Towards an easy access to amphiphilic rod-coil miktoarm star copolymers†

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Water-soluble stimuli-responsive AB_2 miktoarm star copolymers were prepared by atom transfer radical polymerisation of styrene followed by chain-end modification, polymerisation of either γ-benzyl-L-glutamate *N*-carboxyanhydride or *tert*-butylacrylate and a final step of hydrolysis.

Water-soluble amphiphilic block copolymers find widespread applications as surfactants, templates for the controlled growth of inorganic compounds or in drug and gene delivery systems.[1] Depending on their molecular parameters, these block copolymers can form in a selective solvent various self-assembled structures in the submicron size range (*e.g.* spherical micelles, vesicles or rod-like micelles).[1] In particular, when they are comprised of ionogenic blocks, such copolymers can respond by a change of their size or their shape to a variation of their environment, as it might be the pH, ionic strength or temperature.[1]

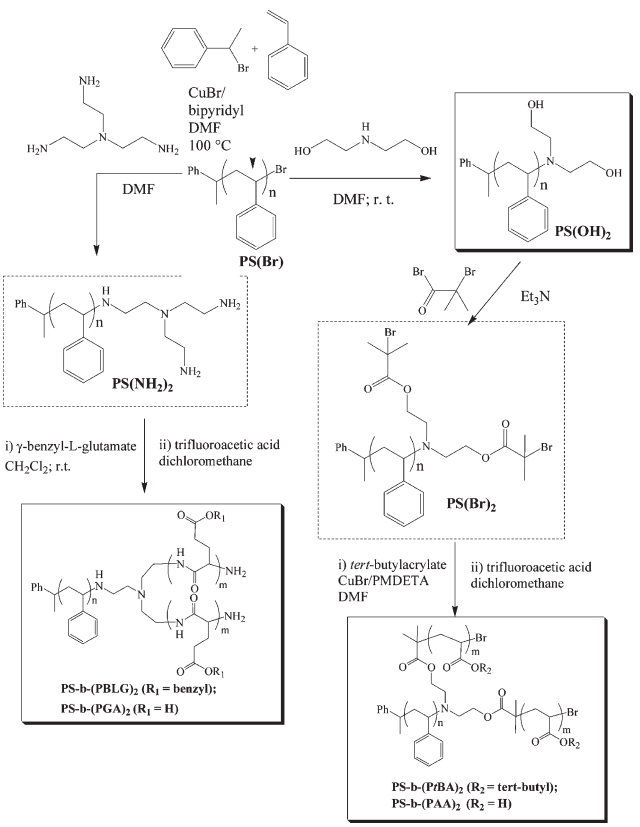
It so happens that the water-soluble stimuli-responsive block copolymers investigated so far are mainly linear. Interest in star-like homologues is driven by the expectation that the presence of a branching point can reduce the conformational entropy of such systems and bring about self-assembled organizations different from those observed with linear counterparts.[2] Among the various AB_x miktoarm star copolymers reported in the literature,[2] only a handful are stimuli-responsive in aqueous media.[3–6] For instance, AB_2-type miktoarm star copolymers, where A was a polystyrene block and B a poly(ethylene oxide) one, were synthesised following an anionic polymerisation route.[3] Armes *et al.* also designed AB_2 systems where A was a statistical copolymer of ethylene oxide and propylene oxide and B a methacrylic block grown by atom transfer radical polymerisation (ATRP) and chemical modification of chain ends.[6]

Here we describe the synthesis of rod-coil water-soluble miktoarm star copolymers comprising a polystyrene block and two poly(L-glutamic acid) (PGA) blocks. The peptide blocks exhibit pH-sensitive secondary structures that were exploited to manipulate the size and the shape of the supramolecular structures arising in water.[7] Very recently, ATRP and ring-opening polymerization of *N*-carboxyanhydrides were combined to derive linear rod-coil block copolymers.[8] The novelty of our work lies in the presence of a branching point separating hydrophobic and hydrophilic blocks, which is expected to influence the overall morphologies of the aggregates formed.

The synthetic scheme of these stars involves the prior preparation of ω-bromo-terminated polystyrenes by ATRP (Scheme 1). Next, the bromo end-groups of these precursors were derivatised into twice as many NH_2 initiating sites from which two additional B blocks of poly(γ-benzyl-L-glutamate) (PBLG) were subsequently grown by ring opening polymerisation of γ-benzyl-L-glutamate *N*-carboxyanhydride.

The first step thus involved ATRP of styrene followed by a newly designed chain-end modification procedure. Styrene was polymerised in bulk at 100 °C in the presence of dimethylformamide (DMF) used as an additive (10% in vol. relative to monomer), CuBr/bipyridyl (1/2 molar) as the catalytic system and 1-phenylethyl bromide as the initiator for ATRP. Under these conditions, both the molar masses and the polydispersities of the samples obtained could be controlled.

Selective chemical chain-end modification of these ATRP-derived PS, denoted by PS(Br), was achieved using a large excess of 1-aminotriethylenetriamine for the nucleophilic substitution of



Scheme 1 Synthetic strategy for miktoarm star copolymers.

† Electronic supplementary information (ESI) available: experimental section. See http://www.rsc.org/suppdata/cc/b5/b500636h/

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the bromo-end group, affording PS capped with gemini amino groups, denoted by $PS(NH_2)_2$ (Scheme 1). PS samples fitted with gemini hydroxy groups, denoted by $PS(OH)_2$, were also obtained upon heating PS(Br) with a large excess of diethanolamine in DMF then end-capped with bromoesters for subsequent ATRP of *tert*-butylacrylate (*t*BA). Esterification of the hydroxy groups of $PS(OH)_2$ in the presence of triethylamine afforded ω,ω′-bis(bromo) PS, denoted by $PS(Br)_2$.

All these chemical modifications were monitored by both ^{1}H NMR and MALDI-TOF mass spectroscopy. The MALDI-TOF mass spectrum of $PS(NH_2)_2$ showed a major population with a series of peaks that perfectly matched the expected distribution (ESI). The two chain ends were clearly identified: one is the phenylethyl moiety from the initiator (m/z = 105), the other the amino groups introduced by the functionalisation agent (m/z = 145). Both MALDI-TOF MS and NMR characterisations provided full evidence that the functionalisation of the PS precursors occurred quantitatively.

$PS(NH_2)_2$ and $PS(Br)_2$ subsequently served as macroinitiators to synthesise miktoarm star copolymers constituted of a PS block and two poly(γ-benzyl-L-glutamate) (PBLG) and two poly(*tert*-butylacrylate) (P*t*BA) blocks, respectively (Scheme 1). PS-b-$(PtBA)_2$ samples were prepared by ATRP of the *tert*-butylacrylate at 60 °C using $PS(Br)_2$ as a macroinitiator, DMF as additive and CuBr/pentamethyldiethylenetriamine as the catalytic system. As for PS-b-$(PBLG)_2$ copolymers, they were obtained at room temperature by ring opening polymerisation of γ-benzyl-L-glutamate in CH_2Cl_2 using $PS(NH_2)_2$ as macroinitiators.

In the two cases described above, characterisation by size exclusion chromatography (SEC) (run both in DMF and THF as eluent) of the products recovered showed monomodal peaks and polydispersity indices less than 1.3 (see Fig. 1). The shift in molar masses when compared to the SEC trace of PS(Br) indicated efficient chain extensions. Compositions and molar masses of these miktoarm star copolymers were determined by ^{1}H NMR, knowing the molar mass of the PS(Br) precursor (see Table 1). Excellent agreement between experimental and targeted molar masses confirmed the formation of well-defined structures and attested to the controlled/living character of the two polymerisation processes carried out to generate PS-b-$(PBLG)_2$ and PS-b-$(PtBA)_2$ miktoarm star copolymers.

A final step of hydrolysis of PS-b-$(PtBA)_2$ and PS-b-$(PBLG)_2$ copolymers using trifluoroacetic acid and hydrogen bromide in dichloromethane afforded the targeted PS-b-$(PAA)_2$ and PS-b-$(PGA)_2$ miktoarm star copolymers, where PAA and PGA refer to poly(acrylic acid) and poly(glutamic acid), respectively. PS-b-$(PAA)_2$ samples were synthesised for the purpose of comparison

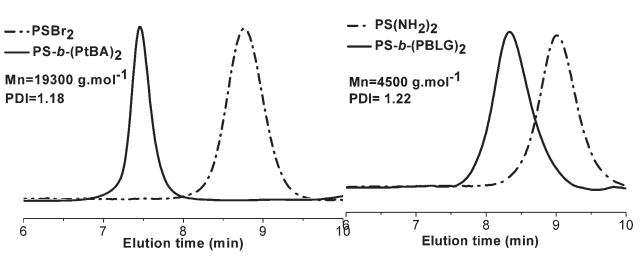

Fig. 1 SEC traces of miktoarm star copolymers.

Table 1 Molecular characteristics of PS-b-$(PtBA)_2$ and PS-b-$(PBLG)_2$ miktoarm star copolymers

Miktoarm star copolymer	Conv[a] (%)	$M_{n\ theo}$[b] (g mol^{-1})	$M_{n\ Mikto}$[c] (g mol^{-1})	PDI
PS_{21}-b-$(PtBA_{13})_2$	16	6270	6030	1.13[d]
PS_{20}-b-$(PtBA_{40})_2$	46	13080	12850	1.17[d]
PS_{20}-b-$(PtBA_{53})_2$	61	16530	16170	1.17[d]
PS_{25}-b-$(PBLG_{18})_2$	98	10680	10850	1.22[e]
PS_{25}-b-$(PBLG_{36})_2$	97	17600	18500	1.26[e]
PS_{25}-b-$(PBLG_{51})_2$	97	24000	25080	1.24[e]

[a] Conversion determined by gravimetry. [b] Theoretical molar mass: $M_{n,theo}$ = (Conv*[monomer]/[macroinitiator]*M_m) + M_i, M_m and M_i are the molar mass of monomer and the macroinitiator respectively. [c] Molar mass determined by ^{1}H NMR. [d] Determined by SEC in THF. [e] Determined by SEC in DMF.

of their aqueous solution properties with those of PS-b-$(PGA)_2$. NMR analysis before and after release of the *tert*-butyl and the benzylic groups, respectively, confirmed the efficiency of this deprotection step (ESI).

Miktoarm star copolymers PS-b-$(PAA)_2$ and PS-b-$(PGA)_2$ could be readily dissolved in water. Their stimuli-responsive behavior as a function of pH was investigated by means of static and dynamic light scattering (SLS and DLS) and ^{1}H NMR. As an example, Fig. 2 shows the average hydrodynamic radius (R_H) of PS_{25}-b-$(PGA_{18})_2$ measured in acidic and basic aqueous solutions. Spherical micelles were obtained in both cases with a narrow size distribution, the PS part constituting the core of the aggregates and the two PGA blocks forming the shell.

The R_H value was lower at pH < 5 (R_H = 11 nm) than that obtained under basic conditions (R_H = 16 nm for pH > 12). At acidic pH, indeed, PGA blocks exhibit a compact α-helical conformation (Fig. 2). On increasing the pH, PGA is electrostatically charged and changes its conformation to a random coil,[7] this α-helix to coil transition being reversible even in highly salted medium. In addition, the change of the micellar size is more significant with this polypeptidic PS-b-$(PGA)_2$ system as compared to micelle based on a pure polyelectrolyte such as PS-b-$(PAA)_2$ in the presence of salt. It turns out that PS-b-$(PGA)_2$ is insensitive to the presence or absence of salt in its pH-responsive behaviour (ESI).

In summary, water-soluble miktoarm star copolymers consisting of two ionogenic (PAA or PGA) hydrophilic blocks connected to a

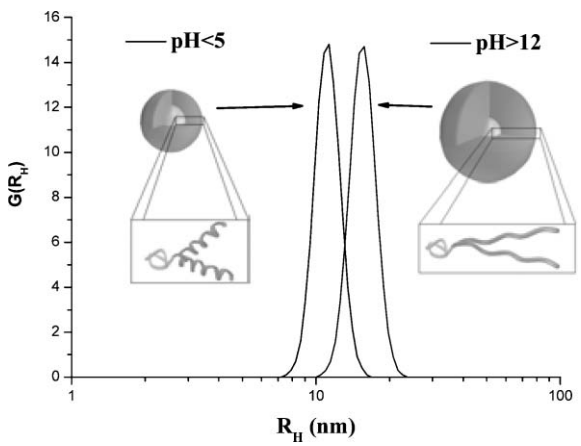

Fig. 2 Size distribution of PS-b-$(PGA)_2$ copolymers.

single PS block were synthesised using a straightforward approach based on the combination of ATRP, selective branching reactions and the same or another living/controlled polymerisation. Preliminary investigations by DLS demonstrated the pH-responsiveness of these AB_2 systems in aqueous media. Further experiments are in progress in order to demonstrate the "miktoarm effect" on the self-assembly and stimuli-responsive properties of these systems.

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