

Synthesis of a novel poly(oxyethylene)-bridged β -cyclodextrin dimer

Sung Ho Choi · Kurt E. Geckeler

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Abstract A novel supramolecular building block based on cyclodextrin and poly(oxyethylene) is reported, in which the poly(oxyethylene) moiety was selected to be the linker for cyclodextrin in order to enhance the biocompatibility. We report for the first time the synthesis of a bridged β -cyclodextrin dimer based on a condensation reaction by using a simple and efficient procedure, which can be employed for applications in supramolecular chemistry as a nanoscaled building block. It is noteworthy that the dimerization of β -cyclodextrin can increase the binding affinity compared to the β -cyclodextrin derivatives. The chemical structure is biocompatible and the dimer can therefore be considered for drug delivery applications.

Keywords Cyclodextrin · Dimer · Poly(oxyethylene) · Supramolecular building block · Biocompatibility

Introduction

Cyclodextrins (CDs) have gained considerable interest because they can form inclusion complexes with various guest molecules and their excellent biocompatibility [1, 2]. Chemical modification of the CD molecule can significantly alter the molecular binding ability and selectivity toward a variety of guests through simultaneous weak interactions [3–8]. Thus, various approaches for the synthesis of modified CDs and bridged CD dimers,

have been reported [9–12]. Very recently, a bridged CD dimer, which contains a long-chain PEG unit, has been reported [13]. However, the procedure for the preparation of the CD dimer is complicated. Thus, a facile and straightforward preparation of CD dimers is of substantial interest. Our research group has been studying various nanoscaled materials as supramolecular building blocks such as fullerenes, carbon nanotubes, and CDs [14–16]. In this paper, we report the direct and simple synthesis of a bridged β -CD dimer, which contains a short PEG unit as a spacer group to attain an enhanced biocompatibility [17].

Experimental details

Synthesis of the β -CD dimer

β -CD (from Cyclodextrin Technologies Development, Inc.) was used after two recrystallizations and drying under vacuum at 80°C overnight. Poly(ethylene glycol) bis(carboxymethyl) ether (average molecular mass: ~250 g/mol) was purchased from Aldrich Chemical Company and used without further purification. Thionyl chloride was purchased from Fluka. N,N'-dimethylformamide (DMF) and pyridine were used after distillation under reduced pressure with CaH₂. Thrice distilled water were deionized water were used throughout the experiments. In order to detect the β -CD dimer synthesized, spray-staining techniques were employed in connection with thin-layer chromatography. For the spray solutions of Dragendorff's reagent, solutions of bismuth nitrate (Fluka), potassium iodide and barium chloride (Aldrich Chemical Company) were mixed.

S. H. Choi · K. E. Geckeler (✉)
Laboratory of Applied Macromolecular Chemistry,
Department of Materials Science and Engineering,
Gwangju Institute of Science and Technology (GIST),
Gwangju 500-712, South Korea
e-mail: keg@gist.ac.kr

The synthesis of the poly(oxyethylene)-bridged β -CD dimer was performed as follows: Solutions of the purified β -CD (**1**) (0.503 g, 0.44 mmol) in anhydrous pyridine (14 ml) and of the PEG diacid chloride (**3**) (0.03 g, 0.105 mmol) in anhydrous DMF (13 ml) were prepared and the latter solution was added dropwise at 0°C in an ice bath under nitrogen. After finishing the dropping procedure, the mixture was stirred for 8 h at 0°C. Then the mixture was allowed to warm up to room temperature and stirred for 2 days. The volume of the resulting mixture was reduced by rotary evaporation. Then an excess of acetone was added to this mixture, the precipitate was collected and washed with acetone (3 times). The crude product was dried under vacuum overnight, then distilled water was added, and the solution freeze-dried overnight. The dried product was purified by column chromatography over Sephadex G-25 with distilled and de-ionized water as the eluent (yield: 0.399 g, 37%).

Characterization

$^1\text{H-NMR}$ spectra were obtained with a JEOL JNM-LA300WB instrument at room temperature in D_2O as the internal reference. Matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) was used for conforming the molecular mass of the β -CD dimer synthesized (α -cyano-4-hydroxyci-

namic acid (CHCA), a low molecular mass peptide was used as the matrix material). Thermogravimetric analysis (TGA) data were recorded on a TA 2050 (TA instruments) in a N_2 atmosphere at a heating rate of $10^\circ\text{C min}^{-1}$ from 30°C to 800°C . Photoluminescence spectroscopy was used for studying the fluorescence quenching phenomena by using an ACTON spectrometer connected to a charge-coupled detector with a Xenon lamp as the excitation source.

Results and discussion

A novel supramolecular cyclodextrin dimer with a poly(oxyethylene) linker has been prepared and characterized. We report for the first time the synthesis of a novel bridged β -cyclodextrin dimer based on a condensation reaction by using a simple and efficient procedure, which can be employed for applications in supramolecular chemistry as a nanoscaled building block. It is noteworthy that the β -cyclodextrin dimer has the potential to increase the binding affinity for guest molecules as compared to cyclodextrin monomers. Also, both the biocompatibility and the hydrophilicity of the poly(oxyethylene) spacer are advantageous.

Figure 1 shows the straightforward synthetic procedure for the bridged β -CD dimer (**4**). For the preparation of the precursor spacer molecule for the β -CDs,

Fig. 1 Synthetic scheme for the β -CD dimer

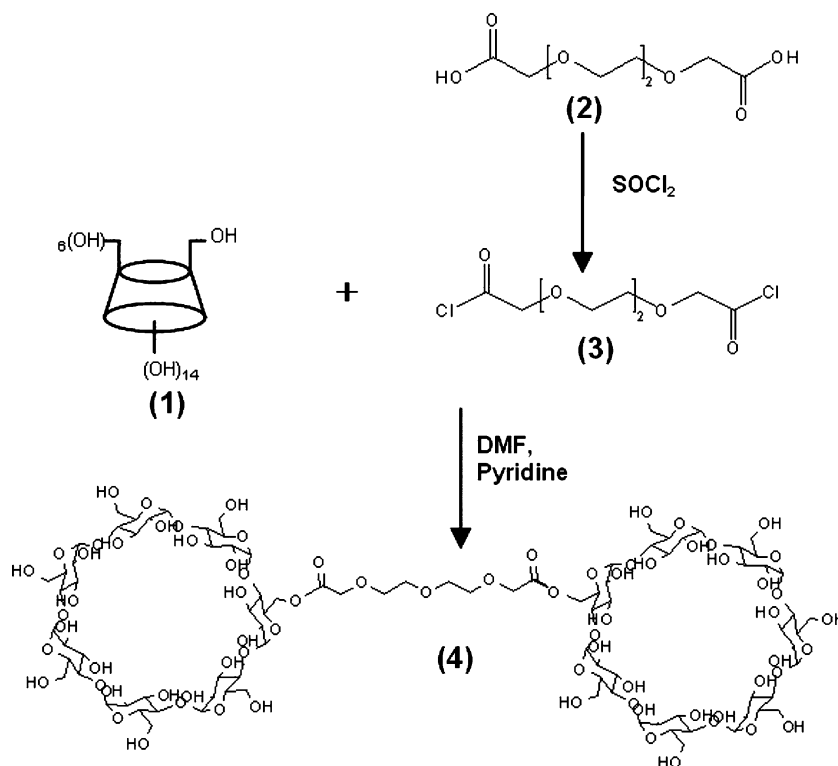
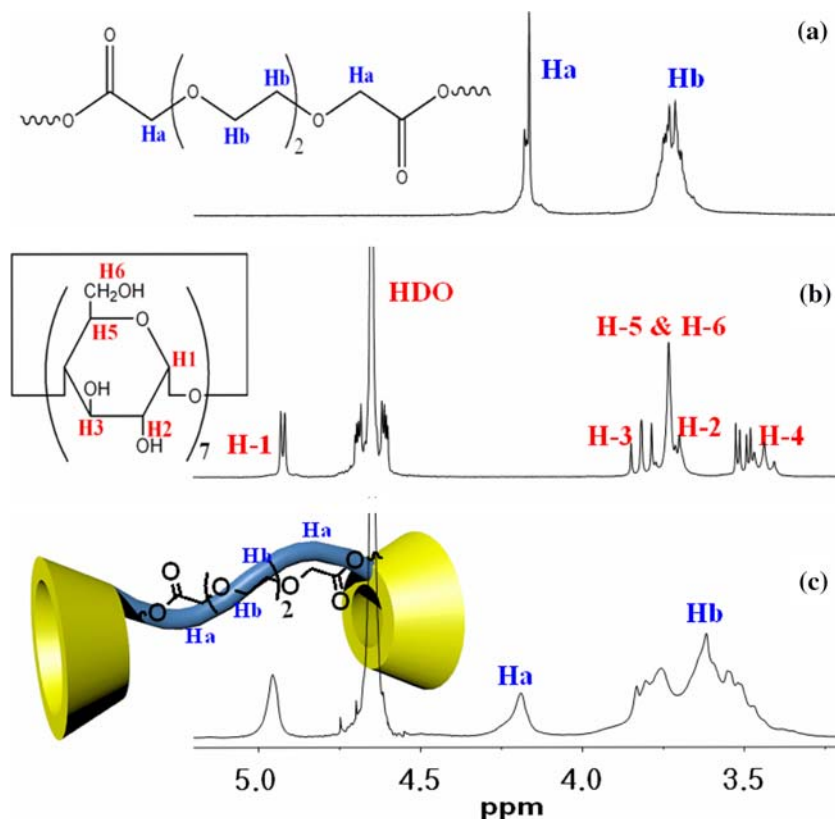


Fig. 2 $^1\text{H-NMR}$ spectra of (a) the PEG diacid chloride (in CDC/3), (b) $\beta\text{-CD}$, and (c) the bridged dimer at room temperature in D_2O



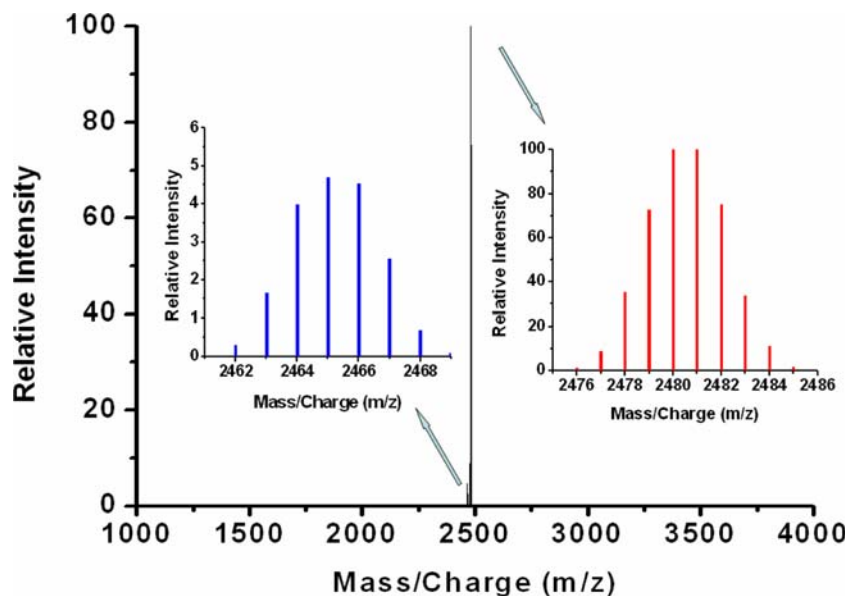
poly(ethylene glycol) bis(carboxymethyl) ether (**2**) was chlorinated with thionyl chloride and then reacted with the CD to yield the POE-bridged CD dimer.

Figure 2 presents the $^1\text{H-NMR}$ spectra of the PEG diacid chloride (a), the pristine $\beta\text{-CD}$ (b), and the bridged $\beta\text{-CD}$ dimer (c) at room temperature. The signals of the bridged $\beta\text{-CD}$ dimer include the peaks from the PEG unit. In particular, both the H2 and H4

protons of the bridged $\beta\text{-CD}$ dimer are overlapped with Hb protons of the PEG units. However, the other Ha protons of the PEG units are clearly shown in the spectrum of the dimer.

MALDI-TOF mass spectroscopy was used to identify the molecular mass of the $\beta\text{-CD}$ dimer synthesized (Fig. 3). The molecular mass was detected to be 2480 g/mol [$\beta\text{-CD}$ dimer: Na^+ ; H^+]. This result can be

Fig. 3 MALDI-TOF MS spectra of the $\beta\text{-CD}$ dimer. The two insets are mass ion spectra



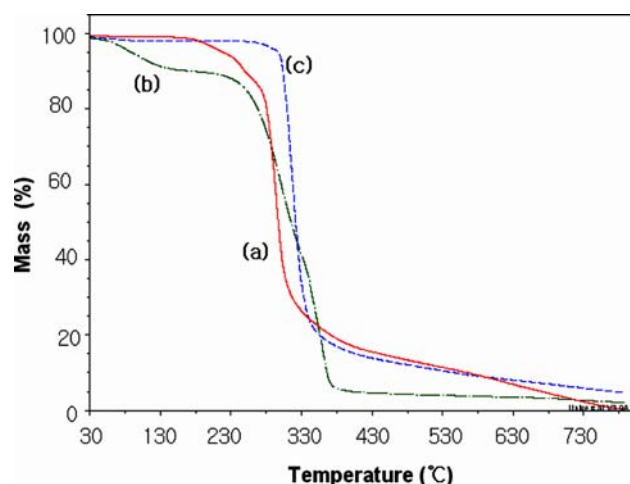


Fig. 4 Thermogravimetric analysis of (a) the bridged β -CD dimer, (b) PEG-bis(carboxymethyl) ether, and (c) pristine β -CD

explained from the data of a previous study [18]. During the detection of the ionized molecules in the MALDI-TOF MS, the two cavities of the β -CD dimer can be occupied with H^+ or Na^+ ions. The molecular mass of the β -CD dimer consisting of two β -CDs and one PEG spacer unit ($n = 2$) was calculated to be 2456 g/mol.

Thermogravimetric analysis (TGA) of β -cyclodextrin, the PEG-bis(carboxymethyl) ether, and the bridged β -CD dimer was performed to understand the details of their decomposition properties and to explore their thermal stability (Fig. 4). Generally, the pristine β -CD has the highest thermal stability among these three compounds and the pristine PEG-bis(carboxymethyl) ether has the lowest thermal stability. As expected, the thermal stability of the bridged β -CD dimer is situated between these two compounds. This result clearly indicates that the β -CD dimer synthesized has an enhanced thermal stability compared with that of PEG-bis(carboxymethyl) ether.

Conclusion

A facile and efficient synthesis of a novel supramolecular building block, the β -cyclodextrin dimer containing a poly(oxyethylene) unit as the bridging unit, is reported. The straightforward and one-step preparation method yields the hydrophilic β -cyclodextrin dimer, which has potential applications in drug delivery systems and nanoscaled supramolecular network systems with multifunctional guest molecules.

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