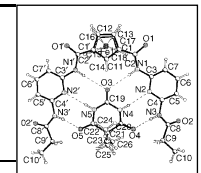
Recent developments in the redox-switched binding of organic compounds



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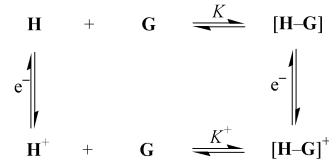
This review summarizes and puts into context recent advances in the field of redox-switched binding processes, with particular reference to the interaction between redox-active compounds and organic compounds, both charged and neutral. Simple homogeneous, two-component systems are discussed at first as a precursor to sections on more advanced systems (*e.g.* multi-component and multi-pole) and binding processes involving components attached to a surface.

1 Introduction

It is now clear that electrochemical oxidation or reduction can influence or trigger a range of physicochemical properties in a molecular system.[1] Systems that demonstrate or undergo such processes are often termed redox switches (electroswitches[1]), particularly if the redox process and the observed effect are reversible. This review focuses on redox-switched binding processes, where the binding affinity of a receptor or host molecule towards a substrate or guest is changed upon its oxidation or reduction. The background to this area has recently been described in a book by Kaifer and Gómez-Kaifer,[2] as have aspects of this area in recent literature reviews.[3–7] Essentially, the change in the binding constant between a host, **H**, and a guest, **G**, upon oxidation or reduction of the host is related to the change in its reversible redox couple upon complexation, as illustrated by the following square scheme (Scheme 1) and eqn. (1).[2,4,5,7]



Scheme 1 Square scheme for a redox-switchable system.

$$K^{+}/K = \exp[-nF(E_{[\mathbf{H}-\mathbf{G}]} - E_{\mathbf{H}})/RT] \quad (1)$$

$E_{\mathbf{H}}$ and $E_{[\mathbf{H}-\mathbf{G}]}$ are the formal electrode potentials of **H** and the complex, [**H**–**G**], respectively (each is usually approximated from the average of the anodic and cathodic peak potentials from cyclic voltammetry), K^{+} and K are the binding constants in the oxidised and reduced form of the receptor respectively, F is the Faraday constant, R is the universal gas constant, T is the temperature and n is the number of electrons transferred (in Scheme 1, $n = 1$). The direction of the change in the electrode potential, either anodic (positive) or cathodic (negative), indicates whether binding is stronger or weaker in a particular oxidation state of the host. From eqn. (1), a negative shift in the redox couple of the host **H** upon complexation (*i.e.* ΔE, where $\Delta E = E_{[\mathbf{H}-\mathbf{G}]} - E_{\mathbf{H}}$, is negative) denotes that guest binding is stronger when **H** is in its oxidised form (*i.e.* $K^{+} > K$). Therefore, if the binding constant is determined for one oxidation state,

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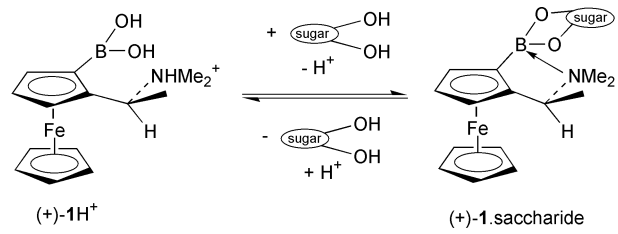
usually through a separate spectroscopic method, then the binding constant in the other oxidation state can be estimated, if ΔE is known. In practice, however, the actual limiting ΔE value can sometimes be difficult to determine, for example, if the binding interaction is relatively weak. Complexation and decomplexation kinetics and their effect on voltammetric behaviour may also play a role. An alternative approach to estimating values of K^+/K is through computer simulations of cyclic voltammograms.[2,3]

Part of the interest in this area of research stems from the fact that a change in redox potential upon complexation enables the binding process to be read out electrochemically and leads to the possibility of developing electrochemical sensors for a range of substrates. This is especially the case if a unique redox response is generated by the binding of a particular species, or if a receptor is highly selective for a desired target. Therefore, in the vast majority of cases, whether such systems demonstrate redox-switched binding or act as electrochemical sensors depends on your viewpoint; *i.e.* if a change in oxidation state affects the binding strength then it follows that complexation must affect the electrochemical properties of the redox-active unit. Such synthetic electrochemical sensors are expected to be viable alternatives to those based on natural receptors (biosensors), due in part to the expected increase in durability of such devices and their increased stability *in vivo*.

There are now numerous examples of supramolecular redox-active receptors in the literature and in most cases, redox-switched binding or electrochemical sensing has been demonstrated with inorganic cations.[8] More recently, redox-active receptors for anions, especially inorganic anions, have been developed,[9] including receptors that respond to cations or anions.[9b] Since these aspects have been largely dealt with elsewhere, this review concentrates on recent examples of the complexation by redox-active receptors of *organic compounds*, be they charged or neutral, including the binding of biologically-relevant molecules and binding interactions at a surface.

2.1 Inorganic redox-active binders

2.1.1 Metallocenes. Ferrocene has been a popular choice as the functional component of a molecular redox switch, owing to its well-characterised and reversible electrochemistry. In addition, ferrocenes can be easily functionalised with a variety of receptor groups and chirality can be readily introduced. This last aspect has been utilised by Shinkai in the development of chiral ferrocene receptors for saccharides.[10] It was shown that ferrocenylboronic acid (+)-**1** bound both linear and cyclic sugars in aqueous solution at neutral pH (Scheme 2), due to the



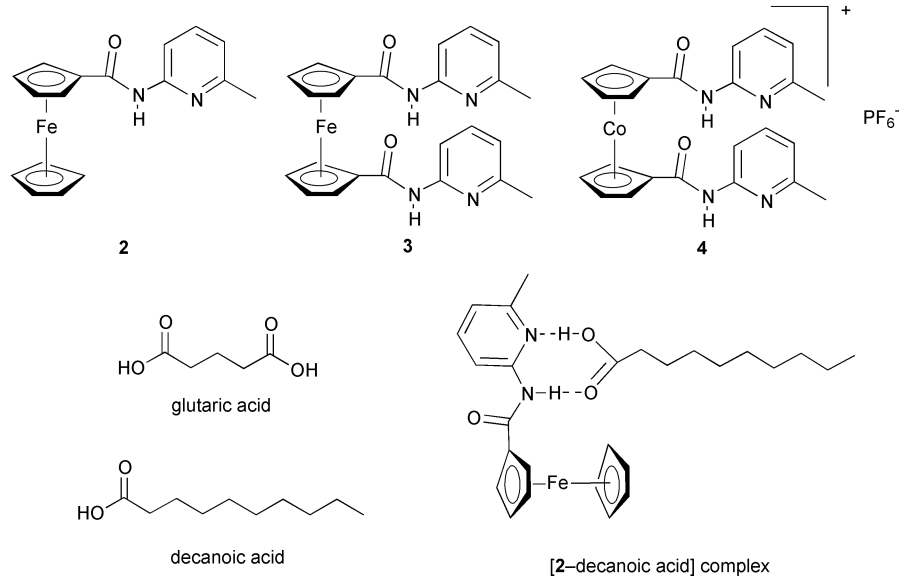
Scheme 2 Complexation formation between ferrocene receptor (+)-**1** and a saccharide.

reversible reaction between the boronic acid moiety of the protonated ferrocene receptor and the sugar to form a boronate ester, as shown in Scheme 2.

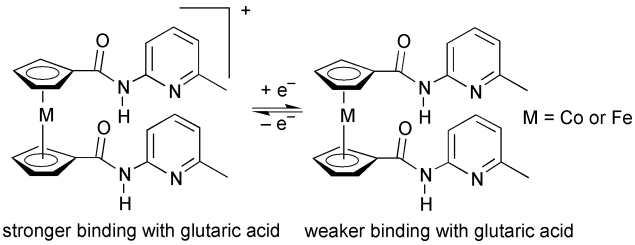
Electrochemical studies revealed that complexation imparted cathodic (*ca.* −50 mV) shifts in the Fe-centred oxidation potential of protonated (+1)-**1** and (−)-**1**, which indicated that the sugars were bound more strongly once the receptors were oxidised. It was thought that this redox-switched process was a result of the acidity of the boronic acid moiety increasing upon oxidation of the ferrocene unit, thereby increasing sugar affinity. Interestingly, chiral discrimination in binding was observed in that (+1)-**1** bound the linear saccharide D-sorbitol more strongly than L-sorbitol (D/L = 1.4); however this effect was only observed for linear sugars and differences in the electrochemical response to the binding of these enantiomers by (+1)-**1** were not apparent.

In the process of developing novel inorganic receptors for neutral molecules, metallocene compounds **2**, **3** and **4** were found to bind mono and dicarboxylic acids in organic solvents through complementary hydrogen bonds with their amide (N–H···O) and pyridine (O–H···N) groups.[11,12] Cyclic voltammetry studies in CH_2Cl_2 revealed cathodic shifts in the reversible waves of the receptors upon complexation, with the redox response to complexation of the mono-acid decanoic acid by **2** and **3** (−25 and −55 mV respectively) being approximately proportional to the number of hydrogen bonds in each complex (two and four respectively). Similar cathodic shifts have been found recently in the complexation through hydrogen bonds of 3-aminopyrazole derivatives by ferrocene dipeptide receptors.[13]

The binding of the dicarboxylic acid glutaric acid by metallocenes **3** and **4** was followed by ^{1}H NMR spectroscopy in $CDCl_3$–DMSO (0.5%), with a competition study confirming



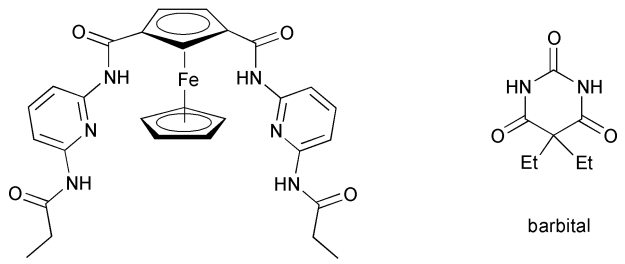
that the charged cobaltocenium analogue **4** bound glutaric acid in a 1:1 complex approximately twenty times more strongly than **3** (log K_3^{red} = 3.66 ± 0.02, log K_4^{ox} = 4.99 ± 0.04).[11] Interestingly, cyclic voltammetry studies in the same solvent mixture revealed identical cathodic shifts of −90 mV in the M^{III}/M^{II} redox couples of each receptor, showing that for each receptor the binding constants were higher in their oxidised forms [log K_3^{ox} = 5.2 ± 0.2, log K_4^{red} = 3.45 ± 0.2 from eqn. (1)]. The similarity of the binding constants for each receptor in their reduced or oxidised forms shows that it is the presence of positive charge and not the different metal that influences the hydrogen-bonding strength (Scheme 3). It is likely that the



Scheme 3 Redox-switched binding of glutaric acid by charged and neutral forms of metallocene receptors **3** and **4**.

positive charge on the metallocenium unit pulls electron density away from the amide units, which increases the acidity of the two N–H protons, thereby increasing their effectiveness as hydrogen bond acceptors.

Recently the ferrocene receptor **5** was synthesised with a view to binding and sensing urea and barbiturate derivatives through hydrogen-bonding interactions.[14] Receptor **5** does



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indeed bind barbital strongly in organic solvents, forming a 1:1 complex (Fig. 1). However the redox response to complexation

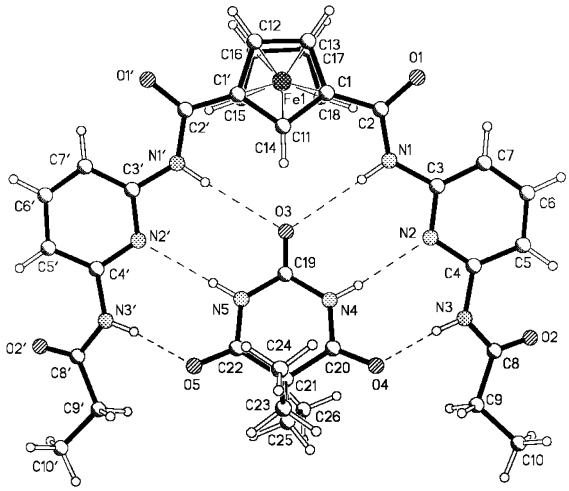
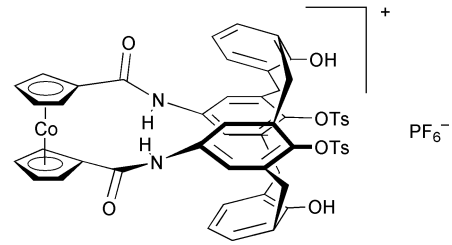


Fig. 1 X-Ray structure of the complex [**5**–barbital].[14]

is not large (*ca.* −20 mV), which shows that the binding enhancement upon oxidation does not appear to be as marked as when the guests are bridged between the Cp rings.[11,12]

Metallocene-based calixarenes have been used on a number of occasions as redox-active receptors for organic molecules. For example, Beer has shown that the two rigidly-held amide units on the upper-rim of calix[4]arene **6** create an ideal site for



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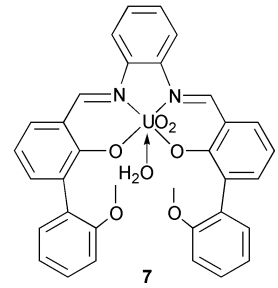
the complexation of bidentate anions such as carboxylates through hydrogen-bonding interactions.[15] The addition of tetrabutylammonium acetate to a solution of **6** in CH_3CN brought about a cathodic shift of −155 mV in the reversible Co(III)/(II) redox couple, which indicated that the anion was effectively stabilizing the positive charge on the cobaltocenium unit, making the complex harder to reduce.

Beer has also utilized a neutral ferrocene-appended calix[5]arene to encapsulate and sense the binding of polar organic molecules such as EtOH and DMF.[16] Electrochemical studies revealed that inclusion of these molecules into the calixarene cavity induced cathodic shifts in the ferrocene-centred redox waves. Anionic calix[6]arenes have been shown by Kaifer and co-workers to bind metallocenes in a 2:1 (host:guest) stoichiometry, with the two metallocene units being bound at the periphery of the receptor.[4] Complexation induced negative shifts in the metallocene-centred redox waves, indicating that, as expected, the anionic host bound the metallocenes more strongly in their oxidised (charged) forms. Kaifer has also investigated the electrochemical behaviour of inclusion complexes of ferrocenes with β-cyclodextrins and hemi-carcerands, as described in a recent review.[17] In each case, complexation leads to positive shifts in the ferrocene-centred redox-waves. In the case of the cyclodextrin complexes, complex dissociation takes place before the ferrocene is oxidised.

2.1.2 Other metal centres. In 1991, Reinhoudt reported a neutral metallocleft **7** containing a uranyl cation and a bound



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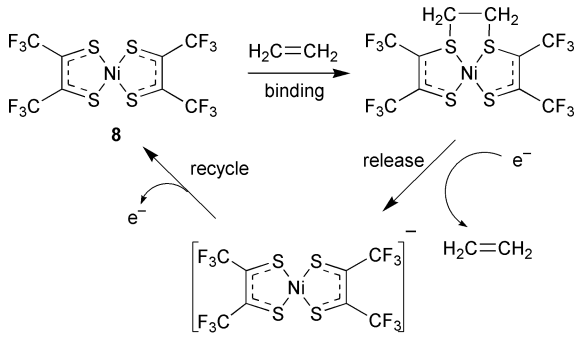
water molecule.[18] Polarographic studies in CH_3CN revealed that displacement of the bound water by benzylamine resulted in a −43 mV shift in the one-electron reduction potential of the U(VI) centre, presumably because the stronger Lewis basicity of the amine meant that it was better at stabilising the oxidised form of the complex with respect to the reduced form.

More recently, a nickel dithiolene complex **8** was shown to bind olefins in a reversible manner through a redox-switch cycle.[19] The complex bound the olefin in its neutral form with the olefin adding across two sulfur atoms. This process could be followed electrochemically by cyclic voltammetry studies in CH_2Cl_2 which revealed that the reversible one-electron reduction wave of **8** was markedly affected by the addition of excess

hex-1-ene. Reduction appeared to reduce the stability of the adduct to such an extent that the olefin was rapidly released from the complex, which could then be oxidised back to the starting material (Scheme 4). Such a process appears to be a

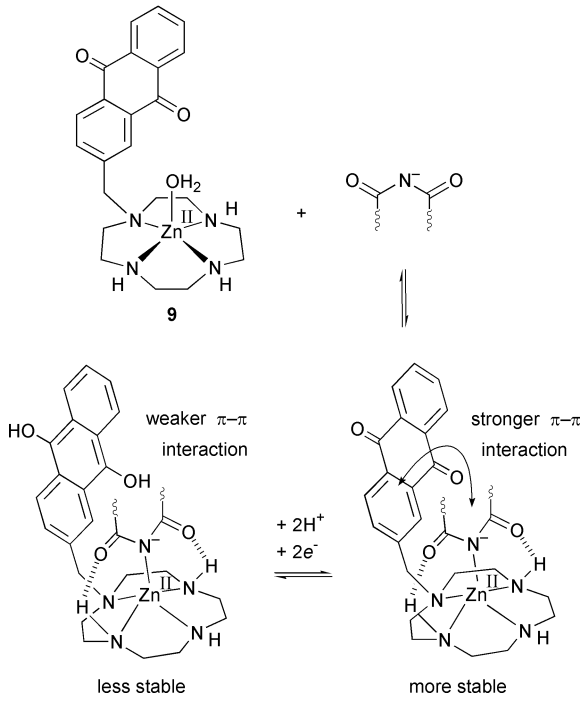


Scheme 4 A redox switch cycle for olefin separation, shown here with ethene.

viable method of separating and purifying ethene from gas streams containing impurities such as CO, H_2S and ethyne which do not interact with the complex.

There has been considerable recent interest in the design of redox-active ligands that can act as electrochemical probes for DNA.[20] Although most of these probes do not rely upon shifts in electrode potential for sensing purposes, redox-switched processes have been demonstrated with some inorganic complexes that can interact with DNA and its components. Bard was the first to report shifts in the metal-centred redox couples of complexes upon addition of DNA.[21] More recently, Palaniandavar demonstrated that the interaction of a series of copper phenanthroline complexes with DNA could be probed by monitoring the shifts of the reversible Cu(II)/(I) redox couple.[22] A cathodic shift of −49 mV in this couple for the complex [Cu(2,9-dimethyl-1,10-phenanthroline)$_2$]$^{2+}$ was observed upon addition of DNA in water at neutral pH, leading to a binding enhancement of 6.8 for the Cu(II) over the Cu(I) species [eqn. (1)], presumably due to increased electrostatic interactions.

A Zn(II)–cyclen complex, **9** (Scheme 5), containing a redox-

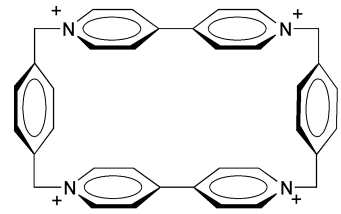


Scheme 5 The complexation of an imide by zinc(II) complex **9**, showing the redox-controlled π–π stacking interaction.

active anthraquinone pendant arm was shown to bind to the DNA base dT in aqueous solution.[23] Potentiometric studies at physiological pH revealed that dT and other neutral imides bound strongly to the receptor in their deprotonated form, due to Zn(II)–N^- coordination and complementary hydrogen bonding between the imido carbonyls and NH groups on the cyclen. A π–π interaction between the anthraquinone pendant arm and dT was also found by NMR studies. Electrochemical studies revealed that the degree of the redox response to complexation was strongly dependent upon the strength of π–π stacking in the oxidised form of the receptor. This was a result of the stacking interaction being dramatically weakened upon reduction of the anthraquinone moiety, due to increased electrostatic repulsion between the dihydroanthraquinone arm and the guest (Scheme 5).

2.2 Organic redox-active binders

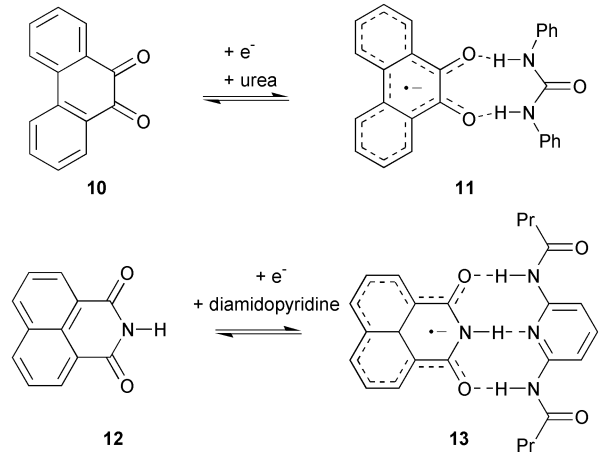
There are a number of examples of redox-switched processes involving organic redox-active molecules. Whereas metallocenes have shown prominence as inorganic redox switches, so the macrocycle cyclobis(paraquat-*p*-phenylene), **CBPQT**$^{4+}$,



CBPQT^{4+}

originally published by Stoddart, has been widely used as an organic redox-active receptor. This compound was reported as an early example of a redox-switched receptor for organic molecules.[24] Studies were carried out in Nafion film to avoid precipitation problems in aqueous solution. Complexation of the aromatic molecules catechol and indole at pH = 7 shifted the two-electron reduction potential of **CBPQT**$^{4+}$ to more negative values. This indicated that the guests were more tightly bound before reduction, as a result of stabilising charge-transfer interactions between **CBPQT**$^{4+}$ and the π-donor guest. Since then an array of complexes of **CBPQT**$^{4+}$ have been studied,[25] including redox-switched interlocked systems[6] and complexes with other redox-active species (see Sections 2.3 and 2.4).

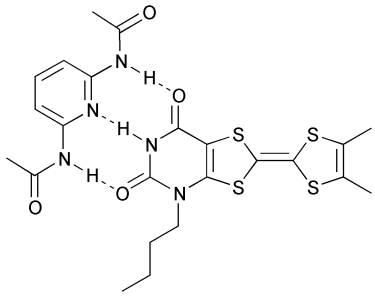
2.2.1 Hydrogen-bonded systems. As with inorganic redox-switched receptors, organic receptors have been used to study host–guest interactions with organic molecules that bind solely through hydrogen bonds. Smith *et al*. found that the redox couple of phenanthrenequinone **10** (Scheme 6), which under-



Scheme 6 Redox-switched binding of 1,3-diphenylurea and 2,6-dipropylamidopyridine by receptors **10** and **12**.

goes a reversible one-electron reduction in aprotic media, was shifted by over +100 mV upon binding 1,3-diphenylurea in dichloromethane to form the complex **11**, with a smaller shift observed in DMF, used to prevent aggregation of the urea.[26] The positive shifts upon complexation and the lack of any significant interaction in the oxidised form (from separate NMR studies) meant that binding was switched on by reduction, due to the location of negative charge at the carbonyl oxygen atoms (Scheme 6). Similar results were found for the interaction between 1,8-naphthalimide **12** and a 2,6-diamidopyridine derivative to form the complex **13**.

The complexation of 2,6-diamidopyridine moieties *via* hydrogen bonds has also been studied by Goldenberg *et al*., who found that a redox-active tetrathiafulvalene (**TTF**) derivative containing a pyrimidine unit formed the complex **14** in CH_2Cl_2



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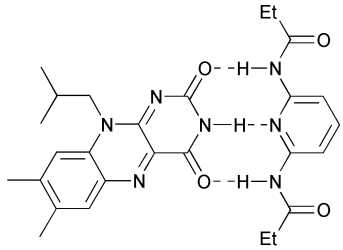
through three complementary hydrogen bonds.[27] The oxidation peak potential of the **TTF** derivative shifted anodically by +30 mV upon complex formation. Complexation therefore removed electron density from the TTF unit, making it harder to oxidise. The positive shift in potential meant that the complex was of the order of 3–4 times less stable in its oxidised form.

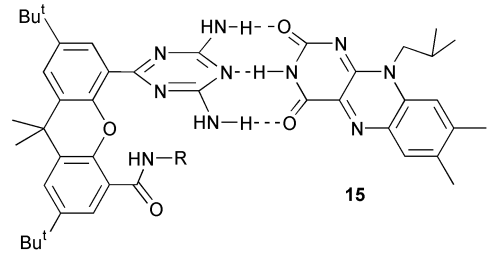
Rotello and Neimz have recently published a review of their work on a series of flavin receptors,[5] which describes how hydrogen bonding and other non-covalent interactions can control the potential at which flavins are reduced, which could explain in part why flavoproteins can display redox activity over such a wide (>500 mV) potential range. Initial studies involved the three point hydrogen-bonding interaction between the flavin **15** and the 2,6-diamidopyridine derivative **16**, where



15 **16**

complexation in CH_2Cl_2 was found to perturb the one-electron reduction potential of the flavin by +155 mV, corresponding to nearly a 500-fold increase in the binding constant [eqn. (1)] upon reduction to the flavin radical anion. Subsequent studies in a range of hydrogen-bonding solvents have shown that formation of the central hydrogen bond to the N–H of the flavin in fact makes reduction more difficult,[28] which shows that it is the bonding to the two carbonyl oxygens that is solely responsible for the large positive shift in potential.

Rotello has also shown that it is not only hydrogen-bond formation that brings about changes in flavin reduction potential: in work with related complexes containing a rigid scaffolding unit, reduction of the flavin **15** when bound to the anthracene receptor **17a** caused a dramatic decrease in the π–π stacking interaction between host and guest, as evidenced by negative shifts in potential upon complexation.[5] In a similar fashion, when a related receptor **17b** containing a thiomethoxy



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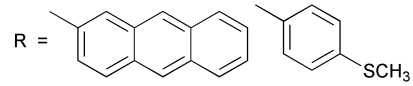
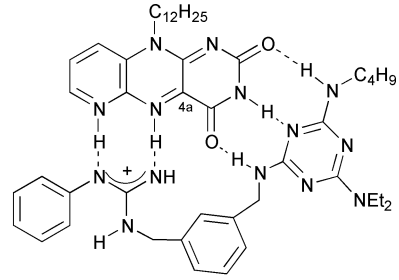


17a **17b**

group was used,[5] reduction of the bound flavin brought about a decrease in the interaction between the sulfur atom and the π system of the flavin.

Yano *et al*. have studied related complexes where aza-flavins are bound through five complementary hydrogen bonds, resulting in high binding constants in relatively polar organic solvent mixtures [*e.g.* $K = 1.3 \times 10^4$ M^{-1} for the complex **18** in $CHCl_3$–MeCN (20%)].[29] As found with Rotello's work, cyclic voltammetry studies revealed large positive shifts in the one-electron reduction potential of 6-azaflavin upon complex formation, indicating a large increase in complex stability in the reduced form [*e.g.* for complex **18**, $E = +220$ mV, $K_{red} \approx 7 \times$



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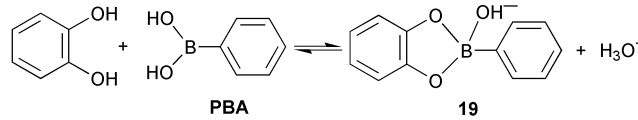
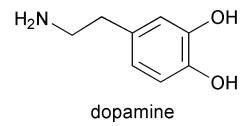
10^7 M^{-1} from eqn. (1)]. As well as stabilising the 6-azaflavin in their reduced forms, hydrogen bonding was also found to accelerate the rates of nucleophilic attack at the C(4a) position of the flavin.

2.2.2 Covalently-bonded systems. As part of a programme to develop novel electrochemical sensors for neurotransmitters, the reaction between catechol and phenylboronic acid (**PBA**) to form the boronate ester **19** in water at neutral pH (Scheme 7)



PBA **19**



dopamine

Scheme 7 The reaction between catechol and phenylboronic acid (**PBA**) to form a boronate ester.

was studied by electrochemistry.[30] Studies revealed large changes in the appearance of the cyclic voltammogram of catechol in the presence of **PBA**. In particular, a new anodic oxidation wave emerged at a potential approximately 400 mV

more positive than the original catechol oxidation wave upon the addition of aliquots of **PBA** to a 1 mM solution of catechol, with a concomitant decrease of the catechol oxidation wave (Fig. 2). The studies revealed that the boronate ester must be

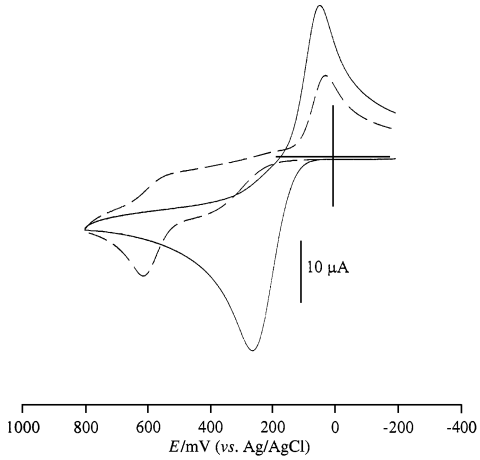


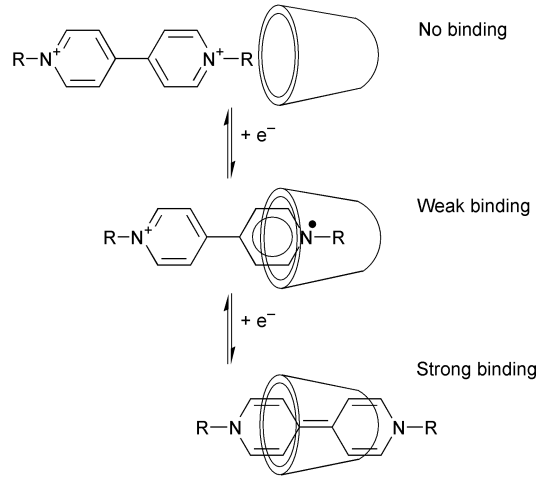
Fig. 2 Cyclic voltammograms, recorded using a glassy carbon electrode in aqueous buffer at pH = 8 and 298 K, of 1 mM catechol (—) and catechol plus 20 mol equiv. of **PBA** (– – –). Sweep rate 100 mV s^{-1}.[30]

very unstable in its oxidised form, since oxidation of the ester appeared to lead to its immediate cleavage to reform **PBA** and oxidised catechol (benzoquinone). Similar results were observed upon the addition of **PBA** to dopamine. Significantly the electrochemistry of ascorbic acid, which is present in large excess to dopamine *in vivo* and normally masks the dopamine oxidation signal, was not affected by the presence of **PBA**, leading to the possibility of developing viable electrochemical sensors for dopamine and related catecholamines.

2.3 Multi-component and multi-pole systems

The examples of inorganic and organic redox-active receptors for organic compounds discussed so far (Sections 2.1 and 2.2) involve the equilibria summarised in Scheme 1. This represents the simplest form of a host–guest system involving a redox-active species, where only two reacting species (components) come together to form a complex, with one of the components able to interconvert between two oxidation states (poles). Such a process can therefore be described as a two-component two-pole system, with redox-switched binding occurring where oxidation or reduction of one component alters the binding affinity between the two species. Recently, as part of the recent drive towards the design of artificial molecular devices and machines,[6] attempts have been made to study more complex systems, where there are more than two types of reacting species or components in the system or where there are more than two oxidation states in which complex formation can be monitored. There are now a number of examples of so-called multi-component and/or multi-pole systems, as described below.

2.3.1 Two-component multi-pole systems. Here complex formation between two reacting components is monitored over three or more oxidation states. The simplest case is a two-component three-pole system, where one component can exist in three oxidation states. An excellent example of this is the study by Kaifer of viologen (4,4′-bipyridinium) complexation by modified and unmodified β-cyclodextrins (β-CDs) in water at pH = 7 (Scheme 8).[4] Viologen can exist in three oxidation states by virtue of its undergoing two reversible one-electron reductions. With a +2 charge (R = water solubilising chain), NMR evidence shows that it is not bound by β-CDs. One-electron reduction results in weak binding, as evidenced by small positive shifts in the +2/+1 reduction potential upon



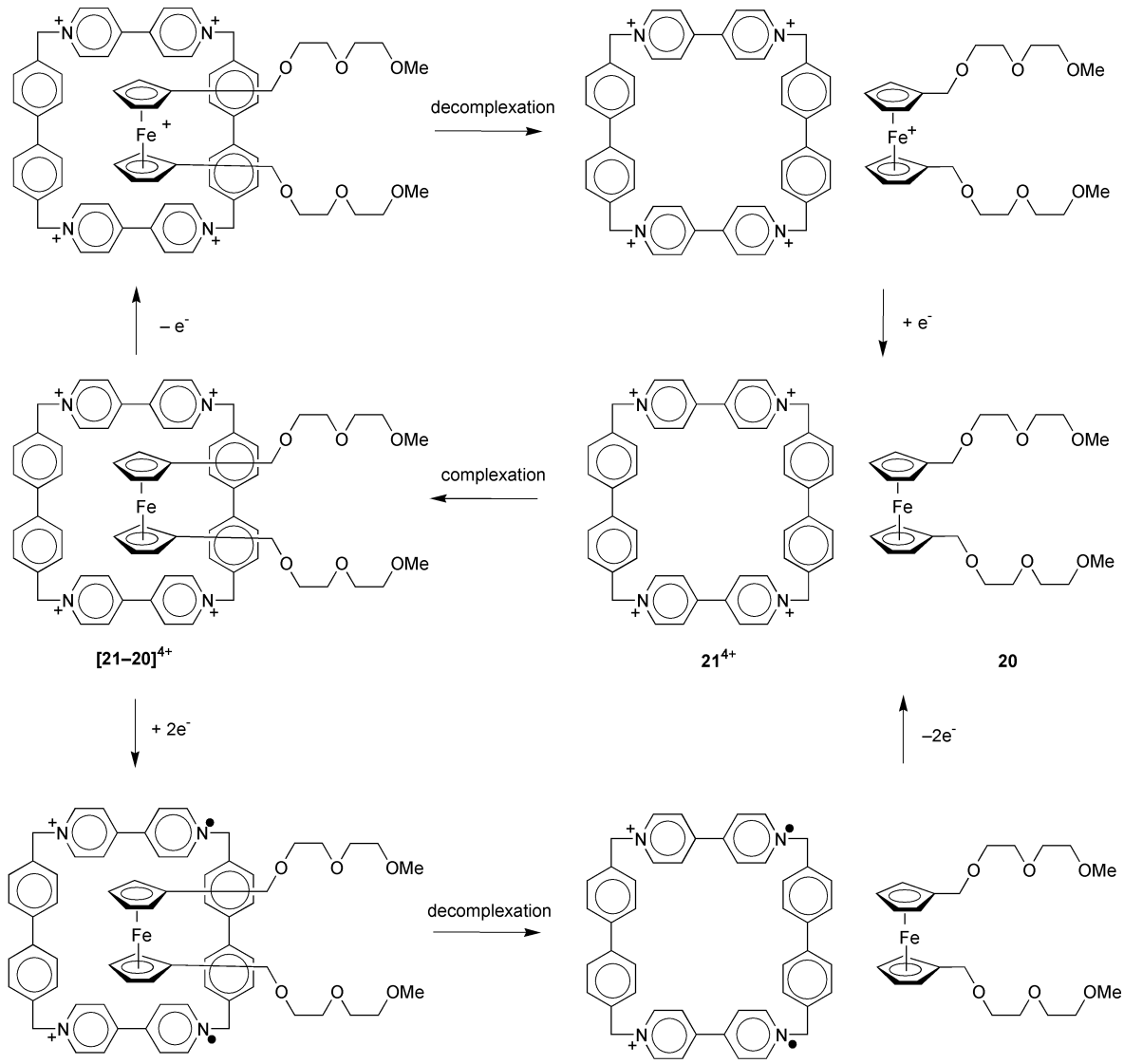
Scheme 8 Redox-switched binding of a β-CD by a viologen over three oxidation states.

addition of β-CD. However the second +1/0 reduction is strongly affected by the presence of β-CD, with large positive potential shifts observed. This result is consistent with the fully reduced neutral viologen being strongly bound by the receptor in water to form a pseudorotaxane complex, due its increased electron density and hydrophobic character.

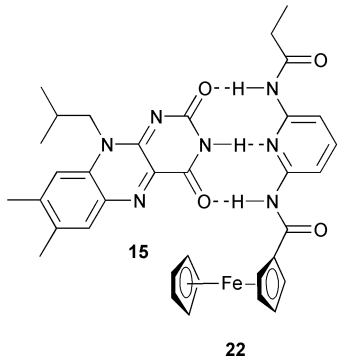
A two-component multi-pole system can also operate where both reacting components are redox-active (*i.e.* host *and* guest). Such a case has been recently been demonstrated by Stoddart and co-workers with the binding in MeCN of the 1,1′-disubstituted ferrocene polyether derivative **20** by the charged macrocycle $\mathbf{21}^{4+}$, a derivative of $\mathbf{CBPQT}^{4+}$.[6] With a +4 charge, the receptor forms a strong complex with **20** in acetonitrile (K_a = 3900 M^{-1} in CD_3CN), with the two polyether chains protruding outwards from the same side of the host. Uncomplexed **20** undergoes a reversible oxidation that is shifted to more positive potentials in the presence of $\mathbf{21}^{4+}$ which indicates a disruption of the host–guest adduct upon oxidation of the guest (Scheme 9). However, $\mathbf{21}^{4+}$ is also redox-active and undergoes two reversible two-electron reductions in MeCN; the first of these (+4/+2) is shifted to more negative potentials in the presence of ferrocene **20**. Once again this observation is consistent with a destabilisation of the host–guest complex, this time upon reduction of the host (Scheme 9). These results therefore indicate that a two-component three-pole system is in operation in which there is only significant complexation in one combination of oxidation states. Interestingly, the second reduction of the receptor unit (2+/0) is unaffected by the presence of **20**, which indicates that reduction takes place on the free cyclophane to form a fourth redox pole in which there is also no host–guest complexation.

A related two-component three-pole system has recently been described by Cooke *et al.* in which the strength of the hydrogen-bonding interaction between two redox-active compounds can be affected either by oxidation of one species or by reduction of the other.[31] The ferrocene receptor **22** was found to form only a weak complex with flavin **15** in $CDCl_3$ solution (K = 45 ± 5) M^{-1}. However, cyclic voltammetry studies revealed a cathodic shift of −34 mV in the ferrocene-centred redox couple of **22** upon addition of excess **15**, which indicated that the ferrocene receptor was more strongly bound to the flavin in its oxidised form $\{[\mathbf{22}–\mathbf{15}]^{+}$, K = 169 ± 17 M^{-1}, eqn. (1)$\}$. Interestingly, the addition of excess **22** to a solution of **15** brought about a +100 mV anodic shift in the reversible redox couple of the flavin, indicating a 50-fold increase in stability upon reduction $\{[\mathbf{22}–\mathbf{15}]^{-}$, K = 2209 ± 221 M^{-1}, eqn. (1)$\}$.

2.3.2 Three-component two-pole systems. In this case there are only two oxidation states of a molecule over which



Scheme 9 Redox-controlled complexation and decomplexation of the complex [**21**–**20**]$^{4+}$.



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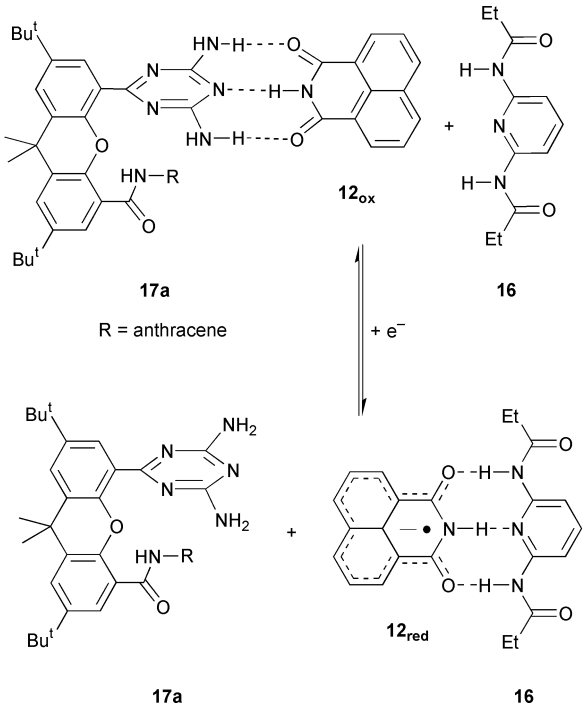
complexation is monitored, but there are two other components in the system that may form a complex with the redox-active species in one (or both) of its redox states. An excellent example of such a situation has been demonstrated by Rotello.[5] Here the 2,6-diamidopyridine derivative **16** and the scaffold receptor system **17a** mentioned earlier (Section 2.2) compete for complexation with the redox-active 1,8-naphthalimide **12**, previously shown by Smith to demonstrate redox-switched hydrogen bonding in a two-component system (Scheme 6).[26] NMR titration experiments revealed that neutral $\mathbf{12}_{ox}$ bound relatively strongly to the anthracene scaffold system **17a** in $CDCl_3$, due to favourable π–π interactions with the anthracene ring, whereas binding was an order of magnitude weaker between $\mathbf{12}_{ox}$ and **16**. As previously found by Smith,[26] a substantial positive shift in the reduction potential of **12** (+143 mV) was observed upon addition of **16**. However, no change in reduction potential was found upon addition of **17a** to **12** due to expected favourable hydrogen-bonding interactions being offset by unfavourable aromatic interactions with the reduced naphthalimide, as described earlier (Section 2.2). The electrochemical data therefore indicated that whereas the strength of the interaction between the reduced naphthalimide, $\mathbf{12}_{red}$, and the scaffold **17a** was no different to that with neutral $\mathbf{12}_{ox}$, the binding interaction between $\mathbf{12}_{red}$ and **16** was now nearly 300 times stronger than that between $\mathbf{12}_{ox}$ and **16** [eqn. (1)]. Therefore, the binding preference of **12** was switched from **17a** to **16** upon its reduction (Scheme 10). These results were verified independently by an NMR competition study and by EPR measurements.

Kaifer has also demonstrated a similar three-component two-pole system where the preference of a cobaltocene derivative for either a β-CD or a calix[6]arene depends upon its metal oxidation state.[4]

2.3.3 Three-component three-pole systems. The cyclophane **CBPQT**$^{4+}$ has been used as a receptor in a three-component three-pole switching system.[6,32] The key to this work is that the redox-active species tetrathiafulvalene (**TTF**) can exist in three oxidation states. Electrochemical and spectroscopic experiments revealed that neutral **TTF**(0) was bound strongly by the **CBPQT**$^{4+}$ in acetonitrile (K_a = 1.0 ± 0.1



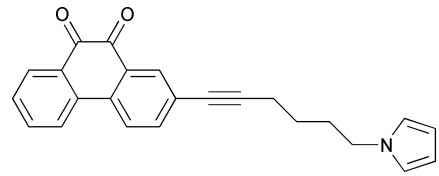
Scheme 10 In the presence of **17a** and **16**, imide **12** forms a stronger complex with **17a** as $\mathbf{12}_{ox}$ but a stronger complex with **16** as $\mathbf{12}_{red}$.

$\times 10^4$ M^{-1}) but not at all when oxidised successively to **TTF**$^{+\cdot}$ and then **TTF**$^{2+}$. Conversely, similar experiments revealed that **TTF**$^{2+}$ was bound strongly by the crown ether 1,5-dinaphtho[38]crown-10 (**23**) in acetonitrile ($K_a = 4.1 \pm 0.4 \times 10^3$ M^{-1}) but not at all as **TTF**$^{+\cdot}$ or **TTF**(0) (Scheme 11). Accordingly, electrochemical experiments in acetonitrile carried out in the presence of both receptors revealed that the **TTF** guest interchanged between the two receptors as **TTF**(0) or **TTF**$^{2+}$, but as **TTF**$^{+\cdot}$ it was bound by neither receptor.

2.4 Redox-controlled recognition at a surface

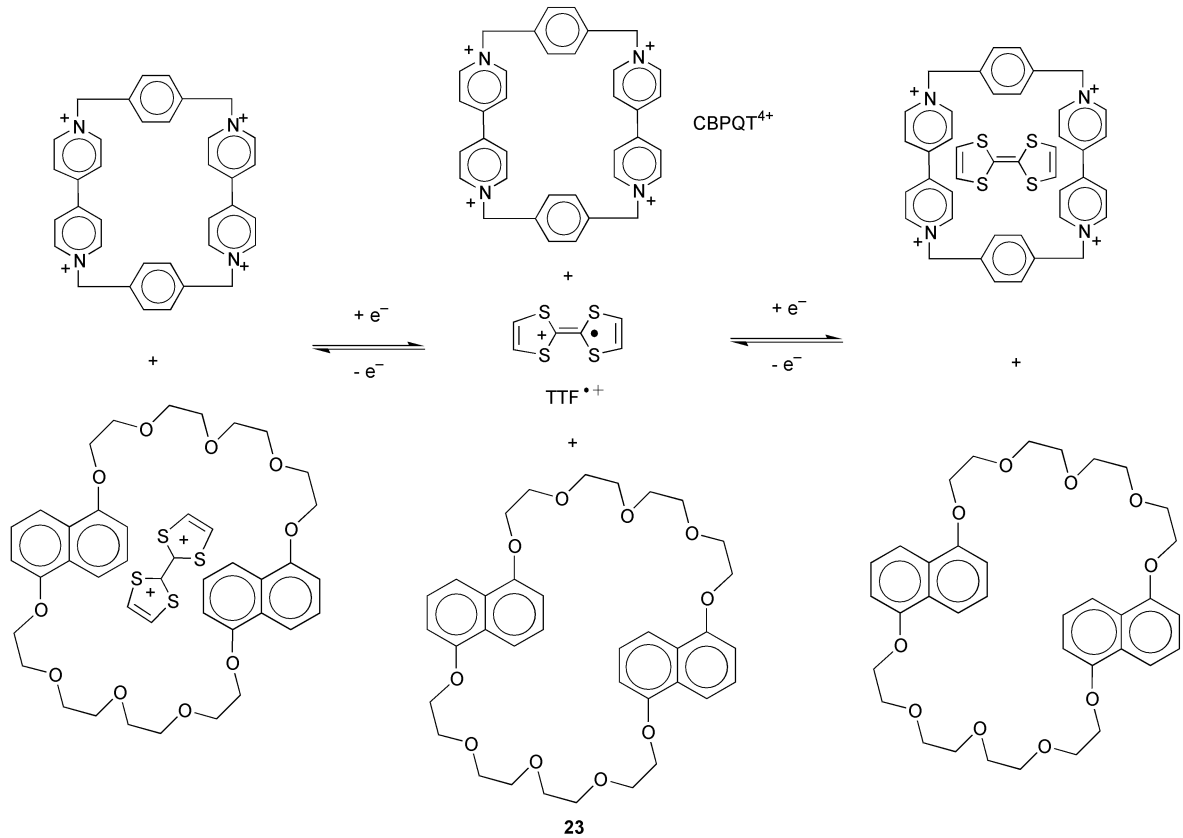
The examples discussed so far in this review describe molecular recognition in solution. One way of utilising such a process for a potential application (*e.g.* for a prototype electrochemical sensor or for an electroactive molecular device) is to immobilise at least one of the reacting components onto a surface. Accordingly, there are now a number of examples of molecular recognition at a surface involving redox-active components.[2–4,33] In principle, either the redox-active species or its target may act as the immobilised component. The following few examples discuss recent advances involving the binding of organic species at a surface by redox-active species and illustrate how effects in solution discussed above can also be observed at the solid/liquid interface.

A common way to immobilise a receptor onto an electrode surface is to generate a polypyrrole film. Recently, Smith has built on previously described studies of hydrogen-bonding interactions in solution[26] with the synthesis of a phenanthrenequinone pyrrole **24** which was electropolymerised at a



24

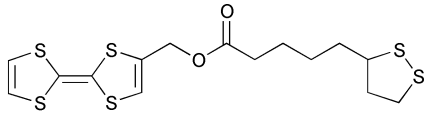
glassy carbon disk electrode.[34] Electrodes derivatised with this polymer were found to be reasonably stable in organic solvents. The derivatised electrode was placed in CH_3CN solutions containing differing amounts of 1-phenyl-3-propylurea. As observed previously in the solution phase, complexation resulted in the redox couple for phenanthrenequinone reduction shifting towards a more positive value, indicating a strong interaction between the surface-confined quinone radical anion and the urea. Interestingly, the surface-confined receptor was



Scheme 11 A three-component three-pole system in which, depending on its oxidation state, **TTF** is either bound by **CBPQT**$^{4+}$, crown ether **23** or by neither receptor.

found to be more selective than the analogous compound in solution, with only aromatic ureas causing a significant shift in potential.

The use of self-assembled monolayers (SAMs) for complexation studies involving redox-active groups at a surface has been explored over the past few years.[3,4] Recently, Cooke *et al*. have demonstrated how a mixed monolayer on a gold electrode containing the thioctic ester derivative **25** interacts with a solution of **CBPQT**$^{4+}$ in CH_3CN.[35] As found in solution studies with this molecule and in related work described earlier,[32] the first oxidation potential of the **TTF** unit of **25** to form the radical



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cation species was shifted anodically in the presence of **CBPQT**$^{4+}$, while the second oxidation potential was unaffected. This behaviour was consistent with the complex at the electrode surface between **25** and **CBPQT**$^{4+}$ dissociating upon the first oxidation of the **TTF** unit.

Rotello has also used SAM chemistry to demonstrate that the redox-controlled recognition of flavin derivatives can take place at a surface in a similar fashion to that in solution.[36] In this case, SAMs of 2,6-diamidopyridine derivatives were formed at the surface of a gold colloid nanoparticle (*ca*. 2 nm in diameter) rather than at an electrode. As expected from previous studies in solution,[5] complex formation between the SAM and flavin **15** was observed (Fig. 3) by NMR spectroscopy. Subsequent

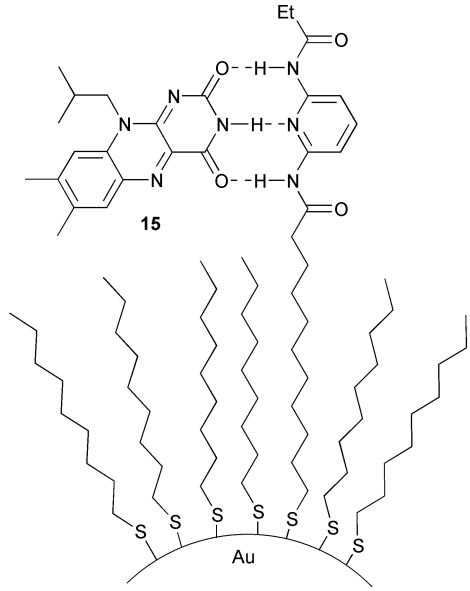

Fig. 3 Complexation of flavin **15** by a diamidopyridine-functionalised gold colloid.

electrochemistry experiments revealed that the redox couple of the flavin was shifted anodically by +81 mV upon complexation, which showed that the binding interaction was at least 20 times as strong [eqn. (1)] upon reduction of the flavin.

3 Summary and future prospects

The examples described in this review show how redox processes may be used to control the binding strength between two or more interacting species and how such processes may be utilised for sensing purposes. Now much of the ground-work has been laid, future work with redox-active species will undoubtedly be directed towards more complex (*e.g*. multi-pole and multi-component) systems. Many of the concepts described here have already been adopted for related redox-switched processes. For example, locking the host and guest together as components of a catenane or a rotaxane results in conformational changes upon oxidation or reduction.[6] More links between redox-switched binding processes and other controllable processes (*e.g*. redox-switched reactivity and catalysis[19,37]) can be envisaged in the future. The fact that many of the effects observed in solution appear to be perfectly reproducible at a surface bodes well for future applications.

4 References

1 J. M. Lehn, *Supramolecular Chemistry, Concepts and Perspectives*, VCH, Weinheim, 1995.
2 A. E. Kaifer and M. Gómez-Kaifer, *Supramolecular Electrochemistry*, Wiley-VCH, 1999.
3 P. L. Boulas, M. Gómez-Kaifer and L. Echegoyen, *Angew. Chem., Int. Ed*., 1998, **37**, 216.
4 A. E. Kaifer, *Acc. Chem. Res*., 1999, **32**, 62.
5 A. Niemz and V. M. Rotello, *Acc. Chem. Res*., 1999, **32**, 44.
6 V. Balzani, A. Credi, F. M. Raymo and F. S. Stoddart, *Angew. Chem., Int. Ed*., 2000, **39**, 3348.
7 P. D. Beer, P. A. Gale and G. Z. Chen, *J. Chem. Soc., Dalton Trans*., 1999, 1897.
8 F. Le Derf, M. Mazari, N. Mercier, E. Levillain, G. Trippé, A. Riou, P. Richomme, J. Becher, J. Garín, J. Orduna, N. Gallego-Planas, A. Gorgues and M. Sallé, *Chem. Eur. J*., 2001, **7**, 447 and references cited therein.
9 (*a*) P. D. Beer and P. A. Gale, *Angew. Chem., Int. Ed*., 2001, **40**, 487; (*b*) J. M. Lloris, R. Martínez-Mánez, J. Soto and T. Pardo, *J. Organomet. Chem*., 2001, **637–639**, 151.
10 A. Ori and S. Shinkai, *J. Chem. Soc., Chem. Commun*., 1995, 1771.
11 J. D. Carr, L. Lambert, D. E. Hibbs, M. B. Hursthouse, K. M. A. Malik and J. H. R. Tucker, *Chem. Commun*., 1997, 1649.
12 J. D. Carr, S. J. Coles, M. B. Hursthouse, M. E. Light, J. H. R. Tucker and J. Westwood, *Angew. Chem., Int. Ed*., 2000, **39**, 3296.
13 P. Saweczko, G. D. Enright and H. B. Kraatz, *Inorg. Chem*., 2001, **40**, 4409.
14 S. R. Collinson, T. Gelbrich, M. B. Hursthouse and J. H. R. Tucker, *Chem. Commun*., 2001, 555.
15 P. D. Beer, D. Hesek, K. C. Nam and M. G. B. Drew, *Organometallics*, 1999, **18**, 3933.
16 P. D. Beer, Z. Chen, M. G. B. Drew and P. A. Gale, *J. Chem. Soc., Chem. Commun*., 1995, 1851.
17 C. M. Cardona, S. Mendoza and A. E. Kaifer, *Chem. Soc. Rev*., 2000, **29**, 37.
18 A. R. van Doorn, M. Bos, S. Harkema, J. van Eerden, W. Verboom and D. N. Reinhoudt, *J. Org. Chem*., 1991, **56**, 2371.
19 K. Wang and E. I. Stiefel, *Science*, 2001, **291**, 106.
20 S. Takenaka, *Bull. Chem. Soc. Jpn*., 2001, **74**, 217.
21 M. T. Carter and A. J. Bard, *J. Am. Chem. Soc*., 1987, **109**, 7528.
22 S. Mahadevan and M. Palaniandavar, *Inorg. Chem*., 1998, **37**, 693.
23 J. H. R. Tucker, M. Shionoya, T. Koike and E. Kimura, *Bull. Chem. Soc. Jpn*., 1995, **68**, 2465.
24 A. R. Bernardo, J. F. Stoddart and A. E. Kaifer, *J. Am. Chem. Soc*., 1992, **114**, 10624.
25 M. B. Nielsen, J. O. Jeppesen, J. Lau, C. Lomholt, D. Damgaard, J. P. Jacobsen, J. Becher and J. F. Stoddart, *J. Org. Chem*., 2001, **66**, 3559.
26 Y. Ge, L. Miller, T. Ouimet and D. K. Smith, *J. Org. Chem*., 2000, **65**, 8831.
27 L. M. Goldenberg and O. Neilands, *J. Electroanal. Chem*., 1999, **463**, 212.
28 A. O. Cuello, C. M. McIntosh and V. M. Rotello, *J. Am. Chem. Soc*., 2000, **122**, 3517.
29 T. Kajik, H. Moriya, K. Hoshino, T. Kuroi, S. Kondo, T. Nabeshima and Y. Yano, *J. Org. Chem*., 1999, **64**, 9679.
30 S. M. Strawbridge, S. J. Green and J. H. R. Tucker, *Chem. Commun*., 2000, 2393.
31 C. Bourgel, A. S. F. Boyd, G. Cooke, H. Augier de Cremiers, F. M. A. Duclairoir and V. M. Rotello, *Chem. Commun*., 2001, 1954.
32 P. R. Ashton, V. Balzani, J. Becher, A. Credi, M. C. T. Fyfe, G. Mattersteig, S. Menzer, M. B. Nielsen, F. M. Raymo, J. F. Stoddart, M. Venturi and D. J. Williams, *J. Am. Chem. Soc*., 1999, **121**, 3951.
33 L. M. Goldenberg, M. R. Bryce and M. C. Petty, *J. Mater. Chem*., 1999, **9**, 1957.

34 Y. Ge and D. K. Smith, *Anal. Chem.*, 2000, **72**, 1860.
35 G. Cooke, F. M. A. Duclairoir, V. M. Rotello and J. F. Stoddart, *Tetrahedron Lett.*, 2000, **41**, 8163.
36 A. K. Boal and V. M. Rotello, *J. Am. Chem. Soc.*, 1999, **121**, 4914.
37 A. M. Allgeier and C. A. Mirkin, *Angew. Chem., Int. Ed.*, 1998, **37**, 894.