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Synthesis and Characterization of Cationic and Anionic Cyclodextrin Oligomers and Their Use in Layer-by-Layer Film Formation

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Ionically modified β-cyclodextrins, which have excellent water-solubility, have been interested in purification technology as well as drug carrier system. The present study summarizes the synthesis and characterization of cationic and anionic β-cyclodextrin (β-CyD) products using by polycondensation. The oligo (β-CyD)s are synthesized from β-CyD, epichlorohydrin (EP) and choline chloride (CC; for cationic polymer) or chloroacetic acid (CAA; for anionic polymer) through one step polycondenstaion process. Unlike the previous studies, we successfully purified the ionic β-CyD condensation products from the β-CyD reaction mixtures and accomplished a great level of structural analysis. The detailed structural analysis of these ionic β-CyD compounds is done by ^{1}H NMR, MALDI-TOF as well as GPC analysis and confirms the formation of oligomers with a few units of β-CyD. We found that the sequence of reactant addition also could effect on the molecular weight of the resulting product as well as the molar ratio of the reactants. Finally, we used the cationic and anionic β-CyD oligomers for fabricating multilayer films by layer-layer process.

Key Words : Cyclodextrin polymer, Polycondensation, Cyclodextrin oligomer, MALDI-TOF, Layer-by-Layer film

Introduction

A great deal of research has been made on cyclodextrin chemistry. Cyclodextrins (CyDs) are cyclic oligosaccharides having glucose units linking together by α-(1,4)-glucosidic bonds. Due to the chair conformation of the glucopyranose units, these cyclodextrins are shaped like a truncated cone rather than perfect cylinders. The primary hydroxyl groups of the sugar residues are oriented at the narrow edge of the cone and the secondary hydroxyl groups at the wider edge. Thus the hydrophobic central cavity can form host-guest inclusion complexes with various hydrophobic guest molecules[1,2] even including polymers. This property of the cyclodextrin has been extensively exploited in chiral recognition by high performance liquid chromatography and capillary electrophoresis.[3,4] Among CyDs, α-, β- and γ-CyDs, which consists of 6-8 glucopyranose units, are commonly found in literatures.[5] Especially, β-CyD is the most widely studied compound due to its optimal size which forms inclusion complexes with variety of drugs.[6] Use of β-CyD as a drug carrier increases water solubility, chemical stability and bioavailability of the drug. However, presence of intra-molecular hydrogen bonding of secondary hydroxyl groups in parent CyD has been considered as the main cause for the low water solubility of these compounds.[7] Therefore, various derivatives of CyDs have been synthesized to improve the water solubility. Among the approaches, introducing ionic fragments on CyDs has used to make potent derivatives which incredibly increases the water solubility and also result in lowering of toxicity.[8] In addition to improved water-solubility, CyDs functionalized with weak acid or base may exhibit reversible supra-molecular complexation behaviors induced by pH-changes.[9,10]

Synthesizing CyD polymers may be attractive due to their binding affinity to guest compounds, catalytic effect, and the processability to give solid thin film.[11-13] The previously reported polymeric CyDs have CyD as side groups or main chain of the polymer. The former method is mostly based on radical polymerization of acrylate derivatives of CyD or the monomers that form complexes with CyD. The later synthetic route is the polycondensation of CyDs, react with bi-functional agents such as epoxy derivatives.[14] This condensation reaction is simpler than synthesizing CyD-containing monomers, and therefore used to achieve polymeric CyD. However, obtaining water-soluble CyD-polymer by polycondensation is limited by the nature of CyD and epoxy produce, networks by crosslinking. Therefore, synthesizing water-soluble CyD-polymer by polycondensation requires elimination of undesirable crosslinking, and facilitating this polymerization kinetic is exceptionally delicate. To this account, Renald *et al*. carried out systematic study on the polycondensation of β-CyD using epichlorohydrin (EP) under basic condition (NaOH aqueous media).[15] The authors reported detailed information on various reaction conditions, for example, ratios of reactants, concentration of NaOH, reaction time and temperature. However, their isolation of the desirable polymeric CyD was rather incomplete (their purification method using dialysis could not exclude unreacted or monomeric byproducts). Therefore, characterization and analysis of the product in their study represents the mixture of monomer, dimer, and so on rather than polymer-only part.

If a reagent having ionic functional groups is added to this polycondensation, it will produce ionic CyD polymers. Polycondensation of CyD with ionic functional groups would create more complicate situations. The synthesis of cationic CyD-polymer has been tried by using choline chloride (for introducing positively charged ammonium units to CyD) with EP and CyD,[16-18] although the products with a few CyD units were reported in these literature. Furthermore, their purification method was not sufficient to remove unreacted monomer (they used a dialysis bag with molecular cut-off 1000, which is lower than the molecular weight of β-CyD). Actually, the authors admitted that there were unreacted compounds in the final product and this might influence all of their measurements.[16] This synthetic method has been repeatedly used without following any further analysis.

In this regard, we carried out the study on the synthesis of ionic CyD polymer by using a proper purification and detailed characterization. For the synthesis of ionic β-CyD polymers, we adapted the previously reported methods with some variation on reaction conditions. We carefully conducted the purification of the reaction mixture by two-step dialysis. The high molecular weight β-CyD products were successfully isolated from unreacted cyclodextrin or partially substituted cyclodextrin fragments, as confirmed by characterization of the compounds by combined analysis with NMR, GPC and MALDI-TOF. The present study describes the details of synthesis and characterization of pure, high molecular weight ionic β-cyclodextrins, which provides useful information for cyclodextrin-related research.

Experimental

Materials and Methods. β-Cyclodextrin (β-CyD), Epichlorohydrin (EP) and Choline chloride (CC) were purchased from Sigma Aldrich (USA). Chloroacetic acid (CAA) was obtained from TCI fine Chemicals (Japan) and NaOH from Oriental Chemical Industries. All the reagents were of AR grade and used as received without further purification. NMR spectra of the synthesized cationic oligomer along with reactants DMSO-d_6 solvents were recorded on JEOL Ltd. (Akishima, Japan) 400 MHz spectrometer. Cationic and anionic β-CyD oligomers were also measured in D_2O solvent for NMR analysis. Mass spectra of synthesized compounds were analyzed by Matric Assisted Laser Desorption/Ionization-Time of Flight (MALDI-TOF) technique. (2,5-Dihydroxybenzoic acid)-10 mg/mL in 50% ACN/water with 0.1% TFA) and α-Cyano-4-hydroxycinnamic acid (7.5 mg/mL in 50% ACN/water with 0.1% TFA) were used as matrix with sample concentration of 1 mg/mL. GPC measurement was performed by Agilent 1100 series with a PLgel with 5 um mixed-C and mixed-D (300 mm × 7.5 mm) columnns. The eluent was THF with the flow rate was 1.0 mL/min and working temperature was 40 °C. For the layer-by-layer film deposition process, cationic and anionic β-CyD oligomers solutions were prepared with a concentration of 0.1 M (based on monomer units) dissolved in de-ionized water. The pH conditions for dipping solutions were adjusted to 3.0 or 7.0 for cationic β-CyD and 3.0 for anionic β-CyD. 0.01 M of HCl or NaOH solution was used for the pH-adjustment of the dipping solutions. The film was deposited on silicon substrates and the substrates were cleaned by soap solution with sonication followed by rinsing with de-ionized water. More detailed deposition process which followed the general LbL process can be found in previously published paper.[12]

Polycondensation of Ionic (β-CD). Ionic β-CD oligomers was synthesized by one-step condensation polymerization. A typical procedure for a molar ratio of β-CD/EP/CC = 1/15/2 is described here.

Synthesis of Cationic β-CyD Oligomer. For the general preparation of cationic β-CyD polymer, the following method was used: 1 g of NaOH (0.025 mol) was dissolved in 20 mL of deionized water, and then 1.135 g (0.001 mol) of β-CyD were dissolved in NaOH solution. The solution was electromagnetically stirred at 25 °C for 24 h. 0.2792 g (0.002 mol) of CC was then fed into the solution rapidly and 1.388 g (1.2 mL, 0.015 mol) of EP was added at the flow rate of 0.1 mL/min. After the completion of EP feeding, the mixture was heated at 60 °C for 6 h. After 6 h, polymerization was stopped by neutralizing with 3 N HCl solution. The solution obtained was dialyzed for 36 h with a dialysis membrane of 3000-3500 molecular weight cut-off (MWCO) against fresh de-ionized water, and the water was kept changed in every 8-10 h. We also used dialysis membrane of 1000 MWCO for the comparison. Yield: 0.74 g (22.2%). In the case of the samples, Cat-8 and Cat-9, EP was added into the β-CyD solution first at 25 °C. And then CC was introduced to the reaction bath followed by heating the mixture at 60 °C for 2 h. The same purification step of dialysis was used.

Synthesis of Anionic β-CyD Oligomer. 1 g of NaOH (0.025 mol) was dissolved in 20 mL of DI- water, and then 1.135 g (0.001 mol) of β-CyD were dissolved in NaOH solution. The solution was electromagnetically stirred at 25 °C for 24 h. 0.189 g (0.002) of CA was then fed into the solution rapidly and 1.388 g (1.2 mL, 0.015 mol) of EP was added at the flow rate of 0.1 mL/min. After the completion of EP feeding, the mixture was heated at 60 °C for 6 h. After 6 h, polymerization was stopped by neutralizing with 3 N HCl solution. The solution obtained was dialyzed for 36 h with a dialysis membrane of molecular weight cut-off 3000-3500. Yield: 0.6 g (19.8%).

Results and Discussion

Synthesis of Ionic β-CD Oligomers. We attempted to synthesize high molecular weight cationic and anionic β-CyDs following the previously reported method with some variations. The representative chemical structures ionic β-CyD polymers are shown in Figure 1.

The polycondensation of cationic β-CyD was carried out with changing the molar ratio of reactants, epichlorohydrin (EP), choline chloride (CC) and NaOH. Anionic β-CyD was also synthesized following the same procedure except using chloroacetic acid (CAA) instead of CC. We varied the

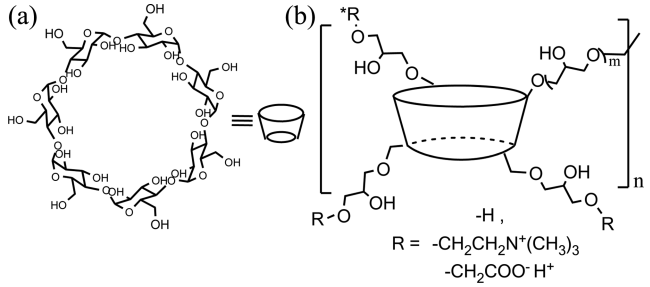

Figure 1. Chemical structures of (a) β-CyD and (b) oligomeric β-CyD having cationic or anionic substituents.

reactant ratios of NaOH and CC or CAA to β-CyD as summarized in Table 1, and some of the reaction conditions were adapted from the previously reported data of the condensation of β-CyD and EP.[14] As our aim was to isolate only high molecular weight fragment, thus unlike previous reports where dialysis bag of 1000 molecular weight cut-off (MWCO) has been used for the purification, we used two step-dialysis using membranes having 3000-3500 MWCO in addition to 1000 MWCO. Any residue of monomeric CyD is considered to change the results on characterization of the product. Therefore, this purification was carefully conducted to ensure there was no monomeric CyD left over. As summarized in Table 1, the molecular weights of most of the products indicate they contain only several β-CyD units, which is somewhat similar to the previous reports.[16-18] Therefore, we will denote the products of this polycondensation as cationic *oligo* (β-CyD) and anionic *oligo* (β-CyD) hereafter.

Among many parameters, the amounts of NaOH and EP appeared very important. Gelation was not reported when the ratio of EP to CyD was less than 10, which means the reactivity of EP toward CyD is not so vigorous. In the previously reported synthesis of cationic β-CyD polymer, the ratio of EP to β-CyD was used as 10-15.[16] It was also reported when the concentration of NaOH was above 33%, polycondensation was not observed.[15] The authors claimed that the most of substitution occurred on the primary hydroxyl groups (6-OH position) under such a high NaOH concentration condition, and it generated so high steric hindrance that blocked the condensation reaction between β-CyDs. They also reported that the reaction became very slow when the NaOH concentration was below 5%. However, this percent concentration seems indirect notation for the comparison between the concentrations of reactants therefore; we used NaOH as mole concentration. We varied the NaOH concentration from 1-25 times compared to the concentration of β-CyD. As shown in Table 1, NaOH concentration affected to the β-CyD condensation. When 1-5 eq. amounts of NaOH was used to deprotonate the hydroxyl groups of β-CyD, no condensation product was obtained. Increasing of the molar ratio of NaOH over 15 eq. to the other reactants started to generate condensed cyclodextrins. The total number of hydroxyl groups present on β-CyD is 21, hence it requires excess base for the de-protonation of hydroxyl groups and 25 eq. moles of NaOH has given the optimum yield (Table 1).

Reaction time and temperature for the polymerization were fixed to 6 h and 60 °C, mostly. Thus reaction time was increased from 6 h to 18 h to check whether increasing reaction time would yield the desired polymeric product. However, increasing reaction time also did not affect significantly on the molecular weight of *oligo*(β-CyD). The highest MW of the purified product was slightly over 3000 in both cationic and anionic *oligo*(β-CyD) when we followed the reported method. These molecular weights can be matched to the dimer cases of the β-CyD. Surprisingly, when we changed the addition sequence of the reactants by adding EP first, and then CC to the β-CyD solution, the MW of the product became up to over 5000. In the previous literatures, the reported method of mixing reactants is adding CC with β-CyD first and followed by a slow addition of EP into the mixture. This is probably due to the consideration of cross-linking that can be generated between EP-reacted β-CyDs. However, as also reported that the reactivity of EP is appeared not so vigorous and our condition that is far below gelation point, the sequence of the reactant addition may not

Table 1. Details of Various Reaction Conditions for The Synthesis of Cationic (Cat) and Anionic (Ani) CyD Oligomers

Ser. No.	β CyD (mmol.)	EP (mmol.)	CC, CAA (mmol.)	NaOH (mmol.)	Yield (%)	Mol. wt.	Rxn (h)
Cat-1	1	15	1	1	0.3 g (–)	1157	6
Cat-2	1	15	1	5	0.03 g (–)	1269	6
Cat-3	1	15	1	15	0.085 g (3%)	2800	6
Cat-4	1	15	1	25	0.43 g (14.7%)	2924	6
Cat-5	1	15	2	25	0.742 g (22.2%)	3335	6
Cat-6	1	15	2	25	0.50 g (16.4%)	3043	18
Cat-7	1	15	4	25	0.23 g (7.9%)	2906	6
Cat-8*	1	15	1	15	0.21 g (4.7%)	4465	2
Cat-9*	1	15	2	25	0.2655 g (4.97%)	5344	2
Ani-1	1	15	1	25	0.55 g (18.5%)	2980	6
Ani-2	1	15	2	25	0.6 g (18.2%)	3296	6
Ani-3	1	15	4	25	0.40 g (12.7%)	3146	6
Ani-4	1	15	2	25	0.6 g (19.8%)	3035	18

All reactions performed at 60°C. *EP was added into the reaction media prior to the addition of CC.

problematic in terms of crosslinking. Rather, presenting EP to β-CyD and giving some time may produce more chance to activate β-CyD toward condensation reaction. We obtained the product within the shorter reaction time (2 h) with this method and the isolated products were readily water-soluble, which indicated no sign of crosslinking. We will discuss more detailed discussion about the products by MALDI-TOF analysis later. Overall, the most reproducible, consistent and comparatively higher yields were observed for the molar ratio of reactants, β-CyD:CC:EP: NaOH, as 1:15:2:25.

Characterization of the Product of Polycondensation of β-CD. Defining the reactivity ratio between the substitution of β-CyD with ionic groups and the condensation to β-CyD polymer is critically important. As summarized in Table 1, we have used various reactant ratios. This effort was not only for increasing the yield but also finding the influence of the reactant ratio toward the ionic substitution or polycondensation of CyD. In order to study this mechanism, we conducted ^{1}H NMR analysis of the product of cationic and anionic (β-CyD) polycondensation. In the previous study on NMR spectroscopy of cationic (β-CyD) products, mostly D_2O was used as the solvent. Thus ^{1}H NMR spectra of cationic and anionic *oligo* (β-CyD)s have been measured in D_2O first. Chemical shift assignments of cationic *oligo* (β-CyD) has been done by comparing the ^{1}H NMR with that of reactants *viz*., β-CyD, EP and CC in the same solvent. Similarly from the NMR spectrum of β-CyD, we can observe that the -CH protons of *oligo* (β-CyD) resonates in the region 3.4-3.9 ppm except for C1H proton which is more deshielded and hence appears down field at 4.93 ppm. The peaks of the -CH protons from EP and CC also can be defined in the region of 2.91-3.96 and 3.2-4.1 ppm respectively (Figure 2(a)).

During the reaction epoxide ring opens to form the glycerol unit and protons of this unit resonates in the 3-3.5 ppm. While the ^{1}H NMR of cationic *oligo* (β-CyD) shows the multiple merged peaks in the region 3-4 ppm due to the overlap of protons from CyD and that of the substituents, it is clear that a single peak around 3.1 ppm is due to -CH_3 protons of the quaternary ammonium substituent introduced by CC. By comparing the integration of this peak (from CC) and C1H of CyD, we could estimate the portion of ionic substitution. We also studied the influence of CC concentration in the reaction mixture on the content of CC in the product. The obtained cationic *oligo* (β-CyD)s contain CC contents as about 1 group in two β-CyD units when the reactant molar ratios of β-CyD:CC was 1:1, and then increased to 3 times when the molar ratio of CC was increased to twice (β-CyD:CC = 1:2). (See S2 in the supporting information). However, the increased CC content in cationic *oligo* (β-CyD) did not increase at the higher CC concentration (β-CyD:CC = 1:4 for Cat-7). In addition, the MW of isolated *oligo* (β-CyD) product started to decrease.

In the case of anionic *oligo* (β-CyD), the ^{1}H NMR was compared with the those of EP and CAA. As the reaction follows the similar way to the synthesis of cationic *oligo* (β-CyD), the protons from glycerol unit were observed near 3-3.5 ppm. The peaks in the region of 3.25-4.1 ppm are associated with the protons from glucose units of β-CyD along with glycerol unit. Other distinctive peaks, which are -CH_2 protons of CAA unit, were observed at 4.14 ppm. This is more up-field region compared to the reactant CAA because these protons are not deshielded as much as the ones placed next to chlorine atom. Details of ^{1}H NMR assignment of cationic *oligo* (β-CyD) and anionic *oligo* (β-CyD) including reactants can be found in the experimental section and supporting information.

NMR analysis of cationic and anionic *oligo* (β-CyD) using D_2O as solvent has a limitation of detecting the changes in conversion of hydroxyl groups. In β-CyD, there are 7 primary and 14 secondary hydroxyl groups present, and they locate at 6-C and 2-, 3-C positions of each glucose unit, respective-

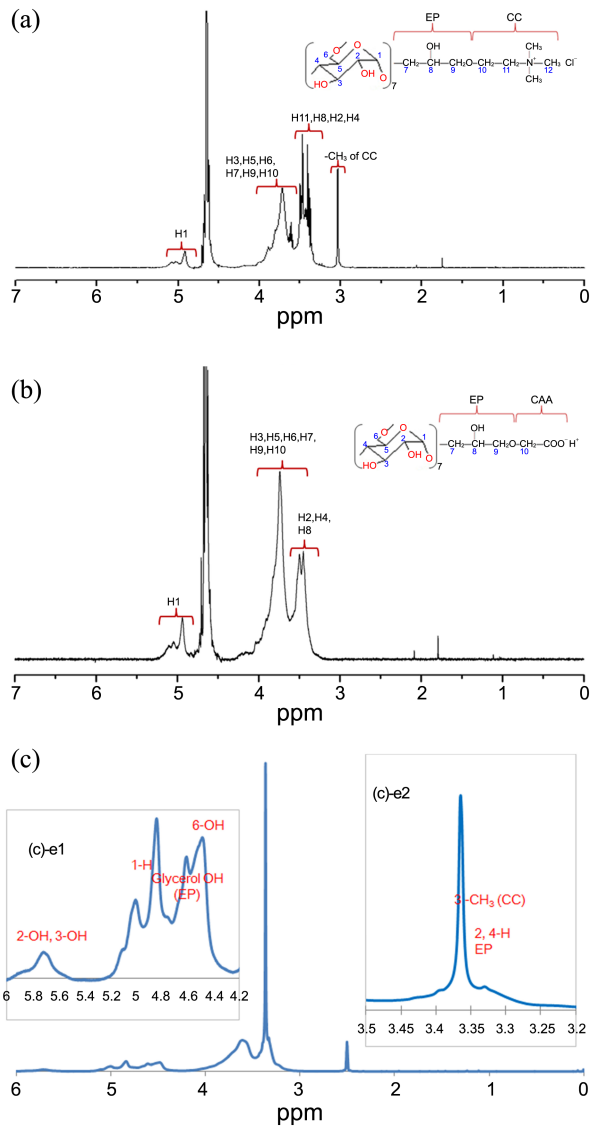

Figure 2. ^{1}H NMR spectra of (a) cationic *oligo* (β-CyD), Cat-5, (b) anionic *oligo* (β-CyD), Ani-2, taken in D_2O solvent, and (c) Cat-5 obtained with DMSO-d_6 solvent. Expanded regions, (c)-e1 and (c)-e2, are taken for the clear appearance of the peaks.

ly. The changes on these hydroxyl groups are important information for understanding substitution and condensation of β-CyD. Therefore, we conducted ^{1}H NMR measurements for reactants and *oligo* (β-CyD) using DMSO-d_6 as the solvent (Figure 2(c)). Under DMSO-d_6 solvent condition, all the hydroxyl groups of *oligo* (β-CyD) as well as β-CyD, 2, 3-OH and 6-OH, are clearly separated in the range of ~4.5 and 5.7 ppm. Our reaction condition using the NaOH molar ratio toward β-CyD as higher than 15 (15 and 25) established the proton abstraction mostly from secondary 2, 3-OH groups. As discussed previously, deprotonation of 6-OH groups is known to be major abstraction of proton under highly basic condition. Even for the case of the highest NaOH concentration, in which the molar ratio of NaOH exceeds to the all 21 hydroxyl groups in a β-CyD, most of deprotonation of hydroxyl group took a place on the 2, 3-positions (~80%) whereas only a small fraction of 6-OH groups (13%) were deprotonated. Since 6-OH groups are on the smaller rim of β-CyD, it was expected that the substitution on 6-OH would not lead to condensation between β-CyDs due to the steric hindrance caused by them. Whereas, increasing the substitution of 2, 3-OH groups on the larger rim of β-CyD may increase the reactivity for polycondensation.

The reaction condition for Cat-3 in Table 1 has been reported previously, and reproduced by many following studies. In those works, the molecular weight of the product was characterized only by GPC. We used GPC measurement for Cat-3 and found Mw is 2306 with a polydispersity as 1.04. We also conducted extensive MALDI analysis of all the products listed in Table 1 with assigning feasible chemical species that correspond to the observed base and molecular ion peaks. The data obtained by GPC and MALDI-TOF are similar, but the effect of eluent and standard calibration of GPC could give influence to create deviation from sample to sample while we obtained rather constant MALDI-TOF data.

In the case of Cat-1 and Cat-2 samples, of which the concentration ratios of NaOH/β-CyD were below 5, the products were nothing but unmodified cyclodextrins that was revealed by MALDI-TOF spectra (given in the supporting information). When the concentration ratio of NaOH to β-CyD was larger than 15, the major product was dimer (Figure 3).

We also conducted the synthesis of anionic β-CyD similarly to the cationic polycondensation. Figure 4 shows the molecular structure analysis of Ani-1 and Ani-2 samples based on MALDI-TOF spectra. Molar ratio of the reactant introducing charged functional groups (CC or CAA) to β-CyD slightly influenced on the substitution degrees of β-CyD by ionic groups. However, it was observed that the increase of feed concentration of such ionic compounds did not affect much the degree of polycondensation. When the concentration of CC or CAA to β-CyD was over 4 (Cat-7 and Ani-3), the MW of the product became smaller than when the ratio was 2.

With the experimental range of reactant ratios and times employed, except for the basicity of the reaction mixture (NaOH concentration), we did not found significant increase of β-CyD units in the product. However, when we changed the addition sequence of the reactants, *i.e.* placing EP prior to the addition of CC to the β-CyD solution, the MW of the product became greater than dimer. Figure 5 shows the MALDI-TOF data of the cationic *oligo* (β-CyD) products obtained by this method. We analyzed all the major peaks,

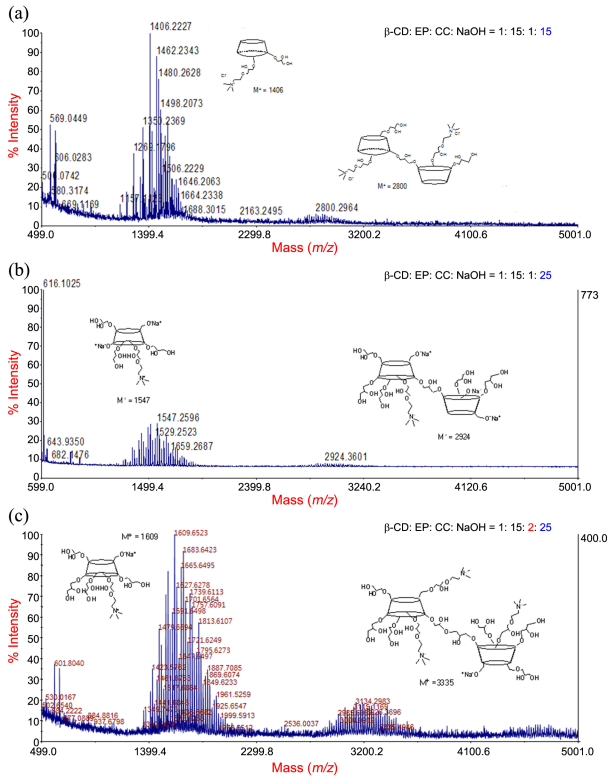

Figure 3. MALDI spectra of the major products of poly-condensation of β-CyD with introducing cationic group by using different ratios of β-CyD: EP: CC: NaOH; (a) Cat-3, (b) Cat-4 and (c) Cat-5.

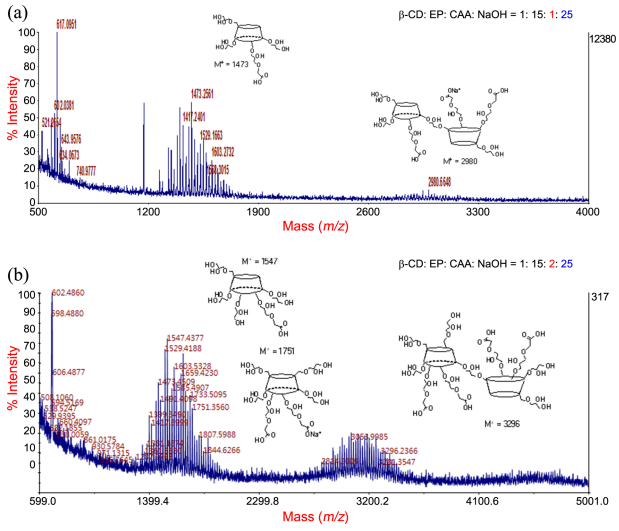

Figure 4. MALDI spectra of the major products of polycondensation of β-CyD with introducing anionic group by using different ratios of β-CyD: EP: CAA: NaOH; (a) Ani-1 and (b) Ani-2.

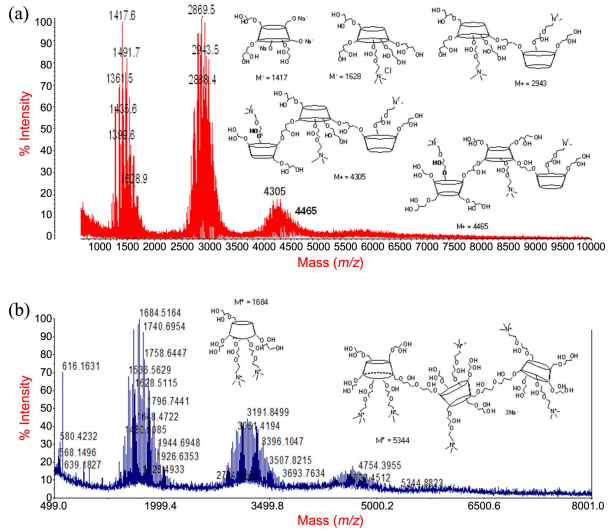

Figure 5. MALDI spectra of the products of cationic *oligo* (β-CyD) syntheses obtained when EP was added prior to CC into the reaction mixture; the reactant ratios of β-CyD: EP: CC: NaOH were fixed as (a) 1:15:1:25 (Cat-8) and (b) 1:15:2:25 (Cat-9).

molecular ion peak and fragments. It suggests that the products are trimers of β-CyD of which the number of ionic substituent corresponds to the feed ratio. However, even with this approach, three units of β-CyDs in the product appear to be the highest number and the yield is not satisfactory. Further study for optimization of the reaction time and temperature needs to be continued in order to increase the yield and β-CyD units of the reaction.

We set out to show the formation of solid thin films using these new cationic and anionic cyclodextrin oligomers by layer-by-layer (LbL) deposition. The multilayers fabricated by LbL process have been utilized in an enormous range of applications.[12,13,19-21] Especially, water-soluble polymers having similar property as weak acid or weak base exhibit highly tunable surface properties as they are processed by LbL deposition technique. Therefore, we used LbL process for the ionic *oligo* (β-CyD)s to fabricate multilayer films. The film deposition was conducted on glass slide and silicon substrates. Because these substrates have slightly negatively charged surface, we used cationic *oligo* (β-CyD) as the first layer, which was followed by the assembly of anionic *oligo* (β-CyD). We studied the multilayer deposition of ionic *oligo* (β-CyD) using two different pH assembly conditions, 3.0/3.0 and 3.0/7.0 for the anionic/cationic *oligo* (β-CyD) solutions. The anionic product has carboxylic acid groups that exhibit variable degrees of ionization by pH condition, whereas the charge density of the cationic (β-CyD) compound (having quaternary ammonium groups) is constant. At the pH condition of 3.0/3.0 for the multilayer, where carboxylic acid groups of anionic CyD oligomer were kept unionized we would expect less ionic interactions between these β-CyDs, whereas the multilayer assembled at 3.0/7.0 would form mainly by ionic interactions. As shown by the graphs in Figure 6, the film thickness did not increase systematically with increasing the repeating cycle of deposition, rather

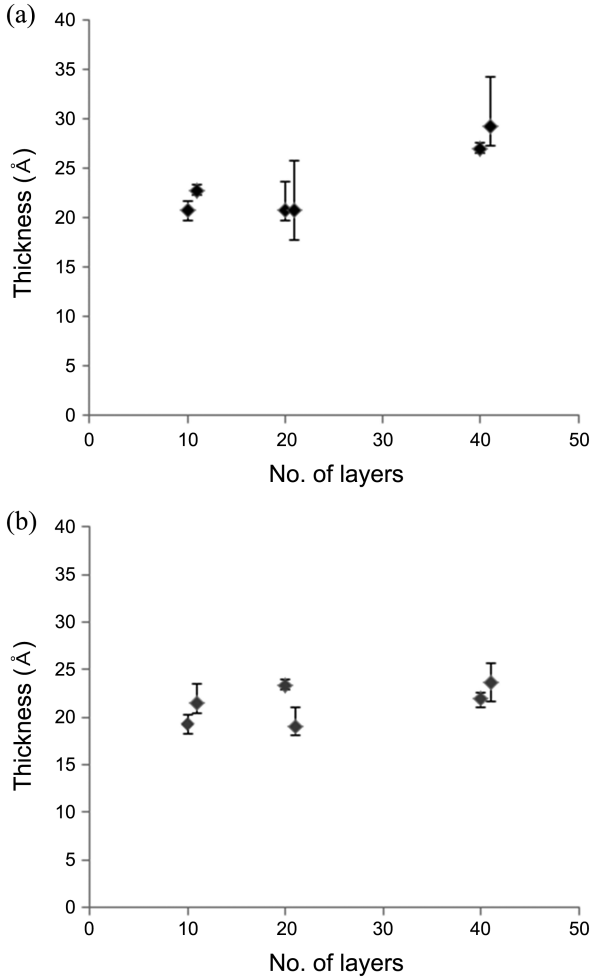

Figure 6. Thickness data of the Cat-*oligo* (β-CyD)/Ani-*oligo* (β-CyD) multilayer films deposited with the pH conditions of anionic/cationic *oligo* (β-CyD) as (a) 3.0/3.0 and (b) 3.0/7.0. Each point indicates of n experiments with ± S.D. (n = 3).

limited to only a couple of molecular layer-thickness. No significant difference in the film thicknesses prepared at these different assembly conditions. The possible reason may be due to the small MW of *oligo* (β-CyD)s, which did not provide enough interactions between molecules to continue the layer-by-layer deposition. Actually, we found a meaningful increase of film thickness on using CyD trimers compared to the corresponding dimers, which is promising for our future study. We now design a new system for the multilayer process by incorporating second molecules which can be assembled with these low MW oligomers.

Conclusion

We have attempted to synthesize and isolate the water soluble high molecular weight ionic β-cyclodextrin. Although we obtained the compounds with small number of β-CyD in repeating units, which are mostly dimer or trimer, we prove that the selective modification of secondary hydroxyl groups of CyD is possible, and structurally well-characterized ionic β-CyD oligomers can be synthesized. Furthermore, we will

continue to study the film formation of these ionic *oligo* (β-CyD)s and expand our study of synthesis using other cyclodextrins.

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