Progress in the studies of electrochemically controllable host-guest interactions*

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Abstract Studies on the electrochemically controllable host-guest interactions have received considerable attention since the middle of the 1980s. In this paper, progress in such studies is reviewed according to the types of the hosts, including cyclodextrin, calixarene, cucurbituril, cyclophane, and so on. In addition, perspectives for the future development and potential applications of the interactions are discussed.

Keywords: host-guest interaction, electrochemistry, cyclodextrin, calixarene, cucurbituril, cyclophane.

Molecular recognition is the chemical basis of many biological processes and biological phenomena, and is one of the most important components of supramolecular chemistry. Effective control of the molecular recognition processes by external stimuli may afford a deeper understanding of the nature of the process and open ways to its potential applications, such as design of novel intelligent materials, new sensors and molecular machines, etc. Therefore, studies on the control of molecule recognition have received considerable attention during the last 20 years[1–6].

In theory, any physical, chemical or biological signals may be employed to control the recognition processes. Among them, photochemistry, pH, temperature and electrochemistry are the mostly studied ones. Compared to other methods, electrochemical approach is most attractive since it does not contaminate the systems to be studied, and is easy to be performed. Therefore, the studies of controllable molecular recognition have become popular in recent years[1–10].

Host-guest interaction is the mostly studied electrochemically controllable molecular recognition processes. The control is based upon the fundamental phenomenon that the interaction strength strongly depends upon the oxidation state of the host or the guest, and thereby the gain or loss of an electron by a host or a guest molecule will modify the stability of a host-guest complex, as illustrated in Fig. 1[1,7,9].

![Strong binding ↔ Weak binding](image)

Fig. 1. Schematic representation of the control of molecular recognition processes by redox reactions.

In this paper, progress in studies on the electrochemically controllable host-guest interaction is reviewed according to the types of the hosts, including cyclodextrin, calixarene, cucurbituril and cyclophane, etc. In addition, possible progress in the future and potential applications of the interactions has also been predicted.

1 Cyclodextrins (CD)

CDs are cyclic oligomers of α-D-glucose, which are linked together by α-(1, 4) bonds. There are three kinds of CDs, which are α-CD (6 glucopyranose units), β-CD (7 glucopyranose units), and γ-CD (8 glucopyranose units), respectively. CDs have a defined “bucket” shape with a hydrophobic internal cavity and all the hydroxyl groups crowding the two cavity openings. In aqueous solution, they can form sta-

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ble inclusion complexes with less polar molecules (guests) that fit tightly inside the CD cavity. Among them, aromatics and derivatives, adamantane and derivatives and some metalloccenes are commonly found guests\cite{1,11-13}. Although the CDs are not electroactive, they do form inclusion complexes with suitable redox active guests. For instance, β-CD can form stable 1:1 complexes with ferrocene (Fc) and Fc derivatives. As early as 20 years ago, Osa\cite{14} and Takahashi\cite{15} revealed that ferrocenecarboxylic acid is effectively bound by β-CD (2200 L/mol), but its oxidized form is not. Shortly after the reports, Breslow\cite{16} and Kaifer\cite{17-19} further studied the interactions between CDs and Fc and Fc derivatives, and obtained similar results. For example, one-electron oxidation greatly diminishes the stability of the inclusion complex between Fc and β-CD. In addition, it was also found that the electrochemical oxidation in the presence of the host takes place only on the free Fc guest. No direct oxidation of the inclusion complex is observed. This finding suggests that electron transfer from the inclusion complex must be thermodynamically or kinetically hindered. Kaifer and co-workers\cite{20} designed complexes of CDs with multi-site guests based on dendrimer skeletons and found that dendrimers having 4, 8, or 16 ferrocene subunits at their surface can act as multi-site guests for complexation by β-CD yielding soluble supra-molecular assemblies with high molecular weights. The complex can be broken up by simple oxidation of the Fc moieties (Fig. 2).

![Fig. 2. Supra-molecular assembly formed between a dendrimer and eight cyclodextrins.](image)

Kaifer et al.\cite{21} synthesized two new Fc derivatives, 7-ferrocenyl-2, 4, 6-heptatrienial and 7-ferrocenyl-2, 4, 6-heptatrienial and investigated their host-guest binding interactions with the receptors α-CD and β-CD in aqueous medium. Electrochemical measurements suggest some degree of site selectivity in the complexation processes, with β-CD binding preferentially to the Fe moiety while α-CD interacts with the unsaturated chain. Osella et al.\cite{22} reported the results of electrochemical study of the host-guest supra-molecular adducts between Fc⁺ (ferrocenium cation), and other mono- and di-substituted Fc derivatives with β-CD and its derivatives in mixed organic-aqueous media. Interestingly, the addition of sulfated β-CD shifts the redox Fc/Fc⁺ couple toward cathodic values, indicating that the oxidized, cationic form Fe⁺ is more strongly bound to the sulfated CD than neutral Fc, probably by means of electrostatic interaction with the external —SO₃ functionalities.

Besides Fc, viologen (4, 4'-bipyridinium) and cobaltocenium (Cob⁺) derivatives are also redox active guests. In 1988, Kaifer and co-workers\cite{23} studied the effects of CDs on the aggregation and electrochemical behaviors of N-ethyl-N'-hexadecyl-viologenbromide (C₁₆VBBr₂) and N-ethyl-N'-octadecyl-viologenbromide (C₁₈VBBr₂). It was demonstrated that in the presence of α-CD, the first reduction couple of both viologens exhibit reversible, diffusion-controlled voltammetric behavior. α-CD also inhibits completely the formation of dimers from the corresponding cation radicals. In striking contrast, the presence of β-CD does not eliminate the precipitation on the electrode surface of the hydrophobic, reduced viologen species. Furthermore, β-CD is unable to prevent the extensive dimerization of the viologen cation radicals. All these findings can be interpreted by assuming that the CDs interact with the long alkyl chain of the viologens forming inclusion complexes. No evidence was obtained to indicate the interaction of either CDs with aromatic viologen moieties. After that, Kaifer's group\cite{24,25} also investigated the complexation between CDs and viologen or Cob⁺ derivatives. It was found that these guests did not interact appreciably with CDs in their most stable oxidation states (2⁺ for the viologens and 1⁺ for Cob⁺). However, reduction considerably increases the affinity of these guests for CDs. In the case of Cob⁺, one-electron reduction yields neutral cobaltocene (Cob), which, like Fc, is an excellent guest for inclusion by β-CD (Fig. 3). One-electron reduction of the viologens leads to cation radical species that are not strongly bound by the CDs. In contrast, two-electron reduc-
tion yields uncharged guests which form very stable complexes with $\beta$-CD and a methylated $\beta$-CD derivative (Fig. 4). Cuadrado et al.\(^{26}\) reported the preparation, characterization of four dendrimers having 4, 8, 16 and 32 peripheral Co(II) subunits and studied their binding interactions with $\beta$-CD. However, these positively charged dendrimers are not complexed by $\beta$-CD in aqueous media, their electrochemical reduction triggers the formation of high molecular weight, multi-site inclusion complexes with this host (Fig. 5). Cuadrado and co-workers\(^{27}\) synthesized a new organometallic compound containing a Co(II) and a Fe residue and characterized its electrochemical behavior by reversible one-electron oxidation of the Fe residue and by one-electron reduction of the Co(II) subunit. The organometallic compound exhibits three accessible oxidation states that can be represented as Fe$^{3+}$-Co(II), Fe-Co$^{3+}$ and Fe-Co. Cyclic voltammetric experiments in the presence of the host $\beta$-CD revealed that the fully oxidized form (Fe$^{3+}$-Co(II)) is not bound, the intermediate oxidation state (Fe-Co$^{3+}$) forms a stable 1:1 complex by inclusion of its Fe site, and the fully reduced form (Fe-Co) presents two binding sites for the host. Park's group\(^{28}\) reported an electrochemical sensor for an electrochemically inactive organic compound using a self-assembled monolayer (SAM) formed on a gold electrode surface from a solution of thiolated $\alpha$-CD. The SAM makes up an array of micro-electrodes which capture electroactive molecules such as FeC. When this SAM-modified electrode is exposed to a solution containing an electrochemically inactive compound, e.g. glucose, the captured FeC molecules are replaced by the guest molecules via an equilibrium established between the two compounds, lowering the current for FeC oxidation. The decrease in current is directly proportional to the amount of glucose added. The glucose sensor they constructed offers a novel concept of how an electrochemically inactive organic compound can be analyzed by using electrochemical method and also a molecular size selective sensor can be designed.

In addition to the three kinds of electroactive guests, Wu et al.\(^{29}\) also studied the $\beta$-CD modified poly(N-acetylaniline) (PNAANI) electrode using hydroquinone as an electroactive probe. In the cyclic voltammogram of hydroquinone at the $\beta$-CD/PNAANI electrode, $\Delta E_p$ ($E_p$, peak potential) of the peaks is sharpening and the area of the peaks is increasing, which may be due to the inclusion of hydroquinone into the cavity of $\beta$-CD immobilized at the electrode surface. Jouni's group\(^{30}\) investigated the behavior of the inclusion complex between 4-amino-
N, N-diphenylamine (ADPA) and CDs by fluorescence and electrochemistry techniques at different pH values and in different oxidation states. It was found that it was possible to control the complexation between ADPA or its oxidation product and CDs by altering pH or the applied potential. This gives a new route to synthesize encapsulated conductive polymers like polyaniline.

Recently, Matsui et al.\cite{31} fabricated Fe nano-tubes by binding Fe carboxylic acid derivative onto template peptide nano-tubes via hydrogen bonding. It was found that the Fe nano-tubes can attach onto the gold electrode by recognizing β-CD in SAMs via host-guest interaction and the attachment and detachment process can be controlled electrochemically.

All these studies indicate that in most of the cases, guest molecules of appropriate size are strongly bound by CDs when they are in their neutral states, but they cannot be bound when they are oxidized. Moieties containing viologen or Cob, however, are very different from those containing Fe, in which the molecular recognition forces can be deactivated electrochemically. The former requires electrochemical activation to trigger significant complexation by the CD hosts\cite{1}. The characteristics of the host-guest pairs are crucial for the design of molecular machines and molecular devices.

2 Calixarenes

The calixarenes constitute another important class of receptors that have attracted considerable attention during recent years\cite{1,32}. They are a group of polyphenolic basket-shaped molecules, usually represented as calix[n]arene (n, the number of phenol units)\cite{12}. The aromatic skeleton of the host molecules can be modified in many ways to modify their binding ability and selectivity to guest molecules or to introduce specific functional groups. Like CDs, calixarenes are electro-inactive, but the electrochemical parameters of redox active guests are often strongly affected by the presence of these hosts, affording a valuable tool to investigate the complex processes\cite{1}.

Kaifer et al.\cite{1} compared the effect of β-CD and calixarene 1 (Fig. 6) on the electrochemical behavior of ferrocene-carboxylate (FeCOO\textsuperscript{−}). Cyclic voltammetry studies demonstrated that the complexation of FeCOO\textsuperscript{−} with β-CD may be detected by a shift in the half-wave potential (E\textsubscript{1/2}) to more positive values and by a decrease in the peak current (i\textsubscript{pa}). The anodic potential shift reveals that the reduced form (FeCOO\textsuperscript{−}) of the guest is more stabilized by complexation than the oxidized form (Fe\textsuperscript{3+} COO\textsuperscript{−}). In contrast, the anionic calixarene host induces a negative shift in the E\textsubscript{1/2}. Therefore, the host interacts more strongly with the oxidized form of the guest (Fe\textsuperscript{3+} COO\textsuperscript{−}), which is anticipated from the anionic character of both the reduced guest (FeCOO\textsuperscript{−}) and the host. Moreover, calixarene addition has a much smaller effect on i\textsubscript{pa} than that observed with β-CD, indicating that the initial form of the electroactive guest (FeCOO\textsuperscript{−}) is not significantly bound by the calixarene host. In addition, Kaifer’s group\cite{33,34} also studied the inclusion complexation of other Fe derivatives and methyl viologen with calixarene 1.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{fig6.png}
\caption{Structures of sulfonatocalix[6]-arene hosts.}
\end{figure}

Atwood and co-workers\cite{35} studied the solid-state structure of the octa-anionic form of calixarene 1 (1\textsuperscript{8−}). In neutral aqueous solution, the anionic host has two identical binding sites (Fig. 6), and thereby formation of ternary complexes (binding two guests) is possible. Kaifer’s group\cite{1,34} identified the 1:2 inclusion complex of 1\textsuperscript{8−} and two Cob\textsuperscript{+} guests in aqueous solution by using \textsuperscript{1}H NMR technique. Reduction of Cob\textsuperscript{+} leads to the dissociation of the ternary complex. In contrast, reduction of the same guest in the presence of β-CD gives rise to the formation of a strong 1:1 β-CD—Cob inclusion complex. This system provides an interesting example of how the redox chemistry of the guest can be manipulated in order to select the host and the stoichiometry of the resulting inclusion complexes. Kaifer et al.\cite{36} also studied the complexation of Cob\textsuperscript{+} by the methylated calixarene.
analogue 2 (Fig. 6). It was found that this host is much less effective than 1. Cyclic voltammetry, $^1$HNMR and simulation studies revealed that $^{26}$- is not an effective host for the same set of Fe derivatives due to its conformational flexibility and lack of pre-organization for binding.

Bond’s group$^{[39]}$ studied the electrochemical behavior of the inclusion complex of C$_{60}$ and two $p$-benzyl-calix[5]arene (referred to as C$_{60}$·L$_2$) in microcrystal state adhered to the electrode surface via cyclic voltammetry. It was shown that the reversibility of the reduction of the inclusion complex is determined mainly by the reversibility of the diffusion of electrolyte cations into the lattice of the crystals. It was also found that the interaction between C$_{60}$ and the calix[5]arene is so strong that one electron reduction of C$_{60}$ cannot break the inclusion complex apart. Bard et al.$^{[40]}$ investigated the electrochemical reduction of tert-butyl-calix[8]arene-C$_{60}$ film. It was demonstrated that complexation of C$_{60}$ within the film results in a negative shift of the peak potential of the first cathodic wave by about 400 mV compared to the reduction of a pure C$_{60}$ film. Moreover, reduction of C$_{60}$ breaks the complex apart, resulting in escaping of C$_{60}$ from the calixarene basket. Webster and co-workers$^{[41]}$ studied the electrochemical properties of C$_{60}$ in the presence of excess of calix[5] arene or calix[3] arene, and they found that C$_{60}$ could be fully included provided the complexation time is enough. The electrochemical behavior of these inclusion complexes is very different from that of the pure C$_{60}$. The cathodic wave potentials are negatively shifted, and the four waves related with C$_{60}$ merge into two waves. Furthermore, some of the reduced C$_{60}$ molecules still exist in the cavity of the host within the time range of the electrochemical scan cycle.

3 Cucurbiturils

Cucurbiturils are a kind of macrocyclic compounds, which are formed via condensation of glycoluril and formaldehyde in the presence of acids. The compounds are usually represented as CB[n] (n, the number of glycoluril unit). The structures are shown in Fig. 7$^{[42]}$. The structures are characterized by symmetry and with two identical openings. Like CDs, the hydrophobic interior of CBs provides a potential site for inclusion of organic molecules. Unlike CDs, however, they can form stable inclusion complexes with various protonated alkyl and arylamines.

The rigid structure and capability of forming stable complexes with molecules and ions make CBs attractive as building blocks for the construction of supramolecular architectures$^{[42, 43]}$.

![CB[n]](n = 5, 6, 7, 8)

Fig. 7. The structure of CB.

Although the synthesis of CB[6] was reported 100 years ago$^{[44]}$, its chemical nature and structure had not been clear till 1981$^{[45]}$. Another 20 years later, CB[6] analogues CB[n] (n = 5, 7, 8) and their derivatives were synthesized by Kim’s group$^{[46]}$, which becomes the basis for the studies of the supramolecular chemistry of CB[n] hosts. As mentioned above, CBs bind guests of various sizes similar to CDs, but the two host families have fundamental differences in host-guest interactions originated from the different functional groups decorating the cavity entrances. The different inclusion behavior between CBs and CDs is illustrated by the electrochemical behavior of N, N'-dimethyl-4,4'-bipyridinium (MV$^2^+$) in the presence of CB[7]$^{[47, 48]}$ or β-CD$^{[27]}$. It was revealed that CB[7] binds MV$^2^+$ strongly (K$_{2+}$: ~2 x 10$^5$ L/mol). One-electron reduction of MV$^2^+$ leads to MV$^{+}$, which still binds tightly to CB[7] with a slightly lower binding affinity (K$_{+}$: ~1 x 10$^5$ L/mol), as indicated by a small negative shift (~ - 20 mV) in the first E$_{1/2}$. However, the large negative shift (~ - 110 mV) in the second E$_{1/2}$ indicates that further reduction of the guest to MV$^0$ substantially decreases its binding affinity to CB[7] (K$_{0}$: ~2 x 10$^2$ L/mol). Therefore, the stabilities of the CB[7] complexes with the three species of MV (MV$^2^+$, MV$^{+}$, MV$^0$) follow the order of K$_{2+}$ > K$_{+}$ > K$_{0}$, which is exactly opposite to that for β-CD (K$_{2+}$ < K$_{+}$ < K$_{0}$), as described earlier.

Similar to CB[7], CB[8] also forms an exclusive 1:1 host-guest complex with MV$^2^+$ with formation constant of 1.1 x 10$^5$ L/mol. However, one-electron reduction of MV$^2^+$/CB[8] leads to rapid generation of a 2:1 inclusion complex (MV$^{+}$)$_2$/CB[8] (Fig. 8)$^{[49]}$. Such redox control of the stoichiometry in the host-guest complexation may provide a working principle for electrochemically controllable molecular
machines. Kaifer et al. found that Fe$^+$ and Cob$^+$ can form highly stable 1:1 inclusion complexes with CB. The association constants are larger than $10^6$ L/mol. The electrochemical reduction of either guest leads to a modest loss in binding affinity, which may suggest that dissociation of the complex into their free components is not necessary, since the reduced guests are still bound to the host. The electron transfer route is shown in Fig. 9, which is completely different from the inclusion complexes. In the inclusion complex, electron transfers via a chemical-electrochemical (CE) mechanism (Fig. 3).

![Figure 8. The redox equation of MV$^2$+/CB(8).](image)

![Figure 9. The mechanism of the redox reaction of CB(7)/Fe$^+$.](image)

4 Cyclophanes

Cyclophanes are macrocycles made of aromatic ring subunits. One of the first attempts to exert redox control on the strength of their binding to guest species was reported by Diederich’s group. Researchers found that the reduced flavin-cyclophane can form cavity-inclusion complexes with naphthalene derivatives. Much of Kaifer’s work has focused on the cyclobis (paraquat-p-phenylene) receptor $3^{4+}$ (Fig. 10), which was first synthesized by Stoddart and co-workers. This tetracationic cyclophane has a very rigid structure with two electron acceptors, viologen subunits. The cavity of the compound is ideally sized to include aromatic rings. Unlike CD or calixarene hosts, $3^{4+}$ is electroactive. Usually the two bipyridinium groups undergo one-electron reduction at similar potential, resulting in a single voltammetric wave. The $E_{1/2}$ of this wave is sensitive to complexation, shifting to more negative values upon inclusion of a π-donor guest due to charge-transfer stabilization of the tetracationic (electron acceptor) from the guest. The host exhibits another cathodic wave at more negative potential, which corresponds to the second one-electron reduction of the bipyridinium groups. This wave can also sometimes be utilized to monitor complexation/decomplexation processes.

Kaifer’s group cooperated with Stoddart’s group and investigated the complexation of the aromatic molecules catechol and indole with $3^{4+}$. It was found that the receptor $3^{4+}$ has a substantial affinity for the two guests. And it is possible to alter the affinity of the host to π-donor guests by manipulating the oxidation state of the receptor’s paraquat groups. Thus this species provides an early example of a redox-switchable receptor for organic molecules. Furthermore, Kaifer and coworkers revealed that benzidine and biphenol derivatives are excellent guests for cyclophane host and that the complexation of benzidine can be used to template the synthesis of rotaxane $4^{4+}$ (Fig. 10).

![Figure 10. Structures of cyclophane $3^{4+}$ and rotaxane $4^{4+}$.](image)

Since benzidine is a better electron donor than biphenol, a larger rotaxane containing both aromatic subunits inserted along the thread appears to be an excellent candidate to illustrate the concept of an electrochemically controllable molecular shuttle. Kaifer’s group synthesized a new rotaxane and determined that at $-40^\circ$C in CD$_3$CN, 84% of the cyclophane beads are centered at the benzidine station and 16% are on the biphenol station. However, after
one electron oxidation of the benzdine station, the tetracationic bead moves away from the positively charged benzdine, looking for the stability offered by the biphenoI subunit. This rotaxane offers a compelling example of reversible electrochemical control on the structure of a moleclle, which behaves in a "switchable" fashion[11]. Kaefer et al.[57] also carried out a number of competition experiments with host 34+, benzdine and biphenoI guests and studied the switching behavior of this tri-molecular system to compare it with that of the uni-molecular rotaxane system. The findings indicate that it is indeed possible to control the tri-molecular system with external stimuli. However, due to the finite binding constant values between the host and the two guests, the trimelecular system behaves rather inefficiently and the binding equilibriums keep a substantial fraction of the host in the un-complexed form. The uni-molecular rotaxane system is more efficient because it eliminates the free host from the system and the host is "forced" to interact with either one of the guests along the rotaxane's linear component[11,57]. A redox active species tetrahiafulvalene (TTF) can exist in three oxidation states. Stoddart’s group[8,58] found that neutral TTF(0) is bound strongly by 34+ in acetonitrile (Ks = 1 ± 0.1 × 10⁴ L/mol) but not at all when oxidized successively to TTF⁺ and then TTF2+. Conversely, TTF2+ is bound strongly by the crown ether 1, 5-dinaptho[38] crown-10 in acetonitrile (Ks = 4.1 ± 0.4 × 10³ L/mol) but not at all as TTF⁺ or TTF(0) (Fig. 11). Therefore, in the presence of both receptors, the TTF guest interchanges between the two receptors as TTF(0) or TTF2+, but TTF⁺ is not bound by either receptor. Stoddart and co-workers[8,59] also reported that a 1, 1-disubstituted Fe-based polyether can form stable inclusion complex with cyclobis(paraquat-4, 4'-biphenylene) in acetonitrile (Ks = 3900 L/mol). Electrochemical studies demonstrated that oxidation of the Fe-based units of the guest and first reduction of the bipyridinium moieties of the host occur at respectively more positive and more negative potentials than in the free component states. Detailed analysis of the electrochemical results showed that such oxidation and reduction processes cause disruption of the adduct and that re-complexation takes place upon back reduction and oxidation of the oxidized Fe and reduced bipyridinium units, respectively. The complexation/de-complexation process is reversible and fast on the time scale of the electrochemical scan.

![Fig. 11. TTF is either bound by 34+, crown ether 1, 5-dinaptho[38] crown-10 or by neither Receptor.](image)

5 Summary and perspectives

Since Osa and coworkers revealed that while ferrocene-carboxylic acid is effectively bound by β-CD, its oxidized form is not in 1985, much work has been done upon the electrochemical control of molecular...
recognition processes. The binding strength between a host and a guest of many host-guest systems studied is more or less affected by redox reactions. Future work in this field will undoubtedly be directed towards the finding of new electrochemically controllable host-guest systems and exploring of the potential applications of these systems. For example, chemical reaction rates and catalysis activities may be adjusted by altering the binding constants between a host and a guest \[60,61\]. Similarly, novel sensing films and devices may be designed and prepared by employing the same idea \[28,62,63\]. Moreover, intelligent fluids and smart soft materials can be also designed and prepared by electrochemical control of the binding affinity of host-guest interactions \[64\]. In a word, based upon electrochemical control of host-guest interactions, development of supra-molecular materials and functionalization of them will have a very bright future.

References


