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Cyclodextrins in Polymer Synthesis: Free-Radical Polymerization of Methylated β-Cyclodextrin Complexes of Methyl Methacrylate and Styrene Controlled by *N*-Acetyl-L-cysteine as a Chain-Transfer Agent in Aqueous Medium

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Introduction

The use of equimolar amounts of cyclodextrins (CDs) to dissolve suitable hydrophobic monomers in water and the free-radical polymerization of such host/guest complexes has been investigated in our group recently.[1−5] Also, some patents describe the use of CDs preferably in catalytic amounts in order to improve, e.g., emulsion polymerizations.[6−8] Generally, the hydrophobic monomers become completely soluble in water due to the formation of host/guest complexes with CD. We found that, during the free-radical homopolymerization of the complexed monomers, the CD slips off from the monomer during chain propagation, and the polymer precipitates while the CD remains in the aqueous phase due to its high water solubility.[1−4] We also described recently that the reactivity ratios of the copolymerization of isobornyl acrylate/CD and butyl acrylate/CD complexes differ significantly from the *r* values of the uncomplexed monomers in organic medium.[4] Additionally, we found that the mean molecular weight is nearly reciprocal proportional to the square root of the water-soluble initiator.[9] To get more information about the polymerization mechanism of CD-complexed monomers, we were encouraged to investigate the influence of chain-transfer agents on the molecular weights of the resulting polymers.

Radical chain-transfer agents, e.g., mercaptans, have been applied over several decades to control the degree of polymerization or to terminate the growing polymer chains, e.g., in the case of telomerizations.[10,11]

Up to now, the chain-transfer activity of mercaptans on the degree of polymerization of CD-complexed monomers has not been evaluated. In this paper we wish to report our investigation on free-radical polymerization of CD-complexed monomers in the presence of *N*-acetyl-L-cysteine as hydrophilic chain-transfer agent in aqueous medium.

Results and Discussion

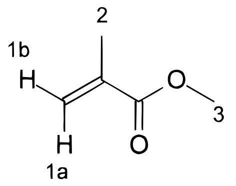
Methylated β-cyclodextrin (me-β-CD) and the hydrophobic monomers methyl methacrylate (**1**) or styrene (**2**) were dispersed in water, yielding the water-soluble host/guest complexes methyl methacrylate/me-β-CD (**1a**) and styrene /me-β-CD (**2a**), respectively, after sonication for several minutes (see Scheme 1).

The complexes were simply identified by thin-layer chromatography. The R_f values of the complexes **1a** and **2a** and the free monomers **1** and **2** differ significantly from each other (Table 1). The spots of the complexes show the same UV activity as the pure monomers, and in addition they react with iodine like me-β-CD. This strongly indicates the existence of stable inclusion complexes even under the conditions of chromatographic flow.

Table 1. R_f Values of me-β-CD, Uncomplexed Monomers 1, 2, and Complexed Monomers 1a, 2a Measured in Methanol

	me-β-CD	**1**	**1a**	**2**	**2a**
$R_{f,\ \mathrm{methanol}}$	0.66	0.85	0.57	0.77	0.61

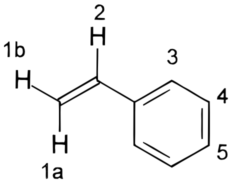
Table 2. Typical ^{1}H NMR Shifts [ppm] of me-β-CD, Uncomplexed Monomer 1, and Complexed Monomer 1a (200 MHz, D_2O)



1, 1a

	C1-*H* of	protons from **1**, **1a**			
monomer	2,6-methylated CD	1a	1b	2	3
1		6.10	5.69	1.91	3.76
1a	5.14	6.05	5.70	1.90	3.69
me-β-CD	5.18				

Table 3. Typical ^{1}H NMR Shifts [ppm] of me-β-CD, Uncomplexed Monomer 2, and Complexed Monomer 2a (200 MHz, D_2O)



2, 2a

	C1-*H* of	protons from **2**, **2a**			
monomer	2,6-methylated CD	1a	1b	2	3−5
2		5.81	5.32	6.16	6.67−6.81
2a	5.13	5.68	5.26	6.65	7.26−7.30
me-β-CD	5.18				

^{1}H NMR spectroscopy was used in order to characterize the complexed monomers. Because of the influence of the CD host on the guest monomers, there are strong differences in chemical shifts up to $\delta = 0.5$ ppm of the host/guest complexes compared to the values of the uncomplexed monomers. Both spectra of unmodified and complexed monomers were measured using D_2O as solvent. Table 2 and Table 3 show that the influence of CD on the styrene guest in **2a** is more significant than on the included methyl methacrylate in **1a**, respectively.

For determination of the chain-transfer constants the complexed monomers **1a** and **2a** were polymerized for 4 h at 80 °C using 0.3% (w/w) of the water-soluble free-radical initiator 2,2′-azobis(2-amidinopropane) dihydrochloride (AAP) (see Scheme 2). The polymerizations were carried out in the presence of different amounts of the highly water-soluble chain-transfer agent *N*-acetyl-L-cysteine from 0 to 3.0 mol %. The degree of

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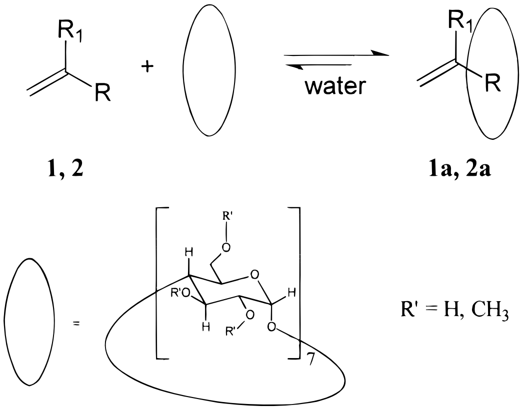
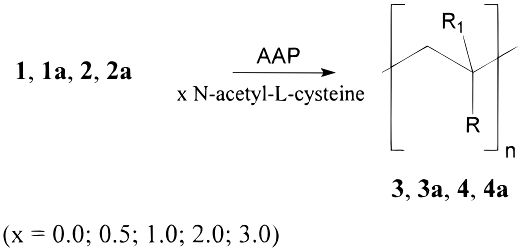
Scheme 1



monomer	R	R1
1, **1a**	-COOCH$_3$	-CH$_3$
2, **2a**	-Ph	-H

Scheme 2



polymer	R	R1
3, **3a**	-COOCH$_3$	-CH$_3$
4, **4a**	-Ph	-H

polymerization $\bar{P}_n$ was determined by size exclusion chromatography (SEC).

To evaluate these results, the polymerizations of both uncomplexed monomers **1** and **2** were also carried out under similar conditions in a solvent mixture of *N,N′*-dimethylformamide (DMF) and water (9:1 vol). The chain-transfer constants $Cs_{\mathbf{1}}$, $Cs_{\mathbf{1a}}$ and $Cs_{\mathbf{2}}$, $Cs_{\mathbf{2a}}$ for the radically initiated polymerization were calculated from experimental results using the method of Gregg and Mayo.[10,11]

Surprisingly, relatively high chain-transfer constants of *N*-acetyl-L-cysteine were found in the case of the complexed monomers **1a** and **2a** in water ($Cs_{\mathbf{1a}} = 1.7 \pm 0.3$ and $Cs_{\mathbf{2a}} = 2.6 \pm 0.3$). In contrast, the chain-transfer constants in DMF/water mixture are significantly lower for **1** and **2**, respectively ($Cs_{\mathbf{1}} = 0.7 \pm 0.1$ and $Cs_{\mathbf{2}} = 0.7 \pm 0.1$).

This means that the molecular weight of polymers obtained from complexed monomers can be controlled more effectively by hydrophilic thiol containing chain-transfer agents than in the case of polymerizations of the corresponding uncomplexed monomers in organic medium.

It is well-known from literature data that the chain-transfer constants depend on different parameters such as temperature, solvent, or type of monomer. According to the literature, the chain-transfer constants of DMF and water may be neglected ($Cs \sim 0$).[12] To evaluate the magnitude of chain-transfer activity of CD, we also investigated the influence of excess of methylated β-CD on the molecular weight of resulting polymer. However, only a very low chain transfer constant was found in this case ($Cs_{\text{me}-\beta-\text{CD}} = 0.004 \pm 0.001$). Thus, the relatively high chain-transfer constants of *N*-acetyl-L-cysteine affecting complexed monomers in water can only be explained by the fact that the kinetic ratio between chain growth and chain transfer is lowered by sterical influences of the CD torus affecting preferably the reactivity of the monomer. In contrast, both monomers in the DMF/water mixture and the mercaptan are not sterically hindered by the CD torus.

Regarding the ^{1}H NMR spectra, there are stronger magnetic interactions between the styrene guest and the me-β-CD-host than in the case of methyl methacrylate (Tables 2 and 3). This indicates that the complexed styrene (**2a**) is sterically hindered more effectively by the CD torus than methyl methacrylate. It seems likely that this is the main reason for the significant higher chain-transfer constant of *N*-acetyl-L-cysteine in the case of complexed styrene monomer compared to the experiment with complexed methyl methacrylate. In contrast, in the case of the uncomplexed monomers (**1**, **2**) both determined chain-transfer constants of *N*-acetyl-L-cysteine are very similar.

From the results described above it can be concluded that polymerization of hydrophobic monomers can be carried out successfully in aqueous medium by using CD as the hydrophilic host component. The degree of polymerization can be controlled effectively by the use of chain-transfer agents such as *N*-acetyl-L-cysteine.

Experimental Part

Materials and Methods. Methyl methacrylate and styrene (Fluka Chemie AG, Buchs, Switzerland, purity ≥99%) were distilled under reduced pressure. *N*-Acetyl-L-cysteine was purchased from Fluka Chemie AG, Buchs, Switzerland, purity ≥99.0%. The β-cyclodextrin (me-β-CD) was obtained from Wacker-Chemie GmbH, Burghausen, FRG, with an average degree of methylation of about 1.8 per glucose unit. 2,2′-Azobis-(2-amidinopropane) dihydrochloride was obtained from Wako Chemicals GmbH, Neuss, FRG. Deuterium oxide (99.9 atom % deuterium) was purchased from Deutero GmbH, Kastellaun, FRG. Water was demineralized before use. If not mentioned otherwise, all materials were used as received. The supersonic treatment was carried out by use of a Bandelin Sonorex RK 1028 transistor. The ^{1}H NMR spectra of all monomers were recorded on a Bruker AC 200 (room temperature) in D_2O. The δ-scale relative to TMS was calibrated by the deuterium signal of the solvent as internal standard. The TLC analysis was carried out with Merck silica gel plates 60 F_{254} with methanol as eluent; the spots were visualized by UV fluorescence and by developing with I_2.

SEC measurements were performed with a setup of the company PSS with chloroform as eluent at 25 °C. Calibration was done with polystyrene standards (PSS) with a range of molecular weight between 374 and 1 000 000 Da. Applying a flow rate of 1 mL/min, 150 μL of a 0.125 wt % polymer solution in chloroform was given onto a column combination consisting of a PSS-SDV 5 μm, 10^3 Å, 8 × 50 mm as precolumn and a set of PSS-SDV 5 μm, 8 × 300 mm with 100, 10^3, and 10^4 Å porosity as analytical columns. Detection of the signals was performed with a TSP UV2000 UV−vis detector (254 nm) and a modified Knauer RI detector. The evaluation was performed using PSS-WinGPC 4.01 software.

Complexation of Monomers. A 38.4 g (29.0 mmol) sample of me-β-CD was dissolved in 70 mL of water, and 2.9 g (29.0 mmol) of **1** was added. The colorless dispersion was sonificated for 10 min, yielding a clear colorless solution of the complexed monomer **1a**. The complexation of **2** was carried out analogously to **1** using 3.0 g (29.0 mmol) of **2**. Tables 1, 2, and 3 show the characterization of the uncomplexed (**1**, **2**) and complexed monomers (**1a**, **2a**), respectively.

Polymerization of Complexes 1a and 2a in Water. A 0.10 g (0.37 mmol) sample of AAP was added to each of the solutions described above. The solutions of the complexes **1a** or **2a** were devided into six parts, and 0, 3.9×10^{-3}, 7.8×10^{-3}, 15.6×10^{-3}, and 23.7×10^{-3} g of *N*-acetyl-L-cysteine were added. The solutions were heated to 80 °C while being stirred under a nitrogen atmosphere. The polymerizations were terminated after 4 h by cooling the reaction mixtures in an ice bath and adding 15 mL of water. The solid precipitates were filtered off. After dissolving the crude polymers in 2 mL of THF, the solutions were poured into 50 mL of water. The obtained colorless polymeric products were free of monomers and me-β-CD according to NMR spectroscopy.

Polymerization of the Uncomplexed Monomers 1 and 2 in DMF/Water Solution. A 2.9 g (29.0 mmol) sample of **1** and 3.0 g (29.0 mmol) of **2** were dissolved in 63 mL of DMF, and 0.1 g (0.37 mmol) of AAP, dissolved in 7 mL of water, was added to the DMF solution. The solutions of **1** and **2** were devided into six parts and 0, 3.9×10^{-3}, 7.8×10^{-3}, 15.6×10^{-3}, and 23.7×10^{-3} g of *N*-acetyl-L-cysteine were added. The solutions were heated to 80 °C while being stirred under a nitrogen atmosphere. The polymerizations were terminated after 4 h by cooling the reaction mixtures in an ice bath and adding 15 mL of water. The remaining colloidal dispersed components were extracted with 3 × 25 mL of chloroform. The combined organic layers were dried over $MgSO_4$, and the solvent was removed by evaporation. The resulting crude polymers were dissolved in 2 mL of THF and poured into 50 mL of water, yielding colorless polymeric products.

Table 4. $\bar{M}_n$ Data [g mol^{-1}] Determined by SEC (Polystyrene Standard, $CHCl_3$) of Polymers Depending on the Concentration of *N*-Acetyl-L-cysteine [mol %]

	$\bar{M}_n$ [g mol^{-1}] [concn of *N*-acetyl-L-cystein]				
polymer	[0.0]	[0.5]	[1.0]	[2.0]	[3.0]
3	5800	5300	3900	3100	2800
3a	49700	31000	13900	4800	1800
4	6400	5200	4000	3200	2800
4a	52000	24700	3300	1800	1400

The $\bar{M}_n$ data determined by SEC of all polymers depending on the concentration of *N*-acetyl-L-cysteine [mol %] are shown in Table 4.

Determination of the Chain-Transfer Constant of Methylated *β*-CD. In 30 mL of water were dissolved 6.7 g (5.0 mmol), 13.3 g (10.0 mmol), and 20.0 g (15.0 mmol) of me-β-CD, and 0.5 g (5.0 mmol) of **1** was added in each case. The colorless dispersion was sonificated for 10 min, yielding a clear colorless solution of the complexed monomer **1a**. To each of the solutions 0.04 g (0.15 mmol) of AAP were added and heated to 80 °C while being stirred under a nitrogen atmosphere. The polymerizations were carried out analogously to the polymerizations of **1a** and **2a**.

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