Purification of Cyclic Polymers Prepared from Linear Precursors by Inclusion Complexation of Linear Byproducts with Cyclodextrins

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Cyclic polymers have been prepared generally by one of three different routes: (1) ring−chain equilibration,[1−4] (2) ring closure of end-functionalized linear precursors under conditions of high dilution,[5−21] and (3) ring expansion by bond insertion.[22−25] With the latter strategy, Grubbs et al. have shown that cyclic polyolefins can be cleanly synthesized by ring-opening metathesis polymerization (ROMP) of cyclooctenes using a cyclic ruthenium-based catalyst.[25] This method is unique because there are no linear precursors or byproducts, and thus purification schemes are not complicated by the need to separate linear and cyclic molecules with similar physical and chemical properties. Not all cyclic polymers will be available by ROMP. Most reported syntheses of cyclic polymers have employed either ring−chain equilibration or ring closure routes. With these routes, product mixtures include linear byproducts from unreacted linear precursor, intermolecular chain extension, or end-capping of the linear precursor at one or both ends by a coupling agent. Purification requires the separation of cyclic products from these linear byproducts.

Linear byproducts are typically removed with fractionation techniques.[10−16,26,27] One of the most effective methods is liquid chromatography at the critical condition (LCCC), in which the conditions (e.g., solvent quality, temperature, solid phase) are adjusted for a given polymer so that the linear species elute at the same time regardless of molecular weight; the separation then only depends on chain architecture. For example, LCCC provides excellent resolution of some cyclic and linear polystyrenes.[27] As long as their characteristic peaks do not overlap, cyclic and linear polymers can be efficiently separated by preparative LCCC after establishing the critical condition. However, baseline resolution will not be possible for all linear/cyclic polymer mixtures.[28] Characteristics that could impede separation include low molecular weights, large polydispersities, and the presence of different functional groups in the linear byproducts vs the ring polymers. Most of the separations using LCCC were demonstrated on mixtures in which both precursor and product were characterized by narrow molecular weight distributions.

Recently, we reported an efficient method to separate cyclic material from charged linear byproducts based on their chemical differences using a macroporous anion-exchange resin.[29] However, this method is not applicable if the linear byproducts do not have charges on either chain end. Some cyclization methods do not proceed through charged linear precursors (e.g., ring-closing metathesis).[17] Here we present a new and versatile method to separate cyclic polymers from linear byproducts by inclusion complexation of the linear byproducts with cyclodextrins (see Scheme 1).

Cyclodextrins (α, β, and γ) form inclusion complexes with a wide variety of low molecular weight compounds as well as linear polymers, both organic and inorganic.[30−40] Cyclodextrins have been used extensively to separate and purify small molecules based on structural characteristics like branching or specific configurations.[41] By comparison, relatively little work has been done to separate and purify polymers using cyclodextrins. Some reports have described the selective complexation of polymers based on differences in their structure,[42] molecular weight[38,43] or stereoregularity.[39] Porbeni et al. suggested the use of γ-cyclodextrin for separating poly(dimethylsiloxane) from its cyclic oligomers.[37] Harada et al. have shown that cyclic oligomers of ethylene glycol larger than four repeat units (i.e., 12-crown-4) do not form inclusion complexes with α-cyclodextrin (α-CD), as they are too large to fit in the cyclodextrin cavity.[30] They have also shown that α-CD forms complexes with poly(oxyethylene) (POE) terminated not only with hydroxyl groups but also with other functionalities, provided the end groups are not larger than the size of the α-CD cavity.[30] Even if end groups are charged, inclusion complexation will occur,[44] and if a given end group or polymer is too large to fit inside the cavity of α-CD, then the larger β- or γ-CD can be used. Thus, inclusion complexation with cyclodextrins can be used to separate a variety of linear byproducts, whether charged or uncharged, from the corresponding macrocycles. This is demonstrated here for purification of cyclic poly(oxyethylene) from its linear precursor and chain-extended byproducts.

Experimental Details

Materials. All materials were obtained from Aldrich unless indicated otherwise. Tetrahydrofuran (THF, anhydrous, 99.9%), heptane (anhydrous, 99.9%), ethyl acetate, tetrahydrofuran (HPLC grade, 99.8%), dimethyl-d_6 sulfoxide (DMSO-d_6), and α-cyclodextrin (α-CD; Wacker) were used as received. α-Hydro-ω-hydroxypoly(oxyethylene) ($M_n \sim 1.5$ kg/mol, $M_w/M_n = 1.04$), *p*-toluenesulfonyl chloride (TsCl, 98%), and potassium hydroxide (KOH, 85%; Fisher) were dried under vacuum prior to use. α-Hydro-ω-hydroxypoly(oxyethylene) is commonly known as poly(ethylene glycol) (PEG).

Instrumentation. ^{1}H NMR spectra were measured with a Bruker DRX 500 on 1 wt % solutions in DMSO-d_6. ^{13}C NMR spectra were measured with a Bruker AMX 400 on 5 wt % solutions in $CDCl_3$. Gel permeation chromatography (GPC) was conducted in THF (1 mL/min) on a Waters system (2690 separations module) using a 2410 differential refractive index detector and three Styragel columns at 303 K (5 μm beads: HR 0.5, 50 Å, 0−1 kg/mol; HR 3, 10^3 Å, 0.5−30 kg/mol; HR 4, 10^5 Å, 5−600 kg/mol). Samples were prepared as 10 mg/mL solutions; injection volumes were 100 μL.

Matrix-assisted laser desorption/ionization time-of-flight (MALDI−TOF) mass spectrometry was conducted on a Micromass TofSpec 2E with two different matrices, dithranol and α-cyanohydroxycinnamic acid (CHCA). Samples were prepared by mixing equal (v/v) amounts of 10 mg/mL solutions of the analyte (in THF) with the matrix (dithranol in THF or CHCA in 1/1 acetonitrile/water v/v). No salt was added, and 1 μL of the final solution was allowed to evaporate on a MALDI plate.

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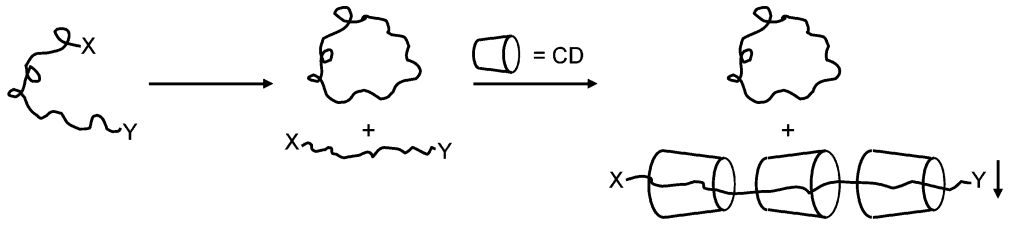
Scheme 1. Purification of Cyclic Polymers Prepared from Linear Precursors by Inclusion Complexation of Linear Byproducts with Cyclodextrins[a]



[a] The X and Y represent functional end groups that may be the same or different, charged or uncharged, and are not necessarily identical in the byproducts and precursor. The CD-included linear byproducts precipitate from solution and are thus separated from the cyclic polymer product.

The measurements were conducted at a background pressure of 10^{-8} Torr using a voltage of 20 kV. The laser wavelength was 337 nm, and 10 laser shots were collected per second. Spectra are an average of 30−50 laser shots.

Synthesis of Cyclic Poly(oxyethylene). Glassware, stir bars, and syringe needles were dried at 120 °C overnight. Round-bottomed flasks with stir bars were sealed with rubber septa and a stopcock adapter and cooled while evacuating and backfilling with dry N_2. Finely ground KOH (2.2 g, 33.3 mmol) was dispersed in a mixture of THF and heptane (75/25 v/v, 100 mL) and stirred under nitrogen at 40 °C. The purpose of the poor solvent, heptane, was to improve ring closure by reducing the end-to-end distance.[11,12] PEG (5 g, 3.33 mmol based on number-average molecular weight) and TsCl (635 mg, 3.33 mmol) were dissolved in 100 mL of THF in a separate flask. This solution was then added dropwise to the KOH dispersion via a syringe pump over a period of 48 h. After stirring for a further 24 h, the mixture was filtered and the solvent was removed initially by rotary evaporation and finally under high vacuum.

Purification. The product obtained above (4.2 g) was dissolved in 42 mL of distilled water (100 g/L). An aqueous solution of α-CD (105 mL, 100 g/L) was added to the product solution at room temperature; the amount added (105 mL) was determined so that the ratio of α-CD to linear byproducts, estimated as 25% of the crude product from the GPC chromatogram, was 10/1 (w/w). The resulting clear solution was ultrasonically agitated for 15 min, became turbid, and was allowed to stand overnight at room temperature. Depending on the concentration and molecular weight of linear byproducts, a white precipitate or gel formed. The mixture was centrifuged and filtered to obtain a clear aqueous solution. Rotary evaporation of this solution gave a solid crude material that contained the cyclic product and some unthreaded α-CD or residual linear byproducts (trapped if gelation occurs). This solid mixture was dissolved in ethyl acetate (200 mL) and filtered to remove the unthreaded α-CD. The filtrate was rotary evaporated to obtain the product which was analyzed using GPC. The procedure was repeated twice to remove the linear byproducts. The pure cyclic product was a white waxy solid (2.5 g, 50%). ^{1}H NMR (500 MHz, DMSO-d_6), δ (TMS, ppm): 3.5. ^{13}C NMR (400 MHz, $CDCl_3$), δ (TMS, ppm): 70.3.

Results and Discussion

Ring closure of α-hydro-ω-hydroxypoly(oxyethylene) was achieved via ether linkage by reaction with tosyl chloride in the presence of solid KOH. End-to-end intramolecular coupling was promoted over intermolecular chain extension by conducting the reaction at high dilution (ca. 10^{-5} M). This synthesis was based on a method reported by Booth et al. for preparation of cyclic poly(oxyethylene).[11,12] They also reported a second method for ring closure via an acetal linkage (reaction of the α,ω-dialkoxide with CH_2Cl_2).[10] We have followed the first method because of the relative chemical stability of the ether linkage compared to the acetal linkage, which is subject to scission under acidic conditions.

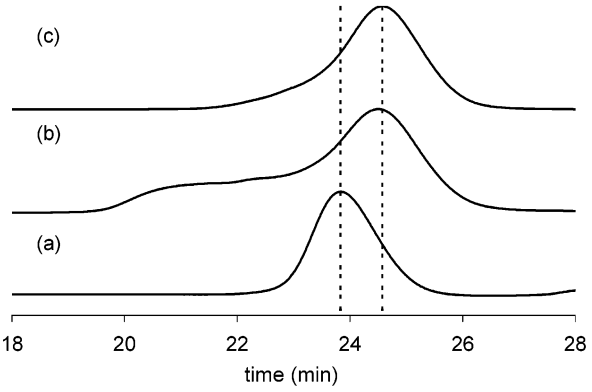


Figure 1. GPC chromatograms for (a) α-hydro-ω-hydroxypoly(oxyethylene) linear starting material, (b) crude product of cyclization, and (c) α-CD-purified product. GPC chromatograms are shown as signal intensity (differential refractive index) vs elution time.

Ishizu and Akiyama reported the cyclization of poly(ethylene glycol)s (M_n = 8 and 20 kg/mol) by reaction of their disodium salts with 1,4-dibromobutane. They reported cyclization with no chain extension even at relatively high concentrations of glycol (10^{-2}−10^{-3} M).[45] We repeated this procedure for PEG ($M_n \sim$ 1.5 kg/mol) without success.

The crude product obtained from the above reaction was a mixture of linear precursor, chain-extended polymer, and cyclic polymer as depicted by the GPC chromatogram in Figure 1b. The GPC chromatogram of the starting material (Figure 1a) contained a single narrow peak. After cyclization, the major peak was found at higher elution time, indicating formation of the cyclic polymer,[2] and a broad shoulder assigned to chain-extended polymer was found at lower elution times (Figure 1b).

The linear precursor and the chain-extended polymer form inclusion complexes with α-CD,[46−48] while the cyclic POE does not.[30] Thus, mixtures of cyclic and linear POE can be separated by a simple precipitation procedure; pure cyclic polymer will be located in the supernatant. Figure 1c shows the GPC chromatogram of the product obtained from the supernatant following precipitation of the linear byproducts with α-CD. It does not contain the broad shoulder at lower elution times, thereby signifying removal of chain-extended byproducts.

α-CD forms complexes with linear POE in a 2:1 stoichiometry (two oxyethylene repeat units to one α-CD).[47] This stoichiometry was used along with a rough estimate of the fraction of linear byproducts present (from GPC) to calculate the amount of α-CD added to purify a given quantity of the crude product mixture.

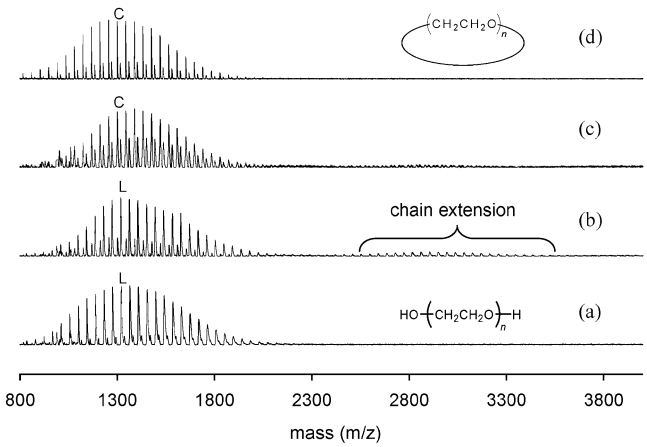


Figure 2. MALDI−TOF mass spectra for (a) α-hydro-*ω*-hydroxypoly(oxyethylene) linear starting material in dithranol, (b) crude product of cyclization in dithranol, (c) crude product of cyclization in α-cyanohydroxycinnamic acid, and (d) α-CD-purified product in dithranol. The peak labeled "L" is the linear species at 1317.6 amu ($n = 29$, Na^+ cationized); this species appears at 1299.6 amu after cyclization and is marked "C". The linear byproducts appear in the crude product more prominently when dithranol is used as the matrix.[50]

Since concentrated solutions of high-molecular-weight linear poly(oxyethylene) and α-CD lead to gelation,[48] initial concentrations were kept low to minimize physical entrapment of cyclic POE and α-CD in the gel. Depending upon the concentration and the amount of α-CD used, purification sometimes resulted in separation of high-molecular-weight species first (disappearance of low-elution-time shoulder from 20 to 22 min) with some low-molecular-weight linear species still present (a small shoulder to the left of the main peak, from about 22 to 23 min). This preferential complexation of α-CD with higher-molecular-weight poly(oxyethylene)s has been reported before.[38] Subsequent recomplexation/precipitation with α-CD removes the remaining linear species. The GPC trace of the purified cyclic POE (Figure 1c) did not change after the second complexation/precipitation. It is slightly broader (polydispersity = 1.10) than the GPC chromatogram of the starting material (polydispersity = 1.04), with a tail at lower elution times (22−23 min) that appears in the same range as the linear starting material. However, removal of linear species was confirmed with ^{1}H NMR spectroscopy (data not shown). Using dry DMSO-d_6, it was possible to detect the hydroxyl end groups of α-hydro-*ω*-hydroxypoly(oxyethylene) as a triplet at 4.5 ppm in the spectrum of the linear precursor and crude cyclization product. This peak was not present in the ^{1}H NMR spectrum of the α-CD-purified product, which contained a single peak at 3.5 ppm. The tail at lower elution times in the GPC trace for the purified product may be due to cyclic polymers formed from the intramolecular coupling of chain-extended intermediates, or perhaps even catenanes.

In addition to ^{1}H NMR spectroscopy, MALDI−TOF mass spectrometry was also used to confirm the absence of linear byproducts in the purified product. Figure 2 shows MALDI−TOF spectra for (a) the linear starting material in dithranol, (b) the crude product of cyclization in dithranol, (c) the crude product of cyclization in CHCA, and (d) the α-CD-purified product in dithranol. Each spectrum contains envelopes of peaks separated by 44 amu, which is the mass of an ethylene oxide repeat unit. The peak labeled "L" in Figure 2a appears at 1317.6 amu and corresponds to a sodium-cationized linear poly(oxyethylene) containing 29 oxyethylene repeat units.[49] Minor peaks in this spectrum correspond to potassium-cationized species.

Figure 2b shows the MALDI−TOF spectrum for the crude product in dithranol. The peak labeled "L" (1317.6 amu) represents unreacted linear precursor. A low-frequency distribution of higher-molecular-weight species is also observed which corresponds to chain-extended linear polymer. Besides the major set of peaks, a minor set of peaks is also observed between 800 and 2000 amu. Each of these minor peaks shows a molecular-weight decrease of 18 amu from the corresponding major peaks in the MALDI−TOF spectrum of the linear starting material (Figure 2a). These peaks are more clearly identifiable in the MALDI−TOF spectrum of the crude product using CHCA as a matrix (Figure 2c).[50] In this spectrum, the peak labeled "C" appears at 1299.6 amu and represents the cyclized product of the $n = 29$ linear precursor (1317.6 amu). The molecular-weight decrease of 18 amu is consistent with loss of a water molecule upon ring closure.

Figure 2d shows the MALDI−TOF spectrum of the α-CD-purified product in dithranol. The peaks due to chain-extended polymer have disappeared. Again, the peak labeled "C" at 1299.6 amu arises from the cyclic poly(oxyethylene) with 29 oxyethylene repeat units.[51] The minor peaks in Figure 2d represent potassium-cationized cyclic species. For example, the minor peak to the right of the peak labeled "C" appears at 1315.6 amu and corresponds to the $n = 29$ potassium-cationized cyclic POE.[52] These minor peaks cannot be due to linear species since they are separated from the major peaks by 16 amu and not 18 amu.

In conclusion, cyclic poly(oxyethylene) prepared from linear precursors has been purified by inclusion complexation and precipitation of linear byproducts using α-CD. Using the method described here, we have also prepared clean cyclic polymers from α-hydro-*ω*-hydroxypoly(oxyethylene)s of $M_n \sim 600$ and 900 g/mol. Since cyclodextrins are capable of forming inclusion complexes with a wide variety of linear polymers (organic, inorganic, hydrophobic, hydrophilic),[30−40] they can be used to separate a wide variety of macrocycles from their linear byproducts even if the physical properties of the two are similar.

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(49) 23 amu (Na^+, ambient) + 18 amu (end groups) + n·44 amu (repeat unit) = 1317.6 amu; n = 29 repeat units.
(50) Matrix effects on MALDI-TOF spectra of linear/cyclic mixtures have been noted. Kricheldorf, H. R.; Schwarz, G. *Macromol. Rapid Commun.* **2003**, *24*, 359.
(51) 23 amu (Na^+, ambient) + n·44 amu (repeat unit) = 1299.6 amu; n = 29 repeat units.
(52) 39 amu (K^+, ambient) + n·44 amu (repeat unit) = 1315.6 amu; n = 29 repeat units.

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