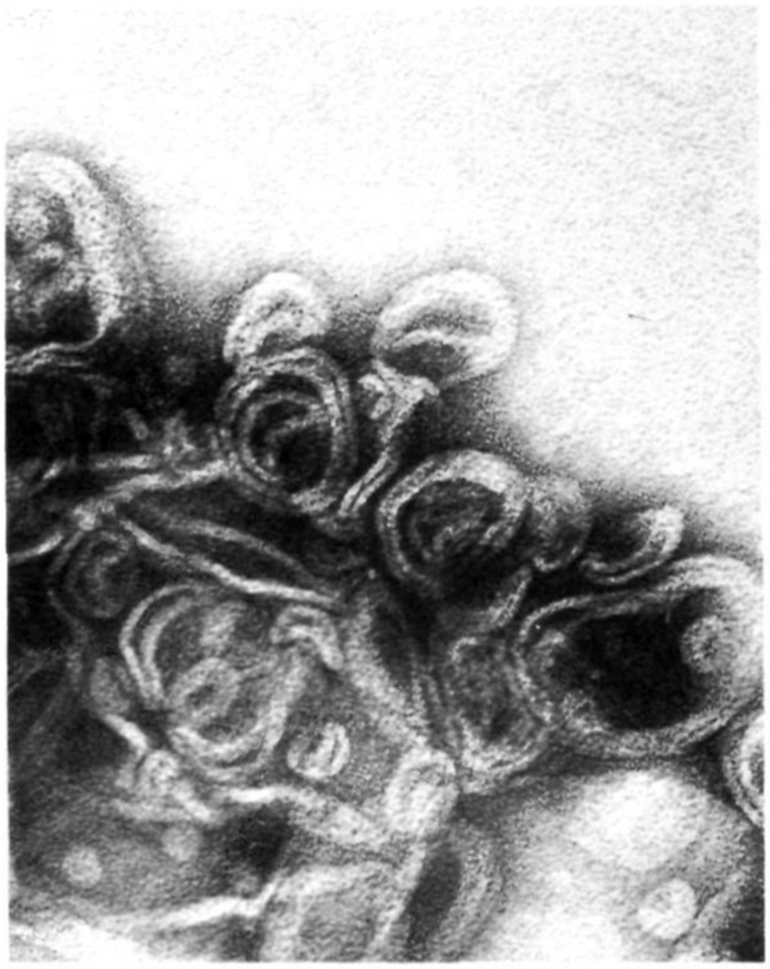

Figure 1. Photoelectromicrograph (76 500 magnification) of vesicles formed from ferrocenylmethyl 3-cholestanyl ether (**6**).

I, and detailed syntheses are provided in the supplementary material.

We anticipated that none of the neutral ferrocene derivatives (**1**–**6**) would show any tendency to aggregate in aqueous solution. Indeed, compounds **2**–**4**, and **6** showed no experimental evidence of aggregation. Tentative evidence for aggregation of **1** and **5** was obtained from light scattering (particle sizes 67 ± 19 nm and 89 ± 23 nm, respectively). Furthermore, definite visual evidence for aggregation of **1** was obtained by electron microscopy, a fact commensurate with a recent report of surface active behavior by **4**.[8] It was anticipated that only oxidation of ferrocene to ferricinium would induce amphiphilicity and prompt aggregation in these systems. Compounds **1**–**5**, when oxidized, afforded roughly spherical particles (EM) that may be vesicles, but the membranes lack definition and other qualities required for a definitive judgment. Dispersions of oxidized **1**–**5** do not scatter light appreciably. The clearest evidence was obtained for **6**, and it is detailed below.

Bulk electrolysis was performed to oxidize **1**–**6** [millimolar concentrations, 25 °C, CH_2Cl_2, 0.1 M tetrabutylammonium perchlorate (TBAP), two-compartment cell, Pt working and counterelectrodes, Ag^0 reference].[9] Potentials for oxidizing the compounds were obtained from cyclic voltammetry experiments. The oxidized species, $\mathbf{6}^+$, was confirmed to be ferricinium by observing the 628-nm visible absorption band. The amount of each oxidized compound was ascertained by using controlled potential electrolysis. About 80% of the ferrocene nuclei were oxidized, and after drying, the vesicles were formed in water (sonication). The vesicles were characterized by dynamic laser light scattering and electron microscopy [$U(OAc)_4$, OsO_4]. Further, the same vesicles were formed when oxidation was done chemically (Ce^{4+}), demonstrating that aggregation is not due to the presence of tetraalkylammonium salt (supporting electrolyte). Once formed, the vesicles were treated with aqueous dithionite solution to reduce Fe^{3+} to Fe^{2+} and thus collapse the aggregates. Compound **6** was isolated (TLC) from this treatment and characterized by mass spectral analysis, demonstrating that the cycle is reversible.

Photoelectromicrographs of vesicles formed from $\mathbf{6}^+$ are shown in Figure 1. On the basis of the magnification scale, it appears that the membrane thickness is about 45 Å. The sizes of these vesicles are obviously not as regular as we found for steroidal lariat ethers,[10] but numerous vesicles of this previously unknown type are clearly in evidence. It is interesting to note that **6** has the smallest redox potential of all of the compounds tested. Thus the observation of vesicles is for the most stable cation in this family. It is also the chemically most stable species, but this is almost certainly a secondary issue. Work is in progress to expand the range of monomers which may produce such aggregates and to explore the dynamics of redox-switched deaggregation.

Acknowledgment. We thank the National Institutes of Health for grants that supported the synthesis (GM 36262) and physical characterization (GM 33940) of these systems. We also gratefully acknowledge helpful discussions with Prof. Angel Kaifer. G.W.G. acknowledges a stimulating seminar presented by R. L. Schowen that led, after discussion with D. Lorenzo, to initiation of these studies.

Supplementary Material Available: Experimental details for the preparation of compounds **1**–**6** and for oxidation and vesicle formation (4 pages). Ordering information is given on any current masthead page.

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[8] (a) Fujihara, M.; Nishiyama, K.; Yamada, H. *Thin Solid Films* **1985**, *132*, 77; *Chem. Abstr.* **1986**, *105*, 106687f. (b) Nakahara, H.; Katoh, T.; Sato, M.; Fukuda, K. *Thin Solid Films* **1988**, *160*, 153.

[9] Detailed experimental conditions are given in the supplementary material.

[10] (a) Echegoyen, L. E.; Hernandez, J. C.; Kaifer, A.; Gokel, G. W.; Echegoyen, L. *J. Chem. Soc., Chem. Commun.* **1988**, 836. (b) Fasoli, H.; Echegoyen, L. E.; Hernandez, J. C.; Gokel, G. W.; Echegoyen, L. *J. Chem. Soc., Chem. Commun.* **1989**, 578.

A Molecular Receptor Based on the Ferrocene System: Selective Complexation Using Atomic Ball Bearings

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Complexation of small molecular species[1-3] has become a dominant theme in organic chemistry during recent years, and nowhere has it been more elegantly demonstrated than in the "molecular cleft" complexing agents of Rebek and co-workers.[4] These workers have stressed the importance of correct functional group orientation and economy of superstructure in achieving complexation. We now report the first alternative family of small molecule complexing agents which incorporate the following novel features. First, the functional groups are incorporated integrally to ferrocene units and are therefore available for complexation on "atomic ball bearings". Second, each ferrocenyl unit has several unused and readily functionalized sites well-oriented for appending a catalytically active group. Third, the inter-ring distance of ferrocene is ~3.2 Å[5] so that a bound aromatic compound, if parallel, should fit tightly face to face with the spacer. Fourth, ferrocene is a redox-active residue,[6] and this makes these receptors potentially even more versatile.

Two successful synthetic approaches were developed. In the first case, two molecules of methyl ferrocenecarboxylate were acylated (Friedel–Crafts method) with a diacyl halide of the form

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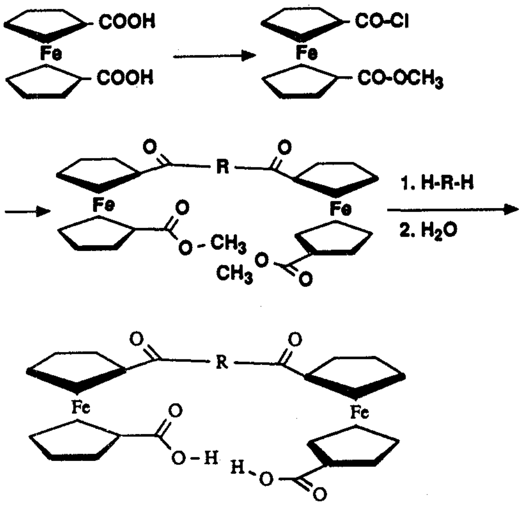
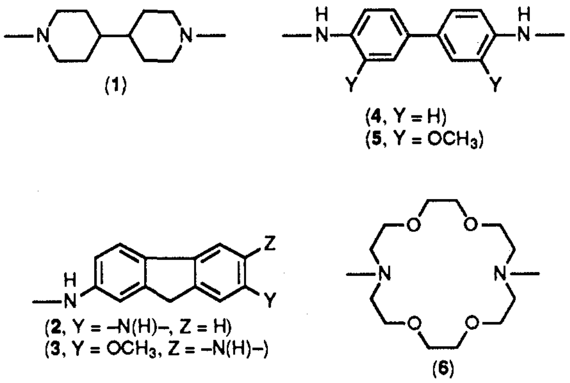
XCORCOX. The compounds reported here, however, were all prepared by the second approach (illustrated herein). Compounds **1**–**6** were obtained as follows: **1**, mp 230 °C dec; **1** diethyl ester for X-ray, mp 181–184 °C; **2**, mp 185–188 °C; **3**, mp 196–200 °C; **4**, mp >440 °C; **5**, mp 171 °C dec; **6**, dimethyl ester, 204–205 °C. Experimental details and complete characterization are provided in the supplementary material. All compounds were fully characterized, and compound **1** was subjected to solid-state structure analysis.[7] The ORTEP plot of the diethyl ester of **1** is shown in Figure 1.



1–6

R designations for **1–6**



Compound **1** (free ligand) is rotated about the bipiperidyl bond to afford the molecule a center of symmetry with the carboxyl groups oriented toward each other but on opposite sides of the saturated spacer. The amide carbonyl groups are nearly coplanar with the ferrocene ring to which they are bound. The estimated cavity size (COOH to COOH) is 7–8 Å, suggesting a good fit for such species as **8** or **9**.

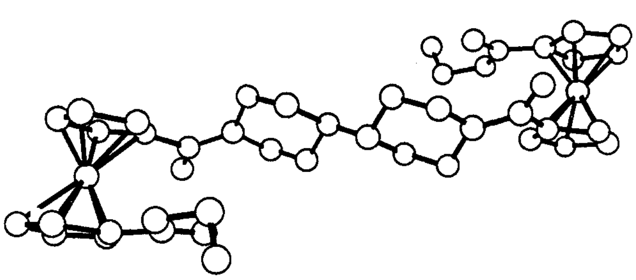
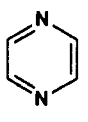


Figure 1. ORTEP plot of **1** as its dimethyl ester.



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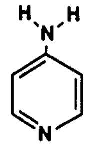

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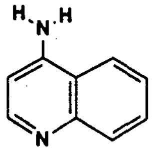

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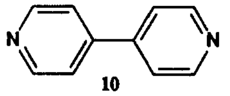

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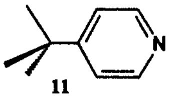

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We expected that both **1** and **3** would bind small molecules selected from among **7**–**11** but that **3** would have the advantage of π-stacking. Unfortunately, differences in solubility prohibit a direct comparison, although the trend is clear. Complexation of **1** in $CDCl_3$ and **3** in THF-d_8 were monitored by 400-MHz ^1H NMR. The flat aromatic surface of **3** was expected to influence and be influenced by appropriately sized guests and the basicity of the amines. The binding constant between **1** and $(CH_3)_2NCH_2CH_2CH_2N(CH_3)_2$ (**12**) ($CDCl_3$) was found to be 431 ± 20 M^{-1}. Binding was determined by using the least-squares method for curve fitting after observation of the proton in italic type (details in supplementary material). The methoxy group of **3** reduced overall molecular symmetry so individual protons could be observed. (The NMR data for **3** are illustrated in the supplementary material.) Compound **3** successfully bound compounds **8** and **9**, but no evidence for binding **7**, **10**, or **11** was obtained. The equilibrium constant for complexation of **8** by **3** in THF-d_8 was determined to be 3200 ± 400 M^{-1} (average of three separate evaluations; see supplementary material). Rebek reported binding constants ($CDCl_3$) for the rigid aromatics pyrazine, quinoxaline, phenazine, and quinazoline with a Kemp triacid/acridine system in the range 700–23000 M^{-1}. The more basic DABCO bound with K_A = 160000.[8]

These novel receptor systems make it structurally possible for an aromatic spacer to be held in an extended π-system and therefore kept planar. The rotational barrier in (unsubstituted) ferrocene is known to be barely more than in ethane so the bottom-ring carboxyl can rotate out of the way to reduce steric hindrance but readily return. Unlike the interesting Kemp acid, several sites on ferrocene can be readily functionalized. When this feature is added to the possibility of altering binding behavior by using redox chemistry, it is seen that the present systems hold considerable promise as a family of molecular receptors having variable properties.

Acknowledgment. We warmly thank the NIH for support of this work through Grant GM-36262 and Prof. Angel Kaifer for insightful and helpful discussions. G.W.G. thanks R. L. Schowen for a stimulating seminar that led, after discussion with D. Lorenzo, to the present study.

Supplementary Material Available: Experimental details for the preparation of **1**–**5** via their dimethyl esters as well as the dimethyl ester of **6** and for complexation studies (10 pages). Ordering information is given on any current masthead page.

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(1) Lehn, J. M. *J. Inclusion Phenom.* **1988**, *6*, 351.

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(5) Ferrocene inter-ring distance in **3** is 3.288 Å.

(6) Medina, J. C.; Gay, I.; Chen, Z.; Echegoyen, L.; Gokel, G. W. *J. Am. Chem. Soc.*, preceding paper in this issue.

(7) Crystal data: $C_{34}H_{36}N_2O_6Fe_2$, FW = 680.36, space group $P2_1/n$, a = 10.204 (1) Å, b = 10.124 (1) Å, c = 16.614 (1) Å, β = 103.204 (7)°, Z = 2, d_{calcd} = 1.469 g·cm^{-1}, Mo Kα (μ = 9.20 cm^{-1}), R = 0.35 for 2113 unique reflections with $I > 3\sigma(I)$ (of 2817 unique data) measured by an Enraf-Nonius CAD4 X-ray spectrometer by ω–2θ scans, 2° < 2θ < 48°.

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