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Ionic Liquids: Versatile Media for Preparation of Vesicles from Polymerization-Induced Self-Assembly

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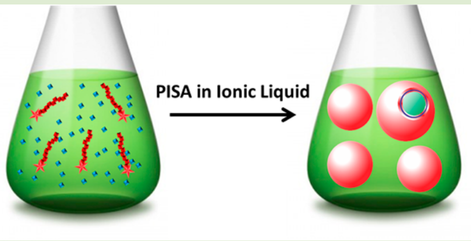
Supporting Information

ABSTRACT: This work reports the development of a new polymerization-induced self-assembly (PISA) system through reversible addition−fragmentation chain transfer (RAFT)-mediated dispersion polymerization in ionic liquids. Three representative monomers (styrene, *n*-butyl methacrylate, and 2-hydroxyethyl methacrylate) were polymerized through chain extension from a trithiocarbonate-terminated poly(ethylene glycol) (PEG) macro-RAFT agent, in a model ionic liquid [bmim][PF_6]. The block copolymers thus prepared could spontaneously form aggregates with vesicular morphologies. Moreover, by regulating the formulation, nanoaggregates with multiple morphologies were generated in ionic liquid via PISA.



Block copolymer vesicles, also known as "polymersomes", are nanoscale sacs with a closed polymeric thin membrane,[1] which have continued to attract increasing scientific interest due to their potential applications in various fields, such as nanoreactors,[2,3] drug delivery,[4−6] biological functional models,[7,8] and so on.[9] Fabrication of polymer vesicles is usually achieved by a widely accepted self-assembly strategy through selective solvation of the asymmetric block copolymer.[10] However, such self-assembly can normally only be prepared in a dilute solution (<1% solid content), while often requiring multiple steps of processing (starting from synthesis and purification of the block copolymer, followed by dissolving in a nonselective solvent and solvent displacement), which limits its commercialization and further applications.

The recent advent of polymerization-induced self-assembly (PISA) has offered an alternative solution for tackling these problems since the synthesis of block copolymers and their self-assembly could be simultaneously performed in a high concentration and the morphology of the formed aggregates could be precisely controlled.[11−13] With the development of controlled/living radical polymerization (CRP), PISA has been extensively studied by several leading groups, such as Pan,[11,14−20] Armes,[12,21−28] Charleux,[13,29−32] Lowe,[33−35] and so on.[36−42] Among the reported work, reversible addition−fragmentation chain transfer (RAFT) polymerization has become the most studied technique for conducting PISA, attracting particular attention due to its versatility of monomer types, as well as good tolerance toward polymerization conditions. Two major polymerization methods, emulsion polymerization and dispersion polymerization, have been applied to conduct PISA, depending on the solubility of core-forming monomer in selective solvent. For example, Charleux and co-workers have made a considerable contribution of PISA from utilizing RAFT emulsion polymerization.[29,30] Through chain extension of a water-immiscible monomer (such as styrene, methyl methacrylate, or *n*-butyl acrylate) from a water-soluble polymer precursor via RAFT polymerization, an amphiphilic diblock copolymer can be produced in situ.[29,30] This PISA approach led to the formation of different morphologies such as spheres, worms, or vesicles, according to the relative volume fractions of the hydrophilic and hydrophobic blocks based on the classic self-assembly theory.[43] On the other hand, dispersion polymerization is also powerful for in situ preparation of block copolymer self-assemblies. Pan et al. first reported PISA in an organic solvent using RAFT-mediated dispersion polymerization.[14] In the presence of different macro-RAFT agents, polymerization of styrene was performed in methanol. With growth of the PS block, a variety of morphologies such as nanorods, fibers, vesicles, or large-compound vesicles could be formed, and their formation mechanisms were also investigated.[15−20] More recently, Armes et al. have developed a promising PISA system based on aqueous RAFT dispersion polymerization of 2-hydroxypropyl methacrylate (HPMA).[21] Poly(glycerol monomethacrylate), or poly[2-(methacryloyloxy)ethyl phosphorylcholine], or poly(ethylene glycol) macro-RAFT agent was used to stabilize the spontaneously formed nanoaggregates, whose morphology could be precisely tuned by the polymerization degree of the hydrophobic poly(HPMA) block, as well as by the solid content.[21,22] Research on PISA via RAFT dispersion polymerization has indeed become an emerging area, with potential applications. However, the monomers reported so far are relatively few due to the limited solvent choice, usually alcoholic solvent,[14−20] water,[21−28] or alkanes.[35,44,45] Thus, more versatile reaction media amenable to conduct PISA are highly desirable.

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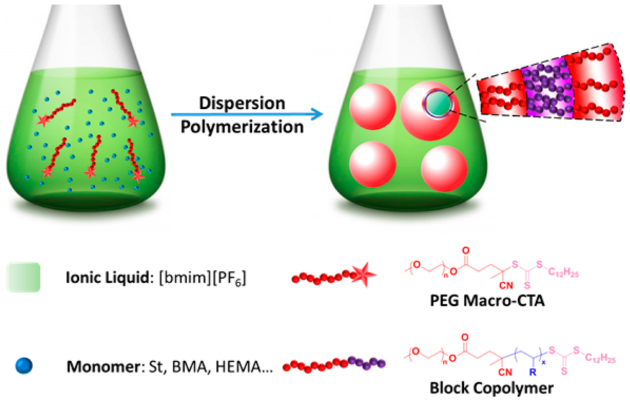
Ionic liquids are room-temperature molten salts and have attracted significant attention as "green" media because of their low vapor pressure, thermal stability, and nonflammability.[46] Due to these attractive properties, they have been used as environmentally friendly media for reaction and separation purposes as an alternative to volatile organic solvents.[47] Moreover, ionic liquids offer great flexibility in their structural and property designs, owing to their almost unlimited possible combinations of cations and anions. As in the field of dispersion polymerization, more monomer types can be performed in ionic liquids since they can provide unprecedented solvation tunability toward both monomers and polymers.[48] In practice, it would certainly broaden the selection of solvent and monomer types for PISA, thus expanding the range of ionic liquid applications.

Herein, we report the development of a new PISA system through RAFT-mediated dispersion polymerization in ionic liquids. An imidazolium ionic liquid, 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF_6]), was chosen as a model ionic liquid system to demonstrate the versatility toward different monomer types. Three representative monomers, styrene (St), *n*-butyl methacrylate (BMA), and 2-hydroxyethyl methacrylate (HEMA), were polymerized through chain extension from a trithiocarbonate-terminated poly(ethylene glycol) methyl ether macro-chain transfer agent (PEG macro-CTA). The block copolymers thus prepared spontaneously formed aggregates with vesicular morphologies, as shown in Scheme 1.

Scheme 1. Schematic Representation of RAFT Dispersion Polymerization for the Preparation of Vesicles from Polymerization-Induced Self-Assembly (PISA) in Ionic Liquid



We designed the polymerization system, where RAFT dispersion polymerization was carried out in an ionic liquid, using trithiocarbonate-terminated PEG as the macro-CTA and corona-forming block. [bmim][PF_6] was selected as a model ionic liquid since it is the most commonly used ionic liquid at room temperature (Tm: −8 °C) and is less moisture sensitive than many other imidazolium analogues.[49] PEG macro-CTA is essentially soluble in [bmim][PF_6], and it was expected to provide sufficient stabilization for the formed aggregates. Dispersion polymerization of St was first conducted since it is the most studied monomer for PISA in alcoholic solvents.[14−20] St is compatible with [bmim][PF_6], but its homopolymer is not, which made the PISA possible. With a designed feed molar ratio (100:1) of St:PEG macro-CTA (**O_{113}−St_{100}**, Table 1), obvious changes in the reaction system during the course of polymerization could be observed. The viscous homogeneous polymerization solution was transparent at the very beginning. Then it turned blue and opalescent within 1 h, and finally white latex-like dispersion with slightly bluish appearance could be obtained after 6 h (Figure 1a). Monomer conversion of the final product reached 94%, as determined from the ^{1}H NMR analysis of the reaction mixture. Methanol was then used to dilute the dispersion product. Methanol is miscible with the ionic liquid, and it is a good solvent for the PEG block but a nonsolvent for the PS block. The number-average particle diameter was around 68 nm, with its distribution shown in Figure 1d, as measured by dynamic light scattering (DLS). Transmission electron microscopy (TEM) was then used to visualize the morphology of the resulting aggregates. As shown in Figure 1e, a typical vesicle morphology could be observed. The statistic average particle diameter of these vesicles was approximately 62 nm, as measured from the TEM images. This was in good agreement with the DLS data. A careful examination of the inset high-magnification TEM image revealed that there was a clear contrast between the pale rim and the dark center, indicating ionic liquid was encapsulated by the vesicle membrane. By varying the target degrees of polymerization (DP) of either block (**O_{113}−St_{200}**, **O_{45}−St_{100}**), vesicles with different particle diameters were also prepared, and TEM images are shown in Figure S1 (Supporting Information). The preparation of polymeric vesicles in ionic liquid from RAFT dispersion polymerization of St via PISA has thus been demonstrated.

Table 1. Experimental Conditions and Results of RAFT Dispersion Polymerization[a]

target composition[b]	conv. (%)[c]	Mn (kD)[c]	D_N/nm (PDI)[d]	morphology
O_{113}−St_{100}	94	15.2	68 (0.03)	vesicles
O_{113}−St_{200}	87	23.5	119 (0.11)	vesicles
O_{45}−St_{100}	90	11.8	212 (0.15)	vesicles
O_{45}−St_{200}	79	18.8	339 (0.27)	multiple
O_{113}−BMA_{100}	93	18.6	118 (0.04)	vesicles
O_{113}−$HEMA_{100}$	95	17.8	162 (0.08)	vesicles

[a] All runs contained 0.01 mmol of PEG macro-CTA, 0.8 mg of AIBN, and 1.5 g of ionic liquid [bmim][PF_6] and were carried out at 80 °C for 6 h. [b] Subscripted numbers refer to target DP of each block. [c] Monomer conversion and theoretical Mn were determined from ^{1}H NMR. [d] Number-average particle diameter and PDI were determined by DLS.

We also conducted dispersion polymerization of BMA. As a typical methacrylic ester polymer with low glass transition temperature, poly(BMA) is incompatible with the ionic liquid. Although solubility of BMA in [bmim][PF_6] was quite low, homogeneous solution could be formed with the help of PEG macro-CTA. During the polymerization, the bluish appearance of the reaction mixture became more obvious, indicating formation of aggregates during the reaction. However, unlike PISA of St, no white latex-like dispersion was observed even at high conversions (93% after 6 h), probably due to the close refractive index between the block copolymer (1.45 and 1.48 for PEG and poly(BMA) block, respectively) and ionic liquid (1.41). After dilution of methanol, the particle size and distribution were measured by DLS, and the result was shown in Figure 1d. It could be found that the particles were mostly located between 100 and 150 nm, with a peak at 118 nm. TEM results showed that the aggregates prepared via PISA

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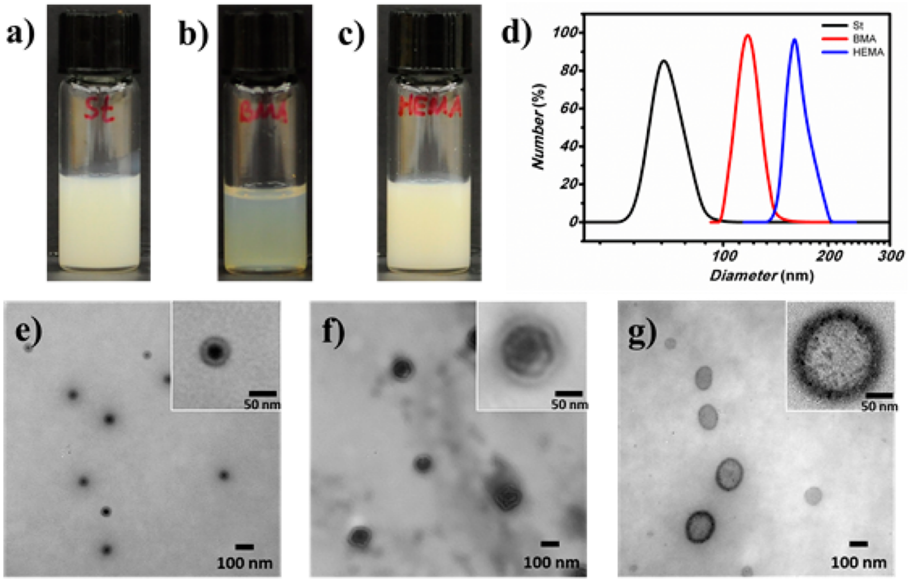

Figure 1. Digital photos of the final product from RAFT dispersion polymerization of (a) St, (b) BMA, and (c) HEMA; (d) DLS data for the prepared dispersions; TEM images (scale bar: 100 nm, inset: 50 nm) of the prepared dispersions from RAFT dispersion polymerization of (e) St, (f) BMA, and (g) HEMA.

had a nice vesicle morphology with a similar average particle diameter around 127 nm. It should be noted that the substantial electron density difference between PBMA and [bmim][PF_6] ensured good contrast for TEM studies.

Finally, HEMA was chosen as a representative hydrophilic monomer, to perform PISA from RAFT dispersion polymerization. The observation during reaction, as well as the final product, was quite similar to that of St. It also reached high conversion (95%) after polymerization for 6 h, as estimated from the ^{1}H NMR result. The block copolymer thus obtained had a molecular weight of 17.8 kDa. Particle size was then examined by DLS, after dilution with acetonitrile. Acetonitrile is miscible with the ionic liquid, and it is also a selective solvent for PEG and poly(HEMA) blocks. The result showed a unimodal distribution with a number-average diameter around 162 nm. TEM visualization further confirmed this result, and clear vesicle morphologies could also be observed.

The above results demonstrated that ionic liquid could be a versatile reaction media for vesicle preparation via PISA. Furthermore, we would like to elucidate if other different morphologies could also be prepared through this PISA process in ionic liquids. It is been reported that morphologies of the resultant aggregates could be tuned by the reaction conditions and the feed molar ratios in the RAFT dispersion polymerization.[16,19] In order to get multiple morphologies, we tried to increase the packing parameter (which is determined by the relative volume fractions of core-forming block) based on the theory of self-assembly.[43] Herein, PEG with lower molecular weight (**O**$_{45}$) was selected as the macro-CTA stabilizer, and the feed molar ratio of monomer to CTA was increased to 200:1. St was used as the model monomer to perform the RAFT dispersion polymerization. After reaction for 24 h, TEM images were taken for analysis of the resulted aggregates. As shown in Figure 2, the multiple morphologies, which include spherical particles (1), normal vesicles (2), rod-like aggregates (3), stretched vesicles (4), large compound vesicles (5), and other complex multiple morphologies, were all evident. The formed nanostructures proved the generality of this PISA approach for the preparation of vesicular nanomaterials in ionic liquids.

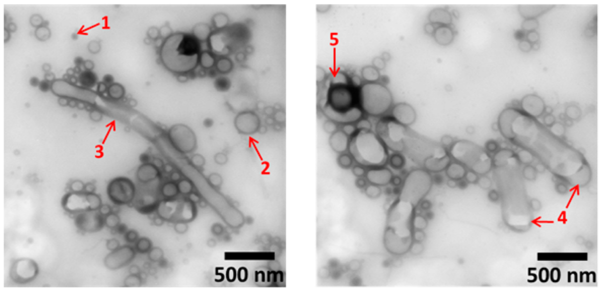

Figure 2. TEM images (scale bar: 500 nm) of the multiple morphologies prepared by RAFT dispersion polymerization of styrene in ionic liquid [bmim][PF_6] with the feed molar ratio of St/O_{45}/AIBN = 400:2:1.

To conclude, we have successfully developed a new polymerization-induced self-assembly (PISA) system through RAFT-mediated dispersion polymerization in ionic liquids. Three representative monomers, St, BMA, and HEMA, were polymerized through chain extension from a trithiocarbonate-terminated PEG macro-CTA, in a model ionic liquid [bmim][PF_6]. The block copolymers thus prepared spontaneously formed aggregates with vesicular morphologies. Moreover, by regulating the formulation, the nanoaggregates with multiple morphologies were generated in ionic liquid via PISA.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Materials, polymerization procedures, characterization methods, and TEM images. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmacrolett.5b00360.

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Notes

The authors declare no competing financial interest.

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