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Sequential Synthesis of Coordination Polymersomes**

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Abstract: *Novel organic–inorganic hybrid liposomes, so-called coordination polymersomes (CPsomes), with artificial domains that exhibit strong lateral cohesion were prepared by a three-step procedure that formed a coordinative interaction leading to a lipid bilayer. First, the lipophilic complex (dabco-C_{18})[Mn(N)$(CN)_4$(dabco-C_{18})] (**1**; dabco-C_{18}^{+} = 1,4-diazabicyclo[2,2,2]octane-$(CH_2)_{17}$–CH_3 cation), was synthesized. **1** has a lipophilic alkyl tail part and a tetracyanometallate head group, which can be used for an expansion to two-dimensional coordination networks. Second, **1** and 1,2-dipalmitoyl-sn-glycero-3-phosphocholine were mixed to prepare the liposomes. Finally, CPsomes were obtained by the addition of transition-metal ions (**M**) to form unilamellar faceted liposomes with plain CP raft domains with Mn–CN–**M** linkages. The concentration of **1** influences the size of the CP raft domains and the shape of the CPsomes. The synthesis of coordination polymers in lipid bilayers is a novel approach for the construction of artificial architectures as raft domains, for example, in cell membranes.*

The dynamic fluid lipid membranes of liposomes provide a platform for the assembly of chemical compounds and chemical reactions.[1–3] Metal complexes in a membrane can be used for magnetic resonance imaging,[1a] catalysis,[1b] as artificial ion channels,[1c,d] and as precursors for nanomaterials.[1e–h] Various surfactants consisting of mononuclear complexes[1a,b] or multinuclear (cluster) polyoxometalates[1h] have been synthesized and investigated for these purposes. One important method for their synthesis entails the control of the assembled structure (domain) of the metal complex surfactants in the liposome matrix.[2] For instance, in a cell membrane, ions induce lateral domain (raft domain) formation, which plays an important role in supporting numerous cellular events in membrane traffic and signal transduction because the domain architectures tune the signal strength and propagation speed by changing the domain sizes.[3] One fascinating approach to form domains in a fluid membrane is the construction of coordination polymers (CPs). Expanding coordination networks on the liposome surface would be useful to enhance lateral cohesion.

CPs that consist of transition-metal ions and linker ligands have been intensively investigated as next-generation materials with various structures and properties.[4] The synthesis of CPs on thin films, such as hard solid substrates, has been reported,[5] whereas a soft lipid membrane has not been used for the synthesis of CPs thus far. The introduction of CPs in a fluid membrane would not only provide new scaffolds for chemical reactions, but also new composite soft materials with controllable domains.

Herein, novel organic–inorganic hybrid liposomes, coordination polymersomes (CPsomes) with Hofmann-type CP raft domains on a 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine (DPPC) lipid bilayer, were synthesized by a sequential process (Scheme 1). The 2D layered Hofmann-type CPs are suitable for domain formation to match the shape of a lipid membrane surface.[6] The Hofmann-type layers are built by linking transition-metal ions **M** with tetracyanometallate ligands $[\mathbf{M}'(CN)_4]^{2-}$ ($\mathbf{M}'$ = Pt, Pd, Ni, Mn≡N). Cyano ligands form stable **M′**–CN–**M** coordination linkages, and the coordination strength can be tuned by switching to metal ions with different electronic configurations for the introduction of CPs into the fluid membrane.[7]

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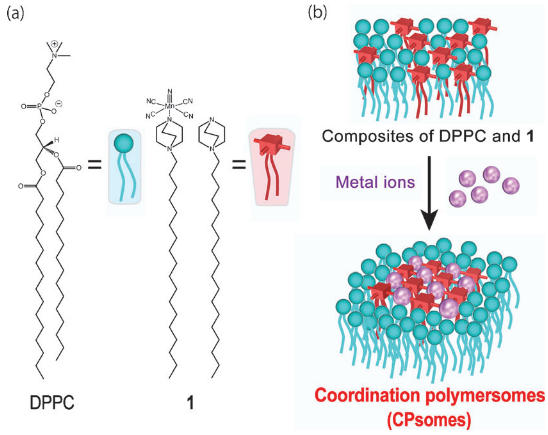


Scheme 1. a) Schematic representations of DPPC and **1**. b) Sequential synthetic procedure for CPsomes.

As a building unit of the CPs, a lipophilic complex, namely (dabco-C_{18})[Mn(N)$(CN)_4$(dabco-C_{18})] (**1**; dabco-C_{18}^{+} = 1,4-diazabicyclo[2,2,2]octane-$(CH_2)_{17}$-CH_3 cation) was synthesized by a two-step ion exchange reaction starting from $(PPh_4)_2[Mn(N)(CN)_4]\cdot 2H_2O$.[8] Complex **1** features a $[Mn(N)(CN)_4]^{2-}$ moiety as the head group and the alkyl chains of two (dabco-C_{18})$^{+}$ cations as the tail group. Single-crystal X-ray structure analysis revealed that one (dabco-C_{18})$^{+}$ ion coordinates to the Mn^{V} center at the axial position of $[Mn(N)(CN)_4]^{2-}$, whereas the other exists as the countercation (Figure 1). The composition of **1**, with an anionic

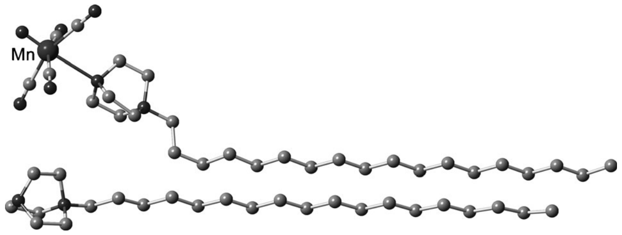


Figure 1. Crystal structure of **1**. Carbon light gray, nitrogen dark gray. H atoms are omitted for clarity.

[Mn(N)$(CN)_4$(dabco-C_{18})]$^{-}$ species and a (dabco-C_{18})$^{+}$ countercation, was also confirmed by ESI-MS spectrometry. **1** behaves as a neutral lipid with two alkyl chains interacting with lipid molecules such as DPPC and has four coordinative cyano ligands in the equatorial positions of $[Mn(N)(CN)_4]^{2-}$ to extend the structure to 2D Hofmann-type coordination networks.[6g,m]

We selected a DPPC lipid molecule (**L**) to construct a basal liposome with **1**. The composites **L**/**1**(x) (**L**/**1** = 1:x, where $x = 0.125$, 0.25, 0.4, 0.5) were prepared by a freeze–thaw method using a mixture of **L** and **1** at a mole ratio of x. Cryo-transmission electron microscopy (cryo-TEM) images of the **L**/**1**(x) liposomes showed approximately 250 nm large sphere-shaped vesicles regardless of the value of x (Supporting Information, Figure S1). The sizes of the composites were also confirmed by dynamic light scattering (DLS; Table S3). For $x > 0.5$, composites were not obtained because powder crystals of **1** precipitated. The effect of the packing parameter of **1** on the vesicle size and stability is shown in Figure S3.

To confirm the formation of **L**/**1**(x) from the perspective of the miscibility between **L** and **1**, the phase transitions of **L**/**1**(x) were investigated by differential scanning calorimetry (DSC; Figure S4). DPPC liposomes (at $x = 0$) changed from the gel phase to a liquid-crystal phase at $T_c = 313.4$ K.[9] For $x < 0.25$, the T_c value of **L**/**1**(x) [$T_c(x)$] increased slightly with an increasing ratio of **1** to **L** [$T_c(0.125) = 314.2$ K and $T_c(0.25) = 314.9$ K]. These composites showed a single abrupt phase transition, which suggests that molecules of **1** were homogeneously dispersed on **L**. The T_c value increased slightly because of a change in the lateral compression pressure produced by electrostatic interactions between $[Mn(N)(CN)_4]^{2-}$ and the head group of **L**.[10] For $0.25 \leq x \leq 0.4$, a peak shift and broadening were observed in the heating process, demonstrating the immiscibility of **1** and **L**. In particular, the immobile phase at the lower temperature had a greater immiscibility, which broadened the phase transition in the heating process, and the mobile phase at the higher temperature had a lower immiscibility to show a homogeneous phase transition in the cooling process. For $x = 0.5$, **L**/**1**(0.5) showed a hysteretic phase transition with a hysteresis width of 7.8 K ($T_c^{\mathrm{up}} = 319.3$ K and $T_c^{\mathrm{down}} = 311.5$ K). The increase in x produced the hysteretic phase transition, indicating that **1** dominated the phase transition of the composite. The surface charge of **L**/**1**(x) also depends on the ratio of **L**/**1**, which was confirmed by the zeta-potential measurements shown in Figure S2. The ratio of **1** to **L** in the composites has an impact on the properties of **L**/**1**(x), such as the distribution of **1** and the phase transition.

CPsomes, **L**/**1**/Mn(0.5), were obtained by adding the equivalent amount of $MnSO_4$ in an aqueous solution to **L**/**1**(0.5). The Mn^{2+} ions were bridged by cyano ligands of **1** in the lipid bilayer (Scheme 1b). Cryo-TEM images of **L**/**1**/Mn(0.5) showed faceted liposomes, demonstrating that the morphology changed from a sphere to a faceted shape (Figure 2), and that the CPs produced CP raft domains with plain surfaces. The formation of stable CPsomes was corro-

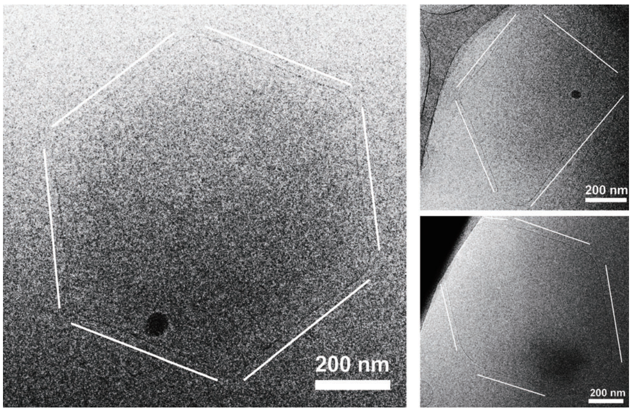


Figure 2. Cryo-TEM images of **L**/**1**/Mn(0.5). White lines indicate the contrasts in the image.

borated by DLS measurements (Figure S3). Changes in the surface charge and size through the formation of CPs on the surface were confirmed by zeta-potential and DLS measurements (for detailed discussions, see Figures S2 and S3). Furthermore, a control experiment was carried out using 1,2-dimyristoyl-*sn*-glycero-3-phosphocholine (DMPC) and an analogous compound, (dabco-C_{16})[Mn(N)$(CN)_4$(dabco-C_{16})] (**2**; dabco-C_{16}^{+} = 1,4-diazabicyclo-[2,2,2]octane-$(CH_2)_{15}CH_3$ cation), which have shorter alkyl chains than DPPC and **1**, respectively. In this case, smaller faceted CPsomes [DMPC/**2**/Mn(0.5)] were obtained in a similar fashion to **L**/**1**/Mn(0.5) (Figure S5). This result suggests that the size of the CPsomes could be controlled by the alkyl chain length and the right combination of lipid species and lipophilic complexes.

The coordination of cyano ligands to the added Mn^{2+} ions in **L**/**1**/Mn(0.5) was confirmed by high-resolution magic angle spinning (HR-MAS) ^{13}C NMR spectroscopy of a suspension of the samples. The NMR spectra provide in situ structural information on **L**/**1**/Mn(0.5). We focused on the ^{13}C atoms of the cyano ligands to study the coordination bonds of $^{13}C{\equiv}N\cdots Mn^{2+}$. A ^{13}C-enriched sample of **1** was prepared by the same method as **1** using $Na^{13}CN$. The ^{13}C NMR spectra of the DPPC liposome, **L**/[^{13}C]-**1**(0.5), and **L**/[^{13}C]-**1**/Mn(0.5) were collected under 12 kHz MAS rotation. **L**/[^{13}C]-**1**(0.5) gave a signal at 151.3 ppm, which was assigned to the ^{13}C atoms of the cyano ligands in $[Mn(N)(CN)_4]^{2-}$;[8] this peak disappeared after adding an $MnSO_4$ aqueous solution to **L**/[^{13}C]-**1**(0.5) (Figure 3a). This disappearance is due to the paramagnetic effect of the Mn^{2+} ions on the ^{13}C atoms, which strongly supports the hypothesis that most of the cyano groups formed $^{13}C{\equiv}N\cdots Mn^{2+}$ coordinative bonds in **L**/[^{13}C]-**1**/Mn(0.5).[11] Infrared spectra of freeze-dried samples also corroborated the formation of $C{\equiv}N\cdots Mn^{2+}$ networks. Although the freeze–dry process led to partial collapse of the CP networks, a shift of the C≡N stretching mode from 2117 cm^{-1} to 2144 cm^{-1} was clearly observed, indicating the formation of Hofmann-type networks in **L**/**1**/Mn(0.5) (Figure 3b).[6g]

To obtain information on the nanoscale morphology, small-angle X-ray scattering (SAXS) measurements were carried out (Figure S7). **L**/**1**(0.5) and **L**/**1**/Mn(0.5) showed no stacking peaks, indicating unilamellar membrane structures, which is consistent with the cryo-TEM images shown in Figure 2.

For faceted liposomes, a correlation between the plain surfaces and the surface charges has been discussed.[12] The formation of plain surfaces stems from a crystallization process that is induced by a change in the charge distribution. As control samples, multilamellar faceted liposomes **L**/Mn were prepared by adding Mn^{2+} ions to **L** liposomes without **1**. Cryo-TEM images revealed that the morphologies and membrane structures of the **L**/**1**/Mn(0.5) CPsomes were different to those of **L**/Mn (Figure S8). In the CPsomes, the accumulation of metal ions in proximity to **1** and the formation of the CP raft domains led to charge localization on the surface. **L**/**1**(*x*) displayed a zeta potential of a 35–45 mV, indicating large repulsion between the head groups, which induces a transformation to unilamellar vesicles. The unilamellar structure was maintained after introducing the metal ions into **L**/**1**(*x*), and the CPsomes thus obtained exhibited unilamellar plain surfaces built by the CPs.

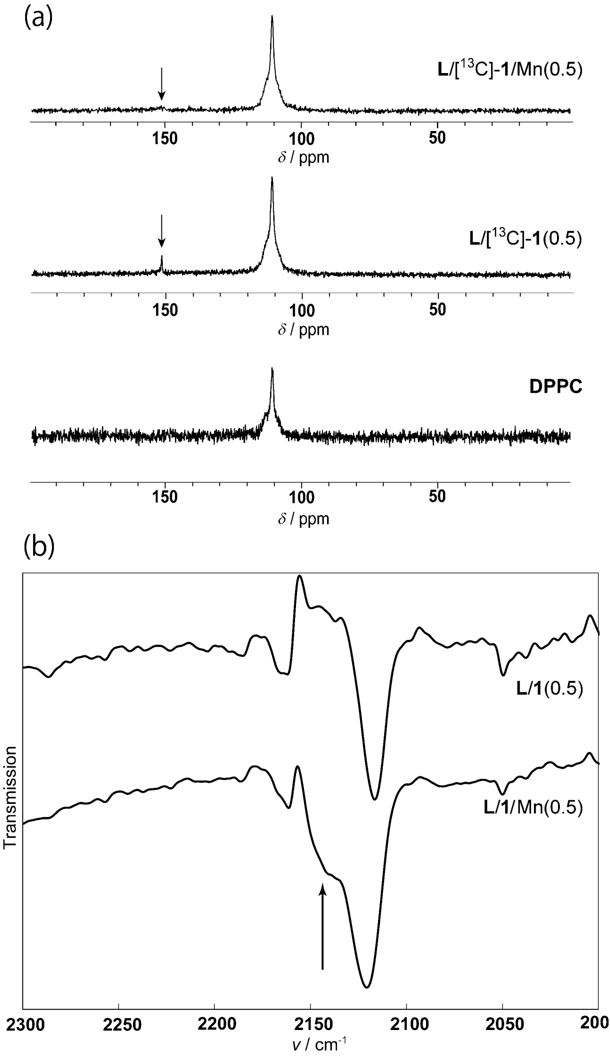


Figure 3. a) HR-MAS ^{13}C NMR spectra and b) infrared spectra of the CPsomes and their precursors.

The size of the CP raft domains changed depending on the **L**/**1** ratio. **L**/**1**/Mn(0.25), which was obtained by adding the correct amount of a $MnSO_4$ aqueous solution to **L**/**1**(0.25), featured smaller CP raft domains than **L**/**1**/Mn(0.5). The differences in the sizes of the CP raft domains of **L**/**1**/Mn(*x*) originate from the different densities and distributions of **1** in the **L**/**1**(*x*) scaffold. The higher density of **1** in **L**/**1**/Mn(0.5) produces larger CP raft domains by the formation of Mn^{V}–CN–Mn linkages. On the other hand, in **L**/**1**/Mn(0.25), **1** was dispersed at a lower density, and the CP raft domains were downsized to give a favorable homogeneous phase (Figure 4a and Scheme 2).

In typical lipid assembly systems under equilibrium conditions, the morphologies transform into nanodiscs and punctuated planes, for example, accompanied with modulating curvatures by changing the composition ratio.[12b] In general, it is hard to control the size of plain surfaces. In the

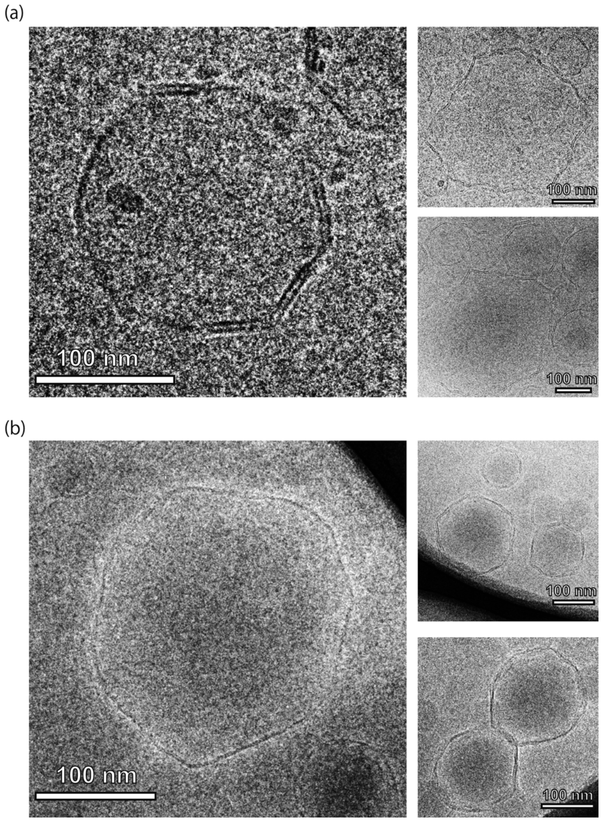
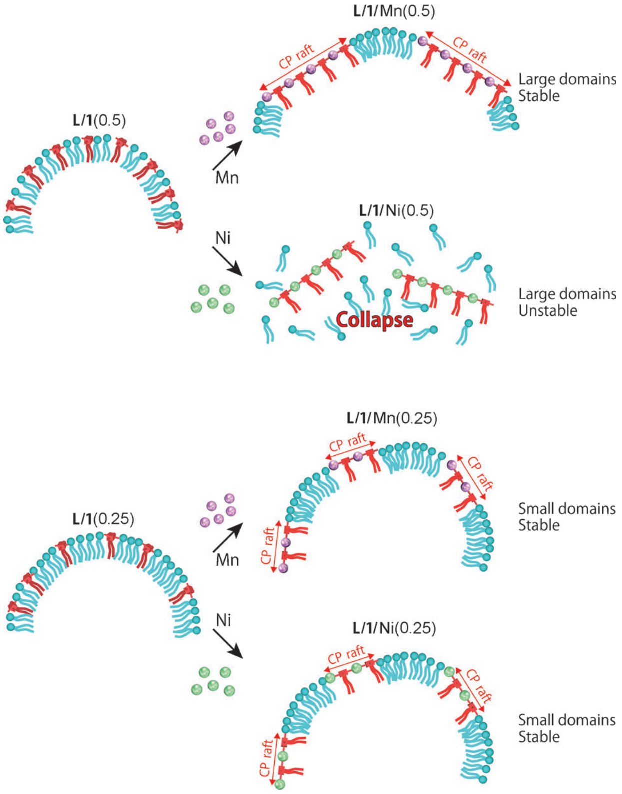


Figure 4. Cryo-TEM images of a) **L**/**1**/Mn(0.25) and b) **L**/**1**/Ni(0.25).



Scheme 2. The formation of CPsomes on the outer surface of **L**/**1**(0.5) and **L**/**1**(0.25) using Mn^{2+} and Ni^{2+} ions. The CP raft domain size is manipulated by changing the concentration of **1**. The stability of the CPsomes is affected by the CP raft domain size.

case of CPsomes, the plain surfaces are formed by extension of the coordination networks, which is a key point for controlling the size of plain surfaces. This method for controlling the domain size has potential for the regulation of the local concentrations of chemical substances and the rates of chemical reactions on the membrane.[3]

To reveal the significance of the coordination bonds in the formation of CPsomes, we studied the influence of the coordination bond strength on **L**/**1**/**M**(x) (**M** = Mn^{2+} or Ni^{2+}). CPsomes with Ni ions were prepared using a $NiSO_4$ aqueous solution instead of the $MnSO_4$ solution. Cryo-TEM images of **L**/**1**/Ni(0.5) showed many fragments that originated from the assemblies (Figure S9). These fragments indicate the collapse of the Ni CPsomes. DSC curves of **L**/**1**/Ni(0.5) had no anomaly, which confirmed that the **L**/**1**/Ni(0.5) CPsomes were too unstable to maintain a liposome structure (Figure S10). This different behavior in the structural stabilities is explained in terms of the Irving–Williams series, in which Ni^{2+} ions form stronger CN−Ni coordination bonds than Mn^{2+} ions.[7] The strong coordination bond provides rigid Ni CP raft domains, which induce the collapse of **L**/**1**/Ni(0.5). For a lower concentration of **1**, stable **L**/**1**/Ni(0.25) CPsomes were obtained by adding a $NiSO_4$ aqueous solution to **L**/**1**(0.25) (Figure 4b and Scheme 2). **L**/**1**/Ni(0.25) was a faceted liposome with CP raft domains that showed an abrupt phase transition (Figure S10). These properties are similar to those of **L**/**1**/Mn(0.25). The CP raft domain size significantly influenced the stability of the CPsomes.

We found that two principal factors control the formation of the CPsomes: 1) the flexibility of the CP raft domains and 2) the CP raft domain size in the CPsomes. Stable CPsomes can be obtained by modulation of the CP raft domain size by a suitable choice of metal ions and bridging ligands with different coordination strengths. This finding leads to a novel approach for the construction of CPsomes from various metal ions and organic ligands.

In conclusion, CPsomes with CP raft domains in the lipid bilayer were successfully obtained by a sequential synthesis approach. The fabricated lipophilic complex **1** was synthesized and integrated with DPPC lipids (**L**) to produce the composites **L**/**1**(x). The CPsomes, **L**/**1**/**M**(x), formed as faceted liposomes by introducing metal ions into **L**/**1**(x), and plain surfaces were produced by CPs as CP raft domains. The size of the CP raft domains could be controlled by modulating the concentration of **1** in the lipid bilayers. The CP raft domain sizes and the coordination bond strength of the CPs were dominant factors in stabilizing the CPsomes. The construction of CPs in a lipid membrane is a novel technique and cannot only be used for obtaining size-controlled CPs, but also for creating composite soft materials with lipid and versatile CPs.

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