

Article

Tailoring Confinement: Nano-Carrier Synthesis via Z-RAFT Star Polymerization

Nadja Förster, Sonja Schmidt and Philipp Vana *

Institute of Physical Chemistry, Georg-August-University Göttingen, Tammannstr. 6, D-37077 Göttingen, Germany; E-Mails: nadja.foerster@gmail.com (N.F.); sonja.schmidt1@stud.uni-goettingen.de (S.S.)

* Author to whom correspondence should be addressed; E-Mail: pvana@uni-goettingen.de; Tel.: +49-551-3912-753; Fax: +49-551-3912-709.

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Abstract: A new pathway to nano-sized hollow-sphere particles from six-arm star polymers with an amphiphilic core-corona structure, synthesized in a four-step-procedure by means of reversible addition-fragmentation chain transfer (RAFT) polymerization is presented, in order to achieve more stable and versatile nano-container systems, which could be applied in the fields of drug delivery or catalyst storage. Star-shaped amphiphilic, diblock copolymers serve as globular platforms for synthesizing uniform hollow structures. By the introduction of monomer units carrying UV-cross-linkable dimethyl maleimido functionalities into the outer sphere of these star polymers, the carrier’s shell could be stabilized under UV-irradiation. After removal of the RAFT-core—constituting the central hub of the star polymer—by aminolysis, the carrier is ready for loading.

Keywords: star polymers; reversible-addition fragmentation chain transfer (RAFT); cross-linking; amphiphilic block copolymers

1. Introduction

We describe here a new pathway to establish nano-sized, amphiphilic carrier systems from star-shaped polymers synthesized by means of reversible addition-fragmentation chain transfer (RAFT) polymerization [1–5]. Methods to synthesize nano-scaled container systems using emulsion

polymerization [6], polymer coating of inorganic or organic templates [7,8], or via self-assembling polymer forming micelles [9,10], are already known. Xu and Liu, for instance, summarized many of the results of research in the field of polymeric micelles from self-assembling amphiphilic copolymers with application in drug delivery in an excellent highlight paper [11]. Many examples given there are based on the storage of hydrophobic drugs in the hydrophobic core of such a micelle. The drug release is triggered by external or internal stimuli affecting the hydrophilic corona. *N*-isopropylacrylamide (NIPAAm)-based copolymers are the mostly used hydrophilic parts. For the hydrophobic core, styrene, *n*-butyl methacrylate, D,L-lactide, and ϵ -caprolactone polymers are frequently applied.

Stability in such self-aggregating systems can be achieved by cross-linking of the outer sphere of the micelles, forming so-called shell cross-linked micelles (SCM). These SCMs are micelles consisting of amphiphilic block copolymers, which have integrated cross-linkable units. After the micelle formation, the cross-linking is triggered by heat, light or changes in pH-value. Large contributions to the topic of SCMs as nano-carriers for drug delivery were achieved by Wooley *et al.* using a multitude of monomers [12,13]. Employing RAFT polymerization, for instance, Chang *et al.* developed thermo-responsive SCMs. They synthesized amphiphilic, linear diblock copolymers from methyl methacrylate (MMA) and NIPAAm with *N*-acryloyxsuccinimide as cross-linkable comonomer [14]. In aqueous solution, these polymer chains form micelles and drug loading takes place. Afterwards the chemical cross-linking via esterification with ethylenediamine was performed. Taking advantage of the thermo-response of PNIPAAm, the drug can actively be set free. Xu *et al.*—as another example—synthesized thermo-responsive ABC-triblock copolymers from α -methoxy(ethyleneoxide), *N*-(3-aminopropyl) methylacrylamide (APMA) and NIPAAm also using RAFT polymerization in aqueous solution [15]. The PAPMA-block was reversibly cross-linked with terephthalidicarboxaldehyde, gaining a “core-shell-corona” system. By decreasing temperature and pH-value, the micelle could be de-cross-linked.

A main drawback of generating nano-carriers via the self-assembly of linear amphiphilic copolymers is the fragile nature of micelle systems. In addition, the size and form of these assemblies not only depend on the macromolecular structure of the block copolymers, but also on the surrounding conditions such as temperature, pH-value or introduced charges. Small disturbances lead to large changes of micelle structures or even the dissociation of the micelles into unimers [15–17]. The combination of a micelle-based system with chemical cross-linking may thus be risky when aiming at an up-scaled process that is obligatory for technical processes, as process parameters are not easily controlled under such conditions.

The use of star-shaped block copolymers from RAFT polymerization as platform for nano-carriers may possibly avoid these problems: Firstly, the copolymer arms are covalently attached to a common core, which greatly enhances stability. Even by changing the surrounding conditions, the covalent bonding remains and keeps up the desired structure. Secondly, many different monomers can be used under very different polymerization conditions, as RAFT is an extremely versatile process. That opens up the possibility of easily tuning the carrier’s characteristics for different applications and of up-scaling the process to technical dimensions. Thirdly, star polymers from controlled radical polymerization are nano-scaled, uniform in shape, and narrowly dispersed with respect to molar mass and they have a spherical shape independent of their concentration [18].

At the beginning of the new century interest in star polymer synthesis via RAFT polymerization grew rapidly. In 2001 one of the first papers regarding this topic was published by Stenzel *et al.* Here the star polymers were generated via the R-group approach (Figure 1, top). In this approach the

core of the multi-functional RAFT-agent is the leaving R-group and therefore the growing radicals are located on the star polymer molecule. This can result in dead arms after disproportionation and star-star-coupling after combination, which is a major disadvantage of this approach [19]. One year later, the same group reported a star polymerization via the so-called Z-group approach (Figure 1, bottom) [20], where the core of the multi-functional RAFT-agent is the stabilizing Z-group. The radical functionality is thereby never located on the star and star-star coupling during the polymerization is therefore avoided. All arms remain in a living state during the process of polymerization, which was proven by our group via NMR studies [21].

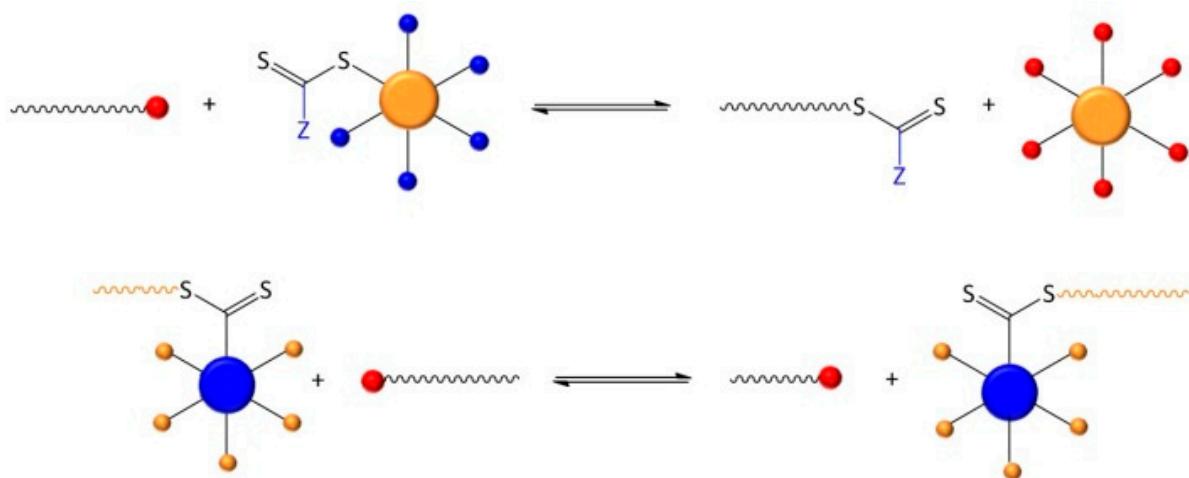


Figure 1. The R-group approach (**top**) and the Z-group approach (**bottom**) of star polymer synthesis via reversible addition-fragmentation chain transfer (RAFT) (red: radical functionalities; orange: R-group; blue: Z-group).

RAFT-agents from pentaerythritol derivatives, as introduced by Mayadunne *et al.* [22], were found to be very well suited for star polymer synthesis and we carried out many projects to find a better understanding of polymerizations with multifunctional RAFT agents using the Z-group approach with the final goal of generating nano-carriers [21,23–27]. The synthesis pathway chosen for these nano-carriers is presented and explored in this present work and is illustrated in Figure 2. Six-functional RAFT-agents were used to synthesize star-shaped polymers with six amphiphilic diblock copolymer arms. The chosen Z-group approach avoids star-star coupling and provides uniform star polymer. In the first polymerization step, a statistical copolymerization of a monomer **A** and a second monomer carrying a UV-cross-linkable group is performed (red block in Figure 2). This first polymer block can principally either be hydrophobic or hydrophilic, but one should make sure that integration of the UV-sensitive monomer does not alter the desired polymer's properties.

Onto the first block of polymer (red), a second block of monomer **B** of opposite polarity (blue) is block copolymerized in order to achieve an amphiphilic character of the star polymer template. The second block does not contain any cross-linkable comonomer. As a consequence of the applied Z-group approach the newly formed block is the inner part of the nano-carrier, *i.e.*, constituting the storage area. Under UV-irradiation of appropriate wavelength, the cross-linking reaction of the outer region is carried out. Finally, the RAFT-core is decomposed via aminolysis [28] to achieve hollow spherical particles. The success of the procedure is monitored by size exclusion chromatography

(SEC)-measurements of the material after the different steps of synthesis as well as by dynamic light scattering (DLS).

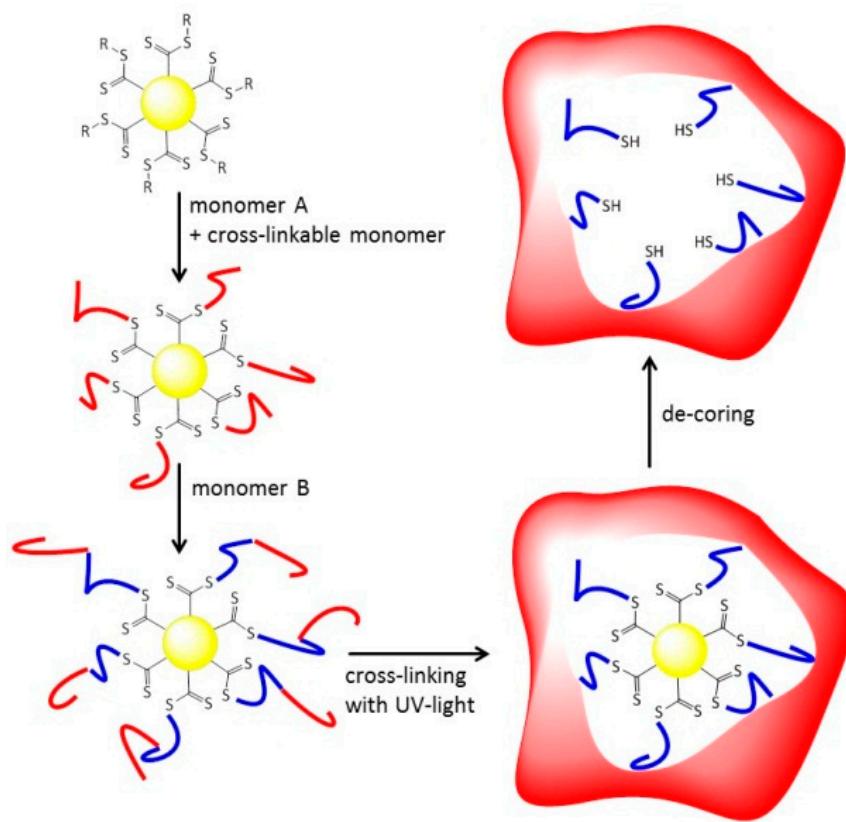


Figure 2. Multi-step process for synthesizing nano-containers via Z-RAFT star polymerization, as presented in this work.

Shell formation can be carried out using chemical linkers, as e.g., in click-reactions or esterification reactions. But the addition of chemicals to the polymer solution can lead to undesired modification or destruction of the polymer. The UV-induced [2+2]-cycloaddition, as applied in this work, provides a destruction-poor pathway for cross-linking, since wavelength and applied energy entry can easily be controlled. There are many UV-cross-linkable groups for monomers, as *N*-alkyl-3,4-dimethylmaleimide (DMI) [29], anthracene [30,31], stilbene [32], cinnamic acid [33,34], uracil derivatives [35], coumarin [36,37] or for polymers alkene groups [38]. All of them cross-link via [2+2]-cycloaddition. The structure of the monomer unit, to which these units are linked, is generally chosen to be identical to that of the main monomer in order to avoid large differences in the polymerization behavior. DMI-based monomers—as also thoroughly investigated by Kuckling *et al.* [29,39–41]—were employed in the present study: For the shell formation of the star polymers *N*-ethylacrylate-3,4-dimethylmaleimide (**1.1**) (see Figure 3) was used in this project as the cross-linkable comonomer. In a recent publication, which presented preliminary research to this present paper, we carefully investigated the Z-RAFT-star copolymerization of *n*-butyl acrylate (BA) and *N*-isopropyl acrylamide (NIPAm), respectively, with **1.1** [42]. It was found that addition of **1.1** slows down the polymerization rate both for BA and for NIPAm polymerization. Double star formation due to radical attack on the 3,4-dimethylmaleimide moiety was found in the case of BA and dead polymer formation, presumably due to aminolysis as

side-reaction, was pronounced in the NIPAm system. These two effects broadened the molar mass distributions, but did not impede the formation of functional star polymers. The composition of the copolymers as well as the reactivity ratios for the applied comonomers were determined for poly(BA-*co*-**1.1**) being $r_{1.1} = 2.24$ and $r_{BA} = 0.95$, and for poly(NIPAm-*co*-**1.1**) being $r_{1.1} = 0.96$ and $r_{NIPAm} = 0.05$. In both cases, the comonomer is consumed preferably at the beginning of the polymerization, thus forming slight gradient copolymer stars with the UV-reactive units being located more probably in the outer sphere, which clearly is beneficial for the chosen nano-carrier synthesis approach.

Polybutylacrylate (PBA) was also chosen for the present study as the hydrophobic part of the star polymer template, as it is known to easily encapsulate hydrophilic drugs [43–46]. BA polymerizes over short periods of time, due to its high k_p -value [47], and was extensively investigated in Z-RAFT star polymerization in our group [21,23,24,48–50]. Poly-*N*-isopropylacrylamide (PNIPAAm) on the other hand, is a hydrophilic polymer with switchable properties: Below a temperature of 32 °C, the polymer is water-soluble; rising the temperature above this critical barrier—the so-called lower critical solution temperature (LCST)—the coil collapses [51] and is no longer soluble in water. As we recently found, the LCST is also highly dependent on the applied pressure and can easily be tuned by the addition of cononsolvents [52]. NIPAAm is also well controllable by RAFT-polymerization and forms block copolymers with BA [53,54].

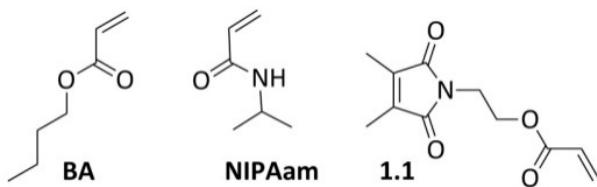


Figure 3. The monomers *n*-butyl acrylate (BA), *N*-isopropylacrylamide (NIPAAm) and *N*-ethylacrylate-3,4-dimethylmaleimide (**1.1**).

2. Experimental Section

2.1. Materials

Butyl acrylate (BA, Aldrich, ≥99%) was freed from inhibitor by passing through a column of neutral aluminum oxide (Aldrich, Brockmann activity I). *N*-isopropyl acrylamide (NIPAAm, Acros Organics, 99%) was recrystallized from *n*-hexane. Azo-bis-(isobutylnitrile) (AIBN, AkzoNobel, 98%) was recrystallized from methanol. Solvents used in synthesis and polymerizations were purchased from different suppliers in *pro analysi* quality and used as received. Tetrahydrofuran (THF) and *N,N*-dimethyl acetamide (DMAc) for SEC-analysis were purchased in HPLC-grade from Sigma-Aldrich (Steinheim, Germany). NMR-solvents were purchased from Deutero (Kastellaun, Germany) or Aldrich (99.8 atom% D) and used as received.

2.2. Synthesis

The comonomer *N*-ethylacrylate-3,4-dimethylmaleimide **1.1** was synthesized in accordance with literature-known procedures: First the precursor dimethylmaleimido ethanol was synthesized in

accordance with the paper of Gupta *et al.* in 98% yield [41]. Afterwards it was used without further purification in a Steglich esterification with acrylic acid (overall yield 80%) [55].

The six-functional RAFT-agents **R₆2** and **R₆3** (see Figure 4) were synthesized as described earlier [23,24].

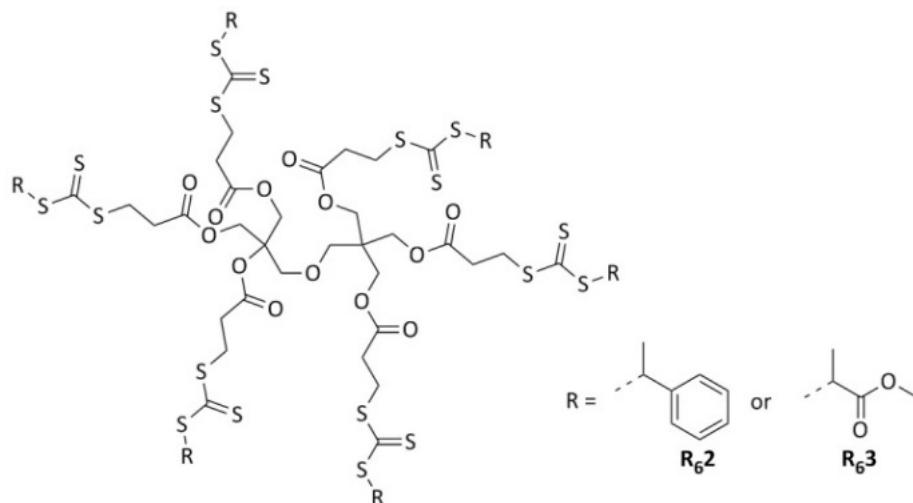


Figure 4. Dipentaerythriol-hexakis(3-S-phenylethyl-tricarbonylpropanoate) **R₆2** for butyl acrylate (BA) and dipentaerythriol-hexakis(3-S-(methyl-2-propanoatothiocarbonyl)propanoate) **R₆3** for *N*-isopropyl acrylamide (NIPAAm) [23,48].

2.3. Polymerizations

Solvents (toluene in BA- and DMF in NIPAAm-polymerizations) and monomers were degassed via at least three pump-freeze-thaw cycles. Along with polymerization vials, RAFT-agent (macroRAFT in case of block copolymerization), initiator, and the comonomer were transferred into an argon-filled glove box (O₂-content below 2 ppm). There, the stock solutions for the polymerizations were prepared, charged to the vials and sealed with Teflon/rubber lids. The vials were inserted into a thermostatted block heater at 60 ± 0.1 °C and removed after preset time periods. After cooling in an ice bath to quench the reaction, the monomer-to-polymer conversion was determined gravimetrically by precipitating the polymer from the reaction mixture (PBA with methanol, PNIPAAm with diethyl ether). The polymer was separated via centrifugation and dried under vacuum.

In the case of block copolymer synthesis with PNIPAAm-based macroRAFT-agents, chloroform was applied as solvent and the reaction mixture was poured into a weighed aluminum dish after quenching. The solvent and remaining BA were removed by evaporation.

2.4. Size Exclusion Chromatography (SEC)

The molecular weight distributions of BA-based polymers were determined with a SEC Analysis Systems 1260 Infinity by PSS Agilent (PSS Agilent Technologies, Mainz, Germany 1260 Iso Pump, Agilent 1260 ALS injector, pre-column PSS SDV, 8 × 50 mm, particle size: 5 μm, three separation columns PSS SDV, 8 × 300 mm, particle size: 5 μm, pore size: 10⁵, 10³ and 10² Å), a UV-detector PSS Agilent Technologies 1260 VWDVL at a wavelength of 310 nm [56] and a RI-detector PSS Agilent

Technologies 1260 RID. As eluent THF was used with toluene (>99.7%, anhydrous, Sigma-Aldrich, Steinheim, Germany) as internal standard (flow velocity $1.0 \text{ mL}\cdot\text{min}^{-1}$ at 35°C). The system was calibrated with polystyrene standards of low dispersity from PSS. Mark-Houwink-coefficients (BA: $K = 0.0122 \text{ cm}^3\cdot\text{g}^{-1}$, $a = 0.7$; Sty: $K = 0.0162 \text{ cm}^3\cdot\text{g}^{-1}$, $a = 0.71$) [57] were used to gain access to the molecular masses of the PBA homopolymers according to the principles of universal calibration. The molecular weight distributions of PNIPAAm samples were determined with a SEC Analysis Systems 1260 Infinity set up by PSS Agilent, similar to the previously mentioned one, containing a PSS GRAM (polyester copolymer network) pre-column, $8 \times 50 \text{ mm}$, and three PSS GRAM separation columns, $8 \times 300 \text{ mm}$, particle size: $10 \mu\text{m}$, pore sizes: 30 , 10^3 and 10^3 \AA , a UV-detector PSS Agilent Technologies 1260 VWDVL applied at a wavelength of 310 nm [56] and a RI-detector PSS Agilent Technologies 1260 RID. As eluent DMAc with 0.1 wt\% LiBr was used (flow velocity $0.8 \text{ mL}\cdot\text{min}^{-1}$ at 45°C). Again toluene was used as internal standard. The system was calibrated with PMMA standards from PSS. McKee *et al.* showed by using NMR-analysis parallel to the SEC measurements that PNIPAAm is equivalent to PMMA in such a solution so that a MMA calibration can be used to estimate the molar mass of PNIPAAm [58].

2.5. Dynamic Light Scattering

DLS measurements were performed on a Zetasizer Nano S (Worcestershire, United Kingdom) by Malvern with a 4 mV He-Ne-laser operating at a wavelength of $\lambda = 633 \text{ nm}$ and a non-invasive back scatter. Measurements were carried out in a Quartz cuvette at 25°C and in total three measurements were conducted.

The attenuator and path length were automatically adjusted by the instrument depending on the quality of the sample. The number of runs was set to 12 with measurement period of 200 s. The presented results are an average of the three measurements.

3. Results and Discussion

3.1. Copolymerizations with *N*-Ethylacrylate-3,4-dimethyl-maleimide

The first step towards the nano-carriers according to the synthesis plan (Figure 2) is the production of star polymers carrying cross-linkable groups. To this end, we developed and carefully explored the synthesis of star polymers from Z-RAFT star polymerization carrying cross-linkable DMI groups in an earlier publication entitled “Photocrosslinkable Star Polymers via RAFT-Copolymerizations with *N*-Ethylacrylate-3,4-dimethylmaleimide” [42]. In addition to kinetic findings—which are not relevant here—the following key outcomes from this earlier study are essential for the present work:

- PBA and PNIPAAm six-arm star polymers can successfully be synthesized in a well-controlled fashion using the RAFT agents **R₆2** in BA-polymerizations and **R₆3** in NIPAAm-polymerizations.
- The formed star polymer shows maximum molar masses of $550,000 \text{ g}\cdot\text{mol}^{-1}$ and typical D -values between 1.2 and 1.8 (when star-star coupling occurs, see below) for PBA and maximum molar masses of $250,000 \text{ g}\cdot\text{mol}^{-1}$ and typical D -values between 1.3 and 1.7 for PNIPAAm.
- Star-star coupling occurs with PBA stars, which originates from sporadic macroradical attack to the DMI-moiety, which results in broadened molar mass distributions at high monomer conversions.

- Star-star coupling does not occur in the NIPAAm system, which, however, shows a much more prominent occurrence of termination leading to dead polymer material.
- The reactivity ratios both for the BA/**1.1**-copolymer system and the NIPAAm/**1.1**-system leads to a gradient along the main chain with a higher content of **1.1** at the outer regions of the star.

Information about the star polymers synthesized in this first step can—in addition to the experimental details described in reference [40]—be deduced from the respective captions of figures showing data of star block copolymers given below.

3.2. Synthesis of Amphiphilic Diblock Copolymer Stars

The next step of the nano-carrier synthesis according to Figure 2 is the generation of the diblock copolymer star using the previously synthesized polymers as macroRAFT agents [42]. The final carrier should be amphiphilic, therefore, the second block's hydrophilicity has to be contrary to the first block. Due to the Z-group approach, none of the six arms of the star polymer is terminated in the first polymerization step but all six RAFT-units are still in the living state and the star polymer can be applied as fully functional macroRAFT agent in the second step. Furthermore, due to the mechanism of the Z-group approach, new monomer units are integrated adjacent to the RAFT-units. Consequently, the newly formed polymer block will form the central part of the star.

Polymer stars with a hydrophobic shell and a hydrophilic center as well as the reverse case were investigated in the present study. It needs to be considered whether the control of the second RAFT-polymerization is reduced, due to the contrasting properties of the polymerizing monomers and the already present star polymers in the system. In the case of a hydrophobic outer sphere, *i.e.*, a BA-block, the block copolymer macroradicals having NIPAAm-units at the active chain end have to penetrate the hydrophobic surrounding of the star's center to reach the RAFT-units near the central core. In order to enhance this penetration, a good solvent for all reaction partners has to be used. If a solvent is used that largely favors one of the polymers, the other one will collapse, consequently closing the pathway for the reaction.

It also has to be mentioned that the determined molecular weights of the copolymer stars are approximate values. On the one hand, there are no standards for such copolymer systems to calibrate the SEC set up. On the other hand, it can be assumed that the solubility of the two polymer blocks is different in the two available SEC solvents (THF and DMAc). The two blocks of the star polymer will therefore not be equally well expanded, which results in deviant hydrodynamic volumes, thus, deviant molecular weights. Figure 5 illustrates the effect of the different SEC-solvents on a BA-based macroRAFT-agent and the resulting diblock copolymer *starpoly*[(BA-*co*-**1.1**)₄₄-block-NIPAAm₅₆] after the copolymerization with NIPAAm. The molecular share of both monomers in the resulting polymer was determined by ¹H-NMR-studies and integration of the monomer-specific singlets in accordance to the procedure shown in reference [59].

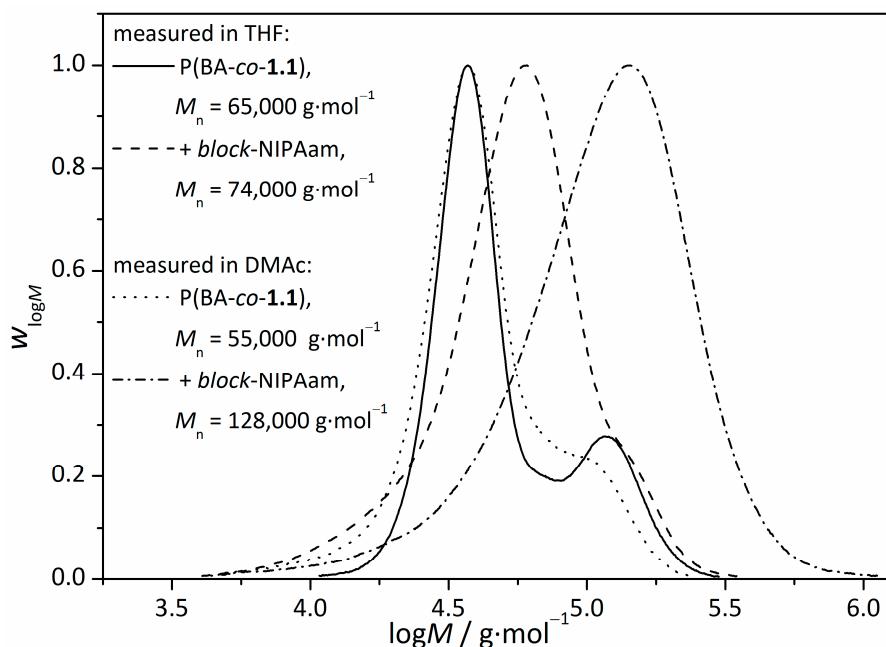


Figure 5. Molecular weight distributions—size exclusion chromatography (SEC)-data—of a macroRAFT agent *starpoly*(BA-*co*-1.1) and the resulting *starpoly*[(BA-*co*-1.1)₄₄-block-NIPAAm₅₆] sample of the polymerization $c_{\text{macroRAFT}} = 0.3 \text{ mmol}\cdot\text{L}^{-1}$, $c_{\text{AIBN}} = 0.7 \text{ mmol}\cdot\text{L}^{-1}$ and $c_{\text{NIPAAm}} = 1.290 \text{ mmol}\cdot\text{L}^{-1}$ in chloroform at 60 °C after 180 min, measured in tetrahydrofuran (THF) and *N,N*-dimethyl acetamide (DMAc).

The molecular weight distributions shown in Figure 5 show that the size of the BA-based macroRAFT (solid line = THF and dotted line = DMAc as solvent for SEC) is determined in both SEC-solvents approximately equally; the evaluated M_n values using a PS-calibration of $65,000 \text{ g}\cdot\text{mol}^{-1}$ and $55,000 \text{ g}\cdot\text{mol}^{-1}$ are in acceptable agreement. In the case of the amphiphilic diblock copolymer originating from this macroRAFT agent, largely different molar masses are observed in the two solvents. Here the polymer appears much smaller dissolved in THF (dashed line), leading to an apparent M_n of $74,000 \text{ g}\cdot\text{mol}^{-1}$, whereas DMAc as solvent gives an apparent M_n of $128,000 \text{ g}\cdot\text{mol}^{-1}$. It can be concluded that THF is a poor solvent for the PNIPAAm-block and that in DMAc both kinds of polymer segments seem to be well dissolved. It can be seen that SEC is a challenging method to characterize such amphiphilic polymer systems, as no calibration standards are available and the solvent quality has a large impact on the determined size and molecular weight. In any case, it can qualitatively be concluded from inspection of Figure 5 that the star-shaped macroRAFT agent of PBA is increasing in molecular weight, *i.e.*, it undergoes block copolymerization. According to the DMAc-SEC, the size is roughly doubled.

Figure 6 shows the *vice versa* situation, that is, the block copolymerization of BA onto a star-shaped PNIPAm. The solid line represents the chromatogram of the *starpoly*(NIPAAm-*co*-1.1), the different broken lines the resulting diblock copolymer stars after 20, 50 and 120 min of reaction time. An increase in the molecular weight can clearly be observed as well as a strong broadening of the molar mass distributions compared to the original macroRAFT agent. Despite the high dispersities, see Table 1, a controlled behavior of the polymerization process can be concluded from the development of the molecular weights with the monomer conversion. As mentioned before, it may

occur that the penetration of macroradicals containing BA units towards the RAFT-units in the center of the star polymer is being slowed down, because of the PNIPAAm surrounding, which directly leads to higher dispersities [60].

As mentioned above, ^1H -NMR spectroscopy was used to evaluate the composition of the star block copolymers and the values are summarized in Table 1. The first sample obtained was a white, amorphous polymer comparable to the starting material. With increasing BA-content, the polymer changes to a transparent material. When larger BA-blocks are obtained ($F_{\text{BA}} > 70 \text{ mol\%}$), the polymer is a transparent, sticky, and rubber-like compound. It was found in further experiments that the control over the reaction is completely lost, if macroRAFT agents with a molecular weight above $100,000 \text{ g}\cdot\text{mol}^{-1}$ are applied. This is a consequence of the low molar proportion of RAFT groups in such systems and may also be due to the shielding of the RAFT-units by the surrounding arms, which becomes apparently too strong.

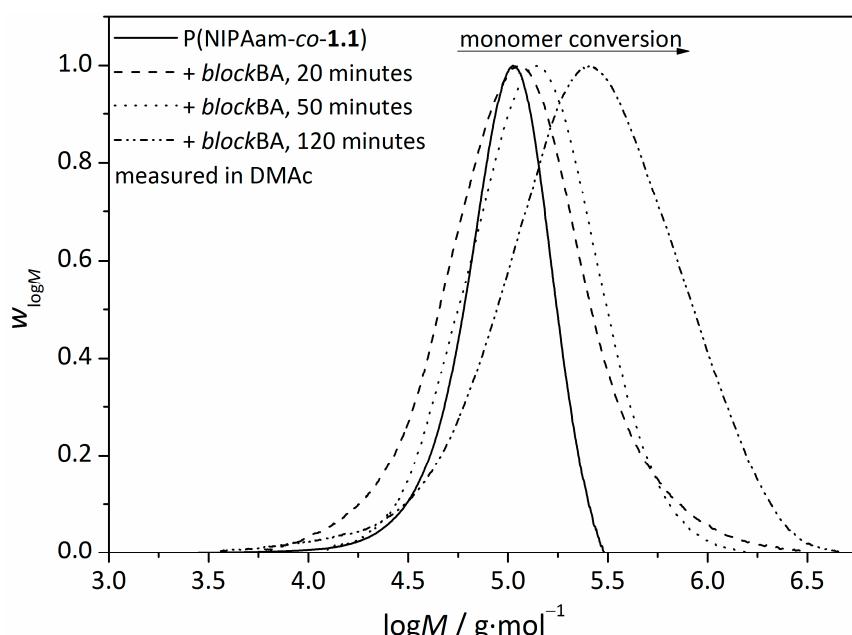


Figure 6. SEC-traces determined in DMAc of the block copolymerization of *starpoly*(NIPAAm-*co*-**1.1**) of $M_n = 70,000 \text{ g}\cdot\text{mol}^{-1}$ (solid line) with $700 \text{ mmol}\cdot\text{L}^{-1}$ BA using $1.2 \text{ mmol}\cdot\text{L}^{-1}$ azo-bis-(isobutylnitrile) (AIBN) in chloroform at 60°C (broken lines).

Table 1. Monomer conversion, molar mass data, and polymer composition of *starpoly*[(NIPAAm-*co*-**1.1**)-block-BA] samples resulting from the block copolymerization of *starpoly*(NIPAAm-*co*-**1.1**) of $M_n = 70,000 \text{ g}\cdot\text{mol}^{-1}$ with $700 \text{ mmol}\cdot\text{L}^{-1}$ butyl acrylate (BA) using $1.2 \text{ mmol}\cdot\text{L}^{-1}$ azo-bis-(isobutylnitrile) (AIBN) in chloroform at 60°C .

t/min	monomer conversion/%	$M_n/\text{g}\cdot\text{mol}^{-1}$	\mathcal{D}	$F_{\text{BA}}/\text{mol\%}$	$F_{\text{NIPAAm}}/\text{mol\%}$
20	4	114,000	1.97	10.1	89.9
50	6	150,000	1.70	38.9	61.1
120	7	210,000	2.67	45.9	54.1

3.3. UV-Induced Cross-Linking of DMI Units in Star Polymers

The next step in the nano-container formation is the cross-linking of the outer regions of the amphiphilic star polymers. For the UV-induced cross-linking step, different UV-lamps were systematically tested and the obtained material was investigated by SEC- and DLS-measurements. The cross-linking of DMI units by irradiation with UV-light was investigated by Kuckling *et al.* for various solvents and different alkyl groups at the nitrogen atom [29]; the mechanism of the reaction is shown in Figure 7.

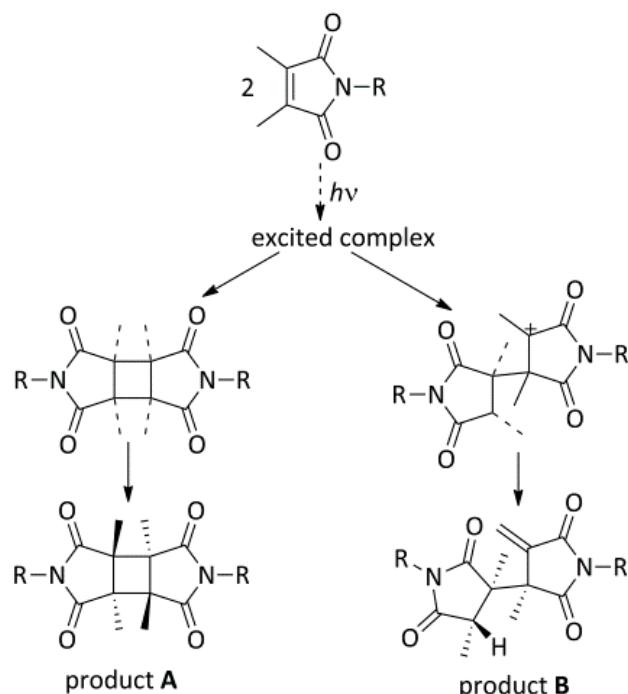


Figure 7. Cross-linking mechanism of *N*-alkyl-3,4-dimethylmaleimide (DMI), redrawn from reference [29].

The cross-linking is induced by UV irradiation with wavelengths above 300 nm [61]. For the investigations here, three kinds of UV-lamps were explored: a Laboratory-UV-Reactor System with a medium pressure mercury lamp by Heraeus Noblelight ($E = 150$ W), a UV-hand lamp by Bender Konrad ($E = 8$ W, $\lambda = 366$ nm) and a UV-lamp system by Müller Elektronik·Optik with a mercury short arc lamp ($E = 100$ W) and a filter to cut off all wavelengths below 305 nm. In order to achieve the desired intramolecular cross-linking for the shell formation and to prevent coupling or even network formation of the star polymers, it was necessary to apply high dilutions of the polymer sample. Concentrations between 10^{-6} and 10^{-7} mol·L⁻¹ of reactive polymer were found to be sufficient [62]. Six-arm diblock copolymer stars for the production of nano-carriers as well as six-arm monoblock polymer stars as model compounds were tested. For the latter, a sample of *starpoly(BA-co-1.1)* from the polymerization with $c_{BA} = 7$ mmol·L⁻¹, $c_{RAFT} = 9$ μ mol·L⁻¹, $c_{1.1} = 0.07$ mmol·L⁻¹ and $c_{AIBN} = 2$ μ mol·L⁻¹ at 60 °C for 195 min, was used.

First, the Laboratory-UV-Reactor System was tested: A *starpoly(BA-co-1.1)* sample with a molecular weight of 336,000 g·mol⁻¹ was dissolved in ethyl acetate ($c_{polymer} = 1.8 \cdot 10^{-6}$ mol·L⁻¹). This star polymer was generated in the presence of a RAFT-agent cocktail consisting both of six- and

mono-functional RAFT-agent. Therefore, the obtained polymer material contains linear and star-shaped polymer side by side as indicated by the bimodal chromatogram in Figure 8 (solid line). The linear polymer in such samples is the exact representative of the individual arms inside the star polymer. This method was developed earlier by us in order to determine the absolute molecular weight of star polymers—which has smaller hydrodynamic volumes in SEC than liner polymer and can thus not be evaluated simply by using conventional calibration by linear polymer standards—via the molar mass evaluation of the linear arm material [49]. The solution was irradiated in the Laboratory-UV-Reactor System ($E = 150$ W) for 25 min resulting in a polymer material with a molecular weight of $50,000\text{ g}\cdot\text{mol}^{-1}$. The corresponding chromatograms obtained with the THF-SEC are shown in Figure 8. A strong reduction in the molecular weight was observed. The material obtained after irradiation (dashed) is approximately six times smaller than the starting material which indicates a complete destruction of the RAFT-units of the star polymer leading to single arm polymer chains. This conclusion is supported by comparison with the chromatogram of the starting material before irradiation, which also contains the polymer generated by the mono-functional RAFT-agent that represents individual arm polymer. The applied UV-lamp emits the characteristic Hg-line spectrum which spans from 185 nm up to visible wavelengths. Even though this lamp has its emission maximum between 305 and 360 nm, *i.e.*, the desired wavelength regime, light of shorter wavelength apparently leads to the destruction of the polymer via the well-known decomposition reaction of thiocarbonylthio-compounds by UV-irradiation [63].

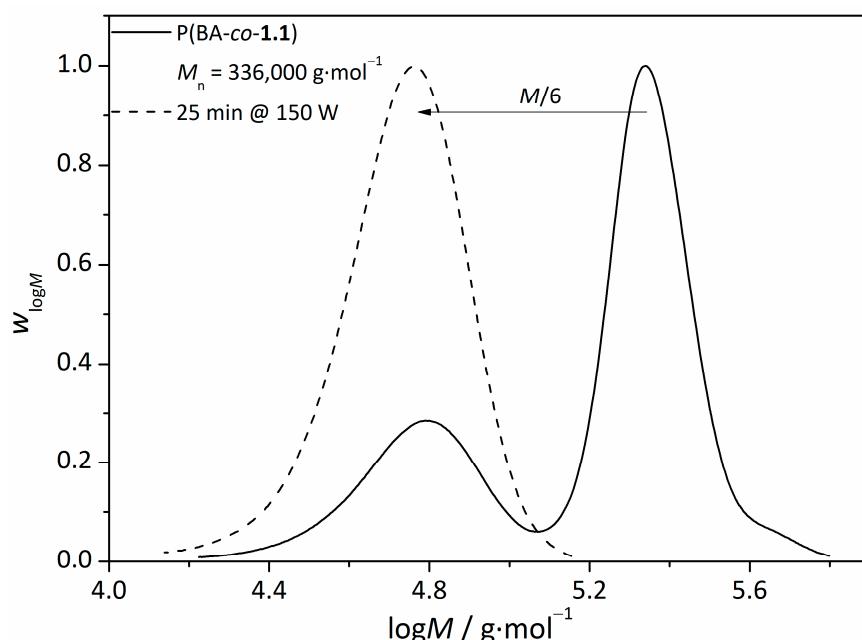


Figure 8. SEC-data, determined in THF, of a *starpoly(BA-co-1.1)* with a molecular weight of $336,000\text{ g}\cdot\text{mol}^{-1}$ (solid line) and the resulting polymer ($M_n = 50,000\text{ g}\cdot\text{mol}^{-1}$) after UV-irradiation (dashed line) for 25 min using a Laboratory-UV-Reactor System with a medium pressure mercury lamp of 150 W in ethyl acetate. The low molar mass portion of the original material (solid line) represents the individual arm polymer and stems from the RAFT star polymerization using a RAFT-agent cocktail consisting both of six- and mono-functional RAFT-agent (for details see text and reference [47]).

In order to avoid destruction, a UV-lamp with lower power was tested in further experiments. The applied UV-hand lamp provides radiation with a wavelength of 366 nm at a power of 8 W. Longer reaction times were anticipated, as the process is performed by a much smaller energy entry. Experiments were carried out with *starpoly*[(NIPAAm-*co*-**1.1**)-*block*-BA] star polymers in chloroform ($c_{\text{polymer}} \approx 2.6 \times 10^{-6} \text{ mol}\cdot\text{L}^{-1}$). Figure 9 shows the chromatograms measured in THF of a polymer sample before (solid line) and after the irradiation for 57 h (dashed line). The here applied *starpoly*[(NIPAAm-*co*-**1.1**)₁₂-*block*-BA₈₈] has an average molecular weight of around 250,000 g·mol⁻¹ (determined in THF) with 64 DMI-units per star (=3.5 mol%). The chromatogram of the material obtained after irradiation (dashed line) shows a shoulder in the region of high molecular weight, similar to those found in polymerizations where star–star coupling occurs. The molecular weight of the material causing the shoulder is indeed roughly two times higher than that of the starting material. The original peak does not change. It can thus be concluded that the stars in principal stay intact and that double stars are formed during the irradiation process. This indicates that the [2+2]-cycloaddition successfully occurs, but is too slow in this system, so that intermolecular reactions—which require long diffusive traveling times of species in order to become in contact with each other—become prominent. This unwanted reaction may even be enhanced by the relatively good solvent conditions, which leads to star polymers being in an expanded state. By reducing the solvent quality via the use of solvent mixtures consisting of good and poor solvents (see below) the intramolecular cross-linking may be enhanced.

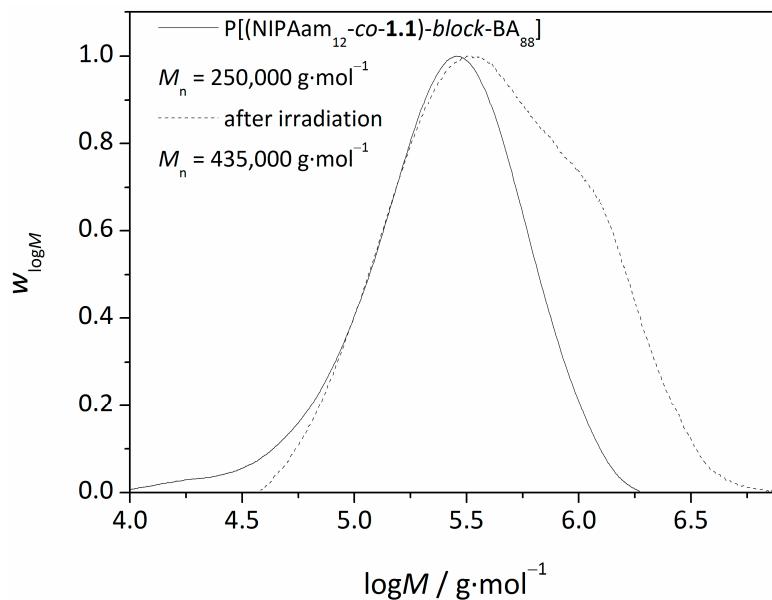


Figure 9. SEC-data, determined in THF, of a *starpoly*[(NIPAAm-*co*-**1.1**)₁₂-*block*-BA₈₈] with a molecular weight of 250,000 g·mol⁻¹ (solid line) and the resulting polymer ($M_n = 435,000 \text{ g}\cdot\text{mol}^{-1}$) after UV-irradiation (dashed line) for 57 h using a UV hand lamp of 8 W in chloroform.

The third applied radiation system was a UV-lamp system with a 100 W mercury-vapor lamp. The emitted spectrum was filtered by a band-pass filter (<305 nm) to avoid possible side reactions induced by shorter wavelengths, e.g., cleavage of the RAFT-agent or the cross-linking product. A light

conductor enabled directed irradiation of the complete sample. Solvent mixtures of lower solvent quality were tested and a mixture of acetone:diethyl ether 3:1 (volume-based) was finally found to be optimally balanced for this PNIPAm-rich system, for which acetone is a good solvent and diethyl ether is a non-solvent. A *starpoly*[(NIPAAm-*co*-**1.1**)₉₀-block-BA₁₀] sample with a molecular weight of 110,000 g·mol⁻¹ was irradiated for 25 min (see Figure 10). The SEC-data of the obtained material was recorded on the DMAc-SEC set up.

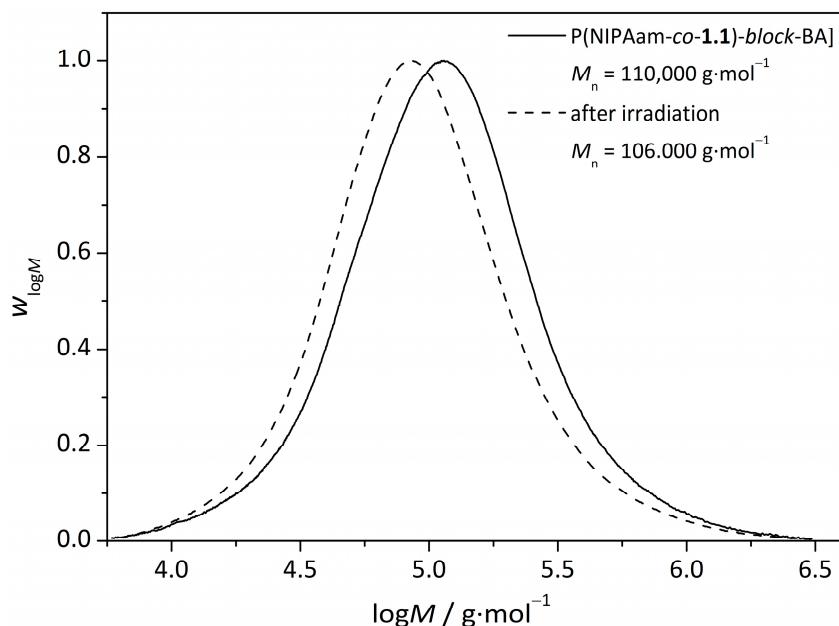


Figure 10. SEC-data, determined in DMAc, of a *starpoly*[(NIPAAm-*co*-**1.1**)₉₀-block-BA₁₀] with a molecular weight of 110,000 g·mol⁻¹ (solid line) and the resulting polymer ($M_n = 106,000 \text{ g}\cdot\text{mol}^{-1}$) after UV-irradiation (dashed line) for 25 min using a UV mercury-vapour lamp of 100 W in acetone:diethyl ether 3:1.

Here a small difference to lower values in the molecular weight before (solid line) and after the irradiation process (dashed line) was observed. In contrary to the previous example, the cross-linking reaction forming the carrier's shell proceeds here in a more coiled state, due to the addition of non-solvent. A reduction in size and therefore in the hydrodynamic radius is therefore a consequence of the collapsed state of the star polymer during the UV-crosslinking process in the poor solvent, which is finally frozen by the applied cross-links. The reduced hydrodynamic volume of this star polymer material being back again in the good solvent is thus strong evidence for the successful intramolecular cross-linking. The formation of larger structures due to self-aggregation of many amphiphilic star polymers forming micellar structures, as described by Štěpánek *et al.* [64], were not observed and the determined molecular weights correspond to the theoretical expected molecular weights of single stars. We hypothesize at this stage already, that by this experiment we could successfully prepare nano-sized hollow spherulitic particles with an amphiphilic core-corona system. This hypothesis will be proven below.

In order to explore this successful cross-linking reaction, which is vital for the full process, more closely, we also studied BA-based monoblock star polymers, which are more easily handled. A sample of 62 mol% BA and 38 mol% **1.1** with a molecular weight of 110,000 g·mol⁻¹ (THF SEC) and a

sample of 92 mol% BA and 8 mol% **1.1** with a molecular weight of 280,000 g·mol⁻¹ (THF SEC) were irradiated for 30 min. The reactions were carried out in a THF:methanol mixture (7:3 volume-based) where THF acts as solvent and methanol as non-solvent. Again, a reduction in the hydrodynamic volume can be observed and the change in size is stronger for blocks with more cross-linkable units than with fewer integrated **1.1**-units (see Table 2).

Table 2. Apparent number of average molecular weights reflecting the hydrodynamic volume before and after the cross-linking with 100 W for *star*(BA-*co*-**1.1**) samples containing various cross-linking group (DMI) densities.

Sample	M_n (before irradiation) g·mol ⁻¹	M_n (after irradiation) g·mol ⁻¹	$\frac{M_n^{\text{before}}}{M_n^{\text{after}}}$
<i>star</i> (BA ₆₂ - <i>co</i> -1.1 ₃₈)	110,000	65,000	1.69
<i>star</i> (BA ₉₂ - <i>co</i> -1.1 ₈)	280,000	180,000	1.56

The amount of **1.1** in the polymer chains has an influence on the strength of the forming cross-linked polymer shell. If only a few **1.1**-units cause the shell-formation, the chains are wrapped loosely around the core and are only fixed by a few points. Therefore, the possibility of expansion in a good solvent is still given to some extent. In the case of many cross-linkers in the system the chains are bound tightly around the core and the structure cannot easily expand in a good solvent environment. Furthermore dynamic light scattering experiments were performed. The SEC-trace and its corresponding size distribution of a sample before and after UV-cross-linking are shown in Figure 11. The measurements reveal that the star polymer exists as a unimolecular particle. After irradiation for 30 min the polymer with the average molecular weight of 139,000 g·mol⁻¹ shows a decrease in particle size from 24–16 nm, which is reflected in the reduction of the apparent molecular weight to 87,900 g·mol⁻¹.

3.4. Removal of the RAFT-Core by Aminolysis

To prove the successful cross-linking and thus the structure of the nano-carriers, the RAFT-cores were removed (see Figure 2). This removal was conducted by aminolysis, as described by Qiu and Winnik [65]. It was expected that the hollow spheres obtained after the aminolysis show approximately the same molecular weight as before, as the polymer material stays unaltered and the RAFT-core is assumed to be negligibly small compared to the polymer material surrounding it. To probe the coring, a UV-crosslinked *starpoly*(BA₆₂-*co*-**1.1**₃₈) was combined with an excess of butyl amine and catalytic amounts of tris(2-carboxyethyl) phosphine hydrochloride (TCP·HCl). The resulting SEC-traces are shown in Figure 12. The chromatograms of the original (solid line), the cross-linked (dashed line) and the de-cored material (dotted line) are plotted together in one graph. For the sample of *starpoly*(BA₆₂-*co*-**1.1**₃₈), no change in size—as expected—due to the core-removal can be observed. The chromatogram of the material after the expulsion of the RAFT-core basically is identical with the one after the cross-linking, apart from the shoulder in the region of high molecular weight, which disappears in the process of aminolysis. This material of higher molecular weight possibly corresponds to star polymers, which are not yet cross-linked. Via aminolysis, the RAFT-units decomposed and the arms, which were not integrated in the shell during the process of cross-linking, were expelled as single chains of smaller molecular weight.

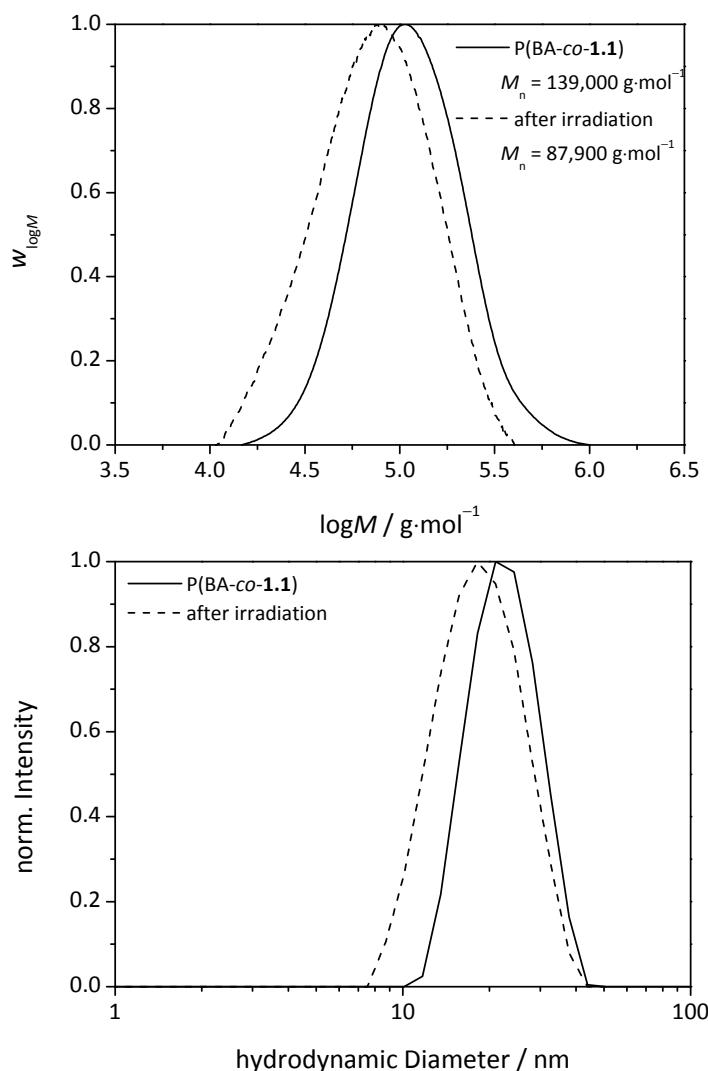


Figure 11. SEC-traces (THF) (**top**) of *star*(BA-*co*-**1.1**) sample from the polymerization of $c_{\text{BA}} = 4882 \text{ mmol} \cdot \text{L}^{-1}$, $c_{\text{AIBN}} = 0.96 \text{ mmol} \cdot \text{L}^{-1}$, $c_{\text{RAFT}} = 0.58 \text{ mmol} \cdot \text{L}^{-1}$, and $c_{\text{1.1}} = 222 \text{ mmol} \cdot \text{L}^{-1}$ in toluene at 60°C for 115 min, and the corresponding size distribution (**bottom**) before (solid line) and after UV-crosslinking (dashed line) for 30 min using a UV mercury-vapor lamp of 100 W in THF:methanol 7:3.

In the case in which intramolecular cross-linking would not have been successful, this RAFT-unit destruction would have led to the complete disintegration of the complete star polymer material. This is clearly not the case, as seen from inspection of Figure 12.

The undisputable proof for a successful de-coring could be obtained via the UV-detection after SEC using $\lambda = 310 \text{ nm}$, which is selective for trithiocarbonates. Figure 13 shows the chromatograms resulting from RI- and UV-detection for the sample before (top) and after the aminolysis (bottom). The signal of the UV-absorbance is very intense before the removal of the RAFT-core as the RAFT-units show a strong absorbance at 310 nm [23]. After the decomposition of the RAFT-core, hardly any absorbance at 310 nm can be observed, which indicates that these units were successfully destroyed. Nevertheless, the comparison with the detected RI-signal reveals that after decomposition of the RAFT-units the size of the polymer entity stays the same. In the case in which pure star polymer without crosslinking would be present, the molar mass would be greatly reduced due to disintegration

into arm polymer chains. These findings clearly prove that with the proposed strategy shell-crosslinked nano-spheres without a RAFT-core are accessible.

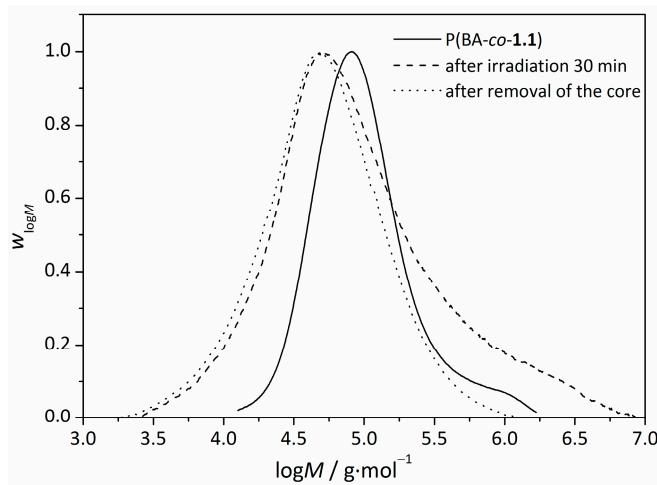


Figure 12. SEC-traces of *star*(BA₆₂-co-1.1₃₈) before irradiation (solid), after irradiation (dashed) and after de-coring by aminolysis with an excess of butyl amine and catalytic amounts of tris(2-carboxyethyl) phosphine hydrochloride (TCP·HCl) (dots).

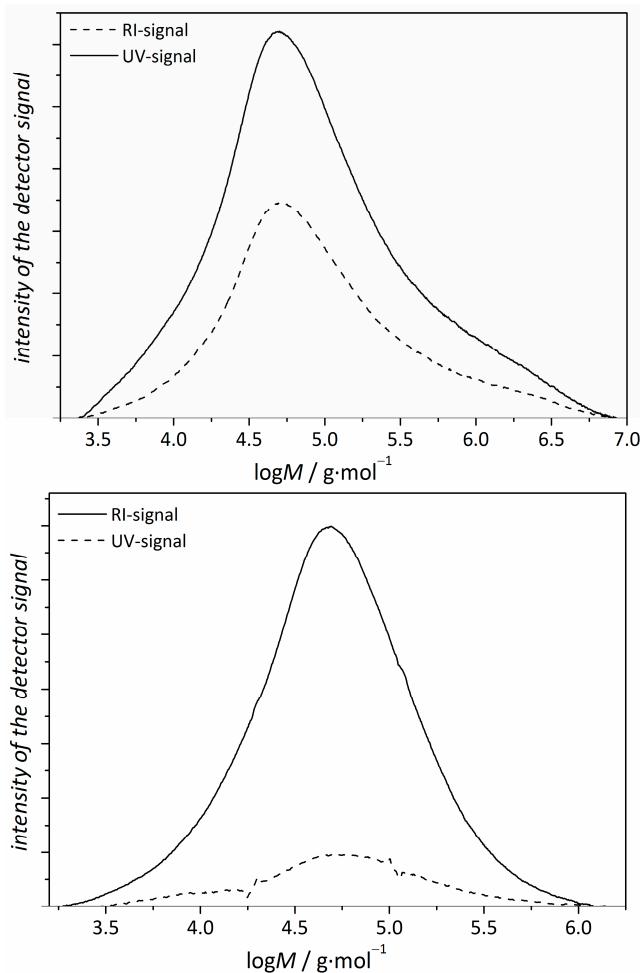


Figure 13. (Top) RI- and UV-chromatograms (at 310 nm) after the cross-linking; **(Bottom)** RI- and UV-chromatograms (at 310 nm) after the de-coring.

4. Conclusions

This paper shows the synthesis of nano-sized hollow spheroid particles with an amphiphilic core-corona system synthesized in a four-step-procedure using the monomers BA and NIPAAm. By means of controlled radical RAFT polymerization, star polymers consisting of six amphiphilic diblock copolymer arms were synthesized. The outer polymer block is composed of a basic monomer and a monomer providing a cross-linkable unit, here *N*-ethylacrylate-3,4-dimethylmaleimide (**1.1**), to enable the shell formation via UV-irradiation. Star polymer samples with different amounts of comonomer were irradiated with UV-light of different energies and over various periods of time to achieve the formation of the carrier's shell. The success of the procedure was monitored via SEC- and DLS-measurements. It was found that less than 3.5 mol% cross-linkable units in the outer block of the star polymer are sufficient to perform the shell closure at energy entries of 100 W over 30 min. The de-coring process to yield the hollow nano-carrier was performed via aminolysis. The success of the process could be proven via SEC using UV-detection, by which the fate of the RAFT groups could be traced.

In total, a successful synthesis strategy towards hollow nano-carriers from Z-RAFT star polymers is presented. In future work, the loading and release mechanism of various compounds has to be tested so that the carrier's capacity for the different possible applications can be determined. In addition, tests will be carried out to verify the nano-carrier's biocompatibility for biomedical applications, for which the modification of the carrier's surface to achieve better biocompatibility has to be considered.

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Author Contributions

Nadja Förster and Philipp Vana designed the experiments; Nadja Förster and Sonja Schmidt performed the experiments and carried out the instrumental analysis; Nadja Förster, Sonja Schmidt and Philipp Vana prepared the manuscript.

Conflicts of Interests

The authors declare no conflict of interest.

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