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

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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-butyl-8-methoxy-12,13,15,16-tetramethyl[2.2]MPCP 8b under various conditions led to transannular cyclization and isomerization reactions, affording the considerably less-strained 5-tert-butyl-8-methoxy[2.2]MPCP 9, 5-tert-butyl-8-hydroxy-14,16,17,18-tetramethyl[2.2]metacyclophane 10 and pyrene derivatives 11 and 12. However, on prolonging the reaction time to 3 h for 8b, the major product is 5-tert-butyl-8-hydroxy[2.2]MPCP 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 (MPCP = 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 deformations of the benzene rings are similar to those of the corresponding rings in para-[2.2]cyclophane 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 3, 4, 6 and 7 on the one hand, and that defined by carbon atoms 12, 13, 15 and 16 on the other, is about 13°. Furthermore, the subtended angle between the 11,12,16-plane and the 10,11-bond vector (or that between the 13,14,15-plane and the 1,14-bond vector) is even larger than the analogous angle in [2.2]paracyclophane. The para bridge moiety of 1 is therefore more highly tilted than that of the isomeric MCPP compound. Introduction of substituents at the intraannular 8-position increases the strain in the molecule in comparison with the unsubstituted [2.2]MPPC 1; the deformation of the para-benzene ring of 8-methyl[2.2]MPPC 2 was estimated at 15° from our previous X-ray crystallographic analysis.[4] Thus, the introduction of a methyl group at the para-benzene ring of [2.2]MPCP also increases the strain in the molecule. Substantial interest exists therefore in the preparation of various polymethyl-substituted [2.2]MPCPs in order to investigate the relationship between strain and the reactivity of such compounds.[5]

We have previously reported the convenient synthesis of 8-methyl- and 8-hydroxy[2.2]MPCPs via the AlCl₃-MeNO₂-catalyzed retro-Friedel-Crafts or trans-tert-butylation of the corresponding tert-butyldiphenyl derivatives in benzene.[6] Those results suggested that the 8-substituted 12,13,15,16-tetramethyl-[2.2]MPPC 3 might also be achieved via the corresponding tert-butyldiphenyl group used as a positional protective group on one of the aromatic rings.[5] Recently, in our laboratory, we have focused on the synthesis and structures of medium-sized [3.3]metacyclophanes and ring-expanded metacyclophanes containing up to three arene rings, with particular interest in their conformations, reactions and potential applications.[7,8] The main objective of the research reported herein however is the synthesis and the Lewis acid-induced isomerization of 5-tert-butyl-8-methoxy-[2.2]MPCP 8b in benzene solution. We report here the convenient preparation of the title compounds and their treatment with various Lewis acid catalysts in benzene. A proposed mechanism to account for the Lewis acid-induced isomerization of [2.2]metaparacyclophanes 8b to the corresponding pyrene derivatives is also presented, as is a DFT computational study of the possible intermediate structures.

Result and Discussion

The syntheses of different hydroxypyrenes by the Lewis acid-induced isomerization of polymethyl-substituted [2.2]MPCPs...
upon irradiation of [2.2]MCP with sunlight in chloroform has previously been described by us.\(^9\) 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 8a and 8b under high-dilution conditions in ethanoic 10% KOH in the presence of a small amount of NaBH\(_4\), to give the desired 2,11-tert-butylation of 8a and 8b in benzene failed under various reaction conditions. For 8b recovered starting compound was obtained whilst 8a afforded only intractable products which were not identified. However, the AlCl\(_3\)-MeNO\(_2\)-catalyzed trans-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.

The structures of 8a–b were elucidated by elemental analyses and spectral data. For instance, the mass spectral data obtained for 8a–b (8a, M\(^+\) = 294.19 and 8b, M\(^+\) = 350.26) were strong evidence for the formation of the desired compounds. The IR spectra of 8a–b show the absorption of the methoxy stretching vibration at around 1700 cm\(^{-1}\). The \(^1\)H NMR spectra (CDCl\(_3\), 300 MHz) of 8a and 8b exhibit singlets at \(\delta\) 1.69 and 1.72 ppm respectively, for their methyl protons at the 15,16-positions which are in the strongly shielding regions of the opposite meta-bridged benzene rings, and at \(\delta\) 2.26, 2.27 ppm for the external methyl protons at the 12,13-positions, respectively. On the other hand, the signals of the internal methoxy protons at the 8-position and two types of aromatic protons for C-4, C-6 and C-5 were observed at \(\delta\) 3.21 ppm and 6.67, 7.29 ppm for 8a, and at \(\delta\) 3.19 and 6.67 ppm for 8b which is in a strongly shielding region of the opposite para-bridged benzene ring. The attempted TiCl\(_4\)-catalyzed trans-tert-butylation of 8a and 8b in benzene failed under various reaction conditions.

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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-hexahydropyrene and [2.2]metacyclophane were produced.[13] 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-\text{tert}-butyl-8-methoxy-12,13,14,16-tetramethyl[2.2]metacyclophane 9 via cation rearrangements-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.[4] 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,[4] the analogous AlCl₃-MeNO₂-catalyzed trans-\text{tert}-butylation of 5-\text{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.,[13] and 15° in 2.[4] 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 sideview.

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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-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 -207.7 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.

| Compounds | DFT optimized energy (kJ mol⁻¹) | ΔE₆ₕ | ΔE₆ₐ | ΔE₆₇ |
|-----------|--------------------------------|-------|-------|-------|
| 6a        | -4387461                       | -15.4 | -38.6 | -23.1 |
| 6b        | -4796323                       | -17.1 | -41.6 | -24.5 |
| 7a        | -5169492                       | -207.7| -236.2| -28.5 |
| 7b        | -5578356                       | -56.4 | -214.8| -158.4|
| 8a        | -                              | -2316822| -| - |
| 8b        | -                              | -272682| -| - |
| 9         | -                              | -263299| -| - |
| 10        | -                              | -2521106| -| - |

Notes:
1. ΔE₆ₕ= E₆ₕ(E₆₇=E₆₅)=E₆₅-E₆₇
2. For compounds 8–10 only boat-boat conformers are possible.

Conclusions
In conclusion, the preparation of 8-methoxy[2.2]MCP using the thiaclophane 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.

Figure 4. DFT B3LYP/6-31G(d) optimized molecular structures of the various conformers of 6–10 MCPs in gas phase. Color code: carbon = grey; oxygen atom = red; sulfur atom = yellow. All hydrogens except phenolic hydrogen (light green) are omitted for clarity.

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-substitutents as well as various methyl substitutents on the para...
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 spectra were obtained on a Nippon Densi JIR-AQ20M spectrophotometer as Br2 disks. Elemental analyses were performed by Shimadzu gas chromatograph, GC-14A; Silicone OV-1, 2 m; programmed temperature columns were prepared by use of Wako silica gel 60 (63–200 μm).

Materials

2,6-Bis(sulfunomethyl)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 was chromatographed on silica gel (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 -2,2,11,11-tetraoxide 7a:

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To a solution of 60 mg (0.17 mmol) of cyclophane 10:

5-tert-Butyl-8-methoxy-14,16,17,18-tetramethyl[2.2]metaparacyclophane (10b): 6-tert-Butyl-9-methoxy-14,15,17,18-tetramethyl-2,2,11,11-tetraoxide (7b) (1 g, 2.03 mmol) was pyrolyzed at 510 °C, analogous to the preparation of 5-tert-butyl-8-methoxy-12,13,15,16-tetramethyl[2.2]metaparacyclophane, yielding 459 mg (62%). Recrystallization from chloroform gave 5-tert-butyl-8-methoxy-12,13,15,16-tetramethyl[2.2]metaparacyclophane (8b) as colourless prisms. M.p. 89–90 °C. \(^{1}H\) NMR (300 MHz, CDCl\(_3\)): \(\delta = 1.27\) (9H, s, t-Bu), 2.12 (6H, s, CH\(_3\)), 2.27 (6H, s, CH\(_3\)), 2.78–2.94 (8H, m, CH\(_3\)), 3.19 (3H, s, OCH\(_3\)), and 6.67 (2H, s, Ar-H) ppm. \(^{13}C\) NMR (100 MHz, CDCl\(_3\)): \(\delta = 15.94, 16.16, 25.38, 29.49, 31.79, 34.05, 61.96, 124.36, 130.09, 131.96, 134.30, 134.66, 143.52 and 157.65\) ppm. FABMS: \(m/z\) calcd. for C\(_{33}\)H\(_{39}\)O\(_3\): 530.2610 [M\(^+\)]; found 530.2519.

Aluminium chloride catalyzed isomerization reactions of 8b:

5-tert-butyl-8-methoxy-14,16,17,18-tetramethyl[2.2]metaparacyclophane 9:

To a solution of 60 mg of 8b and 8 mL of benzene was added a solution of 0.023 mL of MeNO\(_2\) and 8 mg of AlCl\(_3\) at 0°C. After the reaction mixture was stirred at 50°C for 1 h, it was poured into ice-water (5 mL). The organic layer was extracted with CH\(_2\)Cl\(_2\) (10 mL x 2). The extract was washed with water (5 mL), dried (Na\(_2\)SO\(_4\)), and concentrated. The yield was analysed by GC to give 47% of 9 as off-white prisms along with 10 in 38% yield.

5-tert-Butyl-8-methoxy-14,16,17,18-tetramethyl[2.2]metaparacyclophane 10:

To a solution of 60 mg (0.17 mmol) of 8b and 8 mL of benzene was added a solution of 0.023 mL of MeNO\(_2\) and 8 mg of AlCl\(_3\) at 0°C. After the reaction mixture was stirred at 50°C for 3 h, it was poured into ice-water (5 mL). The organic layer was extracted with CH\(_2\)Cl\(_2\) (10 mL x 2). The extract was washed with water (5 mL), dried (Na\(_2\)SO\(_4\)), and concentrated. The yield was analysed by GC to give 88% of 10 as a yellowish crystalline solid along with a very small amount of 11 in 6% yield. 5-tert-Butyl-8-hydroxy-14,16,17,18-tetramethyl[2.2]metaparacyclophane (10) was obtained as colourless prisms. M.p. 78–79 °C. \(^{1}H\) NMR (300 MHz, CDCl\(_3\)): \(\delta = 0.64\) (3H, s, CH\(_3\)), 1.29 (9H, s, t-Bu), 1.83 (1H, s, 5a-H), 2.21 (3H, s, CH\(_3\)), 2.36 (6H, s, CH\(_3\)), 2.50–2.56 (2H, m, CH\(_2\)), 2.69–2.74 (4H, m, CH\(_2\)), 3.26–3.30 (2H, m, CH\(_2\)) and 7.08 (2H, s, Ar-H) ppm. \(^{13}C\) NMR (100 MHz, CDCl\(_3\)): \(\delta = 15.71, 16.20, 16.57, 30.12, 31.59, 32.83, 32.89, 33.99, 53.47, 113.02, 124.84, 125.68, 129.12, 131.50, 133.87, 150.94 and 151.22\) ppm. FABMS: \(m/z\) calcd. for C\(_{33}\)H\(_{32}\)O\(_3\): 336.2453 [M\(^+\)]; found 335.9887.

2-tert-Butyl-6,7,8-trimethyl-4,5,9,10-tetrahydropyrene 11:

Colourless prisms (hexane). M.p. 193–194 °C. IR (KBr) 3040, 2960, 2900, 2850, 1600, 1430, 1360, 1280, 1230, 1200, 870 and 715 cm\(^{-1}\). \(^{1}H\) NMR (300 MHz, CDCl\(_3\)): \(\delta = 1.31\) (9H, s, t-Bu), 2.24 (4H, m, CH\(_2\)), 2.81 (8H, m, CH\(_3\)) and 7.02 (2H, s, Ar-H) ppm. FABMS: \(m/z\) calcd. for C\(_{33}\)Te: 304.2191 [M\(^+\)]; found 304.2211.

Acknowledgements

We thank the OTEC at Saga University for financial support. This work was performed under the Cooperative Research Program of “Network Joint Research Center for Materials and Devices (Institute for Materials Chemistry and Engineering, Kyushu University)”. CR thanks the EPSRC for a travel award. The authors also thank King Saud University, Deanship of Scientific Research, College of Science Research Center. Compute/Calcul Canada via the Acenet facilities and Dr. Oliver Stueker are thanked for ongoing support for the computational work.

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

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