value is in accord with an experimentally determined upper limit of 45 kcal mol^{-1} reported by Kant and Moon[20] and a theoretical value of 46 kcal mol^{-1} calculated by Das.[21]

By use of the technique described above, Fe^-, Co^-, Mo^-, and W^- also have been generated in our laboratory and are presently under investigation. The details of their preparation and their gas-phase reactivity will be reported in forthcoming publications.

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Registry No. $Cr(CO)_5^-$, 51222-95-8; Cr^-, 19498-56-7; CF_3COOH, 76-05-1; PhSH, 108-98-5; $Cr(CO)_6$, 13007-92-6; dimedone, 126-81-8.

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Polymerized–Depolymerized Vesicles. A Reversible Phosphatidylcholine-Based Membrane[1]

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In this communication we report the synthesis and preliminary characterization of a phospholipid vesicle membrane that can be "switched on" (polymerized) and "switched off" (depolymerized) via oxidation and reduction, respectively. This membrane is based on the thiol-bearing lipid 1,2-bis(11-mercaptoundecanoyl)-*sn*-glycero-3-phosphocholine (**2**) whose synthesis is also described herein.

Polymerized forms of phospholipid bilayer vesicles represent a new and unique class of organic polymers that may find broad use as models for biological membranes and as carriers of drugs.[3-9] They have a close similarity to conventional liposomes in terms of their gross morphology, entrapment ability, permeability, and membrane structure but are substantially more stable. If polymerized vesicles could be depolymerized, in a reversible manner, their utility as a membrane model would be significantly increased. Biochemical studies could then be carried out either in the "on" (polymerized) or "off" (nonpolymerized) mode; they could also be conducted during or between a series of "on–off" cycles. In the "on" position, lateral diffusion within the membrane (a parameter of central importance to many biomembrane problems) should be greatly reduced or eliminated. Moreover, the ability to depolymerize a vesicle network would allow one to take apart and recover key components, e.g., membrane proteins.[10] Polymerized vesicles that are susceptible to depolymerization in vivo might also be ideally suited as time-release carriers of drugs. Motivated by these ideas and by the intriguing structural features expected for an ordered network of monomers capable of reversible polymerization, we have begun to focus our efforts on the synthesis of polymerizable–depolymerizable vesicles. In the following report we present preliminary results obtained with the first representative example, a phosphatidylcholine-based membrane, whose reversibility derives from a thiol–disulfide redox cycle.[11]

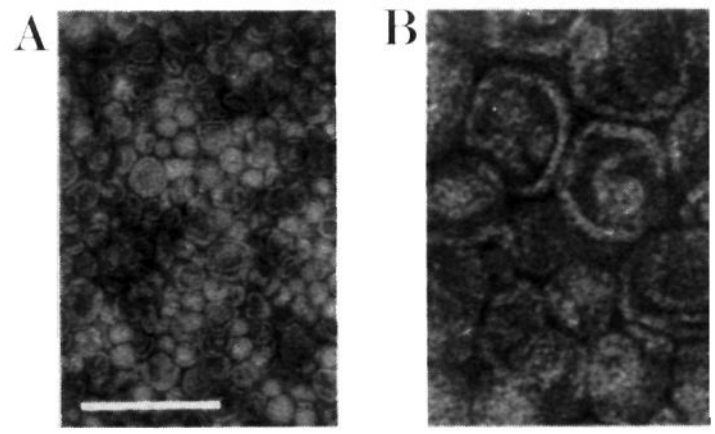
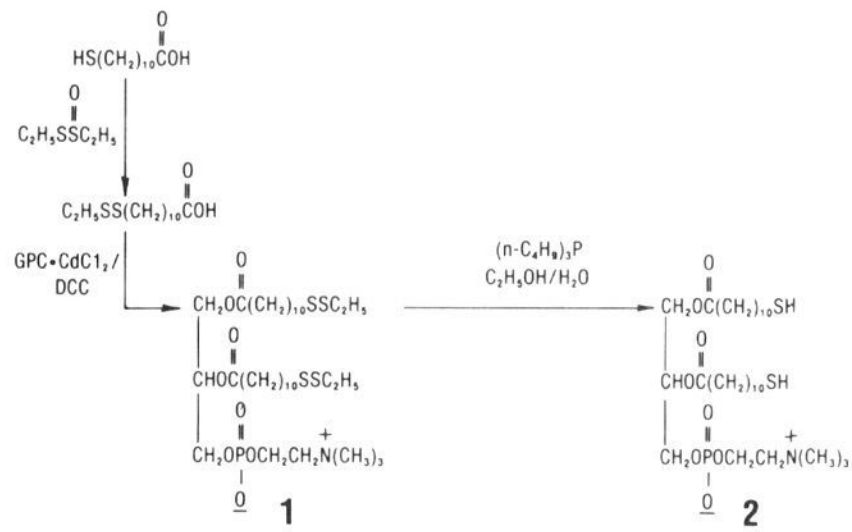


Figure 1. Electron micrographs of UV-polymerized vesicles of **2**. Bar represents 2000 Å; (B) is a 3.9 × magnification of (A).

Scheme I



The synthetic route used for the preparation of **2** is outlined in Scheme I. Oxidation of 11-mercaptoundecanoic acid with ethyl ethanethiosulfinate in chloroform produced an 80% isolated yield of 11-ethyldithioundecanoic acid;[12-14] subsequent esterification with *sn*-glycero-3-phosphocholine–$CdCl_2$ (GPC·$CdCl_2$) furnished a 91% isolated yield of 1,2-bis(11-(ethyldithio)undecanoyl)-*sn*-glycero-3-phosphocholine (**1**). Treatment of **1** in C_2H_5OH–H_2O (1/1) with tri-*n*-butylphosphine afforded a 95% isolated yield of **2**.[15,16]

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Vesicles derived from **2** were prepared by (a) coating the lipid onto the walls of a round-bottomed flask (chloroform evaporation), (b) dispersing the lipid into distilled water (vortex mixing), and (c) irradiating the dispersion with ultrasound at 50 °C under a nitrogen atmosphere to constant turbidity (Heat Systems Model W-375 R bath-type sonicator operating at 275 W). Thin-layer chromatography of the resulting dispersion indicated that no lipid decomposition occurred during the sonication process (R_f = 0.22).[14]

Vesicle polymerization (disulfide formation) was carried out either by direct UV irradiation at 254 nm (30–60 min) or by oxidation with excess H_2O_2 at 40 °C (20 equiv, 3 h).[17-19] In the former case, thin-layer chromatrography indicated the complete disappearance of **2** and a single lipid spot at the origin (R_f = 0). Quantitative analysis for thiol groups using 5,5′-dithiobis(2-nitrobenzoic acid) (Ellman's Reagent) revealed a 95% loss after 0.5 h of irradiation.[20] Electron micrographs recorded on a Philips 400 TEM microscope, using 2% uranyl acetate as a staining agent, confirmed the presence of closed vesicles having diameters ranging between 200 and 800 Å (Figure 1). The estimated thickness of the vesicle membrane is 40–50 Å, which is consistent with the bilayer thickness found in other unilamellar liposomes.[21] With hydrogen peroxide oxidation (pH 7), the starting material was apparently converted to an oligomerized vesicle, whose components had an R_f equaling 0.08 (broad spot); thiol analysis of the product showed that the extent of oxidiation was ca. 55%. Similar hydrogen peroxide mediated oxidation carried out at pH 8.5 produced polymerized vesicles having an R_f equaling 0 and showing a 95% decrease in thiol content.

In contrast to their nonpolymerized analogues, which precipitate on standing within 48 h, photopolymerized vesicles of **2** showed no detectable change in turbidity after 10 days. Improved stability of these polymerized vesicles was further demonstrated by their response to exposure to strong ionic detergent. Thus, addition of 0.16% sodium dodecylsulfate to nonpolymerized and photopolymerized (1 h) dispersions of **2** resulted in an 82% and 12% loss in turbidity, respectively. By using procedures similar to those previously described,[3] photopolymerized vesicles of **2** entrapped ca. 0.02% of [^{14}C]sucrose and retained 75% and 60% of the marker when subjected to dialysis for 2 and 4 h, respectively. Nonpolymerized vesicles of **2** had similar entrapment and retained 54% of the sucrose after 2 h and 46% after 4 h.

Preliminary evidence for substantial reversibility of polymerized **2** has been obtained via reductive regeneration of the lipid monomer. Thus, treatment of freeze-dried, UV or H_2O_2 (pH 8.5) polymerized dispersions of **2** with 40 equiv of tri-*n*-butylphosphine in C_2H_5OH–H_2O (5/1) for 18 h at 40 °C followed by quantitative TLC (phosphorus analysis) indicated at 90% regeneration of **2** (R_f 0.22). Direct reduction of the *aqueous vesicle dispersion* of photopolymerized **2** with 200 equiv of dithiothreitol (50 °C, 3 h) liberated 25% of **2** (quantitative TLC). The turbidity of the resulting dispersion remained unchanged under these conditions, and electron microscopy confirmed the retention of the vesicle structure. Similar reduction of the H_2O_2-polymerized dispersion of **2** regenerated ca. 70% of the monomer; the turbidity of the dispersion was unaltered.

Efforts now underway are aimed at (1) optimizing vesicle oxidation and reduction using chemical, photochemical, and electrochemical means, (2) determining the degree of polymerization within the membrane, (3) synthesizing cross-linked polymerized phosphatidylcholine vesicles based on disulfide formation, and (4) examining the potential utility of this new class of vesicles as membrane models and as drug carriers. Complete details of these studies will be reported in due course.

Registry No. 1, 87050-14-4; **2**, 87050-11-1; **2** homopolymer, 87050-12-2; $C_2H_5SS(CH_2)_{10}C(O)OH$, 87050-15-5; *sn*-glycerol-3-phosphochlorine, 28319-77-9.

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Organometallic Crown Ethers. 1. Metal Acyl Binding to a Crown Ether Held Cation

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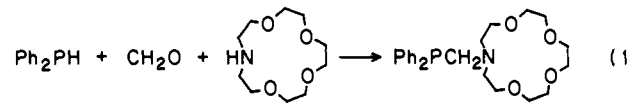
Lewis acids can accelerate alkyl migration to coordinated carbon monoxide by stabilizing the transition state leading to the acyl product.[1] As a means of holding Lewis acidic cations close to transition metals, we have prepared a phosphine functionalized aza crown ether. We now report the binding of a transition-metal acyl ligand to various crown ether held alkali-metal and alkaline-earth cations.[2]

By use of a modification of the Mannich reaction,[5] the combination of diphenylphosphine and monoaza-15-crown-5 with aqueous formaldehyde produces the phosphine aza crown ether **1** as a pure, colorless, air-sensitive oil (reaction 1).[6,7]



(1)

1

1 reacts with $CpFe(CO)_2Me$ (Cp = η^5-C_5H_5) thermally[8] to give the acyl complex **2a** and photochemically[9] to give the methyl

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(2) The earliest reported organometallic crown ethers[3] showed no evidence of interaction between the crown ether held cations and the transition metals. While our work was in progress, J. Powell et al. reported the syntheses of two aminophosphine ligands similar to ours[4a] and the syntheses of *anionic* metal acyl complexes in which the Li^+ counterion is bound to a chelating phosphinite ligand with crown ether properties.[4b,c]

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