Cyclodextrin Methacrylate via Microwave-Assisted Click Reaction

Maricica Munteanu,[†] SooWhan Choi,[‡] and Helmut Ritter*,[†]

Institute für Organische Chemie and Makromolekulare Chemie, Heinrich-Heine-Universität Düsseldorf, Lehrstuhl II, Universitätsstrasse 1, 40225 Düsseldorf, Germany, and S&V Technologies AG, Neuendorfstrasse 20a, 16761 Henningsdorf, Germany

Received August 21, 2008; Revised Manuscript Received October 29, 2008

ABSTRACT: Click reaction of propargyl methacrylate (**1**) with 6I-azido-6I-deoxycyclomaltoheptaose (**2**) was carried out to synthesize mono-(1*H*-1,2,3-triazol-4-yl)(methyl)2-methylacryl-β-cyclodextrin (**3**). The process was investigated by varying the reaction time, temperature profiles, and copper catalyst. Microwave irradiation was compared with conventional heating. The microwave-assisted Cu(I)-catalyzed cycloaddition affords the complete conversion of (**2**) into 1,4-disubstituted triazole in a significant decreased reaction time. Under microwave conditions, the cycloaddition of (**2**) onto poly(propargyl methacrylate) (**5**) was conducted in excellent yields. The regioselectivity of click reactions in dependence of reaction conditions was evaluated by use of NMR spectroscopy. The reactions performed under microwave conditions led exclusively to 1,4-disubstituted triazole, while the conventional heating led to a regioisomeric mixture.

Introduction

In recent years, cyclodextrins have been extensively used in polymer chemistry. For example, they are used to complex water-insoluble monomers and polymers.[1−8] In this field, cyclodextrin monomethacrylates have not yet been studied extensively. Thus, we were encouraged to synthesize such polymerizable cyclodextrin monomers via "click chemistry". This type of coupling introduced by Sharpless and summarized as "all searches must be restricted to molecules that are easy to make"[9] has proven to be a versatile, powerful, and multiapplicable tool, intensively exploited in the past years.[10] Cu(I)-catalyzed Huisgen-type 1,3-dipolar cycloaddition of azides and alkynes extended its area of applications in carbohydrate research, organic and supramolecular chemistry, bioconjugation,[11−14] or drug discovery.[15] According to Huisgen[16] and confirmed by Meldal,[17] thermal 1,3-dipolar cycloaddition of alkynes and azides is not a regiospecific reaction. A structural control can be achieved under mild conditions by using active Cu(I) species.[18,19] The microwave-assisted copper-catalyzed 1,3-dipolar cycloaddition received recently much attention due its ability to afford a complete and regioselective conversion with a significant decrease in reaction time. Although click reactions are known in the cyclodextrin chemistry,[20−24] their use to obtain cyclodextrin monomethacrylate has not been reported. Attempts to synthesize monofunctional cyclodextrin esters led to mixtures, and the desired compound was obtained in low yield afther chromatographic purification.[25] By applying click reaction, cyclodextrin monomethacrylate can be obtained in high yields; the purification by chromatographic methods is not required, and the installation and removal of protecting groups are avoided. The triazol linker is relatively stable toward cleavage, oxidation, or reduction. Since 1,3-cycloaddition of 6-monoazido-6-monodeoxy-β-cyclodextrin with propargyl derivatives under the synergistic effects of copper catalysis and microwave irradiation was less investigated, we decided to explore different reaction parameters in order to provide an easy and efficient way to obtain polymerizable cyclodextrin monomethacrylates. Furthermore, we describe the click reaction of 6I-azido-6I-deoxycyclomaltoheptaose (**2**) onto poly(propargyl methacrylate) (**5**) to obtain a polymer with potential applications in supramolecular chemistry.

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}. 2-Propynyl 2-methacrylate (98%) was purchased from Alfa Aesar GmbH & CoKG, Germany. Sodium azide (99%) was obtained from Aldrich Chemicals, Germany, and used as received. Copper(II) sulfate pentahydrate (99%) was obtained form Carl Roth GmbH & Co. and sodium L(+)-ascorbate (99%) from AppliChem, Germany. α,α′-Azoisobutyronitrile (AIBN) (96%) and *N*,*N*-dimethylformamide (DMF) were purchased from Fluka, Germany. Dimethyl-d_6 sulfoxide (99.9 atom % D) was obtained from Deutero GmbH, Germany. 6I-Azido-6I-deoxycyclomaltoheptaose (**2**) was prepared according to a method described in the literature.[6]

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. ^1H spectra were recorded with a Bruker AC 500 at 20 °C. Chemical shifts were referenced to the solvent value δ 2.51 for dimethyl-d_6 sulfoxide. Matrix-assisted laser desorption/ionization-time-of-flight mass spectrometry (MALDI-TOF-MS) 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. 100 μL of a 0.1% (w/w) polymer solution 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 polydispersity (PD) were calculated by a calibration curve generated by polystyrene standards with a molecular weight range from 374 to 1 000 000 Da. Dynamic light scattering (DLS) experiments were carried out with a Malvern HPPS-ET in the temperature range 17−75 °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

* Corresponding author. Fax: +49-211-8115840. E-mail: h.ritter@uni-duesseldorf.de.
[†] Heinrich-Heine-Universität Düsseldorf.
[‡] S&V Technologies AG.

10.1021/ma8018975 CCC: $40.75
Published on Web 11/25/2008

performed at least five times to obtain statistical information. 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 as well as in standard open vessels under reflux conditions.

Synthesis of the Triazol-CD-Monomer (3). The reaction of 6I-azido-6I-deoxycyclomaltoheptaose (**2**) (116 mg, 0.1 mmol) with 2-propynyl 2-methacrylate **2** (24.80 mg, 0.2 mmol) was carried out in DMF, in the presence of Cu(I) generated in situ by the reduction of copper sulfate (1.2 mg, 0.005 mmol) with sodium ascorbate (1.98 mg, 0.01 mmol). The product was separated by simple filtration after precipitation with acetone (50 mL). We carried out microwave-assisted cycloaddition, by adding 2-propynyl 2-methacrylate (**1**) (24.80 mg, 0.2 mmol) to a solution of 6I-azido-6I-deoxycyclomaltoheptaose (**2**) (116 mg, 0.1 mmol) in 2 mL of DMF in a pressure-resistant test tube. Sodium ascorbate (4 mg, 0.02 mmol) and copper(II) sulfate pentahydrate (2.50 mg, 0.01 mmol) were added to the clear solution. The tube was placed in the CEM monomode microwave and irradiated at 140 °C and 100 W for 30 min. After precipitating the reaction mixture with acetone, 108 mg of product was isolated (84% yield). In order to ensure the equivalence of the reaction parameters, we conducted the reaction under reflux conditions, in oil bath as well as under microwave irradiation. The conventional reaction was performed by preheating the solvent, the reaction mixture being maintained 30 min at reflux temperature, after adding the reagents and catalytic system. The standard open vessel was placed in the CEM monomode microwave, and the reaction was conducted under reflux for 30 min, with a preheating time of 2 min. The product was collected by filtration, after precipitating with 50 mL of acetone (57% yield). By increasing the reaction time under conventional heating, the ratio monomer **3**:monomer **4** was 3:1 after 24 h.

FT-IR (film, cm^{-1}): 3351 (OH), 2927 (CH_2), 1714 (C═O), 1657 (C═C), 1153 (C−O−C), 1078 (OH), 1026 (C−O). ^1H (DMSO-d_6): δ (ppm) 1.86 (3H, CH_3), 3.34 (br, 14H, H-2,4), 3.65 (br, 28H, H-3,5,6), 4.52 (br, 6H, OH-6), 4.84 (d, 6H, H-1), 5.03 (2H, $-CH_2-$), 5.19 (H, $-CH=$), 5.73 (br, 14H, OH-2,3), 6.07 (H, $-CH=$), 8.13 (1H, CH). MALDI-TOF: m/z 1306.5 [M + Na^+].

Homopolymerization of the Triazol-CD-Monomer 3. Mono-(1*H*-1,2,3-triazol-4-yl)(methyl)2-methylacryl-β-cyclodextrin (**3**) (128 mg, 0.1 mmol) was solved in 1 mL of DMF and flushed with argon for 5 min. AIBN (α,α′-azoisobutyronitrile) (1.6 mg, 0.005 mmol) was added under an argon atmosphere. The mixture was heated to 65 °C and stirred overnight. The solvent was removed under reduced pressure to afford 60 mg of product (46% conversion).

FT-IR (film, cm^{-1}): 3303 (OH), 2929 (CH), 1720 (C═O), 1653 (C═C), 1558 (N−H), 1153 (C−O), 1023 (C−O). ^1H (DMSO-d_6): δ (ppm) 1.89 (3H, CH_3), 3.32−3.56 (br, 14H, H-2,4, 28H, H-3,5,6), 4.51 (br, 6H, OH-6), 4.84 (d, 6H, H-1), 5.03 (2H, $-CH_2-$), 5.76 (br, 14H, OH-2,3), 8.13 (1H, CH). $M_n = 1.30 \times 10^4$ g mol^{-1}, PD = 1.4.

Poly(propargyl methacrylate) (5). Propargyl methacrylate (**1**) (1.241 g, 0.1 mol) was solved in 4 mL of dioxane and flushed with argon for 5 min, and AIBN (α,α′-azoisobutyronitrile) (16.4 mg, 0.01 mmol) was added under an argon atmosphere. The reaction was stopped after stirring 2 h at 65 °C (25% conversion). The reaction mixture was precipitated into methanol and filtered, and the solid was dried under vacuum.

FT-IR (film, cm^{-1}): 3284 (≡C−H), 3002 (C−H), 2942 (CH_3), 2135 (C≡C), 1723 (C═O), 1454 (CH_3), 1391 (CH_3), 1261 (C−O), 1128 (C−O−C). ^1H (DMSO-d_6): δ (ppm) 1.9 (3H, CH_3), 3.5 (C≡CH), 4.78 (2H, $-CH_2-$), 5.76 (H, $-CH=$), 6.07 (H, $-CH=$). $M_n = 1.04 \times 10^5$ g mol^{-1}, PD = 1.6.

Coupling Reaction of Poly(propargyl methacrylate) (5) with 6I-Azido-6I-deoxycyclomaltoheptaose (2). A solution of 128 mg of poly(propargyl methacrylate) (**5**) in 10 mL of DMF was prepared, and 6I-azido-6I-deoxycyclomaltoheptaose (**2**) (1.16 g, 1 mmol) was added under vigorous stirring. Sodium ascorbate (19.8 mg, 0.1 mmol) and copper(II) sulfate pentahydrate (12.45 mg, 0.05 mmol) were added to the clear solution. The reaction was conducted under conventional reflux conditions as well as under microwave irradiation. The reaction in oil bath was performed by preheating the polymeric solution, the reaction mixture being maintained 30 min at reflux temperature, after adding 6I-azido-6I-deoxycyclomaltoheptaose (**2**) and catalytic system. The standard open vessel was placed in the CEM monomode microwave, and the reaction was conducted under reflux for 30 min, with a preheating time of 2 min. The product was collected by precipitating the reaction mixture with 100 mL of acetone followed by filtration. The dry polymeric material was dissolved in water, dialyzed 3 days against distillated water using MWCO 3500 membrane, and freeze-dried. The polymer was obtained in a low yield (16%) under conventional heating, while the microwave conditions afforded a higher yield (27%).

FT-IR (film, cm^{-1}): 3317 (OH), 2923 (CH), 1723 (C═O), 1653 (C═C), 1558 (N−H), 1348 (C−N), 1153 (C−O), 1021 (C−O). ^1H (DMSO-d_6): δ (ppm) 1.89 (3H, CH_3), 3.32−3.56 (br, 14H, H-2,4, 28H, H-3,5,6), 4.51 (br, 6H, OH-6), 4.84 (d, 6H, H-1), 5.03 (2H, $-CH_2-$), 5.76 (br, 14H, OH-2,3), 8.13 (1H, CH).

Results and Discussion

We carried out the "click reaction" of propargyl methacrylate (**1**) with 6I-azido-6I-deoxycyclomaltoheptaose (**2**) to synthesize the new monomer mono-(1*H*-1,2,3-triazol-4-yl)(methyl)2-methylacryl-β-cyclodextrin (**3**) useful for the design of polymeric supramolecular architectures. Because of our interest in optimizing the process, we focused on the synergistic effects of microwave irradiation and Cu(I) catalysis. Although the conditions of the microwave-assisted reaction cannot be easily reproduced by the conventional heating, we duplicated some controllable parameters, such as temperature, time, catalyst, and solvent in order to ensure the comparability of the procedures. The active copper(I) catalytic species were generated in situ by reduction of $CuSO_4$ with sodium ascorbate. We used *N*,*N*-dimethylformamide as solvent due its high dielectric constant, high boiling point, and ability to solve both starting materials. We performed also the process in water, but no reaction occurred under microwave irradiation. Regarding our interest to investigate the microwave effect on the Cu(I)-mediated cycloaddition and the possible interaction between the dielectric irradiation and the metal catalysis, we approached three different procedures. Cu(I)-free cycloaddition conducted in *N*,*N*-dimethylformamide took place rapidly under MW irradiation. Applying the conventional heating, we obtained slowly a relatively low conversion, which remained constant with increasing reaction time (Figure 1).

Cu(I)-mediated click reaction conducted under microwave irradiation favored the selective 1,4-conversion in **3** (Figure 2).

The reaction was completed after 30 min. In contrast, the oil bath procedure under similar conditions afforded a mixture of **3** and **4** with a relatively high conversion in **3** after increased reaction time (Figure 3).

The regioisomeric proportion was determined by ^1H NMR spectroscopy. The chemical shifts of the triazole ring protons were used to distinguish isomers **3** and **4**. The H4 proton of the 1,5-disubstituted triazole is located at 8.23 ppm. The resonance of the H5 proton of the 1,4-disubstituted triazol isomer is at 8.13 ppm.

Without any heating, the cycloaddition proceeded regioselectively; however, extremely increased reaction time is required (74% conversion after 1 week).

As mentioned above, the Huisgen cycloaddition is not a selective process, while Cu(I)-mediated reactions afford exclusively 1,4-disubstituted regioisomers.[16,17] As the mild catalyzed reaction resulted in extremely long reaction time, we

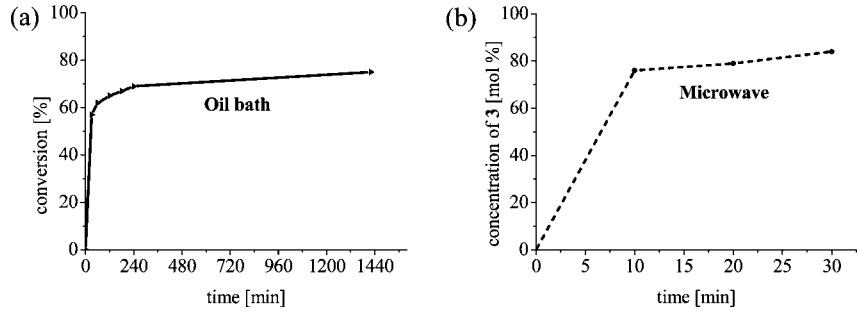


Figure 1. Kinetics of the click reaction under conventional heating (a) and microwave conditions (b). The temperature in microwave and oil bath was 140 °C. Respective reactions were performed in *N,N*-dimethylformamide, using $CuSO_4 \cdot 5H_2O$ and Na ascorbate as catalytic system. Conversion was determined by ^1H analysis of the isolated product.

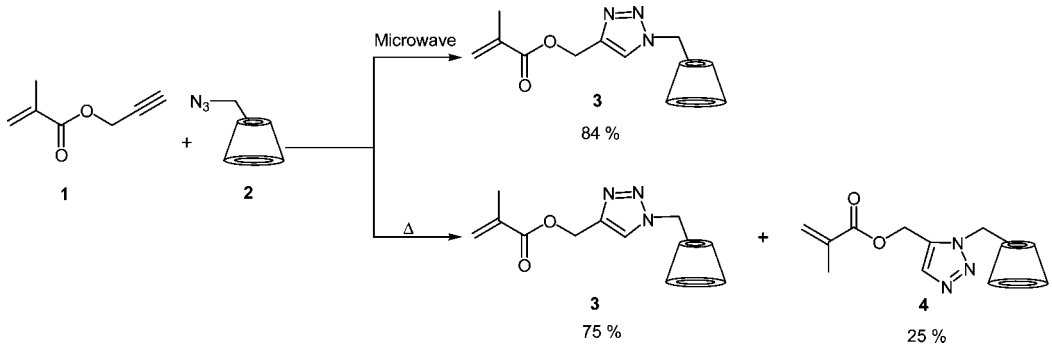


Figure 2. Influence of microwave and conventional conditions conditions on the regioselectivity of the reaction. The reactions were performed at 140 °C in *N,N*-dimethylformamide, using $CuSO_4 \cdot 5H_2O$ and Na ascorbate as catalytic system. The reaction time was 30 min under microwave heating and 24 h in an oil bath.

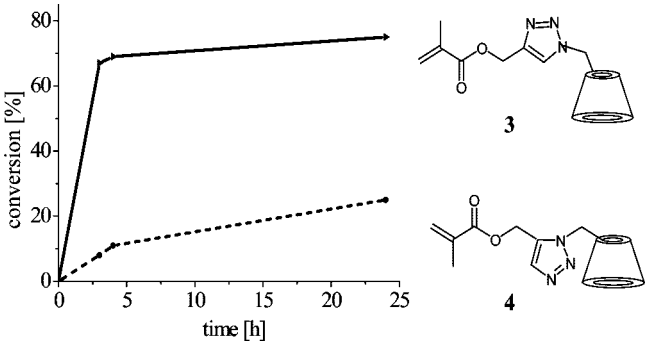


Figure 3. Regiosomeric proportion afforded by Cu-mediated cycloaddition under conventional heating. Reactions were performed in *N,N*-dimethylformamide at 140 °C.

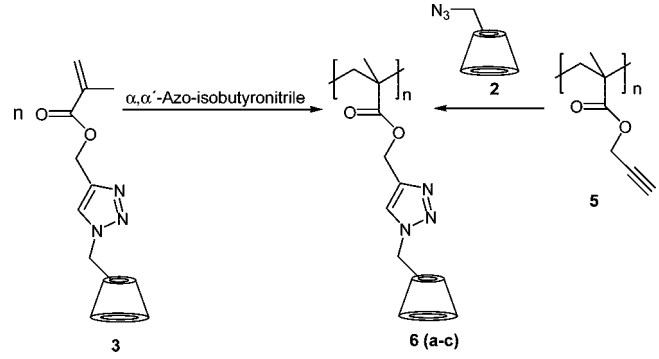


Figure 4. Homopolymerization of monoacrylate cyclodextrin monomer (**3**) and click type coupling reaction of poly(propargyl methacrylate) (**5**) with 6I-azido-6I-deoxycyclomaltoheptaose (**2**). **6a**: the polymer obtained after the coupling reaction in oil bath, in *N,N*-dimethylformamide, at 140 °C, after 30 min; **6b**: the polymer obtained after the coupling reaction under microwave heating, using similar conditions; **6c**: the polymer obtained after the free-radical polymerization of cyclodextrin methacrylate.

pursued the workup under thermal conditions. In order to explore and compare the effects induced by the microwave irradiation and the conventional heating under copper catalysis, we applied a fixed temperature for the same reaction time in both cases. We found that under conventional heating, even mediated by Cu(I), the reaction affords a mixture of 1,4- and 1,5-disubstituted regioisomers, while the tandem Cu(I) microwave assures structural control and a significant higher conversion for the same time. Furthermore, we performed the Cu(I)-mediated click reaction under reflux in MW and also in oil bath. The same reaction time was achieved by preheating the solvent under conventional reflux conditions. A higher conversion of 87% was obtained under microawe irradiation in comparison with 62% obtained under conventional heating. By comparing the results obtained under different reaction conditions (microwave, oil bath, and room temperature, with or without catalyst), we can conclude that the synergy Cu(I) microwave assured the highest conversion in compound **3** with a significant decrease in reaction time (Figure 2).

Attempts to polymerize the monomethacrylate cyclodextrin (**3**) resulted only in water-soluble oligomers (**6**) ($M_n = 1.30 \times 10^4$ g mol^{-1}, PD = 1.4, MALDI-TOF: m/z 9150.1 [M + Na^+]). The reason for the low molecular weight may be due to the bulky cyclodextrin ring. Thus, a polymer analogous coupling of 6I-azido-6I-deoxycyclomaltoheptaose (**2**) onto poly(propargyl methacrylate) (**5**) was carried out (Figure 4). Since atom transfer radical polymerization (ATRP) of propargyl methacrylate was reported to result in high polydispersities (PD > 3) and cross-linked networks,[26] we used classical free-radical-initiated polymerization in dioxane. The obtained polymer ($M_n = 1.04 \times 10^5$ g mol^{-1}, PD = 1.6) was completely soluble in *N,N*-dimethylformamide.

The coupling reaction of **2** onto **5** was monitored by IR and NMR spectroscopy. The successful reaction was confirmed by

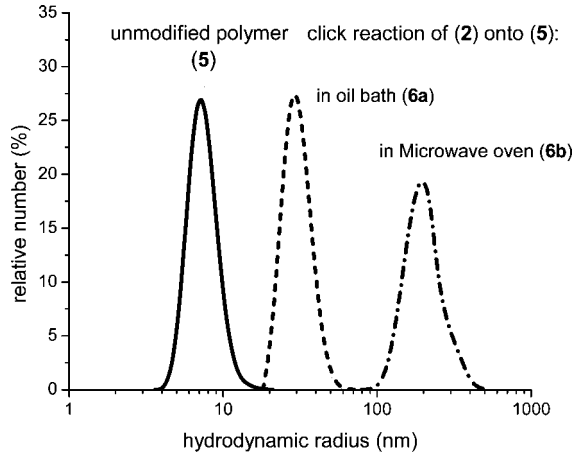


Figure 5. Hydrodynamic volumes of polymer **5** in *N*,*N*-dimethylformamide solution before and after coupling with **2** under conventional reflux conditions (**6a**) and MW irradiation (**6b**) (polymer concentration = 10 g/L, 25 °C).

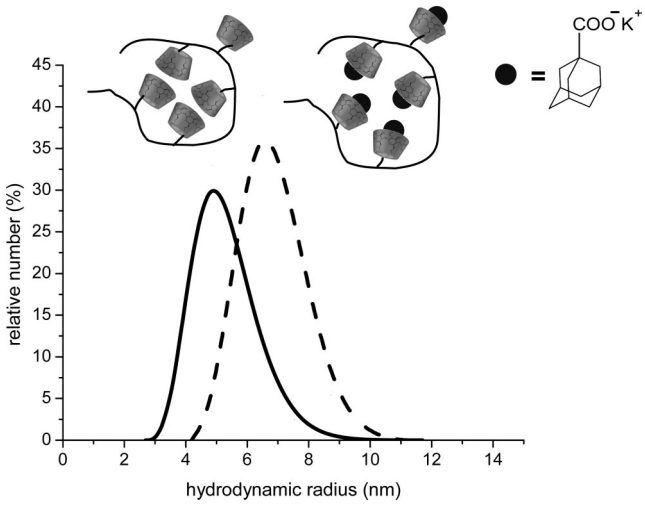
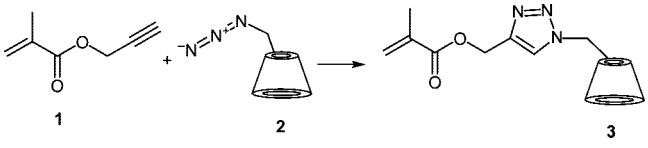


Figure 6. Hydrodynamic volume of poly(methacrylate cyclodextrin) (**6c**) in *N*,*N*-dimethylformamide solution before (—) and after (- - -) complexation with guest molecules (polymer concentration = 10 g/L, 25 °C).

Scheme 1. Synthesis of Triazol-CD-Monomer (3) via "Click Chemistry"



disappearance of the specific IR bands for azide and C≡CH bonds at 2100 and 2135 cm^{-1} and the presence of the peaks for the hydroxyl groups of cyclodextrin at 3317 cm^{-1} as well as of the new peaks at 1558 and 1387 cm^{-1}, indicating the appearance of N−H and C−N bonds. The presence of the triazole ring was also confirmed by NMR spectroscopy at 8.13 ppm.

The size of polymers **6a** and **6b** was investigated in *N*,*N*-dimethylformamide solution by DLS measurements. As expected, the hydrodynamic radius increased significantly after the cycloaddition of **2** onto poly(propargyl methacrylate) (**5**). Surprisingly, however, the yield of the product resulted after microwave coupling reaction was significantly higher compared to conventional coupling under oil bath conditions (Figure 5).

DLS measurements were also carried out for poly(monomethacrylate cyclodextrin) (**6c**) in DMF solution. The low hydrodynamic radius (5 nm) suggests intrachain interactions due to cyclodextrin units. By repeating the measurement using adamantyl carboxylate as guest molecules, we noticed a slightly increased hydrodynamic radius (6 nm), which can be the result of electrostatic repulsion between the carboxylate groups and because of reducing the H-bonds interaction between the dimerized cyclodextrin rings (Figure 6). Similar results were obtained by exposure to LiCl (10%) as a consequence of breaking the intrachain H-bond interactions.

Conclusions

On the basis of the advantages conferred by the MW-assisted Cu-catalyzed "click reaction", we developed an elegant and efficient approach for the synthesis of polymerizable cyclodextrin monomethacrylate, under complete structural control and with an important decrease in the reaction time. IR and NMR measurements correlated with DLS investigations confirmed the polymerization of cyclodextrin monomethacrylates as well as the coupling of 6I-azido-6I-deoxycyclomaltoheptaose (**2**) with the acetylene units placed onto poly(propargyl methacrylate) (**5**). The resulting polymer with a significant content of covalently attached cyclodextrins has potential applications in supramolecular chemistry, drug delivery, and analytics.

Acknowledgment. Financial support by the Deutsche Forschungsgemeinschaft is gratefully acknowledged (DFG, Project RI 410/33-3).

References and Notes

(1) Kretschmann, O.; Steffens, C.; Ritter, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 2708–2711.
(2) Koopmans, C.; Ritter, H. *J. Am. Chem. Soc.* **2007**, *129*, 3502–3504.
(3) Kretschmann, O.; Choi, S. W.; Miyauchi, M.; Tomatsu, I.; Harada, A.; Ritter, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 4361–4365.
(4) Köllisch, H.; Barner-Kowollik, Ch.; Ritter, H. *Macromol. Rapid Commun.* **2006**, *27*, 848–853.
(5) Schmitz, S.; Ritter, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 5658–5661.
(6) Ohga, K.; Takashima, Y.; Takahashi, H.; Kawaguchi, Y.; Yamaguchi, H.; Harada, A. *Macromolecules* **2005**, *38*, 5897–5904.
(7) Harada, A.; Hashidzume, A.; Takashima, Y. *Adv. Polym. Sci.* **2006**, *201*, 1–43.
(8) Wenz, G. *Angew. Chem., Int. Ed.* **1994**, *33*, 803–822.
(9) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, 2004–2021.
(10) (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem.* **2002**, *114*, 2708–2711. (b) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596–2599.
(11) Chittaboina, S.; Xie, F.; Wang, Q. *Tetrahedron Lett.* **2005**, *46*, 2331–2336.
(12) Breinbauer, R.; Köhn, M. *ChemBioChem* **2003**, *4*, 1147–1149.
(13) Gupta, S. S.; Raja, K. S.; Eiton, K. S.; Kaltgrad, E.; Strable, E.; Finn, M. G. *Chem. Commun.* **2005**, 4315–4317.
(14) Wang, Q.; Chan, T. R.; Hilgraf, R.; Fokin, V. V.; Sharpless, K. B.; Finn, M. G. *J. Am. Chem. Soc.* **2003**, *125*, 3192–3193.
(15) Kolb, H. C.; Sharpless, B. *Drug Discovery Today* **2003**, *8*, 1128–1137.
(16) Huisgen, R. *Angew. Chem., Int. Ed.* **1963**, *2*, 565–598.
(17) Tornoe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057–3064.
(18) Kaval, N.; Ermolat'ev, D.; Appukkuttan, P.; Dehaen, W.; Kappe, O.; Van der Eycken, E. *J. Comb. Chem.* **2005**, *7*, 490–502.
(19) Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Noodleman, L.; Sharpless, B. K.; Fokin, V. V. *J. Am. Chem. Soc.* **2005**, *127*, 210–216.
(20) Perez-Balderas, F.; Ortega-Munoz, M.; Morales-Sanfrutos, J.; Hernandez-Mateo, F.; Calvo-Flores, F. G.; Calvo-Asin, J. A.; Isac-Garcia, J.; Santoyo-Gonzalez, F. *Org. Lett.* **2003**, *5*, 1951–1954.
(21) Ortega-Muñoz, M.; Morales-Sanfrutos, J.; Perez-Balderas, F.; Hernandez-Mateo, F.; Giron-Gonzalez, M. D.; Sevillano-Tripero, N.; Salto-Gonzalez, R.; Santoyo-Gonzalez, F. *Org. Biomol. Chem.* **2007**, *5*, 2291–2301.

(22) Chan, T. R.; Hilgraf, R.; Sharpless, K. B.; Fokin, V. V. *Org. Lett.* **2004**, *6*, 2853–2855.
(23) Hoogenboom, R.; Moore, B. C.; Schubert, U. S. *Chem. Commun.* **2006**, *38*, 4010–4012.
(24) Barr, L.; Lincoln, S.; Easton, C. *J. Supramol. Chem.* **2005**, *17*, 547–555.
(25) Harada, A.; Furue, M.; Nozakura, S. *Macromolecules* **1976**, *9*, 701–704.
(26) Sumerlin, B. S.; Tsarevsky, N. T.; Louche, G.; Lee, R. Y.; Matyjaszewski, K. *Macromolecules* **2005**, *38*, 7540–7545.

MA8018975