Electrochemical Anion Sensing: Supramolecular Approaches

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Abstract

Anions play a vital role in a broad range of environmental, technological and physiological processes, making their detection/quantification valuable. Electroanalytical sensors offer much to the selective, sensitive, cheap, portable and real time analysis of anion presence where suitable combinations of selective (non covalent) recognition and transduction can be integrated. Spurred on by significant developments in anion supramolecular chemistry, electrochemical anion sensing has received considerable attention in the past two decades. In this review we provide a detailed overview of all electroanalytical techniques that have been used for this purpose, including voltammetric, impedimetric, capacititive and potentiometric methods. We will confine our discussion to sensors that are based on synthetic anion receptors with a specific focus on reversible, non-covalent interactions, in particular hydrogen- and halogen-bonding. Apart from their sensory properties we will also discuss how electrochemical techniques can be used to study anion recognition processes (e.g. binding constant determination) and will furthermore provide a detailed outlook over future efforts and promising new avenues in this field.

Contents

1. Introduction

Due to their biological, technological, and environmental relevance, an ability to selectively detect anions is of paramount interest for many applications. While cation recognition and sensing has been relatively well established for some decades[1-2] anion binding and sensing remains notably more challenging, mainly due to the more complex geometries of anions, pH dependence and their inherently strong hydration.[3-5] Traditionally, supramolecular anion receptors rely on hydrogen-bonding (HB) and electrostatic interactions to drive anion recognition, while more recently other non-covalent interactions, such as halogen-bonding (XB), have been increasingly exploited, showing enhanced or complementary performance to more traditional approaches.[6-7] An increased understanding of directional bonding approaches and the importance of solvent dynamics at binding sites has, in recent years, facilitated the preparation of synthetic receptors with a fine-tuned anion recognition site that can enable selective binding of specific anionic species.[8] The incorporation of a transducer (e.g. electrochemical/optical) responsive to the presence of the target analyte can then enable not only recognition but also sensing. Electrochemical sensing strategies have received increasing attention due to their real-life potential applicability. Specifically, electrochemical sensory devices are inherently cheap, sensitive and scalable with a number now being commercially available.[9]

In this review we highlight significant advances in the field of electrochemical anion sensing that have been made over the past two decades with some reference to earlier important works where necessary. This includes a brief introduction to all electroanalytical techniques that are relevant to (an)ion sensing applications including voltammetric, impedimetric/capacitive and potentiometric approaches. Electrochemical anion sensors categorized by the specific nature of the supramolecular non-covalent interaction primarily used to reversibly bind small, inorganic anions are then explicitly discussed. Particular highlights include complex receptor designs (e.g. chiral and mechanically interlocked receptors), novel anion-receptive motifs (e.g. C-H hydrogen-bond donors and C-I halogen-bond donors) and other approaches that have not been reviewed in detail elsewhere. Importantly, both theoretical and experimental considerations that are pertinent to the sensory systems are examined with reference to analytical performance, as well as their use as more fundamental tools to elucidate host-guest interactions.

2. Voltammetric Anion Sensing

2.1 General Experimental and Theoretical Considerations

Voltammetric techniques such as cyclic voltammetry (CV), differential pulse voltammetry (DPV) or square wave voltammetry (SWV) are some of the most commonly used electrochemical techniques to study anion binding in solution or at interfaces. Transduction of an anion binding event at a (synthetic) receptor is achieved with the help of a redox transducer, whose electrochemical potential is modulated by the presence of the anion (see Figure 1). Almost invariably this modulation is a cathodic shift of the transducers´ half-wave potential which can be rationalized by a stabilization of the higher oxidation state. Various mechanisms for this stabilization have been proposed, with through-bond and through-space communication between the anion binding site and the redox transducer being the most important ones.[1,10] In both cases an effective transduction of the binding event is only possible if the two sites are spatially and/or electronically coupled.

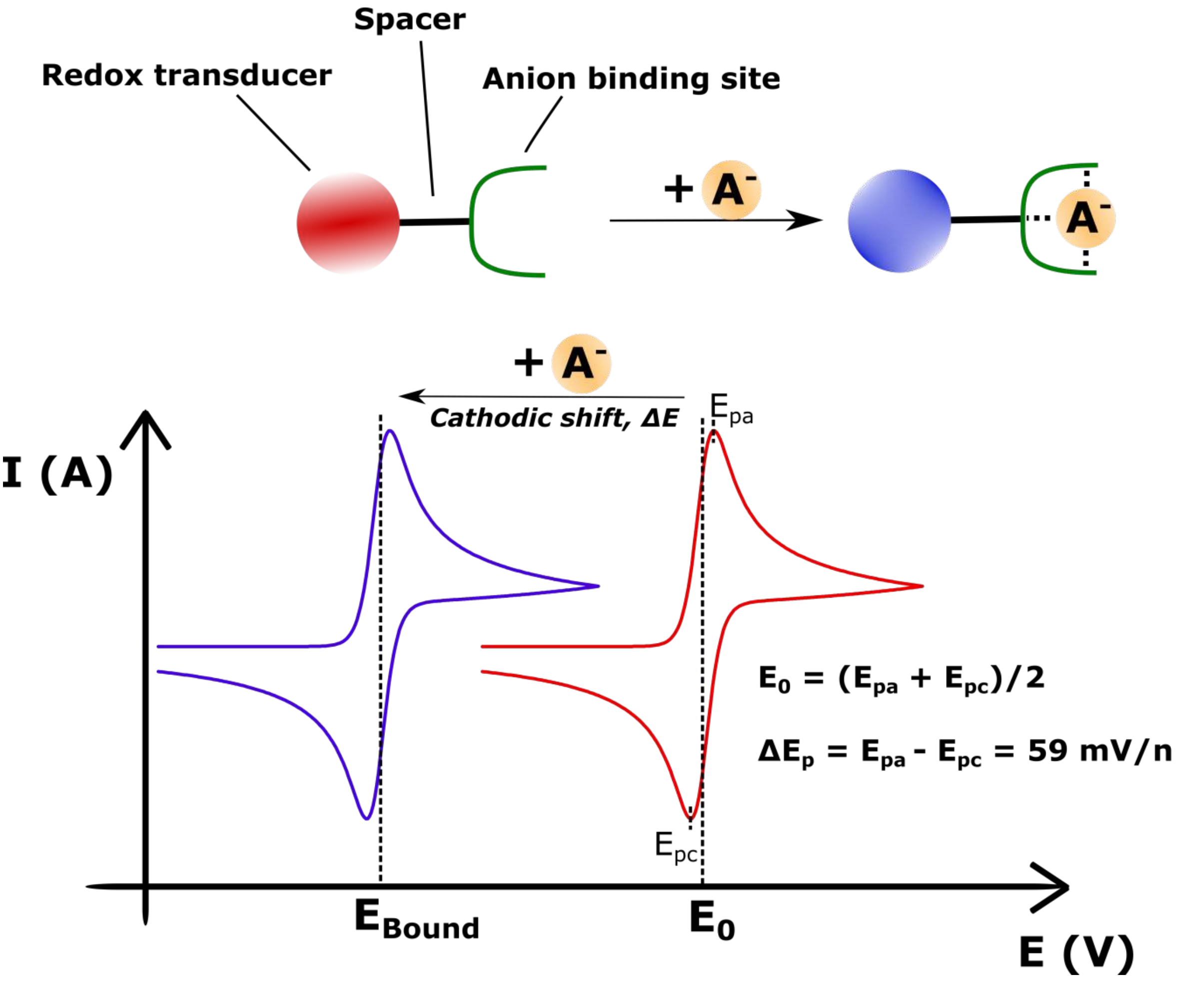


Figure 1. Schematic depiction of the general sensing principle of voltammetric anion sensors. Anion binding induces a cathodic perturbation of the redox transducer that is measureable *via* voltammetric techniques such as CV. The depicted voltammograms represent an ideal, reversible case in which the initial half-wave potential of the transducer E_0 as well as the peak separation ΔE_p can be described by the depicted equations.

While the binding equilibrium in simple host-guest systems can be described by $K = \frac{[HG]}{[H][G]}$ (for a 1:1 stoichiometric host-guest complex system) it should be noted that this is not an accurate description for redox active receptors because the receptor site binding affinity is dependent on the redox state; specifically anion binding is enhanced upon a local oxidation, resulting in the square scheme shown in Figure 2. In fact, it is precisely this change in binding strength that causes the observed voltammetric response, which can, in its most general form, be described by eqn. 1 as derived previously.[1,11] The ratio of K_{Ox}/K_{Red}, where K_{Ox} and

K_{Red} are the (an)ion binding constants of the oxidized and reduced receptor respectively, can be obtained directly from the maximum shift of the transducer in the presence of the target guest and is often called binding enhancement factor (BEF) or reaction coupling efficiency. For [G] >> [H] a special case has been described (eqn. 2) which can be utilised for extraction of both K_{Ox} and K_{Red} from binding isotherms *via* non-linear least square fitting.[12]

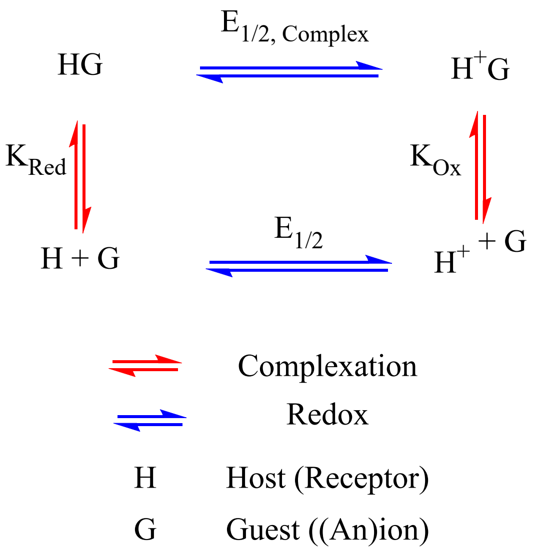


Figure 2. Square scheme for the host-guest equilibria involved in voltammetric (an)ion sensing.

$$\Delta E = -\frac{RT}{nF} * \ln\left(\frac{K_{Ox}}{K_{Red}}\right) \qquad (1)$$

$$\Delta E = -\frac{RT}{nF} * \ln\left(\frac{1+K_{Ox}*[G]}{1+K_{Red}*[G]}\right) \qquad (2)$$

In both cases it should be noted that the response (shift of the receptor's formal potential) is dependent on the relative change in anion binding constants between the different oxidation states (K_{Ox}/K_{Red}, Figure 3). Therefore, a large response is expected in systems where the redox event generates a species in which anion binding is strongly affected. This simple observation again demonstrates why efficient spatial and/or electronic coupling between the anion binding site and the redox transducer are required to induce a measurable perturbation of the formal potential.

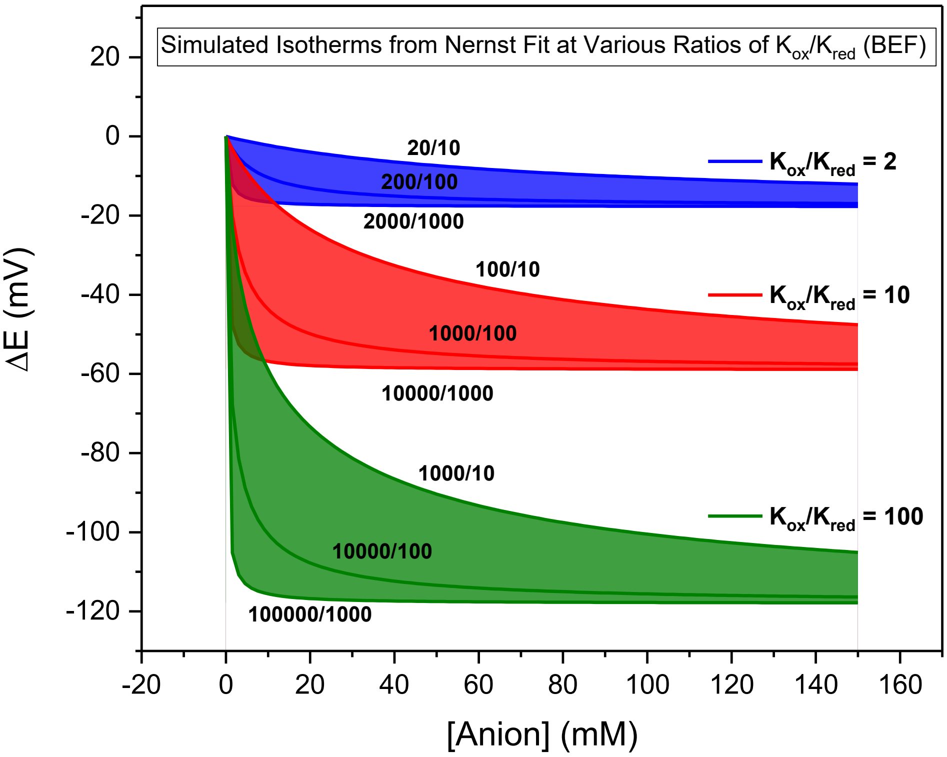


Figure 3. Simulated binding isotherms according to eqn. 2 at various ratios of K_{Ox}/K_{Red} (BEF, binding enhancement factor). The magnitude of the cathodic shift upon anion binding to a redox-active host, according to this model with [G] >> [H] (and fast exchange), is thus mainly determined by the ratio of the binding constants rather than their magnitude.

Advantageously, the (transient) electrochemical generation of an anion receptor with a higher oxidation state allows anion sensing in competitive solvent systems where anion binding in the neutral (reduced) state is not significant. According to the principles discussed above it is precisely in this case, where K_{Ox} is large and K_{Red} is very low (or tends to zero), where we would expect a significant response. Such a “switch-on” transducer (a voltammetry generated higher oxidation state and more potent anion receptor) facilitates anion sensing in competitive media that would not be possible based on other sensory mechanisms (e.g. optical sensors) where typically no additional modulation of the anion binding is possible. However, it should also be noted that, under these circumstances, the use of complementary techniques, such as NMR spectroscopy, is particularly difficult exactly because the binding in the reduced state is difficult to measure (too low) while the oxidised state is often difficult to isolate and/or is paramagnetic. Herein we will not report on any binding constants that were obtained by such complementary techniques as they offer little insight into the electrochemical performance of the sensors and are often conducted in different solvents and in the absence of electrolyte. We will, in select cases, report on the electrochemically determined K_{Ox} and/or K_{Red} binding constants, usually in the form of the BEF (K_{Ox}/K_{Red}). The interested reader can also calculate this ratio from the provided magnitude of the voltammetric perturbation *via* eqn. 1.

In an idealised voltammetric analysis, the reporting signal transduces the specific anion binding event only; in reality a number of dielectric and ion pairing effects can contribute in a manner that is highly dependent on the electrolyte(s) that are used. In order to minimise errors associated with solution phase resistance (i.e. ohmic drop) to voltammetric peak positions a large excess (≥ 100 mM) of a supporting electrolyte is usually employed. It is imperative that this electrolyte does not interfere with the anion binding event. Thus, large non-coordinating anions (like perchlorate (ClO_4^-) or hexafluorophosphate (PF_6^-)) are most commonly used (usually as tetrabutylammonium (TBA) salts). Another important consideration, often overlooked, is the inherent electrostatic (de)stabilisation[13] of the (charged) redox states in the presence of the supporting electrolyte and solvent. For example, the half-wave potential of the simple ferrocene/ferrocenium (Fc/Fc$^+$) couple is strongly dependent on the concentration (and nature) of the supporting electrolyte as well as the solvent.[14] At higher salt concentrations and/or in more polar solvents the charged ferrocenium is more strongly stabilized through charge screening. This effect is particularly dramatic in non-polar solvents such as DCM, where the half-wave potential of Fc/Fc$^+$ is more than 500 mV more cathodic in the presence of 100 mM electrolyte (TBA-tetrafluoroborate) in comparison to the solvent/electrolyte system containing only 1 mM TBABF$_4$. While this stabilization ceases (plateaus) above approximately 100 mM electrolyte in more polar solvents (acetonitrile (ACN) or dimethylformamide (DMF)), these solvent induced cathodic perturbations can be observed in DCM up to 500 mM supporting electrolyte. While this effect has not been investigated in depth for different solvents, electrolytes and redox transducers[15] it is expected that this is a general observation that should be taken into account, especially in non-polar solvents. Thus, to avoid false-positive results, where observed shifts do not arise from a specific binding event but non-specific (electrostatic) stabilization upon addition of target anion, voltammetric anion sensing should ideally be carried out at constant ionic strength and with carefully integrated control experiments with a non-receptive control (the latter revealing any non-specific interactions that might cause voltammetric perturbations).

In the following sections we highlight relevant examples of a variety of redox centre-appended anion sensors and their performance towards the voltammetric sensing of various anions in different solvents. It should be noted that when discussing selectivities, unless otherwise specified, we refer to the selectivities that are observed in the electrochemical experiments, which can differ from those observed by other techniques such as NMR. Furthermore, the absence of a significant electrochemical signal is not always indicative of no binding (i.e. when $K_{Ox}/K_{Red} \approx 1$). Please also note that throughout this review article cathodic responses are represented with a negative sign to indicate a shift to less positive potentials, i.e. $\Delta E = E_{Bound} - E_0$, and that all reported shift values are rounded to two significant figures. This notation is inconsistent across the literature and while the binding of anions almost always induces a cathodic response the opposite effect (anodic response) has also been reported (see below).

Most of the parent redox transducers described in the following sections display fully or quasi-reversible electrochemical behaviour, however this is often not the case for the modified (receptive) transducers and in particular in the presence of anions, especially in non-competitive solvents. For example, while the ferrocene/ferrocenium (Fc/Fc^+) couple is fully reversible in organic solvents, the presence of certain anions (e.g. phosphates) almost always induces a certain degree of irreversibility. The reversibility of a diffusive electrochemical system can most easily be assessed by cyclic voltammetry where in an ideal (fully reversible) system the peak separation between anodic and cathodic peaks is 59 mV/n, where n is the number of electrons transferred. Furthermore, the ratio of anodic and cathodic peak current i_{pa}/i_{pc} should be close to unity (all electrochemically generated species being fully transformed back during the reverse scan) and the peak current should be linearly dependent on the square-root of the scan rate (see Randles-Sevcik equation). Under real measuring conditions, almost all systems display quasi-reversible behaviour (with small deviations from these idealities). For solution-phase voltammetric anion sensing (quasi-)reversibility is not an absolute requirement and irreversible transducers can theoretically be used, which however significantly complicates data analysis and their applicability as useful sensors.

In some cases the voltammetric response of the sensors is not a progressive shift of the transducer´s redox couple but rather a so-called “two-wave” behaviour i.e. the progressive disappearance of the initial wave with a concomitant emergence of a new wave at lower potential. This is attributed to strong binding and a slow (anion-receptor)-exchange (slow ligation on/off rates) which is most commonly observed in non-competitive solvents such as DCM. In this case the BEF (K_{Ox}/K_{Red}) can be obtained directly from the difference in $E_{1/2}$ of these waves, while under the more frequently encountered fast exchange conditions (progressive shift of the wave) the BEF can only be obtained at a plateauing response or from explicit fitting of the binding isotherms. In the slow exchange regime the magnitude of the cathodic perturbation is independent of anion concentration, only the (ratio of) peak currents of the initial and new wave can be utilised to infer the analyte concentration. However, this is usually only possible at substoichiometric quantities of anion (with respect to the number of binding sites), because at 1 equivalent of analyte the receptor is saturated (quantitative binding) and further addition of anions does not perturb the system further (i.e. only the new wave is observed with no additional changes in currents or potentials). In these cases we do not specifically mention the concentration of anions at which the voltammograms were measured.

A final additional consideration is the inherent ability of basic anions to deprotonate receptors in non-polar solvents; this can induce a voltammetric perturbation that does not arise from a non-covalent (e.g. H-bonding) anion binding interaction. Unless pertinent to the discussion this behaviour will not be explicitly highlighted.

2.2 Redox transducers

A number of redox transducers have found application in voltammetric anion sensors, the most common of which are introduced in the following sections. A brief summary of their advantages and disadvantages (for applications as anion sensors) can be found in Table 1.

2.2.1 Ferrocene

Since its discovery in the early 1950s ferrocene (Fc) has been used in a broad range of electrochemical systems and derived sensors,[16-17] due largely to its availability, ease of synthetic modification and favourable electrochemical properties. Most importantly the Fc/Fc^+ couple displays a well-defined, reversible one electron redox couple at moderate potentials and is compatible with a wide range of solvents, electrolytes and analytes. Furthermore it is particularly favourable as a transducer in anion receptors due to the 'switch-on' of binding upon oxidation, and together with the related isoelectronic metallocene, cobaltocenium, were the very first redox transducers employed in anion receptors, as reported by Beer.[18] In fact, the first synthetic redox-active anion sensor, reported in 1989, was based on a cobaltocenium macrocyclic receptor.[19] The cobaltocene/cobaltocenium (Cp_2Co/Cp_2Co^+) couple displays very similar redox-properties as the Fc/Fc^+ couple, with the most marked difference being a significantly lower $E_{1/2}$ (approx. -1.3 V vs Fc/Fc^+). Notably, this can facilitate the sensing of anions whose oxidation potential is incompatible with the Fc/Fc^+ couple (such as iodide), however, this low potential can be incompatible with a variety of solvents. In addition to this, the challenging synthetic manipulation of charged cobaltocenium (derivatives) renders Fc a much more commonly employed transducer.

2.2.2 Tetrathiafulvalene

Tetrathiafulvalene (TTF) is another redox-active molecule that has received considerable attention as a transducer in synthetic anion receptors. In contrast to Fc, TTF exhibits three stable, reversible redox states (TTF, the radical cation $TTF^{+\bullet}$ and the dication TTF^{2+}) allowing for additional tuning of the anion-receptor interaction.[20] However, while the first redox couple ($TTF/TTF^{+\bullet}$) is accessible at potentials similar to those of Fc/Fc^{+}, the second couple ($TTF^{+\bullet}/TTF^{2+}$) has a half-wave potential that is more anodic by ≈350 mV. Depending on the electron-density at the TTF derivative and the solution-phase conditions, this second couple often overlaps with anions possessing a low oxidation potential (e.g. Br^{-}, I^{-} or N_3^{-}). As a consequence only the first couple is usually exploited to transduce an anion binding event. Additionally, TTF possesses rich spectroelectrochemical properties and has found many applications in molecular electronics and in switches.[21] In comparison to Fc however, TTF is much less synthetically accessible and has only rarely been applied within more complex receptive architectures such as those based on macrocyclic, interlocked or dendrimeric systems.

2.2.3 Porphyrin

Porphyrins (free base and metallo-porphyrins) represent an interesting motif for sensing applications due to their rich photophysical and electrochemical properties; the latter is manifested by two quasi-reversible oxidative couples ($P/P^{+\bullet}$ and $P^{+\bullet}/P^{2+}$) at potentials more anodic than that of Fc/Fc^{+} both of which are strongly dependent on the specific substitution/metalation of the porphyrin.[22] Whilst synthetically non-trivial to manipulate, porphyrins possess rich chemistry with respect to substitution patterns and the nature of the coordinated metal. Advantageously, the metal-centre of the metallo-porphyrin can act as an anion binding site which is strongly coupled to the porphyrin resulting in efficient signal transduction. Similarly, anions can directly engage in H-bonding to the central N-H donors of the free base porphyrin. In spite of this only very few porphyrin-based voltammetric anion sensors have been developed.

2.2.4 Complexed Metals

Different metal complexes, in particular those of the first and second row transition metals have been utilised as transducers in electrochemical sensors. Most commonly nitrogenous ligands such as bipyridine (bpy) or terpyridine (tpy) are used to form stable and electrochemically well-behaved transducer complexes. The derivatization of these ligands facilitates the introduction of binding sites into the organic scaffold and further allows tuning of the redox properties of the complex by variation of the electron density. Most commonly the redox couples are reversible one-electron metal-centred oxidative couples at moderate to high potentials. It is worth noting that at, very low potentials, additional ligand-centred reductive couples are often observed, albeit rarely used to transduce anion binding. If the metal is coordinatively unsaturated, an anionic analyte may directly bind to the metal, which, according to the principles established in Section 2.1, should result in an increased voltammetric response. Additionally, different types of ligands can be incorporated *via* sequential complexation, enabling, for example, a tuning of the number of receptive sites or incorporation of additional functionalities. Examples of voltammetric receptors containing different metal complex transducers and their redox characteristics are reviewed in Sections 2.3.1, 2.3.2 and 2.3.4.

2.2.5 Organic transducers

A diverse class of redox-transducers are those based on organic redox-active functionalities. While these are arguably the most synthetically adaptable and tuneable transducers they have received considerably less attention. This may be attributed to their complex electrochemical behaviour, which is often solvent and/or pH dependent. One such transducer are the tri(alkyl/aryl)amines which can be (reversibly) oxidized at moderate to high potentials and have found some application in anion sensors as discussed in Sections 2.3.1 and 2.3.4. Similarly, (hydro)quinones have received considerable attention in various electrochemical studies, but their use in anion sensors has been limited by their relatively complex solvent and pH dependent electrochemistry which arises from two proton coupled one-electron reductions. Indeed, early studies of quinone-based anion sensors produced responses that were difficult to rationalise[23-24] impeding their further use.[25] Another solely organic electrochemically active motif that has been extensively studied in switches and interlocked structures, but has found little use in anion sensors, is the bipyridinium motif found in diquat(DQ)/paraquat(PQ).[26] This dicationic transducer can be reversibly reduced at low potentials in two one-electron steps ($DQ^{2+}/DQ^{+\bullet}$ and $DQ^{+\bullet}/DQ$) thus deactivating anion binding. While this facilitates sensing of anions with low half-wave potentials, such as iodide, it has found limited use in voltammetric sensors most likely because of the demanding synthetic pathways required.

Table 1. Comparison of different redox transducers for application in derived voltammetric (anion) sensors.

Transducer	Advantages	Disadvantages
Ferrocene	-Well-defined, reversible redox couple -Synthetically very adaptable	
TTF	-Two-stage oxidation -Rich spectro(electro)chemistry -Conducting[a]	-Synthetically challenging -Moderate/high oxidation potential -Reversibility often compromised[b]
Porphyrin	-Highly tuneable by metal substitution -Rich photophysical properties -Biomimetic	-High oxidation potential(s) -Reversibility often compromised[b]

Metal complexes	-Highly adaptable through metal or ligand substitution -Often luminescent (double readout)	- Synthetically often challenging
Organic	-Tuneable redox potentials	-Solvent or pH-dependent redox properties -Synthetically can be challenging

a – relevant for molecular electronics. *b* – in particular for the second oxidation process; reversibility often solvent dependent.

2.3 Solution-phase voltammetric anion sensing

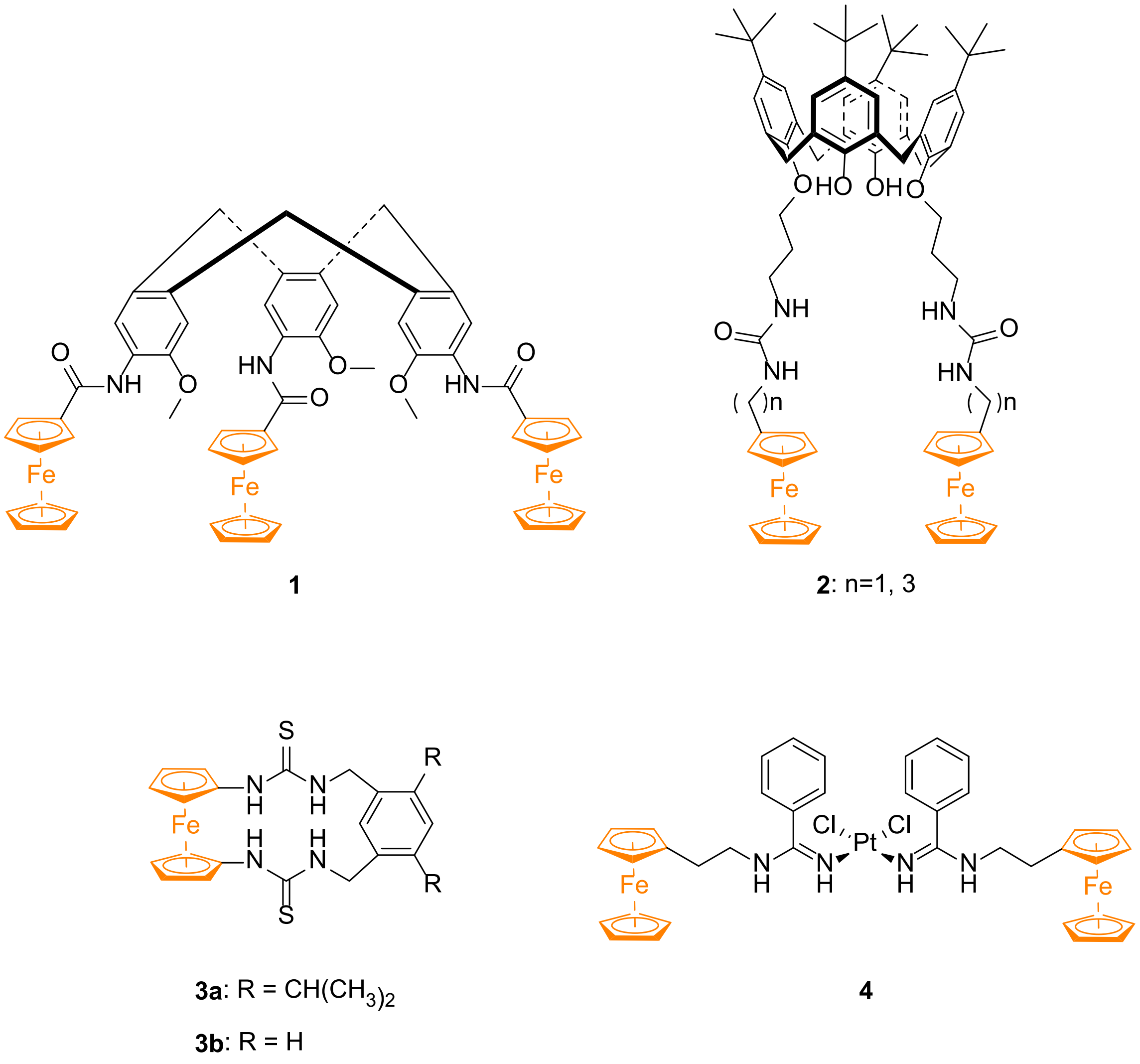
2.3.1 Redox-active receptors based on N-H hydrogen bond donors

N-H hydrogen bond (HB) donor groups are not only ubiquitous in nature but have found wide-spread use in all areas of chemistry, including anion-supramolecular chemistry in which they are arguably the most commonly used anion receptive motif. Almost invariably early voltammetric anion sensors, but also recent examples, are based on N-H hydrogen bond donors. A large variety of such systems, mainly containing amide and urea binding sites, were reported in the 1990s and have been reviewed extensively.[27-28] Many of these early systems and the majority of more recent examples in the last two decades, utilise an integrated Fc redox transducer with amine[29-32], amide[33-37], imidazole[38-42], amide/urea macrocycle[43-44], thiourea[45], amidine[46], guanidine[47-48], cyclotriveratrylene-amide[36], calix[4]pyrrole[49], calix[4]arene-amide[50-51], calix[4]arene-urea[52-53] or calix[4]arene-amine/imine[54] conjugates (see Figure 4 for examples). Their sensory performance does not significantly deviate from those of earlier systems; most display a progressive cathodic shift of the respective Fc/Fc^+ redox couple upon anion addition with some displaying a “two-wave” behaviour, of which a representative example, as assessed by SWV, is shown in Figure 5. Furthermore the majority of these sensors are electrochemically reversible and their anion selectivity largely dictated by the nature of the N-H hydrogen bonding binding site as well as anion basicity. In the following we will briefly highlight some representative examples of such receptors, before discussing N-H HB sensors based on non-Fc transducers in more detail.

In 2001 Reynes *et al.* reported a detailed comparison of acyclic and cyclic ferrocenylamide based sensors including the cyclotriveratrylene receptor **1** (Figure 4)**.**[36] As in almost all of the sensors discussed in this review, **1** displayed only one redox couple indicating that all three ferrocene transducer groups were simultaneously, independently oxidized. This system displayed a particularly interesting response to 1 equiv. of anions. F^- and HSO_4^- induced only small perturbations with a one-wave (progressive shift) behaviour. This was also highly solvent dependent where F^- only perturbed the Fc/Fc$^+$ couple in ACN (-60 mV) with no perturbation in the less competitive solvent DCM. Conversely, HSO_4^- induced a small response in DCM (-20 mV) while no shifts were measured in ACN. **1** responded to the biologically relevant oxoanions $H_2PO_4^-$ and ATP^{2-} in both ACN (-140 mV and -160 mV, respectively) and DCM (-230 mV for both anions) displaying a "two-wave" behaviour. A similar system based on bis-Fc-containing calix[4]arene-urea receptors **2** was later studied where the cathodic perturbations (of approximately -100 mV) induced in the presence of 2 equiv. of $H_2PO_4^-$ in DCM were independent of linker length (n=1,3).[52] Additionally, the replacement of the urea motif in **2** with an amide, a poorer HB donor, elicited a similar electrochemical response, indicating that binding in this non-competitive solvent was driven almost entirely by electrostatic interactions between the anion and the Fc$^+$ moieties, a behaviour that has been exploited in numerous systems containing no specific anion binding sites (see Sections 2.3.5 and 2.3.7).

Apart from the ubiquitously used amide and urea binding sites, thioureas have been incorporated into various Fc-based voltammetric sensors, such as **3a** and **3b**.[45] Both displayed significant responses to the basic F^-, OAc^-, $H_2PO_4^-$ and $HP_2O_7^{3-}$ (1 equiv. in DMSO) of between -90 to -150 mV for **3a** and -120 to -200 mV for **3b**. The response of the less electron-rich **3b** was larger by at least -20 mV in all cases. Neither receptor showed any response to 10 equiv. of Cl^-, Br^-, HSO_4^- and NO_3^-.

In a more recent study Nieto *et al.* assembled a bis(ferrocenyl-amidine) receptor **4** *via* Pt(II)-mediated nucleophilic addition.[46] The Fc/Fc$^+$ couple of this sensor displayed a "two-wave" behaviour upon addition of $H_2PO_4^-$ in ACN/DCM 5:1, as shown in Figure 5. In this slow-exchange, strong binding regime these voltammograms can often be used to infer the stochiometry of the receptor-anion complex. In this case the new wave at lower potential (-90 mV more cathodic) is only fully developed at 2 equiv. of $H_2PO_4^-$ suggesting formation of a 1:2 stochiometric host-guest complex.



1

2: n=1, 3

3a: R = $CH(CH_3)_2$

3b: R = H

4

Figure 4. Representative voltammetric anion sensors based on Fc and typical N-H anion binding sites.

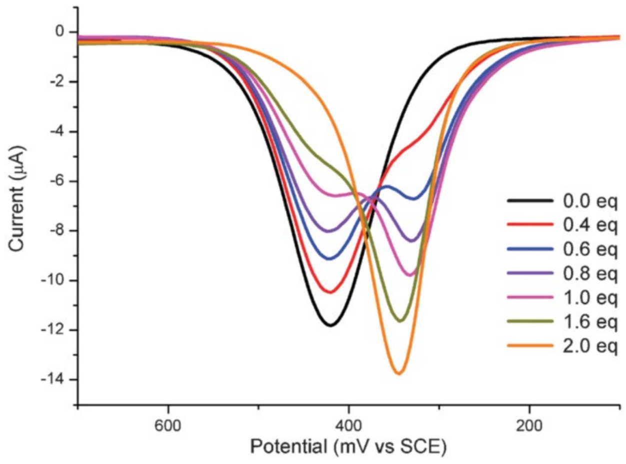
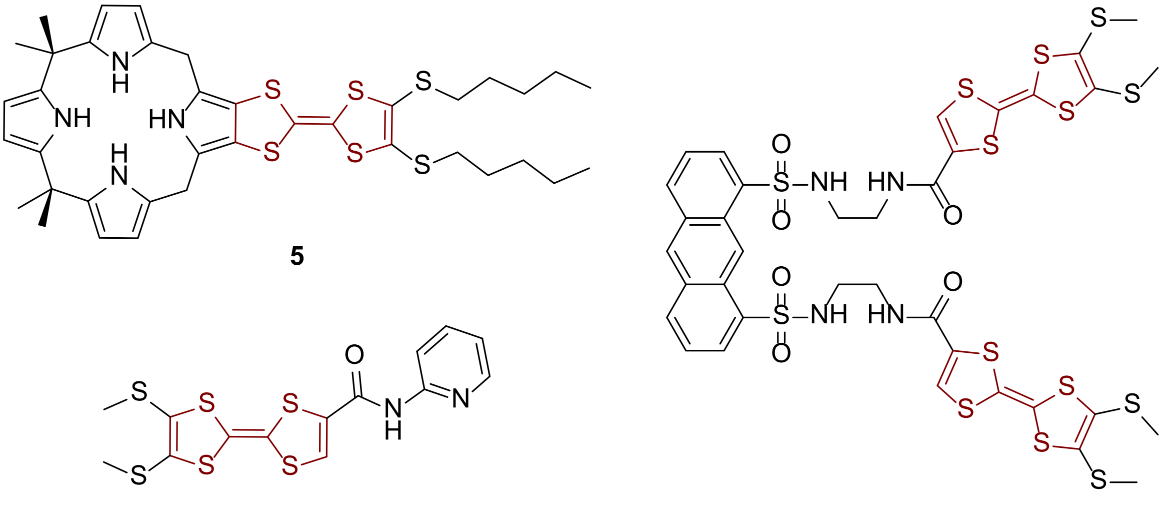


Figure 5. Representative evolution of a SWV upon addition of anions (two wave behaviour). In this specific case receptor **4** was titrated with $H_2PO_4^-$ in ACN/DCM 5:1. Reproduced from Ref.[46] Copyright 2011 The Royal Society of Chemistry.

While in a preliminary report an amide-functionalised TTF had been demonstrated to voltammetrically respond to chloride[55], the first in depth investigation of a TTF-containing anion receptor was reported by Becher and coworkers in 2003.[56] A calix[4]pyrrole receptor was employed which was directly linked to TTF at one of the pyrrole units (**5**, Figure 6). Voltammetric anion sensing was then carried out in ACN by monitoring the perturbations of the first redox couple ($TTF/TTF^{+\bullet}$). Both Br^- (-34 mV) and Cl^- (-43 mV) induced significant cathodic shifts at low concentrations (0.5 mM, 1 equiv.).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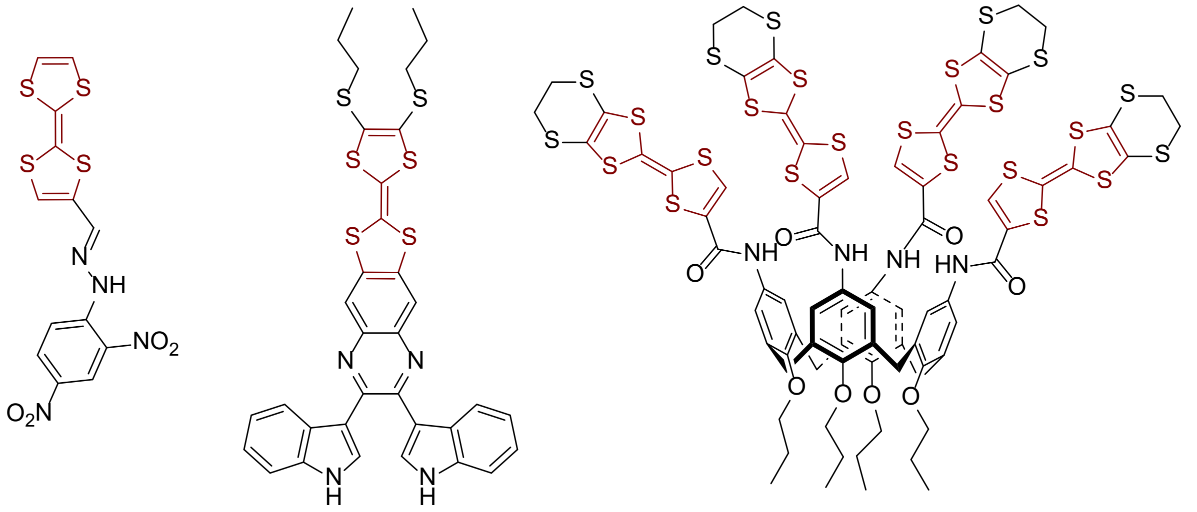
6

7

Figure 6. Early examples of TTF voltammetric anion sensors based on calix[4]pyrrole and amide binding sites.

Other early examples were published by Zhu's group who directly conjugated amide-binding sites to the TTF core to afford the simple mono-amide TTF receptor **6**[57] as well as the more complex amide-sulfonamide receptor **7** (Figure 6).[58] The former was utilised for the selective sensing of $H_2PO_4^-$ in DCM whereby both TTF couples underwent significant perturbations; the first couple shifted cathodically by -100 mV in the presence of 2 equiv. $H_2PO_4^-$, while, interestingly, the second couple shifted *anodically* by 160 mV.[57] This unexpected behaviour was rationalised by destabilisation of the TTF^{2+} by formation of a 2:1 TTF-anion complex. The addition of other anions such as F^-, Br^-, Cl^- or OAc^- did not induce any significant perturbations while the voltammetric behaviour in the presence of HSO_4^- was more complex, most likely due to protonation of the pyridine moiety. A similar complex behaviour was also observed for **7,** whereby addition of 2 equiv. of F^-, Cl^- or OAc^- induced cathodic perturbations of both TTF couples with splitting of the first couple.[58] The addition of $H_2PO_4^-$ induced the appearance of a new wave -170 mV more cathodic than the first couple while the second wave was only perturbed minimally. Interestingly, the addition of HSO_4^- led to significant cathodic perturbations only for the second couple. The presence of the anthracene backbone of the receptor furthermore enabled fluorescent anion sensing whereby only F^- led to a significant luminescence switch-on. A similar TTF-monoamide-BODIPY system was also employed for the voltammetric and fluorimetric sensing of fluoride in DCM.[59]

It should be noted that the "selective" sensing of fluoride, or other basic anions, in many of the systems discussed arises from receptor deprotonation rather than a specific hydrogen-bonding interaction. Precisely this behaviour was exploited by Xiong *et al.* who reported a 2,4-dinitrophenylhydrazone-TTF sensor (**8**, Figure 7). Upon addition of F^- to **8** in DCM large *anodic* shifts of up to 400 mV (both couples) were observed. This interesting behaviour arises because deprotonation of the hydrazone leads to conjugation and subsequent intramolecular electron transfer from the electron rich TTF to the electron deficient dinitrophenyl group. This latter moiety furthermore allows optical fluoride detection whereby both electrochemical and optical sensing of F^- was achieved with good selectivity over OAc^-, $H_2PO_4^-$, Br^-, Cl^- and NO_3^-.



8 **9** **10.cone**

Figure 7. TTF-containing sensors based on different receptive motifs including 2,4-dinitrophenylhydrazone, diindolylquinoxaline and calix[4]arene (only cone conformation shown).

A similar dual signalling approach was also reported by Sessler, whereby a diindolylquinoxaline-TTF **9** was used as a sensor for F^- and $H_2PO_4^-$.[60] Large cathodic shifts of the TTF/$TTF^{+\bullet}$ redox couple of -280 mV and -110 mV in the presence of F^- and $H_2PO_4^-$ were observed, respectively (2 equiv. in DCM). Sessler and Kim also investigated a calix[4]arene based receptor **10** modified with four TTF units. Two different conformations of the receptor (cone and 1,3-alternate) were isolated and studied with both displaying four redox couples in DCM. The presence of multiple of redox waves, in the apparently degenerate TTF units, was attributed to intramolecular interactions between the redox sites.[61] Interestingly, the addition of anions induced *anodic* perturbations of all couples, attributed to inhibition of electron transfer between the calix[4]arene core and the TTF units. Impressively, **10.cone** demonstrated anodic perturbations of 450 mV in the presence of 1 equiv. of $HP_2O_7^{3-}$ with smaller shifts seen for $H_2PO_4^-$ (220 mV), F^- (240 mV), OAc^- (210 mV) and Cl^- (33 mV). The performance of **10.alt** in the presence of these anions was markedly different with shifts of

160, 170, 270, 40 and 26 mV, respectively. Dai's group later reported diamino-diamido TTF anion receptors capable of voltammetric sensing of other oxanions (sulfate and oxalate) in more competitive solvent systems such as ACN/MeOH (9:1) or ACN/DMF (9:1).[62-63]

While an early study[64] demonstrated the potential of porphyrin as a transducer for anion sensing, its use has been, as noted above, limited. One rare example was reported in the "picket fence" tetra-amide-imidazolium Zn-porphyrin **11** (Figure 8).[65] Addition of 5 equiv. of Cl^- (-180 mV), HSO_4^-(-140 mV) and NO_3^- (-95 mV) led to the expected cathodic perturbation of the $P/P^{+\bullet}$ couple in ACN while ClO_4^- induced no shifts and $H_2PO_4^-$ led to precipitation. In a later study similar systems based on the tetra-amide-porphyrin scaffold were studied whereby the specific influence of the nature of the metal-centres (Fe(Cl), Co(PF_6), Ni, Cu, Zn, Cd or Hg) on the sensory performance was systematically investigated.[66] The photophysical and electrochemical properties of **12** are strongly dependent on the nature of the metal centre. For example, the half-wave potential for the first couple differed by 360 mV between the **12.Cd** (lowest $E_{1/2}$) and **12.Fe(Cl)** (highest) in 1:1 DCM/ACN. While addition of 5 equiv. of ClO_4^- resulted in no perturbations, addition of Cl^-, $H_2PO_4^-$ or NO_3^- induced significant cathodic shifts in almost all systems. The largest shifts for all anions were observed for **12.Hg** with some significant variance between receptors for different anions. Interestingly, the addition of these anions to the unmodified tetraphenylporphyrin (TPP) compounds TPP.Cu, TPP.Zn and TPP.Cd led to significantly larger cathodic perturbation for all anions with all tested compounds. While the anion binding constants (and selectivity) to the amide-containing receptors **12** is certainly larger than those of the TPPs this again importantly demonstrates that the response of these systems is not driven by the magnitude of the binding strength but the *relative difference* in binding between the differently charged states, which, apparently, in the case of the metallated TPPs, is larger.

The sensory properties of the free-base porphyrinogen derivative **13** have also been investigated.[67] In ortho-dichlorobenzene both porphyrin couples were cathodically perturbed upon addition of anions (up to 3 equiv.) with maximum shifts of -600 mV (F^-), -580 mV (OAc^-), -570 mV ($H_2PO_4^-$), -70 mV (NO_3^-) and -60 mV (ClO_4^-). These substantial responses can most likely be attributed to the choice of the extremely apolar solvent, the good electronic communication (coupling) between the binding site and the transducer and potentially deprotonation of the receptor.

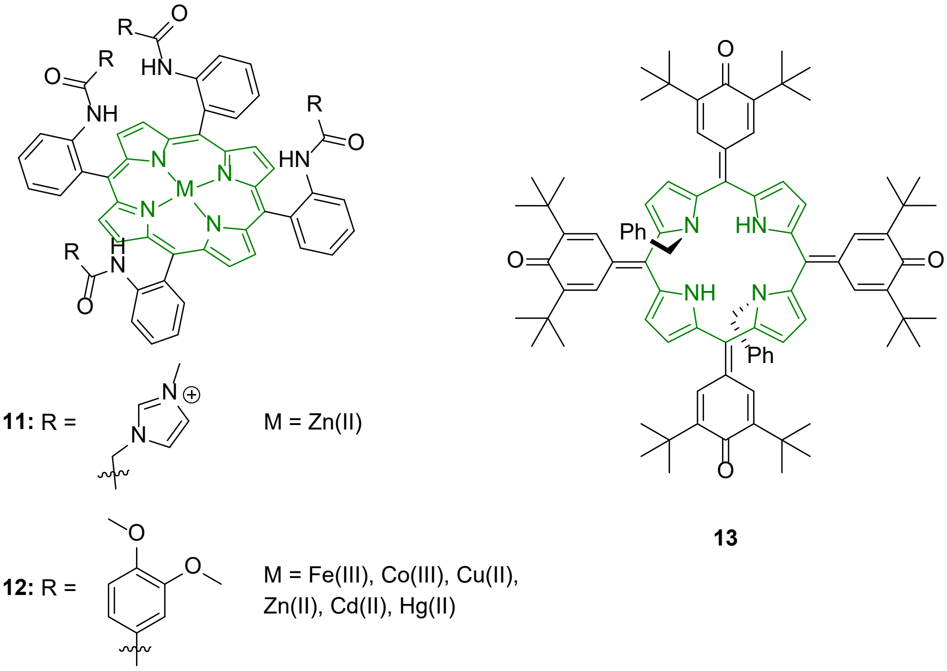


Figure 8. Porphyrin-based receptors for voltammetric anion sensing.

A variety of other redox-receptors based on metals have also been reported, whereby an advantageous double readout (electrochemical, luminescent) is often feasible. Most of these receptors are based on transition metal complexes of ruthenium or osmium with receptor modified nitrogenous ligands, such as bipy, terpy, imidazole or pyrazole (for example receptors **14** and **15**, Figure 9, in which anion sensing was reported *via* the M^{2+}/M^{3+}

couple).[68-72] In a rare example of a receptor containing two redox transducers Beer and coworkers reported tetraamide macrocycles **16a-b** containing both a Ru(bpy)$_3^{2+}$ as well as either a Fc or a Cp_2Co^+ transducer.[73] Cl^- sensing in ACN was achieved both *via* the metallocene as well as bpy redox couples, with cathodic perturbation of **16a** of -40 mV and -60 mV for the couples, respectively (anion in excess). Interestingly, the cobaltocenium analogue **16b** exhibited an even larger perturbation of both couples of -90 mV and -110 mV, respectively.

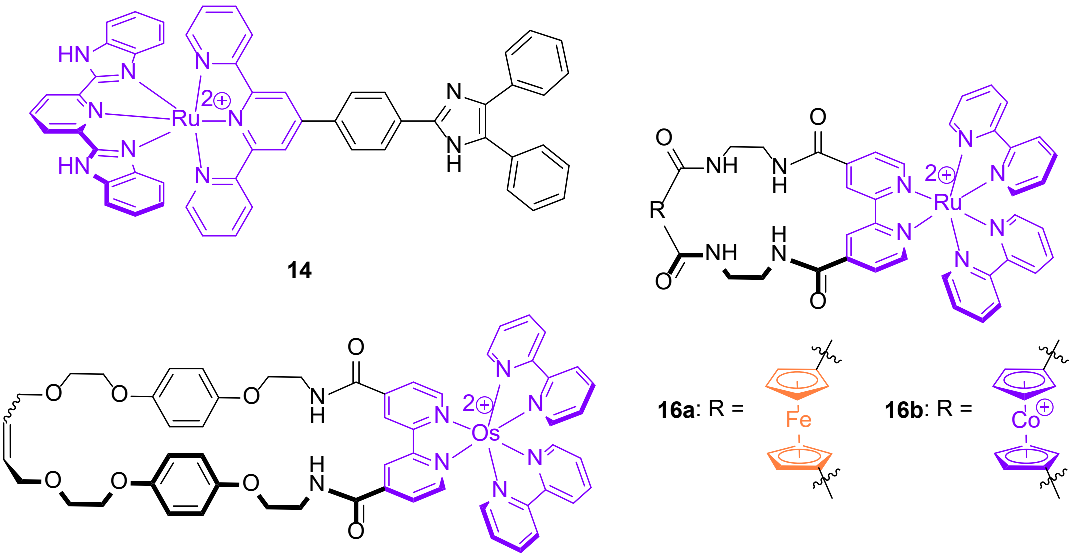

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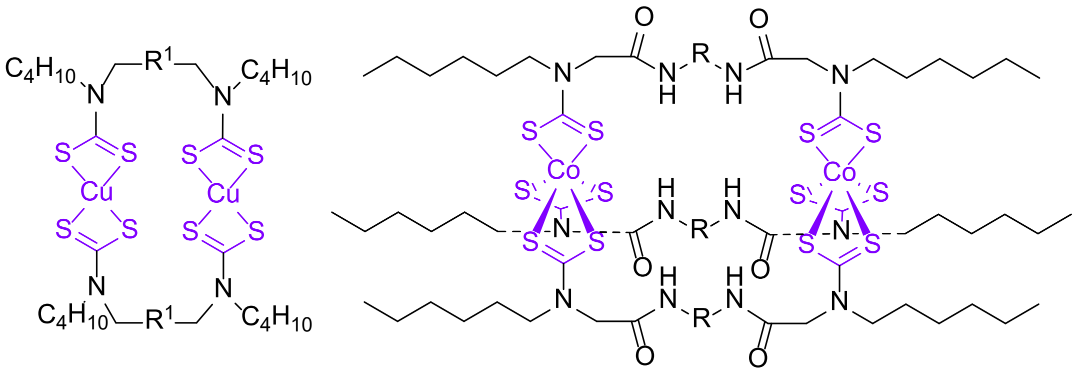
Figure 9. Ruthenium- and osmium-containing voltammetric anion sensors.

The scarcely utilised redox-active dithiocarbamate-metal motif has been investigated by Beer and co-workers in a variety of acyclic and macrocyclic receptors (Figure 10).[74-76] For example simple macrocycles **17** containing two dithiocarbamate (DTC) copper(II) moieties have been shown to sense anions through electrostatic interactions only.[76] **17a** and **17c** display two quasi-reversible overlapping Cu$^{2+/3+}$ oxidation waves at moderate potentials while **17b** shows only one, albeit broad, wave. Significant cathodic shifts are only observed for **17b** in the presence of the large, tetrahedral anions ReO_4^- and $H_2PO_4^-$ (-85 mV each) with a negligible response towards Cl^-, Br^- and NO_3^- in all cases (5 equiv. in DCM/ACN 4:1). This indicates that both electrostatic interactions and size-complementarity govern anion binding in these bimetallic macrocycles.

The DTC motif has also been extended to other metals, such as Co(III), in generating a reporting signal. The amide Co-DTC cryptands **18** were reported to respond to Cl^-, BzO^-, HSO_4^- and $H_2PO_4^-$ through perturbations of the $Co^{3+/4+}$ couple.[74] Both receptors showed the largest response to $H_2PO_4^-$, which was greatest for **18a** (-130 mV), while in all other cases **18b** was more responsive (-50/60 mV; all at 10 equiv. in DCM).



17a: R = *m*-phenyl

17b: R = 2,7-napthyl

17c: R = 3,3'-biphenyl

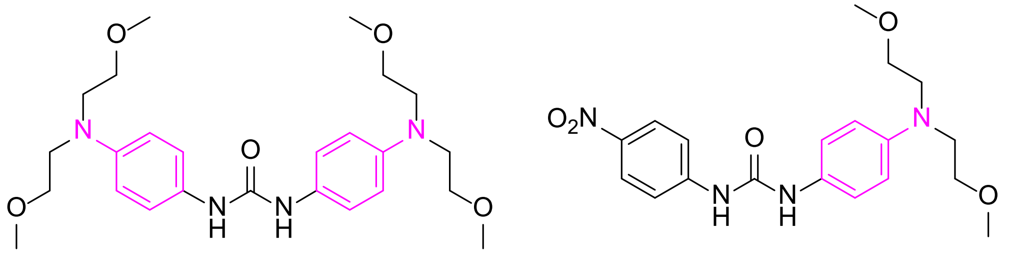
18a: R = *o*-phenyl

18b: R = *m*-phenyl

Figure 10. DTC-containing macrocyclic and cryptand anion sensors.

Other purely organic redox-active anion receptors containing a p-phenylenediamine transducer have been reported (**19-20**, Figure 11).[77] Both of these urea-based hosts displayed a one-electron oxidation at potentials approximately 100-200 mV higher than Fc/Fc^+ with an additional, more anodic, oxidation being observed for the symmetric receptor

19. Binding studies with OAc^-, BzO^-, NO_2^- and Cl^- in ACN revealed the appearance of a new couple at lower potentials, whose potential was significantly more cathodic (by -140 to -250 mV) for the three former anions, while Cl^- elicited much smaller responses for both receptors (-16 mV and -34 mV). The largest response of the unsymmetric receptor **20** in the presence of OAc^- (-250 mV) corresponds to a large BEF (K_{Ox}/K_{Red}) of 14500.



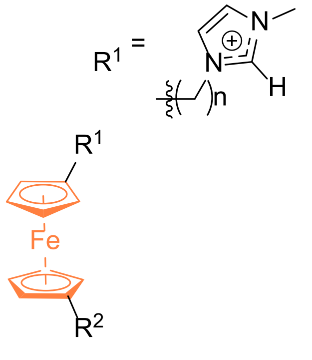
19 **20**

Figure 11. Redox-active urea anion receptors.

2.3.2 Redox-active receptors based on C-H hydrogen bond donors

C-H hydrogen bonding has recently gained significant attention as a potent interaction to drive anion recognition.[78] While often weaker than N-H bond donors, C-H bonds are much less prone to deprotonation, a problem, as highlighted in examples above, that is often observed for N-H bond donors in less-competitive media when binding more basic anions such as F^- or OAc^-. A prominent C-H H-bond motif is provided by imidazolium. The first example of an imidazolium-based C-H H-bonding voltammetric sensor was published as early as 2000 in which simple Fc-imidazolium receptors were shown to respond to anions.[79] More systematic studies on acyclic[80-84] and cyclic[85] imidazolium-based sensors have only been conducted more recently. For example Jin and coworkers reported in-depth studies of a series of mono-and bis(imidazolium)-substituted ferrocenes **21a-f** with varying ferrocene-methylene- imidazolium group linker length (Figure 12).[80,84] Unsurprisingly, the magnitude of the cathodic shifts of **21a-d** were strongly dependent on the methylene linker length whereby the magnitude of the Fc/Fc$^+$ cathodic shift response upon F$^-$, Cl$^-$ and HSO_4^- addition (10 equiv. in ACN) diminished significantly with increasing distance between the ferrocene and imidazolium binding sites. Interestingly, this attenuation was observed to be dependent upon the nature of the anion; for example, the response of **21a-d** towards F$^-$ decreased from -230 mV, to -160 mV, -28 mV to -12 mV while the Cl$^-$ response magnitude was significantly lowered from -65 mV, to -21 mV, -13 mV, to -10 mV.

The incorporation of imidazolium into a bipy-ligand allowed the facile assembly of the highly-preorganized cage-like-receptor **22** after complexation with Co(II) (Figure 12).[86] Initial experiments in ACN revealed significant cathodic perturbation of the Co^{2+}/Co^{3+} couple upon addition of up to 1.5 equiv. Cl$^-$ (-140 mV) or Br$^-$ (-120 mV). Due to the relatively high half-wave potential of the receptor (+100 mV vs. Fc/Fc$^+$) the analysis of other anions with moderate oxidation potentials was not possible in ACN prompting the use of ACN/H_2O 4:1 for further studies. In this solvent system a significant and well-defined response was observed for a wider range of anions in the order Cl$^-$ > Br$^-$ ≈ OCN$^-$ > SCN$^-$ ≈ I$^-$ with shifts of up to -120 mV, as can be seen in Figure 13.



21a-d: n = 0,1,3,4, R^2 = H

21e-f: n = 0 or 4, R^2 = R^1

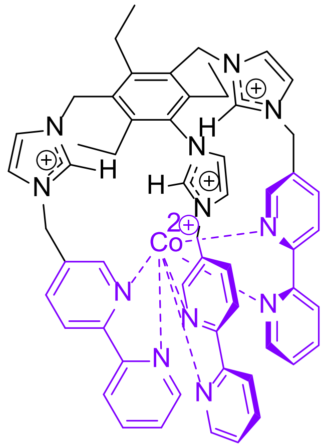


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Figure 12. Imidazolium C-H bond donors in Fc- and Co(bpy)$_3$-containing sensors.

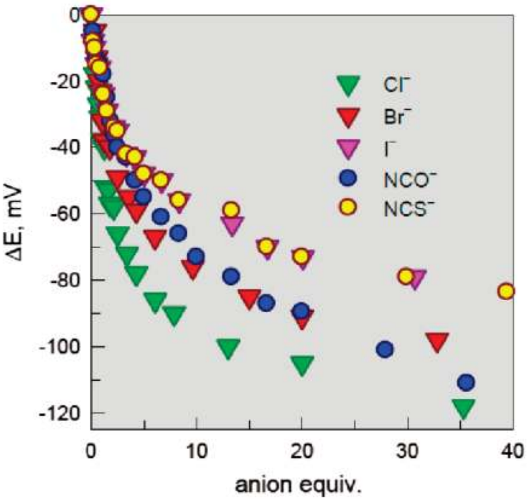

Figure 13. Electrochemical binding isotherms of cage **22** upon addition of various anions in ACN/H_2O 4:1. Reproduced with permission from Ref.[86] Copyright 2008 American Chemical Society.

Another potent C-H bond donor motif recently investigated is 1,2,3-triazole.[87] The heterocycle's widespread use can largely be attributed to the ease of preparation (*via* click chemistry from an azide and alkyne) and the potent polarised C-H bond in the 5-position. Furthermore the C-H hydrogen bond donor potency can be easily enhanced *via* methylation at the 3-position, yielding the cationic triazolium.

Early examples of triazole-containing voltammetric anion sensors were reported by Astruc (Fc-triazole dendrimers discussed separately, *vide infra*), and Tárraga and Molina. The simple Fc-triazole-pyrene receptor **23** (Figure 14) exhibited a cathodic shift of -100 mV in DCM only for $HP_2O_7^{3-}$, while $H_2PO_4^-$, HSO_4^-, OAc^-, NO_3^-, F^-, Cl^- and Br^- elicited no response.[88] Kim's group utilised the bis(Fc-triazole) receptor **24** to also selectively sense $H_2PO_4^-$ and $HP_2O_7^{3-}$ with selectivity over all halides, PF_6^-, ClO_4^-, HSO_4^- and OAc^- (2 equiv. in DCM).[89] The phosphorus oxoanions induced cathodic shifts of the Fc/Fc$^+$ transducer of ≈-200 and ≈-180 mV, respectively. DFT calculations show that Cl^- is bound by a total of three HB´s; two from the triazole moieties (H_a) as well as one from the internal aryl proton (H_b) (Figure 15). Interestingly, the calculated structure for the **24-$H_2PO_4^-$** host-guest complex reveals the formation of two further HB´s from the α-protons of the Fc`s cyclopentadienyl (H_c, Figure 15) a rarely considered, yet potentially important contribution to anion binding. The design of the receptor was later elaborated on by the introduction of additional amide binding sites between the triazole and Fc moieties.[90] Under equivalent conditions as for the aforementioned system this sensor responded to $H_2PO_4^-$ more weakly with a cathodic shift of -130 mV.

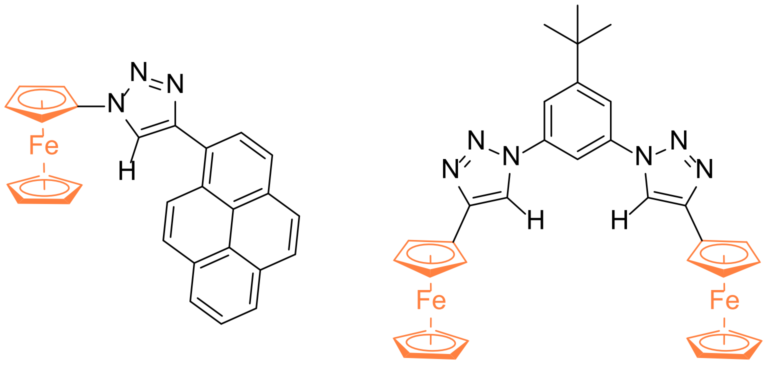

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Figure 14. Early examples of simpe Fc-triazole based voltammetric anion sensors.

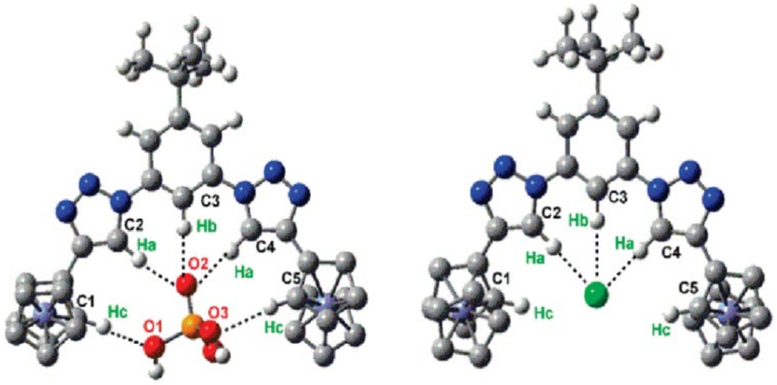


Figure 15. Calculated structures of **24-H$_2$PO$_4^-$** and **24-Cl$^-$** at the B3LYP/6-31-G* level of computation. Reproduced with permission from Ref.[89] Copyright 2011 American Chemical Society.

Tárraga and Molina also conducted an in depth study on a range of related ferrocene triazole receptors **25-32** (Figure 16).[91] All receptors displayed Fc/Fc$^+$ cathodic shifts in the presence of $HP_2O_7^{3-}$, $H_2PO_4^-$, F$^-$ and OAc$^-$ in ACN (**27** and **30** in ACN/DCM 1:1 due to solubility issues) with no response to HSO_4^-, NO_3^-, Cl$^-$ and Br$^-$ in almost all cases (a response was observed for Cl$^-$ and Br$^-$ for receptor **26**). The receptors **25**, **26** and **29** exhibited two redox waves where the more anodic one was assigned to the N-substituted Fc (N-Fc) and the other the C-substituted Fc (C-Fc) (Figure 17). Interestingly, the anion-receptor complexes of **25** and **26** displayed only one wave at a significantly more cathodic potential (with the exception of the **25-F$^-$** adduct) (Figure 17). The overall magnitude of anion binding induced cathodic perturbation of N-Fc in **25**, **26** and **29** was comparatively much larger than that of the C-Fc (by up to one order of magnitude in some cases). For example the C-Fc of **29** was not responsive to OAc$^-$, while the N-Fc exhibited a -100 mV response in the presence of the same anion. It should be noted that this contrasting responsive behaviour most likely does not arise from a better "communication" between the binding site and the N-Fc but from a pronounced "anion binding switch-on from **29^{2+}** to **29^{3+}**" when all three Fc moieties are oxidized. The authors furthermore showed that the response of **28** to the basic anions $HP_2O_7^{3-}$, $H_2PO_4^-$, F^- and OAc^- arises from deprotonation. The positively charged triazolium receptors **26** and **32** exhibited larger cathodic shift magnitudes towards all tested anions in comparison to their neutral analogues **25** and **31**.

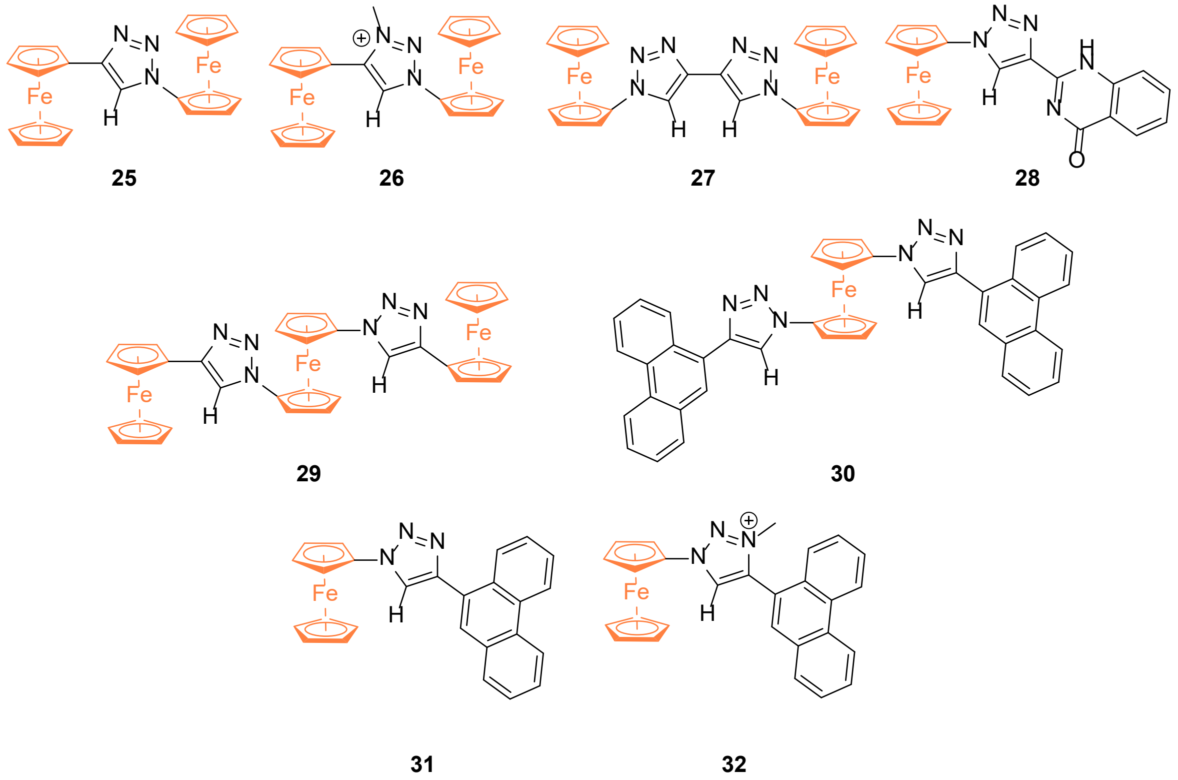


Figure 16. Structures of various Fc-triazole receptors.

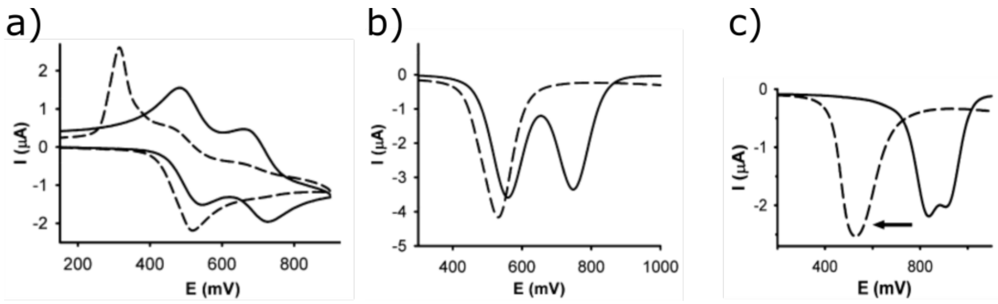
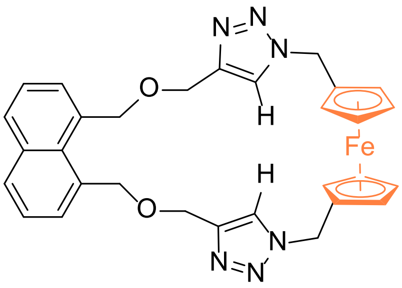


Figure 17. a) SWVs and b) CVs of **25** in ACN, 0.1 M $TBAPF_6$ (solid lines) and in the presence of $H_2PO_4^-$ (dashed lines). C) SWVs of **26** in ACN, 0.1 M $TBAPF_6$ (solid lines) in the presence of a) $H_2PO_4^-$ (dashed lines). Reproduced with permission from Ref.[91] Copyright 2013 American Chemical Society.

The incorporation of Fc and triazoles into macrocyclic structures has also been investigated by White *et al.*[92] and Li *et al.*[93] who prepared two different macrocyclic receptors and acyclic analogues **33-36** (Figure 18). Large cathodic shifts of up to -240 mV (for **34**) were observed for all receptors in the presence of 2 equiv. $H_2PO_4^-$ in DCM with much smaller shifts measured for Cl^-, F^- and OAc^- (max. -32 mV for F^- with **33**).



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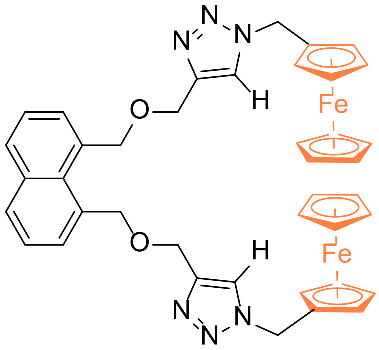

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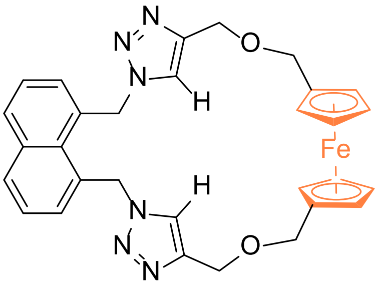

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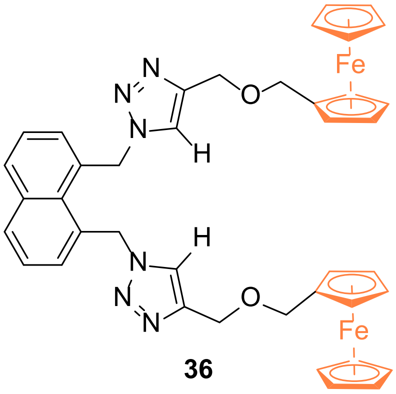

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Figure 18. Macrocyclic and acyclic Fc-triazole receptors.

Sensing of $H_2PO_4^-$ and $HP_2O_7^{3-}$ in DCM was also achieved with a Fc-triazole-modified styrene polymer which, interestingly, showed an enhanced response in comparison to a model monomer and moderate selectivity over Cl^- and Br^-.[94] Another example of a receptor exploiting triazole HB donors is a recent report on a Fc-based calix[4]arene **37** (Figure 19).[95] A selective *anodic* voltammetric response of the Fc/Fc$^+$ couple was observed for F$^-$ in DCM/ACN 1:1, albeit with significant loss of reversibility. This behaviour is analogous to that observed for the similar TTF-appended calix[4]arene receptor **10**.[61]

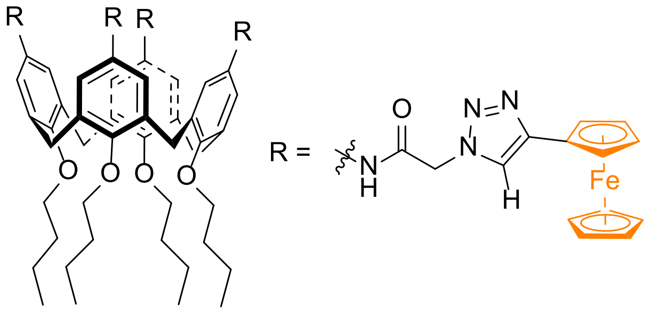

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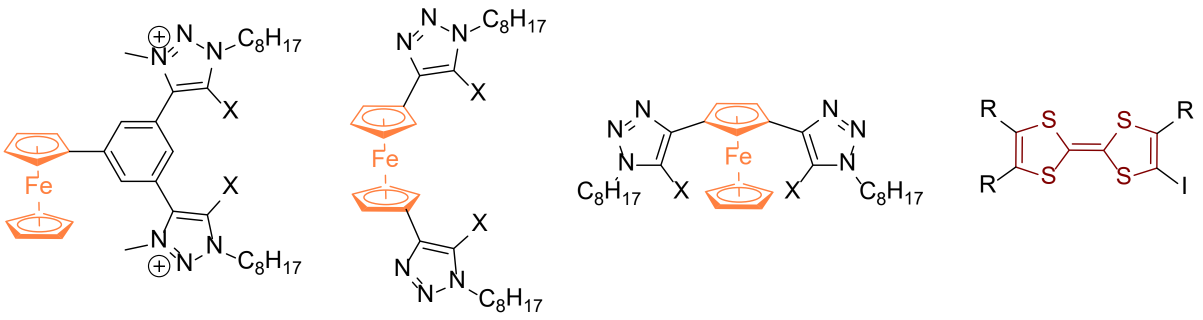
Figure 19. Fc-triazole-appended calix[4]arene.

2.3.3 Redox-active receptors based on C-I halogen-bond donors

The proto-triazole/triazolium motifs can be modified to the halogen-bonding (XB) 5-iodo-1,2,3-triazole and corresponding charge assisted XB triazolium donor analogues which have recently been utilised in anion receptors.[96] Based on this motif, Beer and coworkers reported the first example of a XB-receptive voltammetric anion sensor in 2015[97] wherein a range of neutral and cationic XB and HB receptors were prepared (Figure 20) and studied in ACN. Both receptors **38a** and **39a** displayed moderate cathodic perturbations in the presence of 10 equiv. Cl$^-$ (-32 and -30 mV, respectively) and Br$^-$ (-19 and -18 mV, respectively) the magnitudes of which were notably much larger for these XB receptors in comparison to the halide cathodic responses of the HB analogues **38b** and **39b.** The XB 1,3-bis-triazole-ferrocene receptor **40a**, an analogue of receptor **39a**, demonstrated selectivity for N$_3^-$ (-40 mV) over Cl$^-$, Br$^-$ and OAc$^-$ (max -22 mV for Br$^-$) in ACN/H$_2$O 99:1 at 10 equiv.[98] Importantly, the enhanced cathodic responses for all the XB ferrocene receptors mentioned above (in comparison to their HB analogues), was attributed to better electronic communication of anion binding through the XB interaction and/or stronger binding, Molina and coworkers also studied the XB analogue of their previously discussed HB receptor **29** (Figure 16) in ACN/DCM 1:1 where the cathodic response of the XB-sensor in the presence of anions (vide supra) was comparatively smaller in all cases, which is not necessarily a reflection of weaker binding.[99]



38a: X = I
38b: X = H

39a: X = I
39b: X = H

40a: X = I
40b: X = H

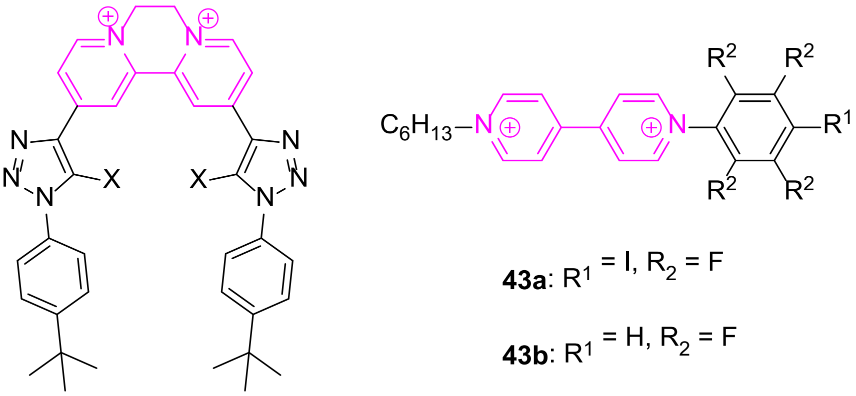
41a: R = H
41b: R = Me

Figure 20. Halogen-bonding voltammetric anion sensors based on Fc or TTF.

Recently, Schöllhorn and Fave used halogen-bonding to drive anion recognition at iodo-modified TTFs **41**.[12,100] The simple substitution of a C-H bond by C-I in the TTF core enabled voltammetric sensing of Cl^- and Br^- in DMF via cathodic perturbations of both TTF couples.[12] Importantly, this work is one of the rare examples of a rigorous analysis of electrochemical binding isotherms and binding constants as described above (eqn. 2) with determination of both K_{Ox} and K_{Red} (rather than just their ratio). Data fitting revealed binding constants of 20 (**41a**), 425 (**41a**$^{+\bullet}$) and 6730 M^{-1} (**41a**$^{2+}$) for Cl^- as well as 5 (**41a**), and 131 M^{-1} (**41a**$^{+\bullet}$) for Br^-. No perturbations of the TTF redox couples were observed in the presence of NO_3^-, OTf^-, ClO_4^- or for the parent TTF with any of the studied anions. Later in depth studies of the methylated iodo-TTF **41b** conclusively proved that the observed behaviour can be attributed to the specific halogen-bonding interaction between the receptors and anions.[100] Furthermore the authors assessed the influence of various other parameters, such as solvent and electrolyte influences and electrode nature and size (all of which are rarely studied) on the binding and sensing performance of **41b**. For example, it is often assumed that non-coordinating electrolyte anions do not interfere with anion sensing/binding. However, the authors demonstrated that the electrochemical voltammetric anion sensing performance of the system using different "non-coordinating" electrolyte anions such as BF_4^-, MsO^-, TfO^-, NO_3^-, ClO_4^- , PF_6^- or $BARF^-$ ([tetrakis[3,5-bis(trifluoromethyl)phenyl]borate) can vary significantly. For example, the magnitude of the cathodic shift for Cl^- (100 equiv.) in the presence of different electrolytes ranged between -36 and -49 mV while K_{Ox} ($K_{TTF+\bullet}$) ranged between 180 and 470 M^{-1} and K_{Red} was negligible (<20 mV) in all cases. The best performance was observed for $BARF^-$ indicating that smaller, commonly used "non-coordinating" anions such as BF_4^- or PF_6^- can indeed compete with binding/signal transduction under these conditions.[100]

XB-donors have also been investigated in viologen-based sensors (Figure 18). For example Beer and coworkers incorporated halogen- and hydrogen-bonding triazoles into the diquat motif to afford **42** which allowed facile sensing of halides in ACN.[101] Unsurprisingly, in light of the XB ferrocene receptors, the XB receptor generally outperformed the HB receptor, with cathodic shifts of the $DQ^{2+}/DQ^{+\bullet}$ couple of -80, -30 and -10 mV as well as -40, -15 and -20 mV for Cl^-, Br^- and I^- for **42a** and **42b**, respectively (at 10 equiv.). Recently Schöllhorn and coworkers reported the examination of a similar paraquat-based system **43**[100] which exhibited Cl^- and Br^- induced cathodic shifts of the $PQ^{2+}/PQ^{+\bullet}$ of -31 and -20 mV for **43a** in DMF (100 equiv.), respectively. The HB analogue **43b** showed smaller responses of -19 and -

10 mV, while interestingly the perfluorinated **43c** outperformed **43b** with shifts of -25 and -12 mV. Even phenylsubstituted **43d** responded to Cl^- (-19 mV), but not to Br^-. These observations suggest that HB interactions are minimal and that the response is mainly driven by electrostatic, anion-π and, in the case of **43a**, XB interactions.



42a: X = I

42b: X= H

43a: R^1 = I, R_2 = F

43b: R^1 = H, R_2 = F

43c: R^1 = R_2 = F

43d: R^1 = R_2 = H

Figure 21. Redox-active halogen- and hydrogen-bonding bipyridinium anion receptors.

2.3.4 Redox-active receptors based on boranes and boronic acids

Boronic acids and other boron derivatives have long been employed as potent receptors for diols (e.g. sugars) or hard inorganic anions (e.g. fluoride or cyanide). The latter react with a Lewis-acidic boron centre *via* formation of a negatively charged, (pseudo)tetrahedral boronate, for example: $ArB(OH)_2 + F^- \rightleftharpoons ArB(OH)_2F^-$. This equilibrium usually lies far to the right and there is a high selectivity for F^- over the other halides and other anions. However, depending on reaction conditions and pH, a variety of other equilibria have to be considered, whereby further substitution can occur to yield $ArB(OH)F_2^-$ or $ArBF_3^-$.[102]

The first example of a voltammetric fluoride receptor based on a boronic acid was reported in 1995 by Shinkai and coworkers who used ferroceneboronic acid (**44**, Figure 22) as a simple yet effective sensor.[103] The authors demonstrated that **44** displayed a cathodic perturbation upon exposure to fluoride in neutral water (up to -150 mV at 1 M). Importantly, no significant shifts were observed in the presence of 1 M Cl^-, Br^-, SCN^-, SO_4^- or $H_2PO_4^-$. Similarly, the voltammetric response of cyclic boronic esters **45** and **46** towards F^- were studied.[104] The former showed a large cathodic shift of ≈-530 mV in the presence of excess F^- in DCM while the latter underwent hydrolysis to afford the parent calixarene and $FcB(OH)F_2^-$. In order to achieve electrochemical CN^- detection the groups of Aldridge and Fallis later also developed the electron-rich borane sensors **47a** and **47b**.[105] Sensor **47a** responded to CN^- in ACN (-560 mV), while also giving a response to F^-. Interestingly, additional functionalisation of the lower Cp ring by permethylation lowered the half wave-potential of [**47b·CN**$^-$] to such a degree that it was oxidised by air, allowing not only electrochemical, but also colorimetric detection of F^- and CN^-. Other dual-signalling sensors based on Fc-containing boron receptors have also been reported more recently.[106-107]

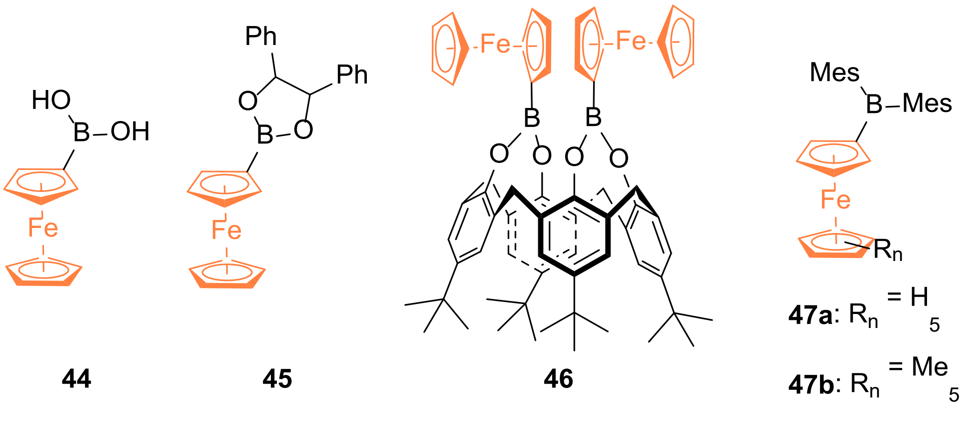
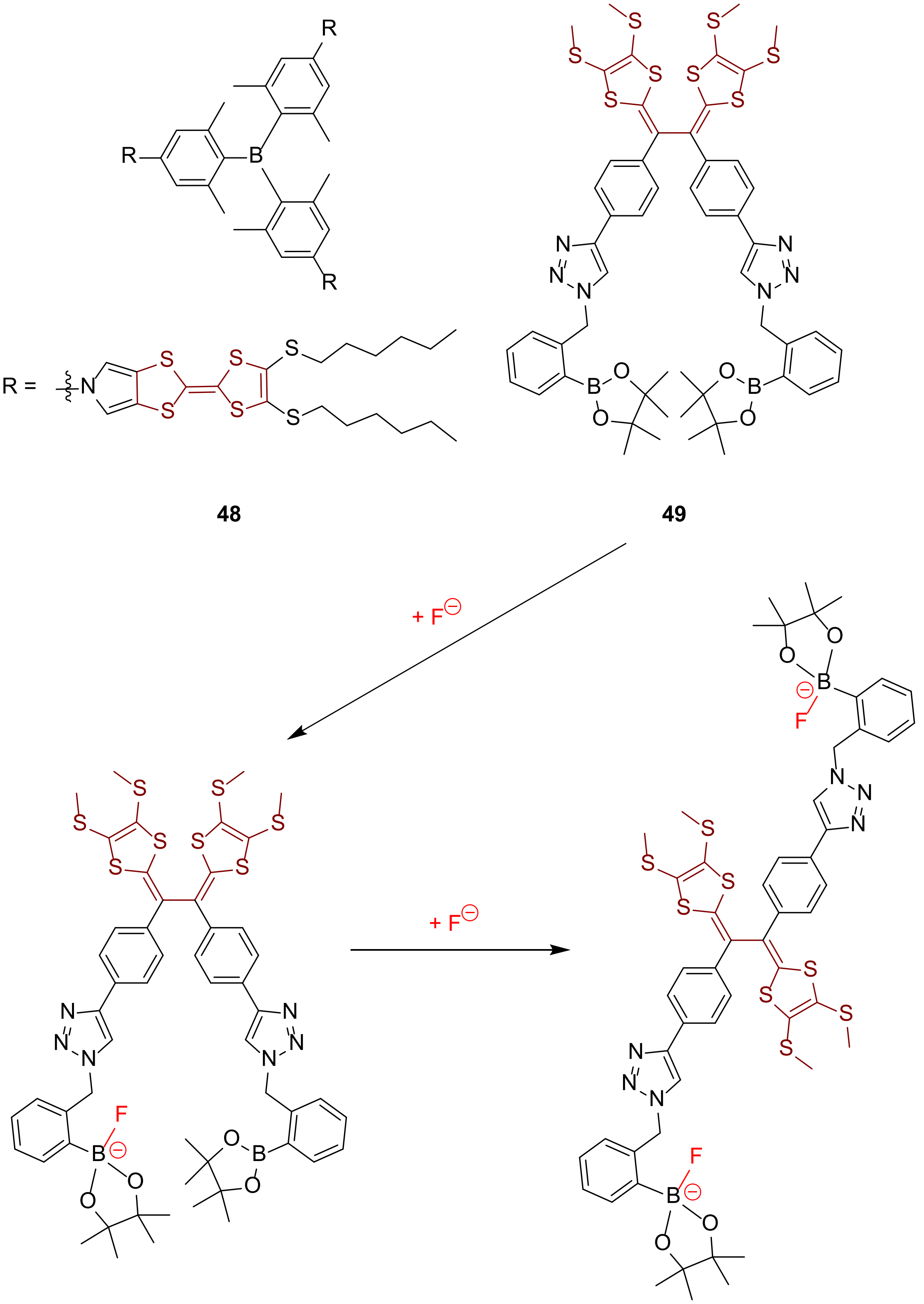


Figure 22. Ferroceneboronic acid and borane based voltammetric anion sensors.

In addition to ferrocene, a variety of other redox-transducers have been incorporated into boron-based receptors. For example, electrochemical and optical detection of F^- was achieved with the TTF-appended trimesitylborane **48** (Figure 23).[108] Addition of 1 equiv. of F^-

induced a -60 mV cathodic shift of the first oxidation peak of **48** in THF, with no further changes at higher fluoride concentrations. The second oxidative couple ($TTF^{+\bullet}/TTF^{2+}$) experienced some cathodic perturbation also, albeit smaller. Interestingly, a mono-substituted derivative of **48** with only one appended pyrrolo-TTF group displayed significantly different behaviour under the same conditions with the appearance of a new wave, cathodically shifted by -140 mV, for only the oxidation of the first couple. More recently a voltammetric fluoride sensor based on the TTF-vinylogue molecular tweezer **49** was reported.[109] CV studies in DCM revealed one quasi-reversible couple which up upon addition of up to 1 equiv. of F^- shifted cathodically, by up to -140 mV. Further addition of an additional equivalent of F^- induced irreversible oxidation with the appearance of two new waves, one at higher and lower potentials, and a concomitant disappearance of the initial (shifted) anodic wave. This behaviour was rationalised by a conformational change induced by electrostatic repulsion between the boronate moieties resulting in a step-wise oxidation of the receptor.

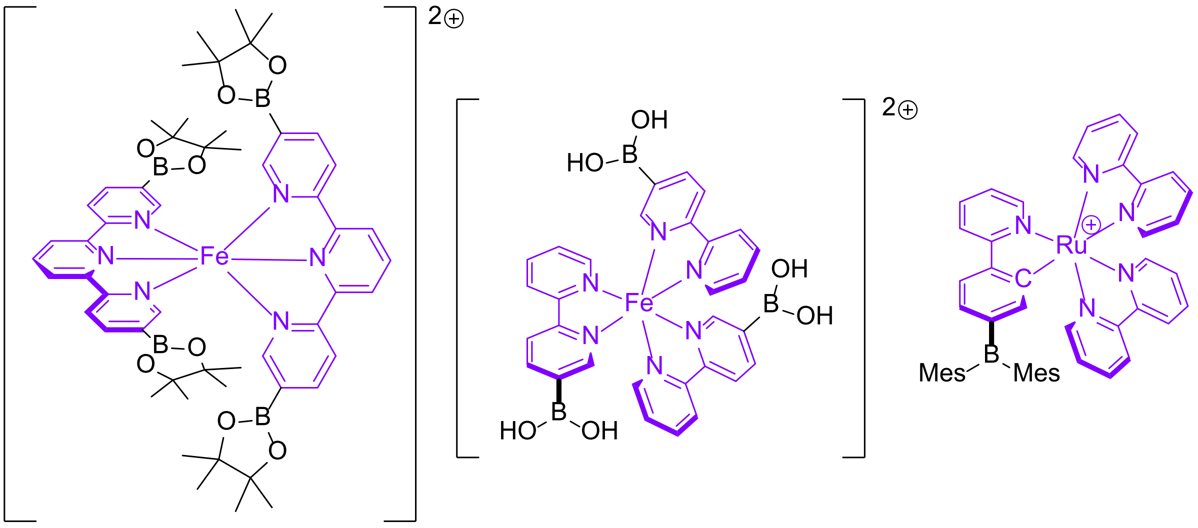


48 **49**

Figure 23. TTF and boron-containing voltammetric receptors for fluoride sensing including the proposed conformational change of molecular tweezer **49** upon sequential binding of F⁻.

In the early 2000s Fabre *et al.* reported a $Fe(tpy)_2^{2+}$ based sensor **50** (Figure 24) for the detection of F^- in MeOH/H_2O 1:1.[110] The $Fe^{2+/3+}$ couple shifted cathodically by up to -160 mV in the presence of 10 mM F^-, corresponding to K_{Ox}/K_{Red} = 560. Cl^- elicited a much smaller response of -20 mV and Br^-, NO_3^- and SO_4^{2-} induced even smaller perturbations. It should be noted that the binding stoichiometry could not be conclusively determined, but, based on UV-Vis studies the authors suggested 1:1 and 1:2 host-guest complex formation. Fabre´s group also investigated the sensory properties of the related bipyridyl analogue **51** in pure aqueous buffer.[111] Electrochemical fluoride binding studies were then carried out at three different pH values of 0.5, 2.1 and 3, whereby the cathodic perturbation in the presence of 20 mM F^- was significantly smaller at the lowest pH (-100 mV) in comparison to pH 2.1 (-150 mV) and pH 3 (-140 mV). This is most likely a reflection of the moderate pK_a of HF (≈3.0) resulting in a significantly lower concentration of free F^- at lower pH. This study is an important illustration of the influence of solution phase conditions, such as pH, on the sensing performance of such systems, in particular when employing receptors whose properties are pH dependent and/or anions that possess moderate pK_a´s. Further complications for the real-life application of boronic acid based receptors for the sensing of F^- is the strong interference from sugars, which have also been shown to elicit a response in many of the discussed boronic-acid based sensors. The immobilization of a derivative of **51** onto an electrode has also been investigated as discussed in Section 2.4.2.

More recently Gabbaï´s group reported another redox-active metal complex **52** based on a dimesityl boron binding site.[112] The $Ru^{2+/3+}$ couple possesses a moderate half-wave potential of +51 mV (vs Fc/Fc^+, in DMF) which was observed to shift -200 mV cathodically in the presence of 1 equiv. of CN^- while addition of 1 equiv. of F^- induced a more complex behaviour with the appearance of an additional new wave -240 mV more cathodically perturbed (Figure 25). Both waves displayed significantly reduced peak currents, which was further exacerbated by the addition of another 5 equiv. of F^-. The authors suggested that this was caused by precipitation of **52·F** at the electrode. Addition of the F^- scavenger $Al(NO_3)_3$ led to the almost complete recovery of the initial voltammetric behaviour of free **52** showing that such systems can generally be regenerated, albeit only when stoichiometric quantities of scavengers are used.



50 **51** **52**

Figure 24. Redox-active metal complexes based on boron-containing ligands.

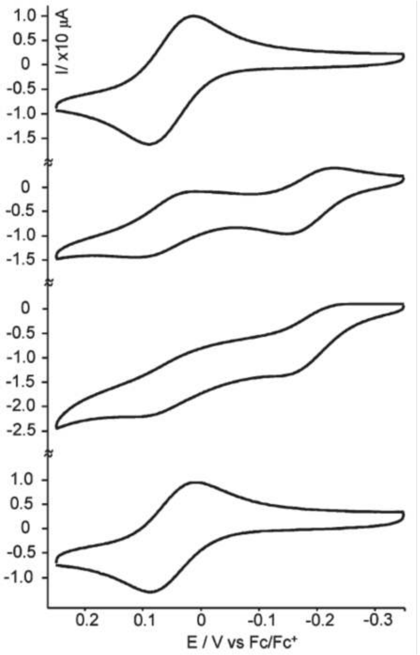
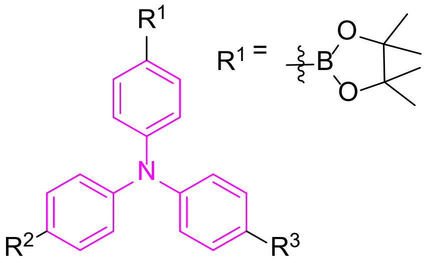
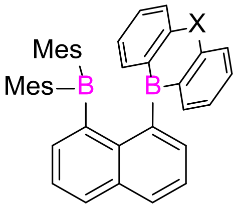


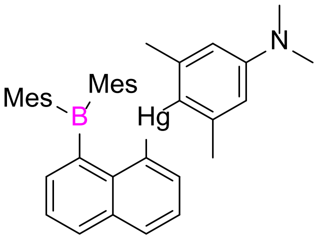
Figure 25. CVs of **52** in DMF, 0.1 M TBAPF$_6$ upon sequential addition of 1 and 6 equiv. of F$^-$ and subsequent recovery after addition of Al(NO$_3$)$_3$. Reproduced with permission from Ref.[112] Copyright 2010 American Chemical Society.

Both aforementioned groups have reported the voltammetric behaviour of other organic boron-containing fluoride receptors. For example, the redox response of mono-, di- and triboronic ester substituted triphenylamines **53a-c** (Figure 26) were investigated.[113] All receptors responded to increasing concentrations of fluoride in DCM by a decrease in the peak currents of the original couple and the emergence of a new couple at lower potential. In the case of the di- and trisubstituted **53b** and **53c** the simultaneous emergence of two and three new waves were observed, respectively, indicating fluoride binding at all boronic ester groups. The third new couple of **53c** was shifted cathodically by -670 mV. The binding enhancement upon one-electron oxidation was large in all cases, in particular for the binding of the first fluoride ion with $K_{Ox}/K_{Red} \geq 44200$ for all receptors. Vinyl derivatives of these receptors were later also studied for the voltammetric fluoride sensing in solution and at functionalised electrodes.[114]

Gabbaï later studied dimesytilboryl naphtalenes **54-56** as voltammetric sensors relying directly on redox processes at the boron centre.[115-116] For example **54a** and **54b** displayed two reversible reductive waves at approx. -2.2 and -2.6 V (vs. Fc/Fc^+) in THF which were attributed to stepwise, one-electron reduction of the two borane moieties, reflective of the coordinative unsaturation.[115] Incremental addition of up to 1 equiv. of F^- led to the concomitant, progressive loss of redox reversibility of both waves indicating that F^- acts as a bridging ligand and coordinates to both boron centres simultaneously rendering both saturated and redox inactive (a representative crystal structure of the related **56-μ_2-F^-** can be seen in Figure 27). None of the other halides nor OAc^-, NO_3^- or NO_2^- invoked any voltammetric response under the same conditions. A similar voltammetric behaviour was also reported for **55** whose single reductive couple disappeared after addition of 1 equiv. of F^- in THF.[116] The symmetric diborane **56** however showed two separate reduction waves indicating strong intramolecular electronic coupling between both boron centres. The addition of 1 equiv. of F^- induced the same behaviour as noted above, but only for the more anodic wave, while the other wave shifted cathodically by -50 to -60 mV. Further addition of F^- up to 2.25 equiv. induced only modest perturbations, with a small reduction in peak currents, but no full loss of redox activity. This indicates that binding of a second F^- bridging ligand is much less favourable than binding of the first F^-, in good agreement with the strong electronic coupling between both sites.







55

53a: $R^2 = R_3 = H$

53b: $R^2 = R_1$, $R^3 = H$

53c: $R^2 = R_3 = R^1$

54a: X = O

54b: X = S

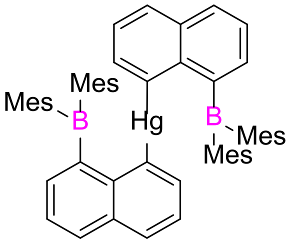


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Figure 26. Boron-containing, organic voltammetric anion sensors.

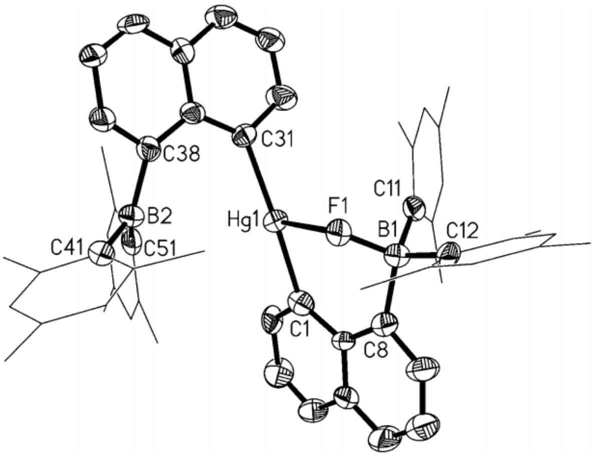
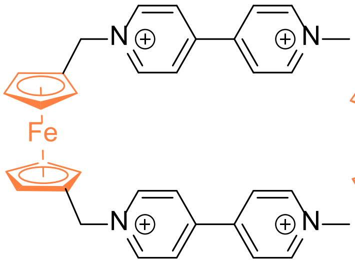


Figure 27. ORTEP view of **56-μ$_2$-F$^-$**. Mesityl groups are shown as thin lines and H-atoms are omitted for clarity. Reproduced with permission from Ref.[116] Copyright 2008 The Royal Society of Chemistry.

2.3.5 Redox-active receptors based on other anion binding motifs

The voltammetric sensing of ATP^{2-} in water has been reported by Reynes *et al.* employing viologen-functionalised Fc receptors **57-59** (Figure 28).[117] Anion recognition was largely driven by electrostatics and charge transfer interactions of the electron rich guest with the electron deficient viologens. While the viologen motif itself is also electroactive and could be used as a transducer (see Section 2.3.3) the Fc/Fc$^+$ redox couple was monitored instead (transduction *via* the viologen was inhibited due to redox associated electrode adsorption). Small cathodic shifts were observed for **57** in the presence of 2 equiv. HSO_4^-, $S_2O_4^-$ and ATP^{2-} (all -10 mV) and for **58** with $S_2O_4^-$ (-10 mV), $PhPO_4^{2-}$ (-10 mV) and ATP^{2-} (-25 mV; all in pure water). No response was observed for either receptor in the presence of $H_2PO_4^-$, HPO_4^{2-}, SO_4^{2-}, CF_3COO^-, F^- or Cl^-. The incorporation of pyrrole furnished **59** which was electropolymerised onto a carbon electrode to give polymeric films. This interface showed an enhanced voltammetric response to the target anions (-35 mV for ATP^{2-}, -20 mV for HSO_4^- and -10 mV for $S_2O_4^-$ at 1 mM). The voltammetric response of this interface towards ATP^{2-} is illustrated in Figure 29. Further examples and discussions about surface-confined voltammetric receptors can be found in Section 2.4.



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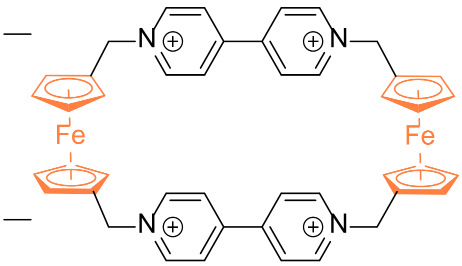

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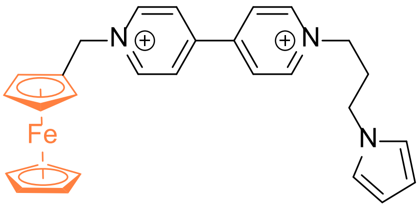

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Figure 28. Viologen-Fc conjugates for voltammetric sensing of ATP^{2-} in water.

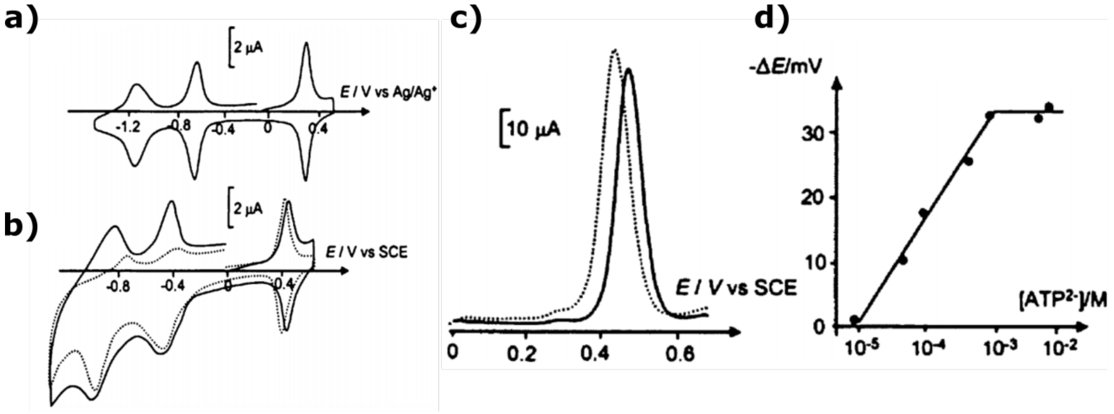
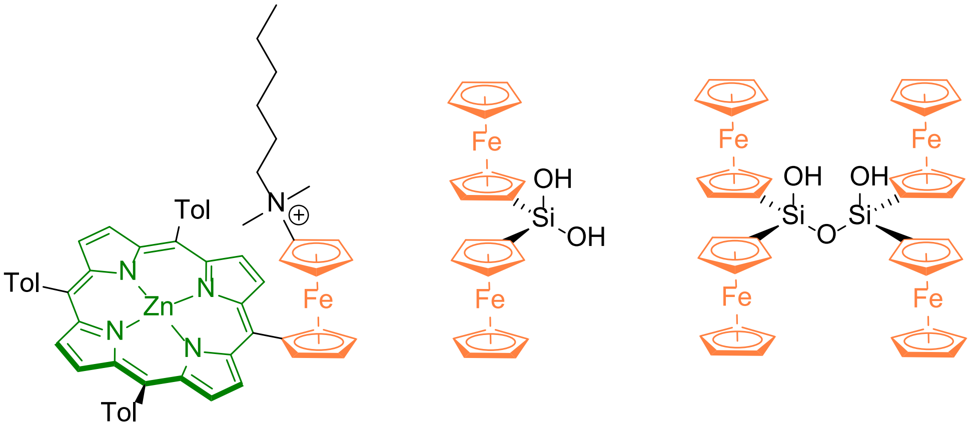


Figure 29. 59$_{Film}$ on GC electrode. a) CV in ACN, 0.1 M TBAPF$_6$. b) and c) CV and SWV in H_2O, 50 mM KNO_3 without ATP^{2-} (full line) and with 1 mM ATP^{2-} (dotted line). d) The corresponding binding isotherm of ATP^{2-}. Reproduced with permission from Ref.[117] Copyright 2004 The Royal Society of Chemistry.

Electrostatically driven anion recognition was also explored by the same group using the ferrocenylmethyl trimethylammonium cation.[118] This very simple sensor responded not only to $H_2PO_4^-$ and ATP^{2-} in DCM with large perturbation of -470 mV and -280 mV, respectively, but even in the more competitive ACN large shifts of -300 mV and -240 mV were observed (all at 1 equiv.). In pure MeOH only ATP^{2-} induced a modest response of -30 mV. The authors later improved on this design through the incorporation of an additional Zn-porphyrin site to produce **60** (Figure 30).[119] The additional axial coordination of anions to the Zn-center not only alters the selectivity of this sensor, but also allows additional binding modulation *via* the redox-active properties of the metallo-porphyrin. The addition of $H_2PO_4^-$ in DCM induced significant shifts of the Fc/Fc$^+$ couple (-240 mV), but also led to significant loss of electroactivity of both transducers. In contrast the Fc transducer remained quasi-reversible in the presence of Cl$^-$ (-130 mV shift). A more interesting behaviour was observed in the presence of NO_3^- and HSO_4^- however; both anions induced cathodic perturbation for the Fc/Fc$^+$ as well as the P/P$^{+\bullet}$ couple. The former was equally perturbed by both anions (≈-80 mV at 20 equiv.) while only the P/P$^{+\bullet}$ couple showed a larger but different response of -90 mV and -140 mV for NO_3^- and HSO_4^-, respectively. The authors reported another interesting observation: the $P^{+\bullet}/P^{2+}$ couple, which was initially observed to disappear during the titration, actually coalesces with the $P/P^{+\bullet}$ couple to from a new two-electron wave (P/P^{2+}).[119] Therefore, in such porphyrin systems consideration should be given that the response of the "first" wave might actually correspond to a two-electron oxidation.



60 **61** **62**

Figure 30. Fc-porphyrin-alkylammonium receptor and silanol-functionalised ferrocenes.

Cuadrado and coworkers recently introduced Fc-containing silanols **61** and **62** as an interesting class of novel redox-active anion sensors (Figure 30).[120] Investigations of **61** in DCM/ACN 1:1 revealed two separate Fc couples that shifted cathodically by -90 and -100 mV in the presence of 1 equiv. OAc^- as shown in Figure 31a-b. Sensor **62** was investigated in DCM/ACN 1:2 showing more complex behaviour with three waves, where upon addition of 1 equiv. OAc^- the first and second couple merge at a potential that is almost equivalent to the original potential of the first wave (-60 mV shift for second couple; Figure 31c-d). The most anodic third wave also shifts cathodically by -60 mV. Addition of Cl^- induces cathodic perturbation of both receptors albeit with smaller magnitude (-40 mV for **61** and -20 mV for **62** (for the most anodic wave in both cases)).

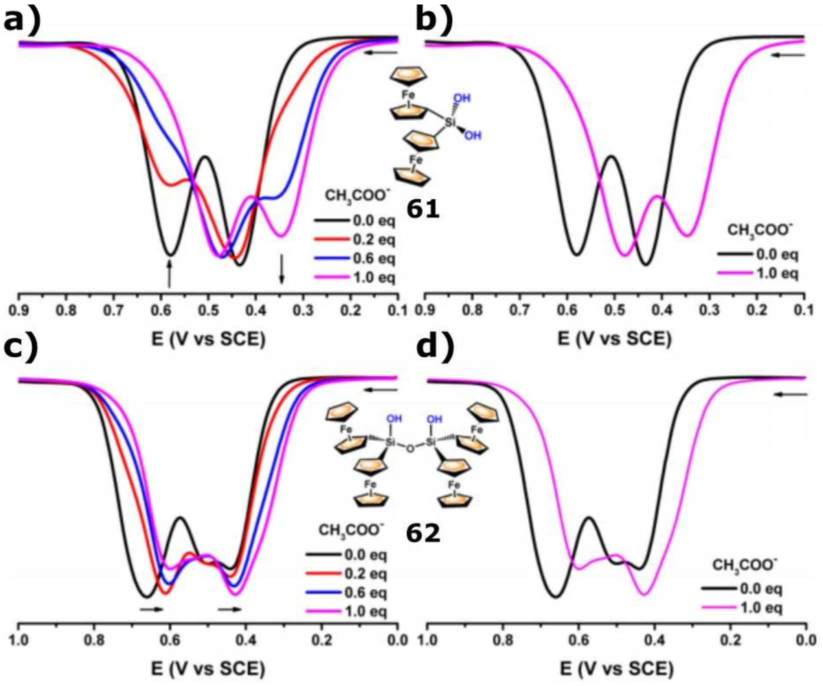
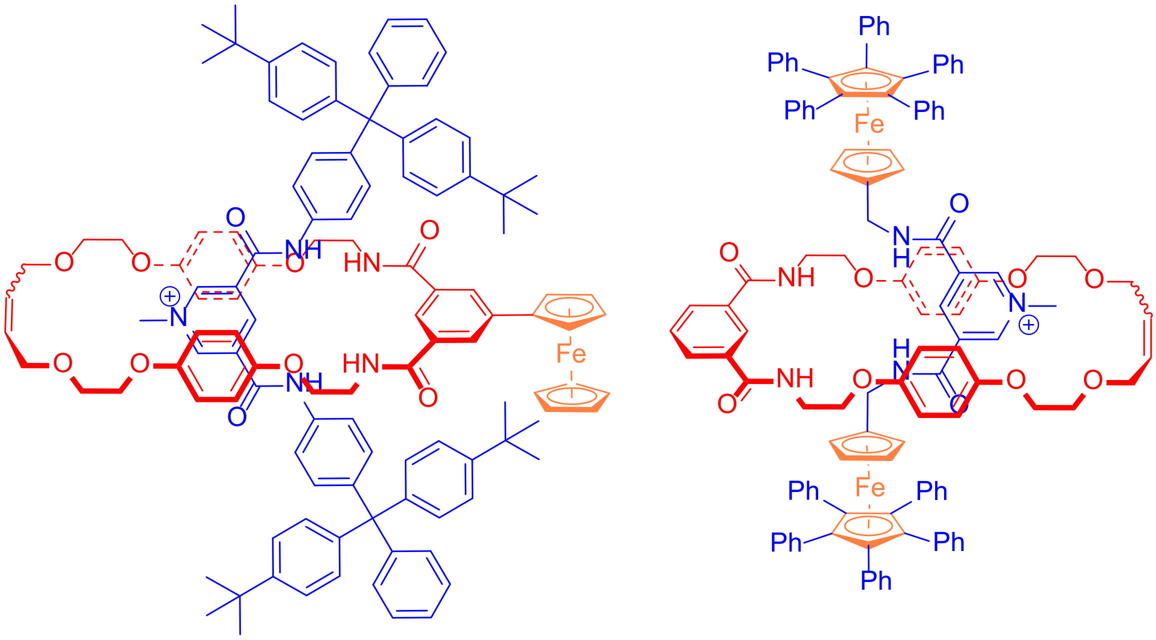


Figure 31. SWVs of a) and b) **61** in DCM/ACN 1:1 and c) and d) **62** in DCM/ACN 1:2 upon addition of OAc^-. Reproduced with permission from Ref.[120] Copyright 2016 American Chemical Society.

2.3.6 Redox-active mechanically interlocked receptors

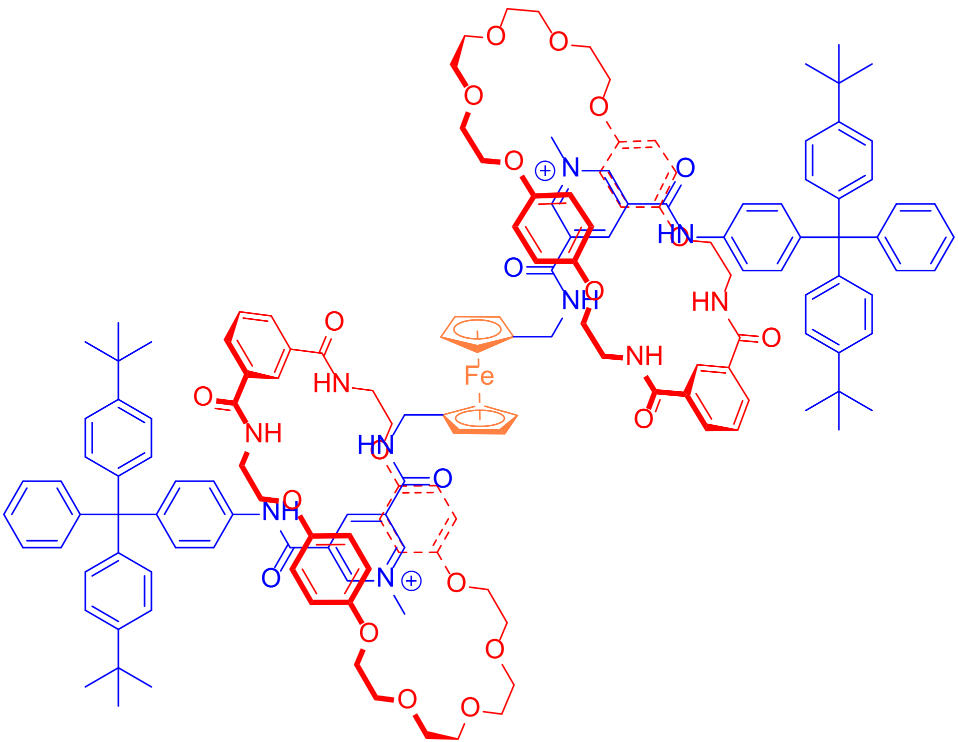
In recent years mechanically interlocked receptors such as rotaxanes or catenanes, have been increasingly studied in the field of anion recognition.[8,121-122] This can mainly be attributed to their unique 3-dimensional binding cavities, which often not only leads to enhanced anion binding strength, but, importantly, imbues much enhanced selectivities over simpler acyclic or macrocyclic systems. The more intimate three-dimensional control over local dielectric/hydration is also of increasing importance when seeking to conduct anion sensing in competitive (aqueous) media. The first example of a solution-phase redox-tagged interlocked structure for anion sensing was reported by Evans and Beer in 2011, whereby a rotaxane **63** was employed, comprising a pyridinum-bisamide axle and a 5-ferrocenylisophtalamide-based macrocycle (Figure 32).[123] Voltammetric studies in ACN revealed significant cathodic perturbations for Cl^-, $H_2PO_4^-$, BzO^- and HSO_4^- of up to -100 mV (for $H_2PO_4^-$ at 10 equiv.) while the maximum shift for Cl^- (-20 mV) was already observed at 1 equiv. indicative of strong binding. The Fc-transducer has not only been incorporated into the macrocyclic component but has also been used as a stopper in the axle component of a [2]rotaxane **64**.[124] This system displayed a similar behaviour to the previous example, whereby addition of 1 equiv. Cl^- in ACN/DCM 1:1 was sufficient to induce plateauing of the response (-20 mV shift), which was not observed for the axle alone. The relatively small shifts that are observed in these systems are most likely a reflection of the strong binding in the neutral state (K_{Red} large) which is not significantly modified through the introduction of an additional charge upon oxidation of Fc moiety. This is not necessarily detrimental in sensing applications, where the overall magnitude of the output is not always important (as long as the output is reproducible and signal-to-noise is low) and is often offset by the largely enhanced selectivities of these interlocked systems.



63 **64**

Figure 32. Fc-containing [2]rotaxanes.

The incorporation of a Fc-transducer into the axle of a [3]rotaxane has also been achieved, yielding **65** (Figure 33).[125] This system displays much larger cathodic perturbation in the presence of Cl^- (-55 mV at 2 equiv. with negligible further shifts at higher equiv.) indicating that a 1:2 stoichiometric host-guest complex is formed whereby two anions bind in each of the cavities (quantitative binding). A much more complex behaviour was observed in the presence of SO_4^{2-} where, depending on the anion concentration, “two-wave” behaviour (slow exchange) was observed, with shifts of up to -270 mV (5 equiv.). A similar sensory behaviour towards Cl^- as in the previous examples, was also observed for the Fc-containing [2]catenane **66**.[126]



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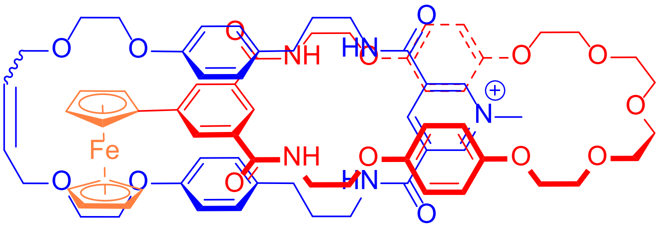
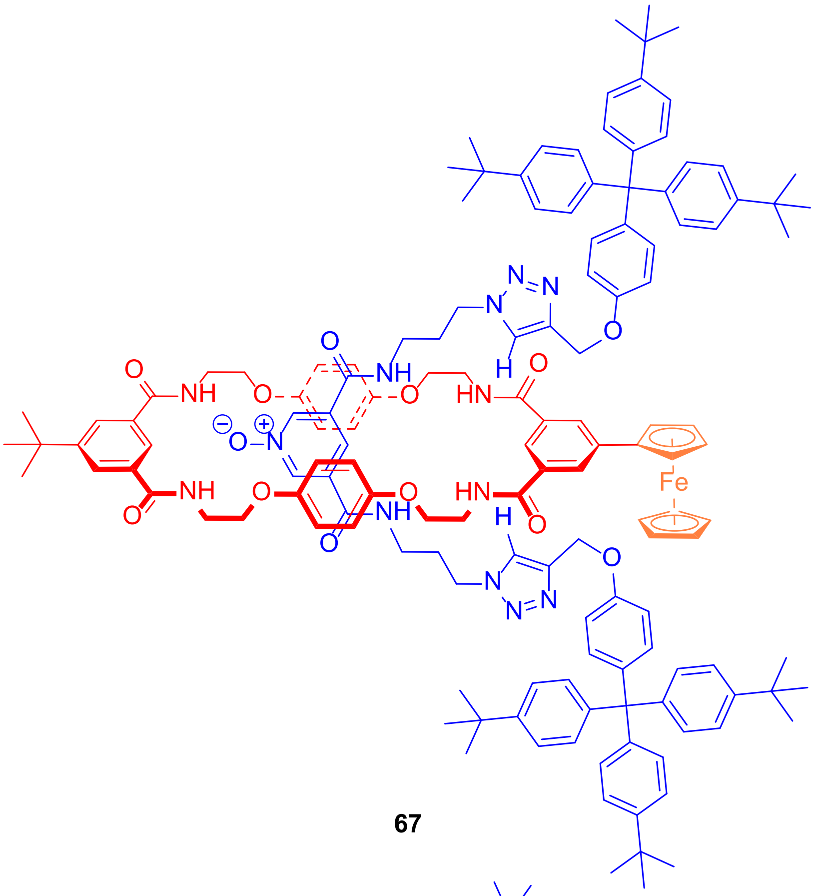


66

Figure 33. Fc-containing [3]rotaxane and [2]catenane.

Lim *et al.* later also reported a range of neutral redox-active [2]rotaxanes based on a pyridine-N-oxide axle.[127] Rotaxane **67** (Figure 34) displayed cathodic shifts in ACN/DCM 1:1 that were larger for all tested anions (Cl^-, Br^-, OAc^- and $H_2PO_4^-$) than those observed for the macrocycle alone. Recently, a redox-active all-halogen bonding rotaxane **68** was utilised for the selective sensing of Br^- over Cl^- and SCN^- in ACN/acetone/H_2O 45:45:10.[128] The only non-

Fc transducer that has been used in voltammetric, interlocked anion sensors is porphyrin which Brown *et al.* introduced into the axle or macrocyclic component of [2]rotaxanes (as free-base porphyrin).[129] These sensors are structurally very similar to the Fc-containing [2]rotaxanes **63** and **64**, whereby the Fc transducer was replaced with the free-base porphyrin. Preliminary electrochemical studies in DCM/ACN 1:1 revealed cathodic perturbations of the P/$P^{+\bullet}$ couple in the presence of 2 equiv. Cl^- of -50 and -25 mV for the porphyrin-stoppered and porphyrin-macrocycle rotaxanes, respectively.



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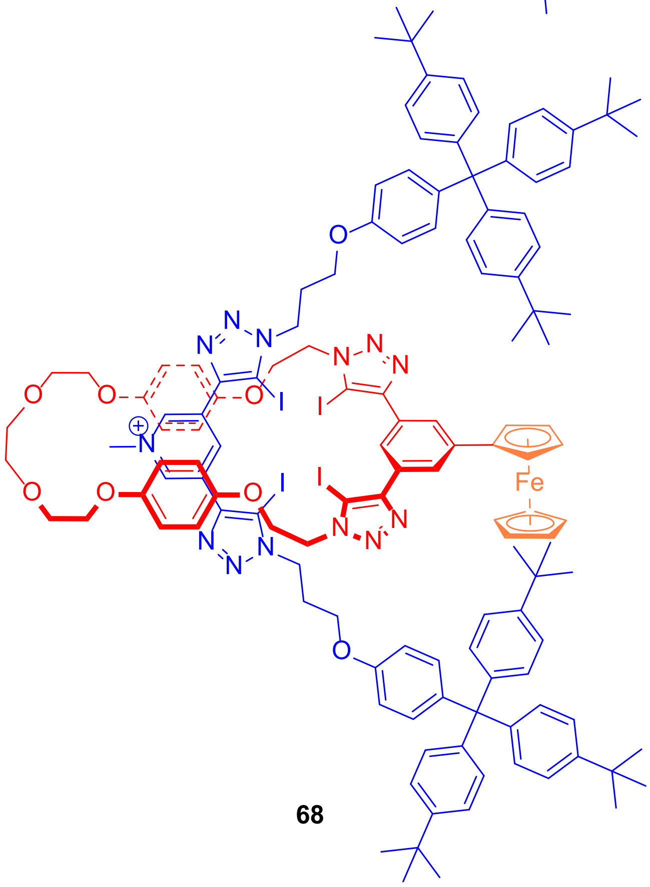

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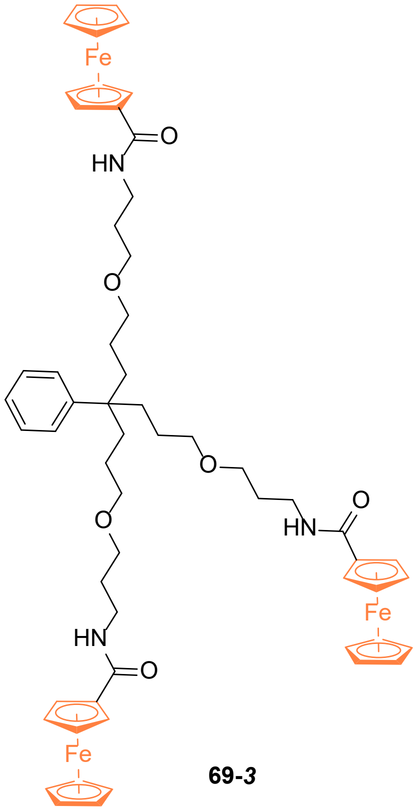
Figure 34. Neutral and all halogen-bonding redox-active [2]rotaxanes.

2.3.7 Redox-active dendritic and nanoparticle based sensing configurations

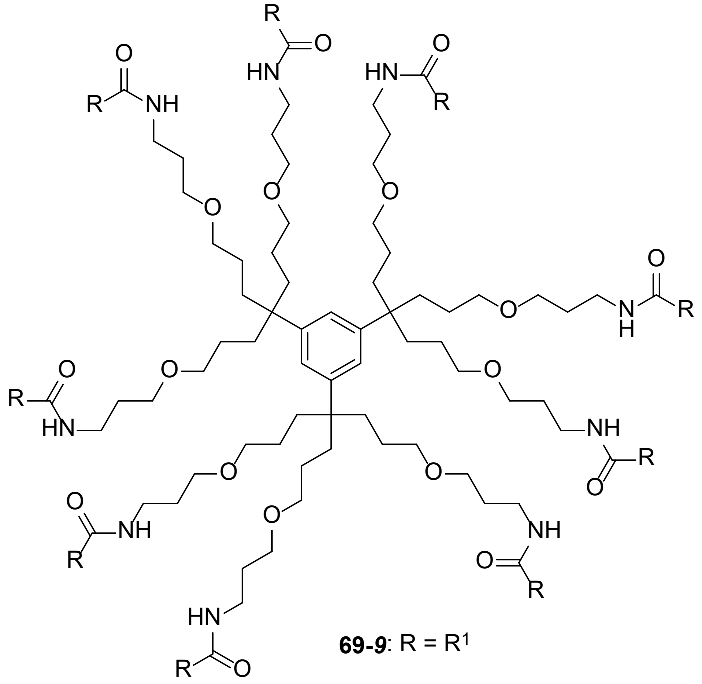
Dendrimers have found numerous applications in a myriad of fields including catalysis, medicine, imaging and sensing.[130-132] In 1997 Astruc and coworkers reported the first use of Fc-amide functionalised dendrimers **69-*n*** for voltammetric anion sensing (Figure 35).[133] The authors demonstrated that the cathodic shift of these dendrimers in the presence of $H_2PO_4^-$, HSO_4^-, Cl^- and NO_3^- was strongly dependent on the number of dendrimer branches, with a significantly increased response observed on increasing the number of branches from 1 to 3, 9 and 18, attributed to cooperative effects. While the non-dendrimeric control compound comprising of one Fc-amide branch only responded to $H_2PO_4^-$ (-45 mV at 1 equiv. per branch in DCM) **69-*3*** also responded to HSO_4^- (-30 mV) and with a much larger response for $H_2PO_4^-$ (-110 mV). Increasing the number of dendrimer branches allowed for a broader range of anions to be sensed including Cl^- (**69-*9***) and additionally NO_3^- (**69-*18***). The cathodic response of **69-*18*** to $H_2PO_4^-$ of -315 mV was seven times larger than that of **69-*1*** corresponding to an extremely large binding switch-on of K_{Ox}/K_{Red} of 219000. These observations show that in addition to electrostatic and other non-covalent interactions (i.e. hydrogen-bonding) local topological effects play a significant role in these systems, which is often rationalised by formation of suitable binding pockets in the higher-generation dendrimers.

Importantly, these and all subsequently discussed redox-active dendrimers display a single redox wave, irrespective of their size (and number of terminal redox groups) and even in very large dendrimers almost all branches are redox active. This indicates that, on the time scale of voltammetric experiments, electron transfer to the whole dendrimer is facile which can be attributed to fast tumbling in addition to electron-transfer between discrete Fc-units.[134-135]

Based on their initial work Astruc´s group also investigated the analogous cobaltocenium terminated dendrimers **70-*9*** and **70-*18***.[136] The former showed, in comparison to **69-*9*** slightly enhanced cathodic shifts of the Cp_2Co^+/Cp_2Co couple in the presence of $H_2PO_4^-$, HSO_4^- and Cl^-. These studies were, due to solubility constraints, conducted in the more polar solvent system ACN/DMF (2:15). Interestingly, the higher generation **70-*18*** elicited much smaller responses to the same anions (i.e. a negative dendrimeric effect), whereby quantitative analysis was hampered by adsorption and precipitation. The former is a frequently observed problem; especially the larger dendrimers often significantly adsorbed onto the electrode surface. While this can lead to more complex voltammetric behaviour, it can be utilised to form interfacial voltammetric sensors, as discussed in Section 2.4.3.



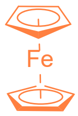
69-*3*



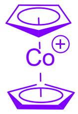
69-*9*: R = R^1

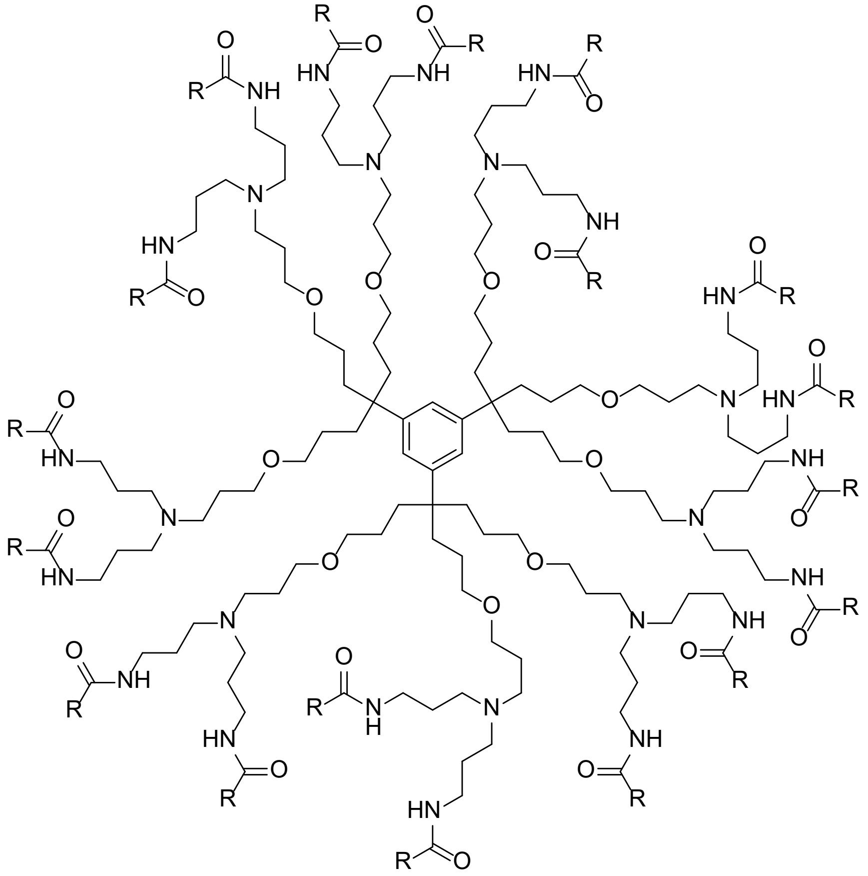
70-*9*: R = R^2

R^1 =



R^2 =





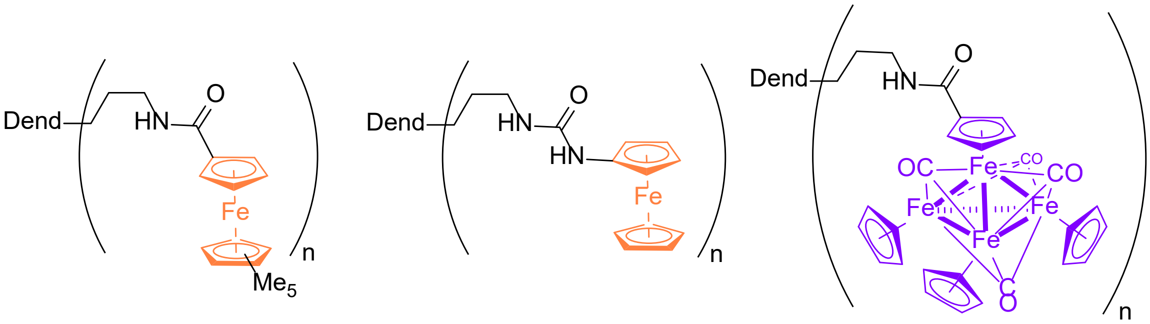
69-*18*: R = R^1

70-*18*: R = R^2

Figure 35. First dendrimeric voltammetric anion sensors based on Fc and cobaltocenium.

The sensory behaviour of five generations of pentamethylamidoferrocenyl dendrimers **71-*n*** (Figure 36) derived from a polyamine core have been investigated in detail by Daniel *et al*.[137] In this work pentamethylation of the Fc transducer was sufficient to significantly reduce decomposition as well as adsorption problems that are observed in the corresponding unmethylated receptor, enabling quantitative binding studies with $H_2PO_4^-$ in both DMF and DCM even for the large G_4 and G_5 dendrimers **71-*32*** and **71-*64***. However, only very small dendrimeric effects were observed; in all cases the cathodic shifts observed were around -150 mV, irrespective of solvent or dendrimer generation. Additionally these shifts were significantly smaller than those observed with the parent, unmethylated receptors, which is most easily rationalised by decreased H-bond donor strength due to higher electron-density of **71-*n***. The response of **71-*4,8,16,32*** towards ATP^{2-} in DCM was slightly smaller (≈-130 mV), with no significant dendrimeric effect. In comparison to $H_2PO_4^-$ however, the equivalence point in this case was already reached at 0.5 equiv. of ATP^{2-} per branch, indicating 2:1 complexation between the Fc^*-amide and ATP^{2-}. Such a 2:1 binding stoichiometry has also been observed for the monovalent $H_2PO_4^-$ with the urea-dendrimers **72-*4,8,16,32*** in DMSO.[138] This series of receptors showed complex dendrimeric effects with larger response of **72-*8*** and **72-*16*** in comparison to either **72-*4*** or **72-*32***. In analogy to the previous examples these sensors also showed good selectivity towards $H_2PO_4^-$ over Cl^- and HSO_4^-. The sensing of $H_2PO_4^-$ and ATP^{2-} has also been carried out with amidoferrocene-terminated dendrimers that have not been assembled covalently, but rather *via* H-bonding between primary amines and phenols.[139-140] Another voltammetric $H_2PO_4^-$ sensor was produced by immobilisation of simple amidoferrocene receptors onto single wall carbon nanotubes (SWNTs) displaying large cathodic shifts of -230 mV in DCM (diffusive conditions), indicating similar cooperative, “dendritic” effects.[141]

An interesting redox-transducer, the tetra nuclear iron cluster $[\mathrm{CpFe}(\mu_3\text{-}\mathrm{CO})]_4$, was incorporated into dendrimers **73-*9,16,27*** which were shown to be competent ATP^{2-} sensors.[142] The reversible one-electron oxidation of $\mathrm{Fe}_4/\mathrm{Fe}_4^+$ at potentials close to $\mathrm{Fc}/\mathrm{Fc}^+$ was used in transduction, where **73-*16*** showed the largest response to ATP^{2-} in DCM (-170 mV) while the shifts for **73-*9*** and **73-*27*** were smaller with -40 mV and -110 mV, respectively. The smaller response for the larger dendrimer was rationalised by the larger distance between adjacent branches in **73-*27***, which was constructed based on a different core, detrimental to 2:1 complexation. However the large **73-*27*** was better suited for the formation of redox-active films on Pt electrodes which were used as a reusable ATP^{2-} sensor (see also Section 2.4.3). Interestingly these receptors are the first dendrimer-based voltammetric sensors that display selectivity for ATP^{2-} over $\mathrm{H_2PO_4^-}$.

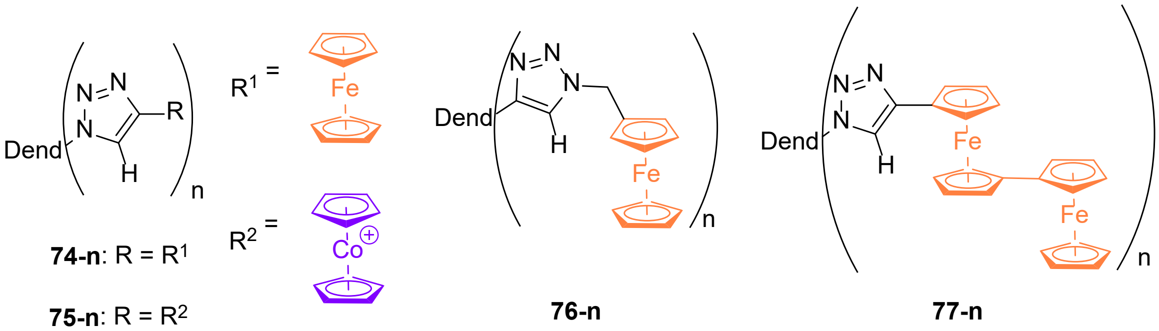


71-n **72-n** **73-n**

Figure 36. Amide and urea dendrimers based on different iron-containing transducers.

More recently dendrimers have been assembled *via* “click” chemistry, significantly expanding their structural diversity.[143] The 1,2,3-triazole motif can not only be used as an anion binding site, but has also been used for the recognition and sensing of cations through binding *via* the N-lone pair of the triazole. The first example of a redox-active triazole dendrimer was reported by Astruc´s group who demonstrated **74-*9,27,81*** as voltammetric sensors for $H_2PO_4^-$ and ATP^{2-} and also for Pd^{2+}, Pt^{2+}, Cu^{2+} and Cu^+ (Figure 37).[144] In DCM all analytes, apart from Cu^+, showed a small, but significant negative dendrimeric effect with the response being largest for **74-*9*** (up to -200 mV for for $H_2PO_4^-$). However in all cases, the response of **74-*27*** was still significant (e.g. -160 mV for $H_2PO_4^-$). In a later study the analogous cobaltocenium dendrimers **75-*9,27,81*** exhibited a markedly different response with a positive dendritic effect: only **75-*81*** responded to $H_2PO_4^-$ (-150 mV).[145] However, these latter studies were, for solubility reasons, performed in DMF. In both DMF and ACN these dendrimers showed much poorer reversibility than **74** with significant adsorption, even for the smaller dendrimers. Fc-dendrimers **76-*27,81,243*** with a different triazole connectivity also displayed a positive dendritic effect in DCM, however only for $H_2PO_4^-$ (-260 mV for **76-*243***), while ATP^{2-} induced the same response of -180 mV for all generations.[146] All receptors showed significant irreversibilities and strong adsorption, with the latter being exploited to form films on Pt. These films showed, in comparison to diffusive sensing conditions, an enhanced response towards ATP^{2-}, with a modest positive dendritic effect (-200 mV for **76-*27*$_{\mathbf{film}}$** and -220 mV for **76-*243*$_{\mathbf{film}}$**).

The use of biferrocene as a transducer in the triazole-dendrimers **77-*9,27,81,243,729*** enabled anion as well as cation sensing through different redox couples (Figure 37).[147] The strong coupling between the Fc groups induced stepwise oxidation, where oxidation of the more electron-rich outer Fc moiety occurs at potentials some 300 mV lower than that of the inner Fc (Figure 38). The addition of ATP^{2-} to **77-*81*** in DCM caused splitting of the first wave, with appearance of a new wave at lower potentials, indicating electrostatic interactions with the outer Fc (the second wave at higher potentials was highly irreversible). Conversely, upon Pd^{2+} addition only the inner Fc was perturbed indicating coordination at the adjacent triazole. Such receptors can potentially be exploited for the simultaneous detection of anions and cations if electrochemical reversibility can be retained (see Section 5). $H_2PO_4^-$ sensing in DMSO using small biferrocene-amide dendrimers has also been reported by Villena *et al.*[148]



74-n: R = R1

75-n: R = R2

76-n

77-n

Figure 37. Metallocene-terminated triazole dendrimers.

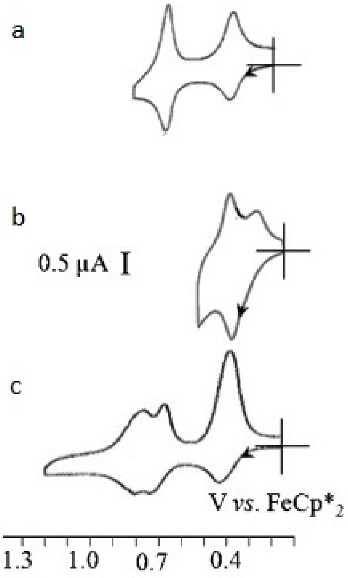


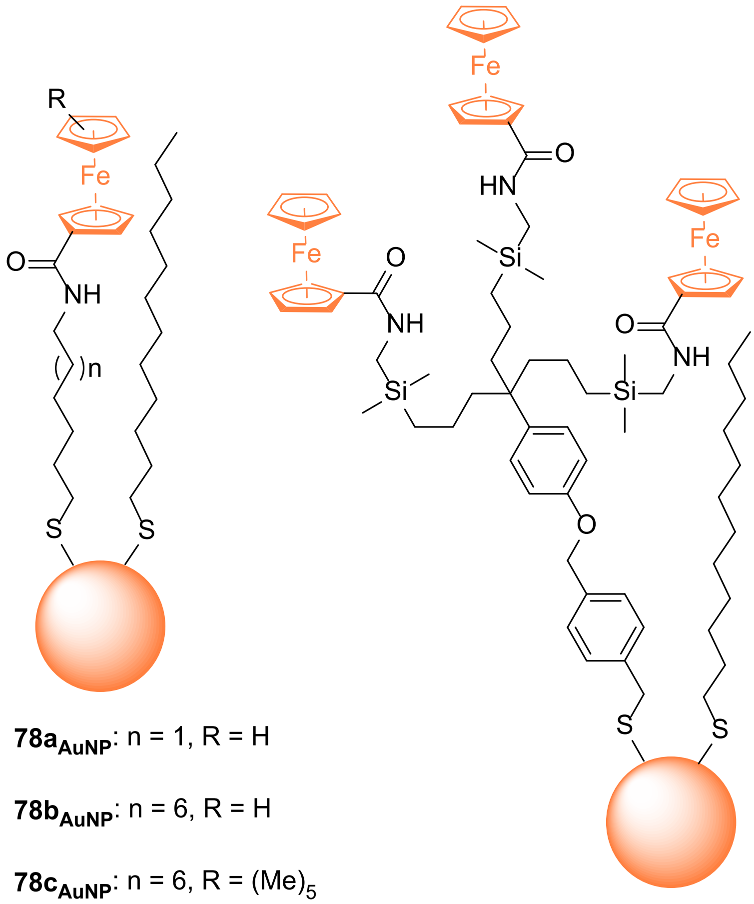
Figure 38. CVs of **77-81** in a) DCM, 100 mM $TBAPF_6$. b) After addition of ATP^{2-} inducing perturbations of the first wave (second wave not shown due to irreversibility). c) After addition of Pd^{2+} inducing perturbations of the second wave. Reproduced with permission from ref.[147] Copyright 2010 Wiley-VCH.

In the early 2000s Astruc and coworkers also reported the first redox-receptor modified nanoparticles (NPs) for solution-phase anion sensing. These systems were prepared by formation of self-assembled monolayers on gold NPs via thiol-chemistry, akin to the direct electrode modification discussed in detail in Section 2.4. For small NPs these systems are topologically similar to dendrimers and generally display similar behaviour such as enhanced responses over their “0th” generation monomers/ligands as well as, depending on size and solution phase conditions, often significant adsorption onto the electrode. Advantageously a large number of closely-spaced redox-receptors can easily be introduced into these NPs without additional synthetic steps that are required to form large, higher generation, dendrimers.

In the first report of such a sensor mixed SAMs of dodecanethiol and amidoferrocenylthiols of various length were formed on small Au NPs (2 nm core diameter, Figure 39).[149] In DCM the reversible Fc couple of **78a$_{\mathbf{AuNP}}$** and **78b$_{\mathbf{AuNP}}$** was cathodically perturbed by ≈-220 mV in the presence of $H_2PO_4^-$. The magnitude of this shift was not only independent of the chain length of the receptor ligands, but, interestingly, also independent on the proportion of this ligand (between 7-38%) with respect to the diluent C_{12}-SH ligand. This is in marked contrast to earlier dendrimeric systems such as **69-*3,9,18*** where a significant positive dendrimeric effect was observed (*vide supra*). This suggests that, even at relatively low receptor loading, cooperative effects can enhance the response of these NP systems and that they resemble large dendritic sensors. In a later study, the influence of the modification of the second Cp ring was studied where it was shown that the response of the permethylated **78c$_{\mathbf{AuNP}}$** was significantly smaller (-130 mV), while that of the acetyl-modified **78d$_{\mathbf{AuNP}}$** was larger (-280 mV), attributed to electronic effects influencing the $H_2PO_4^-$ anion binding strength.[150]

While **78$_{\mathbf{AuNP}}$** also responded to HSO_4^-, albeit a smaller cathodic perturbation of ≈-30mV was observed in comparison to $H_2PO_4^-$, the dendrimer functionalised Au NP platform **79$_{\mathbf{AuNP}}$** selectively responded to $H_2PO_4^-$ (-210 mV) over HSO_4^- as well as Cl^-, Br^- and NO_3^- in DCM.[151]

An analogous sensor without the amide binding site also displayed a significant response of -110 mV indicating that, akin to many dendrimeric sensors, electrostatic interactions dominate in non-polar solvents. This was then exploited in related non-receptive Fc-dendrimer modified Au NPs to sense $H_2PO_4^-$ and ATP^{2-}.[152] Selectivity of ATP^{2-} over $H_2PO_4^-$ was later achieved with Au NPs functionalised with $[Fe_4(\mu_3\text{-}CO)_4(\eta^5\text{-}C_5H_5)_3(\eta^5\text{-}C_5H_4CONH(CH_2)_{11}SH]$ (the same redox-transducer as in **73**) with a response of -150 mV and -60 mV in DCM, respectively.[153]



$\mathbf{78a_{AuNP}}$: n = 1, R = H

$\mathbf{78b_{AuNP}}$: n = 6, R = H

$\mathbf{78c_{AuNP}}$: n = 6, R = $(Me)_5$

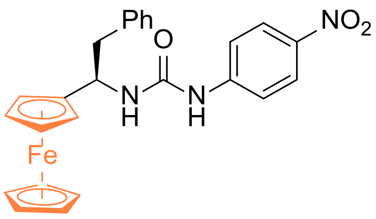
$\mathbf{78d_{AuNP}}$: n = 6, R = $(OAc)_1$

$\mathbf{79_{AuNP}}$

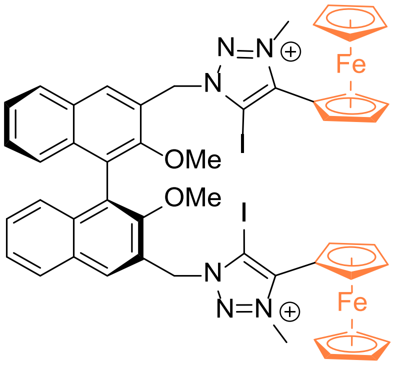
Figure 39. Schematic representation of gold nanoparticles modified with mixed SAMs of dodecanethiol and different amidoferrocenyl-containing thiols (for simplicity each ligand is only shown once, the actual ligand ratio is not 1:1).

2.3.8 Redox-active chiral receptors

Chiral anions, such as α-amino carboxylates, play a vital role in a number of physiological processes. Suitably designed comparably simple synthetic receptors and sensors can serve as powerful tools to both detect these species and to elucidate the fundamental processes that govern their chiral influence.[154] In the early 2000s the groups of Tucker and Moody attempted to prepare a Fc-based chiral anion sensor.[155] While this system was able to bind and respond to chiral carboxylates, no enantiodiscrimination was observed. The same groups later revisited and improved on their initial receptor design and investigated a range of similar chiral receptors based on Fc-urea derivatives.[156] Receptor **80** (Figure 40) was found to be able to electrochemically differentiate between the enantiomers of N-benzenesulfonyl proline, albeit with very small difference in response in ACN (cathodic shifts of -83 mV for the S enantiomer vs. -78 mV for R). A better voltammetric enantioselective response was achieved more recently utilising the (S)-BINOL-based XB receptor **81**.[157] This system displayed significantly different cathodic perturbation for the enantiomers of N-Boc-Alanine (-57 mV (S), -63 mV (R)), N-Boc-Leucine (-55 mV (S), -77 mV (R)) and BINOL-phosphate (-55 mV (S), -38 mV (R)) in ACN.



80



81

Figure 40. Fc-containing receptors for the enantioselective sensing of chiral anions.

2.4 Surface-confined voltammetric sensors

The immobilisation of redox-active (anion) receptors onto conducting (electrode) surfaces is of interest because it facilitates not only continuous anion sensing under flow, but also multiplexed sensing (very difficult to achieve in solution), and the facile integration into various device formats. Anion binding has also been shown to benefit from surface confinement through a combination of receptor preorganisation and cooperative effects.[158-159] Furthermore, these interfaces can usually be reused after a simple washing step, utilise a much lower receptor-to-target ratio and require a lower quantity of the receptor. Another advantage over solution-phase sensing is that surface-confined receptors do not need to be soluble in the sensing medium. This is particularly relevant when seeking to sense anions in pure water, which, under diffusive conditions, necessitates the introduction of hydrophilic solubilising groups or the use of highly charged receptors, both of which are often synthetically challenging or otherwise undesired, and is reflected in the low number of such sensors that have been prepared that operate in water (see above). However, synthetic efforts have to be invested to facilitate immobilisation of receptors onto electrode surfaces, often by incorporation of suitable anchor groups into the redox-tagged receptors. Additionally, the characterisation of the receptive interface or processes thereat (e.g. binding events) is considerably more difficult than solution-phase studies, where a variety of other techniques (NMR, UV/Vis, fluorescence) are available to obtain supplementary information. Another impediment to voltammetric studies at interfaces is the increased impact of any (redox) instability of immobilised redox groups given the small number of molecules that are being repeatedly probed in any experiment and which cannot be diffusively replenished. In contrast to solution-phase (i.e. diffusive) voltammetry the redox behaviour (and reversibility) cannot be described by the Randles-Sevcik equation, instead the peak currents of electroactive films are directly proportional to the scan rate. Furthermore, under ideal conditions, the peak separation $E_{pa} - E_{pc}$ should be 0 (at low scan rates) and the full width at half maximum height (FWHM) is 90 mV (for an exemplary CV of a redox-active films see Figure 43). For further information on electroactive films the interested reader is referred to an excellent review by Meade and coworkers.[160]

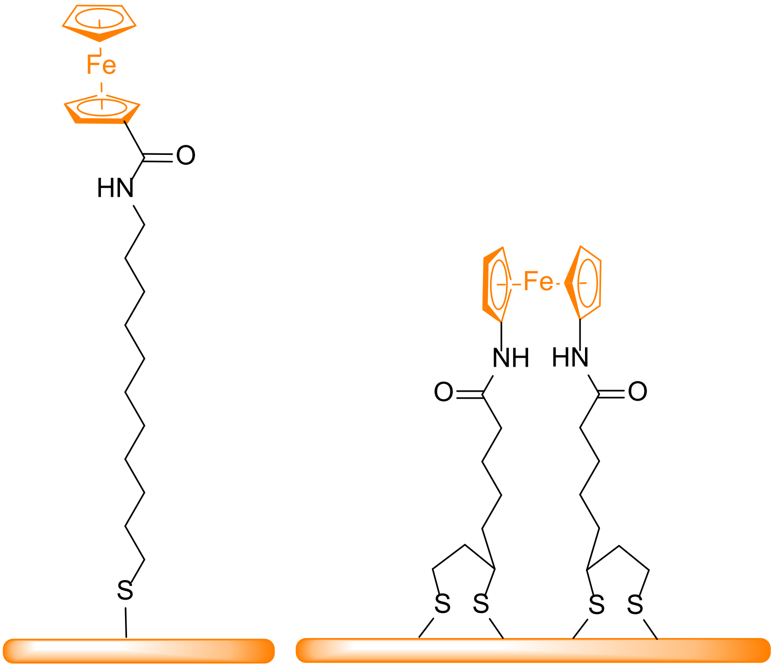
Despite some of these complications a variety of redox-active anion receptive films have been successfully utilised as potent voltammetric anion sensors. Most commonly the immobilisation of redox-active receptors is achieved by formation of self-assembled monolayers (SAMs) on gold electrodes through Au-S bonds (from thiols or disulfides), but other approaches have also been employed, as will be discussed in the following sections. As has been the case for solution-phase voltammetric sensors, the most commonly used transducer is Fc.

2.4.1 SAMs of redox-active anion receptors

The first example of a SAM-based redox-active anion sensor was reported by Astruc and coworkers in 1999, where a simple amide-containing Fc receptor was self-assembled on gold (**82_{SAM}**, Figure 41).[161] This system showed significant cathodic perturbation (-290 mV) in the presence of 1 mM $H_2PO_4^-$ in DCM. However, it was reported that these interfaces were voltammetrically unstable (loss of Fc redox signal after repetitive scanning) and that reversibility was further compromised in the presence of the target anion.

In another early example, sensing of Cl^-, Br^- and $H_2PO_4^-$ was achieved in 2:1 DCM/ACN at **83_{SAM}** containing a Fc transducer and amide anion binding sites.[162] Notably, the presence of 8-9 mM $H_2PO_4^-$ induced large cathodic shifts of -300 mV, with smaller, but significant, perturbations being observed for Cl^- and Br^- (-100 and -30 mV, respectively). Importantly, these responses were significantly larger in magnitude than those observed under diffusive conditions (i.e. in solution), which is commonly observed in these interfacial sensors and, in analogy to the previously discussed dendrimeric sensors, can often be attributed to cooperative or topological effects that arise from the high density of adsorbed receptor molecules.

While this and the following examples mainly rely on N-H H-bond donors, the voltammetric sensing of $H_2PO_4^-$ and ATP^{2-} in ACN has also been reported at SAMs of simple (Fc-methyl)trialkylammonium cations, only relying on electrostatic interactions.[163]

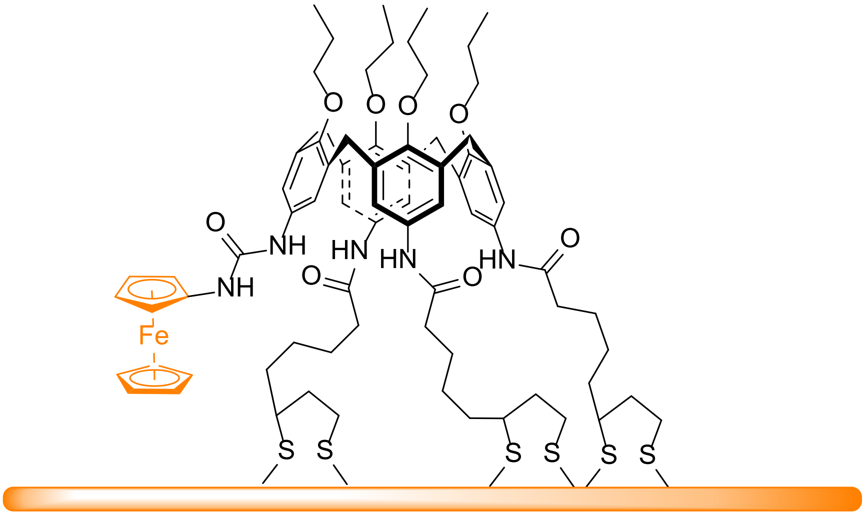


$\mathbf{82}_{\mathbf{SAM}}$ $\mathbf{83}_{\mathbf{SAM}}$

Figure 41. Early redox-active anion receptive interfaces.

A more advanced receptor design, $\mathbf{84}_{\mathbf{SAM}}$, based on urea- and amide-modified calix[4]arene was later developed for anion sensing in more competitive solvent systems (Figure 42).[164] This interface was highly responsive to $H_2PO_4^-$ (-250 mV), BzO^- (-180 mV) and Cl^- (-120 mV) in

DCM/ACN 1:1 (Figure 43); once again, this response was enhanced in comparison to diffusive sensing under comparable conditions. Interestingly, this interface was also responsive to 5 mM ReO_4^- in pure water with moderate cathodic perturbations of -20-30 mV while no such perturbations were observed for other anions. $H_2PO_4^-$ sensing was also reported at SAMs of a tetraferrocenyl-modified cyclic peptide with a cathodic response ("two-wave" behaviour) of -200 mV in ACN.[165]



84_{SAM}

Figure 42. Interfacial calix[4]arene-based voltammetric anion sensor**.**

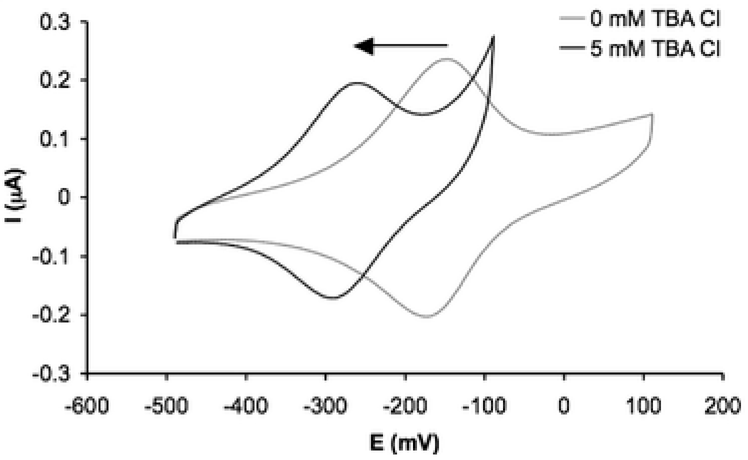
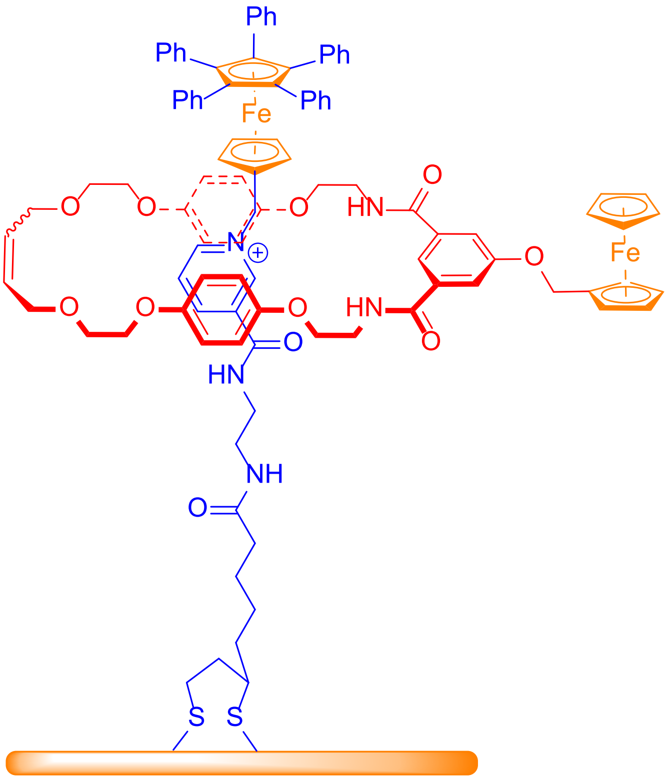


Figure 43. CVs of **84_{SAM}** on gold electrode in the presence of 0 and 5 mM TBACl. Solvent: 1:1 ACN/DCM containing 100 mM $TBABF_4$. Reproduced with permission from ref.[164] Copyright 2010 The Royal Society of Chemistry.

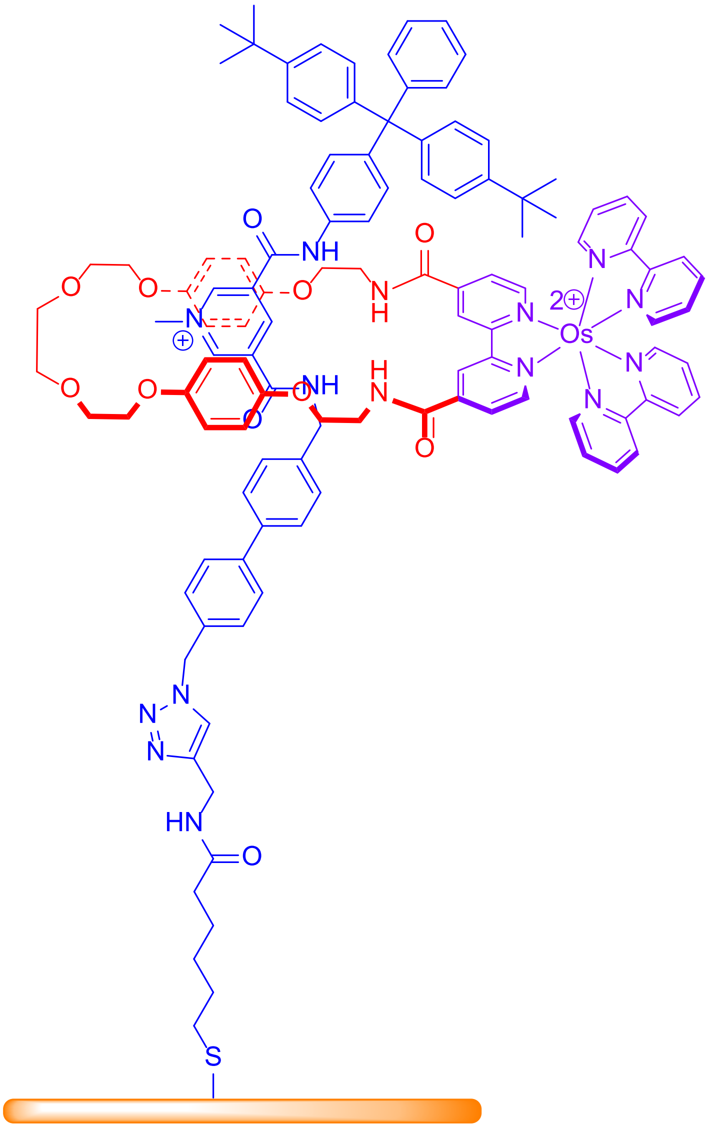
Analogous to voltammetric sensors in solution, the use of mechanically interlocked receptors on surfaces has received some attention. The first example, **85_{SAM}**, reported in 2007, utilised a surface-confined rotaxane for the selective voltammetric sensing of chloride in ACN (Figure 44).[166] This structure was assembled *via* exposure of gold to a redox-active pseudo-rotaxane containing Fc in both the axle (as a stopper) as well as the macrocycle. Importantly, only minor cathodic perturbations (< -10 mV) were observed for a variety of anions to SAMs of the axle alone or for the axle in solution. Diffusive studies of the macrocycle revealed a response to $H_2PO_4^-$ (≈-45 mV) and HSO_4^- (≈-15 mV) but small perturbations for OAc^- and Cl^- (< -10 mV). Only in the surface-confined rotaxane does the macrocycle-Fc show a significant response to Cl^- (≈-40 mV, with good sensitivity (LOD of 0.2 μM)) while being unresponsive to the other oxoanions, clearly highlighting the important role of the interlocked anion binding cavity for the selective response of chloride over larger anions such as dihydrogenphosphate.



85_{SAM}

Figure 44. Redox-active SAM based on interlocked rotaxane containing two Fc transducers.

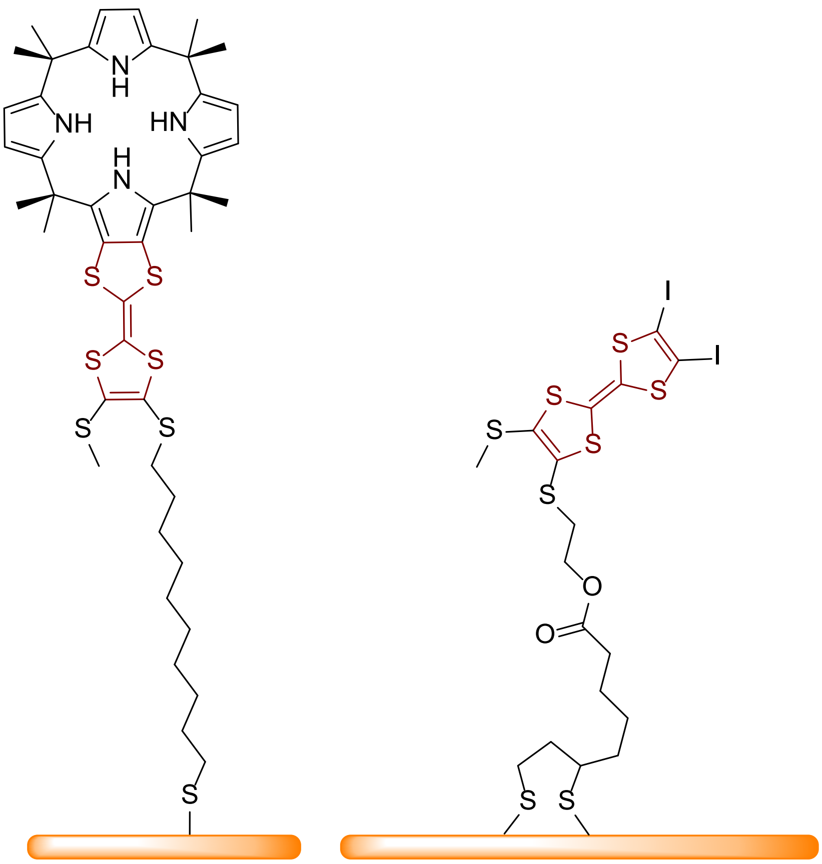
A redox-active surface-confined rotaxane sensor based on the $Os^{2+/3+}$ bipyridyl redox couple has also been reported (**86_{SAM}**, Figure 45).[72] In contrast to the previous examples, immobilisation of the interlocked receptor was achieved *via* click reaction of an alkyne-terminated SAM with an azide-functionalised pseudo-rotaxane. The osmium-couple was then exploited as a transducer for chloride binding in ACN with modest perturbations (-14 mV at 50 µM Cl^-), but good selectivity over OAc^-.



86_{SAM}

Figure 45. Os(bpy)₃-based redox-active rotaxane SAM.

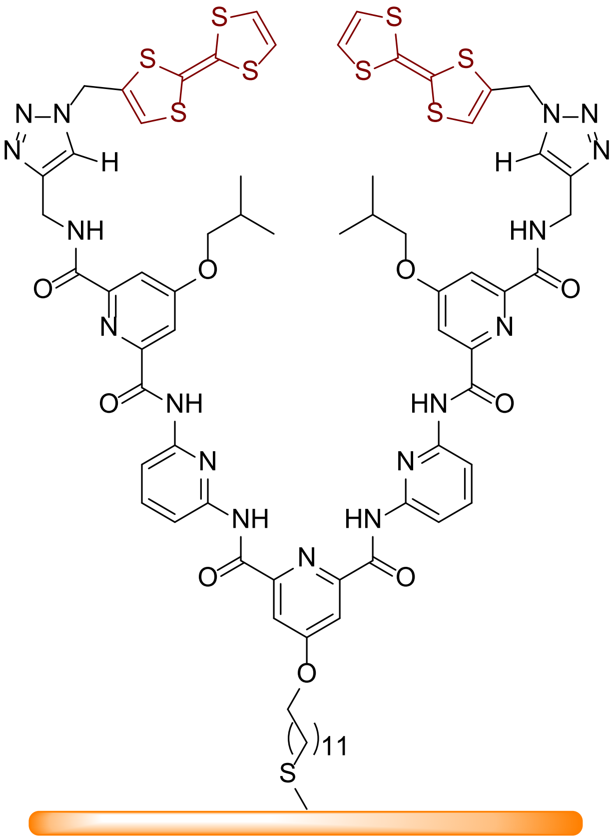
Another redox transducer used in surface-confined anion receptors is tetrathiafulvalene (TTF). In an early example, a TTF-modified calix[4]pyrrole SAM **87_{SAM}** (Figure 46) was utilised as a chloride sensor.[167] In contrast to previous examples, the voltammetric response in DCM was reported to be substantially greater under diffusive conditions (-170 mV) than in **87_{SAM}** (≈-30 mV). This was rationalised by reference to potential conformational restrictions in the SAM where the cone-conformation (in which stronger binding/response is observed in solution) is disfavoured over the 1,3-alternate conformation. It should however be noted that these TTF systems are often not fully reversible and are particularly prone to rapid voltammetric degradation, in particular in the presence of coordinating anions. This problem was also observed in a recent study in which iodo-TTF derivatives were immobilised on gold to form **88$_{\text{SAM}}$**.[168] This XB anion receptive interface was capable of sensing Cl^- and Br^- via perturbations of the first TTF oxidation wave in ACN. Cathodic shifts of around -150 mV were observed for both anions, where a second redox couple emerged at lower potentials. Importantly, this work is a rare example of an in-depth investigation of anion binding constants at redox-active SAMs. From various electrochemical simulations and data fitting, K_{Ox} and K_{Red} of chloride to **88$_{\text{SAM}}$** were estimated to be around and 570000 M^{-1} and 1000 M^{-1}, respectively, much larger than binding constants obtained under similar conditions in solution indicating, as has been the norm, an enhanced interfacial binding.



87_{SAM} **88_{SAM}**

Figure 46. Redox-active anion sensory interfaces based on tetrathiafulvalene.

Another recent study reports the use of a TTF-appended foldamer **89_{SAM}** for the voltammetric sensing of Cl^- and HSO_4^- in DCM (Figure 47).[169] In this solvent system two well-defined TTF redox couples were observed, in good agreement with previous works and supportive of simultaneous, independent oxidation of both TTF-appendages. Addition of 600 µM Cl^- or HSO_4^- led to cathodic shifts of the first couple by ≈-30 mV and ≈-90 mV, respectively (in the presence of 100 mM $TBAPF_6$ electrolyte). The authors further studied the influence of the electrolyte concentration (10, 100 and 500 mM) on the redox properties of the system showing that the half-wave potential was strongly affected by $TBAPF_6$ concentration with the lowest $E_{1/2}$ observed at 500 mM $TBAPF_6$. It was further shown that the magnitude of response to the tested anions was significantly larger at lower concentration of supporting electrolyte. These observations are in good agreement with earlier studies[14] and the general concepts outlined in Section 2.1. Despite the rather advanced receptor design utilised in this study the authors unfortunately did not comment on the use of this platform in more competitive solvent systems.

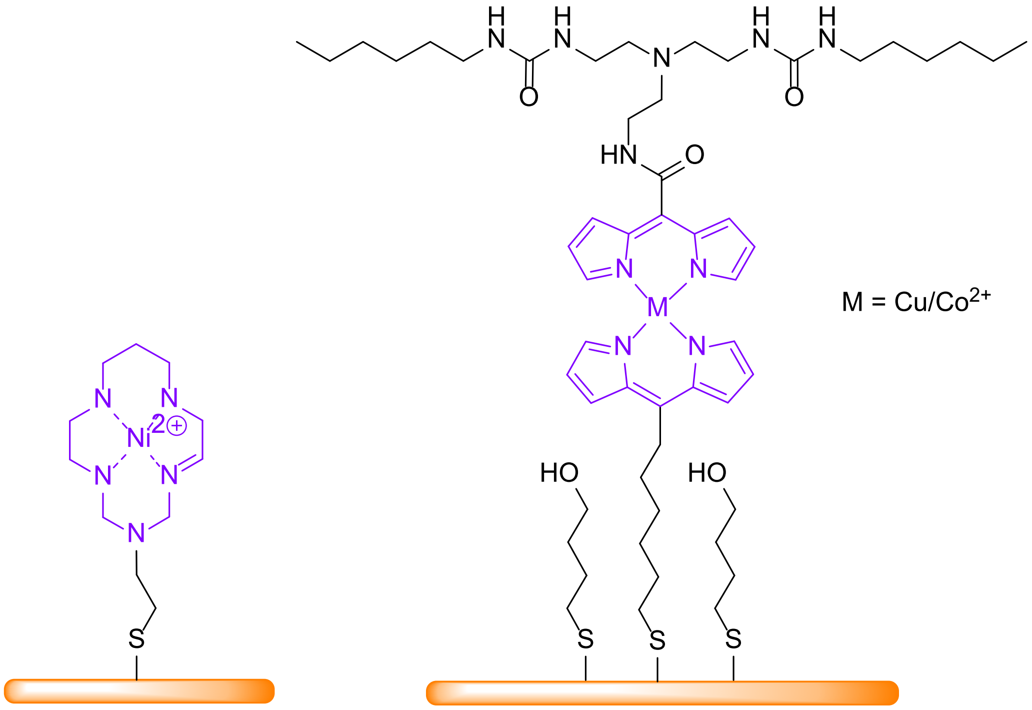


89_{SAM}

Figure 47. TTF-foldamer SAM on gold.

Based on the promising solution-phase electrochemical properties of a simple nickel-azamacrocycle complex[170] Ohsaka and coworkers developed an analogous interfacial sensor (**90_{SAM}**, Figure 48).[171] Exploiting the highly charged $Ni^{2+/3+}$ redox couple as a transducer and anion binding (ligation) site this interface was capable of responding to a variety of anions in pure water. Especially the oxoanions SO_4^{2-} (-110 mV), $H_2PO_4^-$ (-88 mV), AMP^- (-90 mV), ADP^-

(-180 mV) and ATP^{2-} (-240 mV) induced large perturbations at a concentration of 1 mM while chloride induced much smaller cathodic shifts (-20 mV). Further investigations also revealed, as expected, a different binding stoichiometry for sulfate (1:1) and dihydrogenphosphate (2:1). Relying only on electrostatic/dative interactions these simple systems are, similarly to analogous solution-phase sensors (Section 2.3.5), often not very selective. Another metal-containing interface, incorporating redox active dipyrromethene receptors containing copper(II) or cobalt(II), was recently reported for the voltammetric sensing of Cl^-, Br^- and SO_4^{2-} in water.[172] This interface was assembled in a step-wise fashion, where a mixed SAM of 4-mercaptobutanol and a dipyrromethene-thiol was initially formed on gold. Subsequent metallation with Co(II) or Cu(II) was then followed by complexation with an additional receptor-containing dipyrromethene ligand to afford **91.Cu/Co$_{SAM}$**. The sensor, containing urea, amide and amine groups was demonstrated to respond to the three target anions in pure water at pH 4.0. Specifically, a clear shift in the oxidation potential of up to -57 mV, -17 mV and -40 mV as well as -150 mV, -47 mV and -61 mV for Cl^-, Br^- and SO_4^{2-} at **91.Cu$_{SAM}$** and **91.Co$_{SAM}$**, respectively, was observed. The enhanced response at **91.Co$_{SAM}$** most likely arises from a strong binding switch on (Co^{2+} to Co^{3+}) while binding at **91.Cu$_{SAM}$** was observed to be decreased (Cu^{2+} to Cu^+). The step-wise assembly of this interface facilitates the use of different dipyrromethene-tagged receptors without the need to isolate the final thiolated receptor, enabling facile construction of different interfaces containing different metals and/or receptors. This has recently been exploited to immobilise a novel dipyrromethene-tagged anion-receptive, cyclic peptide for the voltammetric sensing of sulfate in water.[173] However, it should be noted that the assembly on the surface will often not fully convert all (metallated) ligands to the final receptor complex, resulting in interfaces that are not homogeneous and that contain different redox active species which can result in non-ideal voltammetric behavior, as observed in both studies.[172-173]



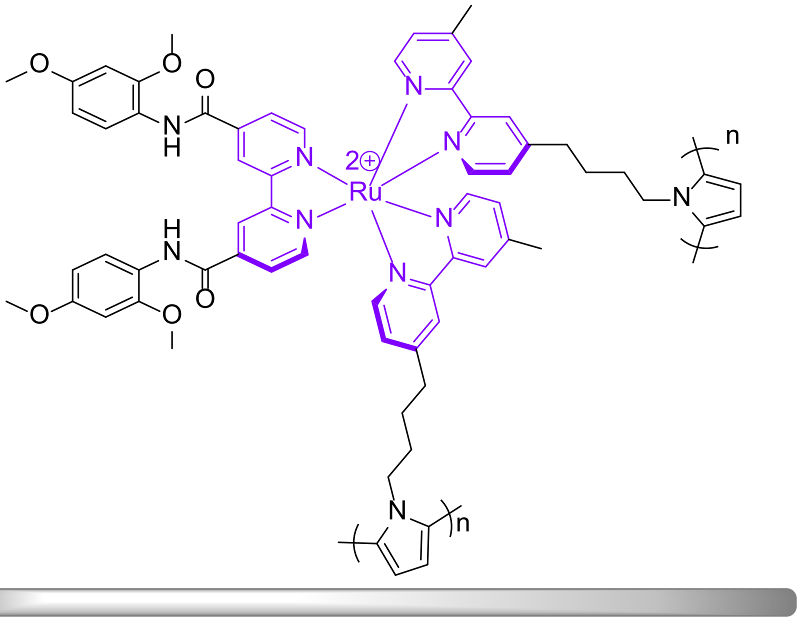
$\mathbf{90}_{\mathbf{SAM}}$ $\mathbf{91.Cu/Co}_{\mathbf{SAM}}$

Figure 48. Metal-containing receptors for voltammetric anion sensing in water.

2.4.2 Polymeric anion receptive interfaces

Another commonly employed strategy to modify (conducting) interfaces, so as to be specifically responsive, is (electro)polymerization. The incorporation of electropolymerisable groups, such as pyrrole- or thiophene-derivatives allows facile generation of polymeric films on any electrode surface and is thus more versatile than self-assembly on gold. Additionally, film thickness can often be controlled easily by adjusting the polymerisation conditions (e.g. potential window or number of scans). While such films are structurally less well-defined than SAMs, their potentially higher conformational flexibility might be advantageous when sensing larger analytes which might be sterically excluded from densely packed SAMs. They also offer the potential for a greater baseline signal.

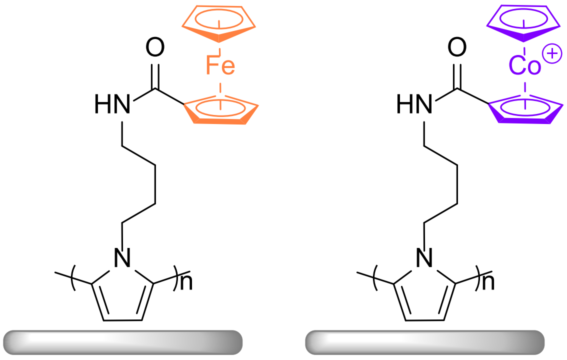
To the best of our knowledge the first example of such an interface, and the first example of any redox-active anion responsive interface, was reported by Moutet and coworkers in 1996.[174] They used a redox-active Ru(bpy)$_3$-based receptor containing two different ligands, one with a bis-amide binding site as well as a pyrrole-modified ligand which was utilised to electropolymerize the receptor onto a Pt electrode (**92$_{\text{film}}$**, Figure 49). This film displayed a reversible Ru$^{2+/3+}$ redox couple at high potential in ACN and three reductive couples at lower potential, ascribable to ligand centred reductions. The most positive of these three couples, corresponding to the **92$_{\text{film}}$$^{2+/+\bullet}$** couple, displayed moderate cathodic perturbations of up to -40 mV in the presence of Cl$^-$, while Br$^-$ and I$^-$ did not induce any measurable response. The voltammetric behaviour in the presence of F$^-$ was more complex with disappearance of this couple, possibly due to receptor deprotonation.



92$_{\text{film}}$

Figure 49. Polymeric anion sensing film on Pt based on Ru(bpy)$_3$-pyrrole receptor.

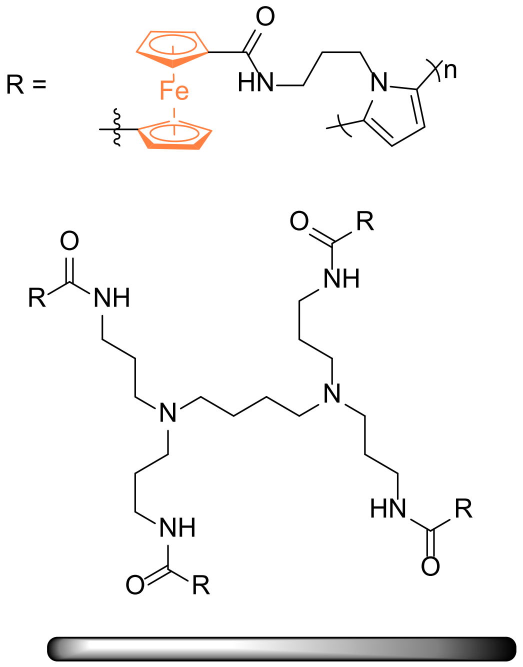
The same group also formed films of the a much simpler Fc-amide-pyrrole receptor on Pt electrodes (**93**$_{\text{film}}$, Figure 50).[175] This interface was responsive to 1 mM of $H_2PO_4^-$ or ATP^{2-} with shifts of -220 mV and -180 mV in ACN and -260 mV and -240 mV in DCM, respectively. The response to HSO_4^- was much smaller (-30 mV and -60 mV in ACN and DCM) while NO_3^- failed to induce any response. In alignment with subsequent observations at redox-active SAMs these responses were significantly larger than the shifts observed under diffusive conditions (using the same receptor). At the same time del Peso *et al.* investigated the sensory properties of the same receptive interface with a cobaltocenium transducer (instead of Fc).[176] Under similar conditions (in ACN), **94**$_{\text{film}}$ displayed similar cathodic perturbations as its Fc-analogue: -210 mV in the presence of 0.1 mM $H_2PO_4^-$. Interestingly, and in contrast to **93**$_{\text{film}}$, **94**$_{\text{film}}$ did exhibit a large response to HSO_4^- (-250 mV), though this was difficult to rationalise chemically. Moutet and coworkers not only studied the sensory behaviour of simple Fc-alkylammonium SAMs[163], as described in Section 2.4.1, but also of analogous Fc-alkylammonium containing pyrrole-based polymeric films, showing good responses to $H_2PO_4^-$, ATP^{2-}, HSO_4^- and F^- in ACN.[177-178]



93$_{\text{film}}$ **94**$_{\text{film}}$

Figure 50. Polymeric anion responsive films on Pt based on metallocene-pyrrole receptors.

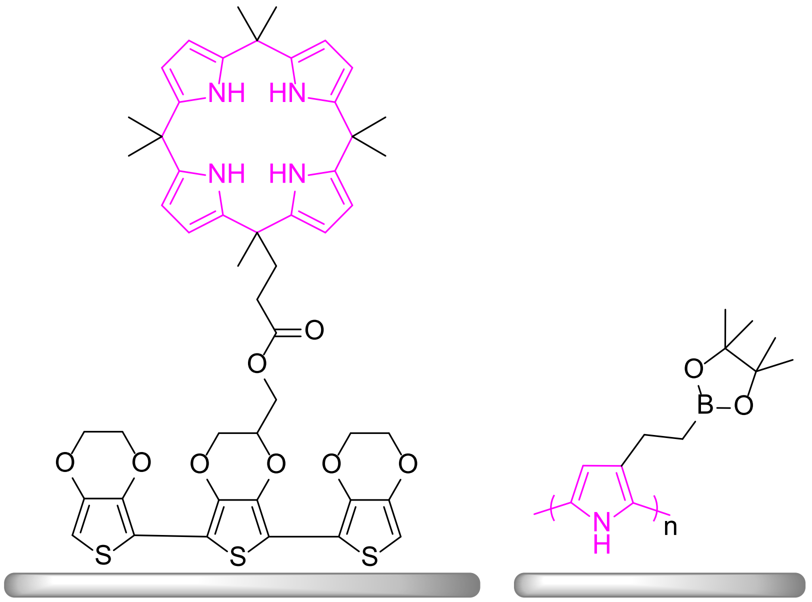
Martínez *et al.* achieved sensing of $H_2PO_4^-$ in pure water utilizing a Fc-amide-pyrrole dendrimer interface, **95_{film}** (Figure 51).[179] The authors reported that these films were voltammetrically unstable in ACN (with any electrolyte) and in aqueous $LiClO_4$. Interestingly a stable and reproducible voltammetric behaviour was only observed when using $Li[B(C_6F_5)_4]$ as electrolyte in pure water. Addition of μM concentrations of $H_2PO_4^-$ induced significant cathodic perturbations of the Fc/Fc^+ couple of up to -110 mV. Unfortunately the authors did not systemically investigate anion selectivity, but did show that the dendrimeric structure of the receptor was integral to the sensing performance of the films in that a similar non-dendrimeric Fc-bis(amide-pyrrole) film did not respond to phosphate in the same aqueous medium.



95_{film}

Figure 51. Polymeric anion responsive films on GC based on Fc-pyrrole dendrimer.

An electropolymerizable porphyrin-receptor was reported by Swager and coworkers using a doubly strapped free-base porphyrin film to sense F^-.[180] Bithiophene groups in the straps facilitated electropolymerisation while anion binding was achieved by the porphyrin core and additional amide binding sites. These films displayed two reversible redox couples in DCM, where the more anodic couple was identified as the P/P$^{+\bullet}$ couple while the other couple was ascribed to the conjugated polymer back-bone. As expected, addition of 0.3 mM F$^-$ induced significant perturbations only for the former, receptive couple with cathodic shifts of -69 mV. More recently Sessler and coworkers reported the sensing properties of calix[4]pyrrole (CP)-based anion receptive films **96$_{\mathbf{film}}$**.[181] Conjugation of the receptor to ethylenedioxythiophene (EDOT) enabled the facile electrochemical polymerisation on a wide variety of substrates (Pt or ITO). In order to enhance the conductivity of the polymer film the receptor was copolymerised with (unmodified) EDOT (Figure 52). The resulting copolymer was used for sensitive voltammetric sensing of F$^-$ in water; a new redox couple at more negative potential (at ≈ -1 V) appeared at the expense of the original wave associated with the CP. Importantly, control experiments with pure pEDOT revealed minimal perturbations in the presence of F$^-$, confirming the role of the CP as a receptor in this sensitive sensor (LOD of 11 μM).



96$_{\text{film}}$ **97**$_{\text{film}}$

Figure 52. Anion receptive polymer film generated by electropolymerisation of a 1:1 mixture of EDOT and EDOT-Calix[4]pyrrole on ITO and polypyrrole-boronic acid based sensor.

In analogy to solution-phase studies, boronic acid motifs have been incorporated into polymeric architectures. An early example included the anodic polymerisation of a vinyl-derivative of the triphenylamine-boronic acid receptor **53** (Section 2.3.4) which reportedly responded to F^- by a gradual loss in redox activity.[114] A more reversible sensor was developed based on a pyrrole-boronic acid conjugate which was polymerised onto Pt to produce **97**$_{\text{film}}$.[182] In contrast to previous examples this study exploited the inherent redox-activity of the polypyrrole film as the transducer, omitting the need for an additional redox group. Addition of 2 mM F^- to **97**$_{\text{film}}$ in 1:1 ACN/H_2O induced a selective cathodic perturbation of -260 mV (over Cl^- and Br^-).

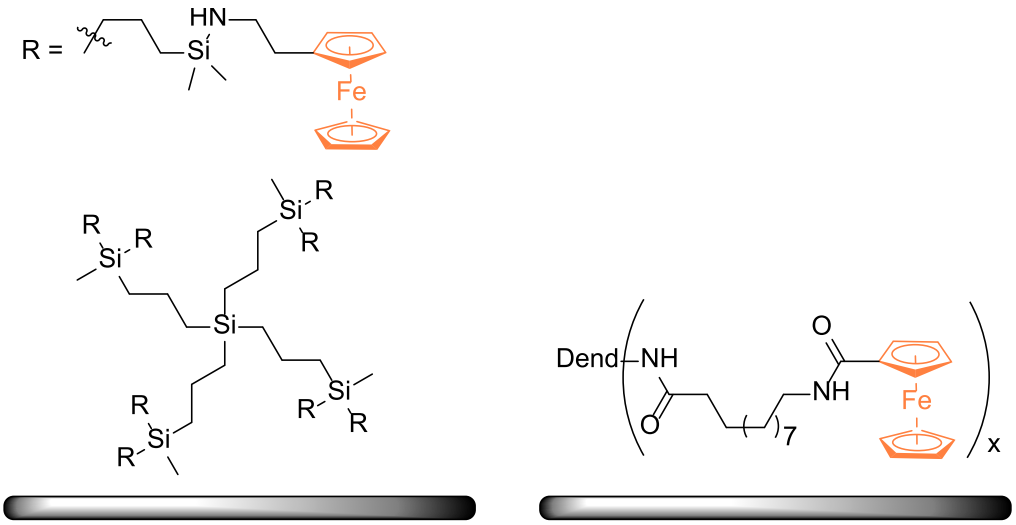
In a more recent study a completely different methodology was utilised to sense F^- at polymeric films. To this end 3-aminophenylboronic acid was oxidatively polymerised onto the electrode.[183] While polyanilines are inherently redox active, F^- sensing was carried out in pure water (pH 3.0) in the presence of $[Fe(CN)_6]^{3-}$ as a solution-phase redox probe. Upon F^- binding to the interface, electrostatic repulsion between the generated boronate and the negatively charged transducer led to reduced Faradaic currents of the latter, as measured by SWV. A current suppression of up to 35% in the presence of 1 mM F^- was observed at this interface which responded to F^- over a wide linear concentration range and a very low LOD of 90 pM. As expected, a large variety of other anions did not significantly interfere with this detection. An analogous voltammetric sensor based on SAMs of 4-mercaptophenylboronic acid has also been reported[184] while phosphate[185-186] and sulfate[187] sensing based on this principle has also been reported.

2.4.3 Physisorbed and drop-casted anion receptive interfaces

As highlighted in Section 2.3.7 redox-active dendrimers (and also nanoparticles) have an observed tendency to physisorb onto electrodes, in particular the larger, higher generation, dendrimers. This can be exploited to conveniently form redox-active responsive films. Most commonly the dendrimers are immobilised onto glassy carbon (GC) or Pt electrodes by either simple exposure of the electrode to the dendrimer solution or by additional application of a potential (either cycling or controlled potential electrolysis) where, depending on the solvent, the charged receptor often physisorbs more strongly (usually reflected in asymmetric diffusive CVs resulting in the cathodic backward scan resembling a stripping peak; see Section 2.3.7).[188]

In pioneering work Casado *et al.* electrodeposited a dendrimer onto GC electrodes to form **98$_{\mathbf{film}}$** (Figure 53).[189] This sensor was subsequently used for sensing of $H_2PO_4^-$ in DCM, with a response of up to -170 mV (at 0.5 mM). This cathodic shift magnitude is, unlike many of the previously described SAM-based sensors, somewhat smaller than that observed under diffusive conditions, indicating that the “enhanced response” of SAM based sensors largely arises from cooperative and topological effects, which in the case of the dendrimers, are (at least in part) already present under diffusive conditions. **98_{film}** was also, more weakly, responsive to HSO_4^- (-85 mV), Cl^- (-30 mV) and Br^- (-10 mV; all at 500 µM). As highlighted previously, the tendency of dendrimers to adsorb onto the electrode is usually dependent on their size, with larger dendrimers interacting more strongly. To this end, Astruc and coworkers investigated the electrode modification by giant alkylferrocenyl dendrimers.[190-191] Even without any specific anion binding site the large sixth and seventh generation dendrimers with 6561 and 19683 Fc-termini respectively, displayed a significant cathodic response to both $H_2PO_4^-$ and ATP^{2-} in DCM, again highlighting the importance of electrostatic interactions and the care that must be taken in assuming anion interactions are confined to integrated receptive sites.[191]

Alonso, Casado, Losada and coworkers reported interfacial sensors based on smaller amidoferrocenyl dendrimers **99-*4,8,16,32*$_{film}$**.[188] The authors not only reported a positive dendrimeric effect but also noted that the peak currents were significantly supressed upon anion binding, indicating electrochemical irreversibility and/or strong ion-pairing (ultimately this signal suppression was used as the reporting function). More importantly however, it was shown that **99-*4*$_{film}$** can be employed to sense low mM $H_2PO_4^-$ and ATP^{2-} in pure water, highlighting the benefit of using dendrimer films as sensors, circumventing solubility issues which have arguably been the major drawback of these systems in solution.



98$_{\text{film}}$ **99**$_{\text{film}}$

Figure 53. Schematic representation of dendrimer films on GC.

An alternative approach to immobilize dendrimers was achieved in a step-wise manner by first immobilising an azide-terminated dendrimer onto an alkyne-modified GC electrode *via* click chemistry (Figure 54).[192] Due to the dendrimer topology, and the large number of azide termini, further modifcation with ethynylferrocene resulted in a covalently immobilised, redox-active dendrimer. Scanning electrochemical microscopy, in which a current at a probing tip is measured as a function of distance to the substrate, was then used to show that $H_2PO_4^-$ binds to this interface in DMF in a manner that facilitated Fc oxidation and thus electron transfer across the interface.

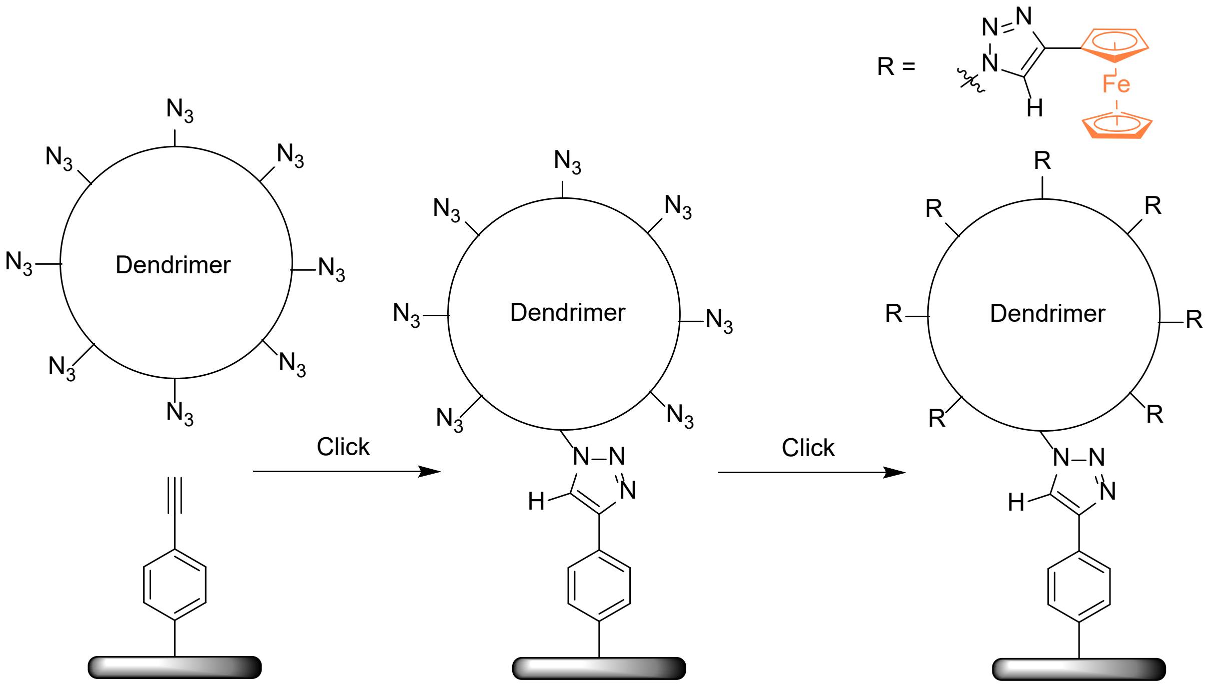


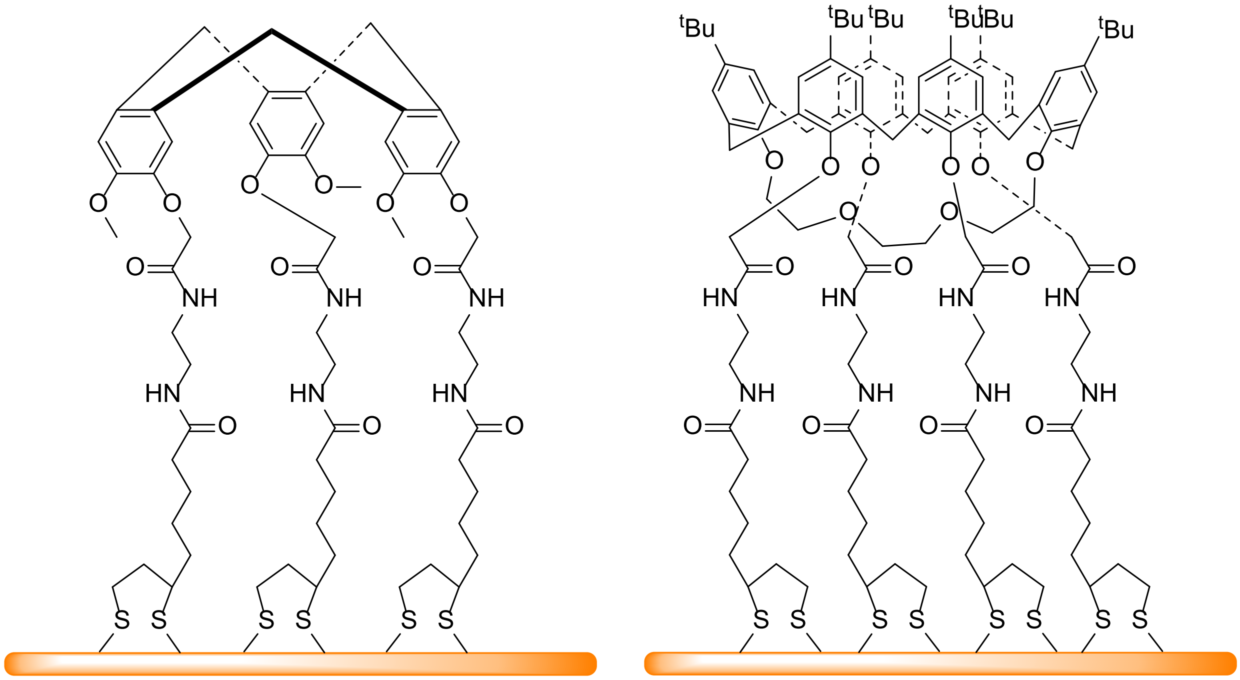
Figure 54. Schematic representation of step-wise modification of a GC electrode with Fc-triazole terminated dendrimer by multiple click reactions.

3. Impedimetric and Capacitive Anion Sensing in Molecular Films

3.1 Faradaic Impedimetric Anion Sensing

Of all electroanalytical techniques electrochemical impedance spectroscopy (EIS) stands out as one which is particularly sensitive to interfacial events. The application of a small amplitude AC perturbation at a fixed bias potential allows facile extraction of a range of interfacial parameters (e.g. resistance and capacitance) with minimal perturbations of the interface. EIS is commonly exploited for sensing of large biomolecules whereby the charge transfer resistance (R_{ct}) of a receptor (e.g. antibody) modified electrode in the presence of a redox probe (most commonly $Fe(CN)_6^{3-/4-}$) is utilised as transducer for analyte binding.[193] This concept has been expanded to the sensing of small molecules and ions also. In particular impedimetric cation sensing at crown ether modified electrodes has received some attention[194-197], though impedimetric anion sensing remains rare. In this section we highlight advances in impedimetric anion sensing in the presence of a redox probe and discuss benefits and limitations. All of the following examples were conducted in pure aqueous media.

Early work in this field was conducted by Echegoyen *et al.* who exploited SAMs of cyclotriveratrylene (CTV)[198] and calixarene-based[199] anion receptors on gold electrodes (**98$_{\mathbf{SAM}}$** and **99$_{\mathbf{SAM}}$**, Figure 55). Sensing of various anions such as phosphate, acetate, fluoride and others was achieved in the presence of either $Ru(NH_3)_6^{2+/3+}$ or $Fe(CN)_6^{3-/4-}$; a decrease or increase in R_{ct}, respectively, was observed upon anion binding (Figure 56). These altered charge-transfer characteristics can be attributed to electrostatic interactions between the surface-captured anion of interest and the solution-phase redox probe, whereby electrostatic attraction facilitates electron transfer, i.e. leads to a lower R_{ct}, and, conversely, repulsion results in an increased R_{ct}.



100$_{\mathbf{SAM}}$ **101**$_{\mathbf{SAM}}$

Figure 55. SAMs of CTV and Calix[6]arene-based anion receptors on gold for impedimetric anion sensing.

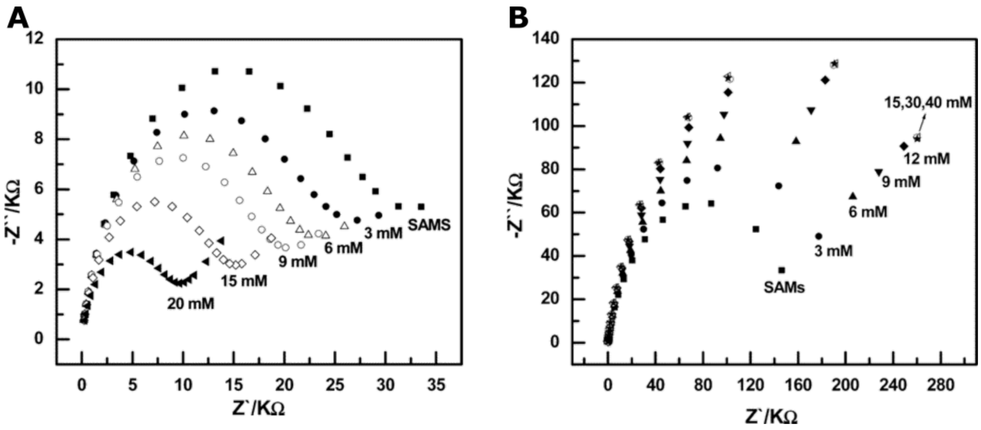
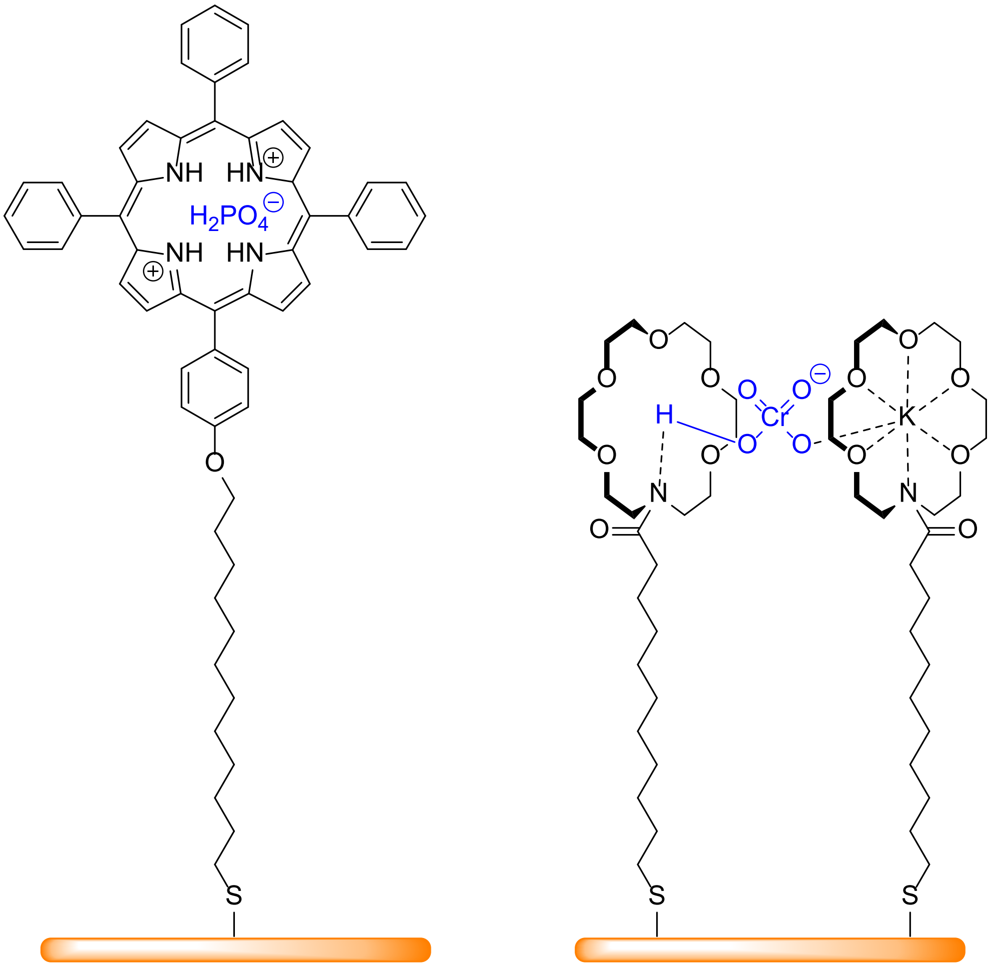


Figure 56. Impedimetric Nyquist plots of **100**$_{\mathbf{SAM}}$ in the presence of increasing [OAc$^-$] utilising $Ru(NH_3)_6^{2+/3+}$ **(A)** or $Fe(CN)_6^{3-/4-}$ **(B)** as redox probes. In both plots the change of the impedance (charge-transfer resistance) can be seen, which arises from electrostatic attraction and repulsion between the bound anion and the redox-probe, respectively. Reprinted with permission from ref.[198] Copyright 2005 American Chemical Society.

The impedimetric sensing of $H_2PO_4^-$ was also achieved at SAMs of free-base porphyrin (**102$_{SAM}$**, Figure 57) with good selectivity over other anions such as NO_2^-, Br^-, NO_3^- and Cl^-.[200] Interestingly, the R_{ct} of this interface decreased upon addition of $H_2PO_4^-$ (in the presence of $Fe(CN)_6^{3-/4-}$). This was rationalised by double-protonation of the porphyrin-core in the presence of the anion, resulting in an overall positively charged SAM with an enhanced electron transfer by virtue of the electrostatic attraction of the solution redox probe. Similarly, the highly toxic $HCrO_4^-$ was detected at azacrown ether modified interfaces **103$_{SAM}$** where the chromate is supposedly sandwiched between azacrown ethers complexed with K^+/H^+.[201] Sensing of the analyte in the presence of $Fe(CN)_6^{3-/4-}$ at pH 5.0 in aqueous KCl was achieved with an exceptionally low limit of detection (LOD) of 78 pM.

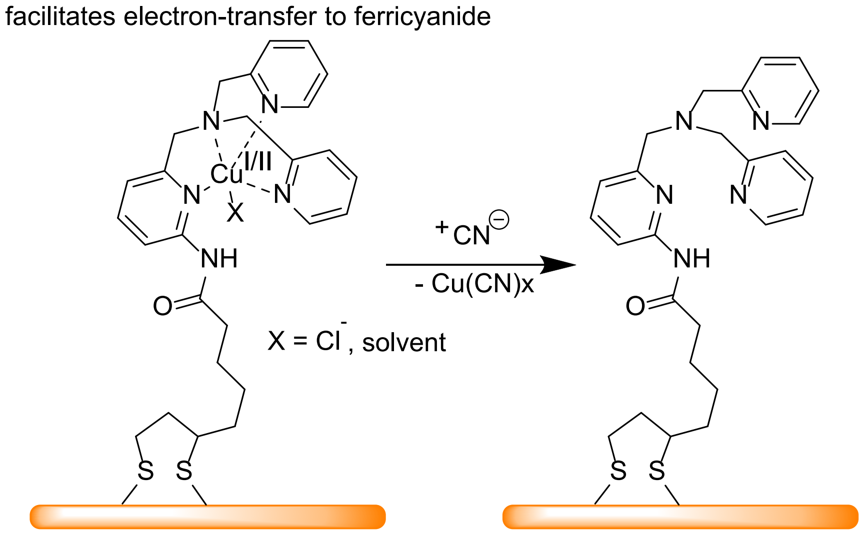


$\mathbf{102}_{\mathbf{SAM}}$ $\mathbf{103}_{\mathbf{SAM}}$

Figure 57. Schematic representation SAMs of phorphyrin and azacrown ether-based anion receptors on gold for impedimetric sensing of phosphate and chromate including proposed binding modes.

While these examples, and a majority of electrochemical sensors in general, are prepared by self-assembly on gold electrodes, impedimetric anion sensing has also been carried out at other interfaces. In a recent report two polyaza-acridine receptors were immobilized on screen printed carbon electrodes by voltammetric deposition (potential cycling) enabling impedimetric sensing of SeO_3^{2-} in the presence of $Fe(CN)_6^{3-/4-}$.[202]

A few reports exist of impedimetric anion sensing that do not rely on specific, supramolecular anion-receptor interactions. For example, a cyanide selective impedimetric sensor was constructed based on a SAM of a copper-tris(pyridyl)amine complex (Figure 58).[203] In the presence of CN^- the chelated copper cation was abstracted from **104_{SAM}** as a $Cu(CN)_x^{(n-1)-}$ complex leaving behind the free ligand-modified interface which, due to the lack of the positive charge, possesses a higher R_{ct} to ferricyanide (reduced electrostatic attraction of the redox probe). Due to this selective, strong abstraction of the metal, a low LOD of 1 nM for CN^- was attainable with excellent selectivity over OAc^-, $H_2PO_4^-$, F^- and NO_3^-. Another metal-based sensor was developed for the impedimetric detection of phosphate at Zr^{4+}-terminated SAMs.[204] To this end a carboxy-terminated SAM of mercaptopropionic acid was first assembled on gold onto which Zr^{4+} was adsorbed. This interface was then shown to sensitively respond to sub-micromolar levels of phosphate at pH 3.0. Good selectivity then allowed phosphate detection in pre-purified serum samples.



104_{SAM}

Figure 58. Schematic representation of Cu-tris(pyridyl)amine-based SAM for impedimetric detection of CN^- by abstraction of Cu.

An interesting indirect approach for the impedimetric sensing of ascorbate has been developed based on the copper(I) catalysed azide-alkyne cycloaddition (CuAAC; Figure 59).[205] An azide-terminated SAM was exposed to a Fc-containing alkyne in the presence of Cu(II). In the presence of ascorbate the Cu(II) was reduced to the catalytically active Cu(I) species thus inducing the interfacial "click" reaction. The enhanced steric bulk on the modified interface was then utilised as an efficient, indirect, impedimetric transducer for the presence of ascorbate with a LOD of 2.6 pM. The use of a redox-tagged alkyne also provided an additional voltammetric means to monitor the reaction progress, however, it should be noted that this approach is somewhat limited by the difficulty of regenerating the original sensory interface.

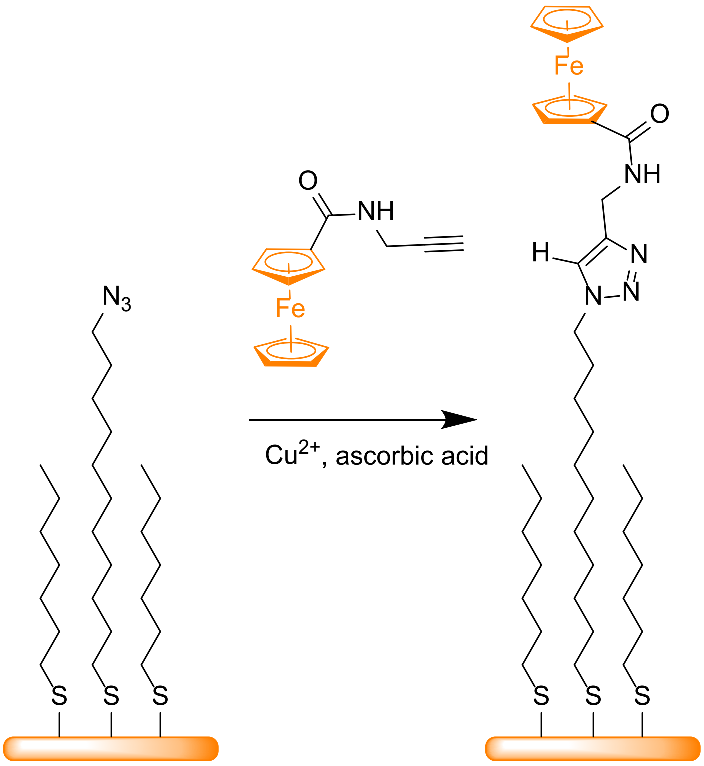


Figure 59. Initial azide-terminated SAM and the SAM after CuAAC click reaction *via in situ* generated Cu(I) from Cu(II) and ascorbate. Ascorbate can thus be indirectly sensed at the latter, more sterically blocking, interface by EIS.

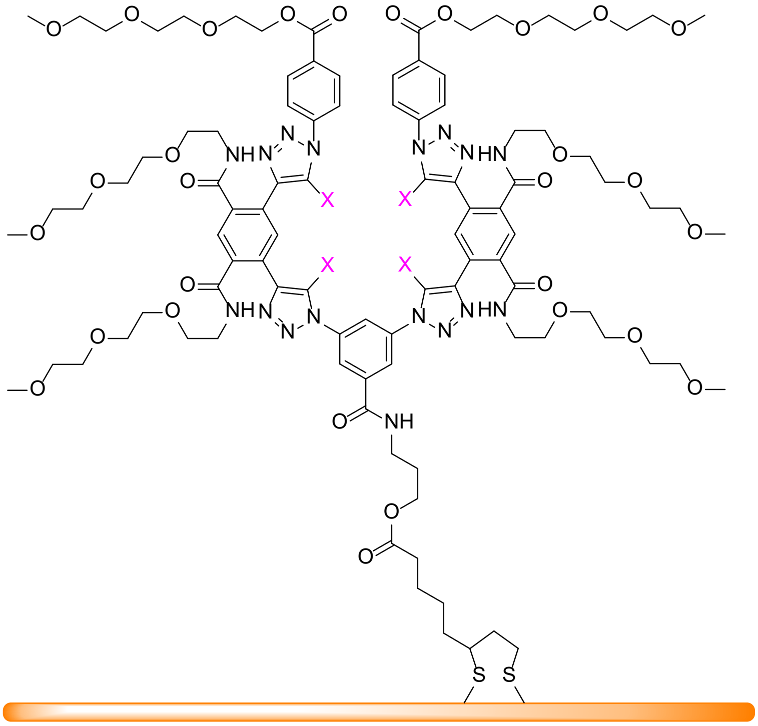
Although impedimetric sensing of cations using bioreceptors (e.g. aptamers) has received considerable attention[206-208], anion sensing based on this strategy is rare. One recent example is of an aptamer-based sensor for As(III) (sensed as meta-arsenite, AsO_2^-) at gold electrodes.[209] Upon binding of AsO_2^- the conformation of this aptamer changed to a folded state in which electron-transfer to the electrode was facilitated leading to a significant decrease in R_{ct}.

While these works demonstrate the large potential of EIS as a sensitive tool for the detection of a variety of anions, progress in this area since its emergence more than a decade ago has been slow. We attribute this mainly to the need for a redox probe which imposes multiple restrictions on sensor design and performance: 1) Faradaic EIS is almost exclusively performed in pure aqueous media due to lack of suitable (charged) redox probes compatible with organic solvents (solubility/unfavourable charge-transfer characteristics). This requires the synthesis of anion-receptors that not only contain anchor groups for surface-immobilisation but that are also capable of anion recognition in pure water. 2) The DC bias potential during the measurement is fixed to the half-wave potential of the redox-probe prohibiting detection of anions that are electroactive close to these potentials. 3) Interactions of the redox-probe with the interface that might lead to baseline instabilities or compete with binding.

The omission of a redox probe thus offers many advantages and has been preliminarily investigated for cation sensing.[196-197] Anion sensing using non-Faradaic approaches to EIS has remained elusive until very recently and will be discussed in the following section.

3.2 Capacitive anion sensing

We have recently reported an anion receptive SAM based on halogen- and hydrogen-bonding foldamers capable of selective anion sensing using impedance-derived capacitance spectroscopy (**105_{SAM}**, Figure 60).[210] In the absence of a redox probe in the aqueous phase, anion sensing was achieved utilising the film capacitance as a sensitive transducer for binding. This capacitance can be easily obtained from the capacitive Nyquist plot (Figure 61) by simple graphical analysis or from data fitting to a suitable equivalent circuit. We not only demonstrated sensitive sensing of the environmentally and biologically relevant charge-diffuse anions ReO_4^-, I^- and SCN^- utilising this new methodology, but also reported on the first examples of a XB-receptive interface showing improved performance over the analogous HB film.



$105a_{SAM}$: X = I

$105b_{SAM}$: X = H

Figure 60. Halogen- and hydrogen-bonding foldamer SAMs for anion sensing in pure water *via* non-Faradaic capacitance spectroscopy.

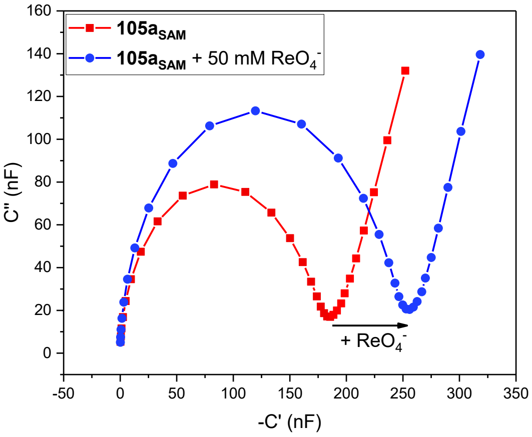


Figure 61. Capacitive Nyquist plots of **105a$_{SAM}$** in the absence and presence of 50 mM ReO$_4^-$ showing an increased capacitance in the presence of bound anion. Measurements were performed at open-circuit potential (≈ 0 V) in the presence of 100 mM electrolyte (x NaCl + y NaReO$_4$, x + y = 100 mM). Chem. Commun., 2019,55, 4849-4852. Reproduced by permission of The Royal Society of Chemistry.

Anion binding to the receptive interface was macroscopically described by a simple Langmuir adsorption model with low limits of detections (as low as 14 µM for I$^-$ at **105a$_{SAM}$**). Importantly, an increase in capacitance upon anion binding can be directly attributed to an increased film dielectric constant due to introduction of a charged species and a concomitant increased film hydration. In contrast to standard Faradaic EIS, where ion binding is transduced due to electrostatic interactions between the surface-confined ion and the charged redox-probe (see Section 3.1), this approach may also facilitate capacitive ion-pair sensing and is entirely “reagentless” in completely omitting diffusive or surface-bound electroactive transducers.

4. Potentiometric Anion Sensing

4.1 General Experimental and Theoretical Considerations

Potentiometry is an electroanalytical technique in which the electromotive force (emf; a potential) is measured between two electrodes immersed in the analyte solution. The potential is measured between an indicator electrode and a reference electrode, ideally quite unresponsive. Potentiometry is the simplest electroanalytical technique and has been studied in some detail for over a century. By far the most common application of this technique is in ion-selective electrodes (ISEs), whereby, through chemical means, the indicator electrode selectively responds to the concentration (or more accurately the activity) of the target analyte. This is achieved through the selectivity of a membrane that separates the inner filling solution of the indicator electrode and the analyte solution (Figure 62). The response of the system is only dependent on the membrane potential of the indicator electrode; all other potentials (e.g. of the reference electrode) are constant or can be corrected for (e.g. junction potentials, see below). A membrane potential arises when a specific ion selectively partitions into the membrane inducing a charge separation at the membrane boundary and therefore a measurable emf. Of paramount importance to the successful application of such systems is, then, that only one specific ion can partition into the membrane. A variety of different membranes have been used for this purpose such as glass membranes in the ubiquitously used pH-probes, crystalline membranes such as LaF_3 (for F^--ISEs) as well as liquid and polymeric membranes. The two latter types rely on the incorporation of ion-exchangers and/or ionophores (ion carriers) to impart selectivity for the desired ion. In this review we will only discuss such systems in which anion selectivity is imparted through the integration of synthetic supramolecular H-bonding hosts.

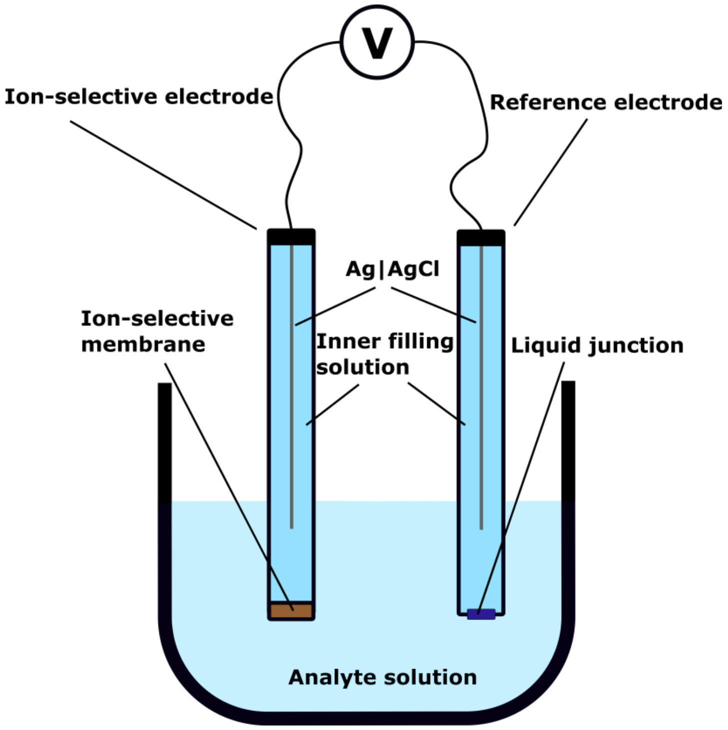


Figure 62. Schematic depiction of a membrane-based ion-selective electrode.

The following discussion briefly describes how the measured potential is related to the concentration of the target analyte. As previously mentioned, the partitioning of the analyte ions into the membrane results in a phase boundary potential whose magnitude can be described accurately by eqn. 3 where E^0 is a constant and a_I and z_I the activity and charge of the ion, respectively.

$$E = E^0 + \frac{RT}{z_I F} \ln a_I \qquad (3)$$

It should be noted that two of such phase boundary potentials develop across the membrane; at both the inner and the outer side such that the overall potential across the whole membrane is $E_{Memb} = E_{Outer} - E_{Inner}$. The inner side of the membrane is in contact with the inner filling solution of the electrode which contains a known, constant amount of the target analyte. The term E_{Inner} is thus a constant and like E^0 does not contribute towards the change in emf that is measured as a function of analyte activity. From this follows that a change in the membrane potential, and also the potential of the whole system (with all junction potentials being constant), is only dependent on a_I at the outer membrane, i.e. a_I in the analyte solution. The overall emf as a function of a_I is hence still described by eqn. 3 whereby the constant E^0 contains all phase-boundary/junction potentials apart from that at the outer membrane interface. From this equation it can be seen that, at room-temperature, a ten-fold change in the ion activity in the sample induces a measurable potential change of 59.2 mV/z_I. This so called "Nernstian response" is however not always observed in reality, whereby, depending on many factors, small deviations from the ideal behaviour can be observed. In this case the response can be described more generally by eqn. 4, where if $S = 59.2\frac{mV}{z_I}$, ideal Nernstian behaviour according to eqn. 3 is obtained again.

$$E = E^0 + S\ loga_I \qquad (4)$$

While an ideal Nernstian response is desirable, arguably more important is the selectivity for the target analyte. The response of an ISE in the presence of an interfering ion "J" can be described by the Nicolskii-Eisenman equation (eqn. 5):

$$E = E^0 + \frac{RT}{z_I F}\ log(a_I + K_{IJ}^{pot} a_J^{z_I/z_J}) \quad (5)$$

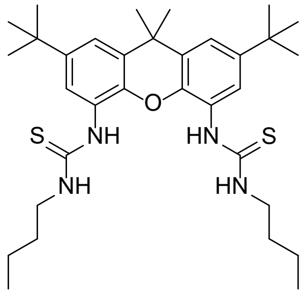
where $K_{IJ}^{pot}$is the selectivity coefficient between the target and interfering ion. A smaller K_{IJ}^{pot}indicates a smaller interference and is ultimately one of the most important parameters that needs to be assessed and tuned. Importantly, depending on the desired application, the ISE does not have to be selective over all potentially interfering anions (i.e. K_{IJ}^{pot} can be >1) as long as the activity of the interfering ion is small enough (i.e. as long as the $K_{IJ}^{pot} a_J^{z_I/z_J}$ term in eqn. 5 is significantly smaller than a_I). The selectivity coefficients of ionophores over various interfering anions are often represented graphically and logarithmically, as depicted in Figure 66 or Figure 72. A negative $logK_{IJ}^{pot}$ indicates that the ion of interest "I" induces a larger response in comparison to the interfering ion "J". For example, a $logK_{IJ}^{pot}$ of -1 represents a response that is 10x smaller for "J" than "I" i.e. 5.7 mV/decade vs. 57 mV/decade, in an ideal case.

In these systems the response selectivity is primarily determined by the ionophore, but not exclusively (the membrane matrix itself can play a role even if it is chosen to be electrostatically neutral, such as polyvinyl chloride (PVC) or fluorinated polymers). One challenge is that associated with the detection of hydrophilic, strongly solvated anions, such as sulfates or phosphates, where the enthalpic penalty associated with their entering the membrane is pronounced. The presence of lipophilic interfering anions such as thiocyanate or salicylate, which can thus more easily partition into the membrane, can also be problematic. Despite some of these shortcomings ISEs are by far the most common and useful electroanalytical devices for ion sensing applications and are generally cheap and easy to produce and operate. A large variety of ISEs for different ions, in particular for cations, are commercially available and widely used, for example in clinical applications. In comparison to other analytical techniques, their somewhat lower precision is offset by a large detection range and fast response time (usually a few tens of seconds). For more details on the concepts discussed above the interested reader is referred to seminal works by Bakker, Bühlmann, Pretsch and others.[211-218]

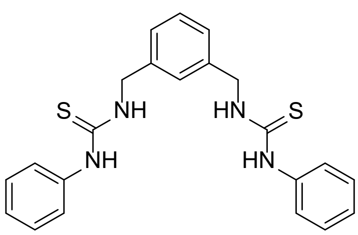
On a final note, potentiometric techniques can also be applied in other formats, namely that presented by field-effect transistors (FETs).[219-221] For example, recently, an organic FET (OFET) based on a SAM of a phenylboronic acid derivative for sensing of F^- in water has been developed.[222] Although the transduction mechanisms of these FET sensors differs from that of ISEs, ultimately the selectivity arises from the same ionophore design principles. In the following section we discuss the development of ionophores and ISEs for anions. As for the impedimetric sensors discussed in Section 3, these systems all operate in aqueous media.

4.2 Ionophores for anion-selective electrodes

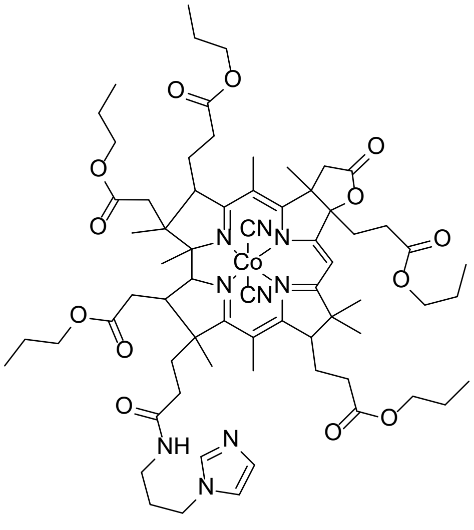
As discussed above, the selectivity of ISEs is largely imparted by synthetic ionophores, which are almost always non-covalently incorporated into the membrane matrix by simple mixing, but can be covalently attached to polymeric backbones. The design of anion receptor ionophores for ISEs largely follows principles that are established for solution-phase anion receptors. For example, size complementarity between the target analyte and the ionophore is of considerable importance. Different ionophore topologies have thus been investigated whereby most commonly multiple reversible covalent, dative or non-covalent interactions are exploited to enable strong and selective binding. While strong binding is not *per se* important for the successful application of a receptor in an ISE, it is beneficial if selective binding of the more hydrated anions is sought (to compensate for the energetic penalty associated with anion-dehydration). This can, for example, be achieved by exploitation of electrostatic interactions, as long as the introduction of charged, or otherwise polar groups, does not render the ionophore too hydrophilic (thus potentially leaching out of the membrane). One complication in design is the difficulty of translating solution-phase binding data (i.e. binding constants/selectivities) to the performance of the receptors as ionophores in ISEs, namely because the membrane environment significantly differs from that of a simple solvent. Furthermore, the difficulty of assessing binding stochiometries and conformations as well as possible interactions with the membrane itself additionally hampers the understanding of processes that govern ionophore performance. While the simple signal output (i.e. the “direct” conversion of ion activity to an emf) is attractive for sensing applications it does not —in contrast to voltammetric or impedimetric techniques— allow extraction of further information on binding processes in the system and is thus of low relevance for fundamental studies. Despite these impediments a variety of anion-selective electrodes based on reversible, non-covalent host-guest systems have been developed and examples of anion-ionophores **106-111**, developed in the 90s, are given in Figure 63.[223-228] As can be seen, many of these host-guest based ionophores rely on hydrogen-bond donors such as thioureas and guanidiniums or metal complexes such as corrin (**108**) or porphyrins (not shown). While, from a supramolecular chemist´s point of view, some of these receptors are structurally rather simple they can display remarkable selectivities and the depicted ionophores for chloride (**106**)[228], sulfate (**107**)[227] and sulfite (**108**)[223] are commercially available. For a more comprehensive overview of earlier examples and further details please see reviews by Reinhoudt[229] and Pretsch.[230]



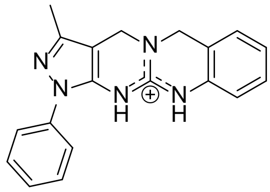
106, for chloride



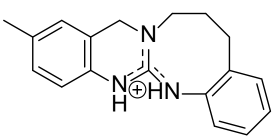
107, for sulfate



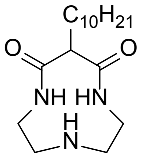
108, for iodide



109, for sulfite



110, for salicylate



111, for phosphate

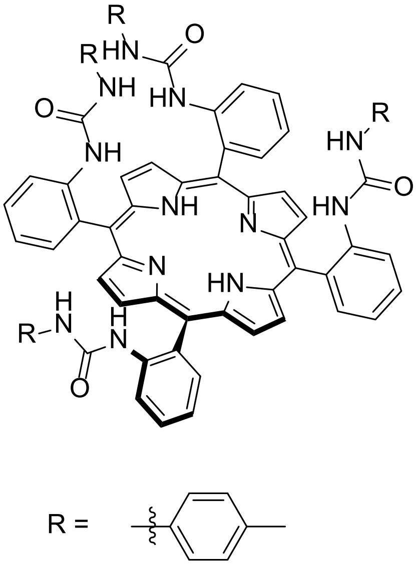
Figure 63. Representative examples of early anion-ionophores for potentiometric sensing of the highlighted anions.

A large number of these (early) anionophores are based on coordinative interactions with metal complexes or reversible covalent bond formation. While ubiquitous, it should be noted that there is some concern regarding the potential toxicity of metal-based ionophores. In the following paragraphs we will not discuss these examples, but will introduce a few more recent examples of anionophores based on other non-covalent interactions, specifically hydrogen-bonding.

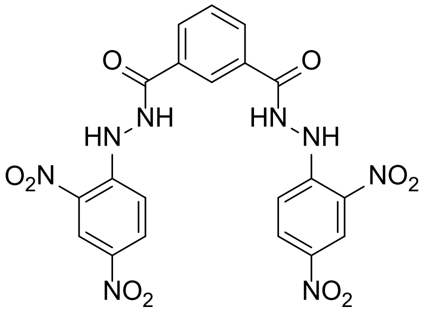
Based on the design principles developed towards the end of the last century, anionophores studied in the last two decades have continued to exploit acyclic and cyclic receptors based on established H-bond donors such as amides,[231] (thio)ureas[232-233] and guanidiniums.[234] In parallel a variety of other receptive moieties and receptor topologies have been established which are highlighted in more detail below.

While metalloporphyrins have long been established as potent ionophores, their free base analogues have been studied as well.[235-237] For example, an ISE based on **112** (Figure 64) was shown to exhibit excellent nitrate selectivity over all tested anions in the following order: NO_3^- > SCN^- > OAc^- > NO_2^- > ClO_4^- > I^- > Br^- > HSO_3^- > HCO_3^-.[237] Additionally a Nernstian response (-57.4 mV/decade) over a wide concentration range (10 µM – 0.1 M) with a low LOD (1.9 µM) was achieved.

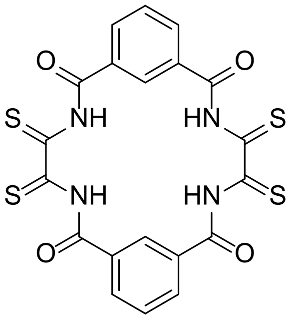
In expanding the toolbox of receptor designs a range of other H-bond donors have been applied in ionophores. The 2,4-dinitrophenylhydrazine motif was investigated in an ionophore for OAc^-.[238] While only possessing moderate selectivity, the sensor was successfully applied to quantify OAc^- in vinegar. A very similar ionophore **113** was applied in a CO_3^{2-} sensor.[239] In this study a new conditioning protocol significantly extended the linear range (6 orders of magnitude) and LOD (down to 80 pM) of the ISE and was successfully applied in artificial sea water with near-Nernstian response (26.9 mV) towards the divalent anion. Another less common H-bond donor motif, the dithioxamide, was utilised in a HPO_4^{2-}-selective electrode based on the cyclic ionophore **114**.[240] This ISE not only possessed a Nernstian response (here 29.6 mV/decade), but also showed excellent selectivity ($log\, K^{pot}_{HPO_4{}^{2-},\ A^-} < -1.55$ in all cases) over all tested anions with a clear anti-Hofmeister bias, i.e. a preference for the more strongly hydrated anions: HPO_4^{2-} > OAc^- > SO_4^{2-} > HSO_4^- > HCO_3^- > NO_3^- > ClO_4^- > I^- > SCN^- > Cl^- > Br^- > F^- >CrO_4^{2-} > MnO_4^- > BrO_3^-.



112



113

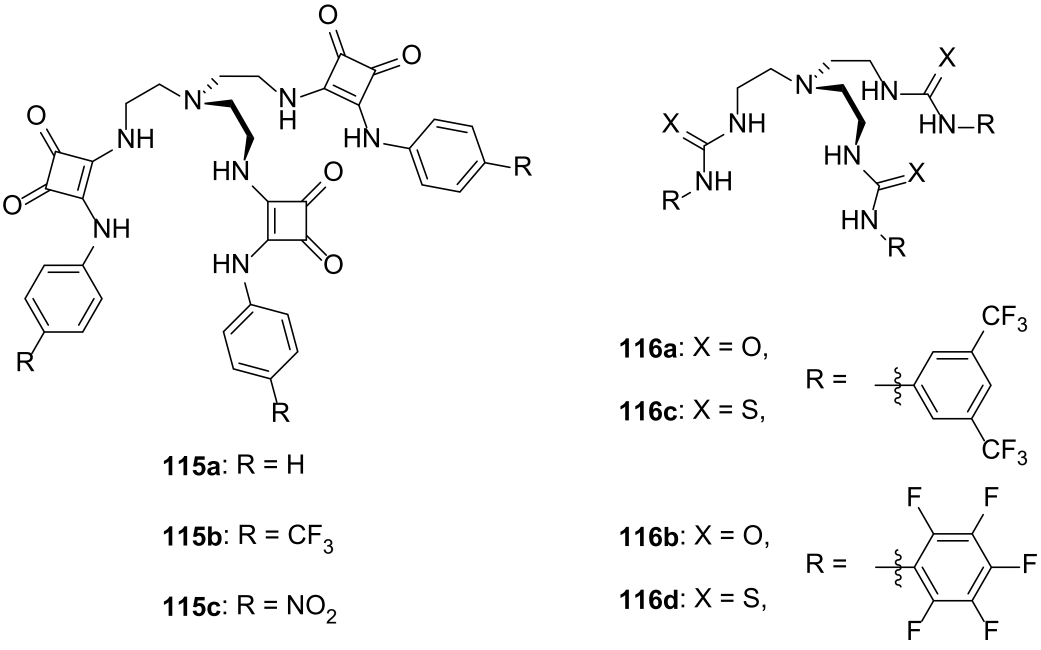


114

Figure 64. Examples of different ionophores based on different topologies and H-bond donors including ureas, hydrazides and dithioxamides.

Urea ionophores with a tripodal topology were first investigated by Bachas and coworkers in 2000 for the sensing of sulfate.[241] A related amide analogue based on the tris(2-aminoethylamine) scaffold was later investigated as a nitrate ionophore,[242] enabling a near-Nernstian response (-54.7 mV/decade) towards nitrate with good selectivities over Br^-, Cl^- and HPO_4^{2-}.

In a more recent study Liu *et al.* have investigated three tris(squaramide) ionophores **115a-c** based on the same scaffold (Figure 65).[243] While a near-Nernstian response for sulfate was achieved with all ionophores only the ISE based on **115c** showed selectivity over $H_2PO_4^{2-}$, Cl^-, Br^- and NO_3^-, though with no selectivity over ClO_4^-, SCN^- and I^-. The performance of the two other ionophores was significantly worse, in particular for **115a**. Importantly, in comparison to Bachas´ original tris(urea) ionophore the sulfate selectivity of **115c** is significantly improved over all tested anions demonstrating the potential of the squaramide motif as a potent motif for the recognition of hydrophilic oxoanions. Similarly, four fluorinated tris((thio)ureas **116a-d** were recently studied as ionophores for Cl^-.[244] As can be seen in Figure 66, in particular **116a** imparted good chloride selectivity, while the thiourea analogues **116c-d** performed worse, with poor selectivity over salicylate. Sufficient selectivities of **116a** over salicylate and bicarbonate enabled Cl^- assaying in undiluted human serum with a response of 49.8 mV/decade and good recoveries (ratio of measured *vs.* actual concentration).



115a: R = H

115b: R = CF_3

115c: R = NO_2

116a: X = O,

116c: X = S,

116b: X = O,

116d: X = S,

Figure 65. Tripodal ionophores based on squaramide-containing or fluorinated receptors.

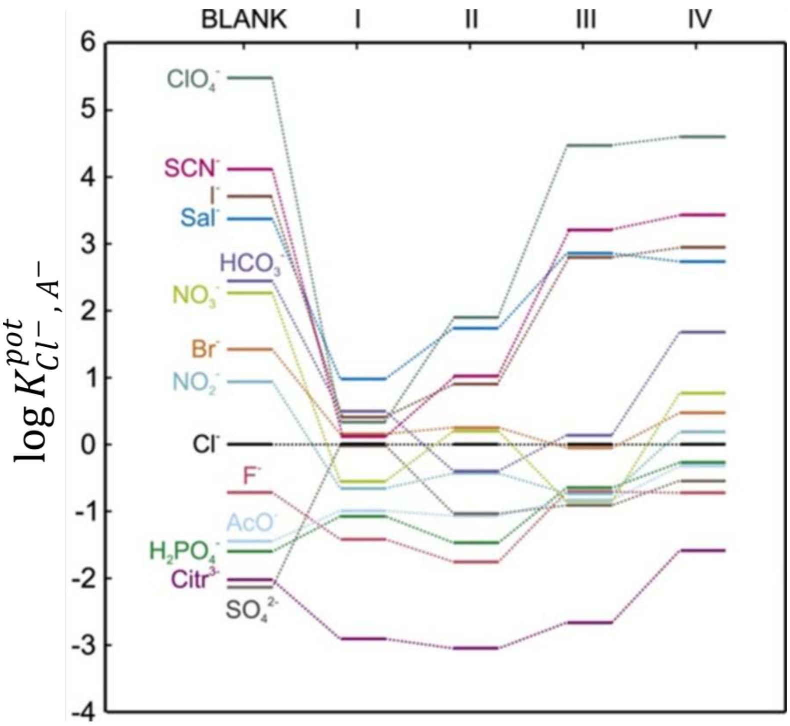
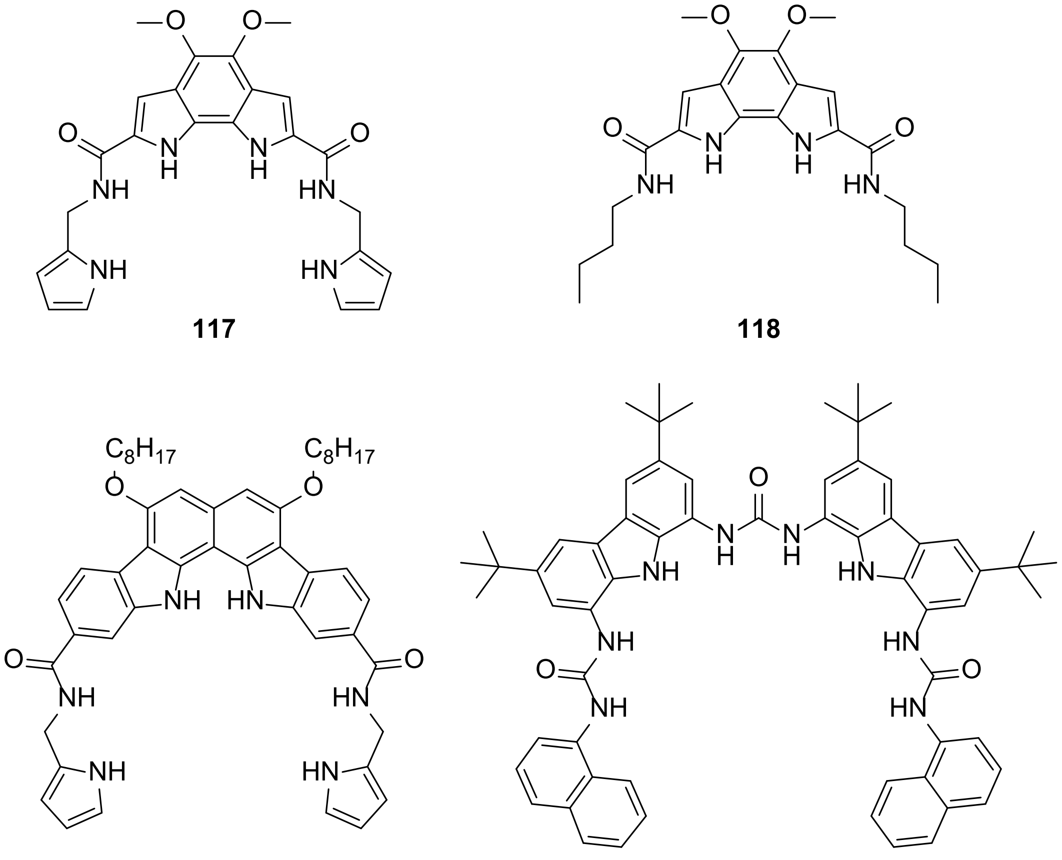


Figure 66. Selectivities of chloride over other anions of ISEs based on fluorinated tripodal receptors **116a-d** (I-IV). Reprinted with permission from ref.[244] Copyright 2018 Elsevier.

Ortuño´s group have developed a series of benzopyrrole and carbazole-based ionophores for the detection of divalent anions in ISEs. In their first study they investigated the amide- and pyrrole appended benzodipyrroles **117** and **118** (Figure 67).[245] While ISEs based on these ionophores still showed a bias towards lipophilic monovalent anions (though greatly reduced) their selectivity towards the divalent anions SO_3^{2-}, SO_4^{2-}, $S_2O_3^{2-}$ and $C_2O_4^{2-}$ was significantly enhanced in comparison to a blank membrane. The pyrrole appended ionophore **117** showed particular improvement of oxalate, sulfate and thiosulfate selectivity while the simpler **118** more significantly improved the selectivity towards sulfite. The larger carbazolocarbazole **119** was later shown to significantly enhance the selectivities towards the dicarboxylates oxalate, adipate, malonate, succinate and glutarate.[246] While this ISE displayed good Nernstian response to all these analytes with low LODs of ≤3.3 µM it should be noted that in contrast to the previous examples this system does not (in comparison to the blank membrane) lower the interference from many of the tested monovalent anions, for example the selectivity towards ClO_4^- over Cl^- actually increases (albeit not as much as for the dicarboxylates). Very recently the urea-carbazole **120** has been utilised as an ISE ionophore for acetate, with reduced interference from SCN^-, I^-, Br^- and NO_3^-, although an interference from ibuprofen, naproxen and benzoate was reported.[247]

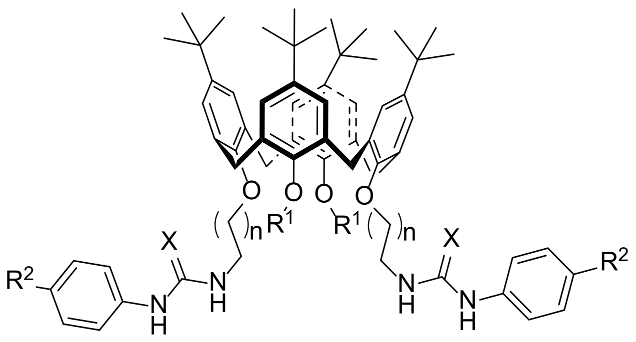


117 **118**

119 **120**

Figure 67. Carbazole-based receptors as ionophores for sensing of divalent anions.

Another class of anionophores that have received considerable attention are those based on calixarenes and calixpyrroles. An early example includes the use of a hexaamide modified calix[6]arene as an ionophore for HPO_4^{2-} with moderate selectivities over other anions.[248] More in depth studies have been conducted on a variety of urea- and thiourea-containing calix[4]arenes **121a-e** (Figure 68). The simple bis-urea ionophore **121a** was utilised in a very potent carbonate selective electrode.[249] The system showed a response of -29.2 mV, as expected for a divalent anion, with excellent selectivities over all tested anions, even ClO_4^- ($log\ K^{pot}_{CO_3{}^{2-},\ ClO_4{}^-} = -1.85$), salicylate ($logK^{pot}_{CO_3{}^{2-},\ Sal^-} = -1.72$) and I^- ($logK^{pot}_{CO_3{}^{2-},\ I^-} = -1.68$). The very similar **121b** has later been explored as an ionophore for NO_3^-.[250] While not as selective against the less hydrophilic anions I^- and SCN^- as the aforementioned ISE this system still displayed good selectivity over Cl^- ($logK^{pot}_{NO_3{}^-,\ Cl^-} = -3.41$) and a "super-Nernstian" response of -72.8 mV/decade. Another slightly adapted receptor **121c-alt** based on a 1,3-alternating calix[4]arene and a nitrophenyl-urea receptor displays a significantly different selectivity.[251] An ISE based on this system has been observed to display a near-Nernstian response (-55.7 mV/decade) towards Cl^- with good selectivities over a large variety of anions including NO_3^- ($logK^{pot}_{Cl^-,\ NO_3{}^-} = -2.60$) and CO_3^{2-} ($logK^{pot}_{Cl^-,\ CO_3{}^{2-}} = -3.65$). While the cone conformer **121c-cone** displays almost identical selectivities,[252] the thiourea analogues **121d-alt/cone** and **121e-alt/cone** differ somewhat with the **121e-alt** being more selective for chloride over almost all tested anions.[252]



121a: X = O, R^1 = H, R_2 = H, n = 1

121b: X = O, R^1 = Pr, R_2 = H, n = 3

121c-alt: X = O, R^1 = Pr, R_2 = NO_2, n = 1

121d-alt/cone: X = S, R^1 = Pr, R_2 = H, n = 1

121e-alt/cone: X = S, R^1 = Pr, R_2 = NO_2, n = 1

Figure 68. Calix[4]arene-based ionophores, shown is only the cone conformation.

Like calixarenes, calixpyrroles have been investigated as ionophores in ISEs. While an early study of a [2]pyridine[2]pyrrole has been investigated for a salicylate selective electrode[253] a more in depth study of various calix[4]pyrroles has been carried out more recently.[254] To this end Sabek *et al.* prepared a range of aryl-appended calix[4]pyrroles **122a-g** where, in addition to hydrogen-bonds, anion-π interactions can drive recognition (Figure 69 and Figure 70). All ISEs based on these ionophores responded to Cl^- with near-Nernstian response and a LOD of ≤10 μM. While ionophores **122a-c** induced sufficient chloride selectivity over SCN^-, NO_3^-, HCO_3^- and lactate to enable Cl^- sensing in biological fluids, the salicylate selectivity is not sufficient. Only the nitrophenyl-containing ionophore **122d** shows sufficient selectivity over all anions. These results indicate that anion-π interactions can play a significant role in governing the selectivities. Interestingly, receptors **122e** as well as receptors **122f-g** did not enable Cl^- sensing in biological samples due to lowered selectivities over salicylate or SCN^-, respectively, in spite of enhanced anion-π interactions. The authors further investigated the predictive power of solution phase selectivities of Cl^- over NO_3^- (in ACN) showing that they are not correlated to the performance of the ionophore in the ISE format.[254] A similar behaviour was also reported by Xiao *et al.* who demonstrated that the use of ionophore **106** in a different sensor format displays altered selectivities.[185] Specifically, a monolayer of **106** was formed by physisorption on highly oriented pyrolytic graphite (HOPG) electrodes whereby anion binding to this film was transduced by a modulation of the redox properties of the solution-phase $[Fe(CN)_6]^{4-}$ probe (decreased peak currents and potential shifts; for further examples of such voltammetric sensors see Section 2.4.2). This interface was most responsive to $H_2PO_4^-$ while the analogous ISE was selective for Cl^- as discussed above.

These observations again demonstrate the difficulty of rationally designing ionophores for specific analytes, as also demonstrated by the wide variation of selectivities of the aforementioned calixarene ionophores. It has to be reiterated that key analytical parameters, including selectivites, can depend strongly on the membrane/interface composition and not only the ionophore itself.

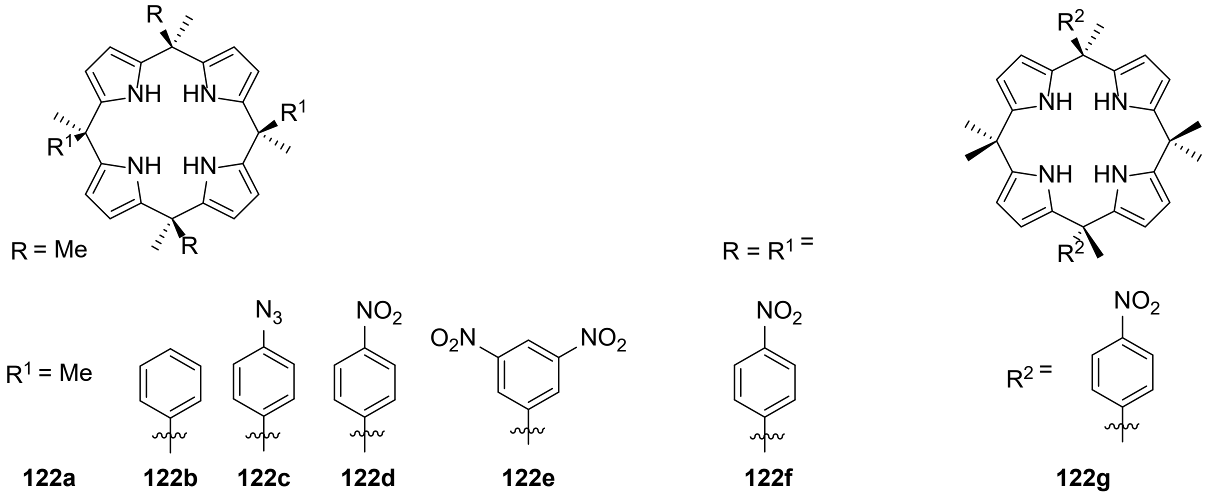


Figure 69. Calix[4]pyrrole-based ionophores for the investigation of anion-π interactions as driving force for anion binding and selectivity.

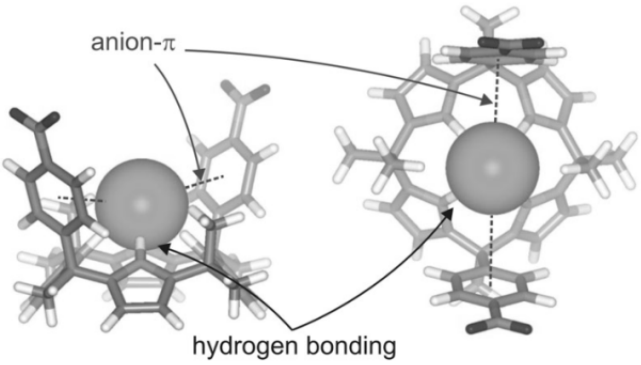
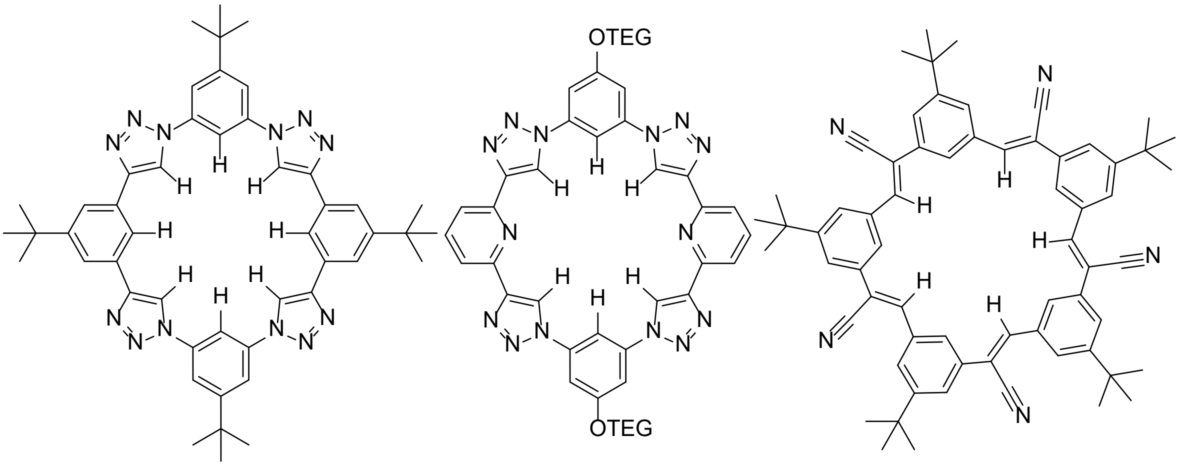


Figure 70. X-ray crystal structure of the **122d-Cl$^-$** host-guest complex in side and top view highlighting HB and anion-π interactions. Reproduced with permission from Ref.[254] Copyright 2015 Wiley-VCH.

More recently the groups of Bachas and Flood investigated the performance of macrocyclic C-H bond donors as anionophores.[255-257] In their first study they investigated the triazolophane **123** (Figure 71) as a potent halide selective ionophore forming 1:1 host-guest complexes as schematically shown in Figure 72a.[255] In good agreement with previous solution-phase studies an ISE based on this receptor displayed a near-Nernstian response for Cl$^-$ (-54.6 mV/decade) and a Nernstian response for Br$^-$ (-60.2 mV/decade). The electrode displayed anti-Hofmeister selectivity towards bromide with good selectivity over salicylate ($logK^{pot}_{Br^-,\ Sal^-} = -1.54$). Furthermore the selectivity over all other interfering ions was large enough to facilitate bromide quantification in spiked horse serum with good recoveries. Using a slightly different membrane composition the ISE could, in the absence of Br$^-$ and salicylate, also be used for Cl$^-$ determination in serum.

A high iodide selectivity was later achieved with a very similar pyridyl-triazolophane **124**.[257] The lone pairs of the two central pyridine units disfavour the formation of a 1:1 complex with halides in favor of a 2:1 host-guest complex. This renders ISE based on this ionophore particularly iodide selective with good selectivities over all tested anions (Figure 73). This iodide sensor showed a near-Nernstian response of (-62.0 mV/decade) with a LOD of 0.25 µM and a large linear range of 0.8 µM to 0.1 M.

Similarly, based on the 2:1 host-guest formation of cyanostar **125** (Figure 72b) the same groups also recently reported a ClO_4^- selective electrode.[256] While most ISE-membranes without an ionophore would inherently show selectivity towards ClO_4^- (Hofmeister bias) this ISE is more selective by at least two orders of magnitude over other anions. For example a very large selectivity over salicylate of $logK^{pot}_{ClO_4^-,\ Sal^-} = -6.50$ was achieved with near-Nernstian response (-56.7 mV/decade), submicromolar LOD and a wide linear range. It was further shown that this ISE could be used to determine ClO_4^- in lake water, tap water and horse serum.



123 **124** **125**

Figure 71. C-H H-bond based anion ionophores. TEG = triethylene glycol.

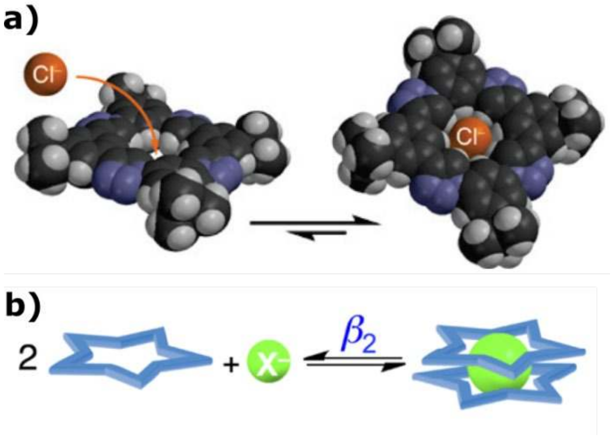


Figure 72. Schematic representation of a) 1:1 chloride binding to triazolophane **123.** Reproduced with permission from Ref.[255] Copyright 2010 American Chemical Society. b) anion binding to cyanostar **125** under formation of a 2:1 host-guest complex. Reproduced with permission from Ref.[256] Copyright 2018 American Chemical Society

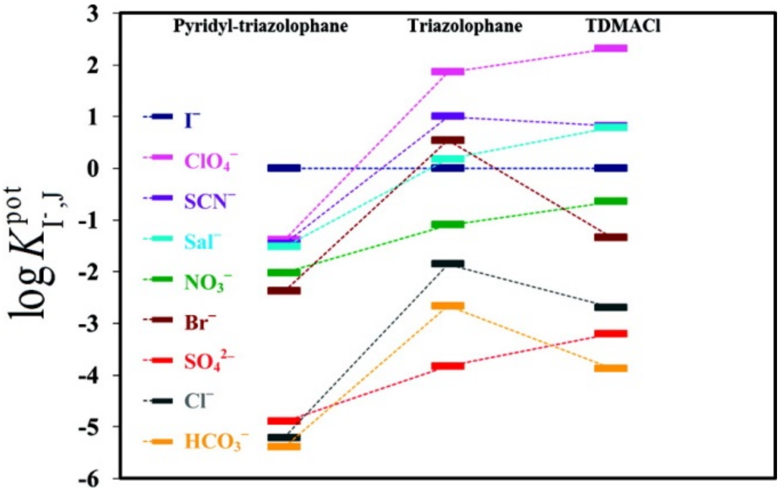


Figure 73. Selectivities of iodide over other anions of ISEs based on pyridyl-triazolophane **124** and triazolophane **123** as well as a control membrane without ionophore (labelled TDMACl). Reprinted with permission from ref.[257] Copyright 2011 American Chemical Society.

Although boron and boronic acid motifs have gained considerable attention in various (electrochemical) sensors as discussed in Section 2, their use in ISEs has been surprisingly limited. While an early report[258] indicated that the simple napthylboronic acid can be utilised as an ionophore for F^-, few follow-up studies have been conducted. A study by Jańczyk *et al.*

showed that different boronic acid derivatives can be utilised to impart good selectivity over the other halides as well as sulfate.[259] The authors further investigated the performance of the ISE at different pH values and showed that significant deviations from Nernstian behaviour arise from the complex binding equilibria in this system. Interestingly, a very different selectivity was observed at a poly(3-aminophenylboronic acid) film that was electrochemically synthesized on a Pt electrode.[260]

As can be seen from works highlighted in this section, more selective anionophores are being continually developed to further improve the performance of ISEs. Despite the century long development of ISEs as potent analytical devices many fundamental studies are still being carried out with substantial challenges remaining in terms of chemically engineering high levels of selectivity.[217] These efforts are focused on various aspects including the development of more real-life relevant, sensitive and compact devices,[214] as well as exploiting new sensor and transduction formats,[261-262] including wearable sensors,[263] paper-based sensors[264-265] as well as other smart devices.[266]

5. Summary and Outlook

As highlighted herein, significant advances have been made in the development of a myriad of electrochemical anion sensors capable of the selective sensing of anions. Importantly, these studies can significantly improve our understanding of (electrochemically mediated) supramolecular host-guest interactions in solution and at interfaces and thus serve as an important tool to investigate such interactions. Voltammetric techniques will undoubtedly remain primary for such fundamental studies offering a high information density while being experimentally accessible. It is likely that ISEs and other potentiometric devices will, due to their low cost as well as ease of use and fabrication, continue to be the most widely applied electrochemical anion sensors for real sample analysis for some time to come. While impedimetric approaches are relatively underdeveloped for ion sensing applications they may be able to combine the advantages of both voltammetric and impedimetric techniques in offering not only a high information density, but saliently a high real-life potential (Table 2).

Despite promising developments there remains much untapped capability in bringing electrochemical anion sensors to academic and industrial applications. We believe that future efforts in the field will focus on the following general points:

Exploitation of other supramolecular interactions: Regardless of the transduction mechanism, almost all electrochemical anion sensors employ receptors based on "traditional" supramolecular interactions such as hydrogen-bonding and electrostatic interactions. The use of other "novel" interactions, such as halogen-, chalcogen- or pnictogen bonding,[267] anion-pi interactions and others promises to be a powerful approach to achieve improved performance.

Multiplexed anion sensing and development of advanced devices: Imperative for the successful application of sensors in various real-life settings is that they are applied in useful formats. Continuing attention will be given to fabricate (shelf-)stable, small and simple devices exploiting microfabrication and microfluidic integration. The simultaneous, multiplexed sensing of different ionic species is highly desirable for many applications (clinical, environmental and industrial e.g. food/beverage testing) and can, for example, be achieved with sensing arrays. In a recent proof-of-concept Swager and coworkers developed a novel chemiresistor platform enabling real-time and wireless detection of multiple anions, albeit only in organic solvents.[268]

Fundamental studies on transduction mechanisms and the influence of electrolytes (relevant for voltammetric and impedimetric sensors): The development of a better understanding of the fundamental processes that govern anion binding and the transduction thereof would greatly advance the field and enable a more rational approach to designing advanced sensors capable of detecting specific anionic targets. In particular the influence of the electrolyte and local hydration on signal transduction and anion binding is of crucial importance when application in real-life samples, where different salt concentrations are encountered, is being sought.

Ion-pair recognition (relevant for voltammetric and impedimetric sensors): The (simultaneous) detection of different ionic species or zwitterions is highly desirable in a variety of applications. In combining both anion and cation recognition sites, cooperative effects can lead to significantly enhanced binding as well as other interesting properties.[269] A variety of such ditopic redox active receptors have been investigated for the (simultaneous) voltammetric sensing of anions and cations.[40,270-276] While fundamentally interesting these sensors are not particularly useful; the oppositely charged ions induce opposing voltammetric shifts that largely cancel each other. While ion-pair sensing has not been investigated *via* Faradaic EIS the same effect is expected. The reliance on electrostatic interactions as a signal transducer precludes efficient sensing of oppositely charged species. This can most likely be circumvented by use of non-Faradaic techniques such as electrochemical capacitance spectroscopy whereby both anions and cations have been separately shown to induce the same response (i.e. increase in capacitance, see Section 3.2).

In the following we also want to highlight future developments that are specifically relevant to each of the discussed electrochemical sensing techniques:

Voltammetric Sensors

Utilisation of novel redox transducers: While voltammetric anion sensors have incorporated a myriad of redox transducers, the utilisation of other transducers could significantly expand the toolbox when designing systems with specific properties. As discussed above, depending on the target anion, a transducer with an appropriate half-wave potential needs to be employed; many transducers, like Fc, TTF or porphyrin, are incompatible with anions possessing a low oxidation potential, such as iodide or bromide. The incorporation of multiple transducers may also present an opportunity to develop novel systems with enhanced control over binding processes.

Voltammetric anion sensing in competitive (aqueous) media: While a few examples of voltammetric anion sensors have been shown to operate in pure water the vast majority remain restricted to non-polar organic solvents. This illustrates the vast potential that lies in exploring sophisticated molecular architectures that enable anion recognition and electrochemical sensing in pure water.

Impedimetric Sensors

Impedimetric/capacitive anion sensing in organic media: In contrast to voltammetric sensors which are largely studied in less polar solvent media, impedimetric techniques are currently restricted to (pure) aqueous media. In Faradaic EIS this restriction arises from the redox-probe itself which needs to possess favourable charge-transfer characteristics (e.g. it needs to be surface sensitive). So far only $Ru(NH_3)_6^{2+/3+}$ or $Fe(CN)_6^{3-/4-}$ have been thoroughly investigated for this purpose and only possess appropriate charge-transfer and solubility properties in water. The exploration of other redox-probes could potentially circumvent this, but in completely omitting the transducer capacitive techniques appear even more promising.

Exploration of novel techniques and methodologies: Having received much attention for biosensing, EIS and derived techniques have not been routinely employed for (an)ion sensing. In particular, capacitive approaches are promising as a simple, sensitive means to transduce (anion) binding events. While redox capacitive sensing of large molecules has been successfully employed in recent years[277-278], redox capacitive (an)ion sensing remains open to exploration.

Potentiometric Sensors

Development of novel ionophores: The selective sensing of many anions, in particular strongly hydrated anions such as sulfate and phosphate, still present a formidable challenge, in particular when the concentration of interfering, hydrophobic anions is large. As highlighted in the previous section the exploitation of ionophores of different topologies has significantly expanded the pool of useful ionophores. A particularly promising ionophore topology which should impart interesting selectivities, but has to the best of our knowledge, not been applied in ISEs, is that presented by mechanically interlocked structures.

Miniaturization and other sensory formats: While many ISEs are routinely employed in *in vitro* diagnostics their *in vivo* application remains limited. This mainly arises from difficulties to miniaturize these systems, a problem that has received considerable attention recently, resulting in, for example, development of solid-contact ISEs in which the internal filling solution is eliminated resulting in more durable and minituarisable ISEs.[217-218] Going forward, it is likely that suitably selective and robust electrochemical anion sensors will play a valuable role in accessible "point of care" diagnostics.

Table 2. Comparison of different electroanalytical techniques in the context of anion sensing and the fundamental study of host-guest interactions.

	Voltammetry	**Impedance/Capacitance**	**Potentiometry**
Advantages	-High information density -Experimentally simple	-High information density -System at equilibrium -Potentially high real-life potential	-High real-life potential -Applicable to any ionophore -Well understood
Disadvantages	-Low real-life potential -Requires receptor and transducer -Highly dependent on solvent/electrolyte conditions	-Experimentally difficult -Often requires receptor and transducer/anchor groups -Transduction mechanisms poorly understood	-Low information density -Molecularly ill-defined systems
Future efforts	-Investigation of electrolyte effects -More routine application in water -Exploitation in switches and other advanced systems	-Implementation in real-life sensors -Study of transduction mechanisms -Development of capacitive approaches	-Development of (more) selective ionophores -Miniaturization and application *in vivo*

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Notes

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Biographies

Robert Hein obtained his B.Sc. from Jacobs University Bremen, Germany in 2016, where he worked in the field of supramolecular chemistry under the supervision of Prof. Werner M. Nau. During his studies he spent a semester abroad at Cornell University (with Prof. Geoffrey W. Coates) and furthermore completed a summer project in the group of Prof. Oren A. Scherman at the University of Cambridge. He is currently pursuing a Ph.D. at the University of Oxford under the guidance of Prof. Paul D. Beer and Prof. Jason J. Davis working on electrochemical, supramolecular anion sensors. Other research interests include the development of novel antifouling interfaces for electrochemical (bio)sensors, surface functionalization *via* diazonium chemistry as well as host-guest chemistry.

Prof. Jason Davis is a Professor of Chemistry and a Tutorial Fellow and Dr Lee's Reader in Chemistry at Christ Church, Oxford. He studied Chemistry at Kings College London, where he was awarded The Victor Gold, Ivor John and Robert Wakeford Memorial Prizes in Chemistry and a First Class honours degree in 1993. He then undertook a DPhil in Chemistry at Oxford (1994-1998) he was elected to an Extraordinary Junior Research Fellowship at The Queens College in 1998 and a Royal Society University Research Fellowship in 1999. He was appointed to a University Lectureship in 2003 and made a full professor in 2014. His research interests are broad and primarily focussed on the design and utilisation of advanced functional interfaces, particularly those associated with diagnostics, sensing, molecular switches and imaging. His group have published more than 160 primary peer reviewed publications, including 3 book chapters, one edited volume and numerous invited reviews spanning molecular imaging, nanotechnology, nanoparticle based molecular imaging, molecular electronics, supramolecular chemistry, molecular machines and fundamental electrochemistry.

Prof. Paul Beer obtained a PhD from King’s College London in 1982 with Dr. C. Dennis Hall. After a Royal Society European Post-doctoral Fellowship with Professor J.-M. Lehn and a Demonstratorship at the University of Exeter, he was awarded a Lectureship at the University of Birmingham in 1984. In 1990, he moved to the University of Oxford, where he was made a University Lecturer and Tutorial Fellow at Wadham College, and became a Professor of Chemistry in 1998. His research interests include coordination and supramolecular chemistry.

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