Synthesis of ATRP-induced dextran-*b*-polystyrene diblock copolymers and preliminary investigation of their self-assembly in water†

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Dextran-*b*-polystyrene diblock copolymers forming miscellaneous spherical self-assemblies in water were obtained by chemical modification of the anomeric extremity of a commercial dextran followed by atom transfer radical polymerisation of styrene.

Naturally occurring polysaccharides such as cellulose, dextran, *etc…* are an abundant source of raw materials that attract an increasing interest due to their biodegradability and renewable character.[1] A convenient and classical means to tailor the physicochemical properties of these natural macromolecules is to modify their backbone by graft copolymerisation. A number of applications have been developed following this approach, through "grafting-from" and "grafting-onto" methods.[2] For instance, atom transfer radical polymerisation (ATRP)[2,3] and ring-opening polymerisation (ROP) of caprolactone[2,4] have been successfully applied to grow grafts from the initiating sites carried by the polysaccharide scaffold. In applications targeting specifically the biorecognition properties of polysaccharides, the biofunctional moiety has to be accessible and precisely placed within the (co)polymer architecture to exhibit bioactivity. For instance, copolymers containing statistically distributed sulfated maltoheptose grafts were obtained by copolymerization of the corresponding macromonomer with methyl methacrylate and found to exhibit anti-HIV activity.[5] Another attractive route that allows one to control the location of the biofunctional entity is to associate the latter with another polymer in a block copolymer architecture. Block copolymers offer, indeed, the unique advantage to self-assemble in nanostructures of well defined morphologies and provide numerous examples of so-called smart materials.[6]

Attempts at synthesizing polysaccharide-based block copolymers are recent and scarce; essentially two routes have been contemplated so far. The first rests on the end-to-end coupling of amino-terminated polymers onto the terminal aldehyde of the polysaccharide block *via* reductive amination.[7,8] Due to the incompatibility between blocks, coupling is often not complete and requires a tedious purification step. The second route relies on the end modification of the synthetic polymer with a small saccharide residue from which the polysaccharide block is grown by enzymatic polymerization.[9,10] Such a synthetic procedure also requires several steps, including tedious purification by dialysis. Surprisingly, a third way which would consist in modifying polysaccharides at their reducing ends to subsequently grow synthetic blocks has not been explored yet. One can mention, however, two examples of a cyclodextrin-based macroinitiators that served to grow a polystyrene (PS) block by controlled radical polymerisation.[11,12] In the current report, we describe the first dextran-based ATRP macroinitiator for the synthesis of dextran-*b*-PS diblock copolymers (Scheme 1) and the preliminary results on the self-assembly of such diblocks in water. The first step in our synthetic endeavor was to introduce an appropriate ATRP[13] site at the anomeric extremity of a commercial dextran of M_n = 6600 g mol^{-1}. Dextran is a highly water-soluble polysaccharide composed of α-D-glucopyranosyl units mainly linked by (1 → 6) bonds and exhibiting a low degree of branching. To generate nanoparticles or gels from dextran for water-bound applications, a hydrophobic chemical modification of the latter polymer is required, most of the chemical modifications carried out involving their primary hydroxyls.[14] The random character of such alterations eventually led to the formation of rather large particles in water, in the range of 100 nm and above.

Here we take advantage of the presence of the terminal anomeric aldehyde to subject a commercial dextran to reductive amination, using a specifically designed coupling agent fitted with ω-amino and α-tertiary bromide groups. This coupling agent was obtained in a three-step sequence from ethylene diamine (**1**): one amino-group was protected in the form of (*tert*-butyloxy)carbonate (BOC) using di-*tert*-butyl dicarbonate (BOC_2O) whereas acylation of the other amine was achieved using 2-bromoisobutyrylbromide in the presence of Et_3N. Finally, the release of BOC under acidic conditions afforded the targeted coupling reagent (**4**) in its protonated form, as confirmed by ^1H and spectroscopy (ESI†).

The coupling reaction on dextran was carried out in a DMSO/water mixture in the presence of triethylamine and sodium cyanoborohydride as reducing catalyst. As evidenced by ^1H NMR, the end-functionalisation of dextran occurred quantitatively after 48 h of reaction at RT and additional 48 h at 60 °C (ESI†).

Before growing the PS block by ATRP from the bromoisobutyramide-ended dextran (**5**), the OH groups of the latter were silylated following an already published procedure[4] to make it soluble in regular organic solvents.

Next, styrene was polymerized from the corresponding silylated dextran-based ATRP macroinitiator (**6**). ATRP experiments were carried out in toluene using CuBr/PMDETA as catalyst (ESI†).

Aliquots were sampled out at various times (t = 20 to 90 min) depending upon the DP_n targeted for the PS block. Five diblock copolymers (**7**) whose DP_n of the PS block ranged from 5 to 775 were synthesized from the same dextran-based precursor.

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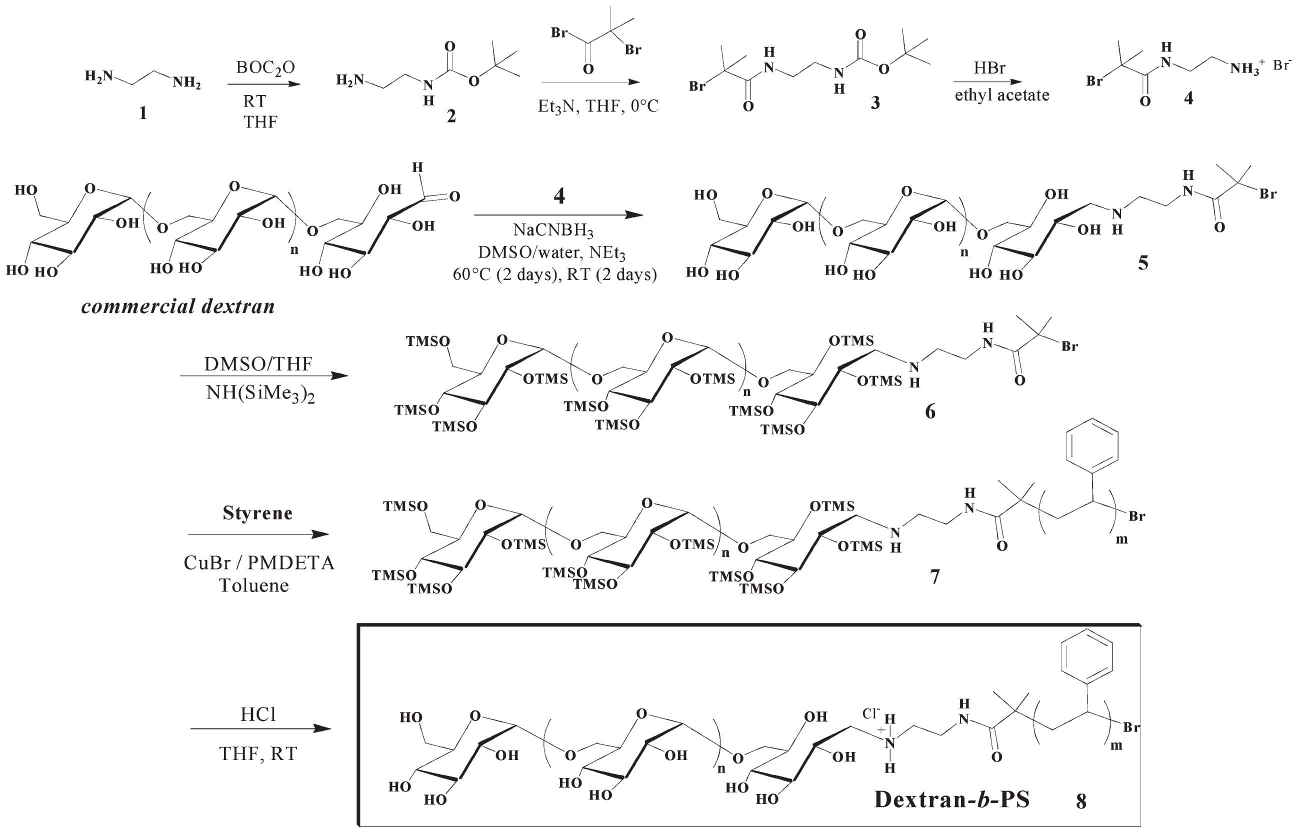

Scheme 1 Synthetic strategy to dextran-*b*-PS block copolymer by ATRP.

Both the silylated macroinitiator and the five silylated-dextran-*b*-PS diblocks were characterized by SEC using THF as eluent. As shown in Fig. 1, all SEC traces are symmetrical with no residual macroinitiator, indicating that initiation of styrene by ATRP occurred efficiently (ESI†).

Finally, these (silylated dextran)-*b*-PS block copolymers were readily desilylated under acidic conditions (Scheme 1), affording the targeted amphiphilic dextran-*b*-PS block copolymers (**8**).

In a preliminary study, the self-assembling properties in water of these diblock copolymers were investigated. Because of its small PS content, copolymer 1 (Table 1) could be directly dissolved in water at ∼90 °C. The nanoparticles thus formed adopted a micelle-like spherical shape with a diameter of 56 nm, as determined by dynamic light scattering (DLS) and 50 nm from atomic force microscopy (AFM) (Fig. 2).

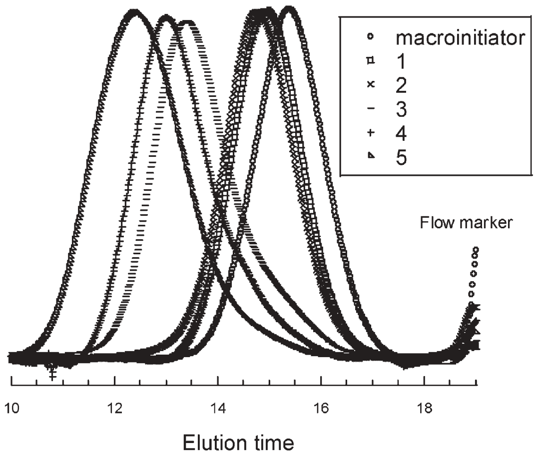

Fig. 1 SEC traces in THF of dextran-based macroinitiator and corresponding (silylated dextran)-*b*-PS block copolymers (**7**) obtained by ATRP.

Samples with larger contents in PS could not be directly transferred in water; they were first dissolved in a DMSO–THF mixture before slowly substituting water for the organic phase, the latter being totally removed by dialysis. Depending on the PS content, various stable morphologies (vesicles and ovoids) could be clearly identified. For instance, copolymer 4 (Table 1) with its 87% content in PS exhibited a vesicular morphology as seen by transmission electron microscopy (TEM) (Fig. 3). DLS and static light scattering measurements on the same sample afforded a ratio of 1 for R_g/R_H, thus confirming the formation of a vesicle.

Table 1 Molecular characteristics of silylated dextran-*b*-PS copolymers[a]

Sample	t/min	T/°C	$M_{n\ SEC}$[b]	$DP_{n\ NMR}$[c]	PDI[b]	Φ_{PS}[d] (vol%)
1	20	90	17500	5	1.4	11
2	40	90	21500	15	1.4	27
3	20	100	55700	145	1.6	78
4	40	100	82200	270	1.7	87
5	90	100	160000	775	1.9	95

[a] Polydispersity of silylated dextran **6** is around 1.4. [b] Determined by SEC in THF (calibration with PS standards). [c] Overall composition determined by ^{1}H NMR spectroscopy knowing the molar mass of commercial dextran (M_n = 6600 g mol^{-1}). [d] Volume fraction in PS calculated using a density (d_{PS} = 1.05 and $d_{dextran}$ = 1.63)

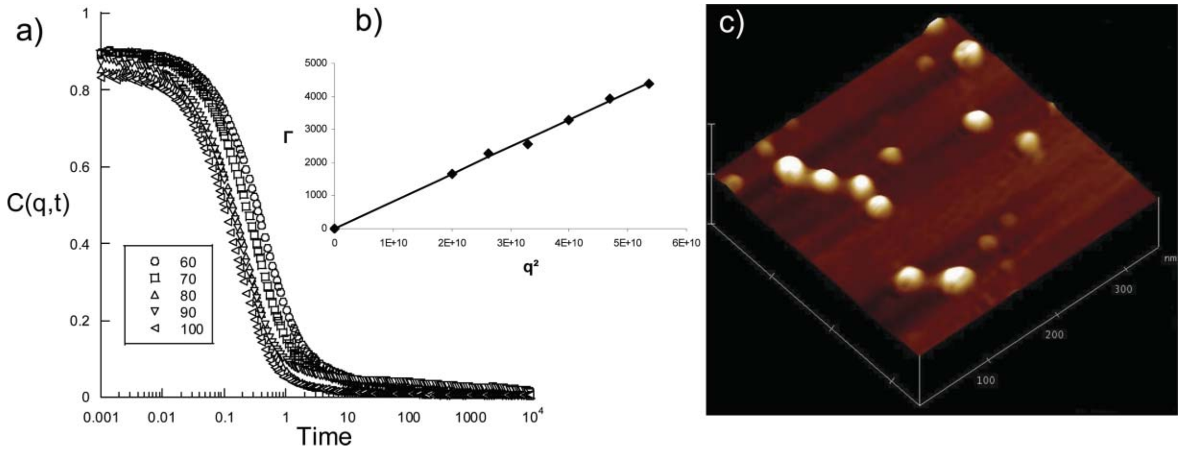

Fig. 2 (a) Correlation functions for concentration of 0.05 mg ml^{-1} of system 1 in water; (b) frequency q^2 dependency; (c) AFM image obtained from a dilution of the same solution by evaporation on a mica surface.

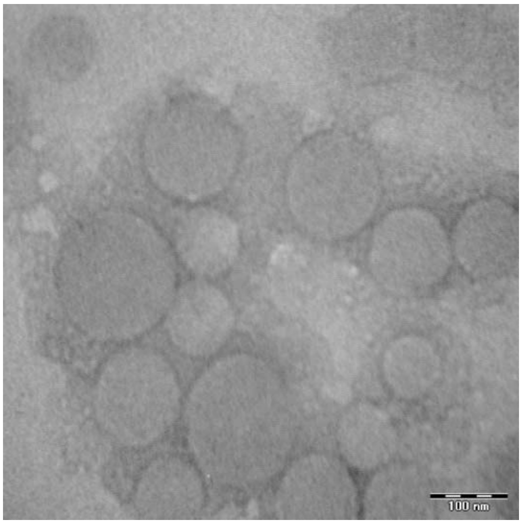

Fig. 3 TEM from a water solution of a dextran-*b*-PS block copolymer (entry 4, Table 1).

In conclusion, hybrid block copolymers comprising dextran as a natural block and polystyrene as the synthetic block were designed by ATRP after the covalent attachment of an ATRP-initiating moiety onto the anomeric group of the commercial polysaccharide. Self-assembly in water of such diblock copolymers led to various, stable spherical morphologies whose size strongly depended on the overall composition. A detailed description of the self-assembling properties of these dextran-*b*-polystyrene copolymers will be the subject of a forthcoming paper.

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