on this phenomenon that behaves as a molecular loop lock, which requires both a key and an activation process to open. Further studies on the novel molecular machine and its applications are in progress.

Experimental Section

3·3 Br**:** The tribromide salt of *N*-(3-(naphthalen-2-yloxy)propyl)-*N*′-(3-(trimethylamino)propyl-4,4′-bipyridinium) ($\mathbf{3}^{4+}\cdot 3\,Br^-$) was prepared according to a reported procedure[5c] with a minor modification. Detailed procedures are described in Supporting Information.

4·3 Br**:** CB[8]·H_2SO_4·16 H_2O (20.0 mg, 11.6 μmol) was added to a solution of **3**·3 Br (7.0 mg, 9.7 μmol) in D_2O (4 mL), and the resulting mixture was sonicated for 1 min. Undissolved solid was filtered off, and the filtrate was slowly evaporated under reduced pressure to yield the title product (18.2 mg, 92 %). ^1H NMR (500 MHz, D_2O, 25 °C, TMS): $\delta = 8.84$ (d, J(H,H) = 6.3 Hz, 1 H; Py), 8.79 (d, J(H,H) = 6.6 Hz, 2 H; Py), 8.76 (d, J(H,H) = 6.3 Hz, 1 H; Py), 6.85–6.78 (m, 2 H; Py, Np), 6.74 (d, J(H,H) = 6.5 Hz, 3 H; Py, Np), 6.65 (d, J(H,H) = 8.9 Hz, 1 H; Np), 6.62 (d, J(H,H) = 4.8 Hz; Np), 6.56 (d, J(H,H) = 8.1 Hz, 1 H; Np), 6.51 (d, J(H,H) = 3.4 Hz, 2 H; Np), 6.06 (d, J(H,H) = 1.9 Hz, 1 H; Np), 5.72 (dd, J(H,H) = 9.2, 15.3 Hz, 16 H; CB[8]), 5.47 (s, 16 H; CB[8]), 5.08–5.02 (m, 2 H; Py-CH_2), 4.91–4.88 (m, 2 H; Py-CH_2), 4.62–4.57 (m, 2 H; OCH_2), 4.21–4.16 (dd, J(H,H) = 9.2, 15.3 Hz, 16 H; CB[8]), 3.66 (t, J(H,H) = 9.1 Hz, 2 H; NCH_2), 3.57–3.56 (m, 6 H; NCH_2), 2.99–2.66 (m, 4 H; CH_2), 1.46 ppm (t, J(H,H) = 7.11 Hz, 9 H; CH_3); HRMS (ESI-MS): m/z: calcd for $C_{80}H_{90}N_{35}O_{17}$ $[M\text{-}3\,Br]^{3+}$: 604.2418; found: 604.2411.

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[6] We previously demonstrated that the 1:1 inclusion complex $MV^{2+}\subset CB[8]$ undergoes disproportionation to form an equal mixture of the 2:1 complex $\mathbf{2}^{2+}$ ($(MV^{+\bullet})_2\subset CB[8]$) and free CB[8] upon chemical or electrochemical reduction and that the reaction is reversible: W. S. Jeon, H.-J. Kim, C. Lee, K. Kim, *Chem. Commun.* **2002**, 1828.

[7] The small, reversible wave at −1.1 V in Figure 1 c, which increases with increasing scan rates, corresponds to the $MV^{+\bullet}/MV^0$ redox couple of free $MV^{+\bullet}$. The subsequent spectroelectrochemical study revealed no absorption bands that correspond to free monomeric $MV^{+\bullet}$ after electrolysis of $\mathbf{1}^{2+}$ in the presence of MV^{2+} (1 equiv, see Supporting Information) which implies that the reaction between $\mathbf{1}^{+\bullet}$ and $MV^{+\bullet}$ that leads to $\mathbf{2}^{2+}$ is relatively slow on the timescale of cyclic voltammetry experiments. The second reduction wave of $\mathbf{1}^{2+}$ in the absence (Figure 1 b) or presence (Figure 1 c) of MV^{2+} is apparently related to the reduction of the 2:1 complex $\mathbf{2}^{2+}$ generated in the first reduction step, but we do not clearly understand this process at the moment.

[8] The bulky cationic unit was introduced at the terminal to prevent the formation of intermolecular CT complexes and intermolecular viologen radical-cation dimers inside CB[8] upon reduction. Another role of the cationic terminal unit is to improve the solubility of the complex after reduction.

[9] The bands at $\lambda = 368$, 550, and 890 nm can also be attributed to $\mathbf{2}^{2+}$ ($(MV^{+\bullet})_2\subset CB[8]$), which may be generated during the reduction process. However, the intensity of the band at $\lambda = 368$ nm increases linearly with increasing concentrations of MV^{2+} (0–1.0 equiv) and is almost twice as high as that of $\mathbf{2}^{2+}$ generated by the reduction of a 1:1 mixture of MV^{2+} and CB[8] at the same concentration (see Supporting Information). These results thus indicate that the amount of $\mathbf{2}^{2+}$ generated during this reduction process is insignificant. Besides the bands that are assigned to $\mathbf{5}^{3+}$, shoulders at $\lambda = 395$ and 610 nm are observed (Figure 2) which can be attributed to the one-electron-reduced species $\mathbf{4}^{2+\bullet}$ and $MV^{+\bullet}$ that are in equilibrium with $\mathbf{5}^{3+}$. It also suggests that the reduction of a 1:1 mixture of $\mathbf{4}^{3+}$ and MV^{2+} first generates $\mathbf{4}^{2+\bullet}$ and $MV^{+\bullet}$, which further react to produce $\mathbf{5}^{3+}$ (see Supporting Information).

[10] Treatment of $\mathbf{4}^{3+}$ with $Na_2S_2O_4$ in the absence of MV^{2+} produces the one-electron-reduced species $\mathbf{4}^{2+\bullet}$, whose UV/Vis spectrum is similar to that of $MV^{+\bullet}$ which indicates that the viologen unit of the guest molecule exists in its radical-cation form. Owing to the paramagnetic nature of the species, the signals for the protons from the stopper unit ($\delta \approx 1.4$ and ≈ 3.5 ppm) are broad. However, the signals are clearly observed in the ^1H NMR spectrum of $\mathbf{4}^{2+\bullet}$ whereas those for the Np unit are not, which indicates that the Np unit is still in close proximity to the viologen radical-cation unit. This result in turn suggests that $\mathbf{4}^{2+\bullet}$ maintains the same "locked" conformation with the one-

electron-reduced viologen and Np units located inside CB[8]. Thus, the molecular loop lock does not open in the absence of the key (MV^{2+}) and the activation process (reduction).

[11] Preliminary electrochemical studies confirmed that this reversible process can also be triggered by electrochemical stimuli. Details of the electrochemical behavior of $\mathbf{4}^{3+}$ and related compounds will be published elsewhere in due course.

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