Tenside-free Preparation of Nanogels with High Functional β-Cyclodextrin Content

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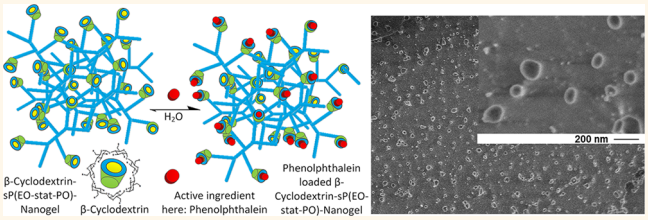
ABSTRACT



We present the preparation of ultrafine (R_h, 50 −150 nm) nanogels through tenside-free condensation of reactive prepolymers with β-cyclodextrin (β-CD) in water. These nanogels possess a maximum content of 60 wt % functional β-CD that can form inclusion complexes as demonstrated by dye sorption with phenolphthalein. Aside of this extremely high uptake capacity to hydrophobic molecules, the nanogels also show good adhesion to surfaces in homogeneous distribution with size of R_h of 25 nm under dry conditions.

KEYWORDS: nanogels · cyclodextrin · reactive prepolymers · host−guest-systems

Cross-linked polymeric hydrogel particles, called nano- or microgels, are functional materials that may be prepared in a wide range of chemical compositions.[1,2] These colloidal polymer networks exhibit pronounced swelling in water, which allows transport processes into the particles and makes them especially interesting for applications such as sequestration or release.[3,4] For that, specific binding activities have to be embedded into the nanogels. Cyclodextrins (CDs) are interesting and versatile binding motives and are well-known for the formation of supramolecular inclusion complexes with many organic molecules.[5] The complexation of sensitive or volatile ingredients, for example, drugs, pharmaceutical products, flavoring agents, perfumes, and insecticides are of particular interest.[6,7] Natural CDs consist of six, seven, or eight D-glucose units which are α-glycosidic linked to a cyclic oligomer and named α, β, or γ-CD, respectively. Since the interior hydrophilic part of the torus-shaped CD facilitates complexation with the guest molecules, the reactive hydroxy groups on the outer part of the molecules can be used for modification, functionalization, and copolymerization. This way, CDs have been used as cross-linker for the creation of three-dimensional bulk hydrogels.[8]

Nanogels offer an increased surface area in combination with shorter diffusion lengths which leads to a higher CD accessibility and faster complexation as compared to three-dimensional bulk gels.[9] Moreover, they can be applied from aqueous solution to form films and coatings. Radical polymerization techniques are usually applied for the preparation of nano- and microgels.[10−13] Accordingly, CDs containing polymeric particles and microgels have been prepared by radical copolymerization with methyl methacrylate (MMA) in organic solution, with *N*-isopropylacrylamide (NIPAm) by mini-emulsion *via* addition of surfactant, and by precipitation polymerization with *N*-vinylcaprolactam (VCL) in aqueous solution.[14−17]

Another method to prepare nanogels with γ-CD or hydroxypropyl-β-CD is by an emulsification/solvent evaporation process. Here, the aqueous phase consists of a fix CD concentration of 20% (w/w) with or without hydroxypropyl methylcellulose (HPMC) or agar at various concentrations. Ethyleneglycol diglycidyl ether (EGDE) acts as crosslinkng agent and is essential for the formation of nanogels.[18] Polydisperse CD-nanoparticles in water and ethanol have also been obtained by self-assembly of a water insoluble polymer, which was made by the reaction of CD and toluene-2,4-diisocanate (TDI) in organic solvent dimethyl sulfoxide (DMSO).[19,20]

The preparation of CD containing nanogels in water without direct polymerization

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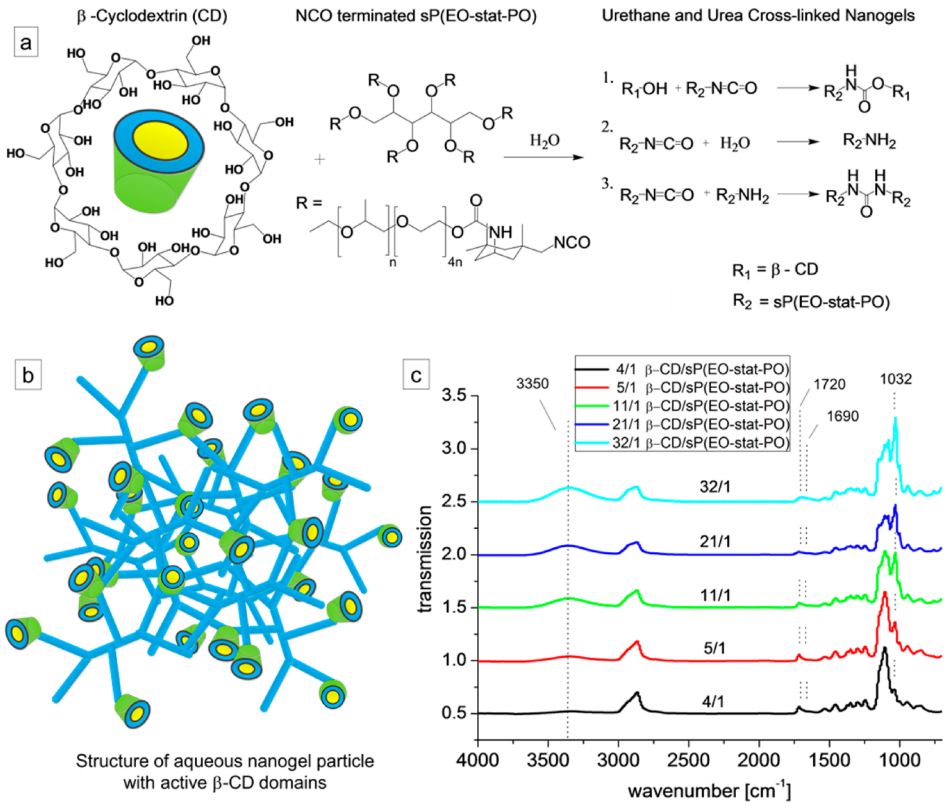

Figure 1. Reaction scheme of β-CD with NCO sP(EO-stat-PO) to urethane and urea cross-linked nanogels (a). Scheme of nanogel structure with active β-CD domains (b). IR-spectra of nanogels with increasing β-CD content (c).

from monomers is often performed by exploiting the complexation ability of CDs, so that the CD molecules act as cross-linkers themselves. This way, the majority of CD molecules is blocked for uptake of guest molecules into the nanogels, and the overall complexation capacity is moderate. We have recently demonstrated a preparation technique for nanogels based on the addition reaction among functional hydrophilic prepolymers.[21] Here we present a new method to design nanogels with high β-CD content *via* polyaddition directly in aqueous surfactant-free solution at room temperature (RT) without the use of organic solvents. The method was optimized to yield nanogels with a hydrodynamic radius between 50 and 150 nm. Owing to the choice of prepolymers and nanogel preparation technique, the nanogels contain up to 60 wt % β-CD that is functional and can take up guest molecules as demonstrated with the sorption of phenolphthalein. Finally, also film formation of these nanogels is demonstrated, enabling the preparation of ultrathin films with strong loading and release capacity for hydrophobic guest molecules.

RESULTS AND DISCUSSION

Amphiphilic 12 kDa six-arm isocyanate (NCO)-terminated star-shaped poly(ethylene oxide-stat-propylene oxide) with 80% EO content (NCO-sP(EO-*stat*-PO))[22] was used as reactive polymeric cross-linker for β-CD (Figure 1a). In water, isocyanates hydrolyze to amine groups that further react with other NCO groups to urea bridges between the prepolymers. This process leads to formation of a three-dimensional polymer network and may be used for the preparation of hydrogels,[23] in which also biopolymers that possess nucleophilic groups such as hyaluronic acid may be embedded resulting in biopolymer−polymer hybrid hydrogels.[24] Here, β-CD was added to aqueous solutions of NCO sP(EO-*stat*-PO). Hence, aside the hydrolysis-aminolysis cross-linking reaction described above, reaction between the NCO groups and the hydroxy groups of β-CD leads to cross-linked polyurethane networks. Since alcoholysis is kinetically favored compared to hydrolysis, the cross-linking *via* β-CD is the main network-forming mechanism. With this method, β-CD-nanogels may be prepared by a simple one-pot preparation method in water without the use of tensides (Figure.1b). This process strongly depends on reaction parameters. The influence of the stoichiometric ratio of the reactant and the concentration has been examined at a constant stirring rate of 300 rpm at room temperature (Table 1). After 24 h reaction and subsequent dialysis against water, between 40 and 70 wt % of educts remained as cross-linked nanogels in solution. Generally, the adoption of sP(EO-stat-PO) in a higher molar ratio to β-CD in the reaction mixture leads to a higher yield of nanogels after dialysis.

TABLE 1. Reaction Recipe and Conditions for the Preparation of Nanogels with β-CD by Constant Stirring Rate of 300 rpm and RT

β-CD 1135 g/mol	sP(EO-*stat*-PO) 12000 g/mol	wt ratio	mol ratio		educts/water
[g] (mmol)	[g] (mmol)	β-CD/sP(EO-*stat*-PO)	β-CD/sP(EO-*stat*-PO)	water [mL]	[wt %] (g/mL)
	0.600 (0.05)	0/1	0/1	20	3 (0.03)
0.375 (0.33)	1.125 (0.09)	1/3	4/1	50	3 (0.03)
0.500 (0.44)	1.000 (0.08)	1/2	5/1	50	3 (0.03
0.750 (0.66)	0.750 (0.06)	1/1	11/1	50	3 (0.03)
1.000 (0.88)	0.500 (0.04)	2/1	21/1	50	3 (0.03)
1.125 (0.99)	0.375 (0.03)	3/1	32/1	50	3 (0.03)
0.250 (0.22)	0.250 (0.02)	1/1	11/1	10	5 (0.05)
0.1125 (0.1)	0.375 (0.03)	1/3	4/1	5	10 (0.1)

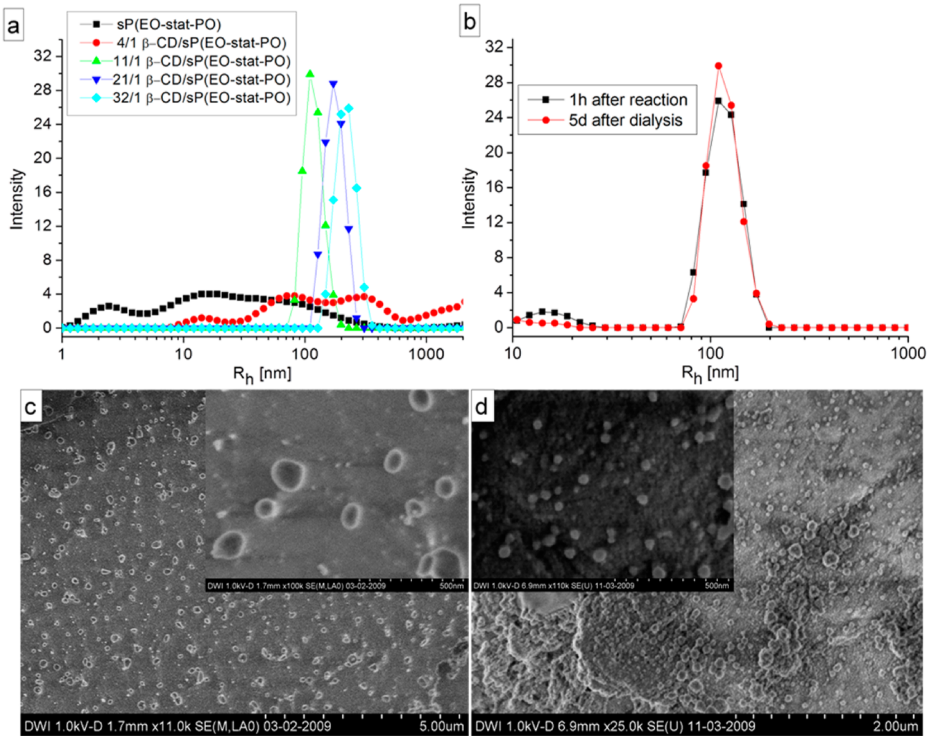

Figure 2. DLS-measurements of nanogels with β-CD units in aqueous dispersion at 25 °C; size distributions of nanogels with different β-CD content (a) and size distribution of nanogels (11 β-CD/1 sP(EO-stat-PO)) in aqueous dispersion 1 h after reaction and after 5 d dialysis (b). Cryo-FESEM images of swollen nanogels containing β-CD in ratio of (11 CD/1 sP(EO-stat-PO)) with a diameter of 100−300 nm (R_h = 50−150 nm) made in 3 wt % aqueous dispersion (c). FESEM images of the nanogels (11 β-CD/1 sP(EO-stat-PO)) made in 3 wt % aqueous dispersion with an average diameter of 50 nm (R_h = 25) in dry collapsed-state coated on aluminum (d).

TABLE 2. Determination of β-CD Content in Nanogel Dispersions after Dialysis by Titration of Phenolphthalein in Aqueous Solution at pH 10.5

mol-ratio β-CD/sP(EO-*stat*-PO)	nanogel concn [mg/mL]	phenolphthalein solution [mL/10 mL]	β-CD content [mg/mL]	β-CD content [μmol/mL]
4/1	8.18	0.45 ± 0.10	0.14 ± 0.05	0.13 ± 0.04
5/1	9.71	1.13 ± 0.15	0.72 ± 0.17	0.63 ± 0.15
11/1	8.37	1.53 ± 0.60	1.22 ± 0.08	1.07 ± 0.07
21/1	7.00	1.98 ± 0.10	1.90 ± 0.16	1.68 ± 0.14
32/1	5.40	2.70 ± 0.23	3.30 ± 0.25	2.91 ± 0.22

Infrared-spectroscopy of freeze-dried purified nanogels shows a higher β-CD content with an increase in the stoichiometric ratio of β-CD to sP(EO-*stat*-PO) in the reaction mixture. This is evidenced by increasing intensity of the typical β-CD hydroxy bands (3350 cm^{-1} and 1680 cm^{-1}) and the characteristic stretching vibration peak of C−O−C from β-CD (1032 cm^{-1}).[25] The absence of a NCO band at

2265 cm^{-1} and the presence of the typical band for urea (1690 cm^{-1}) and urethane (1720 cm^{-1}) confirm chemical cross-linking (Figure 1c).

The stability of the prepared nanogels was characterized at 3 wt % concentration in aqueous dispersion by dynamic light scattering (DLS; Figure 2a). Low β-CD content in the nanogels (β-CD/sP(EO-*stat*-PO) molar ratio of 4/1) leads to particle dispersions with a multimodal, large size distribution over length scales. This corresponds to the multimodal size distribution curve of nanogels prepared from pure sP(EO-*stat*-PO). By increasing the β-CD content to β-CD/sP(EO-*stat*-PO molar ratios of 11/1, 22/1, and 32/1, uniform nanogels with a narrow size distribution and an increasing hydrodynamic radius of R_h = 118.6 ± 12.8 nm (11/1) to R_h = 175.9 ± 5.3 nm (21/1) and further to R_h = 218.8 ± 12.5 nm (32/1) are obtained. Obviously, β-CD supports and stabilizes the formation of more uniform structures and subsequently chemically cross-links the nanogels.

Optical stability of nanogel dispersion with higher β-CD content is given over months in low concentrated aqueous solution. DLS of aqueous nanogels (11/1 molar ratio β-CD/sP(EO-*stat*-PO) in water at RT reflects a monomodal size distribution with R_h = 118.1 nm. After 5 d dialysis R_h remains constant at 118.6 nm, indicating stability of the nanogels (Figure 2b).

Cryo FESEM images of nanogels in swollen state prepared in 3 wt % aqueous dispersion (Figure 2c) reveal uniform particle morphology and confirm the nanogel size of R_h = 50−150 nm as determined by DLS (R_h = 118.6 (11/1)). For studies of collapsed particles, aluminum slides are dip-coated in nanogel dispersions for 15 min, dried, and investigated by FESEM (Figure 2d). In the dry state, the nanogels shrink to an average diameter of 50 nm (R_h = 25 nm). The calculated volumetric (de)-swelling ratio defined as $(R_h^D/R_h^S)^3$ (R_h^D = hydrodynamic radius under dry conditions; R_h^S = hydrodynamic radius for maximally swollen nanogels in water) averages 0.009.[26] Thus, the nanogels exhibit excellent swelling properties in water up to more than four times their own particle size from the collapsed state. Furthermore, they display a good adhesion to the surface and a homogeneous distribution. At higher concentrations (5 wt %), nanogels show an affinity for agglomeration (Supporting Information, Figure S1a). This may be explained by formation of inclusion complexes between β-CD and hydrophobic moieties of the prepolymer that are available at the nanogels surface, as multiple interactions between single nanogels are more probable at higher concentrations. Such β-CD-mediated interfacial phenomena between hydrogels have recently been demonstrated to physically "glue" macroscopic hydrogels.[27] At very high concentration (10 wt %) 3-dimensionally cross-linked bulk hydrogels are formed (Supporting Information, Figure S1b).

The number and availability of inclusion sites of β-CD in nanogels are crucial for their sorption properties

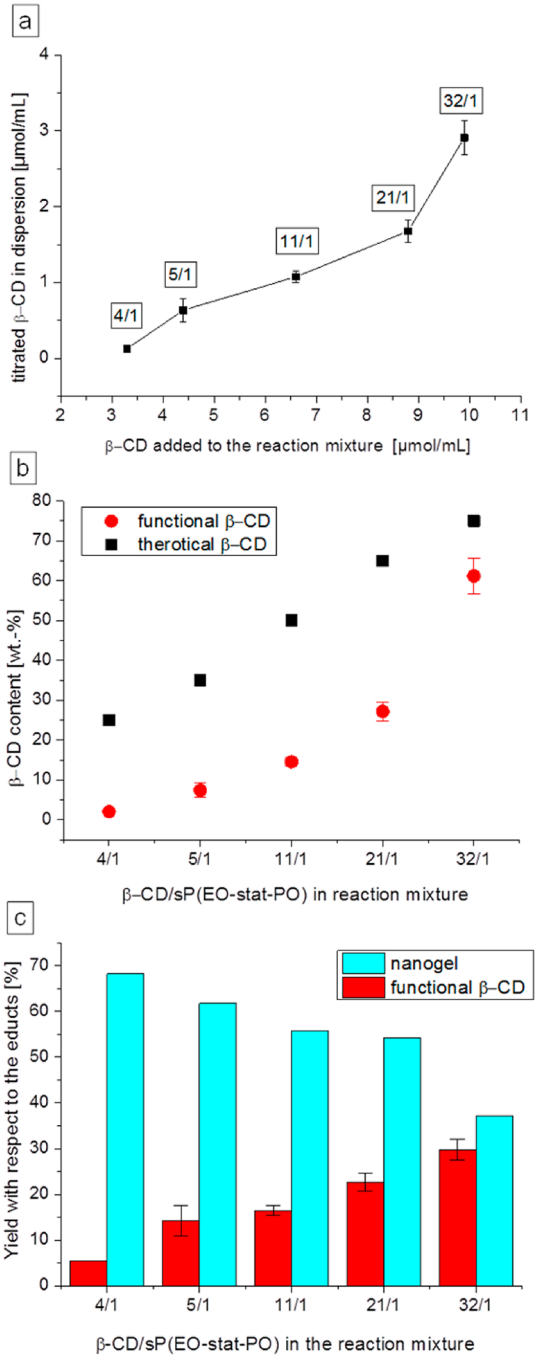

Figure 3. Amount of phenolphthalein-titrated β-CD in nanogel dispersions in comparison with the amount of β-CDs added during preparation of nanogels in different molar ratios to sP(EO-stat-PO) (a). Active β-CD content [wt %] in prepared nanogels based on complexion studies compared with the theoretical content in the reaction mixture (b) Yield of prepared nanogels after dialysis based on liophilisation and yield of active β-CDs based on complexation studies with respect to the educts (c).

in water. β-CDs which are occupied and bound in rotaxane-like structures are not accessible for host molecules. An easy way to characterize the amount of functional β-CD in nanogels is the dye sorption method, for example by using the complexation of phenolphthalein by β-CD. Phenolphthalein shows an

absorbance at 553 nm in alkaline aqueous solution (pH 10.5) due to delocalization of the π-electrons. Upon complexation of phenolphthalein in β-CD, this delocalization is disturbed by lactonization of the ionized form. As a consequence, the absorbance changes and the pink color disappears.[28,29] The creation of colorless 1:1 complexes in alkaline aqueous solution can thus be used for the quantitative determination of β-CD-content in polymeric materials.[30−32] Supporting Information, Figure S2 shows a qualitative proof for complexation of phenolphthalein by β-CD nanogels in alkaline aqueous solution. For quantitative determination of active β-CD in nanogels in comparison to free β-CD, the volumetric titration of phenolphthalein in aqueous dispersion at pH 10.5 has been performed. Aqueous solutions of free β-CD in different concentrations have been titrated in water at pH 10.5 until the transition point to obtain a calibration curve (Supporting Information, Figure S3). Afterward, nanogels containing β-CD have been titrated until the transition point, and the results were compared to the calibration curve obtained from free β-CD. A higher amount of β-CD added during preparation of the nanogels also results in a higher amount of functional β-CD in the nanogels dispersion, with the highest concentration of active β-CD in the case of a molar ratio of 32/1 β-CD/sP(EO-stat-PO) corresponding to a 3.3 mg/mL solution of free β-CD (Table 2 and Figure 3a).

Correlating this value to the expected amount of β-CDs per nanogel reveals, in agreement with the IR-data, an increased β-CD content of nanogels from molar ratio 4/1 to 32/1 β-CD/sP(EO-stat-PO) (Figure 3b). Nanogels prepared with a higher β-CD ratio (32/1 CD/sP(EO-stat-PO)) also show a higher content of incorporated, active β-CD than nanogels prepared with lower ratio (11/1 and 4/1 β-CD/sP(EO-stat-PO)). The maximal content of functional β-CD is reached with the molar ratio 32/1 β-CD/sP(EO-stat-PO) with about 60 wt % functional β-CD in the nanogels. Hence, 60 wt % of each nanogel in this sample are β-CD that are able to take up guest molecules.

However, the yield of the nanogel preparation process, meaning the amount of obtained nanogels with respect to the educts, increases with decreasing amount of β-CD in the reaction mixture. This trend is accompanied with a decreasing amount of functional β-CD in the nanogels (Figure 3c). For the nanogels prepared with the molar ratio 32/1 β-CD/sP(EO-*stat*-PO), 30 wt % of the β-CD added to the reaction mixture for nanogel preparation is incorporated into the gels in a functional way. With decreasing content of β-CD in the reaction mixture, the yield of nanogels with respect to the educts increases, while the amount of functional β-CD in the nanogels as well as the yield of functional β-CD in the nanogels with respect to the amount added to the reaction mixture decreases. Taking into account the IR results that show a continuous decrease of β-CD content with decreasing amount of β-CD in the reaction mixture, we conclude that, although some β-CD may be bound in the nanogels in a nonfunctional manner, most of the nondetectible β-CD is not integrated into the nanogels during preparation and thus removed during dialysis.

CONCLUSIONS

In conclusion, we presented the preparation of β-CD containing nanogels through an aqueous surfactant-free process by reaction between NCO-functional hydrophilic prepolymers and β-CD. This process allows production of uniform nanogels with narrow size distribution and a hydrodynamic radius of 50−150 nm. Coatings on aluminum showed nanogels with a good adhesion to surfaces in homogeneous distribution with size of R_h = 25 nm under dry conditions. The efficiency and the advantages of the nanogels in respect to the uptake of guest molecules were investigated by dye sorption method with phenolphthalein. This method enabled the quantitative determination of complexable β-CD units in colloidal polymeric material. Taking the results together, low β-CD content in the reaction mixture leads to a high yield of nanogels, but with a large, multimodal particle size distribution and low complexation properties. With the use of a high β-CD amount in the reaction mixture, nanogels with small uniform particle size and high uptake properties to hydrophobic molecules can be produced, with a maximum content of 60 wt % active β-CD per nanogel. Owing to this extremely high content of active β-CD in aqueous dispersion, these nanogels are very promising materials for a variety of applications. Ongoing research focuses on the application of these materials for technical surface modification such as textiles as well as sustained release in agriculture and drug delivery.

METHODS

Preparation of β-CD Containing Nanogels. β-CD (Merck) (0.75 g, 0.66 mmol) was dried at 80 °C for about 48 h and dissolved in deionized water (50 mL). Six-arm NCO-terminated star P(EO-stat-PO) prepolymers were synthesized using published procedures.[22] An aqueous β-CD mixture was added to (0.75 g, 0.06 mmol) NCO-terminated prepolymer under stirring. The aqueous phase was stirred continually at 300 rpm over 24 h at RT using a glass paddle connected to an overhead stirrer. The aqueous reactant mixture got a clear nanogel dispersion, which was purified by dialysis in water using a dialysis tube with MWCO of 12 kDa (ZelluTrans-12, 0 S 45 mm. MWCO: Nominal 12000−14000; Carl Roth GmbH, Karlsruhe). The water (2 L) was changed after 24 and 48 h; dialyses were stopped after 96 h. Yield: 40−70%.

Analysis of Reaction. IR spectra were obtained using an FT-IR-spectrometer: Nexus 470 (Thermo Nicolet) (spectral disintegration of 8 cm^{-1}). Nanogel dispersions were dried by liophilization and privileged studied in KBr pellets. IR (KBr): ν/cm^{-1} = 3356 (m, OH), 2870 (m), 1720 (m, ν_s C=O), 1677 (m, N−H), 1638 (m, OH),

1458 (m), 1350 (m), 1301 (m), 1248 (m), 1147 (s), 1101 (s), 1081 (s), 1032 (s, C−O−C), 1004 (s), 945 (m), 863 (m).

Particle Characterization. Analysis of particle size was made by dynamic light scattering measurements (DLS), using a Nano Zetasizer (Malvern) spectrometer. The spectrometer consists of a He−Ne Laser ($\lambda_0 = 633$ nm). Back scattering light was detected using an angle of 173°. Hydrodynamic particle radius and the particle distribution of the hydrodynamic radius were determined. All DLS measurements were made at 25 °C.

FESEM and Cryo-FESEM. Electron microscopic analyses were made using a model S-4800 field emission scanning electron microscope (Hitachi) with a high disintegration and cryo-function.

Swollen particles in aqueous solution were studied by cryo-scanning electron microscopy. A droplet was taken from an aqueous particle dispersion and after shock freezing in liquid nitrogen the freeze droplet was cut and the surface of the cut was sublimated in vacuum.

The morphology of the swollen nanogels was studied at a temperature of −167 °C, accelerating voltage of 1 kV, and 8 mm disintegration. Dry nanogels are studied after coating onto aluminum surface. The Al carrier was dipped 15 min into the aqueous particle dispersion. After being dried at RT and by vacuum, samples coated with nanogels are studied by FESEM at RT and an accelerating voltage of 1 KV and 8 mm disintegration. Particle diameter and radius are determined by enclosed software.

Preparation and Analysis of Phenolphthalein Complexes. A stock solution of 1% phenolphthalein (Merck) in ethanol was made, and aliquots of 2.50 mL were dropped into 250 mL of 0.1 M sodium hydroxide to obtain a 0.25 mmol/L alkali phenolphthalein solution. All aqueous stock solutions were freshly prepared and run within 12 h to ensure that absorbance changes due to any instability of phenolphthalein did not contribute to experimental artifacts. The β-CD stock solution was prepared in water with a β-CD concentration of 8.8 mmol/L. Aliquots of β-CD stock solution were diluted with water to different concentrations with an end volume of 15 mL. Different concentrated β-CD solutions were titrated by 0.25 mmol/L alkali phenolphthalein stock solution under stirring until the transition point from colorless to slight pink. Dispersions of nanogels containing β-CD were used as received after dialysis and diluted in water. A 10 mL aliquot of each prepared nanogel dispersion with known particle concentration was titrated by 0.25 mmol/L alkali phenolphthalein stock solution under stirring until the transition point from colorless to slight pink. For all volume titration a buret was used from Brand Duran; DIN, with a total volume of 50 mL, ± 0.05 mL. Ex +30s UV/vis-absorptions spectra were recorded by Varian Cary 100 UV−vis spectrophotometer of Fa. Varian, Darmstadt, A silica cuvette with a coating thickness of 1 cm was used. Water attended as reference.

Conflict of Interest: The authors declare no competing financial interest.

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Supporting Information Available: Additional figures as described in the text. This material is available free of charge *via* the Internet at http://pubs.acs.org.

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