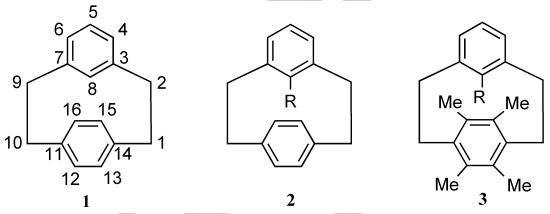
Synthesis, Structures and Lewis-acid Induced Isomerization of 8-Methoxy[2.2]metaparacyclophanes and a DFT Study

Md. Monarul Islam,*[a],[b],[c] Xing Feng,[c] Shofiur Rahman,[d],[e] Paris E. Georghiou,[d] Abdullah Alodhayb[e],[f] Carl Redshaw[g] and Takehiko Yamato*[b]

Abstract: Methyl substituted 8-methoxy[2.2]MPCPs **8a**–**b** were obtained via thiacyclophane and its oxidized products. Lewis acid-catalyzed ($AlCl_3$-$MeNO_2$) 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 substitutents as well as the methyl substitutents on the *para*-linked benzene rings, which increase the strain in the molecules. The ^{1}H 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



atoms,

Figure 1. Structuresof [2.2]metaparacyclophanes.

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 MPCP compound. Introduction of substituents at the intraannular 8-position increases the strain in the molecule in comparison with the unsubstituted [2.2]MPCP **1**; the deformation of the *para*-benzene ring of 8-methyl[2.2]MPCP **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]

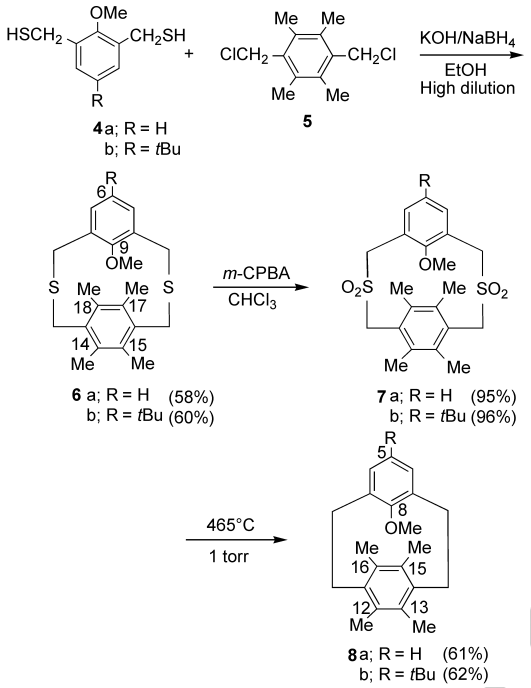
We have previously reported the convenient synthesis of 8-methyl- and 8-hydroxy[2.2]MPCPs via the $AlCl_3$-$MeNO_2$-catalyzed retro-Friedel-Crafts or *trans-tert*-butylation of the corresponding *tert*-butyl derivatives in benzene.[4] Those results suggested that the 8-substituted 12,13,15,16-tetramethyl-[2.2]MPCP **3** might also be achieved via the corresponding *tert*-butyl group used as a positional protective group on one of the aromatic rings.[6] 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 hydropyrenes by the Lewis acid-induced isomerization of polymethyl-substituted [2.2]MPCPs

[a] Dr. M. M. Islam,
Chemical Research Division
Bangladesh Council of Scientific and Industrial Research (BCSIR)
Dhanmondi, Dhaka-1205, Bangladesh.
E-mail: mmipavel@yahoo.com
[b] Dr. M. M. Islam, Dr. Prof. T. Yamato
Department of Applied Chemistry, Faculty of Science and Engineering, Saga University
Honjo-machi 1, Saga 840-8502 Japan
E-mail: yamatot@cc.saga-u.ac.jp.
[c] Dr. M. M. Islam, Dr. X. Feng
School of Materials and Energy
Guangdong University of Technology,
Guangzhou 510006, P. R. China.
[d] Dr. S. Rahman, Dr. Prof. P. E. Georghiou
Department of Chemistry, Memorial University of Newfoundland
St. John's, Newfoundland and Labrador A1B 3X7, Canada
[e] Dr. S. Rahman, Dr. A. Alodhayb
Aramco Laboratory for Applied Sensing Research
King Abdullah Institute for Nanotechnology, King Saudi University
Riyadh, Saudi Arabia.
[f] Dr. A. Alodhayb
Department of Physics and Astronomy, College of Science, King Saud University, Riyadh 11451, Saudi Arabia.
[g] Dr. Prof. C. Redshaw
Department of Chemistry & Biochemistry
The University of Hull
Cottingham Road, Hull, Yorkshire HU6 7RX, UK.

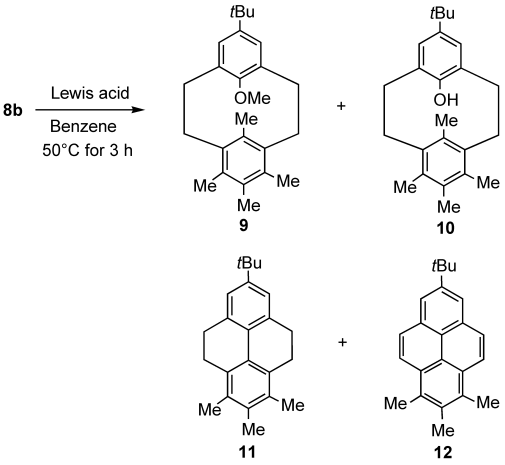
upon irradiation of [2.2]MCP with sunlight in chloroform has previously been described by us.[9] As part of our on-going interest in the synthesis and study of Lewis acid-induced isomerization of polymethyl-substituted [2.2]MPCPs to less-strained pyrene derivatives via polymethyl-substituted [2.2]MCPs, we have undertaken a systematic investigation of 8-methoxy-12,13,15,16-tetramethyl[2.2]MPCP. 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.



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

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.[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 ethanoic 10% KOH in the presence of a small amount of $NaBH_4$, to give the desired 2,11-dithia[3.3]MPCPs **6a** and **6b** in 58 and 60% yields, respectively. Similarly, oxidation of **6a**–**b** with *m*-chloroperbenzoic acid in $CHCl_3$ afforded the corresponding bissulfones **7a** and **7b** in 95 and 96% yields, respectively. Pyrolysis of bissulfones **7a**–**b** under reduced pressure (1 torr) at 465 °C was carried out by a reported method,[11,12] to afford exclusively **8a** and **8b** in 61 and 62% yields, respectively.

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 ^1H NMR spectra ($CDCl_3$, 300 MHz) of **8a** and **8b** exhibit singlets at δ 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 δ 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 δ 3.21 ppm and 6.67, 7.29 ppm for **8a**, and at δ 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. 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]MPCP **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 plausable mechanism for the formation of the isomerization products **9** from **8b** is proposed as shown in Scheme 3.

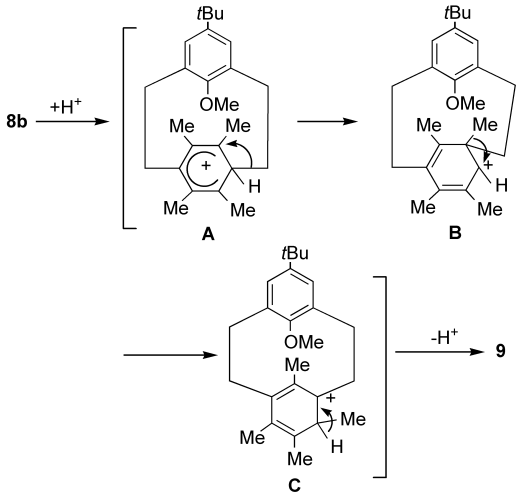


Scheme 2. Treatment of **8b** with Lewis acids in benzene. See Table 1 for the yields obtained under the different conditions.

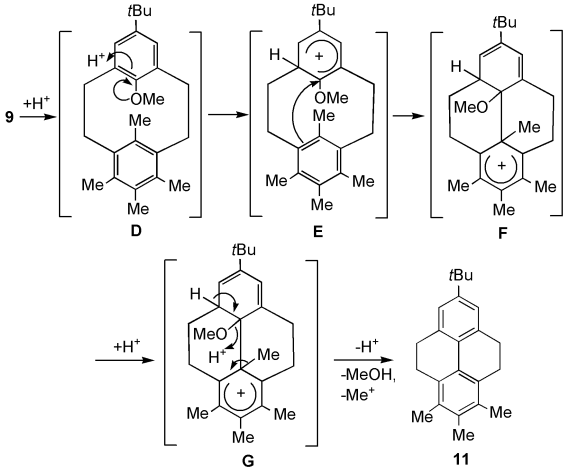
Table 1. Lewis acid catalyzed isomerization and *trans-tert*-butylation reaction of **8b**.

Run	Catalyst	Temp. (°C)	Time (h)	Products Yield (%)[a,b]			
				9	**10**	**11**	**12**
1	$TiCl_4$[c]	0	1	0	0	0	0
2	$TiCl_4$[c]	20	1	0	0	0	0
3	$AlCl_3$-$MeNO_2$	50	1	57[44]	40	3	0
4	$AlCl_3$-$MeNO_2$	50	2	20	74	6	0
5	$AlCl_3$-$MeNO_2$	50	3	3	88[75]	6	3

[a]The product yields were determined by GLC analyses. [b]Isolated yields are shown in square brackets.[c] Starting compound was recovered in quantitative yield.



Scheme 3. Reaction mechanism proposed for the formation of **9**.



Scheme 4. Reaction mechanism proposed for the formation of **11** by a Lewis acid-catalyzed transanular reaction.

Previously, Cram *et. al.* had reported that the isomerization of [2.2]paracyclophane under $AlCl_3$-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 $-CH_2CH_2-$ 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 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 $AlCl_3$-$MeNO_2$catalyzed*trans*-*tert*-butylation of 5-*tert*-butyl-8-methyl[2.2]MPCP afforded only 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 $P2_1/n$ (SI Table S1). Figure 2 shows the molecular structure of **8b** in a top and sideview.

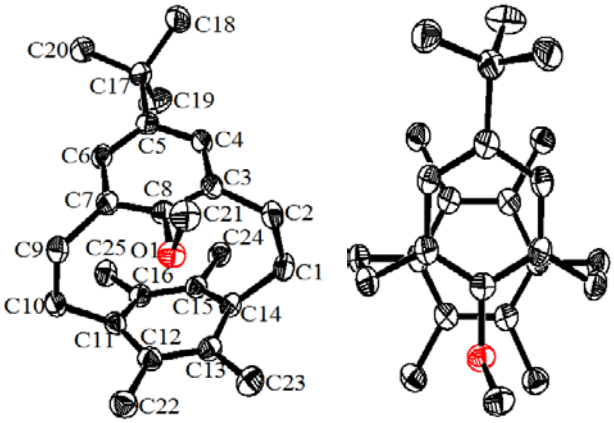


Figure 2. Ortep drawing of **8b** with top (*left*) and side (*right*) views. Thermal ellipsoids are drawn at the 50% probability level. All hydrogen atoms are omitted for clarity.

The mean distance between the mean geometric centres of the benzene rings of **8b** is equal to 3.272 Å as shown in Figure 3. The two benzene units overlap very slightly, with their dihedral angle being only 15.22°.

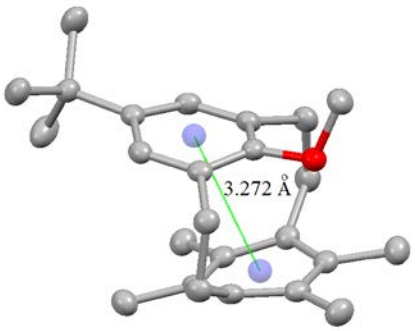


Figure 3. The distance between the geometric centres of the benzene rings of **8b**.

In the crystal-packing diagram of **8b** (SI Figure S7), the intermolecular shortest distance within C(26)H(56)-H(51)C(19) is 2.38 Å, which is shorter than the sum of the van der Waals radii

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]MPCP **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 -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 (kJmole^{-1})			ΔE_a	ΔE_b	ΔE_c
	chair-chair	*chair-boat*	*boat-boat*	kJ mol^{-1}	kJ mol^{-1}	kJ mol^{-1}
6a	-4387461	-4387446	-4387423	-15.4	-38.6	-23.1
6b	-4796323	-4796306	-4796282	-17.1	-41.6	-24.5
7a	-5169492	-5169285	-5169256	-207.7	-236.2	-28.5
7b	-5578356	-5578300	-5578142	-56.4	-214.8	-158.4
8a	-	-	-2316822	-	-	-
8b	-	-	-2725682	-	-	-
9	-	-	-2623299	-	-	-
10	-	-	-2521106	-	-	-

Notes:
1. $\Delta E_a = E_{chair\text{-}chair} - E_{chair\text{-}boat}$; $\Delta E_b = E_{chair\text{-}chair} - E_{boat\text{-}boat}$; $\Delta E_c = E_{chair\text{-}boat} - E_{boat\text{-}boat}$.
2. For compounds **8**–**10** only *boat-boat* conformers are possible.

Conclusions

In conclusion, the preparation of 8-methoxy[2.2]MPCP using the thiacyclophane method appears to be a useful route to such compounds. Similarly, the preparation [3.3]MPCP via a coupling method, followed by a Wolff–kishner reduction proved facile.

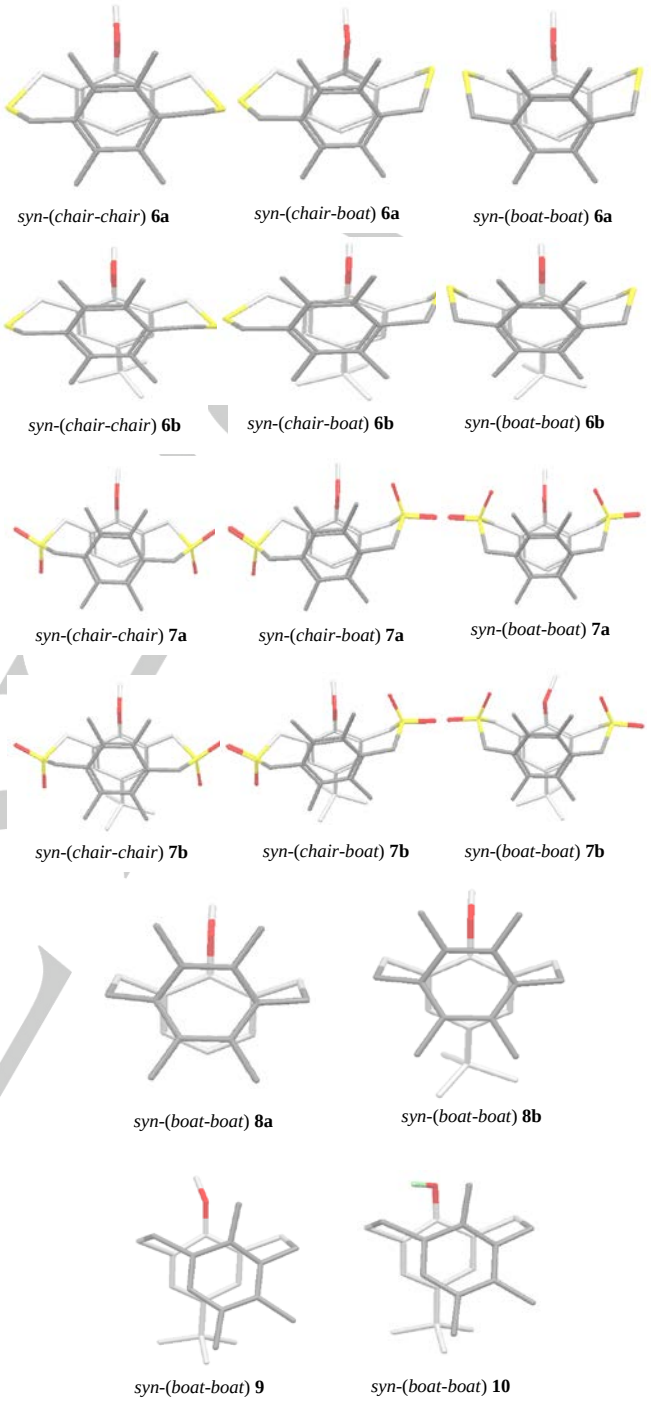


Figure 4. DFT B3LYP/6-31G(d) optimized molecular structures of the various conformers of **6**–**10** MCPs in gas phase. Color code: carbon = grey; oxygen atom = red; sulfur atom = yellow. All hydrogens except phenolic hydrogen (light green) are omitted for clarity.

An X-ray diffraction study of 5-*tert*-butyl-8-methoxy[2.2]MPCP **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 (^{1}H NMR) spectra and ^{13}C 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 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 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 **5** was reported previous.[11]

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 hydroxide (3.32 g, 71 mmol) and sodium borohydride (630 mg) in ethanol (3.2 L). After the addition, the reaction mixture was concentrated and washed by water (50 mL). The residue was extracted with CH_2Cl_2 (100 mL × 3). The CH_2Cl_2 extract was washed with brine and dried by $MgSO_4$. The CH_2Cl_2 extract was concentrated and the residue 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 (**6a**) (2.4 g, 51%) as colourless prisms. M.p. 132–137 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.87 (6H, s, CH_3), 2.35 (6H, s, CH_3), 3.33（3H, s, OCH_3）, 3.19 (2H, d, *J* = 15.3 Hz, CH_2), 3.46 (2H, d, *J* = 13.2 Hz, CH_2), 3.84 (2H, d, *J* = 15.3 Hz CH_2), 4.48 (2H, d, *J* = 13.2 Hz, CH_2), 6.84 (1H, t, Ar-*H*) and 7.12 (2H, d, *J* = 7.5 Hz, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.01, 19.17, 27.34, 30.33, 122.42, 128.45, 131.90, 132.84, 133.12 and 153.00 ppm. FABMS: *m/z* calcd. for $C_{21}H_{26}OS_2$ 358.1425 [M$^+$]; found 358.1378.

Preparation of 6-*tert*-butyl-9-methoxy-14,15,17,18-tetramethyl-2,11-dithia[3.3]metaparacyclophane (6b):

A solution of **4b** (3.6 g, 13.8 mmol) and **5** (3.12 g, 13.8 mmol) in toluene (45 mL) was added drop wise over a period of 4 h from a Hershberg funnel with stirring to a solution of potassium hydroxide (3.32 g, 71 mmol) and sodium borohydride (630mg) in ethanol (3.2 L). After the addition, the reaction mixture was concentrated and washed by water (30 mL). The residue was extracted with CH_2Cl_2 (150 mL× 2), washed by brine and dried by $MgSO_4$. The CH_2Cl_2 extract was concentrated and residue 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 6-*tert*-butyl-9-methoxy-14,15,17,18-tetramethyl-2,11-dithia[3.3]metaparacyclophane **6b** (4.87 g, 79%) as colourless prisms. M.p. 128 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30 (9H, s, *t*-Bu), 1.91 (6H, s, CH_3), 2.35 (6H, s, CH_3), 3.31（3H, s, OCH_3）, 3.19 (2H, d, *J* = 15 Hz, CH_2), 3.445 (2H, d, *J* = 13.2 Hz, CH_2), 3.81 (2H, d, *J* = 15.6 Hz, CH_2), 4.51 (2H, d, *J* = 13.5 Hz, CH_2) and 7.07 (2H, s, Ar-*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.97, 18.16, 26.65, 30.55, 31.70, 34.35, 62.48, 125.49, 131.46, 132.00, 132.54, 133.37, 144.68 and 151.16 ppm. FABMS: *m/z* calcd. for $C_{25}H_{34}S_2O$ 414.2051 [M$^+$]; found 414.2004.

Preparation of 9-methoxy-14,15,17,18-tetramethyl-2,11-dithia[3.3]metaparacyclophane -2,2,11,11-tetraoxide 7a:

To a solution of **6a** (1.5 g, 4.18 mmol) in dry $CHCl_3$ (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% $NaHCO_3$ (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. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.95 (6H, s, CH_3), 2.43 (6H, s, CH_3), 3.39（3H, s, OCH_3）, 3.86 (2H, d, *J* = 14.4 Hz, CH_2), 4.48 (2H, d, *J* = 15.0 Hz, CH_2), 4.69 (2H, d, *J* = 15.9 Hz, CH_2), 4.86 (2H, d, *J* = 14.7 Hz, CH_2), 6.93 (1H, t, Ar-*H*), and 7.70 (2H, d, *J* = 8.4 Hz, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{21}H_{26}O_5S_2$ 422.1222 [M$^+$]; found 423.1300.

Preparation of 6-*tert*-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 $CHCl_3$ (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% $NaHCO_3$ (100 mL), water (50 mL) and ethanol to afford 6-*tert*-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.>300 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30 (9H, s, t-Bu), 1.97 (6H, s, -CH_3), 2.43 (6H, s, CH_3), 3.37 (3H, s, OCH_3), 3.85 (2H, d, J=14.7 Hz, CH_2), 4.45 (2H, d, *J* = 15.0 Hz, CH_2), 4.68 (2H, d, *J* = 13.8 Hz, CH_2), 4.86 (2H, d, *J* = 14.1 Hz CH_2) and 7.67 (2H, s, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{25}H_{34}O_5S_2$ 478.6645 [M$^+$]; found 479.1926.

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

9-Methoxy-14,15,17,18-tetramethyl-2,11-dithia[3.3]metapara-cyclophane-2,2,11,11-tetraoxide (**7a**) (500 mg, 1.18 mmol) was pyrolyzed at 465 °C, analogous to the preparation of 8-methoxy-12,13,15,16-tetramethyl[2.2]metaparacyclophane**,** yielding 212 mg (61%). Recrystallization from dichloromethane gave 8-methoxy-12,13,15,16-tetramethyl[2.2]metaparacyclophane (**8a**) as colourless prisms. M.p. 106–107 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.69 (6H, s, CH_3), 2.27 (6H, s, CH_3), 2.31–2.36 (2H, m, CH_2), 2.82–2.90 (4H, m, CH_2), 3.12–3.17 (2H, m, CH_2), 3.21 (3H, m, OCH_3), 6.67 (2H, s, Ar-*H*) and 7.29 (1H, s, Ar-*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.64, 16.31, 17.32, 21.12, 27.03, 81.67, 83.65, 100.57, 112.74, 137.84, 140.57 and 171.28 ppm. FABMS: *m/z* calcd. for $C_{21}H_{26}O$ 294.1984 [M$^+$]; found 294.1992.

Preparation of 5-*tert*-butyl-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-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]metaparacyclo-phane**,** yielding 459 mg (62%). Recrystallization from chloroform gave 5-*tert*-butyl-8-methoxy-12,13,15,16-tetramethyl[2.2]meta-paracyclophane (**8b**) as colourless prisms. M.p. 89–90 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (9H, s, t-Bu), 1.72 (6H, s, CH_3), 2.27 (6H, s, CH_3), 2.78–2.94 (8H, m, CH_2), 3.19 (3H, s, OCH_3) and 6.67 (2H, s, Ar-*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{25}H_{34}O$ 350.2610 [M$^+$]; found 350.2519.

Aluminium chloride catalyzed isomerization reactions of 8b:

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

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 1 h, it was poured into ice-water (5mL). The organic layer was extracted with CH_2Cl_2 (10 mL x 3). The extract was washed with water (5 mL), dried (Na_2SO_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]metacyclophane (**9**) was obtained as colourless prisms.M.p. 105–107 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.57 (3H, s, CH_3), 1.29 (9H, s, *t*-Bu), 2.18 (3H, s, CH_3), 2.29（6H, s, CH_3, 2.39–2.49 (2H, m, CH_2), 2.58-2.6 (4H, m, CH_2), 3.18–3.25 (2H, m, CH_2), 2.86 (3H, s, OMe) and 7.10 (2H, s, Ar-*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.63, 16.08, 16.39, 31.56, 32.61, 33.29, 34.00, 59.51, 125.50, 130.14, 130.66, 131.89, 133.44, 145.71, 158.56 and 183.18 ppm. FABMS: *m/z* calcd. for $C_{25}H_{34}O$350.2610 [M$^+$]; found 350.2823.

5-*tert*-Butyl-8-hydroxy-14,16,17,18-tetramethyl[2.2]meta-cyclophane 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_2Cl_2 (10 mL × 2). The extract was washed with water (5 mL), dried (Na_2SO_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]metacyclophane (**10**) was obtained as colourless prisms.M.p. 78–79 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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 152.12 ppm. FABMS: *m/z* calcd. for $C_{24}H_{32}O$ 336.2453 [M$^+$]; found 335.9887.

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

Colourless prisms (hexane).M.p.190–191°C (lit.[15] 190–191°C). IR (KBr) 3040, 2960, 2900, 2850, 1600, 1430, 1360, 1280, 1230, 1200, 870 and 715 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.31 (9H, s, *t*-Bu), 2.24 (9H, s, CH_3), 2.81 (8H, s, CH_2) and 7.02 (2H, s, Ar-*H*) ppm. FABMS: *m/z* calcd. for $C_{23}H_{28}$ 304.2191 [M$^+$]; found 304.2211.

2-*tert*-Butyl-6,7,8-trimethylpyrene 12:

Colourless prisms (hexane). M.p. 194–195 °C. IR (KBr) 3040, 2960, 2900, 2850, 1600, 1430, 1360, 1280, 1230, 1200, 870 and 715 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.57 (9H, s, *t*-Bu), 2.69 (3H, s, CH_3), 2.90 (6H, s, CH_3), 7.99 (2H, d, *J* = 9.3 Hz, Ar-*H*), 8.13 (2H, s, Ar-*H*) and 8.27 (2H, d, *J* = 9.3 Hz, Ar-*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.81, 17.27, 31.12, 32.49, 33.63, 34.80, 55.47, 115.02, 126.73, 127.28, 131.02, 133.87, 135.97, 153.34 and 154.19 ppm. FABMS: *m/z* calcd. for $C_{23}H_{24}$ 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

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

[1] a) T. Hylton, V. Boekelheide, *J. Am. Chem. Soc.* **1968**, *90*, 6887–6888; b) S. A. Sherrod, R. L. da Costa, *Tetrahedron Lett.* **1973**, *14*, 2083–2086; c) S. A. Sherrod, R.L. da Costa, R. A. Barnes, V. Boekelheide, *J. Am.Chem. Soc.* **1974**, *96*, 1565–1577.

[2] a) F. Vogtle, *Chem. Ber.* **1969**, *102*, 3077–3081; b) D. T. Hefelfinger, D. J. Cram, *J. Am. Chem. Soc.***1970**, *92*, 1073–1074; c) D. T. Hefelfinger, D. J. Cram, *J. Am. Chem. Soc.* **1971**, *93*, 4767–4772.

[3] A. Renault, C. Cohen-Addad, J. Lajzerowicz-Bonneteau, J. P. Dutasta, M. J. Crisp, *Acta Cryst.,* **1987**, *B43*, 480–488.

[4] T. Yamato, J. Matsumoto, K. Tokuhisa, K. Tsuji, K. Suehiro, M. Tashiro, *J. Chem. Soc.,Perkin Trans. 1,* **1992**, 2675–2682.

[5] a) T. Yamato, K. Tokuhisa, H. Tsuzuki, *Can. J. Chem.* **2000**, 78, 238–247; b) T. Yamato, K. Noda, H. Tsuzuki, *New. J. Chem.* **2001**, *25*, 721–

727.

[6] a) M. Tashiro, T. Yamato, *J. Org. Chem.***1981**, *46*, 1543–1552; b) M. Tashiro, K. Koya, T. Yamato, *J. Am. Chem. Soc.***1982**, *104*, 3707–3710; c) M. Tashiro, T. Yamato, *J. Org. Chem.***1985**, *50*, 2939–2942; d) T. Yamato, T. Arimura, M. Tashiro, *J. Chem. Soc., Perkin Trans. I.* **1987**, 1; e) M. Tashiro, A. Tsuge, T. Sawada, T. Makishima, S. Horie, T. Arimura, S. Mataka, T. Yamato, *J. Org. Chem.***1990**, *55*, 2404–2409.

[7] a) M. M. Islam, T.Hirotsugu, T. Matsumoto, J. Tanaka, T.Yamato, *Can. J. Chem.* **2015**, *93*, 1161–1168; b) T. Akther, M. M. Islam, S. Rahman, P. E. Georghiou, T. Matsumoto, J. Tanaka,C. Redshaw,T. Yamato, *Org. Biomol. Chem.* **2017**, *15*, 3519–3527; c) T. Akther, M. M. Islam, S. Rahman, P. E Georghiou, T. Matsumoto, J. Tanaka, P. Thuéry, C. Redshaw, T. Yamato, *ChemistrySelect*, **2016**, *1*, 3594–3600; d) M. M. Islam, T. Akther, S. Rahman, P. E. Georghiou, T. Matsumoto, J. Tanaka, C. Redshaw, T.Yamato, *ChemistrySelect*, **2017**, *2*, 7255–7262; e) T. Akther, M. M. Islam, T. Matsumoto, J. Tanaka, X. Feng, C. Redshawand T. Yamato, *J. Mol. Struct*. **2016**, 1122, 247–255.

[8] a) M. M. Islam, T. Hirotsugu, P. Thuery. T. Matsumoto, J. Tanaka, M. R. J.Elsegood, C. Redshaw, T. Yamato, *J. Mol. Struct*. **2015**, *1098*, 47–54; b) M. M. Islam,T. Hirotsugu,T. Matsumoto, J. Tanaka,S. Rahman, P. E. Georghiou, C. Redshaw, T. Yamato, *Org. Biomol. Chem.* **2015**, *13*, 9055–9064; c) M. M. Islam,T. Akther, Y. Ikejiri,T. Matsumoto, J. Tanaka,S. Rahman, P. E. Georghiou, D. L. Hughes, C. Redshaw, T. Yamato,*RSC Adv.* **2016**, *6*, 50808–50817; d) T.Akther, M. M. Islam, T. Matsumoto, J. Tanaka, P. Thuery, C. Redshaw, T. Yamato, *Tetrahedron*, **2018**, 74, 329–325; e) T.Akther, M. M. Islam, T. Matsumoto, J. Tanaka, P. Thuery, C. Redshaw,T. Yamato,*Eur. J. Org. Chem.* **2017**, *2017*, 1721–1726; f) M. M. Islam, C.-Z. Wang, X. Feng, S. Rahman, P. E. Georghiou, A. Alodhayb, T.Yamato, *ChemistrySelect*, **2018**, *3*, 13542–13547.

[9] a) A. Paudel, T. Shimizu, T. Yamato, *J. Chem. Res.* 2008, 650–654; b) T. Shimizu, K. Hida, T. Yamato, *J. Chem. Res.* 2009, 443–447; c) A. Paudel, T. Shimizu, T. Yamato, *J. Chem. Res.* 2008, 650–654.

[10] T. Sato, T. Takemura, *J. Chem. Soc., Perkin 2,* **1976**, 1195–1201.

[11] M. Tashiro, T. Yamato, *J. Org. Chem.* **1981**, *46*, 4556–4562.

[12] M. Tashiro, T. Yamato, *J. Org. Chem.* **1983**, *48*, 1461–1468.

[13] D. J. Cram, D. L. Helgeson, D. Lock, L. A. Singer, *J. Am. Chem. Soc.* **1966**, *88*, 1324–1325.

[14] M. J. Frischet al. *Gaussian 09, Revision D.01*; Gaussian, Inc., Wallingford CT, 2013.

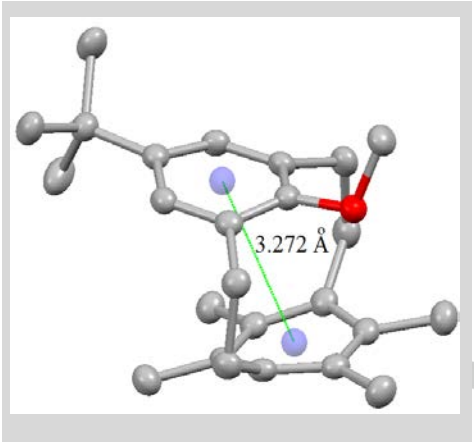
[15] M. Tashiro, T. Yamato, K. Kobayashi, T. Arimura, *J. Org. Chem.*, **1987**, *52*, 3136–3199.

Entry for the Table of Contents (Please choose one layout)

Layout 1:

FULL PAPER

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 transanular reactions are discussed.



M. M. Islam,*[a],[b],[c] X. Feng,[c] S. Rahman,[d],[e] P. E. Georghiou,[d] A. Alodhayb,[e],[f] C. Redshaw[g] and T. Yamato*[b]

Page No. – Page No.

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

Layout 2:

FULL PAPER

((Insert TOC Graphic here; max. width: 11.5 cm; max. height: 2.5 cm))

*Author(s), Corresponding Author(s)**

Page No. – Page No.

Title

Text for Table of Contents