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Ferrocene as a molecular building block in lariat ethers and other complexing agents†

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Several novel ferrocene derivatives have been prepared which possess functional groups on both cyclopentadienyl rings. The ability of these compounds to complex protons and other cations has been assessed by several methods and the results are reported. Evidence is presented for sidearm cooperativity in the complexation phenomenon.

INTRODUCTION

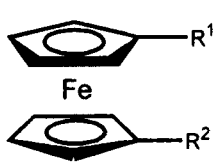
The ferrocene sandwich complex possesses several interesting properties.[1] Ferrocene is an organic-soluble, organometallic compound. Its two parallel cyclopentadienyl rings are spaced approximately one aromatic thickness (≈3.25Å) apart and are electron rich. They may be readily substituted by the Friedel-Crafts reaction, and they rotate relative to one another on a "molecular ball bearing" comprised of an iron atom.[2] The iron atom of ferrocene is formally in the 2+ oxidation state and may be readily oxidized to the formal 3+ state. The resulting cation is formed at an accessible potential and is stable in aqueous solution.

Hall and coworkers[3] incorporated the ferrocene unit into cryptands and they have studied in detail the complexation properties of the resulting structures. Beer and his collaborators[4] have greatly expanded the family of hosts known to contain ferrocene and have recently prepared lariat ethers having three ferrocenyl sidearms.[5] Plenio and coworkers[6] have recently explored selectivity in redox-switchable, ferrocenyl crown ethers as we[7] have done. In most of this work, ferrocene is incorporated as part of a cryptand. We wondered whether the "ball bearing" aspect of ferrocene could be used to advantage as a pivot for a lariat ether sidearm. We report here the preparation of several novel lariat ethers having cation-binding sidearms attached to ferrocene at a ring different from that which secures the macroring. Proton affinities (pK_A values) and cation binding constants are reported for several of these novel structures.

RESULTS AND DISCUSSION

Syntheses

Ferrocene (**1**) readily undergoes substitution by the Friedel-Crafts reaction. Indeed, its reactivity as a nucleophile is greater than for benzene by some 10^6-fold.[8] A broad range of derivatives may thus be prepared.[9] The challenge is differentiating two identical substituents attached to the 1- and 1′-positions of ferrocene. Basic building blocks for the compounds studied here include ferrocene itself, hydroxymethylferrocene (**2**), ferrocenecarboxylic acid (**3**), carbomethoxyferrocene (**4**), ferrocene-1,1′-dicarboxylic acid (**5**), and its dimethyl ester, **6**. All of these compounds can be readily prepared or are commercially available.



1, $R^1 = R^2 = H$

2, $R^1 = CH_2OH$, $R^2 = H$

3, $R^1 = COOH$, $R^2 = H$

4, $R^1 = COOCH_3$, $R^2 = H$

5, $R^1 = R^2 = COOH$

6, $R^1 = R^2 = COOCH_3$

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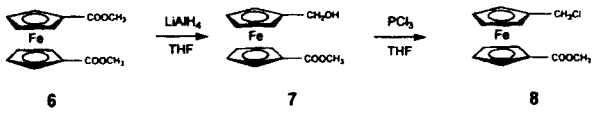
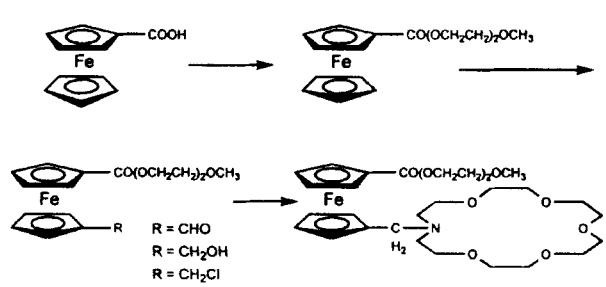


Two general approaches were utilized for the preparation of 1,1′-differentiated ferrocenes. In the simpler cases, commercially available 1,1′-ferrocenedicarboxylic acid (**6**) was partially reduced using $LiAlH_4$ in THF. The half alcohol, half ester (**7**) was obtained in 54% yield and then treated with PCl_3 in THF to afford reactive chloromethyl ester **8**.

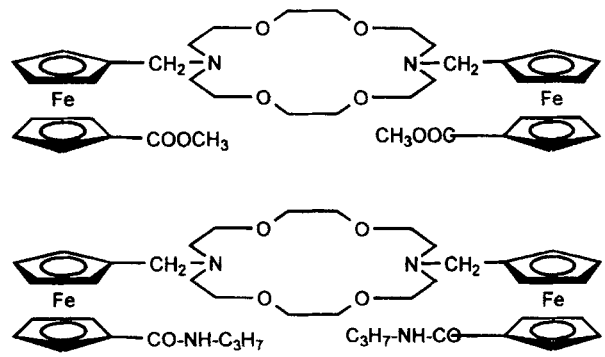
For those ferrocene derivatives having more complex substitution patterns, ferrocenecarboxylic acid was appropriately substituted. Dichloromethylation and hydrolysis afforded the aldehyde which was then reduced. Chlorination of the alcohol gave the labile 1′-substituted-1-chloromethylferrocene. This process is illustrated below for the synthesis of **13** which possesses both a macrocyclic ring and a podand chain.

In the process illustrated above, ferrocenecarboxylic acid chloride was treated with diethylene glycol monomethyl ether to give the podand ester. This was then allowed to react with Cl_2CHOCH_3 and $AlCl_3$ in CH_2Cl_2. Hydrolytic workup gave the aldehyde. The aldehyde was readily reduced in the presence of the ester by using $NaBH_4$ in CH_3OH. The primary alcohol was converted into the very reactive primary chloride by treatment with PCl_3 in THF and C_5H_5N. Finally, chloride was displaced by aza-18-crown-6 (Na_2CO_3, CH_3CN) to give the mixed podand-coronand.

The two bis(crowns) shown as **14** and **15** were prepared by using a similar strategy. In the final step, 4,13-diaza-18-crown-6 is allowed to react with the chloride to form the tertiary amine. In addition to these compounds, related structures have been prepared which are not described in detail here because they have not been characterized in terms of binding. One is a monocrown related to **13** in which the sidearm is $CO\text{-}NH\text{-}C_{14}H_{29}$ rather than $CO(OCH_2CH_2O)_2CH_3$. The second is the analog in which the sidearm is $CO\text{-}N(C_5H_{11})_2$. The third is a diaza-18-crown-6 similar to **14**



Preparation of **13**

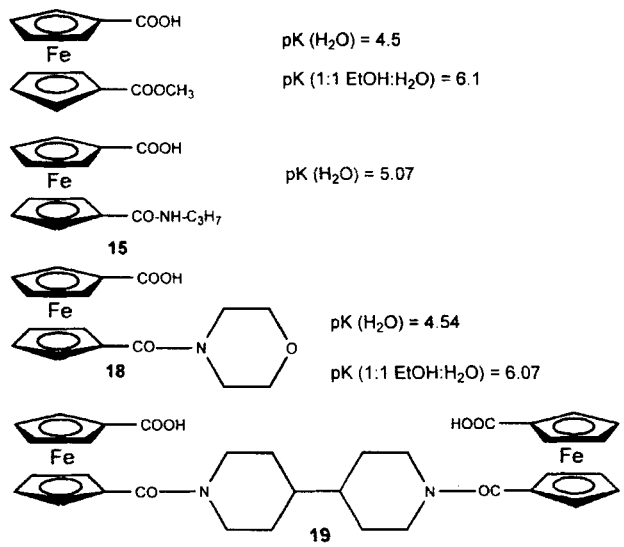


Compounds **14** (top) and **15**

in which the two "lower" sidearms comprise $CO\text{-}N(C_5H_{11})_2$ as well.

Determination of acidity constants. In connection with the use of bis(ferrocenyl) derivatives as molecular complexing agents, we wished to know the relative acidities of the ferrocenyl carboxylic acids. In particular, we were interested to know whether any significant cooperativity would be observed between upper and lower ring substituents or across the molecular cleft of **19** when one of them was carboxyl. Such cooperativity was not anticipated since the ring separation of the two aromatic cyclopentadienides is 3.25Å. The preferred conformation of carboxyl is expected to be planar with the aromatic π-system to which it is conjugated. In the case of **19**, the separation is even greater. Nevertheless, a few constants were determined to calibrate the expectations.

Determination of acidity constants was accomplished by measurement of pH during titration with NaOH (*ca.* 0.1 N). Ten points were typically determined and the pK_A



established from the average. In our system, the experimentally determined pK_A of acetic acid was 4.74 which compares with the published value of 4.75.[10] Data for the compounds studied are given below.

Acidity constant data for a few ferrocene derivatives are available in the literature. In the earliest days of ferrocene chemistry, the pK_A of the carboxylic acid was of interest as an indicator of the chemistry of this novel molecule. The pK_A of ferrocenecarboxylic acid, determined in 2:1 (v/v) ethanol-water is reported to be 6.78.[11] In a similar solvent system, *i.e.* 38 vol-% ethanol-water, the pK_A was reported to be 5.72.[12] The latter authors also determined the pK_A of benzoic acid under these conditions: 6.32. The pK_A's of ferrocenedicarboxylic acid were determined in 2:1 ethanol:water and found to be $pK_1 = 6.51$ and $pK_2 = 7.57$.[13] For reference, the pK_A of benzoic acid under the latter conditions was reported in the same paper to be 6.6. In water, the pK_A of benzoic acid is 4.19.[10]

There is some difficulty in comparing the data obtained as part of this study with literature data. This is because the solvent compositions in the literature and this work range from 33%–50% ethanol in water and data are not readily available in water. Further, even where solvents are similar, literature data do not comport with each other. One observation can be made, however, even within this uncertain context. It appears that in none of the derivatives prepared is there significant cooperativity between functional groups in the upper and lower rings. Moreover, the two carboxyl groups of **19** have pK_A values that are very similar to 1,2-dicarboxyferrocene itself.

Cation complexation. Cation binding constants for ferrocene-substituted crowns **13–15** are recorded in Table 1 along with a number of other data for comparative purposes. All values were determined in anhydrous methanol by ion selective electrode methods as previously described.[14] Calcium complexation constants were obtained by a competitive method previously described.[15]

The ferrocene-derived ionophores add several features to simple crown ethers. They are lariat ethers[16] in the sense that they contain sidearms. The sidearm is special, though, since the ester, amide, and/or ether donor groups are attached at the alternate ring of ferrocene. The sidearm's flexibility results primarily from rotation of the rings relative to each other. Compound **13** possesses both ester and ether donors in its sidechain. The greater flexibility of this chain in **13** relative to the simple esters of **14** makes it a more effective donor for Na^+. The binding is somewhat better than for *N*-benzylaza-18-crown-6 but poor relative to 18-crown-6. Indeed, binding is about a power of ten lower for **13** than for the simple ester $< 18N > CH_2COOCH_2CH_3$.

Binding of diazacrowns **14** and **15** is relatively poor for Na^+ but Ca^{2+} binding by **15** is considerably stronger. Of course, the amide donors in the latter are expected to favor the more charge-dense Ca^{2+} over Na^+. A similar trend is observed for the family of dipeptide-substituted diazacrowns which have been previously studied.[17] The glycyl-glycine case is typical in that Ca^{2+} binding is considerably stronger than for either Na^+ or K^+. This bibracchial lariat ether also contains both amide and ester donors in the sidearms.

The complexation of Ca^{2+} by **14** and **15** was studied by ^{1}H-NMR in methanol-d_4 using ligand:Ca^{2+} ratios of 1:0, 1:0.5, and 1:1. The NMR spectra showed by line broadening that complexation and decomplexation is slow on the NMR time scale. All resonances for the complexed ferrocene ligands were shifted downfield relative to their uncomplexed positions. The NMR spectra suggested that complexation was quantitative. For example, all methylene group resonances in the crown and both ferrocene

Table 1 Cation complexation by crown and lariat ethers[a]

Complexing agent[b]	Na^+	K^+	Ca^{2+}
18-crown-6	4.35	6.08	3.9
$< 18N > CH_2C_6H_5$	3.41	4.88	3.10
$< 18N > CH_2COOCH_2CH_3$	4.67	5.92	ND[c]
$< 18N > CH_2CH_2OCH_3$	4.58	5.67	4.34
$< 18N > (CH_2CH_2O)_2CH_3$	4.33	6.07	4.23
$C_6H_5CH_2 < N18N > CH_2C_6H_5$	2.68	3.38	2.79
$EtOCOCH_2 < N18N > CH_2COOEt$	5.51	5.78	6.78
$R < N18N > R$, $R = CH_2CON(C_5H_{11})_2$	5.69	5.49	ND
R < N18N > R, R = gly-gly-OMe	3.35	3.32	5.36
13 < 18N > CH_2-1-Fc-1'-COOEOEOMe[d] (13)	3.69	ND	ND
R < N18N > R, R = CH_2-1-Fc-1'-COOMe (14)	3.20	ND	ND
R < N18N > R, R = CH_2-1-Fc-1'-CONHPr (15)	3.15	ND	4.86

a. All data are $\log_{10} K_S$ for anhydrous methanol at 25±0.1 °C. b. < 00N > indicates a macrocycle having 00 members. N indicates the presence of that atom as well. c. ND means not determined. d. E means CH_2CH_2.

cyclopentadienyl rings were split into two distinct peaks and broadened upon complexation well before the 1:1 ratio was reached. The methylene groups of $-CONHCH_2CH_2CH_3$ in ligand **15** were considerably broadened upon complexation, clearly indicating amide group participation in the cation complexation.

CONCLUSIONS

The ferrocene unit has been successfully incorporated into several novel lariat ether structures. Complexation of H^+, Na^+, and Ca^{2+} have been assessed for various of the derivatives. NMR evidence confirms that the lariat sidearms participate in binding Ca^{2+} but the complexation constants are not unusually high for any of these derivatives.

EXPERIMENTAL SECTION

^{1}H-NMR were recorded at 300, 500, or 600 MHz in $CDCl_3$ solvents and are reported in ppm (δ) downfield from internal $(CH_3)_4Si$ unless otherwise specified. ^{13}C-NMR were recorded at proportional frequencies as noted above. Infrared spectra were recorded on a Perkin-Elmer 1310 Infrared Spectrophotometer and were calibrated against the 1601 cm^{-1} band of polystyrene. Melting points were determined on a Thomas Hoover apparatus in open capillaries and are uncorrected. Thin layer chromatographic (TLC) analyses were performed on aluminum oxide 60 F-254 neutral (Type E) with a 0.2 mm layer thickness or on silica gel 60 F-254 with a 0.2 mm layer thickness. Preparative chromatography columns were packed with activated aluminum oxide (MCB 80–325 mesh, chromatographic grade, AX 611) or with Kieselgel 60 (70–230 mesh). Chromatotron chromatography was performed on a Harrison Research Model 7924 Chromatotron with 2 mm thick circular plates prepared from Kieselgel 60 PF-254.

All reactions were conducted under dry N_2 unless otherwise stated. All reagents were the best (non-LC) grade commercially available and were distilled, recrystallized, or used without further purification, as appropriate. Molecular distillation temperatures refer to the oven temperature of a Kugelrohr apparatus. Combustion analyses were performed by Atlantic Microlab, Inc., Atlanta, GA, and are reported as percents. Values given for molecular weights were determined by fast atom bombardment mass spectrometric analysis and are reported in Daltons to the nearest integer.

Cation binding constants were measured in absolute CH_3OH at 25.0±1.0 °C using a Corning 476210 electrode and an Orion model 701A "ionalyzer" meter according to the method of Frensdorff[18] as described recently in detail. Values for the equilibrium constants are reported as $\log_{10} K_S$.

Ferrocene (**1**), hydroxymethylferrocene (**2**), ferrocenecarboxylic acid (**3**), carbomethoxyferrocene (**4**), 1,1′-ferrocenedicarboxylic acid (**5**), and 1,1′-dicarbomethoxyferrocene (**6**) were obtained commercially and purified by standard methods if necessary or used as received if appropriate.

1-Carbomethoxy-1′-hydroxymethylferrocene, 7. To a stirred solution of **6** (8.7 g, 0.029 mol) in dry THF (50 mL), was added dropwise a solution of $LiAlH_4$ (1.00 g, 0.026 mol, in 100 mL THF). The suspension was gently shaken during addition to aid dispersion of the $LiAlH_4$. The reaction mixture was heated at reflux temperature for 3 h and then allowed to cool to ambient temperature. Water was added to quench the reaction and the solvent was removed *in vacuo*. The mixture was extracted with CH_2Cl_2 and then chromatographed over alumina (1% MeOH/CH_2Cl_2 as eluent). The product (4.0 g, 54%) was isolated as a sticky oil which was solidified after 2 days drying at high vacuum. ^{1}H NMR: 4.83 (t, 2H); 4.45 (t, 2H); 4.37 (d, 2H); 4.23 (s, 2H); 4.18 (s, 2H), 3.85 (s, 3H), 3.47 (s, 1H).

Alternate intermediate for the formation of 7 by $NaBH_4$ reduction: 1-Carbomethoxy-1′-formylferrocene. To an ice-cold, mechanically-stirred CH_2Cl_2 solution (100 mL) of methyl ferrocenecarboxylate (11.5 g, 0.047 mol) and α,α-dichloromethyl methyl ether (5.4 g, 0.047 mol), was added $AlCl_3$ (12 g) in portions using a solid addition funnel. The reaction was maintained at 0 °C for 0.5 h. Water (100 mL) was added in portions to quench the reaction. The product was extracted (CH_2Cl_2), the organic phase was dried over $MgSO_4$, and the crude product was chromatographed over silica (1% MeOH/CH_2Cl_2 as eluent). The product (3.32 g, 26%) was obtained as a red solid, mp 83–84°C, ^{1}H-NMR: 3.80 (s, 3H); 4.45 (t, 2H); 4.58 (t, 2H); 4.80 (t, 2H); 4.88 (t, 2H); 9.95 (s, 1H).

1-Carbomethoxy-1′-chloromethylferrocene, 8. To a stirred solution of the methyl ester of 1′-(hydroxymethyl)ferrocenecarboxylic acid (2.74 g, 10 mmol) in dry THF (20 mL), was added dry pyridine (0.6 mL), followed by dropwise addition of a solution of PCl_3 (0.069 g) in THF (15 mL). After stirring for 8 h at ambient temperature, the solution was decanted from the precipitate and the precipitate was washed with THF (30 mL). The combined solutions of the product in THF were used in the next reaction without further purification.

Carboxyferrocene 3,6-dioxaheptanoate, 9. To a solution of CH_2Cl_2/THF (1:1 v/v, 200 mL) solution containing ferrocenecarboxylic acid chloride (10 g, 0.04 mol) and diethylene glycol monomethyl ether (4.5 g, 0.037 mol) was added triethylamine (6.0 g, 0.59 mol).

The reaction was stirred for 4 h at ambient temperature and then HCl (3*N*, 150 mL) was added. The product was extracted with CH_2Cl_2 (100 mL). The combined organic material was evaporated *in vacuo*. The product (**9**, 10.5 g, 79%) was obtained by chromatography (alumina, 1% MeOH/$CHCl_2$) as an orange oil. ^{1}H-NMR: 3.48 (s, 3H), 3.68 (t, 2H), 3.63 (t, 2H), 3.78 (t, 2H), 4.12 (s, 5H), 4.33 (t, 2H), 4.37 (t, 2H), 4.74 (t, 2H).

1′-Formyl-1-carboxyferrocene 3,6-dioxaheptanoate, 10. To an ice-cold, mechanically-stirred solution of **9** (9.0 g, 27 mmol) and α,α′-dichloromethyl methyl ether (3.5 g, 30 mmol) in CH_2Cl_2 (250 mL), $AlCl_3$ (8.7 g, 55 mmol) was added portion-wise by use of a solid-addition funnel. Stirring was continued for 10 min after addition, and then allowed to warm to ambient temperature during 15 min. The reaction was quenched by dropwise addition of water (300 mL). The organic phase was evaporated *in vacuo*. Chromatography over silica afforded **10** (3.3 g, 34%) as a red oil. ^{1}H NMR: 9.98 (s, 1H); 4.83 (s, 2H); 4.78 (s, 2H); 4.65 (s, 2H); 4.38 (t, 2H), 4.31 (s, 2H); 3.78 (t, 2H); 3.68 (t, 3H), 3.64 (t, 2H), 3.47 (s, 3H).

1′-Hydroxymethyl-1-carboxyferrocene 3,6-dioxaheptanoate, 11. Sodium borohydride (1.0 g, 26.4 mmol) was added to a solution of **10** (3.2 g, 8.9 mmol) in MeOH (150 mL). The mixture was stirred for 0.5 h, water (200 mL) was added, and the mixture extracted with CH_2Cl_2. The organic phase was evaporated *in vacuo* and the residue chromatographed over silica gel to afford **11** (2.6 g, 81%) as an orange oil. ^{1}H NMR: 5.96 (br, 1H); 4.64 (t, 2H); 4.38 (t, 2H), 4.34 (t, 2H); 4.22 (s, 2H); 4.16 (s, 2H); 3.79 (t, 2H); 3.68 (t, 3H), 3.64 (t, 2H), 3.45 (s, 3H).

1′-Chloromethyl-1-carboxyferrocene 3,6-dioxaheptanoate, 12. To a N_2-purged solution of **11** (2.5 g, 6.9 mmol) and pyridine (0.42 g) in THF (25 mL) was added dropwise PCl_3 (0.48 g). The reaction mixture was stirred at ambient temperature for 3 h. The solution was decanted, the precipitate was washed with THF (15 mL) and the crude product used directly in the next step without further purification.

1′-(N-Aza-18-crown-6)methyl-1-carboxyferrocene 3,6-dioxaheptanoate, 13. The product (**12**) from the above sequence was dissolved in THF (30 mL) and added dropwise to a solution of aza-18-crown-6 (0.80 g, 3.04 mmol) and Na_2CO_3 (1.06 g) in THF (20 mL). The solvent was removed *in vacuo*, CH_3CN (50 mL) was added, and the reaction mixture was refluxed under N_2 for 6 h. The solvent was removed *in vacuo*, water (100 mL) was added, the mixture was extracted with CH_2Cl_2, and then chromatographed over alumina (5% MeOH/CH_2Cl_2 as eluent). The product (**13**) was obtained as an orange oil (1.17 g, 47%). ^{1}H-NMR: 2.67 (t, 4H); 3.38 (s, 3H); 3.48 (s, 2H), 3.56 (t, 4H), 3.60 (t, 2H), 3.65–3.70 (m, 20H) 3.78 (t, 2H); 4.13 (s, 2H), 4.17 (s, 2H), 4.33 (s, 2H), 4.38 (t, 2H) 4.74 (s, 2H). FAB/MS molecular ion determination: calcd. for $C_{29}H_{45}NO_9Fe$: 607.5, Found: 607.

N,N′-bis[(1′-Carbomethoxyferrocenyl)methyl]-4,13-diaza-18-crown-6, 14. To a solution of diaza-18-crown-6 (0.54 g, 2.06 mmol) and Na_2CO_3 (1.06 g) in 20 mL THF, was added dropwise a THF solution (10 mL) of **8** (from 2.74 g of **7**). The solvent was then removed *in vacuo*. Dry acetonitrile (50 mL) was added and the reaction mixture was heated at reflux under N_2 for 6 h. Solvent was removed *in vacuo*, and then extracted with CH_2Cl_2. Chromatography over alumina (5% MeOH/CH_2Cl_2 as eluent) afforded **14** (51%) as a yellow-orange solid, mp 91–93°C. ^{1}H-NMR: 4.73 (t, 2H); 4.34 (t, 2H); 4.16 (s, 2H); 4.13 (s, 2H); 3.84 (s, 3H); 3.59 (s, 4H); 3.55 (t, 4H); 3.47 (s, 2H); 2.68 (t, 4H). FAB/MS molecular weight determination calcd. for $C_{38}H_{50}N_2O_8Fe_2$: 774.5, Found: 774.

In the above procedure, if THF is not removed and substituted by CH_3CN, product yield is much reduced.

Preparation of N,N′-bis[(1′-N-n-Propylaminocarboxyferrocenyl)methyl]-4,13-diaza-18-crown-6, 15. ***N-n-Propyl ferrocenecarboxamide.*** To a solution of ferrocenecarboxylic acid chloride (8.5 g, 0.034 mol) and n-propyl amine (3 g, 0.06 mol) in CH_2Cl_2 (150 mL) was added triethylamine (3 g) and the reaction mixture was stirred at ambient temperature for 3 h. Aqueous HCl (3N, 150 mL) was added then extracted with CH_2Cl_2 (100 mL). The combined organic phase was dried over $MgSO_4$, evaporated *in vacuo*, and then chromatographed (alumina, 2% MeOH/$CHCl_2$ as eluent). The product was obtained (8.6 g, 93%) as yellow needles, mp 128–130 °C. ^{1}H NMR: 0.94 (t, 3H), 1.57 (m, 2H), 3.29 (q, 2H), 4.10 (s, 5H), 4.23 (s, 2H), 4.57 (s, 2H), 5.85 (t, 1H).

N-n-Propyl 1′-formylferrocenecarboxamide. To a mechanically-stirred, ice-cold solution of methyl ferrocenecarboxylate (9.0 g, 0.033mol) and α,α-dichloromethyl methyl ether (4 g, 0.035 mol) in CH_2Cl_2 (250 mL) was added portion-wise $AlCl_3$ (9.0 g) by using a solid-addition funnel. Stirring was continued at 0°C for 0.5 h. Water (100 mL) was added, the mixture was extracted with CH_2Cl_2, the organic phase was dried over $MgSO_4$, and the solvent was evaporated *in vacuo*. The product (6.4 g, 65%) was isolated as a red oil after chromatography over silica (1% MeOH/CH_2Cl_2 as eluent). ^{1}H-NMR: 0.94 (t, 3H), 1.58 (m, 2H), 3.33 (q, 2H); 4.16 (s, 2H); 4.64(s, 2H); 4.77 (s, 2H); 4.79 (s, 2H); 6.20 (t, 1H), 9.95 (s, 1H).

N-n-Propyl 1′-(hydroxymethyl)ferrocenecarboxamide. To a solution of *N-n*-Propyl 1′-formylferrocenecarboxamide, (6.5 g, 21.7 mmol) in MeOH (150 mL), $NaBH_4$ (1.2 g, 31.7 mmol) was added. The reaction mixture was stirred at ambient temperature for 0.5 h. Water (200 mL) was added, the mixture was extracted with CH_2Cl_2, and the solvent was removed *in vacuo*. The alcohol was

obtained (5.7 g, 87%) after chromatography over silica gel as a yellow solid, mp 109–111°C. ^{1}H-NMR: 5.96 (br, 1H); 4.63 (s, 2H); 4.37 (s, 2H), 4.35 (d, 2H); 4.22 (s, 2H); 4.16 (s, 2H); 3.36 (q, 2H); 1.60 (m, 2H); 0.98 (t, 3H).

N-n-Propyl 1′-(chloromethyl)ferrocenecarboxamide. To a solution of *N-n*-propyl 1′-(hydroxymethyl)ferrocenecarboxamide (3.01 g, 10 mmol) and pyridine (0.6 g) in THF (25 mL) was added dropwise PCl_3 (0.69 g). The reaction mixture was stirred under N_2 at ambient temperature for 3 h and then decanted from a yellow precipitate. The solid was washed with THF (15 mL). The combined solution was used directly in the following reaction.

N,N′-bis[(1′-N-n-Propylaminocarboxyferrocenyl)-methyl]-4,13-diaza-18-crown-6, 15. To a solution of diaza-18-crown-6 (0.54 g, 2.06 mmol) and Na_2CO_3 (1.06 g) in THF (20 mL), a solution of *N-n*-Propyl 1′-(chloromethyl)ferrocenecarboxamide (see above, made from 1.5 g of alcohol) in THF (30 mL) was added dropwise, the solvent was removed *in vacuo*, acetonitrile (50 mL) was added and the reaction mixture was refluxed under N_2 for 6 h. The reaction mixture was allowed to cool, solvent was removed *in vacuo*, water (100 mL) was added, the mixture was extracted with CH_2Cl_2, and then chromatography over alumina (5% MeOH/CH_2Cl_2 as eluent) to afford **15** (54%). ^{1}H NMR: 4.56 (s, 2H); 4.23 (s, 2H); 4.10 (d, 4H); 3.55 (s, 4H); 3.53 (s, 2H); 3.51 (t, 4H); 3.30 (q, 2H); 2.65 (t, 4H); 1.57 (m, 2H); 0.94 (t, 3H). FAB/MS molecular weight calcd for $C_{42}H_{60}N_4O_6Fe_2$: 828.65, Found: 828.

1-Carboxy-1′-carbomethoxyferrocene, 16. The following is a modification of the procedure originally described by Nesmeyanov.[19] To monomethyl 1,1′-ferrocenedicarboxylate (3.79 g, 12.5mmol) was added a solution comprised of 200 mL MeOH, 50 mL H_2O, 100 mL CH_2Cl_2 and 5.0 g NaOH. The reaction mixture was stirred at ambient temperature for 6h, then acidified to pH = 2 with 3N HCl. The reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The organic phase was dried with anhydrous $MgSO_4$. The solvent was evaporated *in vacuo* and the crude product was chromatographed over silica using 5% MeOH/CH_2Cl_2 to afford an orange powder (1.5 g, 41%), mp 143–145 °C. Spectral data matched those reported in the literature.

1′-(Carbomethoxy)ferrocenecarboxylic acid chloride. To a mixture of **16** (1 g, 3.5 mmol) and pyridine (catalytic, 50 mg) in CH_2Cl_2 (10 mL) was added oxalyl chloride (8 mL). The reaction mixture was stirred for 4 h at ambient temperature. The solvent was evaporated *in vacuo*, the residue was dissolved in anhydrous diethyl ether (50 mL), filtered, and evaporated to afford the acid chloride (0.88 g, 88%) as a red solid, mp 76–81°C. ^{1}H NMR: 4.92 (s, 4H); 4.56 (s, 4H); 3.85 (s, 3H).

1′-*N*-(Morpholinocarbonyl) ferrocenecarboxylic acid, 18. To a solution of methyl 1′-(chlorocarbonyl)ferrocenecarboxylate (1.0 g, 3.4 mmol, prepared from 16) in CH_2Cl_2 (25 mL) was added morpholine (0.35 g, 4.0 mmol) of morpholine followed by Et_3N (1 g). The reaction mixture was allowed to stir at ambient temperature for 10 h. It was then quenched with water and diluted with CH_2Cl_2. The organic phase was separated, dried over $MgSO_4$, the solvent was evaporated, and the crude product was chromatographed over alumina (1% MeOH/CH_2Cl_2 as eluent) to afford an orange powder (0.95 g, 81%). ^{1}H-NMR: 3.60 (t, 4H); 3.65 (s, 3H), 3.80 (t, 2H), 4.30 (t, 2H); 4.45 (t, 2H); 4.57 (t, 4H), 4.85 (t, 2H).

To a solution of 10% NaOH in a mixture of MeOH: CH_2Cl_2: H_2O (2:1:1, v/v) was added methyl 1′-*N*-(morpholinocarbonyl)ferrocenecarboxylate (0.85 g, 2.4 mmol). The reaction mixture was stirred at ambient temperature for 24 h. The mixture was acidified with 1N HCl, and the product was extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$, the solvent was evaporated *in vacuo* and the product was chromatographed over silica gel (5% MeOH/CH_2Cl_2 as eluent). The product (**18**) was obtained (0.62 g, 77%) as a yellow powder, mp 178 °C (dec.); ^{1}H NMR in DMSO-d_6: 3.49 (t, 8H), 4.27 (s, 2H), 4.41 (s, 2H), 4.46 (s, 2H), 4.59 (s, 2H). *Anal.* calcd. for $C_{16}H_{17}NO_4Fe$, C, 56.00; H, 4.99; N, 4.08, Found: C, 56.14; H, 5.08; N, 4.04.

4,4′-bis(1′-carbomethoxyferrocenylcarbonyl)bipiperidine, 19. To a solution of 1′-(carbomethoxy)ferrocenecarboxylic acid chloride (0.35 g, 1.1mmol) in CH_2Cl_2 (25 mL) was added of 4,4′-bipiperidine (85 mg, 0.51mmol) followed by addition of Et_3N (1 g). The reaction mixture was allowed to stir at ambient temperature for 10 h. It was then quenched with water, diluted with CH_2Cl_2, the organic phase was separated and dried over $MgSO_4$, and the solvent was evaporated. The crude product was chromatographed over alumina (1% MeOH/CH_2Cl_2 as eluent) to afford an orange powder (0.16 g, 46%) mp 181–184 °C. ^{1}H NMR: 1.21 (m, 4H); 1.37 (m, 2H), 1.68 (s, 4H); 1.76 (d, 4H); 2.80 (broad, 4H), 3.81 (s, 6H); 4.31 (t, 4H); 4.50 (d, 4H); 4.57 (d, 4H); 4.86 (t, 4H). IR: 3100 (m), 2860–2960 (m); 1710 (s); 1605 (s); 1455 (s); 1420 (s); 1284 (s); 1150 (s). *Anal.* calcd for $C_{36}H_{40}N_2O_6Fe_2$: C, 61.04; H, 5.69; N, 3.95. Found: C, 61.25; H, 5.96; N, 3.76.

4,4′-bis(1′-Carbethoxyferrocenylcarbonyl)bipiperidine. To a solution of 1-chlorocarbonyl-1′-ethoxyl carbonyl ferrocene [from 1′-carbethoxyferrocenecarboxylic acid (1.5 g, 5 mmol)] in CH_2Cl_2 (25 mL) was added 4,4′-bipiperidine (0.42 g, 2.4 mmol) followed by addition of Et_3N (1.0 g). The reaction mixture was allowed to stir at ambient temperature for 10 h. It was then quenched with water and diluted with CH_2Cl_2. The organic phase was separated and dried over $MgSO_4$; the solvent was evaporated. The crude product was chromatographed

over alumina (1% MeOH/CH_2Cl_2 as eluent) to afford an orange powder (1.02 g, 59%), mp 133–136 °C. ^{1}H NMR: 1.21 (m, 4H); 1.35 (t, 6H), 1.75 (d, 4H); 2.10 (s, 2H); 2.76 (broad, 4H); 4.28 (q, 4H); 4.30 (s, 4H); 4.49 (s, 4H); 4.56 (t, 4H), 4.85 (s, 4H). Anal. calcd for $C_{38}H_{46}N_2O_6Fe_2$: C, 61.98; H, 6.02; N, 3.80. Found: C, 62.04; H, 6.03; N, 3.79.

To 3.79 g (12.5 mmol) the diethyl ester described above was added a solution of 200 mL EtOH, 100 mL H_2O, 100 mL CH_2Cl_2 and 5.0 g NaOH. The reaction was stirred at ambient temperature for 4 hrs, then acidified to pH = 2 with 3N HCl. The reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The organic phase was dried over anhydrous $MgSO_4$. The solvent was evaporated *in vacuo* and the crude product was chromatographed over silica using 5% MeOH/CH_2Cl_2 to afford **19** as an orange powder (1.5 g, 30%). ^{1}H-NMR: 1.37 (t, 6H), 4.28 (q, 4H); 4.40 (s, 4H); 4.48 (s, 4H); 4.56 (t, 4H), 4.65 (s, 4H).

Measurement of dissociation constant (pK_a) values for carboxylic acid derivatives.

Acetic acid. FW = 60.05; Wt = 0.0121g dissolved in 20 mL deionized water, pipet 10.0mL of the solution and titrated by NaOH solution; Concn = 0.1015N. Ave. pK_A = 4.74.

Compound 16 Water: Wt = 0.00741 g; pipet 20 mL deionized water, titrated by NaOH solution 0.1015N. Average pK_A = 4.5.

EtOH/H_2O (50:50, w/w): Wt = 0.0125 g in 20 mL mixed solvent, titrated by NaOH solution Concn = 0.1015N; Average pK_A = 6.11.

Compound 18 Water: Wt = 0.0083 g; F.W. = 343.2; 25 mL deionized water; titrated by NaOH solution 0.1015N. Concn = 9.71×10^{-4}; Average pK_A = 4.54.

EtOH/H_2O (50:50, w/w): Wt = 0.0118 g in 20 mL mixed solvent; Concn = 1.72×10^{-3} M; Average pK_A = 6.07.

Compound 19 EtOH/H_2O (50:50, w/w): Wt = 0.0088 g; F.W. = 680.4; 20 mL EtOH/H_2O (50:50, w/w), NaOH solution 0.1015N; Concn = 6.47×10^{-4} M; pK_1 = 6.4; pK_2 = 7.7.

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