Structure of a Chiral Monopyrido Crown Ether: 1,4:1′,4′:3,6:3′,6′-Tetraanhydro-5,5′-*O*-oxydiethylene-2,2′-*O*-[pyridine-2,6-diylbis(methylene)]-di-D-mannitol

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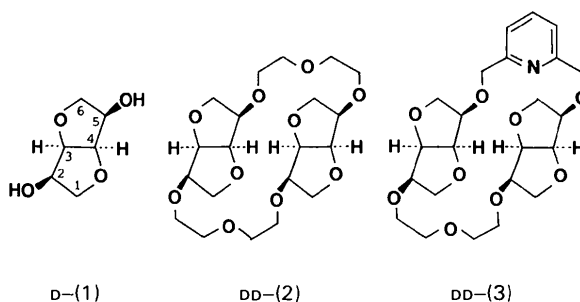*Department of Chemistry, The University, Sheffield S3 7HF, England*

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Abstract. $C_{23}H_{31}NO_9$, $M_r = 465 \cdot 5$, orthorhombic, $P2_12_12_1$, $a = 10 \cdot 384$ (2), $b = 19 \cdot 321$ (4), $c = 11 \cdot 299$ (2) Å, $V = 2267$ Å^3, $Z = 4$, $D_x = 1 \cdot 36$ Mg m^{-3}, Cu $K\alpha$, $\lambda = 1 \cdot 54178$ Å, $\mu = 0 \cdot 84$ mm^{-1}, $F(000) = 992$, room temperature, $R = 0 \cdot 043$ for 2975 observed reflections including Bijvoet pairs with $|F_o| > 3\sigma(|F_o|)$. The title compound [DD-(3)] has gross conformational features similar to those of 1,4:1′,4′:-3,6:3′6′-tetraanhydro-2,2′:5,5′-bis(*O*-oxydiethylene)di-D-mannitol [DD-(2)], *i.e.* with the two dianhydro-mannitolo units adopting a 'face-to-back' geometry with respect to each other. A consequence of this arrangement is the self-filling of the potential macro-cyclic cavity despite the rigidity imposed by the pyridine ring. Significantly, the N atom on the pyridine ring is directed into the centre of the collapsed chiral cavity.

Introduction. As part of a research programme directed towards the synthesis of chiral crown ethers incorporating carbohydrate residues (Stoddart, 1979, 1981; Crawshaw, Laidler, Metcalfe, Pettman, Stoddart & Wolstenholme, 1982), 1,4:3,6-dianhydro-D-mannitol |D-(1)| (Montgomery & Wiggins, 1948; Goodwin, Hodge & Weisleder, 1980) has been identified as a readily available and inexpensive synthetic precursor (Metcalfe, Stoddart, Jones, Crawshaw, Quick & Williams, 1981; Metcalfe, Stoddart, Jones, Crawshaw, Gavuzzo & Williams, 1981). This diol D-(1) may be regarded as a 'chiral triethylene glycol unit' (HO—C^2—C^1—O—C^4—C^3—O—C^6—C^5—OH) that exhibits substantial structural rigidity on account of its two *cis*-fused five-membered rings. The use of the diol D-(1) in the synthesis of a chiral bisdianhydromannitolo-30-crown-10 derivative DD-(2) has already been reported and shown by X-ray crystallography to adopt a 'face-to-back' conformation with respect to the two carbohydrate residues (Metcalfe, Stoddart, Jones, Crawshaw, Quick & Williams, 1981). However, on forming a crystalline 1:1:1 complex with (S)-Ph-CHMeNH₃ClO₄ and H₂O, DD-(2) adopts the expected

'face-to-face' conformation compatible with the creation of a hydrophilic cavity for binding of two guest species simultaneously (Metcalfe, Stoddart, Jones, Crawshaw, Gavuzzo & Williams, 1981). By contrast, we have found more recently in the 1:2 adduct of DD-(2) with BH₃NH₃ that, although the same type of host geometry is adopted, the conformation of one of the polyether chains is subtly modified such that the resulting complexation of the two BH₃NH₃ guest molecules is to both sides of the host (Shahriari-Zavareh, Stoddart, Williams, Allwood & Williams, 1985). Subsequently, our synthetic work has been directed towards changing the constitutions of the polyether chains linking the two carbohydrate residues in DD-(2) with two objectives in mind: introducing (i) rigid spacer groups and (ii) heteroatoms other than O to serve as potential binding sites within the chiral macrocycles. Towards this end, we have incorporated a pyrido ring into one of the two polyether chains (Crawshaw, 1982). Here, we report the results of the structure analysis of this novel macrocyclic compound DD-(3).

D-(1)   DD-(2)   DD-(3)

Experimental. Single crystals of DD-(3) (found: C, 59·3; H, 6·8; N, 3·0%; $C_{23}H_{31}NO_9$ requires C, 59·3; H, 6·7; N, 3·0%), suitable for X-ray crystallography, were grown at room temperature from ethyl acetate–light petroleum (b.p. 333–353 K) and had m.p. 411–414 K and $|\alpha|_D^{20°C} + 193°$ ($c = 0·7$ g dm^{-3} in CHCl₃) (Crawshaw, 1982). Crystal size 0·25 × 0·30 × 0·60 mm. Refined

unit-cell parameters obtained from setting angles of 18 reflections. Nicolet $R3m$ diffractometer. 3051 independent reflections $(\theta \leq 58°)$ measured, Cu $K\alpha$ radiation (graphite monochromator), ω scan. 2975 $||F_o| > 3\sigma(|F_o|)|$ considered observed, index range $h -11/11$, $k\, 0/20$, $l\, 0/12$ (Friedel pairs measured); two check reflections measured every 50 reflections, net count constant; Lorentz and polarization corrections, no absorption correction. Structure solved by direct methods; non-hydrogen atoms refined anisotropically; positions of H atoms calculated (C—H 0·96 Å); H atoms assigned isotropic thermal parameters, U(H) = 1·2 U_{eq} (C), and allowed to ride on parent C atoms. An empirical extinction correction was applied $|g = 0·0087\,(10)|$. Refinement using F magnitudes by block-cascade full-matrix least squares; $R = 0·043$; $wR = 0·064$ $|w^{-1} = \sigma^2(F) + 0·00048F^2|$. $(\Delta/\sigma)_{max} = 0·1$; residual electron density in difference map within $-0·49$ and $+0·56$ e Å^{-3}; atomic scattering factors and dispersion corrections from *International Tables for X-ray Crystallography* (1974). Computations carried out on an Eclipse S140 computer using the *SHELXTL* program system (Sheldrick, 1983).

Discussion. Table 1* lists the fractional atomic coordinates of the non-hydrogen atoms, Table 2 the bond lengths and angles, and selected C—C and C—O torsion angles associated with the dianydromannitolo and macrocyclic rings.

The structure of DD-(3) is illustrated in Fig. 1 which includes the atomic numbering scheme. Fig. 2 shows a space-filling representation of the molecule looking into the macrocyclic cavity.†

DD-(3) crystallizes with *one* independent molecule in the asymmetric unit whereas DD-(2) crystallizes with two (Metcalfe, Stoddart, Jones, Crawshaw, Quick & Williams, 1981). The dominant feature of the solid-state conformation of DD-(3) is the 'face-to-back' arrangement of the two dianhydromannitolo residues. Despite the presence of the two crystallographically independent molecules in DD-(2), this 'face-to-back' conformation is also common to both molecules. The incorporation of the pyrido ring has not noticeably perturbed the gross conformational features of the macrocyclic ring in DD-(3) relative to that in DD-(2). Despite the absence of any complexing stabilization of the polyether chains, there is no evidence (from the

Table 1. *Atom coordinates* $(\times 10^4)$ *and equivalent isotropic temperature factors* (Å^2 $\times 10^3$) *with e.s.d.'s in parentheses*

	x	y	z	$U_{eq}{}^*$
C(1)	11771 (3)	3612 (1)	-930 (3)	66 (1)
O(2)	11968 (2)	4319 (1)	-697 (1)	54 (1)
C(3)	12899 (3)	4633 (2)	-1440 (2)	60 (1)
C(4)	13270 (5)	5318 (2)	-979 (3)	102 (2)
O(5)	12683 (3)	5800 (1)	-1534 (3)	118 (1)
C(6)	12367 (3)	5593 (2)	-2695 (2)	60 (1)
C(7)	12422 (3)	4808 (2)	-2703 (2)	51 (1)
O(8)	11172 (2)	4559 (1)	-2970 (2)	55 (1)
C(9)	10287 (3)	5088 (1)	-2648 (3)	59 (1)
C(10)	10944 (3)	5747 (2)	-2978 (2)	54 (1)
O(11)	10428 (2)	6302 (1)	-2328 (2)	65 (1)
C(12)	10683 (3)	6960 (2)	-2819 (3)	69 (1)
C(13)	10249 (3)	7508 (2)	-2007 (3)	69 (1)
O(14)	8890 (2)	7488 (1)	-1881 (2)	58 (1)
C(15)	8458 (3)	7898 (1)	-926 (3)	63 (1)
C(16)	8603 (4)	7562 (1)	260 (3)	71 (1)
O(17)	7681 (3)	7036 (1)	478 (2)	85 (1)
C(18)	7905 (3)	6385 (1)	-54 (3)	69 (1)
C(19)	6703 (4)	5955 (2)	93 (3)	78 (1)
O(20)	7092 (2)	5261 (1)	122 (2)	67 (1)
C(21)	8445 (3)	5213 (1)	399 (2)	57 (1)
C(22)	8944 (3)	5946 (1)	535 (3)	65 (1)
O(23)	9074 (2)	6072 (1)	1787 (2)	79 (1)
C(24)	8498 (3)	5515 (2)	2422 (3)	63 (1)
C(25)	8669 (3)	4903 (1)	1612 (3)	53 (1)
O(26)	7825 (2)	4368 (1)	1967 (2)	56 (1)
C(27)	7715 (3)	3798 (1)	1145 (3)	55 (1)
C(28)	8961 (3)	3409 (1)	997 (2)	50 (1)
C(29)	9268 (3)	2847 (1)	1705 (3)	61 (1)
C(30)	10409 (3)	2500 (2)	1513 (3)	66 (1)
C(31)	11223 (3)	2740 (1)	645 (3)	59 (1)
C(32)	10887 (3)	3316 (1)	-7 (2)	49 (1)
N	9759 (2)	3634 (1)	144 (2)	51 (1)

* U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

anisotropic thermal parameters) for the disorder* that tends to plague large uncomplexed macrocyclic polyether rings. It is noteworthy that within the polyether link from C(10) to C(18), there is a disruption of the conventional all-*gauche* stabilizing conformation predominant in polyether macrocycles. Although the two C—C bonds adopt characteristic *gauche* conformations, two of the C—O bonds depart from their expected *anti*† geometries. There are also large differences (see Table 2) in the conformations of the two pairs of *cis*-fused five-membered dianhydro rings. These differences may reflect the relative dispositions of the two carbohydrate residues with respect to each other.

The solid-state structures of macrocyclic polyethers containing pyrido rings generally show the pyridyl N atom pointing into the middle of the host cavity towards the complexed guest (Goldberg, 1984), *e.g.* 2,6-pyrido-18-crown-6/*tert*-butylammonium perchlorate (Maverick, Grossenbacher & Trueblood, 1979), a 2,6-pyrido-18-crown-6-dione/H$_2$O (Newkome, Fronczek & Kohli, 1981), and 2,6-pyrido-27-crown-9/guanidinium perchlorate (van Staveren, den Hertog,

* However, a possible minor disorder may occur in the C(4), O(5) region of the macrocycle as evidenced by the very short C(4)—O(5) bond length.

† In the context of this paper '*gauche*' and '*anti*' are synonymous with synclinal and antiperiplanar, respectively.

Reinhoudt, Uiterwijk, Kruise & Harkema, 1984). In free macrocyclic and macrobicyclic polyethers containing pyrido rings, although the smaller molecules, e.g. 2,6-pyrido-18-crown-6 (Grootenhuis, van Staveren, den Hertog, Reinhoudt, Bos, Uiterwijk, Kruise & Harkema, 1984) and 2,6-dimethylylbenzoic acid–2,6-pyrido-18-crown-5 (Goldberg & Rezmovitz, 1978), usually adopt this type of conformation, the larger molecules, e.g.

2,6-pyrido-24-crown-8 (van Staveren *et al.*, 1984) and a |3.3.3|cryptand with N bridgeheads containing a 2,6-pyrido ring in the middle of each chain (Newkome, Majestic & Fronczek, 1981), apparently prefer to have a pyridyl unit filling their cavity with the pyridyl N atom pointing outwards. Thus, these molecules have to reorganize themselves conformationally during complexation of substrates in order to utilize the pyridyl N atom for binding. This is not the situation in the case of DD-(3), which is formally a 2,6-pyrido-30-crown-10 derivative. In this large but bulky macrocycle, the pyridyl N atom is oriented towards a potential cavity for binding substrates. Although complexes of DD-(3) have not been characterized structurally, it is possible that DD-(3) would also adopt a 'face-to-face' geometry on complexation (Crawshaw, 1982). Notably, as in the case of DD-(2), it is one of the dianhydromannitolo residues rather than the pyridine ring that fills the cavity of the macrocyclic ring in DD-(3).

There are three intermolecular contacts ≤3·4 Å. The shortest |3·18 (1) Å| of these is between O(17) and C(13) of the molecule at $-\frac{1}{2}+x$, $1\frac{1}{2}-y$, $-z$ with an associated |H···O| distance of 2·50 Å.

Table 2. *Bond lengths (Å), bond angles (°) and selected torsion angles (°)*

C(1)–O(2)	1·406 (3)	C(1)–C(32)	1·502 (4)
O(2)–C(3)	1·416 (3)	C(3)–C(4)	1·474 (5)
C(3)–C(7)	1·548 (4)	C(4)–O(5)	1·278 (5)
O(5)–C(6)	1·410 (4)	C(6)–C(7)	1·517 (4)
C(6)–C(10)	1·541 (4)	C(7)–O(8)	1·416 (3)
O(8)–C(9)	1·422 (3)	C(9)–C(10)	1·491 (4)
C(10)–O(11)	1·406 (3)	O(11)–C(12)	1·412 (4)
C(12)–C(13)	1·472 (5)	C(13)–O(14)	1·418 (3)
O(14)–C(15)	1·412 (4)	C(15)–C(16)	1·496 (4)
C(16)–O(17)	1·417 (4)	O(17)–C(18)	1·413 (3)
C(18)–C(19)	1·508 (5)	C(18)–C(22)	1·525 (4)
C(19)–O(20)	1·402 (4)	O(20)–C(21)	1·442 (4)
C(21)–C(22)	1·516 (4)	C(21)–C(25)	1·513 (4)
C(22)–O(23)	1·441 (4)	O(23)–C(24)	1·424 (4)
C(24)–C(25)	1·506 (4)	C(25)–O(26)	1·413 (3)
O(26)–C(27)	1·445 (3)	C(27)–C(28)	1·506 (4)
C(28)–C(29)	1·386 (4)	C(28)–N	1·343 (3)
C(29)–C(30)	1·378 (4)	C(30)–C(31)	1·375 (4)
C(31)–C(32)	1·381 (4)	C(32)–N	1·334 (3)

O(2)–C(1)–C(32)	109·2 (2)	C(1)–O(2)–C(3)	113·8 (2)
O(2)–C(3)–C(4)	110·6 (3)	O(2)–C(3)–C(7)	114·9 (2)
C(4)–C(3)–C(7)	102·3 (2)	C(3)–C(4)–O(5)	110·9 (3)
C(4)–O(5)–C(6)	111·1 (3)	O(5)–C(6)–C(7)	106·3 (2)
O(5)–C(6)–C(10)	111·2 (3)	C(7)–C(6)–C(10)	103·2 (2)
C(3)–C(7)–C(6)	103·0 (2)	C(3)–C(7)–O(8)	114·6 (2)
C(6)–C(7)–O(8)	107·8 (2)	C(7)–O(8)–C(9)	107·1 (2)
O(8)–C(9)–C(10)	104·7 (2)	C(6)–C(10)–C(9)	102·8 (2)
C(6)–C(10)–O(11)	113·8 (2)	C(9)–C(10)–O(11)	110·3 (2)
C(10)–O(11)–C(12)	114·2 (2)	O(11)–C(12)–C(13)	110·2 (3)
C(12)–C(13)–O(14)	110·4 (3)	C(13)–O(14)–C(15)	112·2 (2)
O(14)–C(15)–C(16)	114·1 (2)	C(15)–C(16)–O(17)	113·5 (3)
C(16)–O(17)–C(18)	116·9 (3)	O(17)–C(18)–C(19)	107·9 (3)
O(17)–C(18)–C(22)	115·2 (3)	C(19)–C(18)–C(22)	103·4 (2)
C(18)–C(19)–O(20)	106·9 (3)	C(19)–O(20)–C(21)	110·3 (2)
O(20)–C(21)–C(22)	107·2 (2)	O(20)–C(21)–C(25)	111·8 (2)
C(22)–C(21)–C(25)	103·1 (2)	C(18)–C(22)–C(21)	103·5 (2)
C(18)–C(22)–O(23)	113·6 (2)	C(21)–C(22)–O(23)	106·8 (2)
C(22)–O(23)–C(24)	109·2 (2)	O(23)–C(24)–C(25)	103·7 (2)
C(21)–C(25)–C(24)	102·8 (2)	C(21)–C(25)–O(26)	116·8 (2)
C(24)–C(25)–O(26)	109·2 (2)	C(25)–O(26)–C(27)	115·1 (2)
O(26)–C(27)–C(28)	112·5 (2)	C(27)–C(28)–C(29)	121·7 (3)
C(27)–C(28)–N	116·6 (2)	C(29)–C(28)–N	121·8 (2)
C(28)–C(29)–C(30)	119·2 (3)	C(29)–C(30)–C(31)	118·4 (3)
C(30)–C(31)–C(32)	119·9 (3)	C(1)–C(32)–C(31)	121·5 (2)
C(1)–C(32)–N	116·8 (2)	C(31)–C(32)–N	121·7 (2)
C(28)–N–C(32)	118·9 (2)		

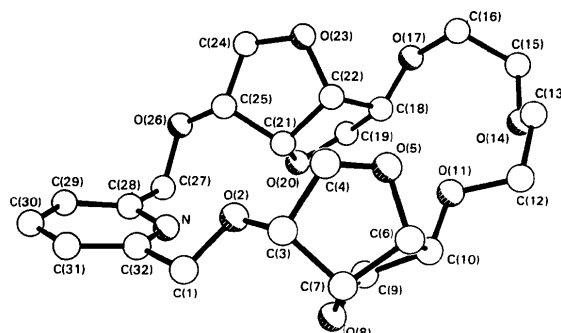|			
C(1)–O(2)–C(3)–C(4)	-167·1 (3)	C(16)–O(17)–C(18)–C(19)	-169·2 (3)
O(2)–C(3)–C(4)–O(5)	-100·0 (4)	O(17)–C(18)–C(19)–O(20)	-151·5 (3)
C(3)–C(4)–O(5)–C(6)	-27·3 (5)	C(18)–C(19)–O(20)–C(21)	19·1 (3)
C(4)–O(5)–C(6)–C(7)	19·3 (4)	C(19)–O(20)–C(21)–C(22)	-1·0 (3)
O(5)–C(6)–C(7)–O(8)	117·5 (2)	O(20)–C(21)–C(22)–O(23)	113·2 (3)
C(6)–C(7)–O(8)–C(9)	-23·6 (3)	C(21)–C(22)–O(23)–C(24)	-9·3 (3)
C(7)–O(8)–C(9)–C(10)	37·8 (3)	C(22)–O(23)–C(24)–C(25)	29·9 (3)
O(8)–C(9)–C(10)–O(11)	-157·8 (2)	O(23)–C(24)–C(25)–O(26)	-163·0 (2)
C(9)–C(10)–O(11)–C(12)	-161·2 (2)	C(24)–C(25)–O(26)–C(27)	169·3 (2)
C(11)–O(2)–C(3)–C(7)	77·7 (3)	C(16)–O(17)–C(18)–C(22)	75·9 (3)
O(2)–C(3)–C(7)–C(6)	110·1 (2)	O(17)–C(18)–C(22)–C(21)	144·8 (3)
C(3)–C(7)–C(6)–C(10)	-121·0 (2)	C(18)–C(22)–C(21)–C(25)	-135·1 (2)
C(7)–C(6)–C(10)–O(11)	140·6 (2)	C(22)–C(21)–C(25)–O(26)	151·6 (2)
C(6)–C(10)–O(11)–C(12)	83·8 (3)	C(21)–C(25)–O(26)–C(27)	53·2 (3)
C(10)–O(11)–C(12)–C(13)	-173·0 (2)	C(25)–O(26)–C(27)–C(28)	64·4 (3)
O(11)–C(12)–C(13)–O(14)	-65·1 (3)	O(26)–C(27)–C(28)–N	-89·6 (3)
C(12)–C(13)–O(14)–C(15)	167·0 (2)	C(27)–C(28)–N–C(32)	178·6 (2)
C(13)–O(14)–C(15)–C(16)	-79·5 (3)	C(28)–N–C(32)–C(1)	-176·9 (2)
O(14)–C(15)–C(16)–O(17)	-75·0 (3)	N–C(32)–C(1)–O(2)	54·3 (2)
C(15)–C(16)–O(17)–C(18)	78·9 (3)	C(32)–C(1)–O(2)–C(3)	173·5 (2)

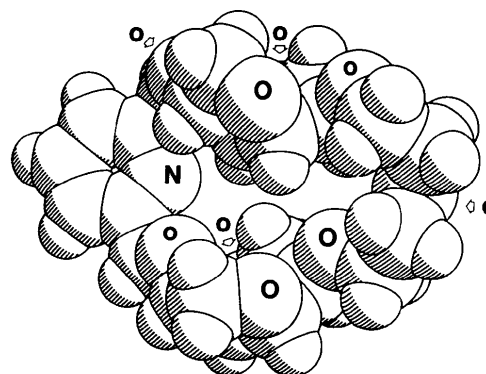Fig. 1. Ball-and-stick representation of the structure of DD-(3) showing the atomic numbering scheme.

Fig. 2. A space-filling representation of DD-(3).

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Structure Analysis of Minaprine Analogs: 3-Morpholinoethylamino-6-phenyl-4-pyridazinecarboxamide Monohydrate (I) and Butyl 3-Phenethylamino-6-phenyl-4-pyridazinecarboxylate (II)

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Abstract. (I): $C_{17}H_{21}N_5O_2.H_2O$, $M_r = 345.4$, orthorhombic, $Pccn$, $a = 7.576$ (1), $b = 29.759$ (3), $c = 31.324$ (4) Å, $V = 7062.5$ Å^3, $Z = 16$ (two molecules in the asymmetric unit), $D_x = 1.30$ Mg m^{-3}, λ(Cu $K\bar{\alpha}$) $= 1.54178$ Å, $\mu = 6.66$ mm^{-1}, $F(000) = 2944$, $T = 293$ K, $R = 0.04$ for 1362 observed reflections. Two cocrystallized water molecules participate in an extensive network of hydrogen bonds. (II): $C_{23}H_{25}N_3O_2$, $M_r = 375.2$, triclinic, $P\bar{1}$, $a = 13.969$ (2), $b = 9.763$ (3), $c = 8.469$ (4) Å, $\alpha = 115.17$ (3), $\beta = 88.57$ (2), $\gamma = 99.88$ (2)°, $V = 1028.2$ Å^3, $Z = 2$, $D_x = 1.21$ Mg m^{-3}, λ(Mo $K\bar{\alpha}$) $= 0.71069$ Å, $\mu = 0.45$ mm^{-1}, $F(000) = 400$, $T = 293$ K, $R = 0.04$ for 1517 observed reflections. The structures studied are characterized by an intramolecular hydrogen bond between the carbonyl O and exocyclic N atoms. In both compounds, this particular N participates in an electronic delocalization specific to the aminopyridazine ring, conferring upon it sp^2 hybridization.

Introduction. This study is part of a more general investigation into conformational and electronic properties of analogs of minaprine (commercial name: Cantor – Clin Midy, France), a potent antidepressant drug (Wermuth, 1985). As the 4-demethyl analog appeared inactive, various substituents were fixed on position 4 in