Tetrahedron 66 (2010) 5653–5659

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis and electrochemical studies of disubstituted ferrocene/dipeptide conjugates with sulfur-containing side chains

Conor C.G. Scully [a,b], Peter J. Rutledge [a,*]

[a] School of Chemistry F11, The University of Sydney, NSW 2006, Australia
[b] Centre for Synthesis & Chemical Biology, University College Dublin, Belfield, Dublin 4, Ireland

ARTICLE INFO

Article history:
Received 7 January 2010
Received in revised form 30 April 2010
Accepted 17 May 2010
Available online 24 May 2010

Keywords:
Amino acids
Peptide synthesis
Bio-organometallic chemistry
Ferrocene
Mercury
Electrochemistry

ABSTRACT

A series of 1,1′-disubstituted ferrocenoyl peptides incorporating dipeptide sidearms has been synthesized and studied electrochemically. The target peptides include ferrocene as an electrochemical reporter, sulfur-containing amino acids (L-methionine, *S*-methyl-L-cysteine, *S*-trityl-L-cysteine, *S*-benzhydryl-L-cysteine) as metal binding agents, and amino acids with non-polar side chains (L-alanine, L-valine, L-phenylalanine) as spacers between reporter and metal binding groups. Ferrocene/dipeptide conjugates were prepared using solution phase peptide synthesis methods employing a BOC-protecting group strategy and HBTU- (*O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate) mediated peptide coupling. The electrochemical properties of these 1,1′-substituted ferrocenoyl peptides have been characterized using cyclic voltammetry. All exhibit fully reversible one electron oxidation steps; forward sweep half wave peaks (E_F), reverse sweep half wave peaks (E_R), peak separations (ΔE_P) and half wave potentials ($E_{1/2}$) are reported. Finally, towards the goal of utilizing ferrocenoyl peptides to detect heavy metals in solution, the response of these ferrocene/dipeptide conjugates to metal cations (zinc(II), mercury(II), cadmium(II), lead(II), silver(I)) has been examined. Monitoring changes in the potential of the Fe(II)/Fe(III) redox couple to follow peptide/metal interactions, we have probed the influence of the spacer unit between the redox reporter and the metal-binding amino acid, and shown that these systems respond to mercury(II) more strongly than to other heavy metal ions.

1. Introduction

The rapid proliferation of heavy industry in developed and developing nations has led to increased levels of pollutants and toxins in the local and global environment.[1] Amongst the most harmful of these are metal pollutants released by mining, incineration and manufacturing, and within this class the heavy metals mercury, cadmium and lead pose a particular threat to the environment due to their extreme toxicity and wide-spread use.[2,3] Plants and animals have developed natural defence mechanisms in response to elevated levels of these metals in the environment, using proteins rich in sulfur-containing amino acids—metallothioneins and phytochelatins—to bind and sequester metal ions such as mercury(II) and cadmium(II).[4–6]

Given the high toxicity and increasing prevalence of mercury and its derivatives, significant efforts have been directed towards the development of methods to detect them in the environment,[7–9] and a variety of sensitive redox-active systems have been reported.[10–13] Ferrocene conjugates have been used widely as chemical receptors to probe the behaviour of metal ions in solution, due in large part to the stable and reproducible redox behaviour of the ferrocene/ferrocenium redox couple and its resulting electrochemical properties.[14–18] Ferrocene bioconjugates have received attention more recently as potential receptors for metal ions, part of an increasing focus on the bio-organometallic chemistry of ferrocene.[19–23] Several ferrocene/peptide systems have been used to detect cations in solution (including Li(I), K(I), Cs(I), Mg(II), and La(III)),[17,24,25] however the application of ferrocenoyl peptides to cation-sensing applications has received only limited attention to date.

We recently reported the synthesis and metal-binding properties of simple sulfur-containing ferrocene/amino acid conjugates, which demonstrated a significantly stronger response to mercury (II) than other thiophilic metals.[23] Our strategy uses sulfur-containing amino acids and peptides based loosely on the metal binding motif of metallothioneins in conjunction with the iron(II)/iron(III) redox couple of ferrocene as an electrochemical reporter. As part of ongoing efforts to utilise amino acid and peptide derivatives for binding and sensing heavy metals, we report here the synthesis and characterization of more complex 1,1′-disubstituted

* Corresponding author. Tel.: +61 2 9351 5020; fax: +61 2 9351 3329; e-mail address: p.rutledge@chem.usyd.edu.au (P.J. Rutledge).

0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.05.070

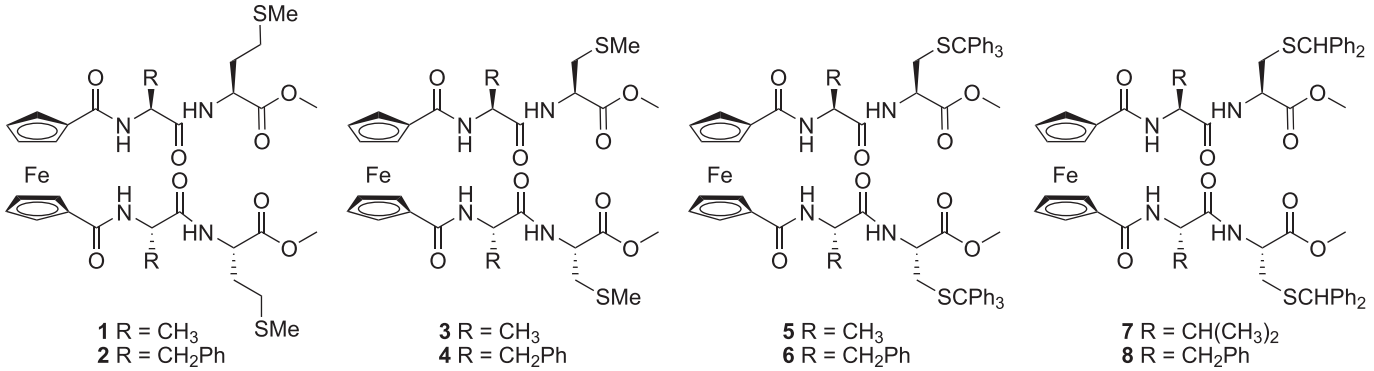


Figure 1. Ferrocenoyl/dipeptide conjugates **1**–**8**.

ferrocenoyl peptides, using electrochemistry to probe the influence of a spacer unit between the redox reporter (ferrocene) and the metal-binding amino acid (L-methionine and L-cysteine derivatives). We have synthesised a family of eight ferrocene-linked dipeptide conjugates **1**–**8** (Fig. 1) and studied their interactions with heavy metal cations by cyclic voltammetry, surveying a range of metal-binding residues (L-methionine, *S*-methyl-L-cysteine, *S*-trityl-L-cysteine and *S*-benzhydryl-L-cysteine) and linkers (L-alanine, L-valine and L-phenylalanine). The linker amino acids incorporate non-polar side chains, which should play little or no direct role in metal binding. However they vary in steric bulk and so will influence the conformation of the peptide in solution, thereby influencing the approach of a metal ion and ultimately the selectivity and sensitivity of these systems in binding heavy metals. By comparing these dipeptide-derived systems to previously reported single-amino acid derivatives[23] the influence of distance between the metal-binding residue and the redox reporter can also be characterised. The electrochemical properties of the 1,1′-substituted ferrocenoyl peptides **1**–**8** have been analyzed using cyclic voltammetry and the interactions of these compounds with the heavy metal cations mercury(II), cadmium(II), lead(II), silver(I) and zinc(II) examined.

2. Results and discussion

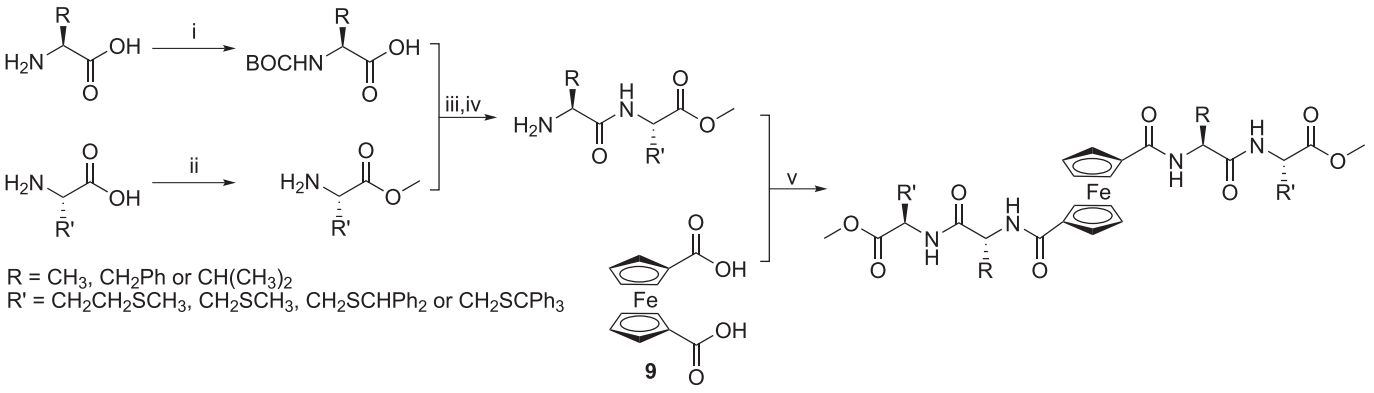
2.1. Synthesis of ferrocenoyl peptides

The 1,1′-substituted ferrocenoyl peptide targets **1**–**8** were obtained from ferrocene-1,1′-dicarboxylic acid **9** and 2 equiv of the corresponding dipeptide (Scheme 1). Ferrocene-1,1′-dicarboxylic acid **9** was synthesized in high yield (75%) following the literature procedure.[26] Protected L-cysteine derivatives *S*-methyl-L-cysteine,[27] *S*-benzhydryl- and *S*-trityl-L-cysteine[28] were prepared using known procedures; L-methionine and *S*-protected L-cysteine derivatives were converted to their methyl esters in high yields (61%–quantitative) by reaction with thionyl chloride and methanol.[29] L-Alanine, L-valine and L-phenylalanine were converted to the *N*-Boc derivatives in excellent yields (85–99%) following a literature procedure.[30]

L-Alaninyl-, L-valinyl- and L-phenylalaninyl-dipeptide methyl esters were synthesised by coupling *N*-Boc-L-alanine, *N*-Boc-L-valine or *N*-Boc-L-phenylalanine with L-methionine methyl ester, *S*-methyl-L-cysteine methyl ester, *S*-benzhydryl-L-cysteine methyl ester or *S*-trityl-L-cysteine methyl ester using *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HBTU) under standard peptide coupling conditions.[31] The resulting *N*-Boc-protected dipeptides were deprotected at the N-terminus in excellent yields (71–94%) by heating for 120 min with *p*-toluenesulfonic acid in refluxing DCM.[28] Deprotected dipeptides were coupled to ferrocene-1,1′-dicarboxylic acid using HBTU, to give the desired conjugates **1**–**8** in moderate to high yield (41–85%).

2.2. Electrochemistry of 1,1′-substituted ferrocenoyl dipeptide compounds

All the compounds synthesized exhibit fully reversible one electron oxidation steps in acetonitrile. The forward sweep half wave peaks (E_F), reverse sweep half wave peaks (E_R), peak separations (ΔE_P) and half wave potentials ($E_{1/2}$) are summarised in Table 1.



Scheme 1. Synthesis of 1,1′-substituted ferrocenoyl peptide targets **1**–**8** (**1** R=CH_3, R′=$CH_2CH_2SCH_3$; **2** R=CH_2Ph, R′=$CH_2CH_2SCH_3$; **3** R=CH_3, R′=CH_2SCH_3; **4** R=CH_2Ph, R′=CH_2SCH_3; **5** R=CH_3, R′=CH_2SCPh_3; **6** R=CH_2Ph, R′=CH_2SCPh_3; **7** R=$CH(CH_3)_2$, R′=CH_2SCHPh_2; **8** R=CH_2Ph, R′=CH_2SCHPh_2); i. Boc_2O, NaOH, *t*-BuOH/H_2O, rt 24 h, 85–99%; ii. $SOCl_2$, MeOH, reflux 4 h, then rt 16 h, 61–100%; iii. HBTU, TEA, DCM/DMF, rt 16 h, 52–88%; iv. TsOH, DCM, reflux 2 h, 71–94%; v. HBTU, TEA, DCM/DMF, 48 h, 41–85%.

Table 1
Basic electrochemical properties of 1,1′-substituted ferrocenoyl compounds

Compound	E_F (mV)	E_R (mV)	ΔE_P (mV)	$E_{1/2}$(mV)
1	820	755	65	788
2	827	760	67	794
3	825	758	67	792
4	837	769	68	803
5	831	765	66	798
6	860	789	71	825
7	827	763	64	795
8	841	773	68	807
10[a]	*856*	*795*	*61*	*826*
11[a]	*868*	*794*	*74*	*831*
12[a]	*883*	*807*	*76*	*846*

[a] Data reported previously,[23] included for comparison.

The half wave potentials measured for these compounds are comparable to ferrocene/peptide conjugates previously reported.[17,23,32] Redox potentials are raised relative to ferrocene itself ($E_{1/2}$=448 mV vs Ag/Ag^+),[24] since covalently bound amino acids exert an electron withdrawing effect on the metallocene, thus making the iron(II) centre more difficult to oxidize. Further to the electron withdrawing effect of the amide, the amino acid side chains also exert their own influence on the redox potential of the ferrocene core. The L-alanine-containing compounds **1**, **3** and **5** do not demonstrate as strong a cationic shift as the equivalent L-phenylalanine-containing conjugates **2**, **4** and **6**, which may be attributable to the more electron rich nature of the phenylalanine side chain; Metzler-Nolte and co-workers have previously observed small residue-dependant shifts in the redox potentials of several sulfur-containing ferrocenoyl peptides.[20] The influence of the through-bond distance between the sulfur and the redox core noted previously with single-amino acid systems (Fig. 2)[23] is also apparent with these dipeptide conjugates, although it is only slight: compare the redox potentials of $Fe(C_5H_4$-CO-Ala-Met-$OMe)_2$ **1** (788 mV) and $Fe(C_5H_4$-CO-Ala-Cys(Me)-$OMe)_2$ **3** (792 mV), or $Fe(C_5H_4$-CO-Phe-Met-$OMe)_2$ **2** (794 mV) vs $Fe(C_5H_4$-CO-Phe-Cys(Me)-$OMe)_2$ **4** (803 mV).

All of the conjugates **1**–**8** have lower half wave potentials than systems in which sulfur-containing amino acids are appended directly to the cyclopentadiene ring. For example compare $Fe(C_5H_4$-CO-Ala-Met-$OMe)_2$ **1** (788 mV) and $Fe(C_5H_4$-CO-Phe-Met-$OMe)_2$ **2** (794 mV) to $Fe(C_5H_4$-CO-Met-$OMe)_2$ **10** (826 mV);[23] $Fe(C_5H_4$-CO-Ala-Cys(Me)-$OMe)_2$ **3** (792 mV) and $Fe(C_5H_4$-CO-Phe-Cys(Me)-$OMe)_2$ **4** (803 mV) to $Fe(C_5H_4$-CO-Cys(Me)-$OMe)_2$ **11** (831 mV);[23] or $Fe(C_5H_4$-CO-Ala-Cys(Trt)-$OMe)_2$ **5** (798 mV) and $Fe(C_5H_4$-CO-Phe-Cys(Trt)-$OMe)_2$ **6** (825 mV) to $Fe(C_5H_4$-CO-Cys(Trt)-$OMe)_2$ **12** (846 mV).[23] This observation can be rationalized using similar electron density arguments.

Peak separations (ΔE_P) evince the reversibility of the redox event. The theoretical peak separation for a diffusion-limited redox event involving the transfer of one electron is 59 mV,[33] however due to uncompensated resistance in the solvent between reference and working electrodes, actual ΔE_P values may be 10–20 mV above this theoretical value.[34] All of the compounds **1**–**8** show peak separations within 12 mV of this theoretical value: $Fe(C_5H_4$-CO-Val-Cys(Bzh)-$OMe)_2$ **7** has the smallest peak separation at 64 mV, and only $Fe(C_5H_4$-CO-Phe-Cys(Trt)-$OMe)_2$ **6** (71 mV) deviates by more than 10 mV from the theoretical value.

2.3. Metal binding studies

The electrochemical properties of ferrocenoyl peptides **1**–**8** were tested in the presence of various thiophilic heavy metals to probe the metal binding properties of these compounds. All respond electrochemically to varying concentrations of mercury(II) nitrate, with corresponding changes in half wave potentials. Much lower responses are observed to cadmium(II) nitrate, zinc(II) nitrate, sliver(I) nitrate and lead(II) triflate. The electrochemical responses of compounds **1**–**6** to these five metals are shown in Figure 3 and their responses to mercury are detailed in Table 2.

Like the single-residue compounds reported previously[23] the ferrocene/dipeptide conjugates **2**–**6** show a significantly stronger response to Hg(II) than to other metals tested. The Phe-*S*-Trt-Cys derivative $Fe(C_5H_4$-CO-Phe-Cys(Trt)-$OMe)_2$ **6** shows the highest redox potential change of these systems, a shift of 64 mV. The response is characterised by a concentration-dependant change in $E_{1/2}$, which reaches this upper limit at a mercury(II) concentration of 51 ppm. Compounds **2**–**5** show similar redox shifts to the single-residue compounds within comparable Hg(II) concentration ranges. In contrast, the response to other metals is much smaller, with none of them causing a shift greater than 10 mV.

Intriguingly the Ala-Met derivative $Fe(C_5H_4$-CO-Ala-Met-$OMe)_2$ **1** exhibits a much smaller response to mercury(II) than the other responsive compounds, a shift of only 9 mV up to saturation at 52 ppm Hg(II). The reason for this discrepancy is not clear. The *S*-benzhydryl-L-cysteine analogues **7** and **8** do not respond at all to mercury (or the other metals tested), a result consistent with that previously observed for the directly linked *S*-benzhydryl-L-cysteine derivative $Fe(C_5H_4$-CO-Cys(Bzh)-$OMe)_2$, but also difficult to explain.[23] As noted previously, the corresponding *S*-benzyl- and *S*-tritylcysteine analogues respond to mercury and it is not obvious why *S*-benzhydryl derivatives do not display properties intermediate between these.

The response to mercury of dipeptide conjugates **2**–**6** show similar saturation effects and sensitivity (Fig. 3, Table 2) to those seen previously for similar systems.[23]. Saturation is observed at concentrations of 35–60 ppm mercury(II), beyond which the redox potential is unchanged by further Hg(II) addition (compare to 53 ppm for the directly-linked $Fe(C_5H_4$-CO-Met-$OMe)_2$ **10**, 40 ppm

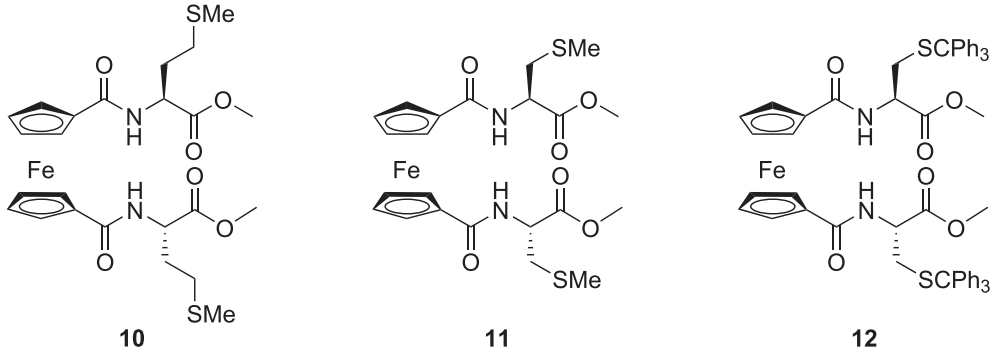


Figure 2. Ferrocenoyl peptides **10**–**12** in which the *S*-bearing amino acid is directly attached to the ferrocene core.

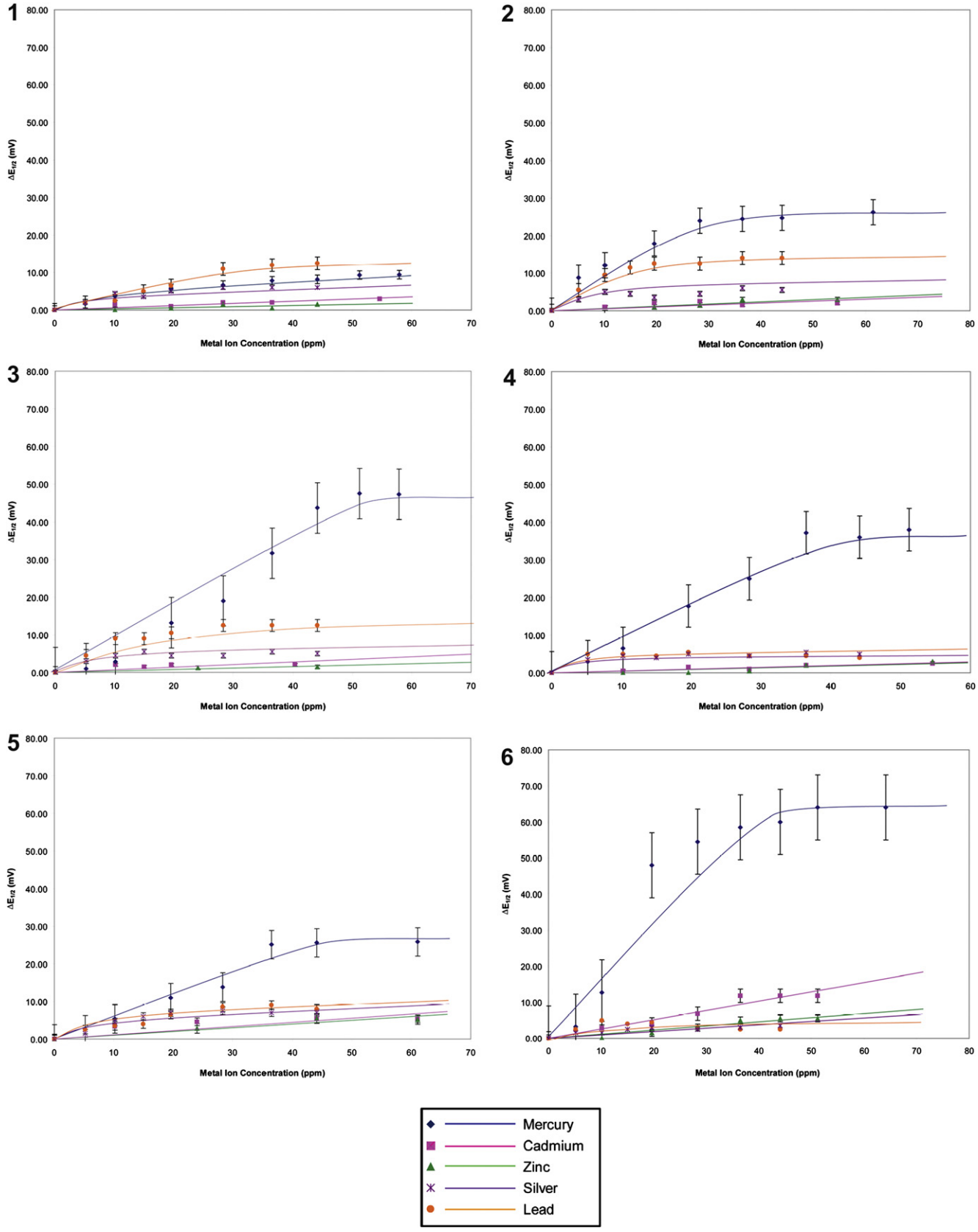


Figure 3. Electrochemical response of compounds **1**–**6** to metal ions mercury(II), cadmium(II), zinc(II), silver(I) and lead(II). The apparent diminution of the generated current as the concentration of mercury(II) increases is due to the increasing interaction of the ligand with the cation. The peak current is proportional to the diffusion constant for the peptide as given in the Randles/Sevcik equation: $i_p=2.69\times10^5 n^{3/2}AD^{1/2}Cv^{1/2}$ (where i_p=peak current (mV); n=no. of electrons transferred; A=electrode surface area (cm^2); D=diffusion coefficient ($cm^2\ s^{-1}$); C=concentration ($mol\ cm^{-3}$); ν=scan rate ($V\ s^{-1}$)). The diffusion coefficient (D) in turn is inversely related to the molecular weight of the ligand/metal complex, which increases as the heavy metal cation is bound.

Table 2
Electrochemical response of ferrocenoyl peptides to Hg(II) in solution

Compound	Max potential shift[a] (mV)	Hg(II) saturation point[b] (ppm)	Sensitivity[c] (mV ppm^{-1})
1	9	52	0.17
2	26	61	0.43
3	47	51	0.92
4	37	36	1.03
5	26	36	0.72
6	64	51	1.25
10[d]	*47*	*53*	*0.89*
11[d]	*69*	*40*	*1.73*
12[d]	*31*	*58*	*0.53*

Compounds **7** and **8** are not shown because no response to mercury was observed for these compounds.

[a] The maximum potential shift is the change in the half wave potential from the value in the absence of mercury(II) to the point at which the system becomes saturated and no further shift is seen.

[b] The Hg(II) saturation point is the concentration of mercury beyond which no further change in half wave potential is observed.

[c] The sensitivity indicates how quickly the half wave potential changes with respect to the concentration of mercury present.

[d] Data reported previously,[23] included for comparison.

for Fe(C_5H_4-CO-Cys(Me)-OMe)$_2$ **11** and 58 ppm for Fe(C_5H_4-CO-Cys(Trt)-OMe)$_2$ **12**). The sensitivity is a measure of how quickly the redox potential changes with respect to increasing mercury concentration and can be calculated from the slope of the mercury response. The sensitivities of compounds **1**–**6** fall in the range 0.15–1.25 mV ppm^{-1}, similar to the values previously observed for compounds **10**–**12** (0.50–1.75 mV ppm^{-1}).[23]

2.4. Conclusions

There are four modes by which the interaction of a guest with a redox active ligand can affect the redox potential of the ligand:[14,35] (i) direct coordination between the redox core and the guest;[36] (ii) through-space electrostatic interactions;[37] (iii) through-bond communication;[38] (iv) redox perturbation by induced conformational change.[39] Given the nature of the guest, ligand and redox core used in this study, mode (i) can be discounted for these systems, and modes (ii) and (iii) should be the most important.

The through-bond distance is increased in the dipeptide conjugates **1**–**6** relative to the single-residue compounds **10**–**12**: any through-bond electronic perturbation has to traverse an extra three bonds to reach the redox core. Electron transfer through covalent bonds is expected to decay exponentially with distance,[40] however the formation of peptide secondary structure provides a means for electron transfer to bypass covalent interactions.[41] Through-space interactions are harder to evaluate in the absence of structural data pinpointing the relative positions of iron and mercury in the ferrocene/peptide/mercury(II) complexes. (While crystal structures are known for several of the ferrocene/peptide conjugates themselves,[23] our attempts to crystallize the Hg(II) complexes of **1**–**12** have proved unsuccessful). Nonetheless comparing the data summarized in Table 2 allows some conclusions to be drawn regarding the nature of the mercury/peptide interactions, the factors affecting the observed changes in redox response, and the influence of the spacer amino acids.

Comparing **1** and **2** to **10** (methionine series) and **3** and **4** to **11** (*S*-methylcysteine series), it is evident that for these *S*-methyl thioethers introducing a spacer lowers the maximum potential shift and the sensitivity, but does not influence the Hg(II) saturation point. This is consistent with the spacer amino acid having moved the metal binding group further from the electrochemical reporter: these groups are three bonds further apart, although the change in through-space distance is harder to evaluate (see above). A different result is apparent when comparing **5** and **6** to **12** (*S*-tritylcysteine series): the sensitivities of both **5** (0.72 mV ppm^{-1}) and **6** (1.25 mV ppm^{-1}) are greater than the directly linked analogue **12** (0.53 mV ppm^{-1}), while the maximum potential shift of **5** (64 mV) outstrips both **6** (26 mV) and **12** (31 mV). Thus through-bond influences alone do not account for the changes observed. The *S*-trityl group is massively more sterically demanding than the side chains of methionine and *S*-methylcysteine; it is plausible that this side chain is afforded greater conformational freedom when positioned further from the ferrocene core, which in turn influences its binding to mercury(II), and the through-space interaction between the mercury guest and iron reporter.

The influence of the side chain on the spacer amino acid (Phe vs Ala) is small and difficult to generalise. For the methionine (**1** vs **2**) and *S*-tritylcysteine series (**5** vs **6**), the Phe-linked compounds show higher maximum potential shift, higher saturation points and greater sensitivity than the corresponding Ala-linked compounds. In the *S*-methylcysteine series (**3** vs **4**) there is less difference in the electrochemical properties of the two compounds, but it is the Ala derivative **3** that shows a slightly higher maximum potential shift and saturation point, although its sensitivity is again lower than the Phe compound **4**. Thus there is not a generalisable difference between the L-alanine and L-phenylalanine spacer units. Although the side chain of phenylalanine is significantly bulkier than that of alanine, there are not sufficient conformational constraints on the dipeptide chain for this to consistently influence metal binding.

Nonetheless it is evident that introducing a spacer amino acid between the ferrocene reporter and metal binding group of ferrocenoyl peptides with sulfur-containing side chains does influence the fundamental electrochemical properties of these systems and subtly alter their response to mercury(II) in solution. Moreover, the greater responsiveness of such ferrocenoyl peptide systems to mercury(II) than to other metal cations is also observed for dipeptide conjugates.

3. Experimental

3.1. Synthesis of building blocks

3.1.1. General procedure for preparation of dipeptides. N-tert-Butyloxycarbonyl-L-Xaa (0.5 mmol) was stirred in DCM (10 mL). Triethylamine (1.0 mmol) was added followed by *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HBTU) (0.5 mmol). This solution was stirred for 15 min after which time L-Yaa methyl ester (0.5 mmol) was added. The reaction was stirred for 16 h, the solvent evaporated in vacuo and the residue dissolved in ethyl acetate (50 mL). This solution was washed with brine (10 mL), saturated aqueous sodium bicarbonate solution (10 mL), water (10 mL), aqueous hydrochloric acid (1 M, 10 mL), water (10 mL) and brine (10 mL). The organic extract was dried ($MgSO_4$) and the solvent was evaporated in vacuo to yield an off-white foam. This was purified by column chromatography (SiO_2, EtOAc/hexane 1:1) to yield *N-tert*-butyloxycarbonyl-L-Xaa-L-Yaa methyl ester as a white foam (52–88%). All compounds were fully characterized using NMR and high resolution mass spectrometry.

3.1.2. General procedure for preparation of ferrocenoyl peptides. Ferrocene-1,1′-dicarboxylic acid (2.5 mmol) was dissolved in acetonitrile (10 mL) and triethylamine (5.0 mmol) and stirred while HBTU (5.0 mmol) was added. Stirring was continued for 15 min before the dipeptide methyl ester *p*-toluenesulfonate salt (5.0 mmol) was added along with additional triethylamine (5.0 mmol) and stirring continued for 24–48 h. The reaction mixture was diluted with ethyl acetate (50 mL) to prevent the formation of emulsions and the organic phase washed with water (50 mL), hydrochloric acid (1 M, 25 mL), water (50 mL), saturated aqueous sodium bicarbonate solution (25 mL),

water (50 mL) and brine (50 mL), then dried ($MgSO_4$). The solvent was evaporated in vacuo to give a brown solid, which was purified by flash chromatography (hexane/ether); yields and characterization data follow below.

3.1.2.1. Ferrocenoyl-1,1′-di-L-alaninyl-L-methionine methyl ester ***1***. Synthesized from ferrocene-1,1′-dicarboxylic acid **9** (0.10 g, 0.36 mmol) and L-alaninyl-L-methionine methyl ester *p*-toluenesulfonate (0.30 g, 0.73 mmol) to give an orange oil (0.15 g, 60%); R_f 0.13 (ether); δ_H (400 MHz, $CDCl_3$): 1.42 (6H, d, *J* 7.5 Hz, 2×CHCH_3), 2.02–2.30 (4H, m, 2×CH_2CH_2S), 2.15 (6H, s, 2×SCH_3), 2.61–2.69 (4H, m, 2×CH_2S), 3.76 (6H, s, 2×CO_2CH_3), 4.30–4.31 (2H, m, 2 of Fe(C_5H_4)$_2$), 4.52–4.53 (2H, m, 2 of Fe(C_5H_4)$_2$), 4.62–4.66 (2H, m, 2×NHCH_{ALA}), 4.70–4.76 (2H, m, 2×NHCH_{MET}), 4.78–4.79 (2H, m, 2 of Fe(C_5H_4)$_2$), 4.86–4.87 (2H, m, 2 of Fe(C_5H_4)$_2$), 6.80 (2H, d, *J* 8.0 Hz, 2×N*H*), 8.35 (2H, d, *J* 7.5 Hz, 2×N*H*); δ_C (100 MHz, $CDCl_3$): 16.6 (2×SCH_3), 17.4 (2×CHCH_3), 29.8 (2×CH_2CH_2S), 36.3 (2×CH_2S), 49.4 (2×NHCH_{ALA}), 52.3 (2×CO_2CH_3), 52.9 (2×NHCH_{MET}), 70.6, 70.9, 71.8, 72.1 (8×CH of Fe(C_5H_4)$_2$), 76.3 (2×C$_{ipso}$ of Fe(C_5H_4)$_2$), 170.6, 171.5, 175.1 (6×*C*=O); ν_{max} ($CHCl_3$ soln): 3319 (m), 1739, 1677 (m), 1537 (m), 1224 (w); *m*/*z* (ES^+): 729 (100%, $[M+Na]^+$); HRMS (ES^+): found $[MH]^+$ 707.18518, $C_{30}H_{43}FeN_4O_8S_2$ requires 707.18717.

3.1.2.2. Ferrocenoyl-1,1′-di-L-phenylalaninyl-L-methionine methyl ester ***2***. Synthesized from ferrocene-1,1′-dicarboxylic acid **9** (0.31 g, 1.13 mmol) and L-phenylalaninyl-L-methionine methyl ester *p*-toluenesulfonate (1.20 g, 2.48 mmol) to give an orange oil (0.66 g, 60%); R_f 0.41 (ether); δ_H (400 MHz, $CDCl_3$): 2.11–2.22 (4H, m, 2×CH_2CH_2S), 2.16 (6H, s, 2×SCH_3), 2.61–2.67 (4H, m, 2×CH_2C$_6$H$_5$), 3.13–3.15 (4H, m, 2×CH_2S), 3.58 (6H, s, 2×CO_2CH_3), 4.31 (2H, s, br, 2 of Fe(C_5H_4)$_2$), 4.55 (2H, s, br, 2 of Fe(C_5H_4)$_2$), 4.75–4.82 (2H, m, 2×NHCH_{PHE}), 4.77 (2H, s, br, 2 of Fe(C_5H_4)$_2$), 4.84 (2H, s, br, 2 of Fe(C_5H_4)$_2$), 4.92–4.96 (2H, m, 2×NHCH_{MET}), 7.12–7.29 (10H, m, 2×C$_6$H$_5$), 8.72 (2H, d, *J* 7.0 Hz, 2×N*H*); δ_C (100 MHz, $CDCl_3$): 15.5 (2×SCH$_3$), 31.3 (2×CH_2CH_2S), 37.0 (2×CH_2S), 37.9 (2×CH_2C$_6$H$_5$), 52.1 (2×NHCH_{PHE}), 52.4 (2×CO_2CH_3), 53.5 (2×NHCH_{MET}), 69.9, 70.8, 71.2, 71.9 (8×CH of Fe(C_5H_4)$_2$), 75.7 (2×C$_{ipso}$ of Fe(C_5H_4)$_2$), 126.7, 128.5, 129.3 (10×CH of C_6H_5), 137.6 (2×C$_{ipso}$ of C_6H_5), 170.7, 171.9, 174.1 (6×*C*=O); ν_{max} ($CHCl_3$ soln): 3352 (m), 2964 (s), 1743, 1670 (m), 1627, 1483 (m), 1226 (w); *m*/*z* (ES^+): 881 (100%, $[M+Na]^+$); HRMS (ES^+): found $[MH]^+$ 859.24885, $C_{42}H_{51}FeN_4O_8S_2$ requires 859.24977.

3.1.2.3. Ferrocenoyl-1,1′-di-L-alaninyl-S-methyl-L-cysteine methyl ester ***3***. Synthesized from ferrocene-1,1′-dicarboxylic acid **9** (0.04 g, 0.15 mmol) and L-alaninyl-*S*-methyl-L-cysteine methyl ester *p*-toluenesulfonate (0.12 g, 0.30 mmol) to yield an orange solid (0.11 g, 82%); R_f 0.10 (ether); mp 95–96 °C; δ_H (400 MHz, $CDCl_3$): 1.44 (6H, d, *J* 7.0 Hz, 2×CHCH_3), 2.18 (6H, s, 2×SCH_3), 3.01–3.11 (4H, m, 2×CH_2S), 3.78 (6H, s, 2×CO_2CH_3), 4.32 (2H, s, br, 2 of Fe(C_5H_4)$_2$), 4.38 (2H, s, br, 2 of Fe(C_5H_4)$_2$), 4.70–4.73 (2H, m, 2×NHCH_{ALA}), 4.81 (2H, s, br, 2 of Fe(C_5H_4)$_2$), 4.88 (2H, s, br, 2 of Fe(C_5H_4)$_2$), 4.89–4.95 (2H, m, 2×NHCH_{CYS}), 6.91 (2H, d, *J* 7.0 Hz, 2×N*H*), 8.34 (2H, d, *J* 7.0 Hz, 2×N*H*); δ_C (100 MHz, $CDCl_3$): 16.3 (2×SCH_3), 17.0 (2×CHCH_3), 30.8 (2×CH_2S), 49.1 (2×NHCH_{ALA}), 51.9 (2×CO_2CH_3), 52.7 (2×NHCH_{CYS}), 70.3, 70.9, 71.7, 72.1 (8×CH of Fe(C_5H_4)$_2$), 75.6 (2×C$_{ipso}$ of Fe(C_5H_4)$_2$), 170.6, 171.2, 174.8 (6×*C*=O); ν_{max} ($CHCl_3$ soln): 3323 (m), 2954 (s), 1743, 1677 (m), 1512 (m), 1220 (w); *m*/*z* (ES^+): 701 (100%, $[M+Na]^+$); HRMS (ES^+): found $[M+Na]^+$ 701.13941, $C_{28}H_{38}FeN_4NaO_8S_2$ requires 701.13782.

3.1.2.4. Ferrocenoyl-1,1′-di-L-phenylalaninyl-S-methyl-L-cysteine methyl ester ***4***. Synthesized from ferrocene-1,1′-dicarboxylic acid **9** (0.04 g, 0.16 mmol) and L-phenylalaninyl-*S*-methyl-L-cysteine methyl ester *p*-toluenesulfonate (0.15 g, 0.32 mmol) to afford an orange oil (0.07 g, 49%); R_f 0.30 (ether); δ_H (400 MHz, $CDCl_3$): 2.07 (6H, s, 2×SCH_3), 2.71–2.95 (4H, m, 2×CH_2C$_6$H$_5$), 2.99–3.20 (4H, m, 2×CH_2S), 3.46 (6H, s, 2×CO_2CH_3), 4.22 (2H, s, br, 2 of Fe(C_5H_4)$_2$), 4.38 (2H, s, br, 2 of Fe(C_5H_4)$_2$), 4.60 (2H, s, br, 2 of Fe(C_5H_4)$_2$), 4.65–4.71 (2H, m, 2×NHCH_{PHE}), 4.73 (2H, s, br, 2 of Fe(C_5H_4)$_2$), 5.04–5.29 (2H, m, 2×NHCH_{CYS}), 7.22–7.48 (10H, m, 2×C$_6$H$_5$); δ_C (100 MHz, $CDCl_3$): 16.3 (2×SCH_3), 36.7 (2×CH_2S), 38.5 (2×CH_2C$_6$H$_5$), 53.3 (2×NHCH_{PHE}), 54.2 (2×CO_2CH_3), 56.9 (2×NHCH_{CYS}), 71.2, 71.9, 72.4, 73.6 (8×CH of Fe(C_5H_4)$_2$), 77.2 (2×C$_{ipso}$ of Fe(C_5H_4)$_2$), 128.0, 129.7, 130.8 (10×CH of C_6H_5), 139.8 (2×C$_{ipso}$ of C_6H_5), 172.9, 173.1, 176.0 (6×*C*=O); ν_{max} ($CHCl_3$ soln): 3323 (m), 2954 (s), 1745, 1672 (m), 1504 (m), 1209 (w); *m*/*z* (ES^+): 853 (100%, $[M+Na]^+$); HRMS (ES^+): found $[MH]^+$ 831.22096, $C_{40}H_{47}FeN_4O_8S_2$ requires 831.21847.

3.1.2.5. Ferrocenoyl-1,1′-di-L-alaninyl-S-trityl-L-cysteine methyl ester ***5***. Synthesized from ferrocene-1,1′-dicarboxylic acid **9** (0.15 g, 0.56 mmol) and L-alaninyl-*S*-trityl-L-cysteine methyl ester (0.50 g, 1.12 mmol) to give an orange solid (0.38 g, 61%); R_f 0.61 (ether); mp 107–110 °C; δ_H (400 MHz, $CDCl_3$): 1.20 (6H, d, *J* 7.0 Hz, 2×CHCH_3), 2.59 (2H, dd, H_B of ABX, J_{BA} 13.0 Hz, J_{BX} 8.0 Hz, 2×(1 of CH_2S)), 2.72 (1H, dd, H_A of ABX, J_{AB} 13.0 Hz, J_{AX} 5.5 Hz, 2×(1 of CH_2S)), 3.58 (6H, s, 2×CO_2CH_3), 4.19–4.20 (2H, m, 2 of Fe(C_5H_4)$_2$), 4.24–4.25 (1H, q, *J* 7.0 Hz, 2×NHCH_{ALA}), 4.35–4.36 (2H, m, 2 of Fe(C_5H_4)$_2$), 4.48 (2H, dd, H_X of ABX, J_{XA} 5.5 Hz, J_{XB} 8.0 Hz, 2×NHCH_{CYS}), 4.67 (2H, m, 2 of Fe(C_5H_4)$_2$)), 4.78–4.79 (2H, m, 2 of Fe(C_5H_4)$_2$)), 6.04 (2H, d, *J* 7.0 Hz, 2×N*H*), 7.12–7.38 (30H, m, 2×(C_6H_5)$_3$), 8.15 (2H, d, *J* 7.0 Hz, N*H*×2); δ_C (100 MHz, $CDCl_3$): 15.9 (2×CHCH_3), 32.4 (2×CH_2S), 47.5 (2×NHCH_{ALA}), 50.8 (2×CO_2CH_3), 51.4 (2×NHCH_{CYS}), 66.2 (2×*C*(C_6H_5)$_3$), 69.1, 69.9, 70.5, 70.8 (8×CH of Fe(C_5H_4)$_2$), 74.9 (2×C$_{ipso}$ of Fe(C_5H_4)$_2$), 125.9, 126.1, 126.7, 127.1, 128.5 (30×CH of C_6H_5), 143.2 (6×C$_{ipso}$ of C_6H_5), 169.9, 170.1, 173.6 (6×*C*=O); ν_{max} ($CHCl_3$ soln): 1751, 1683 (m), 1506 (m), 1220 (w); *m*/*z* (ES^+): 1157 (100%, $[M+Na]^+$); HRMS (ES^+): found $[MH]^+$ 1135.34395, $C_{64}H_{63}FeN_4O_8S_2$ requires 1135.34367.

3.1.2.6. Ferrocenoyl-1,1′-di-L-phenylalaninyl-S-trityl-L-cysteine methyl ester ***6***. Synthesized from ferrocene-1,1′-dicarboxylic acid **9** (0.06 g, 0.22 mmol) and L-phenylalaninyl-*S*-trityl-L-cysteine methyl ester *p*-toluenesulfonate (0.30 g, 0.43 mmol) to yield an orange solid (0.12 g, 44%); R_f 0.75 (ether); mp 128–133 °C; δ_H (400 MHz, $CDCl_3$): 2.27–2.77 (4H, m, 2×CH_2C$_6$H$_5$), 3.00–3.22 (4H, m, 2×CH_2S), 3.78 (6H, s, 2×CO_2CH_3), 4.23 (2H, s, br, 2 of Fe(C_5H_4)$_2$), 4.28–4.31 (2H, m, 2×NHCH_{PHE}), 4.36 (2H, s, br, 2 of Fe(C_5H_4)$_2$), 4.70–4.74 (2H, m, 2×NHCH_{CYS}), 4.70 (2H, s, br, 2 of Fe(C_5H_4)$_2$), 4.78 (2H, s, br, 2 of Fe(C_5H_4)$_2$), 6.38–6.42 (2H, d, *J* 7.5 Hz, 2×N*H*), 7.13–7.38 (40H, m, 8×C$_6$H$_5$), 8.41–8.45 (2H, d, *J* 8.0 Hz, 2×N*H*); δ_C (100 MHz, $CDCl_3$): 32.9 (2×CH_2S), 37.2 (2×CH_2C$_6$H$_5$), 51.9 (2×NHCH_{PHE}), 52.5 (2×CO_2CH_3), 53.5 (2×NHCH_{CYS}), 67.2 (2×*C*(C_6H_5)$_3$), 70.0, 70.7, 71.5, 71.8 (8×CH of Fe(C_5H_4)$_2$), 75.9 (2×C$_{ipso}$ of Fe(C_5H_4)$_2$), 126.8, 127.0, 128.0, 128.2, 128.6, 129.0, 129.7 (40×CH of C_6H_5), 137.7, 144.2 (8×C$_{ipso}$ of C_6H_5), 170.2, 170.4, 173.7 (6×*C*=O); ν_{max} ($CHCl_3$ soln): 2962 (s), 1730, 1654 (m), 1217 (w); *m*/*z* (ES^+): 1309 (100%, $[M+Na]^+$); HRMS (ES^+): found $[M+Na]^+$ 1309.38941, $C_{76}H_{70}FeN_4NaO_8S_2$ requires 1309.38822.

3.1.2.7. Ferrocenoyl-1,1′-di-L-valinyl-S-benzhydryl-L-cysteine methyl ester ***7***. Synthesized according to the general peptide coupling procedure from ferrocene-1,1′-dicarboxylic acid **9** (0.20 g, 0.74 mmol) and L-valinyl-*S*-benzhydryl-L-cysteine methyl ester *p*-toluenesulfonate (0.92 g, 1.48 mmol) to yield a flaky orange solid (0.26 g, 41%); R_f 0.30 (ether); mp 99–101 °C; δ_H (300 MHz, $CDCl_3$): 0.99–1.05 (12H, m, 2×CH(CH_3)$_2$), 2.05–2.16 (2H, m, 2×(CH(CH$_3$)$_2$), 2.82–2.95 (4H, m, 2×CH_2S), 3.69 (6H, s, 2×CO_2CH_3), 4.25 (2H, s, br, 2 of Fe(C_5H_4)$_2$), 4.28–4.31 (2H, s, br, 2×(NHCH_{VAL})), 4.31 (2H, s, br, 2 of Fe(C_5H_4)$_2$), 4.68 (2H, s, br, 2 of Fe(C_5H_4)$_2$), 4.76 (2H, m, 2×NHCH_{CYS}), 4.81 (2H, s, br, 2 of Fe(C_5H_4)$_2$)), 5.33 (2H, s, 2×SCH (C_6H_5)$_2$), 7.14–7.47 (20H, m, 2×SCH(C_6H_5)$_2$); δ_C (75.4 MHz, $CDCl_3$): 19.6, 19.8 (4×CH(CH_3)$_2$), 29.7 (2×CH(CH$_3$)$_2$), 33.8 (2×CH_2S), 51.9

($2\times CO_2CH_3$), 52.4 ($2\times SCH(C_6H_5)_2$), 54.2 ($NHCH_{CYS}$), 60.3 ($NHCH_{VAL}$), 70.1, 70.2, 71.2, 71.7 ($8\times$CH of Fe($C_5H_4)_2$), 76.3 ($2\times C_{ipso}$ of Fe($C_5H_4)_2$), 127.4, 127.5, 127.4, 128.6, 128.7, 129.2 ($20\times$CH of C_6H_5), 140.6, 140.8 ($4\times C_{ipso}$ of C_6H_5), 169.9, 171.0, 173.5 ($6\times C$=O); ν_{max} ($CHCl_3$ soln): 3322, 1745, 1672 (s), 1439 (m), 1200 (s); m/z (ES^+): 1039 (20%, $[MH]^+$), 1061 (100%, $[M+Na]^+$); HRMS (ES^+): found $[MH]^+$ 1039.3469, $C_{56}H_{63}FeN_4O_8S_2$ requires 1039.3431.

3.1.2.8. Ferrocenoyl-1,1′-di-L-phenylalaninyl-S-benzhydryl-L-cysteine methyl ester ***8***. Synthesized from ferrocene-1,1′-dicarboxylic acid **9** (0.2 g, 0.74 mmol) and L-phenylalanine-*S*-benzhydryl-L-cysteine methyl ester *p*-toluenesulfonate (0.92 g, 1.48 mmol) to yield an orange oil (0.39 g, 46%); R_f 0.40 (ether); δ_H (300 MHz, $CDCl_3$): 2.76–2.90 (4H, m, $2\times CH_2C_6H_5$), 3.07–3.18 (4H, m, $2\times CH_2S$), 3.52 (6H, s, $2\times CO_2CH_3$), 4.21 (2H, s, br, 2 of Fe($C_5H_4)_2$), 4.33 (2H, s, br, 2 of Fe($C_5H_4)_2$), 4.68 (2H, s, br, 2 of Fe($C_5H_4)_2$), 4.79 (2H, s, br, 2 of Fe ($C_5H_4)_2$), 4.72–4.86 (4H, m, $4\times$(NHCH)), 5.22 (2H, s, $2\times SCH(C_6H_5)_2$), 7.14–7.42 (30H, m, $6\times C_6H_5$); δ_C (100 MHz, $CDCl_3$): (75.4 MHz, $CDCl_3$): 33.5 (CH_2S), 37.5 ($CH_2C_6H_5$), 52.1 (CO_2CH_3), 52.4 (SCH ($C_6H_5)_2$), 54.2 ($NHCH_{CYS}$), 55.9 ($NHCH_{PHE}$), 70.1, 70.3, 71.1, 71.9 ($8\times$CH of Fe($C_5H_4)_2$), 75.8 ($2\times C_{ipso}$ of Fe($C_5H_4)_2$), 126.7, 127.4, 127.5, 128.3, 128.5, 128.6, 128.7, 129.2 ($30\times$CH of C_6H_5), 137.6, 140.5, 140.8 ($6\times C_{ipso}$ of C_6H_5), 169.5, 170.5, 170.7 ($6\times C$=O); ν_{max} ($CHCl_3$ soln): 3322, 1745, 1673 (s), 1538 (m), 1452 (m), 1222 (s); m/z (ES^+): 1157 (50%, $[M+Na]^+$); HRMS (ES^+): found $[MH]^+$ 1035.3422, $C_{64}H_{63}FeN_4O_8S_2$ requires 1035.3431.

3.2. Cyclic voltammetry

The electrochemical properties of the ferrocene/peptide conjugates **1**–**8** were analyzed by cyclic voltammetry.[33] Experiments were carried out at room temperature (22±2 °C) on a BAS-100 potentiostat using a glassy carbon working electrode and platinum wire auxiliary electrode. The reference electrode was Ag/AgCl (3.0 M NaCl). Titrations were carried out in acetonitrile degassed with argon and the background electrolyte used was 0.1 M tetrabutylammonium perchlorate. All experiments were repeated three times to ensure reproducibility and the working electrode was cleaned between runs by polishing on a microcloth pad with alumina slurry followed by washing with water then acetonitrile. The scan rate was 100 mV s^{-1} in all experiments and iR compensation was applied in all cases. Half wave potentials are reported relative to the Ag/Ag^+ redox potential. Redox potentials are quoted as the half wave potentials ($E_{½}$) and are derived from the formal redox potential ($E^{\circ\prime}$) of the Fe(II)/Fe(III) couple.

Acknowledgements

We wish to thank Professor Robert O'Neil (UCD) and Dr. Aviva Levina for help and advice with electrochemistry experiments. This work was funded in Ireland by University College Dublin and the Centre for Synthesis and Chemical Biology under the Programme for Research in Third Level Institutions (PRTLI) administered by the HEA, and in Australia by the University of Sydney.

Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.05.070.

References and notes

1. Kraepiel, A. M. L.; Morel, F. M. M.; Amyot, M. *Annu. Rev. Ecol. Syst.* **1998**, *29*, 543–566.
2. Florea, A.-M.; Büsselberg, D. *Biometals* **2006**, *19*, 419–427.
3. Valko, M.; Morris, H.; Cronin, M. T. D. *Curr. Med. Chem.* **2005**, *12*, 1161–1208.
4. Kagi, J. H. R.; Schaffer, A. *Biochemistry* **1988**, *27*, 8509–8515.
5. Henkel, G.; Krebs, B. *Chem. Rev.* **2004**, *104*, 801–824.
6. Clemens, S. *Biochimie* **2006**, *88*, 1707–1719.
7. Huang, C.-C.; Yang, Z.; Lee, K.-H.; Chang, H.-T. *Angew. Chem., Int. Ed.* **2007**, *46*, 6824–6828.
8. Nolan, E. M.; Lippard, S. J. *J. Am. Chem. Soc.* **2007**, *129*, 5910–5918.
9. Wegner, S. V.; Okesli, A.; Chen, P.; He, C. *J. Am. Chem. Soc.* **2007**, *129*, 3474–3475.
10. Moon, S. Y.; Youn, N. J.; Park, S. M.; Chang, S. K. *J. Org. Chem.* **2005**, *70*, 2394–2397.
11. Nolan, E. M.; Lippard, S. J. *J. Mater. Chem.* **2005**, *15*, 2778–2783.
12. Wu, Z. K.; Zhang, Y. F.; Ma, J. S.; Yang, G. Q. *Inorg. Chem.* **2006**, *45*, 3140–3142.
13. Lloris, J. M.; Benito, A.; Martinez-Manez, R.; Padilla-Tosta, M. E.; Pardo, T.; Soto, J.; Tendero, M. J. L. *Helv. Chim. Acta* **1998**, *81*, 2024–2030.
14. Beer, P. D.; Gale, P. A.; Chen, G. Z. *Coord. Chem. Rev.* **1999**, *186*, 3–36.
15. Carr, J. D.; Coles, S. J.; Hursthouse, M. B.; Tucker, J. H. R. *J. Organomet. Chem.* **2001**, *637*, 304–310.
16. Siemeling, U.; Auch, T.-C. *Chem. Soc. Rev.* **2005**, *34*, 584–594.
17. Appoh, F. E.; Sutherland, T. C.; Kraatz, H. B. *J. Organomet. Chem.* **2005**, *690*, 1209–1217.
18. Nijhuis, C. A.; Ravoo, B. J.; Huskens, J.; Reinhoudt, D. N. *Coord. Chem. Rev.* **2007**, *251*, 1761–1780.
19. Severin, K.; Bergs, R.; Beck, W. *Angew. Chem., Int. Ed.* **1998**, *37*, 1634–1654.
20. van Staveren, D. R.; Metzler-Nolte, N. *Chem. Rev.* **2004**, *104*, 5931–5985.
21. Moriuchi, T.; Hirao, T. *Chem. Soc. Rev.* **2004**, *33*, 294–301.
22. Kirin, S. I.; Kraatz, H. B.; Metzler-Nolte, N. *Chem. Soc. Rev.* **2006**, *35*, 348–354.
23. Scully, C. C. G.; Jensen, P.; Rutledge, P. J. *J. Organomet. Chem.* **2008**, *693*, 2869–2876.
24. Chowdhury, S.; Schatte, G.; Kraatz, H. B. *Eur. J. Inorg. Chem.* **2006**, 988–993.
25. Huang, H.; Mu, L. J.; He, J. Q.; Cheng, J. P. *J. Org. Chem.* **2003**, *68*, 7605–7611.
26. Rausch, M. D.; Ciappenelli, D. J. *J. Organomet. Chem.* **1967**, *10*, 127–136.
27. Hwang, D. R.; Helquist, P.; Shekhani, M. S. *J. Org. Chem.* **1985**, *50*, 1264–1271.
28. Bodanzky, M.; Bodanzky, A. In *Reactivity and Structure Concepts in Organic Chemistry*; Hafner, K., Rees, C. W., Trost, B. M., Lehn, J. M., Schleyer, P. v. R., Zahruchik, R., Eds.; Springer: Berlin, 1984.
29. McMullen, T. C. *J. Am. Chem. Soc.* **1916**, *38*, 1228–1230.
30. Tarbell, D. S.; Yamamoto, Y.; Pope, B. M. *Proc. Natl. Acad. Sci. U.S.A.* **1972**, *69*, 730–732.
31. Han, S.-Y.; Kim, Y.-A. *Tetrahedron* **2004**, *60*, 2447–2467.
32. Baker, M. V.; Kraatz, H. B.; Quail, J. W. *New J. Chem.* **2001**, *25*, 427–433.
33. Bard, A. J.; Faulkner, L. R. *Electrochemical Methods: Fundamentals and Applications*, 2nd ed.; John Wiley & Sons: New York, NY, 2000.
34. Noviandri, I.; Brown, K. N.; Fleming, D. S.; Gulyas, P. T.; Lay, P. A.; Masters, A. F.; Phillips, L. *J. Phys. Chem. B* **1999**, *103*, 6713–6722.
35. Beer, P. D.; Gale, P. A.; Chen, G. Z. *J. Chem. Soc., Dalton Trans.* **1999**, 1897–1909.
36. Beer, P. D.; Shade, M. *Chem. Commun.* **1997**, 2377–2378.
37. Saji, T.; Kinoshita, I. *J. Chem. Soc., Chem. Commun.* **1986**, 716–717.
38. Beer, P. D.; Blackburn, C.; McAleer, J. F.; Sikanyika, H. *Inorg. Chem.* **1990**, *29*, 378–381.
39. Beer, P. D.; Chen, Z.; Grieve, A.; Haggitt, J. *J. Chem. Soc., Chem. Commun.* **1994**, 2413–2414.
40. Winkler, J. R.; Gray, H. B. *Chem. Rev.* **1992**, *92*, 369–379.
41. Kraatz, H. B.; Long, Y. T.; Abu-Rhayem, E. *Chem.—Eur. J.* **2005**, *11*, 5186–5194.