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Synthesis and conformational studies of novel 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 bridge, which can be viewed as calixarene analogs, have been synthesized by demethylation of [3.3.1]MCP-diones with trimethylsilyl iodide (TMSI) in MeCN. [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 one hydroxyl group forms intramolecular hydrogen bonding with the oxygen of a benzofuran ring. 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 analog, 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 [(S)-(+)-1-(9-anthryl)-2,2,2-trifluoroethanol], which caused a splitting of the corresponding methylene protons to AB patterns. Single crystal analysis revealed the adoption of a hemisphere-shaped cone isomer. DFT calculations were carried out to investigate the energy minimized structure and hydrogen bonds of the synthesized MCPs.

Introduction

The design and synthesis of novel and 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 enantio-selective artificial receptors and asymmetric catalysts.[3] Two principal approaches have been used for the preparation of chiral calixarenes. The first one is synthesis of inherently chiral calixarenes,[4] whilst the second approach is via attachment of chiral moieties at the upper or lower rim of a calixarene macrocycle.[5] Since the first unintentional preparation of inherently chiral calixarenes was reported by Kwang and Gutsche,[6] inherently chiral calixarenes have continued to attract attention.[7] Given their peculiar structures and unique conformational properties, inherently chiral calixarenes have become topical macrocyclic molecules.[8]

The concept of "inherently chirality" was first suggested by Böhmer, whose chirality was based on the absence of planar symmetry or an inversion centre in molecules bearing an asymmetric array of several achiral groups appended to their three-dimensional skeletons.[9] This concept was soon accepted by researchers and further developed by Mandolini and Schiaffino.[10] 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. The synthesis and optical resolution of inherently chiral calixarenes are challenging yet attractive, because of their potential uses in supramolecular chemistry.[11] In this aspect, the design and synthesis of inherently chiral calixarenes with novel structures and superior functions are a topic of great importance. Inherently chiral calixarenes are receiving increasing attention due to their intriguing structures and potential applications in chemical, analytical, biological and material fields.[12]

Most recently, Szumna 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 concave molecules consisting of repeating chiral subunits such as cyclodextrins as 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. Therefore, the development of effective methods for the synthesis of enantiomerically pure inherently chiral calixarenes and the determination of their absolute configuration is of great importance.

It is surprising that reports on the preparation of calixarenes and their analogs containing three arene rings and the characterization of their hydrogen bonding has been very limited.[19] Our group has reported various types of meta cyclophanes[20] and oxahomocalixarenes[21] containing three benzene rings.

We report herein a short and easy route for the synthesis of inherently chiral macrocyclic[1.1.1]MCPs containing both benzene and benzofuran rings in good yield.
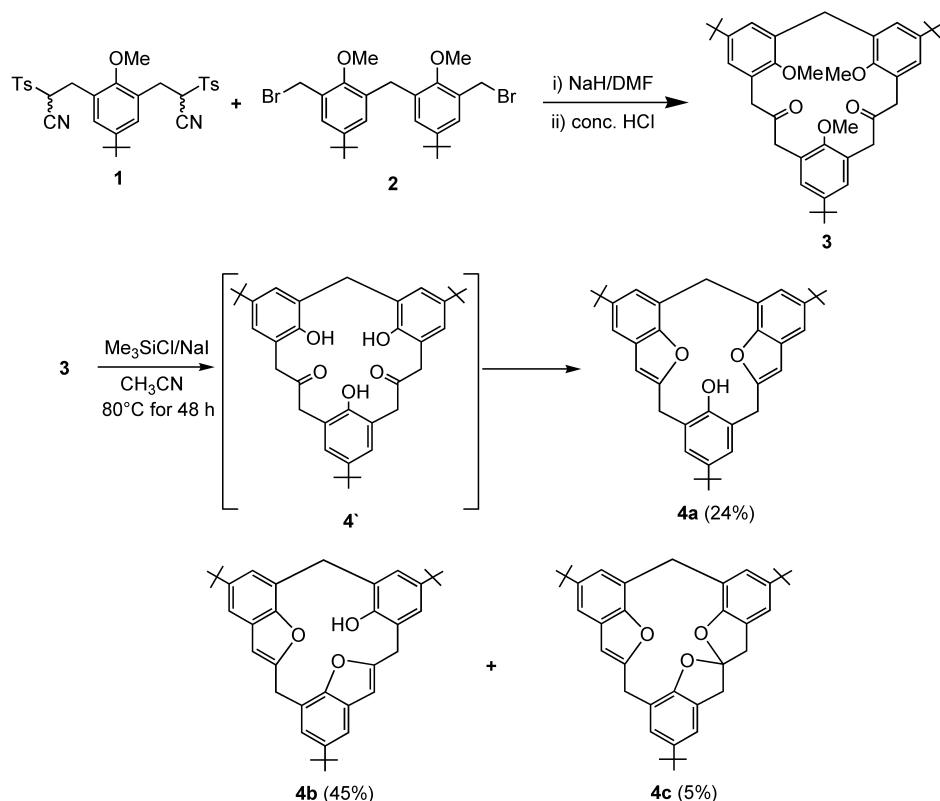
Scheme 1 Demethylation of 6,15,22-tri-*tert*-butyl-9,18,25-trimethoxy[3.3.1]MCP-2,11-dione **3**.

Results and Discussion

As part of our continued interest in the synthesis of novel structures of the inherently chiral calixarenes analogs MCP, we undertook a systematic investigation of [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 phase-transfer conditions.[24]

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$_3$CN 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 lead to hemisphere-shaped calixarene analogs containing a dihydrobenzofuran ring.[25] The structures of **4** (symmetrical or unsymmetrical) were determined by spectroscopic methods (^{1}H NMR and ^{13}C NMR), Mass and elemental analyses. The crude ^{1}H NMR spectrum after reaction with TMSI exhibited two kinds of signal, namely singlets for the hydroxyl groups (exchanged by D$_2$O) and furan moieties. By careful column chromatography, using hexane-CH$_2$Cl$_2$ (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, whilst

hexane-CH$_2$Cl$_2$ (1:1) as eluent gave unsymmetrical-1^5,3^5,5^5-tri-*tert*-butyl-1^2-hydroxy-1(1,3)-benzena-3,5-(2,7)benzofuranacyclohexaphane **4b** (45 %) as the major product. The structures of **4a** and **4b** have been elucidated on the basis of their spectroscopic data. The calixarenes show concentration independent hydroxyl stretching bands in the 3200 cm^{-1} region of the infrared spectrum and a signal at δ 6–7 ppm in the ^{1}H NMR spectrum, indicative of very strong intramolecular hydrogen bonding characteristic of the cyclic nature of calixarenes.[2,26] The ^{1}H NMR spectrum (CDCl$_3$, 300 MHz) of **4a** exhibits the signal for the hydroxyl groups at δ 6.54 ppm (exchanged by D$_2$O). Such data is consistent with the existence of intramolecular hydrogen bonding between the hydroxyl group and the oxygen of the benzofuran ring. The ^{1}H NMR spectrum of macrocycle **4a** exhibits two sets of doublets at δ 3.93 and 4.86 ppm (*J* = 13.3 Hz) for the Ar*CH$_2$*Ar methy-lene protons. These patterns correspond to the "cone" conformer given the two methylene protons Ar*CH$_2$*Ar are in different environments. The remaining two bridge methylene protons appeared as a doublet at δ 3.63 (*J* = 13.8 Hz) and 4.66 ppm (*J* = 13.5 Hz). The structure of **4a** 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 one hydroxyl group present between the two benzofuran rings forms an intramolecular hydrogen bond with the oxygen of the benzofuran ring 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 less than that between H3 (OH) and O2 at 2.523 Å. A concentration variable ^{1}H NMR study of **4a** (CDCl$_3$, 400 MHz) from 0.5 mM to 30 mM at 25 ℃ shows that the hydroxyl proton
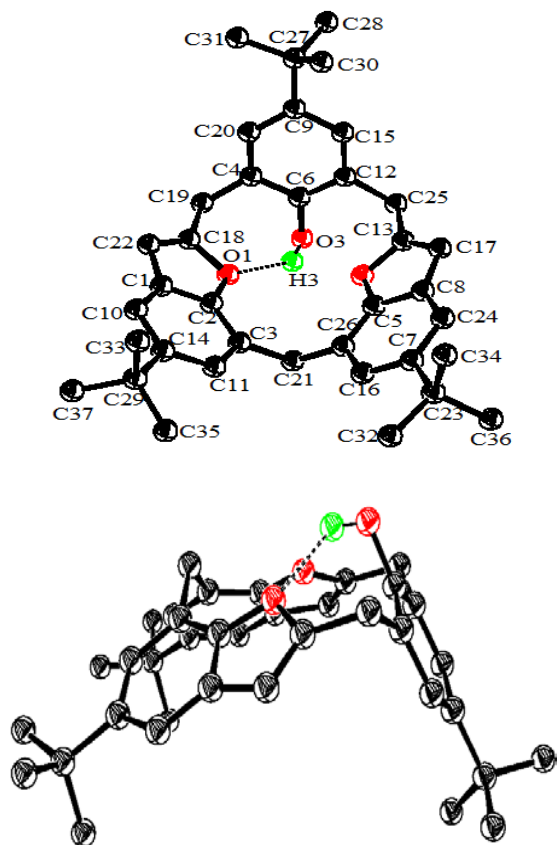

Fig. 1 Ortep drawing of **4a** with top (top) and side (bottom) views. Thermal ellipsoids are drawn at the 50% probability level. All hydrogen atoms except one are omitted for clarity.

peak is concentration independent and always exhibits a peak at δ 6.50 ppm (SI, Fig. S23). On increasing the concentration of **4a** from 0.5 mM to 30 mM only the hydroxyl proton peak intensifies, which is evidence for the intramolecular hydrogen bonding. We also studied the intramolecular hydrogen bonding of **4a** and **4b** in different polar solvents. The ^{1}H NMR spectrum of **4a** (400 MHz) in a mixture of CD$_3$OD and CDCl$_3$ (9:1) led to a shift for the hydroxyl peak at δ 7.66 ppm, indicating that the intramolecular hydrogen bonding is disrupted in polar solvents (SI, Fig. S25). The ^{1}H NMR (CDCl$_3$, 300 MHz) spectrum of macrocycle **4b** possessed three single peaks for the *tert*-butyl protons at δ 1.13, 1.31 and1.32 ppm (relative intensity 1:1:l) and two single peaks for the furan ring at δ 6.36 and 6.39 ppm.

The macrocycle **4b** is fixed in the form of a symmetrical hemisphere-shaped cone conformation at room temperature as observed by the four sets of doublets for the methylene protons at δ 4.02 (J = 14.7 Hz), 4.51 (J = 14.7 Hz), 4.66 (J = 13.2 Hz) and 4.97 (J = 13.2 Hz) ppm. The ^{1}H NMR spectrum (CDCl$_3$, 300 MHz) exhibits a signal for the hydroxyl group at δ 6.55 ppm (exchanged by D$_2$O), indicative of a similar

intramolecular hydrogen bonding between hydroxyl group with oxygen of benzofuran ring. The IR (KBr) spectrum of **4b** shows the absorption for the hydroxyl stretching vibration around 3651 cm^{-1} due to hydrogen bonding. The concentration variable ^{1}H NMR study of **4b** (CDCl$_3$, 400 MHz) from 0.5 mM to 30 mM at 25 ℃ shows that hydroxyl proton peak is concentration independent and always gives peak at δ 6.55 ppm (SI, Fig. S24)
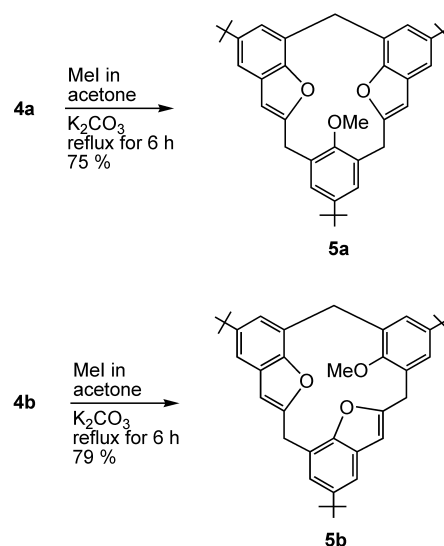
**Scheme 2** *O*-Methylation of hydroxy[1.1.1]MCPs **4** with MeI in the presence of K$_2$CO$_3$.

result to that of **4a**. In the slightly more polar solvent CD$_3$COCD$_3$ (*versus* CDCl$_3$), the hydroxyl peak shifted to 6.86 ppm. The ^{1}H NMR spectrum of **4b** (400 MHz) in a mixture of CD$_3$OD-CDCl$_3$(9:1) led to a shift of the hydroxyl peak at δ 7.68 ppm, indicating that the intramolecular hydrogen bonding is disrupted in the polar solvent (SI, Fig. S26). Along with **4a** and **4b**, we succeeded in isolating another compound **4c** from the hexane eluent of the column chromatography. The structure was somewhat peculiar, containing one furan ring and two dihydrofuran moieties in the cyclophane frame. The presence of the cyclophane structure was evident from the ^{1}H NMR signals observed for the bridge methylene hydrogen atoms that appeared as two pairs of doublets at δ 4.21 and 4.39 ppm. The ^{1}H NMR spectrum of macrocycle **4c** showed three single peaks for the *tert*-butyl protons at δ 1.22, 1.28 and 1.36 ppm (relative intensity 1:1:1). It is difficult to say how the two dihydrofuran moieties were formed, and we tentatively propose that two phenolic oxygens compete at once for nucleophilic attack at the same carbon thereby leading to the formation of the dihydrofuran moieties.
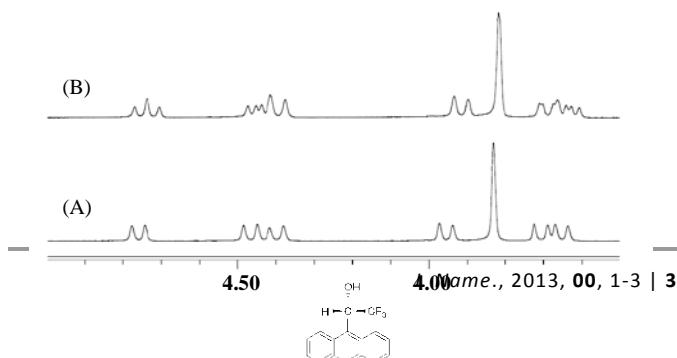
Fig. 2 Partial ^{1}H NMR spectra (CDCl$_3$; 400 MHz); (A) **5b**, (B) **5b** + Perkle's reagent.
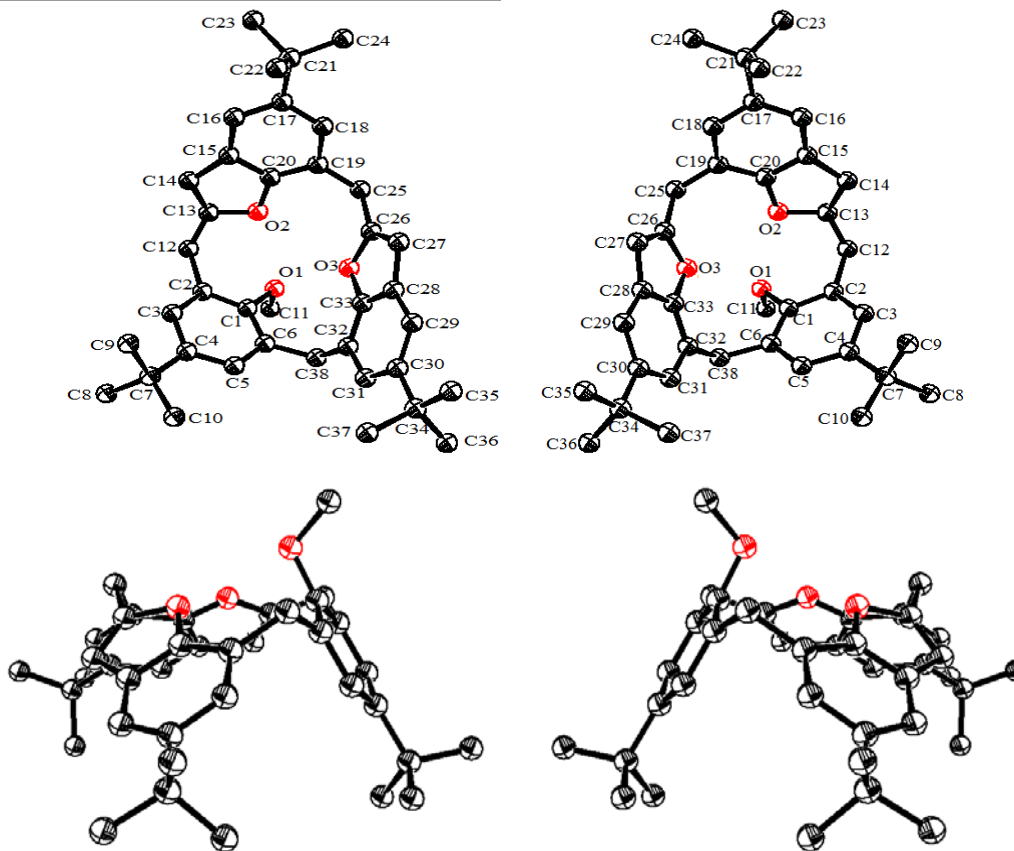

Fig. 3 Molecular structures of the *P*-enantiomer (left) and *M*-enantiomer (right) of **5b** with top (top) and side (bottom) views. Thermal ellipsoids are drawn at the 50 % probability level. All hydrogen atoms are omitted for clarity.

Although we failed to isolate the intermediate **4'**, from examination of the crystal structure of the parent compound **3** (SI, Fig. S27), it is evident that the distance between O3-C5 (3.210 Å) is less than that of O2-C5 (3.510 Å) and O3-C20 (3.685 Å). Thus, the O3 oxygen has a high chance for nucleophilic attack at C5 carbon and after that there is only the one opportunity for the oxygen O1 to attack at the C20 carbon to form the cyclic furan ring. Another factor which leads to the high yield of **4b** is that if O2 oxygen attacks at C5 carbon, then there is also one prior opportunity for the O3 oxygen to attack at the C20 carbon than the O1 oxygen. If O1 oxygen attack occurs at C20 carbon then it would lead to a low yield of the symmetrical-1^5,3^5,5^5-tri-*tert*-butyl-1^2-hydroxy-1-(1,3)-benzena-3,5-(2,7)benzofuranacyclohexaphane **4**a.

O-Methylation of **4b** by MeI in the presence of K$_2$CO$_3$ in acetone afforded the desired calixarene analog, 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**. The ^{1}H NMR spectrum (CDCl$_3$, 300 MHz) of macrocycle **5b** revealed three single peaks for the *tert*-butyl protons at δ 1.11, 1.31 and 1.34 ppm (relative intensity 1:1:l) and two singlet peaks at δ 6.32 and 6.35 ppm for the furan ring. Compound **5b** forms an asymmetric hemi-sphere shaped "cone" conformation at room temperature as by the observation of two sets of doublets for the methylene protons and the

methoxy group is pointed upward and deshielded at δ 3.83 ppm. Inherent chirality is a unique feature associated with MCP and macrocycle **5b** is expected to have a plane of chirality, because it has two types of substituents and bridged linkages which are fixed as 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]. The ^{1}H NMR spectrum of compound **5b** in the absence and the presence of Pirkle's reagent is shown in Fig. 3. Addition of Pirkle's reagent to the racemic mixture (*P*-enantiomer and *M*-enantiomer) splits the signals in the ^{1}H NMR spectrum due to the formation of two diastereomeric complexes.
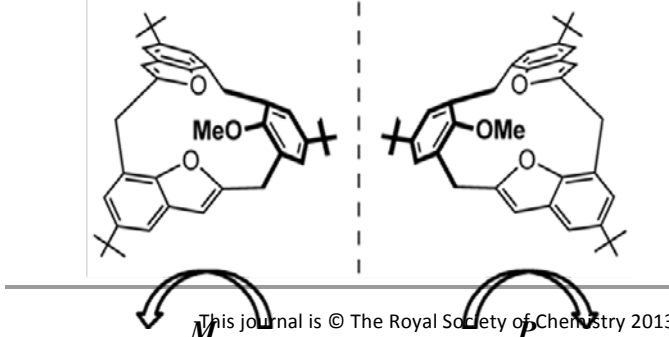
Fig. 4 Schematic diagram of *M*-**5b** (left) and *P*-**5b** (right).
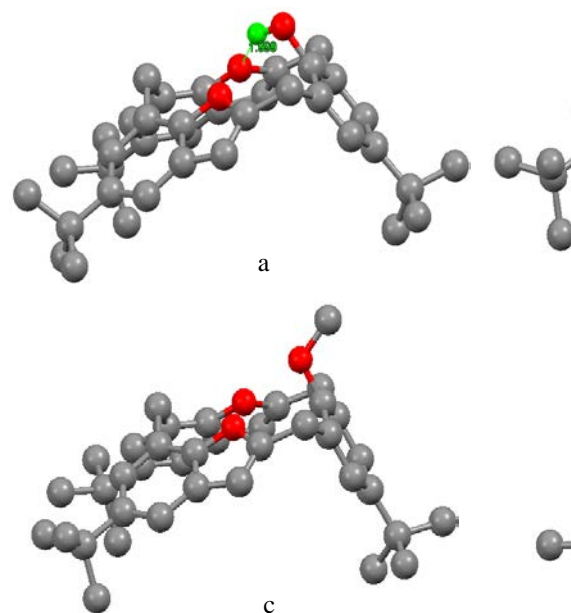
Fig. 5 DFT B3LYP/6-31+G(d) optimized molecular structure of (a) **4a**, (b) **4b**, (c) **5a** and (d) **5b**.

Fortunately, **5b** gave high quality single crystal (CCDC 1049090) from a hexane-CHCl$_3$ 1:1 mixture. The X-ray molecular structure, depicted in Fig. 4, revealed that the macrocyclic skeleton adopts a highly asymmetric hemisphere shaped "cone" 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. 4), it is clear that the methoxy group is pointed upwards and is outside of the two benzofuran rings as predicted from the ^{1}H NMR spectrum. As illustrated explicitly in Fig. 4, *P*-**5b** and *M*-**5b** are mirror images of one another, but they cannot be superimposed.

O-Methylation of **4a** with MeI in the presence of K$_2$CO$_3$ in acetone resulted in the inversion of the arene ring affording the 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 a pair of doublets at δ 3.07 and 3.58 ppm for **5a**. The ^{1}H NMR spectrum of macrocycle **5a** exhibited two singlet peaks for the *tert*-butyl protons at δ = 1.04 and 1.24 ppm (relative intensity 1:2). The methoxy group for compound **5a** shifted to high field as a single peak at δ 1.97 ppm due to the methoxy group residing inside of the two benzofuran rings and experiencing shielding due to the ring current. To better understand the geometry-optimized energy of compounds **4a**, **4b**, **5a** and **5b**, computational studies were carried out. The individual structures for all studies in the gas-phase were fully geometry-optimized using Gaussian 09 with the B3LYP level of density functional theory (DFT) calculations and the 6-31G(d) basis set.[30] The observed geometry-optimized energies (E kJ mole^{-1}) for compounds **4a**, **4b**, **5a** and **5b** are shown in Table 1. From the optimized geometrical molecular structure of compound **4a** (Fig. 5), it is seen that the distance between O1---H3 is 1.999 Å less than that

of O2---H3 which is almost equal to the distance calculated from the single crystal analysis [2.182 Å].

Although we failed to obtain single crystals of **4b**, the hydrogen bond distance was calculated from the DFT optimized structure (Fig. 5) and the distance is 2.018 Å, which is a reasonable distance for the intramolecular hydrogen bonding. The DFT B3LYP optimized structure of **5a** indicated that it adopted a hemi-sphere shaped cone conformation and that the methoxy group is position upwards.

Table 1 DFT B3LYP6-31G(d) optimized energies of the synthesized MCPs.

Compound	Geometry-optimized energy (kJ mole^{-1})
4a	-4360789.8962
4b	-4360792.5746
5a	-4463957.4525
5b	-4463947.4704

However in solution it forms a partial-cone conformation which is evident by the high field shift of the methoxy group at δ 1.97 ppm and methylene bridge pattern in the ^{1}H NMR spectrum (300 MHz, CDCl$_3$). 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 up, outside of the benzofuran rings (Fig. 3 and Fig. 5). DFT B3LYP optimized energies of the synthesized MCPs showed that **4a** and **4b** are more stable due to the presence of the intramolecular hydrogen bonding.

Conclusion

In summary, we have developed an efficient and straightforward strategy for the construction of inherently chiral methylene-bridged calixarene analogs, namely metacyclophanes containing benzofuran rings. The benzofuran rings are formed by a simple intramolecular nucleophilic cyclization reaction of [3.3.1]meta- cyclophane-2,11-dione with TMSI. The ^{1}H NMR spectroscopy and X-ray analysis of **5b** confirmed that it adopted a hemi-sphere shaped cone conformation both in solution and the solid state. We believe that the presently developed novel inherently chiral [1.1.1]metacyclophane will find practical applications as an enantioselective artificial receptor and in asymmetric synthesis; 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) spectra were recorded on a Nippon Denshi JEOL FT-300 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]

Demethylation of 3 withTMSI

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 10 % aqueous sodium thiosulphate solution (80 mL) was added and stirred 1 h at room temperature. Then the mixture was stirred with 10 % HCl (40 mL) for 1 h and extracted with CH_2Cl_2 (3 × 80 mL). The combined extracts were washed with 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)benzofuranacyclohexaphane **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)benzofuranacyclohexaphane **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)benzofuranacyclohexaphane **4a** (96 mg, 24 %) as colourless prisms. M.p. 300–301 °C. IR: v_{max} (KBr)/cm^{-1}: 3543 (OH). ^{1}H NMR (300 MHz, CDCl$_3$): δ= 1.18 (9H, s, *t*Bu), 1.30 (18H, s, *t*Bu × 2), 3.63 (2H,d, J = 13.8, CH_2), 3.93 (1H, d, J = 13.2 Hz, CH_2), 4.66 (2H, d, J = 13.5 Hz, CH_2), 4.86 (1H, d, J = 13.2 Hz, CH_2), 6.36 (2H, s, Ar–H), 6.54

(1H, s, OH, Exchanged by D$_2$O), 6.97 (2H, s, Ar–H),7.23 (2H, d, J = 2.1 Hz, Ar–H) and 7.39 (2H, d, J = 1.8 Hz, 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)benzofuranacyclohexaphane **4b** (181 mg, 45 %) as colourless prisms. M.p. 279–280 °C. IR: v_{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, OH, Exchanged by D$_2$O), 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.

$1^5,2^5,4^5$-tri-*tert*-butyl-1^2-1,2-di-(2,7)dihydrobenzofurana-4(2,7)benzo-furanacyclopentaphane 4c

Recrystallisation from hexane afforded $1^5,2^5,4^5$-tri-*tert*-butyl-1^2-1,2-di-(2,7)dihydrobenzofurana-4-(2,7)benzofuranacyclopentaphane **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_2CCH_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 6b with MeI in the presence of K$_2$CO$_3$

A mixture of **4b** (100 mg, 0.18 mmol) and potassium carbonate (258 mg, 1.8 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$_2$Cl$_2$ (20 mL× 2). The combined extracts were washed with water (10 mL × 2), dried over MgSO$_4$ and condensed under reduced pressure and the residue was chromatographed on silica gel (Wako, C-300; 100 g) by using CHCl$_3$ as eluent to give the 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.

Similarly, symmetrical1^5,3^5,5^5-tri-*tert*-butyl-1^2-methoxy-1(1,3)benzena-3,5(2,7)benzofuranacyclohexaphane **5a** was prepared.

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

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, O*CH$_3$*), 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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Notes and references

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