

Electrochemically Controlled H-Bonding

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1.1 INTRODUCTION

Due to their strength and directionality, hydrogen bonds are one of the most important and useful types of intermolecular interactions available for the construction of supramolecular complexes. The iconic examples of DNA base pairing and the formation of secondary structure in proteins provide ample proof of their utility for the assembly of well-defined, functional structures. Examples¹ of the use of hydrogen bonds in synthetic, solution-phase supramolecular chemistry range from H-bonded dimers² held together by up to 6 H-bonds³ to large “rosette” assemblies constructed from up to 15 components and 72 H-bonds.⁴ A wide variety of open H-bonded structures have also been prepared, including those that self-assemble into capsules of various sizes and shapes^{5,6} and cyclic peptides that assemble into hollow tubes.⁷

Although, from a purely chemical point of view, learning how to create these complicated supramolecular structures has its own value, there are plenty of more practical reasons to investigate this chemistry. In the short term, these include catalysis and sensor applications, and in the long term, molecular electronics and molecular machines. With perhaps the exception of catalysis, all these applications will require some sort of signal transduction to allow for communication with the supramolecular device. This, of course, is one of the main reasons that electrochemistry is useful for supramolecular chemistry. Electron transfer provides a well-understood and very sensitive method to both communicate with supramolecular assemblies and control their structure.⁸

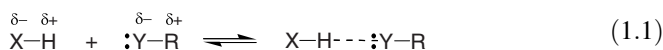
However, although electrochemistry can be used for the above, it will do so only if this functionality is designed into the structure. At minimum, two requirements

must be met. First, a reversible redox couple must be present as part of the structure. Reversible in this context means that both oxidation states are chemically stable under the experimental conditions used and that the electron transfer kinetics are reasonably fast. Second, reduction or oxidation of the redox couple must significantly perturb the strength of important binding interactions holding the assembly together. The most straightforward type of interaction to perturb electrochemically are ion–ion interactions, but the electrostatic nature of a hydrogen bond makes it a close second, while also allowing for neutral molecules as binding partners.

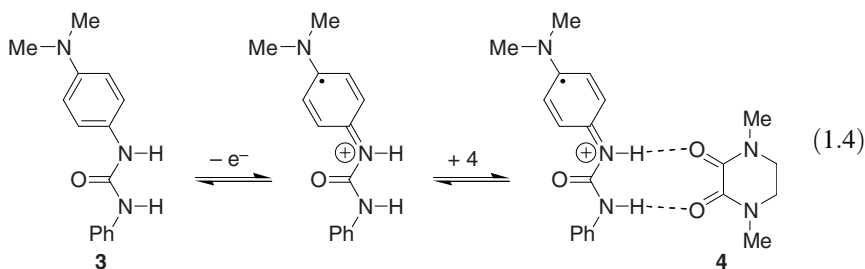
In this chapter, the basic principles behind electrochemically controlled H-bonding will first be described, along with some simple, illustrative examples and a brief discussion of the use of cyclic voltammetry to characterize such systems. Next, some general considerations regarding the design of these systems are discussed: the properties of the redox couple, the structures of host and guest, the choice of solvent and electrolyte, and the possibility for proton transfer. Finally, a selection of electrochemically controlled H-bonding systems will be described, organized by the nature of the binding partner and the type of redox couple.

1.2 BASIC PRINCIPLES

A H-bond is a favorable interaction formed between a relatively positively charged hydrogen atom in a polar bond, X–H, and either a lone pair on a relatively negatively charged atom, Y (Eq. 1.1), or a highly polarizable pi-bonding electron pair (Eq. 1.2).⁹ As this description implies, there is a high degree of electrostatic character associated with H-bonding, although only the very weakest H-bonds are purely electrostatic. Strong H-bonds range in strength from 15 to 40 kcal/mol and are considered to be mainly covalent in character. These bonds are characterized by close to linear X–H–Y bond angles and X–Y distances that are substantially smaller than the sum of the van der Waals radii. These are typically formed from ionic species, for example, N⁺–H or O⁺–H as the H-donor and/or F[–], O[–], or N[–] as the H-accepting atom. Moderate strength H-bonds range in strength from 4 to 15 kcal/mol and are mostly electrostatic in character. They can show a greater range in bond angles, from 130° to 180°, and will have bond lengths that are slightly smaller than the sum of the van der Waals radii. Typical examples are H-bonds formed from neutral oxygen and nitrogen functional groups, for example, N–H and O–H as the donor group and uncharged N and O as the accepting atoms. Weak H-bonds, those less than 4 kcal/mol in strength, are almost purely electrostatic in character and are characterized by a range of bond angles and X–Y distances that may be greater than the sum of the van der Waals radii. These are formed from the weaker H-donors such as C–H and/or weaker acceptors such as pi electron pairs.



Oxidation reactions can also be used to control H-bonding. These have mainly been successful with anionic guests, but a recent example involving the dimethylaminophenylurea **3** gives a large binding enhancement with the cyclic diamide **4** (Eq. 1.4).¹¹ In this case, reversible oxidation of the dimethylaminophenyl group increases the positive charge on one of the urea NHs, greatly increasing its H-donating ability to a good H-accepting guest such as **4**. This results in the binding constant in 0.1 M NBu₄B(C₆F₅)₄/CH₂Cl₂ increasing from 60 M⁻¹ in the reduced state to 2 × 10⁵ M⁻¹ in the oxidized state.



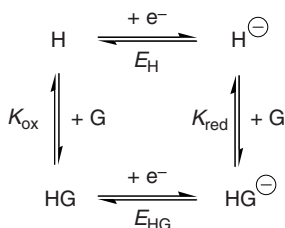
1.2.2 Indirect Perturbation of Hydrogen Bonds

An alternative strategy to control H-bonding electrochemically does not rely on the electroactive unit playing a direct role in the H-bonding, but rather uses it to create additional favorable or unfavorable interactions that either strengthen or weaken an assembly held together through H-bonds. For example, electron transfer can be used to create charged sites that break apart a H-bonded dimer due to electrostatic repulsion. While the focus of this chapter will be on the direct perturbation methods, a well-characterized example of the indirect method will be described later on.

1.3 DETECTION AND CHARACTERIZATION OF ELECTROCHEMICALLY CONTROLLED H-BONDING

The most important and useful technique for studying electrochemically controlled H-bonding and other forms of redox-dependent binding is cyclic voltammetry (CV). By observing how the voltammetry of the electroactive component changes in the presence of possible binding partners, one can readily determine whether redox-dependent binding is occurring and which oxidation state binds the strongest. More careful analysis of this type of data can yield the equilibrium constants for binding and possibly kinetic data as well.

Typically in supramolecular chemistry, the term “host” refers to the larger and more structurally complex of two binding partners, while the term “guest” refers to the smaller, less complex binding partner. However, for the purpose of this discussion, the term “host” will be used to refer to the electroactive binding partner and “guest” to refer to the nonelectroactive binding partner, irrespective of their size or structural complexity.



Scheme 1.2 Equilibria involved in redox-dependent host–guest binding.

With the above definitions, the equilibria involved in the redox-dependent formation of a 1:1 host–guest complex can be described by the square shown in Scheme 1.2. In this representation, the electron transfer reaction of the host by itself is shown on the top horizontal axis and that of the host–guest complex on the bottom axis. Binding of the guest to the oxidized host is on the left vertical axis and binding to the reduced host is on the right. E_{H} is the standard electrode potential for the host by itself and E_{HG} is that of the host–guest complex. K_{ox} is the binding constant of the guest to the host in its oxidized form and K_{red} is that in the reduced form.

Qualitatively, if a guest binds more strongly to the oxidized form of the host, the oxidized host will be stabilized and it will be harder to reduce the host in the presence of the guest. This means that E_{HG} is negative of E_{H} . On the other hand, if the guest binds more strongly to the reduced form, it will be easier to reduce the host in the presence of the guest and E_{HG} is positive of E_{H} .

Quantitatively, it is straightforward to show that if electron transfer and binding are fast and reversible, the four-membered square behaves as a one-electron redox couple with an E that depends on the true E values and the K values (Eq. 1.5). Note that in this equation $[G]$ = the concentration of the free (unbound) guest, which is not equal to the added guest if binding occurs. However, if $[G]$ is greater than 10 times $[H]$, it is reasonable to assume that $[G]$ is approximately equal to the added guest concentration. When $K_{\text{ox/red}}[G] \gg 1$ (large $[G]$ and/or large K), Equation 1.5 reduces to the more often seen Equation 1.6, which relates the maximum change in E to the ratio of binding constants or binding enhancement. A particularly handy form of this equation can be derived by switching to regular logarithms and filling in the constants to give Equation 1.7, which says that at 25°C each 60 mV shift in E corresponds to a 10-fold difference in binding strength between oxidation states.

$$E_{\text{obs}} = E_{\text{H}} + \frac{RT}{F} \ln \left(\frac{1 + K_{\text{red}}[G]}{1 + K_{\text{ox}}[G]} \right) \quad (1.5)$$

$$\Delta E_{\text{max}} = E_{\text{HG}} - E_{\text{H}} = \frac{RT}{F} \ln \left(\frac{K_{\text{red}}}{K_{\text{ox}}} \right) \quad (1.6)$$

$$10^{\Delta E_{\text{max}}/60 \text{ mV}} = \frac{K_{\text{red}}}{K_{\text{ox}}} \quad \text{at } 25^{\circ}\text{C} \quad (1.7)$$

In general, there are two types of limiting voltammetric behavior observed for redox-dependent receptors.¹² First, if there is strong binding in both oxidation

states (K_{ox} and K_{red} are both large), then addition of a half equivalent of the guest results in the current for the original CV wave decreasing by half and the appearance of a new CV wave of approximately equal height. The half-wave potential, $E_{1/2}$, for the original CV wave should be approximately equal to E_{H} , and that of the new wave approximately equal to E_{HG} . Under these circumstances, after addition of 1 equivalent of the guest, only the new CV wave remains, now with a height equal to that of the original host-only wave. Further addition of guest produces no additional changes, unless greater than 1:1 guest–host binding is possible.

In contrast, if the binding constants are small or there is only strong binding in one oxidation state, then generally one CV wave is observed even with less than 1 equivalent of guest. This is the behavior commonly observed for redox-dependent H-bonding systems. As the guest concentration is increased, the $E_{1/2}$ of the CV wave will shift from E_{H} toward E_{HG} .

An example of this typical behavior is shown in Fig. 1.1 with CVs of nitroaniline, **1** ($X = \text{NH}_2$), in the presence of increasing amounts of diphenylurea, **2**.¹⁰ As discussed previously, diphenylurea is expected to bind more strongly to the reduced nitroaniline (Eq. 1.3), making it easier to reduce and resulting in a positive shift in the $E_{1/2}$. This is indeed what is observed. Scan (a) is that of nitroaniline by itself. Addition of half equivalent of diphenylurea, scan (b), results in a broad wave, with a new shoulder appearing at more positive potentials. However, unlike the case in which strong binding is observed in both oxidation states, the position of the new shoulder does not correspond to the maximum shift. With 1 equivalent of diphenylurea, scan (c), the

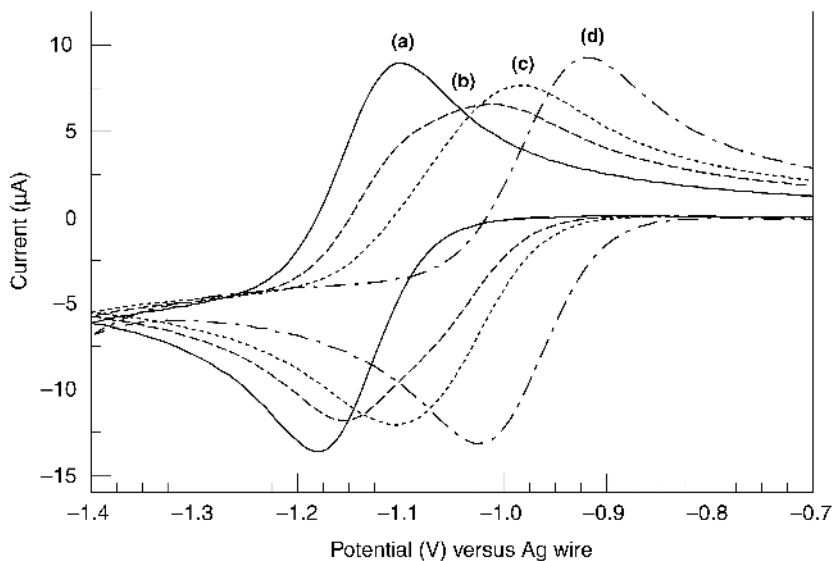


Figure 1.1 CVs of *p*-nitroaniline in 0.1 M $\text{NBu}_4\text{PF}_6/\text{DMF}$ in the presence of different amounts of 1,3-diphenylurea: (a) 0 mM urea, (b) 0.5 mM urea, (c) 1 mM urea, and (d) 10 mM urea. 500 mV/s scan rate.¹⁰

wave sharpens up and moves farther positive. Further additions of diphenylurea result in continued positive shifts in the CV wave.

It is often assumed that if a significant excess of G is added (10–50-fold), then $E_{1/2}$ of the CV wave will be $\sim E_{HG}$, and the binding enhancement can be calculated using Equation 1.6. However, this is not necessarily the case. At the very least, the assumption that saturation binding has been reached should be checked by doubling the concentration of guest and making sure no further change in $E_{1/2}$ is observed.

A more accurate method to determine the binding constants is to do a complete binding titration where the CVs are recorded at a range of guest concentrations as shown in Fig. 1.1. If the CVs are uncomplicated, a smoothly shifting wave with no significant change in wave shape, then it may be possible to obtain binding constants by plotting $E_{1/2}$ versus [G] and fitting the curves to Equation 1.5 using a nonlinear least squares regression method. This can also be done for cases where more than 1:1 guest–host binding is possible.^{13,14}

While the above technique can be used in many cases, it does require uncomplicated voltammetry and that significant $E_{1/2}$ shifts are observed at guest concentrations >10 times the host concentration. If these conditions are not met, then an alternative strategy is needed. The most powerful is to use CV simulation software to fit the experimental CVs to the square scheme or a more complicated mechanism if necessary. This method allows determination of the thermodynamic parameters and possibly the kinetic parameters as well.

An example of the use of CV simulation to determine binding constants and explain more complicated CV behavior is shown in Fig. 1.2. These are CVs observed

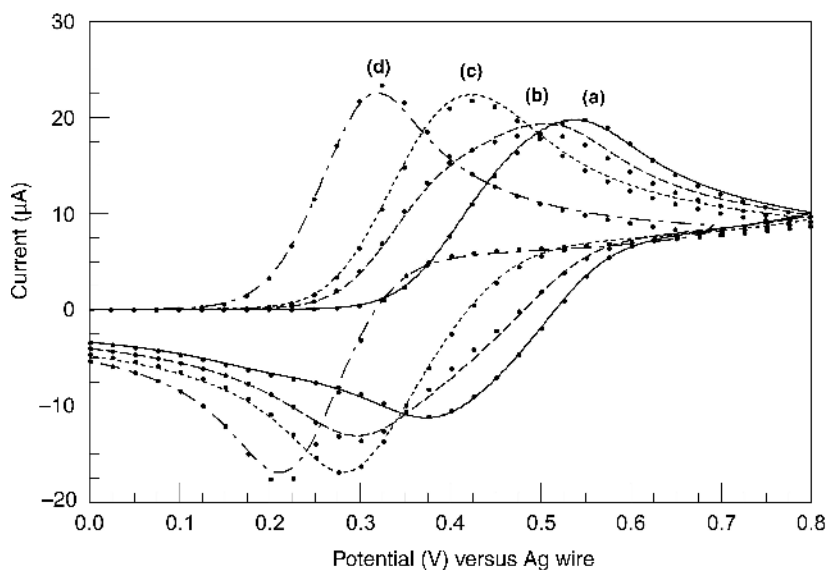
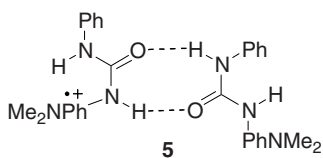


Figure 1.2 Experimental (lines) and simulated (dots) CVs of 1 mM **3** in 0.1 M $\text{NBu}_4\text{B}(\text{C}_6\text{F}_5)_4/\text{CH}_2\text{Cl}_2$ in the presence of different amounts of **4**: (a) 0 mM, (b) 0.5 mM, (c) 1 mM, and (d) 100 mM. 500 mV/s scan rate.¹¹

for oxidation of the electroactive urea, **3**, discussed previously in the presence of the cyclic diamide, **4**.¹¹ Now the guest is expected to bind more strongly to the oxidized form (Eq. 1.4), resulting in a negative shift in $E_{1/2}$ upon addition of guest, the opposite of the effect seen in Fig. 1.1. Note that under the experimental conditions used, the CV wave for the urea by itself, scan (a), is broad. With half equivalent of guest, scan (b), an even broader CV results, with a new shoulder negative of the original wave. With continued addition of guest, the wave now sharpens up and continues to move negative.

In order to explain the original broad wave observed for the urea, it has been proposed that formation of dimer **5** between an unoxidized urea and an oxidized urea is quite favorable. This makes it easier to oxidize the first half of the urea (since the dimer will result) than the second half of the urea (which requires breakup of the dimer). The result is an unusually broad CV wave. Addition of greater than 1 equivalent of the guest breaks up the dimer resulting in a sharper wave. The viability of this mechanism is confirmed by showing that CVs simulated using this mechanism (dots in Fig. 1.2) give good fits to the experimental CVs (lines) with reasonable values for the different reaction parameters.



While cyclic voltammetry is clearly the most important technique for studying electrochemically controlled H-bonding, other physical methods, in particular spectroscopic techniques, can be quite helpful. These can be used to provide structural information on the host–guest complex, and also to provide another means to determine binding constants in at least one of the redox states. For H-bonded supramolecular complexes, the most commonly used technique is simply ^1H NMR, since the chemical shifts of hydrogens involved in the H-bonding will be very sensitive to the presence of the binding partner. However, a significant limitation for the use of NMR in electrochemical H-bonding studies is that it can only be used with diamagnetic systems, and in many cases the stronger binding state is paramagnetic.

1.4 GENERAL CONSIDERATIONS FOR THE DESIGN OF ELECTROCHEMICALLY CONTROLLED HYDROGEN-BONDED ASSEMBLIES

1.4.1 The Redox Couple

First and foremost, the redox couple must be reversible, meaning relatively fast electron transfer reactions and products that are stable in both oxidation states. As discussed previously, for systems in which the hydrogen bonds are to be directly perturbed, the redox reaction must affect the charge distribution on the atoms involved

TABLE 1.1 Shift in Half-Wave Potential, $\Delta E_{1/2}$, for Different *para*-Substituted Nitrobenzenes in the Presence of 1,3-Diphenylurea^a

Substituent	$E_{1/2}$ (V) versus Fc	$\Delta E_{1/2}$ (mV)
NH ₂	-1.870	197
CH ₃ O	-1.698	164
CH ₃	-1.635	156
H	-1.582	153
CF ₃	-1.362	93

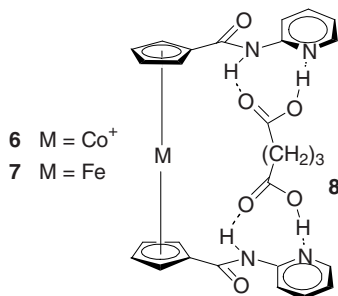
^a1 mM nitrobenzene in 0.1 M NBu₄PF₆/DMF + 50 mM 1,3-diphenylurea. Values are the averages of at least three independent measurements.

in one or more of the hydrogen bonds. This can be done through what can be described as either an inductive or a resonance effect.

The nitrobenzene (Eq. 1.3)¹⁰ and dimethylaminophenylurea systems (Eq. 1.4)¹¹ that were discussed in the previous sections are good examples of resonance effects. In these cases, the electron transfer directly places charge on the atoms involved in H-bonding, which are an integral part of the redox couple. One interesting possibility is to couple this with simple substituent effects in order to further “tune” the binding strength. This hypothesis has only been explored in two systems so far, with mixed results. One is the nitrobenzene system, where the strategy does appear to work, as shown by the data in Table 1.1.¹⁰ This table gives the observed $E_{1/2}$ of the nitrobenzene 0/−1 redox couple, along with the observed $\Delta E_{1/2}$ in the presence of 50 equivalents of 1,3-diphenylurea for five different *p*-substituted nitrobenzenes. As expected, the $E_{1/2}$ values fall in order of the electron-donating/withdrawing strength of the substituents, with the nitrobenzene with the most electron-donating substituent, NH₂, being the hardest to reduce and that with the most electron-withdrawing substituent, CF₃, being the easiest to reduce. Interestingly, the $\Delta E_{1/2}$ values fall in the same order, with the NH₂ derivative giving the largest shift and the CF₃ the smallest. This is consistent with the electron-donating NH₂ forcing more of the negative charge in the radical anion onto the oxygens leading to an increase in H-bond strength, and with the electron-withdrawing CF₃ removing some of the negative charge from the oxygens leading to a decrease in H-bond strength. However, although tuning $\Delta E_{1/2}$ values with substituents appears to be quite effective in the nitrobenzene system, an even more in-depth substituent study for the flavin/amidopyridine H-bonding system,¹⁵ which will be discussed in detail later in the chapter, shows the expected $E_{1/2}$ dependence, but no clear trend in the $\Delta E_{1/2}$ values. It therefore remains to be seen how generally useful this strategy may be.

It is also possible to affect H-bond strength electrochemically without the H-bonding site being an integral part of the redox couple. Good examples of this are found in the many redox-dependent receptors that utilize metallocenes, primarily ferrocene and cobaltocenium, as the redox couple. These are primarily used in ion receptors, but examples of metallocene receptors that show a significant redox dependence with neutral guests are the cobaltocenium and ferrocene diamides,

6 and **7**. Both metallocenes undergo a reversible one-electron transfer reaction between 0 and +1 charge states. However, since cobalt has one more valence electron than iron, the cobalt derivative has the optimum 18 valence electron configuration and is therefore most stable in the +1 state, whereas the iron analog has the optimum 18 valence electron configuration and is most stable in the zero charge state.

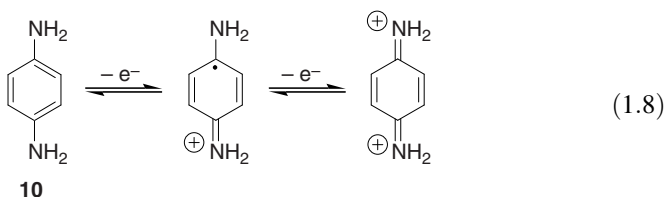
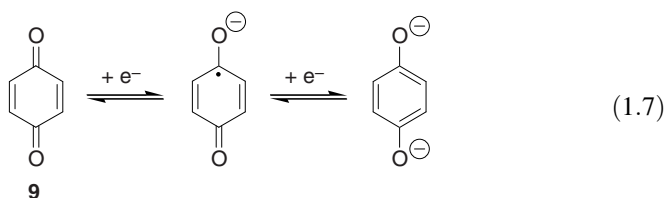


Tucker and coworkers have shown that both of these compounds bind glutaric acid, **8**, through H-bonding between the carboxylic acids and the diamidopyridine.¹⁶¹ ¹H NMR titrations in CDCl₃/DMSO (0.5%) indicate that the cobaltocenium host binds 20 times more strongly than the ferrocene host (K_{ox} of **6** = $9.8 \times 10^4 \text{ M}^{-1}$; K_{red} of **7** = $4.6 \times 10^3 \text{ M}^{-1}$). This is consistent with the positive charge on the cobaltocenium, which would be expected to further polarize the N–H amide bond through an electron-withdrawing effect, resulting in stronger H-bonding to the carbonyl oxygen of the acid. In fact, crystal structures show that the amide H-bonds are shorter in the cobaltocenium derivative than the ferrocene, whereas the pyridine H-bonds are about the same. Reduction of the cobaltocenium to the zero state, and oxidation of the ferrocene to the +1 state would be expected to switch the binding preferences, and indeed the CV studies in CH₂Cl₂/DMSO (0.5%) indicate that this is the case. Addition of excess glutaric acid to both compounds results in the same maximum $\Delta E_{1/2}$ of –90 mV. This corresponds to a 30-fold difference in binding strength between oxidation states, with the +1 state being the stronger binding one in both cases. This indicates that the difference in binding between oxidation states for this system is simply due to the change in charge. Unlike the nitrobenzene example, it is independent of variation in structure (Co versus Fc) or actual $E_{1/2}$ since the $E_{1/2}$ of Co(Cp)₂^{+1/0} is quite negative of the $E_{1/2}$ of Fe(Cp)₂^{+1/0}.

In comparing the two different ways the redox couple can perturb H-bonding strength, there are clearly pros and cons to both. The resonance approach, in which the H-bonding sites are an integral part of the redox couple, is likely to give a stronger redox perturbation than the inductive approach, where the redox couple is simply in conjugation with the H-bonding site. The existing examples bear this out. With neutral guests, where H-bonding is the main binding interaction, the electroactive hosts that have been shown to give the very large $\Delta E_{1/2}$ values are all those in which the H-bonding site is part of the redox couple. The disadvantage is that this really

puts severe limitations on host/guest combinations possible. The advantage of the inductive approach is that the binding site can be designed somewhat independent of the redox couple, making it, in principle, easier to tailor the host for different guests. The other advantage is that very inert redox couples such as the metallocenes can be used, so there is less chance of unwanted reactions taking place.

Another factor to take into consideration when choosing a redox couple is the availability of additional electron transfer equilibria. The redox-dependent hosts considered so far, nitrobenzenes, **1**, the dimethylaminophenylurea, **3**, and the metallocene diamides, **6** and **7**, just undergo one reversible electron transfer reaction. However, many organic redox couples undergo at least two successive electron transfers. The prototypical example are the quinones, **9**, which in aprotic solvents undergo two reversible reductions, first to the radical anion and then to dianion (Eq. 1.8). *p*-Phenylenediamines, **10**, provide a related example of a redox couple that undergoes two reversible oxidations, giving first a radical cation and then a dication (Eq. 1.9). (Note that the dimethylaminophenylurea, **3**, is a phenylenediamine derivative, but the second oxidation is irreversible in this case.) In general, the more highly charged dianions and dications will be significantly more basic or acidic than the mono-ions, and therefore will H-bond more strongly to a given guest, resulting in much larger $\Delta E_{1/2}$ values in the $-1/-2$ or $+1/+2$ redox couple than the $0/-1$ or $0/+1$ redox couples. This phenomena has been particularly well studied with quinones.¹⁷ Addition of weak H-donors, such as alcohols, produces large positive shifts in the $-1/-2$ redox potential with little change in the $0/-1$ potential. Similar results are observed with *p*-phenylenediamines and weak H-acceptors such as tertiary amides.¹⁸



Based on the above discussion, there is an advantage in using redox couples with multiple electron transfer equilibria since this makes incremental control of binding strength possible. However, caution must also be used, since the stronger H-bonding also means that the response will be much less selective, in that weaker H-donors/acceptors could also cause a significant shift. In addition, because the dianions and dications will be more reactive, there is a greater likelihood of proton transfer and other chemical reactions taking place at the second electron transfer, which could

compromise the reversibility of the system. These issues are problematic for practical sensor applications, where the redox response should be highly selective for a particular analyte in a range of different environments. However, this may not be as much an issue in other applications, where the environment can be controlled to prevent unwanted interactions with the more reactive oxidation states.

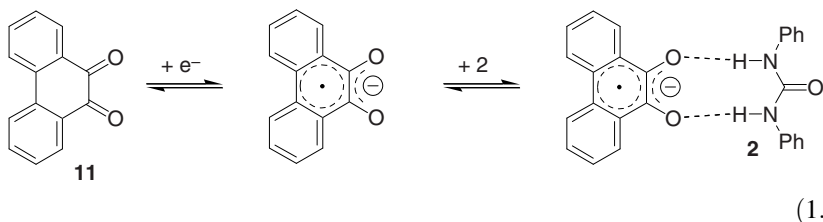
1.4.2 Host/Guest Structure

In order to achieve strong, selective binding with electroactive hosts, just as in other types of molecular recognition, there needs to be a high degree of complementarity between the host and the guest. This means that the binding site needs to have the proper shape, along with the correct positioning of functionality to provide multiple favorable contacts with the target guest. The principle of preorganization is also important, which says that binding strength will be maximized when the host is “preorganized” to fit the guest because this will minimize the entropy loss upon formation of the host–guest complex. For this reason, rigidity in both the host and if possible the guest is generally desirable.

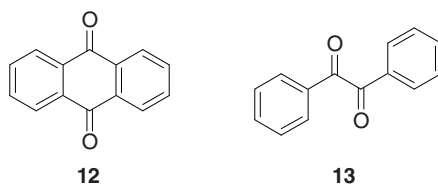
Of course, in order to produce a redox signal for binding, at least one of the binding interactions must be strongly perturbed by a reversible electron transfer reaction. As discussed in the previous section, a greater effect will generally be observed at the second electron transfer (if available), producing a larger $\Delta E_{1/2}$ and making the redox potential of the host sensitive to the guest over a larger range of concentrations. However, this will also likely make the response much less selective, so for sensor applications, the first electron transfer will probably need to be used. This means that a big change in binding strength is needed based on what will typically be a 0/–1 or 0/+1 redox couple.

In looking at existing electrochemically controlled H-bonding systems in which significant $E_{1/2}$ shifts have been observed at the first electron transfer, two minimum features appear necessary. First, there needs to be the possibility of at least two strong, almost linear H-bonds formed between host and guest, and, second, the electron transfer reaction needs to strongly perturb at least one and preferably two H-bonds between host and guest. Examination of the systems discussed so far in this chapter, as well as those yet to be discussed, shows that all obey these basic design principles.

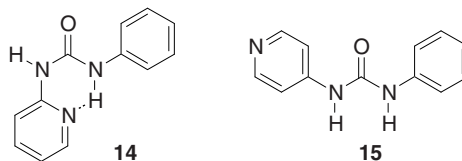
A nice demonstration of the above criteria is provided by a study of the redox-dependent H-bonding properties of 9,10-phenanthrenequinone, **11**, and related compounds.¹⁹ As with nitrobenzenes, diarylureas such as **2** make excellent binding partners, providing appropriately positioned amide NHs to be able to simultaneously H-bond with both carbonyl oxygens. Also like nitrobenzene, reduction of phenanthrenequinone produces a radical anion, with enhanced negative charge on the oxygens. This should result in stronger H-bonding in the radical anion state (Eq. 1.10). Consistent with this, addition of 10 equivalents of 1,3-diphenylurea causes the $E_{1/2}$ of the phenanthrenequinone 0/–1 couple to shift positive by 200 mV in CH_2Cl_2 . Significant positive $E_{1/2}$ shifts are also observed in the more polar DMF. CV simulation of the latter gives $K_{\text{ox}} = 1 \text{ M}^{-1}$ and $K_{\text{red}} = 905 \text{ M}^{-1}$ in 0.1 M $\text{NBu}_4\text{PF}_6/\text{DMF}$.



In order to investigate the structural requirements for the strong redox dependence, $\Delta E_{1/2}$ values were also measured for anthraquinone, **12**, and benzil, **13**, in the presence of 5 equivalents of diphenylurea in DMF. Under these conditions, phenanthrenequinone gives a shift of 61 mV, whereas anthraquinone gives a shift of only 8 mV and benzil 5 mV. Unlike phenanthrenequinone, the urea can only H-bond to one carbonyl oxygen at a time with anthraquinone. Two bifurcated H-bonds are possible, but these together would be much weaker than the two close to linear H-bonds possible with *o*-quinones. A similar situation arises with benzil, since rotation about the central C–C bond will be hindered in the radical anion and the favored conformation will have the oxygens *trans* due to electrostatic repulsion and steric effects.



Another interesting comparison is the difference in $\Delta E_{1/2}$ observed for phenanthrenequinone with the two pyridylureas **14** and **15**. The electronic character of both compounds should be similar, but with **14** a strong intramolecular H-bond will be formed between the 2-pyridyl N and one of the urea NHs. This means that only one NH will be available for H-bonding to the phenanthrenequinone radical anion. This has a huge effect on the $\Delta E_{1/2}$ values, with 5 equivalents of **14** producing only a 16 mV shift in DMF compared to an 85 mV shift with **15**. The latter is actually larger than 1,3-diphenylurea. This can be explained by the greater electronegativity of N compared to C, making the pyridyl group more electron withdrawing than a phenyl group.



1.4.3 Solvent and Electrolyte

In addition to the structures of host and guest, another important consideration for studies of electrochemically controlled H-bonding is the solvent system.

Binding constants for supramolecular assemblies are always strongly solvent dependent because binding of the host to the guest will be in competition with solvation. Since H-bonding has a strong electrostatic component, more polar solvents will solvate the binding sites more effectively than less polar solvents, thereby decreasing the equilibrium constant for host–guest binding, whereas less polar solvents will tend to increase the binding strength. For nonelectrochemical studies, chloroform (more specifically, deuterated chloroform for ^1H NMR studies) seems to be the most common solvent. For electrochemical studies, a less resistive solvent is needed, with dichloromethane being the most common choice. Other aprotic solvents such as acetonitrile or dimethylformamide are also used. Sometimes, these can help to simplify the behavior by decreasing the amount of host–host or guest–guest interaction that occurs in the less polar dichloromethane.

Another important consideration for electrochemical studies is the choice of electrolyte, the ionic compound that is added to maintain electroneutrality and provide a means of charge flow through solution. Because at least one of the oxidation states of the host will be charged, it is possible that ion–ion interactions will play a role in the observed electrochemistry. Indeed, this is useful if the objective is to design a redox-dependent ion receptor, but it can be an interference if the guest is neutral.

The most common electrolyte used today for electrochemical studies in aprotic solvents is tetrabutylammonium hexafluorophosphate, NBu_4PF_6 . The use of NBu_4^+ is a good choice for reduction-based systems since it is a very large cation and is unlikely to interact significantly with the anionic form of the host. For oxidation-based systems, which generally involved cationic intermediates, it is the anion in the electrolyte that is of issue. PF_6^- has generally been considered to also be a large and noncoordinating ion. However, recent evidence suggests that it is not nearly as inert as once believed. In particular, electrochemical studies with organometallic cations show that PF_6^- and other “large” anions such as ClO_4^- and BF_4^- interact with +2 and +3 charged species enough to have a large effect on the observed $E_{1/2}$ values, sometimes also causing distortion in the CV wave shapes and/or precipitation of the cationic products onto the electrode.^{20,21}

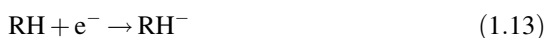
If good H-donor groups are part of the redox couple, it might be expected that even +1 charge species could show strong interactions with these anions. This has recently been shown to be the case with the electroactive urea **3** discussed earlier (Eq. 1.4).¹¹ In the results described previously (Fig. 1.2), the electrolyte was 0.1 M $\text{NBu}_4\text{B}(\text{C}_6\text{F}_5)_4/\text{CH}_2\text{Cl}_2$. $\text{B}(\text{C}_6\text{F}_5)_4^-$ is a very large anion, much larger than the more commonly used PF_6^- . If the same experiments are run with NBu_4PF_6 or NBu_4ClO_4 , much smaller $E_{1/2}$ shifts are observed with the same guest. For example, addition of 1 equivalent of guest **4** to **3** gives $\Delta E_{1/2}$ values of -2 and -16 mV using NBu_4ClO_4 or NBu_4PF_6 , respectively, but the same amount of guest gives -109 mV shift when $\text{NBu}_4\text{B}(\text{C}_6\text{F}_5)_4$ is used as the electrolyte. These results indicate that the smaller anions (which are present at much larger concentrations than the guest) interact strongly enough with the oxidized urea to block interactions with the guest. The much larger anion $\text{B}(\text{C}_6\text{F}_5)_4^-$ does not do this, with the result that significantly larger shifts are observed in the presence of this anion. Based on these results, it would seem prudent

to at least test oxidation-based systems with these very large anion electrolytes, particularly if a less polar solvent such as CH_2Cl_2 is being used.

1.4.4 H-Bonding Versus Proton Transfer

Although it seems to be often pointed out that H-bonding and proton transfer are not the same thing (and obviously they are not), there is clearly a close relationship between the two, with stronger acids generally being better H-donors and stronger bases being better H-acceptors. As the $\text{p}K_{\text{a}}$ of a H-donor guest decreases, the $E_{1/2}$ shift between the guest and the host will increase but so will the possibility of proton transfer.

For organic $0/-1$ or $0/+1$ redox couples, the occurrence of proton transfer is usually quite obvious. Instead of seeing simply a shift in potential of the reversible, one-electron CV wave upon addition of the guest, the wave doubles in size and becomes irreversible. This behavior, which was originally observed upon addition of acids to aromatic anions, is due to an ECEC mechanism. (E stands for electron transfer reaction and C stands for a chemical reaction such as proton transfer.) In the case of reductions, the first step is electron transfer to form a radical anion (Eq. 1.11). Normally, addition of a second electron occurs at a more negative potential because it will be harder to add an electron to an already negatively charged species. However, protonation of the radical (Eq. 1.12) gives an uncharged radical that is typically easier to reduce than the starting species. The result is immediate addition of a second electron (Eq. 1.13) resulting in a two-electron CV wave. Since an acid strong enough to protonate the radical is usually strong enough to protonate the anion product, the final product will generally be the two-electron, two-proton reduced species, RH_2 (Eq. 1.14). The reduction is irreversible because it will be much harder to oxidize RH_2 than R^- . A similar mechanism can be observed with oxidations in the presence of bases capable of removing a proton from the radical cation intermediate.

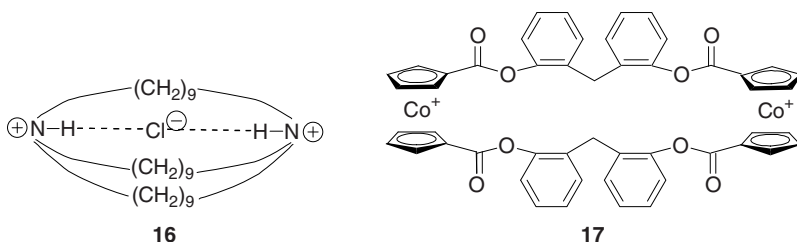


Since the products of the second electron transfers are typically more basic or more acidic than those of the first electron transfer, it is possible to add a guest that is only capable of proton transfer with the product of the second electron transfer. It is important to note that in this case the result of proton transfer may be very similar to that of H-bonding, with simply a positive $E_{1/2}$ shift for the second wave in a reduction or a negative shift for an oxidation. In this case, information about $\text{p}K_{\text{a}}$ values is very helpful for trying to sort out whether it is H-bonding or proton transfer that causes the shift.

1.5 EXAMPLES OF ELECTROCHEMICALLY CONTROLLED H-BONDING SYSTEMS WITH ANIONIC GUESTS

Although the examples of electrochemically controlled H-bonding discussed so far in this chapter have been with neutral guests, the reality is that the majority of the work that has been done in this area has been with ionic, and in particular anionic guests. This work started in the late 1980s, several years before the first reports with neutral guests. It is still an incredibly active area, with numerous new receptors reported each year. Work through the 1990s has been covered in review articles.^{22,23}

The first reported example of anion binding with a synthetic organic macrocycle was the protonated cryptand **16**, reported by Park and Simmons in 1968.²⁴ ¹HNMR evidence was presented showing that this compound binds chloride by a combination of H-bonding and favorable electrostatic interaction. Although numerous other anion receptors have been reported since then, including those that utilize Lewis acid and hydrophobic interactions, the two binding interactions seen in this first example, ion-ion and H-bonding, have turned out to be the mainstays of anion recognition. This leads naturally to electrochemically controlled H-bonding since adding an electroactive group provides a simple way to perturb both electrostatic and H-bonding interactions.

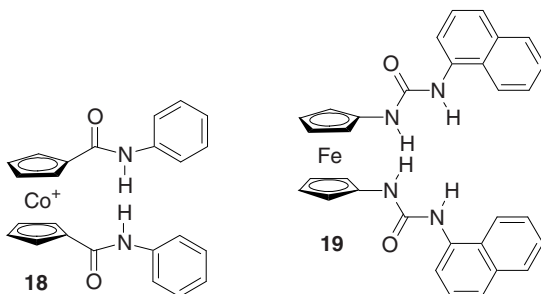


1.5.1 Cobaltocenium

The first redox-active receptor for anions was the bis-cobaltocenium macrocyclic ester **17** reported by Beer and Keefe in 1989.²⁵ FAB-MS and FT-IR evidence indicates that **17** can bind anions in the oxidized state. Reduction of the cobaltoceniums to the zero state would be expected to weaken this interaction, and indeed a modest -45 mV $E_{1/2}$ shift is observed in acetonitrile upon addition of 4 equivalents of Br⁻.

In the above example, binding and redox dependence rely solely on perturbation of electrostatic interactions. A few years later, in 1992, Beer and coworkers reported similar or better redox dependence with halides using simpler acyclic cobaltoceniums.^{26,27} The key was the addition of an amide N-H, providing a H-bonding site. For example, the simple diamide cobaltocene **18** gives a -60 mV shift in $E_{1/2}$ of the cobaltocenium upon addition of 4 equivalents of Br⁻ in acetonitrile, corresponding to at least a 10-fold decrease in binding strength. The analogous N-Me compound results in a smaller than 5 mV shift. A later crystal structure of **18** with Br⁻ clearly

shows the H-bond with the amide NH.²⁸ In addition, a significantly larger shift of -240 mV is observed with **18** and H_2PO_4^- , due to the greater H-bonding capability of this anion compared to simple halides.



1.5.2 Ferrocene

The cobaltocenium anion receptors are examples of electrochemically controlled H-bonding systems in which the electron transfer decreases H-bonding strength. By switching to ferrocene as the redox-active group, anion receptors can be made in which electron transfer increases binding strength. This has proven to be a particular popular strategy and there are now numerous examples of ferrocene-based, redox-dependent anion receptors in the literature. A generally successful strategy, learned from the early cobaltocenium examples, is to simply attach good hydrogen donors, such as amides, secondary amines, guanidiniums, and so on, to one or both cyclopentadienes. A representative example is the diurea-substituted ferrocene, **19**, reported by Molina and coworkers,²⁹ which shows a significant redox-dependent response to F^- ($\Delta E_{1/2} = -208$ mV) and H_2PO_4^- ($\Delta E_{1/2} = -90$ mV) in DMSO, but not to Cl^- , Br^- , AcO^- , NO_3^- , and HSO_4^- . This is an example of a receptor where strong binding is observed in both oxidation states, resulting in two CV waves being observed at less than 1 equivalent of guest.

Most redox-dependent receptors have structural features similar to **17–19**, which are either a macrocyclic or a cleft-type binding site with one or two redox-active groups directly attached. An interesting alternative, introduced by Astruc and coworkers, are the ferrocene-terminated dendrimers, such as **20**.^{30,31} Although each dendrimer contains multiple ferrocenes, just one CV oxidation wave is generally observed, indicating that there is no significant interaction between the ferrocenes. Addition of a good H-bonding anion either causes this wave to shift negative or produces a new CV wave. One of the interesting results is that there is generally a “positive dendritic effect,” in that higher dendrimer generations show a larger maximum shift. For example, Fig. 1.3 shows the effect of different generations of amine dendrimers on the observed $\Delta E_{1/2}$ caused by addition of HSO_4^- . (18-Fc is **20**, which has 18 ferrocenes, 9-Fc is the previous generation with 9 ferrocenes, and so on.) The anions are believed to bind to the amide groups between dendrimer chains as

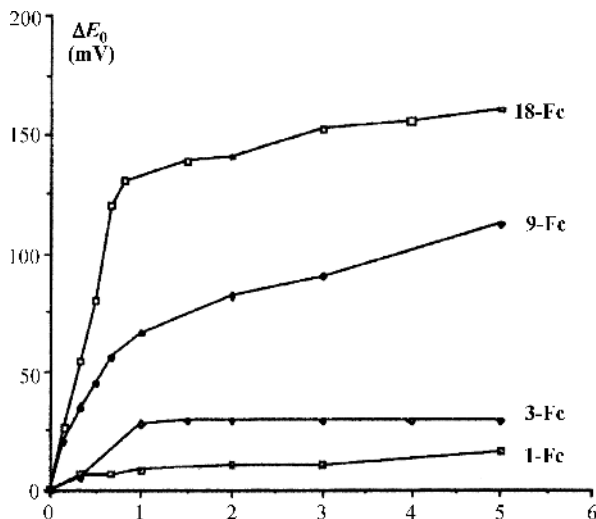
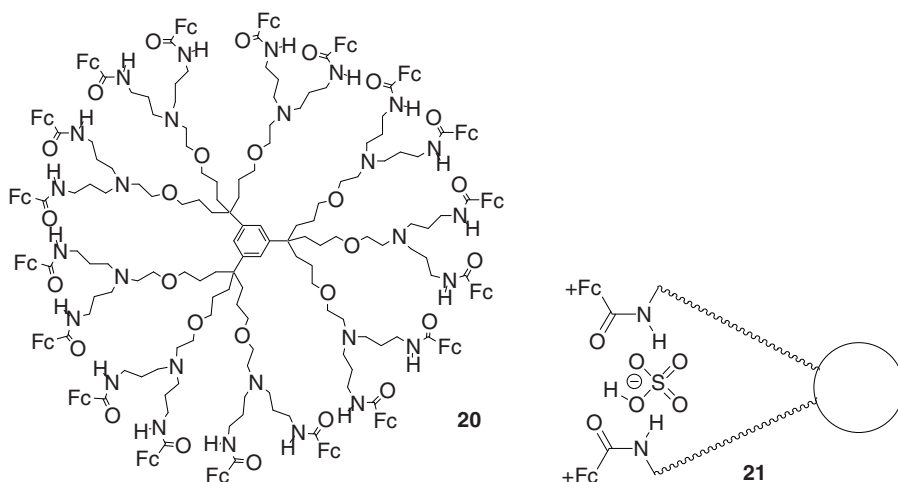


Figure 1.3 Observed $\Delta E_{1/2}$ for the ferrocene 0/+1 CV wave upon addition of NBu_4HSO_4 to different generations of Fc dendrimers in $\text{NBu}_4\text{BF}_4/\text{CH}_2\text{Cl}_2$. The x -axis indicates the number of equivalents of HSO_4^- added per ferrocene unit.³⁰

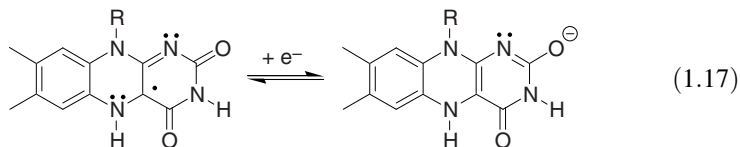
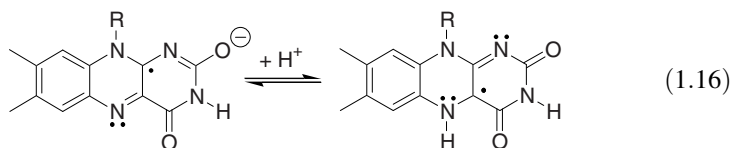
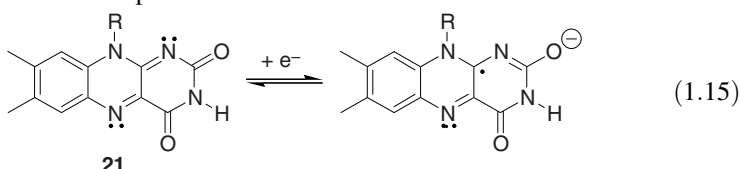
shown in structure **21**. As the dendrimer generation grows, the chains are forced closer together creating a tighter and more preorganized binding cleft that leads to stronger binding and larger potential shifts. Similar effects have been observed with a variety of different ferrocene dendrimers, as well as Au nanoparticles that have amidoferrocene-terminated alkyl thiols attached to their surfaces.³² These type of receptors, where the binding site is a wedge in between outward radiating chains, have been classified as “exo” receptors.



1.6 EXAMPLES OF REDUCTION-BASED, ELECTROCHEMICALLY CONTROLLED H-BONDING SYSTEMS WITH NEUTRAL GUESTS

1.6.1 Flavins

Although the idea of using H-bonding to control redox properties is fairly recent in man's chemistry, nature has been doing this for quite a long time. A nice example is seen in flavoenzymes that use the redox-active flavin group, **21**, to catalyze a wide variety of reactions, such as oxidation of amines to imines and the hydroxylation of aromatic compounds. That one cofactor can catalyze such a range of reactions is possible because the protein environment interacts with the flavin through a variety of intermolecular interactions, including H-bonding, so as to adjust the redox chemistry to be appropriate for each particular task.



The reactions most commonly involved in flavin redox chemistry are shown in Equations 1.15–1.17. One-electron reduction of the flavin (Eq. 1.15) produces a relatively stable radical anion. Protonation of the radical anion produces an unstable neutral radical (Eq. 1.16), which will be rapidly reduced by another electron (Eq. 1.17) to give the flavohydroquinone anion.

In an effort to better understand how the redox behavior of flavins is influenced by hydrogen bonding, Rotello and coworkers reported a study in 1995 where they looked at the electrochemistry of flavin **22** ($R_1 = R_2 = \text{Me}$) in the presence of diamidopyridine **23** ($R = \text{Et}$).³³ This compound hydrogen bonds to the flavin as shown, mimicking the hydrogen-bonding pattern in the active site of a number of flavoproteins. The binding constant of the diamide to the flavin in the oxidized form is 537 M^{-1} in CDCl_3 as determined by ^1H NMR. Reduction of the flavin to the radical anion would be expected to strengthen binding further by increasing the negative charge on the carbonyl oxygens, and, indeed, addition of 5 equivalents of **23** to the flavin in $\text{NBu}_4\text{ClO}_4/\text{CH}_2\text{Cl}_2$ resulted in a +155 mV shift in the $E_{1/2}$ of the flavin 0/–1 potential (Fig. 1.4b), indicating strong stabilization of the radical anion through H-bonding. This result was a nice confirmation of the role that

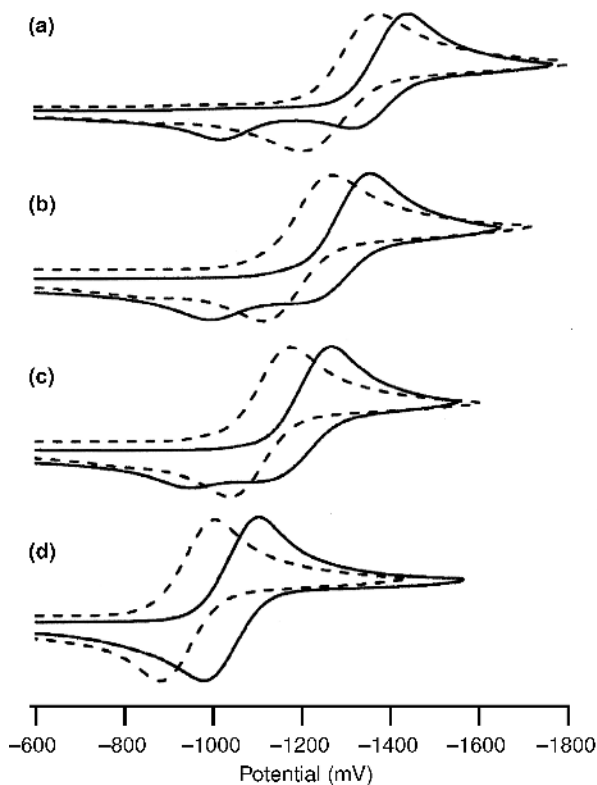
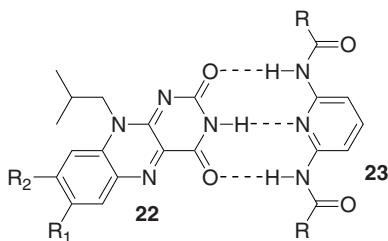
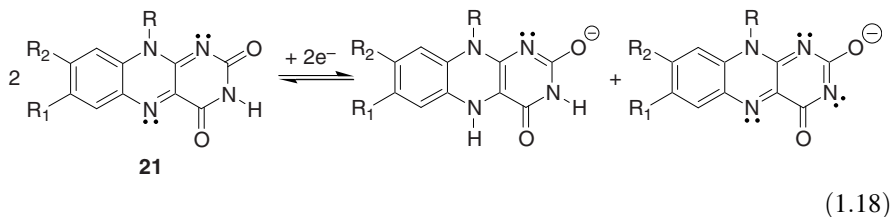


Figure 1.4 CVs of different flavins, **22**, in 0.1 M $\text{NBu}_4\text{ClO}_4/\text{CH}_2\text{Cl}_2$ by themselves (solid line) and in the presence of 50 mM **23** (dashed line): (a) **22**, $\text{R}_1 = \text{Me}$, $\text{R}_2 = \text{NMe}_2$, (b) **22**, $\text{R}_1 = \text{R}_2 = \text{Me}$, (c) **22**, $\text{R}_1 = \text{R}_2 = \text{H}$, and (d) **22**, $\text{R}_1 = \text{R}_2 = \text{Cl}$. 200 mV/s scan rate.¹⁵

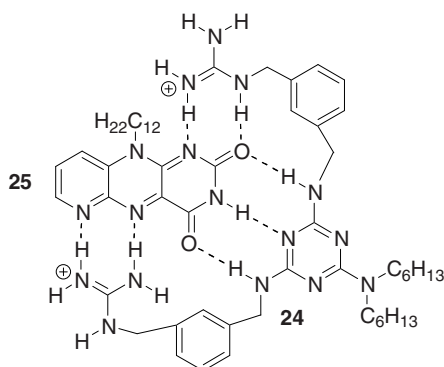
H-bonding plays in the flavoenzymes, but, perhaps more importantly, it really showed how strong an effect intermolecular H-bonding with a neutral binding partner could have on the redox potential of an organic redox couple, and, as a result, ushered in all the work that has followed on electrochemically controlled H-bonding with neutral guests.



Since their initial report on flavins, Rotello and coworkers have reported a number of other detailed studies on this system.^{15,34–44} One of the interesting things about the flavin/diamidopyridine system is that not only does the guest substantially alter the redox potential, but it also changes the nature of the electrode reaction. As shown in Fig. 1.4, in the absence of the guest, the flavin electrochemistry is generally not completely reversible. The return oxidation peak is too small and there is a second oxidation peak that appears at more positive potentials. Addition of the guest both shifts the reduction positive and makes it reversible. A completely reversible wave is also observed, without the guest, when the imide N is methylated, indicating that the irreversibility is due to the presence of the relatively acidic imide NH. Rotello and coworkers have explained this by suggesting that the apparent one-electron reduction of the flavin in aprotic solvent actually corresponds to the two-electron, one-proton reduction to the flavohydroquinone anion (Eqs 1.15–1.17), where the proton source is an oxidized flavin coming in from bulk solution.⁴⁵ Deprotonation of the oxidized flavin prevents its reduction, with the result that the overall process is still one electron/flavin (Eq. 1.18). The return oxidation peak at more positive potentials is then due to oxidation of the flavohydroquinone anion. Addition of the diamidopyridine increases the reversibility of the flavin reduction by preventing the proton transfer both through stabilization of the imide NH on the oxidized flavin and by alteration of the charge distribution in the radical anion.¹⁵

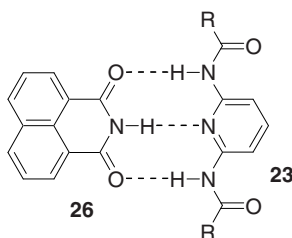


Other groups have also looked at the electrochemistry of flavins with various H-bonding partners. One of the most interesting studies is that by Yano and coworkers who designed the elaborate binding partner **24** for the azoflavin **25**.⁴⁶ The pendant guanidinium groups provide four H-bonds in addition to the three set up to bond to the imide portion of the flavin. This results in very strong H-bonding even in the oxidized state, with $K_{\text{ox}} = 1.9 \times 10^4 \text{ M}^{-1}$ in 20% ACN/ CH_2Cl_2 . Reduction of the flavin to the radical anion increased the binding strength even further, giving a $\Delta E_{1/2} = 317 \text{ mV}$. This corresponds to a binding enhancement of 2.2×10^5 and a $K_{\text{red}} = 4.3 \times 10^9 \text{ M}^{-1}$, certainly one of the largest binding constants that has been reported for these types of H-bonded complexes. Because of the very strong binding in both oxidation states, this is also one of the few examples where two CV waves, one at E_{H} and one at E_{HG} (Scheme 1.1), are observed at less than 1 equivalent of the guest.



1.6.2 Arylimides

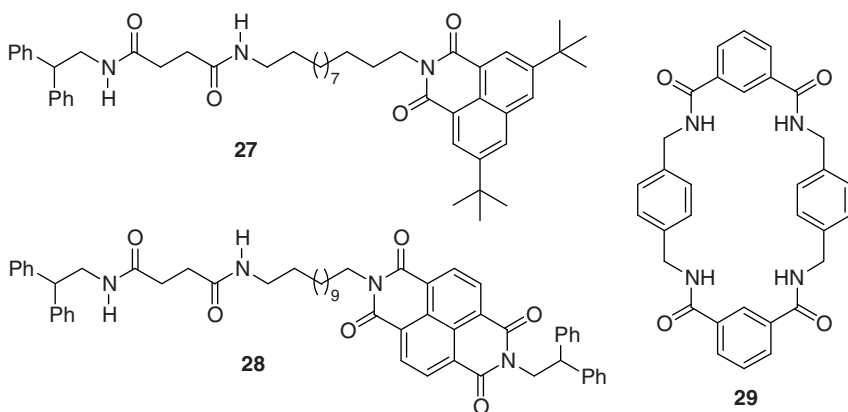
With flavins, the redox-dependent H-bonding site is the imide functional group on one side of the molecule. A year after Rotello's initial report on the flavin/diamidopyridine system, Smith and coworkers reported that a similar type of redox-dependent system can be created by just using a simple aromatic imide such as 1,8-naphthalimide, **26**, with the same type of diamidopyridine guests.⁴⁷ Subsequently, Rotello's group has used aromatic imides in a variety of redox-dependent binding studies.^{48–50} Like the flavins in aprotic solvents, the aromatic imides undergo reversible reductions to radical anions in aprotic solvents, which greatly increases the strength of binding to diamidopyridine or other similarly structured binding partners.



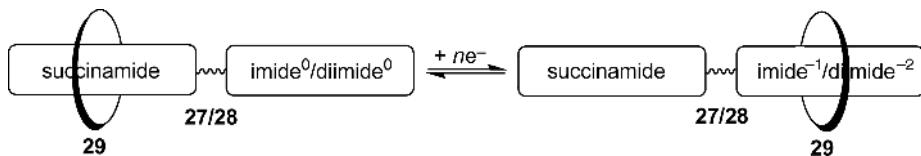
With the flavin and imide systems, the central NH provides an additional H-bond that helps to strengthen the interaction with guest in the oxidized form. However, this is a H-donating group while the carbonyls are H-acceptors, so while reduction would be expected to increase the H-accepting ability of the carbonyls and strengthen the H-bonds between imide carbonyl and amide, it would actually be expected to decrease the strength of the H-bond between the imide NH and the pyridine N. A comparison of the $E_{1/2}$ values of a flavin and its *N*-methyl analog in solvents of varying H-acceptor strength, along with some computational work, supports this hypothesis.⁵¹

Since, from the above analysis, the imide NH actually reduces the redox-dependent binding effect, an alternative way to use imides in H-bonding systems is to eliminate the NH, replacing it with an *N*-alkyl group.^{52,53} Reversible reduction still results, with now just the carbonyl oxygens being involved in the H-bonding. Since it is so straightforward to alkylate at the imide NH, this also provides a simple means to connect additional functionality. Very nice examples of this are the H-bond-based molecular shuttles reported by Leigh, Paolucci, and coworkers.^{54,55}

Molecular shuttles are constructed from at least two separate, but physically interconnected molecular units. The assembly, called a rotaxane, consists of a long linear molecule that is “threaded” through a macrocycle. Bulky groups on either end of the “thread” prevent the macrocycle from slipping off. For a shuttle, the thread will contain at least two binding sites for the macrocycle, with one of these being strongly preferred over the other in the initial state. This preference changes upon external stimulus, such as electron transfer.



The threads of the H-bonding shuttles reported by Paolucci, Leigh, and coworkers contain a succinamide station connected to either an imide, **27**, or a diimide, **28**, station. ¹H NMR clearly shows that the amide macrocycle, **29**, strongly prefers the succinamide station in the oxidized state. However, upon reduction of the imide/diimide, the preference changes, with now the imide/diimide station being strongly preferred. This results in net movement of the macrocycle from the succinamide to the imide/diimide (Eq. 1.19). This behavior can be deduced from the difference in the CVs of the thread by itself and that of the macrocycle-threaded shuttle. With the naphthylimide shuttle, the succinamide station is preferred over the imide 106 to 1 in the oxidized state, but, in the reduced state, the imide is preferred 500 to 1. Switching from an imide to a diimide opens up an additional control element because the diimide now undergoes two reversible reductions, first to the radical anion and then to a dianion. Analysis of the electrochemical data for this system indicates a 200 to 1 preference for the succinamide station in the zero state. This switches to a 2 to 1 preference for the diimide in the -1 state and a 4000 to 1 preference for the diimide in the -2 state.

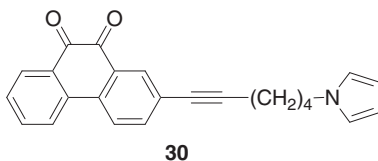


1.6.3 *o*-Quinones

In addition to the arylimides, Smith and coworkers also introduced *o*-quinones, discussed earlier in this chapter, as another example of a redox-dependent H-bonding receptor for neutral guests (Eq. 1.9).^{19,47,56} This system differs from the flavins and the imides in that a strong interaction is only observed in the reduced state, making these receptors function as on/off switches. The groups of Rotello and Cooke have also published several papers exploring the redox-dependent H-bonding properties of *o*-quinones.^{36,57–59}

Many of the applications that can be envisioned for electrochemically controlled H-bonding and redox-dependent binding in general will require that at least one of the components be attached to an electrode surface. It is therefore important to determine whether behavior observed in solution can still be observed when the host is anchored to a surface. This was first tested for a redox-dependent H-bonding receptor with the *o*-quinone system using the phenanthrenequinone pyrrole **30**.⁵⁶

Electrooxidation of the pyrrole unit results in the formation of a pyrrole polymer that coats the electrode surface as it is formed. The amount of polymer deposited can be controlled by the number of CV cycles into the pyrrole oxidation wave. With **30**, thick polymer layers give broad CV waves in the quinone voltage region, but thinner layers produce a well-resolved wave for the quinone 0/–1 reduction, which is reasonably stable when the electrodes are placed into fresh electrolyte solution with no **30**. As in solution, addition of different urea derivatives causes this wave to shift positive. The relative magnitude of the shifts mirror that seen in solution. Furthermore, the $E_{1/2}$ moves back to the original potential when the derivatized electrode is put back into a blank solution containing no urea.



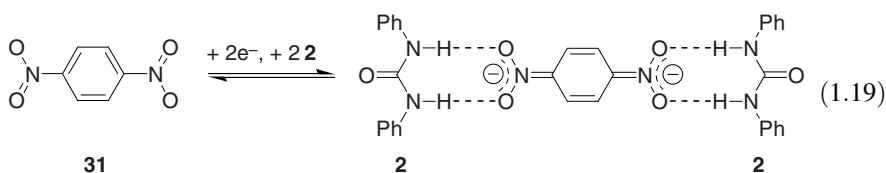
Cooke and coworkers have reported preparation of flavin-modified electrodes using a similar electropolymerization procedure.³⁴ They have also studied electrodes coated with self-assembled monolayers (SAMs) formed from both flavin³⁹ and phenanthrenequinone disulfides.⁵⁹ The monolayers are stable in CH_2Cl_2 solution, and, as with the electrodes formed from **30**, show redox-dependent binding behavior similar to that seen in solution. Interestingly, the phenanthrenequinone SAM

electrodes were also studied in the presence of phenylurea-terminated dendrimers. Addition of excess dendrimer produces a +200 mV shift in the $E_{1/2}$ of the phenanthrenequinone 0/–1 reduction, which is significantly larger than that obtained with phenanthrenequinone dissolved in solution.

1.6.4 Nitrobenzenes

Nitrobenzenes, also introduced by Smith and coworkers¹⁰ and discussed previously, provide yet another example of a simple organic redox couple in which reduction increases negative charge on two convergent oxygens, in this case the nitro oxygens (Eq. 1.3). The use of this group has not been explored as much as the flavin, imide, and *o*-quinone systems. However, the simplicity of its structure and the ease of which it can be introduced into organic structures suggests it may prove to be useful in the construction of more elaborate supramolecular assemblies.

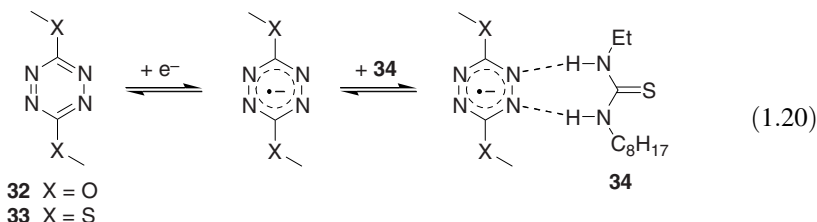
An example of the possible utility of the nitroaromatic group in creating more complicated structures comes from the still very simple case of 1,4-dinitrobenzene, **31**.⁶⁰ Almost all of the redox-dependent H-bonding systems investigated so far involve 1:1 complex formation. The ferrocene dendrimers are one exception. Another is 1,4-dinitrobenzene, where cyclic voltammetry provides very strong evidence for the formation of the 1:2 complex with diphenylurea, **2**, upon reduction to the dianion (Eq. 1.19). This dianion is unusually stable because the negative charge is spread over four oxygen atoms. It is possible that it could function as a simple linker unit that could tie together other units containing, for example, two urea groups, allowing larger and more complex structures to be assembled and disassembled under redox control.



1.6.5 Tetrazines

All of the examples discussed above involve an increase in negative charge on two convergent oxygen atoms. Nitrogen of course is also a good H-accepting atom, but a negatively charged nitrogen would generally be expected to be quite basic, resulting in greater problems with protonation. However, recently Rotello and coworkers have reported that the tetrazine derivatives, **32** and **33**, act as redox-dependent H-bonding hosts for dialkylthioureas (Eq. 1.20).⁶¹ ^1H NMR titrations in CDCl_3 indicate that there is no significant interaction with the thioureas and the tetrazines in their oxidized state. However, addition of 50 equivalents of 1-ethyl-3-octylthiourea, **34**, to solutions of the tetrazines in CH_2Cl_2 produced a +80 mV shift in the $E_{1/2}$ of the 0/–1 reduction of **32** and a +60 mV shift in that of **33**, indicating fairly significant interaction

between the thioureas and the tetrazine radical anions. Computational studies support the formation of H-bonds between the urea N–Hs and two adjacent nitrogens in the radical anion, as indicated in Equation 1.20.



1.7 EXAMPLES OF OXIDATION-BASED, ELECTROCHEMICALLY CONTROLLED H-BONDING SYSTEMS WITH NEUTRAL GUESTS

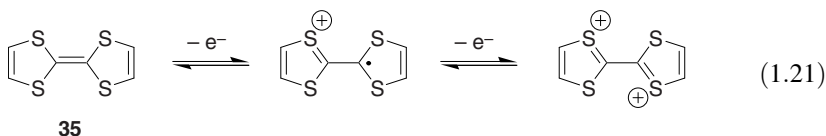
1.7.1 Ferrocene and Phenylenediamines

While using oxidation, in particular the oxidation of ferrocene to ferrocenium, has been a generally successful strategy to increase the strength of H-bonds with anionic guests, it has not as of yet been as successful with neutral H-accepting guests. Undoubtedly, part of the reason for this, as discussed earlier, is that this is such a good strategy for anions that the commonly used electrolyte anions, PF_6^- , BF_4^- , and ClO_4^- , will compete for the binding site, particularly in CH_2Cl_2 . By far, the largest $\Delta E_{1/2}$ values for oxidation-based redox-dependent H-bonding with a neutral guest reported so far are with the dimethylaminophenylurea/diamide system (Eq. 1.4).¹¹ However, this system was studied in the presence of a large anion electrolyte. Much smaller shifts are observed with electrolytes containing PF_6^- and ClO_4^- . The next largest shifts that have been reported for oxidations with neutral guests are with the ferrocene diamide, **7**, reported by Tucker and coworkers. Maximum shifts of -90 mV have been reported with dicarboxylic acid guests,¹⁶ and -60 mV with cyclic ureas.⁶² However, these studies were done in $\text{NBu}_4\text{PF}_6/\text{CH}_2\text{Cl}_2$. It is possible that much larger shifts would be observed in a large anion electrolyte.

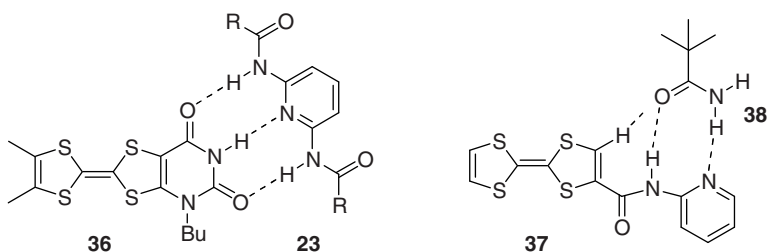
1.7.2 Tetrathiofulvalene

In addition to ferrocene, the oxidative redox couple that has received the most attention in supramolecular chemistry is tetrathiofulvalene (TTF), **35**. This compound undergoes two reversible one-electron oxidations, first to a radical cation and then to a dication (Eq. 1.21). TTF first came to prominence in the 1970s when it was discovered that the charge transfer complex between it and 7,7,8,8-tetracyanoquinonedimethane (TCNQ) shows metallic conductivity. As a result, a large variety of different TTF derivatives have been prepared and characterized. This rich synthetic chemistry, coupled with the electroactivity, has intrigued supramolecular chemists for some time, with the result that the TTF unit has been incorporated into a wide variety of

macrocycles and other supramolecular assemblies.⁶³



Like ferrocene, TTF does not inherently contain good H-bonding functionality, but it is possible to attach good H-bonding sites that will be in conjugation with the TTF. This allows for possible perturbation of H-bond strength through an inductive-type effect. Two examples of this strategy have appeared in the literature. The first is the imide-annealed TTF derivative **36** reported by Goldenberg and Neilands,⁶⁴ which like other imides will H-bond with diamidopyridines. Oxidation of the TTF should decrease the H-bonding by removing electron density from the electron-donating imide carbonyls, and indeed a modest +30 mV $E_{1/2}$ shift for the TTF 0/+1 couple is observed in $\text{NBu}_4\text{PF}_6/\text{CH}_2\text{Cl}_2$, indicating a threefold decrease in binding strength upon oxidation.



Another TTF derivative modified for H-bonding that has been studied is the amidopyridine TTF, **37**, prepared by Cooke, Rotello, and coworkers.⁶⁵ In this case, oxidation of the TTF should increase H-bonding strength by removing electron density from the amide NH, and, in fact, a negative $\Delta E_{1/2}$ of -33 mV is observed upon addition of amide **38**. Interestingly, a computational study suggests that the hydrogen adjacent to the amide group on the TTF ring also likely participates in H-bonding to the carbonyl oxygen of the guest in the +1 state.

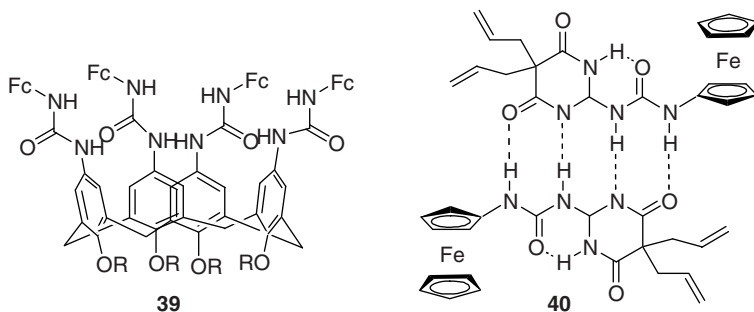
Note that in both of the above cases, the observed $E_{1/2}$ shifts are modest, but the experiments were done in 0.1 M $\text{NBu}_4\text{PF}_6/\text{CH}_2\text{Cl}_2$. Much larger effects might be observed if the work was repeated using a large anion electrolyte.

1.8 INDIRECT ELECTROCHEMICALLY CONTROLLED H-BONDING SYSTEMS

In the previous examples, electrochemical control of supramolecular structure is achieved by using electron transfer to directly affect H-bond strength. An alternative strategy is to not attempt to directly perturb the H-bonds, but instead to use electron

transfer to create an additional, non-H-bonding interaction that either breaks apart or helps form a H-bonded complex. Given the large number of H-bonded complexes that have been prepared, it seems surprising that there are not more examples of this strategy. Perhaps, one of the reasons is that in this case the voltammetry is unlikely to provide unambiguous evidence that the binding is changing, and therefore alternative proof must be provided.

One nice example of indirect control, for which good supporting evidence exists, is the ferrocenylurea calix[4]arene, **39**, reported by Moon and Kaifer.⁶⁶ It has been well established that similar urea-substituted calixarenes form dimeric capsules through H-bonds between the ureas on the two halves in noncompetitive solvents such as chloroform. ¹H NMR evidence shows that **39** also forms dimers in mixed solutions containing up to 3:10 CD₃CN/CDCl₃. Cyclic voltammetry of the complex in 1:10 CH₃CN/CHCl₃ shows a single ferrocene wave indicating that the ferrocenes are noninteracting. The thought was that oxidation of the ferrocenes to ferroceniums should break apart the capsule due to the creation of very unfavorable electrostatic interactions. However, although the CV wave is distorted from an ideal one-electron reversible process, this is not enough to prove that the capsule is breaking apart upon oxidation. More convincing evidence is that the diffusion coefficient of the oxidized calixarene, as measured by an NMR technique, is twice as fast as that of the reduced species. Furthermore, FT-IR spectroscopy shows that the peak for the urea carbonyls goes from 1657 cm⁻¹ in the reduced species, consistent with H-bonded oxygens, to 1783 and 1698 cm⁻¹, in the oxidized species, consistent with non-H-bonded oxygens.



While the above example shows that electrochemically created charge can be used to break apart a H-bonded complex, this is not always the case. This is shown by a study of another ferrocene-containing H-bonded dimer, also by Kaifer and coworkers.⁶⁷ The monomer in this example is based on the well-studied ureidopyrimidine framework that provides a linear AADD (A = H-acceptor; D = H-donor) array capable of forming four linear H-bonds with itself. The version studied by Kaifer, **40**, is modified to prevent the keto-enol tautomerization that complicates the chemistry of these systems. ¹H NMR indicates that, as expected, **40** exists as a dimer in CD₂Cl₂, but as a monomer in the more polar CD₃CN. CVs of **40** in different ratios of CH₂Cl₂ and CH₃CN are shown in Fig. 1.5. In pure CH₂Cl₂, scan (a),

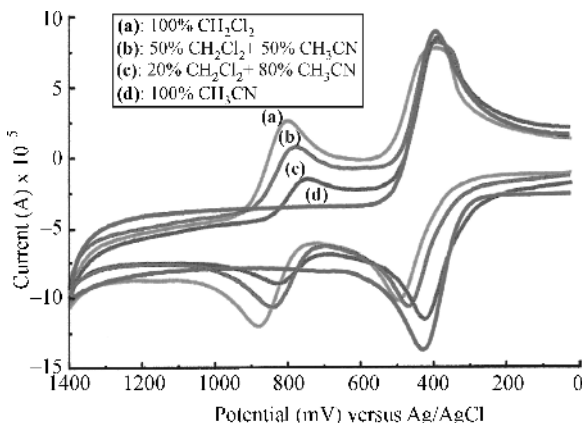


Figure 1.5 CVs of 1 mM **40** in 0.1 M NBu_4PF_6 with different ratios of CH_2Cl_2 and CH_3CN : (a) 100% CH_2Cl_2 , (b) 50% CH_2Cl_2 , 50% CH_3CN , (c) 20% CH_2Cl_2 , 80% CH_3CN , and (d) 100% CH_3CN . 100 mV/s scan rate.⁶⁷ (See the color version of this figure in Color Plates section.)

two reversible CV waves separated by 390 mV are observed. When CH_3CN is added, scans (b) and (c), the first oxidation grows at the expense of the second. In pure CH_3CN , scan (d), only the first wave is observed at a potential close to the first wave in CH_2Cl_2 . These results are consistent with the NMR, with the two-wave voltammogram being due to dimer and the one-wave voltammogram being due to the monomer.

The observance of two well-separated, reversible CV waves for the dimer in this system is a remarkable result. There has to be a very high degree of electronic communication between the two ferrocenes in order to make it so much harder to oxidize the second ferrocene than the first. Given the spatial distance between the ferrocenes, which are on opposite sides of the dimer, this cannot be explained by a through-space interaction, so apparently this electronic interaction is going through the H-bonds. Another surprising feature is that the second wave is reversible. This means that the two monomers dimerize in CH_2Cl_2 even when both are positively charged. Evidently, for this system under these experimental conditions, the four H-bonds are strong enough to overcome the electrostatic repulsion between the monomers.

1.9 CONCLUSIONS

H-bonds, being one of the strongest intermolecular interactions, are used extensively in the supramolecular chemistry of both man and nature. Their high electrostatic character makes it straightforward to perturb their strength electrochemically. There are two main ways to do this. Reduction can be used to make a H-acceptor a better acceptor by increasing the negative charge on a H-accepting atom, or oxidation can be used to make a H-donor a better donor by increasing the positive

charge on a H-donating atom. There are now a number of examples demonstrating the effectiveness of both strategies. In a noncompetitive solvent such as CH_2Cl_2 , it appears possible to change binding strengths by factors of 10^2 – 10^4 , and even 10^5 if additional interactions such as ion–ion can be invoked. The minimum elements required to achieve these large effects appear to be that there are two strong, almost linear H-bonds between host and guest and that at least one of these is strongly perturbed by the electron transfer reaction. Based on the existing examples, the largest effects are observed if the affected H-bonds are an integral part of the redox couple, but significant effects are also possible when the redox couple is simply attached through conjugation with the H-bonding site. Other factors to take into consideration are the solvent and the electrolyte. For reductions, electrolytes with NBu_4^+ as the cation appear to be good choices. For oxidations, especially with neutral guests, the best choices may be electrolytes with very large anions such as $\text{B}(\text{C}_6\text{F}_5)_4^-$, since the more common electrolyte anions such as PF_6^- , ClO_4^- , and BF_4^- may cause interference. Another factor to be aware of is the possibility of proton transfer between host and guest.

Looking toward the future, some basic work in electrochemically controlled H-bonding still remains to be done. In particular, the role of electrolyte needs to be investigated further. The number of different redox couples that have been used successfully is also still rather limited. Nonetheless, it is also clear that much of the groundwork has been laid, and that the next major steps will be to couple what has been learned about how electrochemistry can be used to control the strength of H-bonds in simpler systems with advances in H-bond assembly in solution, in order to construct larger, more sophisticated supramolecular structures operating under electrochemical control. Leigh and Paolucci's work with molecular shuttles and Kaifer's work with redox-active capsules are steps in this direction, but this is really just the beginning.

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