Star-shaped poly[2-(dimethylamino)ethyl methacrylate] and its derivatives: toward new properties and applications

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DOI: dx.doi.org/10.14314/polimery.2014.066

Dedicated to Professor Stanislaw Penczek on the occasion of his 80th birthday

Abstract: The versatility of polymer and hybrid systems containing the polycation PDMAEMA, especially in the star-shaped topology, is reviewed. Different complexation schemes are addressed, including the use of stimuli-responsive counterions. This leads to the use of PDMAEMA stars for nucleotide transfection or advanced hydrogel formulations.

Keywords: stimuli-responsive polymer, star-shaped polymer, micellization, gene transfection, hydrogel, hybrids.

Gwieździsty poli(metakrylan 2-dimetyloaminoetylu) i jego pochodne — nowe właściwości i kierunki zastosowań

Streszczenie: Artykuł stanowi przegląd literaturowy dotyczący właściwości i zastosowania poli(metakrylanu 2-dimetyloaminoetylu) (PDMAEMA) i jego pochodnych. Przedstawiono wszechstronność bazowego polimeru oraz układów hybrydowych zawierających polikation PDMAEMA, zwłaszcza o gwieździstej topologii. Omówiono możliwości wykorzystania wrażliwości polimeru na zmiany temperatury i pH roztworu, a także różne schematy kompleksowania z udziałem przeciwjonów reagujących na wspomniane bodźce. Gwieździste pochodne PDMAEMA mogą znaleźć zastosowanie w terapii genowej do transfekcji nukleotydów, jak również do wytwarzania zaawansowanych preparatów hydrożelowych.

Słowa kluczowe: polimer reagujący na bodźce, polimer gwieździsty, micelizacja, transfekcja genów, hydrożel, hybrydy.

INTRODUCTION

Poly[2-(dimethylamino)ethyl methacrylate] (PDMAEMA) is a very versatile polymer. It combines its weak polyelectrolyte behavior with thermosensitivity [1]. Dependent on the pH, the polymer becomes water-insoluble above a certain temperature owing to a lower critical solution temperature, LCST. Further, it can be easily modified by quaternization leading either to strong polyelectrolytes or to polyzwitterionic species [2, 3]. Again, the polyzwitterionic polymers show — dependent on the salt concentration — either interesting thermoresponsive properties (UCST behavior) [4—6] or they exhibit strong hydration leading to repellent surfaces and therefore efficient lubrication (see Fig. 1) [7]. Derivatives of PDMAEMA with lower water solubility are poly[2-(diethylamino)ethyl methacrylate] (PDEAEMA) and poly[2-(diisopropylamino)ethyl methacrylate] (PDiPrAEMA).

Besides these well-known features of PDMAEMA, we want to further extend its applicability by adding new properties to PDMAEMA-based systems. For example, branched architectures of PDMAEMA, in particular star-shaped ones, show great promise for the efficient gene transfection of non-dividing or differentiated cell lines. Furthermore, this polyelectrolyte behavior can be united with „smart" complexants, like it would be the case for counterions with a switchable valency. Then, the switching behavior of the counterions would be inherited by the macromolecule {*e.g.* the light-sensitivity for $[Co(CN)_6]^{3-}$} [8]. A high local segment density is advantageous for an effective complexation, which does not necessarily rely on electrostatic interactions. The high local segment density can be easily achieved by use of branched or especially star-like architectures. Thus, PDMAEMA provides a versatile platform for various applica-

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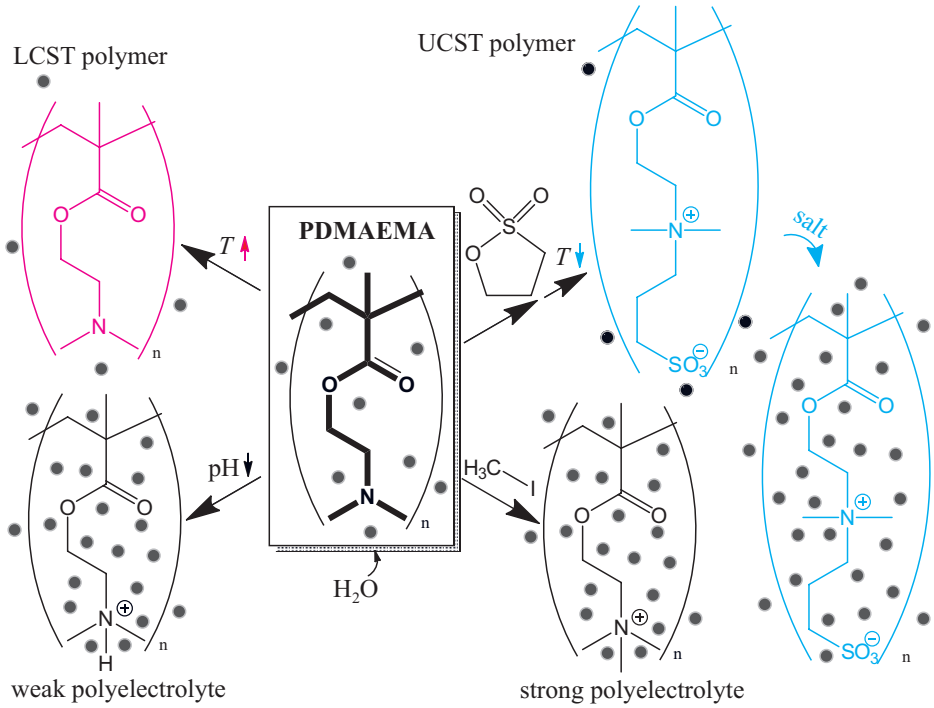

Fig. 1. Versatility of poly[2-(dimethylamino)ethyl methacrylate] (PDMAEMA) including its thermosensitivity and polyelectrolyte properties (degree of hydration is indicated by grey circles, which symbolize water molecules)

tions, which we will address in this review. The first part describes the inherent behavior of PDMAEMA together with changed properties upon interaction with other entities. The second part is devoted to applications with emphasis on the biomedical field as well as on PDMAEMA-based gel formulations.

SYNTHETIC AVAILABILITY

The monomer DMAEMA, as a methacrylic ester, can be polymerized by anionic polymerization [9], group transfer polymerization [10—13] and radical polymerization. Due to their robustness, controlled radical polymerizations are the first choice for the preparation of advanced PDMAEMA-related architectures [14]. Atom transfer radical polymerization (ATRP) [15—18] has been employed frequently, but it needs some attention regarding the complexing abilities of the polymer towards the copper catalyst (use of effective ligands). As alternative preparation methods, radical polymerization with reversible addition-fragmentation chain transfer (RAFT) [19—22] and nitroxide mediated polymerizations [23—25] have been used. These polymerization methods allow the preparation of branched structures. Hyperbranched polymers have been synthesized by self-condensing vinyl copolymerization [26—28]. Cylindrical brushes, another class of polymers with a high segment density, were polymerized by grafting from a linear backbone *via* ATRP [29, 30]. In this review we will mainly focus on star-shaped polymers. Beneficially, their rather small size at still high segment density allows their use for special complexation purposes. Generally [31—34], the stars can be prepared by the core-first [2, 35] and arm-first approach [11, 36] (including macromonomers [37, 38]). These approaches can be extended towards block-like stars [39—44], miktoarm stars [45—50] and pearl-necklace structures [51] by proper macromolecular engineering. Organic-inorganic hybrid structures [52—56] and microgels [57—59] have been also reported.

WEAK POLYELECTROLYTE — PH-DEPENDENT THERMOSENSITIVITY

PDMAEMA belongs to the class of weak cationic polyelectrolytes ($pK_{a,app}$ ~ 6) [1]. Thus, it is fully protonated at low pH, while it is almost completely uncharged at high pH. A conformational change is related to the degree of protonation, since the charged state is by far better soluble in water than the deprotonated polymer. At high degrees of protonation, this leads to an extension of the coil caused by electrostatic repulsion and — more relevant — by the local osmotic pressure of the counterions. These counterions are partly correlated to the polymer backbone and partly confined within the solvated polymeric structure [60—63]. At high pH, PDMAEMA exhibits a thermoresponsive behavior in its (almost) uncharged state, as is known for many other non-ionic water-soluble polymers [64]. It is still water-soluble at low temperature (at least for molar masses up to 10^6 g/mol), but turns insoluble at elevated temperatures [1]. This is termed LCST behavior, since the binary phase diagram (water/polymer) exhibits a lower critical solution temperature. The phase separation temperature at a given concentration, named cloud point, can be modulated with

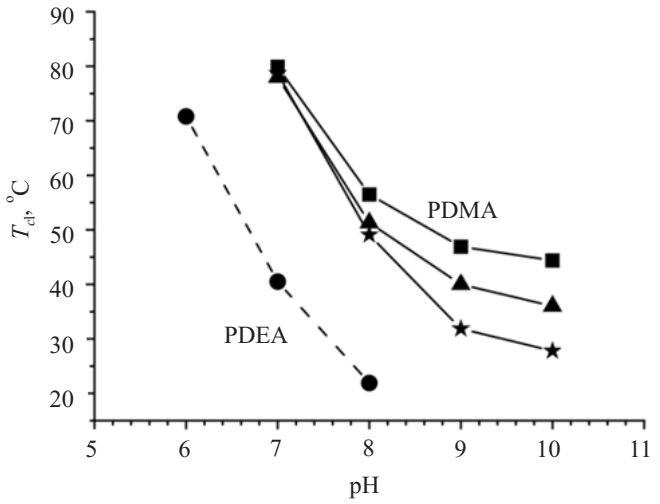

Fig. 2. pH-dependent cloud points, T_{cl}, for (•) PDEAEMA stars and PDMAEMA: (■) linear, *DP* = 108, (▲) star with 3 × 100 units $(DMA_{100})_3$, and (★) star with 18 × 170 units $(DMA_{170})_{18}$. (Reprinted with permission from [66]. Copyright 2010 Elsevier [107])

pH. The LCST decreases with molecular weight at a given pH. This is mainly seen at pH > 8 but independent of topology (Fig. 2) [1]. This is also true for PDEAEMA and PDiPrAEMA. These polymers are more hydrophobic than PDMAEMA, thus lower pH is needed for them to become soluble in water [65]. Although they have been attributed as pH-responsive only, LCST behavior has been found for PDEAEMA [66]. In relation to PDMAEMA of similar molecular weight, the transition temperature of PDEAEMA is shifted towards lower pH at a given temperature and to lower temperature at a given pH, leading to insolubility at all accessible temperatures above pH = 8. When finally going to structural analogues of PDMAEMA by replacing the ester bond with an amide linkage [67—69], hydrophilicity is usually increased by the presence of the polar amide group.

COMPLEXATION WITH MULTIVALENT COUNTERIONS

We turn now to the interaction of anionic species with either the weak polyelectrolyte PDMAEMA or its strong polyelectrolyte analogue poly{[2-(methacryloyloxy)ethyl] trimethylammonium halide} (PMOTAH) [70]. The latter can be easily prepared by quaternization with *e.g.* methyl iodide or dimethyl sulfate [2]. As already mentioned, the star-shaped architecture has some advantages in respect to its linear analogue, like high segment densities and high osmotic pressure of the counterions at the core of the star. This again facilitates complexation in terms of enrichment of the complexant at the center of the molecule. The main reason for this complexation is the entropic gain due to release of a higher number of monovalent counterions. In turn, this can lead to core-corona structures, while the rather uncomplexed corona ensures solubility [71—74]. This could be seen by interpolyelectrolyte complex (IPEC) formation between star-shaped polyelectrolytes with linear oppositely charged polyelectrolytes. The formed complex prevents interstar aggregation in case of sufficiently high arm number, while the IPEC formation between purely linear analogues will cause macroscopic precipitation even at rather low negative-to-positive charge ratios [72]. Thus, the star-shaped topology increases the overall solubility of the interpolyelectrolyte complexes. This principle is even more pronounced, when a solubilizing, non-complexing component is present in the stars [48, 75].

Besides the complexation with linear polyanionic species, PDMAEMA interacts also with inorganic multivalent counterions. This complexation has the advantage that any stimuli-sensitivity of counterions is transferred to the macromolecular complex. Switchable multivalent counterions are easily available in terms of certain metal complexes, whose charge can be manipulated by *e.g.* light or electrochemical stimulus [48]. In contrast, polymeric systems featuring these stimuli-sensitive properties require a more elaborate synthesis. Thus, PMOTAH arms stretch upon illumination in presence of hexacyanocobaltate(III) (Fig. 3).

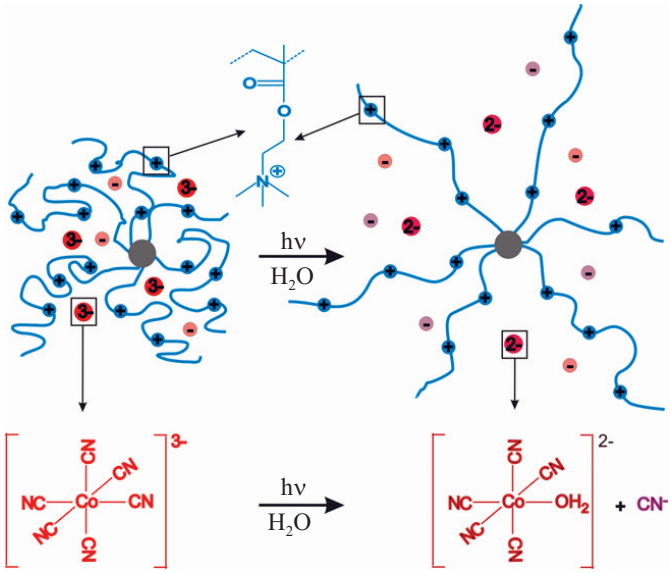

Fig. 3. Illustration of photo-induced stretching of the polyelectrolyte arms. (Adapted with permission from [8]. Copyright 2007 American Chemical Society)

During addition of this trivalent counterion, the PMOTAH star collapses due to complex formation, which is facilitated at the core of the star and which leads to further compaction of the arms [8]. However, the valency of hexacyanocobaltate reduces upon illumination, since the metal complex exchanges one cyano ligand with a water molecule. Then, the total number of counterions increases inside the star. At the same time, the osmotic pressure inside the stars increases and the PMOTAH chains make a transition from a globular to a more coil-like, elongated

state [8]. By deviating from the star-shaped morphology, PMOTAH-based cylindrical brushes adopt a helical shape upon complexation with hexacyanoferrate [76]. Upon illumination, the helices open up like a compressed spring, which could be used as a light-driven nanoactuator. Furthermore, in capsules prepared by a layer-by-layer (LbL) approach containing star-shaped, quaternized PDMAEMA a change in the permeability of the capsule membrane was achieved. The capsules had a low permeability after the addition of multivalent hexacyanocobaltate ions, which could be increased dramatically upon UV illumination [77].

The same complexation principle can be applied for electrochemically-manipulated systems [48]. The valency of hexacyanoferrates can be switched by electrochemical means. While the oxidized ferricyanide is trivalent, the reduced ferrocyanide is a tetravalent counterion. At the same time, the complexing abilities with the cationic polymer change. By use of PMOTAH-based stars, the reversible electrochemical switching between unimers and aggregated polymer is possible. To our best knowledge, this example was the first polymer-related report on switching between unimers and a micellar state by electrochemical means [48].

After having addressed these examples with quaternized PDMAEMA, we turn back to PDMAEMA in its weak polyelectrolyte form. As mentioned before, PDMAEMA is an LCST polymer at intermediate and high pH. At the same time, it is still charged below pH 10 and can interact with multivalent counterions [78]. The presence of multivalent counterions leads to a decrease in solubility upon cooling, similarly to the zwitterionic derivative of PDMAEMA. It is termed a UCST behavior, since the phase-diagram of such polymers exhibit an upper critical solution temperature. In contrast to the mere UCST behavior of polyzwitterions, the presence of multivalent counterions brings an additional thermosensitivity to the inherent LCST behavior of PDMAEMA. Then, a peculiar phase diagram is found, where PDMAEMA is insoluble at high and at low temperature, but is well soluble at intermediate temperatures (at certain pH) [78]. Thus,

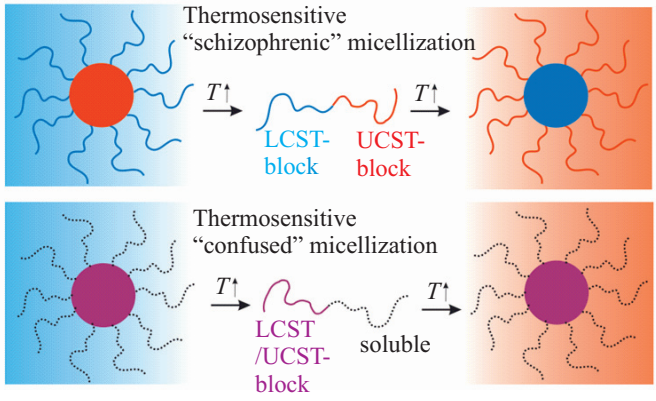

Fig. 4. Comparison of „schizophrenic" micellization and „confused" micellization

UCST and LCST properties are combined in one polymer. In addition, the UCST behavior can be switched off by UV-irradiation.

By help of bis-hydrophilic stars, this property of PDMAEMA was translated into a novel micellization scheme, the so-called „confused micellization" (Fig. 4) [47]. In the analogous well-known „schizophrenic micellization" [79—81], one part of the stimuli-responsive diblock copolymer is located in the corona of a micelle at a certain condition (*e.g.* low temperature), while the same block constitutes the core at a different condition (high temperature). In between, the polymer is typically well soluble. Like a chameleon, the polymer adapts to the different conditions by having three different states. During „confused micellization", the polymer is soluble at moderate conditions as well. However, it responds to low and high temperature in the same way by its UCST and LCST behavior, respectively. Finally, the micellization due to UCST can be reversed by UV-irradiation.

Concluding, PDMAEMA has the advantage that it shows inherent pH- and thermosensitivity, but further stimuli can be simply added to the system by choosing proper multivalent, switchable counterions. This can lead to UCST properties and responsiveness to, *e.g.*, light and electrochemical stimulus.

BIOMEDICAL AND BIOTECHNOLOGICAL APPLICATIONS OF PDMAEMA

In the following, we highlight some of the applications of PDMAEMA, especially in the biomedical field. Ionic interactions are an important force in biomedical applications, because most biomolecules (proteins, nucleotides) carry multiple charges and PDMAEMA can form interpolyelectrolyte complexes (IPECs) with these molecules.

The first of these applications is the delivery of exogenous genetic material into eukaryotic cells (transfection). Gene delivery is a highly challenging task, because cells have several natural barriers that prevent any foreign DNA from entering the cell nucleus. However, in case of some genetic or acquired diseases the introduction of a suitable gene is desirable, because it promises new methods for treatment summarized under the term of „gene therapy" [82]. Polycations in general have shown the capacity to successfully deliver polynucleotides to eukaryotic cells although, as compared to viral „vectors", they are usually less efficient and can exhibit significant cytotoxicity. For more detailed information of the individual steps involved in a successful delivery of genes by non-viral means, the reader is referred to some more detailed literature [83]. In short, for a successful delivery of genes it is necessary to neutralize or revert the negative charges of the nucleic acid, thereby compacting it to a suitable size for cellular uptake. Polycations achieve this through an IPEC formation, leading to particles, so called „polyplexes", with a size up to a few hundred nanome-

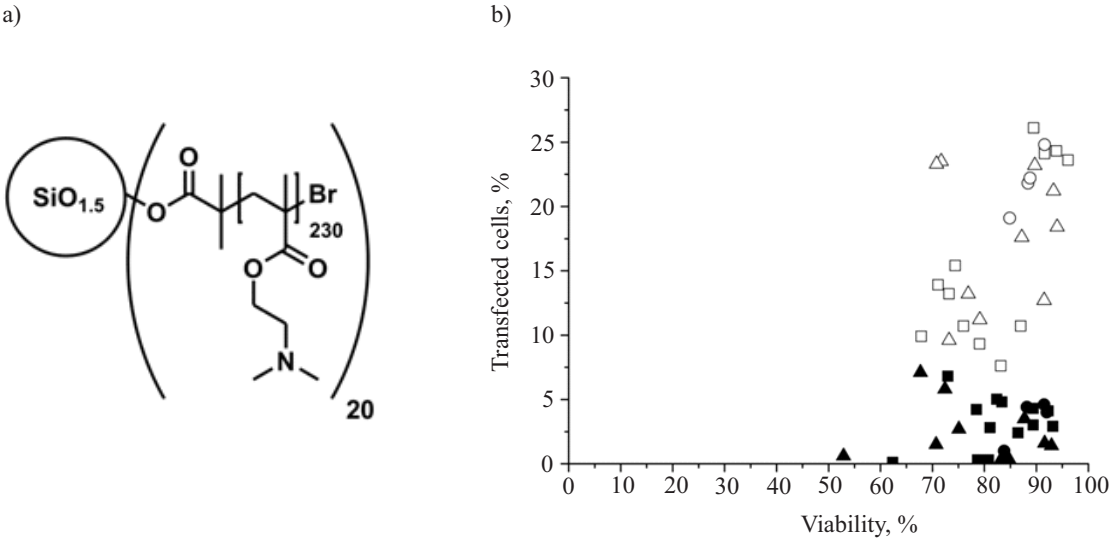

Fig. 5. a) Chemical structure of 20-arm-star PDMAEMA from core-first method by ATRP. b) Analysis of the percentage of transfected cells against the relative viability after transfection in C2C12 cells. Transfection efficiencies in dividing (●, ○), non-dividing myoblasts (■, □) and myotubes (▲, △) are plotted against the viability. Black symbols: PEI, white symbols: Si-PDMAEMA. [Data shown are from individual transfections]. (Reprinted with permission from [93]. Copyright 2012 American Chemical Society)

ters and overall positive charge in case of an excess of the polycation. Simultaneously, by being incorporated in the polyplex the DNA is protected from enzymatic degradation. After successfully entering the cell and escaping from endosomal or lysosomal compartments, the polyplex must dissociate at the right point in the cell so that the nucleic acid is released from the complex and its information can be processed (*e.g.* in the nucleus for DNA and in the cytosol for siRNA). Critical parameters for the evaluation of a transfection agent are the efficiency of gene delivery, characterized by the number of transfected cells and the amount of reporter protein produced after successful delivery. Additionally, the cytotoxicity needs to stay within tolerable levels and finding a good balance between both these parameters has proven a challenging task. PDMAEMA can form polyplexes when complexed with nucleic acids and has successfully transfected cells, but it is generally considered to be less efficient than the „gold standard" poly(ethyleneimine) (PEI) [84, 85]. However, as demonstrated above, synthetic modifications can be performed much more readily using DMAEMA, giving access to more complex architectures (stars, bottlebrushes, *etc.*) and polymers with narrow molecular weight distributions. Several groups found indications for an enhanced transfection when branched structures were used instead of linear ones [13, 28, 35, 40, 86—91]. After testing a library of PDMAEMAs containing linear, 3-arm and 5-arm star-polymers with different molecular weights on their transfection performance and cytotoxicity [92], we discovered a trend towards decreased cytotoxicity with increasing degree of branching, *i.e.* number of arms. Since polymers with higher molecular weight are considered to be more efficient vectors, however, coupled to a significantly increased cytotoxicity, the finding suggests that star-shaped PDMAEMA with a large arm number could give better transfection results combined with low cytotoxicity. Indeed, in a study using a 20-arm star polymer of very high molecular weight (Fig. 5a), we could find extremely high transfection efficiencies in cultured Chinese Hamster Ovary (CHO-K1) cells, while relative cell viability was very high (>90 %) [93]. The superior transfection performance as compared to PEI was not limited to this cell line, but was even found in non-dividing and differentiated cell lines (C2C12 cells and human T lymphocytes). Such cell lines are usually notoriously difficult to transfect by non-viral means, as is evident by the rather weak performance of PEI in the same cell lines. As shown in Fig. 5b, the star-shaped PDMAEMA (open symbols) gave higher transfection efficiency in each individual transfection experiment in C2C12 cells as compared to PEI (filled symbols). Transfections were performed in dividing (circles) and non-dividing (squares) myoblasts as well as in cells differentiated to myotubes (triangles).

Star-like micelles from an amphiphilic polybutadiene-*block*-PDMAEMA diblock copolymer (PB-*b*-PDMAEMA) showed similar transfection results as the 20-arm stars. Thus, we identifed the star architecture as a general design principle for efficient transfection polymers.

In a similar approach, superparamagnetic maghemite nanoparticles (γ-Fe_2O_3 NPs) were coated with a PDMAEMA shell in a core-first approach by first anchoring dopamine-functional ATRP initiators to the NPs and subsequently polymerizing DMAEMA with the resulting multi-functional initiator [53]. This hybrid material showed 2—3 fold higher transfection efficiency as compared to PEI, demonstrating independence of the transfection properties of the star shaped architecture from the core material. Additionally, cells that had taken up this new hybrid transfection agent acquired magnetic properties and

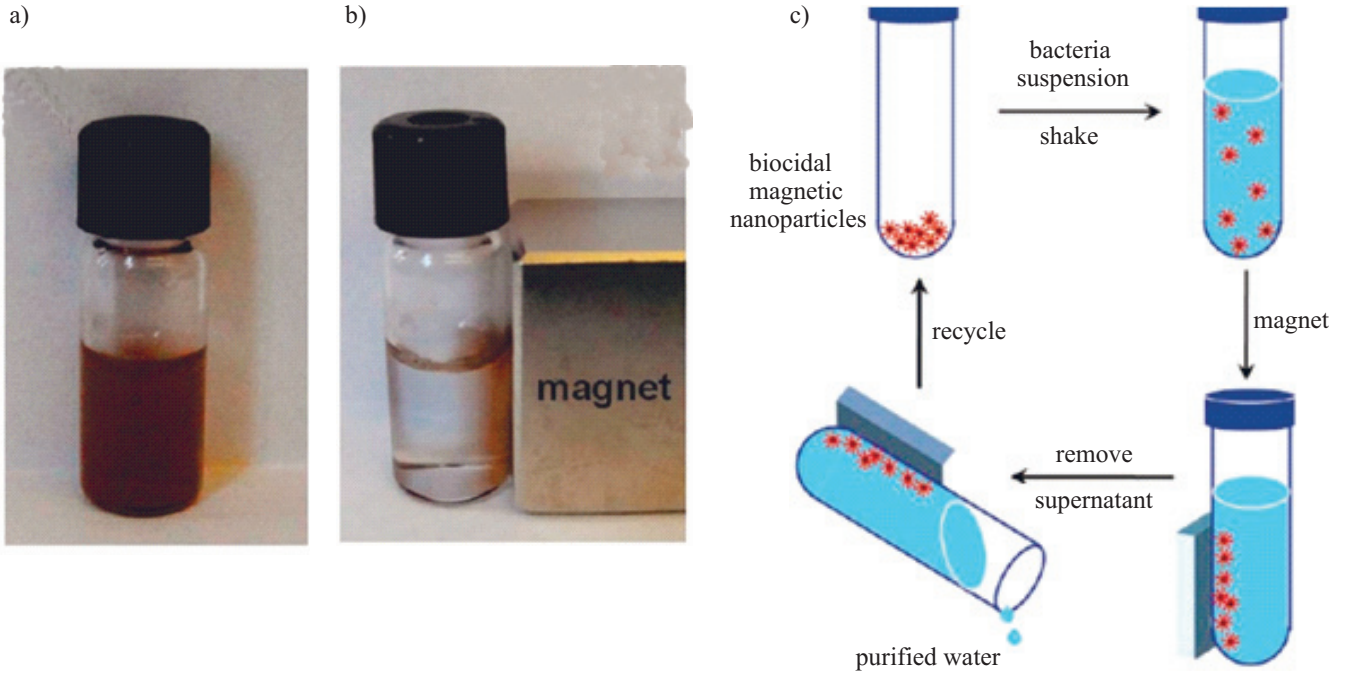

Fig. 6. Images of quaternized PDMAEMA carrying magnetic nanoparticles suspended in water (a) and of the same solution after exposure to a permanent magnet for 10 min (b). Schematic illustration of the exposure/collection/recycling cycle of anti-bacterial nanoparticles (c). (Reprinted with permission from [96]. Copyright 2011 American Chemical Society)

could easily be separated by means of a permanent magnet. The particles therefore offer a new way to identify and select transfected cells out of mixed cell populations, accelerating the development of production cell lines for biotechnology applications. It should be noted that transfection with the magnetic nanoparticles as reported in Ref. [53] is different from so-called Magnetofection™ [94, 95] where gene delivery is performed under application of magnetic fields at a planar surface.

By utilizing the cytotoxicity of amine-containing polymers, especially of quaternary ammonium groups, the group of Matyjaszewski recently introduced magnetic nanoparticles coated with quaternized PDMAEMA as a recoverable anti-bacterial material as depicted in Fig. 6 [96]. Suspended *E. coli* bacteria were efficiently killed after incubation with the nanoparticles, which were subsequently recovered through the application of a magnetic field. Even after repeated administration of the same nanoparticles their bactericidal properties remained unchanged, indicating a good stability of the particles and high recovery rate.

To design enzyme-containing biosensors with a high sensitivity, it is necessary to immobilize a large amount of the respective enzyme on the sensor surface. The layer-by-layer deposition of polyions and enzymes represents a facile method for the production of such sensor systems. Star-like polymer micelles from either PB-*b*-PDMAEMA or its quaternized analogue PB-*b*-PDMAEMAq together with either choline oxidase or tyrosinase were consequently deposited on graphite surfaces and tested as biosensors for the substrate molecules in solution. A large response of the sensors was found when the PB-*b*-PDMAEMA micelles were deposited at high pH, indicating a successful binding of large amounts of enzymes to the surface under these conditions. The response and stability in repeated measuring cycles was higher than for previously tested systems based on poly(diallyldimethylammonium chloride) (PDADMAC) [97].

These examples prove the versatility of PDMAEMA for various applications, especially in the biomedical field. PDMAEMA can easily be adapted to the respective task due to the ease of chemical modification and accessibility of DMAEMA with controlled/living polymerization methods.

HYDROGEL FORMATION FEATURING PDMAEMA

Hydrogels belong to a class of soft matter, which has attracted a lot of attention in recent years. Particularly stimuli-responsive and physically crosslinked gels have many potential applications in biomedicine and have been the subject of intensive research [98—103]. Due to its temperature and pH-sensitive behavior, PDMAEMA can be used in a variety of ways to produce reversible hydrogels [104, 105]. Star-block copolymers have also been used to produce hydrogels. In the case of PDMAEMA, three-arm stars with diblock arms [containing outer poly(DMAEMA-*co*-DEAEMA) blocks] can form free-standing gels at 37 °C and physiological pH at a concentration of 7 wt. % [107]. PDMAEMA and PDEAEMA were combined to create double-responsive star-shaped block copolymers $(PDMAEMA\text{-}b\text{-}PDEAEMA)_x$, where both blocks are responsive to pH and temperature to different

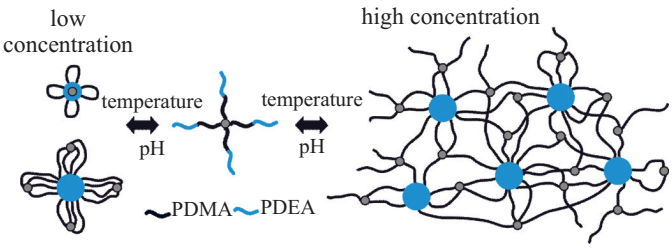

Fig. 7. Aggregation and network formation of double responsive star block copolymers. (Reprinted with permission from [107]. Copyright 2012 Oldenbourg Wissenschaftsverlag GmbH)

extents (Fig. 7) [107]. The collapse of the PDEAEMA outer blocks is first selectively triggered by heating. This has been proven by dynamic light scattering and is due to the significantly lower cloud point of PDEAEMA with respect to that of PDMAEMA at identical pH values.

At high concentrations hydrogel formation was observed under conditions where only the PDEAEMA outer blocks are insoluble. Rheology measurements showed that a minimum DEAEMA fraction is necessary for gel formation and that the DEAEMA fraction strongly influences the properties of the gels. Another factor controlling the gelation behavior of the diblock copolymer stars is the pH value, as the sol-gel transition temperature at a given concentration is shifted to lower values upon increasing the pH. The mechanical properties of some of these gels can be manipulated, as a decrease in the storage modulus was observed in some cases. This occurs only for soft gels, when the temperature is increased above the transition temperature of the inner PDMAEMA block, *i.e.* when the PDMAEMA blocks contract. Here, double-responsive star-shaped gelators were synthesized which formed reversible hydrogels that are still able to respond to a second trigger. However, the hydrogel formation is quite complex, due to the high number of parameters controlling them. This concept of double responsive star-shaped gelators was extended to other polymers and simplified by changing the outer block of the block copolymer stars to a polymer that is only responsive to temperature. This allows for an easier tuning of the sol-gel transition, as only one parameter is involved. The new diblock stars are comprised of PDMAEMA inner blocks and outer blocks of poly(diethylene glycol methyl ether methacrylate) (PDEGMA) [44]. They form hydrogels at relatively low concentrations upon heating above the transition temperature of PDEGMA independent of the pH value. Again, the fraction of DEGMA is an important parameter for the gelation behavior of the (PDMAEMA-*b*-PDEGMA)$_x$ stars. Unexpectedly, the mechanical properties of these gels can also not be changed by heating above the transition temperature of PDMAEMA at pH values around 8. The gels formed in this pH region are strong and too rigid to be affected, similar to the gels formed from (PDMAEMA-*b*-PDEAEMA)$_x$ stars. Only when the pH is increased close to 9, the subsequently formed gels are softer and a decrease in the moduli is observed. Finally, the inner PDMAEMA blocks of the (PDMAEMA-*b*-PDEGMA)$_x$ stars were quaternized to transform them into strong polycations. This leads to an increase in the effective volume fraction of the stars and consequently to a significant decrease of the critical gelation concentration. In addition, the introduction of light-sensitive counterions and even nanoparticles can be envisioned.

CONCLUSIONS

We conclude that PDMAEMA is a very versatile polymer, especially in its star-like topology. It comprises polyelectrolyte behavior, thermosensitivity and pH-responsiveness. Its properties can be adapted to many needs, introducing light-sensitivity or manipulation by electrochemical means. We showed that PDMAEMA stars are the first choice for effective gene delivery or for multiresponsive gels. Even more, we expect other thriving applications of branched PDMAEMA to emerge. Therefore, PDMAEMA can be regarded as the multitasking „chameleon" of polymers: rarely any other polymer shows so many facets.

This original work of the authors was supported by the Deutsche Forschungsgemeinschaft (SFB 481, SPP1259, Mu896/25, SFB 985, PL 571/3-1) and the Fund of the German Chemical Industry (FCI).

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