Metallopolymer−Peptide Conjugates: Synthesis and Self-Assembly of Polyferrocenylsilane Graft and Block Copolymers Containing a β-Sheet Forming Gly-Ala-Gly-Ala Tetrapeptide Segment

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We describe the synthesis and self-assembly of two β-sheet forming metallopolymer-peptide conjugates. The ability of the oligotetrapeptide sequence Gly-Ala-Gly-Ala (GAGA) to form antiparallel β-sheets was retained in PFS-*b*-AGAG (PFS = polyferrocenylsilane) and PFS-*g*-AGAG conjugates with block and graft architectures, respectively. In the solid state, DSC experiments suggest a phase separation between the peptide and PFS domains. In toluene, PFS-*b*-AGAG interestingly forms a fibrous network which consists of a core containing the self-assembled antiparallel β-sheet peptide and a corona of organometallic PFS. The self-assembly of the peptide into antiparallel β-sheets is the driving force for the fiber formation, whereas PFS prevents uncontrolled lateral aggregation of the fibers. The use of an oligopeptide to self-assemble an otherwise random coiled organometallic polymer may be a useful strategy to enhance nanostructure formation. In the cases described here, the conjugates may be used to create nanopatterned ceramics, and the redox properties of the resulting supramolecular aggregates are of significant interest.

Introduction

The introduction of metal centers to polymeric structures offers access to new functional materials with interesting properties and applications.[1] Conjugates of metal complexes or metallopolymers with biomacromolecules are of potential interest for the generation of self-assembled supramolecular materials with novel chemical and physical characteristics, such as redox, catalytic, or anti-cancer activity.[2−6]

Polyferrocenylsilanes (PFSs) are a well-established class of metallopolymers which are available in the form of well-defined and controlled architectures using living polymerization techniques.[7] These organometallic materials have been investigated for a range of potential uses. For example, PFS materials have been used as organometallic precursors to Fe-based ceramics, which can be used to catalyze the formation of carbon nanotubes.[8] Thus, thin films of self-assembled PS-*b*-PFS (PS = polystyrene) diblock copolymers consisting of spherical organometallic PFS nanodomains interspersed in a PS matrix have been shown to serve as precursors to catalytically active iron-rich ceramic nanodomains on thermal or plasma treatment where the PS matrix is volatilized. In addition, self-assembly of PFS block copolymers in selective solvents affords redox active cylindrical structures which can be used to generate wire-like structures.[9]

Over the past decade or so, peptides have frequently been used to mediate the self-assembly of synthetic polymers.[10] Peptides intrinsically have the ability to fold hierarchically into several superstructures, such as helices, β-sheets, and coiled coils, and several authors have shown that this intrinsic folding ability is retained in conjugates of the peptide and a synthetic polymer.[10,11,13−15] We anticipated that the conjugation of such a peptide sequence to PFS would result in nanostructure formation for the PFS−peptide conjugate. These self-assembled supramolecular structures would be of intrinsic interest due to their redox-activity. In addition, if the nanostructure is retained during pyrolysis, this could serve as a simple, alternative approach to enable the nanopatterning of catalytically active Fe-based nanoparticles.

A peptide sequence with a high potential to achieve the above concept is Gly-Ala-Gly-Ala (GAGA). This sequence of four amino acids constitutes the repeating pattern of the crystalline β-sheet domain in *B. mori* silk, which is responsible for the interesting mechanical properties of silk fibers.[12] This very short peptide sequence contains the two most commonly available and cheapest amino acids glycine and alanine and is known to form antiparallel β-sheets through intermolecular hydrogen bonding. If β-sheet formation is retained upon attachment to PFS, we anticipated that the physical cross-linking caused by intermolecular hydrogen bonding might promote the retention of the nanostructures for the PFS−peptide conjugate after pyrolysis.

To the best of our knowledge, only two groups have attempted to use this extremely short sequence to mediate the self-assembly of organic synthetic polymers. Sogah and co-workers prepared a silk-inspired multiblock copolymer by replacing the amorphous peptide domain of spider silk with poly(ethylene glycol) (PEG), while leaving the β-sheet domain (GAGA) untouched.[13] The solid-state structure of the multiblock copolymer was composed of β-sheet nanodomains interspersed in an amorphous PEG phase. In another approach, Sogah et al. prepared segmented block copolymers containing PEG segments and the peptide sequence GAGA derived from *B. mori* silk, templated by phenoxathiin.[14] The peptide segment retained its

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β-sheet structure, and transmission electron microscopy (TEM) experiments showed that it was dispersed in a continuous polyether phase. Recently, van Hest and co-workers described the synthesis and characterization of a well-defined PMMA−poly(AGAG methacrylate)−PMMA triblock copolymer using ATRP and a bifunctional initiator.[15a] IR spectroscopy clearly showed that the β-sheet secondary structure had been introduced. However, no specific structures could be detected by electron microscopy. The same group also recently described the self-assembly of triblock copolymers of poly(ethylene glycol) and poly[$(AG)_3$EG] into well-defined fibrils. Microscopy data suggest an organization in which the fibrils are formed in the β-sheet stacking direction.[15b] In this communication, we report our initial results regarding the synthesis of conjugates of GAGA and PFS and preliminary investigations of their self-assembly behavior.

Experimental Section

Materials and Methods. Glycine, alanine, and benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBOP) were purchased from Novabiochem. All other chemicals were purchased from Sigma-Aldrich Co. and used without further purification.

^{1}H NMR spectra (400 MHz) were recorded on a Varian Unity 400 spectrometer. Molecular weights were estimated by gel permeation chromatography (GPC). The instrument was equipped with Styragel columns HR-1 and HR-5E, a Viscotek model 2501 UV absorbance detector, and a Waters R410 differential refractometer detector. Reagent grade THF was used as the eluent at a flow rate of 0.6 mL/min. The GPC instrument was calibrated using polystyrene standards purchased from American Polymer Standards. FT-IR (Nujol, NaCl) was performed on a Perkin-Elmer Spectrum One IR Spectrometer. Thermal characterizations were performed on a TA instruments 2920 modulated DSC equipped with a cooling unit. The ramp rate for scans was 10 K/min. Transmission electron microscopy (TEM) was performed on a Hitachi H-600 microscope with 75 kV acceleration voltage. The TEM specimens were prepared on a carbon-coated copper grid (200 mesh). Atomic force microscopy (AFM) was performed on a NanoScope III microscope in tapping mode.

Synthesis of Ac-Gly-Ala-Gly-Ala-OH. The peptide Ac-Gly-Ala-Gly-Ala-OH was prepared by solid-phase peptide synthesis (SPPS) using Fmoc-chemistry. The amino acid residues were used as free acids and coupling was facilitated by the use of HBTU (*O*-benzotriazole-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate) and HOBt (*N*-hydroxybenzotriazole) were used as coupling agents. After assembly of the peptide onto a Wang resin, the resin was cleaved by stirring for 1 h in a TFA/DCM (50% v/v) mixture. Subsequent evaporation of solvents and precipitation with diethyl ether resulted in Ac-Gly-Ala-Gly-Ala-OH as a white powder. Typically, after a 1.0 mmol scale synthesis, 254 mg (80%) of the tetrapeptide were obtained. ^{1}H NMR (400 MHz, D_2O, ppm): δ 4.4 (2H, m, C*H*[Ala]), 4.0 (4H, s, CH_2-[Gly]), 2.1 (3H, s, −COCH_3), 1.4 (6H, dd, CH_3[Ala]). FD: $[M]^+$ = 316 g/mol).

Synthesis of Aminopropyl PFS (4). Aminopropyl PFS **4** with an estimated molecular weight of 300 kg/mol and a polydispersity index of 1.5 was prepared according to a previously published report.[16]

Synthesis of Amino-Terminated PFS (7). Amino-terminated PFS **7** was prepared using living anionic ring-opening polymerization of dimethyl-[1]-silaferrocenophane **6**, quenched with 1-(3-bromopropyl)-2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentane and subsequent deprotection of the amine with a THF/methanol mixture.[4] ^{1}H NMR (400 MHz, $CDCl_3$) revealed a degree of polymerization of 18. GPC: M_n = 1230 g/mol, M_w/M_n = 1.1. DSC (10 K/min): T_g = 22 °C.

Synthesis of PFS-*g*-AGAG (5). To a solution of aminopropyl PFS **4** (0.105 mmol, 31.6 mg) in dichloromethane was added 1.1 equiv of Ac-GAGA-OH per amino group (0.127 mmol, 40 mg) as a solution in DMF. The solution was stirred for 5 min. Subsequently, 1.5 equiv of PyBOP in DMF (190 μmol, 107 mg) and 3 equiv of *N*,*N*-diisopropylethylamine (66 μL) were added. The reaction mixture was stirred for 24 h at room temperature. The yellow turbid mixture was filtered, and the residue was thoroughly washed with dichloromethane, tetrahydrofuran, water, and DMF to remove any excess peptide and reagents and any partially reacted polymer derived from **4**. After drying under vacuum, a red solid was isolated in 59% yield (40 mg).

^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 8.1 (2H, t, N*H*[Gly]), 8.0 (1H, t, CH_2CH_2NH), 7.8 (2H, d, N*H*[Ala]), 4.2 (2H, C*H*[Ala]), 4.2 (4H, Cp*H*), 4.0 (4H, Cp*H*), 3.7 (4H, s, CH_2[Gly]), 3.0 (2H, −CH_2-NHCO-), 1.8 (3H, s, CH_3CO-), 1.5 (2H, m, −SiCH_2CH_2-), 1.2 (2H, −SiCH_2-), 1.2 (3H, CH_3[Ala]), 0.8 (3H, CH_3[Ala]), 0.4 (3H, s, −SiCH_3). DSC (10 K/min): T_g = 15 °C, T_m = 115 °C.

Synthesis of PFS-*b*-AGAG (8). To a solution of amino-terminated PFS **7** (50 mg, 0.0112 mmol) in dichloromethane was added a 10-fold excess of Ac-Gly-Ala-Gly-Ala-OH (33 mg, 0.104 mmol) in DMF. The resulting solution was stirred for 5 min. Subsequently, 20 equiv of PyBOP in DMF (116 mg, 0.2066 mmol) and 30 equiv of *N*,*N*-diisopropylethylamine (53 mg, 0.4132 mmol) were added. The reaction mixture was stirred for 24 h at room temperature. Solvents were evaporated, and the residue was taken up in THF. The excess free peptide is not soluble in THF. The mixture was filtered, and the THF solution was concentrated. Precipitation with methanol gave 45 mg of an amber solid (yield: 85%).

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.06−8.04 (1H, d, N*H*[Ala]), 7.70−7.68 (1H, d, N*H*[Ala]), 7.59−7.55 (1H, t, N*H*[Gly]), 7.46−7.42 (1H, t, N*H*[Gly]), 4.22 (4H, s, Cp), 4.02 (4H, s, Cp), 3.24 (2H, CH_2CH_2-NH-), 2.26 (3H, s, CH_3CO-), 1.32 (3H, CH_3[Ala]), 1.23 (3H, CH_3-[Ala]), 0.91−0.87 (3H, t, CH_3CH_2-), 0.67−0.61 (3H, m, CH_3CH-), 0.46 (6H, s, CH_3Si-). GPC (THF, 25 °C): M_n = 1180 g/mol, M_w/M_n = 1.1. DSC (10K/min): T_g = 22 °C, T_m = 63 °C.

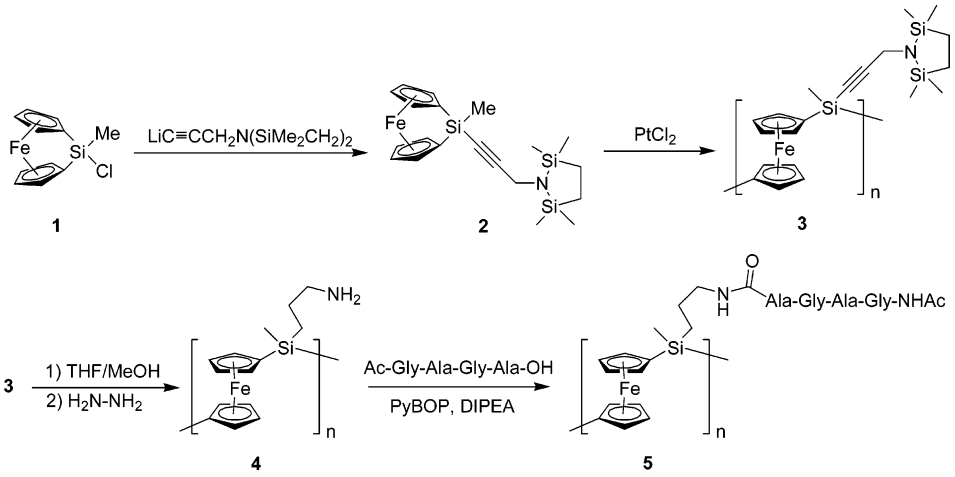
Results and Discussion

Two approaches were followed in order to prepare a β-sheet containing PFS conjugates which differ in the fraction of peptide per ferrocenylsilane repeating unit. In the first approach, the β-sheet forming GAGA sequence was attached to the side chain of every repeating unit of a polyferrocenylsilane resulting in the graft copolymer PFS-*g*-AGAG (Scheme 1). In the second approach, the peptide sequence was attached to a polyferrocenyldimethylsilane end-functionalized with an amino group resulting in the block copolymer PFS-*b*-AGAG (Scheme 2).

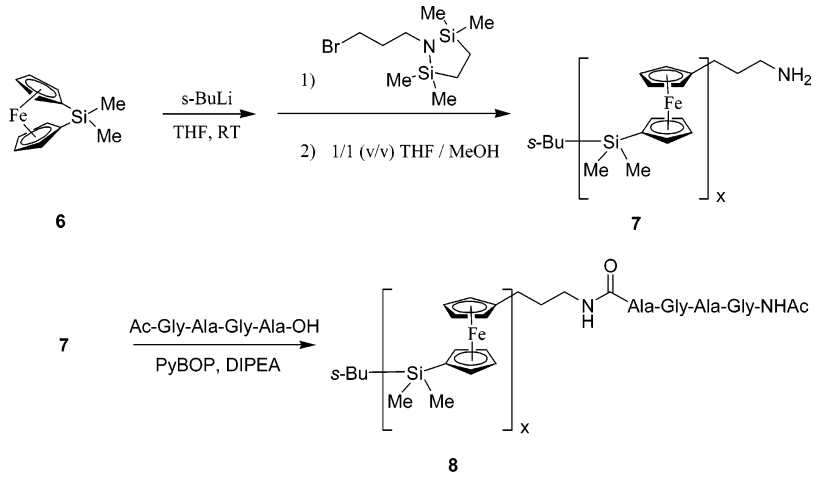
Synthesis of PFS-*g*-AGAG. Polyferrocenylsilane **4** containing a primary amino group in its side chain was prepared according to a previous report by our group.[16] In short, chlorine substitution in chloromethyl [1]-silaferrocenophane **1** with a protected lithiated propynyl reagent resulted in [1]ferrocenophane monomer **2** (Scheme 1).

This monomer was polymerized with $PtCl_2$ at ambient temperature to obtain polymer **3**. Deprotection of the amine and reduction of the triple bond with hydrazine resulted in aminopropyl polyferrocenylsilane **4** containing a primary amino group in the side chain of every repeating unit. Since direct molecular weight estimation of polyelectrolytes is difficult to obtain and was not achieved for **4**, we anticipate that the value is close to its protected amino propyne precursor **3** ($M_n \sim$ 300 kg/mol, polydispersity index = 1.5). The peptide sequence Ac-Gly-Ala-Gly-Ala-OH was prepared by solid-phase peptide synthesis using Fmoc-chemistry. Reaction of **4** with a 1.1-fold excess of Ac-Gly-Ala-Gly-Ala-OH per PFS amino group gave PFS-*g*-AGAG **5** in 59% isolated yield. The conjugate was only soluble in dimethyl sulfoxide (DMSO) and in mixtures of water or organic solvents with trifluoroacetic acid (TFA). However, upon addition of TFA, the solution rapidly turned blue, indicating oxidation of the Fe in the PFS backbone. Lithium bromide is

Scheme 1



Scheme 2



typically used as an additive to dissociate aggregates in aqueous or organic solutes and hence to enhance solubility, but addition of this salt, even in high concentrations (up to 6 M) and at elevated temperature (up to 80 °C), did not result in a soluble conjugate. By comparison of ^{1}H NMR signals in DMSO-d_6 for Si−Me groups at 0.43 ppm and the methylene protons for glycine at 3.7 ppm, we concluded that the peptide was attached quantitatively to the PFS side chain. Unfortunately, it was not possible to determine the molecular weight of bioconjugate **5** by gel permeation chromatography (GPC), because of the lack of solubility in GPC eluents such as tetrahydrofuran, *N*,*N*-dimethylformamide, or water. Based on the quantitative peptide coupling detected by NMR and a molecular weight of around 300 kg/mol for precursor **3**, bioconjugate **5** has a molecular weight of around 600 kg/mol.

Self-Assembly of PFS-*g*-AGAG. First, we investigated whether the introduction of GAGA peptide sequences into the side chain of PFS leads to the formation of β-sheet structural elements in the organometallic polymer PFS. FT-IR spectroscopy is an excellent method to check the secondary structure of peptides and proteins and was therefore employed here. The amide I carbonyl stretching region is highly sensitive to the secondary structure of polypeptides and proteins in solution and the solid state.[17] The sequence GAGA has been shown to have a high tendency to form antiparallel β-sheets in the solid state.[17,18] In the amide I carbonyl stretching region, the FT-IR spectrum (NaCl, Nujol) of the aminopropyl PFS precursor **4** shows no absorptions. PFS-*g*-AGAG **5** shows amide I carbonyl stretching frequencies at 1694, 1651, and 1622 cm^{-1} (Figure 1A). The absorptions at 1694 and 1622 cm^{-1} are typical for antiparallel β-sheet structures, whereas the absorption at 1651 cm^{-1} most probably arises from amorphous peptide domains (random coil). This absorption could also indicate α-helix formation, but since the employed peptide sequence is extremely short,[19] α-helix formation is highly improbable. No evidence for parallel β-sheet structures was observed as indicated by the absence of a band at 1645 cm^{-1}. We anticipated that intermolecular antiparallel β-sheet formation would lead to a "phase-separated" lamellar-like morphology with alternating peptide and PFS layers (Figure 1B). Since the chain length of the peptide is only about 1 nm, the separation of the peptide and PFS phases would be on the nanoscale. Information about whether phase separation occurs in a particular polymer can be obtained from differential scanning calorimetry (DSC) analysis. The DSC thermogram of the aminopropyl PFS precursor **4** showed a transition at 15 °C and a first-order transition at 76 °C (weak), whereas PFS-*g*-AGAG **5** showed transitions at 15 and 115 °C (weak) (Figure 1C). The transition at 15 °C can be assigned to the T_g of PFS, whereas the origin of the weak transition at 76 °C is unclear. The transition at 115 °C can be assigned to the T_m of self-assembled peptide segments.[13] The individual observation of peptide and PFS thermal transitions in DSC thermograms supports our hypothesis of a phase separated structure. Scanning and transmission electron microscopies (SEM and TEM) were used in an attempt to visualize the phase separated structures, but it was unfortunately not possible to obtain thin films of PFS-*g*-AGAG. The bioconjugate is only soluble in DMSO, and drop- and spin-casting of DMSO

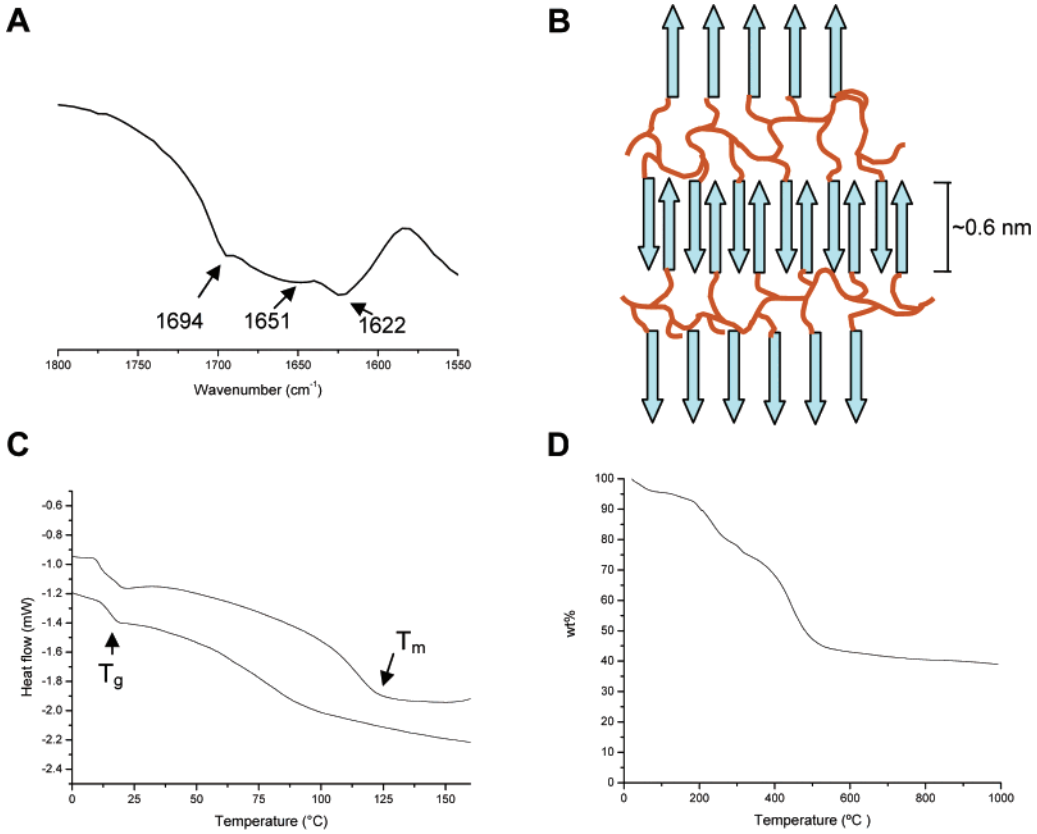


Figure 1. (A) FT-IR spectrum of PFS-*g*-AGAG **5**. (B) Schematic model of PFS-*g*-AGAG **5** self-assembly. The arrows represent the β-sheets. (C) DSC thermogram of PFS-*g*-NH_2 **4** (lower trace) and PFS-*g*-AGAG **5** (upper trace). (D) Thermal gravimetrical analysis of PFS-*g*-AGAG **5**.

solutions of PFS-*g*-AGAG were unsuccessful due to the low vapor pressure of the solvent. Microtome slicing proved unsuccessful as well at this stage. No diffraction peaks were observed in small-angle X-ray scattering (SAXS) experiments.

Pyrolysis of PFS-*g*-AGAG resulted in nearly complete thermal degradation of the peptide segment (Figure 1D). A ceramic yield of 39% was obtained, which is comparable to the ceramic yield of poly(ferrocenyldimethylsilane) (~35%).[20] We are currently investigating if the physical cross-linking of the PFS chains through interchain peptide β-sheet aggregation is sufficient to retain the PFS nanostructure after pyrolysis.

Synthesis of PFS-*b*-AGAG. Dimethyl-[1]-silaferrocenophane **6** was polymerized anionically using *sec*-butyllithium as an initiator (Scheme 2). The living polymer was quenched with 1-(3-bromopropyl)-2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentane and after deprotection of the amine with a THF/methanol mixture, amino-terminated PFS **7** with an average degree of polymerization of 18 by ^{1}H NMR spectroscopy was obtained.[4] The same condensation chemistry as for PFS-*g*-AGAG **5** was used to obtain the PFS-*b*-AGAG conjugate in 85% yield. The conjugate now was soluble in common solvents for PFS, i.e., THF, toluene, and chloroform, but not in common solvents for the peptide segment, DMSO or DMF. The bioconjugate was characterized with ^{1}H NMR spectroscopy and GPC with THF as the eluent to confirm the quantitative attachment of the peptide. The GPC trace (Figure 2A) was monomodal and showed a number-average molecular weight (M_n) of 1180 g/mol. The molecular weight is lower than expected from ^{1}H NMR (DP = 18, M_n = 4670), but this may be explained by the use of polystyrene standards to calibrate the GPC instrument. The GPC trace of the PFS−NH_2 precursor polymer revealed a molecular weight of 1230 g/mol (^{1}H NMR: DP = 18, M_n = 4360). Since we have previously found that side groups with lone pairs of electrons such as amino groups can weakly interact with the GPC column material,[21] this may explain why the molecular weight of the precursor was found to be higher than the bioconjugate.

Self-Assembly of PFS-*b*-AGAG. The FT-IR spectrum of PFS-*b*-AGAG was measured before and after undergoing the 3 heating−cooling cycles in the DSC (Figure 2B). Before annealing, only a broad absorption in the amide I carbonyl stretching region around 1650 cm^{-1} was observed. After thermal annealing, sharp absorptions appeared at 1695, 1655, and 1620 cm^{-1}, which indicates the formation of antiparallel β-sheets (1695 and 1620 cm^{-1}) and the presence of amorphous peptide domains (1655 cm^{-1}). Apparently, the chain mobility found in the isotropic state at elevated temperature is necessary for the peptide domain to assemble. In the case of PFS-*g*-AGAG, the annealing process is not necessary since the peptide sequences are present in much higher density. In this context, it should be noted that the intensities of the IR absorptions between 1700 and 1600 cm^{-1} for PFS-*b*-AGAG were much lower than those for PFS-*g*-AGAG.[22] This is because the latter contains one peptide sequence per ferrocenylsilane unit whereas the former only contains one peptide sequence for every 18 organometallic units.

The DSC thermogram of **8** showed transitions at 22 and 67 °C (Figure 2C). The first transition can be attributed to the T_g of PFS, whereas the second transition may be the T_m for the peptide. The lower T_m for PFS-*b*-AGAG as compared with PFS-*g*-AGAG (115 °C) is an indication that β-sheet formation is less extensive in the former. After thermal annealing, i.e., after undergoing the 3 heating−cooling cycles in the DSC, PFS-*b*-AGAG was not soluble anymore in toluene suggesting the formation of hydrogen bonds between the peptide segments. The hydrogen bonding could however be disrupted by heating

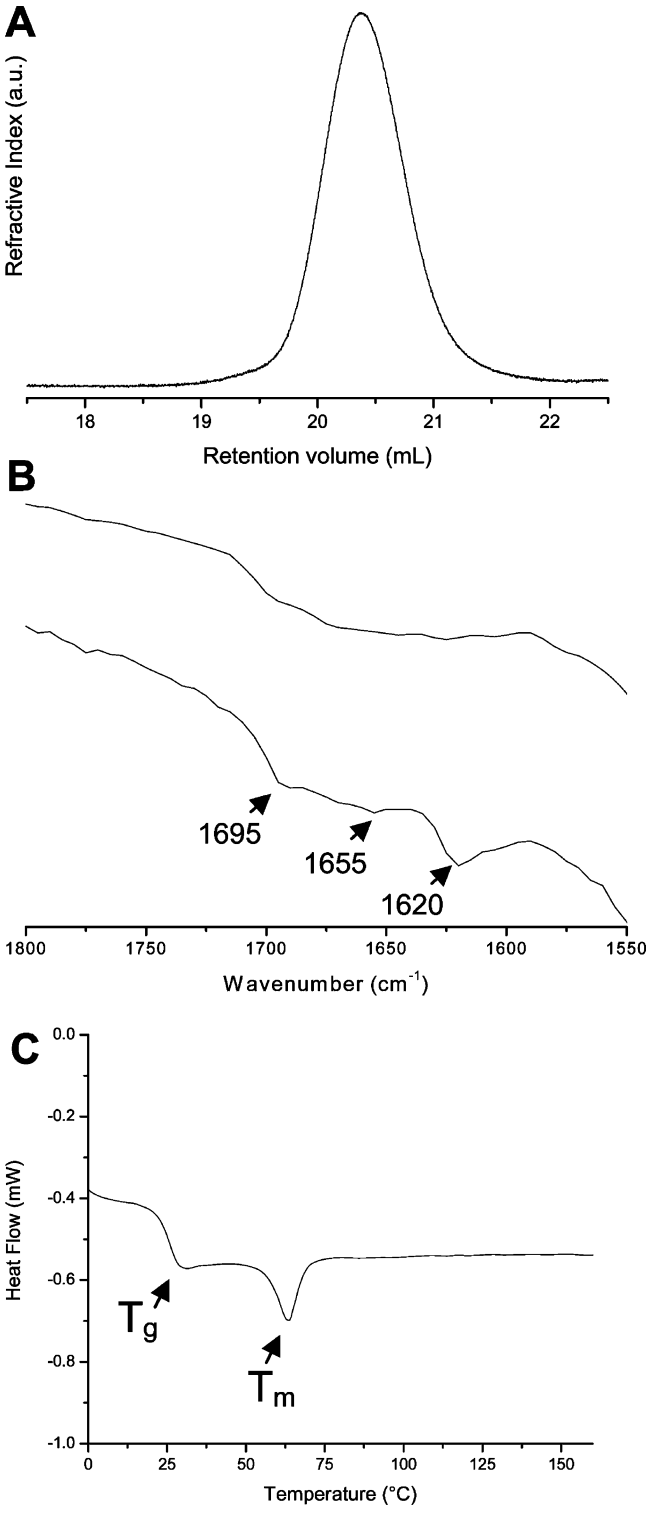


Figure 2. (A) GPC trace of PFS-*b*-AGAG **8**. (B) FT-IR spectra of PFS-*b*-AGAG **8** before (upper trace) and after thermal annealing (lower trace). (C) DSC thermogram of PFS-*b*-AGAG **8**.

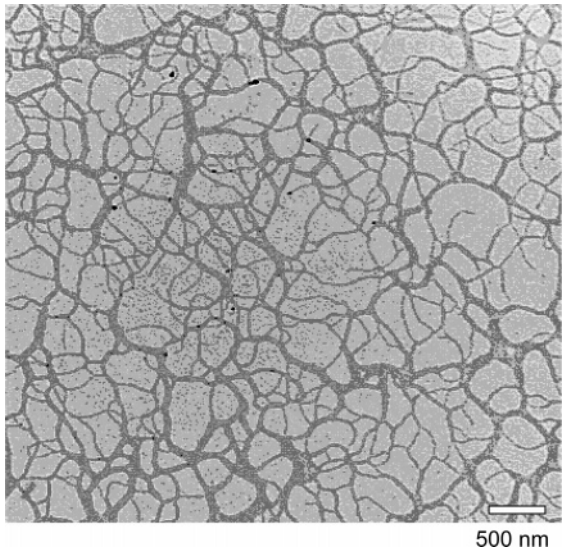


Figure 3. TEM image of PFS-*b*-AGAG **8** in toluene (0.2 mg/mL).

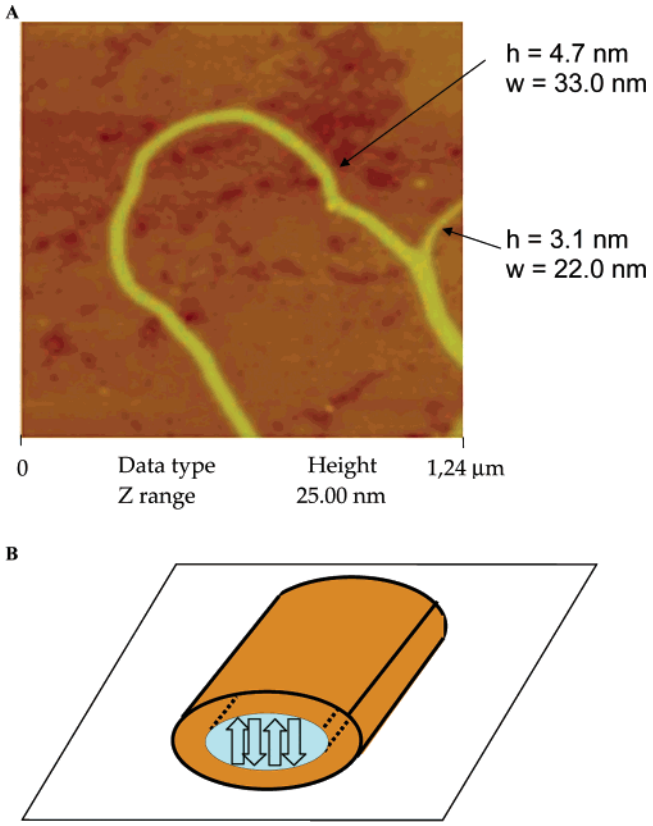


Figure 4. AFM image of PFS-*b*-AGAG **8** in toluene (0.2 mg/mL). (B) Model presentation of a fiber. The orange corona represents the organometallic PFS. The blue core contains the peptide, assembled into antiparallel β-sheets oriented perpendicular to the surface. For reasons of clarity only a few peptide chains (arrows) are shown.

the mixture in toluene above 70 °C. This resulted again in a stable yellow solution. These observations are consistent with the results from FT-IR and DSC analysis. Slow cooling of the hot toluene solution to room-temperature resulted in a viscous solution (concentration = 0.2 mg/mL). Increasing the concentration up to 5 mg/mL did not lead to the formation of an organogel. Transmission electron microscopy (TEM) of the 0.2 mg/mL viscous toluene solution after solvent evaporation, however, showed the formation of a fibrous network (Figure 3). A ^{1}H NMR spectrum of PFS-*b*-AGAG in toluene only showed signals of the PFS, suggesting the formation of a core−shell structure. Since the peptide is insoluble in toluene, it forms the core of the fiber after antiparallel β-sheet formation, while the PFS chains are highly soluble in toluene and wrap around the extended β-sheet core. Atomic force microscopy (AFM) experiments were performed to determine the dimensions of these fibers (Figure 4). A fiber height of 3−5 nm and a fiber width of 22−50 nm were obtained. These findings may suggest that the antiparallel β-sheet forming peptide in the core is

oriented perpendicular to the substrate (mica) (Figure 4B). However, a more detailed study is necessary to confirm this suggestion. Intermolecular hydrogen bonding is the driving force for the assembly of these fibers, while the organometallic PFS wraps around the peptide core and presumably prevents uncontrolled lateral aggregation.

Summary

We have described the synthesis and self-assembly of two β-sheet containing organometallic polymers. The ability of the peptide sequence Gly-Ala-Gly-Ala to form antiparallel β-sheets was retained in both PFS−AGAG conjugates. In the solid state, DSC experiments suggest a phase separation between the peptide and PFS domains. In toluene, PFS-*b*-AGAG interestingly forms a fibrous network which consists of a core containing the self-assembled antiparallel β-sheet peptide and a corona of organometallic PFS. The self-assembly of the peptide into antiparallel β-sheets is the driving force for the fiber formation, whereas PFS prevents uncontrolled lateral aggregation of the fibers. The use of a peptide to self-assemble an otherwise random coiled organometallic polymer may be a useful strategy to enhance nanostructure formation. For example, pyrolysis of these conjugates may lead to nanopatterned ceramics. This, among other options, such as studies of the redox properties of the supramolecular aggregates, will be the subject of further investigations.

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