

Cryptand-based metal-free or complexed amphiphiles which readily form vesicles

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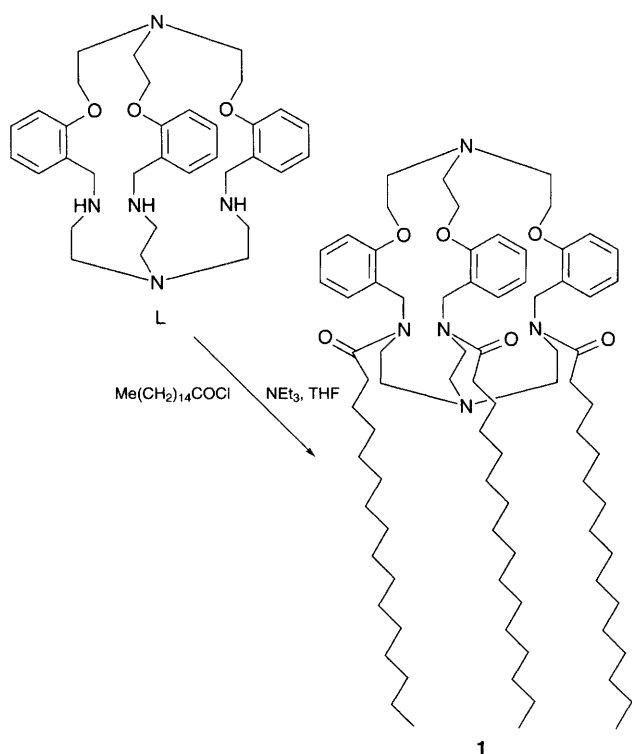
A heteroditopic cryptand with three palmitoyl side groups, both as the free ligand and as its copper complex, acts as an amphiphile and readily forms unilamellar vesicles.

Vesicles made with synthetic amphiphiles are of considerable current interest in view of their use as model systems for membrane structure¹ and functional² studies. In addition, such systems are useful in drug delivery and targeting,³ medical imaging,⁴ catalysis,⁵ energy conversion⁶ and separation.⁷ We report here the first cryptand-based amphiphile composed of three hydrocarbon tails and three head groups in the host molecule with a suitable cavity to entrap transition-metal ions or organic molecular guests; this, both in its free form and as its copper(II) complex, readily forms vesicles. In recent years, synthetic vesicles have been reported with different chemical structures and composition of hydrophilic headgroup and hydrophobic tail(s). Examples include single tail surfactants with large rigid segments,^{8,9} a surfactant with a hyperextended chain,¹⁰ a two-headed single-chain surfactant,¹¹ two-headed two-tail surfactants,¹² and surfactants with identical hydrophobic chains and two hydrophilic headgroups connected through a spacer.¹³ Our cryptand-based amphiphile can be regarded as a new generation of surfactant. The chemical structure of amphiphiles largely influences the physical and functional properties of the vesicles¹⁴ formed from them. Vesicles formed with more than one hydrophobic chains are more efficient in lowering oil–water interfacial tension com-

pared to the more common single-chain systems. Other than their potential uses as vehicles for drug delivery or as anthelmintic agents,¹⁵ cryptand-based vesicles have certain unique features such as a preorganized cavity that can trap a metal ion and/or a small molecule. Hence, they can also serve as potential catalysts (functional aggregates¹⁶).

Compound **1** was synthesized (Scheme 1) by treating the cryptand **L** (ref. 17) with palmitoyl chloride in dry THF in the presence of NEt₃ as base under an argon atmosphere. The isolated pale yellow solid was purified by recrystallization from ethanol.† The copper(II) salt was isolated when copper(II) perchlorate hexahydrate was treated with **1** in ethanol. The coordination of Cu^{II} within the cryptand cavity was established by its EPR and electronic spectral characteristics which match closely those obtained for the well characterized underivatized cryptand complex [CuL][ClO₄]₂.¹⁸

To form vesicles, a solution of the amphiphile (1 mmol dm⁻³) in ethanol was injected into a buffer solution [tris-



Scheme 1

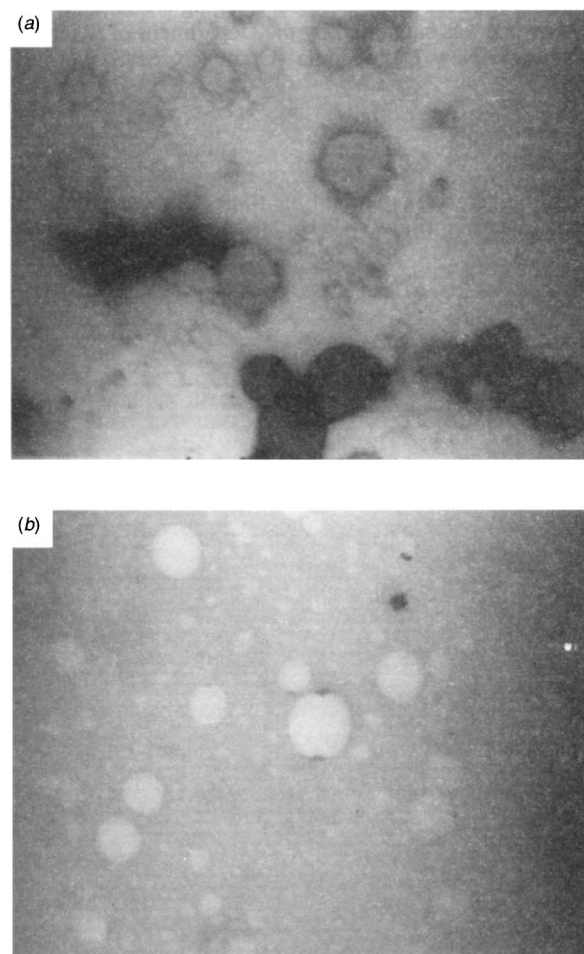


Fig. 1 Negative-stain transmission electron micrographs of vesicles of **1a** (magnification 15000×) and **1b** (magnification 12000×)

HCl, histidine (50 mmol dm⁻³), NaCl, pH 7.4]. Due to reverse-phase hydration in ethanol, the amphiphile molecules form multilamellar vesicles. This multilamellar vesicular suspension was extruded through a polycarbonate membrane of porosity 0.1 µm at a constant temperature of 30 °C. After 5 cycles of extrusion, unilamellar vesicles of almost equal size were obtained (**1a**). The corresponding copper(II) perchlorate salt of the amphiphile also afforded unilamellar vesicles (**1b**) when treated in a similar manner.

The vesicles were characterized by negatively stained (0.5% uranyl acetate) micrographs taken on a JEOL TEM-2000F instrument operating at 30 kV (Fig. 1). The average diameter of the vesicles was approximately 350 nm for the free (**1a**) and 450 nm for the Cu^{II}-bound (**1b**) vesicles. Vesicle dispersions of the free or the Cu^{II}-bound amphiphiles when dried on a glass plate *in vacuo* gave a cast film which was examined by X-ray powder diffraction. The diffraction pattern displayed four peaks (2θ values) at 10.6, 21.3, 31.7 and 45.5° for **1a** and at 10.8, 21.6, 32.2, 45.4 for **1b**. For **1b**, two additional minor peaks appeared at 2θ 15.4 and 40.8°. Gel filtration of aqueous vesicular dispersions of both **1a** and **1b** through a Sephadex G-50 (Pharmacia) column led to ≈ 75% recovery and the profile was sharp in each case. Extruded vesicular dispersions of either **1a** or **1b** in water gave a turbid solution which was optically stable for weeks as judged by the measurement of turbidity at 400 nm. In osmotic gradient experiments, the vesicles were found to be stable for more than 15 days in 100 mmol dm⁻³ sucrose–NaCl medium as the turbidity at 400 nm did not change to any noticeable extent in either case.

In summary, we have shown that vesicular structures are possible with a cryptand/Cu^{II}-cryptate connected to three palmitoyl chains. Synthesis of suitable cryptand hosts to entrap lanthanide ions for use in medical imaging are in progress.

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Footnote

† IR (KBr pellet) 1645s (br) cm⁻¹; ¹H NMR (400 MHz, CDCl₃, 25 °C, SiMe₄): δ 1.2 (m, 87 H), 1.95 (t, 6 H), 2.6 (br s, 6 H), 2.95 (br s, 6 H), 3.5

(br s, 6 H), 4.2 (s, 6 H), 4.95 (br s, 6 H), 7.1 (m, 12 H); mp 60 °C; FAB-MS *m/z* 1275 1⁺ (100%); satisfactory elemental analysis (C, H, N) for C₈₁H₁₃₅N₅O₆.

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