Aminoferrocene Derivatives in Chloride Recognition and Electrochemical Sensing

Konstantinos Kavallieratos, Sharon Hwang, and Robert H. Crabtree*

Sterling Chemistry Laboratory, Department of Chemistry, Yale University, 225 Prospect Street, New Haven, Connecticut 06520-8107

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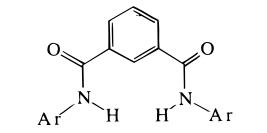
Introduction

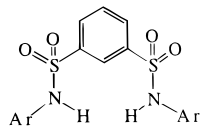
Redox-active anion receptors[1−9] giving potential shifts on binding are useful in chemical sensor applications:[10−15] cobaltocenium,[1−5,16,17] ferrocene,[1−7,18−20] and transition-metal−bipyridyl[8,9] cases are known.

Our readily available isophthalamide (**1**)[21] and disulfonamide (**2**)[22] receptors bind Cl^- and other anions very strongly in CH_2Cl_2,[21,22] suggesting the neutral diferrocenyl analogues **3** and **4** might act as Cl^- sensors because the anion is closely coupled to the ferrocenyl (Fc) group.[23] Related aminomethylferrocene diamide analogues have recently been reported by Beer et al.[24] Amide receptors with two FcNH groups have not yet been reported since $FcNH_2$ is not commercially available and is difficult to prepare.[25−29]



1

Ar = Ph-, 2,4,6-($Me_3C_6H_3$), 4-Me-C_6H_4-



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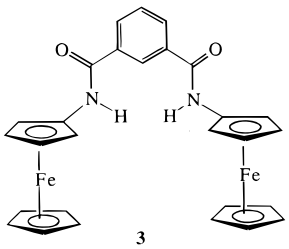
Ar = Ph-



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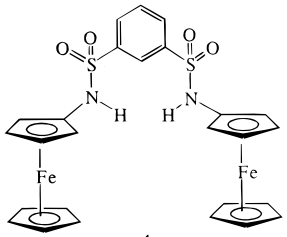

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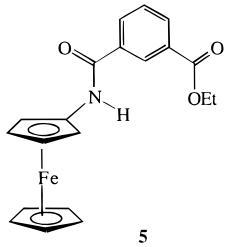
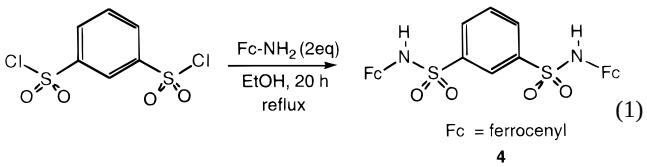


5

We have synthesized **3**−**5**, which, being neutral, are very soluble in organic solvents. The chloride-binding properties of **4** are studied. We also report an improved synthesis of $FcNH_2$.

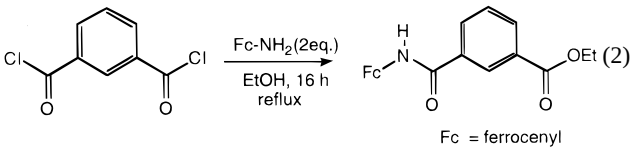
Results and Discussion

Synthesis of $FcNH_2$ and 3−5. $FcNH_2$, synthesized by a known route,[25] but with an improved isolation procedure, gave yields of 21−26% versus 8−14%.[25,30] The disulfonamide **4**, synthesized in good yield (54%) in one step from $FcNH_2$ and 1,3-benzenesulfonyl dichloride in EtOH,[31] was isolated as a yellow powder, soluble in CH_2Cl_2, and was characterized by ^1H NMR, FT-IR, and elemental analysis. Attempts to synthesize receptor **3** in CH_2Cl_2 gave only 8% of **3** but in EtOH gave a 24% yield of the amide ethyl ester **5**; both were fully characterized.



(1)

4



(2)

5

Anion Binding by 3−5 (^1H NMR). Addition of Bu_4NX ($X = Cl^-$) to CD_2Cl_2 solutions of **3** and **4** caused large chemical

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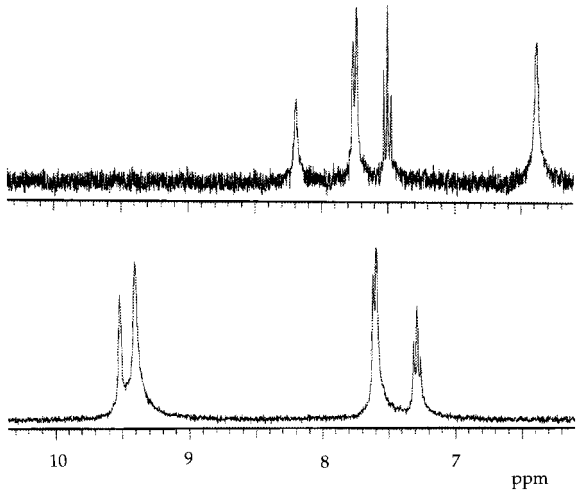

Figure 1. ^{1}H NMR spectra of **4** before and after addition of 10 equiv of $(n\text{-Bu})_4$NCl. The resonance corresponding to the N−H (2H) shows a dramatic downfield shift from 6.4 to 9.4 ppm. Similarly the 2-C−H (1H) shows a smaller downfeld shift from 8.2 to 9.5 ppm. The other aromatic protons are affected only slightly by anion addition.

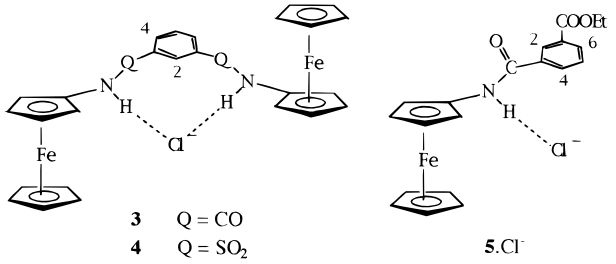

Figure 2. Binding conformation of chloride−receptor complexes based on the NMR data and previous work on similar receptors.[21,22]

Table 1. Chemical Shift Changes ($\Delta\delta_{max}$) for N−H and Aromatic 2-C−H Protons in the ^{1}H NMR Spectrum upon Chloride Addition

compound	$\Delta\delta$ (N−H) (**R**·Cl$^-$) (ppm)	$\Delta\delta$ (2-C−H) (**R**·Cl$^-$) (ppm)
3	3.37	1.07
4	3.13	1.03
5	2.88	0.23

shift changes for protons (N−H and 2-C−H) affected by hydrogen bonding (Figure 1 and Table 1).

Monoamide **5** gave smaller changes for the same protons. The 2-C−H shift (0.23 ppm) being much smaller than the 4-C−H (0.50 ppm) suggests an anti binding conformation. On the other hand, the large shift changes for the 2-C−H protons of **3** and **4** suggest[21,22] a syn−syn binding conformation is adopted
(Figure 2).

No crystals were obtained for X-ray study of any complex of **3** and **4**, but previous studies[21,22] with **1** and **2** strongly suggest that all have a syn−syn binding conformation with two convergent N−H···Cl hydrogen bonds (Figure 2).

Solution and Thin Film FT-IR for Receptors and Adducts. To compare Cl$^-$ binding of **4** and **5** in solution and the solid state, we examined the solution and thin film[32] FT-IR spectra of the receptors and their adducts (Table 2). Free **4** (10^{-1} M), gave ν_{N-H} bands at 3360 and 3228 cm^{-1} (w) for self-associated N−H. The thin film spectrum shows only the 3228 cm^{-1} band. With a slight excess of $(n\text{-Bu})_4$NCl, a new band appears for N−H···Cl$^-$ at 3260 cm^{-1} (thin film, 3258 cm^{-1}).

(32) The thin film is formed by slow evaporation on a NaCl plate of the same solution used for the solution FT-IR study.

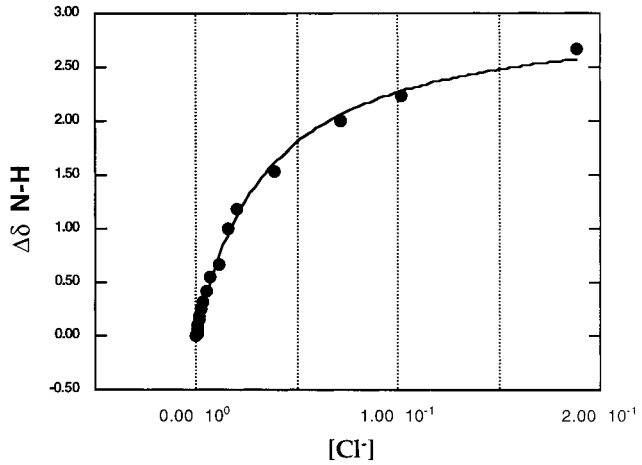

Figure 3. Titration curve of **5** with $(n\text{-Bu})_4$NCl at 19.4 °C in CD_2Cl_2.

Table 2. FT-IR ν_{N-H} Stretching Frequencies in CH_2Cl_2 Solution and a Thin Film for the Free Receptors and Their Adducts (X = Cl)

FT-IR spectrum of	ν_{N-H} (solution) (cm^{-1})	ν_{N-H} (thin film) (cm^{-1})	FT-IR spectrum of	ν_{N-H} (solution) (cm^{-1})	ν_{N-H} (thin film) (cm^{-1})
4	3360 and 3228 (weak)	3228	**5**	3434	3263
			5·X$^-$	3434	3176
4·X$^-$	3360 and 3260	3258			

As before,[22] the self-associated sulfonamide band (3228 cm^{-1}) does not appear in the solution or film spectra of **4**·X$^-$. For the monoamide ferrocenyl receptor we were able to observe the free N−H band in solution at 3434 cm^{-1} and the self-associated N−H band at 3263 cm^{-1} in a thin film. For **5**·Cl$^-$ only a broad N−H···Cl$^-$ band at 3175 cm^{-1} appeared in thin film, but the solution spectra did not show many other differences from that of free **5**, suggesting a much weaker anion complexation.[33]

^{1}H NMR Titrations. Association Constants. The association constants, K_a, were determined for **4** and **5** with Cl$^-$ in a CD_2Cl_2 solution, by a standard NMR titration[34] monitoring $\Delta\delta$(N−H) and $\Delta\delta$(2-C−H) in a dilute receptor CD_2Cl_2 solution of concentration range $(0.5-1) \times 10^{-3}$ M, with the addition of 1.0×10^{-2} to 1.0×10^{-1} M CD_2Cl_2 solutions of $(n\text{-Bu})_4$NCl in the same receptor concentration. One to one binding curves for the N−H protons (Figure 3) were analyzed using a nonlinear regression method.[35] The 1:1 binding isotherm[34] of eq 3 gave consistent fits for both 2-C−H and N−H.

$$\Delta\delta = ([\mathbf{R}]_t + [Cl^-]_t + K_a^{-1} - ((([\mathbf{R}]_t + [Cl^-]_t + K_a^{-1})^2 - 4[Cl^-]_t[\mathbf{R}]_t)^{1/2}))\Delta\delta_{max}/(2[\mathbf{R}]_t) \quad (3)$$

Comparison of the data for Cl$^-$ binding (K_a = 9500 M^{-1} (±30%), **4**·Cl$^-$; 30 M^{-1} (±5%), **5**·Cl$^-$; ΔG_f = −22.3 kJ/mol, **4**·Cl$^-$; −8.3 kJ/mol, **5**·Cl$^-$) demonstrates the importance of the two convergent hydrogen-bonding groups;[36−38] the second N−H increases K_a by >300-fold and ΔG_f by >2-fold. In our previous studies with the organic analogues **1** and **2**,[21,22] we found similar binding constants for the two receptors, suggesting that the higher acidity of the sulfonamide is a secondary factor.

(33) We have found that typically for association constants of <100 M^{-1} the hydrogen-bonded band is normally not observed in dilute solution.

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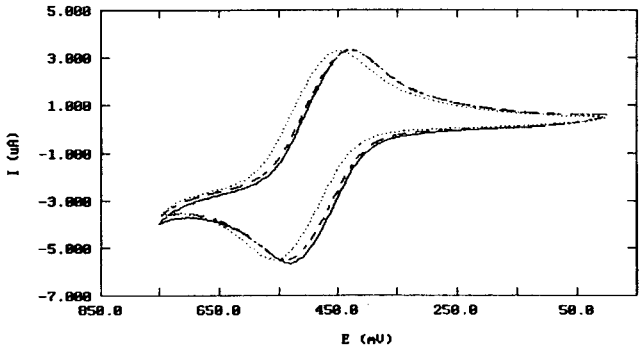

Figure 4. Cyclic voltammograms of **4** (···), **4** + $(n\text{-Bu})_4$NCl (1 equiv) (---), and **4** + $(n\text{-Bu})_4$NCl (5 equiv) (—). The total concentration of **4** is 5×10^{-4} M. The scan rate is 100 mV/s.

Electrochemical Study (Cyclic Voltammetry). The CVs of 5×10^{-4} M solutions of $FeCp_2$ (standard), **4**, and **5** in CH_2Cl_2 were recorded before and after addition of 1 and 5 equiv of solid $(n\text{-Bu})_4$NCl (final concentrations 5 and 25×10^{-4} M Cl^-). $(n\text{-Bu})_4NBF_4$ (0.1 M) was an inert electrolyte. All the waves corresponded to quasi-reversible oxidations. In certain cases,[19,20] Beer saw an EC mechanistic response, but our compounds and conditions (including solvent) are somewhat different and **4** binds halides very strongly; in other cases[23] Beer saw results similar to our results. **4** showed a shift of −20.0 mV after addition of 1 equiv of $(n\text{-Bu})_4$NCl increasing only marginally for 5 equiv of $(n\text{-Bu})_4$NCl, as expected for anion binding[23] (Figure 4). In contrast, control **5** gave only a weak negative shift (<5 mV) for the solution containing 1 equiv of $(n\text{-Bu})_4$NCl and no negative shift for the solution containing 5 equiv of $(n\text{-Bu})_4$NCl, so the two convergent hydrogen-bonding groups are very important for effective sensing. A small nonspecific positive potential shift linearly dependent on $[Cl^-]$ for the Cp_2Fe standard explains why the voltammograms obtained for solutions with 5 equiv of chloride for **4** and **5** show no further increase (**4**) or reversal (**5**) of the previously observed negative shift. The source of this shift—only expected in the case of an interaction with a positive charge[39]—remains unexplained.

Conclusion

The new diferrocenyl sulfonamide receptor **4** is capable of anion binding and electrochemical sensing. With its two convergent N−H···Cl H-bonds, disulfonamide **4** has a much higher anion affinity than the monoamide analogue **5** (NMR, e-chem).

Experimental Section

General Procedures. Solvents (analytical grade) and materials (Aldrich Chemical Co.) were used as received. ^{1}H NMR spectra (GE-Omega 300 MHz) were referenced to residual solvent. FT-IR spectra were recorded on a MIDAC M1200 FT-IR spectrophotometer. Elemental analyses were performed by Atlantic Microlab Inc. (Norcross, GA) or Robertson Microlit Laboratories Inc. (Madison, NJ). High-resolution MS were obtained by Dr. S. Mullen (University of Illinois, Urbana-Champaign). Electrochemical data were obtained using a Princeton Model 243 potentiostat. *O*-Benzylhydroxylamine was prepared[25] from the hydrochloride and distilled.

Aminoferrocene. *N*-Butyllithium (15.9 mL of 2.5 M solution in hexanes, 0.0339 mmol) was added using a gas-tight syringe to anhydrous Et_2O (55 mL). Ferrocene (3.34 g, 18 mmol) was added and the mixture refluxed (6 h) and then stirred (12 h). The mixture was then cooled (−22 °C) and *O*-benzylhydroxylamine added dropwise over 15 min. The mixture was then warmed to room temperature for 45 min. HCl (30 mL, 0.1 N) was added at 0 °C and the acid layer (now orange) discarded. Two more aliquots of HCl (30 mL, 0.1 N) were added, and from the combined green-dark brown extract, an off-white product was crystallized on addition of excess 12 M NaOH dropwise, then filtered, and dried in vacuo. The product was spectroscopically identical to the reported product (^{1}H NMR) (yield 0.75−0.93 g, 21−26%).

***N,N′*-Bisferrocenyl 1,3-Benzenedicarboxamide (3).** Aminoferrocene (100 mg, 0.5 mmol) was added to isophthaloyl dichloride (51 mg, 0.25 mmol) in distilled CH_2Cl_2 (20 mL). Triethylamine (0.05 mL, 0.5 mmoL) was added and the mixture stirred for 3 h. The mixture was then washed with HCl (3 × 10 mL, 0.1 N), and then with water (3 × 10 mL). The CH_2Cl_2 layer was dried with $MgSO_4$. Dropwise addition of hexanes precipitated a yellow solid (10.0 mg) which was filtered and dried in vacuo (7.5% yield). ^{1}H NMR (CD_2Cl_2, 19.2 °C): δ (ppm) 8.58 (s, 1H, ar H-2), 8.04 (d, 2H, ar H-3, $J_{3-1} = 7.5$ Hz), 7.63 (t, 1H, H-1, $J_{1-3} = 7.6$ Hz), 7.42 (br s, 2H, N−H), 4.69 (s, 4H, Fc H-4), 4.15 (s, 10H, Fc H-5), 4.03 (s, 4H, Fc H-6). Anal. Calcd for $C_{28}H_{24}N_2O_2Fe_2$: C, 63.20; H, 4.55. Found: C, 62.93; H, 4.70.

***N,N′*-Bisferrocenyl 1,3-Benzenedisulfonamide (4).** Aminoferrocene (100 mg, 0.5 mmol) was dissolved in EtOH (20 mL) containing $NaHCO_3$ (1 g) and $MgSO_4$ (2 g). 1,3-Benzenedisulfonyl chloride (56 mg, 0.25 mmol) dissolved in ethanol (17 mL) was then added dropwise. The mixture was refluxed for 20 h. The resulting dark brown solution was cooled to room temperature, and after filtration of $MgSO_4$ and $NaHCO_3$, the ethanol was evaporated. The dark brown residue was redissolved in CH_2Cl_2 and the solution washed with HCl (3 × 20 mL, 0.1 N, or until the aqueous layer appeared colorless). The organic layer was then washed with H_2O (3 × 20 mL) and dried with $MgSO_4$. After filtration, slow evaporation of the CH_2Cl_2 gave a bright yellow powder which was filtered and dried in vacuo (66.1 mg, 54% yield). ^{1}H NMR (CD_2Cl_2, 19.2 °C): δ (ppm) 8.19 (s, 1H, ar H-2), 7.75 (dd, 2H, ar H-3, $J_{3-1} = 7.8$ Hz, $J_{3-2} = 0.9$ Hz), 7.50 (t, 1H, H-1, $J_{1-3} = 7.9$ Hz), 6.38 (br s, 2H, N−H), 4.21 (s, 4H, Fc H-4), 4.11 (s, 10H, Fc H-5), 4.03 (s, 4H, Fc H-6). FT-IR (thin film, cm^{-1}): 3228, 3090, 1492, 1178, 1157. Anal. Calcd for $C_{26}H_{24}N_2S_2O_4Fe_2$: C, 51.70; H, 4.00; N, 4.64. Found: C, 51.55; H, 3.99; N, 4.54.

(*N*-Ferrocenyl)-3-(ethylcarboxylate) Benzene-1-carboxamide (5). The compound was prepared as above but from isophthaloyl dichloride (51 mg, 0.25 mmol) and with 16 h of reflux. The product precipitated as an orange powder (22.9 mg 24% yield). ^{1}H NMR (CD_2Cl_2, 19.2 °C): δ (ppm) 8.42 (s, 1H, ar H-2), 8.20 (d, 1H, ar H-3, $J_{3-5} = 7.5$ Hz), 8.06 (d, 1H, ar H-4, $J_{4-5} = 7.3$ Hz), 7.59 (t, 1H, H-5, $J_{5-4,3} = 7.6$ Hz), 7.38 (br s, 1H, N−H), 4.74 (s, 2H, Fc H-6), 4.40 (q, 2H, H-8 $-CH_2-$, $J_{8-9} = 7.0$ Hz), 4.19 (s, 5H, Fc H-7), 4.07 (s, 4H, Fc H-8), 1.42 (t, 3H CH_3-H-9, $J_{9-8} = 7.0$ Hz). FT-IR (thin film, − cm^{-1}): 3263, 3093, 1719, 1600, 1487. Anal. Calcd for $C_{20}H_{19}NO_3Fe$: C, 63.70; H, 5.08; N, 3.71. Found: C, 62.81; H, 4.91; N, 3.60. High-resolution mass spectrometry (FAB): calcd 377.071 433, found 377.071 700.

^{1}H NMR Titration Experiments. Solutions of **4** and **5** in CD_2Cl_2 (5×10^{-4} to 1×10^{-3} M) were titrated by the standard procedure reported in ref 22, but dried $(n\text{-Bu})_4$NCl was used as a titrant (1.0×10^{-2} and 1.0×10^{-1}M).

Cyclic Voltammetry. Solutions (5×10^{-4} M) of **4**, **5**, and ferrocene (control) were prepared in CH_2Cl_2 containing 0.1 M $(n\text{-Bu})_4NBF_4$ as supporting electrolyte. $(n\text{-Bu})_4$NCl was used as a Cl^- source. The CVs were recorded using a Pt working electrode and a Ag/AgCl reference electrode before and after the addition of solid $(n\text{-Bu})_4$NCl in molar ratios of 1:1 and 1:5.

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