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Synthesis and unimolecular micellar behavior of amphiphilic star-shaped block copolymers obtained *via* the Passerini three component reaction†

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A series of new amphiphilic star-shaped block copolymers with hydrophobic cores and hydrophilic shells was synthesized, using the Passerini three component step-growth polymerization (Passerini-3CP). The degree of polymerization of the Passerini hydrophobic cores (20, 10 and 5 repeating units) was controlled and the chain ends were quantitatively functionalized with different sized PEG-aldehydes and/or PEG-isocyanides *via* another Passerini reaction. The encapsulation and phase transfer properties of the star-shaped block copolymers were followed visually and by using UV/VIS-spectroscopy, using Orange II and Para Red dyes as guest molecules. The investigated polymers showed a unimolecular micellar behavior, as shown by dynamic light scattering (DLS) and the mentioned encapsulation experiments.

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Unimolecular micelles show interesting properties for a wide range of applications, including catalysis or the encapsulation of low molecular weight organic guest molecules.¹ These covalently connected core-shell architectures can be based on amphiphilic hyperbranched polymers, dendrimers or star-shaped block copolymers. Unimolecular micelles are characterized by an increased stability in solution, due to their covalently linked structure, thus preventing the usually observed dynamic equilibrium between the individual amphiphilic molecules and the micelle.² The first described systems behaving like unimolecular micelles were based on dendrimers.^{3–5} However, dendrimers often require difficult multi-step organic syntheses. Polymer-based systems with core-shell architecture often show similar properties, but are easier to synthesize and thus constitute suitable alternatives. For example, amphiphilic star-shaped polymers having a defined number of arms and, accordingly, end groups, can be used in different applications, due to their behavior as unimolecular micelles.^{6–10} Most commonly, these amphiphilic star-shaped polymers are synthesized by atom transfer radical polymerization (ATRP) or other controlled/living polymerization techniques (e.g. nitroxide-mediated radical polymerization (NMP), reversible addition-fragmentation chain transfer (RAFT) or anionic polymerization).^{11–13} Additionally, ring-opening

polymerization of lactides and lactones is often used to synthesize star-shaped polymers.¹⁴ In previous work, we have demonstrated that star-shaped block copolymers can be synthesized *via* the Passerini three component reaction (Passerini-3CR) in a step-growth process.¹⁵ The Passerini-3CR is an efficient reaction using a carboxylic acid, an oxo-component (ketone or aldehyde) and an isocyanide in a one-pot procedure under very mild conditions.¹⁶

We recently summarized the manifold and straightforward synthesis possibilities in polymer chemistry using the Passerini reaction, demonstrating a variety of application possibilities and achievable molecular architectures.^{17,18} By using bifunctional components (AA- + BB-type monomers or AB-type monomers), a polymerization process is induced and substituted polyesters, polyamides or poly(ester amide)s can be obtained.^{18–20}

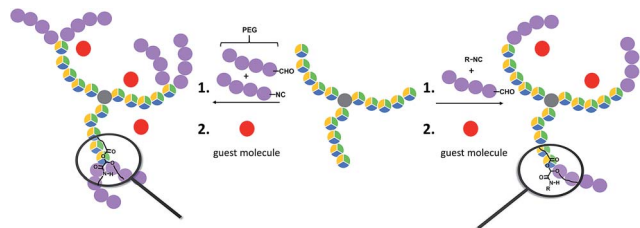
In the case of the star-shaped polymer, advantageously, this approach enables to easily tune the side chains of the polymer cores, thus adjusting its properties. Additionally, this step-growth process led to a control of the molecular weight with 100% end-group fidelity.

Following our previous study, this work describes the synthesis of well-defined amphiphilic star-shaped block copolymers using the Passerini-3CR and the subsequent encapsulation of two different dyes (Scheme 1). This approach is based on the use of a trifunctional carboxylic acid as an irreversible chain transfer agent (ICTA) in combination with the AB-type monomer **3**. We have recently shown that by using an ICTA, an AB-type monomer (combination of aldehyde and carboxylic acid), and an excess of isocyanide, the molecular weights obtained in

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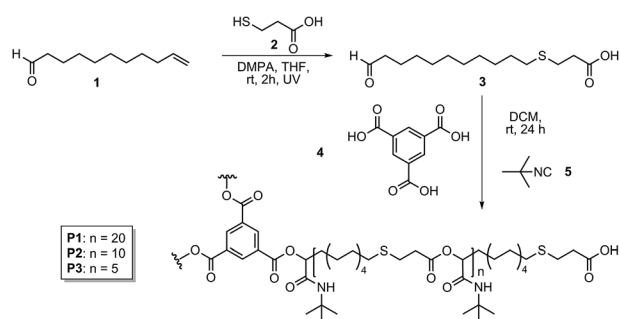
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Scheme 1 Schematic representation of the applied synthesis strategy to obtain the described different polymer architectures (including an indication of their potential for guest encapsulation).

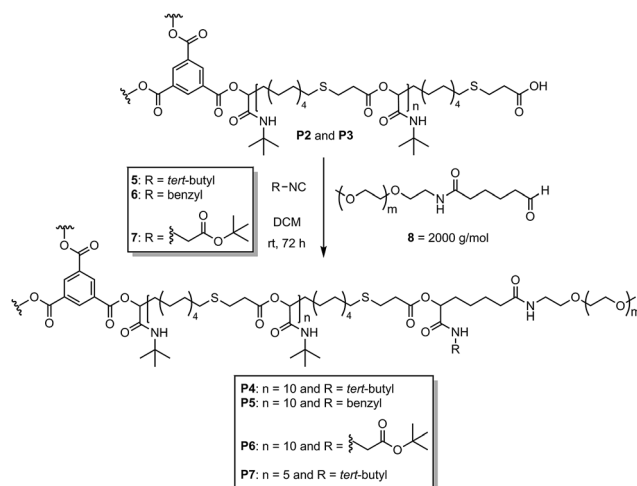
a Passerini-3CP are determined by the ratio of monomer : ICTA (in analogy to the monomer : initiator ratio in living/controlled polymerizations). To investigate potential applications of these star-shaped homopolymers, we now focused on their functionalization with PEG chains, to produce amphiphilic polymers and to study their encapsulation behavior. The synthesis of AB-type monomer **3** and star-shaped homopolymer **P1** has been described in our previous publication (Scheme 2), also demonstrating very high end-group fidelity, which is essential for this investigation.¹⁵ Additionally, two star-shaped homopolymers with shorter arm lengths (**P2** and **P3**, 10 and 5 repeating units) were synthesized using ratios of 30 : 1 and 15 : 1 of [3] : [4] (10 : 1 and 5 : 1 per arm respectively). The molecular weights (M_n) of the star-shaped polymers determined by ¹H NMR end group integration were consistent with the expected molecular weights (Formula S1†) and confirmed a degree of polymerization of 10 and 5, respectively (Table S1†). The observed molecular weight distribution (Fig. S17†) was symmetric and confirmed full monomer conversion. The obtained dispersities (1.23–1.40) are lower than for a classic step-growth polymerization, indicating the presence of both step-growth and chain-growth mechanisms in this system, as expected. The star-shaped homopolymers **P2** and **P3** were subsequently functionalized with a water-soluble PEG-based (polyethylene glycol) shell to obtain water-soluble star-shaped block copolymers with the goal to achieve unimolecular micellar behavior. Two strategies based on the Passerini-3CR were used to produce linear or branched star-shaped block copolymers. For this purpose, the COOH end groups of the star-shaped polymers reacted with a PEG aldehyde and an



Scheme 2 Synthesis of AB-type monomer **3** and subsequent polymerization to obtain homopolymers **P1**, **P2** and **P3** with different number of repeating units.¹⁵

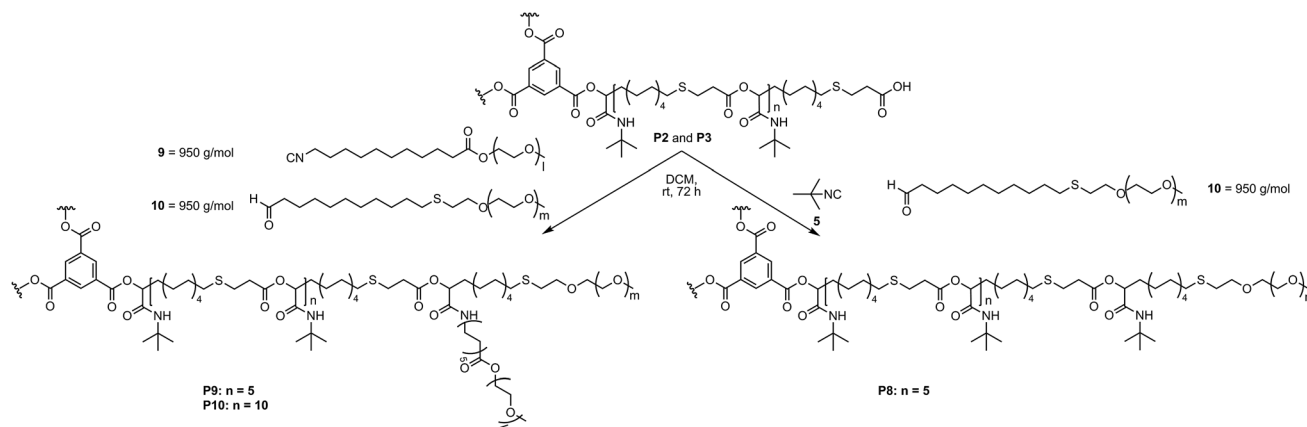
isocyanide or with a PEG aldehyde and a PEG isocyanide in a Passerini-3CR to form a water-soluble shell with either one or two PEG chains per arm. In first tests, **P2** was converted with a commercially available PEG-aldehyde **8** (2000 g mol⁻¹) in a ratio of 1 : 1 (per arm) and an excess of *tert*-butyl isocyanide **5**, benzyl isocyanide **6** or *tert*-butyl-2-isocanoacetate **7** (Scheme 3). After precipitation in diethyl ether, the functionalized polymers **P4**, **P5** and **P6** were obtained in good yields. Complete conversion of the end groups was confirmed by ¹H NMR and SEC measurements (Fig. S10–S12 and S18†). Although the polymer end groups were fully functionalized, the water solubility of the polymers **P4**, **P5** and **P6** were rather poor and insufficient to obtain unimolecular micelles soluble in water. Thus, we used the smaller cores (**P2** and **P3**) and did not continue the investigations with **P1**.

Therefore, **P7** was synthesized using the smaller hydrophobic core **P3** with *tert*-butyl isocyanide **5** and PEG aldehyde **8** in order to increase the hydrophilic fraction of the copolymers. Moreover, in order to investigate the influence of the molecular weight of the PEG chains as well as the effect of branching at the core–shell connection on the aggregation and encapsulation behavior of the star-shaped block copolymers in water, lower molecular weight functionalized PEGs were used. For the preparation of PEG isocyanide **9** (950 g mol⁻¹), first, isocyanide **17** was prepared from amine **11**, which was subsequently transformed to PEG isocyanide **9** *via* a transesterification with methoxy-PEG **18** (Scheme S1†).²¹ PEG aldehyde **10** (950 g mol⁻¹) was synthesized by end group modification of PEG thiol **19** *via* a thiol–ene reaction with 10-undecenal **1** (Scheme S2†). Having the functionalized PEGs in hand, the star-shaped block copolymers **P8**, **P9** and **P10** were synthesized *via* the Passerini-3CR, using *tert*-butyl isocyanide **5** and PEG aldehyde **10**, or PEG isocyanide **9** and PEG aldehyde **10** to obtain polymers with either one or two PEGs (950 g mol⁻¹) and either 5 or 10 repeating units of the core (Scheme 4, compare also Scheme 1). Thus, a small library of five different amphiphilic star-shaped block



Scheme 3 Functionalization of **P2** with different isocyanides **5**, **6** and **7** and PEG aldehyde **8** (2000 g mol⁻¹) to obtain block copolymers **P4**, **P5** and **P6** and additional functionalisation of **P3** with *tert*-butyl isocyanide **5** and PEG aldehyde **8** (2000 g mol⁻¹) to obtain block copolymer **P7**.





Scheme 4 Functionalization of P2 and P3 with *tert*-butyl isocyanides 5 and PEG aldehyde 10 (950 g mol^{-1}) to obtain star-shaped block copolymer P8 and additional functionalisation of P2 and P3 with PEG isocyanide 9 and PEG aldehyde 10 (950 g mol^{-1}) to obtain star-shaped block copolymers P9 and P10.

copolymers was produced and further investigated, allowing the correlation of the different polymer architecture to the performance as unimolecular micelles. The full conversion of the end groups was determined by ^1H NMR measurements (Fig. S14–S16[†]). Due to an increased hydrophilic ratio, polymers P7, P8, P9 and P10 showed improved water solubility. All following evaluations were performed only on these four water soluble polymers. Due to the differences in solubility of the two blocks in water, the formation of aggregates might be expected, contradicting a unimolecular micellar behavior. Nevertheless, dynamic light scattering (DLS) measurements confirmed unimolecularity for the four star-shaped block copolymers in a concentration range from 0.1 mg mL^{-1} and 1.0 mg mL^{-1} (Fig. S20–S23[†]). The measurements were carried out in water and dichloromethane (DCM). Two different preparation protocols, typical for the preparation of micellar solutions, were used for the analysis in water.²²

On the one hand, the sample was directly dissolved in water (without acetone: woA) and on the other hand, the sample was dissolved in 2–3 drops of acetone and then water was added dropwise (with acetone: wA). The values of all four polymers measured woA were slightly higher (13.5–21.0 nm) compared to the values wA (8.7–15.7 nm), which may indicate some aggregation in water. To confirm this and possibly break these aggregates, P7 wA and woA was ultrasonicated for 5 minutes each (P7 showed the largest size difference for the two preparation modes). Afterwards, all samples showed the same value (value of the sample wA: Fig. S24[†]), indeed indicating that small aggregates were present for the woA samples and also indicating that the wA samples indeed represent unimers that cannot be further dissociated. The values measured in DCM were slightly lower (4.2–6.5 nm), which can be attributed to a different swelling behavior of these macromolecules in an aqueous solution. Most interestingly, the guest encapsulation of the star-shaped block copolymers and a phase transfer phenomenon was observed and could be visualized in the following tests, also unambiguously confirming unimolecularity. First, amphiphilic star-shaped block copolymers

were added to the water insoluble dye Para Red, rendering it water-soluble due to encapsulation (Fig. 1 and S26[†]). Polymers with shorter hydrophobic cores and higher hydrophilic parts were better soluble in water and exhibited the best encapsulation behavior of the dye.

In a second test, the water soluble dye Orange II was added to a two-phase water/DCM system (Fig. 1 and S27[†]). After addition of the amphiphilic star-shaped block copolymers and shaking for a few seconds, most of the dye was transferred to the DCM phase. The color change from orange to yellow of Orange II is due to a change of the microenvironment of the dye and confirms that the polymers can encapsulate and phase transfer the investigated guest molecule. This results is a clear proof of the unimolecular behavior of the polymer, since a self-assembled micelle would dissociate in DCM, not being able to phase transfer the dye. Using these initial visual inspections, the best results for both tests were obtained for polymer P9, which shows the highest ratio of hydrophilic : hydrophobic parts (Fig. 1). Therefore, we investigated the phase transfer behavior (water/DCM) of P9 in more detail by a UV/VIS titration experiment (the polymer was titrated to the biphasic mixture of dye and the solvents, Fig. 2). The absorption of the dye in both phases was separately measured and the concentration of P9 was increased after each measurement by addition of further

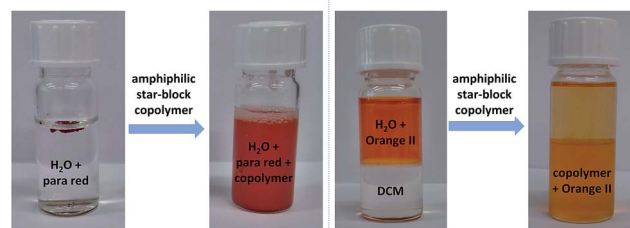


Fig. 1 Visualization of the encapsulation of water-insoluble Para Red in water by block copolymer P9 (left) and visualization of the encapsulation and phase transfer of Orange II from the water to the DCM phase by P9 (right).



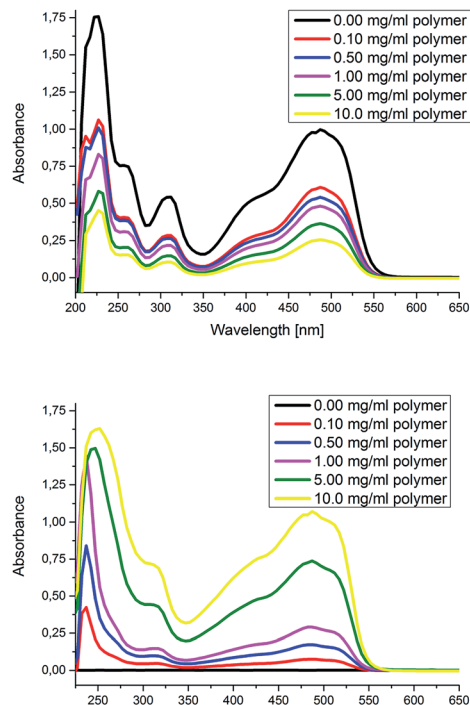


Fig. 2 UV/VIS spectra of the encapsulation and phase transfer of Orange II from the water phase to the DCM phase by block copolymer **P9** (above: absorbance of Orange II in water with increasing concentration of **P9**, below: absorbance of Orange II in DCM with increasing concentration of **P9**).

aliquots. While the absorption of the dye in water decreased with increasing concentration of polymer **P9**, the absorption in DCM increased. This behavior can be explained by an encapsulation and phase transfer of Orange II from the water to the organic phase by the amphiphilic star-shaped block copolymer **P9**. After recording a calibration curve for Orange II in water (Fig. S19[†]), the concentrations in water could be determined as well as the number of encapsulated dye molecules per polymer (Table 1). An average up to 2.5 dye molecules per polymer was able to be encapsulated when 0.10 mg mL⁻¹ of **P9** was added, starting with 0.0225 mg mL⁻¹ of dye in water. However, at this concentration, less than half of the introduced dye phase transfers to the DCM phase. A concentration of **P9** of 10 mg mL⁻¹ was required to encapsulate around 75% of the dye. Finally, the hydrodynamic diameter of polymer **P9** with and without guest molecule was compared *via* DLS (Fig. S25[†]). The slight increase of around 25% and the absence of larger aggregates also indicate that the guest molecules are encapsulated in the polymers.

In conclusion, new unimolecular core-shell architectures were successfully synthesized *via* Passerini-3CR. Controlling the polymerization conditions, amphiphilic three-arm star-shaped block copolymers with Passerini derived cores and different PEG shells were obtained. The unimolecular behavior, the encapsulation of water-soluble and water-insoluble guest molecules as well as the transport abilities from water to an organic phase were demonstrated by UV/VIS spectroscopy and DLS measurements. Thus, these star-shaped block copolymers

Table 1 Concentration of dye (Orange II) in water and DCM with increasing concentrations of block copolymer **P9** and the ratio of encapsulated dye per polymer in DCM measured *via* UV/VIS

Conc. polymer [mg mL ⁻¹]	Conc. dye in water [mg mL ⁻¹]	Conc. dye in DCM [mg mL ⁻¹]	Ratio polymer : dye in DCM
0.00	0.0225	0.00	—
0.10	0.0144	0.0081	1 : 2.50
0.50	0.0128	0.0097	1 : 0.75
1.00	0.0114	0.0111	1 : 0.38
5.00	0.0086	0.0139	1 : 0.10
10.00	0.0061	0.0164	1 : 0.06

are multifunctional materials with a potential for applications in drug delivery systems or as phase-transfer catalysts.

Conflicts of interest

There are no conflicts to declare.

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