Synthesis of Some out,in- and out,out-Macrobicyclic Polyethers derived from Glycerol. Out,in–in,out Isomerism

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Macrobicyclic polyethers containing carbon bridgeheads have been synthesised from achiral and chiral glycerol derivatives. Syntheses based on *cis*-1,3-*O*-benzylideneglycerol yield a mixture of out,out- and out,in-isomers of these macrobicyclic compounds, whereas syntheses based upon 2,3-*O*-isopropylidene-D-glycerol afford stereospecific routes to the out,in-isomers. ^{13}C N.m.r. spectroscopy indicates that the out,in-macrobicyclic polyethers are undergoing out,in–in,out isomerization, and in two compounds the interconversion is slowed sufficiently on cooling for separate bridgehead carbon resonances to be observed. A rationalization is presented for the relative conformational mobility observed in the series of out,in-compounds studied. Added potassium ions produce significant changes in the ^{13}C n.m.r. spectra of certain of the macrobicyclic polyethers, and it is suggested that these changes are a result of complexation of the cation by the bicyclic compound.

In connection with an investigation into the complexing abilities of macrobicyclic polyethers towards metal cations, we have synthesized a series of these compounds containing carbon atoms at the bridgehead positions, starting from derivatives of glycerol. Although the connecting chains about the bridgeheads. Either the chains *a*, *b*, and *c* (see Figure 1), are arranged in the same rotational sense when viewed along each carbon to hydrogen bridgehead-bond, as in (*A*) (the *trans*-fused isomer [2]), or in the opposite rotational sense, as in (*B*)

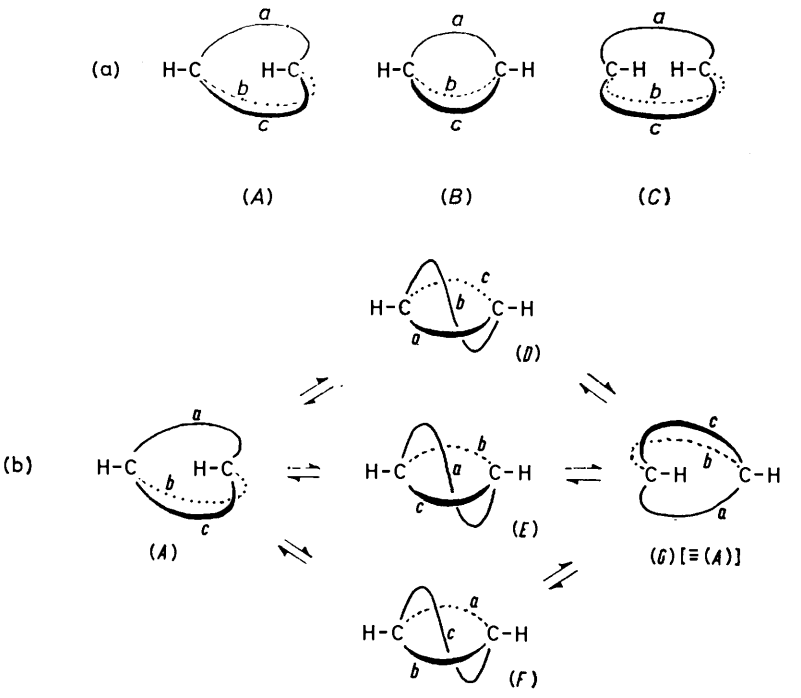
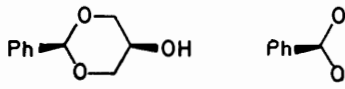


FIGURE 1 (a) Out,in- (*A*), out,out- (*B*), and in,in- (*C*) stereoisomers of a macrobicyclic compound with carbon bridgeheads. (b) Representation of preferred conformations (*A*) and (*G*) [≡(*A*)] of macrobicyclic compound with carbon bridgeheads, and of the possible transition states (*D*), (*E*), and (*F*) for the conformational interconversion (*A*) ⇌ (*G*)

fulfilment of our original objective awaits the preparation of larger amounts of these compounds than we have at present, we wish to report our synthetic routes, and on the interesting conformational properties of some members of this series.[1]

In general, macrobicyclic compounds with tetrahedral, bridgehead carbon atoms may be classified into two types, based on the stereo-arrangement of the inter- and (*C*) (*cis*-fused isomers [2]). Stereoisomers (*B*) and (*C*) are called atropisomers [3] if capable of independent existence, and may, at least in theory, be interconverted by a process in which one chain passes through the ring formed by the other two chains and the bridgehead atoms (homeomorphic isomerization).

As represented in Figure (1a), stereoisomers (*A*), (*B*), and (*C*) may be classed as out,in-, out,out-, and in,in-



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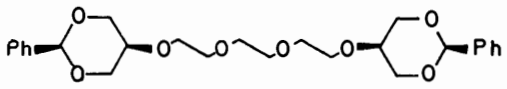

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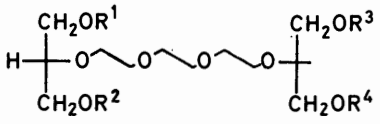
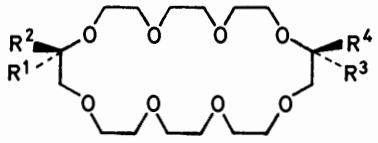
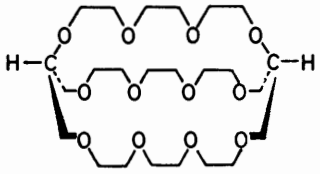




(3) $R^1 = R^3 = H$; $R^2 = R^4 = CH_2Ph$
(4) $R^1 = R^4 = CH_2Ph$; $R^2 = R^3 = H$
(5) $R^1 = R^4 = H$; $R^2 = R^3 = CH_2Ph$
(6) $R^1 = R^3 = (NO_2)_2 \cdot C_6H_3 \cdot CO$; $R^2 = R^4 = CH_2Ph$
(7) $R^1 = R^4 = CH_2Ph$; $R^2 = R^3 = (NO_2)_2 \cdot C_6H_3CO$
(8) $R^1 = R^4 = (NO_2)_2 \cdot C_6H_3 \cdot CO$; $R^2 = R^3 = CH_2Ph$

(9) $R^1 = R^3 = H$; $R^2 = R^4 = CH_2OCH_2Ph$
(10) $R^1 = R^4 = CH_2OCH_2Ph$; $R^2 = R^3 = H$
(11) $R^1 = R^4 = H$; $R^2 = R^3 = CH_2OCH_2Ph$
(12) $R^1 = R^3 = H$; $R^2 = R^4 = CH_2OH$
(13) $R^1 = R^4 = CH_2OH$; $R^2 = R^3 = H$
(14) $R^1 = R^4 = H$; $R^2 = R^3 = CH_2OH$



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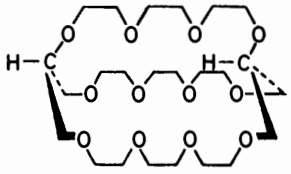

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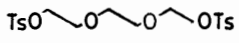


(17)

bicyclic compounds, respectively, the prefixes describing the position of the bridgehead hydrogen atoms with respect to the molecular cavity.*

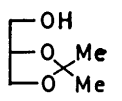
Although this type of isomerism has been investigated fairly extensively, in bicyclic compounds containing nitrogen bridgeheads,[6a-h] in which the added factor of nitrogen inversion must be considered, it has been little studied in systems containing carbon bridgehead atoms. In most of the familiar carbobicyclic systems, for example bicyclo[2.2.1]heptane (norbornane), the chains joining the bridgehead positions are too short to allow the existence of isomers of the type (*A*) or (*C*) in Figure 1. However, Park and Simmons [4] have prepared the in,in- and out,in-isomers of bicyclo[8.8.8]hexacosane by stereospecific routes; the allocation of the in,in- rather than the out,out-conformation to the one isomer was based on theoretical calculations of the thermodynamic stabilities of both atropisomers. Also, Gassman and his coworkers [5] have described an out,in-macrobicyclic compound which was obtained by a ($2\pi + 4\pi$) cycloaddition between hexafluoro-2-butyne and *cis,trans*-cyclododeca-1,3-diene. More recently, syntheses of out,out-isomers of macrobicyclic polyethers have been described.[7,8]

RESULTS AND DISCUSSION

Our initial approach to the synthesis of out,out- † and out,in-macrobicyclic polyethers based on glycerol afforded

* The use of in- and out- as prefixes to describe bridgehead stereochemistry in such macrobicyclic compounds is convenient, and is established by usage, but suffers from the disadvantage that it may be ambiguous. Thus, an out,in-bicyclic compound (*A*) (Figure 1) can assume, at least in theory, out,out-conformations of the type (*D*), (*E*), and (*F*) [Figure 1(b)], and also in,in-conformations. Similarly, it is possible to represent an out,out-bicyclic compound (*B*) in out,in-conformations. In this paper, unless it is stated otherwise, the out,in-, out,out-, and in,in-descriptors of bridgehead stereochemistry will be assumed to describe the stereoarrangements at the bridgeheads of bicyclic systems in those conformations in which the chains are not intertwined [as they are in (*D*), (*E*), and (*F*)] but are as far apart as possible, as in (*A*), (*B*), and (*C*); this system of nomenclature has been tacitly assumed by previous workers.[4,5] When chains *a*, *b*, and *c* are different, then stereoisomers of a macrobicyclic compound are defined unambiguously (except as regards their conformation) by giving the absolute configuration at each bridgehead position using the (*RS*) notation;[2] the *trans,cis* system of nomenclature [2] does not distinguish between (*A*) and its enantiomer. If at least two of the chains are identical then the *trans, cis* designation is sufficient to define a stereoisomer.

† We have no evidence as to whether the preferred conformation of the *cis*-fused bicyclic system prepared in this work is the out,out- or the in,in-form, and arbitrarily refer to it as the out,out-conformation.



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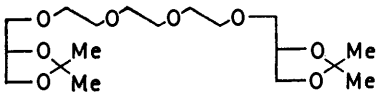

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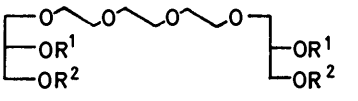
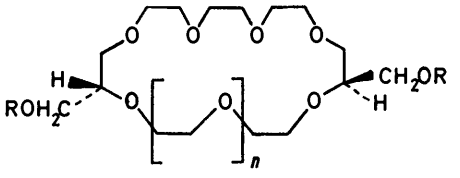
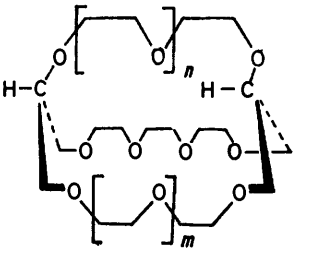


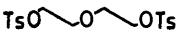
(20) $R^1 = R^2 = H$
(21) $R^1 = R^2 = (NO_2)_2 \cdot C_6H_3CO$
(22) $R^1 = H$; $R^2 = Ph_3C$



(23) $n = 2$; $R = Ph_3C$
(24) $n = 1$; $R = Ph_3C$
(25) $n = 2$; $R = H$
(26) $n = 1$; $R = H$



(27) $n = 2$, $m = 1$
(28) $n = 1$, $m = 1$
(29) $n = 1$, $m = 2$



(30)

both the stereoisomers, and required their separation at the final stage. *cis*-5-Hydroxy-2-phenyl-1,3-dioxan (1), prepared from glycerol and benzaldehyde, was converted into its alkoxide with sodium hydride and reacted with triethylene glycol ditosylate (17) to afford the crystalline polyether (2) in 57% yield. Cleavage of the acetal rings [9] in (2) with diborane in tetrahydrofuran gave, in high yield, a liquid mixture of 2,2'-*O*-linked diglycerol derivatives, comprising, on a statistical basis, the *meso*-compound (3) and the enantiomers (4) and (5) in molar ratios of 2 : 1 : 1. The mixture of diols was characterized by formation of a crystalline mixture of the corresponding bis-(3,5-dinitrobenzoates) (6)—(8), and on treatment with triethylene glycol ditosylate and sodium hydride in 1,2-dimethoxyethane it was converted into the 24-crown-8 derivatives * (9)—(11), isolated in 25% overall yield after chromatographic purification. Hydrogenolysis of the latter mixture over palladium–charcoal catalyst gave, as an oil, a mixture of the bis(hydroxymethyl)-24-crown-8 derivatives (12)—(14) in high yield. Reaction of the latter mixture with triethylene glycol ditosylate in the presence of sodium hydride gave a mixture of products with two predominating, the out,out- (*cis*)- and out,in- (*trans*)-macrobicyclic polyethers (15) and (16), respectively, which should be formed, statistically, in equal amounts.

The foregoing synthesis was performed three times and on each occasion, the mixture obtained was separated only with difficulty by either preparative layer chromatography or column chromatography. On thin layer chromatography on silica gel, the macrobicyclic polyethers ran as elongated zones and a distinct separation between them was not observed. However, pure samples of each isomer were obtained in low yield by taking early and late fractions in the chromatographic separations, and the more mobile of these isomers was identified as the out,in-compound (16) by comparison with the material prepared by the stereospecific route described below. Thus, by elimination, the other isomer was identified as the out,out-isomer, (15).

The difficulty we experienced in separating (15) and (16) prompted the development of an alternative stereospecific route to the out,in-isomers of such macrobicyclic systems, and this route allows ready access to chiral bicyclic compounds. The starting material for these syntheses was the readily available 2,3-*O*-isopropylidene-D-glycerol (18) [11] which on reaction with triethylene glycol ditosylate in the presence of sodium hydride gave the chiral 1,1'-*O*-linked diglycerol derivative (19) as a liquid. Hydrolytic removal of the isopropylidene groups in (19) was ahieved on treatment with aqueous trifluoroacetic acid or aqueous acetic acid, and in both cases the initial product was found to be partially acylated; deacylation was readily achieved on treatment of the crude product with a basic ion-exchange resin or with methanolic sodium methoxide. The tetraol (20) was characterized as its amorphous tetrakis-(3,5-dinitrobenzoate) (21). Selective protection of the primary hydroxy groups in (21) was achieved by reaction with two molar equivalents of triphenylmethyl chloride to give the di-*O*-trityl ether (22), which was reacted with either triethylene glycol ditosylate or diethylene glycol ditosylate (30) to yield the 24-crown-8 derivative (23) or

* For trivial crown nomenclature, see ref. 10.

the 21-crown-7 derivative (24), respectively. Hydrogenolysis of (23) and (24) afforded (25) and (26), respectively.

Treatment of (25) with triethylene glycol ditosylate in the presence of sodium hydride gave the macrobicyclic polyether out,in- (*trans*) 3,6,9,12,16,19,22,25,27,30,33,36-dodecaoxabicyclo[12.12.10]hexatriacontane (16), whose ^{13}C n.m.r. spectrum was almost identical to that of the chromatographically more mobile product obtained in the synthesis commencing with *cis*-5-hydroxy-2-phenyl-1,3-dioxan (1). Two resonances for methylene carbon atoms, which could just be resolved in the spectrum of material obtained from (18), were not separated in the spectrum of material obtained from (1), this minor difference arising most probably from a concentration difference in the two measurements, or the presence of trace amounts of complexed salts in one or other of the samples (see later). Although (25) is a chiral molecule, (16) is achiral; the identity of the two chains linking the primary centres in the two glycerol residues of the latter compound leads to a plane of symmetry in the molecule.

On the other hand, reaction of (25) with diethylene glycol ditosylate yielded the chiral macrobicyclic polyether out,in-(1*S*,14*S*)-3,6,9,12,15,18,21,24,26,29,32-undecaoxabicyclo[12.10.9]tritriacontane (27) which exhibits a small but definite rotation at the sodium D-line of $-1 \pm 0.1°$.

The 21-crown-7 derivative (26) reacted with diethylene glycol ditosylate to afford the chiral polyether out,in-(1*S*,14*S*)-3,6,9,12,16,19,22,24,27,30-decaoxabicyclo-[12.9.7]triacontane (28), having a rotation of $+1.06 \pm 0.02°$ at the sodium D-line. Treatment of (26) with triethylene glycol ditosylate gave a product, presumed to be slightly impure achiral compound out,in-(*trans*) 3,6,9,12,16,19,22,25,27,30,33-undecaoxabicyclo[12.12.7]-tritriacontane (29); an acceptable carbon analysis was not obtained (error, 0.5%), but an accurate determination of the mass of its molecular ion was in good agreement with that calculated for the molecular formula of (29), and its ^{13}C and ^{1}H n.m.r. spectrum were in accord with the expected structure.

Variable-temperature ^{13}C *N.M.R. Spectra of the Macrobicyclic Polyethers.*—The proton-decoupled ^{13}C n.m.r. spectra (15), (16), (27), (28), and (29) had similar features. At room temperature, the signals for bridgehead-carbon atoms in this series lay in the region δ_C 78.5—79.0, and were well separated from the resonances of the methylene-carbon atoms, which occurred between δ_C 69.6 and 72.3. Another feature common to all spectra at room temperature was a single methylene-carbon resonance, between δ_C 69.6 and 70.2, which was to higher field of all of the other resonances and separated from the nearest one by 1.1—1.6 p.p.m. A consideration of the chemical shifts and signal intensities within this series strongly suggests that in each case this highest-field resonance arises from the methylene carbon atoms which are directly attached to those oxygen atoms linked to the bridgehead carbon atoms.

At ambient temperature, all the compounds except (27) showed a single sharp resonance for the bridgehead carbon atoms. This is understandable in the case of (15) if it exists in the conformation shown (or in the in,in-conformation, or in a mixture of the out,out- and in,in-conformers in rapid equilibrium on the n.m.r. time scale), as the bridgehead carbons are related by a plane of symmetry. Since the ^{13}C-$\{^{1}H\}$ n.m.r. spectrum of out,in-bicyclo[8.8.8]hexacosane shows separate signals for the bridgehead carbon atoms, with a separation of *ca.* 3 p.p.m.,[4] the occurrence of a single bridgehead resonance for (16), (28), and (29) indicates that if their favoured conformations are as shown in the formulae, then they are all undergoing a rate process, fast on the ^{13}C n.m.r. time scale, which leads to chemical equivalence of their bridgehead carbon atoms. We consider this process to be out,in–in-out isomerization * $\rightleftharpoons$ G[$\equiv$(A)], achieved by passage of any one chain through the ring formed by the other two chains and the bridgehead atoms, as indicated in Figure 1(b). Formulae (*D*), (*E*), and (*F*) represent the transition states or unstable intermediates for the interconversion. It has been reported [4] that, for bicyclic hydrocarbons, a consideration of models suggests that homeomorphic isomerization is possible when the chains contain about ten methylene groups. However it has not been observed experimentally in cations of 1, $(k + 2)$-diazabicyclo-[*k.l.m*]alkanes containing chains of up to fourteen methylene groups. Presumably, the presence of oxygen atoms in the chains of the (16), (28), and (29) (which if the oxygen atoms were replaced by methylene groups would contain between 7 and 12 methylene units) reduces the inter-chain non-bonded interactions, thus facilitating the isomerization. One of the proposed explanations for changes in the ^{1}H n.m.r. spectrum of 4,7,13,16,21,24-hexaoxa-1,10-diazobicyclo[8.8.8]hexacosane on lowering its temperature involves homeomorphic isomerization.[6g]

The expected number of resonances in the ^{13}C n.m.r. spectrum of (15) in the out,out- or in,in-conformation is eight, and for compounds (16), (28), and (29), assuming they undergo rapid (on the ^{13}C n.m.r. time scale) homeomorphic isomerization, the corresponding numbers are eight, ten, and seven, respectively. In the case of (15), seven resonances can be distinguished at room temperature, but a consideration of their relative intensities indicates that the resonance at δ_C 71.19 is composed of two signals which are accidentally isochronous. For compounds (16) [prepared from (18)] and (28), the expected number of ^{13}C resonances are observed at room temperature, whereas for (29) only six resonances are resolved. However, on measuring the spectrum of (29) at 0 °C, the accidental chemical-shift equivalence that must occur in the spectrum measured at ambient temperatures is destroyed and all seven of the expected ^{13}C signals are observed.

The macrobicyclic polyether (27) is unique in that, in its ^{13}C n.m.r. spectrum at room temperature (see Figure

* For a justification of this deduction see the preliminary communication on this work.[1]

2), the bridgehead carbon resonance, centred on δ_C 78.86, appeared broad ($W_{\frac{1}{2}}$ *ca.* 18 Hz) suggesting that out,in–in,out isomerization is occurring at an intermediate rate on the n.m.r. time scale. This possibility prompted a variable-temperature study of the ^{13}C n.m.r. spectrum of this compound, and of the other macrobicyclic polyethers (16), (28), and (29).

In the spectra of (27) measured at progressively lower temperatures (Figure 2), the low-field signal broadened

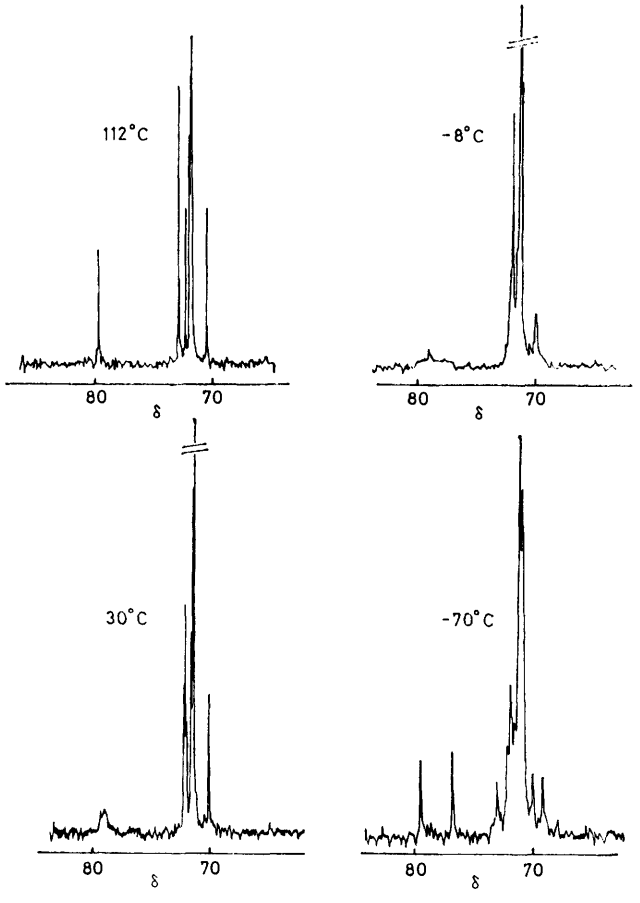


FIGURE 2 ^{13}C N.m.r. spectra of (27) at various temperatures. The spectrum at 112 °C was measured in toluene–[$^2H_8$]toluene and the rest in [$^2H_6$]acetone

further and then two singlets gradually appeared in this region; −70 °C two singlets ($W_{\frac{1}{2}}$ *ca.* 4 Hz) were observed at δ 79.55 and 76.82, having nearly equal intensities (ratio 1 : 1.07). The coalescence temperature was estimated to be near −8 °C, which would correspond to $\Delta G^{\ddagger}$ *ca.* 54 kJ mol^{-1} for the interconversion, assuming that the difference in chemical shifts of the two bridgehead resonances at this temperature is the same as that measured at −70 °C. These figures must be regarded as somewhat tentative; a more accurate determination of the coalescence temperature is difficult because of what appears to be a very large coalescence range. The latter property appears to be a characteristic feature of these macrobicyclic systems and as yet we can offer no explanation for it. Also, it is clear [12] that the estimation of activation parameters by measurement of a rate constant at a single temperature, followed by its conversion to a free energy of activation by the Eyring equation,[13] is fraught with difficulties and pitfalls, and that the most satisfactory method for obtaining such parameters is by line-shape analysis. Nevertheless, we believe the approximate values for (27), and for other compounds (see below) obtained from observations of coalescence phenomena, are of use in making qualitative deductions about the relative conformational mobility of these compounds.

As the temperature of the solution * of (27) was raised, the bridgehead carbon resonance narrowed and, at 112 °C (Figure 3), became a sharp singlet ($W_{\frac{1}{2}}$ *ca.* 1 Hz) at δ_C 79.55, indicating that at this temperature out,in–in,out isomerization is fast on the n.m.r. time scale; ten out of the eleven signals which are expected could be distinguished in this spectrum.

Interestingly, in the spectra of (27) measured at various temperatures, a second coalescence phenomenon may be observed, associated with the highest field signal, initially at δ_C 70.11 in the spectrum measured at 30 °C. At −70 °C two peaks are apparent in this region, at δ_C 69.13 and 69.98, which appear to coalesce near −25 °C; these figures lead to $\Delta G^{\ddagger}$ 53 kJ mol^{-1}, a value very similar to that obtained *via* measurements on the bridgehead resonances.

In the case of the ether (28), lowering the temperature causes the bridgehead-carbon resonance, initially a sharp singlet with δ_C 78.58 at 27 °C, to broaden, and at −80 °C two distinct singlets are observed in this region at δ_C 75.52 and 79.11. The coalescence point for these signals appeared to be near −51 °C, from which a $\Delta G^{\ddagger}$ value of approximately 44 kJ mol^{-1} was calculated for the out,in–in,out isomerization process. It is significant that as with (27) the highest-field signal also broadened as the temperature was lowered. Although the proximity of the peak to the main group of methylene-carbon resonances hindered measurement of the required parameters, a $\Delta G^{\ddagger}$ value of approximately 43 kJ mol^{-1} was indicated, close to that obtained using the bridgehead-carbon resonance as a probe.

Measurement of the spectrum of the ether (16) down to −71 °C produced no significant peak broadening in the spectrum, although at −104 °C in the mixed solvent [$^2H_6$]acetone–dichlorodifluoromethane, the signal for the bridgehead-carbon atoms is considerably broader ($W_{\frac{1}{2}}$ *ca.* 40 Hz) than at 11 °C in the same solvent ($W_{\frac{1}{2}}$ *ca.* 1 Hz).

The room temperature spectrum of the ether (29) showed a sharp singlet resonance for the bridgehead carbon atoms and spectral measurements down to −75 °C showed no significant broadening in any of the signals in the spectra. We conclude that this compound undergoes fast out,in–in,out isomerization on the ^{13}C n.m.r. time scale.

The bridgehead-carbon resonance of the out,out-ether

* Spectra at elevated temperatures were measured in toluene–[$^2H_8$]toluene to alleviate the problem of pressure increase which would occur with [$^2H_6$]acetone in a sealed n.m.r. tube.

(15) did not undergo coalescence, but remained a well defined singlet as spectra were measured at successively lower temperatures, the values of $W_{\frac{1}{2}}$ for this signal at 27, −10, −40, −70, and −80 °C being 2, 3, 6, 8, and 10 Hz, respectively. This is to be expected if the molecule adopts a conformation of the type depicted in (15). However, it is noteworthy that the signal at highest field in the spectrum measured at room temperature is broadened at −40 °C; the fate of this signal at lower temperatures is not clear because of overlap with the group of resonances for the other methylene groups. It should be recognized that interconversion of the out,out-ether (15) and its in,in-atropisomer may be possible, although it would seem unlikely in view of the statement [6c] that the out,out- and in,in-isomers of bicyclo[8.8.8]hexacosane are not interconverted by homeomorphic isomerization up to 200 °C.

A Rationalization of the Relative Conformational Mobilities of (16), (27), *and* (29).—The presence of single, sharp resonances for the bridgehead-carbon atoms in the room-temperature n.m.r. spectra of the out,in-macrobicyclic polyethers (16), (28), and (29) stands in sharp contrast to the observation of separate resonances for the bridgehead carbon atoms in out,in-bicyclo[8.8.8]hexacosane [4] and 11,12-bis(trifluoromethyl)-out,in-bicyclo[8.2.2]tetradeca-11,13-diene.[5] The phenomenon of homeomorphic isomerization in the out,in-macrobicyclic systems containing carbon bridgeheads is most conveniently discussed in terms of the out,in-conformations (*A*) and (*G*) (≡ *A*) and the out,out-conformations (*D*), (*E*), and (*F*) shown in Figure 1. We consider that conformations of the type (*A*) and (*G*) (≡ *A*) represent favoured, low-energy conformations for these compounds and that they interconvert through one or more conformations having a C_2 axis of symmetry of the type (*D*), (*E*), and (*F*), which may represent a transition state or, at least, an unstable intermediate for the conformational interchange. From a consideration of models, steric interactions between chains appear to be minimized in (*A*) and (*G*), and are considerably greater in (*D*), (*E*), and (*F*). Although other intermediates in the conformational interchange (*A*) ⇌ (*G*) [≡ (*A*)] may be envisaged, for example the in,in-conformation, they are probably of higher energy than (*D*), (*E*), and (*F*), and will not be considered further.

The qualitative experimental observations that must be accommodated in any rationalization of the conformational mobilities of the out,in-macrobicyclic polyethers, as indicated by their ability to undergo homeomorphic isomerization, are that (27) and (28) show restricted conformational mobility compared to compounds (16) and (29), and that compound (28) appears to exhibit a greater conformational mobility than (27). As a starting point, it is useful to consider the likely effects of chain lengths in these compounds (as measured by the total number of atoms, carbon plus oxygen, in each chain) on the magnitudes of the free-energy differences between the favoured ground state conformation, assumed to be of type (*A*) in Figure 1(b), and the transition-state conformations, assumed to resemble (*D*), (*E*), and (*F*).

Neglecting such factors as dipole–dipole interactions, reduced steric interactions, *etc.*, which may result from the presence of oxygen atoms in the chains, the following propositions may be made, based on the experimental observations.

(*a*) In transition state conformations (*D*), (*E*), and (*F*) [Figure 1(b)], steric interactions will be greater between the central chain (*b*, *a*, and *c* respectively) and the ring formed by the other two chains and the bridgehead carbon atoms, the smaller the ring is. This is in accord with the observation that those compounds undergoing homeomorphic isomerization most readily, (16) and (29), have the largest rings (26 atoms) in any of the four ethers in their transition-state conformations [see Table and (*E*) in Figure 1].

Total number of atoms (carbon plus oxygen) in chains *a*, *b*, and *c* of the out,in-macrobicyclic polyethers [a]

Compound	Chain *a* [b]	*b*	*c*
(16)	10	12	12
(27)	10	12	9
(28)	7	12	9
(29)	7	12	12

[a] See Figure 1(b). [b] Chain *a* is that one linking the secondary carbon atoms in the two glycerol residues.

(*b*) The most favoured transition-state conformation in Figure 1 is that one in which the chain passing through the centre of the ring is the one linking the secondary carbon atoms of the two glycerol residues in the macrobicyclic polyether. This is in agreement with the fact that (27) isomerizes less readily * than (28). Were this transition state not preferred, it would be expected that (27) would isomerize more readily than (28), since the former has a transition-state conformation available to it, (*F*) in Figure 1, with a ring of 24 atoms, whereas the largest ring in the transition-state conformations for (28) is 23 atoms [conformer (*E*)].

(*c*) Below a certain length for chain *a*, the shorter that chain *a* is, then the lower is the free-energy difference between the favoured conformation and the transition-state conformation. This proposition is a consequence of proposition (*b*) and the observation that (28) isomerizes more readily than (27). For a given interbridgehead distance, there is a minimum length for chain *a* that allows the two bridgehead carbon–hydrogen bonds to lie along the same axis, as in conformation (*A*) of Figure 1. When the length of chain *a* is equal to or longer than this critical length, the free-energy difference $\Delta G_1^{\ddagger}$ between (*A*) and the transition state (*E*) will be given by equation (1) where $G_{(E)}$ and $G_{(A)}$ are the free energies of conformers (*E*) and (*A*), respectively.

$$\Delta G_1^{\ddagger} = G_{(\epsilon)} - G_{(A)} \qquad (1)$$

* By considering only one transition state, an error can be made in assigning the measured $\Delta G^{\ddagger}$ value to that one pathway. However, the maximum error would be $RT \log_e 3$ (*ca.* 2.5 kJ mol^{-1} at 273 K) when three equally energetic pathways are available for the interconversion, and this value is significantly less than the energy differences being compared.

If chain *a* is less than this critical length, the two bridgehead carbon–hydrogen bonds will no longer be able to lie along the same common axis,* but will make an angle θ ($\theta > 0°$) with each other as depicted in conformation (*H*) (Figure 3).

The difference in free energy, $\Delta G_2^{\ddagger}$, between (*H*) and the transition state for conformational inversion, (*I*), is given by equation (2) where $G_{(I)}$ and $G_{(H)}$ are the free

$$\Delta G_2^{\ddagger} = G_{(I)} - G_{(H)} \qquad (2)$$

energies of conformers (*I*) and (*H*), respectively. This difference, $\Delta G_2^{\ddagger}$, is likely to be less than $\Delta G_1^{\ddagger}$; both (*I*) and (*E*) suffer interchain interactions which are likely to be of a similar magnitude, whereas (*H*) possesses interchain interactions of a type not present in (*A*). Thus, conformation (*H*) resembles more closely the transition state, (*I*), leading to conformational inversion, than

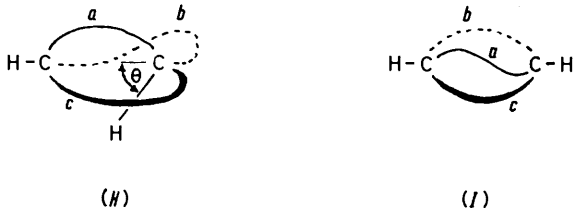


FIGURE 3 Representation of the preferred conformation (*H*) of an out,in-macrobicyclic compound in which chain *a* is short (see text) and of the transition state (*I*) for conformational interconversion.

conformation (*A*) resembles (*E*). Interestingly, in the case of *trans*-fused bicyclic systems, where the two bridgehead carbon atoms are joined directly, for example in *trans*-decalin, the ground state conformer is actually identical to the one with C_2-symmetry.

Effect of Potassium Ions on the ^{13}C *N.M.R. Spectra of* (15), (16), (27), *and* (28).—Consideration of conformations of the type (*D*), (*E*), and (*F*) as transition states or intermediates in the homeomorphic isomerization process, together with a realization that macrobicyclic polyethers are efficient complexing agents for certain metal ions,[6d,e,h,14] led us to investigate the effect that potassium ions have on the conformational interconversions. If a cation were firmly complexed within the cavity of (*A*) and (*G*) it might reasonably be expected that the isomerization process (*A*) ⇌ (*G*) would be slowed if formation of the transition state required prior displacement of the metal ion. Interestingly, if the chains *a*, *b*, and *c* are of a suitable length, cation complexation could occur, conceivably, with conformations of the type (*D*), (*E*), and (*F*), and might lead to stabilization of one or more of these out,out-conformations.

A forceful illustration of the effect of cations was obtained when the spectrum of (27) was measured in the presence of one mol. equiv. of potassium thiocyanate at room temperature. The bridgehead carbon atoms, which in the absence of the salt gave rise to a single broad absorption at this temperature, now gave rise to separate signals of similar intensity at δ_C 77.21 and 77.97. A general shift of all resonances to higher field was also noted. Although we have not carried out coalescence measurements, it would appear that the rate of the process which makes the bridgehead carbon atoms equivalent is slowed significantly, and the apparent $\Delta G^{\ddagger}$ value indicated by this rate must be >64 kJ mol^{-1}, which is a figure, calculated with the usual assumptions, for coalescence of the peaks at 27 °C.

Addition of 1 mol. equiv. of potassium thiocyanate to the solution of (28) caused, at room temperature, an upfield shift of 1.25 p.p.m. in the bridgehead carbon resonance, which remained a sharp singlet. Significantly, the signal at highest field in the absence of the salt, a sharp singlet, was greatly broadened in the presence of the salt. On lowering the temperature of the sample, the bridgehead resonance separated, near 0 °C, into two distinct singlets of similar intensity having chemical shifts of δ_C 76.77 and 77.14 at −20 °C. Near 10 °C, the highest-field signal separated into two singlets of similar intensity and at −20 °C they had δ_C values of 66.25 and 68.27. Calculation of the apparent $\Delta G^{\ddagger}$ from the two coalescence phenomena afforded values of 60 and 52 kJ mol^{-1} from the bridgehead carbon and high-field signals, respectively. We are not sure if the non-identity of these values is due to different rate processes causing the two coalescence phenomena or due to experimental deficiencies, but both figures are considerably greater than that measured (44 kJ mol^{-1}) from coalescence of the bridgehead signals of (28) in the absence of salt.

In the spectrum of (16) measured at successively lower temperatures in the presence of 1 mol. equiv. of potassium thiocyanate, the bridgehead carbon resonance remains as a reasonably sharp singlet down to −30 °C. This signal broadens considerably between −30 and −70 °C, but its separation into two singlet components was not observed in the temperature range studied. The signal at highest field undergoes considerable broadening between 27 and −30 °C, and cannot be seen in the spectrum at lower temperatures. The spectra of the out,out-compound (15) obtained at various temperatures with 1 mol of potassium thiocyanate present show some features for which no satisfactory explanation is, as yet, apparent. At 27 °C, all eight of the expected resonances can be distinguished, but, surprisingly, that one at highest field, which is a sharp singlet ($W_{\frac{1}{2}}$ *ca.* 2 Hz) in the absence of the salt, is broadened somewhat ($W_{\frac{1}{2}}$ *ca.* 8 Hz). At −10 °C, this signal is not discernible in the spectrum (presumably because of further broadening), and on cooling to between −50 and −60 °C the signal for the bridgehead carbon atoms also disappears from the spectrum. Although measurements at −80 °C did not lead to the appearance of peaks in those regions where coalescence had, apparently, occurred, these results are not in disagreement with (15) having conformational mobility.

* We assume that the bridgehead carbon atoms are constrained from moving together, which will obviously not be the case if *a*, *b*, and *c* are large.

In summary, it appears that homeomorphic isomerization of (27) and (28) is hindered by the addition of potassium thiocyanate, and the results are in keeping with the occurrence of complexation between these bicyclic polyethers in conformations of type (*A*) (Figure 1) and potassium ions, coupled with rapid transfer of cations from complexed to uncomplexed species. The apparent decrease in the rate of exchange of magnetic environment for bridgehead carbon atoms which occurs on the addition of the salt is most reasonably interpreted in terms of a reduction in the concentration of uncomplexed polyether, through which the isomerization presumably proceeds.* Significantly, addition of 2 mol. equiv. of potassium thiocyanate to the solution of (28) caused the bridgehead signal to separate *at room temperature* into two singlets, δ_C 77.43 and 77.87, of similar intensity, in contrast to the singlet which is observed at this temperature with only 1 mol. equiv. of salt present.

It is noteworthy that the chemical shift differences of 0.76 and 0.37 p.p.m. between the separated bridgehead resonances of (27) and (28), respectively, in the presence of the salt, are considerably less than those in the absence of salt (2.73 and 3.59 p.p.m., respectively). This reflects, presumably, the different induced chemical shifts caused by the potassium ions. The electric fields experienced by the two bridgehead carbon atoms as a result of a potassium ion occupying the cavity of the bicyclic ether would not be expected to be identical because of the unsymmetrical position of the ion within the cavity, and the unequal shielding effects for the bridgehead atoms, both caused by the in-hydrogen atom at one of the bridgehead positions.

The observation of separate bridgehead resonances for (28) and (29) in the presence of the potassium salt could be rationalized, alternatively, in terms of an out,out-conformation of the type (*D*), (*E*), or (*F*) which contains a potassium ion asymmetrically placed with respect to the two bridgeheads, and which is undergoing slow site-exchange. The observation of two bridgehead resonances for (28) in the presence of 2 mol. equiv. of potassium thiocyanate suggests that if this rationalization were correct, then there are not two similar sites for simultaneous complexation of two cations in this conformation of the bicyclic compound.

EXPERIMENTAL

Column chromatography was performed on Kieselgel 60 (Merck) with the aid of a fraction collector, and preparative layer chromatography was done on Kieselgel PF_{254} (Merck). Optical rotations were measured in chloroform on a Perkin-Elmer 141 polarimeter. ^1H N.m.r. spectra were recorded at 60 MHz with a Perkin-Elmer R12 spectrometer or at 100 MHz with a Varian HA-100 spectrometer for solutions in $CDCl_3$ (unless stated otherwise), using tetramethylsilane as an internal reference. ^{13}C N.m.r. spectra were recorded at 25.05 MHz with a JEOL FX-100 spectrometer on approximately 5% (w/v) solutions in the solvents indicated, using a deuterium lock, and chemical shifts (δ_C) are from tetramethylsilane as an internal reference. Proton-noise-decoupled spectra were measured at spectral widths of 500 and 2 500 Hz, for which, typically, 1 000—2 000 transients were collected (8 192 data points) with a pulse width of 5 μs and a pulse repetition time of 2—4 s. In variable-temperature studies of ^{13}C n.m.r. spectra, temperatures were measured with the meter incorporated in the spectrometer, and the calibration was checked with a thermocouple. Low- and high-resolution mass spectra were obtained on a Hitachi–Perkin-Elmer RMU-6E and on an AEI MS 902 spectrometer, respectively. 1,2-Dimethoxyethane (DME) was dried by distillation from calcium hydride and was stored over sodium wire, and dimethyl sulphoxide (DMSO) was dried over molecular sieves. Sodium hydride, supplied as a dispersion in oil, was freed from oil by washing the dispersion with light petroleum, and the weights of this reagent quoted below refer to the washed and dried material. Organic solutions were dried over anhydrous sodium sulphate. Light petroleum refers to that fraction having b.p. 60—80 °C.

Bis-(cis-2-*phenyl*-1,3-*dioxan*-5-*yl*)-1,4,7,10-*tetraoxadecane* (2).—To a stirred solution of *cis*-5-hydroxy-2-phenyl-1,3-dioxan [16] (1) (9 g) and triethylene glycol ditosylate [17] (17) (9.2 g) in DMSO (30 ml) was added, in portions, sodium hydride (1.2 g) over a period of 0.5 h, and the mixture was then heated at 50 °C for 72 h. After cooling the mixture, methanol (0.5 ml) and dichloromethane (250 ml) were added, sodium tosylate was removed by filtration, and the filtrate was extracted with water (2 × 100 ml). The organic layer was dried and concentrated to afford a syrup which crystallized from benzene–light petroleum to give the *compound* (2) (5.4 g, 57%), m.p. 66—67.5 °C (Found: C, 65.7; H, 7.0. $C_{26}H_{34}O_8$ requires C, 65.8; H, 7.2%); $\delta(CDCl_3)$ 3.35 (2 H, m, 2 × H-5′), 3.64 (4 H, s, 2 × acyclic CH_2), 3.70 (8 H, s, 4 × acyclic CH_2), 3.98 (4 H, dd, $J_{4'e,4'a}$ 12 Hz, $J_{4'a,5'}$ 2 Hz, 2 × H-4′a and 2 × -6′a), 4.32 (4 H, dd, $J_{4'e,5'}$ 2 Hz, 2 × H-4′e and 2 × H-6′e), 5.49 (2 H, s, PhC*H*), and 7.20—7.60 (10 H, complex, Ar-H).

Mixture of meso- *and* (±)-*Stereoisomers of* 4,15-*Bis*-(*hydroxymethyl*)-1,18-*diphenyl*-2,5,8,11,14,17-*hexaoxaoctadecane* [(3), (4), and (5)].—The method used for the reductive cleavage of compound (2) is essentially that of Fleming and Bolker.[9] Compound (2) (8 g) was added to a stirred solution of diborane in tetrahydrofuran (40 ml of an approximately 1M solution) which had previously been cooled to −10 °C. The reaction mixture was kept for 10 min in an ice-bath, then allowed to warm to room temperature, and finally, was heated at 40 °C for 24 h; t.l.c. (EtOAc) indicated the disappearance of starting material. The mixture was cooled, and water was added dropwise until effervescence ceased, and then more water (30—40 ml) was added to dissolve the precipitated boric acid and to hydrolyse esters of boric acid. The aqueous solution was extracted with ether (5 × 100 ml), and the combined extracts were washed with water, dried, and concentrated. Dry methanol (15 ml) was added to the residue and then removed under reduced pressure. The procedure was repeated twice more, to remove any remaining boric acid as its volatile methyl ester, and yielded the mixed *stereoisomers* (3)—(5) (7.2 g, 90%) (Found: C, 64.8; H, 8.0. $C_{26}H_{38}O_8$ requires C, 65.25; H, 8.0%); $\delta(CDCl_3)$ 3.05 (2 H, br s, 2 × OH), 3.45—3.95 (22 H, complex, 10 × CH_2 and 2 × CH), 4.55 (4 H, s, 2 × PhCH_2), and 7.35 (10 H, br s, Ar-H). This product gave a bis-(3,5-dinitrobenzoate) as a yellow solid,

* Rates of exchange between sites *via* *N*-inversion in amines have been reduced by using acid solutions, which reduces the concentration of free amine by partial protonation.[15]

m.p. 110—114 °C (Found: C, 55.6; H, 4.95; N, 6.4. $C_{40}H_{42}N_4O_{18}$ requires C, 55.5; H, 4.9; N, 6.5%).

Mixture of the meso- *and* (±)-*Stereoisomers of* 2,15-*Bis*-*benzyloxymethyl*-1,4,7,10,13,16,19,22-*octaoxacyclotetracosane* [(9), (10), *and* (11)].—To a stirred solution of the mixture of stereoisomers (3)—(5) (4.8 g) and triethylene glycol ditosylate (17) (4.6 g) in DME (100 ml) was added, in portions, sodium hydride (1 g) over a period of 0.5 h. The mixture was stirred at room temperature for 1 h and then at 50 ± 5 °C for another 24 h. Methanol (10 ml) was added slowly to the cooled reaction mixture and the solvents were then removed. The residue was partitioned between chloroform (100 ml) and water (50 ml) and the aqueous layer was extracted with chloroform (3 × 100 ml). The combined organic extracts were washed with water (50 ml), dried, and concentrated. The residue (3 g) was subjected to column chromatography on silica gel (80 g) using ethyl acetate as eluant. The major product was located by t.l.c. (ethyl acetate) and combination of appropriate fractions gave the *compounds* (9), (10), and (11) (1.5 g, 25%) (Found: C, 64.9; H, 8.0. $C_{32}H_{48}O_{10}$ requires C, 64.85; H, 8.2%); δ($CDCl_3$) 3.44—3.94 (34 H, complex, 16 × CH_2 and 2 × CH), 4.48 (4 H, s, 2 × PhCH_2), and 7.26 (10 H, br s, Ar–H).

Mixture of the meso- *and* (±)-*Stereoisomers of* 2,15-*Bishydroxymethyl*-1,4,7,10,13,16,19,22-*octaoxacyclotetracosane* [(12), (13), *and* (14)].—A solution of the mixed stereoisomers (9)—(11) (1 g) in methanol (100 ml), containing a trace of trifluoroacetic acid, was stirred under a slight overpressure of hydrogen in the presence of 10% Pd–charcoal (0.1 g) until gas uptake was complete (36 h). The reaction mixture was filtered through Kieselguhr, and concentrated to yield the mixed *diols* (12), (13), and (14) (0.75 g, 93%) (Found: C, 52.3; H, 8.6%; M^+, 412. $C_{18}H_{36}O_{10}$ requires C, 52.4; H, 8.8%; *M*, 412); δ($CDCl_3$) 3.20—3.45 (2 H, br, 2 × OH) and 3.50—4.50 (34 H, complex, 16 × CH_2 and 2 × CH).

out,out-(cis)- *and out,in*-(trans)-3,6,9,12,16,19,22,25,27,30,-33,36-*Dodecaoxabicyclo*[12.12.10]*hexatriacontane* [(15) *and* (16)].—*First synthesis.* To a stirred solution of the mixed diols (12)—(14) (1.7 g) and triethylene glycol ditosylate (17) (1.9 g) in DME (300 ml) was added sodium hydride (1 g) over a period of 30 min. The mixture was stirred at 50 °C for 24 h, after which time methanol (5 ml) was added, and the solvent was removed to give a white residue, which was partitioned between chloroform (200 ml) and water (100 ml). The aqueous layer was extracted with chloroform (2 × 150 ml) and the combined organic extracts were dried, and concentrated to yield a syrup, which t.l.c. [chloroform–methanol (9 : 1)] indicated to be a mixture of products with two components predominating. The crude material was subjected to p.l.c. in the same solvent with four developments, and component bands were detected using iodine vapour; in no case was a clear separation observed between the major components. Removal of the relevant bands and extraction of the silica gel so obtained with chloroform–methanol (9 : 1 v/v) gave impure component (*A*) (0.28 g) and (*B*) (0.39 g), the former having a greater R_F value than the latter. Solutions of the above two materials in chloroform become brown on storage, presumably a result of the iodine detection procedure, and purification of the impure components (*A*) and (*B*) was attempted by column chromatography using chloroform–methanol (19 : 1 v/v) as eluant. The impure component (*A*) was purified by this treatment to yield a syrup (0.12 g, 6%), identified through comparison of its ^{13}C n.m.r. spectrum with that of material obtained by a stereospecific synthesis from 2,3-*O*-isopropylidene-D-glycerol (see below), as out,in-(*trans*)-3,6,9,12,16,19,22,25,27,30,33,36-dodecaoxabicyclo-[12.12.10]hexatriacontane (16) (Found: C, 55.1; H, 9.0%; M^+, 526. $C_{24}H_{46}O_{12}$ requires C, 54.7; H, 8.8%; *M*, 526); δ($CDCl_3$) 3.20—3.90 (all H, complex); δ_C[$(CD_3)_2CO$] 70.23, 71.37,* 71.39, 71.57, 71.81, and 72.13 (CH_2), 79.00 (CH).

Impure component (*B*) appeared to have undergone decomposition on column chromatography; a comparison of the ^{13}C n.m.r. spectra of material before and after chromatography showed that an increase had occurred in the number of signals.

Second synthesis. The mixed diols (12)—(14) (1.8 g) were treated with triethylene glycol ditosylate (2 g) in DME (300 ml) essentially as described in the first synthesis, but purification of the crude product (3.5 g) was undertaken by column chromatography on silica gel (250 g) using chloroform–methanol (98 : 2 increasing to 95 : 5 v/v) as eluant, rather than by p.l.c. T.l.c. [chloroform–methanol (9 : 1)] of the fractions obtained indicated that the first eluted component (0.13 g, 13%) was chromatographically homogeneous, and on the basis of its ^{13}C n.m.r. spectrum was out,in-(*trans*)-3,6,9,12,16,19,22,25,27,30,33,36-dodecaoxabicyclo[12.12.10]hexatriacontane (16) (Found: C, 54.8; H, 8.85%; M^+, 526.298 2. $C_{24}H_{46}O_{12}$ requires C, 54.7; H, 8.8%; *M*, 526.299 0); δ_C[$(CD_3)_2CO$] 70.31, 71.40,* 71.42 71.59, 71.85, and 72.18 (CH_2), 79.04 (CH).

Later fractions from the column did not afford chromatographically homogeneous material, but ^{13}C n.m.r. analysis suggested that they consisted, essentially, of the less mobile component (*B*) obtained in the first synthesis.

Third synthesis. Reaction of the mixed diols (12)—(14) (1.7 g) with triethylene glycol ditosylate (1.9 g) and column chromatography of the crude product (3.5 g) in a similar matter to that described in the second synthesis gave, in the early fractions, material largely consisting of (16) contaminated with faster-running (t.l.c.) by-products and with a slower-running component. Later fractions from the column contained only this slow-running component (0.1 g, 5%) which, on the basis of its analysis and the non-identity of its ^{13}C n.m.r. spectrum with that of (16), was identified as out,out-(*cis*)-3,6,9,12,16,19,22,25,27,30,33,36-dodecaoxabicyclo[12.12.10]hexatriacontane (15) (Found: C, 54.9; H, 8.8%; M^+, 526.299 8. $C_{24}H_{46}O_{12}$ requires C, 54.7; H, 8.8%; *M*, 526.299 0); δ_C[$(CD_3)_2CO$] 69.69 (*W ca.* 2 Hz), 70.99, 71.19, 71.38, 71.50, and 71.80 (CH_2), 78.65 (CH).

(2S,15S)-1,2:15,16-*Di*-O-*isopropylidene*-4,7,10,13-*tetraoxahexadecane*-1,2,15,16-*tetraol* (19).—To a stirred solution of 2,3-*O*-isopropylidene-D-glycerol[11] (18) (2.65 g) and triethylene glycol ditosylate (17) (4.6 g) in DME (50 ml) was added sodium hydride (1 g) in portions. The temperature of the mixture was then maintained at 50 °C for 24 h, after which time methanol (5 ml) was added dropwise. Solvent was removed under vacuum, and the residue was partitioned between chloroform (100 ml) and water (50 ml). The aqueous layer was extracted with chloroform (3 × 50 ml) and the combined extracts were dried, and then concentrated to give a liquid which was distilled to afford the *compound* (19) (2.1 g, 55%), b.p. 162—165 °C at 0.13 mmHg; $[\alpha]_D$ +14.6° (*c*, 0.7) (Found: C, 57.2; H, 9.0. $C_{18}H_{34}O_8$ requires C, 57.1; H, 9.1%); δ($CDCl_3$) 1.36 (6 H, s, CMe_2),

* In the ^{13}C n.m.r. spectrum of (16) obtained from 2,3-*O*-isopropylidene-D-glycerol, an extra signal could just be resolved in this region.

1.42 (6 H, s, CMe_2), 3.44—3.86 (16 H, complex, 8 × CH_2), and 3.88—4.44 (6 H, complex, 2 × CH_2 and 2 × CH).

(2R,15R)-4,7,10,13-*Tetraoxadecane*-1,2,15,16-*tetraol* (20).—(*a*) A solution of (19) (1.8 g) in trifluoroacetic acid–water (9 : 1, v/v) (10 ml) was concentrated at below 40 °C under reduced pressure to give a syrupy residue, which was dissolved in methanol–water (1 : 1, v/v) (40 ml). This solution was then neutralized to pH paper by the addition of an anion-exchange resin (IR45; HO^- form), and after filtration was concentrated under reduced pressure to give the syrupy title compound which was characterized as its tetrakis-(3,5-dinitrobenzoate) (see below).

(*b*) A stirred solution of (19) (13.5 g) in glacial acetic acid (50 ml) was heated to 80 °C, and water was added dropwise to the heated solution. After 1 h at this temperature, the mixture was cooled, concentrated to dryness, and the residue was dissolved in methanol (300 ml). A small piece of sodium was dissolved in the solution, and the latter was then heated under reflux for 1 h. Solid carbon dioxide was added to the cooled mixture and the solvent was evaporated to give a syrupy residue which was dissolved in chloroform (300 ml), dried, and concentrated to give the title compound (20) (9.7 g, 88%); $[\alpha]_D$ −9.4° (*c*, 1.2); δ($CDCl_3$) 3.35—4.50 (total H, complex), which was characterized as the amorphous tetrakis-(3,5-dinitrobenzoyl) derivative (21), m.p. 48—50 °C, $[\alpha]_D$ −9.9° (*c*, 1.7) (Found: C, 44.8; H, 3.5. $C_{40}H_{34}N_8O_{28}$ requires C, 44.7; H, 3.2%); δ($CDCl_3$) 3.56—3.84 (12 H, complex, 6 × CH_2), 3.94 (4 H, d, 2 × $CHCH_2OR$), 4.70 (2 H, dd, $J_{1.1'}$ 13, $J_{1.2}$ 7 Hz, H-1 and H-16), 4.95 (2 H, dd, $J_{1.2}$ 3 Hz, H-1′ and H-16′), 5.50—5.80 (2 H, br s, 2 × CH), and 9.90—9.92 (12 H, complex, Ar–H).

(2S,15S)-1,16-*Di*-O-*trityl*-4,7,10,13-*tetraoxahexadecane*-1,2,15,16-*tetraol* (22).—To a stirred solution of the tetraol (20) (6.4 g) in pyridine (40 ml) was added, in portions, triphenylmethyl chloride (trityl chloride) (13.2 g). After stirring the mixture at room temperature for 36 h, it was poured into ice–water (200 ml) and the crude product was extracted with chloroform (3 × 200 ml). The combined extracts were dried and concentrated to give a sticky product, from which on column chromatography (ethyl acetate) was obtained, as a syrup, the dityrityl ether (22) (9.9 g, 59%); $[\alpha]_D$ −11.4° (*c*, 1.9) (Found: C, 76.4; H, 6.8. $C_{50}H_{54}O_8$ requires C, 76.7; H, 6.95%); δ($CDCl_3$) 3.02 (2 H, br s, 2 × OH), 3.15 (4 H, d, $J_{1.2}$ 6 Hz, 2 × CH_2OCPh_3), 3.30—3.72 (16 H, complex, 8 × CH_2), 3.72—4.06 (2 H, complex, 2 × CHOH), and 7.00—7.46 (30 H, complex, Ar–H.

(1S,12S)-1,12-*Bis*(*triphenylmethoxymethyl*)-2,5,8,11,14,17,-20,23-*octoxacyclotetracosane* (23).—Sodium hydride (1.5 g) was added in portions to a stirred solution of compound (22) (9.9 g) and triethylene glycol ditosylate (5.8 g) in DME (1 000 ml), and the mixture was heated at 50 °C for 24 h. Methanol (10 ml) was added dropwise to the cooled reaction mixture, the solvent removed under reduced pressure, and the residue so obtained was partitioned between chloroform (300 ml) and water (150 ml). The aqueous layer was extracted with chloroform (3 × 150 ml) and the combined chloroform extracts were dried and concentrated to afford a product which was subjected to column chromatography (ethyl acetate) to give, as a thick syrup, *compound* (23) (4.5 g, 40%); $[\alpha]_D$ −18.1° (*c*, 2.2) (Found: C, 75.0; H, 7.2. $C_{56}H_{64}O_{10}$ requires C, 75.0; H, 7.2%); δ($CDCl_3$) 3.14 (4 H, br d, 2 × CH_2OCPh_3), 3.40—3.84 (30 H, complex, 14 × CH), and 7.00—7.48 (30 H, complex, Ar–H).

(1S,9S)-1,9-*Bis*(*triphenylmethoxymethyl*)-2,5,8,11,14,17,20-*heptaoxacycloheneicosane* (24).—Compound (22) (7.75 g), diethylene glycol ditosylate [17a,17c,18] (30) (4.1 g), and sodium hydride (1 g) were reacted in DME (750 ml) and the product was isolated in the manner described above for the preparation of (23). Column chromatography (ethyl acetate) gave the title compound (24) (5 g, 59%); $[\alpha]_D$ −18.3° (*c*, 6.0) (Found: C, 76.25; H, 7.3. $C_{54}H_{60}O_9$ requires C, 76.0; H, 7.1%); δ($CDCl_3$) 3.12 (4 H, br d, 2 × CH_1OCPh_3), 3.40—3.92 (26 H, complex, 12 × CH_2 and 2 × CH), and 7.00—7.48 (30 H, complex, Ar–H).

(1R,12R)-1,12-*Bis*(*hydroxymethyl*)-2,5,8,11,14,17,20,23-*octaoxacyclotetracosane* (25).—A solution of the dityrityl ether (23) (4.5 g) in ethanol (150 ml) containing 10% Pd–charcoal (0.2 g) and a trace of trifluoroacetic acid was stirred under a slight overpressure of hydrogen at 50 °C for 18 h, after which time t.l.c. indicated the disappearance of rotating material. The reaction mixture was filtered, then concentrated, and the white semi-solid residue was triturated with light petroleum (100 ml) to dissolve triphenylmethane. The light petroleum layer was removed from the oil which remained, and the latter was then subjected to column chromatography with methanol–chloroform (1 : 19 v/v) as eluant to yield, as an oil, the diol (25) (1.3 g, 63%); $[\alpha]_D$ +19.2° (*c*, 0.8) (Found: C, 52.2; H, 8.8%; M^+, 412. $C_{18}H_{36}O_{10}$ requires C, 52.4; H, 8.8%; *M*, 412); δ($CDCl_3$) 3.20 (2 H, br s, 2 × OH) and 3.32—4.06 (34 H, complex, 16 × CH_2 and 2 × CH).

(1R,9R)-*Bis*(*hydroxymethyl*)-2,5,8,11,14,17,20-*heptaoxacycloheneicosane* (26).—A solution of the dityrityl ether (24) (4.4 g) in ethanol (150 ml) was stirred at 50 °C under a slight overpressure of hydrogen in the presence of 10% Pd–charcoal and a trace of trifluoroacetic acid. On disappearance of the starting material (t.l.c. in ethyl acetate), the filtered solution was concentrated and the residue was subjected to column chromatography with methanol–chloroform (1 : 19 v/v) as eluant, to yield the oily *diol* (26) (1.4 g, 74%); $[\alpha]_D$ +12.9° (*c*, 1.2) (Found: C, 51.9; H, 8.7%; M^+, 368.205 5. $C_{16}H_{32}O_9$ requires C, 52.2; H, 8.8%; *M*, 368.204 7); δ($CDCl_3$) 2.98 (2 H, br s, 2 × OH) and 3.50—3.90 (30 H, complex, 14 × CH_2 and 2 × CH).

out,in(trans)-3,6,9,12,16,19,22,25,27,30,33,36-*Dodecaoxabicyclo*[12.12.10]*hexatriacontane* (16).—To a stirred solution of the diol (25) (0.56 g) and triethylene glycol ditosylate (0.63 g) in DME (150 ml) was added sodium hydride (0.2 g) in portions, and the reaction mixture was then heated to 50 °C for 24 h, after which time methanol (5 ml) was added. Removal of solvent gave a residue which was partitioned between chloroform (100 ml) and water (50 ml). The aqueous layer was extracted with chloroform (3 × 75 ml) and the combined organic extracts were dried and concentrated. The crude product so obtained was subjected to column chromatography [eluant: methanol–chloroform (3 : 97, increasing to 5 : 95 v/v)] which afforded the syrupy *compound* (16) (0.13 g, 18%) (Found: C, 54.5; H, 8.9%; M^+, 526.298 9. $C_{24}H_{46}O_{12}$ requires C, 54.7; H, 8.8%; *M*, 526.299 0); δ($CDCl_3$) 3.20—3.90 (total H, complex); δ_C[$(CD_3)_2CO$] 70.16, 71.33, 71.37, 71.38, 71.56, 71.78, and and 72.10 (CH_2), and 78.97 (CH).

out,in-(1S,14S)-3,6,9,12,15,18,21,24,26,29,32-*Undecaoxabicyclo*[12.10.9]*tritriacontane* (27).—Sodium hydride (0.2) was added, in portions, to a stirred solution of the (0.46 g) and diethylene glycol ditosylate (0.45 g) in DME (150 ml). The reaction was performed and the product isolated by a similar procedure to that described for compound (16) above, yielding the syrupy *compound* (27) (0.115

g, 21%); $[\alpha]_D$ −1 ± 0.1° (*c*, 1.0) (Found: C, 54.6; H, 8.8%; M^+, 482.272 4. $C_{22}H_{42}O_{11}$ requires C, 54.8; H, 8.8%; *M*, 482.272 8); δ($CDCl_3$) 3.38—3.88 (total H, complex); δ_C[$(CD_3)_2CO$] 70.11, 71.42, 71.46, 71.55, 71.66, 72.03, 72.15, and 72.25 (CH_2), and 78.86 (br s, $W_{\frac{1}{2}}$ *ca.* 18 Hz, CH).

out,in-(1S,14S)-3,6,9,12,16,19,22,24,27,30-*Decaoxabicyclo*-[12.9.7]*triacontane* (28).—To a stirred solution of diol (26) (1.0 g) and diethylene glycol ditosylate (1.1 g) in DME (200 ml) was added sodium hydride (0.3 g) in portions and the stirred reaction mixture was heated at 50 °C for 24 h. Methanol (2 ml) was then added to the cooled mixture, the solvent was removed under reduced pressure, and the residue was partitioned between chloroform (200 ml) and water (100 ml). The aqueous layer was extracted with chloroform (3 × 100 ml), and the combined extracts were dried and concentrated to give a crude syrupy product. Column chromatography of the latter material [eluant: methanol–chloroform (3 : 97, increasing to 5 : 95 v/v)] gave the syrupy compound (28) (0.55 g, 46%); $[\alpha]_D$ +1.06 ± 0.02° (*c*, 4.7) (Found: C, 54.6; H, 8.6%; M^+, 438.247 3. $C_{20}H_{38}O_{10}$ requires C, 54.8; H, 8.7%; *M*, 438.246 5); δ($CDCl_3$) 3.36—3.94 (total H, complex); δ_C[$(CD_3)_2CO$] 69.72, 71.25, 71.36, 71.38, 71.52, 71.63, 72.17, 72.19, and 72.26 (CH_2), and 78.58 ($W_{\frac{1}{2}}$ *ca.* 1.5 Hz, CH).

out,in-(trans)-3,6,9,12,16,19,22,25,27,30,33-*Undecaoxabicyclo*[12.12.7]*tritriacontane* (29).—Sodium hydride (0.1 g) was added in portions to a solution of the diol (26) (0.27 g) and triethylene glycol ditosylate (0.32 g) in DME (150 ml). The reaction was performed and the product isolated in a similar manner to that described for the preparation of compound (28), to yield the syrupy compound (29) (0.1 g, 30%) (Found: C, 54.3; H, 8.8%; M^+, 482.271 5. $C_{22}H_{42}O_{11}$ requires C, 54.8; H, 8.8%; *M*, 482.272 8); δ[$(CD_3)_2CO$] 3.40—3.86 (total H, complex); δ_C[$(CD_3)_2CO$] 70.09, 71.39, 71.46, 72.08, and 72.18 (CH_2), and 78.80 (CH).

Variable-temperature ^{13}C *Chemical-shift Data for Solutions of the Macrobicyclic Polyethers* (15), (16), (27), (28), *and* (29).—Data are given in the format: compound: temperature (K); δ_C (in [$^2H_6$]acetone unless stated otherwise); where overlap occurs, only prominent peaks are recorded.

(15); 193; 70.22, 71.05, 71.31, and 72.00 (CH_2), 78.60 ($W_{\frac{1}{2}}$ *ca.* 10 Hz, CH): (16); 202; 70.15, 71.06, 71.27, and 71.95 (CH_2), 78.55 ($W_{\frac{1}{2}}$ *ca.* 5 Hz, CH): (27); (*a*) 203; 69.13 * ($W_{\frac{1}{2}}$ *ca.* 4 Hz), 69.98 * ($W_{\frac{1}{2}}$ *ca.* 4 Hz), 70.87, 71.10, 71.67, 71.90, 72.12, and 73.01 (CH_2), 76.82 † and 79.55 † ($W_{\frac{1}{2}}$ for both signals *ca.* 4 Hz, CH). (*b*) 385 {in toluene–[$^2H_8$]toluene (1 : 1 v/v)}; 70.39, 71.64, 71.66, 71.69, 71.74, 71.77, 71.84, 72.15, 72.73 (CH_2), 79.55 ($W_{\frac{1}{2}}$ *ca.* 1 Hz, CH): (28); 192; 67.55, 69.59, 70.55, 71.40, 71.79, 72.63, and 73.68 (CH_2), 75.52 ‡ and 79.11 ‡ ($W_{\frac{1}{2}}$ for both signals *ca.* 10 Hz, CH): (29); (*a*) 223; 69.47, 71.02, 71.08, 71.21, 71.67, and 72.16 (CH_2), 77.99 ($W_{\frac{1}{2}}$ *ca.* 3 Hz, CH). (*b*) 273; 69.93, 71.30, 71.32, 71.39, 72.02, and 72.08 (CH_2), 78.58 ($W_{\frac{1}{2}}$ *ca.* 2 Hz, CH).

^{13}C *Chemical-shift Data for the Macrobicyclic Polyethers* (15), (16), (27), *and* (28) *at Certain Temperatures in the Presence of* 1 *Molar Equivalent of Potassium Thiocyanate.*—Data are given in the format: compound; temperature (K); δ_C values (in [$^2H_6$]acetone); where overlap occurs only prominent signals are noted.

(15); (*a*) 223; 68.66, 69.83, and 70.29 (CH_2), 75.48 (br, $W_{\frac{1}{2}}$ *ca.* 40 Hz). (*b*) 300; 66.27 (br, $W_{\frac{1}{2}}$ *ca.* 8 Hz), 69.34, 69.73, 69.98, 70.27, 70.44, and 70.76 (CH_2), 76.73 ($W_{\frac{1}{2}}$ *ca.* 2 Hz, CH): (16); (*a*) 243; 66.50 (br, $W_{\frac{1}{2}}$ *ca.* 50 Hz), 69.24, 70.12, 70.29, and 70.66 (CH_2), 76.48 ($W_{\frac{1}{2}}$ *ca.* 8 Hz). (*b*) 300; 67.00, 69.66, 70.41, 70.59, 70.70, and 70.95 (CH_2), 77.21 ($W_{\frac{1}{2}}$ *ca.* 5 Hz, CH): (27); 300; 64.35, 68.73, 69.39, 69.83, 70.20, 70.63, 70.94, and 71.34 (CH_2), 77.21 and 77.97 ($W_{\frac{1}{2}}$ for both signals *ca.* 6 Hz, CH): (28); (*a*) 253; 66.25 ** ($W_{\frac{1}{2}}$ *ca.* 5 Hz), 68.27 ** ($W_{\frac{1}{2}}$ *ca.* 5 Hz), 70.34, 70.66, 71.24, 71.93, 72.32, and 73.24 (CH_2), 76.77 § and 77.14 § ($W_{\frac{1}{2}}$ for both signals *ca.* 4 Hz, CH). (*b*) 300; 67.20 (br, $W_{\frac{1}{2}}$ *ca.* 30 Hz), 70.57, 70.62, 70.68, 70.76—73.00 (complex) (CH_2), and 77.33 ($W_{\frac{1}{2}}$ *ca.* 3 Hz, CH): (*c*) 300, with 2 mol. equiv. KSCN; 65.93, 68.24, 70.41, 70.66, 71.97 (br), 72.66, 73.00, 73.60 (br) (CH_2), 77.43 and 77.87 (CH).

We thank Chulalongkorn University and the British Council for financial support (P. K.), and Dr. B. J. Gregory for measurement of some of the ^{13}C n.m.r. spectra in the early part of this project.

[8/2108 *Received*, 7*th December*, 1978]

* Coalescence temperature, T_c, near 248 K.
† T_c Near 265 K.
‡ T_c Near 222 K.

** Coalescence temperature, T_c near 283 K.
§ T_c Near 273 K.

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