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Chiral Naphthafurophanes from Furan Macrocycles

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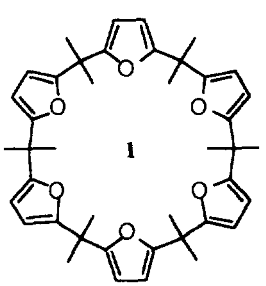
Abstract: *The cycloaddition of two moles of benzyne with any two non diametrically opposite furan units of* **1** *in an* anti *geometry yields a chiral macrocycle. The chiral* anti-*1,3-bis-adduct* **2** *has been isolated, characterised by X-ray crystallography, and converted into the corresponding dinaphthafurophane* **4**. *The X-ray analysis of* **4** *shows the crystals to contain only a single enantiomer i.e.* **4** *undergoes spontaneous resolution on crystallisation.*

In the preceding communication[1] we described the conversion of one or two furan units of the cyclic oligomer of furan and acetone **1**[2] to naphthalenes *via* cycloaddition with benzyne,[3] followed by aromatisation of the adduct(s).[4] In each case both of these adducts have molecular C_S symmetry, *i.e.* they are meso compounds. If, on the other hand, one considers either the 1,2- or the 1,3- analogues, then both meso and chiral forms are possible. The latter originate when benzynes add to the furan units with an *anti* geometry *i.e.* from opposite sides of the mean plane of the macrocycle as represented by an ideal flattened-out all oxygen atoms 'in' conformation. In this communication we describe the single crystal structures of the (±)-*anti*-1,3-bis-adduct **2** [Figure 1 (b)], and that of its aromatised derivative **4** [Figure 2(d)] and discuss the chiral and conformational aspects of these products.



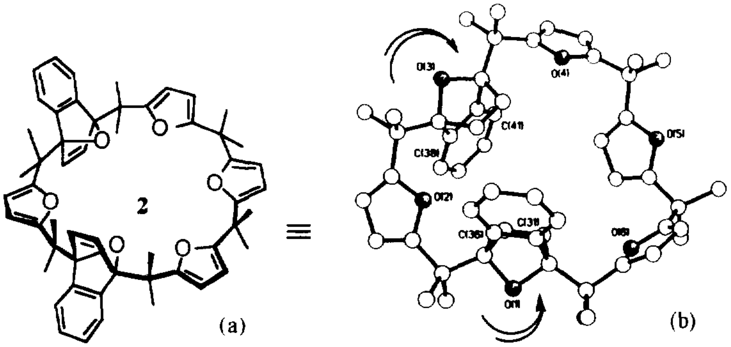


Figure 1. (a) Diagram of the all oxygen atoms 'in' conformation of the (±)-*anti*-1,3-bis-adduct **2** obtained by the cycloaddition of two benzynes to **1**, emphasising the *anti* stereochemistry of the benzo rings observed in its X-ray crystal structure (b). The arrows in (b) indicate the major conformational flips assumed to obtain the representation shown in (a). Intramolecular C–H··· π interactions: C(38)–H···[O(2) furan ring] and C(41)–H···[O(4) furan ring]; the H···π distances and C–H···π angles are 2.71 Å, 135° and 2.95 Å, 132° respectively.

The (±)-*anti*-1,3-bis-adduct **2** was obtained by fractional crystallisation with EtOAc of the concentrated solution that gave the *anti*-1,4-bis-adduct (see preceding communication). The adduct (±)-**2** has been characterised on the basis of its ^{1}H, ^{13}C NMR, and EIMS data[5] and by a single crystal X-ray analysis.[6]

The 1,3- regiochemistry is indicated by the presence in the ^{1}H NMR spectrum of two singlets for the protons of the diametrically opposite furan units, and one AB system for those of the furan units adjacent to the newly formed epoxynaphthalenes. Only four signals having relative intensities 12:12:6:6 were observed for the methyl protons. Assuming a time-averaged flattened-out and all oxygen atoms 'in' conformation [as indicated in Figure 1(a)] the (±)-*anti*- and the *syn*-1,3-bis-adducts have C_2 and C_s symmetries respectively. Thus, in principle, six resonances can be expected for the protons of the six pairs of symmetry-related methyl groups for both stereoisomers. Therefore, even if the observed overlap for two sets of methyl protons did not occur, it would not be possible to assign the *syn*/*anti* stereochemistry by means of ^{1}H NMR spectroscopy. This also implies that one cannot distinguish between either the *meso* compound or the *d*/*l* mixture.

The final *syn*/*anti* assignment of the structure was made by X-ray crystallography [Figure 1 (b)] which confirmed the proposed 1,3-substitution pattern inferred from the ^{1}H NMR analysis and revealed the *anti* configuration for the benzyne addition . The furan rings have their planes inclined by 35° [for the ring containing O(2)], 44° [O(4)], 47° [O(5)] and 71° [O(6)] to the mean plane of the macrocycle – as defined by the six isopropylidene carbon atoms, which are coplanar to within 0.6 Å. Three of the furan oxygen atoms are directed inwards whilst the fourth, that containing O(5), is directed outwards. The two epoxynaphthalene residues are in an *anti* geometry and have their benzo rings inclined by 70 and 74° respectively to the macrocyclic ring plane. There is an absence of any intramolecular C-H···O macrocyclic stabilization. There are however, a pair of weak C-H···π interactions between the C(38) and C(41) aromatic ring hydrogen atoms and their immediately adjacent furan rings. Centrosymmetrically related pairs of molecules pack such that their C(31) to C(36) benzo rings are parallel and partially overlapping with a mean interplanar separation of *ca.* 3.2 Å, indicating a degree of π-π stabilisation of the supramolecular structure. This interaction, which involves the insertion of the benzo ring of one molecule into the macrocyclic cavity of another, indicates a potential for this molecule to act as π-complexing agent for aromatic substrates.

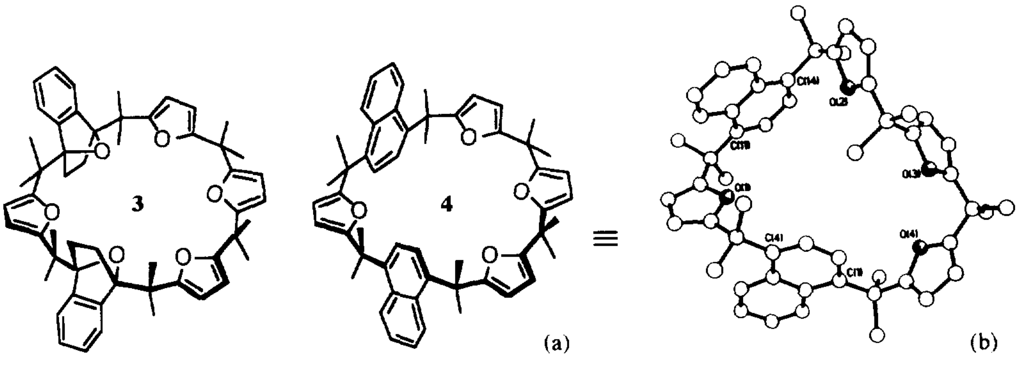


Figure 2. (a) Diagram the dinaphthafurophane **4**, obtained by acid-catalysed dehydration (TsOH, toluene) of (±)-**3**, in which all oxygen atoms are oriented 'in' emphasising the *anti* conformation of the naphthalene units observed in its X-ray crystal structure (b) as previously shown for **2** (Figure 1). The arrows in (b) indicate the major conformational changes assumed to obtain diagram (a).

The (±)-*anti*-1,3-bis-adduct **2** was catalytically hydrogenated (Pd/C, $CHCl_3$, H_2, 1 atm.) to give (±)-**3**[7] which was aromatised by acid promoted dehydration (TsOH, toluene) to the dinaphthafurophane **4**.[8]

The ^{1}H NMR spectrum at of (±)-**3** shows broad signals for most of its protons, indicating a slow conformational mobility. The ^{1}H NMR spectrum of **4**, unlike that of its 1,4-analogue, is consistent with a time-averaged planar conformation. Flipping of the naphthalene units by the passage their C(2)-C(3) carbon bridge through the macro-ring cavity interconverts each chiral conformer **4** of into its enantiomer.[9]

The X-ray analysis of **4**[10] shows the crystals to contain two crystallographically independent molecules both of which have the same chirality and essentially identical conformations with their naphthalene rings in an *anti* orientation. As **4** exists as a racemate in solution, spontaneous resolution has occurred upon crystallisation. The geometry adopted in the solid state can be considered as approximating to an all oxygen 'in' conformation though three of the furan rings [those containing O(2), O(3) and O(4)] are fairly steeply inclined to the macrocycle 'ring plane'. Using the O(1) furan ring to define a datum plane within the molecule, the O(2), O(3) and O(4) containing furan rings are inclined by *ca.* 75, 54, and 37° respectively. The C(4) and the C(11) naphthalene rings are inclined by *ca.* 82 and 70° respectively to the O(1) ring plane, both being folded 'outwards'. In addition to being steeply inclined to the 'ring plane' the two naphthalene rings are sheared and twisted with respect to each other, *i.e.* they swing about a vector linking the two isopropylidene carbon atoms attached to the O(1) furan ring by *ca.* 80°. There are no inter- or intramolecular C–H···O, C–H···π, or π–π interactions. The macrocyclic cavities are occupied by acetone solvent molecules, the host-guest interactions being only normal van der Waals'.

The synthesis[11] of the chiral (±)-*anti*-1,3-adduct **2** from **1** provides support for the prospect of using cyclic oligomers of furan and acetone as precursors of chiral receptors. It is interesting that the configurational chirality present in (±)-**2** (and in (±)-**3**) is also a feature of **4**, though in this instance by virtue of its preferred *anti* conformation, which is a prerequisite for the spontaneous resolution in the solid state. It should also be appreciated that the meso form of **3**, that is the *syn* isomer which was not isolated, would still lead to the conformationally chiral **4** upon aromatisation.

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REFERENCES AND NOTES

1. See preceding communication.
2. For details of the synthesis of **1** see: Kohnke, F. H.; La Torre, G. L.; Parisi, M. F.; Menzer, S.; Williams, D. J. *Tetrahedron Lett.* **1996**, in press; b) Healy, M. D.; Rest, A. J. *J. Chem. Soc., Perkin Trans. I* **1985**, 973-982 and references therein.
3. Benzyne was generated by pyrolysis of benzenediazonium-2-carboxylate: Logullo, F. M.; Seitz, A. H.; Friedman, A. H. *Organic Syntheses, Coll. Vol. 5*, Noland W. (Ed); Wiley, J; New York 1973, pp. 54-55.
4. a) For review of aromarization of Diels-Alder adducts of furan see: Wong, H. N. C. *Acc. Chem. Res.* **1989**, *22*, 145-152; b) For a similar study on the cyclic tetramer of furan and acetone see: Kohnke, F. H.; Parisi, M. F.; Raymo, F. M.; O'Neil, P. A.; Williams, D. J. *Tetrahedron* **1994**, *50*, 9113-9124 and references therein
5. **2**: m.p. 259-260 °C (from EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (s, 6H), 1.40 (s, 6H) 1.47 (s, 12H), 1.55 (s, 12H), 5.50 (s, 2H), 6.09 and 6.19 (AB system, J_{AB} = 3.1 Hz, 2x2H), 6.28 (s, 2H), 6.65-6.73 (m, 8H), 6.82-6.88 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.1, 23.8, 25.6, 25.8, 26.1, 26.7,

37.2, 37.5, 37.5, 94.6, 94.8, 104.0, 104.5, 105.3, 105.7, 120.4, 120.7, 123.5, 123.6, 144.7, 145.2, 151.9, 151.9, 157.9, 158.7, 158.9, 159.4; EIMS: 800 ($M^{+\cdot}$).

6. Crystal data for (±)-**2**: $C_{54}H_{56}O_6$, $M = 801.0$, monoclinic, $a = 13.293(2)$, $b = 14.594(2)$, $c = 23.423(3)$ Å, $\beta = 93.89(2)^\circ$, $V = 4534$ Å^3, space group $P2_1/n$, $Z = 4$, $\rho_{calcd} = 1.174$ g cm^{-3}, $\mu(\mathrm{Cu}K_\alpha) = 5.9$ cm^{-1}. 6719 Independent measured reflections [$2\theta \le 120^\circ$] of which 5534 were considered to be observed [$|F_o| > 4\sigma(|F_o|)$]. Data were measured on a Siemens P4/PC diffractometer, ω scans, CuK_α radiation (graphite monochromator). The structure was solved by direct methods and the non-hydrogen atoms refined anisotropically (based on F^2) to give $R_1 = 0.042$, $wR_2 = 0.099$.
7. (±)-**3**: m.p. 223-225 °C (from $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.90-1.03 (m, 4H), 1.11 (bs, 6H), 1.40 (s, 6H), 1.48 (s, 6H), 1.50 (s, 6H), 1.54 (s, 6H), 1.94-2.05 (m, 4H), 2.52 (bs, 6H), 5.36 (bs, 2H), 5.98 and 6.09 (AB system, 2x2H), 6.20 (s, 2H), 6.82-7.02 and 7.10-7.21 (2xm, 8H and 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.1, 23.5, 24.1, 24.1, 25.6, 26.8, 31.1, 31.2, 37.6, 38.1, 38.5, 89.9, 90.0, 104.0, 104.5, 105.0, 105.7, 119.9, 119.9, 125.2, 125.4, 147.3, 147.3, 158.2, 158.5, 159.1, 159.7; EIMS: 804 ($M^{+\cdot}$).
8. **4**: m.p. 118-130 °C (from toluene/hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 1.42 (s, 12H), 1.61 (s, 12H), 1.79 (s, 12H), 5.48 (s, 2H), 5.82 (m, 4H), 6.23 (s, 2H), 6.93 and 7.04 (AB system, $J_{AB} = 8.1$ Hz, 2x2H), 7.13 (m, 4H), 8.02 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.2, 29.3, 29.7, 37.3, 40.4, 40.9, 103.4, 103.7, 104.3, 104.5, 123.1, 123.3, 123.3, 123.5, 126.2, 126.8, 132.4, 132.6, 141.5, 141.6, 158.0, 158.4, 161.6, 162.2; EIMS: 768 ($M^{+\cdot}$).
9. The other possibility, *i.e.* the passage of the benzo ring through the cavity of the macrocycle is much less likely for steric reasons.
10. Crystal data for **4**: $C_{54}H_{56}O_4 \cdot 1.5\,(CH_3)_2CO$, $M = 856.1$, monoclinic, $a = 10.610(1)$, $b = 43.406(1)$, $c = 10.655(31)$ Å, $\beta = 96.93(1)^\circ$, $V = 4871$ Å^3, space group $P2_1$, $Z = 4$ (2 crystallographically independent molecules), $\rho_{calcd} = 1.167$ g cm^{-3}, $\mu(\mathrm{Cu}K_\alpha) = 5.3$ cm^{-1}. 7489 Independent measured reflections [$2\theta \le 120^\circ$] of which 6878 were considered to be observed [$|F_o| > 4\sigma(|F_o|)$]. Data were measured at -70 °C a Siemens P4 rotating anode diffractometer, ω scans, CuK_α radiation (graphite monochromator). The structure was solved by direct methods and the non-hydrogen atoms refined anisotropically (based on F^2) to give $R_1 = 0.048$, $wR_2 = 0.125$. A definitive assignment of the absolute structure was obtained via the Flack parameter which refined to a value of -0.3(3), *cf.* 1.3(1) for the enantiomeric structure. Computations for both **2** and **4** were carried out using the SHELXTL program system, version 5.03. Further details of the crystal structure investigations can be obtained from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ (UK) on quoting the full journal citation.
11. Adduct (±)-**2** was obtained in low yield (*ca.*5%). Its hydrogenation to (±)-**3** proceeds with quantitative yield, and the aromatisation leading to **4** took place in *ca.* 15% yield. Although these yields are low (no attempt was made to optimise them) all the starting materials are cheap, and the isolation of the products relies on conventional techniques which can be easily used for very large scale preparations.

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