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Ultra-Fast Synthesis of Multivalent Radical Nanoparticles by Ring-Opening Metathesis Polymerization-Induced Self-Assembly

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Supporting Information Placeholder

ABSTRACT: We report a straightforward, efficient, synthesis of radical core-shell nanoparticles (NPs) by polymerization-induced self-assembly. A nitroxide-containing hydrophilic macromolecular precursor was prepared by ring-opening metathesis polymerization of norbornenyl derivatives of TEMPO and oligoethylene glycol and was chain-extended *in situ* with norbornene in ethanolic solution, leading to simultaneous amphiphilic block copolymer formation and self-assembly. Without any intermediate purification from the monomers to the block copolymers, radical NPs are obtained within minutes at room temperature. The high activity of the radical NPs as chemoselective and homogeneous, yet readily recyclable catalysts is successfully demonstrated through oxidation of a variety of alcohols and recovery by simple centrifugation. Furthermore, the NPs show biocompatibility and antioxidant activity *in vitro*.

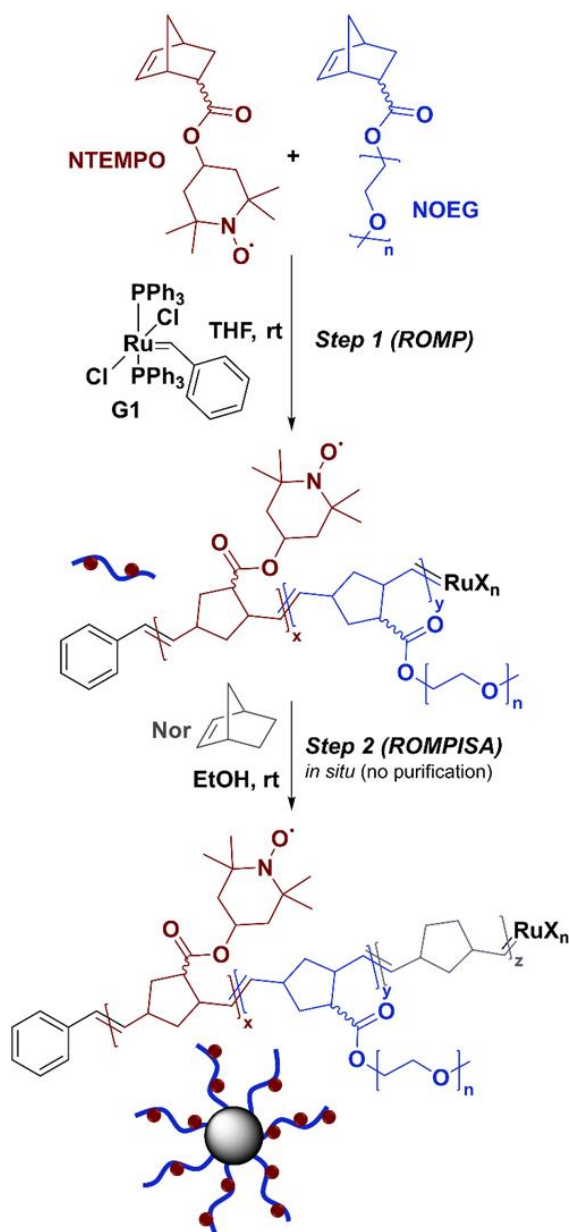
Stable radical compounds with unpaired electrons, such as nitroxides, have long been used in fields as diverse as organic synthesis,^{1–3} controlled radical polymerization,^{4,5} magnetic materials,^{6–8} organic batteries,^{9–13} and biomedicine.^{14–21} The incorporation of nitroxides into polymeric materials enhances their applicability by combination of the chemical and physical versatility of polymers and the unique properties of radical compounds.^{9,10,16,17,22,23} Rational design and control over the activity and the stability of organic radical materials is also an important aspect with regards to the target application. Incorporation of radicals into nanoparticles typically relies on post-synthetic modification, protection/deprotection approaches, and more generally on multistep procedures.²⁵ In this contribution, we demonstrate the synthesis of TEMPO-functionalized nanoparticles (NPs) in one-pot, directly from an unprotected TEMPO monomer by use of the so-called polymerization-induced self-assembly (PISA) method in within a few minutes, and their application as catalyst and antioxidant.

In the last decade, PISA has enabled the straightforward synthesis of block copolymer (BCP) nanoparticles with elaborate and precise macromolecular architecture, colloidal morphology, and functionality.^{24–28} PISA relies on chain extension of a solvophilic “living” macromolecular precursor with a monomer leading to a

second polymer block that is insoluble in the medium, in an emulsion or dispersion polymerization process. An amphiphilic BCP is thus formed *in situ* and undergoes self-assembly. PISA typically uses reversible-deactivation radical polymerization (RDRP) as chain-growth mechanism. RDRP is the most versatile method for PISA because it allows for a wide range of functional monomers and solvents to be used.^{29–32} However, it is often performed at elevated temperatures and, in some cases, leads to (sometimes beneficial) morphological rearrangements when cooled. Ring-opening metathesis polymerization (ROMP), which is feasible in dispersed media at moderate temperature,^{33–35} is an attractive alternative route for conducting PISA.^{36–41} Most importantly, ROMP catalysts exhibit high reactivity yet excellent functional group tolerance,⁴² especially with functionalities which are not well or at all tolerated by RDRP such as alkyne,⁴³ high sulfur content species,³⁶ thiol,⁴⁴ and stable radical.^{17,22,45} It therefore appeared to us that combining the different attributes of ROMP and PISA, i.e., ROMPISA, would be a direct and simple way to access not only radical core-shell nanoparticles but also functional nanoparticles in an ultra-fast one-pot procedure.

To this end, we first performed the ROMP of oligoethylene glycol-based norbornene monomer³⁴ (NOEG) with TEMPO-functionalized norbornene monomer (NTEMPO) to generate a living nitroxide-functionalized solvophilic precursor (Scheme 1). NOEG was selected for (i) its high solubility in a wide range of solvent and (ii) its biocompatibility, potentially enabling application of our radical NPs in the biomedical field. NOEG and NTEMPO monomers were synthesized by esterification of norbornene-monocarboxylic acid with monomethyl ether oligo(ethylene glycol) and 4-hydroxy-TEMPO, respectively (See Supporting Information). A tandem ROMP–ROMPISA methodology was employed, where no intermediate purification is applied between the synthesis of the first solvophilic block (Step 1) and the chain extension (Step 2), the latter leading simultaneously to the formation of nanoparticles (Scheme 1). In analogy to some RDRP-based PISA reports,^{46–48} the present system could therefore be referred to as “ROMPISA with *in situ* macrostabilizer synthesis”. In the initial stage of our study, several hydrophobic core-forming monomers were studied in various PISA conditions (see Supporting Information). Norbornene (Nor) led to the most promising results and was therefore employed for

the PISA study reported in the following. First, copolymerization of **NOEG** and **NTEMPO** monomers was performed in THF with first-generation Grubbs catalyst (**G1**), which exhibits high reactivity towards norbornene-based monomers and high functional-group tolerance.⁴⁵ After full conversion of the monomers, a deoxygenated solution of **Nor** in ethanol was injected to give a final overall concentration of 10–15 wt%. In PISA, the solubility of the first block is a vital parameter. Here, owing to the high hydrophilic character of **NOEG**, the content in **NTEMPO** can be set as high as 74 mol% in the first block while maintaining sufficient solubility. For the PISA process to occur, a good balance between the solubility of P(**NTEMPO-co-NOEG**) and the insolubility of the second polynorbornene (**PNor**) segment could be found for a mixture of a 1:4 v/v THF/ethanol mixture. Therefore, upon addition of a solution of **Nor** in ethanol after full consumption of **NTEMPO** and **NOEG** (Step 1), micellization occurred simultaneously to the growth of the **PNor** block (Step 2), conferring steric stabilization of the final core-shell NPs. Details



Scheme 1. Tandem ROMP-ROMPISA concept developed here for the synthesis of nitroxide-functionalized polymer nano-particles.

of ROMPISA experiments are listed in Table 1.

Both polymerization steps were found to proceed extremely fast. For instance, for Entry 4, ¹H NMR spectroscopy (Figure 1A) evidences the complete disappearance of monomer-related peaks after 5 min and 2 min for Steps 1 and 2, respectively. Furthermore, size-exclusion chromatography (SEC) reveals the formation of a polymer with $M_n = 13300 \text{ g mol}^{-1}$. Similarly, SEC analysis of the PISA product (Figure 1B, full line) shifted to higher molar masses with no residual trace of P(**NTEMPO-co-NOEG**), indicating that all radical precursors were chain-extended to form a pure P(**NTEMPO-co-NOEG**)-*b*-**PNor**. Electron paramagnetic resonance (EPR) of 4-hydroxy-TEMPO as reference, **NTEMPO**, P(**NTEMPO-co-NOEG**) (Table 1, Entry 1), and P(**NTEMPO-co-NOEG**)-*b*-**PNor** NPs (Table 1, Entry 4) displayed characteristic TEMPO like nitroxide 1:1:1 triplet signals indicating a good separation between radicals in these materials (S12).⁴⁹ As already reported, the spectra of polymer and NPs showed broader peaks than those of monomer and reference 4-hydroxy-TEMPO due to the intramolecular spin-spin exchange and dipole-dipole interaction. Interestingly, increasing temperature from 20 °C to 60 °C led to broader peaks of radicals in polymer and NPs. This phenomenon was reversible in that the peaks turned narrow upon decreasing temperature. The reason was related to the energy level-dependent contribution of the electron spins on the Zeeman splitting in Boltzmann distribution rule. Lowering temperature increased difference between high and

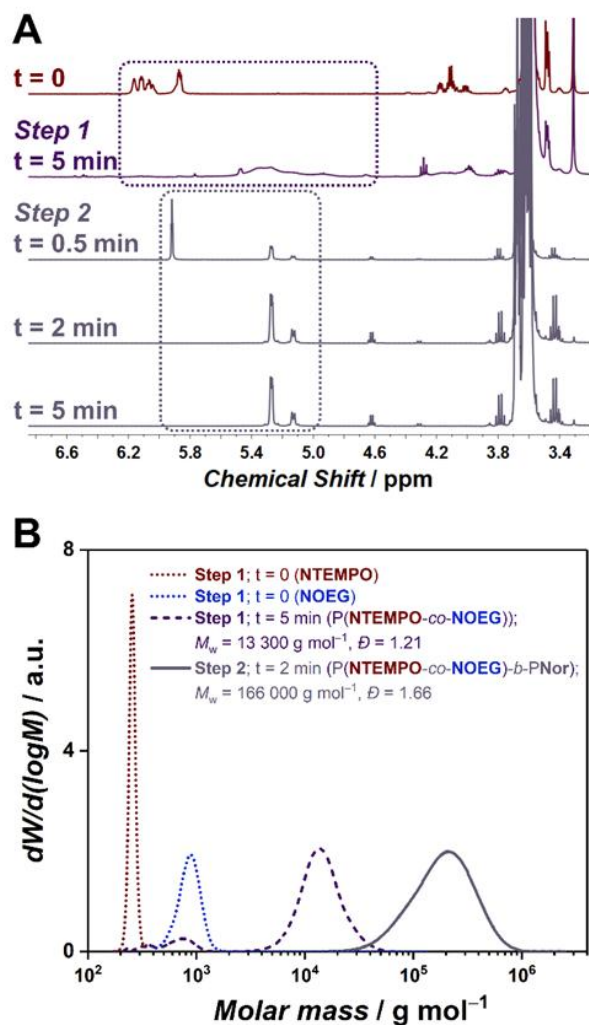







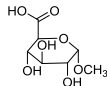
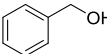

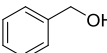



Figure 1. ¹H NMR (A) and SEC (B) monitoring of the entire ROMP-ROMPISA sequence (Table 1, Entry 4).

Table 2. Summary of oxidation reaction of alcohols in the presence of non-functional or TEMPO-functionalized NPs (from Table 1, Entries 2 and 4, respectively).

Entry	Substrate	NP ^δ	Product	Conversion %
a ^α		2		0
b ^α		4		>98
c ^α		4		93
d ^α		4		>98
e ^β		2		0
f ^β		4		> 98

^αCondition: 10 % mol NPs, oxidizing agent/co-catalyst: NaOCl/KBr/NaHCO₃ in water, 0 °C, 1 h, pH 8.6. ^β10 % mol NPs, oxidizing agent/co-catalyst: air/CuBr/Bipyridine/ imidazole in Acetonitrile/Water 1/1 v/v, 40 °C, 48 h. ^δEntry numbers from Table 1.

glucopyranoside) were employed as model alcohols and two distinct TEMPO-catalyzed oxidation protocols were assessed: (i) Anelli's oxidation in water, which involves NaOCl and allows conversion to corresponding aldehydes, carboxylic acids, and ketones⁵³ and (ii) aerobic chemoselective oxidation to aldehydes⁵⁴ with Cu(I) in mixtures of

water and organic solvent. Reaction conditions and results are listed in Table 2. Conversions were determined by ¹H NMR spectroscopy. Importantly, when NPs obtained by ROMP-ROMPISA in the absence of NTEMPO (Table 1, Entry 2) were employed, reactions failed to proceed in both catalytic systems (Table 2, Entries a and e). In contrast, TEMPO-functionalized NPs (from Table 1, Entry 4) drove oxidations to nearly quantitative yields. The kinetics (Figure S13) showed a comparable oxidation rate to that of reaction using water soluble TEMPO-precursor analog (Table 1, Entry 1) and Anelli's oxidation and was much faster than those of other TEMPO-based material catalysts.^{55,56} Moreover, our radical NPs showed a similar chemoselectivity and efficiency as molecular TEMPO for the oxidation of sugars in water.⁵⁷ Here, the primary alcohol of methyl α-D-glucopyranoside was selectively and quantitatively oxidized to carboxylic acid (Table 2, entry d), thanks to a larger solubilization provided by the NP support in comparison to molecular TEMPO, which is poorly soluble in aqueous medium. In the case of Cu(I)/TEMPO system, in which Cu and a radical operate jointly as one-electron oxidants to mediate the two-electron alcohol oxidation reaction,^{3,56} homogeneous dissolution of the catalysts is important to reach completion. Quantitative yields obtained with the radical NPs (Table 2, entry f) therefore indirectly indicate the homogeneous nature of the catalysis mode under which the NPs operate.

Table 1. Summary of conditions and results for the TEMF synthesis of radical nanoparticles.

Entry	NTEMPO/NOEG/ Nor/1	Total solids content ^a %	Conversion %
1	6/9/0/1	-	100
2	0/12/400/1	10	100
3	14/5/10/1	10	100
4	14/5/400/1	10	100
5	14/5/700/1	10	100
6	14/5/700/1	15	100
7	6/9/700/1	15	100
8	14/5/1000/1	15	Partial precipitation

^aTotal solids content of PISA experiments.

low energy level leading well-pronounced EPR signal.⁵⁰

After the synthesis, NPs could be rapidly transferred to water by simple water addition and solvent evaporation. Detailed information on the NPs was subsequently obtained by dynamic light scattering (DLS) and transmission electron microscopy (TEM). DLS studies indicated a narrow, monomodal particle distribution with an average hydrodynamic diameter of 73 nm (Entry 4, Figure S10). On the other hand, the TEM image revealed a spherical morphology with a diameter of about 50 nm (Figure S11). The discrepancy between DLS and TEM is commonly observed for core-shell polymeric NPs and arises from the difference between NPs in solvated and dry states, respectively. One other reason is that DLS addresses an intensity-average diameter, whereas TEM reports a number-average diameter. Therefore, DLS always oversized relative to TEM. Notwithstanding, both DLS and TEM results highlight the uniform structure of the final NPs in aqueous medium.

To investigate the influence of the degree of polymerization of the PNor block on the size and the morphology of the NPs, further PISA experiments were carried out with different [Nor]/[G1] ratios (Table 1, Entries 3-5). As expected, increasing [Nor]/[G1] from 10 to 700 enlarged the NPs size from 12.2 nm to 110 nm, as determined by DLS in water. Increasing the total solids to 15 wt% induced partial formation of two-sphere fusion (Entry 6, Figure S11-6), as observed in RDRP-based PISA.⁵¹ However, within the present study, it was not possible to access long worm or vesicle morphologies with higher [Nor]/[G1] ratios, as precipitation occurred (Entry 8). The reason could be that the solvophilic precursor is sufficiently long to ensure effective steric stabilization and prevent the fusion of spheres and nanorods to form higher-order morphologies.⁵²

To explore the catalytic potential of the new TEMPO-functionalized NPs, we investigated their activity as homogeneous, yet recyclable catalysts for the oxidation of alcohols. Interestingly, the NPs can be dispersed in other solvents such as pure ethanol, Acetonitrile/water (1/1 v/v), or in pure water with concentrations up to 20 wt% enabling the nanoparticles to be employed in different reaction conditions. 1-Propanol, 2-propanol, benzyl alcohol, as well as a carbohydrate (methyl α-D-

The use of our radical NPs as homogeneous catalysts not only guarantees satisfying oxidation rates but also ensures quantitative catalyst recovery and recycling by simple centrifugation, another decisive advantage in comparison to molecular TEMPO. After separation and redispersion, the radical NPs were reused in sequential oxidations of 2-propanol and 1-propanol (Figure 2A). After 6 oxidation cycles, no detectable loss of activity occurred and the NPs maintained their initial colloidal features and chemistry as determined by DLS, TEM, and ^1H NMR (Figures 2B, 2C, and S20, respectively).

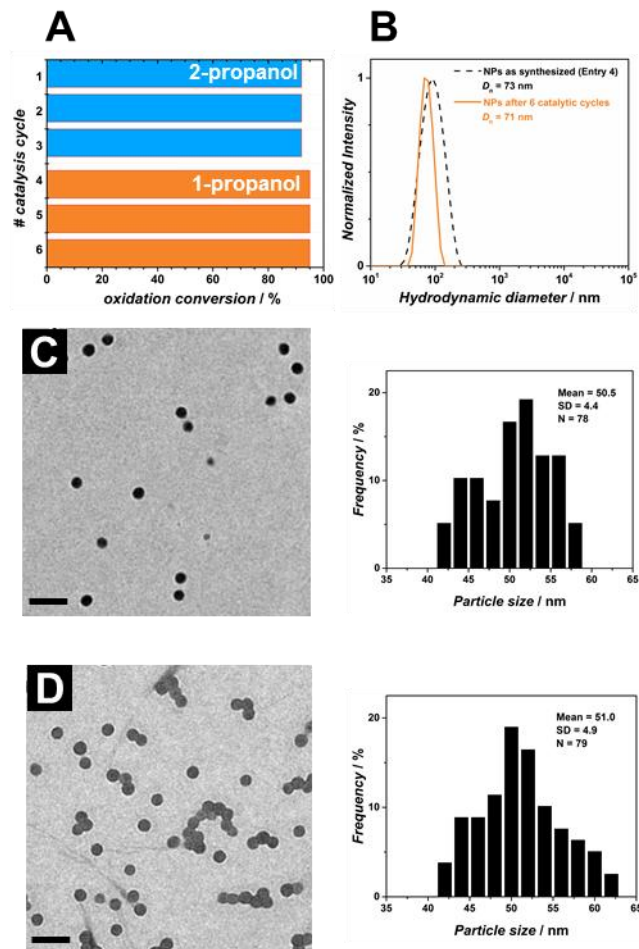


Figure 2. (A) Activity of the radical nanoparticles (Table 1, Entry 4) for the oxidation of 1-/2-propanol upon precipitation-redispersion recycling. (B, C, and D) Comparison of the nanoparticles dimensions and morphologies before and after 6 catalytic cycles (B: DLS; C and D: TEM before and after with histograms, respectively). Scale bars represent 100 nm.

Nitroxide species are employed in the biomedical field as antioxidants or electron paramagnetic resonance/magnetic resonance imaging agents, for instance. Notably, anchoring them to carriers such as polymers or colloidal materials can broaden the range of conditions in which they are applicable. With this in mind, we studied the cytotoxicity of a set of ROMPISA-made NPs with two *in vitro* assays. NPs containing 0, 40, and 74 mol% TEMPO in the shell (Entries 2, 7, and 4) were incubated with murine RAW264.7 macrophages and analyzed for lactate dehydrogenase (LDH) release and water-soluble tetrazolium salt (WST-1) reduction.^{58,59} Increased release of LDH, an enzyme present in the cytoplasm, indicates damage of the plasma membrane of the cells. ROMPISA NPs do not enhance the release

of LDH (Figure 3A, red bars), particularly in contrast to positive control samples such as amino-functionalized polystyrene NPs⁶⁰ even up to a concentration of 100 $\mu\text{g mL}^{-1}$, which is well above clinically relevant doses.⁶¹ Similarly, the WST-1 assay (Figure 3A, green bars) indicates high biocompatibility with no decrease in cellular metabolism, thereby confirming the extremely low toxicity of our ROMPISA nanoparticles. This enabled us to assess their potential as antioxidants. It has been reported that the overproduction of reactive oxygen species (ROS) causes oxidative stress leading to the damage of biomolecules including proteins, lipids, and DNA.^{58,62} The ability of our NPs to quench oxidative species generated by a H_2O_2 / horseradish peroxidase system was evaluated by monitoring the fluorescent oxidation product of 2',7'-dichlorodihydrofluorescein (DCFH₂).⁶³ In this so-called DCFH assay, a decrease of fluorescence indicates reduction of ROS, i.e., antioxidant activity. The NPs devoid of TEMPO

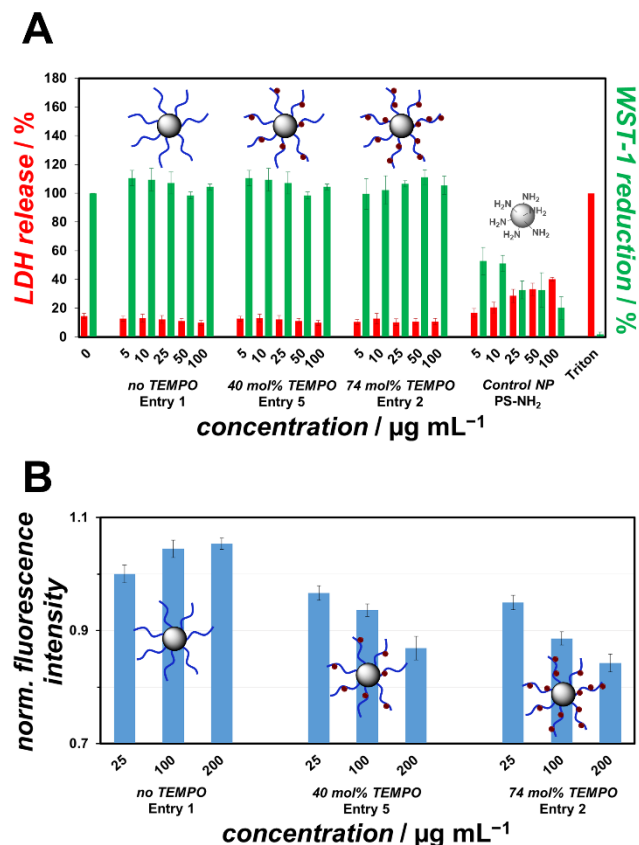


Figure 3. Results of the cytotoxicity study with (A) LDH assay and (B) WST-1 assay, as well as assessment of antioxidant properties with DCFH assay (C) for various ROMPISA-made NPs at different concentrations. Entry numbers correspond to

showed a dose-dependent increase of fluorescence, indicating enhanced catalytic activity, possibly by interaction of the enzyme and/or the substrate DCFH₂ with the particle surface (Figure 3B). In contrast, nitroxide-containing NPs quenched the action of oxidative species in a concentration-dependent manner in terms of both, particle concentration and nitroxide loading.

We presented here a robust and simple method for the synthesis of high-nitroxide-content NPs in a diameter range relevant for antioxidant delivery and offering at the same time a high surface specific area useful for homogeneous supported catalysis (50–110 nm). The nanoparticles were found to be very efficient chemoselective homogeneous catalysts for the oxidation of alcohols with excellent recycling capacity. In addition, they exhibited antioxidant activity with no *in vitro* toxicity. The latter two aspects suggest the potential of our method to produce antioxidant and possibly MRI imaging agents in a straightforward manner. The current synthetic strategy relies on a one-pot tandem ROMP–ROMPISA process, which had so far been reported only in a handful of reports, yet not with such favorable features.^{64–67} Notably, the extremely fast kinetics are unprecedented, allowing production of a pure functional dispersion, without purification at any stage and within a few minutes from the monomers to the core-shell nanoparticles. Additional advantages of our system are the use of a “greener” solvent mixture and of a commercially available core-forming monomer, in PISA-relevant conditions (i.e., > 10 wt%). Considering the industrial relevance of ROMP and PISA, respectively, ROMPISA is an attractive platform for the production of functional nanomaterials. The next step would be to produce nanoobjects of various morphologies in benign conditions, starting from readily available monomers.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Materials, characterization methods, experimental procedures, ROMPISA preliminary studies, additional data (PDF)

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Notes

The authors declare no competing financial interests.

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