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Crystal Structure of *rac*-4-Iodo-5-methoxy[2.2]metacylophane; A Rare Example of a Halogenated Metacyclophane with Planar Chirality

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A racemic mixture of planar chiral 4-iodo-5-methoxy[2.2]metacylophane (**2**) was synthesized by the low-temperature directed *ortho* aryl metalation of 5-methoxy[2.2]metacyclophane (**1**) and subsequent *in situ* reaction with iodine. The crystal structure was determined by the single-crystal X-ray diffraction method at 100 K. The compound crystallized in an orthorhombic system and was characterized as: $Pca2_1$, a = 13.5690(2), b = 14.2212(2), c = 7.5004(1)Å, Z = 4, V = 1447.33(4)Å^3. The crystal structure was solved by direct methods and refined by full-matrix least-squares on F^2 to final values of $R1$ = 0.0281 and $wR2$ = 0.0733 for all 3021 independent reflections.

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The constrained three-dimensional structural framework of *ortho*, *meta* and *para*[2.2]cyclophanes has inspired their long-standing appeal to synthetic, structural and analytical chemists. Their unique physical and chemical properties are induced by the close spatial proximity of their aryl rings with the resulting strain causing a distortion from planarity of the aromatic rings.[1] These intermolecular distances can be considerably smaller than the 3.50 Å of normal stacked aromatic rings.[2] The most common synthetic route to [2.2]cyclophanes utilizes Wurtz coupling conditions, though this approach is restrictive since it lacks functional group tolerance. Additionally, the post-synthesis derivatization of [2.2]metacyclophanes is challenging as, for example, electrophile aromatic substitution reactions cause C-C bond formation between the aromatic rings due to their structurally constrained close proximity.[3] Specific aryl substitution patterns on [2.2]cyclophanes induce planar chirality with the potential for use as scaffolds for asymmetric catalysis.[4] Racemic mixtures of [2.2]metacyclophanes were first synthesised in the 1970's, but have received little research interest in contrast to their isomeric relatives, [2.2]paracyclophanes, which have been utilized as planar chiral scaffolds.[5] Studies have shown that the inversion barrier of [2.2]-metacyclophanes is sufficiently high to permit the resolution of conformationally stable enantiomers.[6] Following optical resolution, several crystal structures of planar chiral [2.2]-metacyclophanes have been reported.[6,7] In this work our goal lies in exploiting chiral iodo-[2.2]metacyclophanes, specifically derivative **2**, since recently chiral aryl iodides have shown considerable promise for asymmetric synthesis (Fig. 1).[8]

Direct substrate metalation with mixed metal bases is a powerful and versatile tool for synthetic chemistry.[9,10] These methods have provided new routes to make and post synthesis modify [2.2]metacyclophanes, thereby allowing an exploration of their substituent/structural relationships. The synthesis of **1** has been previously described in two steps, starting from *m*-xylene and 1-methoxy-3,5-dimethylbenzene.[11] Both steps utilized LiNK metalation conditions (BuLi, KOtBu, TMP(H)) for benzylic deprotonation with subsequent *in situ* oxidative C-C coupling. The transformation of **1** into 4-iodo-5-methoxy[2.2]metacylophane **2** was achieved by a modified protocol from our reported enantioselective route.[12] Briefly, a solution of 5-methoxy[2.2]metacylophane **1** (24 mg, 0.10 mmol) in dry THF (15 mL) at –78°C was treated dropwise with BuLi (2.50 M, 0.080 mL, 0.20 mmol) and stirred for 5 min. KO*t*Bu (1.0 M in THF, 0.20 mL, 0.20 mmol) was added dropwise, the reaction mixture was stirred for 1 h at –78°C and iodine (0.30 mmol) was added. The reaction mixture was allowed warm to room temperature for 2 h and the solvent was removed under reduced pressure. Ethyl acetate (10 mL) was added to the residue, washed with aqueous HCl (2 M, 2 × 10 mL), $Na_2S_2O_3$ (2 M, 2 × 10 mL), dried over sodium sulfate and concentrated to dryness. Purification by silica-gel chromatography eluting with 95:5 pentane:diethyl ether gave **2** as a colorless solid (23 mg, 63%), mp 58 - 60°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.27 (t, J = 6.9 Hz, 1H), 7.11 - 7.02 (m, 2H), 6.56 (d, J = 1.5 Hz, 1H), 4.38 (d, J = 1.8 Hz, 1H), 4.06 (d, J = 1.5 Hz, 1H), 3.93 (s, 3H), 3.59 (dt, J = 12.3, 3.4 Hz, 1H), 3.14 - 2.95 (m, 3H), 2.27 (td, J = 12.3, 3.3 Hz, 1H), 2.20 - 2.03 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.8, 143.0, 140.3, 138.9, 138.7, 136.0, 130.6, 129.0, 126.0, 125.5, 108.6, 87.5, 56.8, 46.0, 40.9, 40.8, 38.5. Enantiomer separation was achieved by analytical chiral HPLC (Chiralpak IA 250 × 4.6 mm i.d.; 254 nm UV detector; eluent 0.5% ethanol in heptane; flow rate

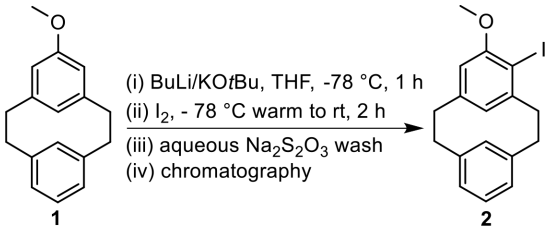

Fig. 1 Chemical structure of 4-iodo-5-methoxy[2.2]metacylophane (**2**), prepared by low-temperature *ortho*-metalation of [2.2]-metacyclophane (**1**) and an *in situ* treatment with iodine.

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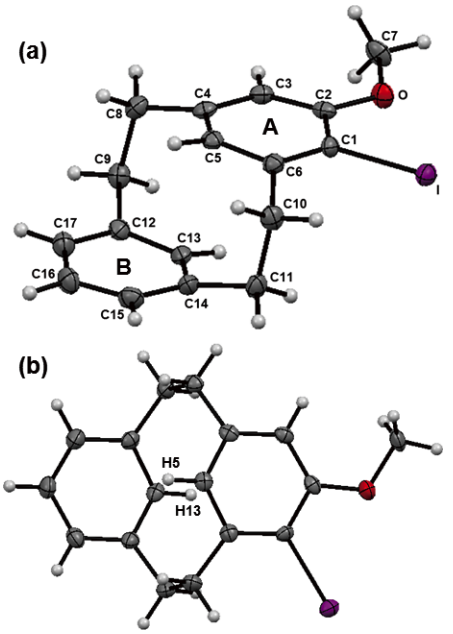

Fig. 2 ORTEP drawing of **2** showing the thermal ellipsoid at 50% probability with the atom numbering scheme.[13,14] (a) Side view showing chair-like conformation of the central ten-membered ring (b) top view structurally constrained aromatic rings with two equatorial internal aromatic proton (H5/H13) signals indicated.

0.8 mL/min) with retention times of 7.0 and 8.2 min.

X-ray quality single crystals grown by the slow room-temperature evaporation of a diethyl ether solution of **2**. X-ray diffraction data for the crystal were collected on an Agilent SuperNova Dual diffractometer with Cu *K*α radiation with the crystal information given in Table S1 and further details described in Supporting Information.

The crystal structure of racemic **2** belongs to the $Pca2_1$ space group with two enantiomers observed per unit cell. Thermal ellipsoid plots are shown in Fig. 2, illustrating the stepwise anti conformation typical of the [2.2]metacyclophane ring system. The out-of-plane bending of the aromatic rings into a boat conformation is a characteristic strained feature of metacyclophanes. This is clearly evidenced by a deviation from a planarity of 7.67(9) and 7.27(9)° for the A and B aromatic rings of **2**, respectively (Fig. 2a). The central ten-membered ring adopts a chair-like conformation, where the two aromatic rings sit in parallel planes, as confirmed by the high ^{1}H NMR shielding of the two internal aromatic proton signals of H5 and H13 at 4.38 and 4.06 ppm, respectively (Fig. 2b). The closest approach of the two benzene rings to one another is 2.632(2)Å, as measured from C5 to C13 (Table 2). The saturated bond length (1.568(6)Å) of the cavity bridging carbons, C8–C9, together with the bond angle C4–C8–C9 of 110.3(3)° further confirm the shortness of the bridge and its effect on the ring strain and conformational rigidity of the molecular framework. The strain induced on the aromatic rings is evident by a divergence in aromatic bond lengths and angles within the A and B rings (Fig. 2). Representative examples include C4–C5 (1.406(6)Å)/C12–C13 (1.414(6)Å), C4–C5–C6 (122.3(4)°/C12–C13–C14 (121.7(4)° and C1–C6–C-5 117.0(4)°/C13-C12-C17 (117.4(4)° (Table 1 and Table S4). Further structural analysis of diversely substituted [2.2]metacyclophanes, made utilizing the direct metalation synthetic strategy described above, are underway and the results will be reported in due course.

Table 1 Selected bond distances (Å) and angles (°) for **2**

Measurement	Data
Intra-annular distance (C5 to C13)	2.632(2)Å
A ring distortion from planarity	7.67(9)°
B ring distortion from planarity	7.37(9)°
C1–I	2.109(4)Å
C4–C5	1.406(6)Å
C4–C8	1.504(6)Å
C8–C9	1.568(6)Å
C9–C12	1.505(6)Å
C12–C13	1.414(6)Å
C2–C1–I	118.3(3)°
C3–C4–C5	118.3(4)°
C5–C4–C8	119.1(4)°
C4–C8–C9	110.3(3)°
C8–C9–C12	110.3(4)°
C9–C12–C13	119.0(4)°
C12–C13–C14	121.7(4)°

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Supporting Information

A CIF format file, Figs. S1 and S2, Tables S1 – S7. These materials are available free of charge on the Web at http://www/jsac.or.jp/xraystruct/.

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