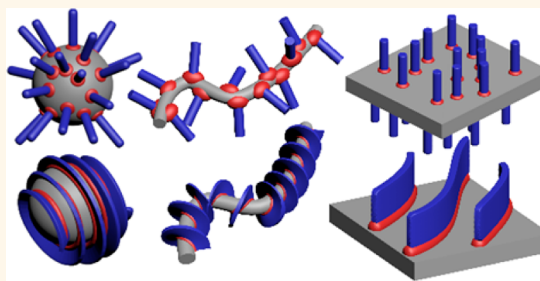


Polymers Zippered-Up by Electric Charge Reveal Themselves

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ABSTRACT In the current issue of *ACS Nano*, Löbbling, Haataja *et al.* craft polymeric nanoparticles with a hierarchy of nontrivial surface structures by combining conventional interpolyelectrolyte complexation with steric control from an uncharged copolymer block. Remarkable cylindrical and lamellar nanodomains are produced on the polyionic coronae of spherical micelles. Here, we discuss generalizing this elegant self-assembly strategy and provide speculative perspectives for its future potential for new nanomaterials.



One are the days when one could comfortably predict what every discipline stood for and what every research group studied; nowadays, chemists work on materials science, materials scientists work on bioengineering, and sometimes there seems no end to the permutation and cross-fertilization between scientific disciplines. Increasingly, the output of scientific papers represents more than any single person could accomplish on their own. A generation ago, when P.-G. de Gennes, the “Newton of his age”, received the Nobel Prize for putting the field of soft matter on strong principles of physics, the spirit of that time was to seek the most general, the most universal, the most fundamental. But today, we care more about useful functionality, about innovations whose value lies in particular materials systems; today, without wishing to over-generalize, nor to draw artificial distinctions, it is fair to say that the concerns of our scientific age have shifted from fundamentals toward complexity. Today, our community is intensely interested in the complexity of strongly correlated systems—what emerges from the balance of numerous interactions that compete without any of them dominating decisively. Often, the best such work marries two (or more) ways of thinking for the first time. A telling statistic is that scientific publications show increasing numbers of coauthors, more than 50% more on

average than a generation ago.¹ As for the number of coauthors: the popular press speaks of “hyperauthorship”² and “rise of the fractional author”.³ As for the mix of coauthors: scientifically, we live in an age of mixed marriages.

We call attention to a beautiful embodiment of this modern pattern: writing in this issue of *ACS Nano* with two equal first authors and eight coauthors *in toto*, a publication that unites four academic institutions and two countries.⁴ Their idea was to build upward from ampholytic triblock terpolymers, designed to form polymer micelles with negatively charged coronae. While their laboratory previously reported such “onion” or “core-shell-corona” structures,⁵ Coulombic attractions with additional charged chains give added value: they zipper the micelles together to form interpolyelectrolyte complexes with cationic/neutral diblock copolymers.

We encourage readers to look at these vivid structures, reproduced in Figure 1: some of them resemble spiky sea urchins, while others resemble the blades of turbines, depending (in rationally understandable ways) on the cationic/neutral ratio of the parent block copolymers. The demonstration of these new structures, which previous workers had neither predicted nor observed, epitomizes the appeal of complexity: the surprise that comes from careful study of complex systems. This

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In this issue of *ACS Nano*, Löbbling, Haataja, and co-workers show how triblock terpolymers and diblock copolymers self-assemble to structural shapes that possess unprecedented hierarchical complexity.

strategic design of charge mixing yields assembled structures efficiently. Driven by thermodynamics, this bottom-up approach to self-assembly is economical and convenient. This approach sidesteps alternatives that might be considered, such as microfabrication and surface

patterning, which can be laborious.^{6,7} Moreover, the size of these structures is dictated by the size of the parent polymers, smaller than 100 nm; these are length scales with which top-down techniques might begin to struggle.⁸

The subtle logic of the work by Löbbling, Haataja *et al.* is to sculpt these electrostatic complexes microscopically by steric control. While it is true that precise Coulombic control is commonplace in ionic crystals such as NaCl and that it can generate surprisingly complex colloid crystals,⁹ previously this had not been achieved for polymer chains. When these macro-ions of opposite charge mix, their high conformational flexibility usually creates complex structures whose molecular arrangement is random; “complex coacervation” results, a kind of phase separation such that the macroions neutralize one another in bulk solution while a population of residual charged groups

remain soluble.^{10–12} A similar limitation underlies film preparation through layer-by-layer (LBL) deposition,^{13,14} versatile and useful as this technique is. The innovation by Löbbling, Haataja *et al.* was to stabilize the chunks of interpolyelectrolyte complexation into regular patterns, capitalizing upon the steric control afforded by attaching a flexible polyethylene glycol (PEG) block to the charged block. Then, when the charged groups bundle into cylinders, the steric influence of PEG chains stabilizes the complexation domains that were formed in coronae of the micelles. There were hints of this approach in prior work: bis-hydrophilic diblock copolymers were formed by joining a nonionic polymer with an ionic chain and mixtures with an oppositely charged linear polyelectrolyte produced micelles.¹⁵ But going beyond this, in the new work reported here, phase segregation on the surface of the micellar nanoparticles is effectively

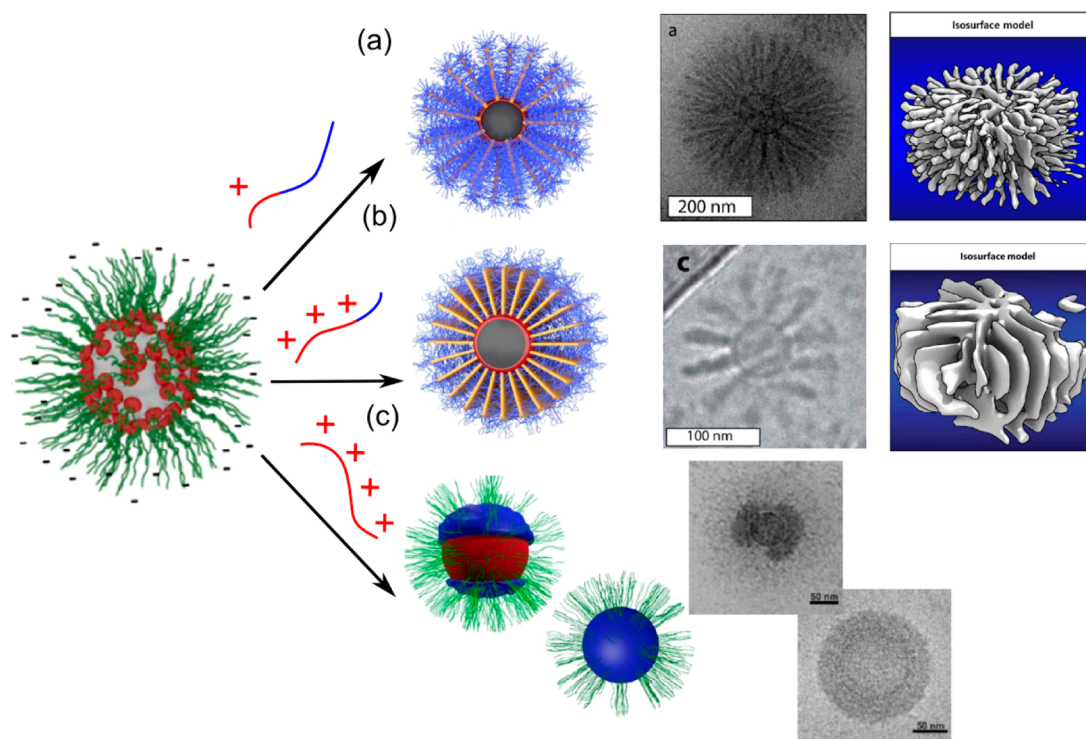


Figure 1. Cryo-transmission electron microscopy and cryo-electron tomography images of different micelle morphologies produced by control of cationic/neutral ratio of polyions. From top to bottom: (a) Löbbling, Haataja *et al.* used cationic/neutral copolymer to fabricate “sea urchin” micelles when the cationic part was short. Reprinted from ref 4. Copyright 2014 American Chemical Society. (b) When a different polymer with a longer cationic part was used, the resultant micelle had a “turbine” structure. Reprinted from ref 4. Copyright 2014 American Chemical Society. (c) By forming complexes with either all-cationic long or short polymer blocks, the resulting micelles could be designed to form either Janus or continuous structures, respectively. Reprinted from ref 17. Copyright 2013 American Chemical Society.

two-dimensional: the charged linear polyelectrolyte chains first group into coronae of micelles.

Remarkably, the phase diagram of this system can be manipulated depending on the chain length of each of the block copolymer segments. This is analogous to the famous hydrophilic–lipophilic balance (HLB) of lipid assembly;¹⁶ the dominant steric influence can be explained simply by the relative volume fraction of PEG chains. Hierarchical structures would arise only for those coronae whose thickness exceeds the diameter of the hydrophobic core of the micelle; in other words, the brushes must be long enough. Then charge–charge domains will develop either as isolated cylindrical bundles or percolated lamellar shells, depending on the PEG chain length (Figure 1a,b). By this logic, it is reasonable to expect that using only charged blocks would produce phase-separated electrostatic domain coronae of micelles (Figure 1c).¹⁷ In addition, micelles with too-thin coronae will just produce homogeneous charge–charge domains (Figure 1c).¹⁷ Overall, this approach to designing block copolymers by a generalization of the HLB idea¹⁸ holds great promise as a versatile, generalizable route to produce nanoparticles with naturally developed surface patterns.

Without definitive characterization of these structures, these hypotheses grounded by physical arguments would be at best guesswork. Going beyond the traditional cryo-transmission electron microscopy (cryo-TEM) characterization of polymeric micelles and coacervates, Löbbling, Haataja *et al.* show the value of cryogenic transmission electron tomography (cryo-ET), which is a three-dimensional (3D) mapping method (Figure 1a,b). The image contrast is sufficiently high between the solvent (water) and the organic phase (micelles). Previously, characterization with such high accuracy (0.1–1 nm resolution) in 3D might, for most material scientists, have seemed just a dream. With this and

other related studies¹⁹ elucidating otherwise-unidentifiable structures, we foresee improved accuracy in interpreting micelle structures using this new 3D imaging tool as use of the technique spreads, though the technique is still troubled by dosage damage from electron beams when it is applied to all-organic materials. It should be interesting to revisit older supramolecular assembly identifications in the literature^{20,21} using this new technique.

Beyond the polymeric micelles studied in this paper, the three-dimensional morphologies of phase-separated polymer blends and nanocomposites may also be interesting candidates for study.

PROSPECTS

The classical block copolymer phase diagrams, predicated on the χ parameter²² to quantify materials incompatibility, can be rationally extended to aqueous systems, although we are at an early stage of doing so with rigorous theoretical

models. Aqueous systems are now fair game for rational design. This comprises a rich playground and exciting new opportunities for crafting new polymeric nanomaterials.²³ There are potentials to impart new, innovative functionality to applications such as biomaterial and drug delivery design.²⁴

From physical reasoning, we envision that interpolyelectrolyte complexation should likewise potentially enable other terpolymer micelles, micelles with added structure. Whereas the study by Löbbling, Haataja *et al.* revolves around using spherical micelles, it is natural to extrapolate further. From the same HLB argument, one can imagine changing the shape of the micellar precursor by changing the length ratio between hydrophobic and hydrophilic blocks. With this strategy, spherical micelles should be easily transformed to wormlike chains (cylindrical micelles) and even bilayers (platelet micelles) if the relative size of the hydrophobic block is increased. Therefore, it seems safe to predict that one can further achieve similar bundles or lamellae on cylinders or plates, provided that these less symmetric micelles are encouraged to form complexes with charged diblock copolymers. Figure 2 shows hypothetical structures when isolated domains and lamellae are produced along a tube or and a flat surface. It will be

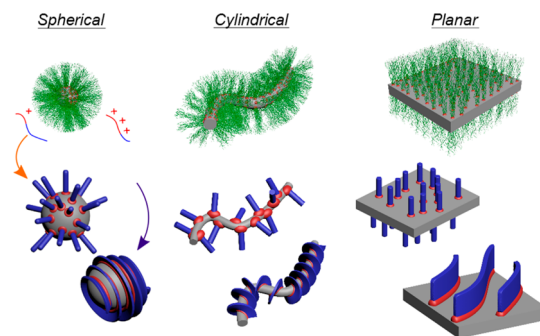


Figure 2. By varying the hydrophobic–hydrophilic block ratio, we envision that additional micellar template morphologies (spherical, cylindrical, and planar) should be possible. As Löbbling, Haataja *et al.* already demonstrated, mixing two different polyions within the same charged micelle generated “sea urchin” and “turbine” corona morphology. Extending this idea, one may imagine mixing such polyions with cylindrical, oppositely charged micelles to give “cactus” or “corkscrew” shapes, depicted schematically in this figure. Similarly, starting with planar micelles, one may obtain “nail bed” or “fish scale” structures, also depicted here.

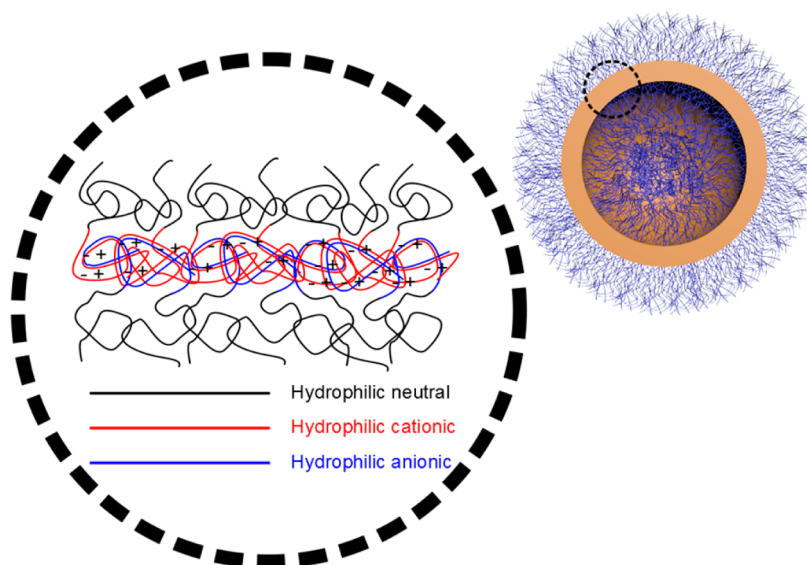


Figure 3. Concept of “catanionic” vesicles inspired by interpolyelectrolyte complexation. While the oppositely charged blocks attract and phase separate into the insoluble inner layer, the neutral hydrophilic blocks stabilize the structure in an aqueous medium.

intriguing to understand how this surface complexation depends on the curvature of the precursor micelles, as can be expected on physical grounds. This can be tested in both experiment and theory.

Second, we envision “catanionic”²⁵ vesicles of block copolymers with interpolyelectrolyte complexes, which, if successful, would be an application with evident use for microencapsulation, for example (Figure 3). The known examples of mixing cationic and anionic surfactants are limited to producing catanionic bilayer vesicles, however.^{25,26} The same success has not yet been met for oppositely charged block copolymers; the pioneering work in this field had succeeded only in crafting spherical micelles by mixing oppositely charged bis-hydrophilic diblock copolymers in which the core was insoluble due to charge neutralization. Now that Löblich, Haataja *et al.* have extended this principle potentially to one-dimensional chains and lamellar layers, with morphology controlled by the ratio between uncharged steric block and charged block, one should expect similar structures to form in the bulk: wormlike chains and bilayer vesicles. This self-assembly, induced by charge mixing, could present advantages relative to the more

conventional assembly driven by hydrophobicity, because of better solubility in aqueous environments. Indeed, recognizing that the strength of interpolyelectrolyte pairing depends on ionic strength in the aqueous solution, this can potentially be used as a novel stimulus response for encapsulation nanomaterials.²⁷

Third, beyond the observation of frozen cryo-electron microscopy states reported in this paper, states in which structural damage is minimized owing to the low temperature, one can dream of observing dynamics *in situ*, without the need for low temperature. Recently, in an explosion of technique development, proteins and nanoparticles suspended in water have been observed in real-time in microfabricated cells with silicon nitride windows²⁸ and in graphene liquid cells.²⁹ With improving detection schemes and improved scanning techniques³⁰ we might see 3D *in situ* electron microscopy soon, to make the “invisible” visible.

As a final speculative observation, we call attention to the fact the promise and pitfalls of this field as it continues to develop so well. On the auspicious side, the numerous parameters that matter in designing triblock copolymers will

give immense freedom to polymer scientists to fabricate micelles of different, tailored morphologies. On the pitfall side, it is important to make the experimental data in the literature readily accessible to researchers. We may take inspiration from the massive protein database in the biology community. In fact, in the literature there is already the suggestion³¹ that a data structure of block copolymer micelles should be established in which the lengths of the different constituent are varied systematically (and to this list, we add the wish to vary the degree of charge). This may help answer basic questions when all the experimental results will have been placed “on the table” and allow scientists to mine data to search for hidden patterns.

Conflict of Interest: The authors declare no competing financial interest.

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