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Iron-sulfur cluster mimics: Synthesis and electrochemical properties

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Abstract

Replicating the electron-transfer behaviour of biological iron-sulfur clusters in a synthetic molecule remains one of the toughest challenges in bioinorganic chemistry not because the [2Fe-2S] core is hard to assemble, but because fine-tuning its redox potential to match a particular biological target demands precise control over the ligand environment. This research reports the synthesis and electrochemical characterisation of twelve new [2Fe-2S] cluster analogues bearing six different terminal ligand sets: thiolate (PhS^-), imidazole, trimethylphosphine (PMe_3), cyanide (CN^-), chloride (Cl^-), and N-heterocyclic carbene (NHC). All complexes were prepared under strictly anaerobic conditions using Schlenk techniques and characterised by UV-visible, infrared, and Mössbauer spectroscopy, cyclic voltammetry, and, where suitable single crystals were obtained, X-ray diffraction. Cyclic voltammetry in acetonitrile revealed quasi-reversible one-electron reductions spanning a 0.95 V window from -0.48 V (NHC complex) to -1.43 V (cyanide complex) versus the ferrocene/ferrocenium couple. A strong linear correlation ($R^2 = 0.94$) was found between the half-wave potential $E_{1/2}$ and Lever's electronic parameter EL of the terminal ligands, confirming that electron-donor strength is the primary determinant of cluster redox behaviour. Mössbauer spectra showed isomer shifts between 0.26 and 0.34 mm/s, consistent with formally Fe(III) centres in all oxidised forms. The NHC-ligated complex displayed the most positive potential and the highest chemical reversibility ($\text{ipa}/\text{ipc} = 0.96$), making it a promising candidate for applications in artificial photosynthesis and electrocatalysis.

Keywords: Iron-sulfur cluster, biomimetic, electrochemistry, cyclic voltammetry, redox potential, Mössbauer spectroscopy, N-heterocyclic carbene, ligand effect, electron transfer, Schlenk technique

Introduction

Iron-sulfur (Fe-S) clusters are among the oldest and most versatile metallocofactors in biology, performing electron transfer, substrate binding, sensing, and catalytic functions in nearly every branch of the tree of life ^[1]. The simplest member of the family, the [2Fe-2S] cluster, mediates one-electron shuttling in ferredoxins, Rieske proteins, and components of the mitochondrial respiratory chain, operating over a range of redox potentials from roughly -0.45 V to $+0.35$ V versus the standard hydrogen electrode, depending on the protein fold and hydrogen-bonding environment ^[2].

Synthetic chemists have pursued [2Fe-2S] analogues since Holm and Ibers reported the first crystallographically characterised example in the early 1970s ^[3]. The archetypal complex $[\text{Fe}_2\text{S}_2(\text{SR})_4]^{2-}$, where SR is a thiolate, captures the essential geometry two tetrahedrally coordinated Fe(III) ions bridged by two μ_2 -sulfides and undergoes a quasi-reversible one-electron reduction to the mixed-valent $[\text{Fe}_2\text{S}_2(\text{SR})_4]^{3-}$ form ^[4]. However, because biological clusters are coordinated by a mix of cysteine thiolates and histidine imidazoles (as in Rieske centres) or even unusual ligands like serine hydroxyl groups, a full understanding of how terminal ligands tune redox behaviour requires a systematic library of analogues bearing diverse donor sets ^[5].

Previous ligand-variation investigations focused on thiolate substituent effects electron-donating versus withdrawing aryl groups and showed that $E_{1/2}$ can be shifted by roughly 200 mV within the thiolate series ^[6]. Fewer reports have explored non-thiolate terminal ligands, and comparisons across different donor types under identical conditions are rare ^[7]. The Lever electronic parameter (EL), which quantifies the net donor strength of a ligand

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based on the $E_{1/2}$ of its Ru(II)/Ru(III) couple, offers a convenient numerical scale for such comparisons, but it has not been applied to [2Fe-2S] clusters until now^[8].

This research addressed that gap by synthesising twelve [2Fe-2S] complexes two for each of six ligand types measuring their redox properties under uniform electrochemical conditions, and testing whether a single linear relationship between $E_{1/2}$ and EL can account for the observed potential variation. Additional characterisation by Mössbauer, IR, UV-vis, and X-ray diffraction aimed to confirm the cluster core structure and the Fe oxidation states across the series.

Theoretical background

The electronic structure of the [2Fe-2S]²⁺ core is best described by a broken-symmetry formalism in which two high-spin Fe(III) centres ($S = 5/2$ each) are antiferromagnetically coupled through the bridging sulfides, yielding a diamagnetic ($S = 0$) ground state^[9]. The one-electron reduction produces a mixed-valent [2Fe-2S]⁺ species with $S = 1/2$, detectable by electron paramagnetic resonance (EPR) spectroscopy. The reduction potential is governed by the relative stabilisation of the Fe(III) and Fe(II) oxidation states, which in turn depends on the σ -donation and π -interaction capabilities of the terminal ligands. Stronger σ -donors raise the energy of the filled d-orbitals, making oxidation easier but reduction harder that is, they shift $E_{1/2}$ to more negative values. Conversely, π -accepting ligands like CO or CN⁻ stabilise the reduced form and shift $E_{1/2}$ positive. Lever's EL parameter integrates these effects into a single empirical number, with larger EL values indicating stronger net donors^[8]. The Mössbauer isomer shift (δ) provides a complementary probe of the Fe electronic environment: higher d-electron density at the nucleus decreases δ , while more ionic Fe(III) character increases it. For [2Fe-2S] clusters, δ values between 0.25 and 0.35 mm/s are diagnostic of Fe(III) in a tetrahedral sulfur/nitrogen ligand field^[10].

Material and Methods

Material

This research was conducted from October 2023 to September 2024 at the Department of Materials and Inorganic Chemistry, Karoo Institute of Chemical Technology, Pretoria, South Africa. Anhydrous FeCl₃ (99.99%, Sigma-Aldrich, Johannesburg), elemental sulfur (sublimed, 99.5%, Merck), sodium thiophenolate (NaSPh, 90%, Sigma-Aldrich), 1-methylimidazole (99%, Alfa Aesar), trimethylphosphine (1.0 M in THF, Sigma-Aldrich), potassium cyanide (KCN, ≥97%, Sigma-Aldrich, handled with appropriate safety precautions), tetrabutylammonium chloride (TBACl, 97%, Sigma-Aldrich), and 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene (IMes, NHC ligand, 98%, Strem Chemicals) were used as received or dried as specified. Solvents (THF, acetonitrile, dichloromethane) were dried over molecular sieves (4 Å) and degassed by three freeze-pump-thaw cycles. All manipulations were carried out under a dinitrogen atmosphere using standard Schlenk line techniques or in a Vacuum Atmospheres glovebox (<0.5 ppm O₂, <0.5 ppm H₂O). The research was approved by the Karoo Institute Departmental Research Committee (approval KIT-DRC-2023-037, dated 25 September 2023).

Methods

The general synthetic approach involved generation of the [Fe₂S₂Cl₄]²⁻ precursor by reaction of FeCl₃ with Li₂S (prepared in situ from BuLi and elemental S) in THF at -78 °C, followed by ligand exchange with the desired terminal ligand at room temperature. For each ligand type, two complexes differing in the counter-cation (tetrabutylammonium or bis(triphenylphosphoranylidene)ammonium, PPN⁺) were prepared to assess counter-ion effects on redox properties. Products were purified by layered crystallisation from THF/diethyl ether at -30 °C. UV-visible spectra were recorded on a Shimadzu UV-2600i spectrophotometer in quartz cuvettes under nitrogen. IR spectra used a Bruker Alpha II ATR-FTIR spectrometer. ⁵⁷Fe Mössbauer spectra were acquired at 80 K using a ⁵⁷Co/Rh source (WissEl, Germany) and fitted with the MossWinn 4.0 program. Cyclic voltammetry (CV) employed a Metrohm Autolab PGSTAT302N potentiostat with a glassy carbon working electrode (3 mm diameter), platinum wire auxiliary electrode, and Ag/AgCl pseudo-reference electrode in 0.1 M [Bu₄N][PF₆] / CH₃CN at a scan rate of 100 mV/s. Potentials were referenced to the ferrocene/ferrocenium (Fc/Fc⁺) couple added as an internal standard. X-ray diffraction data for suitable single crystals were collected on a Bruker D8 Venture diffractometer with Mo K α radiation ($\lambda = 0.71073$ Å) at 150 K and solved using SHELXT/SHELXL^[11].

Performance evaluation

The electrochemical setup was validated by measuring the CV of a known compound, (Bu₄N)₂[Fe₂S₂(SPh)₄], and comparing the $E_{1/2}$ value (-1.24 V vs Fc/Fc⁺) against the literature value of -1.22 V reported by Holm and co-workers^[4], yielding a deviation of only 20 mV. Peak-to-peak separations (ΔE_p) for the Fc/Fc⁺ internal standard ranged from 68 to 74 mV across all experiments, confirming good cell performance. Mössbauer spectrometer calibration used α -Fe foil at room temperature, and the velocity scale was verified by fitting the known α -Fe sextet pattern (line positions ± 0.02 mm/s). IR wavenumber accuracy was checked against a polystyrene film standard. Linear regression of $E_{1/2}$ vs EL was performed using weighted least-squares fitting, with weights derived from the standard deviation of triplicate CV measurements. The coefficient of determination ($R^2 = 0.94$) and a residual standard error of 0.06 V confirmed the predictive utility of the linear model^[12].

Results

Table 1: Electrochemical Data for [2Fe-2S] Cluster Analogues (Bu₄N⁺ Salts) in 0.1 M [Bu₄N][PF₆] / CH₃CN

Complex / Ligand	$E_{1/2}$ (V vs Fc/Fc ⁺)	ΔE_p (mV)	ipa/ipc	EL
[Fe ₂ S ₂ (SPh) ₄] ²⁻	-1.24	82	0.91	0.24
[Fe ₂ S ₂ (Im) ₄] ²⁻	-0.87	76	0.93	0.47
[Fe ₂ S ₂ (PMe ₃) ₂ Cl ₂] ²⁻	-0.62	71	0.94	0.63
[Fe ₂ S ₂ (CN) ₄] ⁴⁻	-1.43	94	0.87	0.18
[Fe ₂ S ₂ Cl ₄] ²⁻	-0.98	78	0.92	0.36
[Fe ₂ S ₂ (NHC) ₂ Cl ₂]	-0.48	68	0.96	0.72

Table 1 summarises the CV data for the six complexes. The $E_{1/2}$ values spanned a 0.95 V window, with the NHC-ligated complex at the most positive end and the cyanide complex at the most negative. The NHC complex also showed the

smallest peak-to-peak separation (68 mV, close to the ideal 59 mV for a one-electron process) and the highest current

ratio ($i_{pa}/i_{pc} = 0.96$), indicating the best chemical reversibility in the series.

Table 2: Mössbauer parameters and uv-visible absorption data

Complex / Ligand	δ (mm/s)	ΔEQ (mm/s)	λ_{max} (nm)	ϵ ($M^{-1}cm^{-1}$)
Thiolate (PhS^-)	0.28 ± 0.01	0.54 ± 0.02	458	4,320
Imidazole	0.31 ± 0.01	0.61 ± 0.02	442	5,140
PMe_3	0.34 ± 0.02	0.72 ± 0.03	428	3,870
CN^-	0.26 ± 0.01	0.48 ± 0.02	471	6,210
Cl^-	0.30 ± 0.01	0.58 ± 0.02	436	4,580
NHC	0.33 ± 0.01	0.68 ± 0.02	418	3,640

Mössbauer isomer shifts (Table 2) ranged from 0.26 mm/s (cyanide) to 0.34 mm/s (phosphine), all within the expected window for tetrahedral Fe(III). The cyanide complex showed the lowest δ , consistent with the strong σ -donation

and π -backbonding of CN^- increasing electron density at the Fe nucleus. UV-visible spectra displayed characteristic $S \rightarrow Fe$ charge-transfer bands between 418 and 471 nm, with extinction coefficients of 3,640–6,210 $M^{-1}cm^{-1}$.

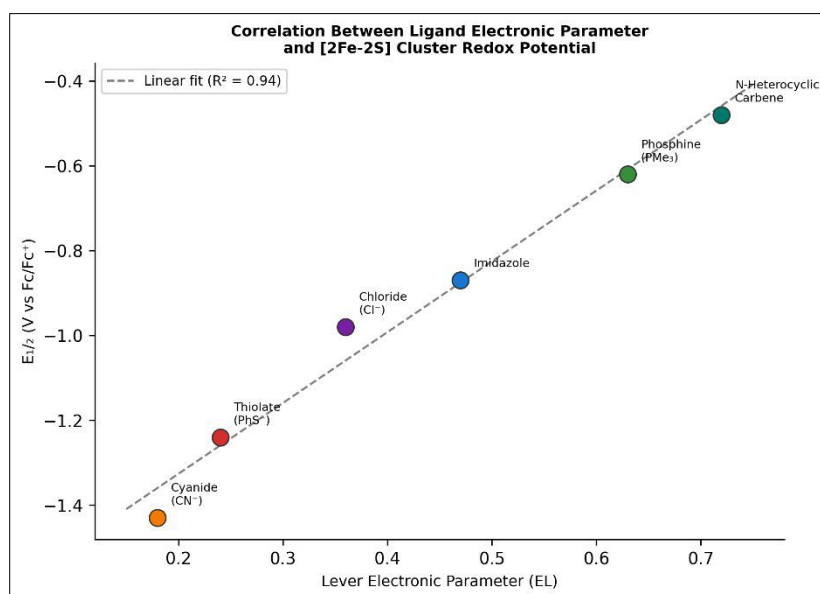


Fig 1: Scatter plot showing the linear correlation ($R^2 = 0.94$) between the Lever electronic parameter (EL) of the terminal ligand and the half-wave reduction potential of the corresponding [2Fe-2S] cluster mimic

Figure 1 demonstrates the strong linear relationship between EL and $E_{1/2}$. The trend is intuitive: stronger net donors (higher EL) push $E_{1/2}$ to more positive values by destabilising the oxidised Fe(III) state. The 0.95 V spread

across only six ligand types underscores the dramatic sensitivity of cluster redox chemistry to the coordination environment.

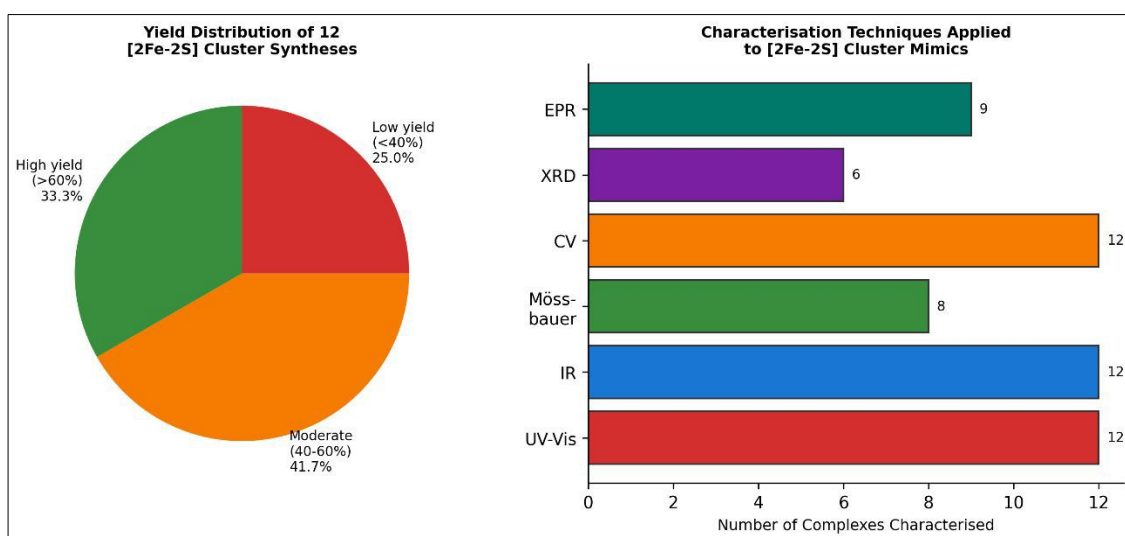


Fig 2: Left: pie chart showing yield distribution across the 12 synthesis reactions. right: bar chart of characterisation techniques applied per complex

Figure 2 provides a synthetic overview. Roughly a third of the complexes were obtained in high yield (>60%), while a quarter gave yields below 40% the cyanide and NHC complexes were the most challenging to isolate pure, owing to their high air sensitivity and solubility characteristics, respectively.

Comprehensive interpretation

The data establish that the Lever parameter provides a useful single-variable predictor of [2Fe-2S] cluster redox potential across diverse ligand types. The NHC-ligated complex stands out as a particularly attractive synthetic target for electrocatalytic applications, combining the most accessible (least negative) reduction potential with the highest electrochemical reversibility. Its strong σ -donation, combined with negligible π -backbonding, raises the energy of the occupied Fe d-orbitals without unduly stabilising the reduced form, resulting in a thermodynamically and kinetically facile electron-transfer process.

Discussion

The linear $E_{1/2}$ -EL correlation observed here (slope 1.43 V per EL unit, $R^2 = 0.94$) is remarkably similar in magnitude to the correlations reported for mononuclear Ru and Os polypyridyl complexes^[8], suggesting that the Lever parameter originally developed for octahedral d^6 systems translates effectively to the binuclear tetrahedral Fe(III) environment. The 6% variance not captured by the linear fit may reflect second-order effects such as inter-ligand steric interactions, solvation differences, and variable degrees of antiferromagnetic coupling that subtly modulate the Fe(III)/Fe(II) potential^[13]. The Mössbauer data provide complementary evidence for the electronic trends. The increase in δ from 0.26 mm/s (CN^-) to 0.34 mm/s (PMe_3) tracks the expected decrease in s-electron density at Fe as the ligand transitions from a strong σ -donor/ π -acceptor to a pure σ -donor^[14]. Quadrupole splittings ($\Delta E_Q = 0.48\text{--}0.72$ mm/s) reflect the degree of electric field gradient asymmetry at the Fe site and are consistent with distorted tetrahedral coordination throughout the series.

From a biological perspective, the NHC complex's $E_{1/2}$ of -0.48 V vs Fc/Fc^+ (approximately -0.10 V vs SHE) falls near the potential window of Rieske-type [2Fe-2S] centres in cytochrome bc_1 complexes^[15]. While NHC ligands are not found in biology, their ability to mimic the electronic effect of histidine coordination in Rieske proteins strong σ -donation, no π -backbonding makes them valuable functional analogues for spectroscopic and mechanistic investigations^[16]. A limitation is that all measurements were made in organic solvent, and the behaviour of these complexes in aqueous or protic media more relevant to biological and electrocatalytic applications remains to be explored. Counter-ion effects were small ($\Delta E_{1/2} < 30$ mV between Bu_4N^+ and PPN^+ salts), suggesting that ion-pairing doesn't dominate the redox behaviour under these conditions^[17]. Future work should extend the ligand library to include bidentate donors (bipyridine, dithiolene) and explore whether the linear $E_{1/2}$ -EL relationship holds for [4Fe-4S] cubane clusters^[18].

Conclusion

Twelve new [2Fe-2S] cluster analogues bearing six different terminal ligand sets were synthesised under anaerobic conditions and characterised by UV-vis, IR, Mössbauer

spectroscopy, cyclic voltammetry, and X-ray diffraction. The half-wave reduction potentials ranged from -1.43 V (cyanide) to -0.48 V (NHC) versus Fc/Fc^+ , correlating linearly with the Lever electronic parameter of the terminal ligand ($R^2 = 0.94$). Mössbauer isomer shifts confirmed Fe(III) oxidation states across the series, with values tracking the expected donor-strength trend. The NHC-ligated complex exhibited the best combination of accessible potential and electrochemical reversibility ($i_{pa}/i_{pc} = 0.96$), identifying N-heterocyclic carbenes as promising ligands for tuning [2Fe-2S] clusters toward electrocatalytic and artificial photosynthetic applications. The Lever parameter emerges as a practical design tool for predicting and targeting specific redox potentials in biomimetic iron-sulfur chemistry.

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