terglycosidic NOE contacts were found for this linkage in D_2O solution.[11]

The presented material proves the existence of a strong intramolecular hydrogen bond involving the OH8 proton of sialic acid residues in aqueous solution, analogous to that found in DMSO solution.[2h] This hydrogen bond is probably the main source of rigidity of the glycerol side chain in sialic acids that has been reported for various sialyl oligosaccharides in different solvents.[15a-e] Thus, we have shown that exchangeable protons of carbohydrates in H_2O can be analyzed by NMR spectroscopy, and that some OH protons serve as long-range sensors in conformational analysis of carbohydrates. Studying OH protons may yield unique information about hydrogen bonding and other three-dimensional structural features such as interproton distances that will add a new dimension to structural studies of complex carbohydrates in aqueous solution.

Acknowledgment. This research was supported by NIH Grants P41-RR-05351 and P01-AI-27135.

---

(15) (a) Brown, E. B.; Brey, W. S.; Weltner, W. *Biochim. Biophys. Acta* **1975**, *399*, 124-130. (b) Christian, R.; Schultz, G.; Brandstetter, H. H.; Zbiral, E. *Carbohydr. Res.* **1987**, *162*, 1-11. (c) Czarniecki, M. F.; Thornton, E. R. *J. Am. Chem. Soc.* **1977**, *99*, 8273-8279. (d) Poppe, L.; Dabrowski, J.; Von der Lieth, C. W.; Numata, M.; Ogawa, T. *Eur. J. Biochem.* **1989**, *180*, 337-342. (e) Sabesan, S.; Bock, K.; Lemieux, R. U. *Can. J. Chem.* **1984**, *62*, 1034-1045.

Redox-Switched Molecular Aggregates: The First Example of Vesicle Formation from Hydrophobic Ferrocene Derivatives

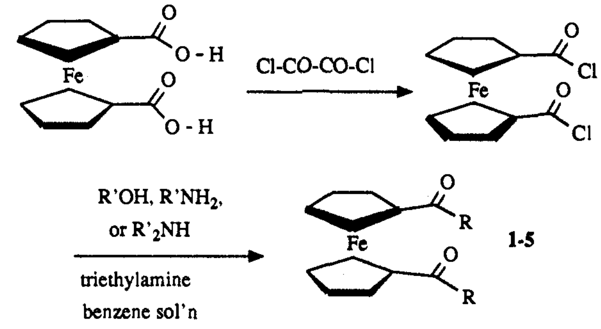
Julio C. Medina, Isabelle Gay, Zhihong Chen,
Luis Echegoyen,* and George W. Gokel*

Department of Chemistry, University of Miami
Coral Gables, Florida 33124

Received May 2, 1990
Revised Manuscript Received October 15, 1990

Ferrocene is a remarkable organometallic compound in many respects. Although containing an integral metal, formally in the Fe(II) state, it dissolves readily in hydrocarbon solvents such as hexane and must be considered extremely nonpolar. Our interest in redox-switched systems[1] led us to consider the ferrocene system as a neutral-cation redox pair that is an alternative to the nitrobenzene and anthraquinone neutral-anion redox pairs we have studied extensively. We are not the first to recognize the potential of ferrocene for its use either in switchable complexation or in molecular aggregation. Hall and co-workers,[2] Beer and co-workers,[3] and Saji and co-workers[4] have made several cation complexing agents based on compounds containing one or more ferrocene nuclei. Saji[5] has recently demonstrated that certain ferricinium salts aggregate into micelles. We report here a novel class of ferrocenyl steroids and present the first evidence for aggregation of these systems and particularly for vesicle formation controlled by redox-switched ferrocene amphiphiles.

Scheme I



Scheme II

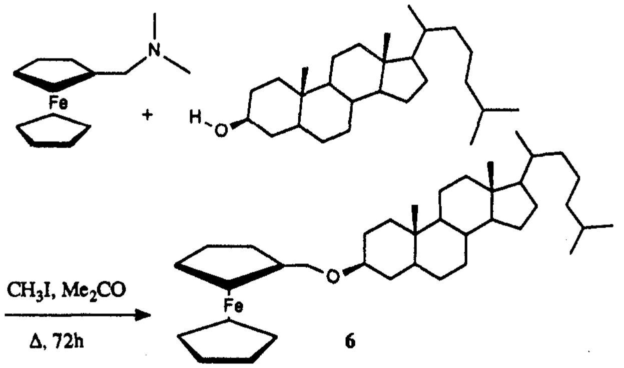


Table I. Ferrocenyl-Derived Amphiphile Precursors[a]

compd no.	substituent site	substituent identity	yield, %	$[\alpha]_D$[b]	mp, °C	$E°_{1/2}$,[c] mV
1	1,1′	$COOC_{17}H_{35}$	69		65-67	972
2	1,1′	COO-dihydrocholesteryl	27	24.4	287-291	941
3	1,1′	COO-cholesteryl	45	−0.44	267-269	945
4	1,1′	$CONHC_{18}H_{37}$[d]	64		105-107	806
5	1,1′	$CON(C_{18}H_{37})_2$	77		32-34	711
6	1	CH_2O-dihydrocholesteryl	7	11.8	134-136	509

[a] All structures are new compounds and had combustion analyses within ±0.4% of theory for C and H as well as IR, NMR, and mass spectra (see supplementary material) in accord with their assigned structures. [b] In CH_2Cl_2, $c = 1-4$. [c] Determined vs Ag/AgCl in CH_2Cl_2. [d] Reference 8.

Synthesis of the ferrocenyl amphiphiles was accomplished by two approaches shown herein as Schemes I and II. Compounds **1-5** were prepared by heating, under reflux (6 h), commercially available (Aldrich) 1,1′-ferrocenedicarboxylic acid with oxalyl chloride and a catalytic amount (1.1%) of pyridine and then treating the dichloride (52%, mp 92-94 °C) with the alcohol or amine in benzene solution containing triethylamine. The ester and amide derivatives were obtained according to Scheme I as follows: **1**, R = $OC_{17}H_{35}$, 69%; **2**, R = *O*-cholestanyl, 27%, **3**, R = *O*-cholesteryl, 45%; **4**, R = $NHC_{18}H_{37}$, 64%; and **5**, R = $N(C_{18}H_{37})_2$, 77%.

Compound **6** was prepared by treating [(dimethylamino)-methyl]ferrocene with dihydrocholesterol (cholestanol) in the presence of methyl iodide and acetone[6] as shown in Scheme II. Methyl iodide induces the Menschutkin reaction[7] followed by carbocation formation and alcoholysis to give the product shown in 7% yield. The syntheses and physical properties of compounds **1-6** (including **4**, previously reported[8]) are summarized in Table

---

* Address correspondence concerning design and synthesis to G.W.G. and concerning aggregate formation and characterization to L.E.

(1) (a) Kaifer, A.; Echegoyen, L.; Gustowski, D.; Goli, D. M.; Gokel, G. W. *J. Am. Chem. Soc.* **1983**, *105*, 7168. (b) Gustowski, D. A.; Echegoyen, L.; Goli, D. M.; Kaifer, A.; Schultz, R. A.; Gokel, G. W. *J. Am. Chem. Soc.* **1984**, *106*, 1633. (c) Gustowski, D. A.; Gatto, V. J.; Kaifer, A.; Echegoyen, L.; Godt, R. E.; Gokel, G. W. *J. Chem. Soc., Chem. Commun.* **1984**, 923. (d) Kaifer, A.; Gustowski, D. A.; Echegoyen, L.; Gatto, V. J.; Schultz, R. A.; Cleary, T. P.; Morgan, C. R.; Rios, A. M.; Gokel, G. W. *J. Am. Chem. Soc.* **1985**, *107*, 1958. (e) Delgado, M.; Echegoyen, L.; Gatto, V. J.; Gustowski, D. A.; Gokel, G. W. *J. Am. Chem. Soc.* **1986**, *108*, 4135. (f) Echegoyen, L.; Gustowski, D. A.; Gatto, V. J.; Gokel, G. W. *J. Chem. Soc., Chem. Commun.* **1986**, 220. (g) Echeverria, L.; Delgado, M.; Gatto, V. J.; Gokel, G. W.; Echegoyen, L. *J. Am. Chem. Soc.* **1986**, *108*, 6825. (h) Echegoyen, L. E.; Yoo, H. K.; Gatto, V. J.; Gokel, G. W.; Echegoyen, L. *J. Am. Chem. Soc.* **1989**, *111*, 2440.

(2) Hall, C. D.; Sharpe, N. W.; Danks, I. P.; Sang, Y. P. *J. Chem. Soc., Chem. Commun.* **1989**, 417.

(3) (a) Beer, P. D.; Bush, C. D.; Hamor, T. A. *J. Organomet. Chem.* **1988**, *339*, 133. (b) Beer, P. D.; Sikanyika, H.; Blackburn, C.; McAleer, J. F. *J. Orgnanomet. Chem.* **1988**, *350*, C15. (c) Beer, P. D.; Blackburn, C.; McAleer, J. F.; Sikanyika, H. *Inorg. Chem.* **1990**, *29*, 378.

(4) Saji, T.; Kinoshita, I. *J. Chem. Soc., Chem. Commun.* **1986**, 716.

(5) Saji, T.; Hoshino, K.; Aoyagui, S. *J. Chem. Soc., Chem. Commun.* **1985**, 865.

(6) Gokel, G. W.; Marquarding, D.; Ugi, I. K. *J. Org. Chem.* **1972**, *37*, 3052.

(7) Takayama, C.; Fujita, T.; Nakajima, M. *J. Org. Chem.* **1979**, *44*, 2871.

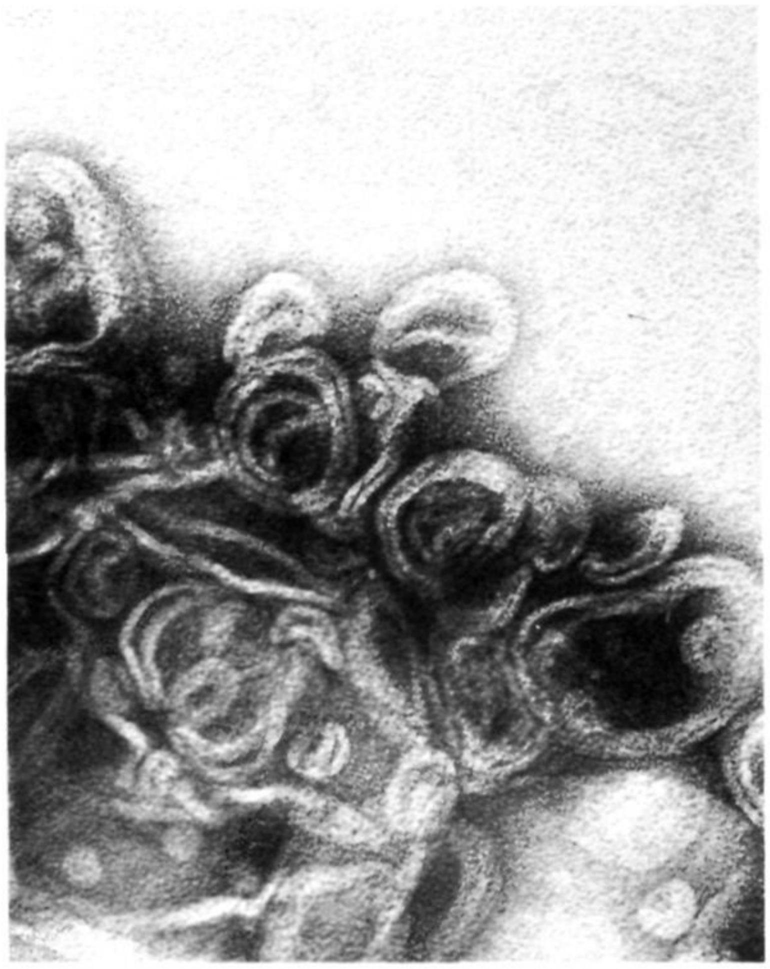


Figure 1. Photoelectromicrograph (76 500 magnification) of vesicles formed from ferrocenylmethyl 3-cholestanyl ether (**6**).

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.

---

[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

Julio C. Medina,[†] Chensheng Li,[†] Simon G. Bott,[‡]
Jerry L. Atwood,[‡] and George W. Gokel*[,†]

Department of Chemistry, University of Miami
Coral Gables, Florida 33124
University of Alabama, Tuscaloosa, Alabama 34567

Received August 6, 1990

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

---

[†] University of Miami.

[‡] University of Alabama.