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Solvent-mediated morphological transformations in peptide-based soft structures

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ABSTRACT

Self-assembly is routinely used for the design and fabrication of new and advanced materials. Biological building blocks such as short peptides undergo self-assembly to reveal a variety of hierarchical structures such as nanotubes, fibers, and spherical structures. Peptide-based soft spherical structures are potentially useful for a variety of applications including vehicles for drug delivery and biological molecules. This report describes a tripalmitoylated triskelion ditryptophan peptide conjugate (**5**) that self-assembles to form hollow spheres along with pores on the surface when higher concentration of the dichloromethane was used, but forms fiber structures when heated in toluene solvent.

1. Introduction

Molecular self-assembly is a tunable methodology for the design and fabrication of functional materials with applications ranging from electro-optics to nanomedicine.[1] The latter application requires biocompatibility, which can be achieved by self-association of biomolecular building blocks. 'Bottom-up' approaches using natural building blocks have played a key role in the discovery of new materials and scaffolds,[2–11] and importantly, self-assembling peptide-based hollow cylinders, spheres and gelatinous scaffolds are particularly useful as substrates for electronics, optics, energy storage, tissue-cell attachment, neurite outgrowth, and formation of active nerve connections, to name a few.[11] These novel architectures also inspire us toward an interest in fundamental phenomenon specific to confined nanospaces.[12]

The important interactions, which are responsible for well formed molecular scaffolds are π–π stacking, Van der Waals forces, hydrogen bonding, etc.[13] These interactions facilitate self-assembly and allow stable growth of supramolecular architectures.

We have recently reported a dipeptide triskelion conjugate that formed caged structures in methanol–water and exhibited ability to entrap guest molecules in solution.[14,15] As one long-term goal to develop synthetic virus like particles, we wished to lipidate the core with long alkyl chains. In the meantime we also became aware of several reports that reveal the lipid-like peptide self-assembled structures, depending on the composition of a mixture of solvent.[16] The presence of primary amino groups in synthetic triskelion offered significant scope for modification as an entry into other interesting material properties of this conjugate and with this premise, we expanded the physico-chemical properties of these molecules by introducing three palmitoyl chains at the N-terminal arms of the triskelion conjugate. Herein, we report synthesis of a tripalmitoylated peptide **5** and its ultrastructures in the different solvent regimes.

2. Results and discussion

2.1. Synthesis of compound 5

Compound **5** was synthesized by solution phase peptide synthesis method as described in Scheme 1.

Palmitic acid was coupled with tryptophan ethyl ester hydrochloride in the presence of DCC and HOBt to produce compound **1**, followed by hydrolysis of the C-terminal ester group to produce compound **2**. Compound **2** was coupled with tryptophan ethyl ester hydrochloride in the presence of DCC and HOBt to yield compound **3**, which on ester group hydrolysis produced **4**. Compound **4** was converted to its active *N*-hydroxysuccinimide ester and its conjugation with tris (2-aminoethyl) amine gave the target compound **5**. Detailed experimental procedures are given in Section 4.

2.2. Formation of hollow spheres

With three palmitoyl group and six tryptophan moieties, compound **5** shows high degree of hydrophobicity and is able to adapt lipid-like conformation.[17,18] Freshly prepared solution of **5** (0.5 mM) in 60% dichloromethane–methanol displayed formation of hollow spheres with an average diameter of ~500 nm. Scanning electron micrographs revealed that these hollow spheres morphed during drying process and changed their shape to bowl-like structures with a depression on the spherical surface (Fig. 1a–c). Atomic force microscopic image also revealed similar morphology for compound **5** (Fig. 1d). After observing soft hollow spheres in 60%

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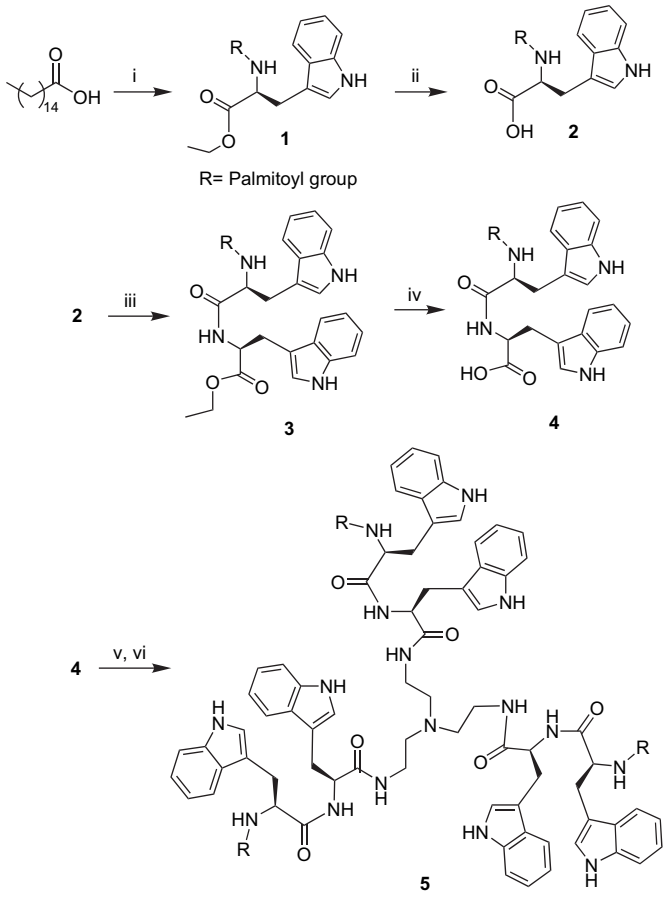

Scheme 1. Synthetic route for compound **5**. (i) Tryptophan ethylester hydrochloride, DCC, HOBt, DMF, 0 °C–rt, 18 h; (ii) 1 N NaOH, MeOH, 3 h; (iii) tryptophan ethylester hydrochloride, DCC, HOBT, DMF, 0 °C–rt, 18 h; (iv) 1 N NaOH, MeOH, 3 h; (v) DCC, *N*-hydroxysuccinimide, DME, 0 °C, 2 h; (vi) TREN [tris (2-aminoethyl) amine], DMF, rt, 24 h.

dichloromethane–methanol we decided to vary the methanol concentration to see its effect on the morphology of **5**. In 80% dichloromethane, we observed hollow spheres with multiple pores with an average diameter 1–10 μm (Fig. 2a–d). SEM image of the cracked and opened-up hollow spheres further confirmed that the structures are hollow in nature. These porous structures clearly indicate that after the formation of hollow spheres, trapped volatile solvent dichloromethane escapes from the surface during the drying process to reveal porous channels.[19] This observation is similar to engendering porosity in polymer samples with the help of porogens. The use of volatile solvents as porogens has been reported in contest polymeric materials such as aqueous solution of poly(*o*-methoxy aniline).[20] We believe self-assembly of compound **5** in dichloromethane–methanol traps volatile solvents in the interior core of the hollow spheres, and while drying, volatile solvent moves toward the surface resulting in shrunken hollow spheres. Escape of solvent from the spheres leads to pore formation.

2.3. Morphological studies in other solvents

Self-assembly of compound **5** was evaluated in other pure and mixed solvents (Table 1) to investigate the morphological changes induced by solvent change. Formation of hollow spheres also dominated in other solvents such as in chloroform–methanol mixture (data not shown) and in DMF (Fig. 3b). Uniformly distributed hollow spheres were observed in case of dichloroethane–methanol (80:20) (Fig. 3a) and dichloromethane–trifluoroethanol (80:20) solvent mixture (data not shown).

However, room temperature solubility of **5** in toluene proved to be rather poor. Therefore, we decided to heat up **5** in toluene until it dissolved completely at 85 °C (0.85 mg in 500 μL toluene), and the microscopic analysis of toluene solution indicates appearance of dense fibrous morphology (Fig. 4). AFM image and TEM image suggested that fibers were composed of small particles fused together to reveal ribbon-like fibers (Fig. 4d) with an inclination toward formation of gel-like structure (data not shown). Interestingly, control experiments with non-palmitoylated triskelion revealed lack of fibril formation in toluene. Table 1 represents different morphologies obtained in various solvents.

It appears that when compound **5** is heated in toluene, a morphological conversion occurs from small spherical structures to fibers. Eventual coalescence during the cooling phase leads to the fusion of spherical structures to fibers with a tendency toward gelation (data not shown). Three palmitoyl chains connected at the N-terminal of the molecule may facilitate the fusion process by interdigitating between each other leading to the coalescence of spherical structures.

2.4. Encapsulation of the guest molecule and rupture of the hollow spheres

After morphological studies, we planned to evaluate entrapment of guest molecules within the confines of these hollow spheres. Rhodamine B dye was chosen as a guest molecule. Compound **5** was dissolved in 1 μM rhodamine B solution and incubated for 24 h. The solution was loaded on a glass slide and dried, followed by fluorescence microscope imaging. The fluorescence micrographs indicated the entrapment of rhodamine B inside the hollow spheres (Fig. 5a).

Fluorescence micrograph suggested rupture of the hollow spheres and release of the dye (Fig. 5b) by simple acidification with methanolic HCl, further lowering down the pH, hollow spheres ruptured completely (Fig. 5c and d). The reason behind the loss of structural integrity may be attributed due to the protonation of tertiary nitrogen on lowering down the pH of the solution. Finally, electrostatic repulsion between two positive charged molecule results in the rupturing of hollow spheres.

3. Conclusion

In conclusion, we have showed the N-terminal modification of the triskelion ditryptophan peptide conjugate by introducing three palmitoyl chains, which is known to be a cell penetrating group, leads to intriguing morphological changes governed by solvent interactions. It is anticipated that such fine-tuning of the self-assembly may lead to the construction of a wide array of nanostructures thereby fostering innovations in the development of functional peptide scaffolds.

4. Experimental

4.1. General

Dichloromethane, *N*,*N*-dimethylformamide, methanol, triethylamine, and 1,2-dimethoxy ethane were distilled following standard procedures prior to use. *N*,*N*′-Dicyclohexylcarbodiimide (DCC), *N*-hydroxybenzotriazole (HOBT), *tert*-butyloxycarbonyl carbonate, and L-amino acids were purchased from Spectrochem, Mumbai, India, and used without further purification. Tris (2-aminoethyl) amine (TREN) was purchased from Sigma. ^{1}H and ^{13}C NMR spectra were recorded on JEOL-JNM LAMBDA 400 model operating at 400 and 100 MHz, respectively. HRMS spectra were recorded on Waters Q-TOF Premier Micromass MS Technology.

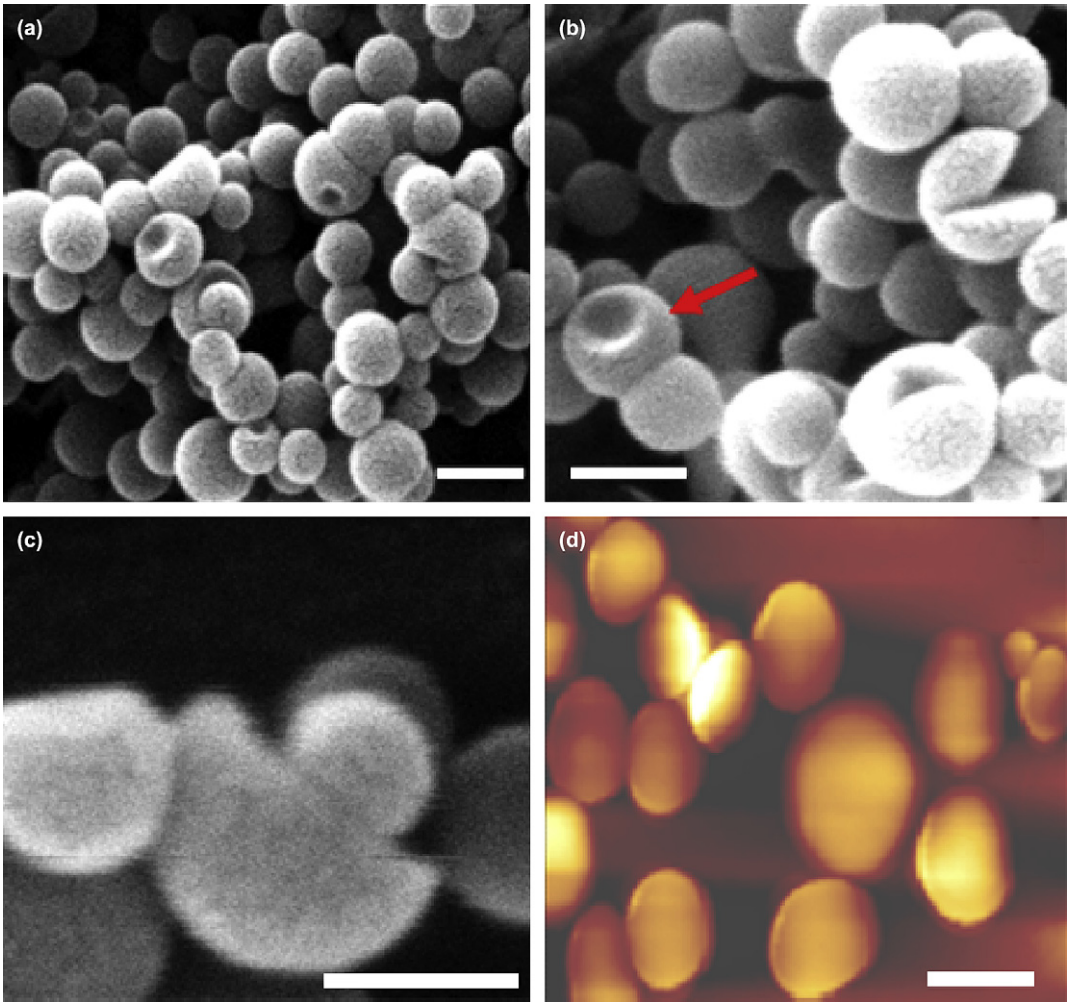

Figure 1. (a,b) SEM micrograph of **5** formed in dichloromethane–methanol mixture. Red arrow indicates the bowl shaped hollow spheres with a surface depression; (c) magnified image of a bowl; (d) AFM image of the hollow spheres. Scale bar corresponds to 500 nm.

4.2. Synthesis of the compound 1

Palmitic acid (1 g, 3.89 mM) and *N*-hydroxy benzotriazole (0.525 g, 3.89 mM) were dissolved in dry DMF and reaction mixture was cooled to 0 °C under nitrogen atmosphere. Solution of DCC (0.96 g, 4.67 mM) in dichloromethane was added into the reaction mixture at 0 °C under nitrogen atmosphere. The reaction mixture was stirred at 0 °C for 1 h. After 1 h tryptophan ethyl ester hydrochloride (1.04 g, 3.89 mM) was added into the reaction mixture followed by triethylamine (0.65 mL, 4.67 mL) and reaction mixture was stirred for 24 h at room temperature. Reaction mixture was filtered to remove *N*,*N*′-dicyclohexylurea (DCU) and filtrate was concentrated in reduced pressure. The residue was dissolved in dichloromethane and organic layer was washed with 1 N HCl (3×30 mL), 10% $NaHCO_3$ (3×30 mL), and brine (30 mL). Organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude compound was purified through silica gel column chromatography by using dichloromethane and methanol (97:3) to give pure compound **1** (1.5 g, 3.1 mM). Mp: 56–58 °C, R_f [5% methanol in dichloromethane]=0.6, $[\alpha]_D^{25}$ +0.11 (*c* 6.1, dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$, TMS, δ ppm): 0.84–0.87 (m, 3H), 1.13–1.23 (m, 26H), 2.09–2.13 (m, 2H), 3.28–3.34 (m, 2H), 4.06–4.17 (m, 2H), 4.90–4.95 (m, 1H), 5.96–5.98 (m, 1H), 6.95 (s, 1H), 7.06–7.10 (m, 1H), 7.14–7.18 (m, 1H), 7.31–7.33 (d, 1H, 8 Hz), 7.51–7.53 (d, 1H, 8 Hz), 8.31 (br s, 1H); ^{13}C NMR (100 MHz; $CDCl_3$, δ ppm): 13.98, 22.61, 24.83, 25.41, 27.54, 29.27, 29.57, 31.83, 33.67, 36.47, 52.93, 61.34, 109.66, 111.28, 118.37, 119.33, 121.91, 122.77, 127.63, 136.07, 172.04, 172.97; FTIR (KBr, cm^{-1}): 1647 (amide II), 1741 (amide I), 3307 (–NH str); HRMS calcd for $C_{29}H_{46}N_2O_3$ (M+H): 471.3508. Found $(M+H)^+$: 471.3586.

4.3. Synthesis of the compound 2

Compound **1** (0.81 g, 1.7 mM) was dissolved in methanol (10 mL) and 1 N NaOH (1.6 mL) was added into the solution at room temperature. The reaction mixture was stirred for 3 h at room temperature. Reaction mixture was concentrated to completely remove methanol under reduced pressure. The residue was acidified with 1 N HCl (5 mL) and extracted with dichloromethane (3×20 mL). The combined organic layer was washed with water followed by brine (20 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to get compound **2** (0.72 g, 1.62 mL), which was directly used for the synthesis of **3**.

4.4. Synthesis of the compound 3

Compound **2** (0.7 g, 1.58 mM) and *N*-hydroxy benzotriazole (0.256 g, 1.89 mM) were dissolved in dry DMF and reaction mixture was cooled to 0 °C under nitrogen atmosphere. Solution of DCC (0.389 g, 1.89 mM) in dichloromethane was added. The reaction mixture was stirred at 0 °C for 1 h. After 1 h tryptophan ethyl ester hydrochloride (0.425 g, 1.58 mM) was added into the reaction

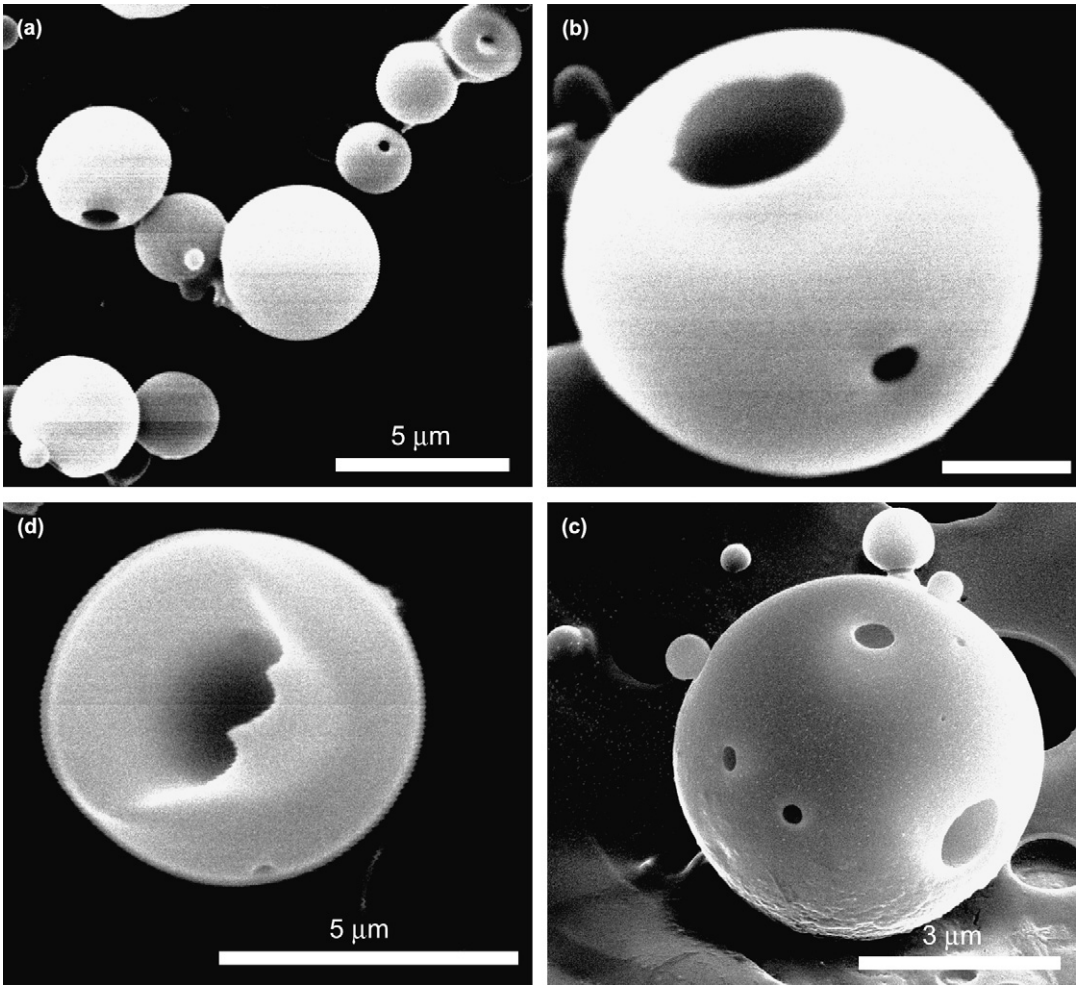

Figure 2. (a) SEM micrograph of hollow spheres of compound **5** formed in dichloromethane–methanol mixture (80:20); (b,c) magnified image showing multiple pores; (d) cracked and opened-up spheres.

mixture followed by triethylamine (0.26 mL, 1.89 mM) and reaction mixture was stirred for 24 h at room temperature. Reaction mixture was filtered to remove DCU and filtrate was concentrated under reduced pressure. The residue was dissolved in dichloromethane and organic layer was washed with 1 N HCl (3×30 mL), 10% $NaHCO_3$ (3×30 mL), and brine (30 mL). Organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude compound was purified through silica gel column chromatography by using dichloromethane and methanol (98.5:1.5) to give pure compound **3** (0.88 g, 1.3 mM). Mp: 68–78 °C, R_f [5% methanol in dichloromethane]=0.8, $[\alpha]_D^{25}$ −0.03 (*c* 9.9, dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$, TMS, δ ppm): 0.83–0.87 (m, 3H), 1.14–1.17 (t, 3H), 1.23–1.31 (m, 26H), 1.88–1.96 (m, 2H), 3.01–3.14 (m, 3H), 3.29–3.34 (m, 1H), 3.47 (m, 1H), 4.0–4.08 (m, 2H), 4.69–4.76 (m, 1H), 6.15–6.20 (dd, 2H), 6.60–6.61 (d, 1H, 4 Hz), 6.75 (s, 1H), 6.92 (s, 1H), 7.02–7.12 (m, 2H), 7.15–7.19 (m, 1H), 7.23–7.25 (m, 2H), 7.27–7.31 (d, 1H, 8 Hz), 7.61–7.68 (d, 1H, 8 Hz), 8.31–8.39 (d, 2H); ^{13}C NMR (100 MHz; $CDCl_3$, δ ppm): 13.97, 14.08, 22.64, 24.82, 25.44, 27.27, 28.1, 29.12, 29.26, 29.31, 29.43, 29.61, 29.66, 31.86, 33.75, 36.45, 52.88, 53.5, 61.43, 109.13, 110.21, 111.28, 118.22, 118.81, 119.27, 119.64, 121.96, 122.06, 123.12, 123.59, 127.28, 127.5, 135.98, 136.14, 170.01, 171.26, 173.2; FTIR (KBr, cm^{-1}): 1493 (amide II), 1629 (amide I), 3326 (–NH str); HRMS calcd for $C_{40}H_{56}N_4O_4$ (M+H): 657.4302. Found $(M+H)^+$: 657.4389.

Table 1
Solvent responsive morphological transformation

Solvent	Hollow spheres	Fiber
DCM–MeOH (60:40)	+ (Bowl shape)	−
DCM–MeOH (80:20)	+ (Hollow/multiple holes)	−
Chloroform–methanol (60:20)	+	−
Dichloroethane–methanol (80:20)	+ (Array of hollow spheres)	−
Dichloroethane–trifluoroethanol (80:20)	+ (Array of hollow spheres)	−
DMF	+	−
Toluene	−	+

4.5. Synthesis of the compound 4

Compound **3** (0.74 g, 1.1 mM) was dissolved in methanol (10 mL) and 1 N NaOH (1.5 mL) was added into the solution at room temperature. The reaction mixture was stirred for 3 h at room temperature. Reaction mixture was concentrated to remove methanol under reduced pressure. The residue was acidified with 1 N HCl (5 mL) and extracted in dichloromethane (3×20 mL). Combined organic layer was washed with water followed by brine (20 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to get compound **4** (0.68 g, 1.08 mM), which was directly used for the synthesis of **5**.

4.6. Synthesis of the compound 5

Compound **4** (0.5 g, 0.79 mM) and *N*-hydroxysuccinimide (0.1 g, 0.87 mM) were dissolved in 1,2-dimethoxy ethane (20 mL) and

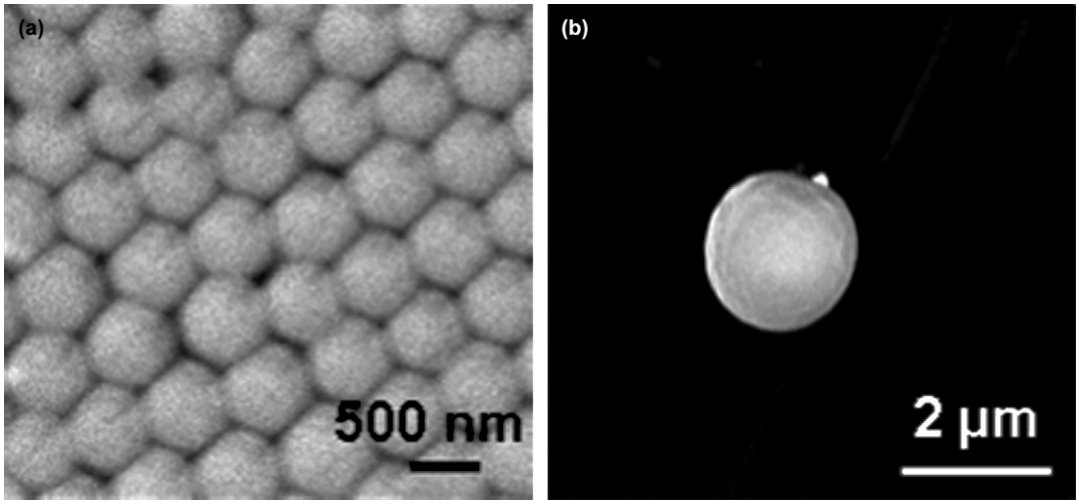

Figure 3. (a) SEM micrograph shows the uniformly arranged hollow spheres of **5** in 1,2-dichloroethane–methanol mixture (80:20); (b) spherical morphology in DMF.

reaction mixture was cooled to 0 °C under nitrogen atmosphere. Solution of DCC (0.18 g, 0.87 mM) in 1,2-dimethoxyethane (2 mM) was added into the reaction mixture drop-wise and reaction mixture was stirred for 2 h at 0 °C followed by storing overnight 0 °C. Reaction mixture was filtered and the filtrate was concentrated under reduced pressure. Solid was washed with diethyl ether

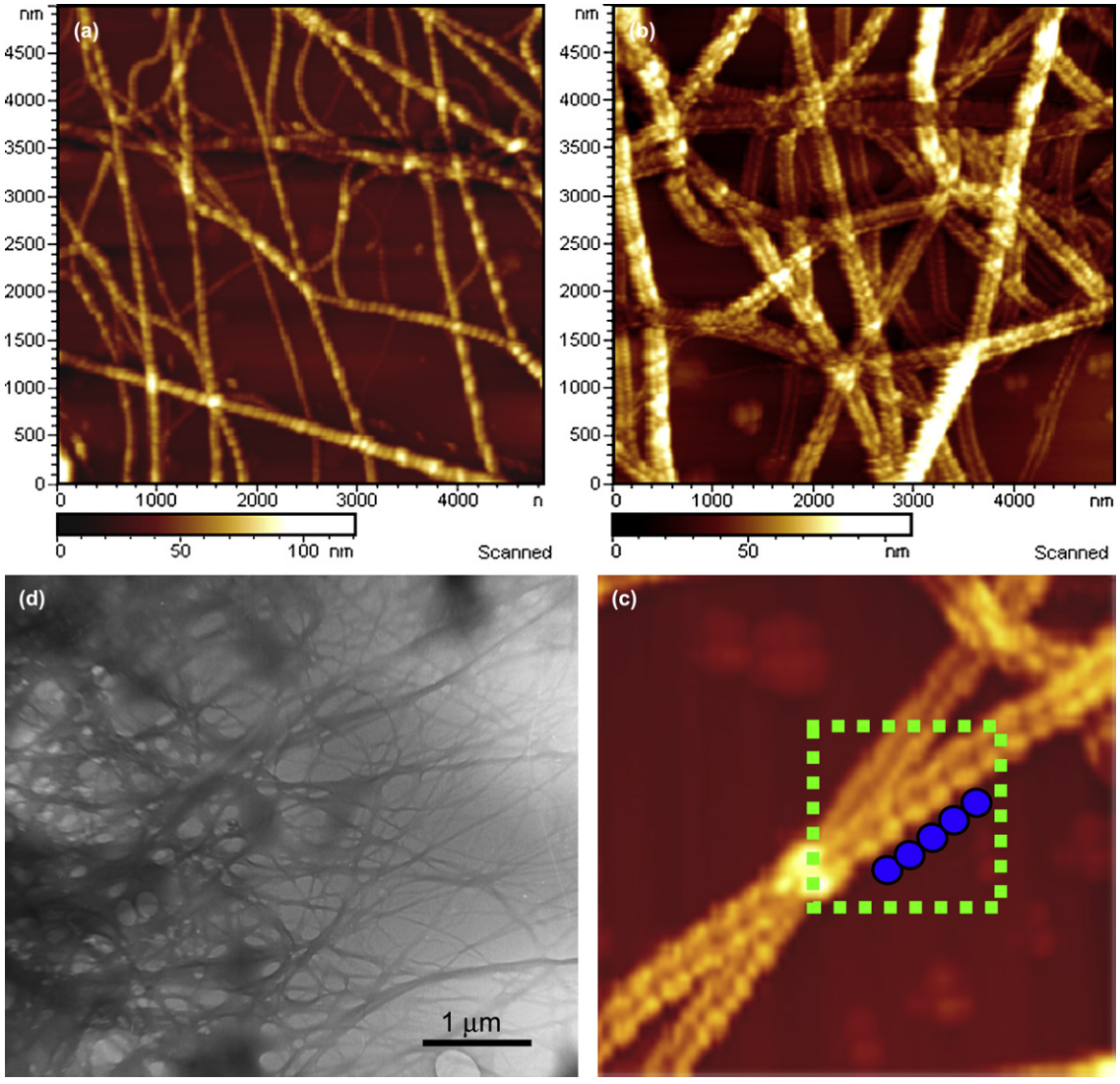

Figure 4. Compound **5** in toluene (a, b) AFM image of the fiber; (c) magnified image of the fiber and green marked area indicates puncated spherical structures as substructures of fibrous structure (blue artwork). (d) TEM image shows the dense fibrous network.

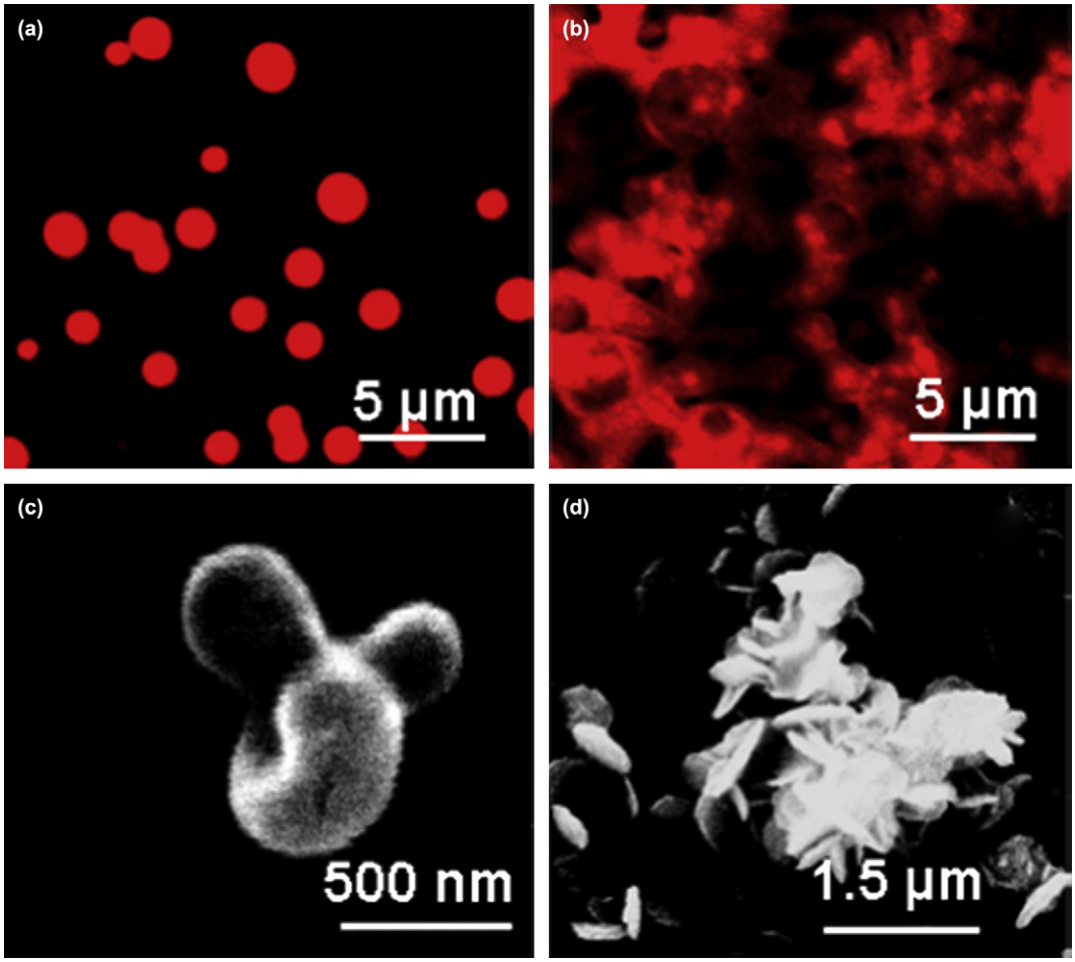

Figure 5. (a) Fluorescence microscopy image of hollow spheres in presence of the rhodamine B dye (60% dichloromethane–methanol); (b) rupture of fluorescent spheres at pH 6.2; (c) SEM image shows the opened-up spherical structures at pH 6.2 and (d) complete rupture at pH 4.2.

and dried under high vaccum pump. Crude compound (0.54 g, 0.74 mM) was dissolved in dry DMF (3.5 mL) at room temperature under nitrogen atmosphere. Solution of ethylenediamine (31 μL, 0.2 mL) in dry DMF (0.5 mL) was added into the reaction mixture drop-wise under nitrogen atmosphere at room temperature. The reaction mixture was stirred at room temperature under nitrogen atmosphere for 24 h. The reaction mixture was concentrated under reduced pressure and dissolved in dichloromethane. Organic layer was washed with 1 N HCl (3×10 mL), 10% $NaHCO_3$ (3×10 mL), and brine solution. Organic layer was dried over anhydrous sodium sulfate and concentrated. The crude compound **5** was purified through silica gel column chromatography by using dichloromethane–methanol (97:3) solvent system to give pure compound (0.25 g, 0.12 mM). Mp: compound decomposes at 198 °C, R_f [10% methanol in dichloromethane]=0.6, $[\alpha]_D^{25}$ −0.02 (*c* 2.0, *N*,*N*′-dimethylformamide). ^{1}H NMR (400 MHz, DMSO, TMS, δ ppm): 0.81(m, 6H), 1.1–1.2 (merged peaks, 78H, palmitoyl chain H), 1.9 (m, 6H), 2.2 (m, 6H), 3.0 (m, 12H), 3.3 (merged with DMSO peak, 12H), 4.5 (m, 6H), 6.9 (m, 6H), 7.01 (m, 6H), 7.07 (s, 6H), 7.26–7.28 (d, 6H, *J*=8.0 Hz), 7.5 (m, 6H), 7.6 (br s, 3H), 7.8 (m, 6H), 10.7 (m, 6H); ^{13}C NMR (100 MHz; DMSO-d_6, δ ppm): 13.97, 22.14, 25.15, 27.39, 27.82, 28.61, 28.77, 28.88, 28.98, 29.12, 31.34, 35.26, 37.04, 52.95, 53.47, 61.0, 109.78, 110.21, 11.23, 118.15, 118.20, 118.40, 120.79, 123.53, 127.37, 136.05, 171.14, 171.50, 172.49; FTIR (KBr, cm^{-1}): 1515 (amide II), 1649 (amide I), 3301 (–NH str); HRMS calcd for $C_{120}H_{168}N_{16}O_9$ (M+H): 1978.3180. Found $(M+H)^+$: 1978.3280; purity of the compound was >99% checked by FPLC (C-18 column, eluent A: 0.1% TFA in water and eluent B: 0.1% TFA in acetonitrile, flow rate 0.8 mL/min).

5. Microscopic sample preparation

5.1. Optical microscopy

Gel solution of the compound **5** in toluene was loaded onto the glass slide and image was captured under cross-polarized light by Labomed Digi 3 microscope.

5.2. Scanning electron microscopy

Incubated solution (20 μL) was coated atop metal slides. A gold coating was applied to the top of the sample to make it conductive for analysis. Samples in different solvents and gel in toluene were analyzed by SEM. SEM measurements were performed on FEI QUANTA 200 Microscope equipped with a tungsten filament gun. Micrograph was recorded at WD 10.6 mm, in varied magnification. Concentration of the samples used was 0.5 mM in 60% dichloromethane–methanol and for the gel 0.85 mg in 1 mL toluene.

5.3. Atomic force microscopy

Samples were imaged with an atomic force microscope (Molecular Imaging, USA) operating under Acoustic AC mode (AAC), with the aid of a cantilever (NSC 12(c) from MikroMasch). The force constant was 0.6 N/m, while the resonant frequency was 150 kHz. The images were taken in air at room temperature, with the scan speed of 1.5–2.2 lines/s. The data acquisition was done using PicoScan 5® software, while the data analysis was done with the aid of visual SPM.

The mixture of the peptide solution was incubated for 0–7 days in 60% dichloromethane–methanol and micrographs were recorded for selected incubation periods. Sample solution (10 μL) was transferred onto freshly cleaved mica surface and uniformly spread with the aid of a spin-coater operating at 200–500 rpm (PRS-4000). The sample-coated mica was dried for 30 min at room temperature, followed by AFM imaging. In similar way gel solution was spread over freshly cleaved mica surface and dried for 30 min, followed by AFM imaging.

5.4. Transmission electron microscopy

Solutions of compound **5** (3 μL) in 60% dichloromethane–methanol were loaded on carbon coated copper grid, dried and stained with uranyl acetate, followed by imaging. Gel solution of compound **5** (2 μL) in toluene was loaded onto the carbon coated copper grid, dried and negatively stained with uranyl acetate followed by imaging.

5.5. Fluorescence microscopy

Compound **5** (1 mM) was dissolved in 10 μM rhodamine B solution in 60% dichloromethane–methanol and incubated for 2 days at 37 °C. After 2 days, 10 μL incubated solution was loaded onto the glass slide and followed by fluorescence microscopic imaging. Solution of compound **5** was acidified with the methanolic HCL solution and pH was measured. These dye entrapped vesicular structures were examined on a fluorescent microscope (Zeiss Axioskop 2 Plus) provisioned with an illuminator (Zeiss HBO 100) and a rhodamine filter (absorption 540 nm/emission 625 nm). This filter optimized visualization of rhodamine-treated (positive resolution) compared with untreated (negative resolution) spherical structures that were virtually invisible in this light.

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