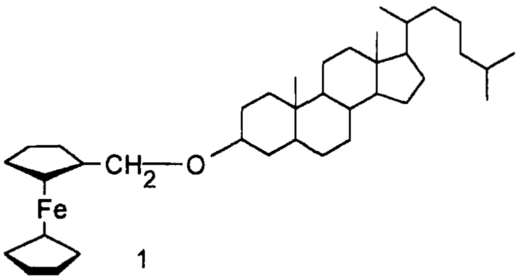
Redox-Switched Vesicle Formation from Two Novel, Structurally Distinct Metalloamphiphiles

Servando Muñoz and George W. Gokel*

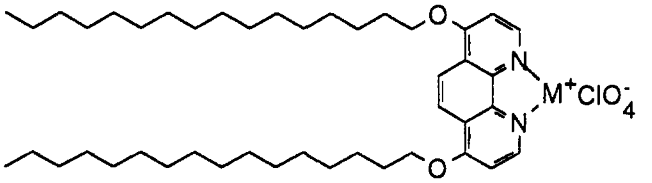
Department of Chemistry
University of Miami
Coral Gables, Florida 33124

Received February 19, 1993

The concept of redox-switched aggregate formation has proved intriguing, but to date,[1-6] the unique example of such vesicle formation involved a steroidal ferrocene (**1**) as the amphiphile.[7] In the latter case, oxidation of ferrocene from iron(II) to iron(III) converted a structure containing both a nonpolar headgroup (ferrocene) and tail (steroid) to an amphiphile (steroidal ferrocenium cation). Sonication of a dilute aqueous solution of Fc^+–CH_2O-3-cholestanyl led to multilamellar vesicles that were characterized by light scattering and electron microscopy. Reduction by chemical ($Na_2S_2O_4$, $NaBH_4$) means converted the ferrocenium cation to ferrocene, and the vesicles collapsed. We now report two metalloamphiphiles, **2** and **3**, that are structurally unrelated either to each other or to **1**, that afford redox-switched vesicles, demonstrating that the phenomenon is general.



1



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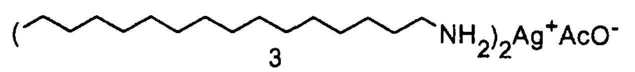
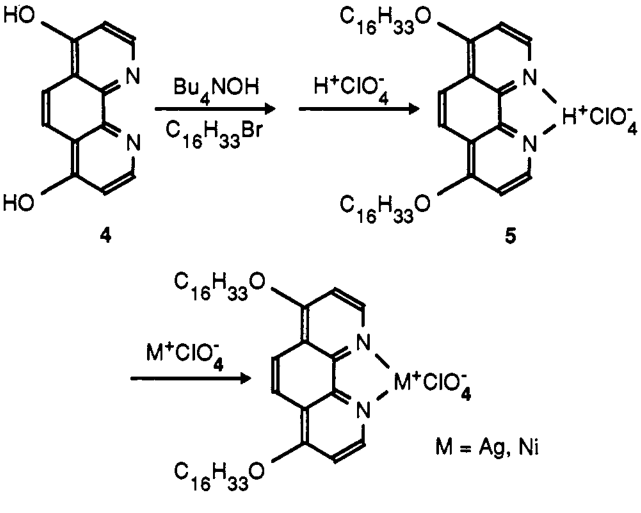


3

Commercially available, crude 4,7-dihydroxy-1,10-phenanthroline (**4**) was heated in refluxing THF with 2 equiv each of $C_{16}H_{33}Br$ and $(n\text{-Bu})_4NOH$ for 20 h followed by precipitation with $HClO_4$ from EtOH to afford 4,7-bis(hexadecyloxy)-1,10-phenanthrolinium perchlorate, **5**·$HClO_4$. The crude material was purified by Soxhlet extraction using hexane and then chloroform, chromatography over alumina (free base, eluant 5% MeOH in $CHCl_3$), and three crystallizations (1:1 EtOH/$CHCl_3$, EtOH, 1:1 EtOH/hexane) to give **5**·$HClO_4$ as a white solid (30%), mp 163–165 °C. The corresponding nickel and silver complexes were prepared by dropwise addition of **5** in anhydrous EtOH to an excess (60:1 $MClO_4$/**5**) of the metal perchlorate in the same solvent. The nickel and silver complexes of **5** were both isolated in quantitative yield, the former as a green solid and the latter as colorless crystals (Scheme I).

Scheme I



Vesicles of either the Ag(I) or Ni(II) complex of **5** (1×10^{-4} M) were prepared[8] according to the reverse phase evaporation protocol of Szoka and Papahadjopoulos.[9] The resulting suspension of heterogeneous, multilamellar vesicles was homogenized in a bath sonicator for 30 min at 10 °C. Dynamic light-scattering measurements indicated the presence of large, probably unilamellar vesicles whose hydrodynamic diameter measured approximately 1500 Å. When a 10^{-5} M aqueous solution of **5**·$Ni(ClO_4)_2$·$4H_2O$ in 0.010 M tris-HCl buffer at pH 8.0 was reduced, the vesicles collapsed completely. This dramatic demonstration of redox-switching was achieved as follows. When vesicles derived from **5**·$Ni(ClO_4)_2$·$4H_2O$ (as described above) were treated with a 5×10^{-4} M solution of Na_2SO_4 (a salt but not a reducing agent) in water, no effect on the vesicles was detected. Although, practically speaking, the high dilution under which this and the following experiment were conducted should have precluded simple osmotic lysis or electrolyte-induced flocculation, we felt the confirmation was useful. Thus, when an identical experiment was conducted in which $Na_2S_2O_4$ (a reducing agent) was substituted for Na_2SO_4, no residual vesicles could be detected by light-scattering methods, indicating complete collapse of the organized assemblies.

Reduction of transition metal complexes of 1,10-phenanthroline involves either a metal- or ligand-centered orbital, according to the energy separation between the d* and π^* acceptor orbitals.[10]

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(2) Beer, P. D.; Bush, C. D.; Hamor, T. A. *J. Organomet. Chem.* **1988**, *339*, 133.

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

(7) Medina, J. C.; Gay, I.; Chen, Z.; Echegoyen, L.; Gokel, G. W. *J. Am. Chem. Soc.* **1991**, *113*, 365–366.

(8) The procedure used for the formation of large unilamellar vesicles was similar to that described by Szoka and Papahadjopoulos. A 5-mL round-bottomed flask was charged with a solution containing 10 mg of the surfactant monomer in 3.0 mL of $CHCl_3$ and 1.0 mL of 0.010 M tris(hydroxymethyl)-aminomethane hydrochloride buffer at pH 8.0. The resulting two-phase system was dispersed for 5 min at 10 °C using a bath sonicator to produce a homogeneous emulsion. After the $CHCl_3$ was removed *in vacuo*, the heterogeneous suspension of multilamellar vesicles was transferred to a 25-mL volumetric flask, diluted to the mark using the aqueous buffer, and further sonicated for 30 min at 10 °C to produce a homogeneous, hazy suspension of metalloamphisomes. The analyte for dynamic light scattering was obtained by dissolving 200 μL of the stock vesicle suspension in 3.00 mL of tris buffer.

(9) Szoka, F.; Papahadjopoulos, D. *Proc. Natl. Acad. Sci. U.S.A.* **1978**, *75*, 4194.

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Ordinarily, reduction occurs at the ligand rather than at the metal center. One or, possibly, two electrons can be delocalized across the polyheteroaromatic matrix, as shown below. Two-electron reduction gives an intramolecular ion pair of inherently low charge density. Reduction of the hydrophilic headgroups diminishes or eliminates monomer amphiphilicity and ultimately deaggregates the assemblies.

$$\mathrm{Ni^{2+}(Phen)^0 + e \rightarrow [Ni^{2+}(Phen)^-]^+ + e \rightarrow [Ni^{2+}(Phen)^{2-}]^0}$$

The second molecular system capable of redox switching that we have developed is a silver diamine complex, **3**. Thus, bis(hexadecylamine)silver nitrate was converted, for solubility reasons, to the corresponding acetate, $[CH_3(CH_2)_{15}NH_2]_2Ag^+AcO^-$, **3**. Dispersion (2 mM surfactant concentration) in water using a bath sonicator for 15 min at 40 °C afforded vesicles of diameter $\approx$2300 Å (light scattering). The surfactant in this case is a silver diamine complex, and upon addition of 10^{-2} M formalin solution at pH 10, they gave the classic Tollens reaction[11] in which Ag^+ is reduced to Ag^0 and formaldehyde is oxidized to formate. Loss of silver cation from the aggregate monomer and conversion to silver metal leads to irreversible collapse of the metalloamphisomes with concomitant coating of the reaction vessel by a fine silver film (silver mirror).

The two methods described differ in that reduction of the nickel(II) phenanthroline surfactant is potentially reversible while loss of silver as a metallic mirror is not. In principle, however, addition of fresh Ag^+ could regenerate the surfactant, and/or addition of an agent that could oxidize silver but not the amine could lead again, after sonication, to vesicles.

We have now demonstrated that ferrocenyl-steroid-based, redox-switched vesicle formation is not a chemical curiosity but rather the prototype of a new class of aggregates that can readily be returned to the monomeric state by judicious application of an appropriate chemical reagent. The three examples disclosed so far all rely on reduction as the "collapse switch", but oxidation of a neutral or anionic head group should, in principle, be equivalent and functional. Studies to confirm this are underway.

Acknowledgment. We thank the NIH for a grant (GM 36262) that supported this work.

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