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Cyclodextrins in Polymer Synthesis: Free Radical Copolymerization of Methylated β-Cyclodextrin Complexes of Hydrophobic Monomers with *N*-Isopropylacrylamide in Aqueous Medium†

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ABSTRACT: Methylated β-cyclodextrin (me-β-CD) was used to form water-soluble host/guest complexes with the hydrophobic monomers *n*-butyl methacrylate (**1**), cyclohexyl methacrylate (**2**), isobornyl acrylate (**3**), isobornyl methacrylate (**4**), and styrene (**5**), respectively. The free-radical copolymerizations of the water-soluble *N*-isopropylacrylamide (NIPAAm) with these complexed monomers were carried out in water at different molar ratios.

Introduction

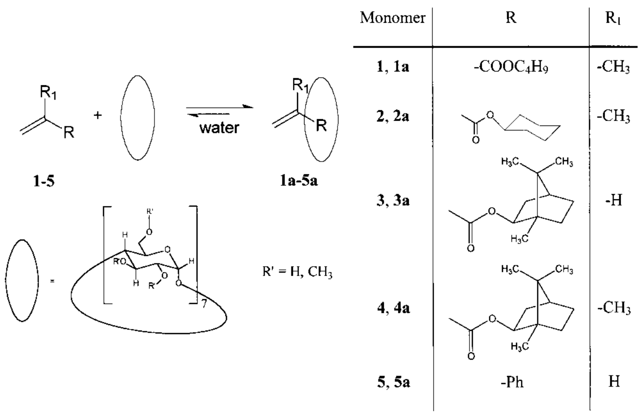
We have shown recently that the free radical polymerization in aqueous phase of cyclodextrin complexed, hydrophobic monomers, e.g., methylated β-cyclodextrin (me-β-CD) complexes of styrene or (meth)acrylates which are soluble in water, leads to insoluble polymers in high yields.[1−6] This means that, during the free-radical polymerization of the complexed, hydrophobic monomers, the CD slips off from the monomer during chain propagation and remains in the aqueous phase due to its high water solubility and the polymer precipitates.[1−6] We also described recently that the reactivity ratios of the copolymerization of isobornyl acrylate/CD and *n*-butyl acrylate/CD complexes differ significantly from the *r* values of the uncomplexed monomers in organic medium.[4] Additionally, we could show that the molecular weight of the polymers obtained from complexed monomers is approximately reciprocal proportional to the square root of the initiator concentration.[7] Also some patents describe the use of CDs preferably in catalytic amounts in order to improve, e.g., emulsion polymerizations.[8−10]

Polymers from *N*-isopropylacrylamide (NIPAAm) are well-known and have been of great interest because of their LCST-behavior. They are used for pharmaceutical and medical applications.[11−14] During the last year some papers described the polymerizations and characterizations of homo-PNIPAAm and copolymers with water-soluble comonomers such as 2-hydroxyethyl methacrylate and its monolactate, respectively, or itaconic acid.[15−19] In the case of hydrophobic comonomers it is necessary to copolymerize in organic solvents or to use the emulsion polymerization. However, the different solubilities of the monomers in water make the copolymerization of water-soluble and water-insoluble monomers by emulsion polymerization often difficult. Rimmer et al. polymerized butyl methacrylate in the presence of β-cyclodextrin in place of surfactant in a kind of emulsion polymerization.[20]

Up to now, the knowledge about the copolymerization of complexed, hydrophobic monomers and the water-soluble NIPAAm has not been described yet. This has been object of our present investigations.

Results and Discussion

Methylated β-cyclodextrin (me-β-CD) and the hydrophobic monomers *n*-butyl methacrylate (**1**), cyclohexyl methacrylate (**2**), isobornyl acrylate (**3**), isobornyl methacrylate (**4**) and styrene (**5**), respectively were mixed in water yielding the water-soluble host/guest complexes *n*-butyl methacrylate/me-β-CD (**1a**), cyclohexyl methacrylate/me-β-CD (**2a**), isobornyl acrylate/me-β-CD (**3a**), isobornyl methacrylate/me-β-CD (**4a**), and styrene/me-β-CD (**5a**), respectively after sonification for several minutes.



We described some typical characteristics of the complexes **3a** and **5a** elsewhere.[4,6] The other complexes were simply identified by thin-layer chromatography. The R_f values of the complexes **1a, 2a**, and **4a** and of the free monomers **1, 2**, and **4** differ significantly from each other (Table 1). The spots of the complexes have got lower R_f values but show the same UV activity as the pure monomers and in addition they interfere with iodine like me-β-CD. This strongly indicates the existence of stable inclusion complexes even under the conditions of chromatographic flow. ^{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 the

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† Dedicated to R. C. Schulz on the occasion of his 80th birthday.

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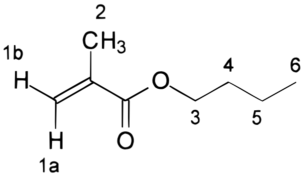
Table 1. R_f Values of Me-β-CD, Uncomplexed Monomers 1, 2, and 4, and Complexed Monomers 1a, 2a, and 4a Measured in Methanol

	me-β-CD	**1**	**1a**	**2**	**2a**	**4**	**4a**
$R_{f,\text{methanol}}$	0.66	0.94	0.50	0.80	0.54	0.82	0.53

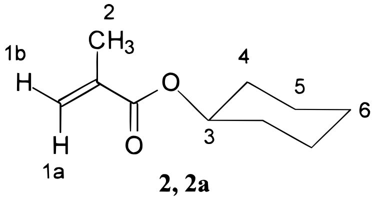
Table 2. Typical ^{1}H NMR Shifts (ppm) of Uncomplexed Monomer 1 and Complexed Monomer 1a (200 MHz, D_2O)



1, 1a

	proton signals from **1**, **1a**						
monomer	**1a**	**1b**	**2**	**3**	**4**	**5**	**6**
1	5.84	5.30	1.72	3.90	1.43	1.24	0.72
1a	5.99	5.68	1.88	4.15	1.64	1.37	0.94

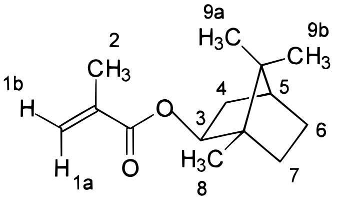
Table 3. Typical ^{1}H NMR Shifts (ppm) of Uncomplexed Monomer 2 and Complexed Monomer 2a (200 MHz, D_2O)



2, 2a

	proton signals from **2**, **2a**				
monomer	**1a**	**1b**	**2**	**3**	**4−6**
2	5.99	5.41	1.82	4.71	1.79−1.07
2a	5.94	5.69	1.85	4.85	1.80−1.40

Table 4. Typical ^{1}H NMR shifts (ppm) of Uncomplexed Monomer 4 and Complexed Monomer 4a (200 MHz, D_2O)



4, 4a

	proton signals from **4**, **4a**										
monomer	**1a**	**1b**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9a**	**9b**
4	5.86	5.77	1.71	4.56	1.64	1.56	0.78	1.02	0.86	0.69	0.69
4a	5.86	5.62	1.81	4.50	2.14	1.68	1.18	*a*	0.92	1.10	1.02

[a] Overlayed by H-2.

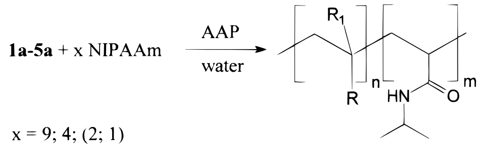
chemical shifts up to $\delta = 0.4$ ppm of the host/guest complexes compared to the values of the uncomplexed monomers. Tables 2−4 show the magnetic influence of CD on the butyl methacrylate guest in **1a**, on the cyclohexyl methacrylate guest in **2a**, and on the included isobornyl methacrylate in **4a**, respectively.

The host/guest-complexes **1a**−**5a** were copolymerized with NIPAAm in water in molar ratios of 1:9 (90 mol % of NIPAAm) and 1:4 (80 mol % of NIPAAm), respectively for 12 h at 80 °C using 5,5 mol % of the water-soluble free-radical initiator 2,2′-azobis (2-amidinopropane) dihydrochloride (AAP). In addition, styrene was also copolymerized with NIPAAm at molar ratios of 1:2 (66.7 mol % of NIPAAm) and 1:1 (50 mol % of NIPAAm), respectively.

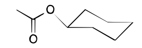
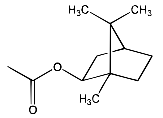
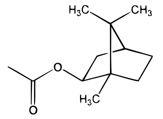
Table 5. Content of Incorporated NIPAAm Sequences in Copolymers Obtained from Complexed Monomers and NIPAAm (1b−5b) and Obtained from DMF/Water (5c) (90, 80, 66.7, and 50 mol % of NIPAAm)

	incorporated monomer content of NIPA for (initial concentration of NIPAAm in Am in copolymer (±3) [mol %])			
polymer	(90)	(80)	(66.7)	(50)
1b	91	86		
2b	95	90		
3b	92	83		
4b	94	83		
5b[a]	96	84	66	47
5c[a]	94	90	82	33

[a] Chemical shift of HN protons of PNIPAAm are in the same range as the phenyl protons.



1b-5b

Polymer	R	R1
1b	-$COOC_4H_9$	-CH_3
2b		-CH_3
3b		-H
4b		-CH_3
5b	-Ph	H

For characterization ^{1}H NMR spectroscopy and size exclusion chromatography (SEC) were used. The compositions of the copolymers were determined by ^{1}H NMR spectroscopy. The integrated characteristic peaks of the incorporated NIPAAm at $\delta = 3.9$ ppm were compared with the integrated signals of each comonomer ($\delta_{\mathbf{1a}} = 3.4$, $\delta_{\mathbf{2a}} = 4.6$, $\delta_{\mathbf{3a}} = 4.6$, $\delta_{\mathbf{4a}} = 4.5$, $\delta_{\mathbf{5a}} = 7.7{-}6.7$ ppm). The resulting ratios of incorporated monomer-sequences in copolymers are summarized in Table 5.

In all cases the content of hydrophilic comonomer-sequences (NIPAAm) in the copolymers (**1b**−**5b**) is slightly higher than the initial monomer concentration at ratios below 80 mol % of initial concentration of NIPAAm. For comparison the copolymerizations of uncomplexed styrene (**5**) with NIPAAm at the same initial concentrations of 90, 80, 66.7, and 50 mol % of NIPAAm, respectively were also carried out under similar conditions in a solvent mixture of *N*,*N*′-dimethylformamide (DMF) and water (9:1 v/v) without me-β-CD. The resulting ratios of incorporated NIPAAm in copolymer **5c** are shown in Table 5.

Surprisingly it was found by means of the SEC data that for all molar ratios of the incorporated monomer

Table 6. $\bar{M}_w$ Data of 5b and 5c Determined by SEC (Polystyrene Standard, THF) Depending on the Molar Ratios

polymer	$\bar{M}_w$ for (initial concentrations of NIPAAm in monomer mixture [mol %]) (90)	(80)	(66.7)	(50)
5b	107 600	126 900	134 100	207 100
5c	23 400	30 400	30 500	43 700

units the weight averages $\bar{M}_w$ of the copolymers **5b** obtained from complexed styrene (**5a**) and NIPAAm are about 3−7 times higher than in the case of the corresponding copolymers **5c** obtained from uncomplexed styrene and NIPAAm in DMF/water solution (Table 6). Similar phenomena were found and described with several other host/guest monomer systems elsewhere.[4,6] In addition the weight averages $\bar{M}_w$ increase with increasing content of styrene from 107 600 to 207 100 in the case of **5b** but only from 23 400 to 43 700 in the case of **5c**. In all cases UV-signal and RI-signal of SEC-elution curves deviate only slightly by about 10% of the maximum and monomodalic SEC curves were found. This strongly points out that the copolymerizations of NIPAAm with hydrophobic monomers can be carried out in aqueous medium.

It is well-known that the molecular weight of polymers obtained via precipitation polymerizations are in general much higher than those of the corresponding polymers prepared in solution.[2] From the SEC diagrams it is also obvious that the polymers do not contain free me-β-CD. In contrast to that the NMR spectra indicate that about 5% (w/w) of me-β-CD still remains in the polymers and cannot be removed by extraction.

From the results described above it can be concluded that free radical copolymerizations of me-β-CD complexed hydrophobic monomers and water-soluble monomers can be carried out successfully in aqueous medium yielding high molecular weight copolymers.

Experimental Part

Materials and Methods. Isobornyl acrylate (elf atochem ATO, Puteaux, France, purity ≥ 99%), isobornyl methacrylate (Merck KGaA, Darmstadt, Germany, purity > 95%), butyl methacrylate, cyclohexyl methacrylate, and styrene (Fluka Chemie AG, Buchs, Switzerland, purity ≥ 99%) were distilled under reduced pressure. *N*-Isopropylacrylamide was purchased from Acros Organics N.V./S.A., Geel, Belgium, 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), chloroform-d_1 (99.8 atom % deuterium) and dimethyl sulfoxide-d_6 (99.8 atom % deuterium) were 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 ^{1}H NMR spectra of the styrene-copolymers were recorded on a Bruker AC 200 (room-temperature) in DMSO-d_6 and the other copolymers in $CDCl_3$. 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 solvent, the spots were visualized by UV fluorescence and by developing with I_2. The FT-IR spectra were recorded on a Nicolet FTIR-5 SXB. SEC measurements were performed with an setup of the company PSS with tetrahydrofuran as eluent at 25 °C. Calibration was done with polystyrene-standards (PSS) with a range of molecular weight between 374 und 10^6. Applying a flow rate of 1 mL/min, 150 μl of a 0.125 wt % polymer solution in DMF were 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 were 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. In the case of copolymerization by molar ratio of 9:1 0.98 mmol of me-β-CD were dissolved in 30 mL of water and 0.98 mmol of each monomer **1**−**5** were added. The colorless dispersions were sonificated for 10 min, yielding clear colorless solutions of the complexed monomers **1a**−**5a**.

The complexation of the monomers for copolymerization with a molar ratio of 4:1, 2:1, and 1:1 were carried out analogously to the molar ratio 9:1 but 2.21 (4:1), 4.42 (2:1), and 8.84 mmol of me-β-CD (1:1), respectively were dissolved in 52, 92, and 172 mL of water and 2.21, 4.42, and 8.84 mmol of each of the monomers **1**−**5** were added.

Tables 1−4 show the characterization of the uncomplexed (**1**, **2**) and complexed monomers (**1a**, **2a**), respectively.

Copolymerization of the Complexes with NIPAAm (1a-5a) in Water. An 8.84 mmol sample of NIPAAm was added to each of the solutions described above, and 5.5 mol % of AAP was added in each case. The solutions were heated to 80 °C while being stirred under nitrogen atmosphere for 12 h. The solid precipitates were filtered off. The crude copolymers were washed with 2 × 50 mL of hot water. The obtained colorless polymeric products were free of monomers but small amounts of me-β-CD were found in all cases (<5%) according to NMR spectroscopy. In all cases the yields of copolymers were close to 80%. The copolymers were slightly soluble in water.

^{1}H NMR ($CDCl_3$, 200 MHz), δ/ppm. 1b: 7.0−5.8 (N*H*); 3.91 (NH−C*H*(CH_3)$_2$); 3.44 (O−CH_2); 2.4−0.8 (CH, CH_2, CH_3). **2b:** 7.1−5.7 (N*H*); 4.64 (O−C*H*); 3.94 (NH−C*H*(CH_3)$_2$); 2.4−0.7 (CH, CH_2, CH_3). **3b:** 7.0−5.0 (N*H*); 4.57 (O−C*H*); 3.95 (NH−C*H*(CH_3)$_2$); 2.5−0.6 (CH, CH_2, CH_3). **4b:** 6.9−5.6 (N*H*); 4.54 (O−C*H*); 3.95 (NH−C*H*(CH_3)$_2$); 2.4−0.6 (CH, CH_2, CH_3).

^{1}H NMR (DMSO-d_6, 200 MHz) δ/ppm. 5b: 7.7−6.7 (Ph and N*H*); 3.84 (NH−C*H*(CH_3)$_2$); 2.3−0.6 (CH, CH_2, CH_3).

FT-IR (KBr): $\tilde{\nu}$/cm^{-1}. 1b: 3440 (NH stretching); 2970, 2935, 2875 (CH stretching, aliphatic); 1730 (C═O stretching, ester); 1650 (C═O stretching, secondary amide); 1540 (NH bending). **2b:** 3435 (NH stretching); 2970, 2935, 2860 (CH stretching, aliphatic); 1725 (C═O stretching, ester); 1650 (C═O stretching, secondary amide); 1540 (NH bending). **3b:** 3440 (NH stretching); 2975, 2935, 2880 (CH stretching, aliphatic); 1720 (C═O stretching, ester); 1655 (C═O stretching, secondary amide); 1550 (NH bending). **4b:** 3430 (NH stretching); 2970, 2935, 2880 (CH stretching, aliphatic); 1720 (C═O stretching, ester); 1650 (C═O stretching, secondary amide); 1540 (NH bending). **5b:** 3430 (NH stretching); 3080, 3060, 3025 (CH stretching, aromatic); 2970, 2925, 2850 (CH stretching, aliphatic); 1650 (C═O stretching, secondary amide); 1540 (NH bending); 760, 700 (out-of-plane bending C−H aromatic, monosubstitution).

Copolymerization of Uncomplexed Styrene (5) with NIPAAm in DMF/Water Solution. Samples of 8.84 mmol of NIPAAm and 0.98 (9:1), 2.21 (4:1), 4.42 (2:1), and 8.84 mmol of styrene, respectively, were dissolved in 20, 34, 61, and 114 mL of DMF and 5.5 mol % samples of AAP dissolved in 10, 17, 31, and 57 mL of water, respectively, were added.

The solutions were heated to 80 °C while being stirred under nitrogen atmosphere for 12 h. The solvent was removed by evaporation. After addition of 50 mL of water and heating to 50 °C, the precipitated copolymers were filtered off and washed with 2 × 25 mL of hot water, yielding colorless polymeric products. In all cases the yields of copolymers were close to 80%.

^{1}H NMR (DMSO-d_6, 200 MHz) δ/ppm. 5c: 7.7−6.7 (Ph and N*H*); 3.84 (NH−C*H*(CH_3)$_2$); 2.3−0.6 (CH, CH_2, CH_3).

FT-IR (KBr): $\tilde{\nu}$/cm^{-1}. 5c: 3435 (NH stretching); 3080, 3065, 3025 (CH stretching, aromatic); 2970, 2925, 2850 (CH stretching, aliphatic); 1650 (C=O stretching, secondary amide); 1540 (NH bending); 760, 700 (out-of-plane bending C−H aromatic, monosubstitution).

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References and Notes

(1) Jeromin, J.; Noll, O.; Ritter, H. *Macromol. Chem. Phys.* **1998**, *199*, 2641.

(2) Jeromin, J.; Ritter, H. *Macromol. Rapid Commun.* **1998**, *19*, 377.

(3) Jeromin, J.; Ritter, H. *Macromolecules* **1999**, *32*, 5236.

(4) Glöckner, P.; Ritter, H. *Macromol. Rapid Commun.* **1999**, *20*, 602.

(5) Ritter, H.; Storsberg, J. *Adv. Mater.*, in press.

(6) Glöckner, P.; Metz, N.; Ritter, H. *Macromolecules*, in press.

(7) Ritter, H.; Storsberg, J. *Macromol. Rapid Commun.* **2000**, *21*, 236.

(8) Lau, W. Rohm and Haas Company. Eur. Pat. Appl.; *Chem. Abstr.* **1996**, *125*, 59402.

(9) Leyrer, R. J.; Wildburg, G.; Haunschild, A. BASF A.G. Ger. Offen.; *Chem. Abstr.* **1996**, *129*, 68159.

(10) Leyrer, R. J.; Mathauer, K.; Roser, J.; Wildburg, G. BASF A.G. Eur. Pat. Appl.; *Chem. Abstr.* **1997**, *127*, 109383.

(11) Heskins, M.; Guillet, J. E. *J. Macromol. Sci. Chem.* **1968**, *A2*, 1441.

(12) Cho, C. S.; Cheon, J. B.; Jeong, Y. I. *Macromol. Rapid Commun.* **1997**, *18*, 361.

(13) Spafford, M.; Polozova, A.; Winnik, F. M. *Macromolecules* **1998**, *31*, 7099.

(14) Chen, G.; Imanishi, Y.; Ito, Y. *Macromolecules* **1998**, *31*, 4379.

(15) Neradovic, D.; Hinrichs, W. L.; Kettenes-van den Bosch, J. J.; Hennink, W. E. *Macromol. Rapid Commun.* **1999**, *20*, 577.

(16) Erbil, C.; Akpinar, F. D.; Uyanik, N. *Macromol. Chem. Phys.* **1999**, *200*, 2448.

(17) Bergbreiter, D. E.; Koshti, N.; Frels, J. D. *Polym. Prepr.* **1999**, *2*, 246.

(18) Han, S. J.; Yoo, M. K.; Sung, Y. K.; Lee, Y. M.; Cho, C. S. *Macromol. Rapid Commun.* **1998**, *19*, 403.

(19) Zhang, X. Z.; Zhuo, R. X. *Macromol. Chem. Phys.* **1999**, *200*, 2602.

(20) Rimmer, S.; Tattersall, P. I. *Polymer* **1999**, *40*, 6673.

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