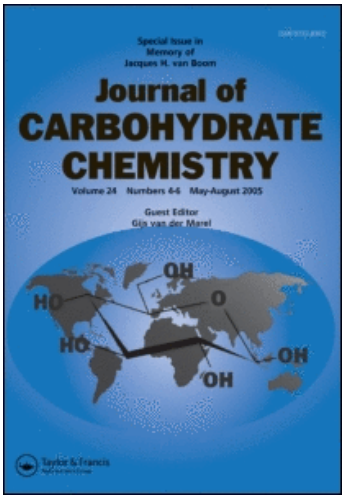


Journal of Carbohydrate Chemistry

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

Synthesis and Polymerization of Carbamate-Linked Cyclodextrin Methacrylate Monomers

Frank Bachmann[a]; Jens Höpken[b]; Rachel Kohli[b]; Dieter Lohmann[b]; Josef Schneider[c]
[a] Ciba Spezialitätenchemie Grenzach GmbH, [b] Ciba Vision Novartis, Basel [c] Novartis Pharma AG, Basel

To cite this Article Bachmann, Frank , Höpken, Jens , Kohli, Rachel , Lohmann, Dieter and Schneider, Josef(1998) 'Synthesis and Polymerization of Carbamate-Linked Cyclodextrin Methacrylate Monomers', Journal of Carbohydrate Chemistry, 17: 9, 1359 — 1375
To link to this Article: DOI: 10.1080/07328309808002359
URL: http://dx.doi.org/10.1080/07328309808002359

J. CARBOHYDRATE CHEMISTRY, 17(9), 1359-1375 (1998)

SYNTHESIS AND POLYMERIZATION OF CARBAMATE-LINKED CYCLODEXTRIN METHACRYLATE MONOMERS

Frank Bachmann,[1]* Jens Höpken,[2] Rachel Kohli,[2]
Dieter Lohmann,[2] Josef Schneider[3]

1. Ciba Spezialitätenchemie Grenzach GmbH, Postfach D-79630 Grenzach-Wyhlen
2. Ciba Vision Novartis, Postfach, CH-4002 Basel
3. Novartis Pharma AG, Postfach, CH-4002 Basel

Received December 30, 1997 - Final Form July 22, 1998

ABSTRACT

A one-step synthesis for cyclodextrin methacrylate monomers was examined starting from α-, β- and γ-cyclodextrin. The reaction of 2-isocyanatoethyl methacrylate as well as allylisocyanate with the corresponding cyclodextrin gave the monofunctionalized carbamate-linked cyclodextrin methacrylates **2**, **6** and **9** and allylcarbamates **11** and **14** in moderate yields. By NMR spectroscopic means, it could be proven that in all cases only the primary 6-hydroxyl groups of the cyclodextrins reacted with the isocyanate group. For the synthesis of a β-cyclodextrin monoallyl compound, a substitution reaction of purchasable 6-*O*-monotoluenesulfonyl-β-cyclodextrin with allylamine gave 6-*N*-allylamino-6-deoxy-β-cyclodextrin **18** in high yield. The reaction of 2-isocyanatoethyl methacrylate with α-cyclodextrin to the 6-*O*-carbamoyl-2-methylpropenoylethyl-α-cyclodextrin (**2**) was optimized so that the monomer **2** could be prepared on a larger scale without chromatographic separation. The aqueous radical homopolymerization of **2** with the peroxodisulfate/bisulfite redox initiator gave the water soluble cyclodextrin polymer **19** in good yield. Its molecular weight was determined by gel permeation chromatography to be M_n = 101,800 corresponding to an average degree of polymerization P_n = 90.

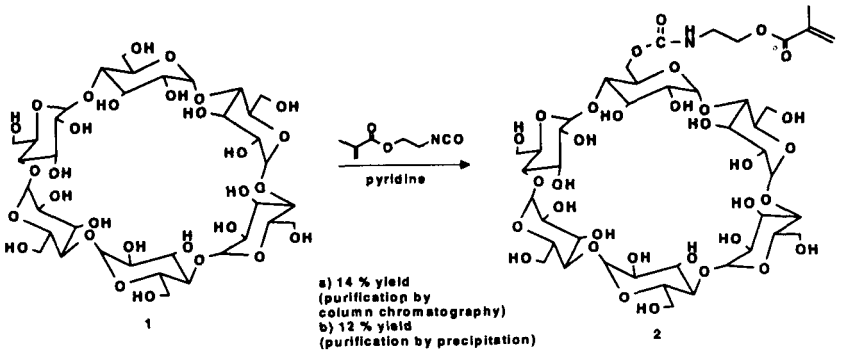
INTRODUCTION

Cyclodextrins (CD's) are cyclic oligosaccharides composed of α-1,4-linked glucopyranose residues; most common are the derivatives with six (α-CD), seven (β-CD) and eight (γ-CD) glucose units in the main chain.

The synthesis of selectively modified polymerizable cyclodextrin derivatives has become a field of considerable importance during the last decade. The synthesis of CD monomers and polymers are of interest because the unique properties of CD - especially the ability to include organic molecules into their hydrophobic cavity - may lead to novel polymeric materials. Furthermore, the modification of surfaces with CD residues may be achieved by radical polymerization of suitable vinyl derivatives.

In order to obtain CD-polymers, various synthetic routes have been developed. Nozakura[1] and Croft[2] synthesized several acrylic esters of α- and β-CD by reaction of *m*-nitrophenyl acrylate with the corresponding CD-derivative. The preparation of a permethacrylated β-CD derivative with methacrylic anhydride was reported by Bowen.[3] Vetter[4] prepared numerous vinyl esters of CD derivatives by reaction of divinyl esters of dicarbonic acids with CD in aqueous buffered solution. The acylation reactions of those activated esters occur regioselectively at the secondary 2-OH or 3-OH position probably mediated by partial inclusion of the divinylates. Several monofunctionalized CD-monomers substituted at the primary 6-OH position were prepared by reaction of 6-amino-6-deoxy-β-CD with acrylic acid derivatives[5] or by substitution reaction of commercially available 6-*O*-toluenesulfonyl-β-CD with allyl amine.[6] Similarly, the synthesis of a polyvinylamine with a CD side chain[7] was performed. The synthesis of CD-monomers could also be accomplished via synthesis of suitably protected CD derivatives.[8,9,10] The preparation of CD-polymers was reviewed by Szejtli.[11] Quite recently, several novel syntheses of CD-polymers were published, for example CD-polyrotaxanes,[12,13] water soluble polymers made by polycondensation with epichlorohydrin[14] as well as a β-CD-2-hydroxyethyl methacrylate copolymer.[15]

We studied the reaction of unprotected carbohydrates with isocyanates carrying a polymerizable group.[6,16,17] 2-Isocyanatoethyl methacrylate (IEM) is readily available and often used in the synthesis of polymethacrylates. This report describes the results of the



Scheme 1

reaction of α-, β- and γ-CD with the unsaturated isocyanates IEM and allyl isocyanate and some preliminary results on the radical polymerization of the resulting CD monomers.

RESULTS AND DISCUSSIONS

Synthesis of CD monomers. There are numerous reports on the application of isocyanates carrying a polymerizable vinyl group in the synthesis of carbohydrate monomers. Due to the higher reactivity of isocyanato groups to amino functions as compared to hydroxylic functions, the reaction of the aminosaccharides D-glucamine and D-glucosamine with IEM as reported by Bamford et al.[18] proceeded selectively to the monofunctionalized derivatives.

Several methacrylate derivatives with urea linkages were prepared by Klein et al.[19,20,21] mostly by reactions in aqueous solutions.

In the absence of amino groups, the difference in the reactivity of the primary hydroxylic groups in contrast to the secondary hydroxylic functions can be utilized for the preparation of monofunctionalized derivatives. We reacted common mono- and disaccharides with IEM in an organic medium. With pyridine as a solvent, for example, the corresponding monofunctionalized derivatives containing a carbamate linkage were obtained in yields of up to 60 %.[22]. The reaction of one molar equivalent of IEM with α-CD in pyridine gave the monofunctionalized derivative **2** as the main product (Scheme 1).

With regard to the six primary hydroxyl groups present, the reaction proceeded with remarkable selectivity in comparatively good yields (14 %) with the di- and trifunctionalized derivatives **3** and **4** as by-products. In comparison, the reaction of the non-cyclic hexasaccharide maltohexaose with IEM gave only complex mixtures. The isolation of monomethacrylate **2** could be performed by column chromatography using acetonitrile/water mixtures. Alternatively, a purification of **2** without chromatography was accomplished. A repeated precipitation using the solvents toluene, acetone and acetonitrile furnished the pure compound **2**. The isolated yield for **2** was low but during work-up most of the starting material could be recovered. Although di- and trisubstitution of the CD-molecule inevitably led to by-products, our isolation process allowed a comparatively simple scale-up. Through scale-up of the reaction 100 g amounts of pure **2** - an attractive water soluble CD monomer - became easily available in a one-step procedure without use of protective groups.

The reaction of β-CD with IEM as claimed in a Japanese patent[23] proceeded in a similar manner and gave the monomethacryloylethyl carbamate **6** which is soluble in DMF or DMSO but, in contrast to **2**, not soluble in water. As by-products the di- and trifunctionalized derivatives **7** and **8** were formed so that column chromatography had to be applied to separate the mixtures.

NMR studies on the cyclodextrin methacryloyloxyethyl carbamates synthesized revealed that exclusively the primary 6-hydroxyl group was carbamoylated. This is remarkable because inclusion of the isocyanate into the hydrophobic cavity of the CD followed by carbamoylation would favour a reaction with the secondary OH groups. For example, the reaction with methacryloyl chloride and α-CD occurred at the secondary OH-2.[1,2] In the esterification of CD with divinylesters,[4] the acylation took place at the secondary OH functions. The structures of the carbamates **2**, **3**, **6** and **7** were investigated by 2D-NMR spectroscopy. The ^{1}H NMR spectra of α-CD monocarbamate **2** and β-CD monocarbamate **6** are shown in the Figures 1 and 2.

The ^{1}H NMR data of the cyclodextrin 2-methacryloyloxyethyl carbamates **2**, **3** and **6** compared to β-CD[24] are listed in Table 1. All hydrogen signals of the CD saccharide protons and of the monomethacryloxyethylcarbamate residue could be clearly assigned. The formation of the carbamate disturbs the symmetry of the CD molecule. The chemical

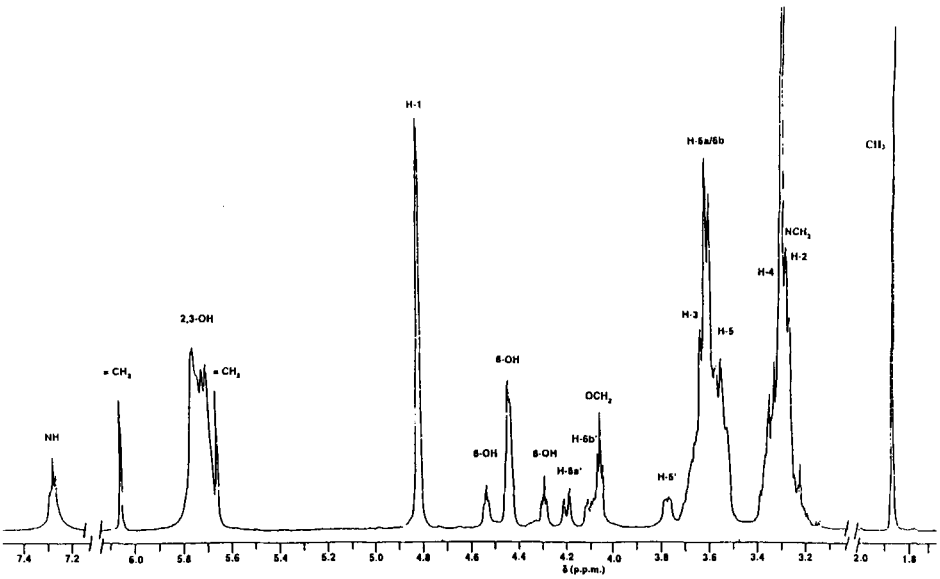


Figure 1. ^{1}H NMR spectrum of α-CD methacrylate monomer **2** in DMSO-d_6

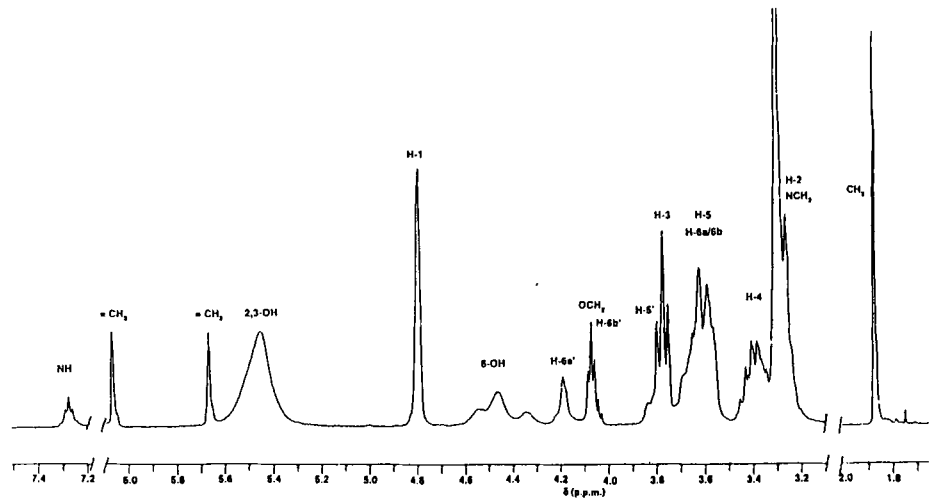


Figure 2. ^{1}H NMR spectrum of β-CD methacrylate monomer **6** in DMSO-d_6

TABLE 1. ^{1}H NMR Data of α- and β-cyclodextrin carbamates **2**, **3**, and **6** in DMSO-d_6

Compound	2	3	6	β-CD(5)[24]
	Chemical Shift (δ/ppm)			
H-1	4.81	4.80	4.82	4.81
H-2	3.28	3.26	3.28	3.29
H-3	3.75	3.75	3.60	3.65
H-4	3.40	3.40	3.32	3.36
H-5	3.58, **3.82**	3.59, **3.82**	3.55, **3.78**	3.54
H-6a,6b	3.60, **4.05, 4.18**	3.60, **4.05, 4.18**	3.60, **4.05, 4.18**	3.55,3.64
NH	7.28	7.25 - 7.35	7.28	
NCH_2	3.25	3.24	3.25	
OCH_2	4.08	4.08	4.05	
$=CH_2$	5.67, 6.06	5.68, 6.07	5.66, 6.05	
CH_3	1.85	1.87	1.85	
2,3-OH	5.30 - 5.60	5.50 - 5.65	5.60 - 5.80	
6-OH	4.30, 4.46, 4.55	4.30, 4.45, 4.55	4.30, 4.43, 4.74	

a. significant chemical shifts in bold are the protons from the glucopyranose unit linked with the IEM residue

shifts of H-1, H-2, H-3 and H-4 are nearly identical with those for pure β-CD. The carbamate formation at the 6-OH group was indicated by the significant chemical shifts of H-5 and H-6a/H-6b. Whereas in non-substituted glucopyranose units the signals for H-5 and H-6a/6b appear between 3.5 - 3.6 ppm, the signals of H-5', H-6a' and H-6b' of the glucopyranose unit bearing the carbamate show a downfield shift of Δδ 0.2 ppm for H-5' and approximately Δδ 0.5 - 0.6 ppm for H-6a' and H-6b'. The methacrylate group gave the characteristic signals at 5.67 and 6.06 ppm for the double bond, the methylene groups were located at 3.25 and 4.08 ppm. The deuterium exchangeable signals between 4.30 and 4.60 ppm were assigned to the 2,3-hydroxyl groups, the 6-hydroxyl groups were found at 4.30 and 4.70 ppm. The ^{1}H NMR spectra of the monocarbamate **2** and the dicarbamate **3** are very similar. Only the primary 6-OH hydroxyl groups were able to react with the isocyanate. Therefore the integration of the 6-OH or the H-5' signals led to a reliable conclusion on the degree of substitution. For all bis- and triscarbamates numerous regioisomers are possible but cannot be differentiated by NMR spectroscopy.

From the ^{13}C NMR data (Table 2), the assumed structures could be confirmed. The ^{13}C NMR signals for C-1, C-2, C-3, C-4 were nearly identical to β-CD, a downfield

TABLE 2. ^{13}C NMR Data of α- and β-cyclodextrin carbamates **2, 3, 6, 7** in DMSO-d_6

Compound	2	3	6	7	β-CD (5) [24]
	Chemical Shift (δ/ppm)				
C-1	102.1	102.0	102.0	101.0	102.0
C-2	72.0	72.1	72.5	72.0	72.5
C-3	73.2	73.2	73.1	72.8	73.1
C-4	82.2	82.1	81.5	81.0	81.6
C-5	72.2, **69.4**	72.2, **69.2**	72.2, **69.3**	72.2, **69.0**	72.1
C-6	60.2, **63.4**	60.1, **63.2**	60.0, **63.2**	59.7, **63.2**	60.0
O**C**ONH	165.2	167.9	166.4	166.4	
N**C**H_2	39.5	39.4	39.2	39.0	
O**C**H_2	63.4	63.3	63.4	63.2	
CO_2	171.0	171.0	171.4	171.0	
=**C**H_2	126.3	126.0	126.0	125.7	
CH_3	18.1	17.9	18.1	18.0	
C=CH_2	134.2	134.2	135.6	135.6	

a. significant chemical shifts in bold are the carbons from the glucopyranose unit linked with the IEM residue

shift Δδ = 3.5 ppm for C-6' and a simultaneous upfield shift Δδ = - 3.0 ppm for C-5' were observed.

The reaction of γ-CD with IEM was also successfully accomplished to yield the monofunctionalized carbamate **9.** After chromatographic separation **9** was isolated in 20 % yield. As a side product, the dicarbamate **10** was obtained.

The reaction of IEM with hydroxypropyl-β-cyclodextrin led to complex mixtures. A mass spectroscopic investigation of the reaction mixture showed the formation of the mono- and difunctionalized vinyl derivatives. A preference of the hydroxypropyl group towards other primary groups of the CD was not observed under the conditions used, therefore a preparative isolation was not performed.

Similarly, the introduction of one allyl group can be performed by reaction with allylisocyanate. The reaction of allylisocyanate with α-CD furnished the monoallyl derivative **11** in 18 % yield; small amounts of bis- and trisallyl-functionalized derivatives **12** and **13** could be isolated as by-products. With β-CD low selectivities and low yields of the corresponding allyl CD derivatives **14, 15** and **16** were obtained. For the preparation

of an allyl β-CD derivative the substitution reaction of commercially available mono-*O*-(*p*-toluenesulfonyl)-β-CD **17** with allylamine was clearly favoured and gave the 6-*N*-allylamino-6-deoxy-β-CD **18** in 86 % yield.

All CD monomers synthesized were isolated as colourless hygroscopic solids without a sharp melting point. Satisfactory elemental analysis could be obtained by previous equilibration and subsequent determination of water. The thermal behaviour was investigated by DSC. Around 100 °C, most compounds showed an endothermic peak probably due to loss of water. Above 150 °C, a gradual decomposition took place. All synthesized cyclodextrin monomers are shown in Scheme 2.

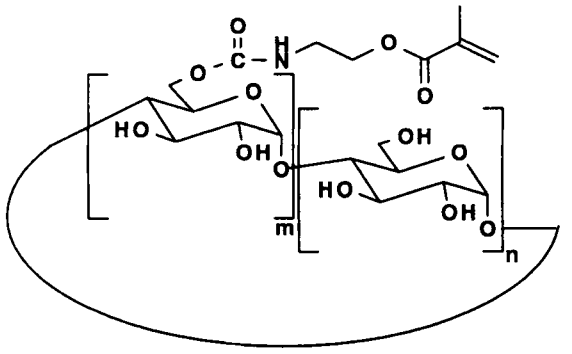
Polymer synthesis. The mono-functionalized derivatives **2**, **6** and **9** are suitable monomers for radical homopolymerizations. The bis-substituted derivatives **3**, **7** and **10** are considered to be used as hydrophilic crosslinkers in the synthesis of hydrogels. The allyl derivatives **11**, **14** and **18** represent attractive monomers for copolymerization reactions. Copolymerizations have been performed with monomers important in technical applications such as hydroxyethyl methacrylate (HEMA), acrylamide and other well-known hydrogel-forming comonomers; the results will be published elsewhere.

The optimum reaction conditions for radical homopolymerization of α-CD monomer **2** were found to be in aqueous solution at room temperature with the redox initiator system ammonium peroxodisulfate/sodium disulfite (Scheme 3).

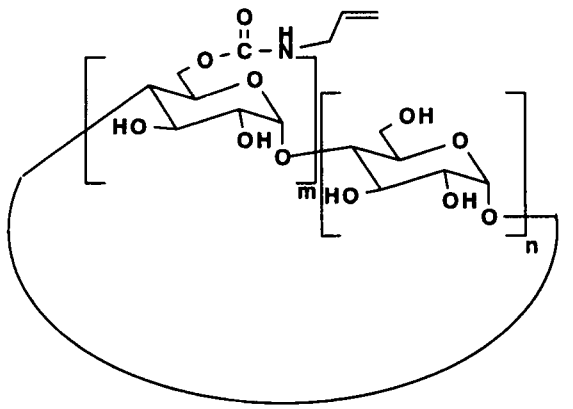
The polymerization reactions had to be performed under strict exclusion of oxygen. The resulting polymer **19** was isolated by precipitation in methanol. A further purification was performed by dissolving the primary precipitate in water, followed by micro-filtration and subsequent lyophilisation. The polymethacrylate **19** is water-soluble and partially soluble in polar aprotic solvents such as DMSO. It is insoluble in organic solvents such as toluene or chloroform.

β-CD methacryloyloxyethyl carbamate **6** is not water-soluble, therefore it has to be polymerized in organic solvents. With the initiator azo-isobutyronitrile (AIBN) in DMF, some oligomeric material **20** was detected by GPC which was not further characterized.

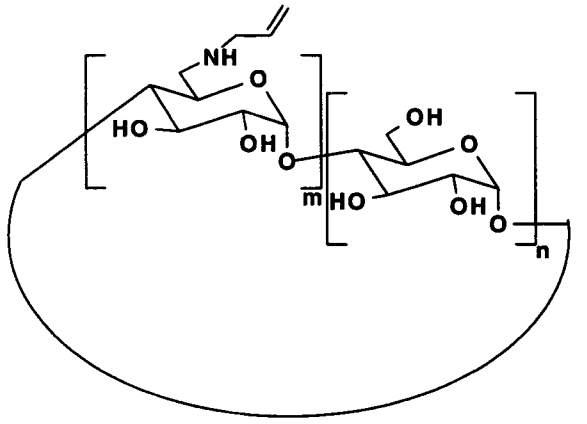
The radical homopolymerization of γ-CD methacryloyloxyethyl carbamate **9** using similar reaction conditions for the monomer **2** also gave oligomers only in low yields.



	Compound	Yield
m = 1, n = 5	2	14
m = 2, n = 4	3	11
m = 3, n = 3	4	1
m = 1, n = 6	6	11
m = 2, n = 5	7	21
m = 3, n = 4	8	4
m = 1, n = 7	9	20
m = 2, n = 6	10	3

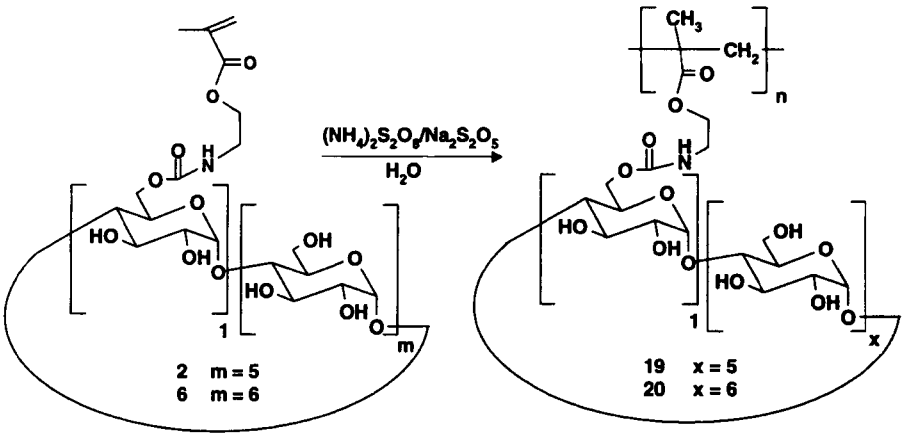


m = 1, n = 5	11	18
m = 2, n = 4	12	3
m = 3, n = 3	13	2
m = 1, n = 6	14	7
m = 2, n = 5	15	8
m = 3, n = 4	16	6



m = 1, n = 6	18	86

Scheme 2



Scheme 3

Table 3: Molecular weights of synthesized CD-containing polymers

Compound	M_w	M_n	U (M_w/M_n)	P_n
19	921,000	101,800	9.04	90
20	2,680	2,100	1.28	<3

*Amount of redox initiator for all polymerizations: 0.1 mg $(NH_4)_2S_2O_8/Na_2S_2O_5$/100 mg saccharide

After 12 hours reaction time (even with higher amounts of catalyst (up to 5 mg/100 mg cyclodextrin), considerable amounts of monomer **9** were still found in the reaction mixture.

The molecular weight distributions and molecular weights were measured by GPC using a light scattering detector. The results are listed in Table 3.

Generally, the homopolymerization of a methacrylate bearing a cyclodextrin moiety seemed to be worse for mono- and disaccharide derivatives[6] due to steric hindrance of the methacrylate group by the bulky cyclodextrin moiety. The molecular weights were determined by GPC combined with a multi-angle-laser-light-scattering (MALLS) detector. With the α-CD monomethacryloyloxyethyl carbamate **2**, M_n values about 100,000 were achieved. However, formation of polymer aggregates in solution could not be excluded. The dispersity of polymer **19** was found to be comparatively high (M_w/M_n = 9.0). There

are only few examples in the literature of water soluble cyclodextrin homopolymers with reported data about molecular weights. Nozakura et al.[1] homopolymerized *N*-acrylyl-6-aminocaproyl-α-cyclodextrin and obtained molecular weights M_n = 8,000 - 10,000 measured by vapour pressure osmometry.

The GPC chromatogram of the α-cyclodextrin homopolymer **19** revealed that besides the polymer fraction with a molecular weight of about 10^5 (on-line light scattering detector) a considerable amount of oligomeric material with a large dispersity (on-line RI detector) was formed. Further molecular modeling studies of the polymer conformation should give some additional information on the polymerization potential of the cyclodextrin monomers.

The use of CD methacryloyloxyethyl carbamates will be checked in further radical polymerization studies as well as UV initiated grafting onto surfaces.

EXPERIMENTAL

General methods. All reactions of low molecular weight compounds were followed using thin layer-chromatography (TLC) with silica gel foils GF_{254} (Merck) and visualized by spraying with sulfuric acid/ethanol (vol. ratio 1:5) and subsequent heating. ^1H and ^{13}C NMR spectra were recorded on Bruker spectrometer AM-250 and AM-400 with tetramethylsilane as internal standard. If necessary, the signals were assigned by 2D ^1H, ^1H ^1H-COSY and ^1H, ^{13}C -COSY (with ^1H-detection as HSQC experiment) NMR experiments. Molecular weights were determined by GPC using the following components: Shimadzu LC-9a pump, columns Zorbax PFM 60 and PFM 300 (DuPont), Wyatt Technology Optilab 903 refractive index detector, and MALLS system Wyatt Technology DAWN-F (633nm laser). Double distilled H_2O was used as solvent with a flow rate of 1.0 mL/min. DSC curves were measured with a Perkin-Elmer differential scanning calorimeter DSC-7. Optical rotations were measured with a Perkin-Elmer 241 polarimeter at 20 °C; denoted is the specific rotation $[\alpha]_D$ in the unit 100 deg g^{-1} with concentration *c* in g $100^{-1}mL^{-1}$. Mass spectrometry was performed on a Finnegan MAT 90 run in FAB mode (Xe atom bombardment at 8 keV) or by chemical ionization (Cl; 150 eV; positive mode, $(M + NH_4)^+$ ions, or negative mode, $(M + Cl)^-$. Chromatographic

separations were performed by flash technique at 2 - 4 bar with silica gel 60 (230 - 400 mesh, Merck) with the described distilled solvents (ratio of mixtures always given as volume ratios). As solvent, acetonitrile/water mixtures were used (solvent A: acetonitrile/water 9:1, solvent B: acetonitrile/water 8:2, solvent C: acetonitrile/water 7:3). For preparative separations, 0.1 vol. % saturated aqueous ammonia was added to the corresponding solvent.

6-*O*-Carbamoyl-2-methylpropenoylethyl-α-cyclodextrin (2). Procedure A: α-CD (5 g, 5.14 mmol) was suspended in pyridine (50 mL) at 40 °C and IEM (797 mg, 5.14 mmol) was added dropwise. The reaction mixture was then carefully concentrated in vacuo. After the chromatographic separation (200 g silica gel, gradient solvent A → C), the corresponding fractions containing the pure compound were collected and carefully concentrated to remove the acetonitrile. The same amount of water was added and the solution was filtered and lyophilized. The monocarbamate **2** and the di- and tricarbamate **3** and **4** were obtained as colourless hygroscopic solids (650 mg, 14 %) for **2**, (600 mg, 11 %) for **3**, (60 mg, 1 %) for **4.**

Procedure B: IEM (797 mg, 5.14 mmol) was added to a solution of α-cyclodextrin (5 g, 5.14 mmol) in pyridine (50 mL). The reaction mixture was stirred for 24 h, the suspension was filtered, with pure α-CD (3.9 g) being recovered from the filter cake. The filtrate was diluted with toluene (200 mL), a white precipitate (1.34 g) flocked out which was filtered and dried. To the dried residue dissolved in water (10 mL) was added acetone (60 mL) to give a suspension which was filtered and concentrated. The residue was dissolved in a small amount of methanol (5 mL). After addition of a few drops of acetonitrile, a white precipitate was formed which was filtered and dried (708 mg, 12.2 %), mp > 150 °C (dec.); $[\alpha]_D$ + 72.8° (*c* 1.23, water); R_f 0.24 [α-CD R_f : 0.12 (solvent B)], NMR (DMSO-d_6): s. Table 1; FAB MS *m/z* : 1126 $(M - H)^-$, 1162 $(M + Cl)^-$.

Anal. Calcd for $C_{43}H_{69}NO_{33}$ (1128.02): C, 45.79; H, 4.61; N, 1.24. Found: C 45.39, H, 4.69; N, 1.31

6,6'-Di-*O*-carbamoyl-2-methylpropenoylethyl-α-cyclodextrin (3). $[\alpha]_D$ + 41.9° (*c* 1.23, water), R_f 0.46 (solvent B); ^1H NMR (DMSO-d_6): s. Table 1; FAB MS for $C_{50}H_{78}N_2O_{36}$ (1283.16) *m/z* : 1281 $(M - H)^+$, 1317 $(M + Cl)^-$.

6,6',6''-Tri-*O*-carbamoyl-2-methylpropenoylethyl-α-cyclodextrin (4). $[\alpha]_D$ + 51.4° (*c* 1.03, water), R_f 0.60 (solvent B); FAB MS for $C_{57}H_{87}N_3O_{39}$ (1438.10) *m/z* : 1463 $(M + Na)^+$, 1475 $(M + Cl)^-$.

6-*O*-Carbamoyl-2-methylpropenoylethyl-β-cyclodextrin (6). To a solution of β-CD (**5**) (1.0 g, 0.881 mmol) in pyridine (15 mL) at 0 °C was slowly added IEM (2.74 g, 1.76 mmol). The solution was stirred for 2 days at room temperature. The resulting suspension was diluted with toluene (100 mL) and concentrated to give a white solid (26.7 g). The residue was dissolved in acetonitrile/water/methanol 1:1:1 (30 mL) and separated by chromatography (silica gel 2 kg, solvent B) to obtain monomethacrylate **6** (1.24 g, 11 %), bismethacrylate **7** (2.63 g, 21 %) and trismethacrylate **8** (0.6 g, 4 %); mp > 150 °C (dec.); $[\alpha]_D$ + 162.8° (*c* 0.81, dimethyl sulfoxide); R_f 0.16 (solvent B); NMR data s. Table 1 and 2; FAB MS *m/z* : 1290 $(M - H)^+$.

Anal. Calcd for $C_{49}H_{79}NO_{38}$ (1290.16): C, 45.62; H, 6.17; N, 1.09. Found: C 45.89, H, 6.26; N, 1.11

6,6'-Di-*O*-carbamoyl-2-methylpropenoylethyl-β-cyclodextrin (7). $[\alpha]_D$ + 87.7° (*c* 1.36, dimethyl sulfoxide); R_f 0.32 (solvent B), FAB MS for $C_{56}H_{88}N_2O_{41}$ (1445.31) *m/z* :1445 $(M)^+$, 1622 $(M + Na - H)^+$.

6,6',6''-Tri-*O*-carbamoyl-2-methylpropenoylethyl-β-cyclodextrin (8): $[\alpha]_D$ + 87.7° (*c* 0.59, dimethyl sulfoxide); R_f 0.47 (solvent B); FAB MS for $C_{63}H_{97}N_3O_{44}$ (1600.47) *m/z* : 1600 $(M)^+$, 1622 $(M + Na - H)^+$.

6-*O*-carbamoyl-2-methylpropenoylethyl-γ-cyclodextrin (9). To a solution of γ-cyclodextrin (20 g, 15.4 mmol) in pyridine (250 mL) at room temperature was slowly added IEM (7.2 g, 46.25 mmol) and the solution was stirred for two days. The resulting slightly muddy brown solution was filtered and diluted with toluene (300 mL). A nearly colourless solid precipitated which was filtered and dried at 40 °C in vacuo. The raw product obtained (30 g) was suspended in a mixture of water/acetonitrile. Chromatography (200 g silica gel, first 1 L of acetonitrile, then 1 L solvent A, 2 L solvent B and 2 L solvent C) of the suspension gave the pure compound **9** (4.47 g, 20 %) and some dicarbamoylated **10** (0.742 g, 3 %), mp > 200 °C (dec.); $[\alpha]_D$ = +68.9° (*c* 1.09, water); R_f 0.36 (solvent C), ^{13}C NMR (D_2O): δ = 18.5 ($\underline{C}H_3$), 40.5 ($N\underline{C}H_2$), 62.8 (C-6, $O\underline{C}H_2$),

67.0 (C-6'), 73.0 (C-5'), 74.3 - 75.7 (C-2, C-3, C-5), 81.3 (C-4), 104.3 (C-1), 128.2 (C=$\underline{C}H_2$), 136.7 ($\underline{C}$=CH_2), 158.6 ($\underline{C}$ONH), 169.8 ($\underline{C}O_2$); FAB MS *m/z* : 452 $(M)^+$.

Anal. Calcd for $C_{55}H_{89}NO_{43}$ (1452.30): C, 45.49; H, 6.18; N, 0.96. Found: C 45.69, H, 6.22; N, 1.13

6,6'-Di-*O*-carbamoyl-2-methylpropenoylethyl-γ-cyclodextrin (10). $[\alpha]_D$ + 93.8° (*c* 0.92, water); R_f 0.52 (solvent C); ^{13}C NMR (D_2O): δ = 20.3 (CH_3), 42.5 (NCH_2), 62.3 (C-6, OCH_2), 67.0 (C-6'), 73.0 (C-5'), 74.0 - 76.0 (C-2, C-3, C-5), 83.0 (C-4), 104.9 (C-1), 130.0 (C=$\underline{C}H_2$), 138.5 ($\underline{C}$=CH_2), 160.0 (CONH); FAB MS for $C_{62}H_{98}N_2O_{46}$ (1607.46) *m/z* : 1629.7 (M + Na)$^+$.

6-*O*-Allylcarbamoyl-α-cyclodextrin (11). To a stirred suspension of α-CD (20 g, 20.5 mmol) in pyridine (200 mL) allylisocyanate (4.7 g, 56.56 mmol) was added dropwise. An additional amount of allylisocyanate (1.7 g, 20.45 mol) in pyridine (50 mL) was added after 2 h. After stirring overnight the suspension was filtered, and the resulting solution was diluted with toluene (400 mL). The mother liquor was filtered, concentrated and the residue separated by chromatography to **14** to give **11** (3.9 g, 18 %), **12** (606 mg, 2.5 %) and **13** (502 mg, 2 %) as colourless solids.

Data for **11**: mp > 160 °C (dec.); $[\alpha]_D$ = +87.9° (*c* 0.84, dimethyl sulfoxide); R_f 0.15 (solvent B); ^{13}C NMR (DMSO-d_6): δ = 45.6 ($\underline{C}H_2$NH), 63.0 (C-6, O$\underline{C}H_2$), 66.8 (C-6'), 73.0 (C-5'), 74.6, 74.9, 76.6 (C-2, C-3, C-5), 84.1 (C-4), 104.6 (C-1), 118.2 (CH=$\underline{C}H_2$), 137.3 ($\underline{C}$H=CH_2), 160.7 (O$\underline{C}$ONH); EI MS for $C_{40}H_{65}NO_{31}$ (1055.95) *m/z* : 1054 (M - 2H)$^+$.

6,6'-Di-*O*-allylcarbamoyl-α-cyclodextrin (12). $[\alpha]_D$ = +104.1° (*c* 1.27, dimethyl sulfoxide); R_f 0.30 (solvent B); ^{13}C NMR (DMSO-d_6): δ = 45.1 ($\underline{C}H_2$NH), 62.4 (C-6, O$\underline{C}H_2$), 66.3 (C-6'), 72.5 (C-5'), 74.0, 74.4, 75.9 (C-2, C-3, C-5), 83.9 (C-4), 104.1 (C-1), 117.6 (CH=$\underline{C}H_2$), 136.7 ($\underline{C}$H=CH_2), 160.2 (O$\underline{C}$ONH); EI MS for $C_{44}H_{70}N_2O_{32}$ (1139.04) *m/z* : 1139 $(M)^+$, 1161 (M + Na)$^+$.

6,6',6''-Tri-*O*-allylcarbamoyl-α-cyclodextrin (13). $[\alpha]_D$ = +77.4° (*c* 1.05, dimethyl sulfoxide); ^{13}C NMR (D_2O): δ = 46.3 ($\underline{C}H_2$NH), 63.7 (C-6, O$\underline{C}H_2$), 67.5 (C-6'), 73.6 (C-5'), 75.2, 75.6, 77.1 (C-2, C-3, C-5), 85.3 (C-4), 105.0 (C-1), 118.9 (CH=$\underline{C}H_2$), 137.9 ($\underline{C}$H=CH_2), 161.3 (O$\underline{C}$ONH); EI MS for $C_{48}H_{75}N_3O_{33}$ (1222.13) *m/z* : 1222 M^+.

6-*O*-Allylcarbamoyl-β-cyclodextrin (14). To a solution of β-CD (2.0 g, 1.76 mmol) in pyridine (20 mL), a solution of allylisocyanate (293 mg, 3.52 mmol) in pyridine (2 mL) was added dropwise and the reaction mixture stirred overnight (TLC-control ether/ammonia (25 %)/2-propanol 2:3:2). The resulting yellow reaction mixture was diluted with toluene (50 mL) and concentrated to give a yellow solid (3.3 g). The raw product was dissolved in a mixture of acetonitrile/water 1:1 (20 mL) and cleaned by column chromatography (500 g silica gel, solvent acetonitrile/water 5:1) to give **14** (140 mg, 7 %), **15** (192 mg, 8 %) and **16** (154 mg, 6 %) as colourless solids;

Data for **14**: mp > 160 °C (dec.); $[\alpha]_D$ = + 73.8° (*c* 0.84, dimethyl sulfoxide); R_f 0.39 (solvent C); ^{13}C NMR (DMSO-d_6): δ = 42.6 ($\underline{C}H_2NH$), 59.9 (C-6), 63.3 (C-6'), 69.3 (C-5'), 72.0 (C-2), 72.2 (C-5), 73.0 (C-3), 81.8 (C-4), 102.0 (C-1), 115.0 (CH=$\underline{C}H_2$), 135.5 ($\underline{C}H$=CH_2), 161.0 (O$\underline{C}$ONH); FAB MS for $C_{46}H_{75}NO_{36}$ (1218.10) *m/z* : 1240 (M + Na)$^+$, 1348 (M + Na + thioglycerin)$^+$.

6,6'-Di-*O*-allylcarbamoyl-β-cyclodextrin (15). $[\alpha]_D$ + 104.1° (c 1.27, water), R_f 0.43 (solvent C), FAB MS for $C_{50}H_{80}N_2O_{37}$ (1301.19) *m/z* : 1302 (M + H)$^+$, 1324 (M + Na)$^+$, 1410 (M + thioglycerin)$^+$, 1432 (M + Na + thioglycerin)$^+$.

6,6',6''-Tri-*O*-allylcarbamoyl-β-cyclodextrin (16). $[\alpha]_D$ + 77.4° (*c* 1.05, water), R_f 0.53 (solvent C), FAB MS for $C_{54}H_{85}N_3O_{38}$ (1384.28) *m/z* : 1385 (M)$^+$, 1407 (M + Na)$^+$, 1515 (M + Na + thioglycerin)$^+$.

6-*N*-Allylamino-6-deoxy-β-cyclodextrin (18). A solution of 6-mono-*O*-(*p*-toluenesulfonyl)-β-CD **17**[25] (2.0 g, 1.55 mmol) in allylamine (20 g, 0.355 mol) was stirred for 4 h at 70 °C. The resulting yellow solution was cooled to room temperature and diluted with methanol (20 mL). After addition of acetonitrile (60 mL), a colourless solid precipitated which was filtered and dried in high vacuo (1.57 g, 86 %); mp > 200 °C (dec.); $[\alpha]_D$ + 122.0° (*c* 0.93, water); R_f 0.10 (diethyl ether/ammonia/2-propanol 5:6:6); ^{13}C NMR (DMSO-d_6): δ 51.6 ($\underline{C}H_2NH$), 59.9 (C-6), 72.0 (C-2), 72.4 (C-5), 73.0 (C-3), 81.5 (C-4), 102.0 (C-1), 115.0 (CH=$\underline{C}H_2$), 137.7 ($\underline{C}H$=CH_2); FAB MS for $C_{45}H_{75}NO_{34}$ (1174.10) *m/z* : 1174 (M)$^+$.

Poly (6-*O*-Carbamoyl-2-methylpropenoylethyl-α-cyclodextrin) (19). The polymerization had to be carried out with degassed solvents in an argon atmosphere.

Acetonitrile (20 µL) was added to a suspension of **2** (100 mg, 89 µmol) in water (200 µL). An aqueous solution of ammonium peroxodisulfate (20 µL) and sodium disulfite solution (20 µL) was used as radical initiator system. The solution was stirred for 20 h (TLC-control) and poured into an exess of methanol (40 mL). The precipitate was filtered (0.45 nm Millipore Membrane), dissolved in water and lyophilized to give a colourless powder (88 mg, 88 %); mp > 160 °C (dec.); $[\alpha]_D$ + 75.6° (*c* 1.11, water); ^{1}H NMR (D_2O) δ 0.7 -1.5 (br, m, -C-C$\underline{H}_2$), 1.8 - 2.1 (br, CH_3), (2.8 - 3.2 (br, m, H-2, NCH_2), 3.5 - 4.5 (m, br, H-3, H-4, H-5, H-6a, H-6b, H-5', H-6a', H-6b', OCH_2), 5.1 -5.3 (H-1); ^{13}C NMR (D_2O) δ 45.9 ($\underline{C}H_2NH$), 62.5 - 63.2 (C-6, O$\underline{C}H_2$), 74.6, 75.9 (C-2, C-3, C-5, C-5'), 83.8 (C-4), 104.2 (C-1), 176.0, 179.3 (O$\underline{C}$ON, O$\underline{C}$O).

The molecular weight determinations for **19** were performed with the described GPC equipment. Wyatt Technology's ASTRA software was used to calculate molecular weights from the light scattering and refractive index signals. A refractive index increment (dn/dc) of 0.136 mL/g was obtained for **19** when the "mass method" was used which is normalizing the refractive index signal to the total injected mass of the polymer. In a second calculation using the obtained dn/dc constant of 0.136 mL/g ("dn/dc method"), the total injected mass was compared with the mass calculated from the signal intensity using the calibration constant of the refractive index detector. The deviation was found to be below 3 %. $(C_{43}H_{69}NO_{33})_n$ $(1128.01)_n$; M_w = 921,100, M_n = 101,800, M_w/M_n = 9.04.

Radical polymerization of 6-*O*-carbamoyl-2-methylpropenoyl-β-cyclodextrin (6). Azoisobutyronitrile (10 mg) was added to a solution of 6-*O*-carbamoyl-2-methyl-propenoylethyl-β-cyclodextrin (**6**) (100 mg, 0.077 mmol) in anhydrous dimethylformamide (600 µL). Argon was passed through the solution and the reaction mixture was heated to 75 °C and stirred overnight. The resulting yellow solution was poured into methanol (100 mL), the colourless precipitate (7 mg, 7 %) was filtered and dried. $(C_{49}H_{79}NO_{38})_n$ $(1290.16)_n$; M_w = 2680, M_n = 2100, M_w/M_n = 1.28.

REFERENCES AND NOTES

1. A. Harada, M. Furue and S. Nozakura, *Macromolecules*, **9**, 701 (1976).
2. A. P. Croft, *Tetrahedron*, **39**, 1425 (1976).
3. R. L. Bowen, *Polym. Prepr.*, **38**, 98 (1997).

4. D. Vetter, EP 624166, *Chem. Abstr.*, **123**:202724h (1994).
5. S. Lincoln, J. Coates, C. Easton, S. Van Eyk, B. May, P. Singh, M. Williams and M. Stile, WO 9002141, *Chem. Abstr.*, **114**:88647 (1989).
6. F. Bachmann, D. Lohmann and P. Chabrecek, EP 668294, *Chem. Abstr.*, **124**:37797 (1995).
7. G. Crini, G. Torri, M. Guerrini, B. Martel, Y. Lekchiri and M. Morcellet, *Eur. Polym. J.*, **33**, 1143 (1997).
8. M. Yoshinaga, WO 9209637, *Chem. Abstr.*, **118**:41122q (1992).
9. M. Yoshinaga, WO 9118023, *Chem. Abstr.*, **117**:10191m (1991).
10. M. Yoshinaga, JP 04025503, *Chem. Abstr.*, **117**:10192n (1991).
11. J. Szejtli, Cyclodextrin Polymers in *Topics in Inclusion Sci., Cyclodextrin Technology*, Kluwer Academic. Publ. 59 (1988).
12. O. Noll and H. Ritter, *Macromol. Rapid Commun.*, **18**, 53 (1997).
13. G. Wenz, M. B. Steinbrunn and K. Landfester, *Tetrahedron*, **53** (1997) 15575.
14. E. Renard, G. Barnathan, A. Deratani and B. Sebille, *Macromol. Symp.*, **122**, 229 (1997).
15. K. Sreenivasan, *Polym. Int.*, **42**, 22 (1997).
16. F. Bachmann, D. Lohmann and P. Chabrecek, WO 9613511, *Chem. Abstr.*, **125**:88086 (1996).
17. F. Bachmann, D. Lohmann and P. Chabrecek, unpublished results.
18. C. H. Bamford, K. G. Al-Lamee, I. P. Middleton, J. Paprotny and R. Carr, *Bull. Soc. Chim. Belg.*, **99** (11), 919 (1990).
19. J. Klein, A. Haji Begli and S. Engelke, *Makromol. Chem. Rapid Commun.*, **10**, 629 (1989).
20. J. Klein, M. Kunz and J. Kowalczyk, *Makromol. Chem.*, **191**, 517 (1990).
21. J. Klein, J. Kowalcyk, S. Engelke, M. Kunz and H. Puke, *Makromol. Chem., Rap. Commun.*, **11**, 477 (1990).
22. F. Bachmann, D. Lohmann and P. Chabrecek, Poster No. P2 at the 2nd General Meeting of the Swiss Society of Biomaterials, Winterthur (1996).
23. H. Kimizuka, K. Iwata and H. Suzuki, JP 06308108, *Chem. Abstr.*, **122**:177435.
24. T. Axenrod, B. Liang, Y. He, L. Yuan and S. Bulusu, *Magn. Reson. Chem.*, **29**, 1018 (1991).
25. 6-Mono-*O*-(*p*-toluenesulfonyl)-β-CD was obtained from Cyclolab Laboratories, Budapest, Hungary.