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Stimuli responsive amphiphilic block copolymers for aqueous media synthesised via reversible addition fragmentation chain transfer polymerisation (RAFT)

Murat Mertoglu[a], Sébastien Garnier[a], André Laschewsky[a,b,*], Katja Skrabania[a], Joachim Storsberg[b]

[a]*Institut für Chemie, Universität Potsdam, P.O. Box 601553, D-14415 Potsdam, Germany*
[b]*Fraunhofer Institute für Angewandte Polymerforschung FhG-IAP, Geiselbergstr. 69, D-14476 Golm, Germany*

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Abstract

A series of RAFT agents was synthesised, and used to prepare various ionic, non-ionic and zwitterionic water-soluble polymers, in organic as well as in aqueous media. The RAFT process proved to be a powerful method to prepare functional polymers of complex structure, such as amphiphilic diblock and triblock copolymers. This includes polymers containing one or even two stimuli-sensitive hydrophilic blocks. Switching the hydrophilic character of a single or of several blocks by changing the pH, the temperature or the salt content demonstrated the variability of the molecular designs suited for stimuli-sensitive polymeric amphiphiles, and exemplified the concept of multiple-sensitive systems.

Keywords: Water-soluble block copolymers; RAFT; Polyelectrolytes

1. Introduction

Stimuli-responsive polymers have been investigated for the development of 'smart' materials in various fields. The term 'stimuli-responsive' implies that marked changes of key properties can be induced by an external stimulus. In the strict sense, the induced property changes should be reversible if the stimulus is suppressed, or if a second 'reverse' stimulus is applied. Many types of stimuli are theoretically useful, but mostly, the choice is limited for practical reasons. In aqueous systems, stimuli-sensitive systems are generally aimed at changing the hydrophilic character of functional groups into a hydrophobic one, or vice versa [1]. Both chemical and physical stimuli (which may be coupled) can be employed for that purpose. Chemical stimuli include for instance acid–base reactions, complexation, bond breaking or making, redox and electrochemical reactions, or photochemical reactions. Physical stimuli comprise, e.g. changes of the pH-value, of ionic strength, of temperature or pressure, light, or electrical and magnetic fields [2].

The simplest stimuli-responsive polymers are based on acid–base reactions, or on pH changes, respectively. Typical examples are polymeric amines or polymeric carboxylic acids, which by protonation/deprotonation become charged and thus undergo a pronounced change of their hydrophilicity. Such pH-responsive polymers excel by their reversibility [1], but open systems are required in order to allow for more than a few switching cycles. Otherwise, salts accumulate during successive protonation/deprotonation events and finally overthrow the system. Though photochemical reactions have been considered alternatively for switching in aqueous media [3–9], these reactions are generally troubled by an insufficient bistability or reversibility on the one hand, and by relatively small changes of the hydrophilicity on the other hand. Another alternative that has been explored are responsive polymers based on redox

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* Corresponding author. Address: Institut für Chemie, Universität Potsdam, Karl-Liebknecht-Strasse 24-25, P.O. Box 601553, D-14415 Potsdam, Germany. Tel.: +49 331 568 1327; fax: +49 331 568 3163.
E-mail address: andre.laschewsky@iap.fhg.de (A. Laschewsky).

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reactions. Such systems show often efficient stimuli responsiveness, as strongly hydrophilic ionic groups are added or removed to/from the system [10–13]. But again, good bistability and reversibility in combination with marked changes of the hydrophilic–hydrophobic balance are hard to achieve simultaneously. In particular, most organic redox systems are chemically sensitive to oxygen from air, or to good nucleophiles (like water) in one of the two oxidation states, thus hampering their application severely.

Due to the difficulties in an efficient switching of the hydrophilic–hydrophobic balance by chemical reactions, the interest has moved more to systems driven by physical stimuli. Thermal transitions dominate this field by far up to now [1,2,14–19], as most non-ionic polymers exhibit a lower critical solution temperature (LCST) in aqueous solution. In contrast, upper critical solution temperatures (UCST) are rarely found in aqueous solution, and have been confined mainly to polyzwitterions [20–23].

Much interest in aqueous solutions of stimuli-sensitive polymers derives from their potential application for the controlled transport and delivery of active substances, such as drugs, in biotechnology, medicine, (phyto)pharmacy, or cosmetics [19]. One main strategy aims at a permeability control of polymeric matrixes or barrier coatings. The other main strategy concentrates on the controlled formation and destruction of hydrophobic micro domains in aqueous media. The latter approach implies typically the interconversion of amphiphilic and non-amphiphilic compounds. Though amphiphilic homopolymers and statistical copolymers of the polysoap type [24,25] were the main stimuli-sensitive micellar polymer systems investigated for long, studies concentrate nowadays on amphiphilic block copolymers.

Amphiphilic block copolymers are typically diblock copolymers consisting of a hydrophobic block aggregating in aqueous solution, and of a hydrophilic block that prevents the aggregates from precipitation [25–29]. Such polymers can be considered as 'macro-surfactants' due to their structural similarity to low molar mass surfactants (Scheme 1(a)). They have gained much impetus in recent years due to the uprise of the so-called controlled free radical polymerisation methods, such as nitroxyl-mediated free radical polymerisation, atom transfer free radical polymerisation (ATRP), or reversible addition fragmentation chain transfer (RAFT) [29–34]. By virtue of the higher chemical tolerance of free radical polymerisation compared to other polymerisation methods, these methods offer a more convenient, and a much more versatile access to block copolymers bearing polar and hydrophilic moieties. The increased variability of monomer units for block copolymer synthesis has stimulated the efforts to convert macro-surfactants from static structures to dynamic ones, in which the amphiphilicity responds to environmental changes [1,22,23,35–42]. For instance incorporating a stimuli-sensitive hydrophilic block, one can switch in water from soluble to insoluble, and thus control the amphiphilic behaviour: if the other block is hydrophobic (Scheme 1(b)), the polymer behaves as surfactant in the ground state, and as oily compound after applying the stimulus. Inversely, if the other block is hydrophilic (Scheme 1(c)), the compound behaves as molecularly dissolved 'double-hydrophilic' polymer in the ground state, but becomes amphiphilic after switching. If both blocks are stimuli-sensitive though different (Scheme 1(d)), the polymer can pass through all three states, namely double-hydrophilic, amphiphilic and oily, depending on the switching states.

Scheme 1. Schematic representation of diverse types of stimuli-sensitive macro-surfactants: (a) hydrophilic and hydrophobic blocks fixed (classical structure), (b) hydrophilic block stimuli-sensitive, (c) hydrophobic block stimuli-sensitive, (d) both blocks stimuli-sensitive (ooo, hydrophilic segment; 〰〰, hydrophobic segment; □□□, ☒☒☒, switchable segments).

Within this general frame, we are exploring convenient access routes to different stimuli-sensitive block copolymers, and investigate different possibilities to trigger the switching, and study their stimuli-sensitive behaviour in aqueous systems. Here, the synthesis of different stimuli-sensitive amphiphilic block copolymer designs (Scheme 1) by the RAFT method is studied. The RAFT method [33,34] was chosen for polymer synthesis as this technique generally provides very clean polymers, because the amphiphilic behaviour of surfactants can be very sensitive even to small amounts of impurities (such as residual catalysts in ATRP etc.). The various copolymers were designed such that the amphiphilicity is sensitive to different physical stimuli, namely to changes of the pH-value, of the temperature, and of added salts. Preliminary experiments concerning their stimuli-sensitive amphiphilic behaviour were performed.

2. Experimental

2.1. Materials

2-(4-Pyridine)ethanesulfonic acid was a gift from Raschig AG (Ludwigshafen, Germany). Carbon disulfide (99%), benzyl bromide (>98%), butyl acrylate (M1) (>99%), poly(ethylene glycol) Monomethyl ether acrylate

($M_r=454$) (M2), dimethylacrylamide (>99%) (M4), and *N*-isopropyl acrylamide (97%) (M6) were purchased from Aldrich. 4-Vinyl styrene sulfonate (90+%) (M7) and 4-vinylbenzyl chloride (>90%), benzyl magnesium chloride (1.3 M in THF), anhydrous magnesium sulfate (98+%), $CDCl_3$ (99.8 Atom, D%) and D_2O (99.8 Atom, D%) were purchased from Acros organics. Poly(ethylene glycol) methyl ether methacrylate ($M_r=430$) (Bisomer MPEG350 MA, M3) was obtained from Laporte (UK). Initiators 2,2′-azobis (2-methylpropionamidine) dihydrochloride (V-50), 2,2′-azobis (2-methyl-*N*-phenylpropionamidine)dihydrochloride (V-545) and 2,2′-azobis (2-methylpropionitrile) (V-60) were gifts of Wako Pure Chemical Industries. Solvents used for synthesis and purification were all analytical grade. Column chromatography was run on silica gel 60 (0.040–0.063 mm, Merck). Dialysis tubes 'Zellu Trans' (nominal molar mass cut off 1000 and 3500, respectively) were from Roth (Germany).

2.2. Synthesis

4-Vinylbenzoic acid (M8) was synthesised as described [43]. Cumyldithiobenzoate (CTA1) was synthesised as described [44] via acid catalysed addition of dithiobenzoic acid to α-methylstyrene. 4-Thiobenzoylsulfanyl-4-cyanopentanoic acid (CTA2) was synthesised by heating the mixture of 4.25 g (13.9 mmol) bis(thiobenzoyl) disulfide and 5.84 g (20.8 mmol) 4,4′-azobis (4-cyanopentanoic acid) in ethylacetate at 80 °C under inert atmosphere as described before [45]. The synthesis of potassium 2-(2-thiobenzoylsulfanylpropionylimino)-naphthalene-6,8-disulfonate CTA3 is described elsewhere [46].

2.2.1. Synthesis of benzyl dithiophenylacetate (CTA4)

40.3 ml (80.6 mmol) of 1.3 M benzyl magnesium chloride in THF were added with stirring over 30 min at ambient temperature under argon flow to a large excess of CS_2 (10.0 ml, 165 mmol). The exothermic reaction yielded a dark red mixture. After 60 min, 9.6 ml of benzyl bromide (80.6 mmol) were added slowly. Then, the reaction was maintained for 3 h at 60 °C. The reaction mixture was poured into 250 ml of ethylacetate and washed with 250 ml water. The red organic phase was washed with 250 ml brine, dried over magnesium sulfate, purified by column chromatography (silicagel, eluent: pentane). The yellow fraction was collected, and the solvent removed under reduced pressure, to give a yellow oil. Storage at −4 °C yielded orange crystals. Yield: 12.22 g (58%). Elemental analysis ($C_{15}H_{14}S_2$, $M_r=258.05$) calcd: C, 69.71; H, 5.47; S, 24.81; found: C, 69.65; H, 5.41; S, 24.89. MS (CI, CH_4/N_2O, *m/z*) signal at 258.8 $(M+1)^+$. ^1H NMR (300 MHz in $CDCl_3$, δ in ppm): $\delta=4.30$ (s, 2H, S–CH_2–), 4.39 (s, 2H, –CH_2–C=S), 7.15–7.36 (m, 10H, =CH–aryl). ^{13}C NMR (75 MHz in $CDCl_3$, δ in ppm): $\delta=41.9$ (–CH_2–S–), 57.8 (–C–(C=S)), 127.3, 127.7, 128.5, 128.7, 129.1, 134.9, 136.8 (=C–aryl), 234.8 (–C(=S)–S–). FTIR (KBr, selected bands, in cm^{-1}): 3082, 3058, 3026, 2885, 1492, 1450, 1412, 1119, 1022, 750, 710, 696, 609. UV–vis (in hexane): bands at $\lambda_{max1}=309$ nm ($\varepsilon=$ 15,300 l mol^{-1} cm^{-1}), $\lambda_{max2}=463$ nm ($\varepsilon=45$ l mol^{-1} cm^{-1}).

2.2.2. N-Acryloyl pyrrolidine (M5)

The synthesis of M5 modified the procedure of Parrod and Elles [47]. Sixty grams (0.663 mol) of acryloylchloride in 200 ml of dry benzene are cooled to 4 °C, and a mixture of 47.14 g (0.663 mol) pyrrolidine and 67.1 g (0.663 mol) of dry triethylamine in 50 g of dry benzene are added over a period of 2 h while stirring and cooling. Then, the mixture is allowed to stir at room temperature for an additional 1 h. Then, the reaction is filtrated, the filter residue is washed three times with 50 ml of benzene, and the combined benzene solutions are collected and evaporated. The residue (92 g) is distilled over CaH_2 in vacuo (bp: 76 °C 4.6×10^{-1} Torr) to yield 66.8 g (80.5%) of pure M5 as a colourless liquid, which solidifies upon storage in the refrigerator. ^1H NMR (300 MHz, δ in ppm): 1.78–2.00 (m, 4H, –CH_2–CH_2–), 3.48 (m, 4H, CON–CH_2–), 5.60 (dd, 1H, =CH–), 6.28–6.45 (m, 2H, =CH_2). ^{13}C NMR (75 MHz, δ in ppm): 164.5 (–C(=O)N<), 129.0 (CH_2=), 127.5 (=CH–), 47.0 and 46.5 (–CH_2–N–CH_2–, *cis* and *trans* position of amide), 26.5 and 24.5 (–CH_2–CH_2–).

2.2.3. 4-(2-Sulfoethyl)-1-(4-vinyl-benzyl) pyridinium betain (M9)

18.72 g (0.1 mol) of 2-(4-pyridine)ethanesulfonic acid and 4.0 g (0.1 mol) of NaOH were dissolved in 120 ml of $HCONH_2$ at ambient temperature. A drop of nitro benzene and 15.26 g (0.1 mol) of 4-vinylbenzylchloride were added slowly under nitrogen atmosphere, and stirred for 65 h at ambient temperature. The cooled solution was precipitated into acetone, filtered, and the filtrate dried in vacuo, to give 29.8 of crude compound containing NaCl. Crystallisation from dry ethanol provided the salt free monomer. Elemental analysis ($C_{16}H_{17}NO_3S$ $M_r=303.38$) calcd: C, 63.34; H, 5.65; N, 4.62; S, 10.57. Found: C, 62.70; H, 5.55; N, 4.71; S, 9.98. MS (FAB, matrix MNBA, negative ions) signal at 301.9 $[M-1]^-$. ^1H NMR (Bruker 300 MHz in D_2O, δ in ppm): 3.18–3.27 (m, 4H, –CH_2–CH_2–SO_3), 5.23 (d, 1H, $CH_{(cis)}H_{(trans)}$=CH–), 5.61 (s, 2H, –CH_2–N^+), 5.74 (d, 1H, $CH_{(cis)}H_{(trans)}$=CH–), 6.63 (m, 1H, =C*H*–), 7.30 and 7.40 (d+d, 2H+2H, CH phenylene), 7.84 (d, 2H, CH(3) pyrid) 8.65 (d, 2H, CH(2) pyrid). ^{13}C NMR (Bruker 75 MHz in D_2O, δ in ppm) 161.3 (C pyrid), 144.1 (–CH=N^+), 139.4 (C4 phenylene), 136.3 (=CH), 132.9 (C1 phenylene), 129.9 (C3 phenylene), 128.9 (=*C*H–C=N^+), 127.7 (C2 phenylene), 116.4 (CH_2=), 64.2 (–CH_2–N^+), 50.2 (–CH_2–SO_3), 31.0 (–*C*H_2–C–SO_3). FT-IR (KBr, selected bands in cm^{-1}): 3506, 3357, 1683, 1639,1197, 1054, 692, 617.

2.3. Polymerisation

Table 1 lists the type and the amounts of monomer, initiator and RAFT agent engaged, the solvents and the

Table 1
Summary of polymerisation conditions used

Sample	Monomer (mmol)	Macro RAFT agent ($\times 10^5$ mol)	Initiatior ($\times 10^5$ mol)	Polymerization temperature (°C)	Solvent used for polymerisation	Polymerization time (h)
p(M1)	M1 (175.5)	CTA4 (74)	V-60 (15)	66	20 ml THF	0.5
p(M1-*b*-M5)	M5 (6.3)	p(M1) 0.43 g (2.5)	V-60 (1.1)	66	5 ml dioxane	1.5
p(M2)	M2 (10.1)	CTA3 (35)	V-545 (7.5)	48	12 ml 0.5 M (aq) NaBr	5
p(M2-*b*-M9)	M9 (11.0)	p(M2) 1.34 g (9.6)	V-50 (3.35)	55	20 ml 0.5 M (aq) NaBr	5
p(M2-*b*-M9-*b*-M8)	M8 (1.2)	p(M2-*b*-M9) 1.68 g (4.3)	V-50 (1.5)	55	13 ml 0.5 M (aq) NaBr pH = 6.5	15
p(M3)	M3 (42.9)	CTA2 (28)	V-50 (7.4)	55	19 ml water	15
p(M3-*b*-M1)	M1 (3.0)	p(M3) 1.50 g (2.2)	V-50 (0.72)	55	20 ml water	6
p(M4)	M4 (125.0)	CTA2 (6.5)	V-545 (1.7)	48	15 ml water	5
p(M4-*b*-M9)	M9 (12.7)	p(M4) 1.33 g (4.3)	V-50 (1.9)	53	25 ml 0.5 M (aq) NaBr	3
p(M4-*b*-M9-*b*-M8)	M8 (0.7)	p(M4-*b*-M9) 0.60 g (1.0)	V-545 (0.75)	53	15 ml 0.5 M (aq) NaBr pH = 6.5	15
p(M5)	M5 (8.0)	CTA1 (8.0)	V-60 (1.6)	70	5 ml toluene	23
p(M5-*b*-M4)	M4 (2.7)	p(M5) 0.30 g (2.7)	V-60 (0.53)	70	7 ml toluene	25
p(M6)	M6 (8.8)	CTA1 (8.8)	V-60 (1.8)	70	1 ml toluene	18
p(M6-*b*-M5)	M5 (5.0)	p(M6) 0.25 g (5.0)	V-60 (1.0)	70	4 ml toluene	25
p(M7)	M7 (125.0)	CTA3 (22.5)	V-545 (4.5)	55	30 ml 0.5 M (aq) NaBr	7
p(M7-*b*-M9)	M9 (11.0)	p(M7) 1.00 g (4.6)	V-545 (1.0)	55	25 ml 0.5 M (aq) NaBr	5
p(M7-*b*-M9-*b*-M8)	M8 (2.4)	p(M7-*b*-M9) 1.32 g (2.6)	V-545 (6.0)	55	25 ml 0.5 M (aq) NaBr pH = 6.5	17
p(M9)	M9 (8.3)	CTA3 (8.4)	V-545 (1.7)	55	25 ml 0.5 M (aq) NaBr	5

reaction temperatures. Samples were deoxygenated by bubbling N_2 for 30 min for polymerisations in water, and by three freeze-pump-thaw cycles for such in organic solvents. Organic solvents and monomers M1, M2, M3 and M4 were passed trough basic aluminium oxide to remove inhibitors prior to polymerisation. Polymer polyM1 was isolated by lyophilisation in benzene. All other polymer samples were dialyzed against water with tubes having nominal molar mass cut off of 1000, and then lyophilised. Conversions were estimated from the polymer yield after lyophilisation.

2.4. Methods

NMR spectra were taken with an apparatus Bruker Avance, using 1,4-dioxane as internal reference (67.4 ppm in D_2O in ^{13}C NMR). IR-spectra were taken from KBr pellets using FT-IR spectrometer Bruker IFS 66/s. Mass spectra were recorded by a spectrometer TSQ7000 (Thermo Finnigan). UV–vis spectra were recorded with a spectrophotometer Cary-1 (varian) equipped with temperature controller (Julabo F-10). Number average molar masses M_n of the homopolymers/macro RAFT agents were determined by end group-analysis using the absorption of dithioester end groups at visible band ($\varepsilon_{CTA1} = 45\ l\ mol^{-1}\ cm^{-1}$, $\varepsilon_{CTA2} = 115\ l\ mol^{-1}\ cm^{-1}$, $\varepsilon_{CTA3} = 110\ l\ mol^{-1}\ cm^{-1}$ and $\varepsilon_{CTA4} = 106\ l\ mol^{-1}\ cm^{-1}$), assuming that all polymer chains bear exactly one dithioester end group [46,48]. Number average molar masses M_n of the block copolymers were calculated from their composition, assuming that M_n of the first block is identical to the value of the macro RAFT agent employed. Size exclusion chromatography (SEC) in tetrahydrofurane was performed at 20 °C using a Waters 515 HPLC isocratic pump equipped with a Waters 2414 refractive index detector, a Waters 2487 UV detector and a set of Styragel columns (HR 5, HR 45, HR 3500–100,000 Da) from Waters. Flow rate: 1.0 ml min^{-1}. SEC in *N*-methylpyrrolidone (NMP (>99%, Fluka)) with 0.05 mol l^{-1} LiBr was performed at 70 °C using a TSP (Thermo Separation Products from Thermo-Finnigan GmbH, Dreieich, Germany) equipped with a Shodex RI-71 refractive index detector and a TSP UV detector. SDV-10E3 columns (styrene divinyl benzene from MZ-Analysentechnik combined with a styrene divinyl benzene from Polymer Laboratories) were used for the analysis of polyM1-*block*-polyM5 (flow rate: 0.800 ml min^{-1}). All SEC systems were calibrated by polystyrene standards (PSS GmbH, Mainz, Germany). Turbidimetry used a temperature controlled turbidimeter model TP1 (E. Tepper, Germany) with heating and cooling rates of 1° min^{-1}. Dynamic light scattering was performed with a high performance particle sizer (HPPS, from Malvern Instruments) using a light scattering apparatus equipped with a He–Ne (633 nm) laser and a thermo-electric Peltier temperature controller (temperature control range: 10–90 °C). The measurements were made at the scattering angle

$\theta = 173°$ ('backscattering detection'), using CUMMULANTS to analyse the autocorrelation functions. Aqueous solutions of polymers were filtered using a Sartorius Ministar-plus 0.5 μm disposable filter and were placed in a polystyrene or glass cuvette for analysis. Temperature dependent DLS experiments were run with a heating program from 25 to 90 °C in steps of 1 °C, equilibrating the samples for at least 2 min at each step.

3. Results and discussion

Amphiphilic thermoresponsive diblock polymers of various structures were prepared and studied (Fig. 1, Table 2). Poly(butyl acrylate) polyM1 was employed as permanently hydrophobic unit, as the polymer shows a low glass transition temperature ($T_g = -52$ °C) [49], in order to avoid the problem of 'frozen' micellar structures [27,28]. The polymers of poly(ethylene glycol) acrylate M2, and *N*,*N*-dimethylacrylamide M4 served as non-ionic, permanently hydrophilic blocks, whilst poly(styrene sulfonate) polyM7 was used as ionic, permanently hydrophilic block. Monomers poly(ethylene glycol) methacrylate M3, *N*-acryloylpyrrolidine M5, *N*-isopropylacrylamide M6, vinylbenzoic acid M8 and the sulfobetaine M9 were used to construct the stimuli-sensitive blocks (Fig. 2). The non-ionic polymers of M3, M5, and M6 exhibit a LCST, i.e. they are water-soluble at low, but insoluble at high temperatures. The carboxylic acid M8, however, produces pH-sensitive polymers which are only water-soluble at high pH [50,51]. The new zwitterionic monomer M9 (Fig. 3) gives polymers with a particular switching behaviour. Alike many polyzwitterions [20,21,52,53], polyM9 is insoluble in aprotic solvents, including dimethylformamide, NMP and dimethylsulfoxide, but even so in formamide, chloroform and methanol, or their mixtures, though it dissolves in trifluoroethanol. In particular, the solubility of polyM9 in aqueous solvents is sensitive to the type and the concentration of inorganic salts added: Whereas the polymer does not dissolve in pure water or in 0.01 M HCl, it is readily soluble in 0.5 M aqueous NaBr, NaCl or $NaClO_4$.

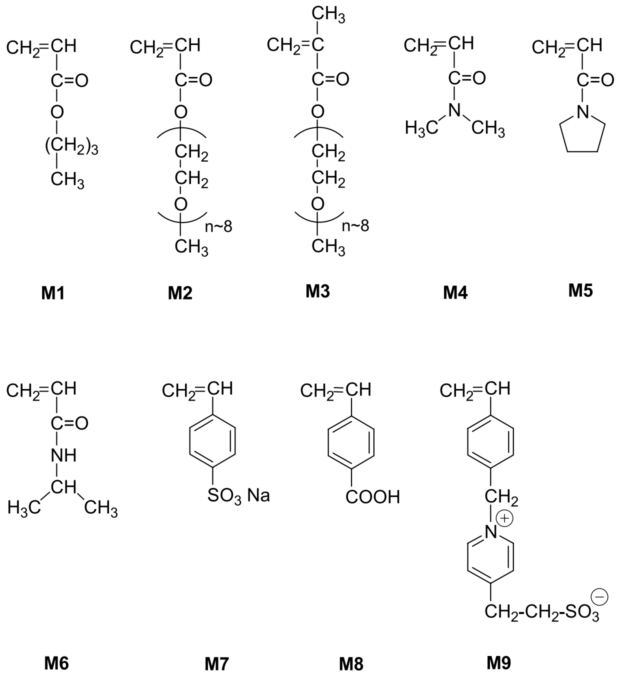


Fig. 1. Monomers used.

With this set of different building blocks, various stimuli-sensitive diblock copolymers were prepared, for all classes of amphiphiles sketched in Scheme 1. Copolymers polyM3-*block*-polyM1, and polyM1-*block*-polyM5 are examples of thermally sensitive macro-surfactants with a switchable hydrophilic block, i.e. they are functional at low temperatures only (Scheme 1(b)). PolyM5-*block*-polyM4 represents a thermally sensitive macro-surfactant with a switchable hydrophobic block that accordingly is functional at high temperatures only (Scheme 1(c)). PolyM2-*block*-polyM9, polyM4-*block*-polyM9, and polyM7-*block*-polyM9 are macro-surfactants with a switchable hydrophobic block according to Scheme 1(c), too. But the stimulus is a pH-change for the first polymer, and a change of salt content in the three other polymers. PolyM6-*block*-polyM5 is one of the rare examples [22,23,37,41,42,54–57] for thermally sensitive macro-surfactants with two switchable blocks (Scheme 1(d)). It behaves as amphiphile at intermediate temperatures only, whereas it is double-hydrophilic at low, and double-hydrophobic at high temperatures.

In addition to the various stimuli-sensitive diblock copolymers, the triblock copolymers polyM2-*block*-polyM9-*block*-polyM8, polyM4-*block*-polyM9-*block*-polyM8, and polyM7-*block*-polyM9-*block*-polyM8 were synthesised. All these triblock copolymers contain the same sequence of two orthogonally stimuli-sensitive blocks, namely the pH-sensitive block polyM8, and the salt-sensitive block polyM9, but they differ in the nature of the third, permanently hydrophilic block. The variation of the latter concerns the use of non-ionic bulky hydrophilic groups (polyM2), non-ionic small ones (polyM4), and ionic small ones (polyM7), respectively.

The polymers were prepared by the RAFT method, under the conditions listed in Table 1. The general characteristics of the homopolymers used as macro RAFT agents, and of the various block copolymers are given in Table 2, and selected ^{1}H NMR spectra are shown in Figs. 3 and 4. The choice of the RAFT agent (Fig. 2) depended on the polymerisable moiety of the monomers, and on the solvent employed. CTA1 and in particular CTA2 can be used rather generally and are useful for methacrylates [44], whereas CTA3 and CTA4 are best suited for acrylic and styrenic monomers [46]. Highly polar monomers such as M7 and M9 require aqueous solvents and thus water-soluble RAFT agents such as CTA2 and CTA3, whilst the non-ionic monomers can be polymerised in organic solvents with the hydrophobic RAFT agents CTA1 and CTA4, which are

Table 2
Characterisation of homo- and block polymers

Sample	Conversion (%)	Weight percent of newly added block (by ^{1}H NMR)	Weight percent of newly added block (by elemental analysis)	$M_n \times 10^{-4}$ (g mol^{-1})	PDI	DP$_n$ of the blocks
p(M1)	35	–	–	1.7^{a}		
				1.2^{b}	1.1^{b}	
p(M1-*b*-M5)	41	62	62	3.2^{c}		95-157
				2.7^{d}	1.2^{d}	
p(M2)	76	–	–	1.4^{a}		31
p(M2-*b*-M9)	70	65^{e}	66	3.9^{c}		31-82
p(M2-*b*-M9-*b*-M8)			13	4.5^{c}		31-82-29
p(M3)	96	–	–	6.9^{a}		160
				1.5^{b}	1.08^{b}	
p(M3-*b*-M1)		10	7	7.7^{c}	1.1^{b}	160-62
p(M4)	37	–	–	3.1^{a}		318
p(M4-*b*-M9)	38	49^{e}	49	6.1^{c}		318-99
p(M4-*b*-M9-*b*-M8)			8	6.6^{c}		318-99-29
p(M5)	78	–	–	1.5^{a}		120
p(M5-*b*-M4)	81	51		3.7^{c}		120-153
p(M6)	44			1.0^{a}		88
p(M6-*b*-M5)	66	70		4.3^{c}		88-197
p(M7)	87	–	–	2.2^{a}		107
p(M7-*b*-M9)	70	^{e}	60	5.0^{c}		107-92
p(M7-*b*-M9-*b*-M8)		^{e}	24	6.6^{c}		107-92-94
p(M9)	80	–	–	2.4^{a}		79

[a] Calculated by end-group analysis of visible band.

[b] According to SEC in THF, polystyrene standards.

[c] Calculated from the averaged compositional data according to elemental analysis and ^{1}H NMR, assuming that M_n of the macro RAFT agent employed is preserved in the block copolymer.

[d] According to SEC in NMP, polystyrene standards.

[e] ^{1}H NMR signals could not be evaluated quantitatively.

more convenient to prepare. The naphthalene labelled CTA3 offers the particular advantage of enabling two independent end-group determinations by UV–vis spectroscopy, due to the characteristic bands of the naphthalene moiety at 251 nm and of the dithiobenzoate group at ca. 480 nm [46]. The dithiophenylacetate CTA4 was prepared as it is expected to minimise the retardation period at the beginning of the polymerisation reaction, which is typically observed for RAFT with dithiobenzoates [34]. The origin of the retardation effect is still a matter of debate [34,58,59], but in any case, it complicates the polymerisation process when the reaction must be stopped at, for instance, incomplete conversions. This, however, is crucial in order to guarantee high end group functionality as needed for the efficient preparation of block copolymers.

With an appropriate RAFT agent chosen that fits to the polymerisable moiety and dissolves in the solvent used (in function of the monomer polarity), all polymerisations proceeded smoothly. The full solvent polarity range from brine via THF and dioxane to toluene was tolerated, and monomers of strongly differing polarity and with different functional groups could be polymerised successfully. In particular, monomers bearing highly hydrophilic anionic, zwitterionic and non-ionic groups could be polymerised, as were macro monomers M2 and M3. The number average molar masses of the homopolymers determined by end

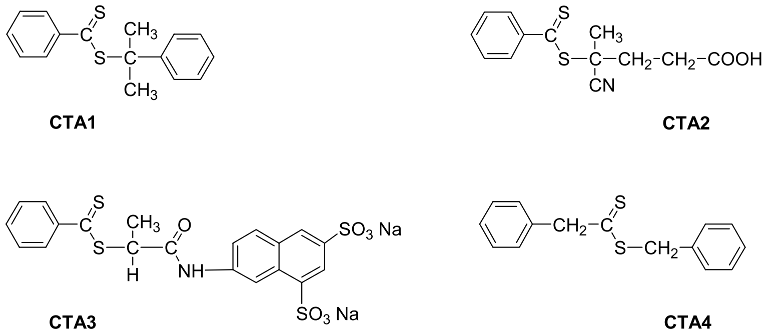


Fig. 2. RAFT agents used.

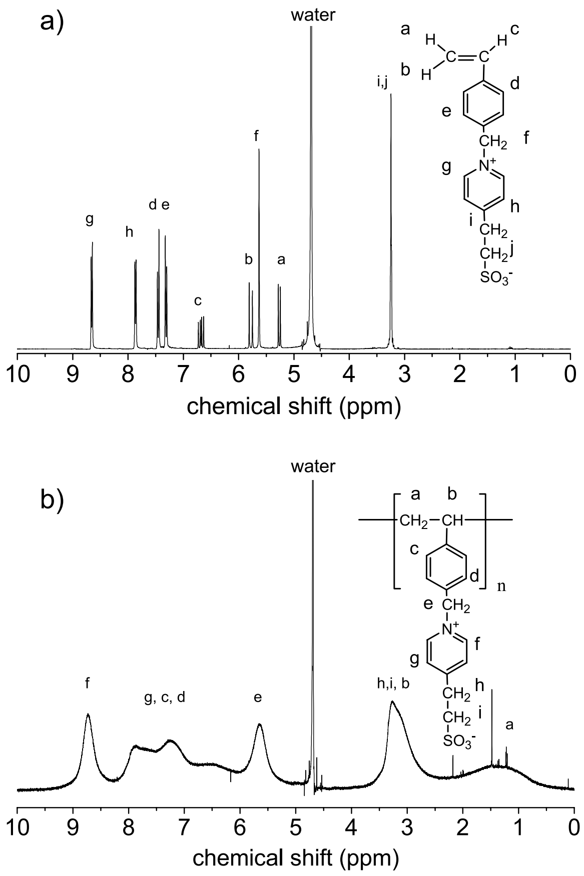


Fig. 3. ^{1}H NMR spectra of (a) M9 and (b) polyM9 in D_2O.

group analysis via the absorbance of the dithioester group (Table 2) match well to the theoretically expected ones, according to the stoichiometric ratio of monomer to RAFT agent employed and the conversion achieved, in agreement with a controlled free radical polymerisation process. This finding suggests also a high degree of preservation of the dithioester end groups, as needed for their use as macro RAFT agents in the successive synthesis of block copolymers. This general conclusion was corroborated by SEC studies in the case of polyM1, the only polymer that could be easily passed over a standard SEC set up with THF as eluent. The SEC trace shows a monomodal, narrow molar mass distribution with a polydispersity index of 1.1. Also, the value of M_n of 12,000 g mol^{-1} according to calibration with poly(styrene) (which is a good standard for polyM1 in THF [60]) agrees well with the theoretically expected value of 10,700 g mol^{-1}, demonstrating the efficient polymerisation control with CTA4. The polymer of macro monomer M3 could also be passed over a standard SEC column in THF, showing a monomodal molar mass distribution with a narrow polydispersity index of 1.08 for the sample. But as the calibration with poly(styrene) standards is not meaningful, only apparent M_n values are obtained that underestimate the true molar mass by far [46] (Table 2).

For the synthesis of the block copolymers, the solvents were chosen such that the macro RAFT agent and the monomer could be dissolved simultaneously (Table 1). Copolymers polyM3-*block*-polyM1 and polyM1-*block*-polyM5 exemplify that the polar or the apolar block can be equally well employed as macro RAFT agent for the preparation of amphiphilic block copolymers. Noteworthy, polyM3-*block*-polyM1 could be synthesised in aqueous solution, implying that polyM3 acts not only as macro RAFT agent but also as efficient compatibiliser for the sparingly water-soluble butyl acrylate M1. Moreover, the active end groups are sufficiently preserved even after the synthesis of diblock copolymers, so that their isolation and reengagement as macro RAFT agents in the third polymerisation cycle enables the preparation of triblock copolymers (Tables 1 and 2).

The successful synthesis of block copolymers was demonstrated by the preparation of monophasic, clear aqueous solutions of all samples under conditions where the block copolymers behave as amphiphiles, i.e. where water-soluble and water-insoluble blocks coexist. Nevertheless, the molecular characterisation of the block copolymers was difficult. Compositional analysis of the copolymers by integration of the signals of the ^{1}H NMR spectra was only possible when a good common solvent for all blocks was found, as for polyM1-*block*-polyM5 and polyM3-*block*-polyM1 in $CDCl_3$, or for polyM5-*block*-polyM4 and polyM6-*block*-polyM5 in D_2O (Fig. 4). Otherwise, the signals of the incompatible block are so much broadened—or even subdued—that meaningful integration was impossible. If the elemental contents of the monomers used were sufficiently different, elemental analysis presented a good alternative method. But due to the pronounced hygroscopic character of the copolymers, elemental analysis was best evaluated by the ratios of C/N and/or C/S contents. Molar mass determination of amphiphilic copolymers by SEC is troubled by numerous difficulties (major risk of polymer aggregation, and of adsorption to the column material; lack of appropriate standards, etc.). In the few cases where the copolymers could be successfully eluted through SEC columns, the measured polydispersity indexes were rather low (1.10 for polyM3-*block*-polyM1, and 1.2 for polyM1-*block*-polyM5), corroborating the successful preparation of block copolymers. But the M_n values derived from calibration with polystyrene standards are only apparent. Therefore, the molar masses were estimated from the average copolymer composition, assuming that the molar mass of the first block is identical to the one of the macro RAFT agent engaged. The resulting analytical data of the block copolymers are listed in Table 2.

In preliminary investigations, the stimuli-sensitive amphiphilic behaviour of the various copolymers was studied by ^{1}H NMR spectroscopy, turbidimetry, and by dynamic light scattering (DLS). The latter two methods are sensitive to the formation of aggregates in the nanometer range, as typically formed by amphiphilic block copolymers in aqueous solution. Therefore, changes in the amphiphilic

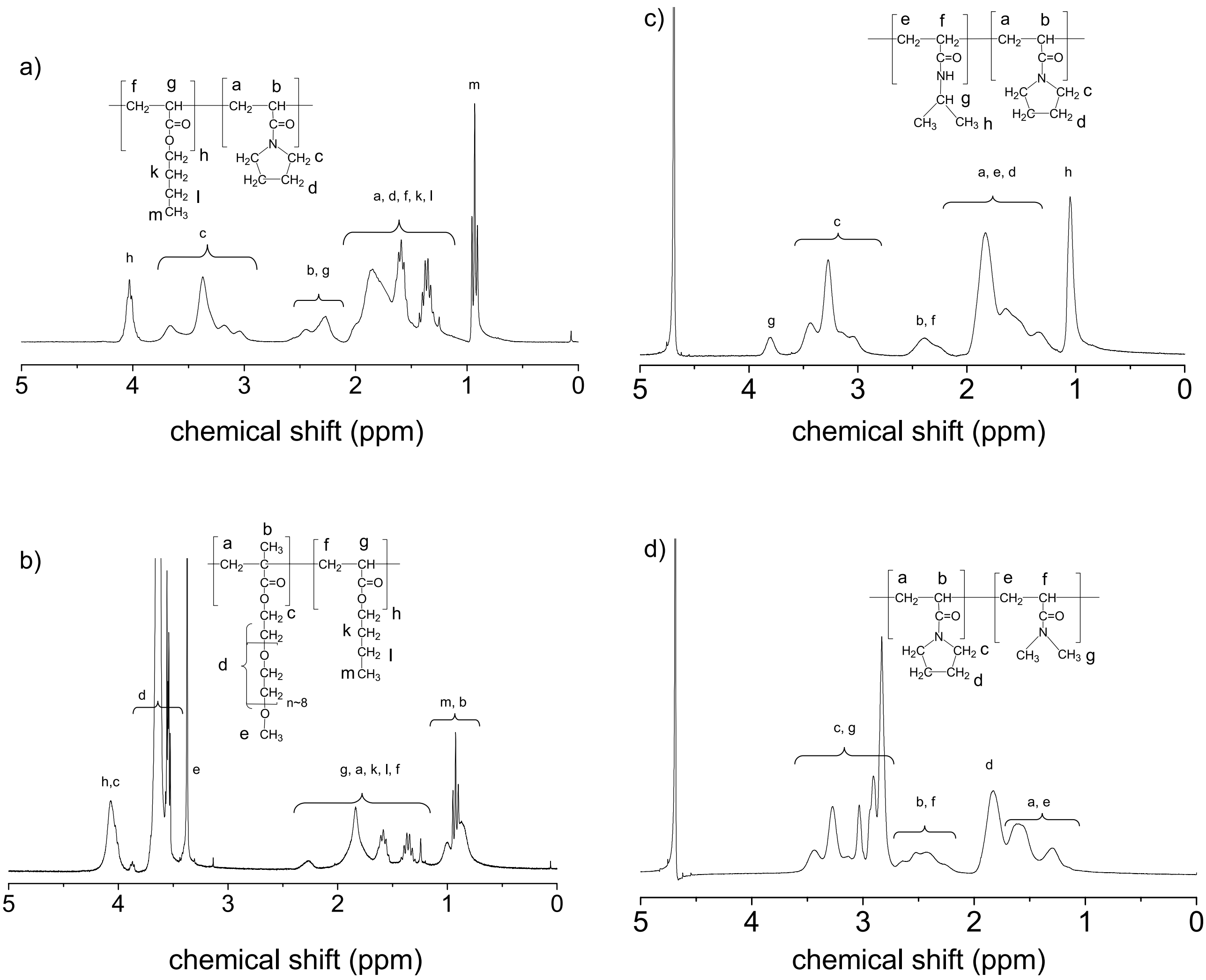


Fig. 4. ${}^1H$ NMR spectra of selected block copolymers. (a) PolyM1-*block*-polyM5 in $CDCl_3$, (b) polyM3-*block*-polyM1 in $CDCl_3$, (c) polyM6-*block*-polyM5 in D_2O, (d) polyM5-*block*-polyM4 in D_2O.

character of the copolymers should be reflected by changes of their hydrodynamic radii, and of their aggregate sizes. ${}^1H$ NMR spectroscopy is an easy qualitative test for the aggregation of the copolymers in D_2O, as the proton signals of the aggregating blocks become strongly broadened or even disappear eventually in the spectra, while the signals of the water-soluble block(s) persist.

First, the block copolymers polyM3-*block*-polyM1 and polyM1-*block*-polyM5 with a rather classical structure (Scheme 1(b)) were investigated. Both copolymers are amphiphilic at ambient temperature, but their hydrophilic blocks are expected to exhibit a LCST, i.e. they should become water-insoluble at elevated temperatures. Homopolymer polyM3 displays a cloud point at about 83 °C (Fig. 5(b)), whereas polyM5 shows a cloud point at 51 °C. No aggregates were detected by DLS at ambient temperature for the homopolymers. As none of these copolymers can be directly dissolved in water, they were first dissolved in a water-miscible organic solvent, which is good solvent for each of the blocks. In the case of polyM3-*block*-polyM1, THF was chosen as common organic solvent, whilst in the case of polyM1-*block*-polyM5, NMP was selected. Subsequently, the solutions were dialyzed extensively against water. This technique allows the continuous and slow exchange of solvents, avoiding the formation of large aggregates [27,28]. Indeed, the procedure resulted in transparent aqueous solutions of the block copolymers, for which DLS indicated the presence of aggregates in the nanometer range.

The distribution of the hydrodynamic radii of the aggregates obtained from polyM3-*block*-polyM1 as analysed by DLS is shown in Fig. 5(a). The thermal behaviour of these aggregates was followed by turbidimetry. Fig. 5(b) depicts the evolution of turbidity showing a cloud point at about 93 °C. The process is reversible upon cooling, with a small hysteresis of about 1 °C between the heating and cooling cycle. Interestingly, the precursor homopolymer polyM3 shows a cloud point of 83 °C under the identical conditions (Fig. 5(b)), i.e. the aggregated block copolymer

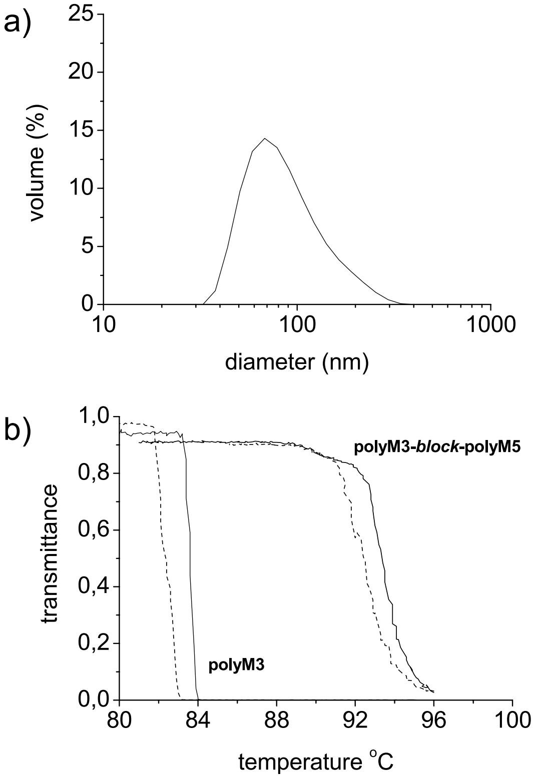


Fig. 5. (a) DLS analysis of particles prepared from polyM3-*block*-polyM1 in H_2O (1 wt%) at 25 °C. (b) Temperature dependent turbidity of 1 wt% aqueous solutions of polyM3 and polyM3-*block*-polyM1 (solid line, heating; dotted line, cooling; rate 1 °C/min).

exhibits a higher transition temperature. Such a behaviour matches well with the reported increase of LCST in tethered polymer brushes on surfaces [61], and may be explained by a hindered collapse of the polymer chains in confined geometry.

The aggregate size distribution of polyM1-*block*-polyM5 in aqueous solution is shown in Fig. 6(a) at 7 days and 3 months, respectively, after dialysis. Presumably, micellar aggregates with a diameter of 42 nm are observed in the solution, but a notable amount (ca. 10% by volume) of much larger aggregates coexist still 7 days after the preparation. These large aggregates almost disappeared after 3 months of storage at ambient temperature with no change of the micellar size, suggesting that the system needs a time long time to equilibrate, despite the low glass transition temperature of the hydrophobic block. This observation goes along with reports that amphiphilic block copolymers have much longer diffusion and exchange rates in water than analogous low molar mass surfactants [62,63]. Moreover, this observation demonstrates that the micellisation of the amphiphilic block copolymer, though kinetically slow, is thermodynamically favoured, as otherwise the larger aggregates would grow instead of disappear upon storage.

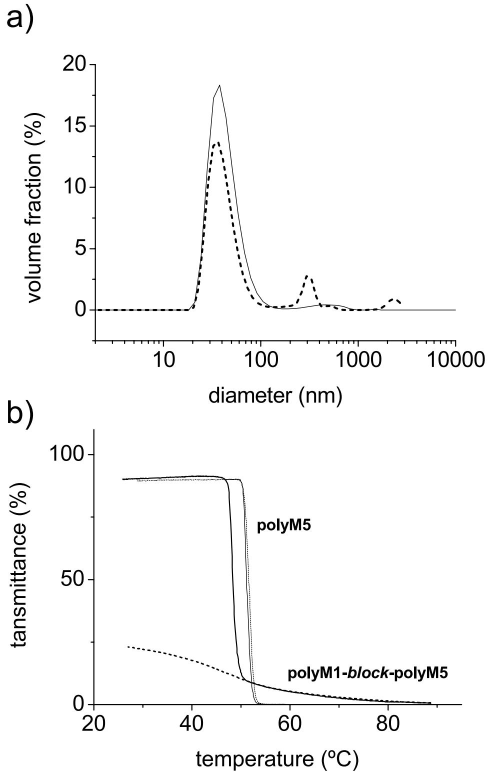


Fig. 6. (a) DLS analysis of particles prepared from polyM1-*block*-polyM5 in H_2O ($1.0\ g\ l^{-1}$) at 25 °C, 7 days (dotted curve) and 3 months after dialysis (solid curve). (b) Temperature dependent turbidimetry of 1 wt% aqueous solutions of polyM5 and polyM1-*block*-polyM5 (solid line, heating; dotted line, cooling).

The temperature sensitivity of the aggregation behaviour of polyM1-*block*-polyM5 was investigated with turbidimetry (Fig. 6(b)) and DLS (Fig. 7), in comparison to the behaviour of the homopolymer polyM5. As illustrated in Fig. 6(b), the solution of polyM5 shows a sharp increase of the turbidity at 51 °C upon heating which is reversible upon cooling. In contrast, the solution of polyM1-*block*-M5 shows a sharp increase of the turbidity at 46 °C, but this thermal transition is not reversible, as the solution remains turbid upon cooling. The DLS experiments shown in Fig. 7 provide some more information on the thermal switching. Obviously, polyM5 is molecularly dispersed in water below the cloud point and forms large aggregates (much bigger than 1 μm in diameter) above 50 °C, which rapidly sediment. The solution rapidly becomes clear upon cooling and the aggregates disappear. However, the micelles of polyM1-*block*-M5 with about 40 nm in diameter aggregate to bigger colloids of rather defined size (ca. 250 nm diameter) above the cloud point, which do not further aggregate and sediment only very slowly. Noteworthy, this secondary aggregation process is not reversible. DLS measurements performed after 10 days of annealing at 25 °C, after passing the sample over the cloud point, still show the presence of large aggregates of about 200 nm in diameter with a decreasing count rate, typical for sedimenting samples.

The irreversibility of the thermal transition as well as the lower cloud point of the block copolymer polyM1-*block*-M5

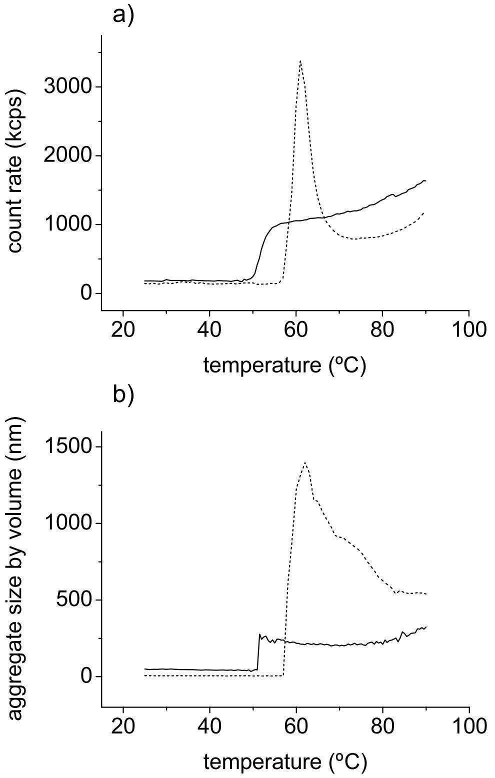


Fig. 7. Temperature sensitive aggregation behaviour of aqueous solutions ($c=1.0\ \mathrm{g\,l^{-1}}$) of homopolymer polyM5 (dotted curve) and block copolymer polyM1-*block*-polyM5 (solid curve), as followed by DLS. (a) Count rate, (b) average diameter of the colloids.

compared to the homopolymer polyM5 contrasts with the behaviour of the pair polyM3-*block*-polyM1/polyM3 (see above). Though the marked differences in aggregation behaviour are obvious, we can only speculate about the reasons at present. Compared to polyM3-*block*-polyM1, polyM1-*block*-polyM5 disposes of a larger hydrophobic block, and a smaller switchable hydrophilic one. Possibly, the overall more hydrophobic character of this block copolymer leads to larger and more stable aggregates when the hydrophilic block collapses beyond the cloud point. Thus, the redispersion of the copolymer is kinetically prevented, keeping in mind that the bulk compound does not disperse freely in water. The argument of the overall more hydrophobic character may be put forward, too, to explain the lower cloud point of polyM1-*block*-polyM5 compared to polyM5, whilst the pair polyM3-*block*-polyM1/polyM3 behaves oppositely. Clearly, more systematic studies on different temperature-sensitive block copolymers are needed to clarify this diversified behaviour.

The other synthesised block copolymers (Table 2) represent structures according to Scheme 1(c) and (d), and thus are all directly water soluble under appropriate conditions, i.e. when all blocks are water-soluble. Aggregation can only take place if at least one of the hydrophilic blocks is switched to a water-insoluble state. A priori, such block copolymers seem more attractive as stimuli-sensitive macro-surfactants than copolymers of type b in Scheme 1 (such as polyM1-*block*-polyM5 and polyM3-*block*-polyM1). This is not only by virtue of the ease of the preparation of their aqueous solutions, but also due to their potentially easier recovery: typically, surfactants in water are aimed at solubilising hydrophobic compounds. If the hydrophobic solubilisate ought to be separated later on, this is achieved by breaking the solution/emulsion via a stimulus-driven switching of the amphiphilic character of the emulsifier. Then, it will be much more practical to have the emulsifier stay in its inactive form in the aqueous phase, thus separating it from the solubilisate, than to have it go into the organic phase together with solubilisate [64].

Qualitatively, aggregation of these copolymers is easily detected by ^{1}H NMR spectroscopy in D_2O, as the proton signals of the aggregating blocks become strongly broadened or even disappear eventually in the spectra while the signals of the water-soluble block(s) persist. All the block copolymers made pass successfully this qualitative test of stimulus-sensitive switching, let it be by temperature change, pH change, or adjustment of the salt content.

PolyM5-*block*-polyM4 is a thermally sensitive macro-surfactant with a switchable hydrophobic block that is functional at high temperatures only (Scheme 1(c)). Measuring the temperature dependent aggregation in aqueous solution (Fig. 8) by turbidity, a cloud point was observed at 61 °C, i.e. about 10 °C higher than the cloud point of the precursor homopolymer polyM5 under the identical conditions (see also above and Figs. 6 and 7). The clouding is reversible, too, so that cooling yielded clear solutions again. In both respects, the behaviour of polyM5-*block*-polyM4 is analogous to the behaviour of polyM3-*block*-polyM1 discussed above, presumably for analogous reasons. However, according to the DLS studies (Fig. 8), the temperature-induced aggregation leads to large aggregates but which sediment only very slowly, different to the behaviour of the homopolymer polyM5 that flocculates above the cloud point. The structure of the large aggregates, for instance whether they are clusters of micelles [27,65], or

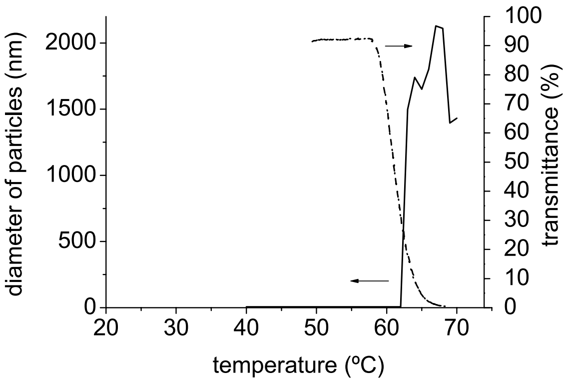


Fig. 8. Temperature sensitive aggregation behaviour of polyM5-*block*-polyM4 in 0.3 wt% aqueous solutions followed by turbidity (dashed curve, heating; dotted curve, cooling), and by DLS (solid curve).

vesicles [27,66], etc. is an open question at present and will require additional studies.

Copolymers polyM2-*block*-polyM9, polyM4-*block*-polyM9, and polyM7-*block*-polyM9 represent a new type of amphiphilic diblock copolymer with a stimulus-sensitive associating block according to Scheme 1(c), which is sensitive to the concentration and type of added salts. The key feature of these diblock copolymers is the insolubility of the zwitterionic block polyM9 in pure water, as polyM9 requires the presence of certain salts to become soluble (‘salting-in’ behaviour). DLS studies of these copolymers in aqueous NaBr and in pure water are exemplified in Fig. 9. To induce aggregation, the copolymers are first dissolved in brine, etc. and then dialyzed. PolyM2-*block*-polyM9 and polyM4-*block*-polyM9 form small aggregates in pure water, with a diameter of about 32 and 41 nm, respectively. If the polymer concentration is increased, the size of the aggregates grows, too. The aggregates are stable upon heating until at least 70 °C. But the aggregates redissolve in semi-concentrated solutions of certain salts such as NaBr. The efficiency of the anion in dissolving the aggregates increases from $ClO_4^- > Br^- > Cl^-$, i.e. it follows the Hofmeister series as frequently reported for other poly (sulfobetaine)s [20,67]. Typically, the salt controlled dissociation does not exhibit a sharp transition at a precise salt concentration, but the size of the aggregates decreases continuously with increasing salt content. The final particles with diameters well below 10 nm appear to be individual macromolecules. The analogous copolymer polyM7-*block*-polyM9 of similar size (Table 2), disposing with polyM7 of a permanently hydrophilic ionic block, behaves surprisingly differently. Whereas the block copolymer exhibits a hydrodynamic radius of about 10 nm in 0.5 M aqueous NaBr alike the two other copolymers containing M9, the polymer seems to collapse onto itself in pure water, forming extremely small, compact colloids (Fig. 9(c)). Speculating on the reasons, we presume an attractive interaction between the anionic and the zwitterionic monomer units in this copolymer, which leads to dense polymer coils and aggregates when not screened by salt. This hypothesis is based on the ^{1}H NMR spectra of block copolymers polyM7-*block*-polyM9 in 0.5 M NaBr in D_2O (Fig. 10), which show a marked broadening of the signals with increasing length of the zwitterionic block. The results for the block polymers containing polyM9 blocks are related to the observations on the salt-induced modification of aggregation of other block copolymers containing a permanently polyzwitterion block [37,68]. But the particular structure of M9 with a hydrophobic polymerisable moiety and a rather hydrophobic betain group renders the amphiphilic transition much more pronounced for systems containing polyM9.

PolyM6-*block*-polyM5 is one of the rare examples for thermally sensitive macro-surfactants with two switchable

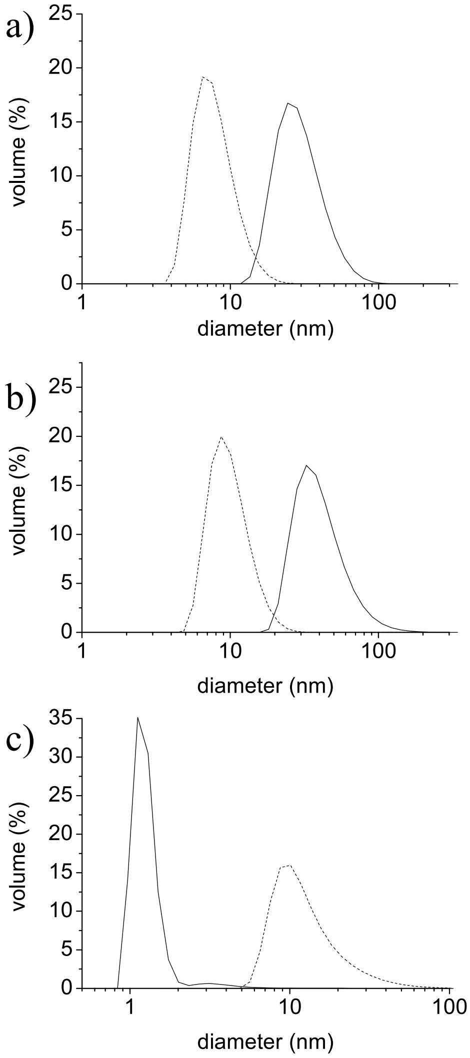


Fig. 9. DLS studies of 0.5 wt% solutions of diblock copolymers in 0.5 M aqueous NaBr (dotted lines) and after dialysis of these salt solutions against water (solid lines). (a) PolyM2-*block*-polyM9, (b) polyM4-*block*-polyM9, and (c) polyM7-*block*-polyM9.

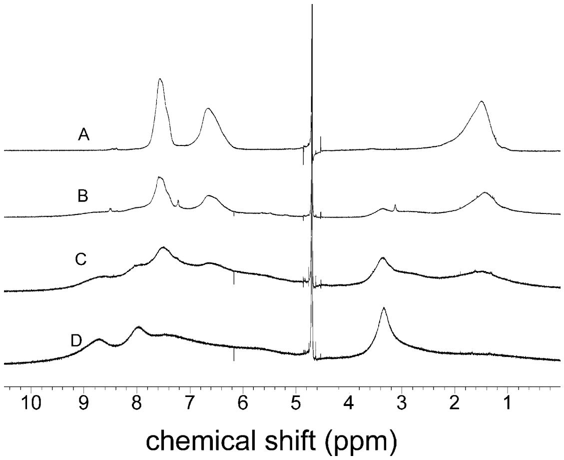


Fig. 10. ^{1}H NMR spectra of polyM7 in D_2O (A), and polyM7-*block*-polyM9 in 0.1 M NaBr in D_2O, with growing size of the polyM9 block as $M_n = 8 \times 10^3$, 13×10^3, and 23×10^3 for (B), (C) and (D), respectively. The size of the polyM7 block is $M_n = 22 \times 10^3$ for all samples.

blocks (Scheme 1(d)) [22,23,37,41,42,54–57]. It behaves as amphiphile at intermediate temperatures only, whereas it is double-hydrophilic at low, and double-hydrophobic at high temperatures. The temperature sensitivity of the aggregation behaviour was investigated with turbidimetry and DLS (Fig. 11), and compared to the behaviour of the two homopolymer blocks polyM5 and polyM6. Whereas the solution of polyM5 shows a sharp increase of the turbidity at 52 °C (Figs. 6(b) and 7) and the one of polyM6 at 30 °C (not shown), the apparent cloud point of polyM6-*block*-polyM5 is in between at 41 °C. But a closer look to Fig. 11 reveals that the transmittance is already partially reduced in the temperature range between 30 and 41 °C and passes through a local minimum, suggesting a two-step aggregation process. Both polyM5 and polyM6 flocculate from their solution when heated beyond their cloud points. But the solution of polyM6-*block*-polyM5 was stable in the range between 30 and 41 °C, and the copolymer precipitated only slowly when heated above the cloud point. Interestingly, cooling of the turbid solutions below 41 °C provided completely transparent solutions, i.e. only one dissociation step is detected by turbidimetry. The temperature dependent DLS experiments in Fig. 11 show that indeed a two-step thermal switching is achieved. Above 30 °C, i.e. above the cloud point of polyM6, aggregates are formed whose hydrodynamic diameter passes through a maximum of about 500 nm at 36 °C before dwindling to a value of about 50 nm. Above the cloud point of 41 °C, the size of the aggregates increases strongly again, reaching permanently 300 nm and more. It is interesting to notice that the thermal transition temperature of the polyM6 block in the copolymer is very close to the one of homopolymer (as often observed for block and graft copolymers of M6 [22,37,42]), while the second thermal transition of the polyM5 block takes place about 10 °C lower than the one of the homopolymer. From these findings it is obvious that polyM6-*block*-polyM5 exhibits a two-step aggregation in water. But the detailed behaviour seems complex and is not easy to understand on the basis of the few current observations. In particular the initial strong increase and subsequent decrease of the aggregate size in the intermediate temperature range, where the copolymer should be amphiphilic, is difficult to rationalise at present. Perhaps, transitions between micellar and vesicular aggregates are involved. More investigations are necessary to clarify the double thermally sensitive behaviour of the block copolymer.

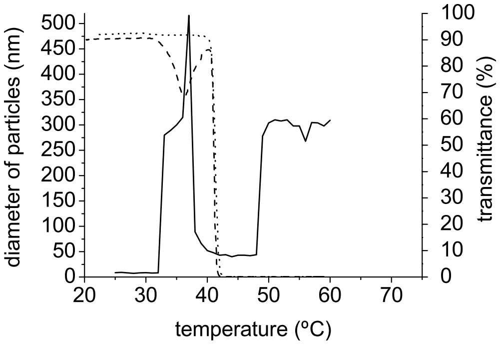
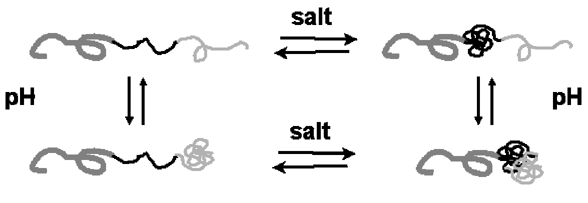


Fig. 11. Temperature sensitive aggregation behaviour of polyM6-*block*-polyM5 in 0.3 wt% aqueous solutions, followed by turbidity (dashed curve, heating; dotted curve, cooling), and by DLS (solid curve).

In the light of the salt sensitive aggregation of block copolymers polyM2-*block*-polyM9, polyM4-*block*-polyM9, and polyM7-*block*-polyM9 (Fig. 9), and of reports on the pH-sensitive aggregation of block copolymer polyM7-*block*-polyM8 [51,52,69], the synthesised triblock polymers polyM2-*block*-polyM9-*block*-polyM8, polyM4-*block*-polyM9-*block*-polyM8, and polyM7-*block*-polyM9-*block*-polyM8 were expected to be sensitive to two orthogonal stimuli, namely pH changes and salinity changes of their aqueous media. DLS measurements were used to follow their stimuli-sensitive behaviour, applying neutral and acidic pH, and varying the concentration of NaBr from 0 to 0.5 M. As the sequence of aggregation steps may be varied for two independent stimuli (Scheme 2), we also looked into the effect of changing the order of the transitions. Fig. 12 illustrates the effects on induced aggregation by applying the ‘salt switch’ first (rendering the central block water-insoluble), whereas Fig. 13 shows the effect of applying the ‘pH-switch’ first (rendering one of the external blocks water-insoluble). These preliminary experiments exemplify that the behaviour encountered is rich and complex. In particular, it becomes evident that detailed molecular parameters are important, beyond having an ABC triblock copolymer in which the blocks B and C can change their water-solubility reversibly by an external stimulus.

Copolymer polyM2-*block*-polyM9-*block*-polyM8 shows a hydrodynamic diameter of ca. 10 nm in 0.5 M aqueous NaBr at ambient pH. When the NaBr is removed by dialysis, the polyzwitterion central block collapses, and a compact structure with a diameter of 3 nm is observed (Fig. 12(a)). Possibly, the two external hydrophilic blocks prevent the molecules from intermolecular association and thus, molecular micelles are formed. Adjusting subsequently the pH to 1, the block polyM8 becomes hydrophobic additionally, resulting in the formation of aggregates with a diameter of about 10 nm. Noteworthy, the scattering signal is much stronger than for the original polymer, indicating the presence of small, but compact aggregates (Fig. 12(a)). When the switching sequence is reversed (Fig. 13(a)), the collapse of the small external polyM8 block does not change



Scheme 2. Idealised model for the behaviour of the salt- and pH-sensitive triblock copolymers, when exposed to different sequences of stimuli.

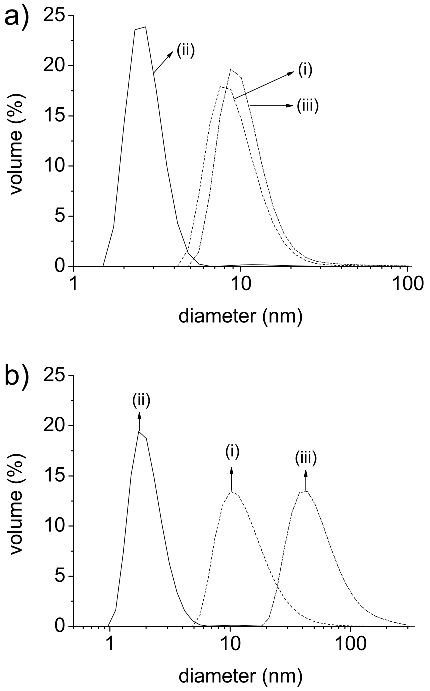


Fig. 12. DLS analysis of the triblock copolymers (a) poly(M2-*b*-M9-*b*-M8), (b) poly(M7-*b*-M9-M8). (i) 0.5 wt% solutions of block-polymers were prepared in 0.5 M (aq) NaBr (dashed line), (ii) polymer solutions were dialyzed against DI water (pH = 5.8) (straight line), (iii) pH of solutions were arranged to pH 1 by addition of 1 M (aq) HCl (dash dot dash).

the size of the structure notably, though increasing the scattering intensity. The subsequent collapse of the central polyM9 block induced by dialyzing the NaBr, however, leads to aggregate growth resulting in particle diameters of about 30 nm. Apparently, the small hydrophobic domains created by the first transition favour intermolecular aggregation during the collapse of the second, central block.

Though structurally synthesised according to the same design (permanently hydrophilic block-betaine block-carboxylate block), copolymer polyM7-*block*-polyM9-*block*-polyM8 behaves even qualitatively differently. As for the previously discussed triblock copolymer, when NaBr is removed by dialysis, the polyzwitterion central block collapses, and a compact structure with a diameter of 2.5 nm is seen (Fig. 12(a)). But adjusting subsequently the pH to 1, thus rendering the polyM8 block water-insoluble, too, results in the formation of larger aggregates with a diameter of about 45 nm. (Fig. 12(b)). When inverting the switching sequence, (Fig. 13(c)), the collapse of the external polyM8 block induces directly colloids with 56 nm diameter, whereas the subsequent collapse of the central polyM9 block after dialyzing the NaBr, leads to a shrink of the aggregates diameter to about 45 nm. It seems that the second transition takes place only within the aggregates, thus reducing the hydrodynamic radius.

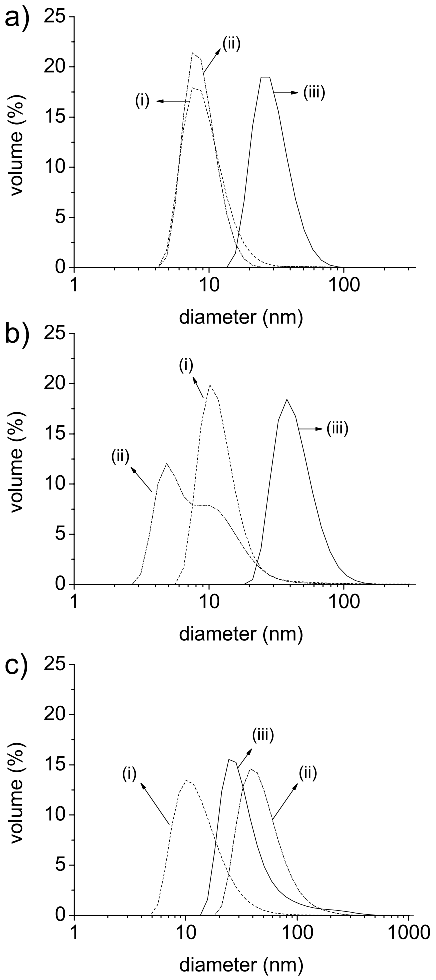


Fig. 13. DLS analysis of the triblock copolymers (a) poly(M2-*b*-M9-*b*-M8), (b) poly(M4-*b*-M9-*b*-M8), (c) poly(M7-*b*-M9-M8). (i) 0.5 wt% solutions of block-copolymers were prepared in 0.5 M (aq) NaBr, (ii) polymer solutions were dialyzed against 0.5 M (aq) NaBr having pH of 1.8, (iii) polymer solutions were dialyzed against DI water having pH of 2.5.

On the basis of the few preliminary studies, it is difficult to explain the strongly contrasting behaviour of polyM2-*block*-polyM9-*block*-polyM8 and polyM7-*block*-polyM9-*block*-polyM8. Except for the central block of polyM9 which has a similar size (Table 2), the size and the shape of the external blocks vary strongly in the two samples. The specific interaction of the polyM7 and polyM9 blocks in the latter triblock copolymer (Fig. 10) may also play a role. In any case, it is obvious that the detailed molecular structure affects the switched aggregation markedly. This individuality is corroborated by the behaviour of the third analogously designed triblock copolymer, polyM4-*block*-polyM9-*block*-polyM8 (Fig. 13(b)). For this polymer, acidifying of the polymer solution reduces the diameter of the structure, and broadens the size distribution, whereas the subsequent dialysis, removing the salt, induces aggregation to particles of 45 nm in diameter.

Taken together, the preliminary switching experiments on the double-sensitive triblock copolymers demonstrate that indeed two-step switching is possible, while maintaining homogeneous, clear solutions with aggregate sizes in the nano-particle range. It becomes clear that the sequence of switching is of major importance for the induced aggregation of a given polymer. However, the association behaviour encountered varies strongly for different polymers, even when having the same block architecture.

4. Conclusions

The RAFT process is a powerful method to prepare functional polymers of complex structure, even when containing strongly hydrophilic moieties, and even when performed in aqueous solution. Amphiphilic diblock and triblock copolymers thus become conveniently accessible. Preliminary studies on the switching of the hydrophilic character of single or several blocks by changing the pH, the temperature or the salt content demonstrated the variability of the molecular designs suited for stimuli-sensitive polymeric amphiphiles. Furthermore, they gave a first idea of the wealth of aggregated structures, which can be obtained. In particular, the usefulness of added salt as alternative stimulus was demonstrated for polyzwitterion blocks, and the opportunities of multiple-sensitive systems were exemplified.

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