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Cyclodextrin-*click*-cucurbit[6]uril: Combi-Receptor for Supramolecular Polymer Systems in Water

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ABSTRACT: We describe the synthesis of a combi-receptor via the click reaction of 6I-azido-6I-deoxycyclomaltoheptaose onto (propargyl-O)$_6$cucurbit[6]uril under microwave-assisted conditions. The process was investigated by ^{1}H NMR, FT-IR spectroscopy, and MALDI-TOF mass spectrometry. The ability of the synthesized compound to act as a molecular receptor and supramolecular building block in combination with NIPAM- and adamantane-containing methacrylates was investigated by turbidity measurement and dynamic light scattering (DLS).

Introduction

The molecular recognition based on macrocyclic receptors such as cyclodextrins (CDs) and cucurbiturils (CBs) is of great interest in supramolecular chemistry.[1] Similar to CDs, CBs can hold small organic molecules through hydrophobic interaction. Unlike CDs, however, the carbonyl groups at the portals allow CB[6] to form stable complexes with various ions and molecules through charge−dipole as well as hydrogen-bonding interactions.[2,3] Because of their host−guest chemistry, CDs and CBs proved to be very attractive not only as molecular receptors but also as building blocks for the construction of supramolecular architectures.[4−9] Combinations of CDs and CBs are also used for the design of supramolecular structures.[10−12] Recent progresses in the field of supramolecular chemistry are also the contribution of click chemistry, a versatile and powerful tool that affords the modular assembly of new molecular entities.[13,14] Both CDs and CBs have already found applications in click chemistry. Click reactions are known in CD chemistry,[15−19] whereas the use of CB[6] is based on its remarkable ability to catalyze 1,3-dipolar cycloadditions in a regioselective manner within the cavity.[20,21] However, the coupling of CBs and CDs via "click reaction" has not been reported. Therefore, we describe herewith the first synthesis of a dual CD-*click*-CB receptor by the successful cycloaddition of 6I-azido-6I-deoxycyclomaltoheptaose (**3**) onto (propargyl-O)$_6$CB[6] (**2**) under microwave-assisted conditions (Scheme 1). Furthermore, the ability of the CD-*click*-CB receptor to recognize and include guest molecules was investigated by turbidity measurement and dynamic light scattering (DLS).

Experimental Section

Materials. Cyclodextrin (β-CD) was obtained from Wacker-Chemie GmbH (Burghausen, Germany) and used after drying overnight in vacuum oil pump on P_4O_{10}. *N*-Isopropylacrylamide (NIPAAM) 97% and sodium azide (99.5%) were obtained from Aldrich Chemicals (Germany) and were used as received. Copper(II)-sulfate pentahydrate (99%) was obtained form Carl Roth GmbH & Co., and sodium L(+)-ascorbate (99%) was obtained from AppliChem (Germany). α,α′-Azoisobutyronitrile (96%) and *N*,*N*-dimethylformamide (DMF) were purchased from Fluka (Germany). Dimethylsulfoxide-d_6 99.9 atom % D was obtained from Deutero GmbH and DMSO p.a. from Carl Roth GmbH & Co. (Germany). Commercially available reagents and solvents were used without further purification. 6I-Azido-6I-deoxycyclomaltoheptaose and 6-acrylamido-*N*-adamantyl-hexane amide were prepared according to methods described in literature[22] or applied previously by us.[23]

Measurements. IR spectra were recorded with a Nicolet 5 SXB FTIR (Fourier transform infrared) spectrometer equipped with an ATR unit. The measurements were performed in the range of 4000−300 cm^{-1} at room temperature. ^{1}H NMR spectra were recorded with a Bruker AC 500 at 20 °C. Chemical shifts were referenced to the solvent value δ 2.51 for DMSO-d_6. Matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOFMS) was performed on a Bruker Ultraflex TOF mass spectrometer. Ions formed with a pulsed nitrogen laser (25 Hz, 337 nm) were accelerated to 25 kV, the molecular masses being recorded in linear mode. 2,5-Dihydroxybenzoic acid (DBH) in acetonitrile/water (25 mg·mL^{-1}) was used as a matrix. The samples (1 mg·mL^{-1} in water) were mixed with the matrix solution at volumetric ratios of 1:2. Gel permeation chromatography (GPC) analyses were performed on a GPC system from PSS with PSS-WIN-GPC software 4.01, 6.1 with *N*, *N*-dimethylformamide as eluent. The flow rate was 1 mL·min^{-1}, and the column temperature was maintained at 60 °C. A 0.1% (w/w) polymer solution (100 μL) was given to a hydroxyethyl methacrylate (HEMA) column combination that consisted of a precolumn of 40 Å and main columns of 40, 100, and 3000 Å porosities. The number-average molecular weight (M_n) and the polidispersity (PD) were calculated by a calibration curve generated by polystyrene standards with a molecular weight range from 374 to 1 000 000 Da. DLS experiments were carried out with a Malvern HPPS-ET apparatus at a temperature value of 20 °C. The particle size distribution was derived from a deconvolution of the measured intensity autocorrelation function of the sample by the general purpose mode algorithm included in the DTS software. Each experiment was performed five times to obtain statistical information. Cloud points were determined by transmission changes (at 500 nm) of the

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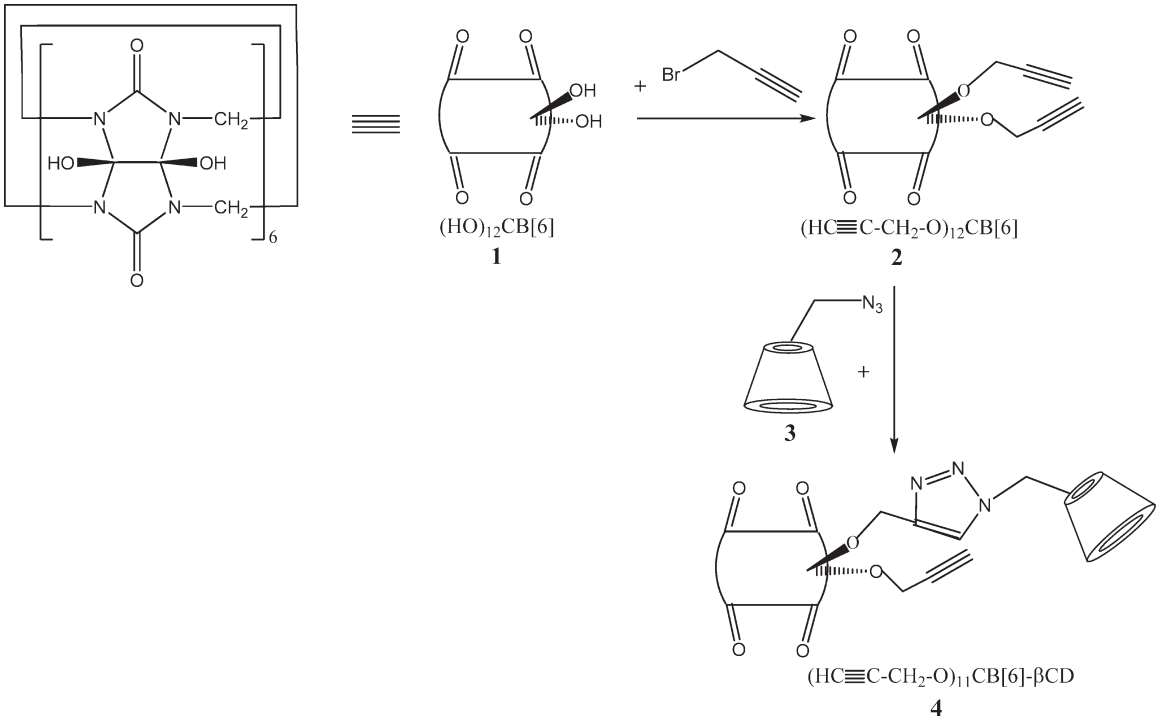
Scheme 1. Synthesis of CD-CB Receptor via *click* Chemistry



solutions heated at 0.1 $K \cdot min^{-1}$ in a magnetically stirred cell; values of the cloud points were defined as the temperature at which the transmission decreases by 50%. Microwave-assisted synthesis was performed using a CEM Discover synthesis unit (monomode system). The temperature was measured by infrared detection with continuous feedback temperature control and maintained at a constant value by power modulation. Reactions were performed in closed vessels under controlled pressure.

Synthesis of Perhydroxycucurbit[6]uril (CB[6]OH) (1). PerhydroxyCB[6] was prepared according to a method described by Kim.[24] FT-IR (film): 1745 (C=O), 1437 (C−H), 1372 (N−H), 1264 (O−H), 1102 (C−O), 985 (C−H), 906 (−CH=CH_2). ^{1}H NMR (DMSO-d_6, δ): 4.43 (d, 12H, CH_2), 5.33 (d, 12H, CH_2), 7.96 (s, 12H, OH). MALDI-TOF: m/z 1227.238 [M + K^+].

Synthesis of (Propargyl-O)$_6$CB[6] (2). Sodium hydride (0.304 g, 7.6 mmol) was solved in 20 mL of dry DMSO and stirred for 15 min. PerhydroxyCB[6] (0.76 g, 0,63 mmol) was added to the solution cooled to 0 °C, and the reaction mixture was stirrred at room temperature for 8 h. After the solution was cooled to 0 °C, propargylbromide (1.50 g, 12.6 mmol) was added, and the mixture was stirred overnight at room temperature. The reaction was stopped by the addition of 125 mL of cold water. The precipitate was collected by filtration and washed with water and ether on the filter (47% yields). FT-IR (film): 3280 (HC≡), 2924 (CH), 2112 (HC≡), 1728 (C=O), 1454 (C−H), 1409 (CH_3), 1319 (N−H), 1029 (CH), 906 (−CH=CH_2). ^{1}H NMR (DMSO-d_6, δ): 1.23 (s, 12 H, HC≡), 2.04 (s, 24 H, −CH_2−), 4.43 (d, 12H, CH_2), 5.34 (d, 12H, CH_2). MALDI-TOF: m/z 1667.3 [M + Na^+].

Synthesis of CD-*click*-CB (4). The microwave-assisted click reaction of (propargyl-O)$_6$CB[6] (82 mg, 0,05 mmol) with 6I-azido-6I-deoxycyclomaltoheptaose (116 mg, 0.1 mmol) was carried out in DMSO in the presence of Cu(I) generated in situ by the reduction of copper sulfate (0.002 mmol) with sodium ascorbate (0.005 mmol). The tube was sealed and placed in the CEM monomode microwave and irradiated at 140 °C and 100 W for 40 min. The product was separated by simple filtration after precipitation with 50 mL of acetone (86 mg, 71%). FT-IR (film): 3382 (OH), 2920 (CH_2), 2112 (HC≡), 1739 (C=O), 1644 (−CH=CH_2), 1473 (C−H), 1365 (N−H), 1318 (O−H), 1150 (C−O−C, OH), 1080 (C−O−C), 995. ^{1}H NMR (DMSO-d_6, δ): 1.23 (s, 11 H, HC≡), 2.04 (s, 24 H, −CH_2−), 3.35 (br, 14H, H-2,4), 3.64 (s, br, 28H, H-3,5,6), 4.43 (d, 12H, CH_2), 4.54 (br, 6H, OH-6), 4.83 (d, 6H, H-1), 4.92 (H, H-1), 5.43 (d, 12H, CH_2), 5.73 (br, 14H, OH-2,3), 8.14 (1H, CH). MALDI-TOF: m/z 2843 [M + K^+].

Copolymer (5) Synthesis. *N*-Isopropylacrylamide (1.13 g, 10 mmol) and 6-acrylamido-*N*-adamantyl-hexane amide (159 mg, 0.5 mmol) were dissolved in DMF (4 mL). The solution was flushed with argon for 30 min, and AIBN (8.5 mg, 0.05 mmol) was added under an argon atmosphere. The mixture was heated to 65 °C and stirred overnight. The solvent was removed under reduced pressure. The dry polymeric material was dissolved in water, dialyzed, and freeze dried (M_n = 3.6 × 10^4 $g \cdot mol^{-1}$, PD = 1.6.)

Results and Discussion

The synthesized compounds were characterized by ^{1}H NMR, FT-IR spectroscopy, and MALDI-TOF mass spectrometry. The successful microwave-assisted cycloaddition of (propargyl-O)$_6$-CB[6] onto 6I-azido-6I-deoxycyclomaltoheptaose was IR spectroscopically proven by the disappearance of the azide band at 2100 cm^{-1}. We identified the characteristic peaks of CB[6] at 1739 and 1473 cm^{-1} corresponding to C=O and C−N stretching vibration, respectively, the peaks corresponding to OH stretching at 3370 cm^{-1} and C−O−C stretching and OH bending at 1150 cm^{-1} for CD. Furthermore, the formation of triazole ring was confirmed by the appearance of the new peak at 1644 cm^{-1} as well as by ^{1}H NMR data, the triazolic proton being distinguished at 8.14 ppm (Figure 1).

The MALDI-TOFMS measurement confirmed the molecular masses of all synthesized compounds. DLS measurements accomplished in THF indicated a hydrodynamic diameter of CB-*click*-CD compound of nearly 2.5 nm. In comparison, the outer diameter of β-CD is about 1.5 nm, and that of CB[6] is only 0.6 nm. An increased hydrodynamic diameter of 112 nm obtained

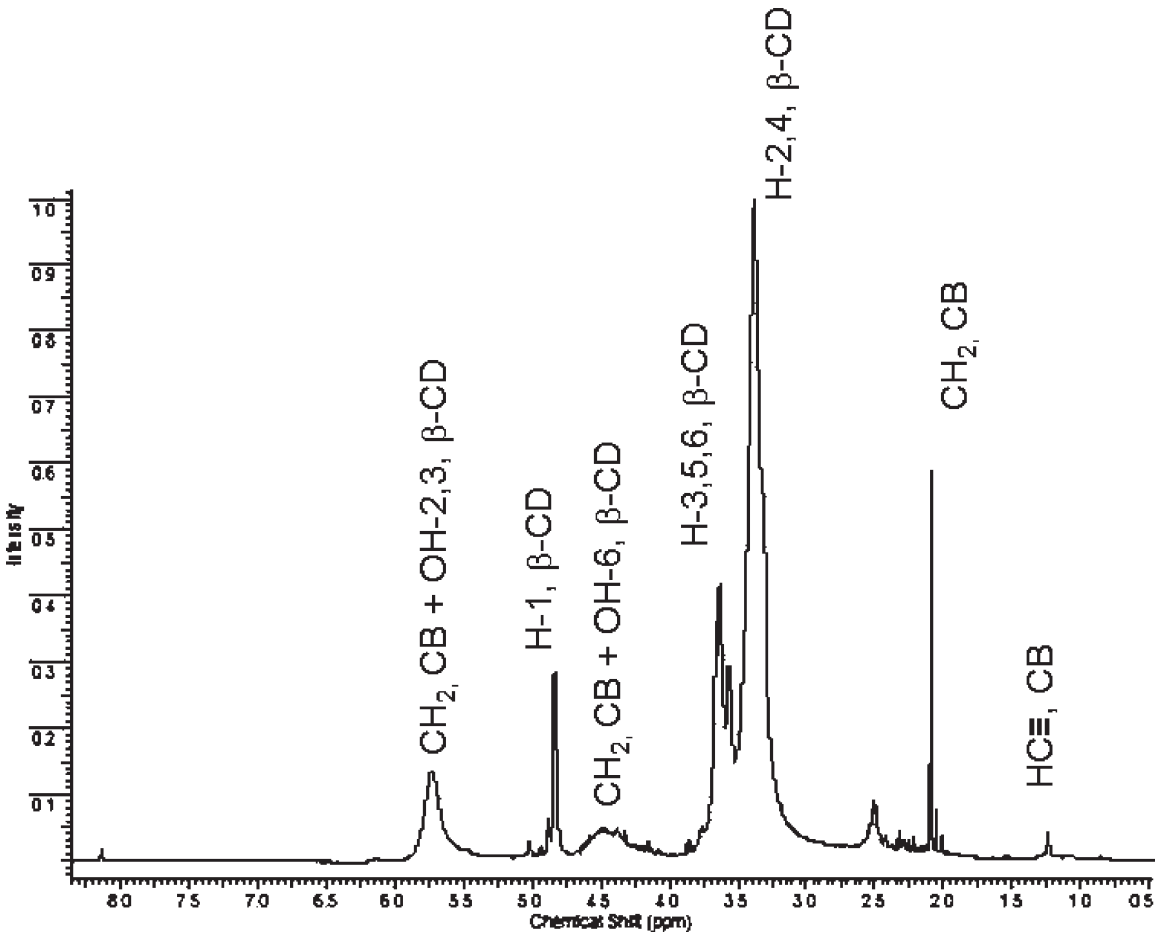


Figure 1. ^{1}H NMR spectrum of the CB−CD heterodimer.

by performing the DLS measurements in aqueous solution suggested the formation of heterodimer aggregates.

Additionally, the ability of the synthesized CD-*click*-CB compound **4** to act as a receptor and supramolecular building block was investigated. We performed DLS and cloud point measurements for an adamantane-containing copolymer **5**, which was then complexed with an equivalent ratio of **4**. The increasing of the hydrodynamic diameter of copolymer **5** from 15 to 31 nm in the presence of **4** suggests the inclusion of adamantane moiety into CD. By the addition of *N*,*N*′-dimethyl-4,4′-bipyridinium (methyl viologen, MV^{2+}), the hydrodynamic volume decreased to 20 nm as a result of the shrinkage effect of the complexed copolymer because of the interaction of the dicationic 4,4′-bipyridinium nucleus with CB (Figure 2).

The turbidity point of the copolymer **5** at 23 °C is significantly lower than that of the unmodified poly(NIPAAM) itself (34 °C) because of the influence of hydrophobic adamantyl units. To investigate the effect of CD-*click*-CB compound **4** on the cloud point of the adamantane-containing copolymer **5**, we performed turbidity measurements in the presence of an equivalent amount of CD-*click*-CB (Table 1, Figure 3). The upward shift of cloud point temperature from 23 to 29 °C confirms the inclusion of the hydrophobic adamantyl units by CD-*click*-CB. Relative to the cloud points of poly(NIPAAM) itself, this value also suggests the presence of the hydrophobic CB units.

To investigate the influence of the CB moiety, we further measured the cloud point of the copolymer complexed with CD-*click*-CB in the presence of MV^{2+}. As the DLS measurements already confirmed, the CB units can interact with the guest MV^{2+}. The complex formed by CD-*click*-CB with MV^{2+} has increased stability and precipitates above the turbidity point of copolymer **5**. In terms of the phase transition temperature, this can be assumed to be the decrease in turbidity point to 25 °C (Table 1).

Because the adamantane moiety belongs to the best guest of *β*-CD known so far,[25] with a high complex stability constant around 5000 M^{-1},[26] an equimolecular mixture of the copolymer **5** with CD-*click*-CB **4** led to a stable supramolecular complex. Regarding the possible influence of MV^{2+}, the literature data suggest no inclusion of the dicationic 4,4′-bipyridinium nucleus in the CD host,[27,28] whereas a weak interaction with the CB[6] is confirmed by a complex constant of 21 M^{-1}.[29] As control experiments, we performed turbidity and DLS measurements for the copolymer **5** in the presence of MV^{2+} and *β*-CD/MV^{2+}, using the same concentrations of **5** and MV^{2+} as those for the first experiment. In both cases, the cloud point and hydrodynamic radius were not modified by MV^{2+}, but the combination *β*-CD/MV^{2+} increased the turbidity point up to 35 °C. In our former work, we showed that the addition of *β*-CD to this copolymer also led to a cloud point of 35 °C, which correlates to the LCST of pure poly(NIPAAM).[30] Also, the DLS measurement proved the formation of aggregates with a hydrodynamic diameter around 300 nm. We can conclude that because only *β*-CD interacts with the polymer chain in the control experiment, MV^{2+} can influence the turbidity point and hydrodynamic radius of the polymer **5** by interacting with CB[6]. Ion−dipole interactions are possible between the dicationic 4,4′-bipyridinium guest and the carbonyl groups at the portals of CB[6]. The successive supramolecular interactions have a shrinkage effect on the polymer network, confirmed by the DLS and turbidity measurements.

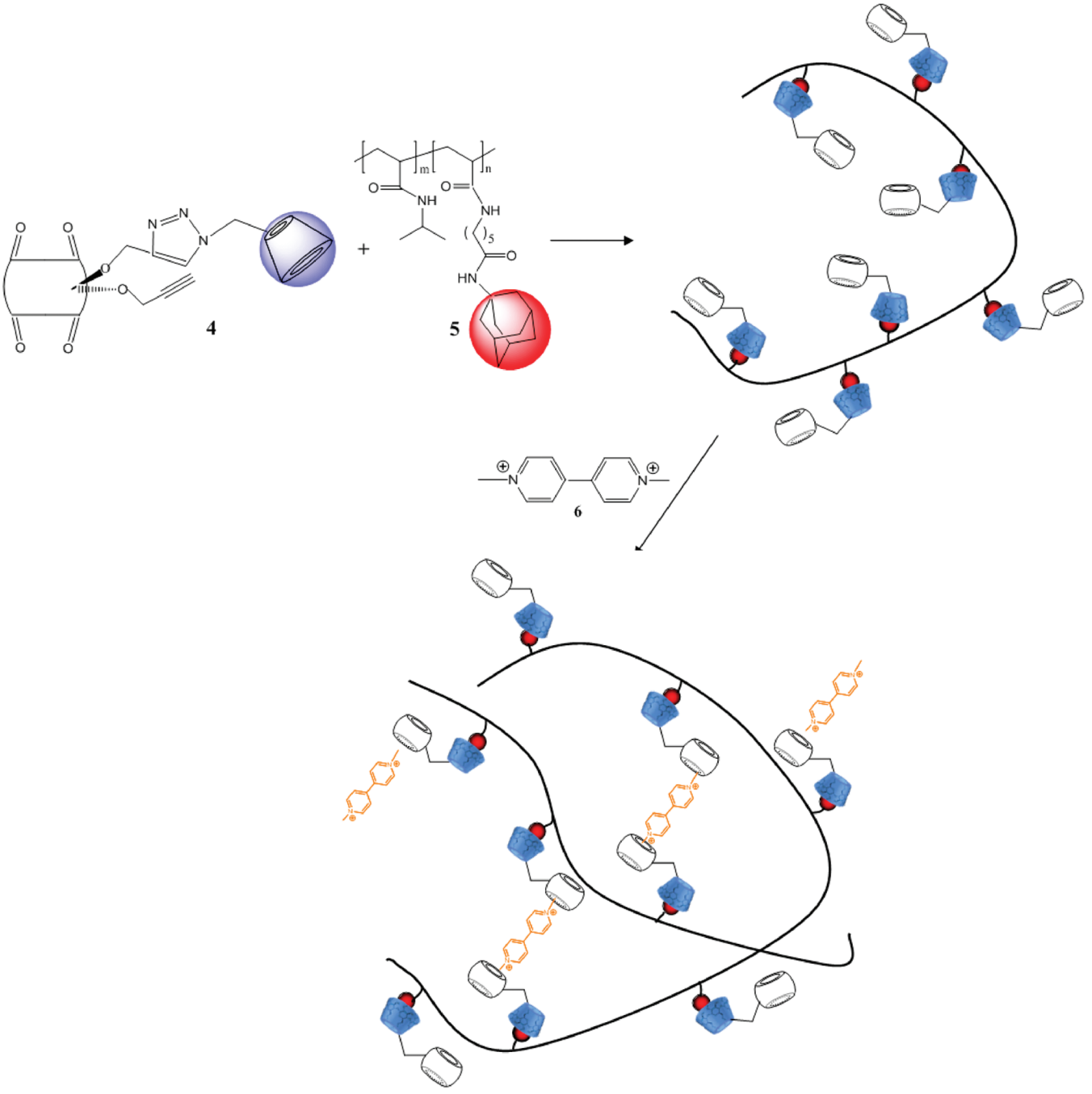


Figure 2. Supramolecular interaction of CD-*click*-CB with the adamantane-containing polymer network.

Table 1. Experimental Cloud Point Temperature Dependence on the Balance of Hydrophobic/Hydrophilic Interactions of CB−CD with the Copolymer and the Influence of CB−CD on the Hydrodynamic Volumes of Copolymer[a]

compound	turbidity point (°C)	hydrodynamic diameter [nm]
copolymer **5**	23	15
copolymer **5** + CD-*click*-CB **4**	29	31
copolymer **5** + CD-*click*-CB **4** + MV^{2+} **6**	25	20

[a] DLS measurements were performed at 20 °C, below the turbidity point of the copolymer, using the following concentrations of copolymer and guests: C_P = 20 g L^{-1}, $C_{CD\text{-}CB}$ = 26 g L^{-1}, $C_{MV^{2+}}$ = 2 g L^{-1}. Turbidity measurements were performed in aqueous solutions using the following concentrations of copolymer and guests: C_P = 10 g L^{-1}, $C_{CD\text{-}CB}$ = 13 g L^{-1}, $C_{MV^{2+}}$ = 1 g L^{-1}.

Conclusions

A cyclodextrin-cucurbit[6]uril (CD-*click*-CB) combi-receptor was synthesized via copper-catalyzed Huisgen 1,3-dipolar cycloaddition. DLS and turbidity measurements were performed after complexing an adamantane-containing copolymer with the synthesized heterodimer and the dicationic 4,4′-bipyridinium guest MV^{2+}. As a control experiment, the same polymer was investigated in the presence of MV^{2+} and β-CD/MV^{2+}. Because the dicationic 4,4′-bipyridinium guest can influence the polymer chain only in the presence of CD-*click*-CB compound, this could be valuable not only by being a molecular receptor, because of its dual complexing ability, but also by controlling the shrinkage of polymer networks by supramolecular interactions.

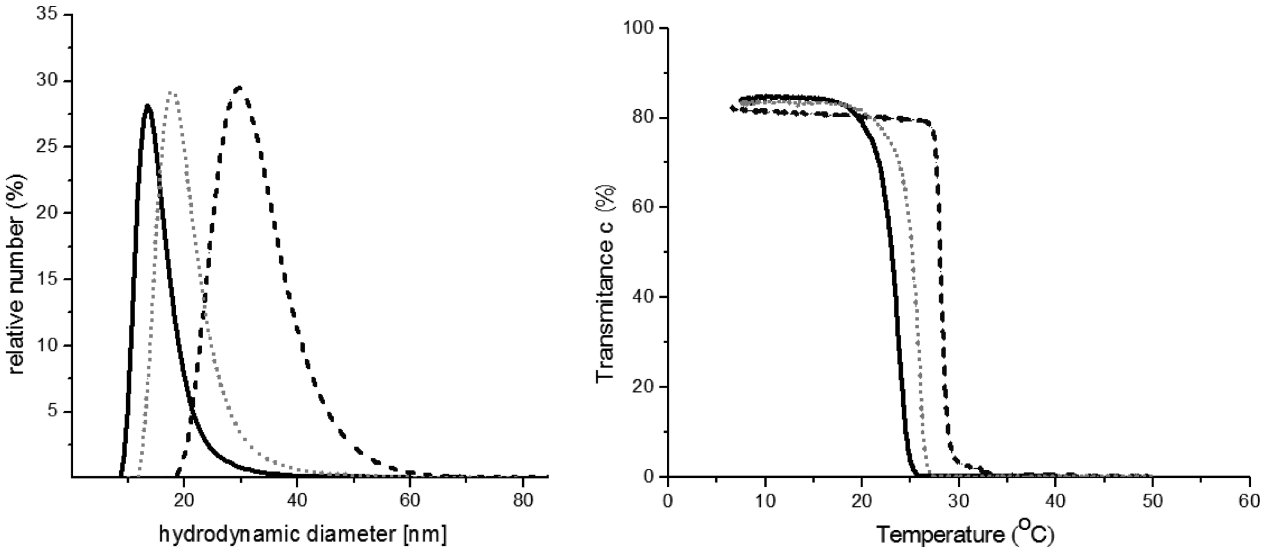


Figure 3. (a) Effect of CB−CD compound on hydrodynamic volume and (b) the change of phase transition temperature of the copolymer (—, copolymer **5**; —, copolymer **5** + CD-*click*-CB **4**; ···, copolymer **5** + CD-*click*-CB **4** + MV^{2+} **6**).

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