Synthesis of In, Out-3,6,9,12,16,19,22,25,27,30,33,36-dodecaoxabicyclo[12.12.10]hexatriacontane and the Chiral Cryptand In, Out-(−)-3,6,9,12,15,18,21,24,26,29,32-Undecaoxabicyclo[12.10.9]tritriacontane. Out, In–In, Out Isomerism

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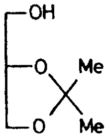
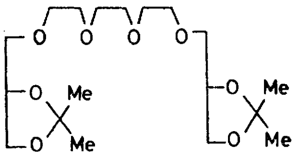
Summary In, out-isomers of two macrobicyclic polyethers have been prepared by a specific route and have been shown by ^{13}C n.m.r. spectroscopy to undergo in, out–out, in isomerization; in the case of the smaller cryptand, the interconversion may be slowed sufficiently by cooling for the bridgehead carbon atoms to be distinguished spectroscopically.

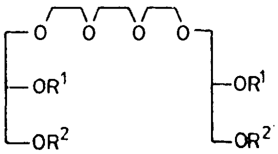
Recently the first macrobicyclic polyethers with bridgehead carbon atoms were prepared[1] from pentaerythritol and from 1,1,1-tris(hydroxymethyl)ethane. We now describe the syntheses of two, carbon-bridgehead macrobicyclic polyethers starting from 2,3-*O*-isopropylidene-D-glycerol (**1**). The novelties of our synthetic route are (i) it affords a specific preparation of in, out-isomers of the bicyclic systems, (ii) it can be used to prepare chiral [2]cryptands, and (iii) it gives [2]cryptands in which two of the three rings which may be traced within their molecular framework contain the uninterrupted repeating sequence of C–C–O units so favourable[2] for complexation of alkali and alkaline earth metal cations.

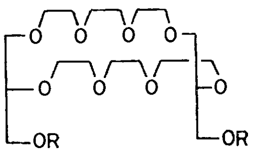
Reaction of 2,3-*O*-isopropylidene-D-glycerol[3] with sodium hydride and triethyleneglycol ditosylate[4] in 1,2-dimethoxyethane (DME) at 50 °C for 24 h gave the ether (**2**) (55%), b.p. 162—165 °C at 0·125 mmHg, $[\alpha]_D$ + 14·6°.† Hydrolysis of (**2**) with trifluoroacetic acid–water (9 : 1) afforded the tetrol (**3**) (90%) which was characterized as its amorphous tetra-3,5-dinitrobenzoate (**4**), $[\alpha]_D$ − 9·9°. Reaction of (**3**) with 2·2 moles of trityl chloride in pyridine yielded, after chromatography (ethyl acetate), the ditrityl ether (**5**) (59%), $[\alpha]_D$ − 11·4°. Treatment of (**5**) with sodium hydride and triethyleneglycol ditosylate at 50 °C for 24 h in DME, and chromatographic purification (ethyl acetate) of the crude product gave the macrocyclic ether (**6**) (40%), $[\alpha]_D$ − 18·1°. Hydrogenation of (**6**) in ethanol at 50 °C over 10% Pd–charcoal gave the diol (**7**) (63%), $[\alpha]_D$ + 19·2° after chromatography (CHCl$_3$–MeOH 19 : 1). Reaction of (**7**) with sodium hydride–triethyleneglycol ditosylate and chromatographic separation of the products (CHCl$_3$–MeOH 19:1) gave the bicyclo-hexatriacontane derivative (**8**) (18%). Treatment of (**7**) with sodium hydride and diethylene glycol ditosylate[4] followed by similar chromatographic isolation afforded the chiral bicyclo-tritriacontane derivative (**9**) (21%), $[\alpha]_D$ − 1 ± 0·1°.

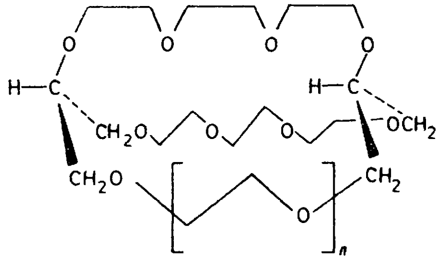
The ^{13}C–{^{1}H} n.m.r. spectrum of (**8**) in (CD$_3$)$_2$CO at 30 °C is relatively simple and six of the seven signals it contains lie in the region δ 70·16 to 72·09 p.p.m. A single sharp resonance (half-height width, W_H *ca.* 1 Hz) is observed at

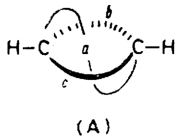

(1)


(2)

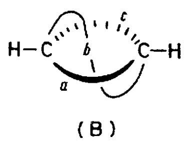

(3) R^1=R^2=H
(4) R^1=R^2=3,5-(NO$_2$)$_2$·C$_6$H$_3$·CO
(5) R^1=H, R^2=Ph$_3$C


(6) R = Ph$_3$C
(7) R = H

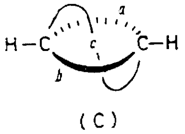

(8) n = 3
(9) n = 2



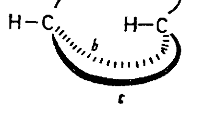
(A)
out,out



(B)
out,out



(C)
out,out



(D)
out, in

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† All compounds, which were liquids unless stated otherwise, were characterized by elemental analysis and physical methods. Rotations were measured in CHCl$_3$, and chromatography was performed on silica gel.

δ 78·97 p.p.m. (from Me_4Si) for the bridgehead carbon atoms, suggesting that they are rendered chemically equivalent (and thus isochronous) by an isomerization process which is fast on the n.m.r. time scale.‡ We consider§ this process to be out, in-in, out isomerization[5] achieved by passage of any one chain through the ring formed by the other two chains and the bridgehead atoms (homeomorphic isomerization[6]); a total of eight lines in the ^{13}C n.m.r. spectrum of rapidly interconverting (**8**) might be expected in the absence of accidental overlap. For bicyclic hydrocarbons, such an isomerization is possible (based on a consideration of models) only when the chains contain about ten methylene groups, but it has not been observed experimentally in cations of the l, $(k + 2)$-diazabicyclo[$k.l.m$]alkanes containing chains of up to fourteen methylene groups.[5] Presumably, the presence of oxygen atoms in the chains of (**8**) (which, if oxygen atoms were replaced by methylene groups would contain 10, 12, and 12 methylene units) reduces the interchain non-bonded interactions, thus facilitating the isomerization. It is noteworthy that one of the proposed explanations for the changes which are observed in the ^1H n.m.r. spectrum of 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane on lowering its temperature involves homeomorphic isomerization.[7] At -104 °C [solvent: $(CD_3)_2CO$–CF_2Cl_2], the ^{13}C-signal for the bridgehead carbon atoms in (**8**) is considerably broader (W_H *ca.* 40 Hz) than at 11 °C in the same solvent (W_H *ca.* 1 Hz).

The ^{13}C–$\{^1H\}$ n.m.r. spectrum of (**9**) at 30 °C in $(CD_3)_2CO$ contained eight signals in the region δ 70·11 to 72·55 p.p.m., and most significantly, a broad absorption (W_H *ca.* 18 Hz) at δ 79·0 p.p.m. for the bridgehead carbon atoms, suggesting that out, in–in, out isomerization was occurring at an intermediate rate on the n.m.r. time-scale. At progressively lower temperatures, this low-field signal broadened further, and then two distinct signals appeared in this region; at -70 °C two singlets (W_H *ca.* 4 Hz) were observed at δ 79·55 and 76·82 p.p.m. having nearly equal intensities (ratio, 1 : 1·07).¶ The coalescence temperature was estimated to be near -8 °C, corresponding to $\Delta G\ddagger$ *ca.* 54 kJ mol^{-1} for the interconversion. At 112 °C (solvent: $C_6H_5CH_3$–$C_6D_5CD_3$), only a sharp singlet (W_H *ca.* 1 Hz) was observed at δ 79·55 p.p.m. for the bridgehead carbon atoms of (**9**), indicating out, in–in, out isomerization was fast on the n.m.r. time scale; ten out of the eleven signals which are expected could be distinguished in the spectrum.

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‡ In the ^{13}C–$\{^1H\}$ n.m.r. spectrum of in, out bicyclo[8.8.8]hexacosane, separate signals are observed for the bridgehead carbon atoms with a separation of *ca.* 3 p.p.m. (see ref. 5). In the ^{13}C–^1H n.m.r. spectrum of the in, out-bicyclic compound obtained (P. G. Gassman, S. R. Korn, and R. P. Thummel, *J. Amer. Chem. Soc.*, 1974, **96**, 6948) from the $(2\pi + 4\pi)$ cyclo-addition between hexafluoro-2-butyne and *cis*, *trans*-cyclododeca-1,3-diene, the bridgehead carbon signals were separated by 12·6 p.p.m.

§ Four types of conformation may be considered which place the bridgehead hydrogen atoms either outside or inside the molecular cavity, that is (A), (B), and (C) (out, out) each having a C_2 axis of symmetry, and (D) (out, in); steric interactions in CPK models of the in, in-conformations corresponding to (A), (B), and (C) suggest these stereo-arrangements may be neglected here. A single resonance for bridgehead carbon atoms in these macrobicyclic ethers could arise from a mixture of the conformers (A), (B), (C), and (D), in which the conformers are interconverting rapidly (on the n.m.r. time scale) and in which (D) is undergoing rapid conformational inversion (out, in-in, out-isomerization). A consideration of CPK models of conformations (A), (B), and (C) for (**8**) ($a \neq b = c$) and (**9**) ($a \neq b \neq c$) suggests that such species are of higher energy than the out, in-type of conformation, (D), as a result of significant steric interactions between the chains. We consider that (A), (B), and (C) may represent intermediate stages during the conformational inversion of (D) but that a stereo-arrangement similar to type (D) represents the preferred, minimum energy conformation for (**8**) and (**9**).

¶ The low temperature spectrum of (**9**) supports the deduction based on CPK-models that conformers (A), (B), and (C) do not form a major part of the conformational population for this compound. The occurrence of only two signals of nearly equal intensities for bridgehead carbon atoms in the spectrum of a system containing conformers (A), (B), (C), and (D) which are interconverting *slowly* on the n.m.r. time scale, and in which (D) is inverting slowly, would require an unlikely number of accidental chemical-shift equivalences. Alternatively, if chemical-shift equivalence does not occur, either (A), (B), and (C) are present in very minor proportions and (D) is the major conformer, or the bridgehead carbon signals must arise from two out of the three conformations described by (A), (B), and (C), and (D) is absent. In the latter case such an over-riding preference for two conformations is not easily rationalized and thus the former alternative appears more reasonable. The possibility that the two bridgehead signals represent averaged signals for two sets of conformers [for example set (AD) and set (BC)] undergoing rapid interconversion *within* each set and slow interconversion between the sets is invalidated since interconversions between (A), (B), and (C) each proceed through a conformation of type (D).

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[6] C. H. Park and H. E. Simmons, *J. Amer. Chem. Soc.*, 1968, **90**, 2429.
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