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Reversible Calcium(II)-Ion Binding through an Apparent pK_a Shift of Thermosensitive Block-Copolymer Micelles

*Johannes P. A. Custers, Sjoerd F. G. M. van Nispen, Aydin Can, Victor R. de La Rosa, Samarendra Maji, Ulrich S. Schubert, Jos T. F. Keurentjes, and Richard Hoogenboom**

Abstract: *There is an increasing need for smart materials capable of removing multivalent ions from aqueous streams without the inconvenience of brine regeneration as in ion-exchange processes. Herein, we present a thermoresponsive micellar system consisting of polystyrene–poly(methoxy diethyleneglycol acrylate) block copolymer surfactants modified with carboxylic acid end groups (PS-PMDEGA-COOH) that can be used to switch between the adsorption and desorption of divalent calcium(II) cations by a mild temperature trigger, thus providing a new type of thermoregenerable ion-adsorbing materials. The switch of calcium(II)-binding capacity is demonstrated to result from a shift in the pK_a value of the carboxylic acid groups by the collapse and redissolution of the PMDEGA block and the associated change in local polarity.*

Hardness ions, such as calcium(II), cause problems in many processes by forming unwanted salt depositions. For different applications, ranging from household applications, such as laundry and dish washing, to drinking-water processes, the softening of water streams is essential.[1,2] The current technology to bind multivalent ions is commonly based on the use of ion-exchange resins.[3,4] The regeneration of ion-exchange resins typically involves consecutive washing steps involving brine or acid and caustic, thus leading to a large amount of waste salt.[5,6] The disposal of these salts causes salinization of surface waters and soil, which is an increasing burden for the environment. Upcoming regenerate-disposal legislation has led several US states, such as California, to already install partial softener bans to deal with the salinization of surface waters. Therefore, the need for salt-free water softening is growing.

A promising approach is the use of smart polymer systems in which a thermal trigger is used as a switch between the adsorption and desorption of multivalent ions, such as calcium(II).[7] A few examples have been reported in which the lower critical solution temperature (LCST) of poly(*N*-isopropyl acrylamide) (PNIPAAm) is used to switch between adsorption and desorption.[8] However, most of these systems deal with ion adsorption at elevated temperatures (40–50 °C) and ion desorption at ambient temperature levels (10–20 °C) and are thus not practical for many applications, since ions often need to be adsorbed from natural water sources, generally found at ambient temperature levels. Furthermore, for systems based on a thermal switch, it would be ideal to use wastewater streams with slightly elevated temperatures for regeneration.

In the search for alternative ion-absorbing materials, we have now developed a micellar system capable of adsorbing calcium(II) ions from water at ambient temperatures (10–20 °C) with the ability to desorb the bound ions at slightly elevated temperatures (40–50 °C). Low-grade waste heat can, thus, be used to regenerate these micelles. The micellar system is based on amphiphilic block-copolymer surfactants synthesized by atom-transfer radical polymerization (ATRP). The surfactants consist of a hydrophobic polystyrene (PS) block and a thermoresponsive hydrophilic poly(methoxydiethylene glycol acrylate) (PMDEGA) block modified with a carboxylic acid (COOH) end group (Scheme 1). In this way, high-molecular-weight anionic surfactants (PS-PMDEGA-COOH) are formed at neutral pH levels.

The main feature of these polymeric surfactants is that the PMDEGA block exhibits a reversible thermosensitive LCST phase transition in aqueous solution with a cloud-point temperature (T_{CP}) slightly above room temperature (38 °C).[9,10] Below its T_{CP} value, the PMDEGA block is water-soluble and hydrophilic, whereas at temperatures above the T_{CP} value, PMDEGA becomes hydrophobic and insoluble in water. At temperatures below the T_{CP} value of PMDEGA and neutral pH levels, micelles of PS-*b*-PMDEGA with a carboxylic acid end group have a negatively charged micellar surface and are therefore capable of adsorbing multivalent cations, such as calcium(II). Since PMDEGA is thermoresponsive,[11–13] the micellar corona collapses and dehydrates upon an increase in the temperature to a value above the T_{CP} value. At these temperatures, the micellar system becomes hydrophobic and microscopic phase separation occurs. Locally, in the environment close to the micelle, a decrease in the dielectric constant occurs as a result

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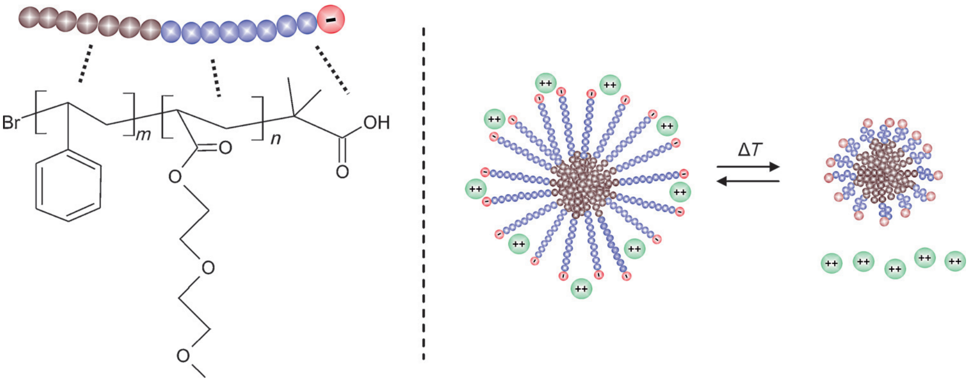
[*] Dr. J. P. A. Custers, Dr. S. F. G. M. van Nispen,
Prof. Dr. J. T. F. Keurentjes
Process Development Group, Eindhoven University of Technology
PO Box 513, 5600 MB Eindhoven (The Netherlands)

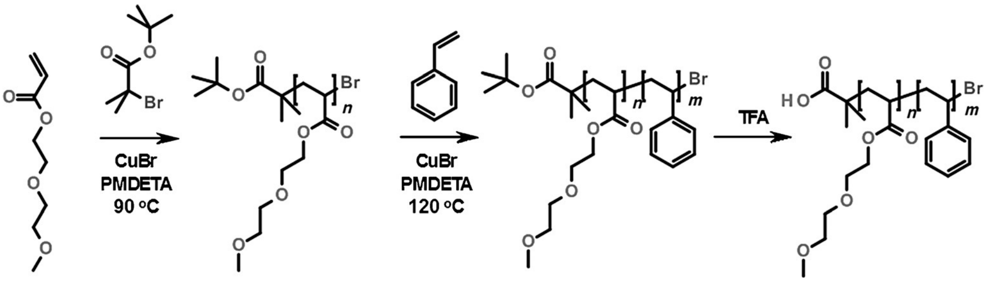
A. Can, Prof. Dr. U. S. Schubert
Laboratory of Organic and Macromolecular Chemistry (IOMC)
Friedrich-Schiller-University Jena
Humboldtstrasse 10, 07743 Jena (Germany)
and
Jena Center for Soft Matter (JCSM), Friedrich-Schiller-University Jena
Philosophenweg 7, 07743 Jena (Germany)

Dr. V. R. de La Rosa, Dr. S. Maji, Prof. Dr. R. Hoogenboom
Supramolecular Chemistry Group, Department of Organic and Macromolecular Chemistry, Ghent University
Krijgslaan 281 S4, 9000 Ghent (Belgium)
E-mail: Richard.Hoogenboom@ugent.be
Homepage: http://www.sc.ugent.be

Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under http://dx.doi.org/10.1002/anie.201505351.



Scheme 1. Right: Mechanism of thermoreversible cation binding for a polymeric surfactant consisting of polystyrene, poly(methoxydiethylene glycol acrylate), a carboxylic acid end group. Left: Chemical structure of the polymeric surfactant.



Scheme 2. Synthesis of thermoreversible amphiphilic polystyrene-*block*-poly(methoxydiethylene glycol acrylate) with a carboxylic end group by ATRP with *tert*-butyl α-bromoisobutyrate as the initiator. PMDETA = *N*,*N*,*N*',*N*'',*N*''-pentamethyldiethylenetriamine.

Table 1: Characterization of the synthesized polymers.

Polymer sample	M_n[a] [g mol^{-1}]	$Đ$[a]	X_{DEGA} [%][b]	$X_{styrene}$ [%][b]	DP_{DEGA}[c]	$DP_{styrene}$[c]
PMDEGA-*t*Bu[d] (**1**)	12 900	1.22	57	–	74	0
PS-PMDEGA-*t*Bu[d] (**2**)	19 000	1.38	64	53	79	50
PS-PMDEGA-COOH[e] (**3**)	19 000	1.41	64	53	79	50

[a] The number-average molecular weight (M_n) and dispersity ($Đ$) were determined by size-exclusion chromatography analysis relative to polystyrene standards. [b] X is the conversion of the monomer, as determined by ^{1}H NMR spectroscopy. [c] DP is the degree of polymerization. [d] *t*Bu represents the tertiary butyl end group on the PMDEGA block. [e] COOH represents a carboxylic acid end group on the PMDEGA block.

of the removal of water. It was anticipated that the change in the dielectric constant would change the effective pK_a value of the carboxylic acid end groups towards higher values. This apparent pK_a shift is proposed to lead to partial release of the bound calcium(II) ions at neutral pH values through competitive protonation and the resulting decrease in surface charge density.

In the field of biology, the pK_a values of amino acid side chains present in proteins are known to shift from those of the free amino acids as a result of both electrostatic interactions and hydrophobic effects.[14,15] In fact, it has been reported that the most effective pK_a shift in water arises from competition between hydrophobic and hydrophilic species.[16] Such pK_a shifts as a result of variation in hydrophobicity have also been described for fatty acids,[17] aliphatic amines,[18] and peptide hydrogels,[19] as well as for thermoresponsive ionic polymers, such as poly(dimethylaminoethyl methacrylate) (co)polymers[20,21] and ionically modified PNIPAAm.[22–24] Thermoresponsive ionic polymers have also been demonstrated to enable the temperature-controlled absorption of carbon dioxide.[25,26] However, to the best of our knowledge, no examples have yet been reported in which such a pK_a shift has been used as a switch between the adsorption and desorption of multivalent cations, nor for the softening or decalcifying of water.

The polymerization of mDEGA by ATRP with *tert*-butyl α-bromoisobutyrate as the initiator resulted in a defined polymer, PMDEGA-*t*Bu (**1**), with a dispersity ($Đ$) of 1.22 (Scheme 2). This specific initiator was selected to enable facile removal of the *tert*-butyl group to generate the desired carboxylic acid end group. The PMDEGA-*t*Bu polymer **1** was subsequently used as a macroinitiator for the ATRP of styrene to yield the PS-PMDEGA-*t*Bu block copolymer (**2**). Hydrolysis of the *tert*-butyl ester group of **2** with trifluoroacetic acid (TFA) then gave the final product PS-PMDEGA-COOH (**3**) with a carboxylic acid end group. Table 1 lists the structural details of the polymers, and further experimental details are included in the Supporting Information.

In a previous study, we found that divalent calcium(II) ions do not bind to isolated carboxylate groups.[7] The sequestering of calcium(II) ions only occurs when polymeric surfactants aggregate into micelles, thus bringing the carboxylic acid end groups into close proximity. Therefore, we formed PS-PMDEGA micelles by direct dissolution of the polymer in water. A cryoTEM image of a 0.30 wt % aqueous solution of **2** clearly revealed the presence of mostly spherical micelles with a PS-core diameter of 20–30 nm (Figure 1; the contrast in cryoTEM only enables visualization of the PS core and not the hydrated corona). Static light scattering (a Zimm plot) revealed a similar value of 22 nm for the PS core (see the

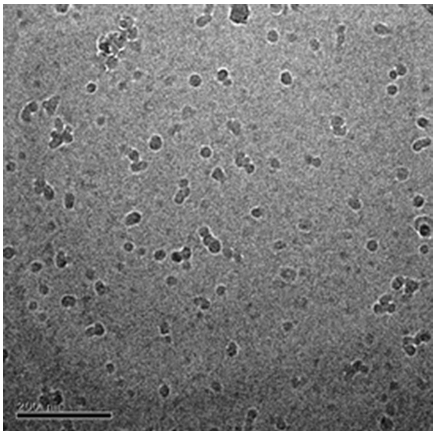


Figure 1. CryoTEM micrograph of a 0.30 wt% solution of PS-PMDEGA-*t*Bu (**2**; scale bar: 200 nm).

Supporting Information). Dynamic light scattering (DLS) showed that the obtained micelles of PS-*b*-PDEGA had an average hydrodynamic size of 35 nm, which did not depend significantly on the concentration of the micelles in water, thus indicating that the corona has a hydrodynamic thickness of approximately 5 nm.

Determination of the T_{CP} value is important, because it will indicate the proposed switching temperature between the absorption and desorption of calcium(II) ions. Therefore, we compared the thermoresponsive behavior of PS-PMDEGA-*t*Bu (**2**) and PS-PMDEGA-COOH (**3**) micelles to study the influence of the presence of carboxylic acid groups. Plots of the optical transmittance of the micellar solutions at 490 nm as a function of temperature (Figure 2) show that the T_{CP} value shifted to a higher value for **3**. This shift can be attributed to the higher hydrophilicity of the copolymer end groups that form the outer layer of the micelles and thus strongly influence the hydration behavior of the PMDEGA corona.[27,28]

Surprisingly, the turbid solution of the more hydrophobic polymer PS-PMDEGA-*t*Bu (**2**) was found to be more stable that than of PS-PMDEGA-COOH (**3**). In fact, further coagulation of the polymer-rich phase-separated droplets of **3** was observed from around 46 to 52 °C (see photographs in Figure 2). It may be speculated that this further coagulation is a first hint that the carboxylic acid end groups indeed undergo a pK_a shift during the LCST transition, and that the resulting larger fraction of protonated acid groups enables further coagulation, possibly driven by hydrogen bonding, into large aggregates that phase segregate to the bottom of the vial, so that higher transmittance is observed.

The ability of the PS-PMDEGA-COOH (**3**) micelles to bind and release calcium(II) ions was investigated in a dialysis experiment: A dialysis bag was placed in a beaker containing an aqueous solution of PS-PMDEGA-COOH micelles and $CaCl_2$. Under these conditions, the calcium(II) and choride ions can freely enter the dialysis bag, in contrary to the PS-PMDEGA-COOH micelles. At equilibrium, the concentration of calcium(II) inside the dialysis bag represents the concentration of free calcium(II), not bound to the micelles. During this experiment, an excess of calcium(II) (0.5 mM) was used in relation to the COOH groups (0.3 mM), as we took into account that two COOH groups bind one calcium(II) ion in the presence of NaCl (0.3 mM). These conditions were chosen to mimic drinking-water conditions and to provide a proof-of-concept demonstration of the decalcifying capability of our system. Alteration of the temperature of the water to values above and below the T_{CP} value led to a significant variation in fractional calcium(II) binding (Figure 3; see the Supporting Information for more experimental details). At 20 °C there was almost complete fractional binding, whereas at 38 °C significantly decreased binding of the calcium(II) ions by the PS-PMDEGA-COOH micelles was observed.

The large difference in fractional binding between 20 and 38 °C indicates a substantial shift in micellar surface charge density between those temperatures, most likely as the result of a large effective pK_a shift of the end groups. On the basis of

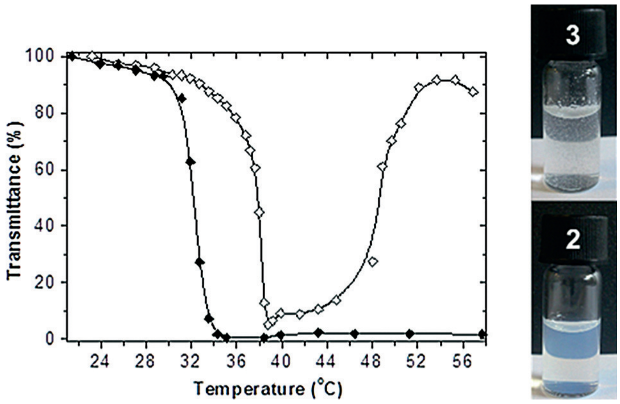


Figure 2. Left: Optical transmittance of a 0.25 wt% aqueous solution of PS-PMDEGA-*t*Bu (**2**; ◆) and a 0.28 wt% aqueous solution of PS-PMDEGA-COOH (**3**; ◇) as a function of temperature . Right: Photographs of solutions of PS-PMDEGA-COOH (**3**; top) and PS-PMDEGA-*t*Bu (**2**) after heating to 50 °C.

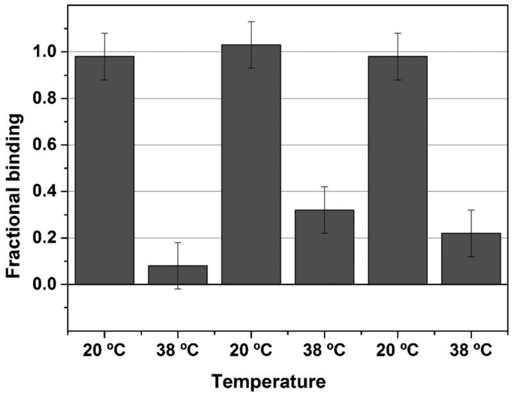


Figure 3. Fractional binding of carboxylic end groups with calcium(II) ions as a function of the changing temperature of the aqueous solution. At the start, the pH value was adjusted to 7 by NaOH at 20 °C. The experimental error in the fractional binding was found to be 0.1 for all temperatures. The concentration of end groups was 0.3 mM, and the initial concentrations of $CaCl_2$ and NaCl were 0.5 and 0.3 mM, respectively.

the assumptions that calcium(II) ions are either bound or free (two-state approximation) and that free calcium(II) ions are present at the same concentration in- and outside the dialysis bag, we can estimate that the apparent pK_a value at 20 °C is about 5 (pH 7.0) and at 38 °C is about 7.8 (pH 7.3). These values correspond to an effective calculated pK_a shift of about 2.8 (see the Supporting Information). To confirm this hypothesized pK_a shift, we performed pH titrations for PS-PMDEGA-COOH (**3**) below (at 26 °C) and above (at 48 °C) the T_{CP} value (Figure 4; see also the Supporting Information).

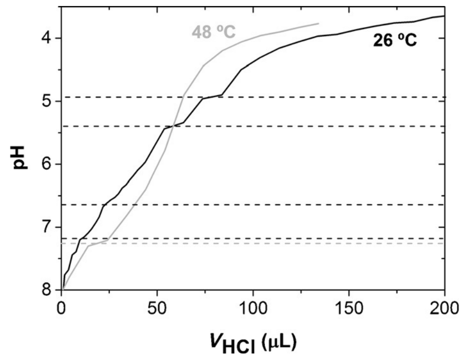


Figure 4. pK_a titrations of PS-PMDEGA-COOH (**3**) micelles below (26 °C) and above (48 °C) the cloud-point temperature. The pH value is plotted as function of the volume of HCl solution added, and was normalized to start at pH 8. The dotted lines indicate the individual pK_a values.

An important first observation is that the pH value of the micellar solution in milliQ water was hardly affected by the temperature-induced phase transition, being 6.38 at 26 °C and 6.50 at 48 °C. Furthermore, the pK_a titration below the T_{CP} value revealed two major transitions with pK_a values of 4.9 and 5.4, which are in the expected range for carboxylic acids in an aqueous environment. Furthermore, two faint pK_a shifts were observed at 6.7 and 7.2, which may represent the protonation of carboxylate groups that are hidden in hydrophobic parts of the micelles. This latter assumption was confirmed by the pH titration above the T_{CP} value, which clearly showed a single pK_a value at 7.3, in perfect agreement with the estimated value. Thus, these pH titrations unambiguously confirmed that crossing of the T_{CP} value induces a large pK_a shift of approximately 2 units that is proposed to induce the change in calcium(II)-binding ability of the PS-PMDEGA-COOH micelles. A second important observation is that the addition of much less HCl is required to reach pH 4 above the T_{CP} value than below the T_{CP} value, thus indicating that not all carboxylic acid groups are available above the T_{CP} value but that a significant fraction is hidden inside the collapsed PMDEGA corona (Figure 4).

The appearance of multiple pK_a values during the titration below the T_{CP} value is rather intriguing and might indicate that the (de)protonation of the carboxylic acid groups induces a rearrangement of the micelles to produce a small pK_a shift in the remaining carboxylate groups. Since this rearrangement of the polymer chains in the corona of the micelles should affect the topology of the micelles, we investigated the particle-size distribution at different pH values throughout the titration (see Figures S6 and S7 in the Supporting Information). Below the T_{CP} value, two subtle but sharp transitions towards marginally larger sized and better defined particles were indeed observed around pH 4.9 and 5.4 upon the addition of HCl. This observation supports a rearrangement of the micelles during the carboxylate protonation as the origin of the distinct pK_a transitions observed, although it does not shed light on the exact conformational changes of the polymers in the corona during these transitions. Above the T_{CP} value, DLS revealed one sharp transition from well-defined micelles with a diameter of approximately 23 nm to large near-micron-sized particles at pH values below 5.4.

However, in addition to this pK_a-induced change in the electrostatic driving force for calcium(II) ions to move in and out of the dialysis bag between the two temperatures, there could be a change in the distribution of calcium(II) because of a difference in chemical potential simply caused by the occurrence of polymer phase separation inside the dialysis bag, thus leading to a shift in osmotic pressure, as was recently proposed for LCST-driven osmotic pumps.[29] To exclude this possibility that there is no effective pK_a shift at 38 °C and thus hardly any proton counterions, so that calcium(II) counterions dominate the surface of the hydrophobic collapsed micelles, we used a simple Donnan equilibrium model for 2:1 electrolytes to estimate the equilibrium ion distributions for two cases (see the Supporting Information). A fractional binding of 0.14 was found at 38 °C for the case in which there are mainly H counterions (protonation) and a fractional binding of 0.75 for the case in which there are mainly calcium(II) counterions. Since the mean experimental fractional binding at 38 °C is about 0.19 (Figure 3), this result supports our hypothesis that an apparent pK_a shift is mainly responsible for the observed reversible calcium(II) binding.

In conclusion, we have demonstrated the ability of micellar solutions of PS-PMDEGA-COOH to reversibly switch between the adsorption and desorption of calcium(II) ions upon heating from ambient temperatures towards a moderate temperature of 38 °C. The driving mechanism is a hydrophobically induced pK_a shift of around 2 units, which results in an affinity change for multivalent cation adsorption, as was confirmed by pH titrations. These results may open up new possibilities for a variety of ion-binding applications, such as the development of softening resins that can be regenerated by low-grade waste heat without the need for a chemical-treatment step. Future research should be directed towards further enhancement of the calcium(II)-binding ability by variation of the block lengths of the polymer. Furthermore, competitive binding experiments should be carried out with other components that may be present in water, such as magnesium(II). Related studies on the binding of calcium(II) and magnesium(II) to palmitic acid revealed significantly stronger binding of calcium(II), and similar results may be expected for our system, as the interacting carboxylate groups are the same.[30]

Keywords: calcium(II) binding · responsive polymers · self-assembly · smart materials · thermoreponsive polymers

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