

Stereospecific Syntheses of Macrobicyclic Polyethers with Carbon Bridgeheads from Chiral Glycerol Derivatives

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The [3.3.3]cryptand (**3**), prepared stereospecifically from 2,3-*O*-isopropylidene-D-glycerol D-(**1**) and 2,3-di-*O*-benzyl-L-glycerol L-(**2**), has been separated chromatographically at -5°C into slowly interconverting *in-in* *ii*-(**3**) and *out-out* *oo*-(**3**) conformational diastereoisomers [$\Delta G_{ii \rightarrow oo}^{\ddagger} = \text{ca. } 24 \text{ kcal mol}^{-1}$ (1 kcal = 4.184 kJ) in CD_3COCD_3 at $+38^{\circ}\text{C}$]; an X-ray structural analysis has shown (**3**) to form a crystalline 1 : 1 complex with $\text{Ba}(\text{SCN})_2$ in which the Ba^{2+} ion is encapsulated by *oo*-(**3**) and the two SCN^- ions in an 11-co-ordinate manner.

Since the preparation of the first macrobicyclic polyethers with carbon bridgeheads was reported¹ from pentaerythritol, two reports have appeared^{2,3} describing the incorporation of glycerol units at the bridgehead positions. A stereospecific

synthesis starting from 2,3-*O*-isopropylidene-D-glycerol⁴ D-(**1**) provides² a route to *in-out* isomers, whereas a non-stereospecific approach,³ employing 1,3-dichloropropan-2-ol as the bridgehead synthon, relies upon an isomer separa-

tion† at an intermediate stage in the synthetic procedure, which affords, subsequently, only *out-out* isomers carrying fused benzo- and cyclohexano-rings.⁵ In the search for a way of preparing unsubstituted *in-in* and *out-out* isomers, without having to resort to difficult isomer separations (*cf.* ref. 2), we have devised a stereospecific route where D-(1) constitutes one bridgehead and 2,3-di-*O*-benzyl-L-glycerol‡ L-(2), the other bridgehead. Here, we illustrate our approach with reference to the synthesis§ (see Scheme 1) of the

† The recently reported (Y. Nakatsuji, T. Mori, and M. Okahara, *Tetrahedron Lett.*, 1984, **25**, 2171) separation of *cis* and *trans* isomers of several bis(bromomethyl) dimethyl crown ethers could also provide a synthetic entry into macrobicyclic polyethers with carbon bridgeheads. *Note added in proof.* Indeed, after the present communication had been accepted for publication, Nakatsuji *et al.* published a communication (*J. Chem. Soc., Chem. Commun.*, 1984, 1045) in which they reported on the syntheses of the [3.3.3]-, [3.3.2]-, and [3.2.2]-cryptands with CMe bridgeheads and evaluated the abilities of these macrobicyclic polyethers to complex with Na⁺ and K⁺ ions in methanolic solution.

‡ The compound L-(2) was synthesised by a modification of a literature route (B. Wickberg, *Acta Chem. Scand.*, 1958, **12**, 1187). The optical purity of L-(2) was checked by conversion into its trityl derivative, [α]_D -8.8° (c, 5.0, CHCl₃). Recently, D-(1) and L-(1) have become commercially available from Aldrich.

§ All new compounds gave satisfactory analytical and n.m.r. spectroscopic data. D-(4) δ (¹H, 220 MHz, CDCl₃) 1.35, 1.41 (2 × 3H, 2 × s, CMe₂), 2.44 (3H, s, SO₂C₆H₄Me), 3.40–3.75 (9H, m, CH₂OCH₂CH₂OCH₂ and CHH in ring), 4.04 (1H, dd, *J* 6, 8 Hz, OCHH in ring), 4.16 (2H, t, *J* 5 Hz, CH₂OSO₂C₆H₄Me), 4.28 (1H, quintet, *J* 6 Hz, CH), 7.35, 7.81 (2 × 2H, 2 × d, *J* 8 Hz, SO₂C₆H₄Me); DL-(5) δ (¹H, 220 MHz, CDCl₃) 1.38, 1.45 (2 × 3H, 2 × s, CMe₂), 3.45–3.87 (16H, m, CH₂OCH₂CH₂OCH₂CH₂OCH₂CH(OCH₂Ph)CH₂OCH₂Ph and OCHH in ring), 4.07 (1H, dd, *J* 6.0, 8.5 Hz, OCHH in ring), 4.30 (1H, quintet, *J* 6.0 Hz, CH in ring), 4.58, 4.73 (2 × 2H, 2 × s, CH₂OCH₂Ph and CHOCH₂Ph respectively), 7.20–7.42 (10H, m, 2 × Ph); DL-(6) δ (¹H, 220 MHz, CDCl₃) 2.75, 2.95 (2 × 1H, 2 × br. s, 2 × OH), 3.45–3.70 (16H, m, 8 × OCH₂), 3.81 (2H, quintet, 2 × OCH superimposed), 4.56, 4.72 (2 × 2H, 2 × s, CH₂OCH₂Ph and CHOCH₂Ph, respectively), 7.25–7.40 (10H, m, 2 × Ph); (7) δ (¹³C{¹H}, 25.15 MHz, CD₃COCD₃) 64.5, 71.2, 71.3, 71.8 (CH₂), 73.8 (CH); δ (¹H, 220 MHz, CD₃OD) 3.40–3.72 (16H, m, 8 × OCH₂), 3.78 (2H, quintet, *J* 5.5 Hz, 2 × OCH); (8) δ (¹³C{¹H}, 25.15 MHz, CD₃COCD₃) 65.9, 71.1, 71.3, 73.8 (CH₂), 70.4 (CH), 87.0 (C), 127.7, 128.4, 129.4, 145.1 (Ph); δ (¹H, 400 MHz, CDCl₃) 3.10, 3.18 (4H, AB portion of 'ABX system', *J*_{AB} 9.5, *J*_{AX} 5.5, *J*_{BX} 6.0 Hz, 2 × CH₂OCPH₃), 3.50, 3.65 (4H, AB portion of 'ABX system', *J*_{AB} 10, *J*_{AX} 3.0, *J*_{BX} 7.0 Hz, 2 × OCH₂CH), 3.54 (2H, br. s, 2 × OH), 3.57–3.68 (8H, m, 4 × OCH₂), 3.96 (2H, br. m, 2 × OCH), 7.17–7.43 (30H, m, 2 × CPh₃); (9) δ (¹³C{¹H}, 25.15 MHz, CD₃COCD₃) 64.7, 70.7, 71.3, 71.6, 72.4 (CH₂), 79.5 (CH), 87.2 (C), 127.7, 128.5, 129.4, 145.1 (Ph); δ (¹H, 400 MHz, CDCl₃) 3.11, 3.17 (4H, AB portion of 'ABX system', *J*_{AB} 9.5, *J*_{AX}, *J*_{BX} 5.5 Hz, 2 × CH₂OCPH₃), 3.55–3.80 (22H, m, 10 × OCH₂, 2 × OCH), 7.19–7.45 (30H, m, 2 × CPh₃); (10) δ (¹³C{¹H}, 25.15 MHz, CD₃COCD₃) 62.6, 70.2, 71.4, 71.5, 71.5, 72.3 (CH₂), 80.9 (CH); δ (¹H, 400 MHz, CDCl₃) 3.30 (2H, br. s, 2 × OH), 3.60–3.85 (26H, m, 12 × OCH₂, 2 × OCH); *ii*-(3) δ (¹³C{¹H}, 25.15 MHz, CD₃COCD₃, -40°C) 69.7 (CH₂-a), 71.2 (2 × CH₂-b, 2 × CH₂-c), 71.9 (CH₂-d), 72.9 (2 × CH₂-e), 77.2 (CH-f); δ (¹H, 400 MHz, CDCl₃, -5°C) 3.53–3.62 (8H, AB portion of 'ABX system', *J*_{AB} 10, *J*_{AX}, *J*_{BX} 6.0 Hz, 4 × CH₂-e), 3.62–3.72 (16H, m, 4 × CH₂-b, 4 × CH₂-c), 3.74, 3.91 (8H, AA'BB' system, 2 × CH₂-a, 2 × CH₂-d), 4.35 (2H, quintet, *J* 6.0 Hz, 2 × CH-f); *oo*-(3) δ (¹³C{¹H}, 25.15 MHz, CD₃COCD₃, -40°C) 70.0 (CH₂-k), 71.2, 71.5, 71.5, 71.7 (2 × CH₂-l, 2 × CH₂-m, CH₂-n, 2 × CH₂-o), 79.9 (CH-p); δ (¹H, 400 MHz, CDCl₃, -5°C) 3.50–3.92 (all protons); *oo*-(3)·Ba(SCN)₂ δ (¹³C{¹H}, 62.90 MHz, CD₃COCD₃) 68.6 (CH₂-k), 70.7, 71.9, 72.9 (2 × CH₂-l, 2 × CH₂-m, 2 × CH₂-o), 71.5 (CH₂-n), 77.0 (CH-p); δ (¹H, 400 MHz, CDCl₃) 3.52, 3.69–3.76, 3.84, 4.31 (16H, ABCD system, *J*_{AB} *J*_{AC} *J*_{BD} 10, *J*_{AD} *J*_{BC} 2.5 Hz, 4 × CH₂-l, 4 × CH₂-m, 3.59 (2H, br. t, *J* 4, 1 Hz, 2 × CH-p), 3.69–3.76, 3.90 (12H, AA'BB' system and B portion of 'ABX system', 2 × CH₂-k, 2 × CH₂-n, 4 × CHH-o), 3.99 (4H, A portion of 'ABX system', *J*_{AB} 10, *J*_{AX} 4 Hz, 4 × CHH-o).

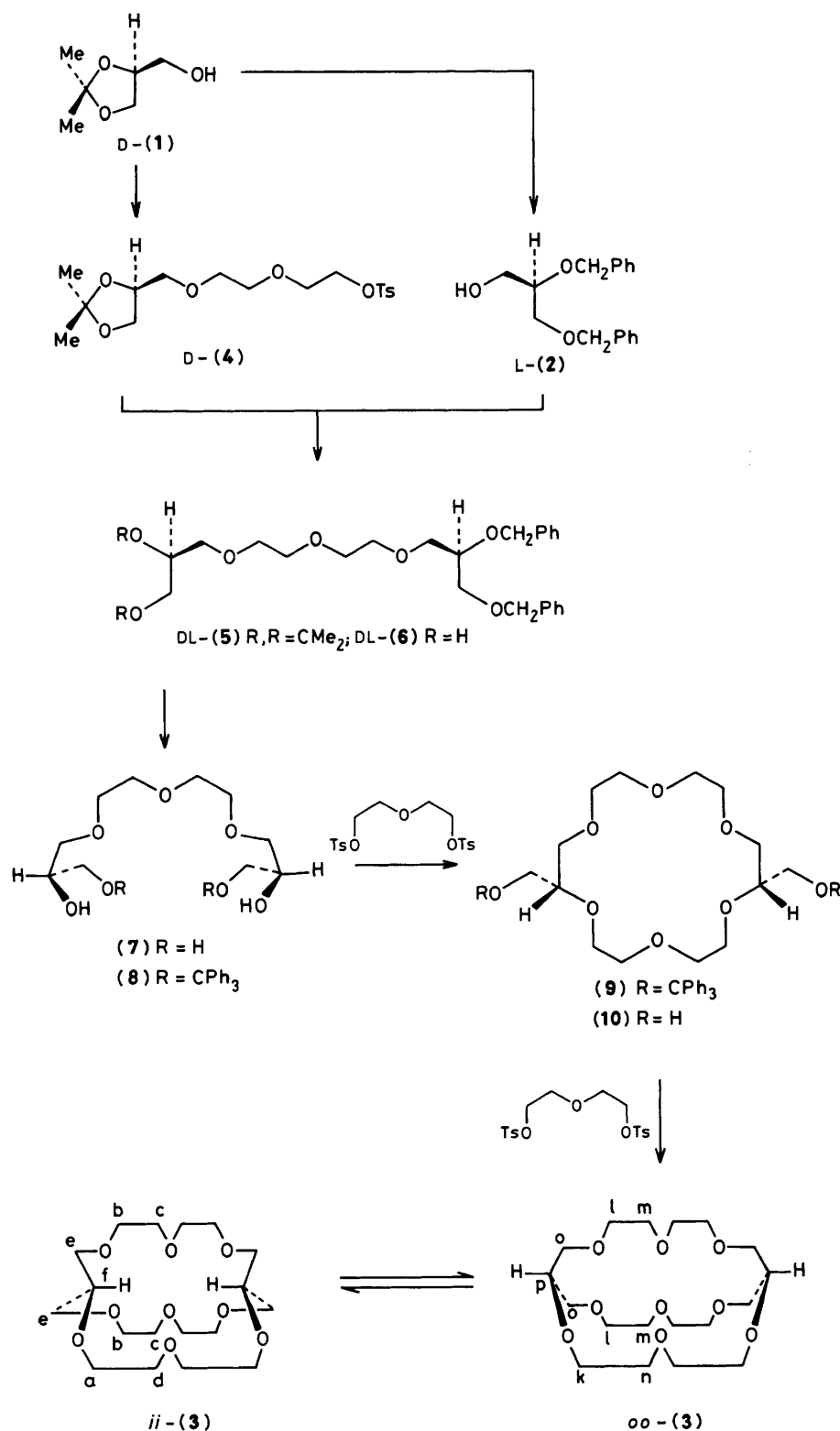
[3.3.3]cryptand (3), which exists as chromatographically separable *in-in*, *ii*-(3), and *out-out*, *oo*-(3), isomers and then report on (i) the characterisation of *oo*-(3) by X-ray crystallography of its Ba(SCN)₂ complex and (ii) our preliminary investigations on the thermodynamic and kinetic stabilities of *ii*-(3) and *oo*-(3) in solution by ¹H and ¹³C n.m.r. spectroscopy.

Reaction [NaH, tetrahydrofuran (THF)] of D-(1) with 2.3 mol. equiv. of Ts[OCH₂CH₂]₂OTs (Ts = tosyl)⁶ afforded (44%) the toluene-*p*-sulphonate D-(4), [α]_D +4.6° (c 2.0, MeOH), after SiO₂ chromatography (CH₂Cl₂–Et₂O–light petroleum). The reaction (NaH, THF) between D-(4) and L-(2) yielded (74%) the acyclic polyether DL-(5), [α]_D +5.2° (c 4.35, MeOH). Methanolysis (Zerolit 325/H⁺) of DL-(5) gave the diol DL-(6), [α]_D -0.10° (c 4.57, MeOH), in quantitative yield after SiO₂ chromatography (Et₂O–MeOH). Hydrogenolysis (Pd/C, MeOH) of DL-(6) also proceeded quantitatively to give the *meso*-tetraol (7). Tritylation (Ph₃CCl, 4-*N*,*N*-dimethylaminopyridine, Et₃N, CH₂Cl₂)⁷ of (7) yielded (60%) the ditrityl ether (8) after SiO₂ chromatography (Et₂O–light petroleum). Reaction (NaH, Me₂SO) of (8) with Ts[OCH₂CH₂]₂OTs afforded the crude 18-crown-6 derivative (9), which was most easily purified by a stepwise sequence of precipitations that rely upon consecutive complexations of (9) with BH₃NH₃⁸ and MeCN.⁹ Thus, addition of pentane to a CHCl₃–MeOH solution of crude (9) and BH₃NH₃ yielded a precipitate, which was isolated and refluxed in Me₂CO–H₂O (2 M NaOH) to regenerate purified (9). Addition of MeCN to this sample afforded a crystalline (9)·2MeCN complex, m.p. 48–50°C. Single crystals suitable for X-ray crystallography[¶] were obtained from a MeCN solution by layering with pentane. The crystal structure (Figure 1) of (9)·2MeCN confirmed the *cis* stereochemistry of the 18-crown-6 derivative (9). Heating (*ca.* 50°C) of (9)·2MeCN *in vacuo* afforded pure (9) as an oil. This efficient isolation procedure avoids column chromatography and permits the isolation of (9) in 48% yield from (8). Deprotection (HCl, MeOH, CH₂Cl₂) of (9) gave (100%) the diol (10), which was treated (NaH, Me₂SO) with Ts[OCH₂CH₂]₂OTs to afford the [3.3.3]cryptand (3) in 20% yield. The *out-out* isomer *oo*-(3) was characterised as its Ba(SCN)₂ complex by stirring (16 h) a solution of (3) in CH₂Cl₂ with excess of the salt and then layering pentane on top of the extract to afford single crystals of (3)·Ba(SCN)₂·CH₂Cl₂, m.p. 90°C, suitable for X-ray crystallography.[¶] The crystal structure (Figure 2)

¶ *Crystal data:* for (9)·2MeCN, C₅₆H₆₂O₈N₂, *M* = 891.1, monoclinic, space group *Cc*, *a* = 7.593(2), *b* = 16.819(7), *c* = 38.89(1) Å, β = 93.77(2)°, *U* = 4955 Å³, *Z* = 4, *D_c* = 1.20 g cm⁻³. The structure was solved by direct methods and the positions of the MeCN hydrogen atoms were clearly located in a ΔF map. The non-hydrogen atoms were refined anisotropically and the MeCN methyl groups were refined as rigid bodies. Refinement converged to *R* = 0.049, *R_w* = 0.053 for 3186 independent observed reflections [$\theta \leq 58^\circ$, $|F_o| > 3\sigma(|F_o|)$].

For *oo*-(3)·Ba(SCN)₂·CH₂Cl₂, C₂₁H₃₆O₉N₂Cl₂S₂Ba, *M* = 732.9, orthorhombic, space group *P2₁2₁2₁*, *a* = 10.846(2), *b* = 13.980(5), *c* = 20.132(6) Å, *U* = 3053 Å³, *Z* = 4, μ (Cu–K α) = 136 cm⁻¹, *D_c* = 1.60 g cm⁻³. The structure was solved by the heavy atom method and the non-hydrogen atoms were refined anisotropically using absorption corrected data to *R* = 0.056, *R_w* = 0.060 for 2272 independent reflections [$\theta \leq 58^\circ$, $|F_o| > 3\sigma(|F_o|)$]. There is disorder both in the dichloromethane and in the region around C(13) in the host.

In both cases, data were measured on a Nicolet R3m diffractometer using the ω -scan routine with graphite-monochromated Cu–K α radiation. The atomic co-ordinates are available from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.



Scheme 1. Ts = tosyl.

demonstrates the *out-out* stereochemistry of the hydrogen atoms at the bridgehead positions of this [3.3.3]cryptate.

T.l.c. (Al₂O₃-EtOAc) of (3) indicated the presence of a major fast-moving (fraction 1) and a minor slow-moving

(fraction 2) component: n.m.r. spectroscopic data revealed that these components are slowly interconverting (*t*₁ = ca. 2 h at 20°C) conformational diastereoisomers, *i.e.* atropisomers. Fractions 1 and 2 were separated in the form of oils by Al₂O₃

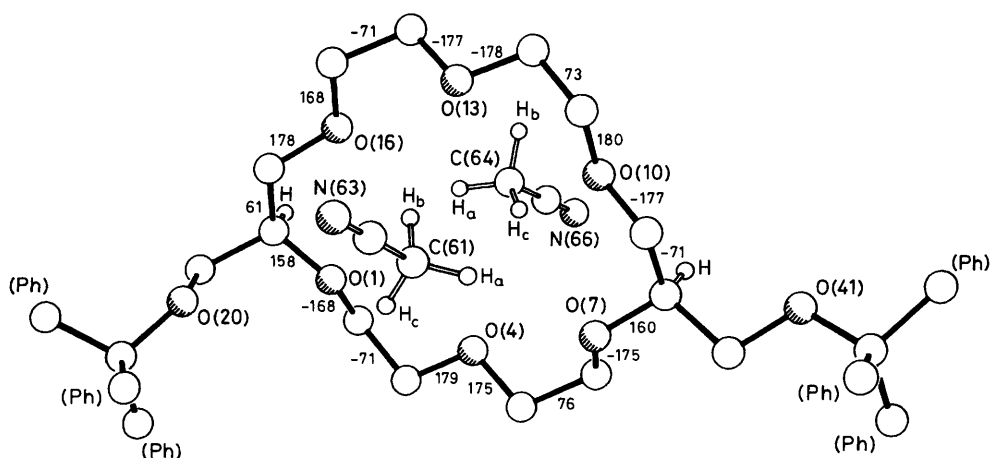


Figure 1. The solid state structure of $(9) \cdot 2\text{MeCN}$, omitting the phenyl rings associated with the trityl groups for the sake of clarity. The torsional angles ($^\circ$) around the macrocyclic ring are shown beside the relevant bonds. The shortest distances $R[\text{C}(61) \dots \text{O}]$ are 3.24 and 3.20 Å to O(1) and O(13), respectively, and $R[\text{C}(64) \dots \text{O}]$ are 3.17 and 3.31 Å to O(4) and O(10), respectively. All other $[\text{C}(\text{Me}) \dots \text{O}]$ distances are greater than 3.42 Å. Although the angle (174°) between the two axes of the MeCN guest molecules reflects a near parallel alignment, the individual MeCN axes deviate by 39° $[\text{C}(61)\text{N}]$ and 35° $[\text{C}(64)\text{N}]$ from the normal to the mean plane of the six ring oxygen atoms. The $[\text{C}(61) \dots \text{C}(64)]$ distance between the two MeCN guest molecules of 3.952 Å may be compared with that of 3.93 Å for the $[\text{C}(\text{Me}) \dots \text{C}(\text{Me})]$ distance in $\{[\text{trans-Ir}(\text{CO})(\text{MeCN})(\text{PPh}_3)_2]_2^+ \cdot 18\text{-crown-6}\}[\text{PF}_6]_2$ (H. M. Colquhoun, J. F. Stoddart, and D. J. Williams, *J. Am. Chem. Soc.*, 1982, **104**, 1426).

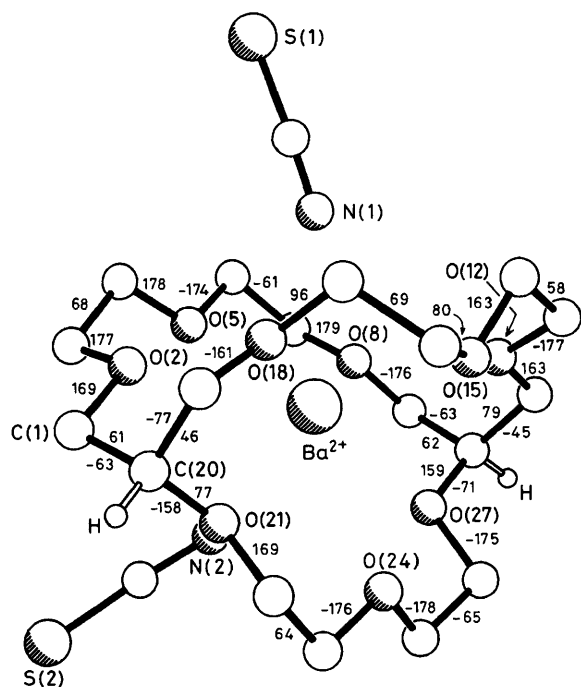


Figure 2. The solid state structure of $oo\text{-(3)} \cdot \text{Ba}(\text{SCN})_2$. The torsional angles ($^\circ$) are shown beside the relevant bonds. The barium co-ordination distances are as follows: O(2), 2.866; O(5), 2.932; O(8), 2.862; O(12), 2.917; O(15), 3.067; O(18), 2.921; O(21), 2.814; O(24), 2.929; O(27), 2.862; N(1), 2.848; N(2), 2.813 Å. Note the rare 11-fold co-ordination of the Ba^{2+} ion: for another example involving a barium $[\text{3.2.2}]$ cryptate thiocyanate dihydrate, see B. Metz, D. Moras, and R. Weiss, *Acta Crystallogr., Sect. B*, 1973, **29**, 1388.

chromatography (EtOAc) at -5°C and were characterised as the *in-in*, *ii*-(3), and *out-out*, *oo*-(3), isomers, respectively, on the basis of the following evidence.

(i) Chromatographic mobility: whereas the *X*-ray structure

(Figure 2) of $oo\text{-(3)} \cdot \text{Ba}(\text{SCN})_2$ reveals that the 18-membered ring in the host incorporating O(2), O(5), O(8), O(27), O(24), and O(21) adopts an all-*gauche* conformation with local pseudo D_{3d} symmetry, molecular model inspection shows that this complex-forming conformation is denied to both 18-membered rings in *ii*-(3); thus, *oo*-(3) should form complexes with guest species readily and, as a consequence, exhibit low chromatographic mobility characteristic¹⁰ of 18-crown-6 derivatives which can assume this conformation.

(ii) ^1H N.m.r. spectroscopic data in CDCl_3 : whereas *ii*-(3) gives rise to a low field quintet at δ 4.35 for the bridgehead protons (H-f), the signal for H-p in *oo*-(3), and for the methine protons in the precursors (9) and (10), resonate at much higher field, *i.e.* below δ 3.92; at equilibrium at ambient temperature, *ii*-(3) : *oo*-(3) is 58 : 42.

(iii) $^{13}\text{C}\{^1\text{H}\}$ N.m.r. spectroscopic data in CD_3COCD_3 : whereas the bridgehead carbon atoms (CH-f) in *ii*-(3) resonate at δ 77.2, the signal for these carbon atoms (CH-p) in *oo*-(3), and for the methine carbon atoms in the precursors (9) and (10) appear at δ 79.9, 79.5, and 80.9, respectively, *i.e.* at lower field; at equilibrium at $+38^\circ\text{C}$, *ii*-(3) : *oo*-(3) is 68 : 32. Employing the signals for CH-f in *ii*-(3) and CH-p in *oo*-(3) as quantitative ^{13}C probes, direct equilibration experiments¹¹ afforded a $\Delta G^\ddagger_{ii \rightarrow oo}$ value of *ca.* 24 kcal mol⁻¹ (1 kcal = 4.184 kJ) at $+38^\circ\text{C}$. We propose that conformational interconversion between *ii*-(3) and *oo*-(3) involves passage of the 7-atom chain containing O(21), O(24), and O(27) through the 20-membered ring $[\text{C}(1) \text{---} \text{C}(20)]$.

(iv) ^{13}C Chemical shift changes on complexation: the upfield shifts exhibited by most of the resonances in *oo*-(3), when it forms a 1 : 1 complex with $\text{Ba}(\text{SCN})_2$, are in accordance with the previously observed² effect on $^{13}\text{C}\{^1\text{H}\}$ spectra of macrobicyclic polyethers when 1 mol. equiv. of KSCN is present.

(v) ^1H Chemical shift changes on complexation: in particular, the appearance of a high field quintet at δ 3.59 for the bridgehead protons (H-p) in $oo\text{-(3)} \cdot \text{Ba}(\text{SCN})_2$ is in accord with expectation.

The control of stereochemistry illustrated here in the preparation of *ii/oo*-(3) is capable of further development, *e.g.* in the stereospecific synthesis of *macropolycyclic* polyethers from carbohydrate precursors.

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