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Synthesis and conformational studies of chiral macrocyclic [1.1.1]metacyclophanes containing benzofuran rings

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Macrocyclic [1.1.1]metacyclophanes (MCPs) containing benzene and benzofuran rings linked by methylene bridges and which can be viewed as calixarene analogues, have been synthesized by demethylation of [3.3.1]MCP-diones with trimethylsilyl iodide (TMSI) in MeCN. The [3.3.1]MCP-diones are synthesized by using (*p*-tolylsulfonyl)methyl isocyanide (TosMIC) as the cyclization reagent in *N,N*-dimethylformamide (DMF) with an excess of sodium hydride. ^{1}H NMR spectroscopy revealed that the remaining hydroxyl group on the phenyl ring is involved in intramolecular hydrogen bonding with the oxygen of one of the benzofuran rings. *O*-Methylation at the lower rim of monohydroxy[1.1.1]MCP in the presence of K_2CO_3 in acetone afforded a novel and inherently chiral calixarene analogue, namely the macrocyclic [1.1.1]MCP, possessing C_1 symmetry. The inherent chirality of the two conformers was characterized by ^{1}H NMR spectroscopy by addition of an excess of Pirkle's chiral shift reagent, which caused a splitting of the corresponding methylene protons to AB patterns. Single crystal X-ray analysis revealed the adoption of a hemisphere-shaped *cone* isomer. DFT calculations were carried out to investigate the energy-minimized structures and the hydrogen bonds of the synthesized MCPs.

Introduction

The design and synthesis of new functional macrocycles such as cyclophanes[1] and calix[*n*]arenes[2] have been of particular synthetic and theoretical interest among scientists for a number of decades. Chiral calixarenes have attracted recent attention due to their potential use as enantioselective artificial receptors and asymmetric catalysts.[3] Two principal approaches have been used for the preparation of chiral calixarenes. The first approach involves the synthesis of inherently chiral calixarenes directly,[4] whilst the second approach is via the attachment of chiral moieties at the upper or lower rims of a calixarene macrocycle.[5] Since the first unintentional preparation of inherently chiral calixarenes was reported by No and Gutsche,[6] inherently chiral calixarenes have continued to attract attention,[7] and given their peculiar structures and unique conformational properties, inherently chiral calixarenes have become topical macrocyclic molecules.[8] Furthermore, these types of chiral calixarenes have significant potential applications in the chemical, analytical, biological and material fields.[9]

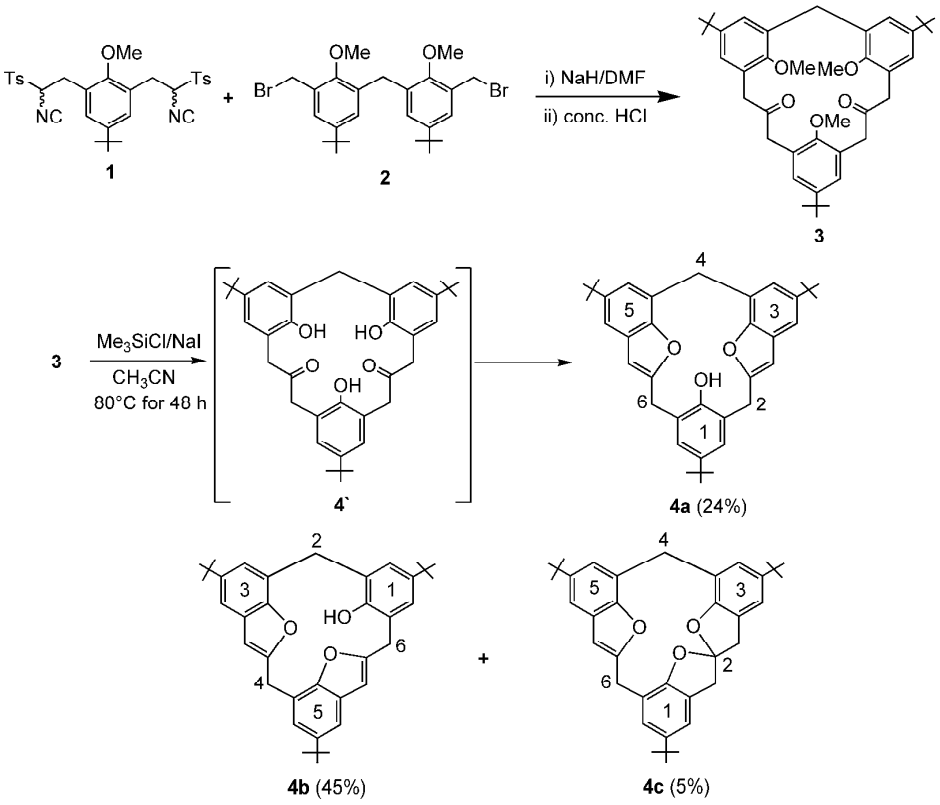
The concept of "inherently chirality" as applied to calixarenes in particular, was first suggested by Böhmer, based on either the absence of planar symmetry or the absence of an inversion centre in molecules bearing an asymmetric array of several achiral groups appended to their three-dimensional skeletons.[10] This concept was soon accepted by researchers and further developed by Mandolini and coworkers.[4b] Indeed, inherently chiral macrocycles with diverse structures could be obtained from asymmetric arrays of one or several functionalities on the cyclophane/calixarene skeletons in appropriate positions.[11] The synthesis and optical resolution of inherently chiral calixarenes are challenging, but because of their potential uses in supramolecular chemistry remains attractive.[12] The design and synthesis of inherently chiral calixarenes with novel structures and superior functions therefore is a topic of great importance.

More recently, Szumna has modified the definition as '*...inherent chirality arises from the introduction of a curvature in an ideal planar structure that is devoid of perpendicular symmetry planes in its bi-dimensional representation*'.[13] A wide variety of concave molecule-based inherently chiral macrocycles such as calixarenes,[14] resorcinarenes,[15] heteracalixaromatics,[16] cyclotriveratrylenes,[17] and so on,[13] have been reported and many of these have shown excellent chiral recognition and asymmetric catalytic abilities. An inherently chiral element can also be added to such concave molecules consisting of repeating chiral subunits such as cyclodextrins which were reported by Sollogoub.[18] However, access to inherently chiral calixarenes is frequently not straightforward due to regio-control and conformational problems involved at the synthetic stage, and consequently low yields result. The development therefore, of effective methods for the synthesis of enantiomerically-pure inherently chiral calixarenes and the determination of their absolute configurations is of great importance.

It is surprising that reports on the preparation of calixarenes and their analogues containing only three arene rings and the characterization of their hydrogen bonding has been very limited.[19] Our group has previously reported various types of metacyclophanes (MCPs)[20] and oxahomocalixarenes[21] containing three benzene rings. We report herein a short and easy route for the synthesis of inherently chiral, three arene-based, macrocyclic [1.1.1]MCPs containing both benzene and benzofuran rings in good yields.

Results and Discussion

As part of our continued interest in the synthesis of inherently chiral calixarenes analogues, we undertook a systematic investigation of



Scheme 1 Demethylation of 6,15,22-tri-*tert*-butyl-9,18,25-trimethoxy[3.3.1]MCP-2,11-dione **3**.

[1.1.1]MCPs containing both benzene and benzofuran rings, which were synthesized by intramolecular cyclization. The macrocyclic MCP framework **3** was synthesized by the reaction between the TosMIC [(TosMIC = (*p*-tolylsulfonyl)methyl isocyanide)] adduct **1** and 1,1-bis(3-bromomethyl-5-*tert*-butyl-2-methoxyphenyl)methane **2**. Vögtle and co-workers[22] reported the preparation of carbocyclic [3n]MCPs using TosMIC[23] as the cyclization reagent, which was applied in a new cyclization procedure without the need for phase-transfer conditions.[24]

The structure of **3** has been established by elemental and spectral analyses. For instance, the mass spectral data for **3** (M^+ = 612.43) strongly supports a cyclic trimeric structure. The IR spectrum of **3** reveals the absorption of the carbonyl stretching vibration at around 1700 cm^{-1}. The ^1H NMR spectrum of macrocycle **3** exhibits two doublets at δ 3.32 and 4.27 ppm (J = 12.6 Hz) for the ArCH_2Ar methylene protons, four doublets at δ 3.25, 3.42, 3.64 and 4.02 ppm for the ArCH_2COCH_2Ar methylene protons. In this case, two methoxy groups are located above (δ 3.51 ppm), and one is located in the opposite direction and is in the π-cavity which is formed by two benzene rings, and is shielded such that its signal appears up-field at δ 2.05 ppm. A single crystal of **3** was grown from a mixture of hexane and CH_2Cl_2, and its structure was investigated by X-ray crystallography (CCDC 1028494) to confirm the conformation. The crystal structure was found to belong to the monoclinic crystal system with the space group $P2_1/c$ (SI Table S1). The crystal structure of **3** is shown in Figure 1. It is clear that the O3-C27 methoxy group is located between the two aromatic rings that are forced inwards to each other and is pointing downwards between the benzene rings. This methoxy group is shielded due to the ring current. The other two methoxy groups (O1-C32 and O2-C34) are pointing up and are situated away from the macrocyclic cavity.

Treatment of 6,15,22-tri-*tert*-butyl-9,18,25-trimethoxy-[3.3.1]MCP-2,11-dione **3** with TMSI generated *in situ* from TMSCl and NaI in CH_3CN afforded the furan moiety by nucleophilic intramolecular cyclization. Sawada and co-workers reported that treatment of tetrahydroxy-tetramethoxy [2.1.2.1]MCPs with TMSI leads to hemisphere-shaped calixarene analogues containing a dihydrobenzofuran ring.[25] The structures of **4** (symmetrical or unsymmetrical) were determined by spectroscopic methods (^1H NMR and ^{13}C NMR), mass and elemental analyses. The ^1H NMR spectrum of the crude product from the reaction with TMSI exhibited two types of signals, namely, singlets for the hydroxyl groups (exchanged by D_2O) and for the furan moieties. By careful column chromatography, using hexane-CH_2Cl_2 (8:2) as eluent, the symmetrical-1^5,3^5,5^5-tri-*tert*-butyl-1^2-hydroxy-1-(1,3)-benzena-3,5-(2,7)benzofuranacyclohexaphane **4a** (24 %) was isolated. When hexane-CH_2Cl_2 (1:1) was the eluent, the unsymmetrical-1^5,3^5,5^5-tri-*tert*-butyl-1^2-hydroxy-1(1,3)-benzena-3,5-(2,7)ben-zofuranacyclohexaphane **4b** (45 %) was eluted as the major product. The structures of **4a** and **4b** were elucidated on the basis of their spectroscopic data. In general, a calixarene having free phenolic hydroxyl groups on its narrow-rim shows concentration-independent hydroxyl stretching bands in the 3400-3200 cm^{-1} region in the infrared spectra and signals in the δ = 6-7 ppm region in the ^1H NMR spectra. This spectroscopic evidence is indicative of the intramolecular hydrogen bonding characteristics of the cyclic nature of these macrocycles.[2,26] The ^1H NMR spectra of **4a** ($CDCl_3$, 400 MHz) and **4b** ($CDCl_3$, 300

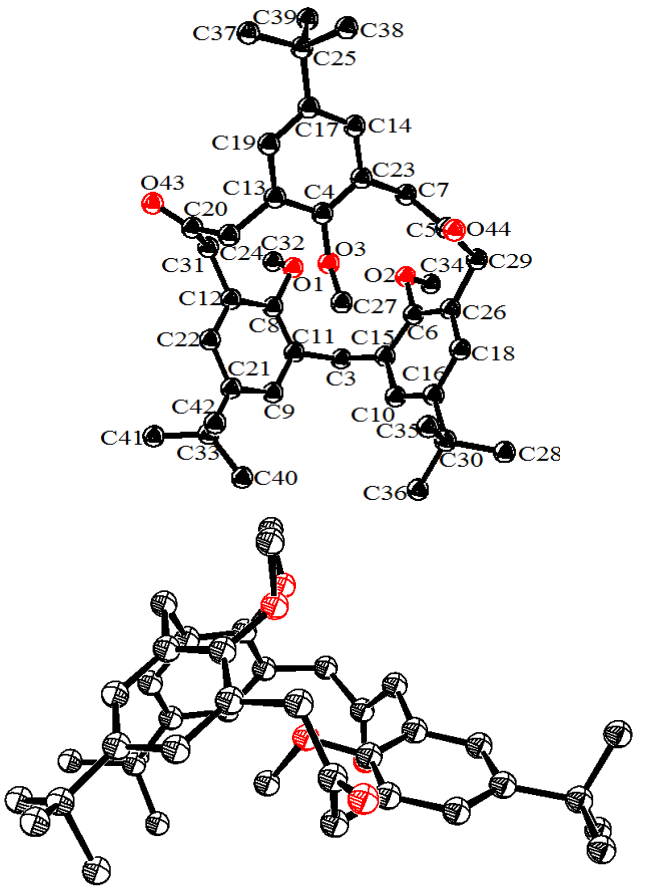


Fig. 1 Ortep drawing of **3** with top (top) and side (bottom) views. Thermal ellipsoids are drawn at the 50 % probability level. All hydrogen atoms are omitted for clarity.

MHz) each exhibit signals at the same positions, at δ = 6.55 ppm for their hydroxyl groups both of which are exchanged with D_2O.

The chemical shift can be interpreted as being consistent with the existence of intramolecular hydrogen bonding between the hydroxyl groups and the oxygens of the benzofuran rings. A concentration-variable ^{1}H NMR study of **4a** and **4b** ($CDCl_3$, 400 MHz) from 0.50 mM to 30 mM at 25 ºC shows that the chemical shift of the hydroxyl proton is concentration-independent and always exhibits a signal at δ 6.50 ppm for **4a** (SI, Fig. S24) and at δ 6.55 ppm for **4b** (SI, Fig. S25). The intramolecular hydrogen bonding of **4a** and **4b** in polar solvents was also studied. The ^{1}H NMR spectrum of **4a** (400 MHz) in CD_3COCD_3 led to a shift for the hydroxyl proton signal at δ 7.16 ppm, and with **4b** to a shift for the hydroxyl proton signal at δ 6.85 ppm, indicating that the intramolecular hydrogen bonding is disrupted in polar solvents (SI, Fig. S26 & SI, Fig. S27) and formation of hydrogen bonds with acetone-d_6 results.

The ^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of macrocycle **4a** exhibits two doublets at δ 3.93 and 4.86 ppm (J = 13.2 Hz) for the ArCH_2Ar methylene bridge protons. The remaining two bridge methylene protons each appeared as two-proton doublets at δ 3.63 and 4.66 ppm (J = 14.0 Hz). The structure of **4a** (Fig. 2) was also established by single crystal X-ray analysis (CCDC 1049029), the crystals for which were grown from a hexane-$CHCl_3$ 1:1 mixture by slow evaporation. The crystal structure was found to belong to the orthorhombic crystal system with space group Pccn (SI Table S1) and is fully consistent with the ^{1}H NMR data of **4a**. It is clear that the hydroxyl group situated between the two benzofuran rings forms an intramolecular hydrogen bond with the oxygen atom of one of the benzofuran rings, as predicted from the ^{1}H NMR spectroscopic data. The distance between H3 (OH) and Ol is 2.182 Å, which is a reasonable distance for intramolecular hydrogen bonding and which is less than the distance between H3 (OH) and O2 (2.523 Å). The ^{1}H NMR ($CDCl_3$, 300 MHz) spectrum of **4b** possessed three singlet signals for the *tert*-butyl protons at δ 1.13, 1.31 and1.32 ppm (relative intensity 1:1:l) and two singlet signals for the furan ring at δ 6.36 and 6.39 ppm. The macrocycle **4b** is fixed in the form of an asymmetrical hemisphere-shaped *cone* conformation at room temperature in solution as observed by the five doublets for the methylene protons at δ 3.63 (J = 13.8 Hz), 4.02 (J = 14.7 Hz), 4.51 (J = 14.7 Hz), 4.66 (J = 13.8 Hz) and 4.97 (J = 13.2 Hz) ppm and is evidence for the magnetically inequivalent methylene protons.

Along with **4a** and **4b**, a third compound **4c**, was isolated from the hexane eluent of the column chromatography. The structure was somewhat peculiar, containing one furan ring and a spiro bisdihydrofuran moiety within the cyclophane frame.

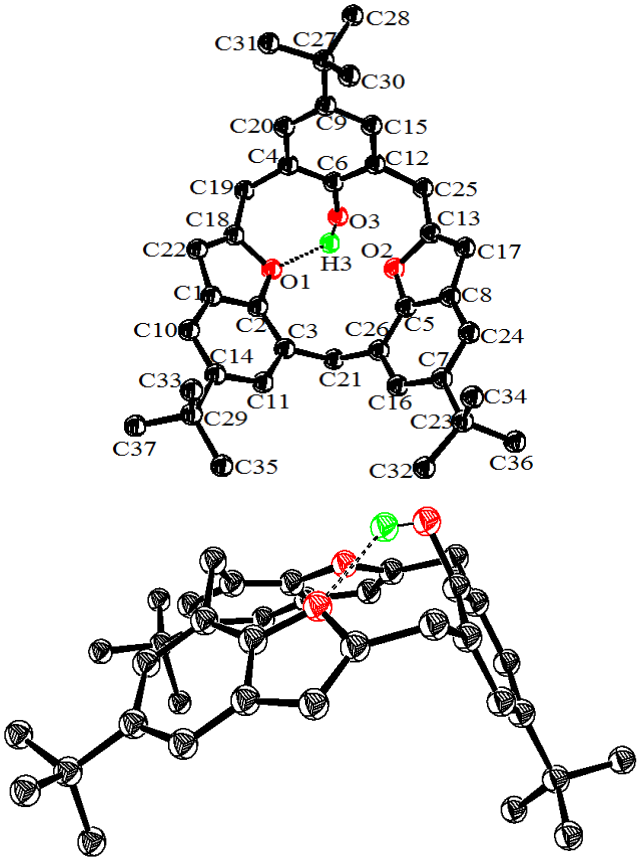
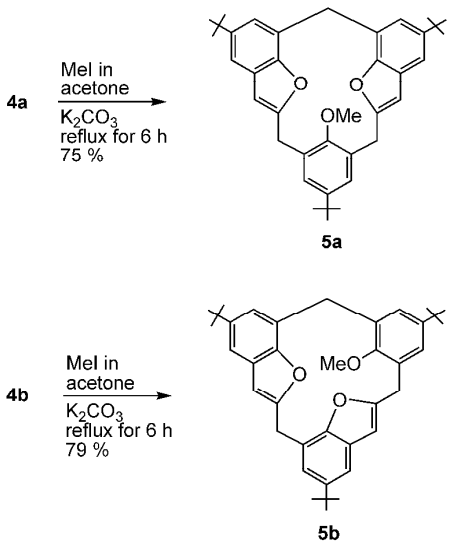


Fig. 2 ORTEP drawing of **4a** with top (top) and side (bottom) views. Thermal ellipsoids are drawn at the 50 % probability level. All hydrogen atoms except one are omitted for clarity.



Scheme 2 *O*-Methylation of hydroxy[1.1.1]MCPs **4a-b** with MeI in the presence of K_2CO_3.

The presence of the cyclophane structure was evident from the ^{1}H NMR signals observed for the bridge methylene hydrogen atoms which appeared as two doublets at δ 4.21 and 4.39 ppm (J = 13.5 Hz). The ^{1}H NMR spectrum of macrocycle **4c** showed three singlets for the *tert*-butyl protons at δ 1.22, 1.28 and 1.36 ppm (relative intensity 1:1:1). The mechanism of precisely how the two dihydrofuran moieties were formed can only be conjecture at this stage. We tentatively propose that two phenolic oxygens compete at once for nucleophilic attack at the same proximal carbonyl carbon thereby leading to the formation of the spiro bisdihydrofuran moieties in **4c**. Although intermediate **4'**, could not be isolated, it is evident upon examination of the crystal structure of the parent compound **3** (SI, Fig. S28), that the distance between O3-C5 (3.210 Å) is shorter than those of O2-C5 (3.510 Å) and O3-C20 (3.685 Å). Thus, the O3 oxygen has a higher chance for initial nucleophilic attack on the C5 carbon and subsequently there is only the one opportunity for the O1 oxygen to undergo nucleophilic addition at the C20 carbon to form the second furan ring. Another factor which leads to the higher yield of **4b** (45 %) is that when the O2 oxygen attacks the C5 carbon, there is also a preferred subsequent opportunity for the O3 oxygen, rather than O1, to attack the C20 carbon. Attack of the O1 oxygen at the C20 carbon leads to the lower yield obtained (24 %) of the symmetrical-1^5,3^5,5^5-tri-*tert*-butyl-1^2-hydroxy-1-(1,3)-benzena-3,5-(2,7)benzofurana-cyclohexaphane **4a**.

O-Methylation of **4b** with MeI in the presence of K_2CO_3 in acetone afforded the desired calixarene analogue, namely the inherently chiral metacyclophane 1^5,3^5,5^5-tri-*tert*-butyl-1^2-methoxy-1-(1,3)benzena-3,5-(2,7)benzofuranacyclohexaphane **5b**. Its ^{1}H NMR spectrum ($CDCl_3$, 300 MHz) revealed three singlet signals for the *tert*-butyl protons at δ 1.11, 1.31 and 1.34 ppm (relative intensity 1:1:l) and two singlets at δ 6.32 and 6.35 ppm for the furan ring. Compound **5b** forms an asymmetric hemispherical shaped *cone*-type conformation at room temperature, as revealed by the presence of two doublets at δ 3.95 (J = 14.1 Hz) and 4.75 (J = 13.5 Hz) ppm, each containing one proton and two double doublets for the remaining methylene protons, and the fact that all methylene protons are magnetically slightly inequivalent. The methoxy group is deshielded at δ 3.83 ppm, indicating that it is located outside (*exo*) of the ring. Inherent chirality is a unique feature associated with some MCPs and **5b** is expected to have a plane of chirality. This is because it has two different types of substituents and bridged linkages which are fixed in a C_1 symmetrical conformer and does not undergo a conformational change at or near ambient temperature.

Böhmer and co-workers[27] demonstrated the chirality of dissymmetric calix[4]arenes with C_2 and C_4 symmetry by interaction with Pirkle's reagent [(*S*)-(+)-1-(9-anthryl)-2,2,2-trifluoroethanol].

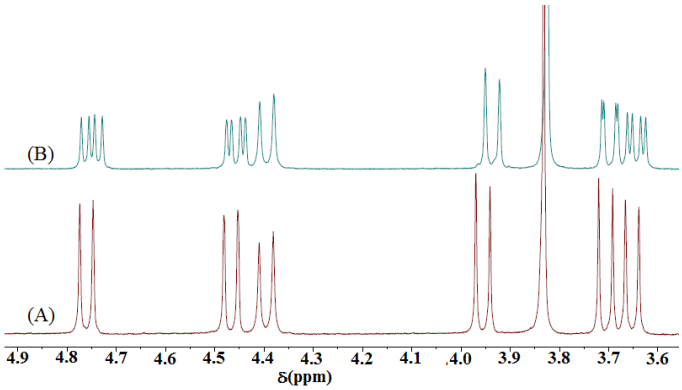


Fig. 3 Partial ^{1}H NMR spectra ($CDCl_3$; 500 MHz); (A) **5b**, (B) **5b** + Pirkle's reagent.

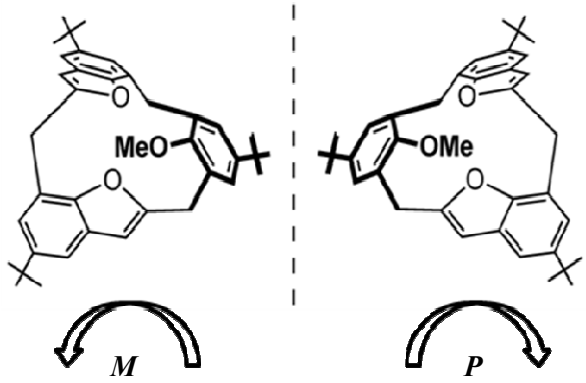


Fig. 4 Schematic diagram of *M*-**5b** (left) and *P*-**5b** (right).

The ^{1}H NMR spectra of compound **5b** in the absence and in the presence of Pirkle's reagent are shown in Fig. 3. Addition of Pirkle's reagent to the racemic mixture (*P*-enantiomer and *M*-enantiomer, Fig. 4) splits the signals in the ^{1}H NMR spectrum due to the formation of two diastereomeric complexes. Fortunately, **5b** afforded high quality crystals from a hexane-$CHCl_3$ 1:1 mixture. The single-crystal X-ray structure (CCDC 1049090) depicted in Fig. 5, revealed that the macrocyclic skeleton adopts a highly asymmetric hemisphere-shaped *cone*-type conformation. The crystal structure was found to belong to the monoclinic crystal system with space group C2/c (SI Table S1). From the single crystal analysis (Fig. 5), it is clear that the methoxy group is pointed upwards and is *exo* to the two benzofuran rings as was predicted from the ^{1}H NMR spectrum. As illustrated explicitly in Fig. 4, *P*-**5b** and *M*-**5b** are mirror images of each other and cannot be superimposed.

O-Methylation of **4a** with MeI in presence of K_2CO_3 in acetone resulted the inversion of the arene ring affording the non-symmetrical *partial-cone* methoxy[1.1.1]MCPs **5a**. This is

evident from the ^{1}H signals observed for the bridge methylene hydrogen atoms that are split and appear as five doublets at δ 3.07, 3.58, 3.88, 4.32 and 4.68 ppm for **5a**. The splitting pattern of methylene protons suggest that one of the benzofuran moiety is inverted to the other side of the macrocycle making the whole structure unsymmetrical in solution and this corresponds to the presence of three magnetically inequivalent CH_2 bridges. The methoxy group for compound **5a** is shifted to high field as a singlet at δ 1.97 ppm due to the methoxy group residing inside of the one benzofuran ring and experiencing shielding due to the ring current of the aromatic ring. Although three conformations are possible, these ^{1}H signals correspond to an unsymmetric *partial-cone* structure. The variable temperature NMR (VT-^{1}H NMR, 300 MHz) of **4b** (Fig. S35) and **5b** (Fig. S36) in 9:1 (v/v) CD_3CN:CD_2Cl_2 was studied by changing the temperature from 298 to 358 K and revealed that these calixarene analogue metacyclophanes are rigid and do not undergo clear and unambiguous conformational changes under this temperature.

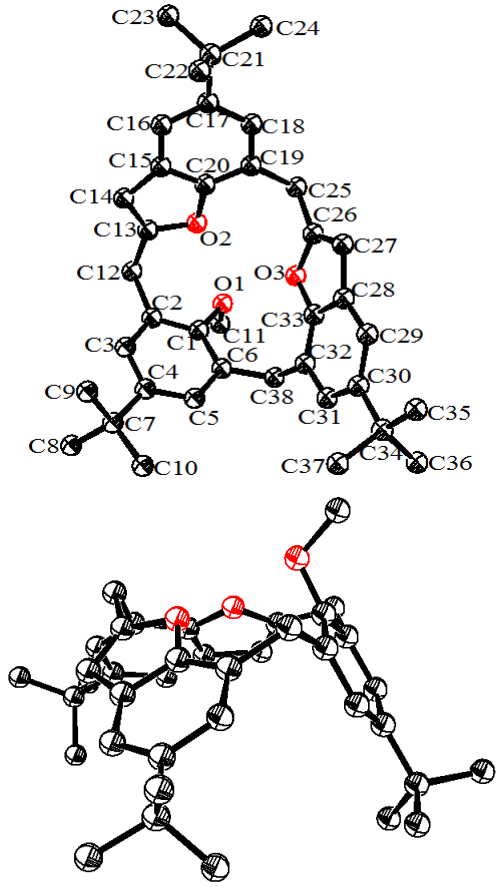


Fig. 5 Molecular structures of **5b** with top (top) and side (bottom) views. Thermal ellipsoids are drawn at the 50 % probability level. All hydrogen atoms are omitted for clarity.

Density functional theory (DFT) computational studies were carried out to determine the geometry-optimized energies of compounds **4a**–**b** and **5a**–**b**. The starting structures were generated with the initial geometries based upon the X-ray structures of **4a** and **5b** and from the presumed structures of **4b** (derived from **4a**) and **5a** using *SpartanPro'10* with the MMFF94 method.[30] The generated structures were then imported into *Gaussian-09*[31] and were geometry-optimized in the gas-phase with either the B3LYP or ωB97xD with 6-31G(d) basis set. The calculated energies (kJ mole^{-1}) for **4a**, **4b**, **5a** and **5b** are shown in Table 1. Compounds **4b** and **5b** were energetically more-favoured (in the gas-phase) by 3.792 or 3.083 and 89.974 or 74.718 kJ mole^{-1} respectively, than the corresponding structures of **4a** and **5a**, using B3LYP/6-31G(d) or ωB97xD/6-31G(d) respectively (details in the supporting information). As can be seen in Fig. 6(4a), for compound **4a** the O1---H3 distance is 2.026 Å, which is shorter than that for the O2---H3 (2.460 Å) distance and is very close to the distance (2.182 Å) calculated from the single crystal X-ray analysis.

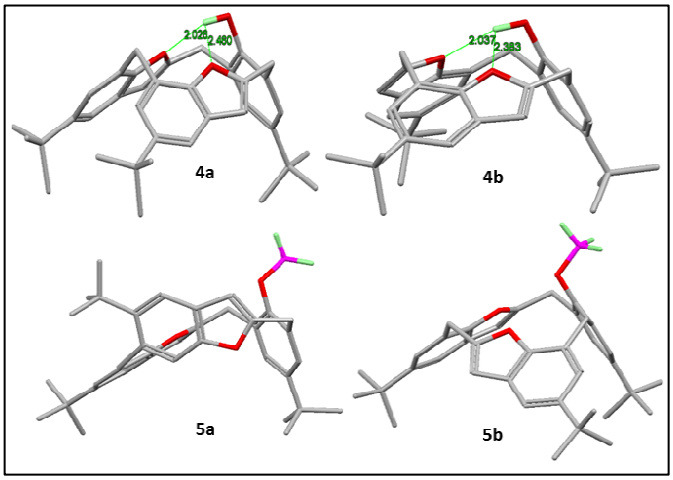


Fig. 6 Geometry-optimized (ωB97xD/6-31G(d)) structures of **4a–b** and **5a–b** (Ellipsoid). Colour code: carbon = dark grey; oxygen atom = red, methoxy carbon = magenta. All hydrogens except methoxy hydrogens and phenolic hydrogens (light green) are omitted for clarity.

Table 1 DFT geometry-optimized energies of the synthesized MCPs.

	ΔE(kJ mol^{-1})^a	ΔE(kJ mol^{-1})^b
4a	$\Delta E_{(4b\text{-}4a)}$ = –3.792	$\Delta E_{(4b\text{-}4a)}$ = –3.083
4b		
5a(*exo*)	$\Delta E_{(5b\text{-}5a)}$ = –89.974	$\Delta E_{(5b\text{-}5a)}$ = –74.718
5b(*exo*)		
5a(*endo*)	$\Delta E_{(5a exo\text{-}5a endo)}$= –14.897	$\Delta E_{(5a exo\text{-}5a endo)}$= –4.650
5b(*endo*)	$\Delta E_{(5b exo\text{-}5b endo)}$= –14.685	$\Delta E_{(5b exo\text{-}5b endo)}$= –7.951

Notes: a: Based on DFT using the B3LYP/6-31G(d) basis set-up; b: Based on DFT using the ωB97xD/6-31G(d) basis set-up.

Both the single crystal and DFT-optimized structures of **5b** indicate that it adopts a hemisphere-shaped *cone* conformation and that the methoxy group is pointed above and *exo* to the benzofuran rings (Fig. 5 and Fig. 6).

Conclusion

In summary, we have developed an efficient and straightforward strategy for the construction of inherently chiral methylene-bridged calixarene analogues, namely metacyclophanes (MCPs) containing benzofuran rings. The

benzofuran rings are formed by the simple intramolecular nucleophilic cyclization reaction of [3.3.1]metacyclophane-2,11-dione with TMSI. ^{1}H NMR spectroscopy and X-ray analysis of **5b** confirmed that it adopted a hemisphere-shaped *cone*-type conformation both in solution and in the solid state. The results from DFT computations were consistent with the observed experimental results. We believe that the presently developed novel inherently chiral [1.1.1]metacyclophane will find practical applications as an enantioselective artificial receptor and such studies are now in progress in our laboratory.

Experimental

General

All melting points (Yanagimoto MP-S1) are uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) and ^{13}C NMR spectra were recorded on a Nippon Denshi JEOL FT-300 NMR spectrometer and Varian-400MR-vnmrs400 spectrometer. Chemical shifts are reported as δ values (ppm) relative to internal Me_4Si. Mass spectra were obtained on a Nippon Denshi JMS–01SA–2 mass spectrometer at ionization energy of 70 eV; *m/z* values reported include the parent ion peak. Infrared (IR) spectra were obtained on a Nippon Denshi JIR-AQ2OM spectrophotometer as KBr disks. Elemental analyses were performed by Yanaco MT-5. G.L.C. analyses were performed by Shimadzu gas chromatograph, GC-14A; Silicone OV–1, 2 m; programmed temperature rise, 12 °C min^{-1}; carrier gas nitrogen, 25 mL min^{-1}. Silica gel columns were prepared by use of Merk silica gel 60 (63–200 μm).

Materials

6,15,22-Tri-*tert*-butyl-9,18,25-trimethoxy[3.3.1]metacyclophane-2,11-dione **3** was prepared by the reaction of 2,6-bis(bromomethyl)-4-*tert*-butylanisole TosMIC adduct **1** with 1,1-bis(5-*tert*-butyl-2-methoxyphenyl)-methane **2** according to a reported procedure. [20d,28,29]

Stepwise cyclization of TosMIC adduct 1 and dibromide 2. To a suspension of NaH (0.508 g, 21.6 mmol) in DMF (75 mL) a solution of **1** (2.0 g, 3.40 mmol) and **2** (1.79 g, 3.40 mmol) in DMF (15 mL) was added dropwise over a period of 6 h. After the suspension was stirred for an additional 5 h at room temperature, it was quenched with ice-water (300 mL). The reaction mixture was extracted with CH_2Cl_2 (3 × 100 mL, washed with water (100 mL), dried over $MgSO_4$, and concentrated *in vacuo* to 15 mL. Concentrated HCl (6 mL) was added to the solution which was then stirred for 15 min. The organic layer was again extracted with CH_2Cl_2 (3 × 100 mL), washed with water (2 × 100 mL), dried over $MgSO_4$, and concentrated and condensed under reduced pressure. The residue was chromatographed on silica gel using $CHCl_3$ as eluent to give crude **3** as a pale yellow solid. Recrystallization from benzene afforded 6,15,22-tri-*tert*-butyl-9,18,25-trimethoxy[3.3.1]metacyclophane-2,11-dione **3** (0.95 g, 45 %) as pale yellow prisms. M.p. 195–196 °C. IR: ν_{max} (KBr)/cm^{-1}: 1700 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (18H, s, *t*Bu × 2), 1.32 (9H, s, *t*Bu), 2.05 (3H, s, O*Me*), 3.25 (2H, d, *J* = 14.1, *CH*$_2$), 3.32 (1H, d, *J* = 12.6 Hz, *CH*$_2$), 3.42 (2H, d, *J* = 15.9 Hz), 3.51 (6H, s, O*Me*), 3.64 (2H, d, *J* = 15.9 Hz, *CH*$_2$), 4.02 (2H, d, *J* = 14.1 Hz, *CH*$_2$), 4.27 (1H, d, *J* = 12.6, *CH*$_2$), 7.05 (2H, d, *J* = 2.4 Hz, Ar–*H*), 7.20 (2H, s, Ar–*H*) and 7.22 (2H, d, *J* = 2.7 Hz, Ar–*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.45, 31.33, 31.41, 31.45, 31.52, 37.40, 41.99, 58.81, 60.75, 126.08, 126.37, 126.79, 127.01, 127.02, 134.13, 145.95, 146.52, 154.02, 154.61 and 207.54. FABMS: *m/z*: 612.43 [M$^+$]. $C_{40}H_{52}O_5$ (612.86): calcd C 78.39, H 8.55; found: C 78.65, H 8.67.

Demethylation of 3 with TMSI

To a solution of **3** (368 mg, 0.6 mmol) in CH_3CN (20 mL), NaI (1.8 g, 12.0 mmol) was added. After adding trimethylsilyl chloride (1.6 mL, 12.0 mmol), the mixture was stirred at 80–85 °C for 48 h. The reaction mixture was quenched with 40 mL ice water and aqueous 10 % sodium thiosulphate solution (80 mL) was added and stirred 1 h at room temperature. Then the mixture was stirred with aqueous 10 % HCl (40 mL) for 1 h and extracted with CH_2Cl_2 (3 × 80 mL). The combined extracts were washed with aqueous 10 % $NaHCO_3$ (40 mL), water (40 mL × 2) and dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel using hexane-CH_2Cl_2 (8:2) as eluents to give crude symmetrical 1^5,3^5,5^5-tri-*tert*-butyl-1^2-hydroxy-1-(1,3)-benzena-3,5-(2,7)benzofuranacyclo-hexaphane **4a** and hexane-CH_2Cl_2 (1:1) as eluents to give unsymmetrical 1^5,3^5,5^5-tri-*tert*-butyl-1^2-hydroxy-1-(1,3)-benzena-3,5-(2,7)benzofuranacyclo-hexaphane **4b**.

Symmetrical 1^5,3^5,5^5-tri-*tert*-butyl-1^2-hydroxy-1-(1,3)-benzena-3,5(2,7) benzofuranacyclohexaphane 4a

Recrystallisation from hexane afforded symmetrical 1^5,3^5,5^5-tri-*tert*-butyl-1^2-hydroxy-1-(1,3)-benzena-3,5(2,7)benzofuranacyclo-hexaphane **4a** (96 mg, 24 %) as colourless prisms. M.p. 300–301 °C. IR: ν_{max} (KBr)/cm^{-1}: 3543 (OH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.18 (9H, s, *t*Bu), 1.30 (18H, s, *t*Bu × 2), 3.63 (2H, d, *J* = 14.0, *CH*$_2$), 3.93 (1H, d, *J* = 13.2 Hz, *CH*$_2$), 4.66 (2H, d, *J* = 14.0 Hz, *CH*$_2$), 4.86 (1H, d, *J* = 13.2 Hz, *CH*$_2$), 6.36 (2H, s, Ar–*H*), 6.55 (1H, s, O*H*, Exchanged by D_2O), 6.97 (2H, s, Ar–*H*),7.24 (2H, d, *J* = 1.6 Hz, Ar–*H*) and 7.39 (2H, s, Ar–*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.02, 31.26, 31.41, 31.84, 34.12, 34.59, 102.14, 114.85, 122.09, 122.82, 125.34, 128.08, 129.84, 145.73, 146.04, 150.46, 150.79 and 158.92 ppm. FABMS: *m/z*: 534.34 [M$^+$]. $C_{37}H_{42}O_3$ (534.73): calcd C 83.11, H 7.92; found: C 82.95, H 7.81.

Unsymmetrical 1^5,3^5,5^5-tri-*tert*-butyl-1^2-hydroxy-1-(1,3)benzena-3,5-(2,7)-benzofuranacyclohexaphane 4b

Recrystallisation from hexane afforded unsymmetrical 1^5,3^5,5^5-tri-*tert*-butyl-1^2-hydroxy-1-(1,3)-benzena-3,5-(2,7)benzofuranacyclo-hexaphane **4b** (181 mg, 45 %) as colourless prisms. M.p. 279–280 °C. IR: ν_{max} (KBr)/cm^{-1}: 3651 (OH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.13 (9H, s, *t*Bu), 1.31 (9H, s, *t*Bu), 1.32 (9H, s, *t*Bu), 3.63 (2H,d, *J* = 13.8, *CH*$_2$), 4.02 (1H, d, *J* = 14.7 Hz, *CH*$_2$), 4.51 (1H, d, *J* = 14.4 Hz,*CH*$_2$), 4.66 (1H, d, *J* = 13.8 Hz, *CH*$_2$), 4.97 (1H, d, *J* = 13.2 Hz, *CH*$_2$), 6.36 (1H, s, Ar–*H*),6.39 (1H, s, Ar–*H*), 6.55 (1H, s, O*H*, Exchanged by D_2O), 6.91 (1H, d, *J* = 2.1 Hz, Ar–*H*), 7.03 (1H, d, *J* = 2.4 Hz, Ar–*H*), 7.12 (1H, d, *J* = 1.8 Hz, Ar–*H*), 7.21 (2H, d, *J* = 0.9 Hz, Ar–*H*) and 7.31 (1H, d, *J* = 1.8 Hz, Ar–*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.27, 31.35, 31.50, 31.82, 31.88, 32.40, 34.05, 34.56, 34.67, 101.69, 103.85, 114.67, 115.90, 120.52, 121.44, 122.09, 122.21, 124.63, 125.20, 125.35, 128.24, 128.84, 129.68, 131.53, 145.52, 146.22, 146.28, 148.79, 156.31 and 159.07 ppm. FABMS: *m/z*: 534.33 [M$^+$]. $C_{37}H_{42}O_3$ (534.73): calcd C 83.11, H 7.92; found: C 82.80, H 7.91.

1^5,3^5,5^5-Tri-*tert*-butyl-1,3-di-(2,7)dihydrobenzofurana-5-(2,7)-benzo-furanacyclohexaphane 4c

Recrystallisation from hexane afforded 1^5,3^5,5^5-tri-*tert*-butyl-1,3-di-(2,7)dihydrobenzofurana-5-(2,7)benzofuranacyclohexaphane **4c** (20 mg, 5 %) as colourless prisms. M.p. 251–252 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22 (9H, s, *t*Bu), 1.28 (9H, s, *t*Bu),1.36 (9H, s, *t*Bu), 3.38–3.50 (4H,m, *CH*$_2$C*CH*$_2$), 3.59 (1H,d, *J* = 15.3, *CH*$_2$), 3.66 (1H, d, *J* = 15.0 Hz, *CH*$_2$), 4.21 (1H, d, *J* = 15.3 Hz,*CH*$_2$), 4.39 (1H, d, *J* = 13.5 Hz, *CH*$_2$), 6.33 (1H, s, Ar–*H*),6.99 (2H, s, Ar–*H*),7.15 (2H, d, *J* = 6.3 Hz, Ar–*H*) and 7.30 (2H, s, Ar–*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.93, 31.57, 31.70, 31.78, 31.93, 34.33, 34.42, 34.57, 37.71, 37.81, 101.46, 114.58, 118.80, 119.86, 120.68, 120.88, 121.20, 121.69, 124.26, 125.14, 125.59, 125.90, 126.58, 128.51, 139.31, 144.31, 144.52, 145.23, 154.63, 156.04 and 156.56 ppm. FABMS:

m/z: 534.34 [M^+]. $C_{37}H_{42}O_3$ (534.73): calcd C 83.11, H 7.92; found: C 82.94, H 7.75.

O-Methylation of 4b with MeI in the presence of K_2CO_3

A mixture of **4b** (100 mg, 0.18 mmol) and potassium carbonate (260 mg, 1.80 mmol) in dry acetone (12 mL) was heated at reflux for 1 h under N_2. Then MeI (0.12 mL, 1.8 mmol) was added and the mixture heated at reflux for 12 h. After cooling of the reaction mixture to room temperature, it was quenched with water, and extracted with CH_2Cl_2 (20 mL× 2). The combined extracts were washed with water (10 mL × 2), dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The residue was chromatographed on silica gel (Wako, C-300; 100 g) by using $CHCl_3$ as eluent to give crude **5b** (78 mg, 79 %) as a colourless solid. Recrystallization from hexane gave unsymmetrical 1^5,3^5,5^5-tri-*tert*-butyl-1^2-methoxy-1-(1,3)-benzena-3,5-(2,7)benzofurana-cyclohexaphane **5b** as colourless prisms. M.p. 247–248 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.11 (9H, s, *t*Bu), 1.31 (9H, s, *t*Bu), 1.34 (9H, s, *t*Bu), 3.67 (2H, dd, *J* = 13.5, 14.4 Hz, CH_2), 3.83 (3H, s, OCH_3), 3.95 (1H, d, *J* = 14.1 Hz, CH_2), 4.43 (2H, dd, *J* = 14.1, 14.4 Hz, CH_2), 4.75 (1H, d, *J* = 13.5 Hz, CH_2), 6.32 (1H, s, Ar–*H*), 6.35 (1H, s, Ar–*H*), 6.91 (1H, d, *J* = 2.4 Hz, Ar–*H*), 6.97 (1H, d, *J* = 2.4 Hz, Ar–*H*), 7.06 (1H, d, *J* = 1.8 Hz, Ar–*H*), 7.18 (1H, d, *J* = 1.8 Hz, Ar–*H*), 7.20 (1H, d, *J* = 1.5 Hz, Ar–*H*) and 7.29 (1H, d, *J* = 1.8 Hz, Ar–*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ= 30.83, 31.28, 31.36, 31.63, 31.89, 31.93, 34.04, 34.51, 34.60, 62.16, 101.08, 102.93, 114.41, 115.46, 120.74, 121.12, 121.47, 124.86, 125.39, 126.60, 128.56, 128.87, 129.74, 131.94, 145.19, 145.37, 146.00, 151.27, 151.58, 156.39, 157.01 and 158.38 ppm. FABMS: *m/z*: 548.37 [M^+]. $C_{38}H_{44}O_3$ (548.33): calcd C 83.17, H 8.08; found: C 82.93, H 8.15.

Symmetrical 1^5,3^5,5^5-tri-*tert*-butyl-1^2-methoxy-1-(1,3)-benzena-3,5-(2,7) benzofuranacyclohexaphane 5a

Symmetrical1^5,3^5,5^5-tri-*tert*-butyl-1^2-methoxy-1(1,3)benzena-3,5(2,7)benzofuranacyclohexaphane **5a** was prepared in a similar manner to that used for **5b**. Recrystallisation from hexane afforded symmetrical1^5,3^5,5^5-tri-*tert*-butyl-1^2-methoxy-1-(1,3)-benzena-3,5-(2,7)benzofuranacyclohexaphane **5a** (72 mg, 75 %) as colourless prisms. M.p. 271–272 °C.^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.04 (9H, s, *t*Bu), 1.24 (18H, s, *t*Bu × 2), 1.97 (3H, s, OCH_3), 3.07 (1H, d, *J* = 10.8, CH_2), 3.58 (1H, d, *J* = 13.5 Hz, CH_2), 3.88 (2H, d, *J* = 13.8 Hz, CH_2), 4.32 (1H, d, *J* = 14.4,CH_2), 4.68 (1H, d, *J* = 13.5,CH_2), 6.25 (2H, s, Ar–*H*), 6.99 (2H, s, Ar–*H*), 7.12 (2H, d, *J* = 6.9 Hz, Ar–*H*) and 7.22 (2H, s, Ar–*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.58, 29.91, 31.42, 31.58, 31.76, 33.93, 34.14, 58.24, 101.47, 114.25, 124.30, 125.20, 126.80, 127.57, 128.14, 136.34, 143.14, 149.14, 154.16 and 158.38 ppm. FABMS: *m/z*: 548.37 [M^+]. $C_{38}H_{44}O_3$ (548.33): calcd C 83.17, H 8.08; found: C 82.92, H 8.08.

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