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Solution-Phase Self-Assembly of Complementary Halogen Bonding Polymers

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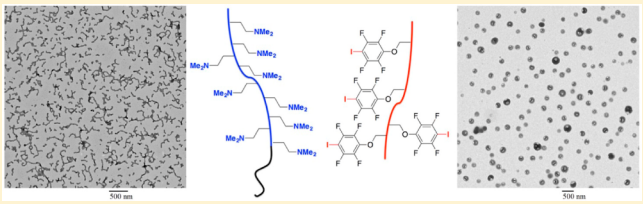
Supporting Information

ABSTRACT: Noncovalent halogen bonding interactions are explored as a driving force for solution phase macromolecular self-assembly. Conditions for controlled radical polymerization of an iodoperfluoroarene-bearing methacrylate halogen bond donor were identified. An increase in association constant relative to monomeric species was observed for the interaction between halogen bond donor and acceptor polymers in solution. When the polymeric donor was combined with a block copolymer bearing halogen bond-accepting amine groups, higher-order structures were obtained in both organic solvent and in water. Transmission electron microscopy, dynamic light scattering and nuclear magnetic resonance spectroscopic data are consistent with structures having cores composed of the interacting halogen bond donor and acceptor segments.



INTRODUCTION

Self-assembly of macromolecules into higher-order structures such as micelles and vesicles is of fundamental interest, and applications of the resulting structures in medicine, nanotechnology, catalysis, and materials design have been demonstrated or proposed. Block copolymers often generate higher-order structures due to solubility differences between the blocks.[1] Variations in block size, polydispersity and assembly conditions can influence the structures obtained.[1−3] A complementary approach to obtaining such structures employs noncovalent or reversible covalent interactions (e.g., metal−ligand complexation, ion-pairing or hydrogen bonding) between functionalized polymers: straightforward tuning of the dimensions and/or types of structures, and modulation of the assembly with external stimuli, are possible using this strategy.[4] Here, we show that halogen bonding interactions between complementary polymers can be used to drive macromolecular self-assembly in both organic solvent and in water.

Halogen bonding (XB) is the noncovalent interaction between a covalently bound, electrophilic halogen (the donor) and a nucleophilic moiety (the acceptor).[5] While the first systematic studies of XB were carried out decades ago, recent research activity has yielded new insight into the nature of the interactions and has generated applications in crystal engineering,[6] medicinal chemistry,[7] ion binding and transport,[8] templated synthesis[9] and catalysis.[10,11] This work has also pointed toward distinctions between XB and the more widely exploited hydrogen bonding (HB) interaction, including the relatively stringent directionality (preference for a 180° noncovalent bond angle) of XB[12] as well as apparent, subtle differences in the dependence of interaction strengths on acceptor structure and solvent.[13] Other features of XB that are potentially complementary to those of HB include the hydrophobic nature of commonly employed halogen bond donor groups (e.g., iodoperfluoroorganics) and the ability to vary the donor strength by changing a single substituent, exploiting the trend in donor ability R−F ≪ R−Cl < R−Br < R−I. The distinct features of XB, and the fact that applications of XB in polymer chemistry are sparse, motivated us to explore interactions between polymeric halogen bond donor/acceptor pairs. Precedent for this work includes the incorporation of iodoperfluorophenyl groups into molecularly imprinted polymers,[14] the layer-by-layer assembly of an iodoperfluoroarene-functionalized polyacrylate with poly(4-vinylpyridine),[15] interactions of poly(4-vinylpyridine) with halogen bond donors,[16] the use of XB to trigger formation of a supramolecular gel,[17] and the alignment of star-poly(ethylene oxide) into lamellar structures ordered up to the millimeter scale.[18]

RESULTS AND DISCUSSION

Polymer Synthesis. The syntheses of the macromolecules employed in this study are depicted in Scheme 1. A block copolymer of ethylene oxide and 2-(dimethylamino)ethyl methacrylate (PEO-*b*-PDMAEMA) was chosen as the acceptor.[19] It is well established that amphiphilic block copolymers of PEO can undergo controlled assembly under a wide range of conditions.[20] Here, the hypothesis was that halogen bond donor−acceptor pairs would form the core of assemblies, with the noninteracting PEO blocks at the periphery. Sterically unhindered amine groups such as those present in the PDMAEMA segment are known to participate in favorable halogen bonding interactions with iodoperfluoroalkanes and -arenes.[13b,c] Atom-transfer radical polymerization[21] (ATRP) using PEO-derived macroinitiator **1** was employed to prepare the target macromolecules PEO-*b*-PDMAEMA (**2b**−**2e**). A

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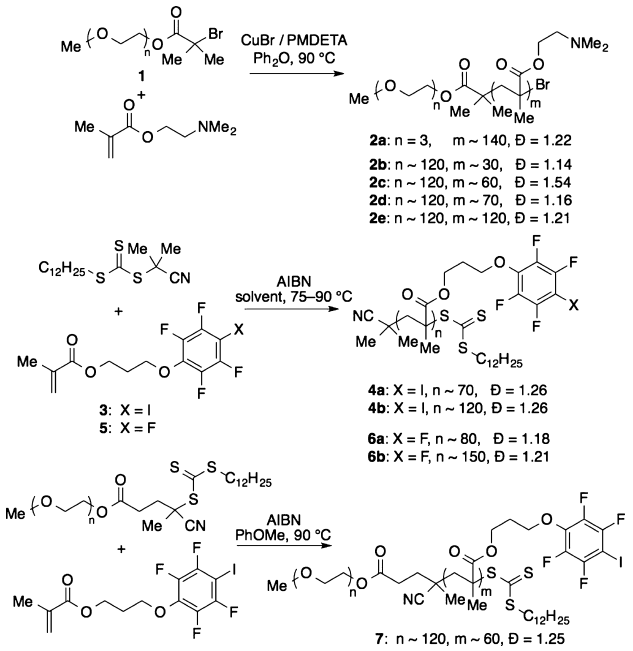
Scheme 1. Preparation of Polymeric Halogen Bond Acceptors (2a–2e), Donors (4a, 4b, 7) and Perfluorinated Controls (6a, 6b)[a]



[a]PMDETA and AIBN denote pentamethyldiethylenetriamine and azobis(isobutyronitrile), respectively. The polymerization solvent was toluene for **4a**, anisole for **4b** and **6b**, and benzene for **6a**.

PDMAEMA homopolymer (**2a**) was produced using a triethylene oxide-derived initiator. Degrees of polymerization were determined by ^{1}H NMR spectroscopy using the signal corresponding to the terminal methoxy group of the PEO segment for reference, and dispersities were determined by gel permeation chromatography (GPC).

An iodotetrafluorophenoxy substituted polymethacrylate was targeted as the donor. Whereas the uncontrolled radical polymerization of an iodoperfluorophenoxy-functionalized acrylate of similar structure to **3** has been reported,[15] a material of low dispersity was needed for the present application. We thus investigated controlled radical polymerizations of **3**, with identification of conditions that would be compatible with the weak C–I bond of the halogen bond donor monomer being an important consideration. Control experiments revealed that in the presence of exogenous iodopentafluorobenzene (C_6F_5I), Cu(I)-mediated ATRP of methyl methacrylate was unsuccessful. Low monomer conversions were observed, along with the formation of decafluorobiphenyl, presumably by Ullman-type homocoupling of C_6F_5I.[22] On the other hand, reversible addition–fragmentation chain-transfer polymerization (RAFT)[23] proved to be a viable method. Using a trithiocarbonate as chain transfer agent, the halogen bond donor polymers **4a** and **4b** were generated. Using the signal in the ^{1}H NMR spectrum corresponding to the methylene group adjacent to the trithiocarbonyl moiety, degrees of polymerization of roughly 70 and 120 were determined for **4a** and **4b**, respectively. No degradation of the iodotetrafluorophenoxy groups was observed by ^{19}F NMR spectroscopy. GPC analysis gave a polydispersity of 1.26 for both **4a** and **4b**. Using a PEO-derived macro-chain transfer agent, donor copolymer **7** was obtained. Monomer **5**, having pentafluorophenoxy in place of iodotetrafluorophenoxy groups, was subjected to the same protocol to generate control polymers **6a** and **6b** lacking the ability to act as halogen bond donors.

^{19}F NMR Spectroscopic Studies of Interpolymer Halogen Bonding Interactions in Toluene. ^{19}F NMR spectroscopy was used to study the association between polymers **2a** and **4b** in toluene solution. Halogen bonding of iodoperfluoroarenes with Lewis bases is signaled by upfield changes in ^{19}F NMR chemical shift for the fluoro substituents *ortho* to the iodo group.[13b–d] The concentration dependence of these changes can be used to determine association constants for XB interactions.[24] Spectral changes of this type were observed upon addition of **2a** to **4b** in toluene, and the data could be fit to a 1:1 binding model based on the concentration of monomer units (Figure 1). An association constant (K_a) of

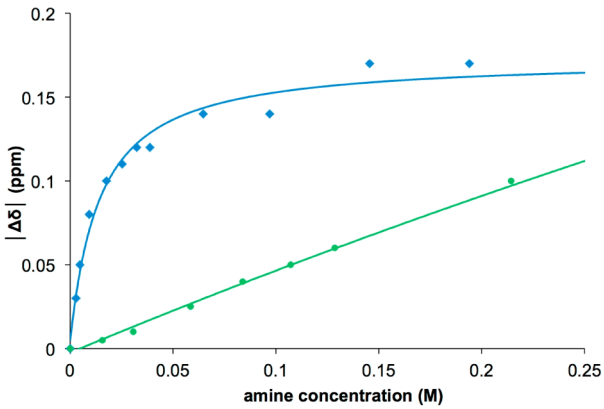


Figure 1. Plot of change in ^{19}F chemical shift ($|\Delta\delta|$) versus amine concentration for interactions between polymers **2a** and **4b** (◆, blue), and the corresponding methacrylate monomers (●, green). The curves represent the equations of best fit to 1:1 binding models (K_a = 74 and 0.5 M^{-1}, respectively). Data are fit to the concentration of monomer units.

72 M^{-1} was determined by taking the average value from three separate titration experiments. Under the same conditions, the association constant between the corresponding methacrylate monomers (K_a < 2 M^{-1}) was roughly 2 orders of magnitude lower than that of the polymers. These data indicate that **2a** and **4b** interact through halogen bonding interactions with an appreciable degree of chelate cooperativity.[25] It should be noted that although the amine concentration needed to reach saturation in the polymer–polymer titration was significantly lower than that for the monomer–monomer titration, the maximum change in chemical shift ($\Delta\delta$) obtained at saturation was also lower for the polymeric system. The maximum value of $\Delta\delta$ obtained from curve-fitting of the monomer titration data was −1.1 ppm, which is consistent with our previous results for halogen bonding interactions of iodoperfluoroarenes in non-polar solvents.[13b] In contrast, the maximum $\Delta\delta$ for the **2a–4b** titration was −0.2 ppm. This result suggests that the maximum occupancy of donor sites for the polymer system is roughly 20%, perhaps due to steric hindrance and/or entropic penalties associated with arranging the polymers such that all donor and acceptor sites can interact. Related screening effects have been invoked in studies of hydrogen bonded polymer blends.[26]

Assembly of Complementary Halogen Bonding Polymers in Aqueous Solution. Having established that the complementary macromolecules could interact through halogen bonding in solution, we turned our attention to the formation of assemblies in the presence of a poor solvent for

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the interacting blocks. Given the hydrophobic nature of the halogen bond donor–acceptor pair used here, assembly in aqueous medium was investigated.

Using a syringe pump, water was added slowly to a DMSO solution of donor polymer **4b** and acceptor polymer **2d** (1:1 ratio of halogen bond donor and acceptor groups), resulting in a polymer repeat unit concentration of 0.5 mM in a 20% (v/v) solution of DMSO in water. This solution was then dialyzed against water using a regenerated cellulose membrane with a molecular weight cutoff of 6000–8000 Da. Transmission electron microscopy (TEM) revealed wormlike structures with average diameters of roughly 40 nm (σ = 5 nm), generally less than a micron in length and in numerous instances showing branching (Figure 2). Individual spherical particles and small groups of fused spheres were also evident by TEM.

A closer examination of the TEM images shown in Figure 2 revealed undulations in the wormlike structures. These features are of similar diameter as the individual spheres present in the sample, suggesting that the worms grow by aggregation of spheres, and that the structures become kinetically trapped before the polymer chains can reorganize into smooth architectures. Further support for the formation of well-defined aggregates was provided by dynamic light scattering (DLS) analysis, which revealed a monomodal distribution of particles with a mean apparent hydrodynamic diameter of roughly 150 nm (Supporting Information, Figure S12).

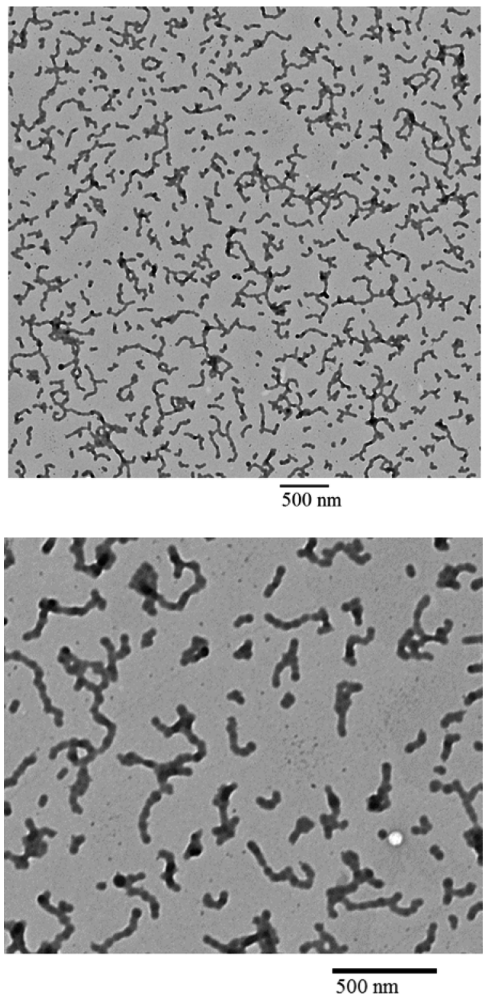

Figure 2. TEM micrographs of branched worms formed from the assembly of acceptor copolymer **2d** and donor homopolymer **4b** by slow addition of water to a DMSO solution of the polymers, followed by dialysis against water. TEM was conducted by loading 2 μL of the dialyzed solution onto a carbon/Formvar grid and wicking away the solvent.

Experimental evidence points toward a key role for halogen bonding in the formation of the structures described above. Pentafluorophenoxy-functionalized polymer **6b**, having a similar degree of polymerization as **4b** but lacking the ability to act as a halogen bond donor, did not generate organized assemblies when combined with **2d** under the conditions used for the **2d**/**4b** pair. Furthermore, the interactions between polymers **2d** and **4b** could be inhibited by addition of 1-iodoperfluorohexane, which is a better halogen bond donor than the iodoperfluoroaryl substituents of the polymer.[13b,c] Addition of $C_6F_{13}I$ (36 mM concentration) to the DMSO solution of the polymers prior to addition of water prevented the formation of structures of the type shown in Figure 2. This effect was not observed when perfluorohexane (C_6F_{14}) was employed in place of $C_6F_{13}I$, suggesting that it is the halogen bond donor ability of the latter, and not its fluorous nature, that perturbs the interaction between polymers. It should be noted that addition of $C_6F_{13}I$ to an aqueous suspension of already formed assemblies (generated from **2d** and **7**, see below) did not result in disruption of the aggregates. It may be that the hydrophobic iodoperfluoroalkane is unable to efficiently access the cores of the assemblies in aqueous suspension.

The nature of the assemblies was found to depend on the structures of the polymers employed. Using acceptor homopolymer **2a** with donor copolymer **7** (that is, switching the position of the PEO stabilizing block from the acceptor to the donor) resulted in a sample without apparent organization. It thus appears that a stabilizing block on the acceptor component is important for the formation of the wormlike structures shown in Figure 2. Furthermore, PEO is essential as a stabilizing block, as the complementary homopolymers did not give rise to organized structures. The combination of copolymers **2d** and **7**, both bearing PEO blocks, gave rise to structures similar to those obtained from **2d** and **4b**, although with a bimodal distribution as judged by DLS (perhaps reflecting the presence of larger branched aggregates). Variation of the acceptor block length was also investigated. Copolymer **2e**, having a PDMEAMA segment with a mean degree of polymerization (DP_n) of 120 (versus 70 for **2d**) gave rise to similar structures as **2d** when combined with **4b**. Using **2b**, with a shorter PDMEAMA segment (DP_n = 30), also gave rise to branched wormlike structures, but with a larger mean diameter (60 nm, σ = 8 nm) than those obtained using **2d** (40 nm, σ = 5 nm). The fact that different polymer compositions did not lead to variations in morphology as would be predicted by the theory of the packing parameter[1,27] appears to further support the hypothesis that the assemblies are formed under kinetic control.

The assembly conditions were also found to influence the nature of the structures obtained (see the Supporting Information for full details, TEM micrographs and DLS data). Inducing the assembly of **4b** and **2d** by dialysis from acetone to water (rather than from DMSO to water using the syringe pump–dialysis sequence described above) yielded aggregates several microns in size and without apparent organization, as judged by TEM. Employing dialysis from acetone to water, but using PEO-functionalized copolymer **7** in place of **4b**, generated a complex mixture of spheres, vesicles

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and wormlike structures (Figure 3). It may be that the increased solubility of donor polymer **7** conferred by the PEO

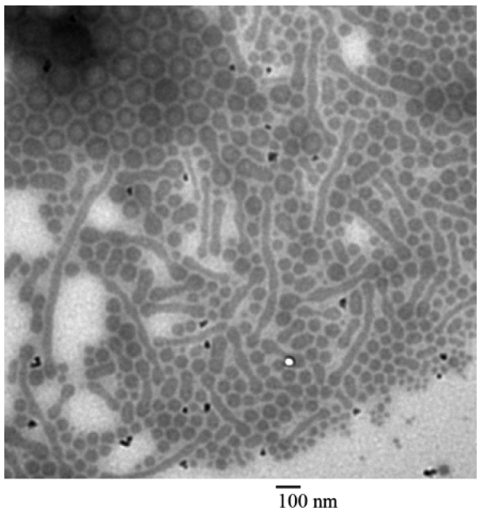

Figure 3. TEM micrograph of assemblies obtained from acceptor copolymer **2d** and donor copolymer **7** by dialysis of an acetone solution of the polymers against water. TEM was conducted by loading 2 μL of the dialyzed solution onto a carbon/Formvar grid and wicking away the solvent.

block facilitates the formation of organized structures. Similar complex mixtures were obtained from combinations of **7** with **2b** (having a shorter PDMAEMA block), or with a PDMAEMA homopolymer, by dialysis from acetone to water. Addition of water by syringe pump to an acetone solution of **7** and **2b**, followed by dialysis, yielded a slightly more homogeneous sample consisting of spheres and wormlike assemblies up to a few microns in length, but with relatively few vesicles. Tetrahydrofuran, *N*-methylpyrrolidinone and *N*,*N*-dimethylformamide were also explored as initial nonselective solvents, but provided inferior results to those obtained using acetone or DMSO.

Assembly of Complementary Halogen Bonding Polymers in Organic Solvent Mixtures. The formation of assemblies from the complementary halogen bonding polymers was further investigated in organic solvent mixtures. A DMSO solution of PEO-*b*-PDMAEMA **2b** and polymeric donor **4a** (1:1 ratio of halogen bond donor and acceptor groups, 2.4 mM repeat unit concentration) was subjected to dialysis against acetonitrile using a regenerated cellulose membrane with a molecular weight cutoff of 6000−8000 Da. After dialysis, TEM revealed spherical particles having an average diameter of 160 nm (σ: 50 nm, Figure 4). DLS of the assemblies from **2b** and **4a** revealed a monomodal distribution of assemblies having roughly similar dimensions to those inferred by TEM (diameter: 160 nm, σ: 50 nm: Figure 4).

NMR spectroscopy proved to be useful for studying the polymer−polymer interactions under the assembly conditions in organic solvent: whereas two signals were evident in the ^{19}F NMR spectrum of **4a** in acetonitrile, these peaks underwent broadening to the point of disappearance in dialyzed solutions of **4a** and **2b**. Presumably this broadening results from modulation of relaxation times due to restricted rotation and/or tumbling in the assembly cores.[28] ^{1}H NMR spectroscopy (with solvent suppression) revealed that whereas the signals corresponding to the aminoethyl groups of **2b** and the

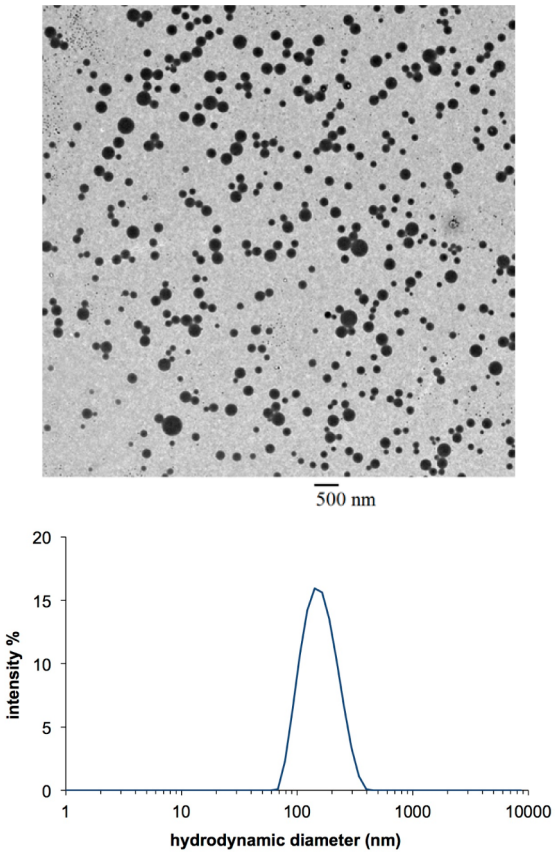

Figure 4. TEM micrograph and DLS data for assemblies obtained by dialysis of a DMSO solution of acceptor copolymer **2b** and donor homopolymer **4a** into acetonitrile. TEM was conducted by loading 2 μL of the dialyzed solution onto a carbon/Formvar grid and wicking away the solvent.

propylene groups of **4a** were no longer discernible in the dialyzed solution of the two polymers, those corresponding to the PEO blocks persisted. These ^{19}F and ^{1}H spectroscopic data are consistent with a model in which the cores of the assemblies are composed of interacting halogen bond donor- and acceptor-functionalized poly(methacrylate) moieties, while the stabilizing PEO segments of **2b** are solvent-exposed. Consistent with this hypothesis, energy-dispersive X-ray spectroscopy revealed that the cores of the assemblies are rich in iodine (Figure S29).[29]

Experiments similar to those described for the aqueous assemblies were conducted to probe the role of halogen bonding in the assembly behavior. Control polymer **6a** did not give rise to well-defined assemblies as judged by TEM when combined with **2b** and subjected to dialysis from DMSO to acetonitrile. Furthermore, the changes in the ^{19}F and ^{1}H NMR spectra that accompanied the formation of assemblies of **2b** and **4a** were not observed for the corresponding solution of **2b** and **6a**. Disruption of the assemblies by addition of a competitive halogen bond donor was also possible: upon addition of $C_6F_{13}I$ (100 mM) to the postdialysis mixture, the TEM features shown in Figure 4 were no longer prominent, having been largely replaced by poorly defined aggregates. DLS analysis of assemblies of **2b** and **4a** in the presence of $C_6F_{13}I$ revealed a shift toward particles of larger hydrodynamic diameter with a broader distribution, and the signals corresponding to the methacrylate pendant groups reappeared in the ^{19}F and ^{1}H

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NMR spectra. The changes revealed by TEM and DLS were not observed when fluorous C_6F_{14} was used in place of the competitive donor $C_6F_{13}I$. Changes in the ^{19}F and ^{1}H NMR spectra were observed upon addition of C_6F_{14} to the assemblies, but these were significantly less dramatic than those obtained using $C_6F_{13}I$. The combination of these results suggests a plasticizing effect of C_6F_{14} on the assemblies, as compared to full-fledged disruption by $C_6F_{13}I$.

When polymer **2c** having a longer acceptor block was subjected to dialysis from DMSO into acetonitrile with **4a**, assemblies with vesicle-like TEM contrast patterns were observed (diameter: 240 nm, σ: 50 nm: Figure 5). The formation of these assemblies was also evident by DLS (diameter 330 nm, σ: 100 nm: Figure 5). The vesicle-like structures displayed the hallmarks of XB-driven assembly (no assembly upon replacing iodinated **4a** with fluorinated **6a**, disruption by addition of $C_6F_{13}I$, ^{19}F and ^{1}H NMR spectroscopic effects consistent with halogen-bonded core segments) discussed above. It should be noted that in addition to its longer acceptor block, **2c** differs from **2b** in terms of its relatively high dispersity, due to the presence of a small shoulder peak in the GPC trace corresponding to high molecular weight material. Copolymer **2d**, having a similar degree of polymerization as **2c** but lacking the high-molecular-weight shoulder (Figure 6), also gave rise to vesicle-like assemblies, but these were less uniform than those obtained from **2c** (Figure S19). Similarly, copolymer **2e**, with a higher degree of polymerization but lower polydispersity than **2c**, gave rise to less uniform vesicle-like structures than those obtained from **2c** (Figure S20). Hence, the high molecular weight component present in **2c** may play a role in the assembly process. It has been noted that polydisperse diblock copolymers (or mixtures of block copolymers having different block lengths) can give rise to structures with different morphologies and distributions than those derived from the corresponding monodisperse samples.[2]

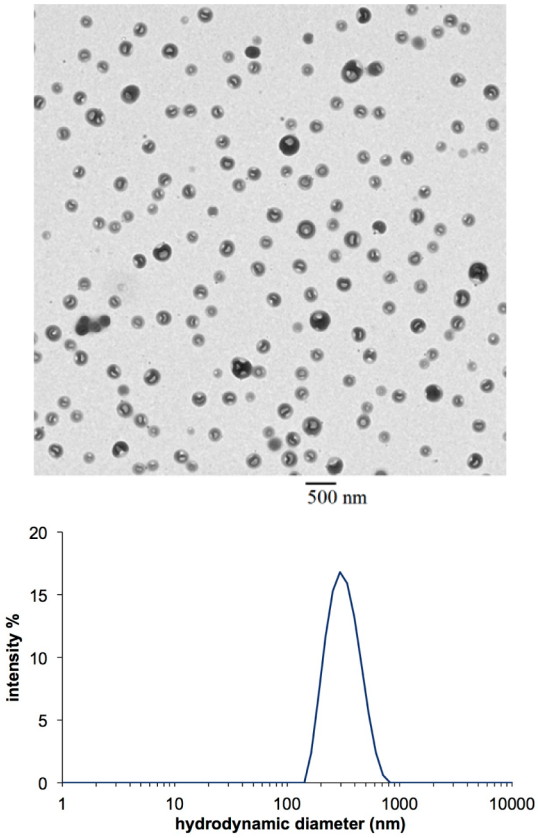

Figure 5. TEM micrograph and DLS data for assemblies formed by dialysis of a DMSO solution of acceptor copolymer **2c** and donor homopolymer **4a** into acetonitrile. TEM was conducted by loading 2 μL of the dialyzed solution onto onto a carbon/Formvar grid and wicking away the solvent.

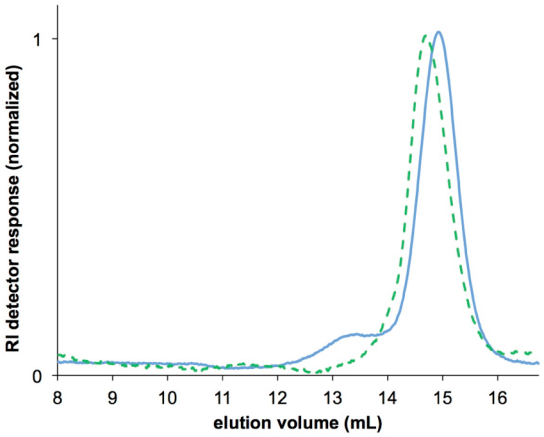

Figure 6. GPC traces (refractive index (RI) detection) showing the difference in chain length distribution between acceptor copolymers **2c** (solid, blue) and **2d** (dashed, green).

■ CONCLUSION

The results described above demonstrate that controlled RAFT polymerization may be employed to generate halogen bond donor-functionalized polymers, and that these species give rise to a variety of supramolecular structures when combined with polymeric acceptors. Both the increased association constant between the complementary polymers relative to that of the monomers, and the observation of assembly under relatively dilute conditions, point toward an important role for multivalency in this system. As is generally the case for block copolymer assembly in solution, solvophobic effects clearly contribute significantly to the driving force and influence the nature of the structures obtained. At present, it appears that the structures obtained are under kinetic control, with similar morphologies being obtained from copolymers having different compositions. However, the ability to direct polymer self-assembly using a noncovalent interaction that is complementary to hydrogen bonding in several respects—the hydrophobic nature of the donor groups, the propensity of XB donors to interact with soft Lewis bases, and the distinct solvent effects on the two interactions, among others[13]—may offer new opportunities, such as the prospect of employing XB in concert with HB to achieve hierarchical self-assembly. Given the diverse ways in which noncovalent interactions have been employed in polymer chemistry, including supramolecular polymerization,[30] the formation of stimulus-responsive and self-healing materials,[31] and the stabilization of polymer blends,[32] further applications of XB in macromolecular self-assembly are worthy of exploration.

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■ ASSOCIATED CONTENT

Supporting Information

Full experimental details and characterization 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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