Synthesis of Perfluorodicyclohexano-18-crown-6 Ether

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Two isomers of perfluorodicyclohexano-18-crown-6 ether, the *cis–syn–cis* and *cis–anti–cis* isomers, have been prepared and their structures have been established by X-ray crystallography.

Perfluoro crown ethers[1] are becoming important for ^{19}F NMR imaging applications[2] in humans and are particularly effective as brain and spinal diagnostics when administered to the cerebrospinal fluid compartment. Scale-up of the synthesis of perfluoro 15-crown-5[1] and other biological applications of these new compounds[3] are being studied. We report here the synthesis and crystal structures of two structural isomers of perfluorodicyclohexano-18-crown-6 ether: the *cis–syn–cis* **1** and *cis–anti–cis* **2** isomers (see Figs. 1 and 2).

Presently such complex oxygen-containing fluorocarbons

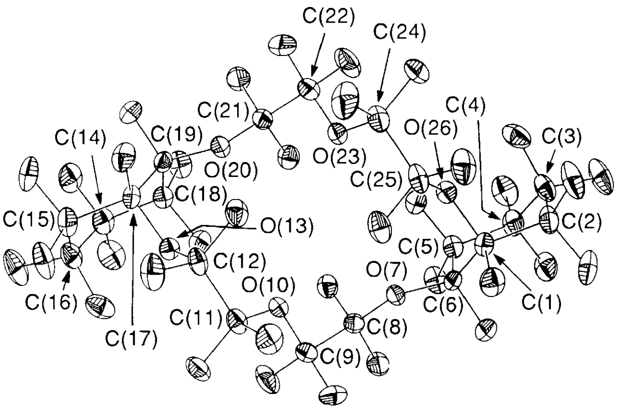

Fig. 1 View (ORTEP) of *cis-syn-cis* **1** showing the atom numbering scheme. Distances (Å) between neighbouring oxygen atoms are as follows: O(13)–O(20) 2.662, O(20)–O(23) 2.713, O(23)–O(26) 2.665, O(26)–O(7) 2.667, O(7)–O(10) 2.707, O(10)–O(13) 2.667. Distances (Å) from oxygen atoms to the centroid of the molecule are as follows: O(7) 2.536, O(10) 2.129, O(13) 3.177, O(20) 2.543, O(23) 2.141, O(26) 3.181.

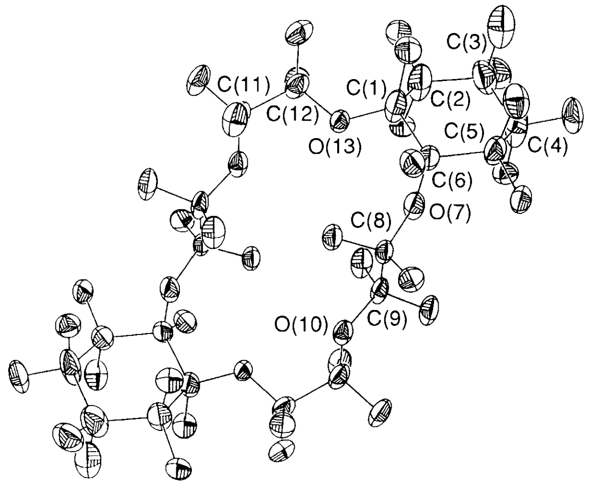

Fig. 2 View (ORTEP) of *cis-anti-cis* **2** showing the atom numbering scheme. Distances (Å) between neighbouring oxygen atoms are as follows: O(10′)–O(13) 2.727, O(13)–O(7) 2.702, O(7)–O(10) 3.525. Distances (Å) from oxygen atoms to the centroid of the molecule are as follows: O(7) 3.156, O(10) 2.403, O(13) 3.332.

are inaccessible by synthetic techniques other than the controlled elemental fluorine reaction techniques developed in this laboratory.[4] A solution of the starting material, dicyclohexano-18-crown-6 ether (mixture of *cis–syn–cis* and *cis–anti–cis* isomers; Aldrich), in dry acetonitrile was dried over 4 Å molecular sieves and the crown ether recrystallized before use. In a typical experiment, a solution of dicyclohexano-18-crown-6 ether (*ca.* 1 g) in dry methylene chloride was mixed with NaF (20 g) to make a slush, and the methylene chloride removed *in vacuo*. The dry material was finely ground and dispersed in a disk reactor[5] over copper turnings, which distribute the organic substrate on NaF powder evenly to increase the surface area exposed to fluorine, and dissipate heat from the hydrogen–fluorine exchange reaction. The NaF powder also scavenges the HF generated. The disk reactor was connected to a cryostat, and purged with He for several hours before the reaction. Helium was also used to dilute the fluorine reagent gas. The fluorination proceeded following the conditions shown in Table 1.

Table 1 Fluorination conditions for dicyclohexano-18-crown-6 ether

t/day	Flow rate/cm^3 min^{-1}		*T*/°C
	He	F_2	
1	100	1	−100
1	100	1	−90
1	100	1	−80
1	50	1	−80
1	50	2	−80
1	20	2	−80
1	20	4	−80
1	10	4	−80
1	0	4	−80
1	0	4	−60
1	0	4	−40
1	0	4	0
1	0	4	Room temp.
1	0	4	40
1	60	0	Room temp.

The NaF powder was collected and extracted (×2) with Freon 113 (1,1,2-trichlorotrifluoroethane; 100 ml). The extracts were washed (×3) with 5 mol dm^{-3} NaOH (100 ml) and the Freon 113 was distilled off carefully leaving a viscous oil. The oil was distilled *in vacuo* (0.5 mmHg; 125 °C), and the distillate separated by GC on a perfluoropolyether column.[6] The two perfluoro-isomers were identified primarily by GC/CIMS. Both isomers gave parent peaks at *m*/*z* 1020.

Single crystals of each isomer were grown and preliminary X-ray results showed that they have different solid state structures. The *syn* isomer **1** has a twisted bent-ellipse ring structure with two cyclohexano groups at two ends while the *anti* isomer **2** has an ellipse ring structure with two cyclohexano groups symmetrically distributed on two sides. Distances between oxygen atoms and the centre of the molecule, and between adjacent oxygen atoms in both isomers are given in Figs. 1 and 2.† All cyclohexano groups are in the chair form. The ^{19}F NMR spectra of both isomers show a complex pattern [δ(CFCl$_3$) −80 to −85] and a broad band (−120 to −145) which correspond to the fluorine atoms attached to the ring and to the cyclohexano groups, respectively. Variable temperature ^{19}F NMR spectra are complex and will be discussed in detail elsewhere.[7] The IR spectra of both isomers are virtually identical [ν_{max}/cm^{-1} (neat liquid) 1192 vs, br, 1042 m, 974 vs, 709, 632 and 485].

More detailed investigation of the new perfluoro crown ethers by GC–high resolution mass spectrometry using a capillary column showed that the two isomers have the same elemental compositions (**1**, calc. 1019.9120, found 1019.9196; **2**, found 1019.9072), and were formed in a ratio of *ca.* 0.54 : 1 (GC peak area). Yields of isolated crystalline solids based on starting material are: **1**, (m.p. 54–55 °C), 8.2%; **2**, (m.p. 49–50 °C), 12.3%. A trace amount of a third isomer (*m*/*z*)

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† *Crystal data* [−75 °C; Nicolet R3 diffractometer, graphite-monochromated Mo-Kα radiation (λ 0.7107 Å). The *syn* isomer **1** is monoclinic, space group *C*2/*c*, *a* = 27.051(2), *b* = 10.0876(10), *c* = 23.526(3) Å, β = 100.920(8)°, *V* = 6303.5(11) Å^3, D_c = 2.15 g cm^{-3}, *Z* = 8. The structure was solved by direct methods and refined by full-matrix least-squares to *R* = 0.0425, R_w = 0.0499 using 3935 reflections with $F_o \geq 4\sigma(F_o)$. The *anti* isomer **2** is also monoclinic, space group *C*2/*c*, *a* = 32.211(5), *b* = 6.0447(6), *c* = 18.828(3) Å, β = 124.782(9)°, *V* = 3012.4(8) Å^3, D_c = 2.25 g cm^{-3}, *Z* = 4. The molecule is located on a crystallographic inversion centre. The structure was solved by direct methods and refined by full-matrix least-squares to *R* = 0.0964, R_w = 0.114 using 1832 reflections with $F_o \geq 4\sigma(F_o)$. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

1019.9202 was obtained after separation on the capillary column.

Besides the possibility of serving as ^{19}F NMR imaging agents and as macrocyclic ligands, the compounds are of interest in the biomedical and oxygen-carrier areas as they contain sizable pockets and are physiologically compatible with human and other mammalian tissue.[8]

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