



Macromolecular Nanotechnology

Structural characterization of nanoparticles formed by fluorinated poly(2-oxazoline)-based polyphiles

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ABSTRACT

We report on the self-assembly behavior of poly(2-methyl-2-oxazoline)-block-poly(2-octyl-2-oxazoline) comprising different terminal perfluoroalkyl fragments in aqueous solutions. As reported previously [Kaberov et al. (2017)] such polyphiles can form a plethora of nanostructures depending of the composition and on the way of preparation. Here we report, for the first time, detailed information on the internal structure of the nanoparticles resulting from the self-assembly of these copolymers. Small-angle neutron and X-ray scattering (SANS/SAXS) experiments unambiguously prove the existence of polymersomes, wormlike micelles and their aggregates in aqueous solution. It is shown that increasing content of fluorine in the poly(2-oxazoline) copolymers results in a morphological transition from bilayered or multi-layered vesicles to wormlike micelles for solutions prepared by direct dissolution.

In contrast, nanoparticles prepared by dialysis of a polymer solution in a non-selective organic solvent against water are characterized by SAXS method. The internal structure of the nanoparticles could be assessed by fitting of the scattering data, revealing complex core-double shell architecture of spherical symmetry. Additionally, long range ordering is identified for all studied nanoparticles due to the crystallization of the poly(2-octyl-2-oxazoline) segments inside the nanoparticles.

1. Introduction

Owing to their versatile properties, poly(2-alkyl/aryl-2-oxazoline)s (PAOx) and their derivatives currently receiving significant scientific attention [1–3]. Due to their biocompatibility and nontoxicity, PAOx are widely studied as materials for biomedical applications such as drug, protein, radionuclide or gene delivery [4–7] as well as for the preparation of non-fouling surfaces that resist non-specific adsorption of proteins, bacteria, and higher organisms [8]. Living cationic ring-opening polymerization (CROP) is usually used for the synthesis of polyoxazolines [9,10] and allows not only controlling the molecular weight and dispersity of the resulting polymers but also to obtain PAOx of desired architecture. One can vary the nature and ratio of monomers, use different functional initiators or terminate agents thereby introducing fragments with different functionality and controlling the hydrophilic to hydrophobic balance [11–13].

Varying the ratio and the order of hydrophilic and hydrophobic blocks constituents of amphiphilic PAOx leads to a plethora of self-assembled structures such as spheres [14], vesicles [15], rod- or wormlike micelles, cylinders and corresponding aggregates in solution. Usually, poly(2-methyl-2-oxazoline) (MeOx) or poly(2-ethyl-2-oxazoline) (EtOx) are used to build hydrophilic blocks since these are biocompatible and reveal “stealth-like” behavior [16–18]. More complex structures, for example, multicompartiment micelles, could be obtained upon self-assembly of triblock terpolymers in water or organic solvents [19,20]. Especially interesting are the so-called polyphiles - triblock copolymers that combine hydrophilic, hydrophobic and fluorophilic blocks [21–25]. Due to the immiscibility of the lipophilic and fluorophilic hydrophobic segments the resulting copolymers can form particles of complex morphologies depending on the polymer architecture and solvent [20,26,27]. Such nano- and microparticles containing fluorinated fragments are of high interest for potential application as

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magnetic resonance imaging contrast agents [28,29].

While the synthesis and the self-assembly behavior of di- and triblock PAOx containing hydrophilic and hydrophobic blocks were widely studied, there is not much information about triblock PAOx that contain fluorinated moieties. Schubert and co-authors reported on the investigation of nanostructures formed by triblock terpolymers consisting of poly[2-ethyl-2-oxazoline-block-2-(1-ethylpentyl)-2-oxazoline-block-2-(Xfluorophenyl)-2-oxazoline] (X = di, tri, tetra and penta). The authors studied the influence of the fluorination degree of these polymers on their self-assembly ability. A transition from rod-like micelles to highly complex round-shaped super-aggregates was observed by cryo-TEM with increasing fluorine content [30]. Water-soluble polymer surfactants based on 2-methyl-2-oxazoline with both fluorinated terminal group $C_8H_{17}CH_2CH_2$ (constant length) and hydrocarbon terminal group of different lengths C_nH_{2n+1} ($n = 6, 8, \dots, 18$) were synthesized by Nuyken and co-authors [31]. It was shown by the fluorescence spectroscopy of polymer solutions with solubilized pyrene that micelle core composition and first micellization point depends on the ratio between hydrophobic and fluorocarbon parts of polymer.

Recently we reported on the synthesis and solution properties of a novel quasi-triblock fluorine-containing copolymers based on 2-oxazolines [32]. Our synthetic approach provides an easy way to attach a C_nF_{2n+1} perfluorinated terminal chain to a poly(2-methyl-2-oxazoline)-block-poly(2-octyl-2-oxazoline) (PMeOx-b-POctOx) diblock copolymer through termination and to combine hydrophilic, hydrophobic and fluorophilic moieties along one polymer chain. Preliminary investigations of the self-assembly of the synthesized polymers in water using dynamic light scattering and cryo-TEM revealed the coexistence of bilayer and multi-layer vesicles as well as rod-like micelles. The shape and the size of the nanoparticles in solution could be controlled by the way of preparation. Spherical micelles with diameters ranging from 15 to 20 nm were observed in solution for the polymers assembled by solvent exchange. However, more detailed insights into the internal structure (size of the core and the shell thickness) of the formed nanoparticles and their dependence on the length of the fluorinated fragment or the method of preparation were not investigated.

Here, we report on the in depth evaluation of the internal structure of nanoparticles formed by the self-assembly of quasi-triblock fluorine-containing copolymers, namely PMeOx-POctOx- C_8F_{17} , PMeOx-POctOx- $C_{10}F_{21}$, PMeOx-POctOx- $C_{12}F_{25}$, as well as the non-fluorinated PMeOx-b-POctOx reference diblock copolymer. We describe the influence of the length of the perfluorinated terminal chain and of the preparation methods on the features of the self-assembled polymers. To achieve a comprehensive characterization of the morphology of the resulting nanoparticles, we combined both small-angle X-ray scattering (SAXS) and small-angle neutron scattering (SANS) experiments.

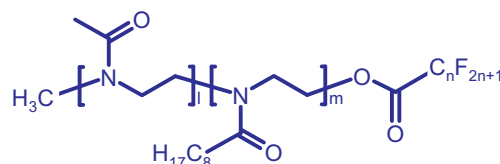
2. Experimental section

2.1. Materials

2-Methyl-2-oxazoline (MeOx, 99%, Acros Organics) was dried over BaO and distilled before use. 2-(n-octyl)-2-oxazoline (OctOx) was synthesized according to procedure described elsewhere [32]. Perfluorinated acids (nonanoic, undecanoic, tridecanoic) and p-toluenesulfonate were purchased from Sigma-Aldrich and used as received. Acetonitrile (ACN, Lachner) was dried by refluxing over BaO and distilled before use. Water was deionized with a MilliPore Milli-Q® gradient installation. All other chemicals were used as received.

2.2. Polymer synthesis

All copolymers were synthesized separately by the CROP. The detailed procedure was described in our previous work [32]. In brief, the first monomer MeOx and the initiator (p-toluenesulfonate) were dissolved in acetonitrile and stirred at 140 °C in pressure reactor under



Scheme 1. Chemical structure of quasi-triblock copolymers, $n = 8, 10$ or 12 .

Table 1

Composition and characteristics of fluorinated quasi-triblock poly(2-oxazolines) and reference nonfluorinated diblock copolymer.

Polymer	Composition	M_n , g/mol	\bar{D}
P0	PMeOx ₃₀ -b-POctOx ₂₀	6300	1.11
P1	PMeOx ₃₀ -b-POctOx ₂₀ - C_8F_{17}	6000	1.08
P2	PMeOx ₃₀ -b-POctOx ₂₀ - $C_{10}F_{21}$	5000	1.09
P3	PMeOx ₃₀ -b-POctOx ₂₀ - $C_{12}F_{25}$	5000	1.14

inert atmosphere for 35 min ($\approx 98\%$ of conversion). After cooling down the reaction mixture, the second monomer OctOx was added and the mixture was stirred at 140 °C for another 45 min to form diblock copolymer.

The perfluoroalkyl fragments were attached to copolymers by termination of polymerization with corresponding perfluorinated carboxylic acids in the presence of triethylamine at 70 °C. To obtain the model PMeOx-b-POctOx diblock copolymer, the polymerization was quenched with 1 M KOH in methanol.

The chemical structures of the polymers are shown in Scheme 1. The molecular weights of the polymers range from 5 to 6 kDa, and the polydispersities of the samples according to the reference [32] in range from 1.08 to 1.14 (Table 1).

2.3. Preparation of samples

All solutions for SAXS experiments were prepared using deionized water in the range of concentrations from 0.1 to 5 wt%. All solutions for SANS experiments were prepared using D₂O (99.9%, Sigma-Aldrich) as solvent to reduce the incoherent scattering. The concentration of all SANS solutions was 2 wt%. Scattering from pure H₂O or D₂O was measured separately and subtracted from solution scattering data.

Samples for SAXS and SANS experiments were prepared in two ways: by direct dissolution in H₂O or D₂O or by solvent exchange.

2.3.1. Solvent exchange method

Briefly, 5 mL of 2.5 wt% polymer solution in methanol was placed in dialysis tubing with MWCO 3.5–5 kDa (Spectra/Por, Spectrum Laboratories, Inc.) and dialyzed against 5 L of deionized water with mild stirring at 25 °C. The deionized water was refreshed 5 times and the total dialysis time was 24 h. Samples were stored in sealed containers at 4 °C.

2.4. Small-angle X-ray scattering

SAXS experiments for samples prepared by direct dissolution were performed on the high brilliance beamline ID02 at ESRF (Grenoble, France). The SAXS setup utilizes a pinhole camera with a beam stop placed in front of a two-dimensional Frelon CCD detector. The X-ray scattering patterns were recorded for sample-to-detector distances of 2.5 and 31 m, using a monochromatic incident X-ray beam with an energy of $E = 12\,460$ eV ($\lambda = 0.1$ nm). The available scattering vector range was $q = 0.001$ – 2.76 nm⁻¹ ($q = 4\pi \sin \theta/\lambda$, where 2θ is the scattering angle). Online corrections were applied for the detector, and the sample-to-detector distance, center, transmission, and incident intensity were calibrated. The isotropic scattering was azimuthally re-grouped to determine the dependence of the scattered intensity $I(q)$ on

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