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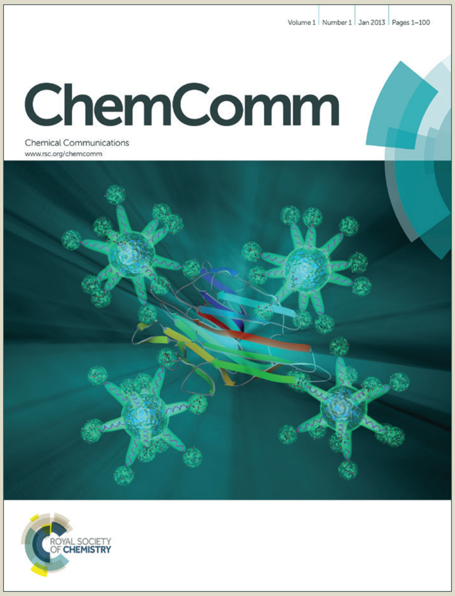

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Mechano-Responsive Polymer Solutions Based on CO_2 Supersaturation: Shaking-induced Phase Transitions and Self-Assembly or Dissociation of Polymeric Nanoparticles

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Mechanical stimulation of supersaturated aqueous CO_2 solutions is accompanied by a pH increase within seconds. In solutions of tailored homo- and AB diblock copolymers this is exploited to induce micelle formation, or, taking advantage of an aqueous upper critical solution temperature transition, nanoparticle disassembly.

Stimulus responsive polymers, materials that respond with often drastic physical changes to subtle applied environmental stimuli, present an intriguing research field.[1] Stimulus-triggered switching of components of copolymers has especially been exploited in the assembly (and dissociation) of defined nanostructures setting the stage for application in drug delivery,[2] biotechnology,[3] detection and sensing,[4] among others. In many cases, stimulus responsive polymers only exhibit their “smart” behaviour in a specific environment. Poly(*N*-isopropylacrylamide), one of the best-documented thermoresponsive polymers, for example, exhibits lower critical solution temperature (LCST) behaviour in water, upper critical solution temperature (UCST) behaviour in dimethylsulfoxide–water[5] and is either soluble or insoluble, but not thermoresponsive, in most other solvents. Of a variety of physical and chemical stimuli that have been investigated to evoke reversible or irreversible responses in tailored smart polymers, mechanical stimuli are attracting increasing attention.[6] In most cases the design of mechano-responsive polymers requires the careful positioning of mechanophores into a polymeric matrix.[7] These are molecules that respond to mechanical stimulation through conformational changes or through scission of a predetermined covalent bond resulting in subsequent chemical reactions.[8] Strong forces required for activation of mechanophores are typically applied through manipulation (e.g. stretching) of bulk samples. Mechanical stimulation of polymer solutions, on the other hand, for example through sonication or shaking, represents an intriguing—and, primarily, simple—technique to prompt the response of a smart polymer. As such, mechano-responsive polymer solutions offer potential to avoid more complex protocols for example in inducing morphological changes through self-assembly or for the development of shock or impact sensors. However, while sonication-assisted aggregation[9] or shaking-induced gelation[10] are well-documented for low molecular weight (organo-)gelators, only few mechano-responsive polymer solutions have been described.[11, 12] For example, Fan et al.[11] described copolypeptide copolymers which formed gels in dimethylformamide that underwent a gel-to-sol transition upon sonication, due to break down of interactions within the copolypeptide block.

Carbon dioxide has been investigated as a gaseous stimulus to trigger reversible responses of pH responsive (co)polymers. CO_2 dissolves in water, forming (in part) carbonic acid which dissociates with a pK_{a1} of 3.60.[13] Interestingly, the $HCO_3^- + H_3O^+ \leftrightarrows CO_2\,(aq) + 2\,H_2O \leftrightarrows CO_2\,(gas)$ equilibrium can be shifted to the right side, and thus the initial pH of the solution restored, by displacing dissolved CO_2 with another gas. Addition and displacement of CO_2 can therefore be applied to reversibly protonate and deprotonate chemical groups of appropriate basicity. Tertiary amines[14] including several amidines,[15] as well as organic carbonates,[14] have lent themselves perfectly to the design of reversibly CO_2 responsive materials.[16, 17] In all of these cases, CO_2 was administered at (partial) pressures of 1 atm and removed by displacement with another gas. To the best of our knowledge supersaturated CO_2 solutions produced at higher pressure[18] have not been used in the smart polymers arena. Under ambient conditions supersaturated solutions are metastable and, in the absence of nucleation sites (such as gas cavities or pits in the container wall) lose dissolved CO_2 slowly.[19] Mechanical stimulation, however, greatly increases the nucleation rate causing bubble formation and rapid loss of CO_2 (as is commonly observed in the effervescence of agitated carbonated beverages) until a certain lower level of supersaturation is reached at which bubble formation ceases.[20] Herein we demonstrate how the pH change associated with mechanical stimulation of supersaturated CO_2 solutions presents a cheap and simple approach to realise an entirely novel type of mechano-responsive polymer solutions. We highlight the versatility of this concept by demonstrating a variety of morphological responses triggered through mechanical stimulation. Depending on the chemical design of functional (co)polymers, shaking (or evacuation of) their solutions in commercial soda water can be applied to induce polymer precipitation, polymer dissolution by means of shifting an aqueous UCST transition, formation of micelles, or dissociation of micelles.

We chose commercial, drinking-quality, bottled soda water as a cheap source of supersaturated CO_2 solutions. Typically sealed at pressures of ~3 bar,[19] we did not find significant differences in shaking-induced pH changes between different brands. One type had an initial pH of 4.35 which was reproducible after keeping in a closed bottle for several weeks. During shaking for 20 s in a conical flask intense effervescence was observed resulting in a pH change to 5.26. Importantly, the initial pH could be adjusted up to ~7 by the addition of aqueous sodium carbonate solution without impairing the occurrence of a shaking-induced pH increase by ~1, see Figure 1. Of note, pH increases occurred within seconds and as a result of mechanically triggered CO_2 effervescence, independent of the presence of other gases. Similar agitation of water saturated with CO_2 through bubbling at ambient pressure[15] did not cause a significant pH increase, demonstrating the need for supersaturated solutions in order to confer mechano-responsiveness.

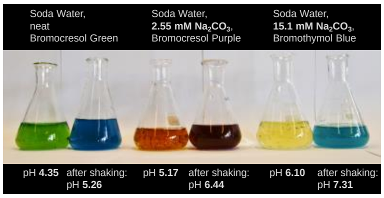

Figure 1. Photograph of soda water containing different amounts of added sodium carbonate to adjust the initial pH without (left flasks) and after (right flasks) shaking for 20 s. Traces of pH indicating dyes were added to elucidate the pH shift.

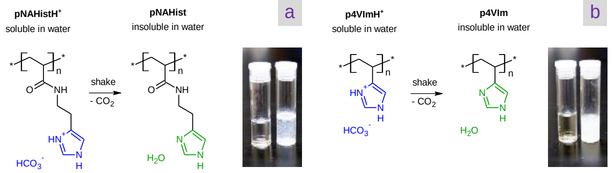

Figure 2. Structures of homopolymers indicating deprotonation[21, 22] upon removal of dissolved CO_2 with photographs of vials before (left) and after (right) shaking soda water solutions containing (a) pNAHist (2.77 g/L), Na_2CO_3 (10 mM, pH 6.08 →7.22 through shaking) and (b) p4Vim (1.26 g/L), Na_2CO_3 (7 mM, pH 7.15 → 7.89 through shaking)

In order to exploit the observed pH increase to trigger switching of a responsive polymer, we first directed our attention to polymers that (a) have a pK_a between pH 5–8 and (b) are water-soluble when protonated and water-insoluble in their basic state. The imidazole-functional species poly(*N*-acryloyl histamine), pNAHist, and poly(4-vinylimidazole), p4VIm, are suitable examples. Both homopolymers dissolved in soda water containing added Na_2CO_3 forming clear solutions that could be kept in closed containers for 3 weeks without any observable change. In response to vigorous agitation for 20 s, however, both solutions turned cloudy followed by macroscopic precipitation of polymer, see Figure 2.

The mechanically triggered collapse of pNAHist was subsequently exploited for the shaking-induced formation of polymeric nanoparticles. An AB diblock copolymer poly(*N*-acryloyl histamine$_{0.45}$-*b*-dimethylacrylamide$_{0.55}$), p(NAHist-*b*-DMA), prepared by RAFT polymerisation[23] and comprising 55 mol% of a hydrophilic pDMA block dissolved unimerically in soda water containing added Na_2CO_3 as confirmed by dynamic light scattering (DLS), see Figure 3 (right side, curve A). Stored in a sealed vial containing little air no changes were observed after 3 weeks (curve D). Shaking the solution for 20 s, however, resulted in the formation of well-defined micelles with hydrodynamic diameters of 40.2 ± 0.8 nm measured by DLS (curve B), and 27.8 nm dried solids diameter measured by transmission electron microscopy (TEM, Figure 3, middle). This morphology change was driven by the response of the pNAHist block causing microphase separation into insoluble cores stabilised by a pDMA corona.[15] Very similar nanoparticles of 40.1 ± 0.9 nm hydrodynamic diameter (curve C) were found after evacuating a round bottom flask containing p(NAHist-*b*-DMA) solution in soda water for several seconds. Intense bubbling was observed when the flask was connected to a pump. Slight mass difference before and after evacuation suggested that only a small amount of water had evaporated and that bubbling had been caused by loss of dissolved gases—including CO_2. These experiments document successful formation of nanoparticles by way of mechanical stimulation of otherwise stable solutions. Micellar solutions were likewise found to be stable with no observed change in particle size or size distribution after several weeks (curve E).

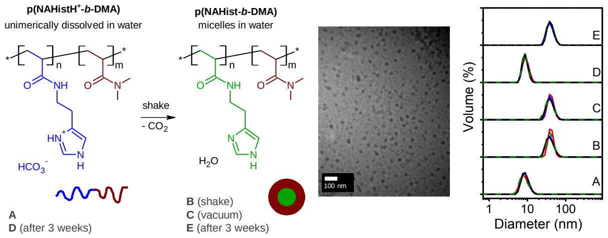

Figure 3. Structure of diblock copolymer p(NAHist-*b*-DMA) (M_n = 8.2 kg/mol, $Đ_M = M_{w,SEC}/M_{n,SEC}$ = 1.20) (left side); volume distribution measured by DLS (right side; 4 separate superimposed measurements each) of p(NAHist-*b*-DMA) unimers (1 g/L) in soda water containing added Na_2CO_3 (10 mM, pH 6.14) (A, d_{vol} = 9.0 ± 0.2 nm), the same solution after shaking for 20 s (B, pH 7.24, d_{vol} = 40.2 ± 0.8 nm), solution A after applying vacuum for 3 s (C, d_{vol} = 40.1 ± 0.9 nm), solution A after keeping for 3 weeks (D, d_{vol} = 9.2 ± 0.2 nm) and micellar solution B after keeping for 3 weeks (E, d_{vol} = 40.1 ± 0.5 nm); and TEM image of micellar solution B (d_n = 27.8 ± 5.2 nm) (middle).

Having successfully demonstrated the ability to mechanically induce soluble-to-insoluble phase transitions we also explored the possibility of triggering the reverse response—shaking-induced dissolution of a homopolymer or nanoparticles. Similar reasoning as above would necessitate a polymer that is water-insoluble in its protonated state and, when deprotonated at a pH between 5–8, becomes water soluble. Carboxylic acid-functional (co)polymers such as poly(methacrylic acid) appeared to have too low pK_a values and thus did not exhibit significant solubility changes in the pH range available by soda water shaking experiments. Instead, we took further advantage of the well-matching pK_a of tertiary amine-functional polymers. In its (partially) protonated state poly[2-(dimethylamino)ethyl methacrylate], pDMAEMA, shows a UCST transition in water[24] in the presence of small amounts cobaltate ions. These trivalent anions crosslink the positively charged polymer side groups through electrostatic interactions that are broken at elevated temperature.[25] In our experiment RAFT-prepared pDMAEMA dissolved in soda water containing added Na_2CO_3 and a small amount of $K_3[Co(CN)_6]$ exhibited a UCST cloud point of 45.8 °C resulting in a two phase mixture at room temperature, see Figure 4. Shaking of this sample for 20 s accompanied by CO_2 effervescence resulted in dissolution of the polymer forming a transparent solution. Thermal characterisation revealed a significantly shifted UCST cloud point of 13.7 °C due to reduced ionization and associated lower cobaltate-induced crosslinking.[25] UCST transitions were thermo-reversible if the amount of dissolved CO_2 was remained unchanged. To the best of our knowledge, this is the first reported example of a mechano-sensitive aqueous UCST transition and further enhances the potential applications of (co)polymers exhibiting aqueous UCSTs.

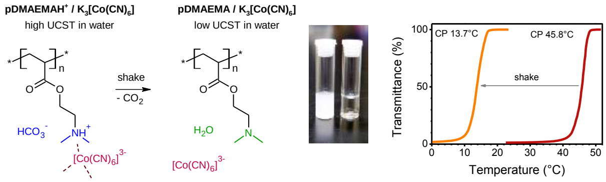

Figure 4. Structure of pDMAEMA homopolymer ($M_{n,SEC}$ = 22.3 kg/mol, $Đ_M$ = 1.14) showing cobaltate crosslinking in the protonated state (left); temperature dependent transmittance of soda water solution containing pDMAEMA (0.67 g/L), Na_2CO_3 (15.3 mM) and $K_3[Co(CN)_6]$ (1.48 mM) (pH = 7.0) before (red curve) and after (orange curve) shaking for 20 s indicating shifting of aqueous UCST transition (right); photograph of same samples at room temperature before (left vial) and after (right vial) shaking.

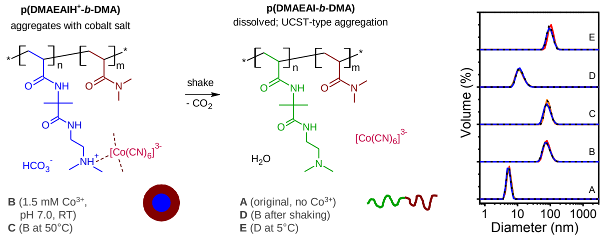

Figure 5. Structure of a p(DMAEAI-*b*-DMA) copolymer highlighting coordination of the tertiary amino functional side groups to trivalent cobaltate ions in the protonated state and loss of protonation and coordination upon removal of carbonation (left); DLS-measured volume distribution (right side; 5 separate superimposed measurements each) of p(DMAEAI-*b*-DMA) unimers (1.46 g/L) in soda water (A, d_{vol} = 5.9 ± 0.1 nm), after addition of Na_2CO_3 (16.1 mM) and $K_3[Co(CN)_6]$ (1.50 mM) showing larger aggregates due to cobaltate crosslinking (B, d_{vol} = 79.7 ± 1.3 nm), solution B at 50 °C indicating insolubility of the cobaltate-coordinated DMAEAI block at this temperature (C, d_{vol} = 84.5 ± 1.4 nm), solution B after shaking for 20 s showing dissolution of large aggregates indicating disruption of most cobaltate coordination (D, d_{vol} = 18.4 ± 1.5 nm) and solution D at 5 °C showing reformation of large aggregates suggesting UCST behaviour of the partially cobaltate-coordinated DMAEAI block (E, d_{vol} = 100.6 ± 2.9 nm).

Finally, we applied the observed shaking-dependent cobaltate crosslinking to a novel species for which aqueous UCST behaviour had previously not been documented. Well-defined poly[(2-(dimethylamino)ethyl 2-acrylamido isobutyramide)$_{0.54}$-*b*-DMA$_{0.46}$], p(DMAEAI-*b*-DMA), comprising 54 mol% of a tertiary amine-functional bisamide block and—similar to the design of the above-mentioned polymer—a permanently water-soluble pDMA block, dissolved molecularly in soda water containing added Na_2CO_3 (see Figure 5, right side, curve A). Addition of $K_3[Co(CN)_6]$ caused formation of nanoparticles with a measured hydrodynamic diameter of 79.7 ± 1.3 nm, seemingly containing a loosely crosslinked pDMAEAI core (curve B). The same morphology was observed by DLS at 50 °C, suggesting the absence of a UCST cloud point up to this temperature (curve C). Shaking this mixture, however, resulted in disintegration of the aggregates (curve D), displaying opposite behaviour to the above-described shaking-induced nanoparticle formation. Interestingly, cooling of the shaken, disintegrated, solution below 10 °C caused reformation of nanoparticles (see Figure 5 curve E and supporting information). These results suggest that pDMAEAI displays aqueous UCST behaviour in the presence of trivalent salts with cloud points somewhat higher than those of pDMAEMA under similar conditions. In summary, we describe a simple and cheap methodology to realise mechanically responsive polymer solutions. Based on agitation-induced effervescence of CO_2 from a supersaturated solution (such as drinking quality soda water) solubility changes in tertiary amine-containing (co)polymers lead to homopolymer precipitation and microphase separation in strategically designed AB diblock copolymers resulting in soft matter nanoparticle formation. Taking advantage of an aqueous UCST transition displayed by tertiary amine functional (co)polymers in the presence of trivalent anions, we additionally designed (co)polymer solutions displaying shaking-triggered dissolution of a homopolymer and of polymeric nanoparticles. This facile technique has the potential to replace more complex procedures often applied toward the manipulation of well-defined functional nanoparticles and their associated phase behaviour.

Notes and references

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