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Review

Ferrocene-Based Electrochemical Sensors for Cations

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Abstract: This study investigates novel ferrocene-based electrochemical sensors for metal cation detection through the design, synthesis and characterisation of ferrocene derivatives. Specifically, the re-search determines the redox potentials of ferrocene versus decamethylferrocene to provide in-sight into the redox potential variations between them. The investigation also examines how electrochemical oxidation of the ferrocene moiety can modulate host affinity for transition metals cations via effects such as electrostatic interactions and changes to coordination chemistry. Metal ion coordination to receptors containing functional groups like imine and quinoline is explored to elucidate selectivity mechanisms. These findings advance the fundamental understanding of ferrocene electrochemistry and host-guest interactions, supporting the development of improved cation sensors with optimised recognition properties, sensitivity, and selectivity. Overall, the work lays the necessary groundwork for applications in analytical chemistry and sensor technologies through customised ferrocene-derived materials.

Keywords: ferrocene; electrochemical sensors; metal cation; host-guest interaction

1. Introduction

The landscape of molecular sensing and recognition has been redefined by the versa-tile synthetic chemistry of ferrocene (Fc), an organometallic compound that has emerged as a cornerstone in developing electrochemical molecular receptors for various cationic species [1–5]. The fascination with Fc in this context stems from its well-established synthetic routes and the accessibility of its redox couple, which confers it with exceptional utility for constructing molecular receptors. These receptors often in-corporate Fc functionalities strategically, serving as signalling or reporter groups. The redox responses of these functionalities undergo perturbations upon binding guest molecules. Alternatively, Fc can serve as a structural component, allowing for precise control over the topology of the guest binding site. Remarkably, Fc-based receptors, especially those assuming dual roles, exhibit a diverse range of functionalities that transcend the capabilities of purely organic architectures [6].

The design paradigm for redox-active receptors commonly employs spacer groups that covalently link the host (metal ion binding moieties) to the Fc unit. This strategic arrangement capitalises on the coexistence of the redox-active centre and the receptor functionality within the same molecular entity. This framework enables Fc-based molecular receptors to engage in concurrent or sequential processes of electron transfer and guest binding (guest = metal cations), with their mutual influence being particularly evident between alkali and alkaline earth metal ions and crown ether or similar oxygen-containing ligands. However, recent investigations have revealed that when hosts containing amine functionalities are involved (e.g., cyclen, cyclam), the interplay between electron transfer and molecular recognition takes on a more intricate nature [7–10].

Fc-based molecular receptors can be designed to bind anionic, cationic or neutral guest molecules [11,12]. Nevertheless, this review article explores Fc-based sensors and molecular receptors tailored for cationic species, shedding light on their intricate designs, redox mechanisms, and sensing responses. We examine the foundational reasons underlying the suitability of Fc as a molecular scaffold for this task, considering factors such as the effect of solvents and substituents on Fc redox potential. We discuss the interactions between Fc and crown ethers as opposed to amine-containing

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hosts and illustrate these concepts using concrete sensor examples, outlining the resultant changes in electrochemical potentials. By navigating through relevant literature and dissecting prominent case studies, we aim to provide an overview of the advancements in electrochemical Fc-based sensing platforms. Through this exploration, we unveil the intricate mechanisms governing their operation and emphasise their pivotal role in shaping the modern landscape of molecular sciences.

2. Why Ferrocene?

Ferrocene stands out because of its unique structure: a central iron atom neatly sandwiched between two cyclopentadienyl rings. This structural arrangement leads to some fascinating electrochemical properties that have attracted the curiosity of many researchers. The redox potential of Fc, as discussed below, is known to vary based on its proximity to the host. This observation, though noteworthy, isn't an isolated phenomenon. When diving deeper into the electrochemical behaviour of Fc, it becomes apparent that several other factors also affect the mentioned redox potential. These factors encompass the nature of the solvent, the type of supporting electrolyte used, and the specific substituents connected to the Fc molecule. The ability of Fc to exhibit changes in its electrochemical responses under these varied conditions underscores its versatility and has cemented its place as a subject of intense study in electrochemistry.

In the extensive body of research surrounding Fc, one aspect has been given less prominence than it deserves: the role of the solvent in modulating Fc redox potential. While ferrocene is often put on a pedestal as an internal reference redox scale or system (IRRS), it is crucial to take a step back and consider the entirety of the system, including the solvent. Neglecting or underestimating the influence of the solvent could lead to a biased or incomplete picture of how ferrocene behaves in different experimental setups. These interactions involve intricate electrostatic interplays between the solvent or electrolyte and specific components of the ferrocene molecule. Such interactions encompass the iron centre and the cyclopentadienyl ring components [13]. Research by Yang et al. has shed light on this phenomenon through a comprehensive analysis of the molecular electrostatic potential (MEP) of Fc and its oxidised ferrocenium ion (Fc^+ or $[Fe^{III}(\eta^5\text{-}C_5H_5)_2]^+$) counterpart [14]. The study elucidated the distribution of electrostatic charges, revealing remarkable insights into the solvation behaviour of Fc. The MEP analysis uncovered negative electrostatic potentials concentrated atop the cyclopentadienyl rings alongside a distinctive planetary-like charge distribution encircling the central iron atom. This distribution significantly fosters electrostatic interactions between Fc and positively charged molecules or ions, including those with electron-acceptor functionalities. Notably, the positively charged regions on the sides of the cyclopentadienyl rings facilitate interactions with electron-donating components from the surrounding solvent or electrolyte.

Interestingly, in the case of Fc^+, the MEP analysis distinctly presents positive electrostatic potentials. This configuration favours electrostatic interactions between Fc^+ and negatively charged ions or molecules characterised by electron-donor groups. The discernible MEP differences between Fc and its Fc^+ counterpart assume a pivotal role, elucidating the observed variances in mass transport properties within viscous solvents, such as ionic liquids [15–19]. This intricate understanding of solvation effects and their consequential impact on Fc and Fc^+ behaviour in distinct environments holds significant promise for advancing our comprehension of their behaviour in diverse contexts. One of which is the demystification of Fc as the optimal IRRS. An IRRS is a reversible or nearly reversible redox system that provides a known and stable, solvent-independent reference point in non-aqueous solvents where reliable reference electrodes are difficult to establish or stabilise [19–21]. The IRRS is generally used with a quasi-reference electrode [22–27].

The history of establishing an IRRS that remains unaffected by the solvent for comparing redox potentials in non-aqueous systems is extensive. This chronicle commenced with the introduction of the $Rb|Rb^+$ or $Rb(Hg)|Rb^+$ redox couples and subsequently advanced with the proposition of employing organometallic redox pairs [28]. To streamline the comparative process and enhance simplicity, IUPAC advocated for the adoption of specific IRRS in non-aqueous contexts, namely, Fc/Fc^+ (also referred to as $Fc^{0/+}$) and bis(biphenyl)chromium(0)|bis(biphenyl)chromium(I), BCr/BCr^+ [28]. These selections were made arbitrarily from various published redox systems [28]. It is noteworthy to observe how an initial arbitrary selection of redox systems, including Fc, has permeated the present scientific landscape, leading to the enduring perception of Fc as an incontrovertible IRRS. This underscores the intricate interplay between historical conventions, pragmatic considerations, and the trajectory of scientific understanding that collectively shape the enduring reputation of Fc.

A range of essential attributes characterises an effective IRRS, several initially outlined by Gritzner and Kuta in the IUPAC recommendation [28]. Additionally, a revised set of properties has been introduced by our research group [29]. This updated framework expands and refines the criteria that define a reliable IRRS, reflecting advancements in our understanding and methodological approaches. The evolution of these properties not only demonstrates the maturation of the field but also underscores the commitment to enhancing the accuracy and applicability of IRRS in diverse electrochemical settings.

Decamethylferrocene (DmFc or $[Fe^{II}(\eta^5\text{-}C_5(CH_3)_5)_2]$) exhibits notably diminished solvent-solute interactions in organic solvent systems, a contrast that surpasses at least one order of magnitude in comparison to ferrocene. This divergence arises due to the methyl-substituent groups within the cyclopentadienyl rings of DmFc, which effectively impede both specific and non-specific interactions. This obstruction originates from the hindered accessibility of organic solvent and supporting electrolyte molecules to the metal centre and the cyclopentadienyl ring [13,30–32]. The veracity of this observation is further corroborated by the analysis of X-ray diffraction patterns of DmFc, which substantiates that the inter-ring methyl groups within DmFc adhere to Van der Waals distances [33]. Consequently, owing to its intrinsic characteristics, DmFc proves to be more appropriate than Fc as an IRRS within organic solvents, where it undergoes a reversible one-electron oxidative transfer process, leading to the formation of decamethylferrocenium (DmFc+ or $[Fe^{III}(\eta^5\text{-}C_5(CH_3)_5)_2]^+$), which is reduced back to DmFc when the potential scanning direction is reverted. The DmFc0/+ mid-point potential, E_m, value associated with this electron transfer is lower than that of Fc due to the electron-donating influence imparted by the methyl groups (inductive effect). These methyl groups direct electron density towards the metal ion, facilitating the extraction of an electron by the electrode. Table 1 shows the difference in the E_m values between $Fc^{0/+}$ and $DmFc^{0/+}$, which fluctuates from 0.614 ± 0.005 V in dichloromethane/0.1 M $[Bu_4N][TFAB]$ ($[TFAB] = [B(C_6F_5)_4]^-$) to 0.413 ± 0.005 V in tetrahydrofuran/0.1 M $[Bu_4N][BF_4]$, representing a difference of 0.201 V due to solvent and supporting electrolyte effects. Furthermore, a change of 0.152 V can be observed by transitioning from tetrahydrofuran to 2,2,2-trifluoroethanol as the organic solvent while maintaining constant the nature and concentration (0.1 M $[Bu_4N][ClO_4]$) of the supporting electrolyte. To mitigate uncertainties when comparing E_m in Table 1, all potential values cited are referenced against the $DmFc^{0/+}$ potential scale. Consequently, as the values in this table signify the disparity in E_m, the chances exist for the absolute E_m values of the $Fc^{0/+}$ and $DmFc^{0/+}$ IRRS to exhibit a more significant variation than that presented here.

Table 1. Redox potentials of Fc vs. DmFc0/+ IRRS in different organic solvents containing different supporting electrolytes.

Solvent	Electrolyte	E_m of $Fc^{0/+}$ vs. $DmFc^{0/+}$ (V)	Ref.
1,2-dibromoethane	0.1 M $[Bu_4N][ClO_4]$	0.475±0.007	[13]
1,2-dichloroethane	0.1 M $[Bu_4N][ClO_4]$	0.532±0.001	[13]
1,2-dichlorobenzene	0.1 M $[Bu_4N][ClO_4]$	0.535±0.001	[13]
2-propanol	0.1 M $[Bu_4N][CF_3SO_3]$	0.455±0.003	[13]
2,2,2-trifluoroethanol	0.1 M $[Bu_4N][ClO_4]$	0.575±0.004	[13]
Acetone	0.1 M $[Bu_4N]Cl$	0.451±0.005	[34]
	0.1 M $[Bu_4N][ClO_4]$	0.479±0.004	[13]
	0.1 M $[Bu_4N][PF_6]$	0.487±0.005	[34]
	0.1 M $[Bu_4N][TFAB]$	0.504±0.005	[34]

Acetonitrile (CH_3CN)	0.1 M $[Bu_4N]Cl$	0.501±0.005	[34]
	0.1 M $[Bu_4N][ClO_4]$	0.505±0.002	[13]
	0.1 M $[Bu_4N][PF_6]$	0.509±0.003	[35]
	0.1 M $[Bu_4N][TFAB]$	0.517±0.005	[34]
Acetonitrile:dichloromethane (80:20)	0.1 M $[Bu_4N][PF_6]$	0.512±0.003	[36]
Aniline	0.1 M $[Bu_4N][ClO_4]$	0.527±0.004	[13]
Anisole	0.1 M $[Bu_4N][PF_6]$	0.518±0.005	[34]
	0.1 M $[Bu_4N][TFAB]$	0.607±0.005	[34]
Benzonitrile	0.1 M $[Bu_4N]Cl$	0.524±0.005	[34]
	0.1 M $[Bu_4N][ClO_4]$	0.523±0.001	[13]
	0.1 M $[Bu_4N][PF_6]$	0.530±0.005	[34]
	0.1 M $[Bu_4N][TFAB]$	0.543±0.005	[34]
Benzyl alcohol	0.1 M $[Bu_4N][ClO_4]$	0.508±0.003	[13]
Bromobenzene	0.1 M $[Bu_4N][ClO_4]$	0.489±0.005	[13]
Chlorobenzene	0.1 M $[Bu_4N][ClO_4]$	0.497±0.001	[13]
Chloroform	0.1 M $[Bu_4N][ClO_4]$	0.483±0.001	[13]
Dichloromethane (DCM)	0.1 M $[Bu_4N]Cl$	0.534±0.005	[34]
	0.1 M $[Bu_4N][ClO_4]$	0.532±0.002	[13]
	0.1 M $[Bu_4N][ClO_4]$	0.570±0.002	[2]
	0.1 M $[Bu_4N][PF_6]$	0.548±0.003	[35]
	0.1 M $[Et_4N][BF_4]$	0.541±0.003	[17]
	0.1 M $[Bu_4N][TFAB]$	0.614±0.005	[34]
	0.1 M $[C_4mPyr][FAP]$	0.589±0.003	[17]
	0.1 M $[C_2mim][FAP]$	0.590±0.003	[17]
	0.1 M $[C_2mim][B(CN)_4]$	0.588±0.003	[17]
	0.1 M $[C_4mim][NTf_2]$	0.570±0.003	[17]
	0.1 M $[C_4mPyr][NTf_2]$	0.568±0.003	[17]
	0.1 M $[C_2mim][FSI]$	0.569±0.003	[17]
	0.1 M $[C_3mim][FSI]$	0.568±0.003	[17]
	0.1 M $[C_4mPyr][N(CN)_2]$	0.564±0.003	[17]
	0.1 M $[C_4mim][PF_6]$	0.556±0.003	[17]
	0.1 M $[C_4mim][BF_4]$	0.557±0.003	[17]
	0.1 M $[C_4mim][CF_3SO_3]$	0.556±0.003	[17]
Diethyl ether	0.1 M $[Bu_4N][BArF_{24}]$	0.550±0.005	[34]
	0.1 M $Na[BArF_{24}]$	0.583±0.005	[34]
Dimethyl sulfoxide	0.1 M $[Bu_4N][PF_6]$	0.486±0.005	[34]
	0.1 M $[Bu_4N][TFAB]$	0.493±0.005	[34]
	0.1 M $[Bu_4N][ClO_4]$	0.468±0.001	[13]
Ethanol	0.1 M $[Bu_4N][ClO_4]$	0.473±0.005	[13]
Formamide	0.1 M $[Bu_4N][ClO_4]$	0.510±0.003	[13]
Methanol (MeOH)	0.1 M $[Bu_4N][ClO_4]$	0.497±0.002	[13]
Nitrobenzene	0.1 M $[Bu_4N][ClO_4]$	0.514±0.002	[13]
Nitromethane	0.1 M $[Bu_4N]Cl$	0.505±0.005	[34]
	0.1 M $[Bu_4N][ClO_4]$	0.516±0.004	[13]
	0.1 M $[Bu_4N][PF_6]$	0.510±0.005	[34]
	0.1 M $[Bu_4N][TFAB]$	0.516±0.005	[34]
N-methylformamide	0.1 M $[Bu_4N][ClO_4]$	0.510±0.002	[13]
N,N-dimethylformamide (DMF)	0.1 M $[Bu_4N]Cl$	0.475±0.005	[34]
	0.1 M $[Bu_4N][ClO_4]$	0.458±0.003	[13]
	0.1 M $[Bu_4N][PF_6]$	0.478±0.005	[34]

	0.1 M $[Bu_4N][TFAB]$	0.493±0.005	[34]
N,N-dimethylacetamide	0.1 M $[Bu_4N][ClO_4]$	0.455±0.008	[13]
Propylene carbonate	0.1 M $[Bu_4N][ClO_4]$	0.495±0.002	[13]
Pyridine	0.1 M $[Bu_4N][ClO_4]$	0.517±0.004	[13]
Tetrahydrofuran	0.1 M $[Bu_4N][BF_4]$	0.413±0.005	[34]
	0.1 M $[Bu_4N][CF_3SO_3]$	0.438±0.005	[34]
	0.1 M $[Bu_4N][ClO_4]$	0.423±0.005	[34]
		0.427±0.002	[13]
	0.1 M $[Bu_4N][PF_6]$	0.446±0.005	[34]
	0.1 M $[Bu_4N][BPh_4]$	0.485±0.005	[34]
	0.1 M $Na[BArF_{24}]$	0.502±0.005	[34]
	0.1 M $[Bu_4N][TFAB]$	0.484±0.005	[34]
	0.1 M $[Bu_4N][BArF_{24}]$	0.521±0.005	[34]
Toluene	0.1 M $[Bu_4N][BF_4]$ [a]	0.430±0.005	[34]

Abbreviations: $[Bu_4N]$ = tetrabutylammonium; $[PF_6]$ = hexafluorophosphate; $[ClO_4]$ = perchlorate; $[BF_4]$ = tetrafluoroborate; $[CF_3SO_3]$ = trifluoromethanesulfonate; [TFAB] = tetrakis(pentafluorophenyl)borate; $[Et_4N]$ = tetraethylammonium; $[C_4mPyr]$ = 1-butyl-1-methylpyrrolidinium; $[C_2mim]$ = 1-ethyl-3-methylimidazolium; $[C_4mim]$ = 1-butyl-3-methylimidazolium; [FAP] = tris(pentafluoroethyl)trifluorophosphate; $[B(CN)_4]$ = tetracyanoborate; $[NTf_2]$ = Bis(trifluoromethanesulfonyl)amide; [FSI] = bis(fluorosulfonyl)imide; $[N(CN)_2]$ = dicyanamide; $[BArF_{24}]$ = bis(trifluoromethyl)phenyl)borate; $[BPh_4]$ = Tetraphenylborate. [a] the toluene:$[Bu_4N][BF_4]$ electrolyte is of the 3:1 stoichiometry.

When considering the impact of substituents on the cyclopentadienyl rings, the solvent's role becomes even more pronounced. Substituents modulate the electron density around the iron centre by their electron-donating or withdrawing nature. This change in electron density, in turn, can influence the solvation shell and the nature of solvent interactions with ferrocene and its derivatives (Table 2). For instance, an electron-donating substituent might increase the negative charge density on the cyclopentadienyl ring. In a polar solvent, which already affects the redox potential of Fc through the stabilisation of charged species, the increase in negative charge might result in an even more pronounced shift of its E_m to more negative potential values. However, the effect might be attenuated or manifest differently in a non-polar solvent. Conversely, electron-withdrawing substituents could exacerbate or mitigate solvent effects, contingent on the specific properties of the solvent used and the nature of the substituent. The interplay between solvent effects and substituent-induced electronic modulation offers a dynamic continuum, with each factor potentially amplifying or modulating the other, resulting in a rich variability of electrochemical behaviour.

The influence of substituents on the E_m of Fc is an exciting aspect of molecular electrochemistry that warrants in-depth investigation. It is well-established that the electron density around the central iron atom can be modulated by introducing various substituents on the surrounding ligands. Depending on the electronic nature of the substituent, such modulation can either stabilise or destabilise the oxidised form of the complex, and its effects rest predominantly upon the electronic principles of induction. When an electron-donating group is appended to the cyclopentadienyl ring of Fc, it can engage in inductive donation. This introduces electron density to the π-system of the cyclopentadienyl ring, which in turn delocalises to the central iron atom. Such an enhancement of electron density around the metal cation predisposes it to a greater likelihood of electron loss, making oxidation more favourable, thus shifting the E_m to more negative potential values respect to that of unmodified Fc (Table 2).

In contrast, electron-withdrawing groups operate on induction and resonance withdrawal principles. These groups extract electron density from the cyclopentadienyl ring. Additionally, certain withdrawing groups can engage in resonance structures that pull electron density away from the cyclopentadienyl ring and into the substituent. As a result of this electron density diminishment, the central iron cation becomes less prone to lose an electron, translating to a shifting of the E_m to more positive potential values respect to that of unmodified Fc (Table 2).

Table 2 shows the E_m values of different substituted Fc derivatives versus $Fc^{0/+}$, which is equal to -0.570 V vs. $Fc^{0/+}$ IRRS for DmFc in dichloromethane/0.1 M $[Bu_4N][ClO_4]$ and 0.640 V vs. $Fc^{0/+}$ for 1,1′-bis(trifluoromethyl)ferrocene in the same solvent/supporting electrolyte system, representing a difference of 1.21 V. Furthermore, a change of 0.141 V can be observed for 1,1′,3,3′-tetra(*t*-butyl)ferrocene by transitioning from acetonitrile (0.1 M $[Bu_4N][ClO_4]$) to toluene containing 0.5 M $[Hex_4N][ClO_4]$ as the supporting electrolyte.

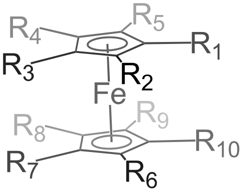
The E_m of Fc is also affected by the distance between the ferrocenyl moiety and substituents that either donate or withdraw electrons [10,37,38]. When analysing a scenario where an electron-withdrawing group is attached to the Fc unit (e.g., Fc-COOH), it becomes evident that increasing methylene groups progressively diminishes the electron-withdrawing effect on Fc—specifically, introducing a single methylene group between the Fc and the carboxylic group results in an E_m shift of 0.245 V towards more negative potential values (Table 2). The magnitude of this shift reduces upon subsequent additions of methylene groups, with further negative shifts of 0.016 and 0.025 V observed following the incorporation of a second and third methylene unit, respectively. In this new scenario (e.g., Fc-$(CH_2)_3$-COOH), the inductive donating property of methylene towards the cyclopentadienyl rings of Fc begins to dominate the resultant E_m of Fc.

The resultant molecule often exhibits compromised stability when the Fc unit is directly linked with electron-donating groups such as amines or hydroxyls. This is exemplified by Fc-NH_2, whose stability depends on various factors such as temperature, pH, and the presence of oxidising agents (e.g., oxygen from air). Consequently, research on these molecule families typically commences with one methylene unit, as seen in Fc-CH_2-OH and Fc-CH_2-NH_2 (Table 2). Interestingly, the observed E_m shift magnitude towards negative values closely aligns with those exhibited by Fc connected to carboxylic groups bearing variable counts of methylene groups as a bridge. As an illustration, the negative E_m shifts of 0.041, 0.032, and 0.040 V are documented upon increasing the number of methylene groups from Fc-CH_2-COOH, Fc-CH_2-NH_2, and Fc-CH_2-OH to Fc-$(CH_2)_3$-COOH, Fc-$(CH_2)_3$-NH_2, and Fc-$(CH_2)_3$-OH, respectively.

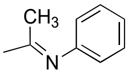
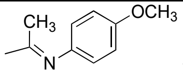
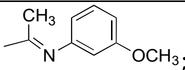
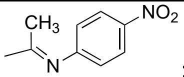
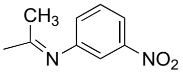
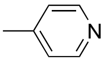
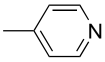
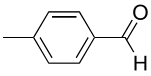
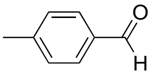
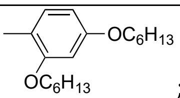
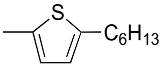
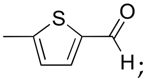
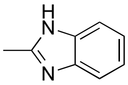
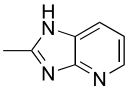
From these observations, it is possible to deduct the pivotal role of methylene group quantity in shaping the overall reactivity and behaviour of ferrocene-based compounds. Expanding the methylene chain effectively serves as a strategic buffer, isolating the electron-withdrawing effects and safeguarding the inherent chemical stability of Fc. Conversely, the judicious placement of electron-donating entities proximal to the ferrocene unit presents opportunities to modulate its E_m and alter its oxidation pathway (see below).

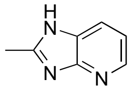
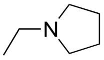
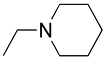
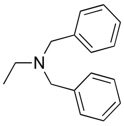
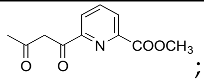
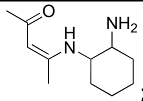
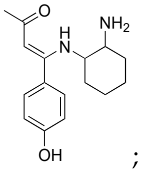
Furthermore, it is essential to consider the spatial orientation and steric hindrance offered by substituents. While electronic effects often dominate, steric factors can influence the approach and interaction of molecules at the electrode surface during redox processes, potentially altering observed redox potentials. Thus, while the electronic properties of substituents provide a foundational understanding of their effects on redox potential, the holistic picture must also account for three-dimensional spatial factors.

Table 2. Redox potentials of substituted Fc in different organic solvents containing different supporting electrolytes.

	**Solvent**	**Electrolyte**	**E_m vs. $Fc^{0/+}$ (V)**	**Ref**
R_{1-10}: H	DCM	0.1 M $[Bu_4N][ClO_4]$	0.000	[2]
R_{1-10}: CH_3	DCM	0.1 M $[Bu_4N][ClO_4]$	-0.570	[2]
R_{1-5}: CH_3; **R_{6-10}**: H	DCM	0.1 M $[Bu_4N][ClO_4]$	-0.270	[2]
$R_{1,10}$: CH_3; **R_{2-9}**: H	CH_3CN	0.1 M $[Bu_4N][ClO_4]$	-0.113	[39]
	CH_3CN	0.1 M $[Bu_4N][PF_6]$	-0.096	[40]
	MeOH	0.1 M $[Bu_4N][ClO_4]$	-0.104	[39]

	Toluene	0.5 M [Hex$_4$N][ClO$_4$]	-0.075	[39]
$\mathbf{R}_{2\text{-}9}$: CH$_3$; $\mathbf{R}_{1,10}$: H	CH$_3$CN	0.1 M [Bu$_4$N][PF$_6$]	-0.406	[40]
$\mathbf{R}_{1,3,7,10}$: *t*-Bu; $\mathbf{R}_{2,4,5,6,8,9}$: H	CH$_3$CN	0.1 M [Bu$_4$N][ClO$_4$]	-0.238	[39]
	CH$_3$CN	0.1 M [Bu$_4$N][PF$_6$]	-0.233	[40]
	MeOH	0.1 M [Bu$_4$N][ClO$_4$]	-0.229	[39]
	Toluene	0.5 M [Hex$_4$N][ClO$_4$]	-0.097	[39]
$\mathbf{R}_1$: *n*-Bu; $\mathbf{R}_{2\text{-}10}$: H	CH$_3$CN	0.1 M [Bu$_4$N][ClO$_4$]	-0.062	[39]
	MeOH	0.1 M [Bu$_4$N][ClO$_4$]	-0.055	[39]
	Toluene	0.5 M [Hex$_4$N][ClO$_4$]	-0.073	[39]
$\mathbf{R}_{1\text{-}10}$: CH$_2$Ph	DCM	0.1 M [Bu$_4$N][ClO$_4$]	-0.070	[2]
$\mathbf{R}_{1,10}$: CF$_3$; $\mathbf{R}_{2\text{-}9}$: H	DCM	0.1 M [Bu$_4$N][ClO$_4$]	0.640	[2]
$\mathbf{R}_1$: CH=CH$_2$; $\mathbf{R}_{2\text{-}10}$: H	CH$_3$CN	0.1 M [Et$_4$N][ClO$_4$]	0.022	[41]
$\mathbf{R}_1$: CH$_2$OH; $\mathbf{R}_{2\text{-}10}$: H	CH$_3$CN	0.1 M [Et$_4$N][ClO$_4$]	0.029	[41]
	CH$_3$CN	0.1 M [Bu$_4$N][ClO$_4$]	-0.012	[39]
	CH$_3$CN	0.1 M [Bu$_4$N][PF$_6$]	0.016	[38]
	MeOH	0.1 M [Bu$_4$N][ClO$_4$]	0.005	[39]
	Toluene	0.5 M [Hex$_4$N][ClO$_4$]	-0.044	[39]
$\mathbf{R}_1$: (CH$_2$)$_2$OH; $\mathbf{R}_{2\text{-}10}$: H	CH$_3$CN	0.1 M [Bu$_4$N][PF$_6$]	-0.046	[38]
$\mathbf{R}_1$: (CH$_2$)$_3$OH; $\mathbf{R}_{2\text{-}10}$: H	CH$_3$CN	0.1 M [Bu$_4$N][PF$_6$]	-0.052	[38]
$\mathbf{R}_1$: (CH$_2$)$_4$OH; $\mathbf{R}_{2\text{-}10}$: H	CH$_3$CN	0.1 M [Bu$_4$N][PF$_6$]	-0.054	[38]
$\mathbf{R}_1$: CH(CH$_3$)OH; $\mathbf{R}_{2\text{-}10}$: H	CH$_3$CN	0.1 M [Et$_4$N][ClO$_4$]	-0.008	[41]
$\mathbf{R}_{1,10}$: CH(CH$_3$)OH; $\mathbf{R}_{2\text{-}9}$: H	CH$_3$CN	0.1 M [Et$_4$N][ClO$_4$]	-0.013	[41]
$\mathbf{R}_1$: CH$_2$CONH$_2$; $\mathbf{R}_{2\text{-}10}$: H	CH$_3$CN	0.1 M [Bu$_4$N][PF$_6$]	-0.003	[38]
$\mathbf{R}_1$: (CH$_2$)$_2$CONH$_2$; $\mathbf{R}_{2\text{-}10}$: H	CH$_3$CN	0.1 M [Bu$_4$N][PF$_6$]	-0.027	[38]
$\mathbf{R}_1$: (CH$_2$)$_3$CONH$_2$; $\mathbf{R}_{2\text{-}10}$: H	CH$_3$CN	0.1 M [Bu$_4$N][PF$_6$]	-0.049	[38]
$\mathbf{R}_1$: COOH; $\mathbf{R}_{2\text{-}10}$: H	CH$_3$CN	0.1 M [Et$_4$N][ClO$_4$]	0.239	[41]
	CH$_3$CN	0.1 M [Bu$_4$N][ClO$_4$]	0.234	[39]
	CH$_3$CN	0.1 M [Li][ClO$_4$]	0.239	[37]
	MeOH	0.1 M [Bu$_4$N][ClO$_4$]	0.233	[39]
	Toluene	0.5 M [Hex$_4$N][ClO$_4$]	0.157	[39]
$\mathbf{R}_1$: CH$_2$COOH; $\mathbf{R}_{2\text{-}10}$: H	CH$_3$CN	0.1 M [Li][ClO$_4$]	-0.006	[37]
$\mathbf{R}_1$: (CH$_2$)$_2$COOH; $\mathbf{R}_{2\text{-}10}$: H	CH$_3$CN	0.1 M [Li][ClO$_4$]	-0.022	[37]
$\mathbf{R}_1$: (CH$_2$)$_3$COOH; $\mathbf{R}_{2\text{-}10}$: H	CH$_3$CN	0.1 M [Li][ClO$_4$]	-0.047	[37]
$\mathbf{R}_1$: COOCH$_3$; $\mathbf{R}_{2\text{-}10}$: H	CH$_3$CN	0.1 M [Et$_4$N][ClO$_4$]	0.243	[41]
	CH$_3$CN	0.1 M [Bu$_4$N][ClO$_4$]	0.237	[39]
	MeOH	0.1 M [Bu$_4$N][ClO$_4$]	0.263	[39]
	Toluene	0.5 M [Hex$_4$N][ClO$_4$]	0.214	[39]
$\mathbf{R}_{1,10}$: COOCH$_3$; $\mathbf{R}_{2\text{-}9}$: H	CH$_3$CN	0.1 M [Et$_4$N][ClO$_4$]	0.470	[41]
$\mathbf{R}_1$: COCH$_3$; $\mathbf{R}_{2\text{-}10}$: H	CH$_3$CN	0.1 M [Bu$_4$N][ClO$_4$]	0.244	[39]
	MeOH	0.1 M [Bu$_4$N][ClO$_4$]	0.271	[39]
	Toluene	0.5 M [Hex$_4$N][ClO$_4$]	0.191	[39]
$\mathbf{R}_{1,10}$: COCH$_3$; $\mathbf{R}_{2\text{-}9}$: H	CH$_3$CN	0.1 M [Et$_4$N][ClO$_4$]	0.482	[41]
$\mathbf{R}_1$: COPh; $\mathbf{R}_{2\text{-}10}$: H	CH$_3$CN	0.1 M [Bu$_4$N][ClO$_4$]	0.250	[39]
	MeOH	0.1 M [Bu$_4$N][ClO$_4$]	0.272	[39]
	Toluene	0.5 M [Hex$_4$N][ClO$_4$]	0.214	[39]
$\mathbf{R}_1$: CONH$_2$; $\mathbf{R}_{2\text{-}10}$: H	CH$_3$CN	0.1 M [Bu$_4$N][PF$_6$]	0.183	[38]
$\mathbf{R}_1$: CHO; $\mathbf{R}_{2\text{-}10}$: H	CH$_3$CN	0.1 M [Bu$_4$N][ClO$_4$]	0.285	[39]
	MeOH	0.1 M [Bu$_4$N][ClO$_4$]	0.304	[39]
	Toluene	0.5 M [Hex$_4$N][ClO$_4$]	0.259	[39]
$\mathbf{R}_1$: CH$_2$NH$_2$; $\mathbf{R}_{2\text{-}10}$: H	CH$_3$CN	0.1 M [Bu$_4$N][PF$_6$]	-0.014	[38]
$\mathbf{R}_1$: (CH$_2$)$_2$NH$_2$; $\mathbf{R}_{2\text{-}10}$: H	CH$_3$CN	0.1 M [Bu$_4$N][PF$_6$]	-0.037	[38]

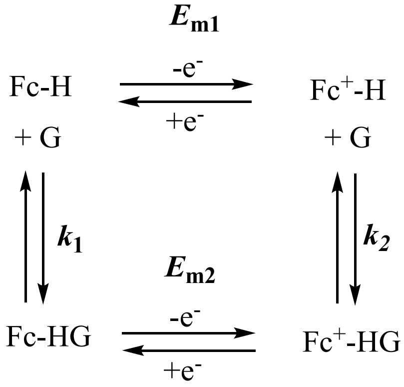
R$_1$: $(CH_2)_3NH_2$; **R**$_{2\text{-}10}$: H	CH_3CN	0.1 M $[Bu_4N][PF_6]$	-0.046	[38]
R$_1$: $(CH_2)_4NH_2$; **R**$_{2\text{-}10}$: H	CH_3CN	0.1 M $[Bu_4N][PF_6]$	-0.060	[38]
R$_1$: $CH_2N(CH_3)_2$; **R**$_{2\text{-}10}$: H	CH_3CN	0.1 M $[Bu_4N][ClO_4]$	-0.004	[39]
	MeOH	0.1 M $[Bu_4N][ClO_4]$	0.046	[39]
	Toluene	0.5 M $[Hex_4N][ClO_4]$	0.009	[39]
	CH_3CN	0.1 M $[Bu_4N][PF_6]$	-0.023	[42]
	DCM:CH_3CN 1:4	0.1 M $[Bu_4N][PF_6]$	0.003	[7]
R$_{1,10}$: $CH_2N(CH_3)_2$; **R**$_{2\text{-}9}$: H	CH_3CN	0.1 M $[Bu_4N][PF_6]$	-0.017	[42]
R$_{1,10}$: $(CH_2)_2N(CH_3)_2$; **R**$_{2\text{-}9}$: H	CH_3CN	0.1 M $[Bu_4N][PF_6]$	-0.077	[42]
R$_{1,10}$: $CH_2N(CH_2Ph)_2$; **R**$_{2\text{-}9}$: H	DCM	0.2 M $[Bu_4N][PF_6]$	-0.001	[9]
R$_{1,10}$: $C(CH_3){=}N(CH_2)_5CH_3$; **R**$_{2\text{-}9}$: H	DCM:CH_3CN 1:1	0.1 M $[Bu_4N][PF_6]$	0.211	[43]
R$_{1,10}$:  ; **R**$_{2\text{-}9}$: H	DCM:CH_3CN 1:1	0.1 M $[Bu_4N][PF_6]$	0.289	[43]
R$_{1,10}$:  ; **R**$_{2\text{-}9}$: H	DCM:CH_3CN 1:1	0.1 M $[Bu_4N][PF_6]$	0.245	[43]
R$_{1,10}$:  ; **R**$_{2\text{-}9}$: H	DCM:CH_3CN 1:1	0.1 M $[Bu_4N][PF_6]$	0.261	[43]
R$_{1,10}$:  ; **R**$_{2\text{-}9}$: H	DCM:CH_3CN 1:1	0.1 M $[Bu_4N][PF_6]$	0.435	[43]
R$_{1,10}$:  ; **R**$_{2\text{-}9}$: H	DCM:CH_3CN 1:1	0.1 M $[Bu_4N][PF_6]$	0.390	[43]
R$_{1,10}$: SH; **R**$_{2\text{-}9}$: H	DCM	0.1 M $[Bu_4N][ClO_4]$	0.200	[2]
R$_1$: $S(CH_2)_2OH$; **R**$_{2\text{-}10}$: H	CH_3CN	0.1 M $[Et_4N][ClO_4]$	0.010	[41]
R$_1$: $SCH_2CH(CH_3)COOH$; **R**$_{2\text{-}10}$: H	CH_3CN	0.1 M $[Et_4N][ClO_4]$	0.039	[41]
R$_1$: $CH(CH_3)SPh$; **R**$_{2\text{-}10}$: H	CH_3CN	0.1 M $[Et_4N][ClO_4]$	0.020	[41]
R$_1$: $CH(Ph)SPh$; **R**$_{2\text{-}10}$: H	CH_3CN	0.1 M $[Et_4N][ClO_4]$	0.043	[41]
R$_1$:  ; **R**$_{2\text{-}10}$: H	CH_3CN	0.1 M $[Bu_4N][ClO_4]$	0.180	[44]
R$_{1,10}$:  ; **R**$_{2\text{-}9}$: H	CH_3CN	0.1 M $[Bu_4N][ClO_4]$	0.350	[44]
R$_1$:  ; **R**$_{2\text{-}10}$: H	CH_3CN	0.1 M $[Bu_4N][ClO_4]$	0.170	[44]
R$_{1,10}$:  ; **R**$_{2\text{-}9}$: H	CH_3CN	0.1 M $[Bu_4N][ClO_4]$	0.180	[44]
R$_1$:  ; R$_{2\text{-}10}$: H	CH_3CN	0.1 M $[Bu_4N][ClO_4]$	0.020	[44]
R$_1$:  ; **R**$_{2\text{-}10}$: H	CH_3CN	0.1 M $[Bu_4N][ClO_4]$	0.090	[44]
R$_1$:  ; **R**$_{2\text{-}10}$: H	CH_3CN	0.1 M $[Bu_4N][ClO_4]$	0.130	[44]
R$_1$:  ; **R**$_{2\text{-}10}$: H	CH_3CN	0.1 M $[Bu_4N][ClO_4]$	0.075	[45]
R$_1$:  ; **R**$_{2\text{-}10}$: H	CH_3CN	0.1 M $[Bu_4N][ClO_4]$	0.085	[45]

$\mathbf{R}_{1,10}$:  ; $\mathbf{R}_{2-9}$: H	CH_3CN	0.1 M $[Bu_4N][ClO_4]$	0.205	[45]
$\mathbf{R}_{1,10}$:  ; $\mathbf{R}_{2-9}$: H	DCM	0.2 M $[Bu_4N][PF_6]$	0.002	[9]
$\mathbf{R}_{1,10}$:  ; $\mathbf{R}_{2-9}$: H	DCM	0.2 M $[Bu_4N][PF_6]$	-0.001	[9]
$\mathbf{R}_{1,10}$:  ; $\mathbf{R}_{2-9}$: H	DCM	0.2 M $[Bu_4N][PF_6]$	-0.001	[9]
$\mathbf{R}_{1}$:  ; $\mathbf{R}_{2-10}$: H	CH_3CN	0.1 M $[Bu_4N][ClO_4]$	0.366	[45]
$\mathbf{R}_{1}$:  ; $\mathbf{R}_{2-10}$: H	CH_3CN	0.1 M $[Bu_4N][PF_6]$	0.100	[46]
$\mathbf{R}_{1}$:  ; $\mathbf{R}_{2-10}$: H	CH_3CN	0.1 M $[BuN][PF_6]$	0.120	[46]

3. Ferrocene-Based Electrochemical Sensors Using Oxygen-Containing Host Molecules

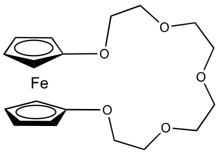
Electrochemical molecular recognition refers to the integrated chemical processes by which a redox-responsive receptor molecule recognises and electrochemically senses a guest species [47]. A suitable recognition requires a potential change larger than the experimental error of the electrochemical technique used. For example, the mid-point potential change (ΔE_m) should be larger than ±0.005 V when cyclic voltammetry is used. However, this change could be larger than ±0.001 V for potentiometric titrations [12].

Oxygen-containing ferrocene derivatives are vital for alkali and alkaline earth metal ions sensing [48,49]. The mechanism of molecular recognition can be described using a squares scheme where Fc-H, Fc^+-H, G, Fc-HG, and Fc^+-HG represent the ferrocene host, ferrocenium host, guest, ferrocene host-guest complex, and ferrocenium host-guest complex, respectively (Scheme 1), were E_{m1} and E_{m2} are the mid-point potentials for the Fc-H/Fc^+-H and Fc-HG/Fc^+-HG redox processes and k_1 and k_2 are the host-guest binding constant for Fc-H and Fc^+-H, respectively [6,47]. The vertical reactions in Scheme 1 represent the guest binding at the host site, which can shift the E_m of Fc pendant group connected to the host. The horizontal reactions represent the electrochemical electron transfer, where $E_{m1} \neq E_{m2}$ for a suitable electrochemical molecular recognition once the guest ion binds to the host. The larger the shift, the better the electrochemical molecular recognition.

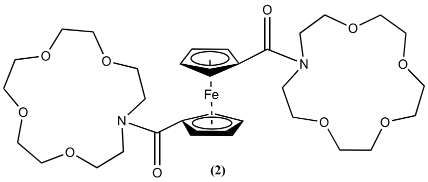


Scheme 1. Square scheme showing coupled electron transfer and guest transfer to and from a ferrocene host molecule.

Crown ethers have gained particular interest as hosts within the family of macrocycles. This is due to their unique interwoven structures composed of oxygen and carbon atoms, making them well-suited for binding a wide range of metal ions [50–52]. The first group of cation receptors known for their redox activity that researchers explored consisted of ferrocene crown ether conjugates **1**-**4** [53–56]. These Fc-based electrochemical sensors were developed for alkali cations such as sodium, potassium, caesium, and lithium, where the electron-rich crown ether acts as the host centre. Inserting a cation to the crown ether of **1–3** significantly results in a substantial E_m shift of Fc to more positive potential values. For example, cyclic voltammograms of 0.2 mM pentaoxa[13]ferrocenophane **1** recorded in CH_2Cl_2/0.1 M $[Bu_4N][PF_6]$ showed a positive E_m shift of 0.17 V after addition of 1 mM $NaClO_4$ [56]. This effect was explained by electrostatic repulsion forces between ferrocenium and the guest Na^+.



(1)



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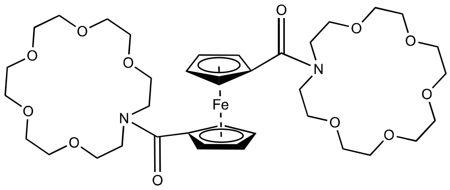

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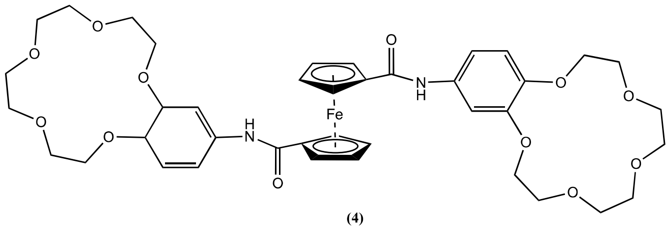

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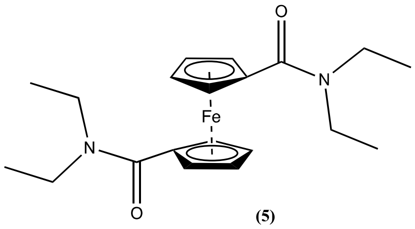
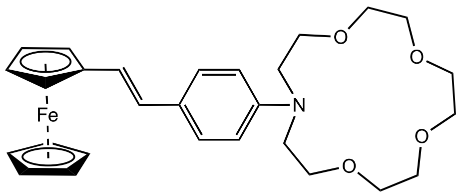


(5)

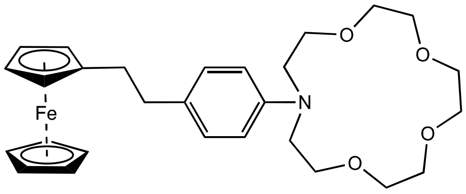
In the case of molecule **2**, the Em of Fc collected in CH_3CN containing 0.2 M $[Bu_4N][BF_4]$ as the supporting electrolyte showed a significant positive shift of 0.040, 0.020 and 0.070 V after one equivalent of Na^+, K^+ and Li^+ ions were added, respectively. Similar shifts of 0.035, 0.020, and 0.075 V were observed for molecule **3** after adding one equivalent of the respective ions [53]. Nevertheless, the E_m of **4** remained unchanged in the presence of Na^+, K^+ and Li^+ ions, which was argued as related to the considerable distance between Fc and host [55]. Notably, the ability to sense alkali cations is not exclusive to the crown ether host. For example, ferrocene amide **5** has a carbonyl oxygen donor, which acts as a host site for Li^+, inducing a positive E_m shift of 0.390 V compared to free **5** [53,57].

Additional investigations into Fc-crown ethers have shown that electronic conjugation can convey a redox reaction when cations bind, even when the binding unit is apart from the Fc reporter group. This can be further explained using molecules **6** and **7** [58]. In molecule **6**, an aza-crown is connected to Fc through an E-stilbene-like linkage. Cyclic voltammetry of **6** in CH_3CN containing 0.2 M $[Bu_4N][BF_4]$ as the supporting electrolyte showed a positive E_m shift of 0.120 V when Mg^{2+} was added. Conversely, for molecule **7**, no discernible cation-induced E_m shift was noticed, which was rationalised as a consequence of the lack of a channel for electronic communication between the host and Fc due to its saturated linker.

Receptor **8**, where an aryl aza-crown is directly bonded to Fc, shows a positive E_m shift of 0.040 V for K^+, 0.090 V for Na^+ and 0.110 V for Mg^{2+} in acetonitrile containing 0.2 M $[Bu_4N][BF_4]$ as the supporting electrolyte [57]. It was hypothesised that the magnitude of the E_m shift of Fc could be related to the charge/radius ratio of cation guests.



(6)



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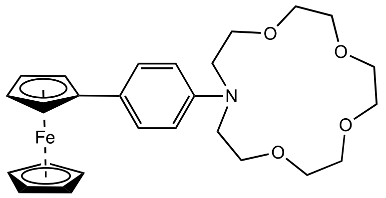

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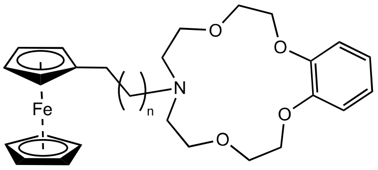

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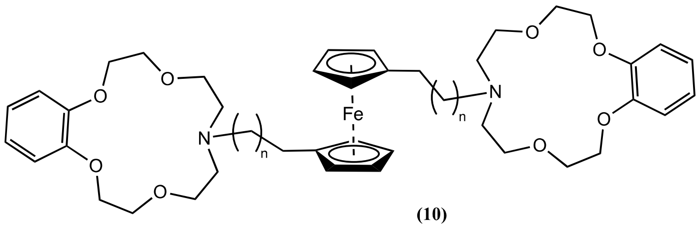
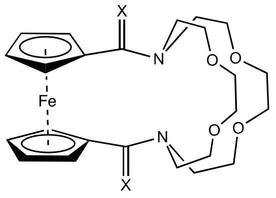


(10)

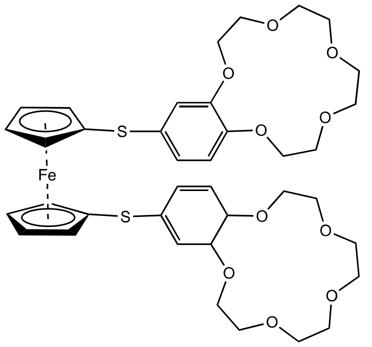
Two series of ferrocene-linked benzoaza[15]crown-5 host molecules **9** and **10** were synthesized with varying alkyl spacer lengths (n = 0, 1, and 3). Cyclic and square wave voltammetry were employed to investigate the electrochemical behaviour of these ligands in the presence of proton and various metal cations [59]. Significant positive E_m shifts were observed upon cation binding, supporting Coulombic origin of the through-space interactions. The ΔE_m varied linearly with the inverse of the distance between Fc and the bound cation, in agreement with Coulomb's law. For the optimal condition (n = 0), **9** ΔE_m of 0.163, 0.068, and 0.040 V and **10** ΔE_m of 0.402, 0.292, and 0.159 V for H^+, Mg^{2+} and Ba^{2+} were observed [59].

Fc connected to cryptands is also well-studied as a molecular sensor for cations [60]. Cyclic voltammetry studies showed a positive E_m shift in the presence of alkaline earth and lanthanide cations [61,62]. Molecule **11** showed the most significant E_m positive shift of 0.295 V for Be^{2+} and 0.254 V for Dy^{3+}. These studies have established a broad correlation between the change in redox potential and the charge density of the cationic species.



(11) X=O

(12) X=H



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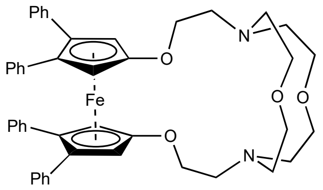
When alkyl amines replaced the amide groups in **11** as in **12**, a more significant E_m shift was observed after cations binding [63]. For example, the Ca^{2+} binding to **11** and **12** showed a positive E_m shift of 0.155 and 0.275 V, respectively. Also, molecule **12** has an exceptional selectivity for Ag^+, displaying a positive ΔE_m of 0.282 V after Ag^+ binding. It was hypothesised that the flexibility of the alkyl linker greatly influences the coupling between Fc and the cryptand host site.

Interestingly, molecule **13**, which has the Fc connected to two crown ether ligands via sulphur, showed a 0.070 V positive ΔE_m for Na^+ binding and a 0.060 V negative ΔE_m for K^+ ion [48]. The source of this anomalous behaviour is due to conformational changes upon K^+ binding. ^{13}C-NMR and FAB-MS confirmed that the larger size of K^+ causes the receptor molecule to form a 1:1 sandwich complex, whereas the smaller size of the Na^+ ion produces a 1:2 host:guest complex. The 1:2 complex may have the two crown ether units in a *trans*-like configuration with respect to the Fc unit. However, the 1:1 sandwich confirmation forces the two crown ether units to the same side of the Fc, forming a *cis*-like configuration, increasing the Fc instability, and justifying the negative ΔE_m observed.

Molecules **14**, **15** and **16** are examples of Fc linked to varying sizes of cryptands via electron donor oxygen atoms [64]. Upon careful analysis of cyclic voltammetry data for these molecules and their respective alkali and alkaline earth metal complexes in CH_3CN, two trends can be observed: *a*) Larger the size of the cryptands (**14** < **15** < **16**), the smaller the positive ΔE_m observed; *b*) the largest positive ΔE_m was observed for metal ions whose sizes are complementary to the cryptand size. For molecule **14**, the most significant positive ΔE_m of 0.380, 0.360 and 0.305 V were obtained for Ca^{2+}, Sr^{2+}, and Ba^{2+}, respectively.



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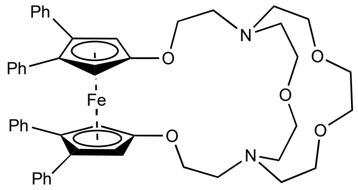

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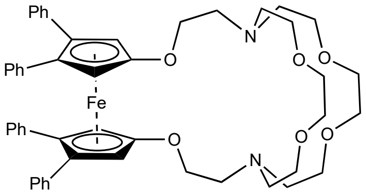
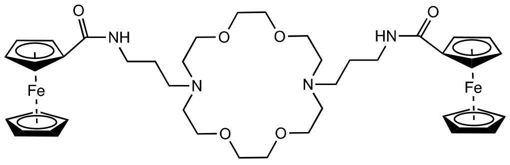


(16)

After complexation with Na^+, **14**, **15** and **16** showed a positive ΔE_m of 0.215, 0.180 and 0.080 V, respectively. This trend supports the theory that the most considerable anodic shift was produced by metal ions whose sizes complement the size of the cryptand connected to the Fc unit.

Host units containing di- or tri-aza crown ethers featuring multiple Fc units (**17** and **18**) have been synthesised [65]. Cyclic voltammetry experiments carried out in CH_3CN/0.2 M $[Bu_4N][BF_4]$ showed that the progressive addition of two equivalent K^+ to solutions of **17** or **18** showed a positive ΔE_m of 0.050 and 0.085 V, respectively.

Receptor **19** was synthesised by connecting Fc to an 8-hydroxyquinoline unit [66]. Cyclic voltammogram of **19** in CH_3CN/0.15 M $[Bu_4N][ClO_4]$ shows a chemically reversible $Fc^{0/+}$ one-electron process. However, **19** exhibits a negative ΔE_m of 0.149 V after adding one equivalent of Hg^{2+}. This shift was attributed to Hg^{2+}, which enhances the electron density at the Fc centre of **19**. Based on fluorescence data, it was hypothesised that the Hg^{2+} ion binds to the oxygen atoms of the ester group, increasing the intramolecular charge transfer, a phenomenon linked to the influence of heavy atoms [67].



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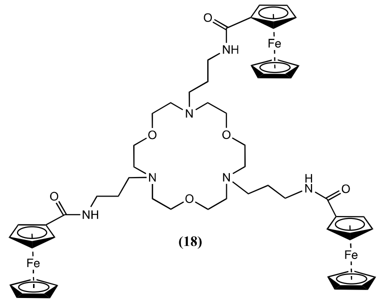

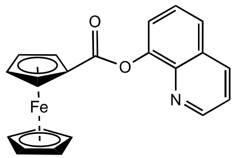

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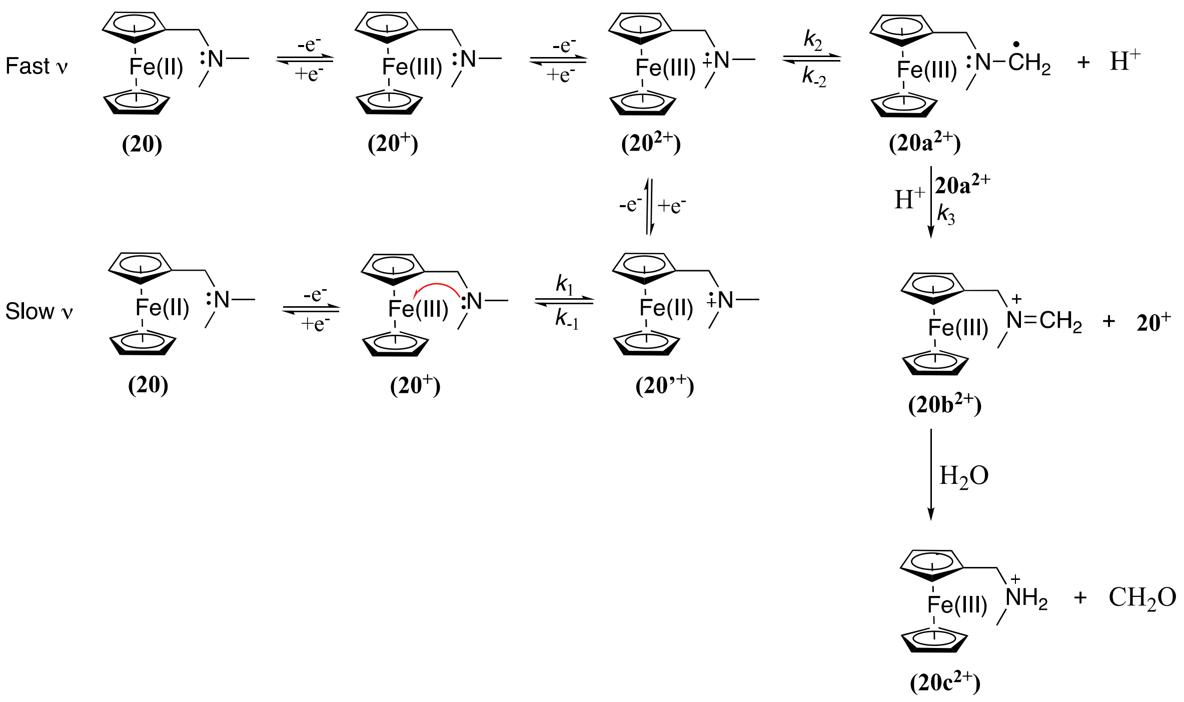
4. Ferrocene-Based Electrochemical Sensors Using Nitrogen-Containing Host Molecules

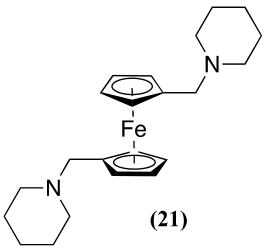
The interaction between Fc and amines has been the subject of extensive research due to its potential wide application range, including the design of metal ion receptors and sensors [8–10,63,68–72]. However, despite numerous studies, the details of this interaction and the oxidation mechanism of ferrocene-bearing amine compounds have remained elusive until recently, where the oxidation mechanism of N,N-dimethylaminomethylferrocene (**20**, $Fc\text{-}CH_2\text{-}N(CH_3)_2$), which can be considered as the parent ligand for many Fc receptors presented in this review, was evaluated and the oxidation product identified (Scheme 2) [7].

At fast scan rates (n), the oxidation process was found to be a simple reversible one-electron oxidation, where the Fc moiety is oxidised to form the ferrocenium cation $\mathbf{20}^+$. This cation is then further oxidised at more positive potentials to form $\mathbf{20}^{2+}$, triggering a reaction sequence that leads to the formation of various intermediate species. Interestingly, the presence of the amine moiety was found to enhance the reactivity of the ferrocenium cation formed on oxidation.



Scheme 2. Schematic representation of the mechanism postulated for the oxidation of **20**.

At slow n, additional steps were observed in the oxidation mechanism. These steps included the direct oxidation of the ferrocenium cation and the formation of a terminal methylene radical **20a**$^{2+}$. This intermediate **20a**$^{2+}$ is formed via two distinct routes: *i*) through direct oxidation of **20**$^{+}$ when the potential scan is extended to more positive values (as observed at high scan rates), and *ii*) through an intramolecular electron transfer from a nitrogen atom to the iron(III) centre (k_1 =0.05 s^{-1}), effectively regenerating the Fc unit and producing a radical cation designated as **20’**$^{+}$, which can then be further oxidised to form **20**$^{2+}$ and subsequently deprotonation to yield **20a**$^{2+}$. A following-up disproportionation reaction regenerates **20**$^{+}$ and forms the iminium derivative **20b**$^{2+}$. Water molecules, either existing as contaminants in the organic solvent or introduced during the extraction of the product, may react with **20b**$^{2+}$ to produce the secondary amine **20c**$^{2+}$ along with formaldehyde as a side product [7]. Although without product identification, a similar mechanism was postulated for **21-26** and related molecules, arriving after oxidation to the corresponding iminium cation [8–10].



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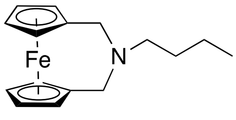

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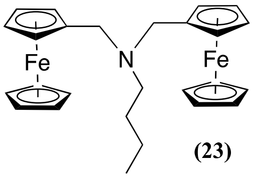

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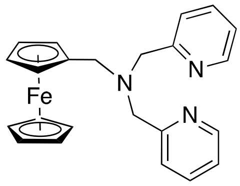

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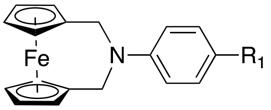

R_1 = Me; *n*-Bu; *t*-Bu; OH

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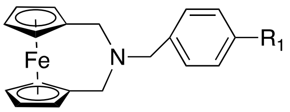
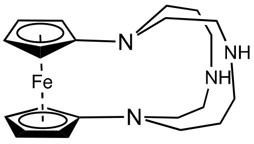


R_1 = Me; CF_3

(26)

The consequence of this finding is that the electrochemical oxidation of the Fc moiety could potentially modify the host affinity for transition metal ions through three distinct mechanisms: *a*) the development of electrostatic repulsion due to the close spatial proximity of the oxidised Fe(III) centre (as part of the ferrocenium ion) to the binding site; *b*) the induction of a positive charge on a host nitrogen atom by substitution of a lone electron pair, which diminishes the host ability to complement the target ion; and *c*) the interaction of the iminium species with water or other nucleophilic molecules leading to the opening of host ring, diminishing the inherent preorganisation of the amine-containing hosts [7]. Consequently, the square scheme described above for oxygen-containing hosts to describe molecular recognition processes may not extend to nitrogen-containing host systems and caution must be taken when conducting such analyses [47,49].

The Fc bridged cyclam **27** was evaluated by cyclic voltammetry in CH_3CN/ $[Bu_4N][PF_6]$ showed a significant positive ΔE_m of 0.360 V for Co^{2+}, 0.380 V for Ni^{2+}, 0.410 V for Cu^{2+}, and 0.470 V for Zn^{2+} [73]. The significant positive E_m shift in the presence of metal ions could be a through-space electrostatic interaction, which causes a substantial perturbation of the E_m of Fc. Molecule **27** was also used as a selective sensor for Cu^{2+}, which showed an ΔE_m of 0.210 V in the presence of Cu^{2+} in 70:30 1,4-dioxane:0.1 M KNO_3 aqueous solution (pH 5.0). However, the E_m was not affected by the presence Ni^{2+}, Zn^{2+}, Cd^{2+}, Hg^{2+} and Pb^{2+} ions [74].



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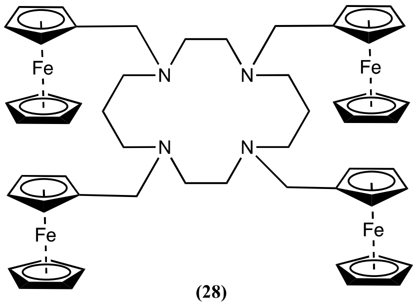

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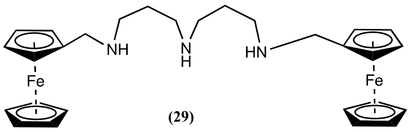
The electrochemical behaviour of **28** in 1:1 DCM:MeOH/$[Bu_4N][PF_6]$ was studied in the absence and presence of Cu^{2+} [75]. The addition of Cu^{2+} resulted in a positive E_m shift of 0.094 V. However, no E_m changes were observed when **28** was in contact with Ni^{2+}, which was hypothesised as related to the slow complexation kinetics.

Acyclic receptor molecules **29-31** were synthesised, and their interaction with transition metals was evaluated [76]. It was observed that the added metal ions may directly coordinate with host molecules or protonate them by acting as an acid. For example, **29** co-ordinates with Ni^{2+} and Cu^{2+}, generating a positive E_m shift of 0.058 and 0.098 V, respectively. Instead, the addition of Zn^{2+} undergoes a protonation pathway of the receptor, causing a positive E_m shift of 0.162 V. In contrast, **30** exclusively follows the protonation pathway due to the large bite angle of the host group. Adding Ni^{2+}, Cu^{2+}, and Ca^{2+} to **30** showed a positive E_m shift of 0.175, 0.169 and 0.160 V, respectively. Meanwhile, the pyridine nitrogen atom in **31** participates in the coordination of metal ions. Its interaction with Ni^{2+}, Cu^{2+} and Zn^{2+} resulted in a positive E_m shift of 0.115, 0.105 and 0.075 V, respectively.



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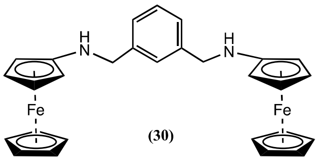

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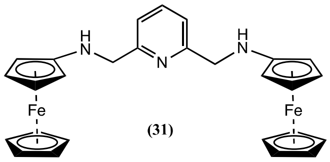

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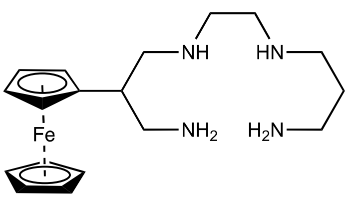
The electrochemical sensor **32** forms a square-planar complex with Ni^{2+}, showing a slight positive E_m shift of 0.025 V in an aqueous 0.1 M $NaClO_4$ solution [77]. However, due to the presence of two electron-deficient amide nitrogen atoms in **33**, the dioxotetraamino host shows a poor tendency towards complexation [77]. This behaviour changes when Ni^{2+} is complexed under basic conditions, where nitrogen deprotonations result in a double negative charge on the ring system of **33**, forming a stable four-coordinated system that generates a negative E_m shift of 0.042 V [11,77].

doi:10.20944/preprints202311.0800.v1



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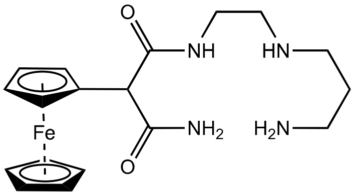

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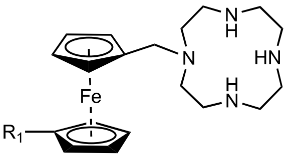
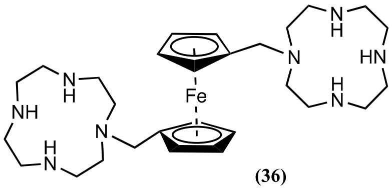
Recently, we synthesised cyclen and cyclam macrocycles bearing ferrocene pendants and investigated their ability to work as electrochemical sensors for transitional metal cations [7]. The cyclic voltammograms **34** in 1:4 CH_2Cl_2:CH_3CN/0.1 M $[Bu_4N][PF_6]$ showed upon addition of Ni^{2+}, Cd^{2+}, Zn^{2+}, Cu^{2+} and Co^{2+} ions a positive E_m shift of 0.054, 0.057, 0.078, 0.100, and 0.120 V, respectively. Similarly, when Zn^{2+} co-ordinates with molecule **35**, a positive E_m shift of 0.098 V was observed.



(34) R$_1$=H
(35) R$_1$=CH$_2$OH



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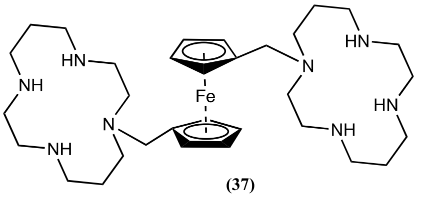

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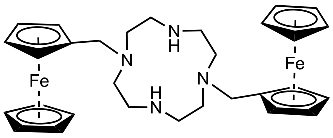

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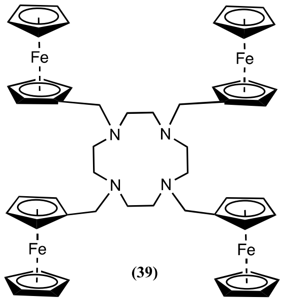

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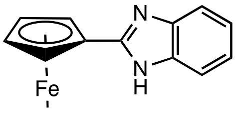
Addition of Ni^{2+}, Cd^{2+}, Zn^{2+}, Cu^{2+} and Co^{2+} ions to a solution of **36** in 1:4 CH_2Cl_2:CH_3CN/0.1 M $[Bu_4N][PF_6]$ generates a positive E_m shift of 0.148, 0.160, 0.203, 0.240, and 0.280 V, respectively. Similarly, cyclic voltammograms of **37** showed a more significant response in the presence of the mentioned ions, generating a positive E_m shift of 0.184 V for Ni^{2+}, 0.179 V for Cd^{2+}, 0.183 V for Zn^{2+}, 0.239 V for Cu^{2+} and 0.259 V for Co^{2+}.

The cyclic voltammetric behaviour of **38**, where two Fc units are linked via the cyclen host group, was studied in detail before and after complexation with 3*d* and 4*d* transition metal cations. The complexation reaction between **38** and Ni^{2+}, Cd^{2+}, Zn^{2+}, Cu^{2+} and Co^{2+} ions resulted in a positive E_m shift of 0.064, 0.060, 0.088, 0.111, and 0.132 V, respectively. Similarly, **39**, where four Fc units are attached to the cyclen host group, was also investigated. Adding Cd^{2+}, Zn^{2+}, Cu^{2+} and Co^{2+} to **39** resulted in a positive ΔE_m of 0.053, 0.047, 0.078, and 0.022 V, respectively. However, no response was observed after the addition of Ni^{2+} ions.

Based on electrochemical data, the charge density of transitional metal ions can be correlated with the ΔE_m observed, except for Ni^{2+}. The magnitude of the E_m shift follows the order **36** ≈ **37** >> **34** ≈ **35** ≈ **38** > **39** and depends on the number of macrocycles linked to Fc. Nonetheless, no significant change in E_m can be obtained by increasing the number of Fc groups attached to a guest macrocycle [7].

The redox behaviour of **40-44** was studied in CH_3CN/0.1 M $[Bu_4N][ClO_4]$ [45]. Receptor **40** showed a positive E_m shift of 0.250 V after adding Pb^{2+}, Zn^{2+}, or Hg^{2+} ions. However, **41** shows a maximum response after adding one equivalent of Pb^{2+}, presenting a positive E_m shift of 0.150 V. Similarly, **41** showed a positive ΔE_m of 0.090 and 0.120 V for Zn^{2+} and Hg^{2+} ions. This shift was very specific, and the cyclic voltammogram of **41** was not affected by the addition of large quantities of Li^+, Na^+, K^+, Ca^{2+}, Mg^{2+}, Ni^{2+} and Cd^{2+} ions. Likewise, **42** showed a positive E_m shift of 0.120 V in the presence of Pb^{2+}. Consequently, the positive E_m shift for the monosubstituted Fc after complexing with Pb^{2+} is **42** < **41** < **40**.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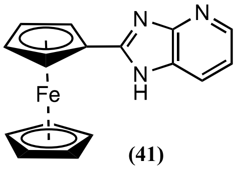
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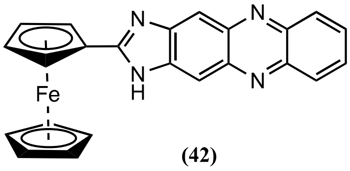
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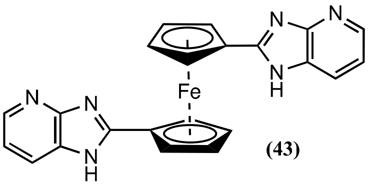
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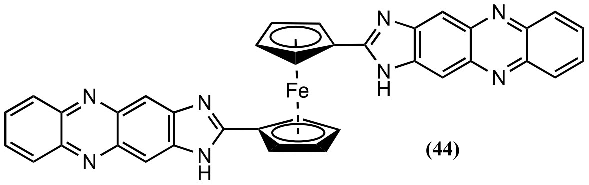
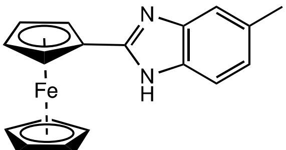

(44)

Receptors **43** and **44** also display selectivity for Pb^{2+} and Zn^{2+}. Molecule **43** showed a positive E_m shift of 0.180 and 0.190 V upon adding one equivalent of Pb^{2+} and Zn^{2+}, respectively. A comparable trend was also found for **44**, which undergoes a positive ΔE_m of 0.110 and 0.170 V for the same cations. The ΔE_m observed for Zn^{2+} starkly contrasts observations made with the related molecules **41** and **42**, which is in agreement with previous works, where the complexation of Zn^{2+} ions to 1,1′-disubstituted ferrocene resulted in a large positive E_m shift with respect to 1-monosubstituted ferrocene [7,78]. The receptor **45**, which differs from **40** by a methyl group in the benzimidazole ring, has been electrochemically studied in CH_3CN/0.1 M $[Bu_4N][ClO_4]$ [79]. It displayed specific sensing capability for Sn^{2+} ions, showing a positive E_m shift of 0.230 V after adding one equivalent of Sn^{2+} ions. Similarly, the ability of **46** and **47** to sense different metal ions was assessed in 1:1 CH_3CN:DCM/0.01M $[Bu_4N][PF_6]$ [80]. In the presence of Hg^{2+} and Pb^{2+}, **46** showed a positive E_m shift of 0.050 and 0.060 V, whereas **47** showed an ΔE_m of 0.150 V for Hg^{2+} and 0.040 V for Pb^{2+} after complexation. Notably, the presence of a 3-pyridyl unit in the sensors, regardless of location, significantly enhanced their ability to detect Hg^{2+} selectively and sensitively. It is worth noting that the 3-pyridyl unit did not directly coordinate with metal ions despite its influence on the improved performance.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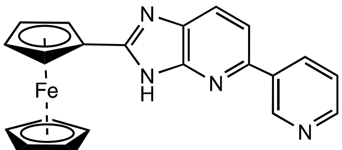
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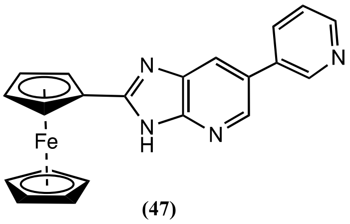
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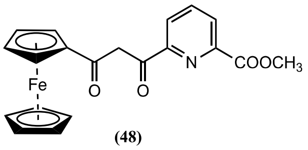
Sensors **48-50** have been synthesised by connecting a Fc unit to a pyridyl moiety using a *β*-diketone bridge [81]. The complexing properties of these sensors towards Zn^{2+}, Hg^{2+}, Co^{2+}, Cu^{2+}, Mn^{2+}, Cd^{2+}, and Ni^{2+} ions were investigated in ethanol/0.1 M $LiClO_4$. The largest positive E_m shifts were obtained after adding Cu^{2+} and Cd^{2+} to a solution of **48,** showing ΔE_m = 0.072 and 0.067 V, respectively. Meanwhile, positive E_m shifts of 0.102 V for Cu^{2+} and 0.109 V for Mn^{2+} were reported for **49**.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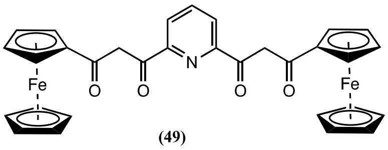
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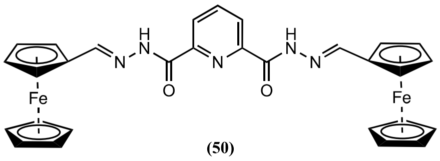
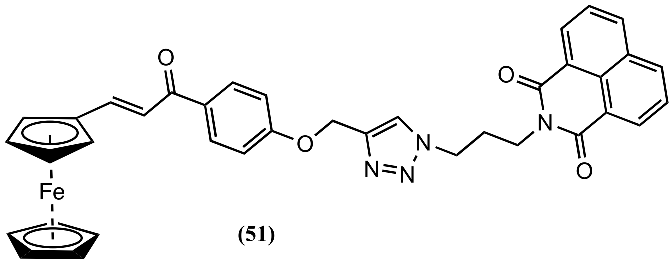

(50)

Similarly, **50** results in a positive E_m shift of 0.053 V for Hg^{2+} and 0.054 V for Mn^{2+} ions. Yet, the receptors **49** and **50** exhibit significantly lower redox potential shifts when treated with Zn^{2+}, Hg^{2+}, Co^{2+}, Cd^{2+} and Ni^{2+} ions.

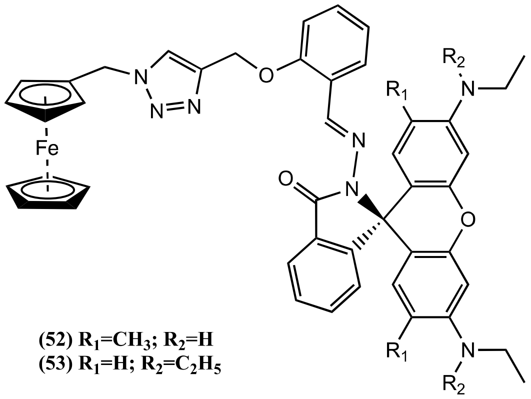
Meanwhile, naphthalimide was connected to a ferrocenyl-chalcone group using a triazole linker, and the electrochemical properties of the resulting molecule **51** to sense Cu^{2+} ion in CH_3CN/0.01 M

$[Bu_4N][ClO_4]$ was evaluated [82]. A 0.5 mM **51** solution showed a positive ΔE_m of 0.020 V upon adding 30 µM Cu^{2+} ion.

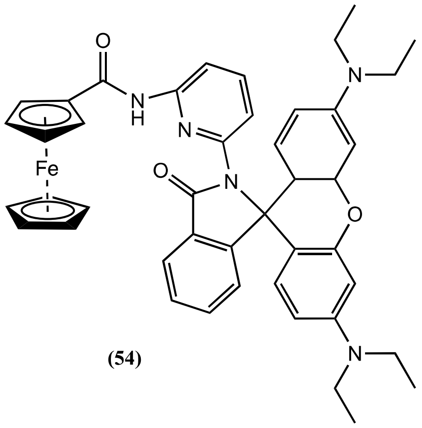


(51)

Two receptors, **52** and **53**, which incorporate Fc and rhodamine containing triazole, were synthesised, and their electrochemical properties to sense metal cations in CH_3CN/0.1 M $[Bu_4N][ClO_4]$ explored [83]. The E_m of these receptors was not affected by the presence of Na^+, Mg^{2+}, K^+, Ca^{2+}, Cr^{2+}, Mn^{2+}, Fe^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Pb^{2+}, Cd^{2+}, and Tl^+ ions. However, introducing one equivalent of Hg^{2+} led to a positive E_m shift of 0.200 and 0.250 V for **52** and **53**, respectively. NMR studies of the **52**-Hg^{2+} complex indicated that Hg^{2+} ions coordinate with the nitrogen atoms of the triazole ring, the imine, the oxygen atoms linked directly to the methylene, and the amide carbonyl group [83]. A similar molecule, **54**, shows a negative ΔE_m of 0.050 V upon adding one equivalent of Hg^{2+}. HR-MS and FT-IR studies suggest that the spirolactam ring undergoes an opening process when Hg^{2+} binds to **54**. Consequently, it is believed that the pyridine nitrogen atom and two amide oxygen atoms of **54** potentially form coordination bonds with Hg^{2+}, creating a chelating complex in conjunction with a solvent molecule [83].



(52) R_1=CH_3; R_2=H
(53) R_1=H; R_2=C_2H_5

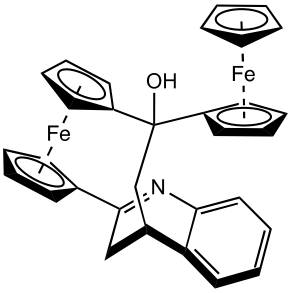


(54)

The strained asymmetric sensor **55** was synthesised and electrochemically evaluated in DCM/0.1 M $[Bu_4N][ClO_4]$ [84]. The cyclic voltammograms revealed two closely spaced, reversible oxidation peaks at 0.510 and 0.740 V vs. SCE. The initial reversible oxidation process was assigned to the oxidation of the single-substituted Fc unit, and the second one to the oxidation of the 1,1′-disubstituted Fc unit. While the addition of Ca^{2+} ions did not cause any E_m changes, a noticeable change was observed upon introducing one equivalent of Mg^{2+} ions, where a positive E_m shift of 0.340 V was observed in the second peak. Meanwhile, a small positive ΔE_m of 0.030 V was reported for the first peak. This sensor was able to distinguish between Mg^{2+} and Ca^{2+} ions without being affected by the presence of excess amount of Li^+, Na^+, and K^+ ions [84].

Molecule **56** was studied in 4:1 DCM:CH_3CN/0.1 M $[Bu_4N][PF_6]$ [85]. The cyclic voltammogram displayed two electrochemically reversible one-electron peaks at E_m = -0.060 and 0.460 V vs. $Fc^{0/+}$. Adding increasing quantities of Zn^{2+} into a solution of **56** led to the partial disappearance of the peak at -0.060 V and the emergence of a new peak at 0.020 V. However, there were no noticeable E_m changes in the second peak of the receptor. Unsymmetrical related molecules **57**-**59** were evaluated with respect to a range of cations, including Li^+, Na^+, K^+, Ca^{2+}, Mg^{2+}, Ni^{2+}, Cd^{2+}, Zn^{2+}, Pb^{2+}, Hg^{2+}, and Cu^{2+} in 4:1 or 3:2 CH_3CN:DCM/ 0.1 M $[Bu_4N][PF_6$ [86]. Each free receptor displayed two reversible one-electron redox processes. Compound **57** shows these processes at 0.050 and 0.250 V vs. $Fc^{0/+}$, **58** at 0.050 and 0.310 V, and **59** at 0.030 and 0.240 V. In all three cases, the initial oxidation process pertains to the Fc unit with a single substitution and the second oxidation wave is associated with the Fc unit bearing two substitutions.

Adding Pb^{2+} ions to **57** generates a positive E_m shift of 0.050 V for the first process and a negative E_m shift of 0.150 V for the second. A similar situation was observed after adding Zn^{2+}, with a positive E_m shift of 0.060 V for the first process and a negative ΔE_m of 0.140 V for the second. In the case of **58**, the second process presented a positive E_m shift of 0.050 V for Cd^{2+}, 0.130 V for Ni^{2+}, 0.150 V for Pb^{2+}, and 0.140 V for Zn^{2+}. Nevertheless, adding Pb^{2+} ions to **59** generates a positive E_m shift of 0.040 V for the first process and a negative ΔE_m of 0.160 V for the second. Similarly, adding Zn^{2+} causes a positive E_m shift of 0.010 V for the first process and a negative ΔE_m of 0.200 V for the second one [86]. As a result of this experiment, the addition of Pb^{2+} and Zn^{2+} to **57** and **59** resulted in a concurrent positive shift of the lower E_m and a negative shift of the higher E_m. This causes a single wave to appear in the cyclic voltammograms of the final complex due to the overlapping of the two oxidation processes part of the receptors. Nevertheless, the most noteworthy change occurs in the higher oxidation process when Ni^{2+}, Cd^{2+}, Zn^{2+}, and Pb^{2+} are added to probe **58**. This process experiences a reduction in intensity until it completely disappears when one equivalent of metal ion is present. Concurrently, the lower oxidation process remains unchanged. This observation implies that the triazole group plays a minor role in interacting with metal cations during complexation. As a result, the primary binding process is likely concentrated in the imine arm of the various receptors, with particular emphasis on receptor **58**, which incorporates an additional quinoline ring [86].



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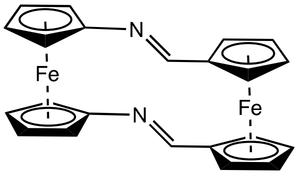

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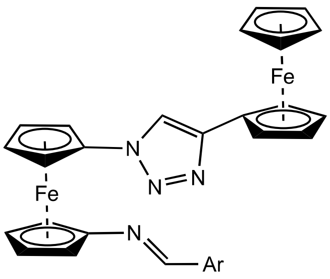

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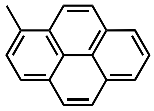

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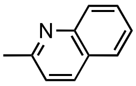

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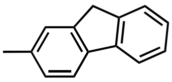

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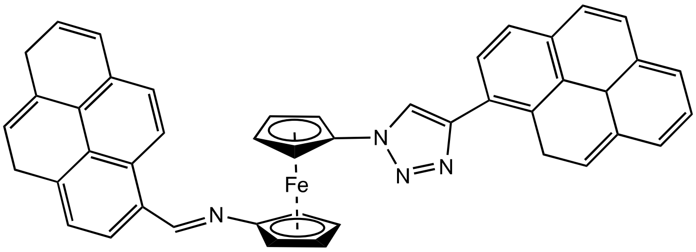

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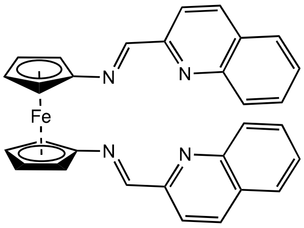
A related molecule **60,** containing one Fc unit, was studied in 4:1 CH_3CN:DCM/0.1 M $[Bu_4N][PF_6]$ [87]. Free **60** showed a one-electron reversible process at 0.195 V vs $Fc^{0/+}$ IRRS. A new reversible process at 0.045 and 0.200 V more positive potential values was observed after adding Zn^{2+} and Pb^{2+}, respectively. Notably, the cyclic voltammetric behaviour of **60** is not affected by adding other ions, such as Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, Ni^{2+}, Cu^{2+}, Cd^{2+}, and Hg^{2+}.

The receptor **61** was studied in CH_3CN containing 0.1 M $[Bu_4N][PF_6]$ as the supporting electrolyte. Meanwhile, receptor **62** was evaluated in 9:1 CH_2Cl_2:DMF/0.1 M $[Bu_4N][PF_6]$ [88]. Each free receptor displayed a characteristic reversible one-electron redox process, with E_m= 0.575 V for **61** and E_m = 0.470 V vs. $DmFc^{0/+}$ IRRS for **62**. The E_m of **61** shifted in the positive direction by 0.333, 0.282, 0.224, 0.274, and 0.361 V after adding Zn^{2+}, Pb^{2+}, Ni^{2+}, Cd^{2+}, and Hg^{2+}, respectively. In contrast, **62** shows a positive $\Delta E_m = 0.260$ V in the presence of Hg^{2+}. Based on NMR and theoretical studies, it was postulated that the coordination of metal ions to receptor **61** occurs via imine and quinoline nitrogens. Similarly, the ferrocene appended phenolic hydroxyl Schiff base **63** was studied in MeOH/0.1 M $[Bu_4N][ClO_4]$ [89]. The addition of Al^{3+}, Cr^{3+}, or Fe^{3+} to a solution of **63** resulted in a positive shift in the E_m of 0.028, 0.044, and 0.015 V, respectively.



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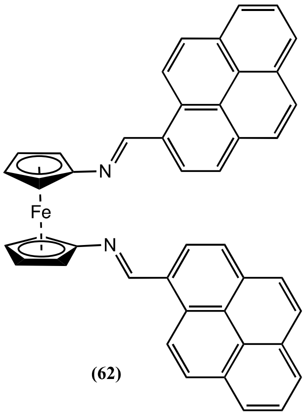

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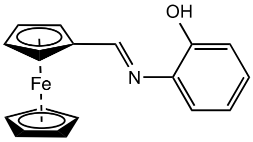
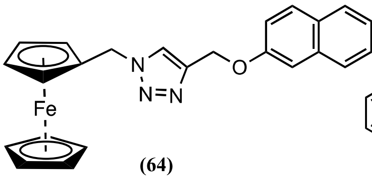


(63)

Cyclic voltammetric experiments were performed using a 3:7 CH_3CN:H_2O/0.1 M $[Bu_4N][ClO_4]$ solution of **64** and **65**. Their ability to detect the presence of Li^+, Na^+, K^+, Ca^{2+}, Mg^{2+}, Cr^{3+}, Zn^{2+}, Fe^{3+}, Ni^{2+}, Co^{2+}, Cu^{2+}, Cd^{2+}, Hg^{2+}, and Pb^{2+} ions was evaluated [90]. Both receptors **64** and **65** displayed a reversible one-electron oxidation process, in which E_m are not perturbed by the presence of the mentioned ions, except for Hg^{2+}, where the addition of one equivalent of this ion generates a positive E_m shift of 0.076 and 0.043 V for **64** and **65**, respectively. No Hg^{2+} ion sensing ability improvement is obtained with **66** or **67**. Receptor **66** can be seen as the dimeric version of **64**, and its E_m shifts by 0.078 V in the positive direction after the addition of Hg^{2+} [91]. However, the E_m of receptor **67** shifts by 0.033 V when exposed to Hg^{2+} ions [92]. Based on ^{1}H-NMR titration analysis, it was inferred that the Hg^{2+} binds to the triazole ring nitrogen atom and the oxygen atom in the OCH_2 bridging group [91].



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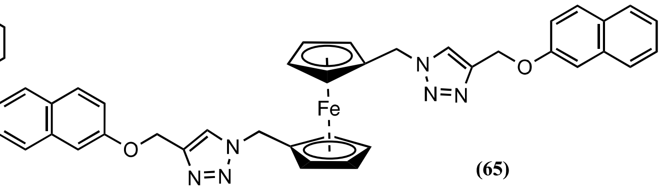

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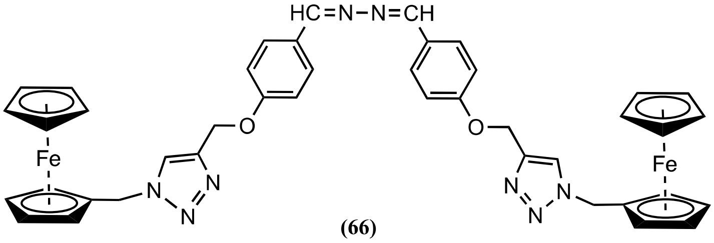

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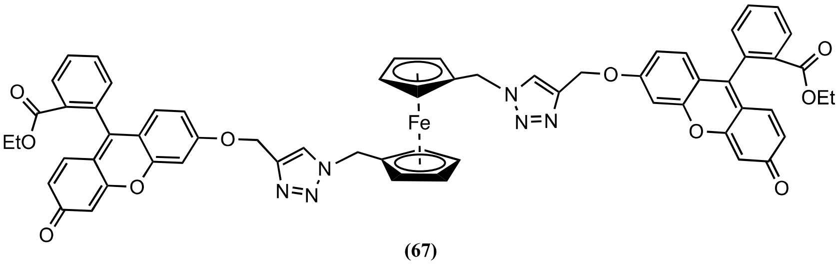

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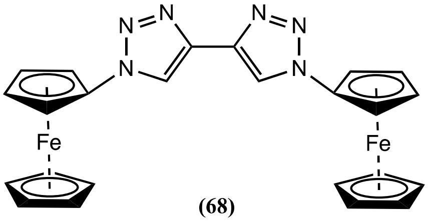
Receptors **68** and **69** containing monosubstituted Fc pendants and **70** and **71** containing disubstituted Fc pendants have been synthesised and electrochemically studied in CH_3CN containing 0.1 M $[Bu_4N][PF_6]$ as the supporting electrolyte [93]. The addition of Ni^{2+}, Hg^{2+}, and Pb^{2+} to **68** resulted in the appearance of a new oxidation process at a more positive ΔE_m of 0.053, 0.025, and 0.014 V, respectively. In contrast, **69** showed a positive E_m shift of 0.072 V upon adding an Hg^{2+} ion. A similar response was observed with the related receptor **70**, which showed a reversible two-electron process at $E_m = 0.544$ V vs. $DmFc^{0/+}$ IRRS for the terminal Fc groups and a reversible one-electron process at $E_m = 0.953$ V vs. $DmFc^{0/+}$ related to the disubstituted central Fc group [93]. The addition of Zn^{2+}, Hg^{2+}, and Pb^{2+} to **70** produced a negligible E_m shift for the terminal Fc groups but an E_m shift of 0.032, 0.076, and 0.022 V, respectively, for the central Fc group. In the case of **71**, only the Hg^{2+} ion produced a significant response, showing a positive E_m shift of 0.035 V after adding one equivalent of the mentioned ion.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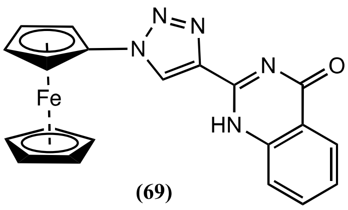
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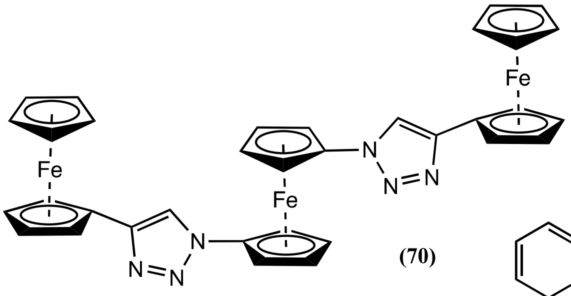
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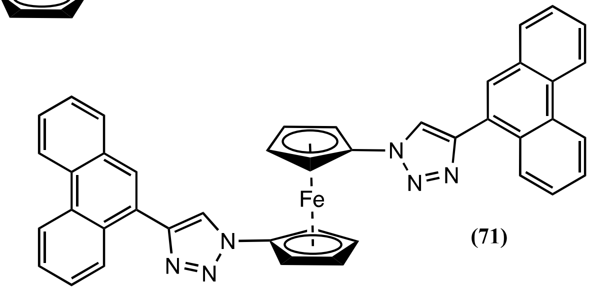
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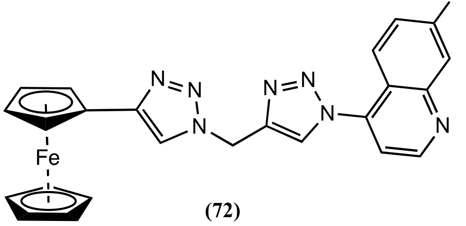
Cyclic voltammetry of **72** in CH_3CN containing 0.01M $[Bu_4N][ClO_4]$ as the supporting electrolyte showed a one-electron reversible process, which E_m shifter positively by 0.065 V after the addition of Fe^{3+} ions to the solution [94]. Meanwhile, Ferrocene quinazolines **73** was studied in 1:1 ethanol:H_2O/0.1M $[Bu_4N][ClO_4]$ [95]. The introduction of Hg^{2+} to this solution caused the appearance of a new irreversible process at 0.136 V more positive to the E_m of **73**. Similarly, adding Pb^{2+} to a solution of **73** resulted in a negative E_m shift of 0.025 V [95].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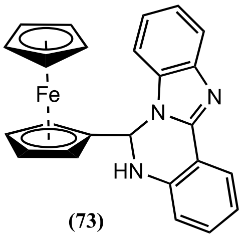
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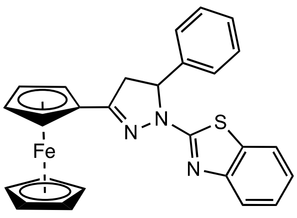
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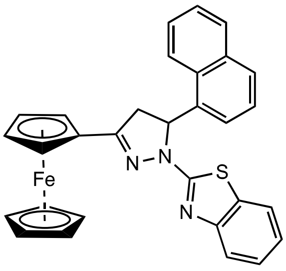
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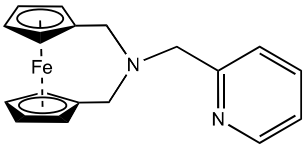
The interaction of **74** and **75** with various metal ions was systematically studied in acetonitrile using cyclic voltammetry and differential pulse voltammetry [96]. The addition of Hg^{2+} ion to this solution produces the appearance of a new process at 0.078 and 0.100 V more positive potentials with the consequent disappearance of the process related to the free **74** and **75** receptors, respectively. Conversely, when one equivalent of Cu^{2+} ions was introduced to the receptor solutions, a single process was observed, showing a positive E_m shift of 0.042 V for receptor **74** and 0.048 V for receptor **75**. The ^{1}H NMR analysis of the **74**-Hg^{2+} complex showed that the ion interacts with the nitrogen atoms in 1H-pyrazoline and 2-benzothiazole. This finding is supported by theoretical computations conducted using density functional theory [96].

Sensor **76** was studied in a CH_3OH/H_2O solution containing 0.1M KNO_3 as the supporting electrolyte [97]. The addition of 0.5 equivalents of Cu^{2+} to this solution resulted in the appearance of two reversible one-electron redox processes. The first one was related to the redox process of the free **76**, and the second, appearing at 0.125 V more positive potentials, was assigned to the **76**-Cu^{2+} complex. When one equivalent of Cu^{2+} was introduced, the redox process of the free **76** disappeared. Interestingly, the E_m of **76** is not affected by the presence of other metal ions, such as Mg^{2+}, Ni^{2+}, Zn^{2+}, Pb^{2+}, and Cd^{2+}.

Receptor **77** was investigated in a 7:3 dioxane:water containing $[Bu_4N][ClO_4]$ as the supporting electrolyte, revealing its pH-dependent behaviour, shifting E_m towards more positive potentials as the pH decreases from 12 to 5 [98]. Additionally, the presence of Mn^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, and Zn^{2+} shifts the E_m of **77** in the positive potential direction by 0.046 V for Cu^{2+}, 0.020 V for Co^{2+}, 0.015 V for Mn^{2+}, 0.013 V for Ni^{2+}, and 0.009 V for Zn^{2+} [98].



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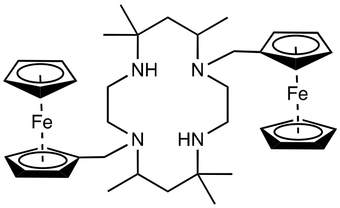

(77)

5. Conclusions

Significant advances have been made in developing Fc receptors capable of selectively sensing metal cations. This review presented a detailed discussion of how oxygen and nitrogen-containing macromolecular receptors featuring Fc moiety can initially form bonds and then exhibit shifts in redox potentials in response to positively charged guest molecules. This interaction occurs through electrostatic perturbation across space or linked conjugated bonds connecting the Fc unit to the metal cation host binding unit. The general factors that affect the magnitude of the redox potential shift upon binding of the cations to the guest site depend on *i*) the complementarity between the ferrocene-containing host and guest cation, encompassing the thermodynamics and kinetics of their binding interactions; *ii*) the charge-to-size ratio of the metal cation; *iii*) the closeness of the binding site to the redox active Fc; *iv*) the type of chemical bond that connects the host to the Fc pendant; and *e*) the nature of the solvent used during the experiment. This review also examined the complexity involved in the interplay between electron transfer and molecular recognition where hosts with amine functionalities such as cyclen and cyclam are utilised.

So far, most cation recognition has been conducted in organic solvents. This presents a significant challenge when attempting to use these ferrocene-based molecular receptors in aqueous solvents, a requirement for ion recognition in biological systems. To add to the complexity, competing redox active molecules against ferrocene probes might also influence the sensor's specificity. These challenges could open an excellent opportunity to enhance the ability of receptors to selectively bind cation guests, particularly in intricate aqueous environments and integrate them into electrochemical device platforms.

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