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Compartmentalization in Hybrid Metallacarborane Nanoparticles Formed by Block Copolymers with Star-Like Architecture

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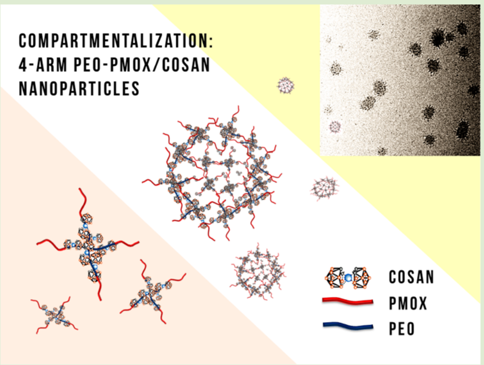
Supporting Information

ABSTRACT: One strategy to control the morphology of hybrid polymeric nanostructures is the proper selection of macromolecule architecture. We prepared metallacarborane-rich nanoparticles by interaction of double-hydrophilic block copolymers consisting of both poly(2-alkyl oxazolines) and poly(ethylene oxide) blocks with cobaltabisdicarbollide anion in physiological saline. The inner structure of the hybrid nanoparticles was studied by cryo-TEM, light scattering, SAXS, NMR, and ITC. Although the thermodynamics of diblock and star-like systems are almost identical, the macromolecular architecture has a great impact on the size and inner morphology of the nanoparticles. While hybrid nanoparticles formed by linear diblock copolymers are homogeneous, resembling gel-like nanospheres, the star-like shape of 4-arm block copolymers with PEO blocks in central parts of macromolecules leads to distinct compartmentalization. Because metallacarboranes are promising species in medicine, the studied nanoparticles are important for targeted drug delivery of boron cluster compounds.



The preparation of new types of hierarchically organized polymer nanoparticles with specific functions has attracted many researchers[1] because of the utilization of such nano-objects in medicine and other applications.[2] Due to advanced synthetic techniques, various architectures of amphiphilic block copolymers are now available for the design of nanostructured particles based on direct self-assembly in solution.[1a,j] Another possibility for preparation is the use of nonchemical procedures because the character of complex nanosystems is often kinetically controlled and far from equilibrium.[3] Double-hydrophilic copolymers are particularly interesting, in which the formation of nanostructures is based on interaction with usually low-molecular-weight agents, such as ions with polyelectrolyte blocks (so-called coassembly).[4a−f] Furthermore, the use of coassembling compounds, such as hexacyanocobaltate and hexacyanoferrates, allows the introduction of less common thermodynamic (UCST), photosensitive, or electroactive properties to block copolymer nanostructures.[4g−i]

Recently, we began a systematic study of the coassembly of neutral hydrophilic polymers of poly(ethylene oxide), PEO, and poly(2-alkyl oxazolines), POX, with the amphiphilic anion [3-cobalt(III) bis(1,2-dicarbollide)](−1), $[CoD]^-$.[5] The interaction of $[CoD]^-$ with neutral polymers is unparalleled in macromolecular chemistry and is based on weak dihydrogen bonding between boron cluster compounds and CH_2CH_2 moieties in polymer backbones.[5,6] Metallacarboranes such as salts of $[CoD]^-$ are fully artificial boron-based inorganic compounds[7] that are intensively studied due to their unique properties and interactions, which open new opportunities in nanochemistry.[8]

The PEO homopolymer interacts with Na[CoD] in NaCl aqueous solutions, and an insoluble nanocomposite with a uniquely organized structure forms as a result.[5b,c] Additionally, POX homopolymers form a complex with $[CoD]^-$. Because Na^+ is not bound by POX, the complex retains solubility in water.[5e] Despite different solution behaviors, both PEO and PEOX metallacarborane complexes exhibit very similar interaction energies (see ITC thermograms and further comments in Figure S3 in Supporting Information, SI). In other words, ITC data suggest that PEO/Na[CoD] and PEOX/Na[CoD] interaction strengths are comparable, and determination of the type of polymer preferred in a mixture would be difficult.

In the case of linear block copolymer poly(ethylene oxide)-*block*-poly(2-ethyl oxazoline), PEO−PEOX (Scheme 1), a

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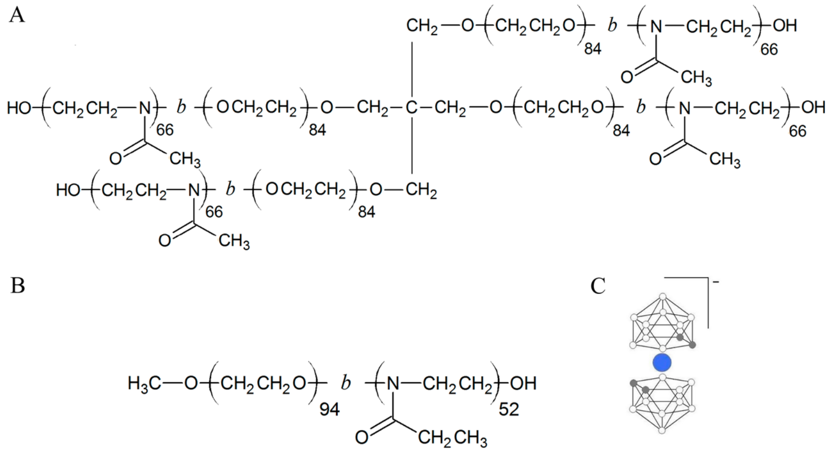
Scheme 1. Structures of (A) [PEO−PMOX]$_4$, (B) PEO−PEOX, and (C) [CoD]$^{-a}$



^{a} Color-coding in (C): transparent, BH groups; grey, CH groups; blue, cobalt atom. Lengths of blocks were determined by means of ^{1}H NMR (details shown in SI).

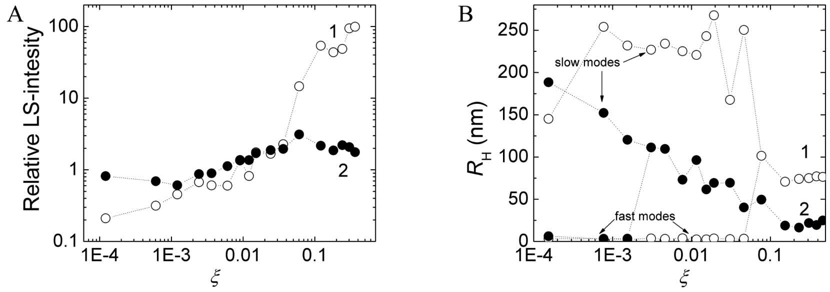


Figure 1. Dependence of (A) relative light scattering intensity (related to intensity of pure polymer solutions) and (B) hydrodynamic radius, R_H, on the addition of Na[CoD] to PEO−PEOX (hollow circles, curves 1) and [PEO−PMOX]$_4$ (black circles, curves 2) solutions (2 g/L) in 0.154 M NaCl. In (B) there are slow and fast modes for both samples at low ξ that eventually merge into one. The values of R_H for pure polymer solutions are as follows: 3 and 161 nm for PEO−PEOX, and 1 and 183 nm for [PEO−PMOX]$_4$.

core/shell structure is expected, with insoluble PEO-complex in the core and water-soluble PEOX-complex in the micellar shell. Nevertheless, no core/shell micelles have been observed.[5e] Homogeneous gel-like nanospheres with high Na[CoD] content forms instead. As no preferential complexation with any block occurs, both PEO and PEOX blocks are intermixed within the nanospheres.

Due to the increasing interest in boron cluster compounds in medical applications (metallacarboranes act as potent inhibitors of HIV protease),[5a] hybrid nanocarriers for targeted drug delivery with well-designed properties are urgently needed. Since nanoparticles of block copolymers used in our previous studies[5] were of quite large dimensions (tens or few hundreds of nanometers), a new concept for the preparation of nanoparticles with controlled size would be very useful. In this paper, we examine nanostructures formed after the addition of Na[CoD] to physiological saline aqueous solutions (0.154 M NaCl) of the star-like block copolymer [poly(ethylene oxide)-*block*-poly(2-methyl oxazoline)]$_4$, [PEO−PMOX]$_4$, which has four arms, as shown in Scheme 1. The results are compared with the previously studied linear PEO−PEOX[5e] to demonstrate that the polymer architecture has a crucial role in the morphology of hybrid nanoparticles.[9]

Both block copolymers were characterized by NMR and GPC to support the structures proposed in Scheme 1 (details on copolymer structure are shown in SI, Table S1 and Figure S1). Additional results of two other linear block copolymers, PEO−PEOX(2) and PEOX−PEO−PEOX (Table S1), are presented in SI and are fully consistent with all findings discussed in the main text (Figures S4, S5, and S8 in SI).

We compare the behavior of block copolymers with PMOX and PEOX blocks, assuming that the pendant alkyl group length in POX segments (i.e., methyl and ethyl) has only a minor impact on the interaction with Na[CoD]. To prove this assumption, we conducted isothermal titration calorimetry, ITC, experiments with PEO−PEOX and [PEO−PMOX]$_4$ (Figure S6 in SI). Interaction of Na[CoD] with each copolymer is exothermic and quite similar, indicating that the interaction of PEOX and PMOX segments with Na[CoD] is nearly identical. The saturation point is located slightly above $\xi = 0.1$ in both cases (ξ is defined as [CoD]$^-$-to-polymer segment molar ratio, where both PEO and POX segments are taken into account), and the overall "thermodynamics" is in fact the same. Additionally, ITC data for PEO and PEOX homopolymers (Figure S3) support our claims that the interaction of polymers with metallacarborane occurs mainly via ethylene units of the backbone.

We monitored the formation of hybrid nanoparticles during consecutive titrations of [PEO−PMOX]$_4$ and PEO−PEOX with Na[CoD] by means of static and dynamic light scattering, SLS and DLS. The dependences of (A) relative light scattering intensity and (B) hydrodynamic radius, R_H, on ξ are shown in Figure 1. Nanoparticle formation is substantially influenced by copolymer architecture. A diblock copolymer suddenly selfassembles into hybrid nanoparticles (R_H approximately 75 nm) at approximately $\xi = 0.1$ by the joining of large and loose preassociates. These large aggregates have also been observed for pure polymer solutions.[5e,10] The process is accompanied by a steep increase of LS intensity, reflecting the saturation of polymeric segments by $[CoD]^-$ and the formation of more compact nanostructures. In the case of star-like copolymers, the "transition" is not as obvious, even though the final step of nanoparticle formation is also observed at approximately $\xi = 0.1$. The resulting nanoparticles are surprisingly fairly small (R_H approximately 20 nm). Further LS results are shown in Figure S4 in SI.

The process of immobilization of PEO and POX segments after interaction with $[CoD]^-$ clusters was directly monitored by the diminishing of corresponding signals in ^{1}H NMR spectra (fraction of frozen polymeric segments shown in Figure S7 in SI together with further comments).[5b,d,e] In the PEO−PEOX system, POX segments are partially frozen, even at low metallacarborane concentration, and both types of segments are substantially immobilized after nanosphere creation at elevated Na[CoD] concentration (PEO approximately 70%, PEOX approximately 60%). In contrast, the incorporation of $[CoD]^-$ in the 4-arm system begins in the "central" area of the macromolecule in which PEO-blocks are located, and PEO segments are frozen to a larger extent than POX from early stages of hybrid nanoparticle formation. Clusters of $[CoD]^-$ are thus accumulated in fairly compact domains, surrounded by more flexible POX segments.

As shown above, NMR data at least partially reveal the degree of complexation of Na[CoD] by both types of block copolymers. Both blocks in linear diblock copolymers are intermixed, as previously discussed.[5e] In the case of star-like block copolymers, the simultaneous interaction of both PEO and POX segments with one bulky metallacarborane cluster is partially restricted due to steric hindrance. Furthermore, the density of PEO segments is fairly high in the central parts of the star, increasing the probability of PEO/Na[CoD] compartment formation.

Direct proof of our above assumptions is based on the visualization of corresponding nanostructures by means of cryo-TEM (Figure 2). AFM scans and further comments on AFM are included in SI for comparison (Figure S8). While the linear architecture of copolymers leads to homogeneous nanospheres with intermixed PEO and POX segments (Figures 2b and S5 in SI), the star-like shape manifests itself in the creation of compartments with dimensions of approximately 4 nm (Figure 2A). The number of compartments within each nanoparticle is in the range of several tens. In other words, $[CoD]^-$ clusters are not distributed evenly, as in linear diblocks, but are concentrated within the central areas of $[PEO{-}PMOX]_4$ star-like macromolecules, glued together by less-compact POX parts, thus, resembling core/shell units. As shown in Figure 2, the size distribution of both types of nanoparticles is quite broad. As we have previously observed,[5b,d,e] nanoparticle formation is kinetically controlled. Size distribution is thus affected by preparation protocol. The inner structure of the nanoparticles, however, remains unchanged.

Based on the proposed structures of both types of nanoparticles, we now seek to determine the types of interaction that keep such nanoparticles in solution. In addition to the role of the large fraction of segments, which are not affected by interactions with metallacarborane and remain mobile and hydrated,[5e] the nanoparticles are stabilized by their negative charge. We conducted electrophoretic light scattering experiments to determine the zeta-potential. In both cases, zeta-potential is approximately −30 mV, which indicates that there are a substantial number of negatively charged $POX/[CoD]^-$ segments in the outer parts of nanoparticles.

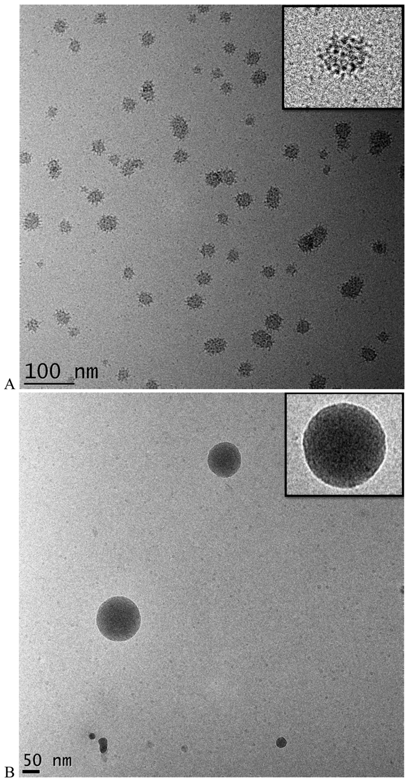


Figure 2. Typical cryo-TEM micrographs of (A) $[PEO{-}PMOX]_4$/Na[CoD], with a zoomed view of a compartmentalized nanoparticle, and (B) PEO−PEOX/Na[CoD], with a zoomed view of a homogeneous nanosphere, both in 0.154 M NaCl, $\xi = 0.4$.

Final proof of our assumptions and qualitative characterization of $[PEO{-}PMOX]_4$/Na[CoD] nanoparticles with various ξ were obtained by SAXS and SANS experiments. Here, we will discuss only the selected SAXS results. In Figure 3 there are representative SAXS curves of hybrid nanoparticles

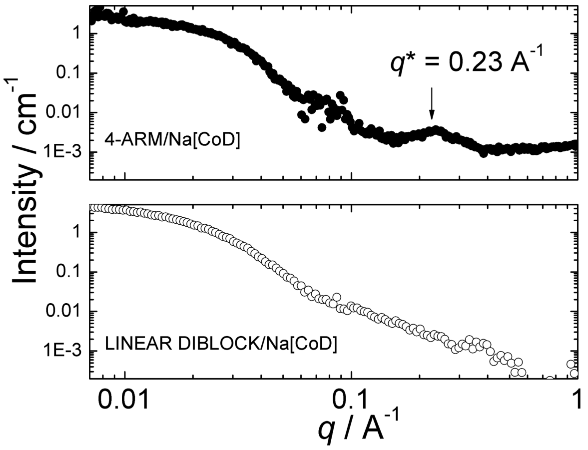


Figure 3. SAXS curves of (top) $[PEO{-}PMOX]_4$/Na[CoD] and (bottom) PEO−PEOX/Na[CoD] nanoparticles in 0.154 M NaCl at $\xi = 0.1$ and 0.15, respectively. The arrow indicates the position of a correlation peak for the star-like system.

for star-like (black points) and linear diblock (hollow points) systems. Further information for [PEO−PMOX]$_4$/Na[CoD] is given in SI and for PEO−PEOX/Na[CoD] in our previous paper.[5e] The most important feature is the presence of a correlation peak at 0.23 Å^{-1} (position not dependent on ξ) for multicompartmentalized nanoparticles that is not present in the case of all studied linear diblocks and triblock (see SAXS section in SI). The peak corresponds to distances between compartments of approximately 3 nm, which is close to the size of nanocompartments visualized by cryo-TEM in Figure 2A. The average number of [CoD]$^-$ clusters per polymer star was calculated from the saturation point of the ITC curve to be approximately 80. Assuming this value, we calculated the aggregation number of star-like macromolecules: N^{agg} = 30 (explained in detail in SI). Thus, metallacarborane clusters are compactly packed within the compartments that are most likely formed by one star-like macromolecule.

In conclusion, we have prepared hybrid metallacarborane-rich nanoparticles with distinct compartmentalization by the mixing of star-like double-hydrophilic polymer [PEO−PMOX]$_4$ with Na[CoD] in physiological saline. Each nanoparticle consists of approximately 30 compartments that are formed by one [PEO−PMOX]$_4$ macromolecule with approximately 80 [CoD]$^-$ clusters densely packed within the central parts of the compartment in which PEO segments are located. From our study, we have clearly demonstrated the tuning of hybrid nanoparticle morphology and size by choice of block copolymer architecture, which could be useful in the design of drug delivery vessels. In a subsequent study, we will extend the set of copolymer structures from star-like with POX in the center of macromolecule to stars with higher number of arms and other types of branched copolymers. The influence of alkyl side groups in POX segments on bonding with [CoD]$^-$ should also be examined in detail.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental section and further NMR, ITC, AFM, SAXS, and SANS data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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