Synthesis, Structures and Lewis-acid Induced Isomerization of 8-Methoxy[2.2]metaparacyclophanes and a DFT Study


Abstract: Methyl substituted 8-methoxy[2.2]MPCPs 8a–b were obtained via thiaclophane and its oxidized products. Lewis acid-catalyzed (AlCl3-MeNO2) reactions of 5-tert-buty1-8-methoxy-12,13,15,16-tetramethyl[2.2]MCP 8b under various conditions led to transannular cyclization and isomerization reactions, affording the considerably less-strained 5-tert-buty1-8-methoxy[2.2]MCP 9, 5-tert-buty1-8-hydroxy-14,16,17,18-tetramethyl[2.2]MCP 10 and pyrene derivatives 11 and 12. However, on prolonging the reaction time to 3 h for 8b, the major product is 5-tert-buty1-8-hydroxy[2.2]MCP 10. These reactions are strongly affected by the size and properties of the C-8 substituents as well as the methyl substituents on the para-linked benzene rings, which increase the strain in the molecules. The 1H NMR spectra and X-ray crystallographic analysis of 8b revealed that it adopts a syn-conformation both in solution and in the solid state.

Introduction

The syn-anti conformational flipping of the meta-bridged benzene rings in [2.2]metaparacyclophane (MCP = metaparacyclophane) 1 has been shown to overcome an energy barrier of ~20 kcal mol−1.[1,2] Single crystal X-ray analysis of 1 shows that the corresponding rings in para- and meta-[2.2]cyclophane, with the para- and meta-bridged rings bent in a boat- and a chair-like conformation, respectively.[3] The angle subtended by the two aromatic planes defined by carbons

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upon irradiation of [2.2]MCP with sunlight in chloroform has previously been described by us.\textsuperscript{[9]} As part of our on-going interest in the synthesis and study of Lewis acid-induced isomerization of polymethyl-substituted [2.2]MPCPs to less-strained pyrene derivatives via polymethyl-substituted [2.2]MCPs, we have undertaken a systematic investigation of 8-methoxy-12,13,15,16-tetramethyl[2.2]MCP. The macrocyclic [2.2]MPCP frameworks were synthesized by the cyclization reaction of bis(mercaptomethyl)benzene with 1,4-bis(chloromethyl)-2,3,5,6-tetramethylbenzene.

The IR spectra of bis(chloromethyl)-2,3,5,6-tetramethylbenzene (6a) under reduced pressure (1 torr) at 465 °C was carried out by a reported method,\textsuperscript{[11,12]} to afford exclusively 2,6-bis(mercaptomethyl)benzenes, as previously reported.\textsuperscript{[4,9,10,11]} The cyclization of bis(chloromethyl)benzene and 2,6-bis(chloromethyl)-2,3,5,6-tetramethylbenzene were prepared from the corresponding bis(chloromethyl)-benzenes, as previously reported.\textsuperscript{[4,9,10,11]}

In the present study, the synthetic route employed and the yields obtained of 5-substituted polymethyl[2.2]MPCPs 8a–b are shown in Scheme 1. 2,6-Bis(mercaptomethyl)benzenes 4a–b were prepared from the corresponding bis(chloromethyl)-benzenes, as previously reported.\textsuperscript{[4,9,10,11]} The cyclization coupling of bis(mercaptomethyl)benzene 4a–b with 1,4-bis(chloromethyl)-2,3,5,6-tetramethylbenzene 7 was carried out under high-dilution conditions in ethanolic 10% KOH in the presence of a small amount of NaBH₄, to give the desired 2,11-tert-butylation of only 8b in benzene at 50°C for 1 h afforded metacyclophane 9 in 47% yields along with the formation of small amounts of 10 and 11. The expected product, 8-methoxy-12,13,15,16-tetramethyl[2.2]MCP 8a was not detected from 8b under the conditions used. Prolonged reaction of 8b for 3 h under the same conditions gave 10 in 88% yield along with minor yields of the other products 9, 11 and 12. These results suggest that 9 might be an intermediate in the formation of 10, 11 and 12 (Scheme 2). Thus, the present Lewis acid isomerization was supposed to be much faster than the trans-tert-butylation of [2.2]MCP. A plausible mechanism for the formation of the isomerization products 9 from 8b is proposed as shown in Scheme 3.

**Scheme 1.** Synthesis of 8-methoxy-12,13,15,16-tetramethyl[2.2]MCPs 8a–b.

![Synthesis of 8-methoxy-12,13,15,16-tetramethyl[2.2]MCPs 8a–b.](image)

**Scheme 2.** Treatment of 8b with Lewis acids in benzene. See Table 1 for the yields obtained under the different conditions.

**Table 1.** Lewis acid catalyzed isomerization and trans-tert-butylation reaction of 8b.

<table>
<thead>
<tr>
<th>Run</th>
<th>Catalyst</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Products Yield (%)\textsuperscript{a,b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>TiCl₄</td>
<td>0</td>
<td>1</td>
<td>0 0 0 0</td>
</tr>
<tr>
<td>10</td>
<td>TiCl₄</td>
<td>20</td>
<td>1</td>
<td>0 0 0 0</td>
</tr>
<tr>
<td>11</td>
<td>AlCl₃-MeNO₂</td>
<td>50</td>
<td>1</td>
<td>57[44] 40 3 0</td>
</tr>
<tr>
<td>12</td>
<td>AlCl₃-MeNO₂</td>
<td>50</td>
<td>2</td>
<td>20 74 6 0</td>
</tr>
<tr>
<td>12</td>
<td>AlCl₃-MeNO₂</td>
<td>50</td>
<td>3</td>
<td>3 88[75] 6 3</td>
</tr>
</tbody>
</table>

\textsuperscript{a}The product yields were determined by GLC analyses. \textsuperscript{b}Isolated yields are shown in square brackets. \textsuperscript{c}Starting compound was recovered in quantitative yield.
Previously, Cram et al. had reported that the isomerization of [2.2]paracyclophane under AlCl₃-catalysis produced the less strained [2.2]MPCP, the corresponding transannular isomerization products, 1,2,2a,3,4,5-hexahydopyrene and [2.2]metacyclophane were produced. In the case of 8b, the protonation (or Lewis-acid complexation) of the ipso-position of a \(-\text{CH}_2\text{CH}_2-\) bridge on the para-linked benzene ring could afford the cation intermediate \(A\), which could isomerize to the less-strained 5-tert-butyl-8-methoxy-12,13,14,16-tetramethyl[2.2]metacyclophane \(9\) via cation rearrangement-aromatization steps as shown in the intermediates \(B\) and \(C\). This novel isomerization reaction might be attributable to the fact that the methoxy groups at the 8-position of the meta-linked benzene ring and the methyl groups at the 12,13,15,16-positions of the para-linked benzene ring increase the strain in the molecule in comparison with the unsubstituted [2.2]MPCP \(1\) and 8-methyl[2.2]MPCP \(2\). The formation of the minor hydropyrene and pyrene products \(11\) and \(12\) respectively, can be accounted for by the mechanism tentatively proposed in Scheme 4 and is analogous to that previously reported by us. Thus, protonation (or, as above, Lewis-acid complexation) at the ortho (or para) position of the methoxy-containing benzene ring of 9 could result in the formation of the stabilized cationic intermediate \(D\) and \(E\) which can then undergo rearrangement-intramolecular cyclization (F)-rearrangement (G) and elimination/aromatization to give \(11\) (Scheme 4). Subsequent elimination-aromatization could, in principle produce the planar and less-strained minor tetrahydropyrene product \(12\). In our previously reported study, the analogous AlCl₃-MeNO₂-catalyzed trans-tert-butylation of 5-tert-butyl-8-methyl[2.2]MPCP \(2\) (R=Me) with none of the similar isomerization reactions as was observed in this present study.

The results reported here can be attributed to the increase of the degree of deformation of the para-benzene ring of 8b, which was estimated to be 17.87° as compared with that of only 13° in 1 as was reported by Cram et al., and 15° in 2. Conclusive evidence for the structure of 8b was provided by a single-crystal X-ray structure determination (Figure 2). A high quality single crystal of 8b (CCDC 1571232) was obtained from hexane solution. The crystal structure was found to belong to the monoclinic crystal system with space group P2₁/n (SI Table S1). Figure 2 shows the molecular structure of 8b in a top and side view.
of the hydrogen (1.20 Å) and oxygen atoms (1.60 Å) or carbon atom (1.70 Å). The X-ray crystallographic study of 8b also shows that the compound is apparently conformationally more rigid than 1. Presumably the methoxy substituent at the 8-position of 8b likely impinges upon the electron cloud of the para-bridged benzene ring. The introduction of the methyl groups to the para-benzene ring of 8b also increases the strain in the molecule in comparison with the unsubstituted 8-methyl [2.2]MCP 2.[4]

DFT Computational Study

The density functional theory (DFT) computational studies were carried out to investigate the conformational characteristics of compounds 6–10. The individual geometry-optimized structures of these molecules were conducted in the gas phase with the B3LYP/6-31G(D) basis set using Gaussian-09.[14] The individual geometry-optimized structures are shown in Figure 4. The calculated optimized energy differences (kJ mole–1) for 6–7 are shown in Table 2 (Calculated energies for 6–10 are shown in SI Tables S2 and the respective xyz files). Compounds 8–10 exhibit only the boat-boat conformation. The DFT geometry-optimized calculation results suggest that the syn-chair-chair-shaped structures are the most favored energetically, among the various conformational isomers of 6–7 in the following order: chair-chair-chair-boat>boat-boat. The syn-chair-chair-6a conformer is -15.4 and -38.6 kJmol–1 more stable than the corresponding chair-boat-6a and boat-boat-6a conformers. The syn-chair-chair-6b conformer is -17.1 and -41.6 kJmol–1 more stable than the corresponding syn-chair-boat-6b and syn-boat-boat-6b conformers. The syn-chair-chair-7a conformer is -20.7 and -236.2 kJmol–1 more stable than the corresponding chair-boat-7a and boat-boat-7a conformers. The syn-chair-chair-7b conformer is -56.4 and -214.8 kJmol–1 more stable than the corresponding syn-chair-boat-7b and syn-boat-boat-7b conformers.

**Table 2.** DFT-computed optimized (kJ mol–1) for the different conformers of 6–10 and energy differences (ΔE, kJ mol–1) for the different conformers of 6–7.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>DFT optimized energy (kJ mol–1)</th>
<th>ΔEa</th>
<th>ΔEb</th>
<th>ΔEc</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>chair-chair</td>
<td>-4387461</td>
<td>-15.4</td>
<td>-38.6</td>
</tr>
<tr>
<td>6a</td>
<td>chair-boat</td>
<td>-4387446</td>
<td>-17.1</td>
<td>-41.6</td>
</tr>
<tr>
<td></td>
<td>boat-boat</td>
<td>-4387423</td>
<td>-20.7</td>
<td>-236.2</td>
</tr>
<tr>
<td>7a</td>
<td>-5169492</td>
<td>-5578356</td>
<td>-56.4</td>
<td>-214.8</td>
</tr>
<tr>
<td>8a</td>
<td>-4387411</td>
<td>-2310822</td>
<td>-272682</td>
<td>-261352</td>
</tr>
<tr>
<td>8b</td>
<td>-4387406</td>
<td>-272682</td>
<td>-263299</td>
<td>-2521106</td>
</tr>
<tr>
<td>9</td>
<td>-4387401</td>
<td>-263299</td>
<td>-2521106</td>
<td>-2521106</td>
</tr>
<tr>
<td>10</td>
<td>-4387396</td>
<td>-2521106</td>
<td>-2521106</td>
<td>-2521106</td>
</tr>
</tbody>
</table>

Notes:
1. ΔEa = Echair-chair – Echair-boat
2. ΔEb = Echair-chair – Eboat-boat
3. ΔEc = Echair-boat – Eboat-boat

An X-ray diffraction study of 5-tert-butyl-8-methoxy[2.2]MCP 8b is described. Lewis acid catalyzed reactions of 8b and 10 under various conditions led to transannular cyclization and isomerization reactions which afforded the considerably less strained pyrene derivatives in good yields. These reactions are strongly affected by the bulk and properties of the 8-substituents as well as various methyl substituents on the para

Conclusions

In conclusion, the preparation of 8-methoxy[2.2]MCP using the thiacyclophane method appears to be a useful route to such compounds. Similarly, the preparation [3.3]MCP via a coupling method, followed by a Wolff–Kishner reduction proved facile.
benzene rings, which increase the strain in the molecules. Further studies on the chemical properties of [2.2]MPCP and [3.3]MPCP are now in progress our laboratory.

**Experimental**

**General**

All melting points (Yanagimoto MP-S1) are uncorrected. Proton nuclear magnetic resonance (1H NMR) spectra and 13C NMR spectrawere recorded on Nippon Denshi JEOL FT-300 NMR and Varian-400MR-vnmrs400 spectrometers. Chemical shifts are reported as δ values (ppm) relative to internal Me4Si. Mass are reported as δ.

**Materials**

2,6-Bis(sulfonmethyl)benzene 4a-b were prepared from the corresponding bis(chloromethyl)benzenes as reported in the literature.[4,9,10] 1,4-Bis-(chloromethyl)-2,3,5,6-tetramethylbenzene (Wako C-300, 300g) (hexane-ethyl acetate, 1:1 v/v, as eluent) to give a colourless solid. Recrystallization from chloroform gave 9-methoxy-14,15,17,18-tetramethyl-2,11-dithia[3.3]metaparacyclophane (6a): m/z 479.1926. To a solution of 4a (3.9 g, 13.2 mmol) and 5 (3.0 g, 13.2 mmol) in toluene (30 mL) was added drop wise over a period of 4 h from a Hershberg funnel with stirring to a solution of potassium tert-butylenzoate (3.84 g, 69–95% purity) at 0°C while stirring. After the solution was stirred for 24 h at room temperature under an argon atmosphere, the solvent was evaporated in vacuo, and the residue was washed with 10% NaHCO3 (100 mL), water (50 mL) and ethanol to afford 9-methoxy-14,15,17,18-tetramethyl-2,11-dithia[3.3]metaparacyclophane (8a): m/z 547.2026. All melting points (Yanagimoto MP-S1) are uncorrected. Proton nuclear magnetic resonance (1H NMR) spectra and 13C NMR spectrawere recorded on 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 Yanoaco MT-5. G.L.C. analyses were performed by Shimadzu gas chromatograph, GC-14A; Silicone OV –1, 2 m; programmed temperature graph, 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 Wako silica gel 60 (63–200 μm).

**Preparation of 9-methoxy-14,15,17,18-tetramethyl-2,11-dithia[3.3]metaparacyclophane 6a:**

A solution of 4a (3.9 g, 13.2 mmol) and 5 (3.0 g, 13.2 mmol) in toluene (30 mL) was added drop wise over a period of 4 h from a Hershberg funnel with stirring to a solution of potassium tert-butylenzoate (3.84 g, 69–95% purity) at 0°C while stirring. After the solution was stirred for 24 h at room temperature under an argon atmosphere, the solvent was evaporated in vacuo, and the residue was washed with 10% NaHCO3 (100 mL), water (50 mL) and ethanol to afford 9-methoxy-14,15,17,18-tetramethyl-2,11-dithia[3.3]metaparacyclophane (8a): m/z 547.2026. To a solution of 4a (1.5 g, 4.18 mmol) in dry CHCl3 (75 mL) was added m-chloroperbenzoic acid (3.84 g, 69–95% purity) at 0°C while stirring. After the solution was stirred for 24 h at room temperature under an argon atmosphere, the solvent was evaporated in vacuo, and the residue was washed with 10% NaHCO3 (100 mL), water (50 mL) and ethanol to afford 9-methoxy-14,15,17,18-tetramethyl-2,11-dithia[3.3]metaparacyclophane-2,2,11,11-tetraoxide (7a) (1.49 g, 85%) as colourless prisms. M.p. >300 °C. 1H NMR (300 MHz, CDCl3): δ = 1.95 (6H, s, CH3), 2.43 (6H, s, CH3), 3.39 (3H, s, OCH3), 3.86 (2H, d, J = 14.4 Hz, CH2), 4.48 (2H, d, J = 15.0 Hz, CH2), 4.69 (2H, d, J = 15.9 Hz, CH2), 4.86 (2H, d, J = 14.7 Hz, CH2), 6.93 (1H, t, Ar-H), and 7.70 (2H, d, J = 8.4 Hz, Ar-H) ppm. 13C NMR (100 MHz, CDCl3): δ = 17.68, 18.62, 52.73, 60.71, 121.60, 123.30, 125.38, 129.03, 135.00 and 135.49 ppm. FABMS: m/z calcd. for C21H26O3S2 422.1222 [M⁺]; found 423.1300.

**Preparation of 6-tet-butyl-9-methoxy-14,15,17,18-tetramethyl-2,11-dithia[3.3]metaparacyclophane-2,2,11,11-tetraoxide 7b:**

To a solution of 6b (1 g, 2.49 mmol) in dry CHCl3 (50 mL) was added m-chloroperbenzoic acid (2.57 g, 10.4 mmol, 69–95% purity) at 0°C while stirring. After the solution was stirred for 24 h at room temperature under an argon atmosphere, the solvent was evaporated in vacuo, and the residue was washed with 10% NaHCO3 (100 mL), water (50 mL) and ethanol to afford 6-tet-butyl-9-methoxy-14,15,17,18-tetramethyl-2,11-dithia[3.3]metaparacyclophane-2,2,11,11-tetraoxide (7b): (0.676 g, 58.3%) as colourless prisms. M.p.&gt;300 °C. 1H NMR (300 MHz, CDCl3): δ = 1.30 (9H, s, t-Bu), 1.97 (6H, s, -CH2-), 2.43 (6H, s, CH3), 3.37 (3H, s, OCH3), 3.85 (2H, d, J = 14.7 Hz, CH2), 4.45 (2H, d, J = 15.0 Hz, CH2), 4.68 (2H, d, J = 13.8 Hz, CH2), 4.86 (2H, d, J = 14.1 Hz CH2) and 7.67 (2H, s, Ar-H) ppm. 13C NMR (100 MHz, CDCl3): δ = 17.67, 18.62, 31.47, 34.90, 52.99, 60.55, 120.60, 125.25, 126.44, 134.99, 135.99, 146.11 and 153.38 ppm. FABMS: m/z calcd. for C23H26O3S2 478.6645 [M⁺]; found 479.1926.

**Preparation of 8-methoxy-12,13,15,16-tetramethyl[2.2]metaparacyclophane (8a):**

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Preparation of 5-tert-buty1-8-methoxy-12,13,15,16-tetramethyl[2.2]metaparacyclophane (8b):

6-tert-Butyl-9-methoxy-14,15,17,18-tetramethyl-2,11-dithia[3.3]metaparacyclophane (7b) (1 g, 2.03 mmol) was pyrolyzed at 510 °C, analogous to the preparation of 5-tert-buty1-8-methoxy-12,13,15,16-tetramethyl[2.2]metaparacyclophane, yielding 459 mg (62%). Recrystallization from chloroform gave 5-tert-buty1-8-methoxy-12,13,15,16-tetramethyl[2.2]metaparacyclophane (8b) as colourless prisms. M.p. 89–90 °C. 1H NMR (300 MHz, CDCl3): δ = 1.27 (9H, s, t-Bu), 1.72 (6H, s, CH3), 2.27 (6H, s, CH3), 2.78–2.94 (8H, m, CH2), 3.19 (3H, s, OCH3) ppm. 13C NMR (100 MHz, CDCl3): δ = 15.94, 16.16, 25.38, 29.49, 31.79, 34.05, 61.96, 124.36, 130.09, 131.96, 134.30, 134.66, 143.52 and 157.65 ppm. FABMS: m/z calcd. for C23H24O 304.2191 [M+]; found 304.2211.

Preparation of 6,7,8-trimethyl-4,5,9,10-tetrahydropyrene 11:

Colourless prisms. M.p. 190–191 °C. IR (KBr) 3040, 2960, 2900, 2850, 1600, 1430, 1360, 1280, 1200, 1200, 870 and 715 cm−1. 1H NMR (300 MHz, CDCl3): δ = 1.31 (9H, s, t-Bu), 2.24 (9H, s, CH3), 2.81 (8H, s, CH2) and 7.02 (2H, Ar-H) ppm. 13C NMR (100 MHz, CDCl3): δ = 14.81, 17.27, 31.12, 32.49, 33.63, 34.80, 55.47, 115.02, 127.63, 127.28, 131.02, 133.87, 135.97, 153.34 and 154.19 ppm. FABMS: m/z calcd. for C23H23O 300.1878 [M+]; found 300.5142.

Supplementary Information Summary

Single-crystal X-ray crystallographic data of 8b; and all DFT computational data and their respective xyz files.

Acknowledgements

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Keywords: Isomerization• Lewis acid • Metaparacyclophane• Transannular reaction • Trans-tert-butylation• Strain

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A simple and effective method for the synthesis of polymethyl[2.2]meta-paracyclophanes and the relationship between the strain and Lewis acid induced isomerization and transannular reactions are discussed.

Synthesis, Structures and Lewis-acid Induced Isomerization of 8-Methoxy[2.2]metaparacyclophanes and a DFT Study

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