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Redox-Responsive, Core Cross-Linked Polyester Micelles

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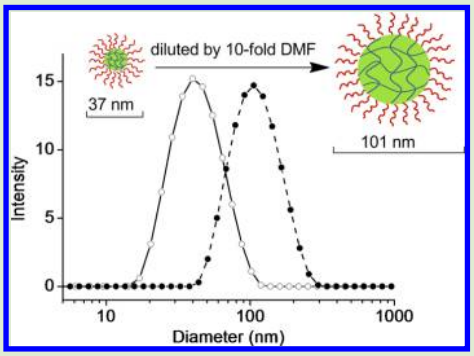
Supporting Information

ABSTRACT: Monomethoxy poly(ethylene glycol)-*b*-poly(Tyr(alkynyl)-OCA), a biodegradable amphiphilic block copolymer, was synthesized by means of ring-opening polymerization of 5-(4-(prop-2-yn-1-yloxy)benzyl)-1,3-dioxolane-2,4-dione (Tyr(alkynyl)-OCA) and used to prepare core cross-linked polyester micelles via click chemistry. Core cross-linking not only improved the structural stability of the micelles, but also allowed controlled release of cargo molecules in response to the reducing reagent. This new class of core cross-linked micelles can potentially be used in controlled release and drug delivery applications.



Polymeric micelles have been extensively used for drug delivery because they can enhance drug solubility, prolong in vivo circulation time, and target specific tissues.[1] Conventional polymeric micelles, which are in thermodynamic equilibrium with their constituent unimers in aqueous solution, dissemble at concentrations below their critical micelle concentrations (CMCs). Undesired micelle disintegrations lead to premature release of the encapsulated cargos before imparting specific functions. When micelles are used in drug delivery and administered systemically, micelle disintegration as a result of significant dilution in blood before reaching the target tissues may result in reduced therapeutic efficacy and undesired side effects.[2]

One effective approach to solve this problem is to stabilize micellar structures by cross-linking.[3] Micelle shell cross-linking approaches have been attempted and the resulting micelles were more stable than uncross-linked (UCL) micelles upon dilution.[2b,3b,3c,4] However, cross-linking of hydrophilic shells may affect the surface mobility, and a highly diluted solution is often required to avoid undesired intermicellar cross-linking.[5] Shell cross-linking can also alter the stealthiness of the micelles.[6] To avoid these problems, core cross-linked (CCL) micelles have been developed as an effective alternative. Most of the existing CCL micelles are based on nondegradable polymeric cores such as polyacrylate or polyacrylamide.[7] Considering the requirement for biocompatibility and biodegradability in clinical applications, CCL micelles composed entirely of polyesters would be ideal candidates as drug delivery vehicles. The choice of the cross-linkers is also important because they directly affect the stability and properties of the resulting CCL micelles. Cross-linkers that respond to external triggers such as redox agents or changes in pH would allow control over the design and disassembly of CCL micelles and the release of encapsulated drugs.

Biocompatible and biodegradable aliphatic polyesters, such as poly(lactic acid), poly(glycolic acid), poly(ε-caprolactone), and poly(lactic-*co*-glycolic acid), have been widely used as hydrophobic cores of copolymer micelles for the encapsulation and delivery of lipophilic drugs.[8] However, these polyesters lack side chain functionality, which prevents core cross-linking of their micelles. It is thus synthetically challenging to modify these conventional polyesters to allow formation of micelles with cross-linkable cores. Effort has been devoted to the synthesis of side chain functionalized polyesters via ring-opening polymerization (ROP).[9] *O*-carboxyanhydrides (OCAs) derived from amino acids is a particularly interesting class of monomers subject to ROP for the synthesis of functional polyesters; significant progress has been made through the work of Bourissou, Dove, and others.[9,10] In this paper, we report the synthesis of 5-[4-(prop-2-yn-1-yloxy)benzyl]-1,3-dioxolane-2,4-dione Tyr(alkynyl)-OCA, **1** (Scheme 1), and monomethoxy poly(ethylene glycol) (mPEG)-initiated ROP of **1** to prepare poly(**1**), a side chain functionalized polyester with pendant alkynyl groups. Poly(**1**) was then used to prepare CCL micelles by cross-linking the polyester alkynyl side chains in the hydrophobic cores via Cu(I)-catalyzed azide−alkyne cyclo-

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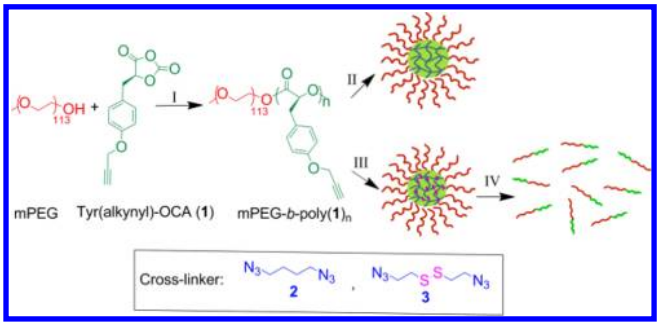
Scheme 1. Preparation of CCL Micelles[a]



[a]Reagents and conditions: (I) 4-dimethylaminopyridine, dichloromethane; (II) cross-linker 2, $CuCl_2$, ascorbic acid sodium salt; (III) cross-linker 3, $CuCl_2$, ascorbic acid sodium salt; (IV) D,L-dithiothreitol (10 mM), under CMC.

additions (CuAAC, so-called "click chemistry"). The reaction is highly chemoselective and can proceed readily under mild conditions without producing byproducts.[11] By utilizing bis(azidoethyl) disulfide, a redox-responsive cross-linker, we developed CCL micelles with responsiveness toward reducing reagents, thus, allowing trigger-induced micelle disruption and controlled release of the encapsulated cargo molecules.

Monomer **1**, a colorless crystalline solid, was synthesized from Boc-L-tyrosine (Boc-L-Tyr-OH) on a multigram scale in ~30% yield (Scheme S1). mPEG-*b*-poly(**1**) was synthesized by ROP of **1** with mPEG (MW = 5000 g/mol) as the macroinitiator and 4-dimethylaminopyridine (DMAP) as the catalyst. The monomer conversion exceeded 95%, evidenced by the complete disappearance of the anhydride FTIR band of **1** (1810 cm^{-1}) in the polymerization solution (Figure S1). Gel permeation chromatography (GPC) analysis revealed that the M_n values of the resulting mPEG-*b*-poly(**1**) copolymers at different monomer to initiator (M/I) ratios agreed well with the expected MWs and that all the copolymers showed narrow molecular weight distributions (MWDs = M_w/M_n, <1.12; Table 1 and Figure S2). These results demonstrated that DMAP-catalyzed ROP of **1** was effective for the synthesis of amphiphilic copolymers to be used for the study of CCL micelles.

Table 1. ROP of Tyr(alkynyl)-OCA (1) by $mPEG_{5k}$[a]

entry	[M]/[I]	$M_{n,cal}$ ($\times 10^{-3}$ g/mol)[b]	$M_{n,GPC}$ ($\times 10^{-3}$ g/mol)[c]	M_w/M_n[c]
1	20	9.0	8.5	1.12
2	30	11.1	12.0	1.06
3	50	15.1	16.1	1.02

[a]All reactions were performed in a glovebox at room temperature with $mPEG_{5k}$ (MW = 5000 g/mol) as the macroinitiator and DMAP as the catalyst ($[mPEG_{5k}]/[DMAP]$ = 1/1) in dichloromethane. Monomer conversion was monitored by FTIR analysis of the OCA anhydride peak (1810 cm^{-1}) until it exceeded 95%. [b]Calculated from the M/I with 100% monomer conversion. [c]Determined by GPC.

Amphiphilic mPEG-*b*-poly(**1**) was first used to prepare UCL micelles consisting of a hydrophobic poly(**1**) core and a hydrophilic mPEG shell. The CMC of mPEG-*b*-poly(**1**), an effective indicator of micellar stability, was determined with Nile Red (NR) as a fluorescence probe.[12] All the micelles had low CMC values (Table 2, Figures S3 and S4), and the CMC values decreased with increasing poly(**1**) block length, indicating that longer poly(**1**) blocks facilitated the formation of micelles owing to increased hydrophobic interactions in the core. Upon identifying the CMCs of mPEG-*b*-poly(**1**), we next prepared the micelles using the nanoprecipitation method and measured the mean hydrodynamic diameters by dynamic light scattering (DLS, Table 2). The particle diameter increased proportionally to the length of the hydrophobic block (poly(**1**)), indicating a longer poly(**1**) block led to the formation of a larger core with enhanced micelle assembly stability.[13] The morphology of the UCL and CCL micelles was further analyzed by transmission electron microscopy (TEM). As shown in Figure S5, both UCL and CCL micelles were well dispersed and adopted spherical shapes; the diameters accorded well with those obtained from the DLS measurement.

We then prepared CCL micelles by introducing 1,4-diazidobutane (**2**, Schemes 1 and S2), a hydrophobic cross-linker, into the hydrophobic core of the micelles followed by **2**-mediated cross-linking of the poly(**1**) blocks by means of click chemistry. We designed a ^1H NMR experiment to test whether cross-linking could occur in the micelle core to form CCL micelles. mPEG-*b*-poly(**1**) and **2** were dissolved in DMF and then water was added to the DMF solution to allow micelles to form. During this process, the hydrophobic cross-linker **2** should migrate into the hydrophobic micelle core which remained swollen in the presence of DMF. $CuCl_2$ and ascorbic acid sodium salt were subsequently added to initiate the click reaction. After removing the copper and DMF by dialysis against deionized water and then removing the water by lyophilization, we dissolved the obtained materials in DMSO-d_6, a solvent that can dissolve both the mPEG and the poly(**1**) block. The ^1H NMR spectrum showed only the hydrophilic proton peaks of mPEG and but not the poly(**1**) block, substantiating formation of CCL micelles and well maintained micelle structure in DMSO (Figure 1b). To validate this conclusion, we prepared and processed micelles using exactly the same materials and conditions without adding $CuCl_2$ and ascorbic acid sodium salt. No click-chemistry induced core cross-linking should happen and the resulting micelles (i.e., the excepted UCL micelles) should not be stable in DMSO-d_6. As expected, the ^1H NMR spectrum of the latter materials was identical to that of mPEG-*b*-poly(**1**) in DMSO-d_6 in which both mPEG and poly(**1**) proton peaks were clearly visible (Figure 1a).

To further demonstrate the cross-linking of the hydrophobic core, we evaluated the change in the diameters of both UCL and CCL micelles upon addition of DMF, a solvent to both mPEG and poly(**1**). The diameters and polydispersity indexes (PDIs) of the CCL and UCL micelles in water were first determined by DLS and found to be nearly identical (Table 2). Upon dilution with 10-fold DMF, the mPEG-*b*-poly$(\mathbf{1})_{20}$ UCL micelles (mPEG-*b*-poly$(\mathbf{1})_{20}$) were completely disrupted, evidenced by the disappearance of the solution DLS signal (Figure 2a). In contrast, the mPEG-*b*-poly$(\mathbf{1})_{20}$ CCL micelles well maintained their structure upon dilution with 10-fold DMF, and the particle diameter increased dramatically to 101 nm from 37 nm of the untreated CCL micelles (Figure 2b), owing to swelling of the core. These results confirmed that cross-linking of the mPEG-*b*-poly(**1**) core allowed the resulting micelles to withstand dissolution in DMF.

In some cases, excessively stabilized cross-linked micelles cannot effectively release their payloads at the target site, thus, compromising the therapeutic efficacy.[14] To make the cross-linking reversible, we used bis(azidoethyl) disulfide (**3**, Scheme

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Table 2. Properties of UCL and CCL Micelles in Water

	UCL micelle			CCL micelles			
sample	diameter (nm)	PDI	CMC ($\times 10^{-3}$ mg/mL)	diameter[a] (nm)	PDI[a]	diameter[b] (nm)	PDI[b]
mPEG$_{5k}$-*b*-poly(**1**)$_{20}$	35	0.17	15.9	37	0.22	39	0.20
mPEG$_{5k}$-*b*-poly(**1**)$_{30}$	41	0.29	10.3	43	0.24	44	0.26
mPEG$_{5k}$-*b*-poly(**1**)$_{50}$	47	0.28	4.8	49	0.30	52	0.27

[a]CCL micelles were prepared with **2** as the cross-linker. [b]CCL micelles were prepared with **3** as the cross-linker. The molar ratio of cross-linker to alkynyl group was kept constant at 0.6.

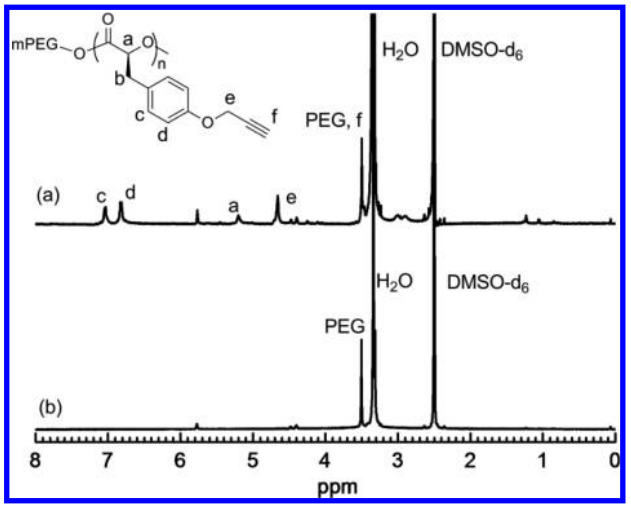

Figure 1. ^{1}H NMR spectra of (a) UCL mPEG-*b*-poly(**1**) and (b) mPEG-*b*-poly(**1**) cross-linked with **2** in DMSO-d_6.

S3), a disulfide-containing cross-linker and an analogue of **2**, to prepare CCL micelles so that they would release cargo molecules in response to external triggers,[15] such as reducing reagent. The resulting CCL micelles using **3** as the cross-linker were similarly prepared as previously described for the CCL micelles prepared with cross-linker **2**. Both CCL micelles had similar particle diameters and stabilities.

To explore the redox-responsive cargo-release profiles, we encapsulated NR as a model hydrophobic drug into the disulfide cross-linked micelles (mPEG-*b*-poly(**1**)$_{20}$, CCL1) and monitored NR release at a concentration (6.0×10^{-3} mg/mL) below the CMC (15.9×10^{-3} mg/mL, Figure S4). In the absence of the reducing agent D,L-dithiothreitol (DTT), the fluorescence intensity of NR remained unchanged (Figure 3), suggesting that the stable micelles tightly restricted NR in their hydrophobic cores. However, in the presence of 10 mM DTT, the fluorescence intensity of NR decreased by 90% within 4 h (Figure 3), indicating that the micelle structure had been disrupted by cleavage of the disulfide cross-linker. These results implied that the disulfide cross-linked micelles could encapsulate hydrophobic cargo molecules at concentrations below the CMC and selectively release the cargo in response to changes in the redox environment.

To fine-tune the release profile of the CCL micelles, we synthesized CCL micelles containing various ratios of cross-linkers **2** and **3**. Specifically, we prepared CCL2, CCL3, CCL4, and CCL5, which had the cross-linker **2**/**3** molar ratios of 2:8, 5:5, 8:2 and 10:0, respectively. NR release from the micelles was decreased as the content of **3** decreased (Figure 3), evidenced by the observation that the NR fluorescence intensities of CCL2, CCL3, and CCL4 decreased by 60%, 15%, and 10%, respectively, within 3 h of treatment with 10

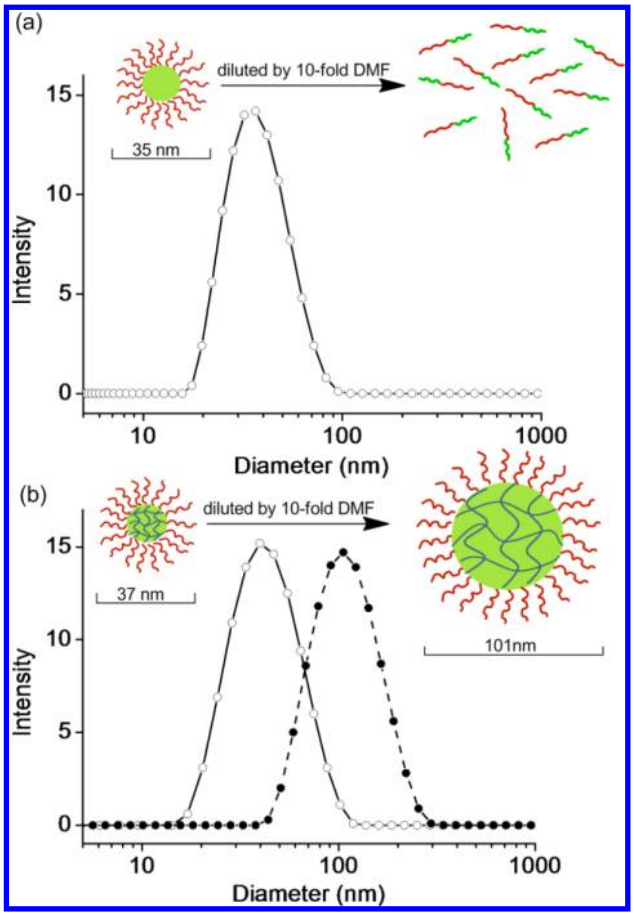

Figure 2. Distributions of hydrodynamic diameters of (a) UCL and (b) CCL micelles in water (○) before and (●) after 10-fold dilution with DMF.

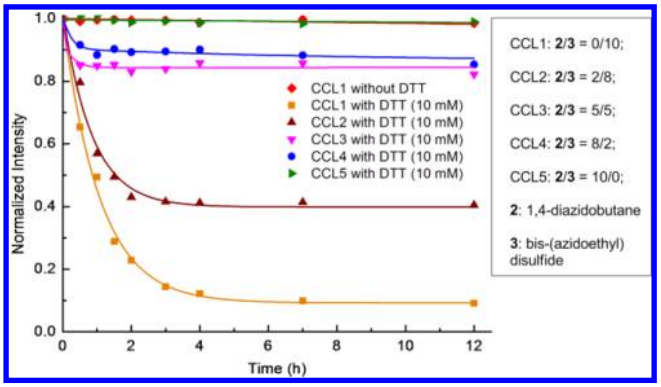

Figure 3. Release of NR from CCL micelles with various proportions of cross-linkers **2** and **3** in the presence or absence of DTT at micelle concentrations below the CMC.

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mM DTT. No NR was released from the CCL5 micelles. These results suggested that micelles containing inadequate amounts of redox-responsive cross-linker **3** were not completely disrupted, and the results again substantiated the importance of **3** in triggering redox-responsive cargo release. This study also suggested that adjusting the cross-linker **2**/**3** feed ratio is a promising approach of modulating drug release profiles to meet specific therapeutic requirements.

In summary, we developed CCL micelles through ROP of *O*-carboxyanhydrides bearing alkyne groups followed by core cross-linking with the use of click chemistry. The CCL micelles not only were structurally stable but also allowed the controlled release of cargo molecules when a redox-responsive cross-linker was introduced. This new class of CCL micelles therefore has potential as a delivery system for the controlled release of pharmaceutical agents.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details including GPC analysis and FTIR and CMC studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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