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Conversion of the Cyclic Hexamer of Furan and Acetone into Naphthafurophanes.

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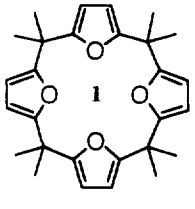
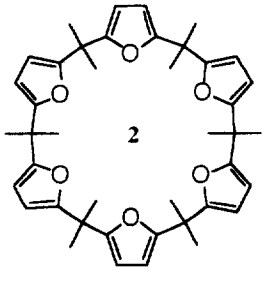
***Abstract**: Furanophane **2** has been converted via benzyne addition/aromatisation into the naphthafurophanes **5** and **8**. The X-ray structure of the diepoxydinaphthofurophane intermediate **6** is also reported. A preliminary dynamic NMR analysis of the conformational behaviour of **8** is presented.* Copyright © 1996 Elsevier Science Ltd

Furan based macrocycles readily self-assemble by the condensation of furan with carbonyl compounds under acidic conditions.[1] These compounds are attractive precursors for the synthesis of large cyclophanes *via* the conversion of (several or all of) the furan units into acene units by means of Diels-Alder reactions with appropriate dienophiles, followed by aromatisation of the adducts.[2]

Following our investigation[3] on the reactions of the cyclic tetramer of furan and acetone **1** with benzynes, we now report an extension of these studies to include the larger cyclic hexamer **2**.



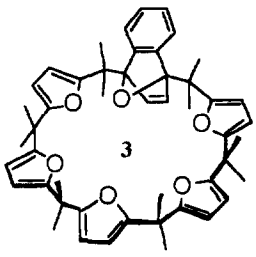


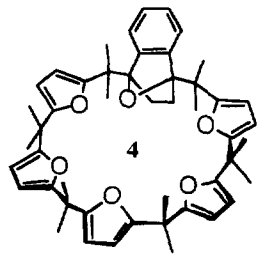
When the furanophane **2** was treated with three moles of benzyne, generated in THF solution by pyrolysis of benzenediazonium-2-carboxylate,[4] a t.l.c. analysis (SiO_2; toluene:hexanes 1:3) revealed that the mixture comprised principally of two major followed by two minor fractions. These were isolated by column chromatography (SiO_2; toluene:hexanes 1:3). The first fraction to be eluted contained the mono-adduct **3**,[5] the second the bis- and tris-adduct(s), the third some other tris- and tetra-adduct(s), whilst the fourth contained only tetra-adduct(s). Trace amounts of penta- and hexa-addition products were detected by MS in the fifth fraction.

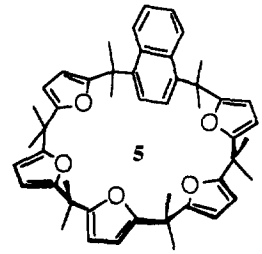
Thus it was immediately evident that, unlike its smaller homologue **1**, which gives a single isomer for each ratio of added benzyne,[3] **2** forms a large number of products which vary both as a function of the

number of added benzynes and of the regio- and stereochemistry of the additions. For example, three regioisomeric bis-adducts can exist which can be referred to as 1,2- 1,3- and 1,4-, these numbers indicating the relative positions of the furan units which have undergone cycloaddition. Regiochemically identical adducts can have various stereoisomers because the benzynes can – in principle – undergo cycloaddition with each furan unit from either side of the mean plane containing **2**. For simplicity we shall assume an ideal flattened-out, all oxygen atoms "in" conformation for the adducts for the purpose of identifying the relative stereochemistry of the benzo rings, *e.g.* the *syn*- or *anti*-1,4-bis-adduct (*vide infra*). The stereochemical complexity arising from this latter factor is lost on aromatisation if these compounds are conformationally mobile, *i.e.* if the 2,3-carbon bridge of each naphthalene unit can pass through the cavity of the macrocycle.[6] However, when we attempted to aromatise simultaneously all of the compounds contained in the crude mixture, by catalytic hydrogenation of the olefinic double bonds of the epoxynaphthalene residues followed by acid-promoted dehydration, we were unable to isolate any of the expected products.

The ^1H and ^{13}C NMR spectra of the mono-adduct **3**[5] are consistent with it having C_s symmetry; thus, six signals are observed for the methyl protons. The protons of one pair of the furan units appear as an AB system whilst those of the other symmetry related pair are coincident, appearing as a singlet. However, all the expected resonances (24 signals) including those of the six methyl and the three quaternary isopropylidene carbon atoms are observed in the ^{13}C NMR spectrum.







The olefinic double bond in the mono-adduct **3** was catalytically hydrogenated (Pd/C, $CHCl_3$, H_2, 1 atm.) to give the epoxynaphthafuraphane **4**[7] which upon acid-promoted dehydration (TsOH in toluene) gave the naphthafuraphane **5**.[8] Unlike the smaller homologue obtainable from **1** the ^1H NMR spectrum of **5** contains only sharp resonances which do not show any broadening at low temperature (-60 °C). The presence of only three resonances for the methyl groups, of two AB systems, and one singlet for the furan units is consistent with a time-averaged planar conformation.

Treatment of the second fraction obtained from the crude mixture with acetone gave a crystalline compound which was characterised as the *anti*-1,4-bis-adduct **6** on the basis of its EIMS, ^1H and ^{13}C NMR spectra[9] and by a single crystal X-ray analysis[10] (Figure 1).

The molecule adopts a C_2 symmetric conformation [about C(10)···C(25)] in which the four furan residues are oriented with their planes essentially normal [83, 90, 90, and 86° for the furan rings containing O(2) O(3), O(5), and O(6) respectively] to the mean plane of the macrocycle, as defined by the six isopropylidene carbon atoms. The furan rings have their oxygen atoms oriented in an up-down-up-down sequence, a conformation equivalent to that observed for the related tetraoxaquaterene **1**[11a]. Each furan ring has at least one of its C–O bonds oriented in an *anti* geometry with respect to one of its adjacent isopropylidene C-Me bonds.[11b,c] The two diametrically opposite epoxynaphthalene units are in an *anti*

geometry with their epoxy oxygen atoms directed outwards. The planes of the benzo rings are steeply inclined (67 and 66°) to the macrocyclic ring plane and are tilted inwards towards the ring centre; the macrocyclic cavity is self-filling. The macro-ring conformation is stabilised by intramolecular C-H···O and C-H···π interactions.

The olefinic double bonds of the *anti*-1,4-bis-adduct **6** were hydrogenated to give the epoxy-naphthalenophane **7**[12] which was then aromatised as for the mono-adduct to give the dinaphthafuraphane **8**.[13]

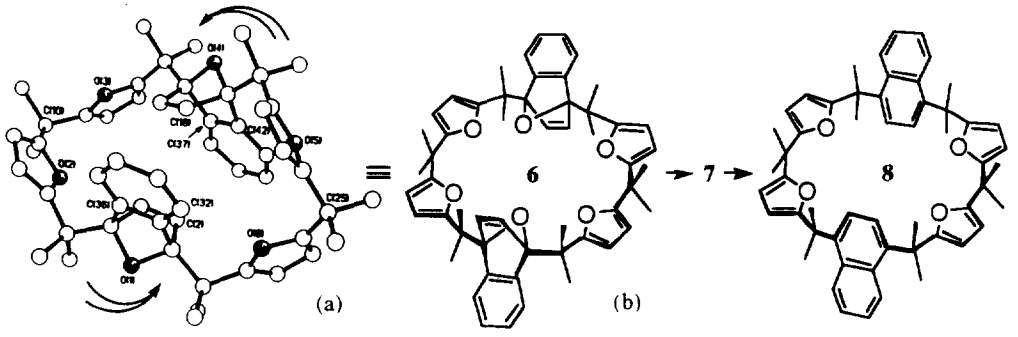


Figure 1. (a) X-ray crystal structure of the *anti*-1,4-bis-adduct **6** and (b) diagram of the corresponding all oxygen atoms "in" conformation which emphasises the *anti*-stereochemistry of the benzo rings. The arrows in (a) indicate the major conformational changes assumed to obtain the representation shown in (b). Intramolecular C-H···O interactions: C(32)-H···O(6) and C(41)-H···O(5); C···O, H···O, and C-H···O distances and angles 3.03, 2.31 Å, 132° and 3.04, 2.29 Å, 134° respectively. Transannular C-H···π interactions: olefinic C(2)-H···[C(37)-C(42) benzo ring] and olefinic C(18)-H···[C(31)-C(36) benzo ring]; the H···π distances and C-H···π angles are 2.76 Å, 140°, and 2.82 Å, 140° respectively.

The ^{1}H NMR spectrum of **7** contains nine sharp signals for the nine sets of symmetry related protons. The ^{1}H NMR spectrum of the dinaphthafuraphane **8** in CD_2Cl_2 at room temperature is characterised by the presence of very broad peaks for the furan protons, but which give a single AX system (δ 5.06 and 5.50; J_{AX} = 3.1 Hz) at +90 °C in $CDCl_2CDCl_2$. On cooling in CD_2Cl_2 the spectrum changes dramatically. At -70 °C, the furan protons appear as two AB systems of equal intensity, with one pair of signals at δ 6.33 and 6.09 (J_{AB} = 3.1 Hz) and the other pair at remarkably high field at δ 4.20 and 3.26 (J_{AB} = 3.1 Hz). The protons at the 2,3-positions of the naphthalene units resonate as another AB system at δ 7.64 and 7.52 (J_{AB} = 7.9 Hz), whilst those at the 5,8- and 6,7-positions appear as separate pairs of signals (δ 7.96 and 7.54) and a multiplet (δ 7.03 - 6.97). These data indicate that the conformational arrangements on either side of each naphthalene unit are different. The high field shifts of two pairs of C(3)-H/C(4)-H furan protons (they are shielded by the naphthalene rings) indicate that two diametrically opposite furan rings are oriented with their oxygen atoms directed away from the macrocycle cavity, whilst the other furan units are oriented with their oxygen atoms directed inwards (as evidenced by the δ values, *vide supra*, observed for their C(3)-H/C(4)-H protons being similar to those found for **6**). We discount the arrangement with adjacent furan rings oriented co-directionally on account of steric considerations. On the basis of these data it is not however possible to establish the relative orientation of the naphthalene units, *i.e.* if their benzo rings are *syn* or *anti*. The ^{13}C NMR spectrum of **8** in CD_2Cl_2 at room temperature contains the expected 13 resonances consistent with a time-averaged planar conformation.

The dynamic behaviour of the dinaphthafuranophane **8** demonstrates that the complexity created by the *syn- / anti-* mode of benzyne addition in the initial adducts is lost in the aromatised products. The successful conversion of the mono- and especially of the *anti*-1,4-bis-adduct into the corresponding naphthafuraphanes

suggests the possibility of converting other polyaddition products of **2** into acenophane derivatives and to extend this methodology[14] (aryne addition/aromatisation) to larger oligomers.

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5. **3**: m.p. 239-241 °C (from $CHCl_3$): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (s, 6H), 1.43 (s, 6H) 1.47 (s, 6H) 1.53 (s, 6H), 1.56 (s, 6H), 1.62 (s, 6H), 5.41 and 5.45 (AB system, J_{AB} = 3.1 Hz, 2x2H), 5.72 (s, 2H), 6.12-6.15 and 6.20-6.23 (AA'BB' system, 2x2H), 6.61 (s, 4H), 7.13 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.0, 25.7, 26.1, 26.3, 26.5, 26.6, 37.2, 37.5, 37.7, 94.6, 103.9, 104.11, 104.3, 104.5, 105.4, 120.2, 123.6, 145.4, 152.0, 158.0, 158.3, 158.7, 158.8, 159.0.; EIMS: 724 ($M^{\cdot+}$).
6. The other possibility, *i.e.* the passage of the benzo ring through the cavity of the macrocycle is much less likely for steric reasons.
7. **4**: m.p. 233 °C (from $CHCl_3$): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (m, 2H), 1.27 (s, 6H), 1.41 (s, 6H), 1.42 (s, 6H), 1.47 (s, 6H), 1.60, (s, 12H), 2.09 (m, 2H), 5.33 and 5.70 (AB system, J_{AB} = 3.1 Hz, 2x2H), 5.61 (s, 2H), 6.09-6.12 and 6.15-6.18 (AA'BB' system, 2x2H), 6.84 (bs, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.2, 23.7, 25.8, 25.8, 26.3, 26.3, 30.8, 37.2, 37.6, 38.08, 89.6, 103.6, 103.8, 104.0, 104.3, 105.2, 119.6, 125.3, 147.2, 158.0, 158.2, 158.7, 158.8, 159.2.; EIMS: 726 ($M^{\cdot+}$).
8. **5**: m.p. 94-95 °C (from acetone): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (s, 12H), 1.49 (s, 12H), 1.83 (s, 12H), 5.01 and 5.41 (AB system, J_{AB} = 3.1 Hz, 2x2H), 5.83 and 5.96 (AB system, J_{AB} = 3.1 Hz, 2x2H), 5.93 (s, 2H), 7.12-7.18 and 7.92-7.98 (AA'BB' system, 2x2H), 7.54 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.2, 26.5, 30.0, 37.3, 37.5, 40.2, 103.4, 103.7, 103.8; 104.4, 104.5, 122.9, 123.6, 126.3, 132.7, 141.5, 157.9, 158.0, 158.0, 158.3, 162.0; EIMS: 708 ($M^{\cdot+}$).
9. **6**: m.p. 218-220°C (from acetone): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (s, 12H), 1.34 (s, 12H), 1.65 (s, 12H), 5.35 (s, 4H), 6.17 and 6.19 (AB system, J_{AB} = 3.1 Hz, 4x2H), 6.61-6.68 and 7.09-7.16 (AA'BB' system, 2x4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.3, 24.7, 26.7, 37.1, 37.1, 37.3, 94.5, 104.0, 106.5, 120.7, 123.5, 143.2, 151.6, 158.6, 159.5; EIMS: 800 ($M^{\cdot+}$). These NMR data were sufficient to establish the 1,4-regiochemistry, but not the stereochemistry.
10. Crystal data for **6**: $C_{54}H_{56}O_6$, M = 801.0, monoclinic, a = 25.770(4), b = 12.394(2), c = 28.616(4) Å, β = 94.65(2)°, V = 9110 Å^3, space group $C2/c$, Z = 8, ρ_{calcd} = 1.168 g cm^{-3}, $\mu(Cu_{K\alpha})$ = 5.9 cm^{-1}. 7171 Independent measured reflections [2θ ≤ 124°] of which 4719 were considered to be observed [$|F_o|>4\sigma(|F_o|)$]. Data were measured on a Siemens P4 rotating anode diffractometer, ω scans, $Cu_{K\alpha}$ radiation (graphite monochromator). The structure was solved by direct methods and the non-hydrogen atoms refined anisotropically to give R = 0.046, R_w = 0.047. Computations were carried out using SHELXTL PC version 4.2. Further details of the crystal structure investigation can be obtained from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ (UK) on quoting the full journal citation.
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12. **7**: m.p.140-142 °C (from $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.96 (m, 2x2H) 1.24 (s, 12H), 1.40 (s, 12H), 1.62 (s, 12H), 1.67 (m, 2x2H), 6.03 and 6.14 (AB system, J_{AB} = 3.1 Hz, 4x2H), 6.84-6.90 and 6.90-6.96 (AA'BB' system, 2x4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.8, 24.0, 26.7, 31.2, 37.2, 38.2, 38.2, 89.6, 103.5, 105.9, 119.7, 125.4, 147.3, 158.7, 159.4; EIMS: 804 ($M^{\cdot+}$).
13. **8**: m.p.140-155°C (from acetone): ^{1}H NMR (300 MHz, +20 °C, CD_2Cl_2): δ 1.5 (s, 12H), 1.8 (bs, 24H), 4.8 (bs, 4H) and 5.5 (bs, 4H), 7.00-7.07 and 7.75-7.82 (AA'BB' system, 2x4H), 7.55 (s, 4H); ^{13}C NMR (75 MHz, +20 °C, CD_2Cl_2) δ 26.3, 30.3, 37.5, 40.0, 103.5, 104.0, 122.8, 123.7, 126.9, 132.4, 141.6, 157.3, 160.0; EIMS: 768 ($M^{\cdot+}$).
14. Naphthafurophane **5** can be obtained in *ca.* 10% yield from **2**, the yield for **8** was considerably lower (*ca.* 2%). Although these yields are low, all starting materials are cheap, and the isolation of the products relies on conventional techniques which can be easily adopted on a very large scale preparations.

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