Host–Guest Systems

DOI: 10.1002/anie.200603753

Cyclodextrin Complexes of Polymers Bearing Adamantyl Groups: Host–Guest Interactions and the Effect of Spacers on Water Solubility

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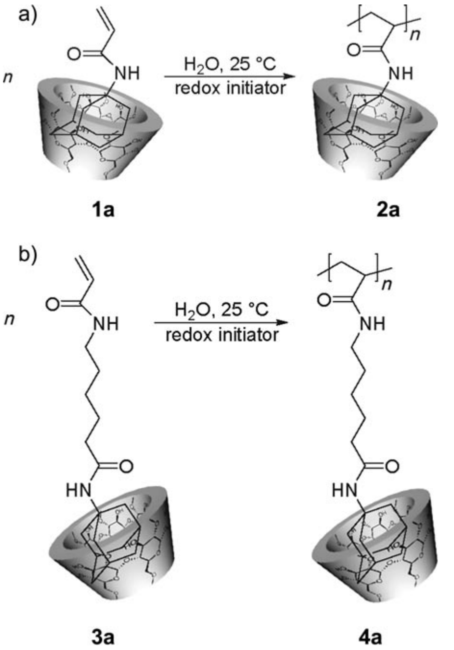
Polymer-inclusion complexes (PICs) with cyclodextrins (CDs) show a broad structural variety[1–4] and are of interest for many different applications, for example, drug delivery systems[5] and stimuli-responsive hydrogels.[6,7]

We have demonstrated that the lower critical solution temperature (LCST) of *N*-isopropylacrylamide(NIPAAM)-based copolymers bearing adamantyl groups can be influenced through complexation of the adamantyl moieties by cyclodextrins (CDs).[8,9] Recently, we reported on the synthesis of a PIC consisting of randomly methylated β-CD and a polymethacrylamide which showed a reversible phase transition in aqueous solution as a result of a dissociation/complexation process.[10] Unfortunately, this system was not optimal in terms of chemical stability and the guest moiety used. We report herein on the pseudo-LCST behavior of PICs consisting of poly(adamantylacrylamide)s and Me-β-CD. In contrast to the previously reported system, the newly synthesized polyacrylamides are expected to be much more stable against hydrolysis. Additionally, the incorporated adamantyl moieties are well suited for inclusion into β-CD. With this optimized system we will demonstrate the influence of spacer groups and concentration on the phase-transition process.

It is known that Me-β-CD-complexed hydrophobic monomers can be polymerized in water by means of a free-radical mechanism by use of water-soluble azo or redox initiators.[11] In most cases, the Me-β-CDs slip off the growing macroradicals which leads to precipitation of the polymeric material. In contrast, polymerization of Me-β-CD-complexed 1-adamantylacrylamide (**1a**) and 6-acryloylaminohexanoic acid 1-adamantylamide (**3a**) resulting the formation of the water-soluble polymer/Me-β-CD-complexes **2a** and **4a**, respectively (Scheme 1). The polymerization was carried out in water at 25 °C using 1 mol % of the redox initiator system $K_2S_2O_8/Na_2S_2O_5$.

The molecular weights of the purified Me-β-CD-free polymers **2** and **4** were determined by MALDI-TOF mass spectrometry (Figure 1). Interestingly, the obtained polymer/Me-β-CD complexes **2a** and **4a** show thermosensitive solubility properties in water that strongly depend on the distance between the Me-β-CD-complexed adamantyl groups and the polymer backbone.



Scheme 1. Free-radical polymerization of monomer/Me-β-CD complexes **1a** and **3a** in water at 25 °C using the redox initiator system $K_2S_2O_8/Na_2S_2O_5$.

Figure 2 shows the transmittance of an aqueous solution of **2a** as a function of temperature. The measurement was performed at a concentration of 100 gL^{-1} using a heating/cooling rate of 1 $K min^{-1}$. It can be seen that in the heating run the transmittance of the solution drops from 100 to 0 % within a temperature range of about 1–2 °C around the cloud point of 44.6 °C. This effect is caused by the dissociation of the polymer/Me-β-CD complex **2a** and the precipitation of the uncomplexed, more hydrophobic polymer; the Me-β-CD molecules remain in the aqueous solution. During the cooling run the transmittance did not return back to the starting level. However, after the solution had been stirred for several days at 5 °C, it became transparent again, indicating the reformation of the polymer/Me-β-CD complex. Apparently the complexation of polymer **2** by Me-β-CD is very slow. At higher concentrations the times for recomplexation are shorter (e.g. 24 h for 150 gL^{-1} **2a** in water).

The incorporation of a flexible spacer between the polymer backbone and the adamantyl groups strongly affects the thermosensitive properties of the supramolecular complex. In Figure 3, the turbidity measurement of a 100 gL^{-1} aqueous solution of polymer/Me-β-CD-complex **4a** is presented. The heating run indicates the cloud point of **4a** at 38.6 °C, which is 6 °C lower than that of **2a** (Figure 2). In the

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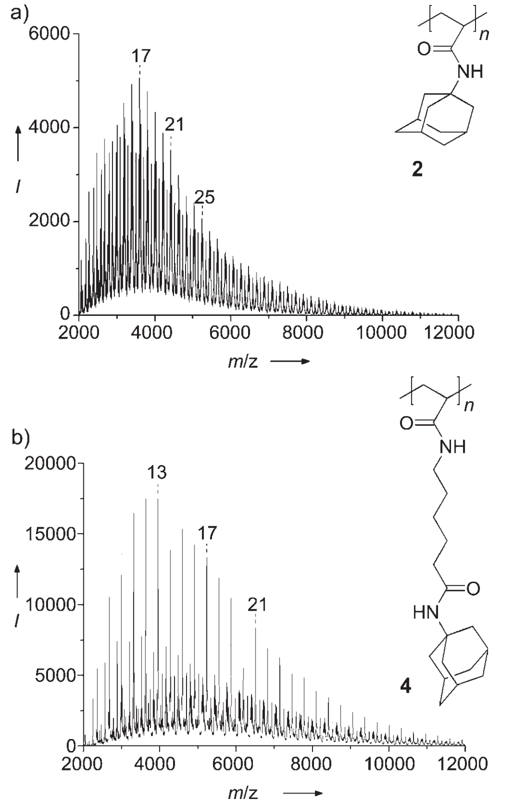

Figure 1. MALDI-TOF mass spectra of Me-β-CD free polymers **2** (a) and **4** (b).

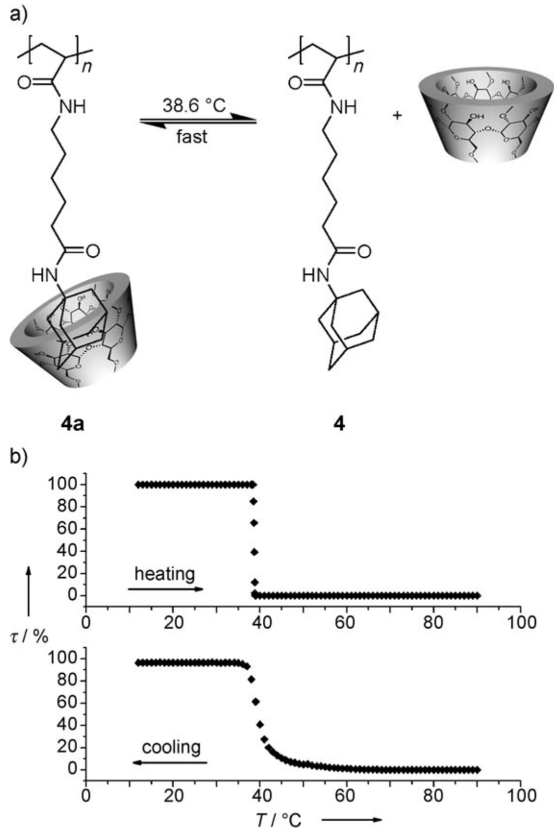

Figure 3. Rapid complexation of **4** by Me-β-CD. Transmittance as a function of temperature for an aqueous solution of polymer/Me-β-CD complex **4a** at a heating/cooling rate of 1 K$\,$min^{-1}. [**4a**] = 100 g$\,$L^{-1} (13.75 g$\,$L^{-1} polymer, 86.25 g$\,$L^{-1} Me-β-CD).

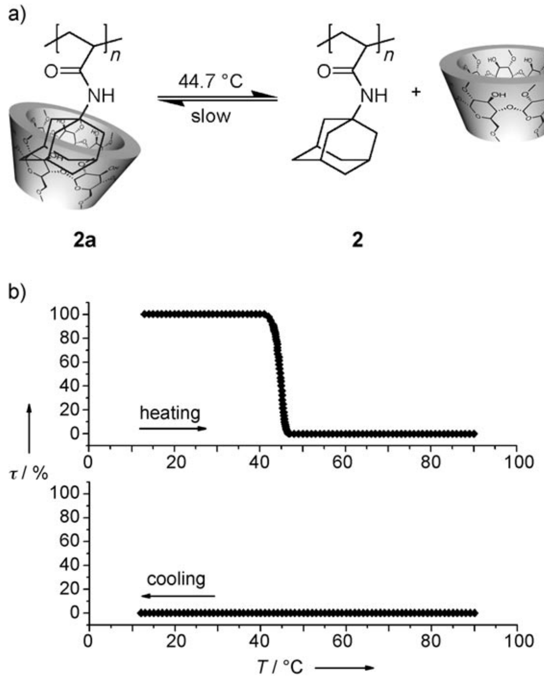

Figure 2. Slow complexation of **2** by Me-β-CD. Transmittance as a function of temperature for an aqueous solution of polymer/Me-β-CD complex **2a** at a heating/cooling rate of 1 K$\,$min^{-1}. [**2a**] = 100 g$\,$L^{-1} (13.35 g$\,$L^{-1} polymer, 86.65 g$\,$L^{-1} Me-β-CD).

cooling run the transparency recovers from 0 to almost 100% at about the same temperature as in the heating run. Apparently recomplexation of the spacer-containing polymer **4** is significantly faster than that of polymer **2**,which contains directly attached adamantyl groups. These results correlate with the degree of mobility of the adamantyl groups attached to the polymer.

It is interesting to note that, in contrast to the polymer/Me-β-CD complexes **2a** and **4a**, the monomer/Me-β-CD complexes **1a** and **3a** are completely stable in the temperature range of 10–90°C. The driving force for the decomplexation of the polymer/Me-β-CD complexes is the entropy gain upon dissociation of the highly mobile Me-β-CD molecules. Owing to the relatively high mobility of the monomer/Me-β-CD complexes, dissociation does not affect the degrees of freedom significantly. Adding potassium adamantane carboxylate to aqueous solutions of **2a** and **4a** leads to irreversible precipitation of the polymeric material as a result of the thermodynamically favored complexation of the monomeric guest within the investigated temperature range.

In Figures 4 and 5 the influence of the complex concentration on the turbidity temperature is demonstrated for polymer/Me-β-CD complexes **2a** and **4a**, respectively. In both cases a stepwise increase of the concentration of the polymer/Me-β-CD complex from 50 to 250 g$\,$L^{-1} leads to a linear

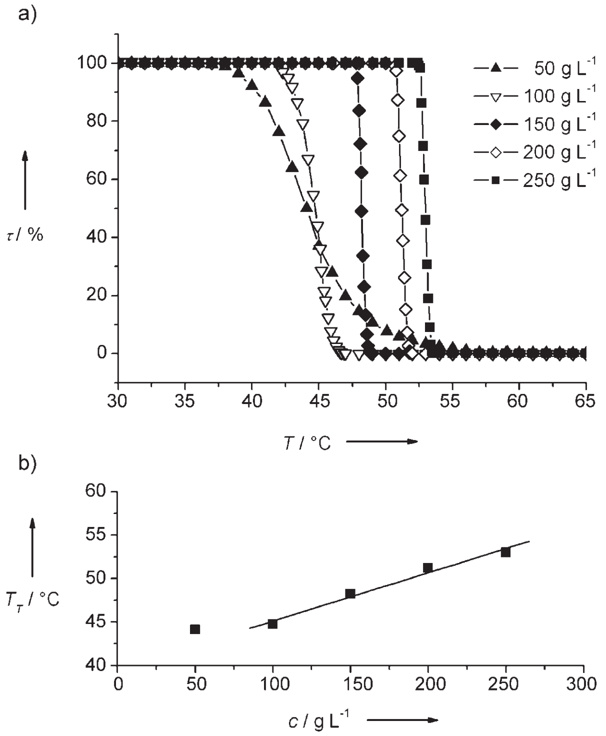

Figure 4. a) Transmittance τ as a function of temperature for a series aqueous solutions of **2a** at a heating/cooling rate of 1 $\text{K}\,\text{min}^{-1}$.
b) Turbidity temperatures plotted against the concentration of **2a** in water.

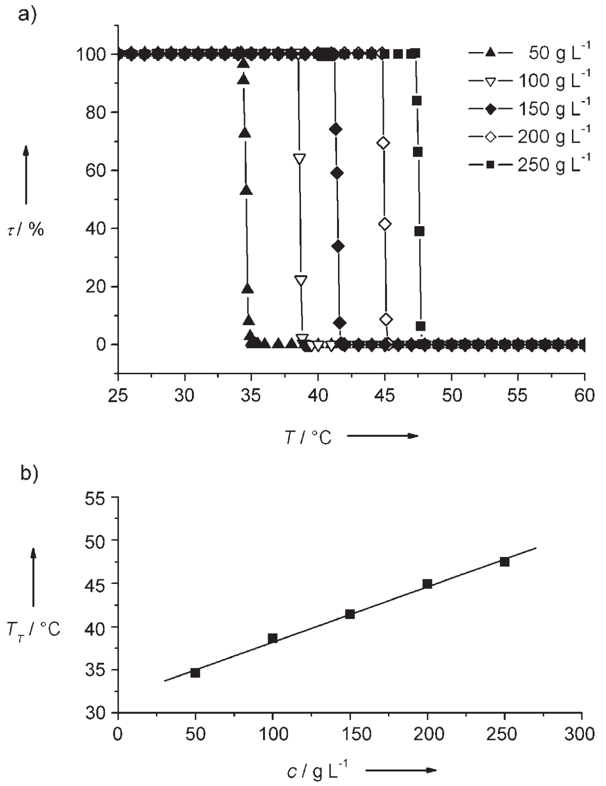

Figure 5. a) Transmittance τ as a function of temperature for a series of aqueous solutions of **4a** at a heating/cooling rate of 1 $\text{K}\,\text{min}^{-1}$.
b) Turbidity temperatures (T_T) plotted against the concentration of **4a** in water.

increase of the turbidity temperatures (Figure 4b and 5b). This result was expected since dissociation processes in highly concentrated solutions are higher in energy, which in case of the polymer/Me-β-CD complexes is directly related to the corresponding turbidity temperatures.

Differences in the phase-transition behavior of **2a** and **4a** become obvious when the heating runs of aqueous solutions of the polymer/Me-β-CD complexes at low concentrations are analyzed. The phase transition of an aqueous solution of **2a** at 50 $\text{g}\,\text{L}^{-1}$ occurs within 15 min in a temperature range of 40–55 °C (Figure 4a), whereas the transparency of an aqueous solution of **4a** at the same concentration decreases from 100–0% within 1 min at about 35 °C (Figure 5a). Similar phase-transition intervals were observed for solutions with concentrations above 100 $\text{g}\,\text{L}^{-1}$.

The polymer/Me-β-CD complex **4a** is more hydrophobic than **2a** because of the incorporated alkyl spacers. Additionally, intermolecular interactions of the hydrophobic side groups of **4a** can easily lead to the formation of aggregates during the decomplexation process. These aggregates have limited solubility which might lead to a fast precipitation of the whole polymeric material, including the shorter polymer chains.

In case of **2a**, aggregate formation is more difficult owing to the direct linkage of the complexed adamantyl units to the polymer backbone. Since **2a** is less hydrophobic than **4a**, precipitation, especially in the case of shorter polymer chains, is retarded and therefore the decrease of the transparency in more dilute aqueous solutions of **2a** observed is slower.

The obtained results clearly show that the thermosensitive properties of the investigated polymer/Me-β-CD complexes **2a** and **4a** are strongly affected by the length of the adamantly-group-bearing side chains and the complex concentration in aqueous solution. Variation of these parameters allows the synthesis of tailormade systems such that the dissociation/complexation process can be controlled within a desired temperature range. Currently, we are studying the suitability of such systems as supramolecular building blocks in, for example, temperature-sensitive hydrogels and optical temperature sensors.

Experimental Section

Materials: 1-Adamantylamine, 6-aminohexanoic acid, acryloyl chloride, triethylamine, ethyl chloroformate (monomer synthesis, Aldrich), randomly methylated β-cyclodextrin (Me-β-CD) (pharmaceutical grade, Wacker), sodium disulfite (J. T. Baker), and potassium peroxodisulfate (Acros) were used as received. THF was dried and distilled before use. Water was distilled before use.

Measurements: MALDI-TOF-MS was performed on a Bruker Ultraflex time-of-flight mass spectrometer equipped with a 337-nm nitrogen laser. Turbidity measurements were carried out using a TP1 turbidity photometer from TEPPER-Analytik. The turbity measurements were recorded in the temperature range from 10 to 90 °C and at a heating/cooling rate of 1 K min^{-1}. The relative transmittance of the samples was determined by use of a power-regulated semiconductor laser ($\lambda = 670$ nm) and a silicon photodiode. Cloud points were determined by transmission changes (at 500 nm) of the solutions heated 1 $°\text{C}\,\text{min}^{-1}$ in a magnetically stirred cell; values of the cloud points were taken as the temperature at which the transmission decreases by 50%.

The synthesis of monomers **1** and **3** were reported previously.[9]

Synthesis of polymer/Me-β-CD complexes **2a** and **4a**: To a solution of Me-β-CD (40 wt %) in distilled water was added the adamantyl-containing monomers **1** and **3**, respectively. In the case of monomer **1**, the molar ratio Me-β-CD/monomer was 1:1. For monomer **3**, 1.5 equiv Me-β-CD was required for quantitative encapsulation of the monomer. After the solutions became completely transparent indicating a successful complex formation, they were degassed by three freeze–pump–thaw cycles. The reaction mixtures were allowed to warm up to 25 °C before the redox initiator system $K_2S_2O_8/Na_2S_2O_5$ (1 mol %) was added under argon atmosphere. The mixturea were stirred for 24 h which resulted in almost quantitative conversion of the monomers (monitored by HPLC).

For MALDI-TOF analyses the solutions were treated with a small amount of trifluoroacetic acid which led to instant precipitation of the polymeric material. The precipitate was filtered off and washed several times with hot water.

For turbidity measurements the aqueous polymer/Me-β-CD solution was freeze-dried without further purification and redissolved in water.

Received: September 13, 2006

Keywords: cyclodextrins · host–guest systems · LCST · supramolecular chemistry

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