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An Easy Way to Sugar-Containing Polymer Vesicles or Glycosomes

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Amphiphilic block polymers made of synthetic and biological units, referred to as hybrid polymers or "molecular chimeras",[1] are raising considerable attention, which is due to their fundamental importance and potential applicability in materials science and biomedicine. A lot of studies have been devoted to peptide hybrid polymers,[2] by far less developed are sugar-containing polymers or synthetic glycopolymers. Numerous contributions exist in the literature on synthesis of glycopolymer architectures,[3] but only very few deal with aggregation behavior and colloidal properties.[4−8]

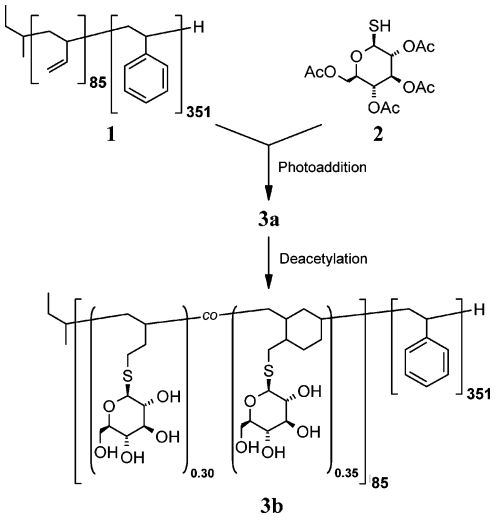
Well-defined amylose-based block copolymers were produced by phosphorylase-catalyzed enzymatic polymerization[9−11] and/or by coupling techniques,[12−15] and oligosaccharide-terminated polymers by atom transfer radical polymerization (ATRP).[16] Polymers with pendent monosaccharide moieties were synthesized through controlled ionic, radical, and metathesis polymerization of functional monomers[3] or by chemical modification.[17] The latter strategy is especially interesting for the generation of a library or toolbox of functional polymers. The chemical modification reaction described by Haddleton et al.[17] is based on "click chemistry" and involves the Cu(I)-catalyzed Huisgen 1,3-dipolar cycloaddition of an azidosugar derivative onto an alkyne side chain polymer made by ATRP. Conversion of the alkyne groups into triazoles was achieved at close to 100% yield.

Here, we report on another easy and efficient route to amphiphilic glycopolymers, which unlike ATRP and "click chemistry" manages without transition metal ions: free-radical addition of a 1-thioglucose derivative onto a 1,2-polybutadiene-based block copolymer (Scheme 1).[18,19]

The starting point is a 1,2-polybutadiene$_{85}$-*block*-polystyrene$_{351}$ (**1**, the subscripts denoting the average number of repeating units), prepared by sequential anionic polymerization of 1,3-butadiene and styrene with Li^+ as the counterion in tetrahydrofuran (THF). The polydispersity index (i.e., the ratio of weight- over number-average molecular weight) of the sample is 1.15.[19] A degassed mixture of **1**, 2,3,4,6-tetra-*O*-acetyl-*β*-D-1-thioglucopyranose (**2**), and azoisobutyronitrile (AIBN) (molar ratio: [C═C]/[SH]/[AIBN] = 1:6:0.33) in dry THF was stirred for 5 h under irradiation with a mercury lamp.[20] The resulting polymer **3a** was isolated by precipitation into methanol and filtration; gravimetric yield was nearly quantitative.

In the ^{1}H NMR spectrum of **3a** (Figure 1a), the signals of the sugar moieties show at δ = 2.0 (acetyl) and 3.5−5.3 ppm (CH and CH_2) and that of the thioether linkage at 2.6 ppm (SCH_2). Proton resonances of the polymer backbone and of aromatic rings appear at δ = 0.8−2.2 and 6.3−7.3 ppm, respectively. Although double bonds seem to be absent, as suggested by the lack of characteristic signals at δ = 4.9 and 5.4 ppm (cf. spectrum of **1** in Figure 1a), **3a** contains just 55 glucose units (as calculated from the sulfur content determined by elemental analysis). A less than quantitative degree of functionalization (65%) at full conversion of double bonds indicates the presence of cyclic units, which are distributed randomly along the polybutadiene backbone.[19] As shown by size exclusion chromatography (SEC), the molecular weight distribution of **3a** is as narrow as that of **1** (Figure 1a).

Scheme 1. Synthesis of a Glycopolymer through the Radical Addition Pathway (Ac = acetyl)



The acetyl protecting groups in **3a** were removed by alkaline hydrolysis:[20] A solution of **3a** in a mixture of chloroform and 0.5 M sodium methoxide in methanol 9:1 (v/v) was stirred for 1 h at room temperature. After neutralization with Amberlite 200C ion-exchange resin, filtration, and evaporation of solvent, the product **3b** was suspended in water and freeze-dried (isolated yield: ∼94%). The success of the deacetylation reaction was proven by FT-IR spectroscopy, the spectrum of **3b** showing the characteristic broad (O−H) absorption at $\tilde{\nu} \approx 3340$ cm^{-1} of hydrogen-bridged hydroxyl moieties and lacking the signals at 1747 (ν(C═O)) and 1218 cm^{-1} (ν(C−O)) of acetyl groups (Figure 1b). The chemical structure of **3b** is depicted in Scheme 1.

For a first investigation of the aggregation behavior of **3b** in dilute solution, the polymer was directly dissolved in THF. The solution appeared slightly turbid at a polymer concentration of 0.02 wt %. As indicated by dynamic light scattering (DLS), the solution contained very large aggregates with an apparent hydrodynamic radius of $R_h \approx 250$ nm (Figure 2a). Analysis of a dried sample by transmission electron microscopy (TEM) revealed that these aggregates were vesicles ("glycosomes");[21−23] the polymer membrane measures about 15 nm across (see Supporting Information). Actually, one would have expected formation of small spherical micelles because the weight fraction of the nonsoluble glucose units is just 0.17.[24] The appearance of a structure with lower interfacial curvature might be explained by an increased bending energy of the glucose core owing to hydrogen bonding interactions (FT-IR).[25]

Addition of water (up to 4 wt %) led to the destruction of the large aggregates, as monitored by DLS (see Figure 2a), and clearing

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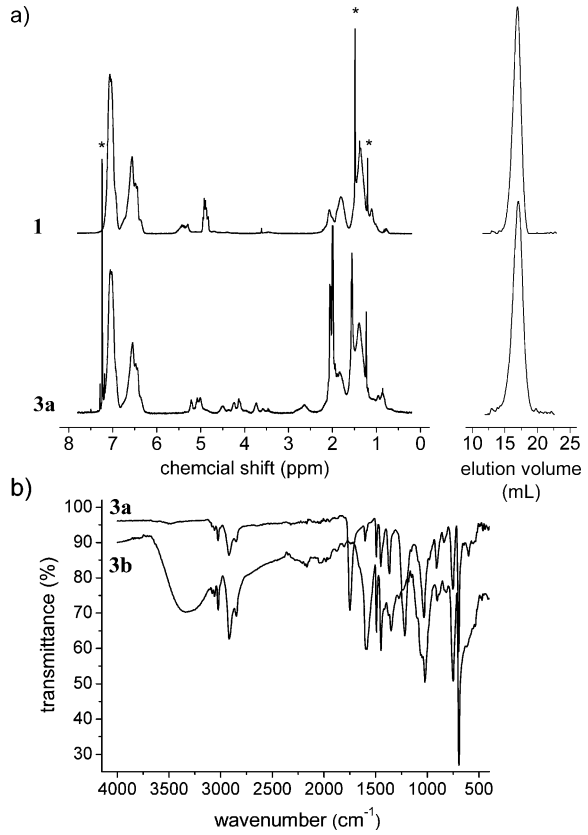

Figure 1. (a) ^{1}H NMR spectra (400.1 MHz, $CDCl_3$, ∗ solvent) (left) and SEC traces (eluent, $CHCl_3$; detector, RI) (right) of precursor polymer **1** and the acetylated glucose-grafted polymer **3a**; (b) FT-IR spectra of solid samples of polymers **3a** and **3b**.

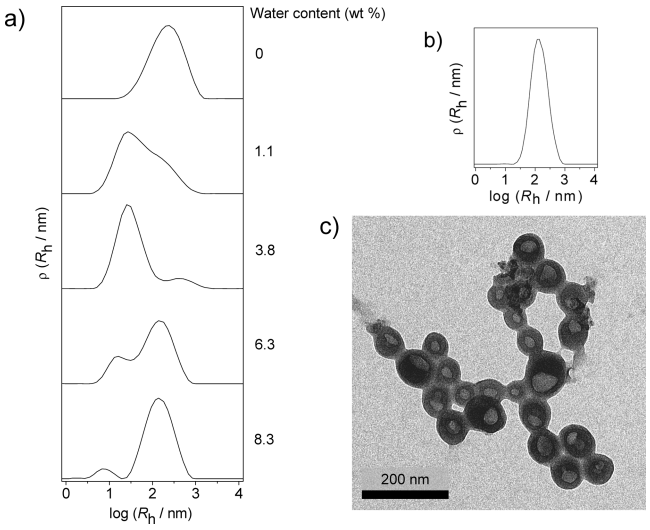

Figure 2. Intensity-weighted size distributions of aggregates (DLS) formed by glycopolymer **3b** in (a) different THF/water mixtures at ∼0.02 wt % and in (b) pure water at 0.003 wt %; (c) TEM image of collapsed vesicles, prepared from a 0.003 wt % solution of **3b** in water.

of the solution. A new species was formed instead, the size of which ($R_h \approx 15-30$ nm) is characteristic for a small micelle or a nonaggregated polymer coil. Upon further increasing the water content to 6 wt % and above, another aggregated species with $R_h \approx 120$ nm appeared, and the solution turned slightly turbid again. These aggregates remained stable in pure aqueous solution after the complete evaporation of THF (Figure 2b). TEM confirmed the presence of vesicles with a ∼20 nm thick polymer membrane (Figure 2c). Vesicles with a stabilizing glucose corona in water are expected for a copolymer with the chemical composition of **3b**. The internal structure of the membrane is not known yet—we hypothesize that polymer chains assembled into an interdigitated structure rather than into a bilayer (see Supporting Information).[23]

In summary, we described a simple and effective free-radical addition route toward well-defined amphiphilic glycopolymers. This reaction, which is done under mild conditions (photoinduced generation of radicals at room temperature) in the absence of toxic transition metal ions, can be applied directly to commercial thiosugar derivatives and polybutadiene-based block copolymers.

The glucose-grafted polybutadiene-*block*-polystyrene prepared (17 wt % glucose) was found to self-assemble into vesicles in both organic and aqueous media. Glucose units are building the membrane and polystyrene the corona of vesicles ("glycosomes") in THF, whereas in water, vesicles with the inverse structure are formed. This material is interesting as a model system for bioinspired structure formation and as a drug carrier.

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Supporting Information Available: Details of experiments and analytical instrumentation as well as additional TEM images and schematic illustration of the vesicle structure. This material is available free of charge via the Internet at http://pubs.acs.org.

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