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Novel triphilic block copolymers based on poly(2-methyl-2-oxazoline)–*block*–poly(2-octyl-2-oxazoline) with different terminal perfluoroalkyl fragments: Synthesis and self-assembly behaviour

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ABSTRACT

We report on the synthesis and solution properties of novel fluorine-containing copolymers. 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) copolymer and to combine hydrophilic, hydrophobic and fluorophilic moieties into one segmented polymer. A series of such quasi-triblock copolymers was prepared with variation of the length of the fluorinated chain end. Using a variety of experimental methods including dynamic light scattering and transmission cryo-electron microscopy, we prove that all of the synthesized copolymers self-assemble into nanostructures in aqueous milieu. The structures and shapes of the nanostructures are controlled by the length of the perfluoroalkyl chain. Single-layer and multi-layer vesicles as well as rod-like micelles are observed in aqueous solutions. The supramolecular structures described represent a potential platform for ^{19}F magnetic resonance imaging contrast agents.

1. Introduction

Molecules composed of fragments with different natures are prospective substances for the formation of phase-separated materials with controlled properties. It was reported earlier that block copolymers based on hydrophilic and hydrophobic polymers are able to form self-assembled structures in aqueous solution. The morphology of these structures can be controlled by a number of factors: polymer composition, concentration, presence of additives and co-solvents, etc. [1,2]. Varying these parameters can lead to structures ranging from simple spherical and cylindrical micelles to more complex bicontinuous and bilayer (lamellae, vesicles) structures.

The main goal of contemporary research in this area is to develop combinations of different monomers, which enable the creation of a plethora of different self-assembled structures. The main criteria for such monomers are the simplicity of the synthesis, the ability to control polymerization with a narrow dispersity of the resulting polymers and the possibility for easy

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structure tuning. Poly(2-alkyl-2-oxazoline)s exhibit all of these characteristics, making them appealing candidates. It is known that poly(2-methyl-2-oxazoline) and poly(2-ethyl-2-oxazoline) exhibit "stealth" behaviour and possess excellent biocompatibility and non-immunogenicity, comparable with poly(ethylene oxide) [3,4], which could make them useful in medicine, for example, as nanocontainers for the targeted delivery of drugs [5–8]. It was shown that these polymers do not accumulate in body tissues [9–11].

Polymerization of 2-alkyl-2-oxazolines via the cationic ring-opening polymerization (CROP) mechanism was discovered in the 1960s [12–17]. This mechanism includes all of the common steps of chain-growth polymerization: initiation, propagation, and termination. In the absence of termination and chain transfer agents (first of all, moisture and other chain transfer inducing functional groups and impurities), the CROP of 2-oxazolines can proceed as living polymerization. The living CROP of 2-oxazolines is ideally suited for the preparation of amphiphilic block copolymers because both hydrophilic and hydrophobic poly(2-oxazoline)s are readily accessible by varying the side-chain substituent of the monomer [16] and block copolymers can be easily prepared by sequential addition of the second monomer after full conversion of the first monomer. Furthermore, functional groups can be introduced during initiation and termination [18]. For example, Binder and Gruber reported the synthesis of a series of block copolymers with poly(2-methyl-2-oxazoline) as the hydrophilic block combined with a variety of hydrophobic 2-oxazolines to form the hydrophobic block [19]. These amphiphilic copolymers self-assemble in aqueous solution, and with increasing molecular weight and mass fraction of the hydrophobic block, the size of the aggregates also increased. The insertion of long alkyl fragments by initiation and/or termination of the living CROP of 2-oxazolines also allows the preparation of amphiphilic structures that self-assemble into micelles. Volet and Amiel reported the self-assembly of poly(2-methyl-2-oxazoline)s synthesized with a lipophilic initiator [20]. Winnik et al. demonstrated the formation of micellar aggregates in aqueous solutions of a range of poly(2-ethyl-2-oxazoline)s and poly (2-isopropyl-2-oxazoline)s with terminal n-octadecyl chains and discussed their thermoresponsive behaviour [21]. Moreover, in studies of Tiller and co-workers, the antimicrobial activity of *N*,*N*-dimethyldodecylammonium-modified poly (2-oxazoline)s was shown [22].

Currently, considerable interest is paid to fluorinated substances. Perfluorohydrocarbons are components of many commercial intravascular oxygen carriers and tissue oxygenation fluids, such as Fluosol®, Perftoran®, Oxyfluor® [23], etc. One of the main upcoming applications of perfluorinated substances is as contrast agents in ^{19}F Magnetic Resonance Imaging (MRI). The ^{19}F atoms have 100% natural abundance, and their MR sensitivity is 83% that of ^{1}H atoms. Perfluorocarbons are immiscible with blood, but they could be injected as emulsions and since there are almost no endogenous fluorine atoms in body tissues (except bones and teeth) ^{19}F MRI allows imaging without significant background signal [24–26]. Perfluoroalkane chains are hydrophobic, but they are also lipophobic - alkanes and perfluoroalkanes are immiscible beginning from C_6. Moreover, perfluoroalkyl chains are much less flexible and polarizable in comparison to alkyl chains due to the larger fluorine atoms and high electron density, resulting in a greater ability to crystallize and form more ordered structures [27].

One can expect that the insertion of perfluorinated fragments into amphiphilic block copolymers will promote additional complexity and decrease critical micelle concentrations due to their strong hydrophobic character and immiscibility with hydrocarbon hydrophobic domains. Indeed, Laschewsky and co-workers reported that linear acrylic block copolymers with different side chains - hydrophilic, hydrophobic and fluorophilic - form micellar aggregates with complex phase-separated structure of the hydrophobic core in aqueous solution [28–30]. In the work of Hillmyer and Lodge, miktoarm star block copolymers with poly(ethylene oxide), polyethylene, and poly(perfluoropropylene oxide) arms were found to form multicompartment micelles in dilute aqueous solution [31]. Depending on the relative lengths of the blocks, discrete multicompartment micelles or wormlike structures with segmented cores were observed.

The synthesis and polymerization of fluorinated 2-phenyl-2-oxazolines was studied in detail by Schubert et al. [32]. In later works, the synthesis of amphiphilic triblock poly(2-oxazoline)s with poly(2-(2,6-difluorophenyl)-2-oxazoline) fluorophilic block and the formation of multicompartment structures were demonstrated [33,34]. Jordan and co-workers reported the synthesis of amphiphilic block copolymers of 2-fluoroalkylethyl-2-oxazoline and 2-methyl-2-oxazoline [35]. It was shown by small-angle neutron scattering and TEM that these copolymers form elongated core–shell micelles in aqueous solution, which should be associated with the high stiffness and hydrophobicity of the perfluorinated chain. It was also shown that mixing this copolymer with a hydrophilic/lipophilic block copolymer leads to the coexistence of lyophilic and fluorophilic micelles rather than the formation of mixed micelles. Furthermore, Thünemann and colleagues reported the synthesis of poly(2-methyl-2-oxazoline) bearing a perfluoroalkyl chain at the α-terminus resulting from initiation and a regular alkyl chain at the ω-terminus resulting from end-capping [36]. It was demonstrated that these chain-end functionalized polymers self-assembled into cylindrical micelles, and it was speculated that the addition of a fluorinated dopant may lead to the formation of cylindrical micelles with a phase separated hydrophobic core.

In this study, we report the synthesis of poly(2-oxazoline) diblock copolymers with hydrophilic and hydrophobic blocks as well as terminal perfluoroalkyl chains of which the chain length is varied. We propose a simple method for the insertion of perfluorinated fragments into the polymer by termination with a perfluorinated carboxylic acid instead of making real triblock copolymers. The rather broad range of available perfluorocarboxylic acids allows us to easily vary the length of the fluorophilic fragment in contrast to polymerization of perfluorinated monomers. The effect of the fluoroalkyl chain length on the aqueous self-assembly behaviour of the copolymers was studied by a number of physico-chemical methods and will also be discussed.