Novel Cationic Ring-Opening Polymerization of Cyclodextrin: A Uniform Macrocyclic Monomer with Unique Character

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Summary: Cyclodextrin (CD) derivatives were found to act as uniform macrocyclic monomers for cationic ring-opening polymerization, yielding poly[(1→4)-D-glucopyranoside]s. Interestingly, as demonstrated in the polymerization of *O*-permethylated α-, β-, and γ-CDs, more strained monomer (α- > β- > γ-) proved less reactive. This finding comes from the unique molecular shape of CD; the monomer having larger cavity (γ- > β- > α-) is favorable for the polymerization. In place of ordinary initiators such as oxonium salts and MeOTf, a combination of HI with an activator of $ZnCl_2$ was found to work as the initiator effectively controlling the polymerization; the glucan obtained from *O*-permethylated γ-CD showed a unique molecular weight distribution, which has large, regular intervals corresponding to the molecular weight of the uniform macrocyclic monomer (= 1634).

Keywords: cationic polymerization; cyclodextrin; polysaccharides; ring-opening polymerization; uniform macrocyclic monomer

Introduction

A molecule of cyclodextrin (CD) has a unique cylinder-like shape; the wall consists of cyclic oligo[α-(1→4)-D-glucopyranoside], which is usually hexa-, hepta-, or octa-mers termed α, β, and γ, respectively, and the inside cavity is relatively hydrophobic in water to form inclusion complexes with various molecules.[1] Thus there have been a large number of studies using CD derivatives as host molecules, disclosing unique features of CDs, and recently, supramolecular chemistry of CDs is an attractive subject.[2] Such works are promoted by the facile availability of three CDs having different cavity sizes as well as by biochemical interest

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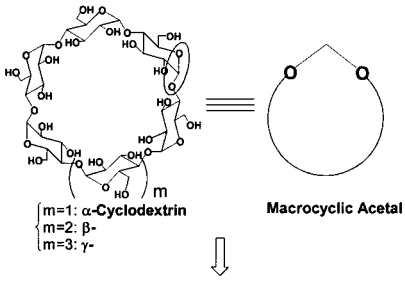
in cyclic oligosaccharides. Industrial application of CDs is also extensive especially for food, medicines, and cosmetics.[1]

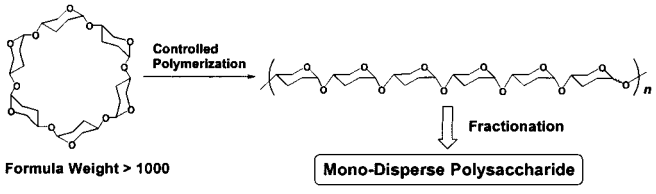
Herein, we disclose another new aspect of CD; in this study, CD derivatives are examined as uniform macrocyclic monomers for ring-opening polymerization. The glycoside bond forming CD is a kind of acetal linkage, so that CD is topologically identical to a macrocyclic acetal. Since cyclic acetal is known to be polymerizable with the aid of cationic initiators, CD could be expected to act as a macrocyclic monomer, producing linear glucan.



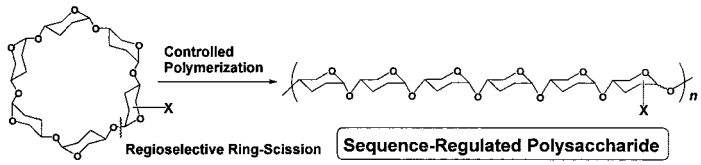
Polysaccharide has been prepared by ring-opening polymerization of sugar anhydride or orthoester as well as by enzymatic or chemical polycondensation.[3] In this project, three unique features arising from the character of CD are discussed:

1) special polymerization behavior due to the unique character of CD, which forms inclusion complexes with various molecules;

2) molecular weight distribution of the product polymer with large, regular intervals, because a CD monomer is a uniform oligomer possessing a large, exact molecular weight;

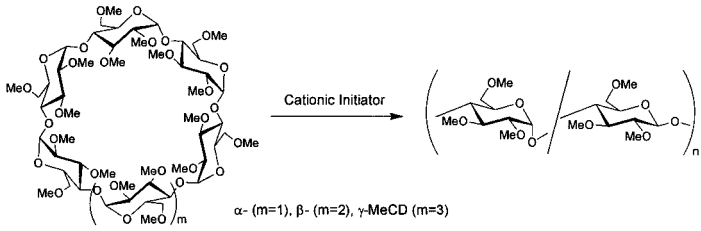


3) production of a sequentially regulated glucan, when one of the glucose components in a CD monomer is modified to achieve regioselective cleavage of the ring;



A literature survey disclosed that enzymatic and chemical ring-opening reactions of CD derivatives are known. Free CDs are converted by cyclodextrin glucanotransferase into amylose via the reverse process of the formation.[4] Restricted acetolysis or thiolysis of OH-protected CD derivatives gives the corresponding maltooligosaccharide derivatives, one of which was modified and subjected to polycondensation.[5] However, the direct chemical ring-opening polymerization of CD derivatives has never been investigated.

Ring-Opening Polymerization of *O*-Permethylated CD with Ordinary Initiator



Because the free OH groups of CD disturb the cationic polymerization, all of them should be transformed to inert groups. For the initial attempt, we employed *O*-permethylated CDs (MeCDs) as the monomers, since the methyl ether is the smallest protective group and its use minimizes the steric hindrance. Three MeCDs were prepared from α-, β-, and γ-CDs, respectively, and subjected to polymerization with ordinary initiators.[6] As shown in Table 1, MeCDs were found to be capable of acting as macrocyclic monomers for cationic ring-opening polymerization. Oxonium salts such as $Et_3O^+X^-$ (X = PF_6, $SbCl_6$, BF_4) and MeOTf are effective initiators in CH_2Cl_2, and a protic acid of HOTf initiates the polymerization even in a less polar solvent of toluene. Increasing the amount of the initiator from 10 mol%

Table 1. Cationic ring-opening polymerization of *O*-permethylated cyclodextrins (MeCDs) with ordinary initiators ([MeCD] = 0.1 M)

Run	MeCD	Initiator (mol%)	Solv.	Temp /°C	Time /h	Yield[a] /%	M_w[b]	M_n[b]	α-Linkage[c] /%
1	α–	Et_3OPF_6 (5)	CH_2Cl_2	r.t.	182	94	13900	5500	76
2	α–	Et_3OPF_6 (10)	CH_2Cl_2	r.t.	68	87	15000	8500	78
3	α–	Et_3OPF_6 (20)	CH_2Cl_2	r.t.	38	88	8900	5500	72
4	α–	Et_3OPF_6 (10)	CH_2Cl_2	0	63	0	-	-	-
5	β–	Et_3OPF_6 (10)	CH_2Cl_2	r.t.	18	83	20200	10100	80
6	β–	Et_3OPF_6 (20)	CH_2Cl_2	r.t.	21	91	9500	5600[d]	72
7	β–	Et_3OPF_6 (10)	CH_2Cl_2	0	135	83	30200	15700	76
8	γ–	Et_3OPF_6 (10)	CH_2Cl_2	r.t.	21	95	19400	9800	76
9	α–	Et_3OSbCl_6 (10)	CH_2Cl_2	r.t.	39	71	8900	5600	73
10	β–	Et_3OSbCl_6 (10)	CH_2Cl_2	r.t.	19	89	10500	6400	80
11	β–	Et_3OBF_4 (10)	CH_2Cl_2	r.t.	40	83	21200	11700	74
12	γ–	Et_3OBF_4 (10)	CH_2Cl_2	r.t.	18	75	16100	8900	-
13	α–	MeOTf (5)	CH_2Cl_2	r.t.	64	46	9200	4900	88
14	α–	MeOTf (10)	CH_2Cl_2	r.t.	62	66	7500	5100	81
15	α–	MeOTf (20)	CH_2Cl_2	r.t.	67	83	6500	4300	84
16	β–	MeOTf (10)	CH_2Cl_2	r.t.	118	66	10000	6200	85
17	γ–	MeOTf (10)	CH_2Cl_2	r.t.	188	75	8800	5400	83
18	α–	Et_2OBF_3 (10)	CH_2Cl_2	40	33	(40)	-	-	-
19	α–	MeI/$AgBF_4$ (10)	CH_2Cl_2	r.t.	137	63 (60)	10800	7000	83
20	α–	HOTf (10)	PhMe	r.t.	24	28 (45)	4900	3500	87
21	β–	HOTf (10)	PhMe	r.t.	15	67 (89)	8700	5400	87
22	γ–	HOTf (10)	PhMe	r.t.	1.4	53 (74)	12100	7400	95

[a] The hexane-insoluble polymer; the monomers were almost quantitatively converted except for runs 4 and 18-22, where the monomer conversions are shown in parentheses. [b] Estimated by GPC (polystyrene standards, $CHCl_3$). [c] The proportions of the α-glycoside linkage, which were evaluated by the ^1H NMR spectra. [d] M_n=4500 (VPO, benzene, 40°C).

to 20 mol%, as expected, produces lower molecular weight polymer, while decreasing it to 5 mol% does not cause the molecular weight to increase (runs 1-3, 5-6, and 13-15). This finding suggests that there is a chain transfer reaction involved, which becomes prominent when the propagation reaction is slow.

The ^{1}H NMR spectra showed that the resultant poly[(1→4)-D-glucopyranoside]s consist of not only α- but also β-glycoside linkages, whose relative contents are given in Table 1.[6] In the propagation reaction, one of six, seven, or eight α-glycoside linkages of MeCD monomers is cleaved and then re-formed as the α- or β-glycoside linkage in the polymer main chain. Assuming that the glycoside linkage formed newly by the propagation exclusively has the β-form, the proportion of the α-glycoside linkage in the product polymer could be theoretically evaluated to be 83, 86, and 89% for α-, β-, and γ-MeCD, respectively. The observed values shown in Table 1 are 72-95% and independent of the monomer. Thus an undesired reaction, which involves the inversion of the α-glycoside linkage to the β-form, could take place during the polymerization (*vide infra*).

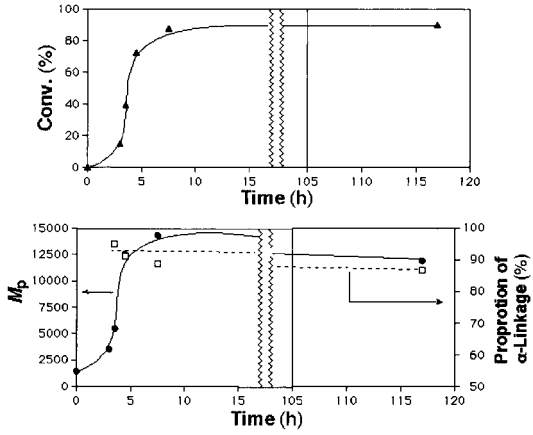


Figure 1. Monomer conversion, molecular weight (at a peak top of a GPC profile in $CHCl_3$, calibrated with PSt standards; M_p) of the polymer fraction, and the proportion of the α-glycoside linkage contained in the polymer, as a function of time in the polymerization of β-MeCD initiated with Et_3OPF_6; reaction conditions: [β-MeCD] = 0.1 M, [Et_3OPF_6] = 0.01 M, in CH_2Cl_2, at r.t.

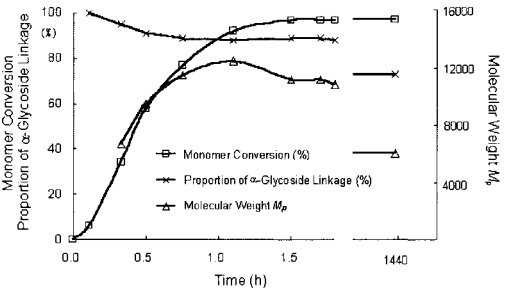
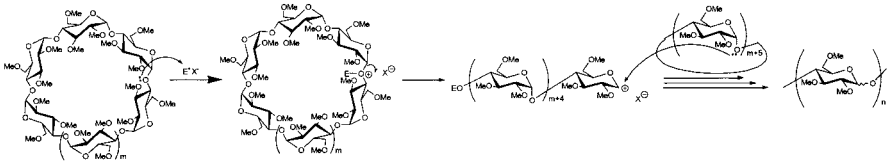


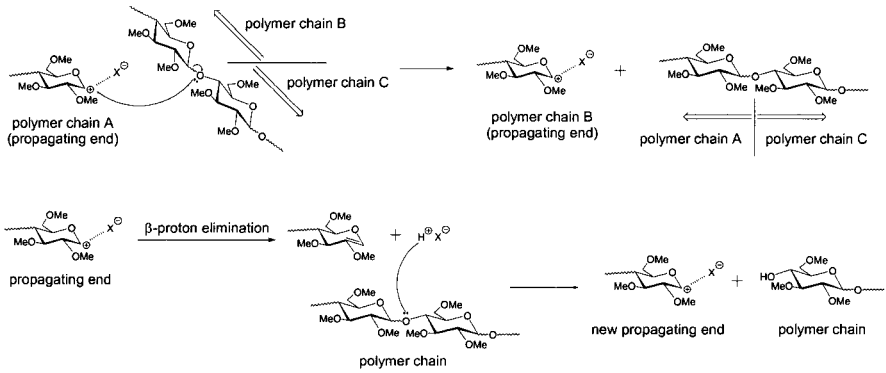
Figure 2. Monomer conversion, molecular weight (at a peak top of a GPC profile in $CHCl_3$, calibrated with PSt standards; M_p) of the polymer fraction, and the proportion of the α-glycoside linkage contained in the polymer, as a function of time in the polymerization of β-MeCD initiated with HOTf; reaction conditions: [β-MeCD] = 0.1 M, [HOTf] = 0.01 M, in CH_2Cl_2, at r.t.

GPC and ^1H NMR analyses of the reaction mixtures revealed the time-dependence of the monomer conversion, the molecular weight of the polymer fraction, and the relative content of the α-glycoside linkage in the product polymer (Figures 1 and 2). There is observed somewhat of an induction period in Figure 1, but not in Figure 2. It is speculated that Et_3OPF_6 could not directly initiate the polymerization due to its steric bulkiness (*vide infra*) and HPF_6 generated during the induction period could act as the actual initiator. The molecular weight of the polymer fraction increases with increasing monomer conversion and afterward decreases during the prolonged reaction time. The proportion of the α-glycoside linkage in the polymer also gradually decreases with time even after the monomer has been consumed. These findings suggest the chain transfer reactions shown in the following schemes, which decrease the content of the α-glycoside linkage and the molecular weight, respectively.

Initiation and Propagation Reactions



Chain Transfer Reactions to Polymer



These chain transfer mechanisms are supported by another experiment; *O*-permethylated amylose (Mw = 54000, Mn = 26000) that is prepared from natural amylose underwent reduction in molecular weight (Mw = 7400, Mn = 4400) and contamination with the β-glycoside linkages, when it was treated with Et_3OBF_4 in CH_2Cl_2 at r.t. for 71 hr.

It is interesting to investigate the relative reactivity of three MeCDs. As shown in Table 1, β-MeCD is polymerizable even at 0°C but α-MeCD is inert under the same conditions (runs 4 and 7). The relative reactivity was examined by subjecting the mixture of two MeCDs to the competitive polymerization in a reaction tube. As seen in Figure 3, the polymerizability increases in the order of α- < β- < γ-, which is identical with increase of the ring size of MeCD and with decrease of the ring strain.[6] This finding is interesting because, in ring-opening polymerizations of analogous monomers having difference in ring size, a more strained monomer usually shows higher polymerizability. To elucidate why the more strained monomer (α- > β- > γ-) is less reactive in the polymerization of MeCDs, the characteristic shape of the CD molecule should be regarded.

As shown in the above scheme, the CD ring is opened by electrophilic attack onto the glycosyl oxygen with an initiator or a propagating end of the oxycarbocation. The CPK space-filling molecular models of MeCDs reveal that the glycosyl oxygen atoms are located at the inside of the cavity of CD. Accordingly, *electorophiles have to go into the cavity of MeCD to open the CD ring for the polymerization*, which means that the larger size of the CD ring is more favorable.

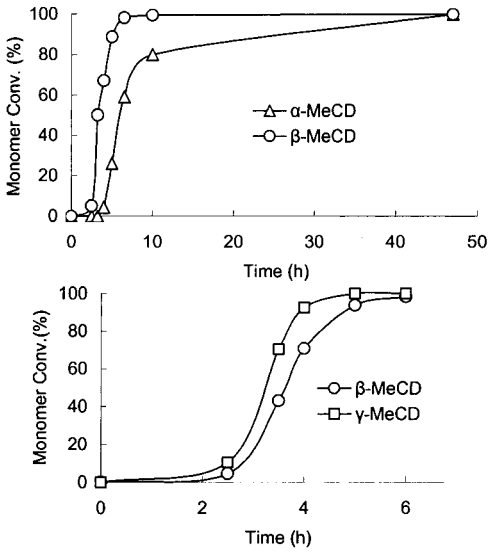
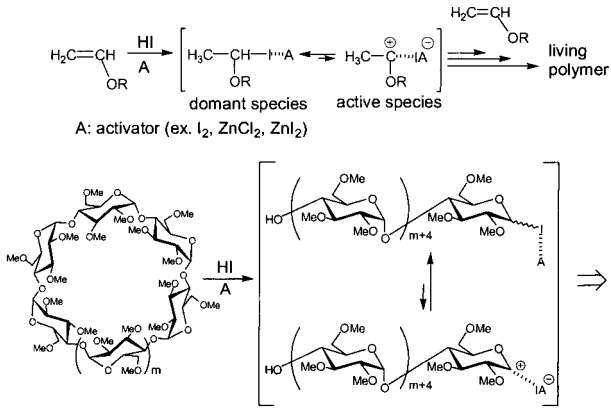


Figure 3. Monomer conversion, which was evaluated from ^{1}H NMR spectra of the reaction mixtures, as a function of time in the competitive polymerizations between α- and β- and between β- and γ-MeCDs initiated with Et_3OPF_6; reaction conditions: [α-MeCD] = [β-MeCD] = [γ-MeCD] = 0.05 M, [Et_3OPF_6] = 0.01 M, in CH_2Cl_2, at r.t.

Controlled Polymerization of MeCD

In order to achieve the second feature expected for this polymerization (*vide supra*), which gives unique glucan having large, regular intervals in the molecular weight distribution, it should be required to exclude the chain transfer reactions mentioned above. Thus we planned to use the knowledge about living cationic polymerization of vinyl ether, since MeCD and vinyl ether are polymerized *via* analogous propagating ends of an oxycarbocation. Herein the combinations of HI with an activator have been applied to control the cationic ring-opening polymerization of MeCD.



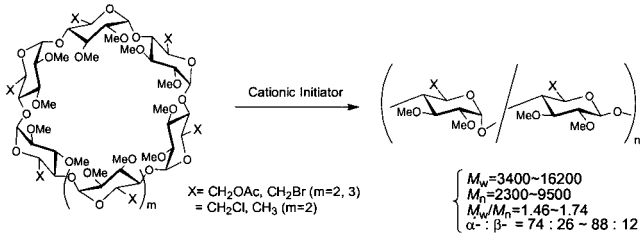
Various reaction conditions were examined: activator: I_2, $ZnCl_2$, or ZnI_2; solvent: CH_2Cl_2 or PhMe; temp.: r.t. or 0°C. The resultant polymers were analyzed with GPC and MALDI-TOF-MS.[7] Consequently, HI-$ZnCl_2$ (10 mol%) in CH_2Cl_2 at 0°C proved most effective to control the polymerization, which however, should still be stopped at moderate monomer conversion to avoid chain transfer to polymer. When the conversion of γ-MeCD was 45%, the high resolution GPC elution profile showed the formation of the "macro" oligomers (DP = 1-5) that were separately detected due to a relatively large difference in molecular weight. Using the MALDI-TOF-MS analysis, the obtained glucan was found to have the unique molecular weight distribution; there are large, regular intervals, each of which were identical to the molecular weight of γ-MeCD.[7]

Ring-Opening Polymerization of Other CD Derivatives

The poly[(1→4)-D-glucopyranoside] obtained from MeCD could not be transformed further, since the *O*-methyl groups cannot be restored to the hydroxyl groups without affecting the polymer chain. Thus the polymerizability of *O*-peracetylated and *O*-perbenzylated CDs has been investigated, since the acetyl and benzyl groups are easily deprotected back to the hydroxyl groups. Unfortunately, however, these CD derivatives proved inert under the same polymerization conditions as mentioned above for MeCDs and reactions forced by heating resulted in polymers consisting of unidentified structures. This is ascribable to the steric

hindrance and the reactivity of the acetoxy and benzyloxy groups; the bulky substituents cover the cavity mouth of CD and obstruct the ring-opening reaction *via* the electrophilic attack onto the glycoside oxygen located inside, and the acetoxy and benzyloxy groups are more reactive toward an electrophile to induce side reactions.

Thus partly modified MeCDs were examined for the polymerization. The primary hydroxyl groups at C-6 positions of the glucose units in CD are more reactive than other secondary hydroxyl groups and can be selectively transformed to various functional groups. Additionally, the C-6 positions are located at the smaller mouth of the CD cavity, so that the polymerization would be less affected by the steric bulkiness at the C-6 positions. Therefore, several CD derivatives, composed with 6-*O*-modified 2,3-di-*O*-methylglucose units, were prepared and subjected to polymerization. Consequently, the CD derivatives shown below proved polymerizable, but less reactive than MeCD.[8] The product glucan could undergo further transformation at the C-6 positions.



As mentioned in the Introduction, there is a third unique feature expected for the polymerization of CD derivatives: production of a sequentially regulated glucan. In order to realize this expectation, a CD derivative, one of whose glucose components is selectively modified at the C-2 position, was designed, since a substituent at the C-2 position exerts the strongest influence on the reactivity of the adjacent glycoside bond. The electronic, steric, and neighboring effects of the C-2 substituent could induce regioselective bond cleavage at the vicinal C-1 position, resultantly yielding a sequentially regulated glucan. We have already succeeded in preparing several mono-2-*O*-modified *O*-permethylated cyclodextrins.[9] The substituent effects upon the polymerization are under investigation.

Conclusions

OH-Modified cyclodextrin derivatives have proved polymerizable; they undergo cationic ring-opening polymerization to yield linear glucan. Representative study using *O*-permethylated cyclodextrins has disclosed unique features of this polymerization: unusually, the less strained monomer is more reactive; there are large, regular intervals in the molecular weight distribution of some product polymers. The former finding comes from the unique molecular shape of cyclodextrin, which has a cavity; the larger cavity of the less strained monomer is favorable for electrophile to enter the cavity for the ring-opening reaction. The latter finding has been achieved by the controlled polymerization of *O*-permethylated γ-cyclodextrin, which is a uniform, giant monomer.

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