Synthesis and Characterization of Large (30–60-Membered) Aliphatic Crown Ethers

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We report a new synthetic approach to large (30–72-membered) crown ethers based on isolation of the small and large cyclic polyethers made by combination of 1 mol or 2 mol each, respectively, of oligo(ethylene glycol)s and oligo(ethylene glycol) ditosylates. The advantages of this approach are the use of readily available glycols [up to hexa(ethylene glycol)] as starting materials and the ability to optimize the procedure for selective production of either macrocycle, producing yields superior or comparable to previous methods. At higher reaction temperatures the large crown ether is preferentially formed. This approach has been used to produce the crown ethers on 100-g scales. Purification was achieved by a combination of filtration through silica gel, treatment with a polymeric acid chloride, and recrystallization techniques, avoiding standard column chromatography. The pure crown ethers, 60-crown-20, 48-crown-16, 42-crown-14, 36-crown-12, and 30-crown-10, were characterized by melting points, ¹H- and ¹³C-NMR, elemental analysis, and/or MS, GC–MS, and TGA–MS. Melting points were as much as 26 °C higher than previously reported for these crown ethers. All the aliphatic crown ethers larger than 18-crown-6 decompose upon heating in air at ca. 200 °C.

Introduction

The first viable syntheses of cyclic polyethers, crown ethers, were reported by Pedersen in 1967.[1] Since the first syntheses of dibenzo-18-crown-6, 18-crown-6, and other crown ether macrocycles,[1–4] there has been a tremendous growth in the research activities pertaining to synthesis of macrocyclic molecules analogous to the crown ethers.[5,6] The interest in such macrocycles is derived from the knowledge that such compounds show selectivity in complexing with a variety of neutral and ionic substrates. Modifications of such crown ether structural parameters as size of the cavity, number of ether oxygen atoms, length of aliphatic chains connecting ether oxygens, aromatic groups in the structure, and substitution of oxygen by heteroatoms such as N or S as a part of aliphatic or aromatic units have been reported.[5,6] The selectivity of the complexation is dependent on the above-mentioned parameters as well as other chemical interactions that may be present, thus giving new directions to the subject of molecular recognition. Other variations in structures of such macrocyclic molecules include three-sided enclosed cavities (cryptands)[5,6] or Mobius strips, the one-sided, one-edged "isomer" of a cylinder with a single 180° twist about a long axis.[7]

Our interest in large (>24-membered) crown ethers stems from the fact that such macrocycles are ideally suited for the synthesis of polyrotaxanes **1**, as we have recently

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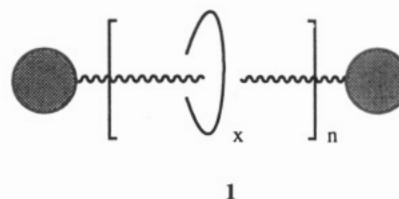
demonstrated.[8] For successful syntheses of polyrotaxanes by polymerization in the presence of macrocycles, the selected macrocycles should meet the following requirements: (1) must have more than 22 members to be threaded by a polymethylene backbone;[9] (2) should be chemically different from the linear component in order to maximize differences in physical properties between the two components; (3) should possess no reactive functionalities that might interfere with the polymerization

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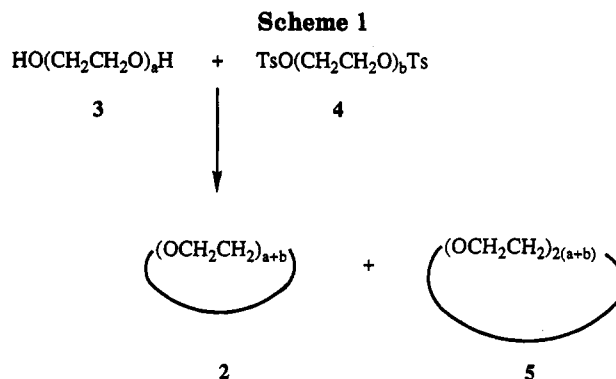
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process; (4) may contain donor centers capable of coordination with the monomer and/or polymer; and finally (5) should be easily prepared in multigram quantities.

While methodologies for the construction of macrocycles still continue to generate considerable interest in both the synthetic organic[5] and polymer chemistry areas,[10] scale-up of these processes is often difficult. Among the general strategies for ring closure, the high-dilution principle[11] and the template method[12] have proved to be most profitable in that the formation of linear oligo- or polycondensation products is suppressed or minimized. The rigid group principle[13] (which restricts the rotational possibilities by having a number of atoms composing the open-chain precursor held in the form of a rigid group), the cesium effect,[14] and the gauche effect[12] have also been used.

A variety of aliphatic as well as aromatic crown ethers and analogues with heteroatoms containing less than 27 atoms have been synthesized and characterized by NMR, X-ray crystal structure analyses, and complexation with either neutral or ionic substrates.[5,6] However, there are relatively few examples of aliphatic and aromatic crown ethers and analogs containing more than 27 atoms reported in literature. Macrocycles containing greater than 27 atoms are generally needed for significant threading of linear species to take place, as in polyrotaxane syntheses.

By a one-pot method in which an oligo(ethylene glycol) is reacted with 1 equiv of *p*-toluenesulfonyl chloride in the presence of a base, forming the monotosylate in situ, syntheses of crown ethers of various sizes from 12-crown-4 to 60-crown-20 have been reported.[15] Crown ethers of larger sizes, up to five times the size of the precursor linear glycol, were also formed, but the yields of higher homologous crowns were generally much lower;[15] for instance, 30-crown-10 was formed in 12% yield from penta(ethylene glycol). From glycols up to the decamer yields of 30–60 membered crowns were all less than 8%. An important conclusion of this study is that the large crown ether macrocycles could be prepared under appropriate conditions. The major drawback of this approach is the necessity to prepare and purify oligo(ethylene glycol)s with more than six oxyethylene units. This is not a trivial task, since fractional distillation or other purification methodologies become more and more difficult as the molecular weight is increased.

The other approach to large crown ethers 2 with (*a* + *b*) ethyleneoxy units is by condensation of 1 mol of an appropriate oligo(ethylene glycol) 3 having "*a*" units with 1 equiv of a oligo(ethylene glycol) ditosylate 4 having "*b*" units in the presence of a base[16] (Scheme 1). The metal hydride used, in some cases, affects the yield of the macrocycle 2 greatly; Na is preferred over K for 27–36-membered crowns, giving up to 37% better yields. Less than 1 g of each macrocycle was prepared. 27-Crown-9, 30-crown-10, and 36-crown-12 were reported as oils, while

Scheme 1

$$HO(CH_2CH_2O)_aH \quad + \quad TsO(CH_2CH_2O)_bTs$$

$$3 \qquad\qquad\qquad\qquad 4$$

$$(OCH_2CH_2)_{a+b} \quad + \quad (OCH_2CH_2)_{2(a+b)}$$

$$2 \qquad\qquad\qquad\qquad 5$$

other macrocycles were reported as low melting solids. The macrocycles were purified by column chromatography. The results, however, do not include the larger macrocycles 5 with 2(*a* + *b*) oxyethylene units which undoubtedly formed by condensations of 2 equiv of glycol 3 with 2 equiv of ditosylate 4.

No matter which approach toward unsubstituted crown ethers is used, the first step involves the preparation of pure oligo(ethylene glycol)s. Homologous impurities in the glycol lead to homologous impurities in the crown ethers, exacerbating the purification problem. As noted above, this is a serious problem if the glycol contains more than six ethylenoxy units, i.e., 3, *a* ≥ 7.

Thus, there are two problems associated with all reported syntheses of large (≥27-membered) crown ethers: (1) the necessity of producing pure high molecular weight oligo(ethylene glycol)s and derivatives, e.g., deca(ethylene glycol)s 3 (*a* = 10) and its ditosylate as precursors to 60-crown-20 (2, *a* + *b* = 20), and (2) the expense associated with the classically employed method of chromatographic purification of the large quantities of crown ethers required for use as solvents in syntheses of polyrotaxanes 1. This paper outlines the approaches we have developed to surmount these two problems and then provides some new characterization results for the large crown ethers produced in pure form.

Results and Discussion

To avoid the synthesis and purification of high molar mass glycols, we adopted the idea of selectively producing the larger ("dimeric") macrocycle 5 from two glycol units 3 and two ditosylate units 4 (Scheme 1). This approach in principle allows the production of macrocycles as large as 72C24 (first number indicating the number of atoms in the ring, "C" crown, and the second number the number of oxygen atoms in the ring) using readily available and purifiable glycols, up to hexa(ethylene glycol) (3, *a* = 6). Glycols containing up to four ethyleneoxy units are cheap and readily available. The pentamer and hexamer are commercially available, but expensive; however, their syntheses can be accomplished in good yields from the cheaper lower homologs, and they can be purified by conventional vacuum distillation.

Linear Precursor Syntheses. Okahara and co-workers claimed to have developed a facile (80% yield) synthesis for hexa(ethylene glycol) (3, *a* = 6).[17] Their strategy consisted of a Williamson-type condensation reaction of tri(ethylene glycol) (3, *a* = 3) with tri(ethylene glycol) monotosylate, generated in situ by the reaction of

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Table 1. Syntheses of Large Crown Ethers According to Scheme 1[a]

a	b	initial diol concn (mol/L)	T (°C)	yields pure (NMR yields) (%)	
				2	5
3	3	0.072	25	40	13 (15)
4	2	0.12	25	37	18 (25)
4	3	0.12	25	22	27
4	3	0.12	67	17	41
4	3	0.67	67		52[b]
3	4	0.097	25		10
3	4	0.097	48		21
3	4	0.097	67		32
4	4	0.097	25		22
4	4	0.67	67		40[b]
6	4	0.12	25	25	37
6	4	0.58	101[b,c]		48

[a] In THF using NaH as base using procedure A (see Experimental Section) unless specified otherwise. [b] In THF (or dioxane if so noted) using NaH as base using procedure B (see Experimental Section): Half of ditosylate added over 0.5 h, stirred 16 h. Solution diluted ca. 9× relative to initial concentration. Rest of ditosylate added over 10 h. [c] Refluxing dioxane.

the former with tosyl chloride in the presence of an appropriate base. This reaction was tried numerous times but produced very low yields (10–33%) in our hands.

By use of Pedersen's classical method[2] tetra(ethylene glycol) (3, a = 4) was converted to tetra(ethylene glycol) dichloride followed by reaction of the dichloride with the disodium salt of ethylene glycol. The yields of pure hexa(ethylene glycol) (3, a = 6) were reproducibly in the range of 25–35%.

After we began this work, Bartsch et al. reported phase transfer catalyzed synthesis of hexa(ethylene glycol) (3, a = 6) in 80% yield.[18] An organic phase consisting of excess ClCH₂CH₂OTHP (THP = 2-tetrahydropyanyl) as solvent and tetra(ethylene glycol) (3, a = 4) was stirred with 50% aqueous sodium hydroxide in the presence of tetrabutylammonium hydrogen sulfate at 65 °C for 3 days. By use of this procedure, in the present study, hexa(ethylene glycol) (3, a = 6) was obtained in yields as high as 92%.

Bis(p-toluenesulfonate)s 4 were prepared by reacting oligo(ethylene glycol)s 3 with p-toluenesulfonyl chloride in the presence of sodium hydroxide in tetrahydrofuran at 0 °C as reported by Ouchi et al.[19] However, the reactions were found not to be complete in the reported 2 h and hence were allowed to proceed for 10–48 h. Under that condition, the reactions were complete and isolation and purification were simplified; i.e., no column separation was necessary. Yields were over 90%.

Crown Ether Syntheses and Purification. The one-pot systematic syntheses of large crown ethers on 0.3 mol scales were generally done in THF using NaH as base, at modest (ca. 0.1–0.7 M in glycol initially) dilution. Two crowns were obtained from each reaction. 2 was formed by "two-piece combination" involving two S_N2 processes and 5 was formed by "four-piece combination" involving four S_N2 displacement reactions (Scheme 1).

Results of syntheses according to Scheme 1 are summarized in Table 1. Highest yields of the large macrocycle 5 were obtained when the ditosylates were equal in length to, or shorter than, the glycols. Alternate syntheses using

the shorter glycols and the longer ditosylates produced lower yields of 5, especially when the glycols were shorter than tri(ethylene glycol). This phenomenon was also observed by Ouchi et al. in the syntheses of 20-crown-6; the yield increased from 26% with butanediol and penta(ethylene glycol) ditosylate to 42% when the diol and ditosylate were reversed.[19]

The total yield of the two crown ethers 2 and 5 ranged from 30% to 65% depending on the system (Table 1). The relative yields of the two crown ethers are determined by several variables such as ring sizes, concentrations, temperature, and template ion used. Generally, at lower temperatures, e.g., 25 °C, the yield of the smaller crown is higher. This is probably because of the shorter end-to-end distance and resultant higher collision probability. On the basis of this idea, higher temperature should favor the formation of the larger ring. Indeed, higher yields of 42C14 were obtained at higher temperatures both when tri(ethylene glycol) reacted with tetra(ethylene glycol) ditosylate and when tetra(ethylene glycol) reacted with tri(ethylene glycol) ditosylate. 42-Crown-14 was the focus of this effort because it is the largest macrocycle which can be constrained by the readily available tris(tert-butylphenyl)methyl end blocking groups[20] on polyrotaxanes 1. 60-Crown-20 was obtained in higher (48%) yield at 101 °C than at 25 °C (37%). Use of higher temperatures for other crowns is under study and will be reported separately.

Two synthetic procedures were employed. In procedure A the dialkoxide (ca. 0.1 M) was prepared by the reaction of the glycol 3 with excess NaH; then the ditosylate 4 was added dropwise. In procedure B glycol 3 was treated with excess of NaH to form the dialkoxide (ca. 0.7 M); then 0.5 equiv of ditosylate was added dropwise, and after several hours of reaction the solution was diluted by a factor of 9 and another 0.5 equiv of ditosylate 4 was added and allowed to react for several hours. As Table 1 shows procedure B produced higher yields of large macrocycle 5.

The isolation and purification of crown ethers are potentially difficult since the reaction products are mixtures of crown ethers with different ring sizes and open-chain diols, ditosylates with different molecular weights and small amounts of catenanes from the larger rings. Vacuum distillations are not practical because of the high boiling points and resultant decomposition. 30-Crown-10 (2, a + b = 10) prepared in the early stages of this research was purified by standard column chromatography using silica gel and ethyl acetate. During the column chromatography most of the linear high molecular weight side products were found to stay on the top of the column. After complete elution of 30C10 from the column 60C20 was found to elute. However, to obtain very pure 30C10 it had to be treated three to four times by column chromatography. However, on large scales such as these, column chromatography is expensive in terms of both adsorbant and solvents.

Fortunately, we found the crown ethers generally can be isolated and purified by alternative purification procedures. By careful ¹H-NMR spectroscopy it is possible by using dry DMSO-d₆ as solvent to detect and quantify OH groups of oligo(ethylene glycol)s as a triplet at 4.57

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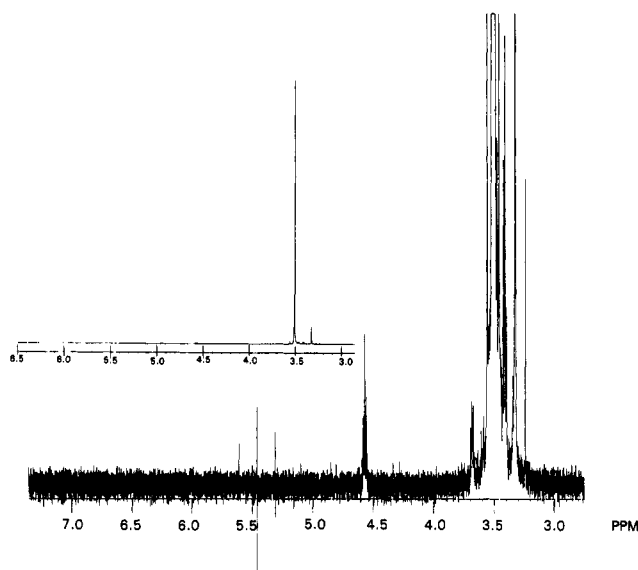
Figure 1. H-NMR (400-MHz) spectrum of crude 42C14 in DMSO-d_6 at 20 °C showing a signal (4.57 ppm) due to OH. The signal at 3.68 is a ^{13}C satellite observed because of vertical expansion; the corresponding high-field signal is obscured by HOD. Note in the unexpanded spectrum that the overall impurity level is low.
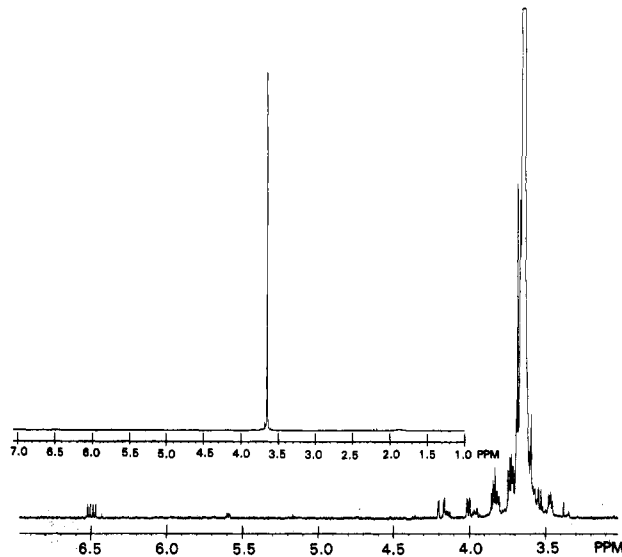
ppm.[21] As Figure 1 shows such signals were observed in impure 42C14. For our use of the crown ethers as solvents in the synthesis of polyrotaxanes 1 with polyester[8] or polyurethane[8] backbones the presence of residual OH moieties in the crown ether will lead to low molecular weights; hence, the glycols must be removed. Also detected in some samples were three signals (doublets of doublets) at 3.97, 4.18, and 6.50 ppm as shown for 42C14 in CDCl$_3$ in Figure 2; these were attributed to vinyl ether end groups in linear species derived by E2 elimination from the tosylates, no doubt exacerbated by excess NaH used in the reactions. Also observed, as exemplified by Figure 2, were impurity signals at ca. 3.70 and 3.85 ppm.

Crude products from large-scale reactions were initially purified by filtration through a short silica gel column to remove linear glycols. The crown ether was then treated with poly(methacryloyl chloride) (6) followed by precipitation into methanol. The glycols and methanol reacted
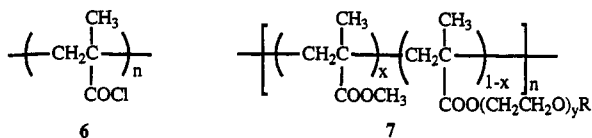
with the poly(acid chloride), and the resultant polyester 7 was completely insoluble in methanol. After removal of solvent from the filtrate, the product was further purified by colum filtration and crystallization from acetone at 0 to −20 °C.

Another method that was found to work well is extraction with hot hexanes. 30C10 (2, $a + b$ = 10) is soluble in hot hexanes while 60C20 (5, $a + b$ = 10) is much less so; thus, very pure 30C10 was obtained by just a few extractions of the crude reaction mixture, followed by recrystallization. The 60C20 thus isolated can be purified by low-temperature recrystallization from acetone. 36-Crown-12 (5, a +

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Figure 2. H-NMR (400-MHz) spectrum of crude 42C14 in CDCl$_3$ at 20 °C showing signals due to terminal –OCH=CH$_2$ (3.97, 4.18, 6.50 ppm) and other impurities (3.66–3.76, 3.83–3.86 ppm). Note the expanded vertical scale which exaggerates the proportions of these impurity signals. The signals at 3.48 and 3.82 ppm are ^{13}C satellites. Note in the unexpanded spectrum that the overall impurity level is low.

Table 2. Melting Points of Crown Ethers

crown	mp (°C)	highest rep. mp (°C)	ref
30C10	42.0–43.8	35.5–36.8	15
36C12	54.5–56.5	36.5–38.0	15
42C14	55.0–57.0	28.5–31.0	16
48C16	49.6–50.8	49.5–50.5	15
60C20	57.0–58.0	46.0–50.5	16

b = 6) can be separated from 18-crown-6 (2, $a + b$ = 6) by exhaustive extraction with hot hexane, in which 36C12 is much less soluble. The hexane-insoluble material upon recrystallization from ethanol or acetone produced pure 36C12. Alternatively, the crude material may be crystallized from methylene chloride initially, yielding the larger macrocycle.

All of these crown ethers were crystalline. Melting points are up to 26 °C higher than any previously reported (Table 2). The availability of larger quantities and improved purification protocols enabled us to obtain this family of crowns in very high purity.

A comparison of the yields obtained in the present work (Table 1) with reported results[16] shows the value of the current methodology. Using concentrations four to seven times greater (to save on solvent cost and facilitate large-scale syntheses), the new method affords the larger crown ethers 36C12, 42C14, 48C16, and 60C20 in yields comparable or superior to the old method with the advantage of avoiding the synthesis and purification difficulties associated with the longer oligo(ethylene glycol)s.

Characterization. All the purified crown ethers show a single peak in the ^{1}H-NMR spectra, even when the chemical shift scale is greatly expanded. For example, Figure 3 shows the absence of hydroxyl signals (4.57 ppm) in 42C14 in DMSO-d_6 solution after purification and Figure 4 demonstrates the absence of vinyl ether signals (3.97, 4.18, and 6.50 ppm) and other impurity signals in CDCl$_3$.

It was difficult to identify the chemical shift differences between the crown ethers when the spectra were taken separately because the instrumental conditions were not always exactly the same. However, the differences are
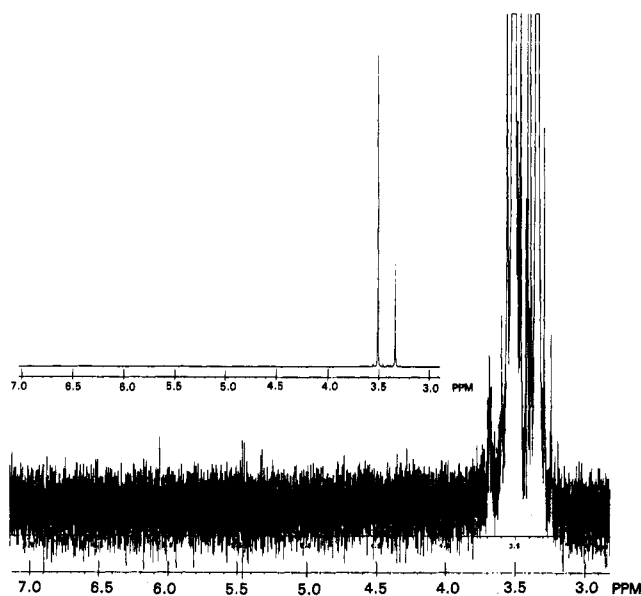
Figure 3. H-NMR (400-MHz) spectrum of pure 42C14 in DMSO-d_6 at 20 °C showing lack of OH signal (4.57 ppm) even on a greatly expanded vertical scale. The signal at 3.35 is due to H_2O.
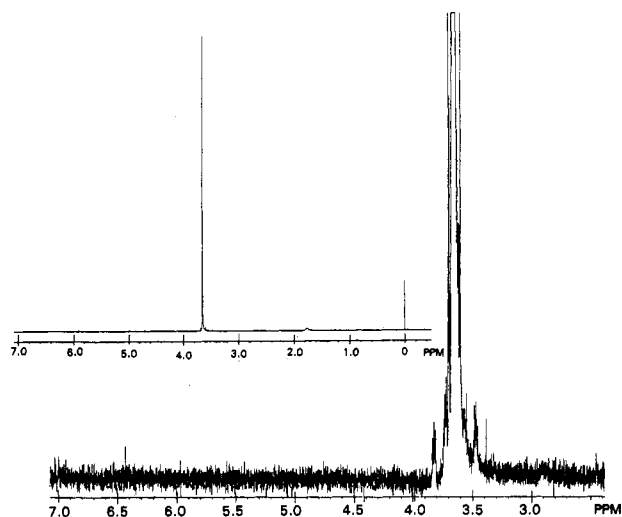
Figure 4. H-NMR (400-MHz) spectrum of pure 42C14 in CDCl$_3$ at 20 °C showing lack of terminal –OCH=CH$_2$ and other impurity signals even on a greatly expanded vertical scale; the signals at 3.48 and 3.82 are ^{13}C satellites, observed due to the vertical expansion.

obvious for synthetic mixtures of pure crown ethers (Figure 5). The chemical shift decreases with increasing ring size, from δ 3.689 for 18C6 to δ 3.646 for 60C20. Likewise, chemical shifts in ^{13}C-NMR decreased from δ 70.67 for 30C10 to δ 70.53 for 60C20, in qualitative but not quantitative agreement with the literature.[16] It is, therefore, not difficult to distinguish the smaller crown from the larger crown produced as per Scheme 1, e.g., 30C10 vs 60C20 or 18C6 vs 36C12 as seen in Figure 5.

Attempts to utilize high pressure liquid chromatography by means of a refractive index detector to provide quantitative purity estimates have been unsuccessful. However, elemental analyses and/or mass spectroscopy (MS) provided confirmation of purity and molecular structures; the corresponding linear glycols would give molecular ions 18 mass units greater than the crown ethers in MS and carbon contents between 1 (60C20) and 2% (30C10) lower. These results also show that no water was
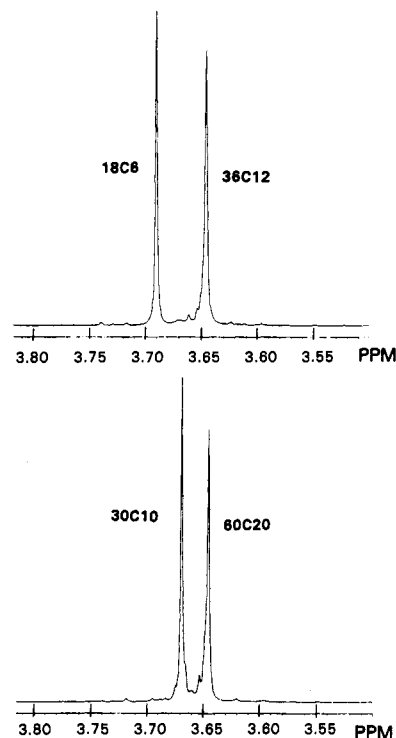
Figure 5. H-NMR (400-MHz) spectra of mixtures of 36C12 and 18C6 (top) and 60C20 and 30C10 (bottom) in CDCl$_3$ at 20 °C.

Table 3. Mass Spectra of Crown Ethers

| crown ether	ionizn[a] technique	parent ion[b] (%)	base peak[b]	other fragments[b] (%)
21C7	EI	308 (48)	89	58 (50), 59 (55), 73 (60), 78 (70), 101 (20), 117 (12), 133 (40), 177 (12), 265 (32)
30C10	CI	441 (100)	89	133 (68), 177 (35)
42C14	CI	617 (8)	133	157 (50), 177 (60), 195 (30)
60C20	CI	882 (28)	89	177 (67), 531 (20), 679 (20)

[a] EI = electron impact, CI – chemical ionization. [b] m/z units.

entrapped in the carefully dried crown ethers. Mass spectral data obtained for 21C7, 30C10, 42C14, and 60C20 are summarized in Table 3. Moreover, infrared spectra of the dry, purified crown ethers showed no OH absorptions. Furthermore, in ^{13}C-NMR no signals were observed at 61.4, 70.2, or 72.5 ppm, as reported for oligo(ethylene glycol)s;[21b] Figure 6 (top) illustrates this for 42C14 and Figure 6 (bottom) shows the ^{13}C NMR spectrum of poly-(ethylene glycol)-600, i.e., 3, $\bar{a}$ = 13.2, for comparison.

The formation of water complexes of crown ethers has been reported to be detected by IR and ^{1}H-NMR spectroscopies.[22] The chemical shifts of the crown ethers are sensitive to solvent. For example, we found that for 42C14 δ = 3.482 ppm in DMSO-d_6, δ = 3.646 ppm in CDCl$_3$, and δ = 3.715 ppm in D$_2$O. The interaction between oxygen atoms in 42C14 and deuterium atoms in the more acidic solvents reduces the electron density on carbons adjacent to oxygen, and consequently the crown ether proton signal shifts downfield due to the deshielding effect.

The shape of the peak also changed with the solvent. In CDCl$_3$ the crown ethers showed shoulders in many cases. The shoulder is due to interactions between the crown ether and trace amounts of water in the CDCl$_3$ solvent, we

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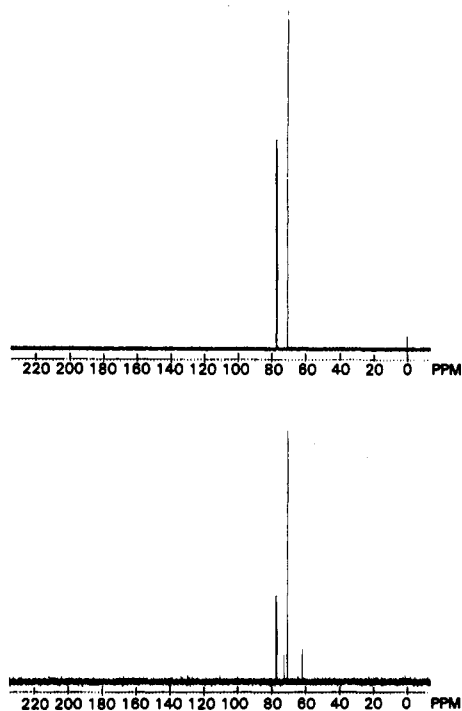
Figure 6. ^{13}C-NMR (100-MHz) spectrum of pure 42C14 in CDCl$_3$ at 20 °C showing a lack of oligo(ethylene glycol) signals. (Bottom) ^{13}C-NMR (100-MHz) spectrum of poly(ethylene glycol)-600 (3, $\bar{n}$ = 13.2) in CDCl$_3$ at 20 °C.

Table 4. Thermogravimetric Analyses of Crown Ethers[a]

crown ether	atm	T_{onset}[b] (°C)	$T_{5\%}$[c] (°C)
30C10	air	172	213
30C10	N$_2$	172	265
36C10	air		214
36C10	N$_2$		374
42C14	air		220
42C14	N$_2$		369
60C20	air	169	205
60C20	N$_2$		376

[a] At 10 °C/min scan rate. [b] Temperature at onset of weight loss. [c] Temperature corresponding to 5% weight loss.

believe. D$_2$O or DMSO-d_6 gave a highly symmetric singlet. In the ^{1}H NMR spectrum of 42C14 there was no significant change in chemical shift or the shape of the peak with the addition of water to a CDCl$_3$ solution. In the case of 18C6, the addition of water shifted the peak from 3.696 ppm (in CDCl$_3$) to 3.681 ppm, but the shape of the peak was maintained as a symmetric singlet. Uncomplexed water peaks were observed at 1.7 ppm when excess dissolved water was present. However, undried 30C10 showed two singlets at 3.675 and 3.671 ppm (in CDCl$_3$). The former, the peak of the tetrahydrate of 30C10, disappeared after the sample had been thoroughly dried under vacuum. Elsewhere, we report X-ray crystal structures of 30C10 and its tetrahydrate.[23]

Differential scanning calorimetric (DSC) analyses of the crown ethers showed that upon rapid cooling from the melt an amorphous glass formed. Then, upon heating, glass–rubber transitions (T_g) were observed at –69 and –67 °C, respectively, for 30C10 and 60C20. Crystallization exotherms occurred at –44 and –43 °C, respectively.

It is important to understand the thermal stability of the macrocycles since in some cases this may limit use of polyrotaxanes 1[8] and related materials. Thus, thermogravimetric analyses were performed. Thermogravimetric analyses (TGA) of some of the crown ethers in air in nitrogen atmospheres are summarized in Table 4. However, although the onset of mass loss can readily be determined, the chemical nature of the evolved compound-(s) cannot be known; i.e., is the compound being volatilized or degraded? To document more completely the thermal behavior of these and related systems, a thermogravimetric analyzer was directly coupled to a mass selective detector (MSD). Six crown ethers have been evaluated by dynamic TGA coupled with MS detection of the volatile products.

The compounds were also evaluated with a gas chromatograph (GC) coupled to an MSD as a reference.

Only one major component was indicated by the GC–MSD of 18-crown-6. The mass spectrum obtained at the maximum of the total ion count (TIC) is shown in Figure 7 (top). It is important to note that the highest molecular weight fragment in the spectrum was m/z 177 (M$^+$ – 87) and the most abundant fragment was m/z 89. These data suggest that the molecular ion of 18-crown-6 (264 amu) does not survive the 70-eV electron source, as recently shown by linked scans for 12-crown-4.[24] In fact, most of the major peaks (m/z = 89, 45, and 133) match those of 18C6 in collision-activated dissociation at 30 eV, derived from the protonated crown.[25] This suggests that self-chemical ionization also occurs under our experimental conditions, as also noted for 12C4 at high pressures;[24] thus, m/z 177 is (M + H)$^+$ – C$_4$H$_8$O$_2$ (dioxane), m/z 89 is probably protonated dioxane, and m/z 45 is CH$_2$CH$_2$OH$^+$.

An additional evaluation of this major chromatographic peak was performed. Because, during the course of a thermogravimetric analysis, there is potentially a wide variation in the flux (mg/min) of sample entering the MSD, the spectra obtained at several positions along the peak were obtained and compared. Although there was a clear transition in the relative intensities of the major peaks, especially m/z 45 vs 89 (increasing with time), after the maximum of the TIC, the spectra obtained all match very well, indicating that nearly the same offgases are produced at the beginning of mass loss as at the end. Samples of 20- and 10-ng quantities of 18-crown-6 at their respective peak maxima each produced a mass spectrum that matched the library spectrum[26] for 18-crown-6 with a quality factor of 95. These data show that over a broad sample size range interpretable mass spectral data are obtained.

The TGA and differential thermogravimetric (DTG) analyses for 18C6 are shown in Figure 7 (bottom). The minimum of the DTG curve occurs at T = 229 °C (t = 9.0 min) and has a width at half-height of 29 °C (1.5 min). The MS TIC peak midpoint is at t = 10.6 min and has a width at half-height of 6.3 min. This indicates that the sample is transferred from the TGA to the MSD fairly quickly at first but is retained to some extent by the cold transfer line. The intensities of the high m/z peaks diminish relative to the low m/z peaks as a function of time (temperature). The best match of this data is with 1,4-dioxane.[26] It thus appears that the 18-crown-6 is decomposing prior to its entrance into the MSD.

(23) Bheda, M. C.; Merola, J. S.; Woodward, W. A.; Vasudevan, V.; Gibson, H. W. *J. Org. Chem.* **1994**, *59*, 1694.

(24) Moini, M. *Proc. 39th ASMS Conf. Mass Spectr. Allied Topics,* May 1991, Nashville, TN, p 879.

(25) Maleknia, S.; Liou, C.-C.; Brodbelt, J. *Org. Mass. Spectrom.* **1991**, *26*, 997.

(26) The spectra obtained using the GC–MSD and TGA–MSD techniques were compared on line with the entries of a spectral data base, the Wiley 130K Mass Spectral Database (G1035A #AA9 Revision A.00.00).
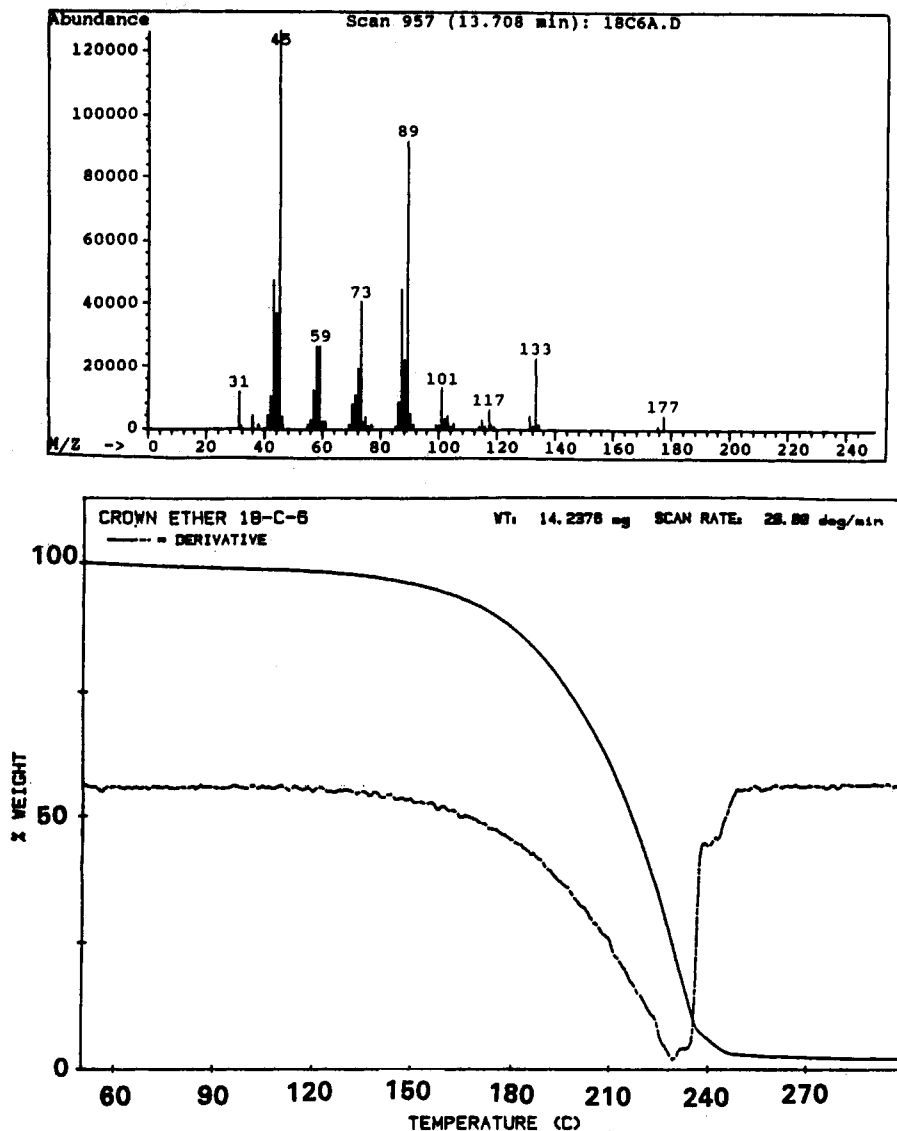
Figure 7. mass spectrum of 18C6 (2, $a + b$ = 6) obtained at the TIC peak maximum for a direct 200-ng GC injection. (Bottom) TGA and DTG obtained for 18C6 (2, $a + b$ = 6).

In an attempt to get more rapid transfer of the TG offgas products into the MSD the transfer line was maintained at 225 °C. Also, the MSD scan parameters were modified so that they would be identical to the parameters that had been used to acquire the GC–MSD data. As was indicated previously, it appears that m/z 88 indicates degradation of the 18-crown-6 within the TGA whereas m/z 89 indicates that the macrocycle entered the MSD intact (Figure 7 (top)). For this reason a selected ion count (SIC) was obtained for these two m/z values. The ratio of intensities was 6 favoring m/z 88. It appears that the predominant components entering the MSD are decomposition products of the crown ether. Additional TG–MSD analyses were performed with the transfer line at 175 °C. Again, the predominant mass spectral peak was m/z 88 instead of 89 by a factor of ca. 8. A final evaluation was performed wherein the transfer line was kept at 140 °C and the 18-crown-6 sample in the TGA was heated to 140 °C. Then, the sample was heated to 220, 230, 240, and 250 °C, each for approximately 2 min. Again m/z 88, not 89, is the most intense signal by a factor of 10. Thus, we conclude that the ratio of crown ether vs decomposition products is a function of temperature and time, as expected.

The mass spectrum at the TIC maximum for a direct GC injection of 15-crown-5 (2, $a + b$ = 5) is shown in Figure 8. The two most abundant peak clusters are m/z 45 and m/z 89 as was the case for 18-crown-6 (Figure 7 (top)). The TIC maximum spectrum (at 18.2 min) for a TGA–MS analysis of 15C5 is nearly identical to the spectrum from the GC–MS analysis (Figure 8). Thus, it seems that 15-crown-5 does not decompose in the TGA before reaching the MSD; it is simply volatile.

Figure 9 (top) shows the mass spectrum at the TIC maximum for a direct GC injection of 30-crown-10 (2, $a + b$ = 10). Again, the two most abundant peaks are m/z 45 and 89. Figure 9 (bottom) shows the analogous data for a TGA–MS analysis of 30-crown-10. With the exception of m/z 28, which is due to nitrogen from a small air leak in the purge system, the major peaks are m/z 88, 58, and 44. The significant differences in mass abundances in these two spectra lead to the conclusion that decomposition is occurring when 30-crown-10 is heated in the TGA.

No GC–MS data were collected for 60-crown-20 (5, $a + b$ = 10). Figure 10 is the mass spectrum at TIC maximum for a TGA–MS run. The most abundant masses are m/z
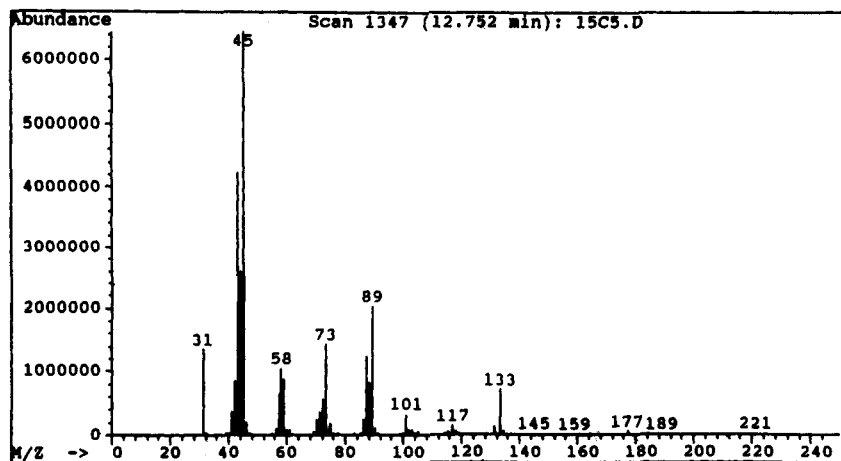
Figure 8. mass spectrum taken at the TIC maximum for a direct GC injection of 200 ng of 15C5 (2, $a + b = 5$) in chloroform.
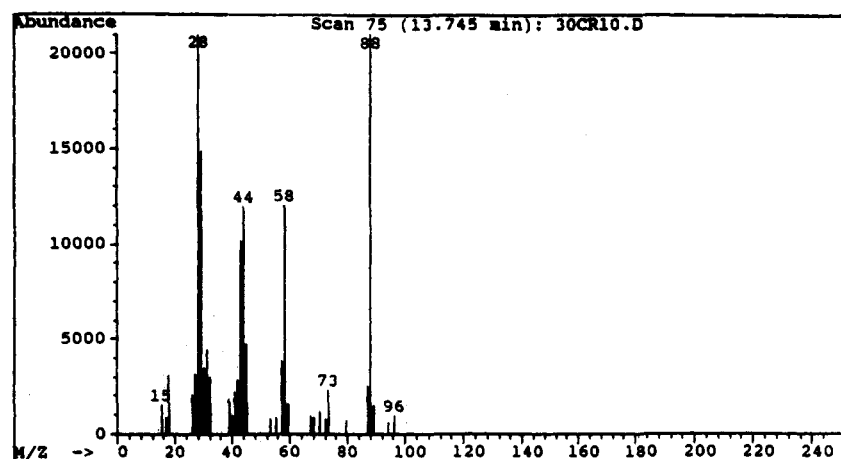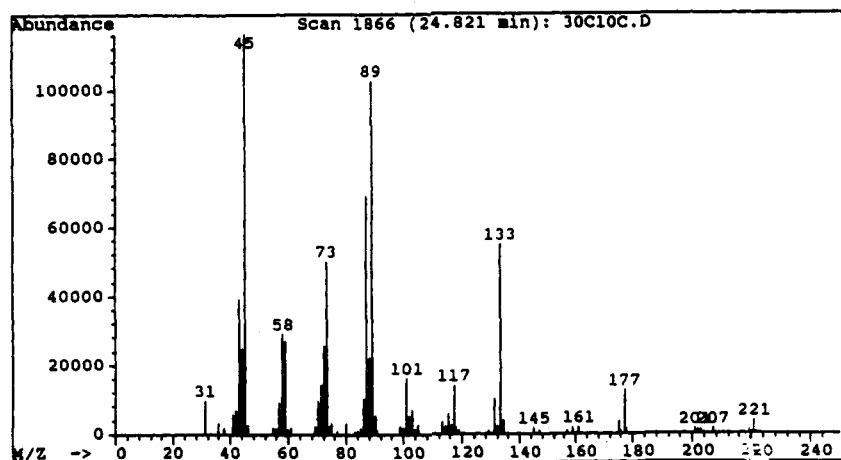

Figure 9. mass spectrum taken at the TIC maximum for a direct GC injection of 200 ng of 30C10 (2, $a + b = 10$) in chloroform. (Bottom) mass spectrum taken at the TIC maximum for a TGA–MS analysis of 30C10 (2, $a + b = 10$).

43 and 127. Also m/z 88 is more prominent than m/z 89. These features indicate that 60-crown-20 is also decomposing in the TGA. M/z 88 corresponds to dioxane and m/z 127 to $C_6H_7O_3$.

Figure 11 is the mass spectrum at TIC maximum for the GC injection of 200 ng of dibenzo-18-crown-6 (DB18C6) (6) in chloroform. The mass spectrum for this ether is quite different from that of 15-crown-5 and its homologues. The most prominent peaks in the DB18C6 spectrum are m/z 136, 121, and 80. The mass spectrum at TIC maximum for the TGA–MS analysis of this crown ether also has

major peaks at m/z 136, 121, and 80. The spectra for direct injection and for evolved TGA gases are very similar. Little or no decomposition occurs for DB18C6 in the TGA; it simply evaporates.

Bis(p-phenylene)-32-crown-4 (BPP32C4) (7) was recently reported by us;[27] it is a predominantly hydrocarbon macrocycle containing only four ether oxygens. BPP32C4 was the most difficult crown ether to analyze. In order to elute this substance from the gas chromatography column,

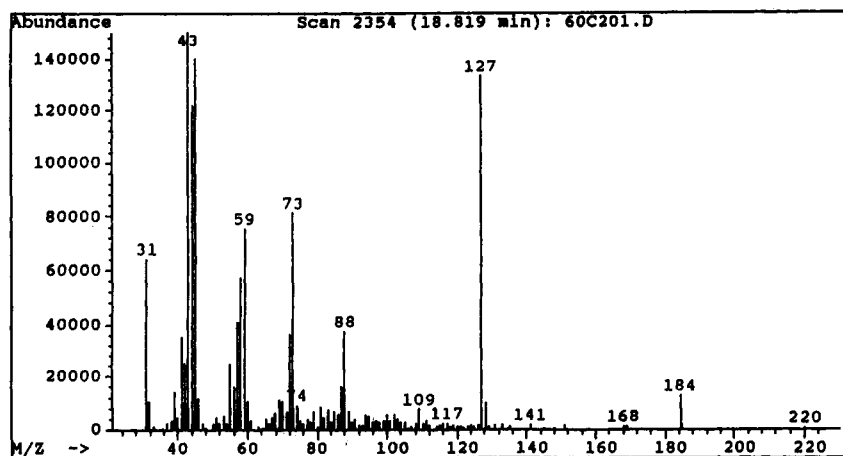(27) Delaviz, Y.; Shen, Y. X.; Gibson, H. W. *Polymer* **1992**, *33*, 212.

Figure 10. spectrum taken at the TIC maximum for a TGA–MS analysis of 60C20 (5, $a + b = 10$).
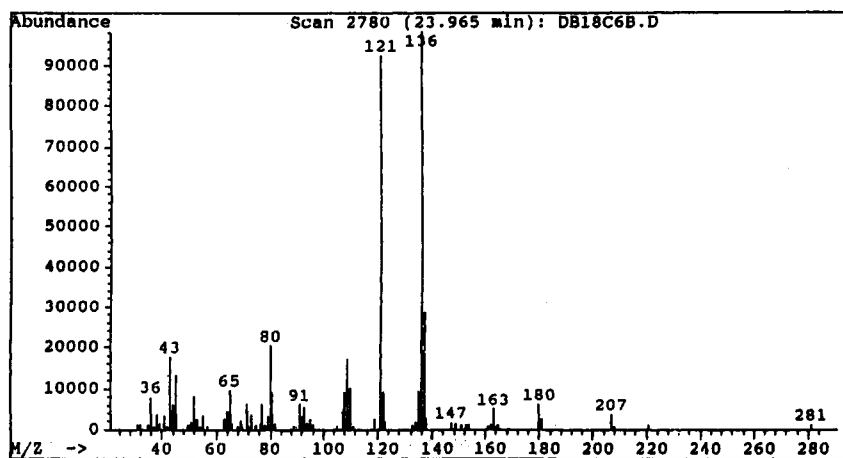

Figure 11. spectrum taken at the TIC maximum for a direct injection of 200 ng of dibenzo-18C6 (6) in chloroform.

the injection port and oven temperature had to be ramped to 280 °C. Even at this temperature, the sample did not elute for several minutes. Figure 12 (top) shows the GC mass spectrum at TIC maximum for BPP32C4. The prominent species in the spectrum are m/z 110 (hydroquinone or 1,7-octadiene?) and 55. A molecular ion signal was recorded at m/z 496. This sample and 15-crown-5 were the only ethers that generated a molecular ion species in the mass spectrometer detector in the GC–MS. Figure 12 (bottom) shows the mass spectrum at TIC maximum for the TGA–MS analysis of BPP32C4. There is scarcely any similarity between this spectrum and that of the direct injection case (Figure 12 (top)). Clearly, BPP32C4 decomposed into a host of different species clustered around m/z 41, 55, 67, 81, 95, and 109. M/z 138 is probably $C_{10}H_{18}$, corresponding to 1,9-decadiene. BPP32C4 was stable enough under electron impact to remain as a molecular ion but was not thermally stable enough in the TGA to produce ions larger than m/z 148, $C_8H_{10}O_2$ (p-dimethoxybenzene?). Nonetheless, as expected, the increased hydrocarbon character of 7 relative to the other crown ethers lends enhanced stability.

Conclusions

Large aliphatic crown ethers with ring sizes of 36–60 atoms have been synthesized from readily accessible precursors, oligo(ethylene glycol)s with six or fewer units, by a one-pot process involving the joining of two glycol and two glycol ditosylate precursors. The process avoids
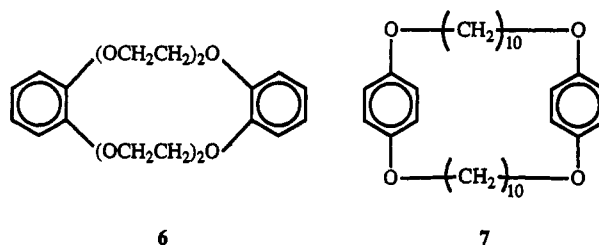
the use of difficult-to-purify higher glycols which were employed in previously reported syntheses by cyclization of one unit each of glycol and ditosylate. Yields by the new approach are comparable or superior to reported values. Purification methods without resort to column chromatography have been developed for separating the mixtures of large and small crowns produced. 36C12, 42C14 and 60C20 have been produced in significantly higher purity than previously reported, as judged by the melting points and careful proton NMR analysis.

It was shown that, within the series of aliphatic crown ethers, only 15-crown-5 exhibits the same spectrum by both GC–MS and TGA–MS. All the larger homologs appear to decompose upon heating in the TGA. Dibenzo-18-crown-6 is thermally stable in the TGA and yields similar spectral features by both techniques. The increased aromatic character of dibenzo-18-crown-6 renders it markedly more stable than 18-crown-6. Bis(p-phenylene)-32-crown-4 requires such high temperatures to vaporize in the TGA that decomposition results; it does
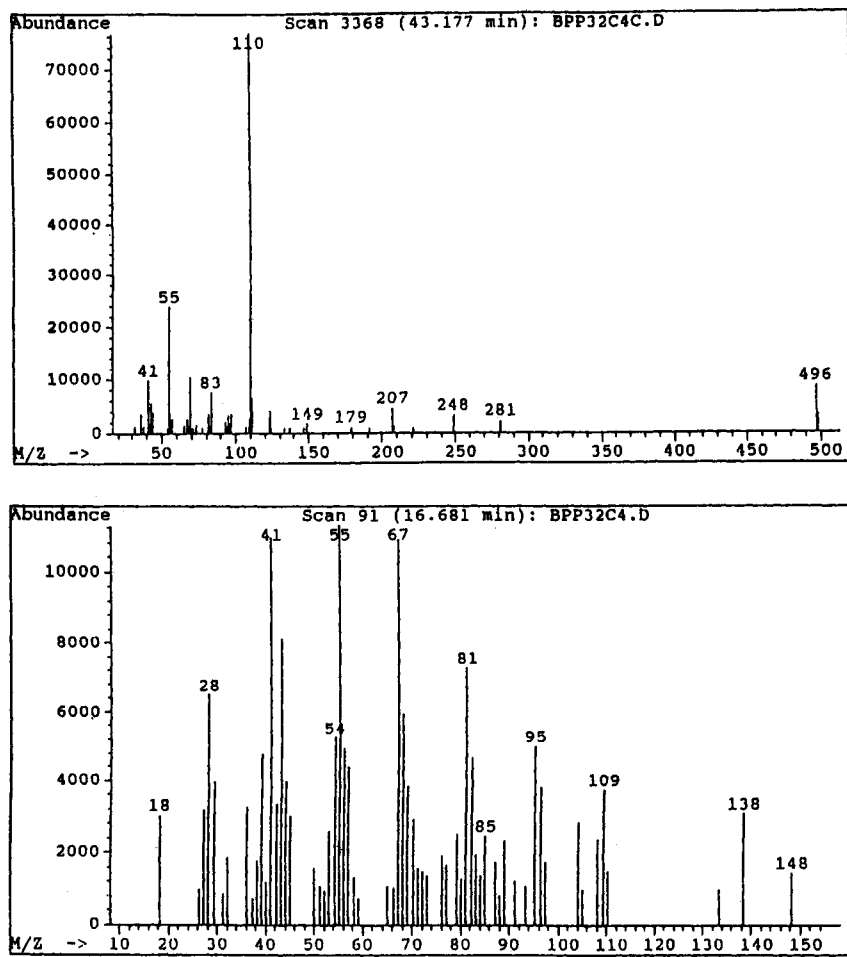
Figure 12. mass spectrum taken at the TIC maximum for a direct GC injection of 200 ng of bis(p-phenylene)-32C4 (7) in chloroform. (Bottom) mass spectrum taken at TIC maximum for a TGA–MS analysis of bis(p-phenylene)-32C4 (7).

produce a molecular ion at 280 °C by direct GC–MS, indicating its enhanced stability.

Experimental Section

General. Melting points were taken in capillary tubes and have been corrected. TGA data were obtained using DuPont TGA 951 and Perkin-Elmer TGA-7 instruments at a scan rate of 10 °C/min. DSC data were obtained using DuPont DSC 912 and Perkin-Elmer DSC-2 instruments at a scan rate of 10 °C/min. Proton and carbon NMR spectra were obtained on a Varian 400-MHz spectrometer using deuterated chloroform solutions with tetramethylsilane as an internal standard, unless otherwise noted; chemical shifts are in ppm. FTIR spectra were obtained on a Nicolet MX-1 instrument. Mass spectral data of Table 3 were obtained using a VGA 7070E analytical mass spectrometer. Elemental analyses were provided by Atlantic Microlab, Inc., Norcross, GA; samples were vacuum dried above the melting point for at least 18 h and protected from the atmosphere.

Ethylene glycol (99%), di(ethylene glycol) (99%), tri(ethylene glycol) (99%), tetra(ethylene glycol) (99%), tri(ethylene glycol) dichloride (99%), hydroquinone (99%), thionyl chloride (99%), and sodium iodide (98%) were purchased and used without further purification. Sodium hydride (60%) in mineral oil was purchased and washed with n-hexane before use. p-Toluene-sulfonyl chloride (98%) was purchased and recrystallized from n-hexane. Tetrahydrofuran was distilled from Na/benzophenone and used immediately.

Tetra(ethylene glycol) dichloride was prepared according to Pedersen[2] in 78% yield after three distillations, bp 148 °C/1.7 Torr (lit.[2] 92%, bp 95 °C/0.4 Torr). IR (ν/max, cm⁻¹): 2905, 1450, 1380, 1342, 1280, 1224, 1110, 1080, 1051, 1000, 950, 900, 832, 748, 661. ¹H-NMR: 3.65 (t, J = 5.9 Hz, 4 H), 3.70 (bs, 8 H), 3.81 (t, J = 5.9 Hz, 4 H). 2-(2′-Chloroethoxy)tetrahydropyran

was prepared according to Buzas[28] in 73% yield, bp 85 °C/12 Torr (lit.[28] yield 71%, bp 89–90 °C/14 Torr).

Hexa(ethylene glycol) (3,a = 6). Bartsch's method[18] utilizing tetra(ethylene glycol) and 2-(2′-chloroethoxy)tetrahydropyran yielded 92% of glycol, bp 216 °C/1–2 Torr (lit.[29] 80%, bp 153–8 °C/0.07 Torr).

Oligo(ethylene glycol) Ditosylates 4. The method of Ouichi[19] was modified by extending the reaction time to 10–48 h. Di(ethylene glycol) ditosylate was produced in 94% yield after two recrystallizations (acetone), mp 89.0–89.5 °C (lit.[19] mp 88–89 °C). Tri(ethylene glycol) ditosylate was isolated in 91% yield after two recrystallizations (acetone), mp 83.5–84.2 °C (lit.[19] mp 80.5–81.5 °C). Tetra(ethylene glycol) ditosylate was obtained in quantitative yield as a colorless viscous oil after the crude product was washed with hot hexane to remove unreacted tosyl chloride.

Poly(methacryloyl chloride) (6). In a 250-mL one-necked flask equipped with a condenser, nitrogen inlet, and magnetic stirrer were dissolved distilled methacryloyl chloride (30.0 g, 0.287 mol) and azobis(isobutyronitrile) (AIBN), 0.47 g, 2.87 mmol, in dried (CaCl₂) toluene (100 mL). The solution was stirred at 90 °C under nitrogen for 20 h. After the solution had been cooled to room temperature, it was precipitated into dried (4-Å molecular sieves) n-hexane (1 L). The polymer was filtered and vacuum dried (18.9 g, yield 63%).

Crown Ethers, General Procedure A. Oligo(ethylene glycol) (3), 300 mmol, was dissolved in 2.4 L of THF in a 5-L flask. Sodium hydride, 48 g, 60% (1.2 mol), was washed with hexane and carefully added to the solution. The mixture was mechanically stirred under dry nitrogen for 0.5–5 h. Oligo(ethylene glycol) ditosylate (4), 309 mmol in 700 mL of THF, was

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(28) Buzas, A.; Egnell, C.; Moczar, M. *Bull. Soc. Chim. Fr.* **1962**, 267.

(29) Cornforth, I. W.; Morgan, E. D.; Potts, K. T.; Rees, D. J. *Tetrahedron* **1973**, *29*, 1659.

added dropwise over a period of ca. 2 h. The reaction was stirred for 48–56 h at the specified temperature. Water, 100 mL, was added dropwise to the reaction mixture to destroy the excess NaH. After filtration THF was evaporated. Excess ditosylate was separated from the water phase by a separatory funnel. Crude crown ether was extracted from the aqueous solution into methylene chloride. The crown ether solution was filtered through a 45- × 2.5-cm silica gel column. Methylene chloride was used as the solvent. The solvent was evaporated after the filtration.

Crown Ethers: General Procedure B. Synthesis of 21C7 (2, *a* + *b* = 7) and 42C14 (5, *a* + *b* = 7). To a three-necked, 1-L round-bottomed flask fitted with a condenser and a mechanical stirrer was added NaH (7.60 g, 80% oil dispersed, 250 mmol), and the resulting mixture was washed with *n*-hexane (2 × 60 mL). THF (or dioxane) (80 mL) was added, and then tetra-(ethylene glycol) (3, *a* = 4) (12.14 g, 62.5 mmol) was added dropwise over a period of 30 min. The reaction mixture was stirred without heating for 40 min. The reaction mixture was heated to reflux, and then tri(ethylene glycol) ditosylate (4, *b* = 3) (14.34 g, 31.3 mmol) in THF (or dioxane) (40 mL) was added dropwise into the refluxing mixture over a period of 50 min with vigorous stirring. After 6 h, THF (or dioxane) (700 mL) was added to dilute the reaction mixture, and tri(ethylene glycol) ditosylate (4, *b* = 3) (14.45 g, 31.5 mmol) in THF (or dioxane) (50 mL) was added dropwise to the refluxing reaction mixture over a period of 50 min. The reaction mixture was allowed to stir for 28 h. Water (5.5 g) was added to destroy excess NaH, followed by filtration and washing the salts formed with THF (50 mL × 2). The solvent was removed by rotary evaporation from the filtrate to afford the crude solid product.

Purification Using Poly(methacryloyl chloride): 42C14. To a 500-mL three-necked flask equipped with nitrogen inlet, a condenser, and magnetic stirrer were added 42C14, mp 52.5–54.9 °C (recrystallized from acetone 3×), 25.0 g, 40.5 mmol, poly-(methacryloyl chloride), 8.90 g, 85.3 mmol of acid chloride, pyridine, 1.5 mL, 18.5 mmol, and freshly distilled, dry THF (250 mL). The mixture was stirred at room temperature for 16 h and 1 h under reflux and precipitated into methanol (500 mL), resulting in a suspension. After the mixture had been boiled on a steam bath, the polymer precipitated completely and was removed by filtration. A yellow oil was obtained after all the solvents had been removed by rotary evaporation. The product was passed through a short silica column (1 × 3.1 cm) and recrystallized in acetone. A colorless solid (20.64 g, recovery 83%) was obtained after vacuum drying.

30-Crown-10 (2, *a* + *b* = 10) and 60-Crown-20 (5, *a* + *b* = 10). The proton NMR spectrum of the crude product indicated three compounds, namely 30C10 (δ = 3.67), 60C20 (δ = 3.64), and a very small amount of presumed catenane (δ = 3.65). The mixture was purified by recrystallization from acetone at –0 to –20 °C. 60C20 formed a white solid gel[30] with some acetone trapped in it, while other compounds remained in the cold solution which was removed using a filtering stick. Powdery 60C20 was obtained after recrystallizations from acetone at 0 °C. IR: same as 30C10 (below). ^{1}H-NMR: 3.646 (s). ^{13}C-NMR: 70.67. Anal. Calcd for $C_{40}H_{80}O_{20}$: C, 54.53; H, 9.15. Found: C, 54.33; H, 9.17. Anal. Calcd for $C_{40}H_{82}O_{21}$ [H(OCH$_2$CH$_2$)$_{20}$OH]: C, 53.43; H, 9.19.

The 30C10 fraction was purified by recrystallization from water at 4 °C. IR (ν/max, cm^{-1}): 2878, 2735, 1762, 1457, 1347, 1299, 1251, 1135, 1115, 1040, 992, 944, 855, 732. ^{1}H-NMR: 3.671 (s). ^{13}C-NMR: 70.53. Anal. Calcd for $C_{20}H_{40}O_{10}$: C, 54.53; H, 9.15. Found: C, 54.44; H, 9.14. Anal. Calcd for $C_{20}H_{42}O_{11}$[H(OCH$_2$CH$_2$)$_{10}$OH]: C, 52.38; H, 9.23.

Mother liquors from both the fractions were combined and upon evaporation of the solvents gave an oily mixture of several compounds including 30C10, 60C20, and possibly catenane (proton NMR analyses showed five to six peaks).

18-Crown-6 (2, *a* + *b* = 6) and 36-Crown-12 (5, *a* + *b* = 6). The crude product was dissolved in ethyl alcohol (400 mL) and filtered. Ethyl alcohol was removed, and the crude product was extracted with hot hexane until TLC showed no more organic

compounds being extracted. The 18C6 was extracted into the hexane layer. After three recrystallizations from hexane, pure 18C6 was obtained, mp 41–42.5 °C, (lit.[2] mp 39–40 °C). Then the hexane insoluble crude product was recrystallized from ethyl alcohol at –20 °C four times to afford 36C12. IR: same as 30C10 (above). ^{1}H-NMR: 3.647 (s).

21-Crown-7 (2, *a* + *b* = 7) and 42-Crown-14 (5, *a* + *b* = 7). The crude product was subjected to low-temperature recrystallization from acetone to give 42C14, which was purified by reaction with poly(methacryloyl chloride) (6), column filtration, and recrystallization from acetone as noted above. IR: same as 30C10 (above). ^{1}H-NMR: 3.647 (s). Anal. Calcd for $C_{28}H_{56}O_{14}$: C, 54.53; H, 9.15. Found: C, 54.36; H, 9.10. Calcd for $C_{28}H_{58}O_{15}$ [H(OCH$_2$CH$_2$)$_{14}$OH]: C, 52.98; H, 9.21. 21C7 was isolated as an oil. ^{1}H NMR: 3.689 (s).

24-Crown-8 (2, *a* + *b* = 8) and 48-Crown-16 (5, *a* + *b* = 8). Low-temperature recrystallization provided crystalline 48C16. IR: same as 30C10 (above). ^{1}H-NMR: 3.646 (s). ^{13}C-NMR: 70.67.

Gas Chromatography–Mass Spectrometry. 15-Crown-5, 18-crown-6, and dibenzo-18-crown-6 were obtained from a commercial source. A solution of each macrocycle was prepared by dissolving 100 mg in 100 mL of chloroform. A 1-mL portion of this solution was diluted to 100 mL to yield a second, less concentrated solution (10 µg/mL). Gas chromatography–mass spectrometry data were obtained with a Hewlett-Packard Model 5971A mass selective detector (MSD) and a Hewlett-Packard Series II gas chromatograph. GC column: HP-1 cross-linked methyl silicone gum, 12 m × 0.2 mm, 0.33-µm film thickness; carrier gas, 99.999% helium; injector temperature, 180 °C; detector (MSD) temperature, 250 °C; column temperature, 50 °C for 3 min, 50–250 °C at 15 °C/min. The MSD parameters were as follows: solvent delay, 2.00 min; low mass, 30; high mass, 300; samplings per scan, 4; threshhold, 500; ionization, 70-eV electron impact.

Thermogravimetry–Mass Spectrometry Data. The TGA–MS system was constructed using two commercially available analytical instruments and a custom designed interface. A Perkin-Elmer thermogravimetric system (Model TGS-2) was coupled to a Hewlett-Packard mass selective detector (Model 5971A). The TGS-2 determines the mass of a sample as a function of time and temperature in a controlled atmosphere. The capillary interface acts as a conduit through which the volatile off-gas species are conveyed. While the samples were being heated the off-gas products were swept dynamically to the MSD by using a physically modified, externally heated TGS furnace tube to reduce adsorption of the off-gas products. The gases next traveled through a deactivated capillary that was sheathed in metal and was independently heated. The species traveled into the analyzer region of the MSD resulting in a spectrum approximately every half second. The MSD provides spectra of the gases as a function of time. The MSD data can be correlated with the TGA data by noting the starting temperature, heating rate, and MSD acquisition start time. Thermogravimetric analyses of crown ethers were obtained by heating ca. 15 mg samples from 50 to 300 °C at 20° per min in a helium atmosphere. MSD parameters: purge, 5 min prior to start of TG and MS data collection; low mass, 10; high mass, 450; sampling per scan, 128; threshhold, 500; ionization, 70-eV electron impact.

(30) Prasad, A.; Marand, H.; Bheda, M.; Gibson, H. W. *Polym. Prepr. Am. Chem. Soc. Div. Polym. Chem.* **1991**, *32*(3), 469.