# Synthesis of Strained Macrocyclic Biaryls for Enthalpy-Driven Ring-Opening Polymerization

**Howard M. Colquhoun,*,† Zhixue Zhu,† Christopher C. Dudman,‡ Caroline A. O'Mahoney,§ David J. Williams,§ and Michael G. B. Drew†**

*School of Chemistry, University of Reading, Whiteknights, Reading, U.K. RG6 6AD, Imperial Chemical Industries plc, The Heath, Runcorn, Cheshire, U.K. WA7 4QE, and Chemical Crystallography Laboratory, Department of Chemistry, Imperial College, South Kensington, London, U.K. SW7 2AY*

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ABSTRACT: Polymerizable macrocyclic biarylene−ether−ketones and biarylene−ether−sulfones are accessible from linear, bis(chloro)-terminated oligomers via nickel-catalyzed, intramolecular coupling under pseudo-high-dilution conditions. Single-crystal X-ray analyses of the resulting cyclo-oligomers reveal extremely distorted and highly strained geometries, with 4,4′-biphenylene units showing deviations of up to 70° from linearity.

## 1. Introduction

Aromatic polyethers such as the poly(ether−ketone)s and poly(ether−sulfone)s exhibit high thermooxidative stabilities, excellent thermomechanical properties and very good impact resistance, leading to their widespread application as high-performance engineering thermoplastics.[1] However, the high melt viscosities of these polymers place limits on their ability to be fabricated into complex shapes, especially at very short length scales, and to be used in composite materials where high levels of reinforcing particles or fibers are present. A potential solution to this problem involves the use of low viscosity macrocyclic precursors, which undergo ring-opening polymerization in situ to give high molar mass polymers without generating byproducts.[2] There is thus considerable current interest in the synthesis of macrocyclic aromatic ethers and in the chemistry of their interconversion with polymeric materials.[3]

Such syntheses (other than those described in preliminary comunications of the present work)[4,5] have focused mainly on activated nucleophilic ($S_NAr$) cyclo-etherification chemistry, carried out under pseudo-high-dilution conditions.[6] For example, homologous series of cyclic ether−ketones have been obtained (i) by self-condensation of 4-fluoro-3′-hydroxybenzophenone[7] or 4-fluoro-4′-hydroxybenzophenone,[8] (ii) by condensation of 1,3-bis(4-fluorobenzoyl)benzene with 4,4′-biphenol,[9] (iii) from 1,2-bis(4-fluorobenzoyl)benzene,[10] or its tetraphenyl derivative,[11] by reaction with a range of bisphenols, and (iv) by condensation of 4,4′-difluorobenzophenone with either resorcinol,[12] bisphenol A,[13] or 3,3′,5,5′-tetramethyl-4,4′-biphenol.[14] Pure, monodisperse macrocycles have been isolated from a number of these "one-pot" reactions by chromatographic fractionation, but an alternative approach involving stepwise construction of long-chain intermediates has also enabled good yields of specific macrocyclic ether−ketones[15] and ether−sulfones[16] to be obtained.

Perhaps as a result of the reversible nature of nucleophilic aromatic substitution, the macrocyclic oligomers so far obtained by this route are almost exclusively strain-free, so that there is no significant enthalpy change associated with their ring-opening polymerization.[7−11,15,16] The latter reaction is then dependent almost entirely on entropic factors—mainly the increase in *conformational* entropy resulting from the opening of a constrained cyclic structure. However, this is opposed by a corresponding decrease in *translational* entropy on polymerization, resulting in a delicately balanced situation whereby quite modest dilutions can shift the thermodynamic equilibrium strongly in favor of cyclic oligomers.[17] Indeed, even in the absence of solvent, the "self-diluting" effect of polymer formation means that significant levels of macrocycles are invariably present at equilibrium.

To provide a higher thermodynamic driving force for ring-opening polymerization, a rather different type of aromatic macrocycle is clearly required, i.e., one having a substantial degree of ring-strain analogous to that of an oxirane or oxetane in aliphatic chemistry. Nucleophilic cyclo-etherification, for the reasons given above, generally fails to yield macrocycles of this type although trace quantities of the strained cyclic *thioethers* [−S-1,4-$C_6H_4$−$SO_2$−Ar−]$_2$ and [−S-1,4-$C_6H_4$−]$_4$ have been isolated from reactions involving displacement of aryl halide substituents by sulfur-based nucleophiles.[18,19] Electrophilic aromatic acylation has also been been briefly described as a route to polymerizable macrocyclic ether−ketones,[20,21] but no evidence for the formation of strained macrocycles has so far been reported for these reactions. In the present paper we describe the first general route to *highly* strained, polymerizable aromatic macrocycles via intramolecular, nickel-catalyzed formation of biaryl linkages.

## 2. Experimental Section

**2.1 Materials.** Reagents and solvents were obtained from Aldrich, Acros, or Lancaster and, other than *N*,*N*-dimethylacetamide, were used as received. The latter was distilled from calcium hydride under dry nitrogen immediately prior to use. The intermediates 4,4′-diphenoxydiphenyl sulfone,[22] 4-chloro-4′-fluorobenzophenone,[23] 2,2-bis(4-phenoxyphenyl)hexafluoro-

* Corresponding author. E-mail: h.m.colquhoun@rdg.ac.uk.
† University of Reading.
‡ Imperial Chemical Industries plc.
§ Imperial College.

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propane,[24] 2,8-diphenoxydibenzofuran,[22] 3,6-dihydroxyxanthone,[22] 4-chloro-4′-hydroxydiphenyl sulfone,[25] and 4,4′-bis(4″-chlorobenzenesulfonyl) diphenyl ether[26] were synthesized according to literature methods. Syntheses of the linear precursor compounds **1**−**4** and **9**−**16** and characterization data for these precursors and for macrocycles **17**−**26** are provided as Supporting Information.

**2.2. Instrumental Analyses.** $^1$H and $^{13}$C NMR spectra were recorded on Bruker DPX-250, A-300, and AMX-400 spectrometers. Spectra were obtained, unless otherwise stated, using a 10:1 v/v mixture of deuteriochloroform and trifluoroacetic acid as solvent. Chemical shifts ($\delta$) are quoted as parts per million (ppm) downfield from TMS, with multiplicities given as singlet (s), doublet (d), double−doublet (dd), triplet (t), multiplet (m), and broad (b). Infrared spectra were obtained from Nujol mulls on a Perkin-Elmer PE1700 FT-IR spectrophotometer. Mass spectra (EI/CI) were recorded on a VG Autospec spectrometer, and FAB-MS spectra were obtained on a Kratos Concept-IS instrument. Matrix-assisted laser desorption/ionization time-of-flight (MALDI−TOF) mass spectra were obtained using Micromass Tofspec 2E and SAI LT3 LaserTof spectrometers, with 1,8,9-trihydroxyanthracene as matrix and sodium trifluoroacetate as cationizing agent. Melting points were measured under nitrogen using a Mettler DSC-20 system, at a heating rate of 10 °C/min, and are quoted as peak values. Elemental analyses were carried out by Medac (UK) Ltd. Thin-layer chromatography (TLC) was performed on Polygram Sil G/UV 254 plates with visualization by UV light at 254 nm, and column chromatography on Merck silica gel 60 (particle size 0.040−0.063 nm). X-ray data were collected on a Siemens P4/RA diffractometer with graphite-monochromated Cu K$\alpha$ radiation using $\omega$-scans, and on a Mar Research image-plate system with Mo K$\alpha$ radiation. Structures were solved by direct methods and the non-hydrogen atoms were refined anisotropically.

**2.3. General Procedure for Ni(0)-Catalyzed Cyclization (Yielding Macrocycles 5, 6, 7, 8, 17, 18, 19, 20, 21, 22, 23, 24, 25, and 26).** The synthesis of macrocycle **6** is given as an example. A mixture of triphenylphosphine (38.0 g, 145 mmol), tetra-*N*-butylammonium iodide (27.0 g, 73 mmol) and the nickel(II) chloride-pyridine complex $Ni(Py)_4Cl_2$ (8.25 g, 19 mmol) in dry DMAc (800 mL) was stirred under nitrogen for 10 min to give a green solution. Finely powdered zinc (13.2 g, 200 mmol) was then added, and the mixture was heated to 60 °C and stirred for a further 0.5 h to give a red-brown suspension of $Ni(PPh_3)_4$. A solution of the linear oligomer **2** (14.0 g, 20 mmol) in dry DMAc (1200 mL) was added dropwise with stirring over 5 h. After the addition was completed, the mixture was stirred at 60 °C for 0.5 h and then cooled and filtered to remove unreacted zinc. The filtrate was poured into 5 M hydrochloric acid (3000 mL), and the precipitate was collected by filtration, washed with aqueous methanol and dried. The solid was then extracted with hot ethanol, the extract filtered hot, and the solid dried. Macrocycle **6** was obtained in 45% yield as a white crystalline solid by column chromatography (4% ethyl acetate in DCM).

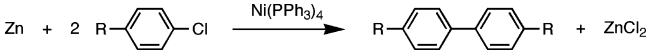
**Macrocycle 5.** Yield: 27.8%. Mp: 387 °C. $^1$H NMR ($CDCl_3$/TFA; 250 MHz), $\delta$ (ppm): 7.74 (d, $J$ = 8.3 Hz, 4H), 7.53 (d, $J$ = 8.3 Hz, 4H), 7.42 (d, $J$ = 8.9 Hz, 4H), 7.38 (d, $J$ = 9.0 Hz, 4H), 7.12 (d, $J$ = 9.0 Hz, 4H), 7.04 (d, $J$ = 8.9 Hz, 4H). $^{13}$C NMR ($CH_3SO_3H$:$CD_2Cl_2$ 1:5, 62.5 MHz), $\delta$ (ppm): 205.9, 167.0, 155.0, 146.0, 138.4, 134.7, 132.6, 131.6, 131.4, 129.6, 128.9, 121.1, 118.4; IR (Nujol) 1677 cm$^{-1}$ ($\nu$CO). MS (FAB): calcd for $C_{41}H_{24}F_6O_4$, *m/z* 694.16; found, 695 [M + H]$^+$. Anal. Calcd for $C_{41}H_{24}F_6O_4$: C, 70.89; H, 3.48. Found: C, 70.67; H, 3.47. Crystal data for **5**: $2(C_{41}H_{24}O_4F_6)\cdot Et_2O\cdot MeOH$, $M$ = 1495.37, monoclinic, space group $P2_1/c$, $a$ = 26.873(1) Å, $b$ = 12.652(1) Å, $c$ = 20.611(1) Å, $\beta$ = 98.84(1)°, $V$ = 6924.7(6) Å$^3$, $T$ = 173 K, $Z$ = 4, $D_c$ = 1.434 g cm$^{-3}$, $\mu$ (Cu−K$\alpha$) = 0.975 mm$^{-1}$, $F$ (000) = 3088; 10905 independent reflections, $R_1$ = 0.053, $wR_2$ = 0.129 for 8259 independent observed reflections [$2\theta \le 124°$, $I > 2\sigma(I)$].

**Macrocycle 6.** Yield: 45.2%. Mp: 354 °C. $^1$H NMR ($CH_3SO_3H$:$CD_2Cl_2$ 1:5, 300 MHz), $\delta$ (ppm): 8.10 (d, $J$ = 8.7 Hz, 4H), 7.86 (d, $J$ = 8.4 Hz 4H), 7.65 (d, $J$ = 8.4 Hz, 4H), 7.46 (d, $J$ = 9.0 Hz, 4H), 7.32 (d, $J$ = 8.7 Hz, 4H), 6.85 (d, $J$ = 9.0 Hz, 4H). $^{13}$C NMR ($CH_3SO_3H$:$CD_2Cl_2$ 1:5, 75 MHz), $\delta$ (ppm): 204.2, 166.8, 158.4, 144.4, 139.1, 137.5, 134.5, 131.2, 130.6, 129.4, 128.0, 123.7, 116.9. IR (Nujol): 1691, 1677 cm$^{-1}$ ($\nu$CO). MS (FAB): calcd for $C_{38}H_{24}O_6S$, *m/z* 608.13; found, 609 [M + H]$^+$. Anal. Calcd for $C_{38}H_{24}O_6S$: C, 74.98; H, 3.97; S, 5.26. Found: C, 74.77; H, 3.72; S, 5.46. Crystal data for **6**: $C_{38}H_{24}O_6S\cdot C_6H_5CH_3$, $M$ = 700.8, monoclinic, space group $P2_1/n$, $a$ = 11.403(2) Å, $b$ = 18.815(3) Å, $c$ = 17.273(3) Å, $\beta$ = 106.63(1)°, $V$ = 3550.9(10) Å$^3$, $T$ = 293 K, $Z$ = 4, $D_c$ = 1.311 g cm$^{-3}$, $\mu$(Cu K$\alpha$) = 1.22 mm$^{-1}$, $F$(000) = 1464; 3648 independent reflections, $R_1$ = 0.043, $wR_2$ = 0.106 for 2915 independent observed reflections [$2\theta \le 100°$, $I > 2\sigma(I)$].

**Macrocycle 7.** Yield: 53.7%. Mp: 353 °C. $^1$H NMR ($CH_3SO_3H$:$CD_2Cl_2$ 1:5, 300 MHz), $\delta$ (ppm): 7.88 (d, $J$ = 8.4 Hz, 4H), 7.72 (d, $J$ = 2.4 Hz, 2H), 7.68 (d, $J$ = 8.9 Hz, 2H), 7.62 (d, $J$ = 8.4 Hz, 4H), 7.52 (d, $J$ = 9.0 Hz, 4H), 7.35 (dd, $J$ = 8.9 and 2.4 Hz, 2H), 7.14 (d, $J$ = 9.0 Hz, 4H). $^{13}$C NMR ($CH_3SO_3H$/$CD_2Cl_2$ 1:5, 75 MHz), $\delta$ (ppm): 205.3, 165.6, 154.8, 148.9, 135.4, 134.2, 131.7, 129.8, 129.4, 128.1, 124.7, 122.1, 116.1, 114.3, 114.1. IR (Nujol): 1674 ($\nu$CO), 1232, 1167 cm$^{-1}$ ($\nu$ C−O−C). MS (FAB): calcd for $C_{38}H_{22}O_5$, *m/z* 558.15; found, 559 [M + H]$^+$. Anal. Calcd for $C_{38}H_{22}O_5$: C, 81.71; H 3.97. Found: C, 81.63; H, 3.93. Crystal data for **7**: $C_{38}H_{22}O_5.0.5C_6H_5CH_3$, $M$ = 604.7, triclinic, space group $P\bar{1}$, $a$ = 9.962(1) Å, $b$ = 12.777(2) Å, $c$ = 13.369(2) Å, $\alpha$ = 69.12(1)°, $\beta$ = 73.45(1)°, $\gamma$ = 89.13(1)°, $V$ = 1517 Å$^3$, $T$ = 293 K, $Z$ = 2, $D_c$ = 1.324 g cm$^{-3}$, $\mu$(Cu K$\alpha$) = 0.70 mm$^{-1}$, $F$(000) = 630; 4075 independent reflections, $R$ = 0.048, $R_w$ = 0.057 for 3555 independent observed reflections [$2\theta \le 116°$, $I > 1.5\sigma(I)$].

**Macrocycle 8.** Yield: 24.9%. Mp: 409 °C. $^1$H NMR ($CDCl_3$/TFA, 250 MHz), $\delta$ (ppm): 8.36 (d, $J$ = 8.9 Hz 2H), 7.68 (d, $J$ = 8.4 Hz, 4H), 7.52 (d, $J$ = 8.4 Hz, 4H), 7.49 (d, $J$ = 8.8 Hz, 4H), 7.32 (dd, $J$ = 8.9. 2.4 Hz, 2H), 7.23 (d, $J$ = 8.8 Hz, 4H), 6.85 (d, $J$ = 2.4 Hz, 2H). $^{13}$C NMR ($CH_3SO_3H$/$CD_2Cl_2$ 1:5, 75 MHz), $\delta$ (ppm): 204.4, 174.4, 167.6, 160.4, 155.8, 144.3, 138.6, 138.1, 130.5, 129.5, 128.9, 128.7, 121.0, 120.7, 110.9, 102.9. MS (FAB): calcd for $C_{39}H_{22}O_6$, *m/z* 586.14; found, 587 [M + H]$^+$. Anal. Calcd for $C_{39}H_{22}O_6$: C, 79.86; H, 3.78. Found: C, 79.90; H, 3.82. Crystal data for **8**: $C_{39}H_{22}O_6$, $M$ = 586.6, triclinic, space group $P\bar{1}$, $a$ = 10.567(3) Å, $b$ = 15.223(4) Å, $c$ = 20.307(7) Å, $\alpha$ = 99.62(3)°, $\beta$ = 103.81(2)°, $\gamma$ = 107.69(2)°, $V$ = 2919.0(2) Å$^3$, $T$ = 293 K, $Z$ = 4, $D_c$ = 1.335 g cm$^{-3}$, $\mu$(Cu K$\alpha$) = 0.732 mm$^{-1}$, $F$(000) = 1216; 5856 independent reflections, $R_1$ = 0.096, $wR_2$ = 0.254 for 3969 independent observed reflections [$2\theta \le 100°$, $I > 2\sigma(I)$].

**Scheme 1. Nickel-Catalyzed Dehalogenative Coupling of Chloroarenes To Yield Biaryls**




## 3. Results and Discussion

Homogeneous, nickel-catalyzed biaryl formation involving zinc-promoted dehalogenative coupling of chloroarenes (Scheme 1)[27] is an extremely versatile reaction, and it seemed to us that this type of chemistry might provide a successful approach to highly strained aromatic macrocycles. In particular, (i) the biaryl-forming reacton is generally irreversible, so avoiding the potential problem of equilibration to larger, unstrained macrocycles, (ii) the kinetics of coupling are rapid—especially when electron-withdrawing aromatic substituents are present—suggesting that the pseudo-high-dilution conditions which favor intramolecular over intermolecular reaction should be readily achieved, and (iii) molecular modeling studies showed that the diarylnickel(III) intermediate, from which the final biaryl product is formed,[27a] would itself be virtually *unstrained*, yet capable of yielding a *highly* strained macrocyclic product on reductive elimination (Scheme 2).

**Scheme 2. Reductive Elimination of a Highly Strained Macrocyclic Ether−Ketone from an Unstrained Diaryl−Nickel(III) Intermediate**

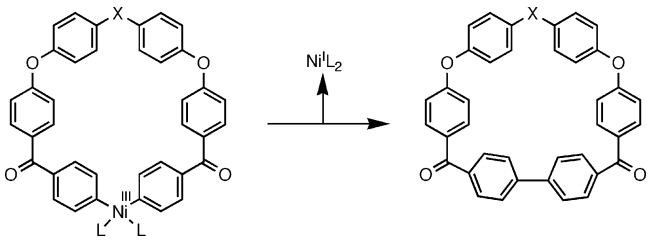
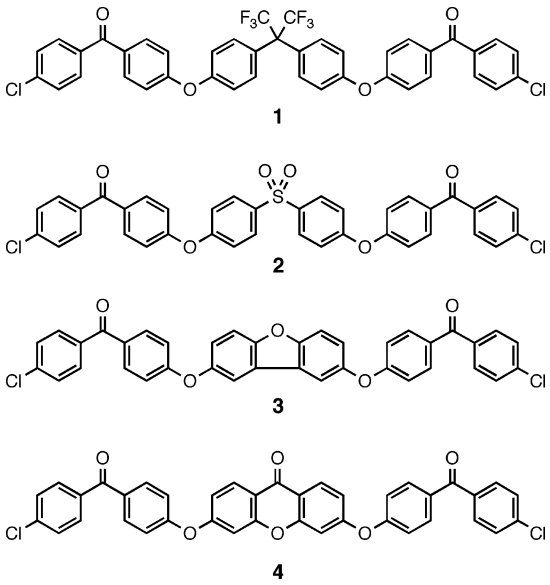



**Chart 1. Linear Precursors to Macrocyclic Aromatic Ether−Ketones**




To test this idea, a linear, bis-4-chloro-terminated oligomer (**1**) was synthesized by reaction of the potassium salt of 4,4′-hexafluoroisopropylidenediphenol with 4-chloro-4′-fluorobenzophenone, a reaction in which nucleophilic attack on the fluoro-substituted (rather than chloro-substituted) aromatic ring occurred with a very high degree of selectivity. Precursor **1** was also synthesized in good yield by Friedel−Crafts acylation of hexafluoroisopropylidenebis(1,4-phenoxyphenylene) with 4-chlorobenzoyl chloride. A series of analogous reactions led to linear oligomers **2**−**4** (Chart 1).

The X-ray structure of linear oligomer **1** is shown in Figure 1. The molecule has crystallographic $C_2$ symmetry about an axis passing through the bridging isopropylidene carbon, whose adjoining aromatic rings are symmetrically skewed and subtend an angle of ca. 111° at this carbon. The diaryl ether unit has an essentially orthogonal conformation, whereas the diaryl ketone fragment is symmetrically skewed. Although the molecule will have substantial conformational freedom in solution, its solid-state structure shows that a conformation favoring intramolecular coupling is clearly favored.

Slow addition of a solution of **1** in *N*,*N*-dimethylacetamide (DMAc) to a solution of $Ni(PPh_3)_4$, generated in situ from $Ni(Py)_4Cl_2$, $PPh_3$, and $Bu_4NI$ by reaction with excess powdered zinc in the same solvent, did indeed result in intramolecular biaryl formation. Macrocycle **5** (Chart 2) was isolated by column chromatography in 28% yield and was characterized by IR, MS, and $^1$H and $^{13}$C NMR spectroscopy and by elemental analysis.

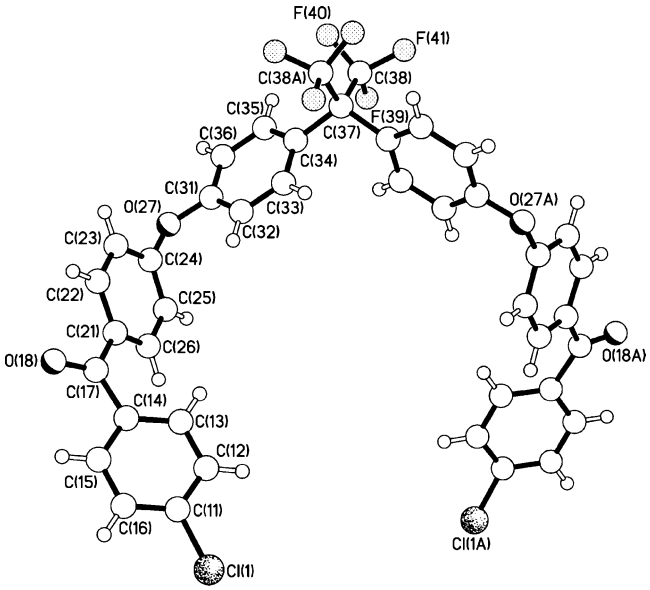
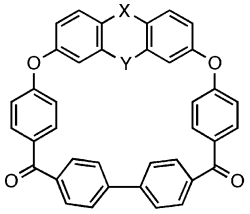



**Figure 1.** X-ray structure of the linear precursor oligomer **1**, displaying a preferred conformation that is preorganized for macrocyclization. The internal valence angles at the bridge-bond atoms C(17), O(27), and C(37) are 122, 116, and 113° respectively.

**Chart 2. Strained Macrocyclic Aromatic Ether−Ketones Obtained by Nickel-Catalyzed Coupling Chemistry**




**5** (X = C(CF$_3$)$_2$, Y = H,H)

**6** (X = SO$_2$, Y = H,H)

**7** (X = O, Y = direct bond)

**8** (X = CO, Y = O)

The macrocyclic structure of compound **5** (Figure 2) was confirmed by single crystal X-ray diffraction, which showed the presence of two independent molecules with very similar conformations in the unit cell. The hexafluoroisopropylidenediphenylene unit has a conformation virtually unchanged from that observed in the linear precursor **1**, with the angle at the bridging carbon atom being ca. 111° in **5**. The conformations of the pairs of diaryl ether units are asymmetrically skewed so as to accommodate the newly formed 4,4′-biphenylene unit. The latter is twisted by about 30° about the biaryl linkage and is severely distorted, with the terminal arene-to-carbonyl bonds [C(29)−C(30) and C(1)−C(39)] subtending an angle of ca. 126°—a deviation of 54° from the conventional linear geometry of a biaryl unit.

The methodology developed for synthesis of macrocyclic ether−ketone **5** was extended to other strained macrocyclic ether−ketones (Chart 2) by replacing the hexafluoroisopropylidene linkage with other linking units such as sulfone (macrocycle **6**). The cyclic structure of **6** was also confirmed by single-crystal X-ray analysis (Figure 3) which showed the diaryl sulfone unit to adopt a conventional open-book conformation (C−S−C = ca. 107°), but with the conformation of the remainder of the macrocycle little changed from that observed in **5**. The increased C−S bond lengths, relative to the corresponding C−C linkages in **5**, brings about a slight relaxation of the overall macrocyclic strain, though the biphenyl unit remains highly distorted, with the biarylarene-to-carbonyl bonds now subtending an angle of ca. 129°.

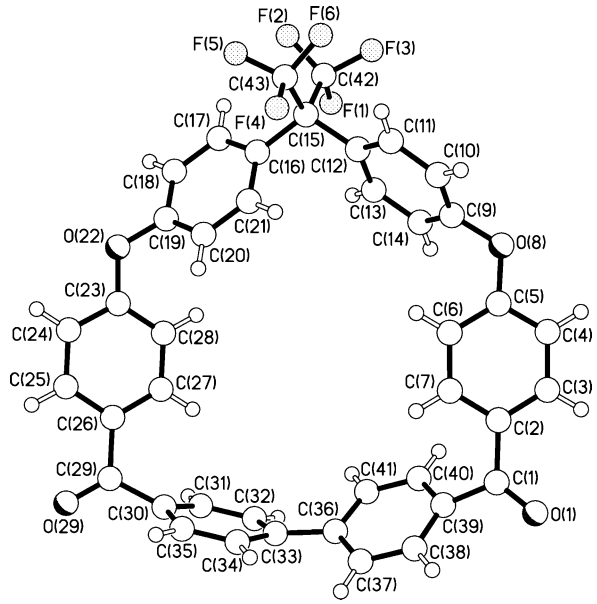



**Figure 2.** Molecular structure of macrocycle **5**. Internal valence angles at C(1), O(8), C(15), O(22), and C(29) are 115 (114), 119 (120), 111 (111), 120 (119) and 115 (116)°, respectively. Values in parentheses correspond to the second independent molecule in the unit cell.

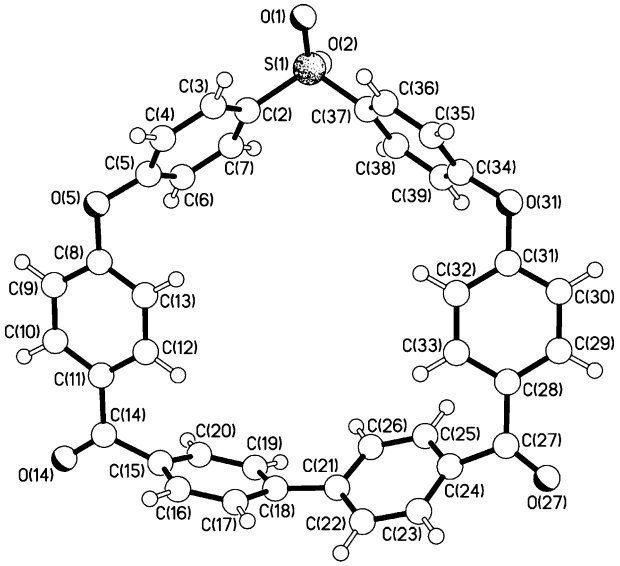



**Figure 3.** Molecular structure of macrocycle **6**. Internal valence angles at S(1), O(5), C(14), C(27), and O(31) are 107, 117, 116, 114, and 116°, respectively.

The unique ability of nickel(0)-catalyzed coupling to generate strained macrocycles of this type was demonstrated by the failure of efforts, in this work, to synthesize macrocycle **6** by electrophilic (Friedel–Crafts) acylation of 4,4′-diphenoxydiphenyl sulfone with 4,4′-biphenyldicarbonyl dichloride under pseudo-high-dilution conditions.

Macrocycles **5** and **6** contain only isolated phenylene rings, so that the structures are still relatively flexible, but the introduction of *fused* aromatic rings such as dibenzofuran and xanthone into the macrocyclic structure should increase the rigidity of the macrocycle, and thus also enhance the glass transition temperature of any polymer resulting from ring-opening polymerization. The first such molecule obtained was the dibenzofuran-based macrocycle **7**. The linear precursor **3** was obtained in high yield from the reaction of 2,8-diphenoxydibenzofuran with 4-chlorobenzoyl chloride and, after purification, this was successfully cyclized to give **7** (mp 353 °C) in 54% yield. The X-ray structure of **7** (Figure 4) showed that replacement of the hexafluoroisopropylidenediphenylene and diphenylenesulfone bridging units in **5** and **6** respectively by the more rigid and more compact dibenzofuran fused-ring system results in an appreciable increase in the level of macrocyclic ring-strain, as reflected in the bowing of the biphenylene unit. Here the two phenylene rings are twisted by ca. 31° and their arene-to-carbonyl bonds subtend an angle of ca. 115°, representing a 65° deviation from linearity. It is surprising to note that in structures of this type, the strain-distortion appears to be almost entirely concentrated in the biphenylenedicarbonyl unit (the internal angle at the two carbonyl-carbon atoms being also significantly contracted, from 120 to ca. 115°) whereas the remainder of the macrocycle is little distorted from ideal geometry.

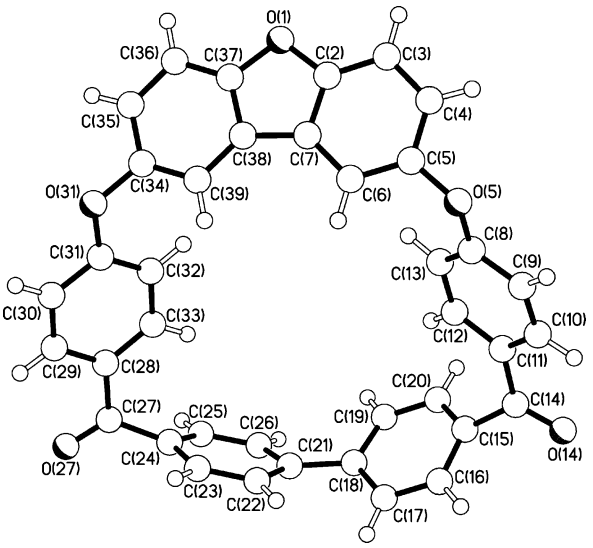



**Figure 4.** Molecular structure of macrocycle **7**. Internal valence angles at O(5), C(14), C(27), and O(31) are 120, 116, 115, and 119°, respectively.

A second example of a strained macrocycle containing a fused-ring system was obtained from the linear precursor **4**, synthesized in 81% yield by reaction of 3,6-dihydroxyxanthone with 4-chloro-4′-fluorobenzophenone. Macrocycle **8** (mp 410 °C) was produced in 25% yield by cyclization of **4** under pseudo-high-dilution conditions and crystallizes with two independent molecules in the unit cell. X-ray analysis (Figure 5) shows that replacement of the dibenzofuran unit by a xanthone residue brings about a significant relaxation of the macrocyclic ring-strain, reflected in an increase in the angle subtended by the two biphenylene-to-carbonyl bonds to ca. 138° (from 115° in macrocycle **7**). The twisting of the biphenylene unit is essentially unchanged at ca. 30°.

**Synthesis of Strained Macrocyclic Ether—Sulfones.** The Ni(0)-catalyzed coupling reaction is known to be favored by electron-withdrawing substitutents,[27] and so should also be applicable to the synthesis of macrocyclic ether–sulfones by replacing the ketone unit with the even more strongly electron-withdrawing sulfone group (Scheme 3). Molecular simulation studies (Cerius-2) indicated that the cyclic dimer **17** would be the smallest cyclic oligomer to be expected from Ni(0)-catalyzed cyclization of precursor **9**. Formation of the

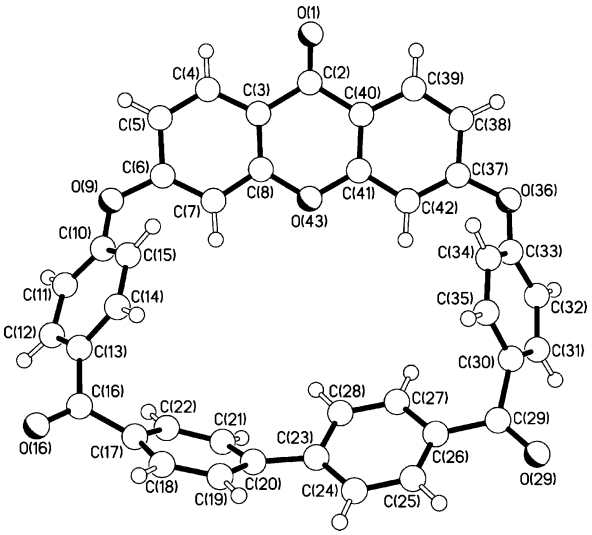



**Figure 5.** Molecular structure of macrocycle **8**. Internal valence angles at O(9), C(16), C(29) and O(36) are 122, 111, 115, and 118°, respectively.

corresponding cyclic monomer would not be expected due to the extreme strain energy associated with such a molecule. Cyclization of **9** was conducted under the same conditions as those used for the synthesis of macrocyclic ether−ketones, but characterization of the crude product by MALDI−TOF mass spectrometry showed that the product in fact comprised mainly a series of linear, H-terminated oligomers up to the linear pentamer. Fractionation by column chromatography *did* afford the pure macrocyclic dimer **17**, but in only 3.9% yield. The formation of linear H-ended oligomers is consistent with previous reports that Ni(0) can promote hydrogenolysis of chloroarenes as a competing reaction with biaryl formation,[27a] and the very low yield of macrocyclic product obtained in this work suggests that syntheses of cyclic biarylene−sulfones are especially susceptible to this side-reaction. Computational modeling of the cyclic diarylnickel(III) intermediates (cf. Scheme 2) for cyclization of analogous ketone- and sulfone-based precursors indicates that the narrower bond angle at sulfone often leads to a more strained intermediate (see Supporting Information), and this may explain why hydrogenolysis competes more effectively with cyclization in sulfone-based systems.

Cyclization of the four-ring ether−sulfone precursor **9** afforded cyclic dimer **17**, but molecular simulation studies suggested that the corresponding reaction of a *five*-ring precursor **10** might possibly yield a cyclic monomer. With the aim of obtaining such a macrocycle, precursor **10** was synthesized by electrophilic sulfonylation of 1,4-diphenoxybenzene with 4-chlorobenzenesulfonyl chloride. Cyclization of precursor **10** was carried out under conditions similar to those used in the synthesis of macrocycle **17**, and the crude product was analyzed by MALDI−TOF mass spectrometry, which again showed that the product mainly comprised linear oligomers, now up to linear hexamer. Chromatographic fractionation *did* afford a pure macrocyclic dimer **18** in 6.2% yield, but no trace of cyclic monomer was obtained, indicating that the proposed monomeric five-ring ether−sulfone macrocycle is in fact too highly strained to be formed.

The cyclization of sulfone-based linear precursors containing four or five *p*-substituted aromatic rings thus afforded only cyclic dimers (**17** and **18**). To synthesize strained cyclic *monomers* of this type it seemed logical either: (a) to move to longer chain (e.g., six-ring) linear precursors, as used successfully in the synthesis of strained macrocyclic polyketones, or (b) to reduce the macrocyclic ring strain by replacing the para-substituted dioxybenzene unit in **17** with a meta- or ortho-substituted aromatic ring. To test the first approach, a six-ring linear precursor **11** was first synthesized by electrophilic sulfonylation of 4,4′-diphenoxydiphenyl sulfone with 4-chlorobenzenesulfonyl chloride in the presence of iron(III) chloride. Although a pure oligomer was obtained in moderate yield, the presence of monosulfonylation products gave rise to difficulty in workup and purification, and so alternative routes to linear ether−sulfone precursors were investigated.

A general method for synthesis of poly(aryl ether−sulfone)s involves nucleophilic aromatic substitution reactions between bis(phenols) and sulfone-activated aromatic dihalides in the presence of potassium carbonate, and this approach has been used in the synthesis of an oligomeric bis(phenol) by nucleophilic substitution of 4,4′-dichlorodiphenyl sulfone with a 20-fold excess of 4,4′-isopropylidenediphenol.[16] Such reactions can in principle yield linear aromatic ether−sulfones with either a single main product (by using a very large excess of bis(phenol)), or else a series of linear oligomers can be formed by working with a smaller excess. In the present work, bis(chlorophenylene)-terminated precursors were required for intramolecular coupling reactions, so that here the activated dihalide (A) was always used in excess over the bis(phenol) (B). If reactant A is excess over reactant **B**, then several bis(chlorophenylene)-terminated precursors (2A + B, 3A + 2B, 4A + 3B, etc.) for macrocycle synthesis can in principle be obtained from a single reaction. Precursor **11** was thus also obtained in 15% yield by nucleophilic aromatic substitution of excess 4,4′-dichlorodiphenyl sulfone with 4,4′-dihydroxydiphenyl sulfone in a 2.2:1 mole ratio. The MALDI−TOF mass spectrum of the crude product confirmed that a series of higher linear oligomers were also formed, but attempted fractionation by column chromatography failed to resolve these.

Nickel-catalyzed coupling of the linear ether−sulfone precursor **11** again yielded a series of linear oligomers, up to the heptamer, but chromatographic fractionation also afforded the target cyclic monomer **19** (mp 400 °C) though in only 8.0% yield. Single-crystal X-ray analysis of **19** (Figure 6) showed that the molecule still has a strained structure, although the degree of distortion of the biphenyl residue is much smaller here than in the corresponding diketone macrocycle **6**. This reduction in ring-strain results from (a) the narrower bond angle at sulfone (C−S−C = ca. 103° in **19**, compared to ketone C−C−C at ca. 115° in **6**), and (b) the increase in bond length on replacing the carbonyl bridges in **6** (C−C = 1.50 Å) by sulfone units (C−S = 1.76 Å). The overall effect of these changes is to open up the total angle subtended by the terminal S−aryl bonds of the biphenylene unit to 146°, from a value of 129° in the diketone analogue **6**. A comparatively rare diaryl sulfone conformation is observed in **19**, where two of these units display a near-orthogonal relationship between their adjoining aromatic rings (cf. the open-book or slightly skewed conformations normally observed).

A cyclic dimer (**20**) was also isolated from this reaction, in 3.1% yield. The $^1$H NMR spectrum of macrocycle **20** shows that the protons are all deshielded

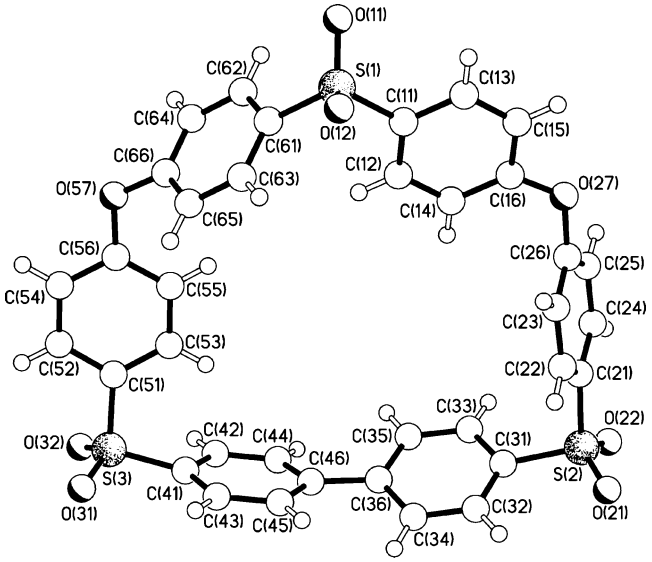



**Figure 6.** Molecular structure of macrocycle **19**. Internal valence angles at S(1), O(27), S(2), S(3), and O(57) are 106, 120, 102, 104, and 118°, respectively.

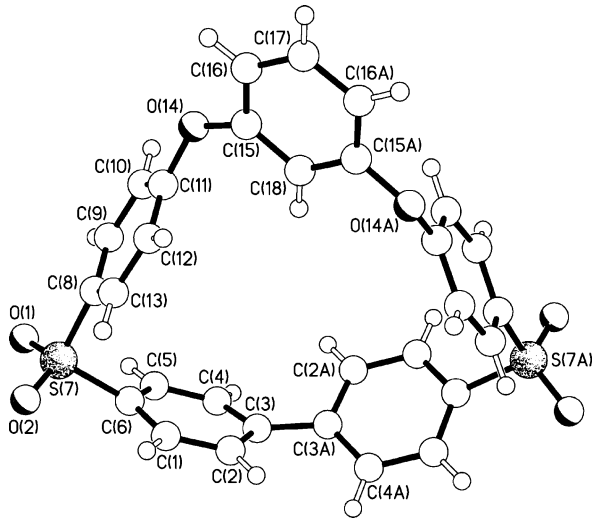
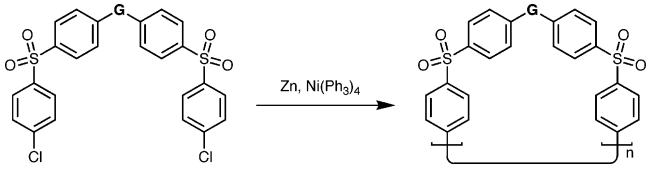



**Figure 7.** Molecular structure of macrocycle **21**. Internal valence angles at S(7) and O(14) are 100 and 123°, respectively.

relative to their positions in the $^1$H NMR spectrum of the smaller cyclic monomer **19**, an effect which probably results from a reduction in transannular ring-current shielding in the larger macrocycle.

Reduction of macrocyclic ring strain by replacing the para-substituted diaryloxybenzene in **10** with a meta-substituted central ring was investigated using precursors **12** and **13**, which were both obtained from the reaction of a slight excess of 4,4′-dichlorodiphenyl sulfone (A) with resorcinol (B). The MALDI−TOF mass spectrum of the crude product showed a series of linear oligomers [(2A + B), (3A + 2B), (4A + 3B) etc.], and chromatographic fractionation of the crude product afforded precursors **12** and **13** in 31.4% and 13.1% yield, respectively. Cyclization of **12** yielded the five-ring cyclic *monomer* **21** (mp 410 °C) in 26.7% yield, in contrast to the result for precursor **10** where only cyclic *dimer* and linear oligomers could be isolated. The X-ray structure of **21** (Figure 7) showed the molecule to have crystallographic $C_2$ symmetry and to be *very* highly strained, more so than any other biarylene-containing macrocycle obtained in this (or indeed in any other) work. Very

**Scheme 3. Synthesis of Macrocyclic Aryl Ether−Sulfones by Ni(0)-Catalyzed Coupling**




**9 - 16** **17 - 26**

| | |
|---|---|
| **9, 17** | (**G** = –O–, n = 2) |
| **10, 18** | (**G** = –O–1,4–$C_6H_4$O–, n = 2) |
| **11, 19** | (**G** = –O–1,4–$C_6H_4SO_2$–1,4–$C_6H_4$O–, n = 1) |
| **20** | (**G** = –O–1,4–$C_6H_4SO_2$–1,4–$C_6H_4$O–, n = 2) |
| **12, 21** | (**G** = –O–1,3–$C_6H_4$O–, n = 1) |
| **13, 22** | (**G** = –O–1,3–$C_6H_4$O–1,4–$C_6H_4SO_2$–1,4–$C_6H_4$O–1,3–$C_6H_4$O–, n = 1) |
| **14, 23** | (**G** = –1,4–$C_6H_4SO_2$–1,4–$C_6H_4$O–, n = 1) |
| **15, 24** | (**G** = –O–3,6–xanthonylene–O–, n = 1) |
| **16, 25** | (**G** = –O–4,4′–$C_6H_4C_6H_4$O–1,4–$C_6H_4SO_2$–1,4–$C_6H_4$O –4,4′–$C_6H_4C_6H_4$O–, n = 1) |
| **26** | (**G** = –O–4,4′–$C_6H_4C_6H_4$O–1,4–$C_6H_4SO_2$–1,4–$C_6H_4$O –4,4′–$C_6H_4C_6H_4$O–, n = 2) |

large strain-induced distortions occur within the 4,4′-biphenylene unit, with the terminal S−C bonds subtending an angle of ca. 110°, i.e., a deviation from collinearity of 70°! This extreme level of strain is reflected both in boatlike deformations of the rings comprising the biaryl unit and in pyramidalization at carbon atoms C(3) and C(6), which lie 0.09 and 0.11 Å respectively out of the planes of their substituent atoms. The internal angles at sulfone are compressed from a conventional value of 105° to only 100°. Despite the small ring size of this macrocycle—comprising only five aromatic rings—there is still a free pathway through its center (defined by van der Waals radii) some 3.6 Å in diameter.

The Ni(0)-catalyzed cyclization reactions so far described all involved relatively short chain (five- or six-ring) precursors, but cyclization of the more extended (8-ring) precursor **13**, isolated as a byproduct from the synthesis of precursor **12**, afforded a macrocyclic biaryl (**22**) in 14.5% yield (Scheme 3). Further investigation of nucleophilic oligomerization as a route to bis(chloro-terminated) macrocycle precursors yielded oligomer **14** in 20.6% yield from the 1:1 reaction of 4,4′-bis(4-chlorobenzenesulfonyl)-biphenyl with 4-chlorophenyl-4′-hydroxyphenyl sulfone. The *unsymmetrical* precursor **14** (Scheme 3) then afforded, on cyclization, a chemically symmetrical cyclic monomer (**23**) in 10% yield. The structure of **23** was confirmed by single-crystal X-ray analysis (Figure 8) which showed that in this molecule the ring-strain is, uniquely, distributed between two 4,4′-biphenylene units (the two pairs of terminal S−aryl bonds subtend angles of 139 and 146°), in contrast to the other macrocycles described here where the ring strain is concentrated at only a single biphenylene unit.

The disulfone analogue of the diketone-macrocycle **8** should still be significantly strained even though, as noted above, the internal angle at sulfone is significantly smaller than that at the carbonyl group. Precursor **15** was therefore synthesized by reaction of 3,6-dihydroxyxanthone with excess 4,4′-dichlorodiphenyl sulfone, and cyclization of this precursor under pseudo-high-dilution conditions afforded cyclic monomer **24** in 14% isolated yield, together with a series of linear oligomers. The cyclic structure of **24** was confirmed both spectroscopically and by single-crystal X-ray analysis (Figure 9). It is clear that macrocycle **24** is indeed less strained than its ketone analogue **8**, as evidenced by the reduced

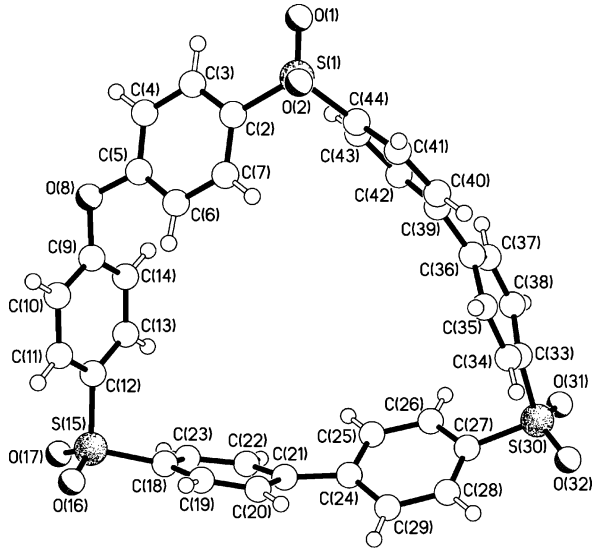



**Figure 8.** Molecular structure of macrocycle **23**. Internal valence angles at S(1), O(8), S(15), and S(30) are 103, 117, 102, and 100°, respectively.

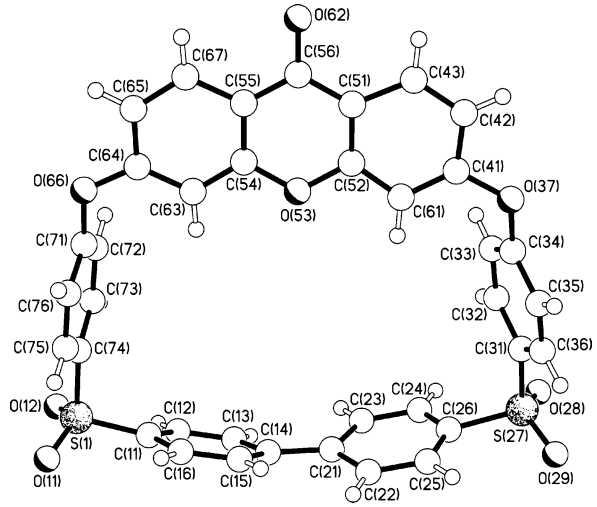



**Figure 9.** Molecular structure of macrocycle **24**. Internal valence angles at S(1), S(27), O(37), and O(66) are 103, 103, 120, and 120°, respectively.

bowing of the biphenylene unit; the total angle subtended by the terminal S−aryl bonds increases from a value of 138° in macrocycle **8** to 148° in macrocycle **24**.

The methodology for synthesis of the strain-free macrocycle **22**, by cyclization of an eight-ring ether−sulfone precursor oligomer (**13**) was also extended to a ten-ring precursor. Nucleophilic substitution of 4,4′-biphenol with excess 4,4′-dichlorodiphenyl sulfone gave a series of linear oligomers, as demonstrated by MALDI−TOF MS, and the 2:3 condensation product **16** was isolated chromatographically in 13.1% yield. Cyclization of oligomer **16** was achieved under the same conditions as those used for the eight-ring precursor **13**, yielding the ten-ring cyclic monomer **25** in 12.5% yield and the 20-ring cyclic dimer **26** in 6.6% yield.

Since all the macrocyclic compounds reported here contain aromatic ether linkages activated toward nucleophilic cleavage by electron-withdrawing carbonyl or sulfone substituents, potential clearly exists for nucleophilically initiated ring-opening polymerization of these macrocycles. Preliminary results[4] have shown that such polymerizations can indeed be achieved using fluoride or phenoxide initiators and that, in keeping with the high levels of ring-strain implicit in the structures reported here, these polymerizations are *highly* exothermic.[4] The following paper analyzes the strain energies associated with macrocycles of this type and describes a more detailed investigation of their ring-opening polymerization chemistry.

## 4. Conclusions

Extremely strained macrocyclic biaryls containing both ether−ketone and ether−sulfone units can be obtained by homogeneous, nickel-catalyzed, intramolecular coupling of short-chain bis(4-chlorophenyl)-terminated oligomers under pseudo-high-dilution conditions. Unstrained macrocycles can be obtained by cyclization of longer-chain precursors. Crystallographic analyses show that the disortions necessary to accommodate the high levels of ring-strain are generally concentrated in the 4,4′-biphenylene unit(s), implying an unsuspected degree of flexibility for this type of molecular fragment.

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**Supporting Information Available:** Text giving synthetic procedures and characterization data for the precursor oligomers **1**, **2**, **3**, **4**, **9**, **10**, **11**, **12**, **13**, **14**, **15**, and **16**, and for macrocycles **17**, **18 19**, **21**, **22**, **23**, **24**, **25**, and **26**, Figure S1, showing energy-minimized models (re-optimised Dreiding-II forcefield) for cyclic organo-nickel intermediates (**A** and **B**) in cyclization of the ketone- and sulfone-based precursors **6** and **11**, respectively, and figures showing thermal ellipsoid plots and CIF files giving full crystallographic data for precursor oligomer **1** and macrocycles **6**, **8**, **19**, **23**, and **24**. This material is available free of charge via the Internet at http://pubs.acs.org. Crystallographic data for compounds **5**, **7**, and **21** were deposited at the Cambridge Crystallographic Data Centre at the time of their publication in preliminary communications, and they have the following CCDC refcodes: RUYYAL, KEGCAA, and RUYXIS respectively.

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