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Cyclic polyethers

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A range of cyclic poly(oxyethylene)s, $\overline{\lfloor(\mathrm{OCH_2CH_2})_{\bar{m}}\rfloor}$, with $\bar{m}$ in the range 23–68, corresponding to rings of 69–204 chain atoms, have been prepared by a modified tosylation method that gave *c.* 75 wt% yields. Gel permeation chromatography and nuclear magnetic resonance were used to monitor the cyclization and purification procedures. Small-angle X-ray studies provided a useful method of characterizing the average molar mass of the cyclics.

(Keywords: cyclic polyethers; cyclo-ethers; large crown ethers)

Introduction

In recent years attention has been paid to the synthesis of large cyclic oligomers, i.e. cyclic molecules of uniform chain length. Useful tabulations can be found in the *Polymer Handbook*[1]. Recent reports concern cyclo-esters[2] and, particularly relevant in the present context, cyclo-ethers (large crown ethers)[3]. However, the main requirement in polymer science is for cyclic polymers with chain lengths long enough to generate characteristic 'polymer' properties, say 200 chain atoms or more. For this purpose, cyclic polymers with narrow chain length distributions suffice, the more so since the linear polymers with which comparison of properties may be made have narrow distributions of chain lengths.

The use of cyclic polymers to gain important insights into polymer properties has been reviewed, e.g. for cyclic poly(dimethylsiloxane)s[4]. An obstacle has been the isolation of samples with narrow chain length distributions by fractional distillation or preparative chromatographic methods[5]. Here we report an efficient method for preparation of cyclic poly(oxyethylene)s which largely circumvents this difficulty.

As described below, cyclic polymers with number-average molar masses (M_n) in the range 1000 to 3000 g mol^{-1} and narrow molar mass distributions were prepared from readily available polyethylene glycols [α-hydro,ω-hydroxypoly(oxyethylene)s, PEG1000 to PEG3000] by ring closure via an ether group, to obtain

$$\overline{\lfloor(\mathrm{OCH_2CH_2})_{\bar{m}}\rfloor}$$

where $m = 23–68$ is the number-average chain length in oxyethylene (E) units, corresponding to rings of 69–204 chain atoms. The method was an adaptation of that first used by Kuo *et al.*[6,7] for synthesis of crown ethers, and later applied to the cyclization of PEG1000 by Vitali and Masci[8]. PEG was reacted with tosyl chloride (*p*-toluenesulfonyl chloride, TsCl) in the presence of powdered KOH dispersed in an inert solvent (tetrahydrofuran, THF).

$$-\mathrm{OCH_2CH_2OH} + \mathrm{TsCl} \rightarrow -\mathrm{OCH_2CH_2OTs} + \mathrm{HCl} \quad (1)$$

$$-\mathrm{OCH_2CH_2OTs} + \mathrm{HOCH_2CH_2O}- \rightarrow -\mathrm{OCH_2CH_2OCH_2OCH_2CH_2O}- + \mathrm{TsOH} \quad (2)$$

Vitali and Masci[8] reported a yield of only 8% for the cyclization of PEG1000. Under more favourable conditions (described below) we have obtained yields of cyclics as high as 80%.

In this communication the notation used is the number-average molar mass of polymer followed by L for linear polymer or R for cyclic polymer, e.g. 1000L.

Experimental and results

Preparation of cyclic poly(oxyethylene). The general method of cyclization was to add very slowly (over 24 h or more) PEG (5 g) plus an amount (from equimolar to threefold excess) of TsCl dissolved in THF (100 cm^3) to a dispersion of KOH in a mixture of THF with heptane (75/25% by volume, 100 cm^3). The purpose of the poor solvent (heptane) was to improve ring closure by reducing (on average) the end-to-end distance of the polymer coil. After stirring for a further 24 h, to ensure complete conversion of any remaining glycol to chain-extended polymer, the mixture was filtered and washed with water (50 cm^3) before removing the solvent, initially by rotary evaporation and finally under high vacuum (10^{-4} mmHg), to obtain a solid product. A small portion of this product was used for preliminary analysis by gel permeation chromatography (g.p.c.), and the remainder was purified by fractionation (see below).

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Gel permeation chromatography. Two g.p.c. systems were used. The system used to monitor the cyclization and purification comprised one 30 cm PL-gel column of porosity 500 Å with THF at 20°C and flow rate of 1 $\text{cm}^3\,\text{min}^{-1}$ as eluent, and a Waters R410 differential refractometer as detector. The system used for more precise analysis comprised three 30 cm PL-gel columns (two mixed bed and one 500 Å) with *N,N*-dimethylacetamide (DMA) at 65°C and flow rate of 1 $\text{cm}^3\,\text{min}^{-1}$ as eluent, and a Knauer HT differential refractometer (at 74°C) as detector. All elution volumes were referenced to internal standards.

Figures 1a and *b* show, respectively, g.p.c. curves (THF system) obtained for the linear precursor (2000L) and the crude product of cyclization. The peak at high elution volume in the g.p.c. curve of the product (compared to that of 2000L) was assigned to cyclic polymer 2000R, and the polymer eluting at lower volumes (up to the exclusion limit of the packing used) was assigned to chain-extended polymer. The fractional yield of cyclic polymer was determined as the area under the 'cyclic polymer' peak relative to the total area. Yields determined in this way are listed in *Table 1*.

Purification. The product was dissolved in toluene (250 cm^3), the solution stirred at 25°C, and heptane slowly added until the solution became cloudy. The cloudy solution was heated until it cleared, and then cooled slowly with gentle stirring to 25°C. A clear, concentrated phase separated from a clear dilute phase and could be removed. G.p.c. served to show that the dilute phase contained predominantly cyclic polymer. If necessary, the separation procedure was repeated until essentially all the high-molar-mass linear polymer was removed. The cyclic polymer was recovered from solution by evaporating the solvent. Loss of cyclic polymer in the purification procedure reduced the yields from those listed in *Table 1* by about 25%, i.e. recoveries of 2.5–3.5 g in total.

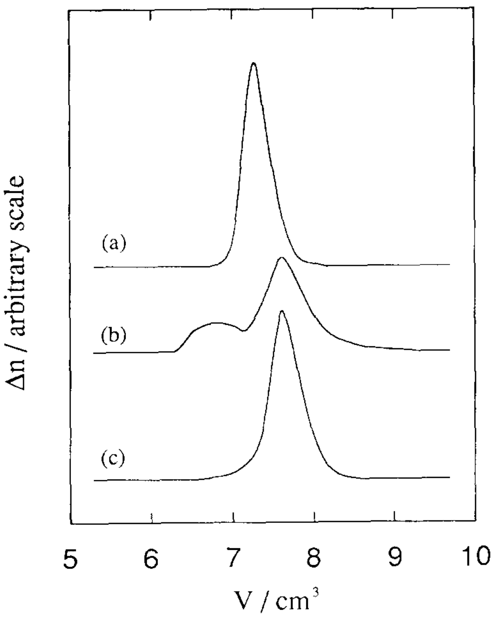

Figure 1 G.p.c. curves (refractive index difference, Δn, *versus* elution volume, V) obtained during the cyclization of PEG2000: (a) the linear precursor polymer, 2000L; (b) the crude product of cyclization; (c) the purified cyclic polymer, 2000R. Peaks resulting from elution of the internal standard (dodecane) and impurities in the solvent are not shown. The curves were obtained with one 30 cm column packed with 500 Å PL-gel. The exclusion limit was 6.35 cm^3

Table 1 Cyclization of polyethylene glycols using toluenesulfonyl chloride[a]

Precursor	Yield (%)
PEG1000	80
PEG1500	75
PEG2000	75
PEG3000	75

[a] Reaction conditions: temperature, 40°C; glycol, 5 g; KOH, 5 g; solvent, THF; non-solvent, heptane (25 vol% in reaction flask); reaction time, 24–46 h; post-reaction time, 24 h

Table 2 Melting points and lamellar spacings of linear and cyclic poly(oxyethylene)s[a]

		Linear		Cyclic	
Precursor	l^b (Å)	T_m (°C)	d (Å)	T_m (°C)	d (Å)
PEG1000	63–66	39	-	33	32
PEG1500	95–99	50	97	47	49
PEG2000	127–132	53	123	51	67

[a] Estimated uncertainties: l, ±5 Å; d, ±3 Å; T_m, ±1°C

[b] l = molecular length along the helix axis calculated assuming 0.93–0.97 Å per chain atom[12,13]

A g.p.c. curve of a purified cyclic polymer is shown in *Figure 1c*. All the samples prepared and purified had similar g.p.c. curves, indicative of narrow chain length distributions. After correction for instrumental spreading, the ratios of weight-average to number-average molar mass (M_w/M_n) were less than 1.1, largely reflecting the widths of the chain length distributions of the precursors.

Nuclear magnetic resonance (n.m.r.) spectroscopy. N.m.r. spectra were recorded by means of a Varian Unity 500 spectrometer operated at 500 MHz for ^{1}H or 125 MHz for ^{13}C spectra, using solutions of *c.* 5 wt% in $CDCl_3$. The spectra of the cyclic polymers contained essentially one peak, at 3.6 ppm (^{1}H) or 70.3 ppm (^{13}C), with resonances assigned[9] to H and C atoms of end groups being of very low intensity (<2% linear polymer).

Melting points. Melting points were determined by differential scanning calorimetry (d.s.c.), defined by the peak of the melting endotherm and corrected for thermal lag. The method used has been described previously[10]. Values are listed in *Table 2*.

Small-angle X-ray scattering. Because of the chemical uniformity of the cyclic polymers, as demonstrated by their n.m.r. spectra, their average molar masses could not be determined by conventional end-group analysis. Confirmation that the chain lengths of the cyclic polymers were the same (within experimental error) as those of their linear precursors was obtained by measuring the lamellar spacings of crystallized cyclic and linear samples by small-angle X-ray scattering (SAXS). The equipment used for X-ray crystallography has been described previously[11]. Samples were crystallized in thin films. Measurements were made with samples held at a constant temperature

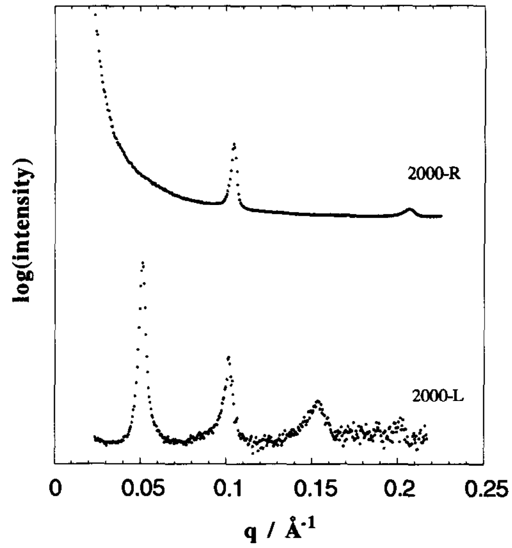

Figure 2 Small-angle X-ray scattering patterns from crystalline cyclic (2000R) and linear (2000L) poly(oxyethylene)s at 20°C

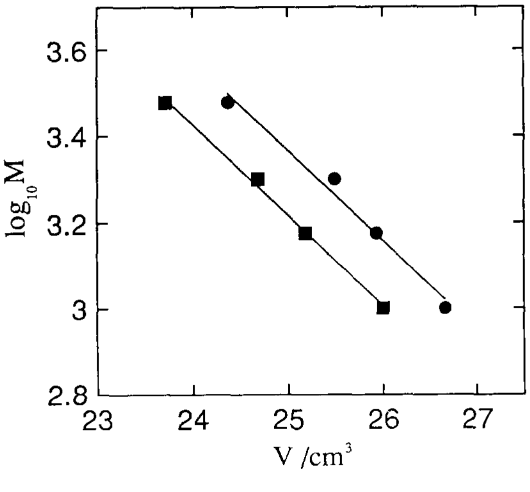

Figure 3 Logarithm of number-average molar mass ($\log_{10} M$) *versus* elution volume in g.p.c. for (●) cyclic and (■) linear poly(oxyethylene)s: DMA system

of 20°C. Both wide-angle (WAXS) and small-angle scattering could be recorded.

Results were obtained for three cyclic polymers (1000R, 1500R and 2000R) and, for comparison, two linear polymers (1500L and 2000L). Sample 3000R was examined, but SAXS from the sample used was too weak to analyse. This was attributed to orientation of lamellar stacks in such a manner as to throw the reflections from the lamellar spacing away from the detector.

Patterns of WAXS served to show that the cyclic polymers crystallized with the same crystal structure as the linear polymers. Given equivalent crystal structure and equivalent orientation of the crystal stems in lamellae, the lamellar spacing of a cyclic polymer should be half that of a linear polymer of equivalent length. As shown in *Figure 2*, in which the SAXS patterns of samples 2000R and 2000L are compared, the periodicity of small-angle reflections from cyclic polymer 2000R was found to be half that of those from linear polymer 2000L, consistent with expectation for a cyclic polymer of the same average molar mass.

Lamellar spacings found for all samples investigated in this way are listed in *Table 2*. Number-average molecular lengths calculated for poly(oxyethylene) in its helical conformation are also listed. The literature[12,13] shows slight variation (from 0.93 to 0.97 Å) in the incremental length along the helical axis of poly(oxyethylene) assigned to one chain atom. However, this uncertainty, noted in *Table 2*, does not affect the present arguments. Comparison of molecular lengths with the measured spacings shows that the helices are orientated normal to the lamellar end surface for the cyclics as well as the linear polymers.

The results of X-ray scattering confirm successful cyclization with insignificant selection among the chain lengths present in the precursor. The high precision of the SAXS experiment provides (under the present circumstances) an accurate measure of chain length, and thereby lends credence to this conclusion.

Elution volume in g.p.c. It is known that cyclic polymers have higher elution volumes in g.p.c. than corresponding linear polymers of equivalent chain length[5]. A plot of $\log_{10} M_n$ against elution volume (DMA system) for the cyclic polymers and corresponding linear polymers was constructed assuming (as confirmed by SAXS) that the average chain lengths of the cyclics were identical with those of the precursors. In order to avoid possible effects of hydroxyl end groups on elution volume[14], this comparison was made against methylated samples[15], i.e. the dimethyl ethers of PEG1000 to 3000, see *Figure 3*. The straight lines through the data points for linear and cyclic polymers are displaced by about 0.15 on the $\log_{10} M$ ordinate, i.e. $M_R/M_L \approx 1.4$. Similar differences have been found in other comparisons of cyclic and linear polymers[5,16].

Discussion

The yield of the cyclic polymer depends on competition between cyclization and chain extension. We write

$$\text{HO–OH} + \text{TsCl} \rightarrow \text{HO–OTs} \quad (3)$$

$$\text{HO–OTs} + \text{TsCl} \rightarrow \text{TsO–OTs} \quad (4)$$

$$2\,\text{HO–OTs} \rightarrow \text{dimer} \quad (5)$$

$$\text{HO–OTs} \rightarrow \text{ring} \quad (6)$$

At high dilution, the bimolecular reactions (3) to (5) are slow compared with the unimolecular reaction (6). Given that reaction (3) occurs at a satisfactory rate, the rates of production of cyclic (R_R) and linear (R_L) products are in ratio:

$$\frac{R_R}{R_L} = \frac{k}{[\text{HO–OTs}]}$$

where k, the ratio of rate constants, $k_R/k_L \propto n^{-3/2}$ (n = number of bonds), is significantly less than 1 (see, for example, ref. 17). However, under the conditions prevailing in our work, the molar concentration of HO–OTs is very small ($<10^{-5}$ mol dm^{-3}), thus ensuring that $R_R \gg R_L$.

Recently[18] we reported an alternative method of ring closure for polyethylene glycol, via an acetal linkage:

$$\llcorner\text{OCH}_2(\text{OCH}_2\text{CH}_2)_m\lrcorner$$

In that case, cyclization was verified by ^{13}C n.m.r. spectroscopy[18] (using the acetal carbon as marker) and by Raman spectroscopy[10]. The method, which was based on Williamson chemistry but with dichloromethane (DCM) as linking agent, involved the following reactions:

$$-OCH_2CH_2OH + CH_2Cl_2 \rightarrow -OCH_2CH_2OCH_2Cl + HCl \quad (7)$$

$$-OCH_2CH_2OCH_2Cl + HOCH_2CH_2O- \rightarrow -OCH_2CH_2OCH_2OCH_2CH_2O- + HCl \quad (8)$$

Yields in the range 80–90% have been recorded for cyclization of PEG1000–3000 by this route. We believe that this reflects the extremely high reactivity of the chloroether formed in reaction (8). The disadvantage in yield from the tosylate method relative to the DCM method may be outweighed in some applications by the fact that the ether closure is chemically stable, whereas the acetal closure is subject to scission under acid conditions.

Concluding remarks

There is reason to suppose that the method described above will prove viable for cyclization of poly(oxyethylene) glycol precursors with M_n greater than $3000\,g\,mol^{-1}$.

Cyclic poly(oxyethylene)s are water soluble, and so have potential for novel interactions with water-compatible systems of interest in colloid chemistry and biochemistry.

Cyclic poly(oxyethylene)s crystallize at temperatures just above ambient, allowing convenient investigation of crystallization rates and crystalline morphologies. Folded chains in lamellae formed under equilibrium conditions offer a convenient system for studying the nature of chain folding in normally helical chains.

Poly(oxyethylene) cyclization chemistry can be simply adapted to the synthesis of cyclic block copolyethers, giving access to a new range of surface-active compounds and providing novel chain architectures for investigation of adsorption from aqueous solution and microphase separation in the bulk state.

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