# Synthesis of star-shaped poly(ε-caprolactone) *via* 'click' chemistry and 'supramolecular click' chemistry†

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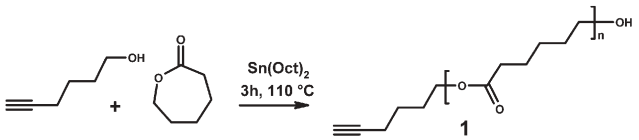
**The synthesis of star-shaped poly(ε-caprolactone) is described *via* azide–alkyne cycloaddition ('click' chemistry) and *via* self-assembly of polymeric ligands into [2 × 2] grid-like metal complexes ('supramolecular click' chemistry)**

Recently, the synthesis of various alkyne functionalized polymers has been described in the literature.[1] The renewed interest in these compounds is driven by their possible application in azide–alkyne cycloadditions (Huisgens reaction).[2] The copper(I) catalyzed azide–alkyne cycloaddition can be performed under mild conditions with excellent yields and selectivities and it is nowadays better known as 'click' chemistry.[3] 'Click chemistry' has been used, *e.g.*, to attach dendrons to polymer backbones,[1a] to prepare block copolymers,[1b] cyclic polymers,[4] end-functionalized polymers[5] as well as side-chain functionalized polymers.[6]

Besides this traditional 'click' chemistry, the concept of 'supramolecular click' chemistry was recently introduced to describe self-assembling supramolecular systems.[7] Like 'click' chemistry, 'supramolecular click' chemistry should also fulfil the stringent conditions as defined by Sharpless[3a] including the requirements that the reactions should be modular, wide in scope and give very high yields. In addition, the starting materials should be readily available. The advantage of 'supramolecular click' chemistry over 'click' chemistry is the reversible character of the supramolecular interactions used. In other words, the self-assembled polymer systems can be switched between the assembled or disassembled state by changing (external) environmental parameters, such as temperature, pH, redox state or concentration. In addition, multiple orthogonal interactions can be used on the same polymer backbone.[8] The supramolecular interactions that have been used for polymer self-assembly include ionic interactions,[9] hydrogen bonding[10] and metal coordination.[11] These supramolecular interactions were applied for the preparation of, *e.g.*, self-assembled block copolymers,[12] graft copolymers[13] and chain-extended polymers.[14]

Star-shaped polymers are of general interest for their lower hydrodynamic volume and the higher number of functional end-groups when compared to linear analogues. In this contribution, we report the synthesis of star-shaped poly(ε-caprolactone) (pεCL) via both 'click' chemistry as well as 'supramolecular click' chemistry using an acetylene functionalized pεCL precursor. This precursor was coupled to a heptakis-azido-β-cyclodextrin by azide–alkyne cycloaddition. Furthermore, the pεCL precursor was attached to a 3,6-di(pyridin-2-yl)pyridazine metal coordinating ligand and self-assembly into [2 × 2] grid-like metal complexes was investigated.




**Scheme 1** Schematic representation of the synthesis of the acetylene-functionalized poly(ε-caprolactone) **1**.

Most of the acetylene functionalized polymers known in literature were prepared using end-group functionalization methods[1a] or *via* the use of protected acetylenes.[1b,15] In contrast, we have investigated the ring-opening polymerization of ε-caprolactone utilizing the unprotected 5-hexyn-1-ol as initiator and tin(II) octanoate as catalyst (Scheme 1).[16]

At first, the polymerization was attempted at 130 °C resulting in polymer coupling as indicated by broad molecular weight distributions (polydispersity index, PDI, > 1.4) and GPC traces with shoulders at higher molecular weights. Lowering the polymerization temperature to 110 °C resulted in PDI values below 1.20, which indicates that the ring-opening polymerization of ε-caprolactone was controlled. The $^1$H-NMR spectrum of the synthesized acetylene terminated pεCL **1** revealed the presence of both the polymer backbone and the acetylene signals (Fig. 1, bottom). The integrals of the acetylene signal (e) and the terminal $CH_2OH$ resonances of the polymer (E′) were obtained

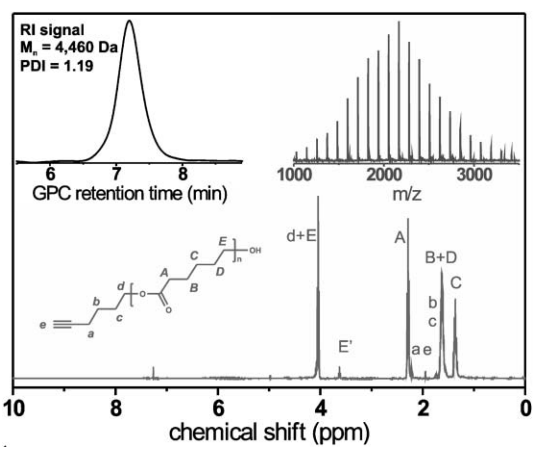



**Fig. 1** $^1$H-NMR spectrum (bottom, $CDCl_3$), GPC trace (top left, $CHCl_3$ : $NEt_3$ : $^i$PrOH = 94 : 4 : 2) and MALDI-TOF-MS spectrum (top right) of the acetylene-functionalized poly(ε-caprolactone) **1**.

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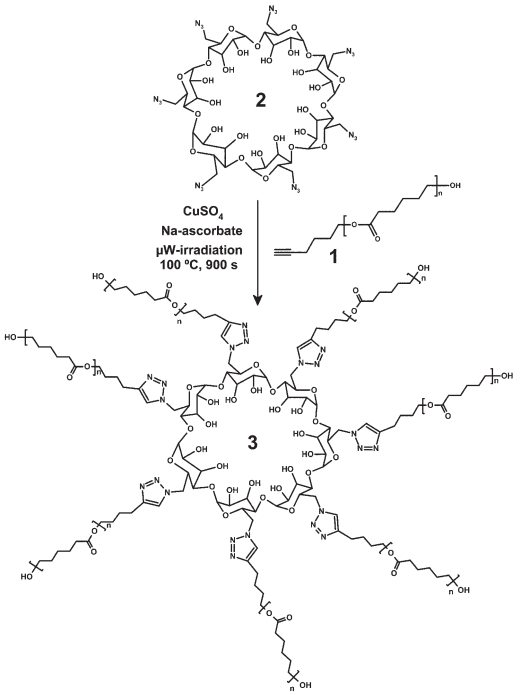



**Scheme 2** Schematic representation of the 'click' reaction of acetylene-functionalized poly(ε-caprolactone) **1** to heptakis-azido-β-cyclodextrin **2** resulting in heptakis-poly(ε-caprolactone)-β-cyclodextrin **3**.

in a 1 : 2 ratio demonstrating that each polymer has an acetylene group attached. Moreover, a monomer to initiator ([M]/[I]) ratio of 20 was calculated from the $^1$H-NMR spectrum which fits to the theoretical [M]/[I] ratio of 20. GPC characterization revealed a $M_n$ of 4460 Da (polystyrene calibration) and a PDI of 1.19 indicating that the polymer was synthesized in a controlled way (Fig. 1, top left).

This was further confirmed by MALDI-TOF-MS that revealed a narrow molecular weight distribution (PDI = 1.03) and a $M_n$ of 2200 Da (Fig. 1, top right). The observed spacing between the signals corresponds to the mass of one monomer unit (114 Da) and end-group analysis confirmed the acetylene end-group.

Subsequently, the acetylene functionalized pεCL **1** was coupled to heptakis-azido-β-cyclodextrin **2** resulting in the formation of the seven-armed star-shaped heptakis-pεCL-β-cyclodextrin **3** (Scheme 2). Up to this moment, the preparation of star-shaped polymers *via* 'click' chemistry has not been reported to the best of our knowledge. Nevertheless, the formation of cyclodextrin analogues[17] and the synthesis of water-soluble cyclodextrins[18] has been performed using a non-catalyzed 1,3-dipolar addition of butyne dicarboxylic acid to an acetylated heptakis-azido-β-cyclodextrin. The 'click' reaction reported here was performed under microwave irradiation at 100 °C as previously reported by Kappe and Van der Eycken.[19] To induce complete functionalization of the β-cyclodextrin, nine equivalents of the acetylene-functionalized pεCL were used in the reaction. After the reaction, the excess pεCL **1** was removed from the star-shaped pεCL **3** by preparative size exclusion chromatography. The GPC traces of the pεCL **1**, heptakis-azido-β-cyclodextrin **2** and heptakis-pεCL-β-cyclodextrin **3** (Fig. 2) clearly reveal the shift in molecular weight after the 'click' reaction demonstrating the successful formation of star-shaped

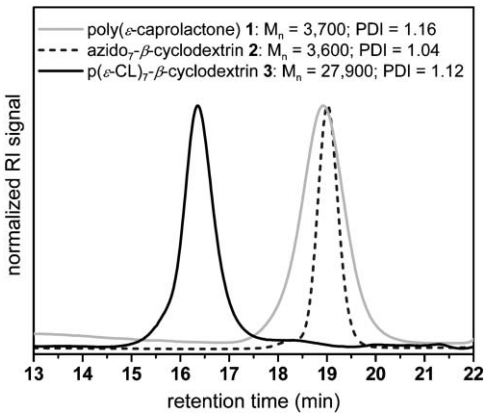
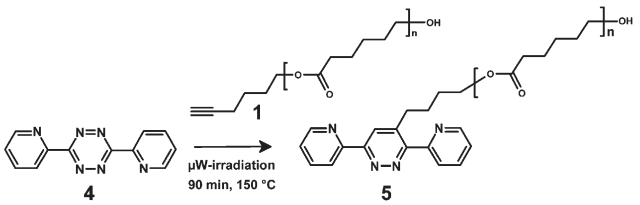



**Fig. 2** GPC traces of acetylene-functionalized poly(ε-caprolactone) **1**, heptakis-azido-β-cyclodextrin **2** and heptakis-poly(ε-caprolactone)-β-cyclodextrin **3** in *N*,*N*-dimethylacetamide with 5 mmol LiCl.

pεCL **3**. In addition, the $^1$H-NMR spectrum in DMSO-$d_6$ revealed the pεCL triazine as well as the β-cyclodextrin signals in the expected ratios corresponding to 150 monomer units per β-cyclodextrin.

For the 'supramolecular click' chemistry approach, the pεCL had to be end-functionalized with a self-assembling supramolecular unit. Therefore, we have chosen to couple it to 3,6-di(pyridin-2-yl)pyridazine (DPP), which self-assembles into [2 × 2] metal complexes with copper(I) ions.[20] Recently, we have demonstrated that poly(L-lactide) functionalized DPPs also self-assembly into polymeric [2 × 2] copper(I) grids.[21] The direct synthesis of poly(ε-caprolactone) functionalized DPP **5** was performed *via* the inverse-electron-demand Diels–Alder reaction between 3,6-di(pyridin-2-yl)-1,2,4,5-tetrazine **4** and the acetylene terminate pεCL as depicted in Scheme 3. This cycloaddition was performed at 150 °C under microwave irradiation in dichloromethane as was previously found to result in faster inverse-electron demand Diels–Alder reactions.[22]

The crude reaction mixture was purified by column chromatography to remove unreacted pεCL **1** and preparative size exclusion chromatography to remove the excess of tetrazine **4**. $^1$H-NMR spectroscopy of the purified pεCL DPP **5** revealed complete functionalization as indicated by the disappearance of the acetylene signal at 1.95 ppm and appearance of the DPP resonances (Fig. 3, bottom). Moreover the integrals revealed a ratio of 1 : 1 for the $CH_2OH$ (E′) resonance of the polymer and the $CCH_2$ (a) signal of the DPP and a [M]/[I] ratio of 20 (Mn = 2,590 Da) proving the successful formation of the DPP pεCL **5**. GPC analysis showed a signal with both UV-vis (290 nm; Fig. 3, top left) and RI detectors proving that the ligand is coupled to the




**Scheme 3** Schematic representation of the synthesis of the DPP-functionalized poly(ε-caprolactone) **5**.

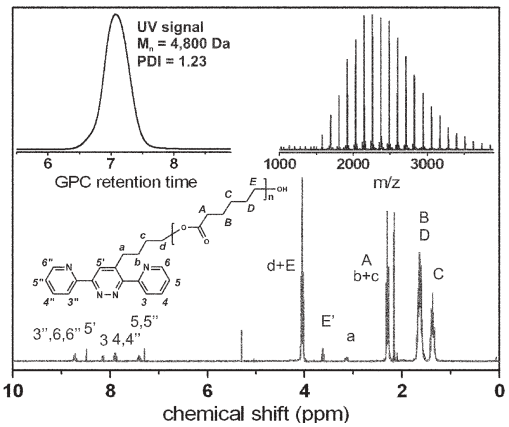



**Fig. 3** $^1$H-NMR spectrum (bottom, $CDCl_3$), GPC trace (top left, $CHCl_3$ : $NEt_3$ : $^i$PrOH = 94 : 4 : 2) and MALDI-TOF-MS spectrum (top right) of the DPP-functionalized poly(ε-caprolactone) **5**.

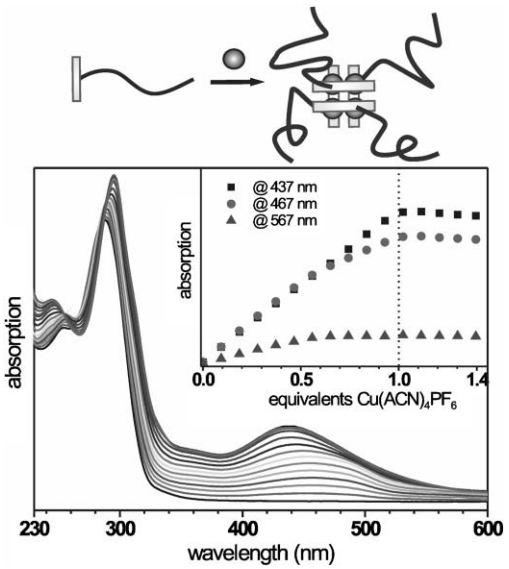



**Fig. 4** Top: schematic representation of the 'supramolecular click' reaction. Bottom: UV-vis spectra obtained during the titration of copper(I) ions to a solution of pεCL DPP **5**. The inset shows the increase of absorption at 437, 467 and 567 nm with the addition of copper(I) ions.

polymer that does not absorb at 290 nm. End-group analysis of the MALDI-TOF-MS spectrum also demonstrated the success of the coupling reaction (Fig. 3, top right). A shift of 208 Da was observed after reaction of pεCL **1** with tetrazine **4**, which fits to the formation of the DPP pεCL **5**.

The 'supramolecular click' reaction of pεCL **5** with copper(I) ions into star-shaped polymeric [2 × 2] grid-like metal complexes (Fig. 4) was investigated by UV-vis spectroscopy. A solution of copper(I) ions was added step-wise to a solution of the DPP pεCL **5** to follow the 'supramolecular clicking'. The spectra resulting from this titration are depicted in Fig. 4 demonstrating the appearance of a metal to ligand charge transfer (MLCT) band at 457 nm. This MLCT shifted to 437 nm after the addition of 0.5 equivalents of copper(I) ions due to a transition from complexes with two ligands and one copper(I) ion into complete polymeric [2 × 2] grid-like complexes.[21b] The increase in absorption at 437, 467 and 567 nm (inset Fig. 4) reached a maximum at 1 equivalent of copper(I) ions corresponding to complete [2 × 2] grid-like complexes. Moreover, the resulting UV-vis spectrum closely resembles the spectra obtained for other [2 × 2] grid-like copper(I) complexes,[20,21] which proves that star-shaped [2 × 2] grid-like complexes are indeed formed from the DPP pεCL **5**. Upon overtitration of copper(I) ions to pεCL DPP **3**, the absorption remained constant indicating that the formed [2 × 2] grids are stable and do not regularly exchange copper(I) ions.

In conclusion, we have demonstrated that both 'click' chemistry and 'supramolecular click' chemistry are versatile approaches for the preparation of well-defined star-shaped pεCL. In addition, the synthesis and self-assembly of pεCL DPP **3** complies with all requirements for 'click' chemistry.

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