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Intramolecular folding of triblock copolymers *via* quadrupole interactions between poly(styrene) and poly(pentafluorostyrene) blocks†

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β-Hairpin formation is one of the fundamental folding actions in biomacromolecules. We present a linear triblock copolymer synthesized *via* reversible addition-fragmentation chain transfer (RAFT) polymerization, that is able to mimic on a very basic level hairpin formation by using π–π stacking interactions between phenyl and 2,3,4,5,6-pentafluorophenyl residues.

The non-covalent self-assembly of synthetic polymers has been investigated as a method to mimic natural processes.[1] However, the synthesis of highly hierarchical and functional three-dimensional structures, such as folded proteins, still remains out of the reach of current synthetic systems.[2] Even at the secondary level of assembly, the two most common motifs in biology, α-helices and β-sheets, are still not fully realized by synthetic polymers. While helical polymers have been reported before,[3] sheet-like polymeric materials still remain elusive.[2c–f,4]

Barner-Kowollik[2c,d,4b] and Meijer[2e] reported single-chain folding of polymers through reversible hydrogen-bonding recognition units, utilizing the specific interaction between thymine and diaminopyridine in conjunction with the interaction between cyanuric acid and Hamilton Wedge, or the self-association of 2-ureidopyrimidinone and benzene-1,3,5-tricarboxamide. These reports suggest that compartmentalized structures with ordered interiors that mimic natural systems, can be constructed using multiple orthogonal self-assembly motifs. Here we introduce a simpler synthetic folding system to mimic β-hairpin like structures.

Our strategy is based on the quadrupole interaction between electron-rich and electron-deficient aromatic systems. This interaction has been well known since the 1960s from the lower melting temperature of mixtures of benzene and hexafluorobenzene.[3a,5] The strength of this quadrupole interaction between aromatic hydrocarbons and aromatic fluorocarbons is weaker than hydrogen bonding in most solvents and the solid state. Coastas reported the association enthalpy of 1 : 1 complex of pentafluorobenzene and benzene to be −4.4 ± 0.2 kJ mol^{-1} using heat capacity measurements.[6] Hunter measured the pentafluorophenyl aniline interaction to be −0.4 ± 0.9 kJ mol^{-1} in chloroform *via* the chemical double-mutant cycles.[7] Nevertheless, this interactions has been applied in crystal engineering,[8] reactant-oriented polymerization,[9] one-dimensional ribbon structure generation[10] and the stabilization of liquid crystalline phases[11] demonstrating the utility of this interaction in materials chemistry.

Here we report the intramolecular folding of a triblock copolymer bearing electron-rich and electron-deficient moieties, which is promoted by the presence of a large number of individual interactions. We hypothesize that due to quadrupole interactions, the linear block polymer can fold into a β-hairpin like structure at low concentrations and in appropriate solvents (Fig. 1).

The intramolecular folding of our block copolymers is based on the quadrupole interactions between styrene and 2,3,4,5,6-pentafluorostyrene (PFS) residues. Styrene is electron-rich,

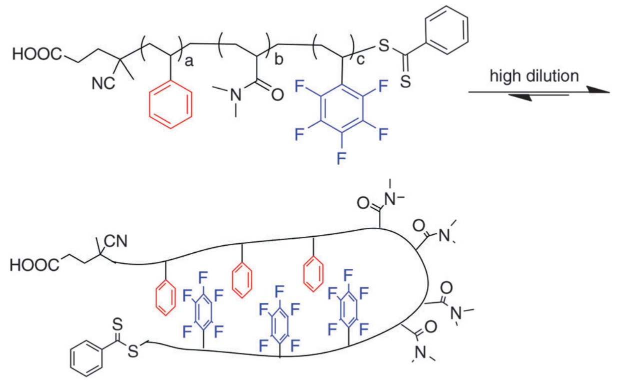

Fig. 1 Schematic representation of the single-chain folding of PS$_{30}$-*b*-PDMAA$_{20}$-*b*-PPFS$_{30}$ block copolymer in solution.

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† Electronic supplementary information (ESI) available: (1) Experimental details, (2) characterizations of the polymers, (3) DLS analyses of the self-assembly, and (4) NMR spectra of poly(styrene), poly(styrene)-*b*-poly(dimethylacrylamide), and poly(styrene)-*b*-poly(dimethylacrylamide)-*b*-poly(pentafluorostyrene) in different solvent. See DOI: 10.1039/c4cc01840k

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whereas PFS is electron-deficient, a fact that also allows for the alternating copolymerization of these two monomers.[12]

A triblock copolymer containing styrene and 2,3,4,5,6-pentafluorostyrene as the A and C blocks was synthesized by reversible addition-fragmentation chain-transfer (RAFT) polymerization,[13] together with a *N*,*N*-dimethylacrylamide middle block, yielding poly(styrene)$_{30}$-*b*-poly(dimethylacryl amide)$_{150}$-*b*-poly(2,3,4,5,6-pentafluorostyrene)$_{30}$ (PS$_{30}$-*b*-PDMAA$_{150}$-*b*-PPFS$_{30}$). The triblock copolymer and its precursors were characterized by gel-permeation chromatography (GPC) and ^{1}H NMR spectroscopy (see ESI†). The dispersity ($Đ$) and apparent molecular weight (M_n^{app}) of the final triblock copolymer are 1.73 and 20.8 × 10^3 g mol^{-1} respectively, as determined by gel-permeation chromatography using poly(styrene) standards.

Table 1 Hydrodynamic radii of poly(styrene)-*b*-poly(dimethylacrylamide) and poly(styrene)-*b*-poly(dimethylacrylamide)-*b*-poly(2,3,4,5,6-pentafluorostyrene) as determined by DLS in different solvents

Radius (nm)	Toluene	DMF	CHCl$_3$^{b}
PS$_{30}$-*b*-PDMAA$_{150}$	8.46 ± 0.07	6.29 ± 0.06	—
PS$_{30}$-*b*-PDMAA$_{150}$-*b*-PPFS$_{30}$	10.06 ± 0.08	4.26 ± 0.09	—
PS$_{30}$-*b*-PDMAA$_{20}$	1.56 ± 0.04	2.32 ± 0.02	2.38 ± 0.04
PS$_{30}$-*b*-PDMAA$_{20}$-*b*-PPFS$_{30}$	2.38 ± 0.09	22.1 ± 0.61^a	2.67 ± 0.08

[a] Micelles formed, not a single chain folding. [b] Higher concentration, 30 mg ml^{-1}, 2.6 mM.

The folding behavior of this PS-*b*-PDMAA-*b*-PPFS block copolymer was investigated by dynamic light scattering (DLS) and a battery of NMR spectroscopy techniques. Other techniques typically used to investigate stacking interactions, such as UV-Vis spectroscopy or WAXS could not be used in this system since styrene, PFS, and the complex are colorless and the polymers do not crystallize. DLS can provide the hydrodynamic size distributions of molecules in solution. Polymer solutions were prepared at very low concentrations of 1 mg ml^{-1} (0.04 mM) in order to avoid intermolecular interactions. Since we expect the folding behavior to be solvent specific, we investigated the self-assembly process in different solvents (Table 1).

In toluene, the quadrupole interaction between styrene and PFS residues is inhibited by the competitive interaction between PFS and the solvent: the hydrodynamic radii (R_h) of the diblock and triblock are similar. In a non-competing solvent such as DMF, the quadrupole interactions draw the styrene and PFS blocks together resulting in triblock copolymers with smaller hydrodynamic radii than the respective diblock polymers despite an increase in molecular weight.

2D ^{1}H–^{1}H NOESY and ^{1}H–^{19}F HOESY NMR spectroscopy experiments were carried out to further confirm the polymer folding. Due to the long middle block (150 repeat units), the NOE and HOE cross-peak signals between PS and PPFS blocks could not be observed. Therefore, a polymer with a shorter

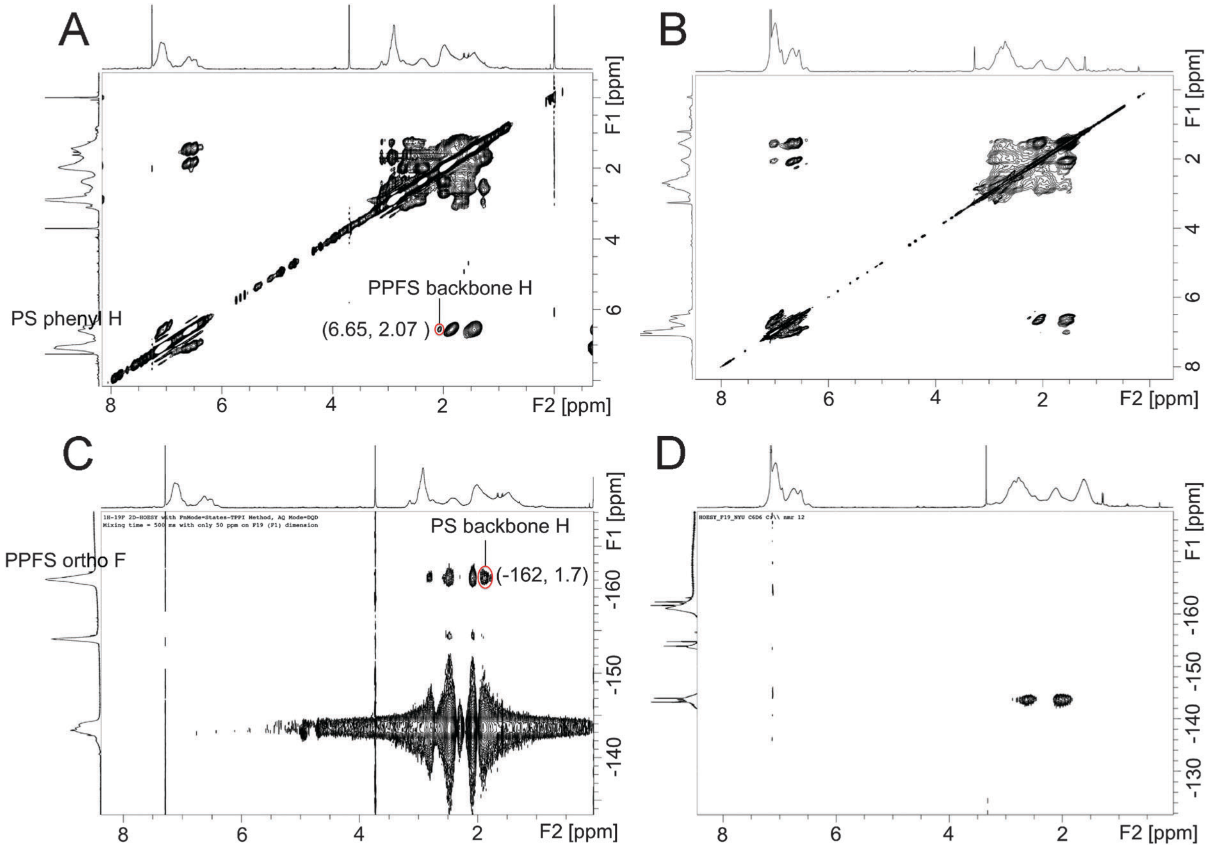

Fig. 2 2D ^{1}H–^{1}H NOESY spectrum of PS$_{30}$-*b*-PDMAA$_{20}$-*b*-PPFS$_{30}$ in CDCl$_3$ (A) and C$_6$D$_6$ (B) and 2D ^{1}H–^{19}F HOESY spectrum of PS$_{30}$-*b*-PDMAA$_{20}$-*b*-PPFS$_{30}$ in CDCl$_3$ (C) and C$_6$D$_6$ (D).

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middle block (PS_{30}-*b*-$PDMAA_{20}$-*b*-$PPFS_{30}$) was synthesized to allow for characterization *via* NOESY and HOESY NMR spectroscopy. GPC analysis of PS_{30}-*b*-$PDMAA_{20}$-*b*-$PPFS_{30}$ revealed $Đ$ of 1.43 and M_n^{app} of 11.5×10^3 g mol^{-1}. We first run DLS analyses of the triblock copolymer with the shorter middle block (PS_{30}-*b*-$PDMAA_{20}$-*b*-$PPFS_{30}$). The results are shown in Table 1. In toluene, the hydrodynamic radius of the triblock copolymer is bigger than its precursor diblock copolymer: the molecular weight more than doubles and no folding is observed. In DMF, we observed the formation of larger aggregates. Since PPFS homopolymers are soluble in this solvent (see ESI†), the aggregates can be ascribed to the interaction between the PS and the PPFS blocks, which is an additional proof for quadrupole interactions. In chloroform, we prepared the samples at different concentrations (ESI,† Table S3) and observed only intramolecular folding when the concentration is below 50 mg ml^{-1}. We observed larger aggregates for sample concentration above 80 mg ml^{-1}. At 30 mg ml^{-1}, (2.6 mM), which is the same concentration as the samples used for the NMR spectroscopy experiments, the hydrodynamic radius of the triblock polymer is only marginally higher than the R_h of the diblock polymer, despite the large increase in molecular weight, indicating the folding of the triblock polymer chain due to π–π interaction. Although the long middle block polymer (PS_{30}-*b*-$PDMAA_{150}$-*b*-$PPFS_{30}$) exhibits a more obvious size difference through the intramolecular folding, the short middle block polymer (PS_{30}-*b*-$PDMAA_{20}$-*b*-$PPFS_{30}$) shows clearer NOE and HOE cross-peak signals in the 2D NMR spectroscopy experiment.

The 2D NMR spectroscopy experiment results are shown in Fig. 2. The NOESY spectrum in Fig. 2A indicates a strong NOE between the aromatic protons on the PS block with the polymer backbone of the PPFS block at (6.65, 2.07 ppm; the signal at 2.07 ppm is unique to the PPFS block) in chloroform. Additionally, a NOE signal can be observed between the backbone protons of PS and PPFS at 1.38, 1.98 ppm (ESI,† Fig. S13). In benzene (Fig. 2B) only a NOE signal can be observed between the aromatic protons of PS and the PS backbone (ESI†), indicating that the quadrupole interaction is inhibited by the interaction of the solvent with the PFS residues.

The HOESY experiments (Fig. 2C and D) give more evidence of the quadrupole interaction. The *ortho*-F of the PFS residues along the PPFS block has several HOE signals with backbone protons of both the PPFS block and PS block at (−162, 1.7 ppm) and with aromatic protons in the PS block (ESI†). By contrast, the only HOE found in benzene is between the *ortho*-F of the PFS residues and the PFS backbone protons, again indicating that no (measurable) quadrupole interaction takes place, and that no folding occurs.

This contribution presents the synthesis of triblock copolymers with arene and perfluoroarene-containing blocks *via* the RAFT polymerization of styrene, *N*,*N*-dimethylacrylamide, and 2,3,4,5,6-pentafluorostyrene. The quadrupole interactions between the electron-rich and electron-deficient blocks were characterized in different solvents using 2D NMR spectroscopy (^{1}H–^{1}H NOESY, ^{1}H–^{19}F HOESY) and dynamic light scattering. We proved that intramolecular single-chain folding of these polymers occurs in chloroform due to this arene–perfluoroarene quadrupole. In DMF, larger aggregates are formed due to intermolecular interactions.

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