Communications to the Editor

Metalization of Lipid Vesicles via Electroless Plating

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The encapsulation of metallic particles and metallic oxides within lipid vesicles has recently been of interest for applications such as catalysis,[1] water splitting,[2] and magnetic control of spin coupling.[3] In this communication we introduce the concept and practice of the deposition of metal on vesicles by using electroless plating techniques.[4,5] Coordination of low valent transition metals to organic functional groups on the surface of the bilayer membrane provides a means of binding metal atoms to vesicles. Chemical reduction produced zero valent atoms which serve as sites for further metal deposition by the chemical reduction techniques of electroless plating. Specifically, this procedure involved the binding of a small amount of tetrachloropalladate to the vesicle bilayer, reduction of the palladium(II) to palladium(0), followed by the deposition of much larger amounts of metal from an electroless plating solution. Electroless plating solutions were used for the deposition of palladium,[6] nickel, cobalt, or copper[7] metal onto the catalytic palladium centers. Since the metallic particles were associated with the vesicles, colloids were formed that were stable in water for much longer periods than the control metal particles formed in water alone. If the vesicles were composed in part of unsaturated lipids, with the olefinic groups on the hydrocarbon chains, the initial evidence suggests the transition metal was directed into the bilayer, rather than staying on the surface. The initial evidence for metal deposition into the bilayer included the observation of an induction period before plating initiated and electron scattering for chemical analysis (ESCA) spectroscopy.

All of the vesicles in this work were prepared by hydration of the desired lipid mixture at a temperature above the lipid phase transition temperature (T_c), followed by sonication $(>T_c)$ of the bilayers to form vesicles.[8] The vesicles prepared ranged in di-

ameter from 500 to 2500 Å and were generally unilamellar.

Nucleation sites were formed by treating previously prepared vesicles, e.g., DMPC/DODAB, 0.3 mL (8.4 μmol/0.5 μmol), with 10 mM sodium tetrachloropalladate, 0.010 mL (0.1 μmol). No change was observed in the appearance of the vesicles. The sample was then reduced with 0.5% dimethylamine–borane (DMAB), 0.10 mL, and the previously white dispersion of vesicles immediately became light brown. A control sample of sodium tetra-chloropalladate in water becomes light gray when treated with dimethylamine–borane. If the vesicles were to be metalized with palladium metal, the vesicles with palladium were then treated with a palladium electroless plating bath,[6] 0.5 mL. The sample began to effervesce and turn black, and the metal remained dispersed throughout the sample, whereas the control without vesicles was a precipitate. Following this general procedure, metalized vesicles of DMPC/DODAB:Pd, Ni, Co, Cu; DMPC:Pd, Ni, Co, Cu; dilauroylPC:Pd; dioleoylPC:Pd, and asolectin[9]:Pd were prepared. Palladium-metalized particles were stable to oxidation as expected. In the absence of precautions the other metalized particles slowly oxidized over several days.

The colloidal dispersion of DMPC/DODAB:Pd was examined by electron microscopy. The palladium particles made from DMPC/DODAB vesicles were approximately 250 Å in diameter and well dispersed. The vesicles before metalization were approximately 300–600 Å in diameter. To further probe the membrane metalization, another set of electron micrographs was obtained from a separate DMPC/DODAB sample. In this sample the vesicle bilayer membranes were stained with 2% uranyl acetate at pH 4.5. This allowed the membrane to be viewed in the micrographs as well as the palladium metal, which was seen alone in Figure 1a made without stain. Both the bilayer membrane and the metal were clearly visible in the micrographs of the stained DMPC/DODAB:Pd particles. Although no free metal was observed in any of the micrographs, some vesicles were not associated with metal. Whether the metal distribution in these micrographs is real or reflects an artifact due to interaction of the negative stain and the metal remains to be demonstrated.

Pd(0) particle formation is not limited to cationic vesicles. Neutral vesicles (DMPC or DLPC) and anionic vesicles (95 mol % DMPC and 5 mol % palmitic acid) can also be utilized. In particular the formation of Pd(0) particles on DMPC membranes was found to proceed in the same manner as that described above for the cationic vesicles. Qualitatively there was no difference in the reactivity of the catalytic Pd(0) prepared in the presence of neutral or cationic vesicles. Thus the association of the negatively charged Pd(II) complex was not inhibited by the vesicle surface charge. Electron micrographs of the DMPC:Pd particles show chains of metal particles, each particle approximately 400 Å in diameter (Figure 1a). The major difference between the Pd(0) produced in these two cases is the apparent association of the particles in the case of the neutral vesicles. Particle association may be inhibited in the case of the cationic vesicles because of the membrane surface charge. Thus the chemistry of the membrane was evident even after the metal was attached to the vesicle. In the same way, cationic, neutral, and anionic membrane vesicles[10]

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(4) Electroless plating solutions consist of three essentials: the metal to be deposited, usually present as aqueous salt; an agent for the reduction of the salt to zero-valent metal; and a sequestering agent that will protect the metal salt from reduction in the solution. Metallic plating onto a substrate occurs only in the presence of catalytic palladium centers, which are deposited separately.

(5) Brenner, A. *Metal Finishing* 1954, *52*, 68; 1954, *52*, 61.

(6) First Choice Electroless Palladium, Callery Chemical Company, Callery, PA 16024.

(7) NiCl$_2$, 0.1 M, or CoCl$_2$, 0.1 M, or CuCl$_2$, 0.1 M; sodium gluconate, 0.1 M; NaH$_2$PO$_2$, 0.2 M in 100 mL of water with 3.5 mL of ammonium hydroxide. (Excess DMAB required for cobalt plating).

(8) In a typical preparation, vesicles of dimyristoylphosphatidalcholine (DMPC) and dimethyldioctadecylammonium bromide (DODAB) were prepared as follows: DMPC, 114 mg (168 μmol), and DODAB, 6 mg (10 μmol), were mixed in chloroform, dried, and then hydrated with 6.0 mL of 100 mM NaCl to yield a milky white dispersion. These extended bilayers were sonicated at 40 °C and 30 W for 15 min to give a slightly cloudy dispersion of vesicles.

(9) Asolectin in a mixture of phosphatidalethanolamine (PE) and phosphatidalcholine (PC) from soya. The lipids are unsaturated.

(10) (a) Okahata, Y.; Kunitake, T. *J. Am. Chem. Soc.* 1979, *101*, 5231. (b) Kunitake, T.; Okahata, Y. *J. Am. Chem. Soc.* 1980, *102*, 549.
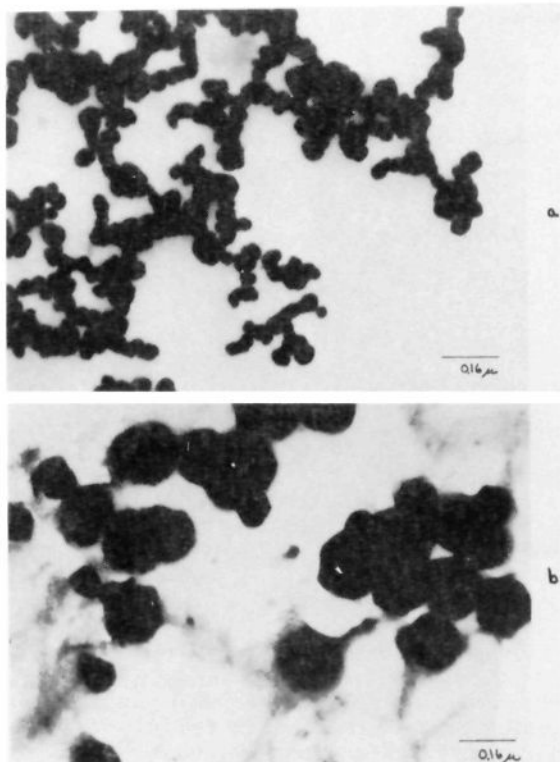
Figure 1. Electron micrograph of a preparation of (a) (top) DMPC:Pd. The particles are approximately 400 Å in diameter and form chains of metal particles. (b) (bottom) DMPC/DODAB:Ni. The stability of the nickel vesicles increased if a reducing agent was entrapped within the vesicles before metal was deposited on the surface. This was achieved if sonication to form the vesicles was carried out in a solution of sodium hypophosphite. The particles appeared as large spheres approximately 1500 Å in diameter.

were successfully used to support catalytic Pd(0) and then form nickel particles by electroless plating (Figure 1b).

The addition of tetrachloropalladate to the unsaturated phospholipid DOPC resulted in the slow formation of Pd(0). This reaction took place in the absence of any added reducing agent. If a Pt(II) salt, tetrachloroplatinate, was added to a sample of DOPC, the solution darkened even more rapidly. These observations indicate that the metal is forming a new complex with the olefin in the phospholipid membrane. The reaction of Pd(II) with olefins in the presence of water is known to rapidly decompose to form aldehydes and Pd(0).[11]

This demonstration of the metalization of both saturated and unsaturated lipid vesicles raises several interesting questions that are currently being explored. These include the following: the nature of the coordination between Pd(II) and the vesicles, the location of the catalytic Pd(0) in both saturated and unsaturated vesicles, and the nature of the deposited metal particles on the saturated vesicles (i.e., is the particle a thin shell of metal associated with most of the vesicle surface or a solid particle that is loosely adhering to the original vesicle surface).

(11) Cotton, F. A.; Wilkinson, G. *Advanced Inorganic Chemistry*, 3rd ed.; Interscience Publishers, John Wiley and Sons: New York, 1972; pp 797–799.

Extremely Short Chiral Synthesis of Bicyclic Alkaloids Having a Nitrogen Atom Ring Juncture

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Bicyclic alkaloids having pyrrolizidine, indolizidine, and quinolizidine skeletons are widely distributed in various plant families.[2] The tumor inhibitory activities of the pyrrolizidine alkaloids have been recognized for the past few decades,[2-4] and there have been a large number of reports on their total syntheses.[5-7] However, the syntheses of optically active pyrrolizidine alkaloids have mostly been performed by employing the chiral building block converted from L-proline derivatives,[7a-f] (*R*)- or (*S*)-malic acid,[7g-m] and carbonhydrates,[7n-p] respectively. Most of the previous chiral syntheses take roundabout ways in spite of their simple structures.

We disclose a new general method for extremely short chiral synthesis of the bicyclic alkaloids having a nitrogen atom ring juncture.[8] Equation 1 shows the synthetic sequence via a highly

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