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# Preparation of a unique glucan with large intervals in molecular weight distribution. Controlled ring-opening polymerization of *O*-permethylcyclodextrin

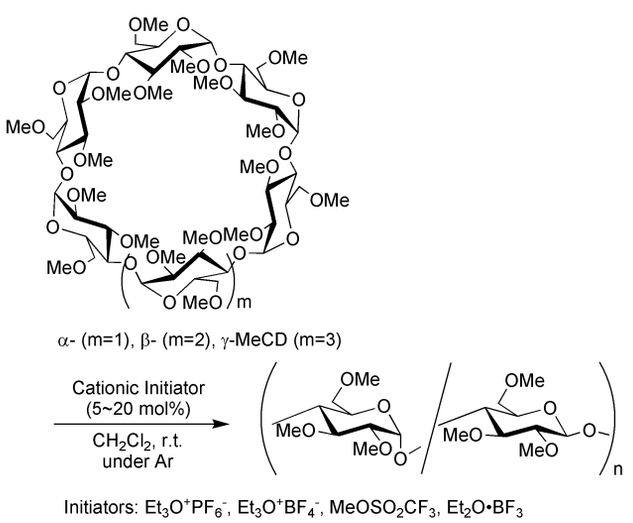
**Masato Suzuki * and Tomofumi Shimazaki**
*Department of Organic and Polymeric Materials, Graduate School of Science and Engineering, and International Research Center of Macromolecular Science, Tokyo Institute of Technology, 2-12-1 O-okayama, Meguro-ku, Tokyo 152-8552, Japan.*
*E-mail: msuzuki@polymer.titech.ac.jp; Fax: +81-3-5734-2888; Tel: +81-3-5734-3552*

***Received 18th October 2002, Accepted 5th December 2002***
***First published as an Advance Article on the web 20th January 2003***

*O*-Permethylated cyclodextrins (MeCDs) were found to be polymerizable with the initiator–activator system of HI–$I_2$ or HI–$ZnX_2$, undergoing ring-cleavage to give linear 1⟶4-glucan. Among several conditions investigated, HI–$ZnCl_2$ in $CH_2Cl_2$ at 0 °C proved most effective to control this cationic ring-opening polymerization (CROP). The MALDI-TOF-MS spectrum revealed that the molecular weight distribution of the glucan obtained from γ-MeCD uniquely consisted of large, regular intervals, each of which were identical to the molecular weight of γ-MeCD (1634).

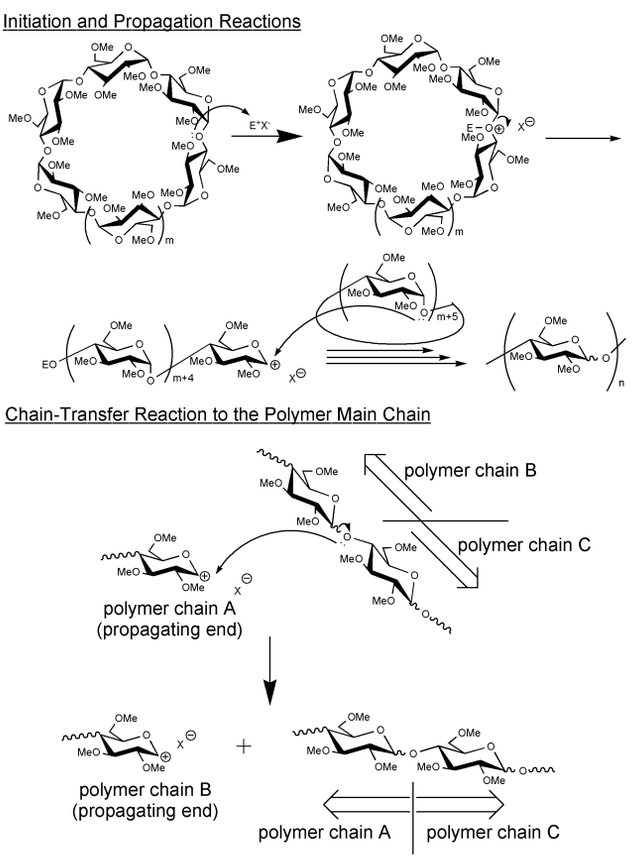
## Introduction

We have very recently reported that *O*-permethylated α-, β-, and γ-cyclodextrins (MeCDs) are able to act as macrocyclic monomers for cationic ring-opening polymerization (CROP) (Scheme 1).[1] The product polymers ($M_w \approx$ 6000–30000, $M_n \approx$ 4000–16000) are the linear 1⟶4-glucans consisting of 2,3,6-*O*-trimethylglucopyranose units, each of which is connected to the other with either α- or β-glycoside bonds (α : β = 72 : 28–88 : 12). The β-glycoside bond has proved to be formed not only in the propagation reaction, which includes bond scission at the α-glycoside linkage of the cyclodextrin (CD) ring and subsequent bond reformation, but also in the chain transfer reaction to the polymer main chain produced (Scheme 2).[1]




**Scheme 1**

We expected the CROP of CD derivatives to have three unique features: 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) when one of the glucose components in a CD monomer is modified to achieve regioselective cleavage of the ring, a sequentially regulated glucan is produced. The first feature has already been confirmed in our previous study,[1] the second is described in this article, and the third will be reported in the near future.




**Scheme 2**

To realize the second interesting feature, the above-mentioned chain transfer reaction should be excluded. Thus we planned to employ the system that is known to effectively conduct the cationic living polymerization of vinyl ether.[2] This idea comes from our observation that a CD derivative and vinyl ether are polymerized *via* analogous propagating ends of an

DOI: 10.1039/b210122j

**Table 1** Polymerization of MeCDs initiated with HI–$I_2$ [a]

| Run | MeCD | HI–$I_2$ [b] | Solv. | Temp./°C | Time/h | Conv.[c](%) | Yield[d](%) | $M_w$ [e] | $M_n$ [e] | $M_w/M_n$ [e] | Glycoside bond (α : β)[c] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | α- | 0.1 : 0.1 | $CH_2Cl_2$ | rt | 113 | 6.3 | — | — | — | — | — |
| 2 | β- | 0.1 : 0.1 | $CH_2Cl_2$ | rt | 72 | 90 | 76 | 7500 | 5100 | 1.47 | 92 : 8 |
| 3 | γ- | 0.1 : 0.1 | $CH_2Cl_2$ | rt | 24 | 95 | 76 | 10100 | 6500 | 1.56 | 93 : 7 |
| 4 | γ- | 0 : 0.1 | $CH_2Cl_2$ | rt | 138 | 0 | — | — | — | — | — |
| 5 | γ- | 0.1 : 0 | $CH_2Cl_2$ | rt | 24 | 9.2 | — | — | — | — | — |
| 6 | β- | 0.02 : 0.1 | $CH_2Cl_2$ | rt | 91 | 5.8 | — | — | — | — | — |
| 7 | γ- | 0.1 : 0.05 | $CH_2Cl_2$ | rt | 24 | 50 | 43 | Trimodal (5500, 3700, 1650)[f] | | | 90 : 10 |
| 8 | γ- | 0.1 : 0.2 | $CH_2Cl_2$ | rt | 24 | 88 | 88 | 12700 | 7000 | 1.82 | 87 : 13 |
| 9 | α- | 0.1 : 0.3 | $CH_2Cl_2$ | rt | 168 | 37 | 35 | 7500 | 4000 | 1.90 | 84 : 16 |
| 10 | γ- | 0.1 : 0.3 | $CH_2Cl_2$ | rt | 24 | 93 | 91 | 13900 | 7500 | 1.85 | 86 : 14 |
| 11 | γ- | 0.1 : 0.5 | $CH_2Cl_2$ | rt | 24 | 96 | 95 | 12500 | 7200 | 1.75 | 78 : 22 |
| 12 | β- | 0.1 : 0.1 | $CH_2Cl_2$ | 0 | 168 | 36 | 34 | Trimodal (5500, 3600, 1750)[f] | | | 93 : 7 |
| 13 | γ- | 0.1 : 0.1 | $CH_2Cl_2$ | 0 | 168 | 79 | 76 | 11600 | 7200 | 1.61 | 90 : 10 |
| 14 | β- | 0.1 : 0.1 | PhMe | rt | 168 | 50 | 43 | 6100 | 3400 | 1.80 | 87 : 13 |
| 15 | γ- | 0.1 : 0.1 | PhMe | rt | 72 | 88 | 53 | 9800 | 6100 | 1.80 | 93 : 7 |
| 16 | γ- | 0.1 : 0.1 | PhMe | rt | 288 | 94 | 86 | 33100 | 12000 | 2.76 | 91 : 9 |

[a] Monomer concentration = 0.1 mmol $ml^{-1}$. [b] Molar ratio to MeCD. [c] Calculated from $^1H$ NMR spectra (see the detail in Experimental section as well as Ref. 1). [d] Polymer precipitated from acetone to hexane. [e] Evaluated by GPC (polystyrene standard, $CHCl_3$). [f] The values in the parentheses correspond to the molecular weights at the peak tops of a GPC profile.

oxycarbocation (Scheme 3). Herein the HI–activator system has been applied to achieve the controlled CROP of MeCDs.[3]




**Scheme 3**

## Experimental section

### Materials

Three MeCDs were prepared from α-, β-, and γ-CDs according to the literature,[4] recrystallized twice from acetone–hexane, and dried at 90 °C under vacuum. The polymerization solvents $CH_2Cl_2$ and PhMe were dried with $CaH_2$ and Na, respectively, and freshly distilled just before use. A $CH_2Cl_2$ solution of HI was prepared by introducing HI gas, which was generated by dropwise addition of an aqueous solution of HI onto $P_2O_5$ and was dried through a $P_2O_5$ column. The concentration (about 0.5 M) of HI was determined by titration with an aqueous NaOH standard solution. $I_2$ was purified by sublimation and dissolved in dry $CH_2Cl_2$ (about 0.3 M). $ZnCl_2$ and $ZnI_2$ were dried under vacuum and dissolved in dry $Et_2O$ (~0.1–0.2 M).

### Polymerization

The typical procedure was as follows: to a solution of MeCD (0.1 mmol) in dry $CH_2Cl_2$ (1 ml) were successively added the $CH_2Cl_2$ solution of HI (0.01 mmol) and the $CH_2Cl_2$ or $Et_2O$ solution of $I_2$, $ZnCl_2$, or $ZnI_2$ under an Ar atmosphere. The mixture was stirred at rt or 0 °C for the hours stated in Table 1; the reaction was monitored by thin layer chromatography (TLC): silica gel 60 $F_{254}$ (Merck KGaA), acetone : hexane = 4 : 3; $R_f$ = 0.51 (α- and β-MeCD), 0.49 (γ-MeCD), and 0 (the product polymer). Afterwards, an aqueous solution of $NaHCO_3$ was added and the aqueous layer was extracted three times with $CH_2Cl_2$ (1 ml). When $I_2$ was used for the polymerization, an aqueous solution of $Na_2S_2O_3$ was added before the extraction. The combined organic phase was dried with $MgSO_4$ and concentrated to dryness. A small portion of the residue was dissolved in $CDCl_3$ and subjected to $^1H$ NMR analysis to determine the monomer conversion as well as the ratio of the glycoside bonds (α : β) forming the polymer (for details see our previous report).[1] Afterwards, the $CDCl_3$ solution was recombined with the reaction mixture, which was then dried again, dissolved in acetone (1.1 ml), and dropped into hexane (30 ml) with stirring. The precipitate was collected and dried *in vacuo* to give a white powdery polymer (the $^1H$ NMR chart is available in Ref. 1).

### Measurement

GPC was carried out using a Shodex® K-804L (Showa Denko) column or a high performance column set of TSKgel®

$G2000H_{XL}$, $G3000H_{XL}$ and $G4000H_{XL}$ (Tosoh). The eluent for GPC was $CHCl_3$ or THF (for high performance analysis), and polystyrene standards were used for the calibration. NMR spectra were measured in $CDCl_3$ by a Bruker DPX 300 spectrometer.

MALDI-TOF-MS was carried out using a PE-Biosystem Voyager-DE™ RP spectrometer, equipped with a nitrogen laser (337 nm) and an extraction voltage of 20 kV, in positive ion and reflectron modes. Two solutions, separately containing the polymer (10 mg) and a matrix of 2,5-dihydroxybenzoic acid (10 mg) in 0.1% $CF_3COOH$ aq. (1 ml), were mixed together in a ratio of 1 : 9. Small aliquots (2 μl) of this mixture were placed on a plate and subjected to measurement. The spectra were the average of 128 shots, calibrated with γ-MeCD (formula weight (FW) = 1633.74) and bovine pancreas insulin (FW = 5733.5, Nacalai Tesque).

## Results and discussion

Table 1 summarizes the CROP of α-, β-, and γ-MeCDs by use of the HI–$I_2$ system, which is one of the typical combinations of initiator and activator used to conduct the living polymerization of vinyl ether. In the presence of 10 mol% of HI and $I_2$, β- and γ-MeCDs successfully gave the polymer in $CH_2Cl_2$ at rt, while α-MeCD was hardly polymerized (runs 1–3). The ratio of the glycoside bonds, α : β, in the product polymer is an index of the relative frequency of the chain transfer reaction (Scheme 2). Higher content of the β-glycoside bond means that the chain transfer reaction to the polymer main chain takes place more frequently; the scission–recombination processes of the glycoside bonds, which are involved not only in the propagation but also in the chain transfer, convert the original α-glycoside bonds of the CD ring to a mixture of α and β anomers. Thus, as compared with the polymerization using the ordinary initiators as shown in Scheme 1 (the β-glycoside bond content in the product polymers = 20–28%),[1] the chain transfer reaction is less significant in the polymerization with the HI–$I_2$ system. Both HI and $I_2$ are necessary to conduct the polymerization (runs 4 and 5), and the lower concentration of HI (2 mol%) made the reaction too slow (run 6). Increasing the amount of $I_2$ (runs 7–11) accelerated the polymerization by increasing the population of the active species (Scheme 3), but this simultaneously promoted the chain transfer reaction to give a higher content of the β-glycoside bond. Compared with run 1, in run 9, the presence of 30 mol% of $I_2$ enabled α-MeCD to polymerize to some extent; the conversion, however, was moderate even after the one week reaction time. The polymerization of β- and γ-MeCDs took place even at 0 °C and also in a less polar solvent of PhMe, although a longer reaction time was required (runs 12–15). A comparison between runs 15 and 16 shows that the molecular weight of the product polymer increases even after consumption of the monomer, which indicates that a polycondensation mechanism is involved in the polymerization. As shown in Scheme 3, the polymer active end is a glycosyl iodide moiety, while the other terminal is a hydroxy group. The reaction between these two groups (polycondensation) evidently occurs to increase the molecular weight. Obviously, the polymerizability of the three MeCDs increases in the order α < β < γ; the same order has been observed in polymerization using ordinary initiators and the explanation for this observation has been discussed.[1]

Trimodal elution profiles in GPC were observed for the polymer samples obtained at runs 7 and 12, suggesting the formation of the "macro" oligomers that were separately detected due to a relatively large difference in molecular weight; this observation could be caused by lower monomer conversion together with a less frequent chain transfer reaction (Scheme 2). Thus, the polymer sample obtained at run 7 was representatively subjected to high performance GPC using a higher resolution column set (Fig. 1). Well-separated peaks were observed,

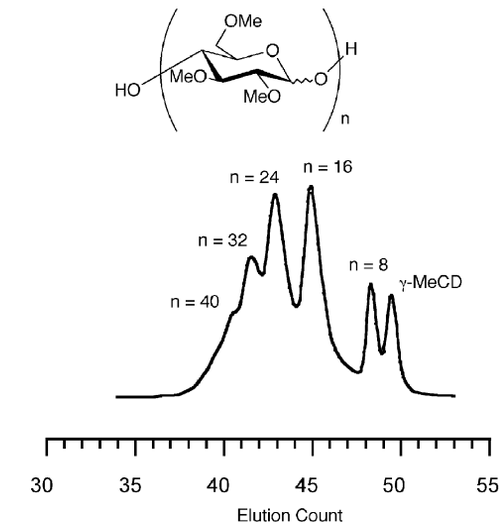



**Fig. 1** A high resolution GPC profile (eluent: THF, detector: RI) of the glucan produced at run 7 in Table 1.

which are assignable to γ-MeCD (the monomer remaining due to insufficient purification), the ring-opened monomer ($n$ = 8), the dimer ($n$ = 16), the trimer ($n$ = 24), the tetramer ($n$ = 32), and the pentamer ($n$ = 40), respectively. This observation suggests that the above-mentioned chain transfer reaction was suppressed in these runs. MALDI-TOF-MS is a powerful tool to investigate this aspect. In Fig. 2(b), the mass spectrum of the

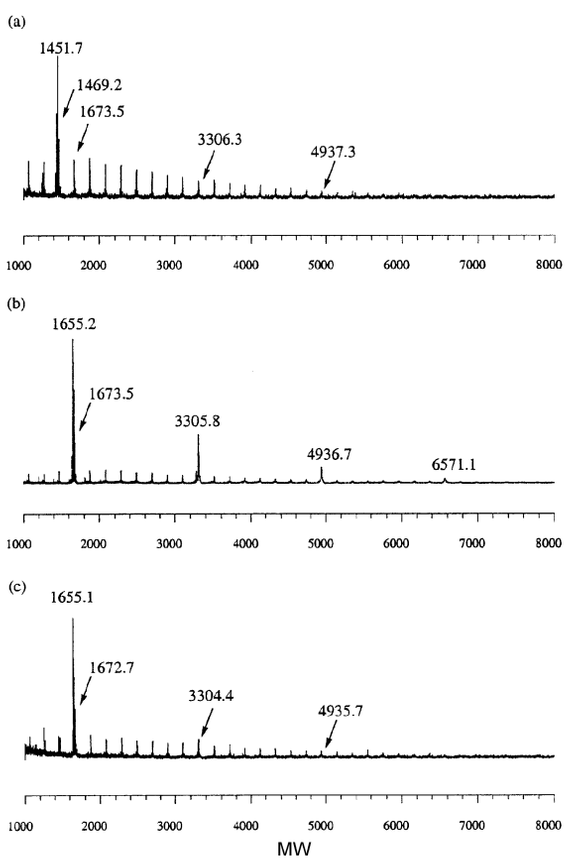



**Fig. 2** MALDI-TOF-MS spectra of the glucans produced at runs 3 (a), 7 (b), and 15 (c) in Table 1.

polymer of run 7, large peaks are observed along with smaller ones between them. The mass values of the major peaks are consistent with the formula weights calculated for the $Na^+$-adducts of γ-MeCD, the ring-opened monomer, the dimer, the trimer, and the tetramer (Table 2).[5] The latter minor peaks are

**Table 2** Theoretical molecular weights of γ-MeCD and the oligomers[a]

| | Molecular weight | Molecular weight + 22.99 (Na) |
|---|---|---|
| γ-MeCD | 1633.7 | 1656.7 |
| Ring-opened monomer ($n = 8$) | 1651.7 | 1674.7 |
| Dimer ($n = 16$) | 3285.5 | 3308.5 |
| Trimer ($n = 24$) | 4919.2 | 4942.2 |
| Tetramer ($n = 32$) | 6553.0 | 6576.0 |
| Pentamer ($n = 40$) | 8186.7 | 8209.7 |

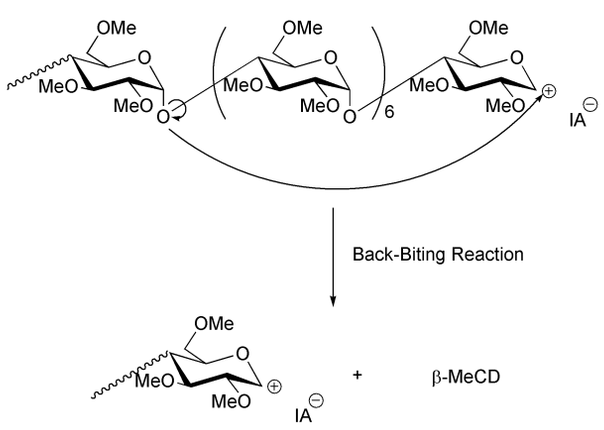
[a] Both terminals of the oligomer are hydroxy groups. The number of the glucose units of the oligomer is shown in parentheses.

**Table 3** Polymerization of MeCDs initiated with HI–$ZnX_2$[a]

| Run | MeCD | X | HI–$ZnX_2$[b] | Solv. | Temp./°C | Time/h | Conv.[c] (%) | Yield[d] (%) | $M_w$[e] | $M_n$[e] | $M_w/M_n$[e] | Glycoside bond (α : β)[c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 17 | β- | Cl | 0.1 : 0.1 | $CH_2Cl_2$ | rt | 168 | 75 | 58 | 7100 | 4800 | 1.79 | 93 : 7 |
| 18 | β- | Cl | 0.1 : 0.1 | PhMe | rt | 168 | 40 | 39 | Trimodal (4900, 3400, 1600)[f] | | | 88 : 12 |
| 19 | γ- | Cl | 0.1 : 0.1 | $CH_2Cl_2$ | rt | 168 | 90 | 75 | 9200 | 5600 | 1.64 | 95 : 5 |
| 20 | γ- | Cl | 0.1 : 0.1 | $CH_2Cl_2$ | 0 | 168 | 45 | 43 | Trimodal (5500, 4000, 1800)[f] | | | 94 : 6 |
| 21 | γ- | Cl | 0.1 : 0.1 | PhMe | rt | 168 | 73 | 64 | 8100 | 5300 | 1.53 | 95 : 5 |
| 22 | γ- | I | 0.1 : 0.1 | $CH_2Cl_2$ | rt | 72 | 9.2 | — | — | — | — | — |
| 23 | γ- | I | 0.3 : 0.3 | $CH_2Cl_2$ | rt | 168 | 75 | 73 | Trimodal (5600, 4000, 1700)[f] | | | 92 : 8 |

[a] Monomer concentration = 0.1 mmol $ml^{-1}$. [b] Molar ratio to MeCD. [c] Calculated from $^1H$ NMR spectra (see the detail in Experimental section as well as Ref. 1). [d] Polymer precipitated from acetone to hexane. [e] Evaluated by GPC (polystyrene standard, $CHCl_3$). [f] The values in the parentheses correspond to the molecular weights at the peak tops of a GPC profile.

located at intervals of the formula weight of the glucose unit. These observations indicate that, in run 7, the chain-transfer reaction occurred to a small extent.[6] Figs. 2(a) and (c) show the mass spectra of the polymers obtained at runs 3 and 15. There are no prominent peaks due to the oligomers but lots of peaks located at intervals of the formula weight of the glucose unit, which means that the chain transfer reaction (Scheme 2) took place extensively during polymerization in these two runs. Additionally, it is noteworthy that the largest peaks in Figs. 2(a) and (c) are observed at different mass values: the latter is ascribable to unreacted γ-MeCD, while the former is interestingly found to be assigned to β-MeCD ionized with $Na^+$ (the calculated mass value = 1452.4). This finding suggests that the polymerization of run 3 included a back-biting reaction to produce β-MeCD (Scheme 4). The propagating end, glycosyl




**Scheme 4**

iodide, could be more activated in the more polar solvent of $CH_2Cl_2$ (run 3), as compared with PhMe (run 15), to promote the back-biting reaction.

The polymerization has been studied further by using other combinations of HI with $ZnCl_2$ or $ZnI_2$. As shown in Table 3, β-, and γ-MeCDs were polymerized. However, the reactions were slower than those using $I_2$ as the activator; especially, 30 mol% of HI–$ZnI_2$ was required to conduct the polymerization at a substantial rate (runs 22 and 23). The polymer obtained at

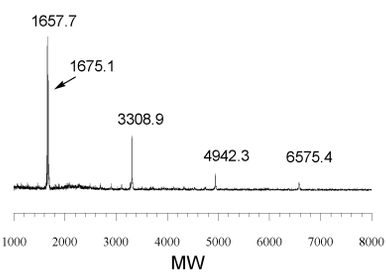



**Fig. 3** MALDI-TOF-MS spectrum of the glucan produced at run 20 in Table 3.

run 20 was analyzed by TOF-MS (Fig. 3); where peaks due to the monomer, the ring-opened monomer, the dimer, the trimer, and the tetramer are observed, while the peaks arisen from the chain transfer reaction are very small. Thus, the combination of HI with $ZnCl_2$ has been found to effectively conduct the well-controlled polymerization of γ-MeCD, giving a unique glucan with large, regular intervals in molecular weight distribution.

## Conclusion

Polymers are usually prepared from small molecules (monomers) as well as polymerizable oligomers or polymers (prepolymers, macromonomers, or macrocyclic monomers). In either case, molecular weight distribution of a product polymer consists of small intervals (= molecular weight of monomer), since, even in the latter case, the starting polymer is polydisperse. Herein, the use of a monodisperse macrocyclic monomer, *i.e.*, the CD derivative (γ-MeCD), has successfully given regular intervals of 1634 to the molecular weight distribution of the product glucan. A literature survey has revealed that one example is known for such a polymer: poly(ethylene glycol)s, which have intervals of 396, 660, or 792 in the molecular weight distribution, had been prepared by polycondensation of the corresponding uniform oligo(ethylene glycol).[7] The large interval would be expected to facilitate the fractionation of the product polymer, giving the glucan with a uniform degree of polymerization, which is presently under investigation.[8]

## Acknowledgements

The authors are grateful to Prof. Mitsuo Sekine and Assoc. Prof. Kohji Seio (Department of Life Science, Tokyo Institute of Technology) for their kind help to measure MALDI-TOF-MS. One of the authors, M. S., expresses his gratitude to The Ministry of Education, Science, Sports and Culture, Japan for the financial support by Grant-in-Aid for Scientific Research (No. 11650904).

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