Published in final edited form as:

Dalton Trans. 2016 September 28; 45(36): 14320–14326. doi:10.1039/c6dt02669a.

The Synthesis and Structures of 1,1'-Bis(sulfonyl)ferrocene Derivatives

Kullapa Chanawanno^a, Cole Holstrom^b, Laura A. Crandall^c, Henry Dodge^d, Victor N. Nemykin^b, Richard S. Herrick^d, and Christopher J. Ziegler^c

^aDepartment of Chemistry, Faculty of Science, Chiang Mai University, Chiang Mai 50200 (Thailand) ^bDepartment of Chemistry & Biochemistry University of Minnesota – Duluth 1039 University Drive, Duluth, MN 55812 (USA) ^cDepartment of Chemistry, University of Akron, Akron, Ohio 44312-3601 (USA) ^dDepartment of Chemistry, College of the Holy Cross, 1 College St, Worcester, MA 01610 (USA)

Abstract

A series of 1,1'-bis(sulfonyl)ferrocene compounds were produced via the 1,1'-bis(sulfonate)ferrocene ammonium salt. This compound can be readily converted to 1,1'-bis(sulfonylchloride)ferrocene. Varying stoichiometry and reaction times, both mono- and bis-sulfonamide derivatives can be synthesized. All new compounds presented in this report have been structurally characterized. The structures of the bis-sulfonamide systems are similar to the well-studied bis(amide) ferrocene compounds. Intermolecular hydrogen bonding is observed, typically between NH and SO groups of neighboring sulfonamides. However in the bis(GABA) derivative, intermolecular NH to CO hydrogen bonding interactions are present.

TOC Image

A series of 1,1'-bis(sulfonylchloride)ferrocene compounds were synthesized from the corresponding ammonium salt, and converted into either mono or bis sulfonamides. These compounds exhibit intermolecular hydrogen bonding.

Correspondence to: Christopher J. Ziegler.

†††Electronic Supplementary Information (ESI) available: Spectroscopic, and crystallographic data for compounds. See DOI: 10.1039/x0xx00000x Crystallographic data for the structures of 2–13 have been deposited with the Cambridge Crystallographic Data Centre as cif files (CCDC 1487629-1487640) Copies of these data can be obtained free of charge via www.ccdc.cam.ac.uk/contents/retrieving.html or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; Email: deposit@ccdc.cam.ac.uk).

Introduction

Ferrocene has been the focus of numerous articles since its discovery due to its extraordinary stability, its ability to act as a scaffold for many types of reactions, and its reversible one electron redox behavior.^{1–8} It has been incorporated into a wide variety of molecules, ranging from candidates for advanced materials^{9–13} to biologically relevant compounds,^{14–18} including as glucose sensors for diabetes testing.¹⁹ The methods used to covalently link ferrocene to other molecules mirror the ways that have been developed for benzene; more common methods derive from the well-known ferrocene aldehyde, acetyl and carboxylic acid reagents.⁴ Each derivative can be prepared in both mono- and bis-forms and syntheses have been improved so that each compound is readily available as a reagent. The mono- and bis-carboxylic acids have been frequently used with great success in appending amino acids and polypeptides to either one or both cyclopentadienyl rings of ferrocene^{20–23}; two decades ago we presented work on a simple bis-amino acid complex and provided early evidence that a 10-member ring with hydrogen bonding was formed that mimicked the bonding near a hairpin loop of a beta sheet (Figure 1).²⁴ This structure was verified in detail in several later papers.^{25,26} Other conformations of 1,1'-dicarboxylic acid substituted ferrocene peptides show one or no intramolecular hydrogen bonds depending on the structure and circumstances.

We have explored new methods for coupling ferrocenes to other compounds; for example, we have used Schiff base formation to append ferrocene to other organometallic moieties.²⁷ Despite the large number of research efforts examining ferrocene chemistry, there has been relatively little research reported on ferrocenesulfonamides. Much of what has been reported has focused on singly derivatized ferrocene systems, via the use of ferrocene sulfonyl chloride. Mono- and bis-sulfonyl ferrocene compounds have been known since the 1950s, with their discovery by Weinmayr²⁸ and Nesmeyanov.²⁹ Later, Knox and Pauson³⁰ introduced an improved synthesis, employing acetic anhydride to help modulate the reaction of chlorosulfonic acid and ferrocene. Rather than isolate the sulfonic acid compounds, which are highly hygroscopic, the ammonium salts were produced, generating crystalline materials that are easier to handle. In 1969, Schlögl and co workers³¹ prepared mono sulfonamide derivatives including a series of amino acids. However, no systematic work on ferrocene

sulfonamides has been reported since. The 1,1'-bis(sulfonate) ferrocene ammonium salt has been employed as a starting material for the synthesis of thiol modified ferrocenes³² and the bis(sulfonate) has been used to generate hydrogen bonding network materials.³³

There are reasons both theoretical and practical for examining ferrocene sulfonamide derivatives: e.g. do they exhibit hydrogen bonding similar to that observed for bis(amino acid) derivatives despite have an sp³-hybridized sulfur atom in place of an sp²-hybridized carbon atom; and can ferrocene sulfonamides find use as pharmaceuticals like organic sulfonamides? To explore this field and hopefully answer important questions, we decided to prepare 1,1'-bis(sulfonamide) ferrocene compounds. In this report, we present the synthesis of 1,1'-ferrocene bis(sulfonyl chloride) and its use to generate both mono-functionalized and bis-functionalized sulfonamide adducts (Figure 2). We have structurally characterized the products of these reactions, and in the GABA modified variant we observe intermolecular hydrogen bonding resembling that seen in beta sheets.

Experimental

All reagents were purchased from Strem, Acros Organics, TCI AMERICA or Sigma-Aldrich and used as received without further purification. All solvents were stored over molecular sieves. ¹H- and ¹³C-NMR spectra were recorded on a Varian Mercury 300 MHz and Varian NMRS 500-01 (500 MHz), respectively. Chemical shifts were reported with respect to residual solvent peaks as internal standard (¹H: CDCl₃, δ = 7.26 ppm; ¹³C: CDCl₃, δ = 77.2 ppm). High resolution electrospray MS (ES-MS; positive mode) spectra were recorded using a Bruker MicrOTOF III mass spectrometer at the University of Minnesota Duluth. Preparations of compounds **1–3** were modified from previous literature reports.^{30,34}

X-ray data collection and structure determination

Single crystal data for **2–13** were collected on a Bruker CCD-based diffractometer with dual Cu/Mo ImuS microfocus optics (Cu K α radiation, λ = 1.54178 Å for compound **6**, Mo K α radiation, λ = 0.71073 Å for compound **2–5** and **7–13**). Crystals were mounted on a cryoloop using Paratone oil and placed under a stream of nitrogen at 100 K (Oxford Cryosystems). The detector was placed at a distance of 4.00 cm from the crystal. The data were corrected for absorption with the SADABS program (and TWINABS for compound **2**).³⁵ The structures were refined using the Bruker SHELXTL Software Package (Version 6.1), and were solved using direct methods until the final anisotropic full-matrix, least squares refinement of F² converged.³⁶ Crystal data and refinement parameters of compounds **2–13** can be found in Table S1 in the supplementary information.

Synthesis of **1**

This compound has been previously reported.³⁰ Ferrocene (4.0 g, 0.022 mol) was dissolved in acetic anhydride (50 mL) yielding an orange solution. Chlorosulfonic acid (5.0 g, 0.043 mol) was slowly added to the rapidly stirred mixture. The solution immediately turned dark blue and then dark brown with rising temperature. The reaction was stirred at room temperature for 12 hr and then set aside to allow precipitation of the product over an additional 6 hr. The solution was then filtered and a dark yellow solid was collected and air-

dried. The resulting solid was dissolved in hot ethanol and allowed to cool, giving yellow crystals. Yield 4.0 g, 53%.

Synthesis of 2

This compound has been previously reported.^{30,34} Compound **1** (3.0 g, 8.7 mmol) was dissolved in ethanol (~200 mL) and ~2 mL of concentrated NH₄OH was slowly added to the mixture. The initially black ethanolic solution gradually turned brown upon stirring. A golden-brown solid started to appear and the mixture was stirred at room temperature for 30 minutes. The solid was filtered and air-dried to yield a yellow. Yield, 3.1 g, 95%. ¹H-NMR (300 MHz, DMSO-d₆): 4.11 (t, J = 1.5 Hz, 4H on C₅H₄), 4.32 (t, J = 1.5 Hz, 4H on C₅H₄). Crystals suitable for X-ray diffraction were obtained by vapor diffusion of ethanol into a solution in methylene chloride.

Synthesis of 3

Compound **2** (3.0 g, 7.9 mmol) was dissolved in dry CH₂Cl₂. Phosphorus pentachloride (3.3 g, 16 mmol) was added and the solution was stirred at room temperature overnight. The yellowish-green solution was extracted with water (3X) and a yellow organic fraction (CH₂Cl₂) was collected and the solvent was removed under vacuum. The resulting orange solid was washed with an excess of hexane and then purified by column chromatography (silica, CH₂Cl₂: hexane) to obtain pure orange crystals of 1,1'-ferrocenedisulfonyl chloride (compound **3**, 2.5 g, yield 84%). ¹H-NMR (DMSO-d₆): 5.03 (s, 4H on C₅H₄), 5.29 (s, 4H on C₅H₄). ¹³C-NMR (CDCl₃): 71.26 (C on C₅H₄), 75.68 (C on C₅H₄), 95.90 (ipso C on C₅H₄). IR: 1367, 1144 cm⁻¹ (ν_{SO}). Crystals suitable for X-ray diffraction were obtained by vapor diffusion of hexane into a solution in methylene chloride.

General synthesis of mono-substituted ferrocenesulfonamides

Compound **3** (200 mg, 0.53 mmol) was dissolved in methanol to give an orange solution. Primary amines (1.5 mol equiv.) and an excess amount of diisopropylethylamine (DIPEA, 15 mol equiv.) were then added to the solution. The reaction mixture was refluxed and monitored by TLC. Reaction completion was reached after several hours. The solvent was removed under vacuum, the residue extracted (CH₂Cl₂/water) and purified by column chromatography (silica, CH₂Cl₂ or 2–5% MeOH:CH₂Cl₂) to afford the pure mono-substituted ferrocenesulfonamides **4–7**.

Cyclopropyl ferrocenesulfonamide 4—Yield, 61 mg, 29 %. ¹H-NMR (CDCl₃): 0.60–0.63 (m, 4H, 2×CH₂ cyclopropyl), 2.27–2.33 (m, 1H, CH cyclopropyl), 4.65 (s, 1H, NH), 4.73 (m, 2H on C₅H₄), 4.90–4.94 (m, 4H on C₅H₄), 5.07 (m, 2H on C₅H₄). ¹³C-NMR (CDCl₃): 6.16 (CH₂ cyclopropyl), 24.23 (CH cyclopropyl), 70.53 (C on C₅H₄), 71.70 (C on C₅H₄), 74.49 (C on C₅H₄), 75.41 (C on C₅H₄), 90.30 (ipso C on C₅H₄). HRMS (ESI): m/z calc. for C₁₃H₁₄ClFeNO₄S₂: 402.9377 found 402.9397 [M]⁺. IR: 3263 cm⁻¹ (ν_{NH}), 1372, 1323, 1143 cm⁻¹ (ν_{SO}). Crystals suitable for X-ray diffraction were obtained by vapor diffusion of hexane into a solution in methylene chloride.

Cyclopentyl ferrocenesulfonamide 5—Yield, 71 mg, 32 %. ¹H-NMR (CDCl₃): 1.34 (m, 2H, CH₂ cyclopentyl), 1.59 (m, 4H, CH₂ cyclopentyl), 1.82–1.84 (m, 2H, CH₂

cyclopentyl), 3.61–3.64 (m, 1H, *CH*cyclopentyl), 4.22 (m, 1H, *NH*), 4.69 (m, 2H on *C*₅*H*₄), 4.88 (m, 4H on *C*₅*H*₄), 5.04 (m, 2H on *C*₅*H*₄). ¹³C-NMR (CDCl₃): 23.21 (*CH*₂ cyclopentyl), 33.62 (*CH*₂ cyclopentyl), 55.27 (*CH* cyclopentyl), 70.53 (C on *C*₅*H*₄), 71.41 (C on *C*₅*H*₄), 74.31 (C on *C*₅*H*₄), 75.44 (C on *C*₅*H*₄), 92.00 (ipso C on *C*₅*H*₄), 95.12 (ipso C on *C*₅*H*₄). HRMS (ESI): *m/z* calc. for C₁₅H₁₈ClFeNO₄S₂: 430.9710 found 430.9685 [M]⁺. IR: 3440 cm⁻¹ (ν_{NH}), 1375, 1324, 1142 cm⁻¹ (ν_{SO}). Crystals suitable for X-ray diffraction were obtained by vapor diffusion of hexane into a solution in methylene chloride.

Allyl ferrocenesulfonamide 6—Yield, 58 mg, 28 %. ¹H-NMR (CDCl₃): 3.60 (t, 2H, *J* = 5.7 Hz, *CH*₂), 4.33 (m, 1H, *NH*), 4.70 (t, *J* = 1.8 Hz, 2H on *C*₅*H*₄), 4.87–4.89 (m, 4H on *C*₅*H*₄), 5.04 (t, *J* = 1.8 Hz, 2H on *C*₅*H*₄), 5.13–5.19 (m, 2H, alkene *CH*₂), 5.65–5.78 (m, 1H, alkene *CH*). ¹³C-NMR (CDCl₃): 45.79 (*CH*₂), 70.57 (C on *C*₅*H*₄), 71.34 (C on *C*₅*H*₄), 74.40 (C on *C*₅*H*₄), 75.40 (C on *C*₅*H*₄), 91.06 (ipso C on *C*₅*H*₄), 95.17 (ipso C on *C*₅*H*₄), 117.91 (alkene *CH*₂), 132.82 (alkene *CH*). HRMS (ESI): *m/z* calc. for C₁₃H₁₄ClFeNO₄S₂: 402.9397 found 402.9369 [M]⁺. IR: 3283 cm⁻¹ (ν_{NH}), 1374, 1325, 1144 cm⁻¹ (ν_{SO}). Crystals suitable for X-ray diffraction were obtained by vapor diffusion of hexane into a solution in methylene chloride.

Mono-GABA ferrocenesulfonamide 7—Yield, 40 mg, 17 %. ¹H-NMR (CDCl₃): 1.78 (quintet, 2H, *J* = 6.6 Hz, *CH*₂), 2.34 (t, 2H, *J* = 6.6 Hz, *H*₂C-C=O), 3.02 (q, 2H, *J* = 6.6 Hz, N-*CH*₂), 3.66 (s, 3H, OCH₃), 4.52 (t, 1H, *J* = 6.6 Hz, *NH*), 4.70 (t, 2H, *J* = 1.8 Hz, 2H on *C*₅*H*₄), 4.70–4.88 (m, 4H on *C*₅*H*₄), 5.04 (t, *J* = 1.8 Hz, 2H on *C*₅*H*₄). ¹³C-NMR (CDCl₃): 24.65 (*CH*₂), 30.88 (*CH*₂), 42.63 (*CH*₂), 51.76 (OCH₃), 70.56 (C on *C*₅*H*₄), 71.30 (C on *C*₅*H*₄), 74.34 (C on *C*₅*H*₄), 75.37 (C on *C*₅*H*₄), 91.03 (ipso C on *C*₅*H*₄), 95.16 (ipso C on *C*₅*H*₄), 173.45 (C=O). HRMS (ESI): *m/z* calc. for C₁₅H₁₈ClFeNO₆S₂: 463.9687 found 463.9643 [M]⁺. IR: 3281 cm⁻¹ (ν_{NH}), 1374, 1326, 1144 cm⁻¹ (ν_{SO}). Crystals suitable for X-ray diffraction were obtained by vapor diffusion of hexane into a solution in methylene chloride.

General synthesis of di-substituted ferrocenesulfonamides

Compound **3** (200 mg, 0.53 mmol) was reacted with 3 mol equiv. of primary amines in similar fashion as for mono-substituted ferrocenesulfonamides. The reaction was carried for at least 24 hours and monitored by TLC until completion was reached. The solvent was removed under vacuum, the residue extracted (CH₂Cl₂/water) and purified by column chromatography (silica, CH₂Cl₂ or 2–5% MeOH:CH₂Cl₂) to afford the pure di-substituted ferrocenesulfonamides **8–13**.

Bis-propyl ferrocenesulfonamide 8—Yield 75 mg, 35 %. ¹H-NMR (CDCl₃): 0.88 (t, *J* = 7.2 Hz, 6H, *CH*₃), 1.51 (q, *J* = 7.2 Hz, 4H, *CH*₂), 2.97 (q, *J* = 7.2 Hz, 4H, N-*CH*₂), 4.45 (m, 2H, *NH*), 4.64 (t, *J* = 1.8 Hz, 4H on *C*₅*H*₄), 4.82 (t, *J* = 1.8 Hz, 4H on *C*₅*H*₄). ¹³C-NMR (CDCl₃): 11.08 (*CH*₃), 23.11 (*CH*₂), 45.19 (N-*CH*₂), 70.70 (C on *C*₅*H*₄), 73.19 (C on *C*₅*H*₄), 90.43 (ipso C on *C*₅*H*₄). HRMS (ESI): *m/z* calc. for C₁₆H₂₄FeN₂O₄S₂: 428.0521 found 428.0455 [M]⁺. IR: 3253 cm⁻¹ (ν_{NH}), 1321, 1191 cm⁻¹ (ν_{SO}). Crystals suitable for X-ray diffraction were obtained by vapor diffusion of hexane into a solution in methylene chloride.

Bis-butyl ferrocenesulfonamide 9—Yield 70 mg, 29 %. $^1\text{H-NMR}$ (CDCl_3): 0.87 (t, $J = 6.9$ Hz, 6H, CH_3), 1.31 (m, 4H, CH_2), 1.45 (m, 4H, CH_2), 2.98 (q, $J = 6.9$ Hz, 4H, N-CH_2), 4.43 (t, $J = 6.9$ Hz, 2H, NH), 4.64 (t, $J = 2.1$ Hz, 4H on C_5H_4), 4.81 (t, $J = 2.1$ Hz, 4H on C_5H_4). $^{13}\text{C-NMR}$ (CDCl_3): 13.52 (CH_3), 19.66 (CH_2), 31.75 (CH_2), 45.14 (N-CH_2), 70.67 (C on C_5H_4), 73.22 (C on C_5H_4), 90.34 (ipso C on C_5H_4). HRMS (ESI): m/z calc. for $\text{C}_{18}\text{H}_{28}\text{FeN}_2\text{O}_4\text{S}_2$: 456.0835 found 456.0774 $[\text{M}]^+$. IR: 3274 cm^{-1} (ν_{NH}), 1321 , 1139 cm^{-1} (ν_{SO}). Crystals suitable for X-ray diffraction were obtained by vapor diffusion of hexane into a solution in methylene chloride.

Bis-pentyl ferrocenesulfonamide 10—Yield 72 mg, 29%. $^1\text{H-NMR}$ (CDCl_3): 0.85 (t, $J = 6.9$ Hz, 6H, CH_3), 1.23–1.26 (m, 8H, CH_2), 1.45 (quin, $J = 6.9$ Hz, 4H, CH_2), 2.96 (q, $J = 6.9$ Hz, 4H, N-CH_2), 4.56 (t, $J = 6.9$ Hz, 2H, NH), 4.64 (t, $J = 2.1$ Hz, 4H on C_5H_4), 4.81 (t, $J = 2.1$ Hz, 4H on C_5H_4). $^{13}\text{C-NMR}$ (CDCl_3): 13.85 (CH_3), 22.12 (CH_2), 28.61 (CH_2), 29.34 (CH_2), 43.39 (N-CH_2), 70.63 (C on C_5H_4), 73.22 (C on C_5H_4), 90.28 (ipso C on C_5H_4). HRMS (ESI): m/z calc. for $\text{C}_{20}\text{H}_{32}\text{FeN}_2\text{O}_4\text{S}_2$: 484.1153 found 484.1156 $[\text{M}]^+$. IR: 3276 cm^{-1} (ν_{NH}), 1321 , 1140 cm^{-1} (ν_{SO}). Crystals suitable for X-ray diffraction were obtained by vapor diffusion of hexane into a solution in methylene chloride.

Bis-dodecyl ferrocenesulfonamide 11—Yield 30 mg, 8.5 %. $^1\text{H-NMR}$ (CDCl_3): 0.88 (t, $J = 7.2$ Hz, 6H, CH_3), 1.23–1.25 (m, 36H, CH_2), 1.45 (m, 4H, CH_2), 2.97 (q, $J = 7.2$ Hz, 4H, N-CH_2), 4.42 (t, $J = 7.2$ Hz, 2H, NH), 4.64 (t, $J = 1.8$ Hz, 4H on C_5H_4), 4.81 (t, $J = 1.8$ Hz, 4H on C_5H_4). $^{13}\text{C-NMR}$ (CDCl_3): 14.07 (CH_3), 22.65 (CH_2), 26.51 (CH_2), 29.07 (CH_2), 29.29 (CH_2), 29.43 (CH_2), 29.49 (CH_2), 29.57 (CH_2), 29.59 (CH_2), 29.73 (CH_2), 31.88 (CH_2), 43.46 (N-CH_2), 70.66 (C on C_5H_4), 73.23 (C on C_5H_4), 90.34 (ipso C on C_5H_4). HRMS (ESI): m/z calc. for $\text{C}_{34}\text{H}_{61}\text{FeN}_2\text{O}_4\text{S}_2$: 681.3423 found 681.3391 $[\text{M}+\text{H}]^+$. IR: 3257 cm^{-1} (ν_{NH}), 1323 , 1132 cm^{-1} (ν_{SO}). Crystals suitable for X-ray diffraction were obtained by vapor diffusion of hexane into a solution in methylene chloride.

Bis-benzyl ferrocenesulfonamide 12—Yield, 85 mg, 31 %. $^1\text{H-NMR}$ (CDCl_3): 4.21 (d, $J = 6.0$ Hz, 4H, N-CH_2), 4.69 (m, 4H on C_5H_4), 4.75 (m, 2H, NH), 4.85 (m, 4H on C_5H_4), 7.29–7.33 (m, 10H on C_6H_5). $^{13}\text{C-NMR}$ (CDCl_3): 47.37 (CH_2), 70.73 (C on C_5H_4), 73.43 (C on C_5H_4), 90.20 (ipso C on C_5H_4), 127.88 (CH on C_6H_5), 127.91 (CH on C_6H_5), 128.69 (CH on C_6H_5), 136.42 (C on C_6H_5). HRMS (ESI): m/z calc. for $\text{C}_{24}\text{H}_{24}\text{FeN}_2\text{O}_4\text{S}_2$: 525.0600 found 525.0598 $[\text{M}]^+$. IR: 3426 cm^{-1} (ν_{NH}), 1322 , 1140 cm^{-1} (ν_{SO}). Crystals suitable for X-ray diffraction were obtained by vapor diffusion of hexane into a solution in methylene chloride.

Bis-GABA ferrocenesulfonamide 13—Yield, 35 mg, 12 %. $^1\text{H-NMR}$ (CD_3OD): 1.71 (quintet, 4H, $J = 7.2$ Hz, CH_2), 2.33 (t, 4H, $J = 7.2$ Hz, $\text{H}_2\text{C-C=O}$), 2.90 (t, 4H, $J = 7.2$ Hz, N-CH_2), 3.63 (s, 6H, OCH_3), 4.64 (t, $J = 1.8$ Hz, 4H on C_5H_4), 4.80 (t, $J = 1.8$ Hz, 4H on C_5H_4). The NH resonance was not observed due to solvent exchange. $^{13}\text{C-NMR}$ (CD_3OD): 26.15 (CH_2), 31.78 (CH_2), 43.39 (CH_2), 52.19 (OCH_3), 71.71 (C on C_5H_4), 74.61 (C on C_5H_4); all quaternary carbons cannot be seen in the spectrum due to limited solubility of the compound in methanol- d_4 . HRMS (ESI): m/z = calc. for $\text{C}_{20}\text{H}_{28}\text{FeN}_2\text{O}_8\text{S}_2$: 545.0709 found 545.0708 $[\text{M}+\text{H}]^+$. IR: 3267 cm^{-1} (ν_{NH}), 1328 , 1141 cm^{-1} (ν_{SO}). Crystals suitable for X-

ray diffraction were obtained by vapor diffusion of hexane into a solution in 5% methanol: methylene chloride.

Results and Discussion

We reproduced the work of Knox and Pauson³⁰ (the first two steps in Figure 2) to produce the 1,1' bis(sulfonato) ferrocene ammonium salt **2** and were able to elucidate its structure which is shown in Figure 3. This compound is made first by treating ferrocene with two equivalents of chlorosulfonic acid, and then reacting the resultant bis-sulfonic acid derivative with ammonium hydroxide. The ferrocene adopts a staggered conformation, with the sulfonate groups in an anti (180°) orientation. The ammonium cations engage in hydrogen bonding interactions with the oxygen atoms of the sulfonate groups. Two of the oxygen atoms per sulfate group exhibit one hydrogen bond interaction apiece (with NH...OS distances measuring ~2.93 and ~2.86 Å) and one oxygen atom engages in two interactions (NH...OS distances measuring ~2.85 and ~2.84 Å). The overall architecture of the solid is comprised of alternating layers of ferrocene dianions and ammonium cations.

The ammonium salt can be converted to the bis-sulfonyl chloride via reaction with PCl₅ in dry CH₂Cl₂ as can be seen in Figure 2. The resultant compound is quite stable to water and readily isolated as a crystalline product. We were able to elucidate the structure of this compound, which is shown with the ammonium cation in Figure 3. The sulfonyl chlorides are oriented in an anti-conformation in the solid state. The bond lengths and angles are as expected for this compound, with an S-Cl bond length of 2.0336(7) Å and S-O lengths of 1.4247(15) and 1.4204(15) Å. Both Cl's are directed away from the ferrocene unit. The crystal structure of **3** was reported previously.³⁷ We solved it again to obtain more accurate data.

With the availability of monofunctionalized ferrocene sulfonyl chloride reagent, there are a few examples of it being used to make sulfonamides. For example, Schlögl³¹ prepared a series monosulfonamides of amino acid ester. Slocum and Achermann³⁴ presented a comprehensive report on N-monosubstituted and N, N-disubstituted sulfonamides, following a 1980 report that examined deuterium exchange on the N,N dimethyl variant.³⁸ A few years later, a study on a series of β-lactam antibiotics linked to ferrocene via sulfonamide groups was presented by Vâ ã and coworkers.³⁹ Fabbrizzi presented a series of reports on cyclams covalently attached to ferrocene^{40,41}; later work by Roglans⁴² used the same linking methodology to attach ferrocene to organometallic chelates. Most recently, sulfonamide modified ferrocenes have been explored as components of electroactive ionic liquids.⁴³

We found that we could selectively functionalize either one or both of the sulfonyl chloride groups on compound **3** to produce sulfonamides simply by controlling the stoichiometry of the amine and the length of the reaction as shown in Scheme 1. Figure 2 shows the mono- and bis-functionalized sulfonamide ferrocenes synthesized for this report, as well as the numbering scheme used. We synthesized four monofunctionalized adducts, as listed in the table, with cyclopropylamine, cyclopentylamine, allyl amine and GABA-OMe (compounds **4–7**). All four compounds have been structurally characterized (Figure 4). In these compounds, the chlorine atom of the sulfonyl chloride group is directed away from the

ferrocene unit. Similarly, in all of the sulfonamides, the R group is directed away from the metallocene, lying above the plane of the Cp unit. Inspection of the relative orientations of the R groups on the Cp rings; in three of the four compounds (cyclopentylamine, allylamine and GABA), the groups adopt an anti-orientation with Cp rings a staggered conformation. An example of an anti conformation can be seen at the top of Figure 5. However, for the cyclopropylamine derivative, in the solid state the rings adopt a nearly eclipsed conformation with a 136.7° angle measured counter-clockwise from the sulfonyl chloride as the substituent with the higher priority to the sulfonamide with the lower priority. Using the nomenclature introduced by Kirin, Kraatz and Metzler-Nolte,²⁵ this is classified as M-1,4' helical chirality (Figure 5). Both enantiomers are present in the unit cell. This distinct structural change results from intermolecular hydrogen bonding in the solid; in the anti-structures, the sulfonamides engage in reciprocal hydrogen bonding between NH and SO groups, forming dimers in the solid state. These hydrogen bond distances exhibit lengths between ~ 2.92 and ~ 3.04 Å as measured by the N-S separation. In the cyclopropylamine structure, hydrogen bonding also occurs between the SO and NH groups (with a N-S distance of ~ 2.92 Å), but instead of forming reciprocal dimers, one dimensional chains of hydrogen bonds form, creating a zig-zag structure in the solid state.

With regard to bis-sulfonamides, we produced the n-propyl amine, n-butyl amine, n-pentyl amine, n-dodecyl amine, benzyl amine, and GABA variants (compounds **8–13**). The structures of these compounds are shown in Figure 6. The structures are as expected for these compounds, with typical bond lengths for the sulfonamide groups. As in the monofunctionalized variants, we observe primarily anti structures, but the bis-GABA derivative shows a 103.9° angle measured counterclockwise between the GABA groups and a concomitant staggered conformation of the Cp rings, as can be seen in Figure 5. This conformation is assigned M-1,5' helical chirality with both enantiomers present in the unit cell.²⁵ Similarly, we can ascribe these changes in conformation to hydrogen bonding differences between the side chains of these compounds.

Part of our interest in these compounds is the use of the ferrocene moiety to organize amino acids for hydrogen bonding. In all of the bis-sulfonamide structures, we do not observe intramolecular hydrogen bonding, but several different types of intermolecular hydrogen bonding are present in the solid state. For all of the compounds except the bis-GABA derivative, we observe hydrogen bonding between the SO and NH groups of the sulfonamides on neighboring compounds. These $\text{NH}\cdots\text{OS}$ hydrogen bonds adopt different connectivity patterns. The bis-propyl, bis-butyl, and bis-pentyl derivatives form one dimensional chains of reciprocal hydrogen bonds with $\text{NH}\cdots\text{OS}$ distances ranging between ~ 2.9 and ~ 3.0 Å. The bis-dodecyl and bis-benzyl hydrogen bonds do not form reciprocal connections; instead each $\text{NH}\cdots\text{OS}$ occurs with a different neighboring molecule, resulting in four connections per molecule. In the bis-dodecyl modified ferrocene, this connectivity results in two dimensional layers of ferrocenes packed between alternating layers of aliphatic dodecyl groups, while in the bis-benzyl structure, the hydrogen bond connections result in a layered network structure. In both of these latter structures, the $\text{NH}\cdots\text{OS}$ distances are very slightly longer, ranging from ~ 2.96 to ~ 3.04 Å. Unlike the rest of the bis-substituted compounds, the bis-GABA derivative exhibits $\text{NH}\cdots\text{OC}$ hydrogen bonds between the

sulfonamide nitrogen atom and the carbonyl of the ester, as can be seen in Figure 7. These interactions are reciprocal, forming one dimensional chains in the solid, and measure ~3.04 Å, similar in length to the NH...OS interactions. Due to the nature of the hydrogen bonding, the one dimensional chains maintain the helical chirality of the individual ferrocene units.

Conclusions

In conclusion, we have explored the synthesis and reactivity of bis(chlorosulfonyl)ferrocenes for the formation of both mono- and bis sulfonamides. The precursors have been previously synthesized, but for this study we were able to structurally characterize both of them. Reaction of the bis(sulfonyl chloride)ferrocene with primary amines results in either the mono- or bis-functionalized adduct, depending on reaction conditions. Although intramolecular hydrogen bonding is not observed in any of the products, all of the sulfonamide adducts exhibit intermolecular hydrogen bonding, typically between the NH and SO units of the sulfonamides. Based on this chemistry, we plan to extend our studies toward the synthesis of ferrocene α -amino acid, ferrocene-peptide and biomolecule conjugates using sulfonamide linking groups.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

C.J.Z. acknowledges the National Institutes of Health (NIH) (grant number R15 GM102805) and the University of Akron for support of this work. KC would like to thank the Royal Thai Government for financial support.

References

1. Cuingnet E, Sergheraert C, Tartar A, Dautrevaux M. *J Organomet Chem.* 1980; 195:325–329.
2. Hüskens N, Gasser G, Köster SD, Metzler-Nolte N. *Bioconjug Chem.* 2009; 20:1578–1586. [PubMed: 19586015]
3. Bariši L, aki M, Mahmoud KA, Liu Y, Kraatz HB, Pritzkow H, Kirin SI, Metzler-Nolte N, Rapi V. *Chem – A Eur J.* 2006; 12:4965–4980.
4. Metzler-Nolte, N., van Staveran, DR. *Ferrocenes.* John Wiley & Sons, Ltd; Chichester, UK: 2008. p. 499-639.
5. Hess A, Sehnert J, Weyhermüller T, Metzler-Nolte N. *Inorg Chem.* 2000; 39:5437–43. [PubMed: 11154558]
6. Hess A, Brosch O, Weyhermüller T, Metzler-Nolte N. *J Organomet Chem.* 1999; 589:75–84.
7. Št pni ka, Petr. *Ferrocenes: Ligands, Materials and Biomolecules.* John Wiley & Sons, Ltd; Chichester, UK: 2008.
8. Phillips, ES. *Ferrocenes: compounds, properties, and applications.* Nova Science Publisher's; Hauppauge, NY: 2011.
9. Shi J, Jim CJW, Mahtab F, Liu J, Lam JWY, Sung HHY, Williams ID, Dong Y, Tang BZ. *Macromolecules.* 2010; 43:680–690.
10. Horikoshi R, Mochida T, Moriyama H. *Inorg Chem.* 2002; 41:3017–3024. [PubMed: 12033913]
11. Atkinson RCJ, Gibson VC, Long NJ. *Chem Soc Rev.* 2004; 33:313. [PubMed: 15272371]
12. Rhoda HM, Chanawanno K, King AJ, Zatsikha YV, Ziegler CJ, Nemykin VN. *Chem – A Eur J.* 2015; 21:18043–18046.

13. Ziegler CJ, Chanawanno K, Hasheminasab A, Zatsikha YV, Maligaspe E, Nemykin VN. *Inorg Chem.* 2014; 53:4751–4755. [PubMed: 24749483]
14. Mahmoud KA, Kraatz HB. *Chem – A Eur J.* 2007; 13:5885–5895.
15. Orlowski GA, Chowdhury S, Kraatz HB. *Langmuir.* 2007; 23:12765–12770. [PubMed: 17975937]
16. Moriuchi, T., Hirao, T. *Bioorganometallic Chemistry.* Vol. 17. Springer-Verlag; Berlin/Heidelberg: 2006. p. 143–175.
17. Hillard E, Vessièrès A, Thouin L, Jaouen G, Amatore C. *Angew Chemie Int Ed.* 2006; 45:285–290.
18. Patra M, Gasser G, Wenzel M, Merz K, Bandow JE, Metzler-Nolte N. *Organometallics.* 2010; 29:4312–4319.
19. Cass AEG, Davis G, Francis GD, Hill HAO, Aston WJ, Higgins IJ, Plotkin EV, Scott LDL, Turner APF. *Anal Chem.* 1984; 56:667–671. [PubMed: 6721151]
20. Bariši L, Rapi V, Metzler-Nolte N. *Eur J Inorg Chem.* 2006; 2006:4019–4021.
21. Kirin SI, Wissenbach D, Metzler-Nolte N. *New J Chem.* 2005; 29:1168.
22. Kirin SI, Noor F, Metzler-Nolte N, Mier W. *J Chem Educ.* 2007; 84:108.
23. Kraatz HB. *J Inorg Organomet Polym Mater.* 2005; 15:83–106.
24. Herrick RS, Jarret RM, Curran TP, Dragoli DR, Flaherty MB, Lindyberg SE, Slate RA, Thornton LC. *Tetrahedron Lett.* 1996; 37:5289–5292.
25. Kirin SI, Kraatz HB, Metzler-Nolte N. *Chem Soc Rev.* 2006; 35:348. [PubMed: 16565751]
26. Chowdhury S, Schatte G, Kraatz HB. *Angew Chemie Int Ed.* 2008; 47:7056–7059.
27. Chanawanno K, Rhoda HM, Hasheminasab A, Crandall LA, King AJ, Herrick RS, Nemykin VN, Ziegler CJ. *J Organomet Chem.* 2016; doi: 10.1016/j.jorganchem.2016.06.004
28. Weinmayr V. *J Am Chem Soc.* 1955; 77:3009–3011.
29. Nesmeyanov NA, Reutov OA. *Bull Acad Sci USSR Div Chem Sci.* 1959; 8:892–894.
30. Knox GR, Pauson PL. *J Chem Soc.* 1958; 692
31. Falk H, Krasa C, Schlögl K. *Monatshefte für Chemie.* 1969; 100:1552–1563.
32. Herberhold M, Nuyken O, öhlmann TP. *J Organomet Chem.* 1995; 501:13–22.
33. Xie J, Abrahams BF, Zimmermann TJ, Mukherjee A, Wedd AG. *Aust J Chem.* 2007; 60:578.
34. Slocum DW, Achermann W. *Synth React Inorg Met Chem.* 1982; 12:397–405.
35. Bruker. 2007
36. Sheldrick GM. *Acta Crystallogr Sect A Found Crystallogr.* 2007; 64:112–122.
37. Starovskii OV, Struchkov YT. *Bull Acad Sci USSR Div Chem Sci.* 1960; 9:936–943.
38. Slocum DW, Beach DL, Ernst CR, Fellows R, Moronski M, Conway B, Bencini J, Siegel A. *J Chem Soc Chem Commun.* 1980; 1043
39. Simionescu C, Lixandru T, Scutaru D, Vâ â M. *J Organomet Chem.* 1985; 292:269–273.
40. De Santis G, Fabbriizzi L, Licchelli M, Mangano C, Pallavicini P, Poggi A. *Inorg Chem.* 1993; 32:854–860.
41. De Blas A, De Santis G, Fabbriizzi L, Licchelli M, Mangano C, Pallavicini P. *Inorganica Chim Acta.* 1992; 202:115–118.
42. Llobet A, Masllorens E, Moreno-Mañas M, Pla-Quintana A, Rodríguez M, Roglans A. *Tetrahedron Lett.* 2002; 43:1425–1428.
43. Gélinas B, Rochefort D. *Electrochim Acta.* 2015; 162:36–44.

Fig. 1.
Conformation of 1,1'-disubstituted ferrocene peptides with two intramolecular hydrogen bonds.

Fig. 2.
General reaction scheme for the synthesis of compounds 1–13.

Fig. 3.
The structures of compounds **2** (left) and **3** (right) with 50% thermal ellipsoids. Non-ionizable hydrogen atoms have been omitted for clarity, and only one of the two NH₄⁺ ions in **2** is shown.

Fig. 4.
The structures of mono-sulfonamide compounds **4–7** with 50% thermal ellipsoids. Hydrogen atoms have been omitted for clarity.

Fig. 5.

Examples of ferrocene geometries for the mono and bis sulfonamides. Most of the complexes exhibit staggered anti conformations, as seen in complex **8**. Compound **4** shows eclipsed rings with a 136.7° rotational angle between substituents, while the bis-GABA complex **13** exhibits staggered rings with a 103.9° rotational angle. Both rotational angles are measured counter-clockwise.

Fig. 6.
The structures of bis-sulfonamide compounds **8–13** with 50% thermal ellipsoids. Hydrogen atoms have been omitted for clarity.

Fig. 7.
Reciprocal hydrogen bonding between GABA units in compound **13**.

Scheme 1.

Synthesis of mono- and di-substituted ferrocenesulfonamides.