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Novel redox active bifunctional crosslinkers from unsymmetrical 1,1′-disubstituted ferrocenes

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ABSTRACT

The synthesis and electrochemistry of novel redox active bifunctional crosslinkers bearing pendant amine and maleimide groups from unsymmetrical 1,1′-disubstituted ferrocene precursors are reported.

1. Introduction

Introduced in the early 1950s,[1] ferrocene and its derivatives continue to receive significant interest from researchers in all fields interfacing with organometallic chemistry.[2] The reversible redox behavior, chemical stability, and synthetic versatility of ferrocene have lead to the development of ferrocenyl molecules as components in asymmetric catalysis,[3] electron transfer[4] and optical devices,[5] liquid crystals,[6] and sensors for chemical and biological targets.[7,8] In addition, synthetic methods enabling the conjugation of ferrocenyl groups to biomolecules have stimulated tremendous advances in bioinorganic chemistry.[2b] For instance, unsymmetrical 1,1′-disubstituted ferrocene derivatives with unique functional groups on each cyclopentadienyl (Cp) ring have been used to assemble electroactive peptide and DNA conjugates.[8a,9] Hence, reliable strategies for the synthesis of unsymmetrical ferrocene derivatives are certain to maintain broad utility in both fundamental and applied research.

As part of an ongoing program toward the development of electroactive self-assembled monolayers (SAMs)[10] as components of biosensor platforms, we have been interested in ferrocenyl molecules with orthogonally reactive functional groups suitable for bioconjugation and immobilization within SAMs. Toward this effort, herein we report the synthesis of novel redox active bifunctional crosslinkers **1** and **2** (Fig. 1) from unsymmetrical 1,1′-disubstituted ferrocenes. The design of the bifunctional crosslinkers includes carboxyl-reactive primary amine groups for eventual surface conjugation to acid-terminated SAMs using established coupling methodologies.[11] The functional groups bridging the pendant amines to one of the ferrocene Cp rings in each molecule were varied from an electron-withdrawing amidoethyl group in **1** to a more electron-donating methylene group in **2**. Different amine bridges were chosen to provide bifunctional crosslinkers with significantly different redox potentials. The alternate ferrocene Cp rings were functionalized with pendant maleimide groups to enable reactivity with sulfhydryl-containing substrates under mild reaction conditions.[12] Therefore, orthogonally reactive bifunctional crosslinkers **1** and **2** should be amenable to selective functionalization with a range of biomolecules, including peptides and proteins with exposed cysteine residues, to generate redox active bioconjugates.

2. Results and discussion

The synthesis of ferrocene derivative **1** is shown in Scheme 1. Previously reported 1,1′-ferrocene dicarboxylic acid monomethyl ester **3**[13] was coupled to *N*-Boc-ethylenediamine to yield **4**. Subsequent removal of the methyl ester with LiOH gave the ferrocene carboxylic acid derivative **5** which was further coupled to *N*-(2-aminomethyl)maleimide to yield **6**, the *N*-Boc-protected precursor of **1**. Removal of the Boc group with trifluoroacetic acid (TFA) afforded the target unsymmetrical 1,1′-disubstituted ferrocene bifunctional crosslinker **1**.

The synthesis of ferrocene derivative **2** is shown in Scheme 2. Compound **7** was prepared from **3** as described previously.[13] Reaction of the primary alcohol in **7** with sodium azide in acetic acid afforded the azide derivative **8** which was subsequently reduced under Staudinger conditions with triphenylphosphine to give the primary amine **9** in high yield. The amine was protected as *N*-Boc derivative **10** which was subsequently treated with LiOH to remove the methyl ester and yield **11**. It should be noted that carboxylic acid derivative **11** may serve as a useful *N*-Boc-protected ferrocenyl alternative to the non-natural amino acid 1-aminoferrocene-1′-carboxylic acid.[14] Compound **11** was further coupled to *N*-(2-aminomethyl)maleimide to yield **12** which was treated with TFA to afford bifunctional crosslinker **2**. We note that the amine functional groups in **1** and **2** were maintained as TFA salts to avoid

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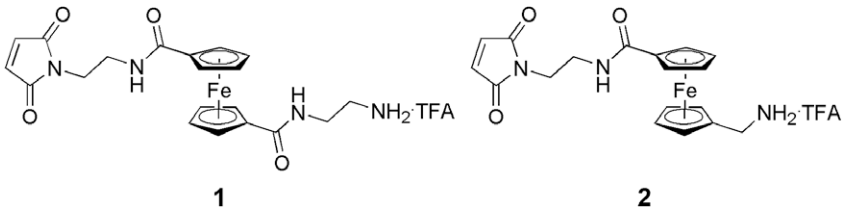
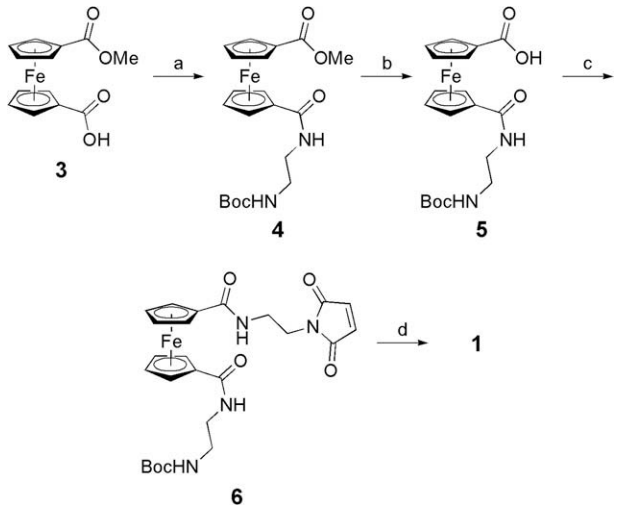


Figure 1. Unsymmetrical 1,1′-disubstituted heterobifunctional ferrocene crosslinkers **1** and **2**.



Scheme 1. Reagents and conditions: (a) *N*-Boc-ethylenediamine, EDC, HOBt, DCM, 86%; (b) LiOH, THF/H_2O, 97%; (c) *N*-(2-aminoethyl)maleimide TFA salt, HATU, TEA, DMF, 88%; (d) TFA/DCM, 98%.

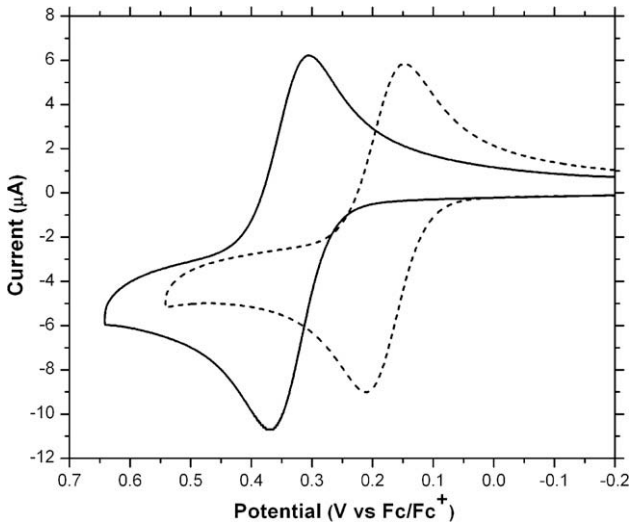


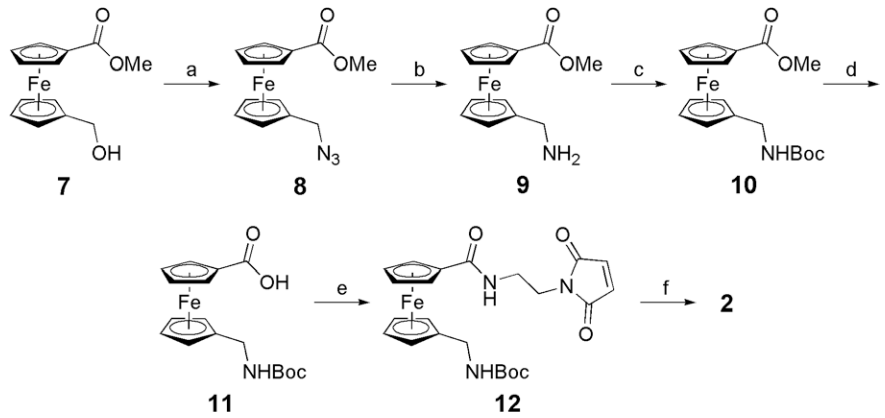
Figure 2. Cyclic voltammograms of *N*-Boc-protected ferrocene derivatives **6** (solid line) and **12** (dashed line) in acetonitrile (5.0×10^{-4} M) containing 0.15 M *n*-Bu_4NClO_4 supporting electrolyte at a glassy carbon working electrode and 100 mV/s scan rate.

any cross-reactivity with maleimides during analysis and storage.[15]

Electrochemical properties of the 1,1′-disubstituted ferrocene derivatives were investigated by cyclic voltammetry in acetonitrile. As shown in Figure 2, *N*-Boc-protected derivative **6** exhibited a reversible one-electron redox wave at $E_{1/2}$ = 338 mV (vs Fc/Fc^+) compared to $E_{1/2}$ = 178 mV (vs Fc/Fc^+) for *N*-Boc-protected derivative **12**. The $\Delta E_{1/2}$ = 160 mV between **6** and **12** was anticipated given the different electronic effects of the amide and methylene Cp substituents, respectively.[16] After removal of the Boc groups, crosslinker **1** exhibited an $E_{1/2}$ = 392 mV (vs Fc/Fc^+) compared to $E_{1/2}$ = 297 mV (vs Fc/Fc^+) for **2**. Positive shifts in the $E_{1/2}$ values for **1** and **2** with respect to their *N*-Boc-protected precursors **6** and **12** can be rationalized by the electron-withdrawing influence of the amine TFA salts on the redox active ferrocene substituents. The magnitude of this potential difference is greater for **2** than for **1** due to a shorter bridge distance between the amine salt and the ferrocene Cp ring.

3. Conclusions

In summary, we have synthesized novel redox active bifunctional crosslinkers **1** and **2** bearing pendant amine and maleimide



Scheme 2. Reagents and conditions: (a) NaN_3, AcOH, 82%; (b) PPh_3, THF/H_2O, 94%; (c) $(Boc)_2$-O, TEA, THF, 99%; (d) LiOH, THF/H_2O, 97%; (e) *N*-(2-aminoethyl)maleimide TFA salt, EDC, HOBt, TEA, 78%; (f) TFA/DCM, 95%.

groups from unsymmetrical 1,1′-disubstituted ferrocenyl precursors. Cyclic voltammetry confirmed reversible one-electron redox processes for **1** and **2** and their corresponding *N*-Boc-protected precursors **6** and **12**. Utilization of these bifunctional crosslinkers toward the preparation of materials with electroactive bioconjugates is ongoing.

4. Experimental

4.1. General

All reagents were purchased from commercial sources. For reaction media and electrochemistry, solvents were dried over neutral alumina via the Dow-Grubbs solvent system[17] acquired from Glass Contours (Laguna Beach, CA) and degassed with argon prior to use. Deuterated solvents were purchased from Cambridge Isotope Laboratories and used as received. Column chromatography was carried out using Silica Gel 60 (particle size: 40–63 μm, Sorbent Technologies, Atlanta, GA). Reactions were monitored by TLC using EMD precoated aluminum plates (Silica Gel 60, F_{254}). Unless otherwise noted, all synthetic manipulations were performed under a dry argon atmosphere using standard Schlenk techniques. NMR spectra were recorded on a Bruker Avance III spectrometer (499.37 MHz for ^{1}H, 125.58 MHz for ^{13}C) and were processed with Bruker TOPSPIN 2.1 software. ^{1}H and ^{13}C chemical shifts are reported in parts per million downfield from tetramethylsilane (TMS). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, pt = pseudo-triplet from a non-resolved doublet of doublets, and m = multiplet), and integration. Electrospray ionization mass spectrometry (ESI-MS) was obtained on a Thermo Finnigan LCQ Advantage mass spectrometer.

Cyclic voltammetry was performed on a CHI model 660A electrochemical analyzer (CHI Instruments Inc.) in a three-electrode system, with a Ag/AgCl quasi-reference wire, a platinum wire counter electrode (Bioanalytical Systems), and a glassy carbon working electrode (d = 2 mm, CHI Instruments). Ferrocene (recrystallized twice from ethanol) was added as an internal standard. Electrochemical measurements in solution were carried out in acetonitrile at 100 mV/s scan rate with tetrabutylammonium perchlorate (n-Bu_4NClO_4) (0.15 M) as the supporting electrolyte.

4.2. Compound 4

To an ice-cooled solution of **3** (0.971 g, 3.37 mmol), *N*-Boc-ethylenediamine (0.744 g, 4.64 mmol), and 1-hydroxybenzotriazole (HOBt) (0.773 g, 5.05 mmol) in dichloromethane (DCM) (50 mL) was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC) (0.969 g, 5.05 mmol), and the reaction mixture was allowed to warm to rt overnight. The solution was concentrated in vacuo and purified by column chromatography (0.5:1.5:8, MeOH:EtOAc:DCM) to yield the product as a pale orange solid (1.25 g, 2.91 mmol, 86%). ^{1}H NMR ($CDCl_3$): δ 1.46 (s, 9H); 3.40 (m, 2H); 3.51 (m, 2H); 3.85 (s, 3H); 4.38 (pt, 2H); 4.46 (pt, 2H); 4.64 (pt, 2H); 4.77 (pt, 2H); 5.41 (br s, 1H); 6.64 (br s, 1H). ^{13}C NMR ($CDCl_3$): δ 28.4, 40.5, 40.8, 52.0, 70.0, 71.6, 71.9, 72.0, 72.7, 78.0, 79.6, 156.9, 169.6, 171.9. ESI-MS m/z: 453.01 $(M+Na)^+$.

4.3. Compound 5

Compound **4** (1.25 g, 2.91 mmol) and LiOH (0.174 g, 7.26 mmol) were combined in THF/H_2O (3/1 v/v, 40 mL). The mixture was stirred at rt for 24 h and concentrated in vacuo to half volume. The mixture was acidified with HCl (0.5 M, 100 mL) and extracted with DCM (4 × 100 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated in vacuo to a crude residue that was purified by column chromatography (9:1, DCM:MeOH + 0.05% AcOH) to yield the product as an orange solid (1.17 g, 2.81 mmol, 97%). ^{1}H NMR (CD_3OD): δ 1.46 (s, 9H); 3.25 (t, J_{H-H} = 6.0 Hz, 2H); 3.39 (t, J_{H-H} = 6.0 Hz, 2H); 4.43 (pt, 2H); 4.47 (pt, 2H); 4.78 (pt, 2H); 4.81 (pt, 2H). ^{13}C NMR (CD_3OD): δ 28.8, 40.8, 41.2, 71.1, 73.1, 73.3, 73.4, 74.3, 78.5, 80.3, 158.7, 172.3, 174.8. ESI-MS m/z: 439.01 $(M+Na)^+$.

4.4. Compound 6

To a solution of **5** (0.060 g, 0.144 mmol), *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(7-aza-benzotriazol-1-yl)uronium hexafluorophosphate (HATU) (0.055 g, 0.144 mmol), and triethylamine (TEA) (42 μL, 0.302 mmol) in DMF (4 mL) was added *N*-(2-aminoethyl)maleimide TFA salt (0.038 g, 0.151 mmol). After 2 h, the reaction mixture was diluted with EtOAc (100 mL) and washed with brine (3 × 50 mL). The organic layer was collected, dried over Na_2SO_4, filtered, and concentrated in vacuo to a crude residue that was purified by column chromatography (2:1, EtOAc:DCM) to yield the product as a light orange solid (0.068 g, 0.127 mmol, 88%). ^{1}H NMR ($CDCl_3$): δ 1.45 (s, 9H); 3.40 (m, 2H); 3.51 (m, 2H); 3.63 (m, 2H); 3.82 (m, 2H); 4.38 (m, 4H); 4.49 (pt, 2H); 4.54 (br m, 2H); 5.58 (br t, 1H); 6.77 (s, 2H); 7.01 (br t, 1H); 7.21 (br t, 1H). ^{13}C NMR ($CDCl_3$): δ 28.4, 37.9, 39.2, 40.6, 40.7, 70.6, 71.0, 71.1, 77.2, 78.0, 78.1, 79.5, 134.3, 156.9, 170.6, 170.8, 171.1. ESI-MS m/z: 539.00 $(M+H)^+$, 561.08 $(M+Na)^+$.

4.5. Compound 1

Compound **6** (0.020 g, 0.037 mmol) was stirred in TFA/DCM (1:1 v/v, 4 mL) for 1 h at rt. The reaction mixture was concentrated in vacuo to yield the TFA salt product as an orange solid (0.020 g, 0.036 mmol, 98%). ^{1}H NMR (CD_3OD): δ 3.22 (m, 2H); 3.49 (m, 2H); 3.60 (m, 2H); 3.73 (m, 2H); 4.46 (br s, 2H); 4.49 (br s, 2H); 4.69 (br s, 2H); 4.76 (br s, 2H); 6.86 (s, 2H). ^{13}C NMR (CD_3OD): δ 38.3, 38.6, 39.2, 41.3, 71.5, 71.6, 73.1, 73.2, 78.0, 78.3, 135.6, 172.4, 172.6, 173.3. ESI-MS m/z: 439.31 $(M+H)^+$.

4.6. Compound 8

A solution of compound **7** (1.11 g, 4.05 mmol) and sodium azide (1.58 g, 24.3 mmol) in acetic acid (30 mL) was heated to 50 °C for 18 h. The reaction mixture was concentrated in vacuo and the residue was suspended in EtOAc (150 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ (5 × 100 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to a crude residue that was purified by column chromatography (0.5:3.5:6, EtOAc:hexanes:DCM) to yield the product as an orange solid (1.00 g, 3.34 mmol, 82%). ^{1}H NMR ($CDCl_3$): δ 3.81 (s, 3H); 4.06 (s, 2H); 4.25 (br s, 4H); 4.41 (pt, 2H); 4.79 (pt, 2H). ^{13}C NMR ($CDCl_3$): δ 49.8, 51.7, 70.1, 70.4, 70.8, 71.7, 71.9, 83.1, 171.6. ESI-MS m/z: 300.06 $(M+H)^+$, 322.08 $(M+Na)^+$.

4.7. Compound 9

Compound **8** (1.00 g, 3.34 mmol) and triphenylphosphine (PPh_3) (1.05 g, 4.00 mmol) were combined in THF (20 mL). After 18 h at rt, H_2O (2 mL) was added and the reaction mixture was heated to 65 °C for an additional 2 h. The reaction mixture was concentrated in vacuo, dissolved in HCl (0.1 M, 200 mL), and washed with DCM (4 × 100 mL). The aqueous phase was treated with aqueous K_2CO_3 until pH 10 and extracted with DCM (5 × 50 mL) which were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo to yield the product as a pale orange solid (0.856 g, 3.13 mmol, 94%). ^{1}H NMR ($CDCl_3$): δ 1.40 (br s, 2H); 3.52 (s, 2H); 3.81 (s, 3H); 4.16 (pt, 2H); 4.19 (pt, 2H); 4.39 (pt,

2H); 4.77 (pt, 2H). ^{13}C NMR ($CDCl_3$): δ 40.5, 51.6, 68.5, 69.2, 70.4, 71.5, 71.6, 92.5, 172.0. ESI-MS *m/z*: 274.07 $(M+H)^+$.

4.8. Compound 10

To an ice-cooled solution of compound **9** (0.850 g, 3.11 mmol) and TEA (0.65 mL, 4.67 mmol) in THF (10 mL) was added pyrocarbonic acid di-*tert*-butyl ester ($(Boc)_2$-O) (1.02 g, 4.67 mmol) in THF (5 mL). After 30 min, the reaction mixture was warmed to rt and stirred for 3 h. The solvent was removed in vacuo and the crude residue was purified by column chromatography (1:1:3, EtOAc:DCM:hexanes) to yield the product as a yellow solid (1.15 g, 3.09 mmol, 99%). ^{1}H NMR ($CDCl_3$): δ 1.48 (s, 9H); 3.84 (s, 3H); 3.99 (d, J_{H-H} = 6.0 Hz, 2H); 4.17 (s, 4H); 4.41 (pt, 2H); 4.77 (pt, 2H); 5.10 (br s, 1H). ^{13}C NMR ($CDCl_3$): δ 28.5, 39.1, 51.8, 69.0, 69.4, 70.6, 71.4, 71.6, 79.3, 87.7, 155.8, 172.2. ESI-MS *m/z*: 373.88 $(M+H)^+$.

4.9. Compound 11

Compound **10** (1.10 g, 2.96 mmol) and LiOH (0.177 g, 7.40 mmol) were combined in THF/H_2O (3/1 v/v, 40 mL). The mixture was stirred at rt for 24 h and then heated to reflux for an additional 24 h. The mixture was acidified with HCl (0.5 M, 100 mL) and extracted with DCM (4 × 100 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated in vacuo to yield the product as an orange solid (1.02 g, 2.85 mmol, 96%). ^{1}H NMR (CD_3OD): δ 1.44 (s, 9H); 3.93 (s, 2H); 4.16 (br s, 2H); 4.20 (pt, 2H); 4.45 (pt, 2H); 4.75 (pt, 2H). ^{13}C NMR (CD_3OD): δ 28.8, 39.6, 61.6, 70.8, 70.9, 71.9, 73.2, 80.1, 89.0, 158.3, 175.9. ESI-MS *m/z*: 381.94 $(M+Na)^+$.

4.10. Compound 12

To an ice-cooled solution of **11** (0.070 g, 0.195 mmol), HOBt (0.036 g, 0.234 mmol), and *N*-(2-aminoethyl)maleimide TFA salt (0.059 g, 0.234 mmol) in DCM (4 mL) were added TEA (70 μL, 0.466 mmol) and EDC (0.049 g, 0.234 mmol). The reaction mixture was allowed to warm to rt overnight and concentrated in vacuo. The crude residue was dissolved in EtOAc (100 mL) and washed with brine (3 × 50 mL). The organic layer was collected, dried over Na_2SO_4, filtered, and concentrated in vacuo to a crude oil that was purified by column chromatography (2:3, EtOAc:DCM) to yield the product as a light orange solid (0.073 g, 0.152 mmol, 78%). ^{1}H NMR ($CDCl_3$): δ 1.48 (s, 9H); 3.61 (m, 2H); 3.81 (m, 2H); 3.97 (d, J_{H-H} = 6.0 Hz, 2H); 4.13 (m, 2H); 4.15 (m, 2H); 4.34 (pt, 2H); 4.63 (pt, 2H); 5.54 (s, 1H); 6.44 (s, 1H); 6.77 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 28.5, 37.6, 38.8, 39.5, 68.8, 68.9, 69.2, 70.9, 76.3, 79.2, 88.2, 134.3, 156.2, 170.8, 171.1. ESI-MS *m/z*: 481.41 $(M+H)^+$, 503.58 $(M+Na)^+$.

4.11. Compound 2

Compound **12** (0.042 g, 0.087 mmol) was stirred in TFA/DCM (1:1 v/v, 4 mL) for 1 h at rt. The reaction mixture was concentrated in vacuo to yield the TFA salt product as a light yellow solid (0.041 g, 0.083 mmol, 95%). ^{1}H NMR (CD_3OD): δ 3.50 (m, 2H); 3.71 (m, 2H); 3.88 (s, 2H); 4.34 (s, 2H); 4.37 (s, 2H); 4.46 (s, 2H); 4.72 (s, 2H); 6.86 (s, 2H). ^{13}C NMR (CD_3OD): δ 38.6, 39.4, 39.6, 70.3, 71.6, 71.7, 72.5, 78.4, 81.8, 135.6, 172.6, 173.3. ESI-MS *m/z*: 382.02 $(M+H)^+$.

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