

Interplay between Molecular Recognition and Redox Chemistry

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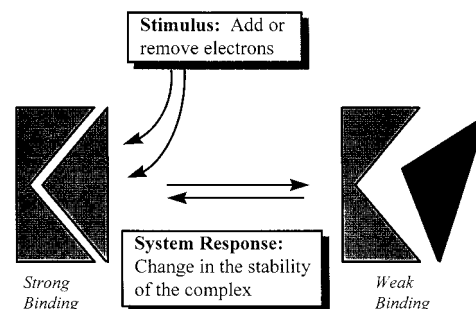
Introduction

Molecular recognition phenomena are centrally important in biochemistry and in the quickly emerging field of supramolecular chemistry.¹ It is not surprising then that the possibility of controlling the strength of molecular recognition interactions through the application of external stimuli has received considerable attention in the last 15 years.² Like many topics in supramolecular chemistry, the idea of exerting direct control on molecular recognition phenomena has a biomimetic origin, but its implications extend into materials science. Effective control of host–guest binding affinity may open the way to several desirable goals, such as responsive or intelligent materials, new sensors, and molecular devices, and may ultimately afford a deeper fundamental understanding of the intermolecular forces responsible for binding.

Photochemical, chemical (pH, ion concentration), and electrical stimuli are all reasonable possibilities to exert control on host–guest systems. Our group has focused its effort in the utilization of electrochemical (redox) conversions to modulate the strength of host–guest interactions. The fundamental idea driving our work is illustrated in Scheme 1. The most attractive aspect of this approach is that electron transfer reactions constitute the simplest type of chemical reactions and are reasonably well understood from a theoretical standpoint.³ Despite this relative simplicity, the gain or loss of an electron by a host (or guest) molecule modifies its charge and electronic distribution and often leads to very significant changes in the magnitude and nature of the intermolecular forces between this molecule and its potential recognition partners.

In this Account I will present a summary of recent work on redox control of host–guest interactions, with emphasis on work performed by my own group. First, I will start with a description of the work in homogeneous solution with three important classes of hosts, namely, cyclodextrins, calixarenes, and cyclophanes. Next, I will briefly discuss the application of host–guest chemistry at the

Scheme 1. Redox Control of Molecular Recognition



electrode–solution interface. The last part of the Account will be devoted to a survey of recent results with encapsulated redox centers and dendrimer systems.

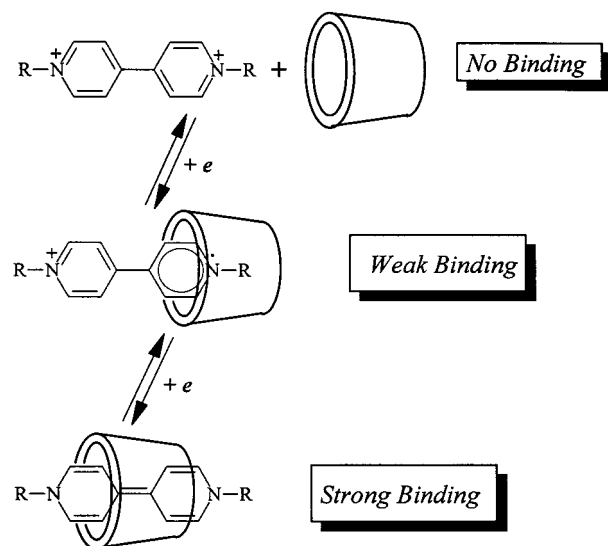
Cyclodextrin Hosts

The cyclodextrins⁴ (CDs) are an important class of natural hosts that, paradoxically, have no known function in living systems. They are cyclic glucopyranose oligomers and have a clearly defined “lampshade” shape with a hydrophobic internal cavity and all the hydroxyl groups crowding the two cavity openings. They are soluble in water and form stable inclusion complexes with those nonpolar guests that fit tightly inside the CD cavity.⁵ Although the CDs are not electroactive, they do form inclusion complexes with suitable redox active guests. For instance, β -CD forms stable 1:1 complexes with ferrocene and ferrocene derivatives. In 1985, Osa, Evans and co-workers demonstrated that while ferrocenecarboxylic acid is effectively bound by β -CD, its oxidized form is not.⁶ My group,⁷ and others,⁸ have investigated a number of ferrocene derivatives and found similar results with all of them; i.e., one-electron oxidation greatly diminishes the stability of the inclusion complex between ferrocene and β -CD. An interesting result from these studies is that the electrochemical oxidation in the presence of the host takes place only on the free ferrocene guest.^{6,7a} *No direct oxidation of the inclusion complex is observed.* This finding suggests that electron transfer from the inclusion complex must be thermodynamically and/or kinetically hindered, a point that will be revisited later.

Recently we have investigated the CD complexation of other redox active guests, such as viologen⁹ (4,4'-bipyridinium) and cobaltocenium¹⁰ derivatives. Due to their charge, these guests do not interact appreciably with CDs in their most stable oxidation states (2+ for the viologens and 1+ for cobaltocenium). However, reduction considerably increases the affinity of these guests for the CDs. In the case of cobaltocenium,¹⁰ one-electron reduction yields the neutral cobaltocene, which, like ferrocene, is an excellent guest for inclusion by β -CD. One-electron reduction of the viologens leads to cation radical species that are not strongly bound by the CDs. In contrast, two-electron reduction (Scheme 2) yields uncharged guests

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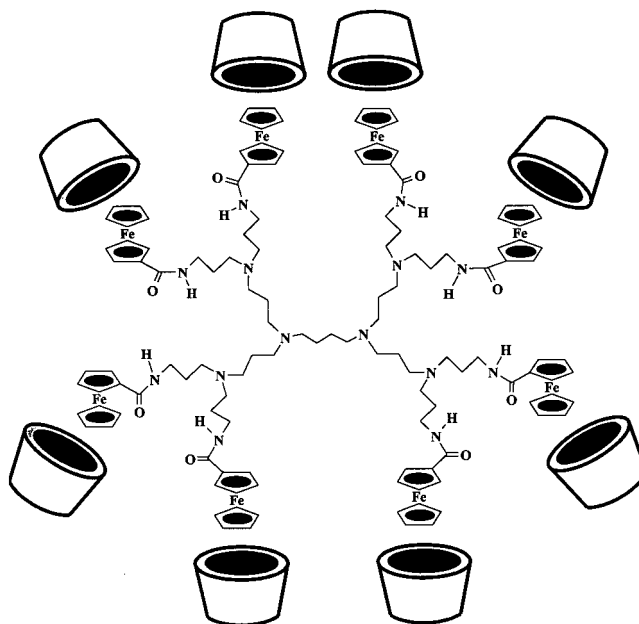
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Scheme 2. Redox Control of the β -CD Complexation of Viologens

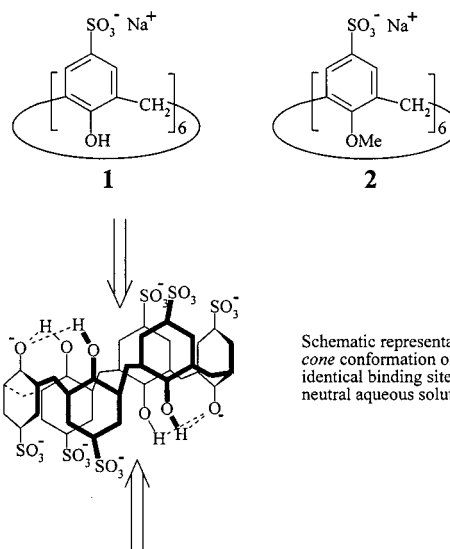
which form very stable complexes with β -CD and a methylated β -CD derivative.⁹ All these studies point to similar conclusions. Neutral subunits of appropriate size are strongly bound by the CD hosts while charged subunits of similar size are not. However, an important distinction can be made between the ferrocene-based guests and those containing viologen or cobaltocenium moieties. Ferrocene guests illustrate a situation in which the molecular recognition forces can be *deactivated electrochemically*, while viologen and cobaltocenium substrates require *electrochemical activation* to trigger significant complexation by the CD hosts.

In collaboration with the group of Cuadrado and Morán, we have recently extended these ideas to the complexation of multisite guests based on dendrimer skeletons.¹¹ Specifically, dendrimers having 4, 8, or 16 ferrocene subunits at their surface act as multisite guests for complexation by β -CD (Scheme 3), yielding soluble supramolecular assemblies with high molecular weights, which can be broken up by oxidation of the ferrocene moieties.

Scheme 3. Supramolecular Assembly Formed between a Dendrimer and Eight Cyclodextrin Hosts



Scheme 4. Structures of Sulfonatocalix[6]arene Hosts



Schematic representation of the *double partial cone* conformation of **1** showing the two identical binding sites exhibited by this host in neutral aqueous solution.

Calixarene Hosts

The calixarenes constitute another important class of receptors that have attracted considerable attention from supramolecular chemists.¹² Their basic aromatic skeleton can be derivatized in many ways to modify their binding selectivity or to introduce specific functional groups. Our group has been particularly interested in the host properties of sulfonatocalix[6]arenes¹³ (Scheme 4), a class of water soluble, anionic receptors with very attractive properties. Like the CDs, calixarenes are electroinactive, 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 complexation processes. Figure 1 shows typical cyclic voltammetric data contrasting the effects of β -CD and calixarene **1** on the electrochemical behavior of ferrocenecarboxylate (FcCOO^-). A comparison of the voltammograms shown in Figure

1A,B demonstrates that the complexation of FcCOO^- with β -CD is detected experimentally by a shift in the half-wave potential ($E_{1/2}$) to more positive values and by a decrease in the peak currents (i_{pa}). The anodic potential shift reveals that the reduced form (FcCOO^-) of the guest is more stabilized by complexation than the oxidized form (Fc^+COO^-). In contrast, the effect of the anionic calixarene on the voltammetric parameters of the ferrocene-containing guest is very different (Figure 1A,C). First, the calixarene host induces a negative shift in the half-wave potential. Therefore, the host interacts more strongly with the oxidized form of the guest (Fc^+COO^-), which is anticipated from the anionic character of both the reduced guest (FcCOO^-) and the host. Second, calixarene addition has a much smaller effect on the peak currents than that observed with β -CD, indicating that the initial form of the electroactive guest (FcCOO^-) is not significantly bound

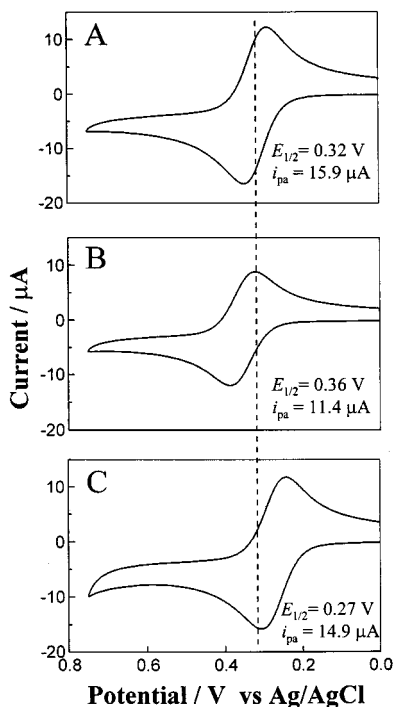


FIGURE 1. Voltammetric response (0.1 V/s) of ferrocenecarboxylate on a glassy carbon working electrode (0.08 cm²): (A) 1.0 mM FcCOO⁻ in 0.1 M pH 7 phosphate buffer, (B) same as in (A) + 3 mM β -CD, (C) same as in (A) + 3 mM calixarene **1**.

by the calixarene host. While these are qualitative observations, the voltammetric data contain information on the thermodynamics and/or kinetics of the complexation reactions. The best and more general methodology to obtain the corresponding equilibrium and/or rate constants relies on the optimization of the fitting between digitally simulated and experimental voltammograms.^{6,9,10} However, this approach may show limitations as the mechanism of the complexation reactions becomes more complicated.

A few years ago we initially reported that host **1** binds effectively a series of ferrocene derivatives,¹⁴ as well as methyl viologen.¹⁵ More recently, we have reported on the complexation of cobalt(III) sepulchrate by the methylated calixarene analogue **2**.¹⁶ However, this host is much less effective than **1**. While comparing the binding affinity of these two calixarene hosts, we soon realized that the solution pH plays an important role in determining the binding ability of **1**. Atwood and co-workers reported in 1992 the solid-state structure of the octaanionic form of **1**,¹⁷ crystallized from neutral aqueous solution. Their findings indicate a double partial cone conformation in which three adjacent sulfonate groups point to each side of the calixarene cavity. The structure is further rigidified by hydrogen bonding of each phenolate oxygen (at neutral pH, two phenol groups are deprotonated) to the neighboring -OH groups, yielding a robust structure with two identical cavity openings, each presenting four negative charges to potential guests (Scheme 4). In a more acidic medium, where all the phenol groups are protonated, this structure may lose some of its rigidity with detrimental effects to its binding properties. This prediction has been

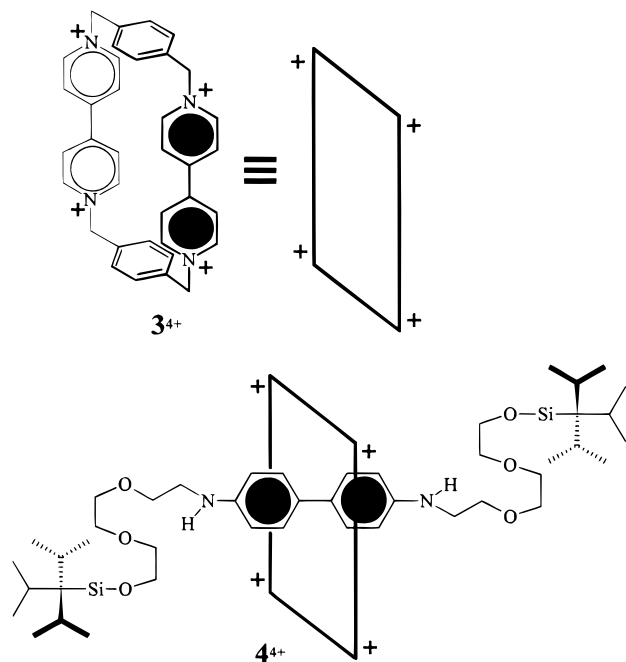
fulfilled by a series of recent voltammetric studies performed with ferrocene guests in buffered media.¹⁸ Our data indicate that **1**⁶⁻ (at pH 2.5) is considerably less effective as a host than **1**⁸⁻ (at pH 7), to an extent that cannot be accounted for by charge differences. Molecular modeling calculations¹⁸ yield a structure similar to that experimentally obtained by Atwood and co-workers for **1**⁸⁻ and a more flattened, puckered conformation for **1**⁶⁻, with less defined binding pockets. Voltammetric and ¹H NMR experiments as well as molecular modeling calculations indicate that the methylated analogue **2**⁶⁻ is an ineffective host for the same set of ferrocene derivative guests,¹⁸ a result of its conformational flexibility and lack of preorganization for binding.

According to Atwood's crystallographic data and to our own molecular modeling work, the octaanionic host **1**⁸⁻ has two perfectly defined and identical binding sites, so that the formation of ternary complexes (binding to two guests) may be anticipated. We have recently obtained ¹H NMR spectroscopic evidence for such a 1:2 complex between **1**⁸⁻ and two cobaltocenium guests in pH 7.0 aqueous solution.¹⁹ This ternary complex is particularly interesting because reduction of the cobaltocenium guests leads to the dissociation of the complex. Reduction of the cobaltocenium in the presence of β -CD gives rise to the formation of strong 1:1 β -CD-cobaltocene inclusion complexes.¹⁹ Therefore, 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. An unrelated example of electrochemical control on host selection has been recently described by Rotello and co-workers.²⁰ Their system is based on hydrogen bonding interactions between two hosts and a redox active guest.

Research publications on calixarenes continue to appear at a very fast pace. Related to the main theme of this Account, several groups have recently reported on redox active calixarene hosts,²¹ which have found interesting applications as cation and anion receptors.

Cyclophane Hosts

Cyclophanes are macrocycles made of aromatic ring subunits.²² Many cyclophanes are known, and one of the first attempts to exert redox control on the strength of their binding to guest species was reported by Diederich's group.²³ Much of our own work has focused on the cyclobis(paraquat-*p*-phenylene) receptor, **3**⁴⁺ (Scheme 5), which was first synthesized by Stoddart and co-workers.²⁴ This tetracationic cyclophane has a very rigid structure, with two electron acceptor, 4,4'-bipyridinium subunits lining a cavity which is ideally sized to include aromatic rings. The considerable binding affinity of this cyclophane for π -donor systems has been extensively utilized by Stoddart's group,²⁵ and others,²⁶ in the preparation of a large number of catenanes, pseudorotaxanes, and rotaxanes. Unlike CD or calixarene hosts, **3**⁴⁺ is electroactive. Usually, the two bipyridinium groups undergo one-electron reduction at similar potentials, resulting in a

Scheme 5. Structures of Cyclophane 3^{4+} and Rotaxane 4^{4+} 

single voltammetric wave. The half-wave potential of this wave is sensitive to complexation, shifting to more negative values upon inclusion of a π -donor guest due to the charge-transfer stabilization of the tetracationic (electron acceptor) form of the host. The host exhibits another cathodic wave at more negative potentials which corresponds to the second one-electron reduction of the bipyridinium groups. This wave can also sometimes be utilized to monitor complexation/decomplexation processes.

Most of our work with this cyclophane focused on its inclusion complexes with biphenyl derivatives²⁷ as well as on fundamental investigations on the origin of guest binding forces.²⁸ In collaboration with Stoddart's group, we showed that benzidine and biphenol derivatives are excellent guests for binding inside the cyclophane host.^{27a} In fact, the complexation of benzidine can be used to template the synthesis of rotaxane 4^{4+} (Scheme 5).^{27b} The anodic behavior of this rotaxane is of substantial interest because each of the one-electron oxidations of the benzidine moiety are severely hindered, both thermodynamically and kinetically, as compared to the same compound lacking the threaded cyclophane component. This reflects the difficulties associated with creating positive charge on the benzidine moiety in the proximity of the tetracationic cyclophane, which acts as the "bead" in rotaxane 4^{4+} . Even more pronounced effects were detected in a second rotaxane prepared around a *p*-phenylenediamine central subunit.^{27b}

Since benzidine is a better electron donor than biphenol, a larger rotaxane containing both aromatic subunits inserted along the thread appeared to be an excellent candidate to illustrate the concept, previously introduced by Stoddart, of an *electrochemically controllable molecular shuttle*.²⁹ We synthesized rotaxane 5^{4+} and determined that, at -40°C in CD_3CN , 84% of the cyclophane beads

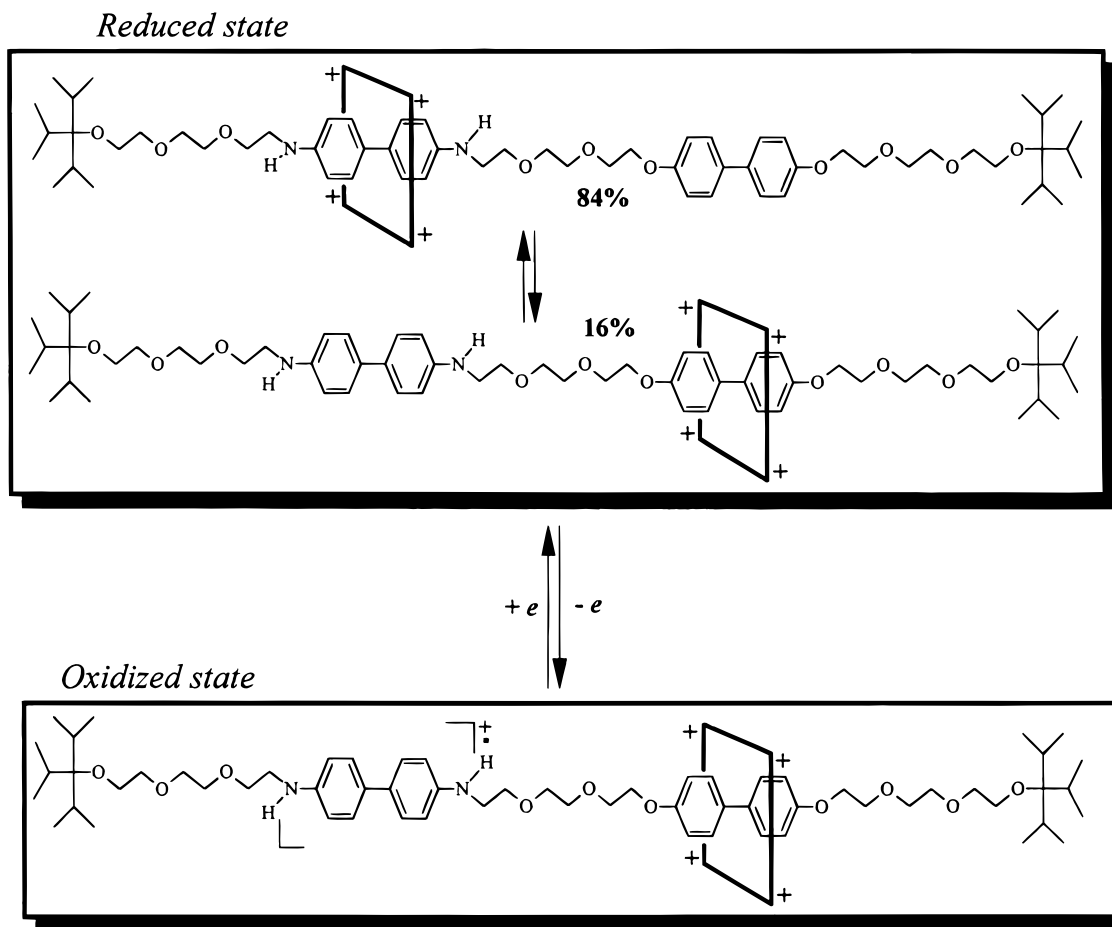
were centered around the benzidine station and 16% were on the biphenol station (Scheme 6).³⁰ However, our voltammetric data indicate that, after one-electron oxidation of the benzidine station, the tetracationic bead moves away from the positively charged benzidine, looking for the stability offered by the biphenol subunit. This rotaxane offers a compelling example of reversible electrochemical control on the structure of a molecule, which behaves in a "switchable" fashion. In fact, a second mechanism—relying on the basicity of the benzidine nitrogen atoms—was found to exert similar control on 5^{4+} . Protonation of the benzidine station leads to the development of positive charge and, again, switching of the cyclophane bead to the biphenol subunit.³⁰ This was verified by detailed ^1H NMR spectroscopic analysis.

Key questions relevant to these efforts follow: Why must one synthesize a complicated rotaxane such as 5^{4+} to observe these effects? Would switching be equally effective with separate molecular components? To answer these questions, we did a number of competition experiments with host 3^{4+} and benzidine and biphenol guests, and studied the switching behavior of this trimolecular system to compare it with that of the unimolecular rotaxane system.³¹ Our findings indicate that it is indeed possible to control the trimolecular system with external stimuli (proton transfer in this case). However, due to the finite binding constant values between the host and the biphenol and benzidine guests, the trimolecular system behaves rather inefficiently since, at the concentration levels used (millimolar range), the binding equilibria keep a substantial fraction of the host in the uncomplexed form. The unimolecular rotaxane system is more efficient precisely 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.³¹

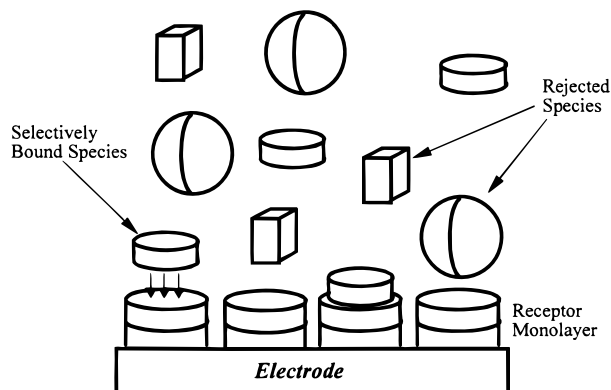
Molecular Recognition at the Electrode—Solution Interface

With conventional metal or carbon electrodes the substrates that undergo electrochemical reaction are determined by the thermodynamics and kinetics of the heterogeneous electron transfer reactions. Therefore, the only parameter that can be used to control selectivity is the applied electrode potential. Conventional electrochemical techniques afford limited selectivity based on favorable potential values. Thus, the idea of setting molecular films as barriers in order to increase the selectivity of the electrodes is very attractive. Over many years, electrochemists have explored this idea, modifying the electrode surface with a variety of polymers and other types of structures. More recently, self-assembled monolayers³² (SAMs) have afforded a powerful molecular building set that can be readily applied to control the molecular architecture of electrochemical interfaces.

In this field, my group's key concern has been the derivatization of electrode surfaces with structures containing active molecular receptors, in the expectation that

Scheme 6. Electrochemical Switching of Rotaxane 5^{4+} 

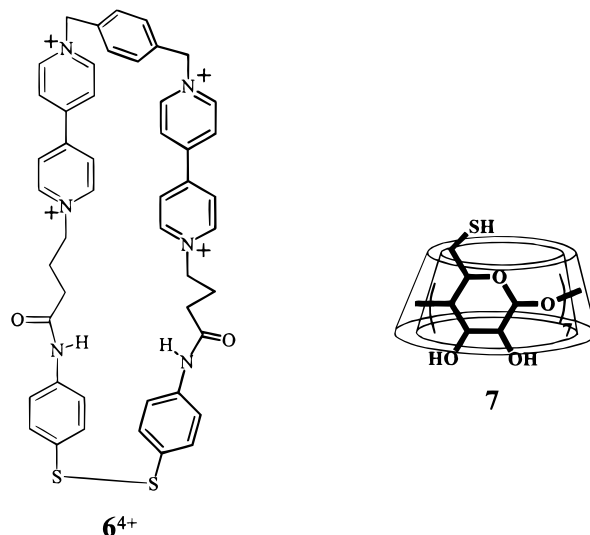
Scheme 7. Idealized Representation of a Self-Assembled Monolayer Containing Preformed Binding Sites



they would impart their binding selectivity to the corresponding electrochemical reactions. This idea is illustrated in Scheme 7. Several other groups have reported extensively in this area,³³ although the majority of the published work has dealt with interfacial molecular recognition in the gas phase. Specifically, we are interested in the development of electrodes derivatized with SAMs containing receptors capable of effective molecular recognition in aqueous solution.

To this end, we decided to utilize the most common type of SAM (that formed by thiolates on gold surfaces) and set out to derivatize the receptors with sulfur func-

Scheme 8. Structures of Interfacial Receptors



tionality. Thus, we synthesized cyclophane 6^{4+} (Scheme 8), which is structurally similar to 3^{4+} but contains a disulfide bridge that is anticipated to serve as its anchoring point to gold. Mixed monolayers of 6^{4+} and decanethiol imparted the anticipated molecular recognition properties to the underlying gold electrodes.³⁴ In our voltammetric experiments with these electrodes, micromolar concentrations of catechol and indole were clearly detected by the

shifts measured on the reduction potential of the viologen groups of the immobilized host.

Another type of SAM, containing cyclodextrins as the molecular recognition component, has also been studied by our group.³⁵ In this case, we used a perthiolated β -CD derivative (receptor **7** in Scheme 8) in which all the primary $-OH$ groups are replaced by $-SH$ groups. The chemisorption of this receptor on gold leads to poor surface coverages ($\sim 65\%$), which forced us to use pentanethiol to complete the coverage of the surface. Gold electrodes covered with mixed monolayers of the thiolated β -CD derivative and pentanethiol were shown to bind ferrocene selectively.³⁵ The dynamic nature of these binding phenomena was verified by experiments in which *m*-toluic acid, an excellent guest for binding by β -CD, displaced ferrocene from the surface-attached cyclodextrin cavities.

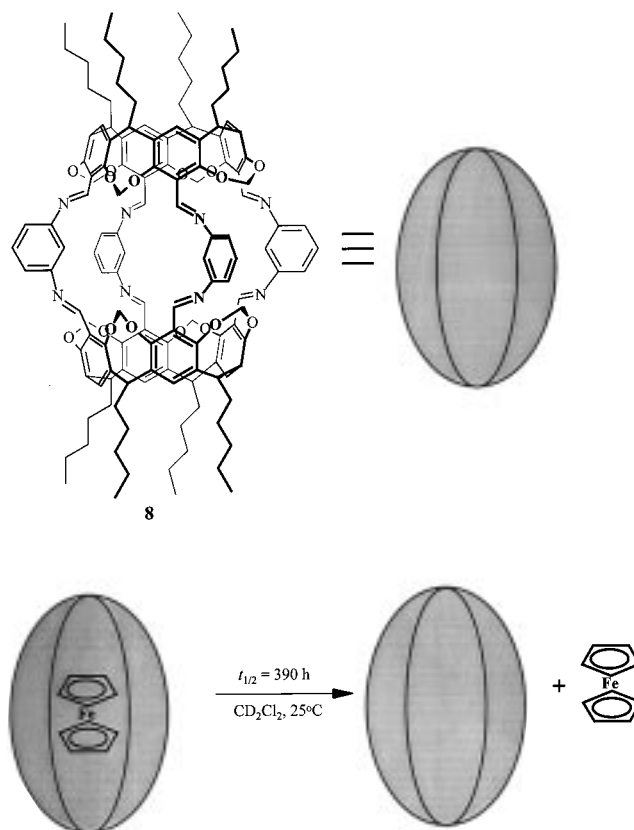
Throughout this work, we have measured several values of binding constants in interfacial situations. In every instance, we have always obtained values 1–2 orders of magnitude higher than the values measured for the corresponding host–guest pairs in homogeneous solution. While additional measurements are desirable to confirm this trend, the findings at hand are very intriguing and might be explained by the degeneracy of binding sites resulting from the spatial accumulation of binding sites at the electrochemical interface. Similar interfacial binding enhancement effects have been described in the biochemical literature.³⁶

The work just described is certainly driven by the possibility of developing novel sensors, but our interest in interfacial binding phenomena has also led to work with entirely different focus. For instance, in collaboration with Echegoyen's group, we have demonstrated that interfacial molecular recognition forces may be utilized for the preparation of monolayer films of fullerene derivatives,³⁷ a result which may open the way for the preparation of new materials. A few years ago, in joint work with Gokel and co-workers, we trapped an inclusion complex formed between **3**⁴⁺ and a bisthiol hydroquinol derivative by attaching the thiol ends of the host-threading guest to a gold surface, yielding what could be termed the first *surface-attached catenane*.³⁸ We have also explored the interfacial host–guest interactions between ferrocene subunits, covalently attached to a SAM, and amphiphilic calixarene hosts, freely diffusing in the solution phase.³⁹ This work has shown that molecular recognition phenomena at electrochemical interfaces hold substantial promise not only for the development of new sensors, but also for the preparation of innovative materials and structures, which might not be accessible by other means.

Encapsulated Redox Centers

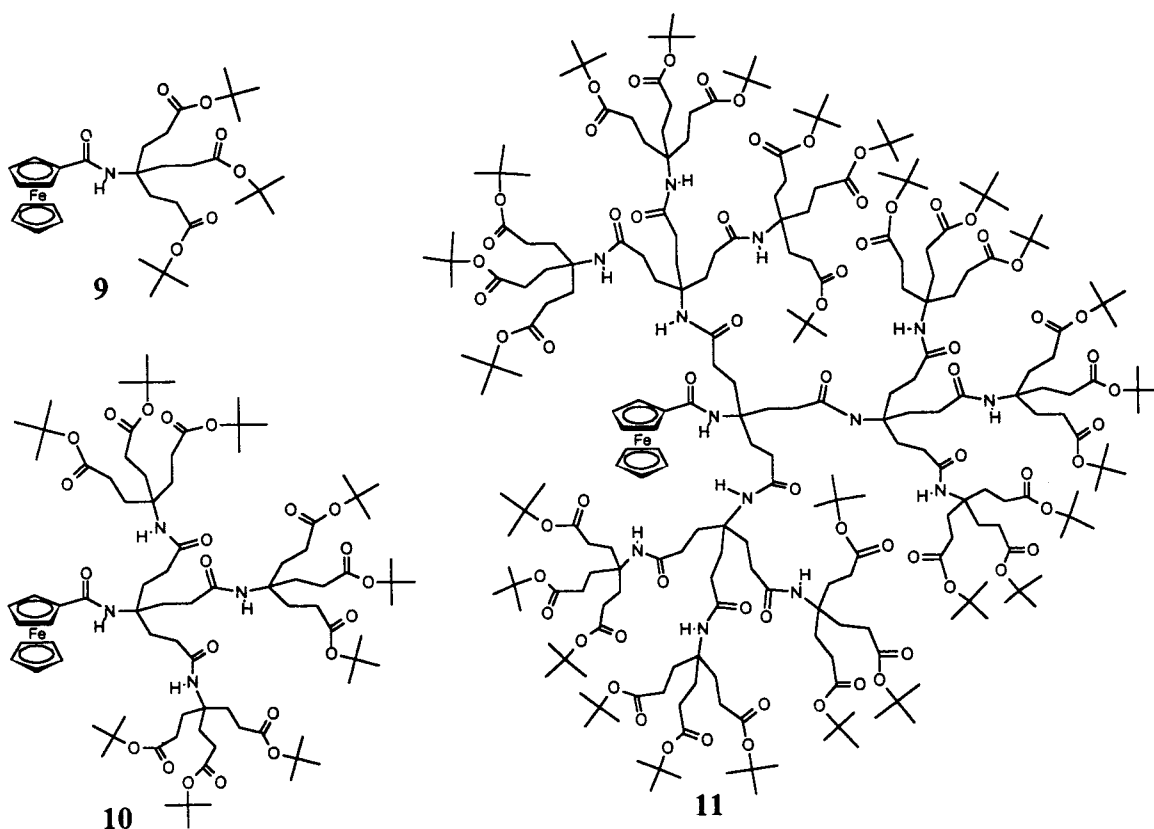
Since the previous sections made clear that electron-transfer reactions may influence supramolecular structures, such as host–guest complexes, we must also expect significant supramolecular effects on the thermodynamics and kinetics of electron-transfer reactions. As a first step to address this issue, we focused on the electron-transfer

Scheme 9. Structure of Hemicarcerand **8** and Its Ferrocene Release Rate



reactions of encapsulated redox centers. It is important to remember here that voltammetric experiments with cyclodextrin inclusion complexes of electroactive guests appear to indicate that dissociation of the complex must precede the actual electrochemical oxidation/reduction process. It is as if the inclusion complexes were electroinactive. Regardless of the sequence of elementary events (dissociation followed by electron transfer or vice versa), redox conversions of the guest usually result in the dissociation of the inclusion complex. Therefore, we considered the preparation of inclusion complexes in which the redox active guest would be “locked” in the host cavity. We selected Cram's hemicarcerands⁴⁰ as the ideal hosts for this purpose because they can encapsulate molecules of reasonable size and the dissociation rate constants for the resulting inclusion complexes (hemicarceplexes) are extremely slow. In particular, hemicarcerand **8** is capable of encapsulating ferrocene, forming an inclusion complex from which ferrocene is released at exceedingly slow rates (see Scheme 9). Interestingly, we found that this ferrocene inclusion complex is indeed electroactive,⁴¹ although its voltammetric behavior is very different from that of free ferrocene. First, the oxidation of ferrocene is thermodynamically hindered in the inclusion complex; its half-wave potential is about 120 mV more positive than that of free ferrocene in the same solvent system ($CH_2Cl_2/0.15$ M TBA⁺PF₆⁻). This is probably due to the inefficient solvation of the oxidized form of ferrocene by the inside walls of the hemicarcerand. Second, the standard rate constant for the heterogeneous

Scheme 10. Structures of Asymmetric Ferrocene-Containing Dendrimers



electron-transfer process decreases by a factor of ~ 50 upon encapsulation.⁴¹ We are currently in the process of investigating other electroactive hemicarceplexes. It is certainly too early to draw extensive conclusions from the results at hand. However, the kinetic slow-down may respond, at least partially, to the increased distance of maximum approach to the electrode surface that the encapsulating host imposes to the ferrocene center.

Dendrimers

Encapsulation of a redox center can be accomplished by noncovalent means, using host–guest chemistry, or by covalently attaching to the redox center large structures with electrically insulating character. Quite naturally, we decided that dendrimers⁴² offered an ideal molecular framework for this purpose and set out to synthesize asymmetric dendrimers prepared starting from a ferrocene nucleus⁴³ which would be located on one of the sides of the dendritic mass, not at its center. These molecules resemble redox proteins, most of which contain an asymmetrically positioned redox active group. In fact, this asymmetric character is very important for nature's control of electron-transfer reactions in living organisms.

We synthesized the series of three asymmetric dendrimers shown in Scheme 10 and studied their electrochemistry.⁴⁴ Interestingly, the half-wave potential for ferrocene oxidation shifts to less positive values with increasing dendrimer generation. This is rather counter-intuitive and difficult to rationalize, but similar trends have been observed by other authors.⁴³ The kinetics of electron

transfer is hindered by increasing dendritic mass, exactly as one would expect on the basis of molecular weight and distance effects. Our investigations with these electroactive dendrimers are still in progress, however, the redox asymmetry of these molecules is certainly remarkable and their similarities to redox proteins offer exciting possibilities.

Concluding Remarks

Chemists have certainly made substantial progress understanding how molecular recognition can be affected by redox reactions. A number of host–guest systems have been found (or prepared) showing varying degrees of redox control on their binding affinity. These phenomena can be expressed in more complicated molecules, such as rotaxanes, yielding switchable molecular systems with very interesting properties. The potential applications of these systems in nanotechnology, for information storage and processing, for instance, are still hampered by the difficulties inherent in establishing connections between the individual molecules and the macroscopic world. On the other hand, interfacial host–guest recognition systems offer very attractive possibilities for the development of novel sensor devices, capable of analyte detection in solution and/or gas phases. Interestingly, we are reaching a point where large molecules with properties resembling those of redox proteins appear accessible. Fundamental and applied research work in all these areas will probably continue to grow.

I am grateful to the National Science Foundation and NATO for continuous support of this research. Some of the work described here would have been impossible without the collaboration of colleagues such as Isabel Cuadrado, Luis Echegoyen, Jeff Evanseck, George Gokel, Moisés Morán, and Fraser Stoddart. The graduate students and postdoctoral associates whose names are given in the references deserve all the credit for the experimental work and my gratitude for their willingness to work so hard.

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