

### Supramolecular Chemistry

# **Supramolecularly Engineered Amphiphilic Macromolecules: Molecular Interaction Overrules Packing Parameters**

Prithankar Pramanik, Debes Ray, Vinod K. Aswal, and Suhrit Ghosh\*

Abstract: We report molecular interaction-driven self-assembly of supramolecularly engineered amphiphilic macromolecules (SEAM) containing a single supramolecular structuredirecting unit (SSDU) consisting of an H-bonding group connected to a naphthalene diimide chromophore. Two such SEAMs, P1-50 and P2-50, having the identical chemical structure and hydrophobic/hydrophilic balance, exhibit distinct self-assembled structures (polymersome and cylindrical micelle, respectively) due to a difference in the H-bonding group (hydrazide or amide, respectively) of the single SSDU. When mixed together, P1-50 and P2-50 adopted self-sorted assembly. For either series of polymers, variation in the hydrophobic/hydrophilic balance does not alter the morphology reconfirming that self-assembly is primarily driven by directional molecular interaction which is capable of overruling the existing norms in packing parameter-dependent morphology control in an immiscibility-driven block copolymer assembly.

Amphiphilic block copolymers<sup>[1]</sup> produce wide-ranging elegant mesoscopic structures<sup>[2]</sup> with close relevance for nanotechnology and biomedicine.<sup>[3]</sup> In a majority of examples the morphology of a block copolymer nanostructure relies on the packing parameters<sup>[4]</sup> determined by the relative length and volume of the hydrophobic and hydrophilic blocks which does not endow precision and structural control at the molecular scale. On the other hand for bio-macromolecules, an alteration in the sequence of a single amino acid or mismatch in one base pair could make vital difference to the overall structure and function. To explore such possibilities in synthetic polymers, we have studied the self-assembly of supramolecularly engineered amphiphilic macromolecules (SEAM; Scheme 1) which consist of a supramolecular structure-directing unit (SSDU) located at the junction of a hydrophilic polymer and a hydrophobic wedge. We asked the question whether in such systems, a specific directional molecular interaction among the single SSDU (Scheme 1)<sup>[5]</sup>

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**Scheme 1.** Structure of the SEAMs and a schematic showing directional molecular interaction-driven distinct self-assembly.

would be able to dictate the formation of a mesoscopic structure by overruling the packing parameters. Here we show that the nanostructures generated from P1-50 and P2-50 (Scheme 1), which differ merely by a single H-bonding group of the SSDU, are fully regulated by the self-assembly motif of the SSDU, and the packing parameters are ignored. Remarkably even in their mixture the individual SSDUs maintain their self-identity which results in self-sorting.

P1-50 and P2-50 were synthesized (see Scheme S1 in the Supporting Information) by RAFT polymerization of the oligo-oxyethylene-attached hydrophilic methacrylate derivative using functional chain-transfer agents containing the corresponding SSDU and the hydrophobic wedge. P1-50 and P2-50 were isolated in 72% and 80% yield, respectively. The polymers were characterized unambigously by <sup>1</sup>H NMR spectroscopy (see Figure S1 in the Supporting Information). By comparing the UV/Vis (Figure S2) and <sup>1</sup>H NMR (Figure S3) spectra of the polymers with those obtained for the SSDU-functionalized chain-transfer agents, it is obvious that the dithioester group remains intact at the other chain terminal of the polymer. Gel permeable chromatography analysis showed (Figure S4) monomodal peaks corresponding to molecular weights corroborating with those values obtained theoretically or estimated from the end group analysis using NMR spectroscopy (Table S1). The SSDU, by design, consists of a naphthalene diimide (NDI) chromophore and a H-bonding functional group (hydrazide and amide, respectively, for P1-50 and P2-50) to facilitate synergistic operation of the H-bonding and aromatic interaction

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(Scheme 1).<sup>[5,6]</sup> UV/Vis spectra of both the polymers in THF show (Figure 1 a) sharp absorption bands with vibronic features indicating non-interacting NDI. In  $H_2O$ , the spectra exhibit a bathochromic shift of 3.0–4.0 nm together with



Figure 1. a) Absorbance b) emission ( $\lambda_{ex}\!=\!340$  nm) and c) FTIR spectra of P1-50 (black) and P2-50 (gray) in solvent (dotted line) (THF-UV and PL, CHCl<sub>3</sub>-IR) and water (solid line);  $C\!=\!1.0$  mg mL $^{-1}$  for absorbance and emission spectra and 10 mg mL $^{-1}$  for FTIR spectra.

a reversal of the intensity for the peaks at 381 and 360 nm and an overall reduction in the intensity, which is indicative of an aromatic interaction among the NDI chromophores<sup>[5]</sup> and is further supported by fluorescence quenching (Figure 1b). A significant upfield shift of the NDI ring protons in the <sup>1</sup>H NMR spectra of the polymers in D<sub>2</sub>O compared to the spectra in CDCl<sub>3</sub> (Figure S5) reconfirmed the  $\pi$ -stacking.

Variable-temperature UV/Vis studies (Figure S6) show no change in the spectral features (except the increase in the baseline intensity) even above 80 °C indicating a very high thermal stability. The increase in baseline intensity at elevated temperatures is attributed to scattering beyond the lower critical solution temperature (LCST)<sup>[7]</sup> of the hydrophilic block which was estimated to be 44 and 42 °C for P1-50 and P2-50, respectively (Figure S6).

Although the hydrophobic content in these polymers is only 6 wt% they still show self-assembly at very low concentrations  $(CAC < 0.5 \text{ mg mL}^{-1})$  and high temperatures indicating the strong impact of the directional interaction between the SSDU involving synergistic H-bonding and aromatic interactions. In fact H-bonding was directly probed by FTIR spectroscopy (Figure 1c). For P1-50 in CDCl<sub>3</sub>, two peaks at 3524 and 3423 cm<sup>-1</sup> are assigned to the OH stretching (from residual water) and non-bonded NH stretching, respectively. In D<sub>2</sub>O, the appearance of a distinct peak at 3334 cm<sup>-1</sup> indicates strong H-bonding among the hydrazide groups. Likewise for P2-50, similar observations were made by comparing the spectra in CDCl<sub>3</sub> and D<sub>2</sub>O confirming Hbonding interactions among the amides in P2-50. TEM images

(Figures 2a, S7) show hollow spherical objects for P1-50 with an average diameter of about 300 nm indicating polymersome formation.<sup>[8]</sup> A similar spherical morphology was also observed in the AFM image (Figure S9). The size obtained from microscopy images corroborates with the dynamic light scattering (DLS) data (Figure 2d) revealing a single peak with a particle size of 300-400 nm. In contrast, TEM images of P2-50 (Figures 2b, S8) reveal a spherical micellar morphology with a relatively small diameter (80-120 nm) corroborating with the DLS (Figure 2e). Intriguingly the DLS data of the P2-50 solution after 100 h show (Figure 2e) complete disappearance of the initial peak at 80-120 nm and the emergence of a new relatively broad peak corresponding to larger particle sizes indicating a morphology transition. Time-dependent DLS studies of over 100 h indicate (Figure S10) a gradual increase in the particle size and a saturation after 72 h. Nonetheless, no such variation was observed for P1-50 (Figures 2d, S10) suggesting stability of its polymersome structure. The intrinsic viscosity of the freshly prepared aqueous solutions of P1-50 and P2-50 were comparable as expected because of the similar spherical morphology. The value remained almost unchanged after 72 h for P1-50 while that for P2-50 showed a five-fold increase (Figure 2 f) further confirming a morphology transition in this case selectively leading to larger entangled structures. This could be clearly visualized in the TEM images of the aged sample of P2-50 revealing cylindrical micelles (Figure 2c, S8)<sup>[9]</sup> with a length and diameter in the range of 1.5 µm-4.5 µm and 50-130 nm, respectively. Likewise the AFM images (Figure S9) also show a transformation of the initially formed spherical structure to elongated fibrils after aging. In these three distinct assembled structures (polymersomes, spherical micelles, cylindrical micelles), organization of the alkyl chains of the hydrophobic wedge is expected to be different.



**Figure 2.** HRTEM images (negative staining with uranyl acetate for a and c) of a) P1-50, b) P2-50 (freshly prepared), and c) P2-50 (aged) in aqueous solution. Dynamic light scattering (DLS) plot of d) P1-50 and e) P2-50 in initial state (black line) and aged state (gray line). f) Intrinsic viscosity in initial state and aged state of P1-50 (black) and P2-50 (gray). g) Variation of GP for the Laurdan dye with time after it is encapsulated in the aqueous solution of P1-50 or P2-50 (Concentration of polymers = 1.0 mg mL<sup>-1</sup> and laurdan dye = 0.01 mM). For HRTEM and DLS, concentration of the polymers were 1.0 mg mL<sup>-1</sup>.

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$$GP = \frac{I_{440} - I_{490}}{I_{440} + I_{490}} \tag{1}$$

where  $I_{440}$  and  $I_{490}$  are the steady-state emission intensities (from the excitation spectra) at 440 and 490 nm, respectively. Laurdan was encapsulated in the aggregates of P1-50 and P2-50 and from time-dependent fluorescence excitation spectra (Figure S11) GP was estimated according to the abovementioned formula. At the beginning, GP for P1-50 was 0.5 (Figure 2g) indicating a highly ordered microenvironment as reported for membranes. The value did not change (Figure 2g) during the tested time span (21 h) supporting stable polymersome assembly. In sharp contrast, for P2-50, values of GP close to zero for freshly prepared solution clearly indicate lack of ordering among the alkyl chains which is expected for micellar structures. Interestingly, in this case the value gradually increases and saturates at about 0.3 after 4 h (Figure 2g) which can be related to the morphology transition from spherical to cylindrical micelles.<sup>[11]</sup> From the increase in GP, it is evident that in cylindrical structure the alkyl chains are organized more effectively than the initially formed spherical aggregates and that could be the driving force for the transformation. Nonetheless, even after prolonged aging the value of GP of encapsulated Laurdan in P2-50 did not reach that of P1-50 indicating the fluidity of the hydrophobic domain is gel-like for P1-50 while liquid-crystal-like in P2-50.[10]

To get more structural insight, small-angle neutron scattering (SANS) experiments were performed in  $D_2O$ . Distinctly different scattering patterns for P1-50 and P2-50 (Figure 3 a) clearly support formation of different mesoscopic structures. Fresh P2-50 data could be well fitted using a spherical core-shell micellar model which considers hydrophilic chains (characterized by the radius of gyration,  $R_{g}$ ) attached to the hydrophobic core of the micelle (characterized by the core radius,  $R_c$ ). The analyzed value of  $R_c$  is found (Table 1) to be larger than the roughly estimated length of the hydrophobic block (ca. 35 Å). This could be arising from the propagation of hydrophobic environment up to some part of the hydrophilic block.<sup>[12]</sup> Upon aging, the shape of the micelles has been found to transform from spherical to long cylindrical ones as evidenced in the DLS/TEM measurements. In this case, the length of these long cylindrical micelles will be reflected in the further lower Q region which is beyond the accessible  $Q_{\min}$  of this SANS instrument (i.e.  $2\pi/$  $Q_{\min} \approx 350$  Å). Nonetheless the inset of Figure 3a highlights the formation of elongated structures through the simulated scattering data for aged P2-50 (considering long cylindrical micelles) extended up to the lower-Q region. On the other hand, P1-50 has been found to form large unilamellar vesicles (LUV). These vesicles have been characterized by the thickness of the hydrophobic component (t; Table 1) as the measurement of the radius of vesicles is limited by the  $Q_{\min}$  of



**Figure 3.** a) SANS data of P1-50 and P2-50 (fresh and aged). Inset: Extended fitted scattering data up to lower-Q re-gion for cylindrical micellar structure of aged P2-50. b,c) SANS profiles for aqueous solutions of P1 and P2 series of polymers. The solid curves are the theoretical fits to the experimental data.

**Table 1:** SANS data of P1-50 and P2-50 in  $D_2O$  (C = 10.0 mg mL<sup>-1</sup>).

SEAM	Structural parameters	Structure
P2-50: fresh	radius of hydrophobic core $R_c = 56.8 \pm 1.9$ Å, polydispersity $\sigma = 0.32$ , radius of gyration of hydrophilic chains $R_g = 16.6 \pm 0.6$ Å	spherical micelle
P2-50: aged	cross-sectional core radius $R_{cs} = 58.4 \pm 2.0$ Å, polydispersity $\sigma = 0.37$ , radius of gyration of hydrophilic chains $R_{g} = 16.6 \pm 0.6$ Å	cylindrical micelle
P1-50	membrane thickness $t = 44.6 \pm 1.6$ Å	unilamellar vesicle

the SANS instrument. Notably the estimated hydrophobic thickness of the vesicle (ca. 45 Å) formed by P1-50 is significantly shorter than twice the length of the hydrophobic segment of P2-50 indicating efficient inter-digitation of the peripheral alkyl chains.

Generally the morphology of block copolymer aggregates depends on the packing parameter (*p*). Spherical micelles, cylindrical micelles or polymersomes are formed when  $p \le 1/$ 3, 1/3 , and <math>1/2 , respectively.<sup>[4]</sup> Contrary tosuch existing norms, the current examples of self-assembly ofSEAMs are unique because P1-50 and P2-50 form distinctlydifferent morphologies although having identical*p*parameters as in both cases the hydrophobic wedge and the hydrophilic polymer are the same. Therefore it is evident that theassembly is not driven by immiscibility, rather it is overruledby specific self-assembly motifs of the particular SSDU. Nowthe SSDU consists of hydrazide and amide in P1-50 and P2-50, respectively, which significantly differs in terms of

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flexibility. The rigid hydrazide groups produce a stiff chain by extended hydrogen bonding which allows the hydrocarbon chains to crystallize and form a bilayer that eventually generates a polymersome structure. On the other hand the flexibility of the amide group due to the presence of the two methylene units between the amide group and the NDI chromophore appears to allow the H-bonded chains adequate flexibility and therefore the supramolecularly assembled P2-50 collapses to a spherical micellar structure (kinetic product) which eventually reorganizes to generate the more stable cylindrical micelles. To what extent does molecular assembly overrule the packing parameter? To answer this question we have studied P1-25 and P1-100 (Scheme 1) where the SSDU remains the same like in P1-50, but the degree of polymerization of the hydrophilic block changes significantly (Table S1). They showed exactly identical SANS profiles (Figure 3b) suggesting polymersome structures in all cases. Likewise, in P2 series (Scheme 1), for all three polymers micellar structures were evident from the very similar SANS pattern (Figure 3c). Microscopy images of P1-25, P1-100, P2-25, and P2-100 (Figures S13-16) corroborate with the results obtained from SANS measurements and therefore are consistent with the hypothesis. For P1-100 or P2-100, the hydrophobic wedge is merely 3 wt% with respect to the entire polymer and still they exhibit facile assembly which reveals the supremacy of directional interaction between the SSDU which ignores the hydrophobicity factor and overtakes the classical norms of block copolymer self-assembly depending on packing parameters.

When mixed together, will P1-50 and P2-50 co-assemble or form self-sorted structures? To probe that by FRET, we have synthesized P1-50-R, P1-50-G, and P2-50-R (Figure 4a) which are structurally similar to P1-50 or P2-50 except for the presence of attached red or green dyes (10-15%). Absorption and emission spectra of these polymers (Figure S17) confirm the successful attachment of the rhodamine dye (R) to P1-50-R and P2-50-R while in P2-50-G the naphthalene-monoimide dve (G) is attached.<sup>[13]</sup> A mixture of P1-50-G + P1-50-R in THF shows negligible emission at the acceptor (R) site when excited at the absorption wavelength of the donor (440 nm) indicating no FRET (Figure 4b) as expected because there is no self-assembly in THF. But in aqueous medium, a strong emission is noticed at 594 nm which is attributed to FRET. This observation confirms co-assembly of the two polymers (as expected in this case because both belong to the P1 series) and puts the appended red and green emitting dye molecules within their Forster distance (52.28 Å).<sup>[13]</sup> Now under identical conditions, P1-50-G + P2-50-R shows a contrasting behavior as FRET is negligible (blue line, Figure 4b) indicating a self-sorted assembly.<sup>[14,15]</sup> Furthermore, the merged fluorescence microscopy image of freshly prepared P1-50-G + P2-50-R (Figure 4c-e) of shows red and green emission from different particles (Figure 4e) confirming self-sorting.<sup>[15]</sup> The control experiment of P1-50-G + P1-50-R, in contrast, shows a yellow emission (Figure 4h) for the merged image indicating that the red and green emissions arise from the same particle. TEM images (Figures S18-19) also show co-existence of polymersome + spherical micelles (fresh sample) or polymersome + cylindrical micelles (aged sample) and thus



**Figure 4.** a) Structure of fluorescently labeled SEAMs. b) Solvent-dependent emission spectra of (P1-50-R + P1-50-G) and (P2-50-R + P1-50-G). The intensity was normalized at the donor (P1-50-G) emission.  $\lambda_{ex} = 440$  nm. c–h) Fluorescence microscopy images of freshly prepared P2-50-R + P1-50-G (left) and P1-50-R + P1-50-G (right). c,f) Green channel emission. d,g) Red channel emission. e) Merged image of (c) and (d). h) Merged image of (f) and (g).

further support the self-sorting between P1-50 and P2-50. This is believed to be a consequence of the fact that due to the mismatch in the spacer length between the H-bonding group and the NDI ring of the two different SSDU, a synergistic effect of H-bonding and aromatic interaction was not achieved.

In summary we have established that a directional molecular interaction can overturn the classical norms of block-copolymer self-assembly driven by packing parameters. Consequently, two such block copolymers with identical chemical structures and the same hydrophobic/hydrophilic balance organized in a distinct manner form either cylindrical micelles or polymersomes depending on whether the SSDU contains an amide or a hydrazide functional group, respectively. On the other hand for same series of polymers containing either an amide or hydrazide group at the SSDU,

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the difference in the packing parameters by varying the degree of polymerization of the hydrophilic block did not alter the self-assembled structure. In a mixture of amide and hydrazide-containing polymers self-sorted assembly was noticed and all existing rules of polymer mixing/segregation were ignored. In the recent past there has been great interest in studying living crystallization driven self-assembly<sup>[9,16]</sup> of block copolymers. Compared to those systems, the present design is a significant step forward because in this case the self-assembly is driven by specific directional molecular interaction among a single SSDU present in the entire polymer chain which brings new opportunities for controllable mesoscopic structure formation of the macromolecules in solution and solid state with precision at the molecular scale.

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#### **Conflict of interest**

The authors declare no conflict of interest.

**Keywords:** amphiphilic polymer · cylindrical micelle · fluorescence · polymersome · supramolecular assembly

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Supramolecularly Engineered Amphiphilic Macromolecules: Molecular Interaction Overrules Packing Parameters



**Amphiphilic block-copolymers**: A directional molecular interaction overrules classical packing parameters and enacts new rules for the self-assembly of supramolecularly engineered amphiphilic polymer assemblies. The self-assembly is governed by a distinct H-bonding motif of a single H-bonding moiety present in the entire polymer chain.

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