Surface Modification of Polymeric Vesicles via Host−Guest Inclusion Complexation

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We have prepared a novel kind of building block (CD-PI-CD) of polyether imide (PI) with β-cyclodextrin (β-CD) at the both ends that self-assembles into vesicles in water. The vesicles are "reactive" in supramolecular chemistry because the host groups of β-CD equally distribute on the inside and outside surfaces of the vesicles. Isothermal titration calorimetry (ITC) and static light scattering (SLS) studies demonstrate that both the inner and outer surfaces of the vesicles can be further modified noncovalently with adamantane-ended polyethlene glycol (Ada-PEG) via a host−guest inclusion interaction between β-CD and adamantane.

Self-assembled polymeric micelles have great potential as multifunctional platforms for nanoreactors and carriers for catalysts, enzymes, and drugs.[1−5] These applications require both a robust structure and the presence of functional molecules on the micelle scaffold. Thus, the design of the building blocks and the surface properties of the micelles are of critical importance for further advances. In this respect, various methods have been developed in the functionalization of the building blocks and/or surface modification of the micelles.[6−11] We noticed that in all cases the functional groups or molecules are always *covalently* connected to the building blocks or the surfaces of the micelles. Among various polymeric assemblies, vesicles have attracted much attention in recent years because they hold greater promise for encapsulation than do ordinary micelles.[12−15] However, there have been only a few reports on the surface modification of vesicles with polymers using click chemistry,[16,17] in part because the vesicles are usually unstable under the conditions necessary for the chemical reactions. In principle, it is even difficult to modify the inner surface of the vesicles via chemical reactions.

Here, for the first time, we report a new strategy for the surface modification of polymeric vesicles via molecular recognition, where the host and guest groups exist at the ends of the building blocks of the vesicles and the ends of the modifier polymers, respectively. Specifically, we synthesized novel building blocks of polyether imide (PI) with β-cyclodextrin (β-CD) at both ends (CD-PI-CD, Scheme 1). We were led to the use of the new building blocks mainly from the success of our research in two respects. First, we found that rigid polymers such as polyimide or rigid-coil polymer pairs can easily self-assemble into vesicles in their common or selective solvents.[18−23] The second is related to the use of inclusion complexation between cyclodextrin and its guest molecules as the driving force for fabricating polymeric micelles, heterogeneous multilayers of nanocrystals, and the reversible aggregation of gold nanoparticles.[24−27]

The novel building block of rigid chains of CD-PI-CD was found to be able to self-assemble easily into nanoparticles when water was added dropwise to its solutions in dimethyl formamide (DMF) under ultrasonication. DMF can then be removed by dialysis of the resultant nanoparticle solutions in DMF−water (20/80 v/v) against water. The dialysis process is very important for the nanoparticles to keep their morphology unchanged during the subsequent surface modification process because of the high hydrophobicity of the PI chains. A TEM image (Figure 1A) of the nanoparticles shows a strong contrast between the center and periphery, which is characteristic of the vesicular morphology.

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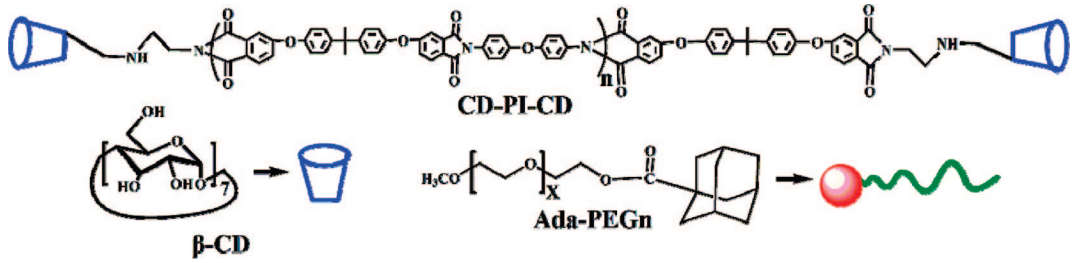
Scheme 1. Chemical Structures of CD-PI-CD, β-CD, and Ada-PEG*n*



Static light scattering (SLS) and dynamic light scattering (DLS) respectively gave 77 nm for the radius of gyration ($\langle R_g \rangle$) and 70 nm for the average hydrodynamic radius ($\langle R_h \rangle$), so $\langle R_g \rangle / \langle R_h \rangle = 1.1$. In addition, from the "molecular weight" of the nanoparticles measured by SLS and the $\langle R_h \rangle$ value, the average density is calculated to be as small as 1.7×10^{-2} g/cm^3. These data further support that CD-PI-CD self-assembled into the vesicles.[28−30]

A close examination of the TEM images gives a thickness of the vesicular shell of about 20 nm, which is comparable to the fully extended chain length of PI.[18,19] Thus, we think that the rigid CD-PI-CD chains pack radially into a monolayer membrane.[18−21] This is similar to those formed by carboxyl-ended polyimide, as we reported previously.[23] Clearly, the terminal CD groups equally distribute on the inside and outside surfaces of the vesicles (Figure 1B). Because the M_w of the vesicles is 1.48×10^7 g/mol and the respective number- and weight-average molecular weights of CD-PI-CD are 1.02×10^4 and 1.89×10^4 g/mol, respectively, it is estimated that one vesicle is composed of about 1000 CD-PI-CD chains on average.

It is well known that the small hydrophobic cavities of β-CD can include many kinds of guest molecules.[31] Here, we used adamantane (Ada)-terminated poly(ethylene glycol) (Ada-PEG*n*, where n = 1.1K, 2K, and 5K denote the M_w of PEG, Scheme 1) as the guest polymer because β-CD and Ada form inclusion complexes in water with a stability constant as high as 5×10^4 M^{-1}.[32,33]

The degree of inclusion complexation was estimated from the enthalpy change (ΔH) during mixing the guest solutions and the host solutions measured by isothermal titration calorimetry (ITC).[34,35] Here, single injection mode (SIM) was used. All of the ITC measurements were performed by titration of the host solutions (0.3 μmol) with 1 equiv of the guest solutions. The heats of dilution of the guest polymer solutions have been measured as a control and subtracted from the corresponding data.

The processes of mixing free β-CD and Ada-PEG*n* were measured first as the reference. Figure 2A shows that the complexation between free β-CD and Ada-PEG1.1K is rather quick because the exothermal process is generally completed in 7 to 8 min with an enthalpy change (ΔH) of ∼−1457 μcal. Very similar results were obtained for free β-CD with Ada-PEG2K (Figure S2A in SI) and Ada-PEG5K (Figure S2B in SI) (i.e., the respective ΔH values were −1430 and −1423 μcal and the heat release proceeded quickly as well). These very similar enthalpy values are also close to that reported in the literature for β-CD and 1-adamantanecarboxylate (∼1500 μcal for 0.3 μmol).[32] On the basis of these results, we may conclude that the attachment of the Ada group to the PEG dose not affect its inclusion complexation with β-CD.

Figure 2B−D presents the exothermal curves of the solutions of the CD-PI-CD vesicles titrated with the solutions of Ada-PEG1.1K, Ada-PEG2K, and Ada-PEG5K, respectively. In the cases of Ada-PEG1.1K and Ada-PEG2K, the ΔH values are −1438 and −1433 μcal, respectively. The agreement of these values with those of free β-CD and Ada-PEG*n* clearly shows that the Ada groups attached to PEG1.1K and PEG2K can form stoichiometric inclusion complexes with the β-CD groups bound to the surfaces of the vesicles. In other words, both the outer and inner surfaces of the vesicles can be fully modified by Ada-PEG1.1K or Ada-PEG2K. However, Ada-PEG5K behaves differently (i.e., the ΔH value obtained over a long duration of 800 min is only −1109 μcal. Because the ΔH value for free β-CD and Ada-PEG5K is −1423 μcal, it is clear that about a quarter of the total β-CD cavities on the vesicle surfaces remained empty. Obviously, the long PEG tails of Ada-PEG5K retard their penetration through the membrane.

Figure 2B−D also displays the kinetics characteristic of the inclusion complexation. For Ada-PEG1.1K or Ada-PEG2K, after the guest solution was added, a quick heat-release peak appeared, and then a long, slow process followed. The time for the first half of ΔH was only 20−30 min whereas the whole exothermal process lasted as long as 130 and 300 min for Ada-PEG1.1K and Ada-PEG2K, respectively. Considering that the penetration of Ada-PEG*n* through the membrane is a precondition for guest−host recognition on the inner surface, the quick and subsequently slow processes are reasonably attributed to the complexation in the outer and inner surfaces, respectively. In the case of Ada-PEG5K (Figure 2D), it takes as long as ∼130 min to reach half

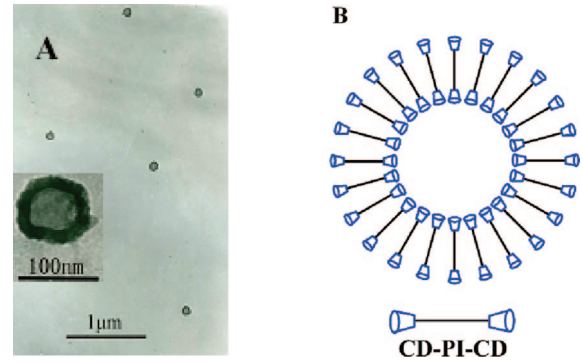


Figure 1. (A) TEM images and (B) schematic representation of the vesicles of CD-PI-CD in water.

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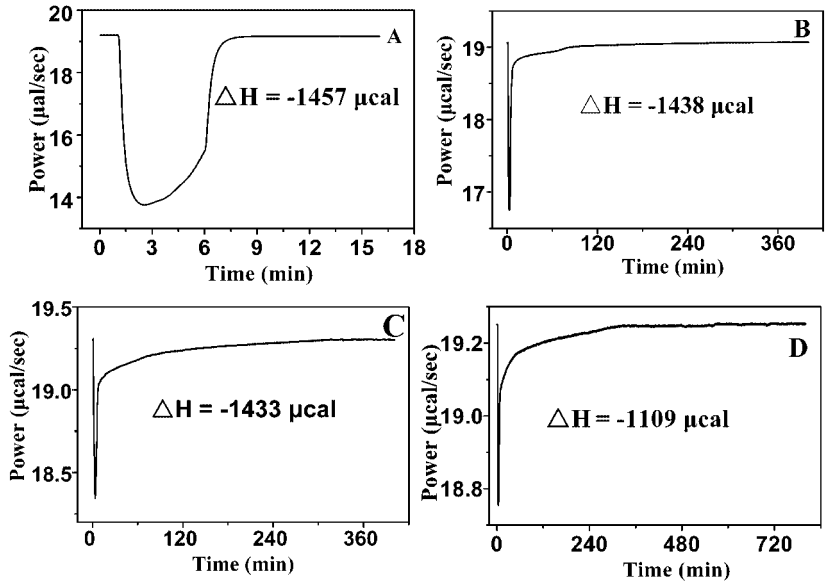

Figure 2. Heat effects observed by ITC in the titration of (A) native β-CD solution by Ada-PEG1.1K and vesicle solution by (B) Ada-PEG1.1K, (C) Ada-PEG2K, and (D) Ada-PEG5K solutions.

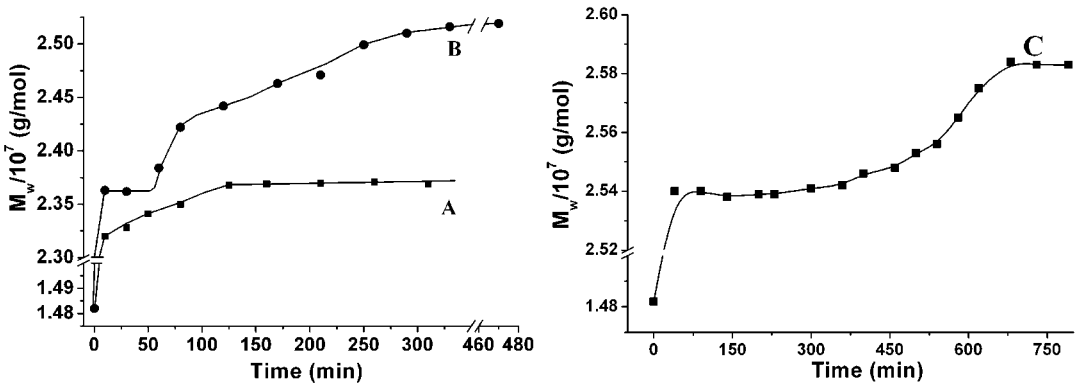

Figure 3. Time dependence of M_w of the vesicles of CD-PI-CD after (A) Ada-PEG1.1K, (B) Ada-PEG2K, and (C) Ada-PEG5K were added. For all of the samples, the final concentration of CD-PI-CD is 0.125 mg/mL, and the molar ratio of CD to Ada-PEG*n* is 1.

of ΔH (-711.5 μcal, calculated from the data in Figure S2B in SI), and the complexation was not complete although the measurement was performed for 800 min.

The surface modification processes were also monitored by SLS showing the changes in the M_w of the vesicles with time. When Ada-PEG1.1K is used as the guest polymer, M_w increases sharply in the initial stage and then gradually increases until it reaches a constant at ~130 min (Figure 3A). This behavior is generally in accordance with the ITC results (Figure 2B). For the case of Ada-PEG2K, M_w increases quickly and then reaches a small plateau at 10−30 min, which is followed by a gradual increase until the final equilibrium is reached (Figure 3B). In comparison with the ITC results in Figure 2C, we know that the time required for M_w to reach the plateau is almost the same as that for ΔH to reach half its value. In addition, the times (~300 min) for the final equilibrium measured by the two methods are also close to each other. This agreement between SLS and ITC indicates that there are two stages in the complexation process. The plateau might be attributed to the completion of the modification of the outer surface, whereas the subsequent slow increase of M_w might be attributed to the modification of the inner surface. In the case of Ada-PEG5K, the two-stage behavior seems to be more obvious because there is a much longer plateau between the fast and slow processes (Figure 3C). Finally. the molecular weight no longer increases at around 700 min; however, this does not indicate a real equilibrium because at this stage about a quarter of the CD cavities on the vesicular surfaces are still empty (Figure 2D). Because of the large size of Ada-PEG5K molecules, the already attached guest molecules would block the channels for the coming guests to penetrate into the inside surface, leading to only a partial modification of the inner surface. The absence of a plateau between the quick and slow processes for the case of Ada-PEG1.1K (Figure 4A) is probably due to the fact that the Ada-PEG1.1K molecules are small, so they can penetrate through the membrane relatively quickly and then the process of the inner surface modification closely follows that of the outer surface. Note that at a given host−guest composition the concentration, composition of the vesicles, and refractive index increment of the solutions continuously vary during the complexation process so that only apparent rather than absolute molecular weights of the vesicles can be obtained here.[36] Thus, one cannot estimate the degree of complexation as a function of time on the basis of the data in Figure 3.

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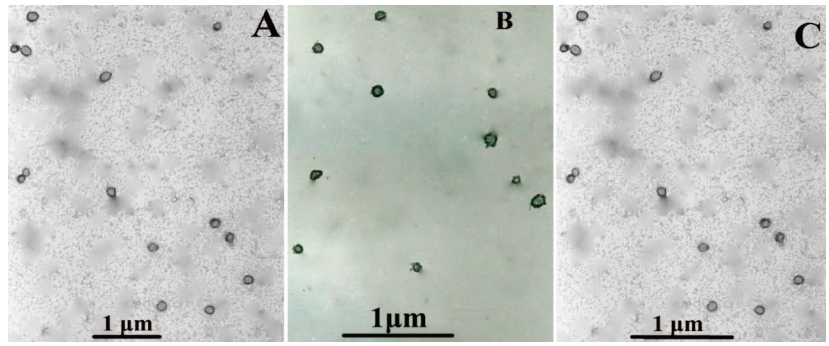
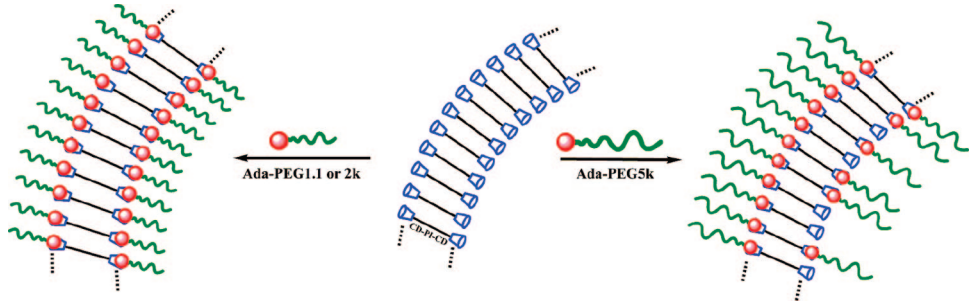


Figure 4. TEM images of the vesicles after (A) Ada-PEG1.1K, (B) Ada-PEG2K, and (C) Ada-PEG5K were added. The samples were made at least 24 h after the addition of Ada-PEG*n*.

Scheme 2. Schematic Representation of the Surface Modification Process of the Vesicles



The inclusion complexation between Ada-PEG*n* and β-CD makes CD-PI-CD and PEG connect with each other to form an amphiphile. One may ask whether this causes disassembly and then reassembly of the vesicles. Our data do not support this speculation. As shown in Figure 3, the molar mass of the vesicles in general increases with time. Furthermore, DLS measurements show that the size distributions of the vesicles remain unimodal with a small change in the polydispersity index ($\mu_2/\langle\Gamma\rangle^2$) ranging from 0.11 to 0.19 during the complexation process (Figure S3 in SI). All of these facts indicate that the vesicles hold their morphology when Ada-PEG*n* chains attach to and penetrate through the membranes. Finally, the vesicular morphology of the resultant assemblies of the vesicles and Ada-PEG*n* was observed by TEM (Figure 4). There is not a significant difference between them and the original vesicles (Figure 2A), expect for a little deformation because such low-molecular-weight PEG chains attached to the vesicles are invisible under TEM.

As schematically summarized in Scheme 2, a novel kind of vesicle, which is reactive in supramolecular chemistry, was prepared through β-CD-ended polyether imide in water. On both the outer and inner surfaces of the vesicles, β-CD cavities are available for further surface modification via inclusion complexation between β-CD and adamantane-monoended PEG. For Ada-PEG2K and Ada-PEG1.1K, both the inner and outer surfaces can be fully modified whereas for Ada-PEG5K the inner surfaces can be only partially modified. We emphasis that our surface modification of the vesicles is completely based on supramolecular chemistry and thus the guest polymers are *noncovalently* connected to the surfaces. This study opens a new, simple, mild avenue to the surface modification and functionalization of the vesicles, which of course would promote their applications in various areas.

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Supporting Information Available: Details of the synthesis procedures of CD-PI-CD, vesicle preparation, characterizations, and methods. This material is available free of charge via the Internet at http://pubs.acs.org.

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