

Review

## Water-Soluble Stimuli Responsive Star-Shaped Segmented Macromolecules

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**Abstract:** Star shaped segmented macromolecules constitute an interesting class of polymeric materials whose properties differ remarkably from those appearing in their linear counterparts. This review highlights the work done in the last decade, dealing with the self-assembly of star-shaped block copolymers and terpolymers of various topologies in aqueous media. This article focuses on a specific class of star shaped macromolecules designated as stimuli responsive. These stars bear block/arms undergo sharp phase transitions upon responding to stimuli, such as temperature, pH, ionic strength and so forth. These transitions impose dramatic transformations on the morphology and, accordingly, in the functionality of the nanostructured associates. The number of arms, the specific functionality and topology of the different arm/blocks and the overall macromolecular architecture of the star polymer, significantly influence their behavior in terms of self-assembly and responsiveness.

**Keywords:** star-shaped segmented macromolecules; stimuli responsive; self-assembly

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## 1. Introduction

Synthetic methods based on “living”/controlled polymerization techniques offer numerous possibilities for designing tailor-made segmented macromolecules with sophisticated architectures and specific functionalities [1,2]. Among the plethora of macromolecular architectures that have so far appeared, star-shaped block copolymers and terpolymers have received a great deal of attention over the years, thanks to their topological symmetry, controllable monomer density and high chain-end functionality, which impart novel intriguing properties.

Water-soluble segmented macromolecules have attracted tremendous interest in the last decade, either in amphiphilic or “double” hydrophilic mode, due to their ability to self-assemble spontaneously in aqueous media forming nanoobjects of unique morphologies and functionalities, useful for various applications in cosmetics, paints, pharmaceuticals, tissue engineering and so forth [3-7].

The aim of this review is to demonstrate the work done in the last decade, dealing with the self-assembly of star-shaped block copolymers and terpolymers in aqueous controlling environments. Particularly, this article focuses on the so-called stimuli responsive star polymers, which are stars bearing block/arms undergoing sharp phase transitions upon responding to a stimulus such as temperature, pH, ionic strength or combinations of these stimuli.

Temperature-responsive, segmented stars are one of the types that have been developed and widely explored in aqueous media. The common feature of these stars is that they bear arms exhibiting thermo-sensitivity in the temperature range of interest. This thermo-sensitivity usually relies on the reversible thermal phase transition of a polymer-solvent mixture characterized by a critical solution temperature. Two cases can be distinguished. The polymer becomes insoluble by increasing temperature above the so called lower critical solution temperature (LCST) which, in fact, is a coil to globule chain conformational transition, or in terms of interactions with the aqueous environment, a hydrophilic to hydrophobic transition. Reverse phenomena occur, in the second case, and the critical temperature is named upper critical solution temperature (UCST).

pH is another very important stimulus which has been taken into account in designing responsive star-shaped copolymers and/or terpolymers. Suitable building arms for this purpose are those exhibiting weak polyelectrolyte (polyacid or polybase) features. The pH-sensitivity of these responsive arms relies on the protonation/deprotonation equilibrium which depends on the  $pK_a$  of the acidic and/or basic moieties of the polymeric chain. Thus at a certain pH, a block polyelectrolyte can be charged at a given degree of ionization and sign (positively or negatively), or it may be completely uncharged (hydrophobic). Accordingly their state controls solubility and the kind of interactions (electrostatic or hydrophobic) that they can develop. For instance, poly(vinyl pyridine) ( $pK_a \sim 5$ ) blocks are water soluble and positively charged at pH lower than 5, whereas, they become hydrophobic above pH 5. On the other hand, poly(acrylic acid) is poorly soluble in water at low pH, capable of developing H-bonding and becomes a negatively charged polyelectrolyte at high pH. Thus pH variation may impose dramatic changes in the conformation of the polyelectrolyte chains (from globule to fully extended), affecting strongly the association ability of the star copolymer.

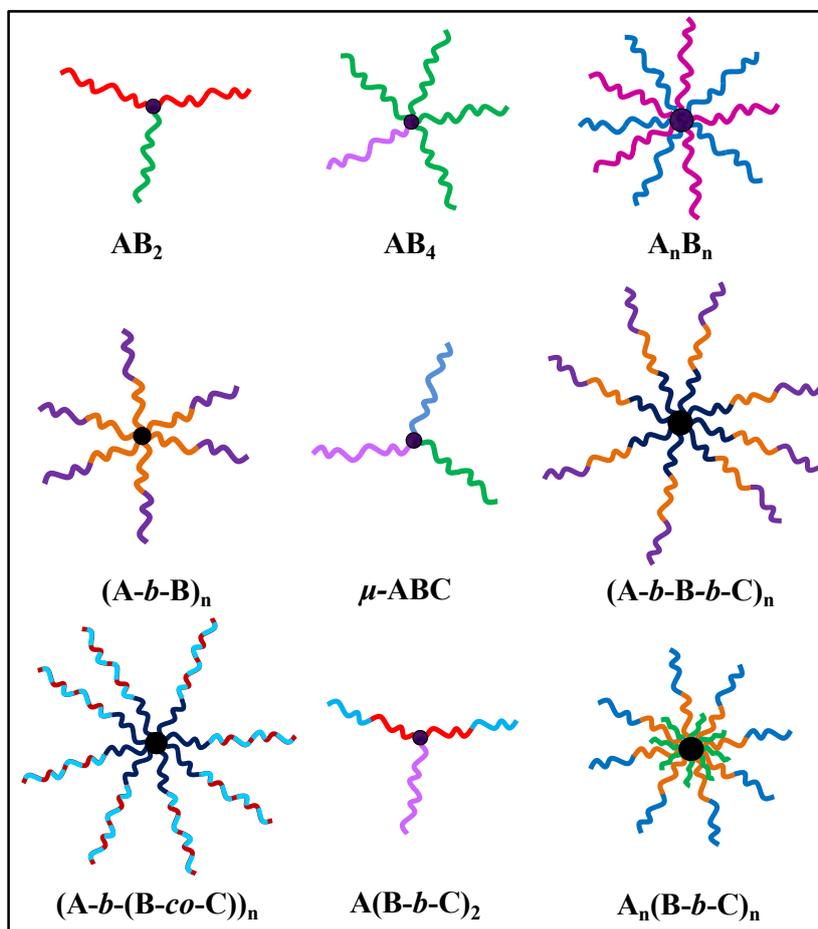
Therefore, these kinds of transitions may induce spontaneous self-organization of a double hydrophilic star and/or impose a dramatic transformation on the morphology and, in turn, on the functionality of the nanostructured self-assemblies, which has been resulted through reversible

hydrophobic association of amphiphilic stars, exhibiting in both cases new properties and, thus, creating novel potential applications.

## 2. Star-Shaped Topologies

Star-shaped polymers comprise of a number of linear macromolecular chains (arms) all linked to a central nodule. Segmented stars are those bearing at least two kinds of segments (block) either as pure arms or as block copolymer arms. A number of synthetic strategies have been developed, based on “living” controlled polymerization methods that have led to a variety of star copolymers, consisting of two different monomers, and terpolymers (comprising three types of repeating units), exhibiting specific block/arm topologies [8-17]. Schematic representation of a number of different segmented stars is shown in Scheme 1; the aqueous solution properties of which are demonstrated in the present review. It should be underlined from the beginning, that the topology (exact position) of the various segments in the star-shaped architecture plays a crucial role in their self-assembly capabilities and resulting morphologies and thus by controlling topology, one could tune the end-properties of these polymeric materials.

**Scheme 1.** Schematic representation of star-shaped segmented polymers:  $A_nB_n$  heteroarm star copolymer,  $AB_2$ ,  $AB_4$  miktoarm star copolymers,  $(A-b-B)_n$  star block copolymer,  $\mu$ -ABC miktoarm star terpolymer,  $A(B-b-C)_2$ ,  $A_n(B-b-C)_n$  heteroarm star block terpolymers,  $(A-b-B-b-C)_n$  star-block terpolymer,  $(A-b-(B-co-C))_n$  block random star block terpolymer.



### 3. Star-Shaped Block Copolymers

#### 3.1. AB<sub>2</sub> Miktoarm Star Copolymers

Stimuli responsive zwitterionic AB<sub>2</sub> miktoarm star copolymers composed by a weak cationic polyelectrolyte PDEAEMA [poly(2-(diethylamino)ethyl methacrylate)] arm and two weak anionic polyelectrolyte PSEMA [poly(succinyloxyethyl methacrylate)] arms were designed and explored in aqueous media. Two copolymers that differed in the PSEMA content *i.e.*, PDEAEMA<sub>50</sub>-(PSEMA<sub>24</sub>)<sub>2</sub> and PDEAEMA<sub>50</sub>-(PSEMA<sub>47</sub>)<sub>2</sub>, were studied [18]. From zeta potential measurements as a function of pH, it was found that the neutralization pH (isoelectric point, *iep*) depends on the PSEMA content. At low pH values below *iep*, the positive charges predominated, due to the protonated PDEAEMA arm, whereas at high pH, the copolymer was negatively charged due to the deprotonation of the PSEMA arms. These stars exhibit the so called “schizophrenic” behavior: at low pH, well-defined large core-shell micelles were formed with PSEMA hydrophobic core and PDEAEMA shell while at basic conditions, inverted core shell micelles were formed with PDEAEMA hydrophobic core and PSEMA shell.

The same architecture, *i.e.*, Y-shaped, AB<sub>2</sub> stars, containing DEAEMA, glycerol monomethacrylate (GMA) or sulfobetaine methacrylate (SBMA), were synthesized by atom transfer radical polymerization (ATRP) using two macroinitiator precursors (denoted as JM) that originated from monoamine-capped poly(alcylene oxides). The pH- or thermo-sensitivity of these copolymers in aqueous solutions was studied using <sup>1</sup>H NMR, dynamic light scattering (DLS) and surface tensiometry [19,20]. The pH sensitive JM<sub>1000</sub>-(DEAEMA<sub>10</sub>)<sub>2</sub> star, in the pH range 2 < pH < 7, did not self associate as DEAEMA was protonated. For pH > 7, self-assembly of the polymer was detected with the micelles formed consisting of hydrophobic, deprotonated DEAEMA cores. The JM<sub>2005</sub>-(GMA<sub>20</sub>)<sub>2</sub> exhibited thermo-responsive micellization due to the thermosensitive propylene oxide-rich JM<sub>2005</sub> block, exhibiting LCST. This block is water soluble at low temperature but precipitates at higher temperatures.

In the same work, the “schizophrenic” thermo-responsive behavior of the Y-shaped JM<sub>2005</sub>-(SBMA<sub>10</sub>)<sub>2</sub> star copolymer was demonstrated. It is known that the PSBMA homopolymer is water-insoluble below 20 °C but turns water-soluble above 20 °C (UCST behavior). Consequently, in sufficiently low temperature (0 °C < T < 10 °C), the PSBMA arms collapsed and the stars self-assembled forming large micelles with PSBMA hydrophobic cores and the propylene oxide-rich JM<sub>2005</sub> arms forming the micelle hydrophilic coronas. At intermediate temperature (12 °C < T < 30 °C), both JM<sub>2005</sub> and PSBMA arms became hydrophilic, leading to the molecular dissolution of the star, existing as unimers. By increasing temperature above the cloud point of the JM<sub>2005</sub> block (30 °C < T < 45 °C), large micelles were spontaneously formed with a hydrophobic JM<sub>2005</sub> core and a PSBMA corona. Finally, above 45 °C, near-monodisperse compact JM<sub>2005</sub>-core spherical micelles were observed.

A well defined polypeptide based, poly(L-lysine), PLL/poly(L-glutamic acid), PLGA, Y-shaped, miktoarm star, PLL-*b*-(PLGA)<sub>2</sub>, was synthesized combining ring opening polymerization (ROP) polymerization and click chemistry and investigated in aqueous solutions by varying pH [21]. It is well known that PLGA and PLL will adopt a random coil conformation in aqueous solution at alkaline and acidic pH conditions, respectively, due to the ionization of side carboxyl groups and protonation of primary amine residues. The water-solubility for PLGA and PLL will considerably decrease in acidic

and alkaline media, respectively, due to the pH-induced coil-to-helix transition. Thus, a pH-sensitive self-association “schizophrenic” behavior of this segmented star polypeptide was revealed in aqueous media. At acidic environment, it formed PLGA-core micelles while at basic solution, it self-assembled in PLL-core micelles, in good agreement with the behavior of their diblock counterpart [22].

### 3.2. $AB_4$ Miktoarm Star Copolymers

A well-defined double hydrophilic  $AB_4$  miktoarm star copolymer, PNIPAM(PDEAEMA)<sub>4</sub> was synthesized by ATRP and its self-assembly and responsive behavior was investigated in aqueous solutions via <sup>1</sup>H NMR and laser light scattering (LLS) [23]. Due to the thermo-sensitivity of poly(N-isopropylacrylamide) (PNIPAM) and pH-sensitivity of PDEAEMA arms, this star exhibits a dual responsiveness. In acidic conditions (pH 4) and at room temperature, the star copolymer was molecularly dissolved in the aqueous solution whereas at specific environmental conditions, it exhibited schizophrenic behavior. More precisely, at elevated temperatures ( $T = 40\text{ }^\circ\text{C}$ ), PNIPAM-core and PDEAEMA-corona micelles were formed, while in basic environment (pH 9) and at room temperature, structurally inverted micelles were observed with a PDEAEMA hydrophobic core and PNIPAM corona.

### 3.3. $A_nB_n$ Symmetric Heteroarm (Miktoarm) Star Copolymers

Symmetric heteroarm star copolymers of the  $A_nB_n$  type (equal number of A, B arms), bearing hydrophobic and hydrophilic pure arms have been studied in aqueous media. Polystyrene/poly(2-vinyl pyridine)  $PS_nP2VP_n$  stars formed unimolecular micelles at low concentrations and in acidic aqueous solutions, in which the P2VP arms were protonated (at  $\text{pH} < 4.8$ ), adopting a stretched chain conformation whereas, the PS hydrophobic arms collapsed in the star nodule [24,25]. At higher concentrations, polymolecular micelles could be formed with aggregation numbers,  $N_{agg}$ , significantly lower than those observed in linear AB counterparts [24-26].  $N_{agg}$  decreased with the number of arms and with increasing length of the soluble arms (P2VP) as compared to insoluble arms (PS).

Thanks to the polyelectrolyte nature of the hydrophilic P2VP arms, the hydrodynamic radius of these micelles is sensitive to the presence of small ions (salt) in the solution. It was observed, that upon increasing the ionic strength, the repulsions between the positively charged 2VP groups were screened, and the shell forming polyelectrolyte arms relaxed from stretched to more coiled conformations, resulting to significant shell thickness decrease [26].

These  $PS_nP2VP_n$  self-assemblies were also sensitive to pH, since deprotonation of the P2VP above pH 4.8 induces precipitation of the copolymers as it turned from amphiphilic to hydrophobic. However reversible onion skin micelles could be stabilized at basic conditions in the presence of P2VP-PEO diblock copolymers, where PEO is poly(ethylene oxide). These micelles comprise three compartments: a compact PS core, a fairly thin and compact middle layer, formed by collapsed non-protonated P2VP arms from the original  $PS_2P2VP_n$  micelles and the P2VP blocks of the P2VP-PEO diblocks and the protective PEO shell. The onion-skin micelles dissociated into original  $PS_nP2VP_n$  micelles and dissolved P2VP-PEO copolymers upon switching pH below 4.8 [26].

The association behavior of another pH sensitive heteroarm star copolymer consisted of a well-defined hexabiphenyl core, six hydrophilic poly(acrylic acid) (PAA) arms and six hydrophobic

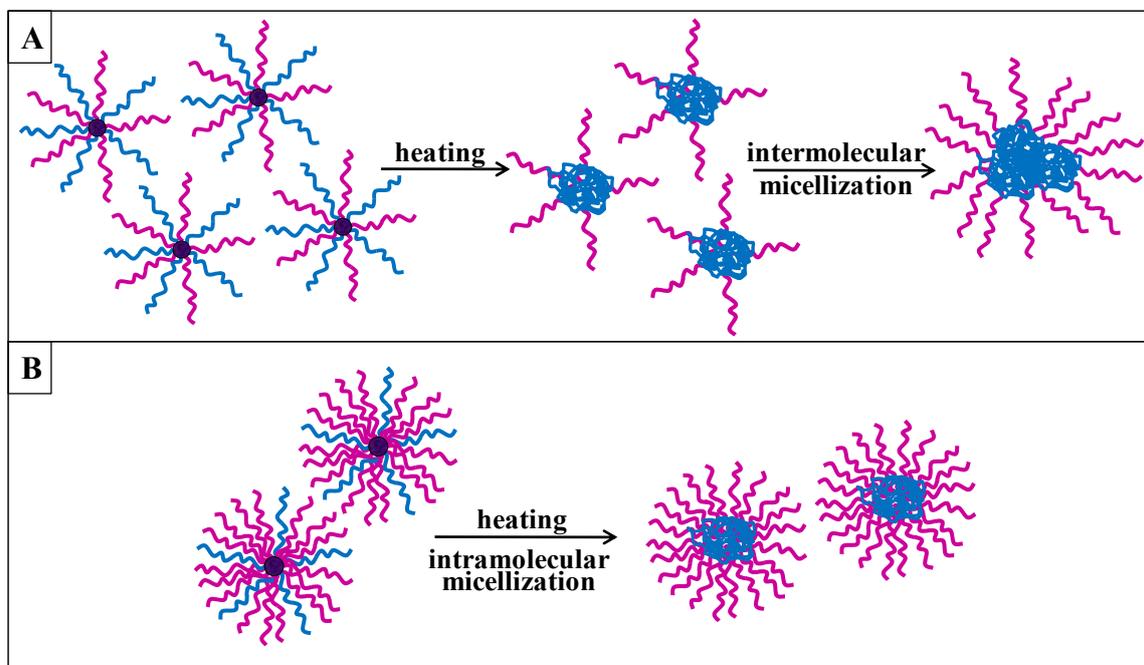
PS arms, (PS<sub>6</sub>PAA<sub>6</sub>) was studied in aqueous solutions by TEM. It was revealed that quite uniform round-shaped objects with PS arms in the core and PAA arms in the periphery were formed while, upon increasing polymer concentration, transition from spherical to cylindrical wormlike micelles occurred [27].

From early studies it was observed that amphiphilic heteroarm stars constituted of hydrophobic and polyelectrolyte arms form very viscous aqueous systems at relatively low concentrations [28,29]. Recently, this issue was explored in PS<sub>8</sub>P2VP<sub>8</sub> acidic salt-free aqueous media [30]. The results showed that intermolecular hydrophobic association prevails in the dilute regime, where colloidal soft nanoparticles constituted of about 6 stars, were formed. Far above the overlap concentration, determined at  $c^* = 0.05$  wt%, (*i.e.*, at about  $40c^*$ ), a fluid to soft solid transition was observed, leading to a colloidal gel due to crowding effects (jamming transition). In the extended concentration regime between the hydrodynamic overlap concentration and the jamming transition, a continuous compaction of the star-like soft nanoparticles prior to interdigitation seemed to occur, in qualitative agreement with the scaling theory for star polyelectrolytes [31].

#### 3.4. $A_nB_m$ Asymmetric Miktoarm (Heteroarm) Star Copolymers

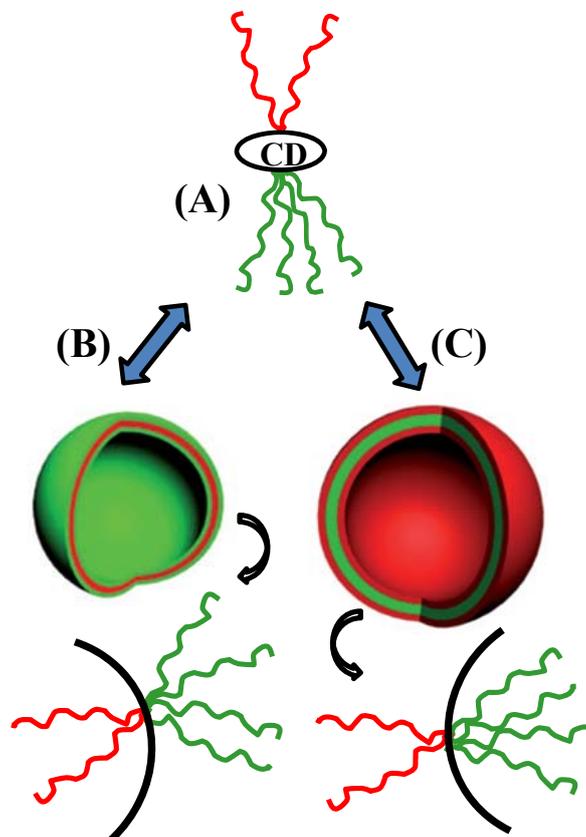
Double hydrophilic PNIPAM<sub>n</sub>-PEG<sub>m</sub> miktoarm star copolymers, were synthesized by combining reversible addition fragmentation chain transfer (RAFT) arm-first technique and aldehyde-aminoxy click reaction [32]. The synthetic method allowed the control of the second generation of PEG arms by varying the feed ratio of the aldehyde-aminoxy click reaction. These star copolymers consisted of biocompatible hydrophilic poly(ethylene glycol) (PEG) arms and the thermo-responsive PNIPAM arms. A thermo-induced micellization behavior in water was observed upon increasing temperature, which depends on the PEG/PNIPAM arm number ratio (Scheme 2). For instance, in the case of the PNIPAM<sub>13</sub>PEG<sub>14</sub> miktoarm stars, that contains a relative small number of PEG arms, optical transmittance measurements showed that the polymer solution turned from transparent and colorless to bluish at  $\sim 31$  °C. At this temperature the PNIPAM blocks became hydrophobic and collapsed into hydrophobic segments. Thus, the double hydrophilic star terpolymer was transformed into an amphiphilic one which leads to intermolecular hydrophobic association and the formation of micelles comprising collapsed PNIPAM cores and stretched PEG coronas. Upon incorporation of high number of PEG arms, *i.e.*, PNIPAM<sub>13</sub>PEG<sub>38</sub>, the hydrophobic/hydrophilic balance was substantially altered towards hydrophilic. Thus, the optical transmittance did not demonstrate any temperature dependence, leading to the conclusion that the PEG content was enough to prohibit any intermolecular aggregation upon heating and this was also confirmed with dynamic light scattering experiments. <sup>1</sup>H-NMR studies revealed that unimolecular micelles were formed in this case [Scheme 2(B)]. Comparing the behavior of symmetric  $A_nB_n$  and asymmetric  $A_nB_m$  heteroarm stars, it is evident that in the latter case the possibility of tuning the number of the hetero-arms provides another means to tune the stimulus-induced self-organization of these star macromolecular architectures.

**Scheme 2.** Thermo-induced micellization behavior of the PNIPAM<sub>13</sub>PEG<sub>m</sub> star copolymer. **(A)** For relative small number of PEG arms, multimolecular micelles were formed. **(B)** For large number of PEG arms, unimolecular micelles were observed. PEG and PNIPAM arms are denoted with magenta and light blue colors, respectively. The scheme was inspired by [32].



Similar “schizophrenic” behavior to that reported for PNIPAM(PDEAEMA)<sub>4</sub> was also demonstrated by a double hydrophilic heteroarm star copolymer comprising 7 PDEAEMA and 14 PNIPAM arms, emanating from the two opposing sides of the rigid toroidal  $\beta$ -cyclodextrine ( $\beta$ -CD) core [(PDEAEMA)<sub>7</sub>-CD-(PNIPAM)<sub>14</sub>] [33]. This Janus type star copolymer (the different arms were segregated at will via chemistry) self assembled into two distinct types of vesicles with inverted nanostructures, by adjusting the pH and temperature values. At pH 4 and at 45 °C, the PNIPAM arms became hydrophobic while the PDEAEMA arms were fully protonated and therefore, vesicular aggregates were formed with a PNIPAM hydrophobic core and hydrophilic PDEAEMA corona. At pH 10 and at 25 °C, the star formed vesicles with deprotonated and hydrophobic PDEAEMA bilayers surrounded by hydrophilic PNIPAM coronas (Scheme 3). Dynamic light scattering results suggested that the thermo-induced vesicles (PNIPAM-core) were much larger than the pH-induced ones (PDEAEMA-core) which seems to be due to the significant asymmetry of the number of the different arms. It should be noticed that the formation of two types of vesicles, possessing “inverted” nanostructures from star-shaped double hydrophilic block copolymers was reported for the first time and it was rather unexpected since vesicles from linear diblock copolymers need a delicate design of relative block lengths and proper hydrophilic/hydrophobic balance [34].

**Scheme 3.** Schematic representation of stimuli-responsive self-assembly of PDEAEMA<sub>7</sub>PNIPAM<sub>14</sub> star copolymer: **(A)** Unimers at pH 4 and 25 °C. **(B)** Vesicles at pH 10 and 25 °C. **(C)** Inverted vesicles at pH 4 and 45 °C. The number of arms has been simplified. The scheme was inspired by [33].



Asymmetric double hydrophilic heteroarm stars were designed bearing two hydrophilic PEO arms and 3 or 4 stimuli responsive poly(dimethylaminoethylmethacrylate) (PDMAEMA) arms respectively [35]. The scope of this study was to take advantage of the unique phase behavior of the PDMAEMA arms that exhibit LCST at high pH (uncharged state), as well as UCST in the presence of trivalent anions [36]. The micellization of the polymers was investigated by light scattering, fluorescence spectroscopy and cryogenic transmission electron microscopy (cryo-TEM). At pH 8, PDMAEMA turned hydrophobic around 55 °C, forming micelles at higher temperatures. At low temperature, trivalent counterions like hexacyanocobaltate(III) allowed additional micellization of the weak polyelectrolyte PDMAEMA, with PEO arms forming the protective corona. The morphology of the aggregates depends strongly on the number and the length of the PDMAEMA arms, giving spherical micelles for the star with 4 shorter PDMAEMA arms and vesicles for the star with 3 longer arms. The unique behavior of this system is that this ionically induced micellization can then be reversed by UV-illumination, leading to disassembly of micelles into unimers upon a photoinduced valency change of the counterion. Therefore, besides pH and thermo-responsiveness, light sensitivity was also incorporated in these stars.

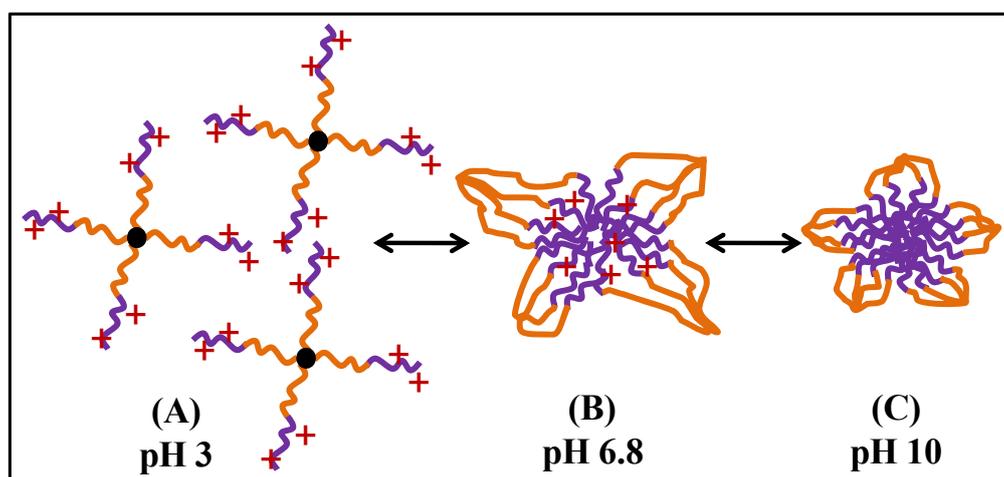
### 3.5. (AB)<sub>n</sub> Star Block Copolymers

Block copolymers attached to a common nodule constitute another type of star copolymers. In this case, the topology of the block (inner or outer position) is critical. A characteristic example of the pH dependent micellization behavior in saline aqueous solutions was demonstrated recently by a four-armed amphiphilic star block copolymer containing poly(methyl methacrylate) (PMMA) inner blocks and PAA outer blocks [37]. At low pH, the star copolymer remains water soluble, forming spherical and elongated micelle-like aggregates, due to the higher content of PAA (PMMA:PAA, 1:2). Upon increasing the pH of the solution, the formerly formed wormlike micelles disintegrated into smaller spherical micelles, owing to the higher ionization degree of PAA blocks, as well as the swelling of the corona due to the higher osmotic pressure by trapped counterions.

Well-defined four-armed amphiphilic star block copolymers, poly(acrylic acid)-block-polystyrene (PAA-*b*-PS)<sub>4</sub>, with PS being the outer block, were found to form hydrogels due to intermolecular association originating from the PS blocks [38]. The increasing length of the PS block was observed to lead to more elastic networks due to increased hydrophobic interaction. Star-block copolymers showed more elastic behavior compared with a triblock copolymer of comparable molar mass and composition. The thermal properties of the gels are changed by increasing the PS block lengths. Gels with short PS blocks soften upon heating at lower temperatures compared with the rheological properties of hydrogels with longer PS blocks.

A well defined pH-responsive star block copolymer consisting of four double hydrophilic PEO-*b*-PDEAEMA block arms was synthesized by ATRP and its self-assembly ability was examined in aqueous solutions [39]. At high pH values (pH 9–10), the PDEAEMA blocks become entirely deprotonated and consequently turned into hydrophobic, leading to the formation of core-shell micelles with a hydrophobic PDEAEMA core, surrounded by the hydrophilic PEO segments which however are not free arm-ends, as they are attached to the star nodule (Scheme 4). By decreasing pH (*i.e.*, pH ~ 6.8), an induced swelling of the micellar core occurred, as the PDEAEMA arms became progressively ionized and started electrostatically repulsing each other. At acidic low pH values (pH 3), the swollen micelles dissociated into unimers as both PDEAEMA and PEO arms became water soluble.

**Scheme 4.** Self-assembly of a four-arm (PEO-*b*-PDEAEMA)<sub>4</sub> star block copolymer in 0.01 M NaCl at (A) pH 3, (B) pH 6.8 and (C) pH 10. The scheme was inspired by [39].



Another paradigm of pH sensitive six-armed amphiphilic star block copolymer, bearing hydrophilic PDMAEMA inner blocks and hydrophobic PS outer blocks, (PDMAEMA-*b*-PS)<sub>6</sub> was designed and studied in aqueous media [40]. The polymer was dissolved in a common good solvent, tetrahydrofuran (THF), followed by dialysis against water. In neutral aqueous solutions, this star self-assembled forming spherical aggregates coexisting with bowl shaped morphologies, due to a possible viscosity control mechanism. The bowl-like morphology has been reported by Eisenberg *et al.* for linear copolymers [41]. This was the first time that such morphology was observed in the aggregation of star block copolymers. In addition, at acidic condition (pH 3), the star copolymer formed large compound spherical micelles with protonated PDMAEMA core, PS matrix and little protonated PDMAEMA moieties on the surface, stabilizing the micelles.

A star block copolymer that exhibited dual pH- and thermo-sensitivity, comprising six block copolymer arms consisted of the hydrophobic poly( $\epsilon$ -caprolactone), PCL, and PDEAEMA was prepared via ROP and ATRP [42]. At room temperature and in acidic aqueous solution (pH < 6.5), the star copolymers self-assembled into spherical micelles with a PCL core and a PDEAEMA shell. It was shown through UV-Vis spectrophotometry, DLS and TEM measurements that this (PCL-*b*-PDEAEMA)<sub>6</sub> star could form larger aggregates or even vesicles, simply by adjusting the external conditions, *i.e.*, pH and/or temperature. Particularly, for a pH range 3.6 < pH < 6.5, the PDEAEMA segments were fully protonated and the molecular chains were completely stretched. At pH 3.6, no LCST was detected by UV-Vis spectrophotometry while at pH 6.5 and 7.4, the star copolymer exhibited LCST at 49.7 °C and 26.3 °C, respectively due to the thermosensitivity of deprotonated PDEAEMA. At pH 6.5, shrunken micelles with a tendency to aggregate were observed, as the DEAEEMA segments started to be dehydrated. For higher pH values (pH 7.4) or upon heating, larger aggregates were formed, due to the fact that the PDEAEMA blocks became so hydrophobic, causing the instability of the hydrophilicity/hydrophobicity balance. Thus, neighboring micelles started interacting with each other to form larger micelles or coalesced vesicles, in order to minimize the total interfacial energy. Such a pH and thermo-responsive system comprising biodegradable PCL inner blocks may be attractive for biomedical applications.

#### 4. Star-Shaped Block Terpolymers

##### 4.1. $\mu$ -ABC Miktoarm Stars

The simplest type of star-shaped terpolymers is the  $\mu$ -ABC miktoarm stars where three different blocks are emanated from a common junction. Extended work reported by Lodge *et al.* has shown that the  $\mu$ -ABC star terpolymers, have the ability to self-organize in a large diversity of nanostructured morphologies, which depends on the nature and relative length of the arms. A series of  $\mu$ -ABC stars composed of one hydrophilic and two highly immiscible hydrophobic (a hydrocarbon and a fluoropolymer) arms were prepared using living anionic polymerization [43]. These  $\mu$ -polyethylene-(poly(ethylene oxide))-poly(perfluoropropylene oxide),  $\mu$ -PEE-(PEO)-PFPO ( $\mu$ -EOF), star terpolymers were found to form a variety of structures when dispersed in water, by varying the relative arm lengths [44-46]. For example, by keeping the PEE and PFPO arm lengths constant while changing the length of the hydrophilic PEO arm, the star terpolymer self-assembled into “hamburger” micelles (for

relatively long PEO chains) or elongated wormlike micelles (for relatively short PEO chains). In the case of “hamburger” micelles, PFPO formed the hamburger while, PEE were the “buns” above and below PFPO. Finally, the long PEO arms shielded the whole hydrophobic core. When shorter PEO arms were used, they were not capable to shield the PFPO/PEE interface. In this case, the PFPO/PEE micelles stacked together to share the PEO arms, resulting to wormlike structures. Further decrease of the PEO length led to ribbon-like micelles, Y-junctions, nanostructured bilayers, toroids and vesicles.

At a second stage, the self-assembly in water was studied, upon varying the PFPO arms length and keeping constant the PEE and PEO arm lengths. In this case, a richer variety of self-assemblies emerged [47]. For short PFPO arms, the star terpolymer demonstrated segmented ribbons and bilayers while, for longer PFPO arms, segmented worms, raspberry-like micelles and multicompartimentalized worms were observed.

Special attention was paid to explore the possible benefits provided by the multicompartiment micelles formed from  $\mu$ -EOF in aqueous media [48]. It was demonstrated that two distinct molecules could be solubilized selectively within the separate nanoscopic compartments. Thus multidelivery nanocarriers could be designed based to  $\mu$ -ABC miktoarm star terpolymers.

In this type of 3-armed terpolymer star architecture, the topology (position) of the different arms does not play any role and the arm conformation approaches that of the linear counterpart, due to the lowest possible monomer density (only 3 arms). This arm “freedom” may interpret the capability of the  $\mu$ -ABC stars to self-assemble in such a diversity of nanostructured morphologies. Therefore the  $\mu$ -ABC star architecture is quite beneficial in designing the self-assembly properties of multifunctional polymeric materials.

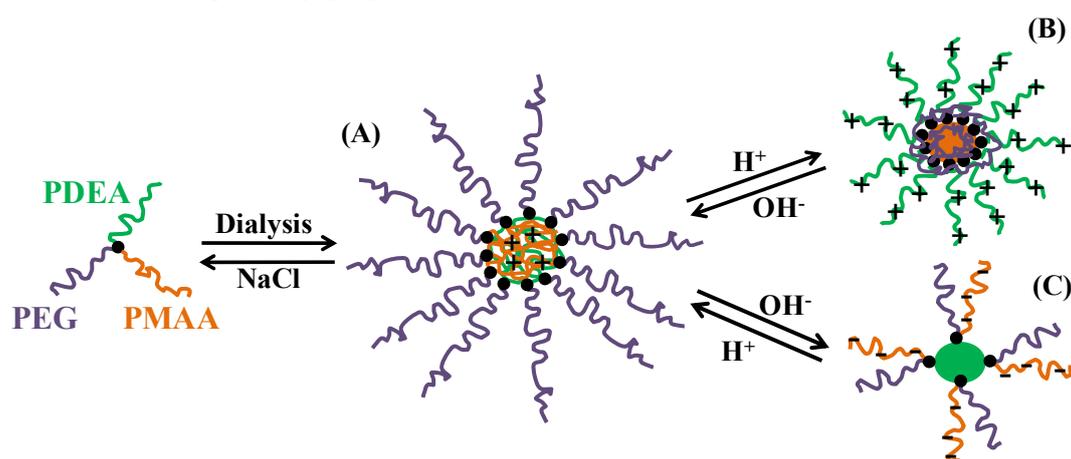
An amphiphilic miktoarm star terpolymer bearing a pH sensitive P2VP arm and two hydrophobic PS, and polybutadiene (PB) incompatible arms, PS-(P2VP)-PB, exhibited an unexpected morphology in aqueous media. Firstly, the terpolymer was dissolved in dioxane. After dialysis against acidic water, multicompartiment micelles (MCMs) were formed as revealed by TEM. These MCMs consisted of a multicompartiment core, comprising hard PS and soft PB nanodomains, surrounded by highly solvated P2VP chains. From cryo-TEM it was observed that these MCMs, due to their unique architecture, could form bridges that originated from the tendency of the hydrophobic PB domains to interact each other. This phenomenon was attributed to the low glass transition temperature of the PB, its accompanying dynamics and the significant exposure of the PB domains to water. It shows a unique way of how MCMs, an emerging class of colloids, can interact with the environment via hydrophobic interactions and can regulate cell interaction or adhesion control. Furthermore, the bridges provide an understanding of the occurring fusion processes in self-assembled aggregates of miktoarm star terpolymers [49].

A number of well-defined poly(ethylethylene)-[poly(ethylene oxide)]-poly( $\gamma$ -methyl- $\epsilon$ -caprolactone) ( $\mu$ -EOC) miktoarm star terpolymers, were prepared and their dispersion in water was studied using cryoTEM and DLS [50]. The structure of the formed micelles was affected by the length of the PMCL arm. It was found that by increasing the PMCL length led to the transition of the initially formed spherical micelles into wormlike. Further increasing of the PMCL length showed a transition from wormlike micelles back to spherical or disk-like structures. Evidences were provided that the micellar cores were indeed internally segregated in the micelles.

Further investigation of the  $\mu$ -EOC stars, revealed that in pH 12 and at 50 °C, cleavage of the PMCL chains transformed the multicompartment micelles from segmented wormlike structures to raspberry-like vesicles or disks. Most of the PMCL chains are cleaved at/or near the juncture with the PEE and PEO arms, producing PEE-PEO diblocks (some with shorter PMCL blocks) and significant amounts of PMCL homopolymer. The striking morphology change was driven by minimization of the unfavorable interfacial energy between three immiscible blocks, under the release of the constraint that the PMCL arms were connected to the other two [51].

A pH responsive triple hydrophilic  $\mu$ -ABC star terpolymer, PEG-(PMAA)-PDEAEMA, containing PEG, a weak polybase PDEAEMA and a weak polyacid poly(methacrylic acid) (PMAA) as arms, was synthesized via the combination of consecutive click reactions and ATRP and its solution behavior was investigated [52]. Due to the multifunctionality of the different arms and the pH sensitivity of the oppositely charged polyelectrolyte arms, this star self-assemble through three types of interactions depending on the environmental conditions. Particularly, at acidic conditions (pH < 4), hydrogen bonding between PEG and the fully protonated PMAA arms predominated, leading to the formation of complex PEG/PMAA core micelles, stabilized in the aqueous solution with protonated PDEAEMA coronas (Scheme 5). At pH 6 in the vicinity of iep, electrostatic interactions between the partially deprotonated PDEAEMA arms and the progressively ionized PMAA segments led to charge-compensated micelles with polyion complexed PDEAEMA/PMAA cores and PEG coronas that sterically stabilize the nanostructures in water. These micelles are very sensitive to the ionic strength of the solution. At increased pH values, *i.e.*, at pH 10, the tertiary amine groups of PDEAEMA blocks were completely deprotonated and became hydrophobic whereas the PMAA blocks were completely ionized. Therefore, hydrophobic PDEAEMA core micelles were formed with hydrophilic PEG and PMAA arms in the corona. The three types of aggregates were fully reversible. The above system demonstrates a nice paradigm of a three armed miktoarm star terpolymer that self-assemble in water via three different driving forces *i.e.*, hydrophobic interactions, interpolyelectrolyte complexation, and hydrogen-bonding.

**Scheme 5.** Schematic representation of the pH dependent formation of three different types of micellar aggregates from a PEG-(PMAA)-PDEAEMA zwitterionic miktoarm star terpolymer: (A) PMAA/PDEAEMA polyion complexes core at pH 6. (B) PEG/PMAA hydrogen-bonded complexes core at pH 2. (C) Hydrophobic PDEAEMA core at pH 10. The scheme was inspired by [52].



A multi-responsive triple hydrophilic PEG-(PDEAEMA)-PNIPAM miktoarm star terpolymer was synthesized via the combination of ATRP and click reaction and its “schizophrenic” micellization behavior was reported [53]. Thanks to the pH responsive PDEAEMA and the thermo-responsive PNIPAM, this terpolymer exhibited both pH- as well as thermo- induced micellization attitude. At acidic aqueous media (pH 4) and at room temperature, it was molecularly dissolved. In an alkaline environment, *i.e.*, pH 10, where the PDEAEMA arms became hydrophobic, the PEG-(PDEAEMA)-PNIPAM miktoarm star formed PDEAEMA hydrophobic core micelles with water soluble PEG/PNIPAM coronas. At pH 4 and at 50 °C (temperature above the LCST of PNIPAM), the PDEAEMA arms were protonated whereas the PNIPAM arms became hydrophobic, leading the terpolymer to supramolecularly self assemble into another type of micelles with hydrophobic PNIPAM core and well solvated PEG/PDEAEMA arms in the coronas.

Another triple hydrophilic  $\mu$ -ABC star terpolymer containing different functional arms of PEG, PNIPAM and poly(L-lysine) (PLys), PEG-(PNIPAM)-PLys, was studied in aqueous solutions in the presence of ionized poly(acrylic acid). A series of PEG-(PNIPAM)-PLys/PAA polyelectrolyte complex (PEC) micelles were prepared through the electrostatic attractive interactions among the oppositely charged PLys arms and PAA chains. The resulting PEC micelles were core-shell spheres with ion-bonded PLys/PAA core and PEG/PNIPAM arms in the shell. Due to the PNIPAM arms, these PEC micelles exhibited thermosensitivity. Increasing temperature above the LCST of PNIPAM led to a three compartment core-shell corona (PLys/PAA-core, PNIPAM-shell and PEG-corona) micelles which had the tendency to aggregate [54].

pH sensitivity was exhibited from another  $\mu$ -ABC star terpolymer, consisting of a ionizable P2VP arm, and the hydrophobic PCL and hydrophilic PEO arms [55]. In low pH values, this miktoarm star was able to form micelles comprised of PCL hydrophobic cores surrounded by a mixed corona containing hydrophilic PEO and positively charged protonated P2VP arms. Upon switching pH above 5, smaller spherical micelles than the ones formed at acidic conditions were observed, since the P2VP arms were entirely deprotonated, and collapsed on the core. Whatever the location of the P2VP blocks, in the core or in the corona, and thus whatever the size and charge of the micelles, these micelles are stable in the whole range of pH. Interaction of these micelles with a negatively charged surface for instance could be triggered simply by adjusting pH. This performance could lead to interesting potential applications.

Different pH responsiveness of self-assemblies in aqueous media of two miktoarm star terpolymers, bearing similar in nature arms with the previous one, *i.e.*, hydrophobic PS, hydrophilic PEO and pH-sensitive PDMAEMA arms, was observed [56]. At low pH, the stars formed spherical micelles with PS cores and mixed hydrophilic PEO and positively charged PDMAEMA arms in the coronas. At intermediate pH (5.2–8.1), the partial deprotonation of the PDMAEMA blocks induced intermicellar attractions. At elevated pH values (pH  $\sim$  9), the spherical core-corona micelles turned into multicompartment micelles due to the entirely deprotonation of the PDMAEMA arms. In this case, the PS cores were bridged by overlapping the PDMAEMA arms, leading to the formation of segmented wormlike micelles.

Thermo-responsive amphiphilic  $\mu$ -ABC miktoarm star terpolymers consisting of two hydrophobic arms (PS and PC and a thermosensitive PNIPAM arm were designed and explored in aqueous solutions [57]. These star terpolymers self-assembled, forming core-shell micelles with mixed PS/PCL

cores and PNIPAM coronas at room temperature. Upon heating the solution at 45 °C, DLS experiments revealed a ~10 nm decrease of the micelles hydrodynamic radius, which could be ascribed to shrinkage of the PNIPAM coronas due to the LCST behavior of PNIPAM.

The same group demonstrated a new double hydrophilic miktoarm star terpolymer, consisting of PEG, the hydrophobic PtBMA and the thermo-responsive PNIPAM arms [58]. At 25 °C, the PEG-(PtBMA)-PNIPAM star terpolymer formed PtBMA core micelles decorated with a mixed PEG/PNIPAM corona. Upon increasing temperature at 50 °C, the micelles size increased, indicating further micellar growth, which can be explained by the fact that at  $T > LCST$ , the PNIPAM arms became hydrophobic and thus water insoluble, leading to the change of the hydrophobic/hydrophilic balance and therefore, to an additional structural rearrangement. As a result, at high temperatures, new type of micelles was formed bearing mixed PtBMA/PNIPAM hydrophobic cores and hydrophilic PEG segments comprising the water soluble coronas.

Recently, the thermo-induced self organization of a PS-(PNIPAM)-PDMAEMA miktoarm star terpolymer was studied [59]. It was shown that in aqueous media, the terpolymer formed core-corona micelles with a PS hydrophobic core and water soluble PNIPAM/PDMAEMA mixed corona. As the temperature increased from 20 to 34 °C, the hydrodynamic radius of the micelles decreased abruptly, owing to the collapse of the PNIPAM chains in the shell. At higher temperatures ( $38\text{ °C} < T < 50\text{ °C}$ ), further size decrease was explained by the collapse of the PDMAEMA arms, forming the outer shell of the formed nanoparticles.

Another example of thermosensitive stars is that of a biodegradable miktoarm star terpolymer composed of the hydrophilic monomethoxy poly(ethylene glycol) (MPEG), the hydrophobic PCL and the thermo-sensitive polyphosphoester (PPE) [60]. While at low temperatures the star terpolymer self-assembled into spherical micelles with a hydrophobic PCL core, at temperatures higher than the cloud point of PPE, larger nanoparticles were formed as the micelles reassembled into short rods.

#### 4.2. $(ABC)_n$ Star Block Terpolymers

A series of potentially pH responsive star terpolymers bearing a large number of ABC triblock terpolymer arms, each composed of the non-ionic hydrophilic methoxy hexa(ethylene glycol)methacrylate (HEGMA), the ionizable hydrophilic DMAEMA, and the neutral hydrophobic MMA, emanating from a common nodule, were synthesized using group transfer polymerization and studied in aqueous media [61]. The uniqueness of these stars is that their behavior is significantly affected by the block topology of the arms. For HEGMA-*b*-MMA-*b*-DMAEMA-*core* and DMAEMA-*b*-HEGMA-*b*-MMA-*core*, both atom force microscopy (AFM) and static light scattering (SLS) techniques revealed the existence of unimolecular micelles and the absence of star aggregation. The third star, HEGMA-*b*-DMAEMA-*b*-MMA-*core*, exhibited the tendency to form polymolecular aggregates. Owing to its large number of arms (40 to 73 arms), the star terpolymer behaved as highly compact soft nanoparticles with their blocks arranged in three concentric compartments, whose topology is determined at will by the block sequence of the arms. It should be underlined that the linear ABC terpolymer counterparts associated in water, resulting, however, in particles with small aggregation numbers, from 2 to 4. Thus, the star rather than the linear architecture provides the means for the preparation of highly compact soft nanoparticles.

Four-arm  $(ABC)_n$  star block terpolymers, each arm of which consisted of hydrophobic PCL, hydrophilic poly(oligo(ethylene oxide) methacrylate) (POEOMA) and thermoresponsive poly(di(ethylene oxide) methyl ether methacrylate) (PMEO<sub>2</sub>MA) segments,  $(PCL-b-POEOMA-b-PMEO_2MA)_4$  and  $core(PCL-b-PMEO_2MA-b-POEOMA)_4$ , were synthesized by a combination of controlled ROP and ATRP [62]. In aqueous solution and at room temperature, these amphiphilic star terpolymers self-assembled into spherical micelles with collapsed PCL segments comprising the hydrophobic core and the hydrophilic POEOMA and PMEO<sub>2</sub>MA segments comprising the corona. Depending on the topology of each block along the arms of the star, the self assembly behavior of these stars was different. When long thermoresponsive PMEO<sub>2</sub>MA moieties were distributed as the outer block, large aggregates were formed at room temperature, as well as at temperatures above the LCST, due to intermicellar interactions. For shorter PMEO<sub>2</sub>MA blocks, the intermicellar interactions were very weak to form larger aggregates in the whole temperature range. In the case of the star terpolymers with the PMEO<sub>2</sub>MA segment being the middle block, the PMEO<sub>2</sub>MA blocks became hydrophobic and collapsed on the inner PCL core at temperatures above LCST. Intramicellar aggregation led to smaller aggregates (comparing to the ones observed in the  $(PCL-b-POEOMA-b-PMEO_2MA)_4$  system) which remained water soluble due to the outer hydrophilic POEOMA blocks.

#### 4.3. $[A-b-(B-co-C)]_n$ Block Random Star Terpolymers

A novel amphiphilic block-random star terpolymer bearing 32 arms consisted of MMA blocks close to the star core and DEAEMA/MAA outer random copolymer blocks,  $core[MMA_{48}-b-(DEAEMA_{31}-co-MAA_{26})_{32}]$ , was prepared by group transfer polymerization (GTP) and studied in aqueous solutions as a function of pH [63]. Due to the high number of arms and the polyampholyte character of the outer blocks, DEAEMA<sub>31</sub>-co-MAA<sub>26</sub>, the star terpolymer formed unimolecular micelles with changeable charge density and sign, simply by varying pH. It was shown by zeta-potential measurements that below and above the isoelectric region of the random polyampholyte (iep region), unimolecular micelles with PMMA hydrophobic cores surrounded by positively or negatively charged coronas respectively, were formed.

#### 4.4. $A(B-b-C)_2$ Asymmetric Heteroarm Star Block Terpolymer

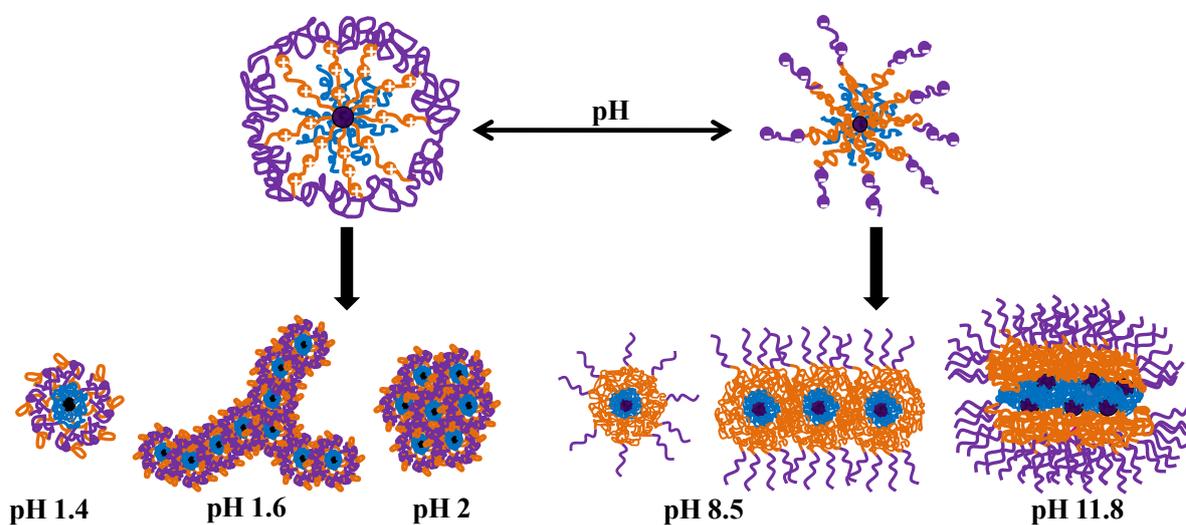
A variety of pH responsive self association phenomena was presented by a novel and amphiphilic 3-arm heteroarm star block terpolymer containing one PS homopolymer arms and two PNIPAM-*b*-P4VP diblock copolymer arms using TEM [64]. The  $PS(PNIPAM-b-P4VP)_2$  star terpolymer was dissolved in a mixture of THF and water (1:9, v:v). At pH 3, sphere-shaped micelles were formed composed of a hydrophobic PS core and hydrophilic PNIPAM-*b*-P4VP coronas. At pH values between  $1 < pH < 3$ , spherical-shaped micelles coexisted with rod-like micelles. The latter was explained by the fact that upon decreasing the pH of the solution, the hydrogen bonding between the PNIPAM moieties and water was destroyed. Therefore, the PNIPAM segments became less hydrophilic, leading thus to the increase of the hydrophobic ratio of the studied system. The corona sizes, as well as the repulsions of the hydrophilic blocks in the corona were reduced, which forced the polymer chains to fuse into

rod-like nanostructures. At even more acidic conditions ( $\text{pH} < 1$ ), nanorods were formed by fusion of small rod-shaped and sphere-shaped micelles.

#### 4.5. $A_n(B-b-C)_n$ Symmetric Heteroarm Star Block Terpolymer

Novel multiarm star-shaped terpolymers of the type  $\text{PS}_n(\text{P2VP-}b\text{-PAA})_n$ , *i.e.*, constituted of  $n$  hydrophobic PS arms and  $n$  P2VP- $b$ -PAA diblock copolymer arms, all emanated from a tightly crosslinked poly(divinyl benzene) (PDVB) common nodule were designed and their aqueous solution properties were explored very recently [65,66]. In fact, the  $A_n(B-b-C)_n$  architecture named *heteroarm star block terpolymer*, is a hybrid between the  $A_nB_n$  *heteroarm star* and a  $(BC)_n$  *star block copolymer*. Due to the pH-dependent properties of the two P2VP and PAA amphoteric blocks, and the specific interactions among them, these stars respond to pH. Turbidimetry and electrophoresis experiments demonstrated the existence of three phases in water solutions: at low pH where protonated P2VP (positively charged) predominated, at high pH where negatively charged PAA predominated and in the intermediate precipitation region where the oppositely charged moieties were neutralized (vicinity of iep). A variety of amphoteric self-assemblies was observed, depending on the pH of the medium (Scheme 6). Below the iep of the diblock polyampholyte arms, in which the terpolymer possesses a bis-hydrophilic nature with interactive arms, core-shell unimolecular micelles, worm-like micelles and multicore large compound micelles (LCM) were formed. A novel association pathway was suggested to account for the formation of the large self-assemblies in this pH window. The LCM arose from coronal interactions without the need of the presence of complexing agents, as reported previously [67]. Above iep, the star terpolymer was transformed to bis-hydrophobic, bearing incompatible segments. In this regime multistar aggregates, network-like large assemblies and finally patchy compartmentalized micelles were observed.

**Scheme 6.** Schematic representation of the pH dependent  $\text{PS}_n(\text{P2VP-}b\text{-PAA})_n$  star conformation and the corresponding self-assemblies. In acidic conditions: pH 1.4, unimolecular micelle; pH 1.6, multicore micelle; pH 2, worm-like micelle. In basic conditions: pH 8.5, unimolecular micelle and network-like assembly; pH 11.8, multicompartment multimolecular micelle. The scheme was inspired by [66].



These multiarmed  $PS_n(P2VP-b-PAA)_n$  star terpolymers can create reversible hydrogels at concentrations above the overlap concentration. Preliminary results of  $PS_{22}(P2VP-b-PAA)_{22}$  aqueous solutions revealed the formation of an elastic physical gel after dialysis of a N,N-dimethylformamide/water (DMF/water) (50/50, v/v) polymer solution against pure water of pH 2. Under these conditions, unimolecular micelles were formed in which the P2VP blocks were partially protonated. Upon increasing the water content (dielectric permittivity augmentation), a sol-gel transition occurred, which was ascribed to the progressive stretching of the P2VP blocks, resulting to a jumbling effect [68].

The surface morphologies of Langmuir-Blodgett monolayers of amphiphilic  $PS_n(P2VP-b-PtBA)_n$  (PtBA: poly(tert butylacrylate)) star terpolymers were examined recently and compared with their  $PS_nP2VP_n$  star copolymer precursors [69]. The  $\pi$ -A isotherms of monolayers at subphases of different pH, exhibited strong pH-dependence leading to the different limiting molecular area which depends on the number of arms. The morphology of  $PS_nP2VP_n$  star copolymers bearing the P2VP segments as free arms was strongly dependent on the subphase pH, while the  $PS_n(P2VP-b-PtBA)_n$  star terpolymer containing the P2VP segments as internal midblocks, maintained nearly constant organization at low pH. The surface morphology comparable studies, suggested that star copolymers with the pH sensitive P2VP free arms can form circular micelles with larger sizes, which can be readily transformed to labyrinth morphologies with dense interpenetrating structures by compression and pH variation. The high number of arms and the presence of the hydrophobic end blocks of star terpolymers promote the formation of robust unimolecular condensed micelles, stable at different compressions and pH conditions.

## 5. Concluding Remarks

In this review, a survey of the works done within recent years on the self-assembly of stimuli responsive water soluble star-shaped block copolymers and terpolymers is demonstrated. Thanks to the great progress of macromolecular engineering, especially the continuous development of the “living”/controlled polymerization methods, a large variety of star-shaped segmented macromolecules of special architectures, bearing different kinds of block/arms in different topologies, have been designed and explored in aqueous media.

The spontaneous self-organization of the star-shaped segmented macromolecules, through a variety of interactions, *i.e.*, hydrophobic, H-bonding, electrostatic, have led to the formation of micellar self-assemblies, with differing properties with respect to the linear counterparts, *e.g.*, critical micelle concentration, aggregation number, morphology.

By incorporating specific sequences in the star-shaped segmented macromolecules that are sensitive to various stimuli, a novel class of responsive star-shaped polymeric materials has emerged, displaying intriguing properties. Thus, star copolymers and terpolymers bearing block/arms that exhibit LCST, pH sensitivity (polyions) or both, undergo sudden and spontaneous morphological transformations on their self-assemblies in aqueous media, upon varying temperature and/or pH. The number of arms, the specific functionality and topology of the different arm/blocks and the overall macromolecular architecture of the star polymer significantly influence their behavior in terms of self-assembly and responsiveness.

The exact position (topology) of the various arms does not always affect the behavior and the self-assembly morphologies, such as in  $A_nB_n$  or  $\mu$ -ABC types, in which morphological variations can be achieved by varying the arm length and/or responding to a stimulus. This is not the case for the  $(AB)_n$  star block copolymers and  $(ABC)_n$  terpolymers, as well as for the  $A_n(B-C)_n$  heteroarm star block terpolymers, in which the topology of segments of a given functionality is critical. For instance, if the outer block is hydrophobic or potentially hydrophobic (stimulus responsive), self-organization will lead to a three dimensional network upon increasing concentration.

Among the plethora of different star architectures, the simplest 3-armed  $\mu$ -ABC miktoarm star terpolymer, exhibits the highest ability to form a large diversity of self-assemblies of unique morphology. The mandatory junction of three segments of different nature at a single point, provokes those topological constraints which create novel morphologies that could not be attained from the linear counterpart.

On the other hand, the multiarmed star-shaped block copolymers ( $A_nB_n$  or  $(AB)_n$  type) of relatively high hydrophilic content tend to form unimolecular micelles at low concentrations, as their architecture can mimic a core/shell micellar structure. The advantage of this behavior is that nano-structured micelles with pre-designed fixed structure, which can survive in selective media at relatively high concentrations without association and at infinite dilution without dissociation, can be prepared.

Comparing the behavior of symmetric  $A_nB_n$  and asymmetric  $A_nB_m$  heteroarm stars, it can be concluded that the possibility of tuning the number of the hetero-arms in the case of  $A_nB_m$ , provides another means to tune the stimulus-induced self-organization of these star-shaped polymeric species.

An interesting class of these stimuli-responsive star copolymers is the so called double hydrophilic or even triple hydrophilic, in the case of star terpolymers, that exhibit “schizophrenic” behavior or exist in molecularly dissolved state at specific environmental conditions and undergo spontaneous and reversible self-organization upon responding to a stimulus. These star-shaped macromolecules are promising candidates for drug delivery applications. For the star terpolymer case, their compartmentalization ability exhibits further potentials for designing multidrug nanocarriers in biological applications.

Due to the large diversity of macromolecules adopting star architecture, the establishment of structure-property relationships, *i.e.*, correlation among the star molecular characteristics such as, number of arms, arm length, segment topology, and specific functionality of each arm/block, with the self-assembly and responsive properties in aqueous media, is quite a motivating topic. Although the studies along this line demonstrated in this review, indicate very interesting and promising results, it is obvious that much more work has to be conducted towards satisfactory understanding of these relationships. The target of designing stars with tunable properties for specific applications currently remains an attractive challenge.

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