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## Studies on Lewis-Acid Induced Reactions of 8-Methoxy[2.2]metacyclophanes: A New Synthetic Route to Alkylated Pyrenes --Manuscript Draft--

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<b>Response to Reviewers:</b>	Dear editor Thank you very much for your E-mail about our manuscript titled "Studies on Lewis-Acid Induced Reactions of 8-Methoxy[2.2]metacyclophanes: A New Synthetic Route to Alkylated Pyrenes", manuscript number: slct.201903048. We deeply appreciate your attention and we have improved the text as suggested by the editorial office as below: (i) We have added space in the entire revised manuscript, where needed. (ii) We removed all title/author/affiliation details from cover sheet of SI. (iii) We removed experimental section from main text to SI and rearranged the number and references. (iv) We mentioned CCDC number of compound 5b in summary, table S1 (SI). (v) We revised the keywords. (vi) We removed issue number and corrected the references.  We therefore, hope that you would be kind enough to consider the revised manuscript for publication.

	<p>Thank you very much for your time and consideration.</p> <p>Yours sincerely,</p> <p>Prof. Dr. Takehiko Yamato (corresponding author)  Department of Applied Chemistry  Faculty of Science and Engineering  Saga University  Honjo-machi 1, Saga-shi, Saga 840-8502, Japan  Fax: (internet.) + 81(0)952/28-8548  E-mail:yamatot@cc.saga-u.ac.jp</p>
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# Studies on Lewis-Acid Induced Reactions of 8-Methoxy[2.2]-metacyclophanes: A New Synthetic Route to Alkylated Pyrenes

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**Abstract:** *Anti*-8-methoxy[2.2]metacyclophanes (MCPs) **5a–b** were obtained via pyrolysis of the corresponding *syn*-thiatetraoxide cyclophanes **4a–b**. Coupling reactions of 4-*tert*-butyl-1-methoxy-2,6-bis(mercaptomethyl)benzenes **1a–b** and 1,5-bis(chloro-methyl)-2,4-dimethylbenzene **2** under high dilution conditions afforded only the *syn*-conformers of 9-methoxy-2,11-dithia[3.3]metacyclophanes **3a–b**, which with *m*-CPBA formed the corresponding *syn*-tetraoxides **4a–b**. Lewis acid (TiCl<sub>4</sub>/AlCl<sub>3</sub>-MeNO<sub>2</sub>) or iodine-catalyzed reactions of **5b** under various conditions led to transannular cyclization to afford tetrahydropyrene **6b** and pyrene derivative **7b** and/or *de-tert*-butylated **6a**. Iodine-catalyzed reaction of **5a** afforded tetrahydropyrene **6a**. These findings suggest the potential for a new route to alkylated pyrenes via strained and alkylated metacyclophanes. Density functional theory (DFT) studies were carried out to investigate the conformational characteristics of **3–5**.

## Introduction

Cyclophanes are macrocycles in which one or more arene rings (most commonly, benzene or substituted benzenes) are linked by methylene (-CH<sub>2</sub>-) group bridges of different lengths.

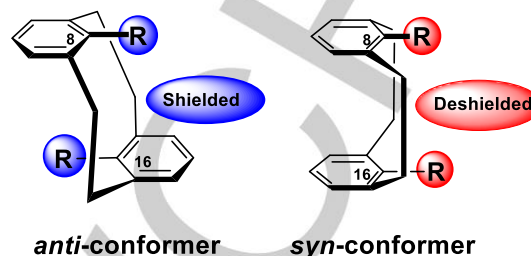


Figure 1. Possible conformers for [2.2]MCPs.

The pioneering work in the cyclophane field was initiated by Cram in 1951,<sup>[1]</sup> and in recent decades cyclophane chemistry has attracted much attention from organic chemists. This is primarily due to cyclophanes having unusual and highly strained geometries, the stereochemical aspects of their structural flexibility such as ring-flipping, ring-tilting, bridge-wobbling as well as *syn-anti* isomerization<sup>[2]</sup> and the structures of many different types of cyclophanes have been reported.<sup>[3]</sup> When the *meta* or *para* positions of the component benzene rings are linked via short bridges, the rings can be forced to adopt *syn* and/or *anti* conformations with respect to each other. Studies on small *meta*- and *para*-cyclophanes have firmly established that a benzene ring can be distorted from planarity to a considerable extent (up to 30°) while fully retaining its aromaticity, as testified by various structural and physical parameters.<sup>[2a,4]</sup> Due to their flexibility, cyclophanes<sup>[5]</sup> have significant importance in theoretical studies and there are continuous efforts to synthesize novel cyclophanes of different sizes with numerous modes of ring attachments.<sup>[6]</sup> Although *syn*- and *anti*-conformers (e.g. see Fig.1) of [2.2]MCPs have been reported, it is still not clear what the effects are of not only internal substituents, but also of having unsymmetrically-substituted benzene rings with respect to the charge-transfer-type interactions between the two aromatic rings as well as steric effects of substituents on the benzene ring(s).

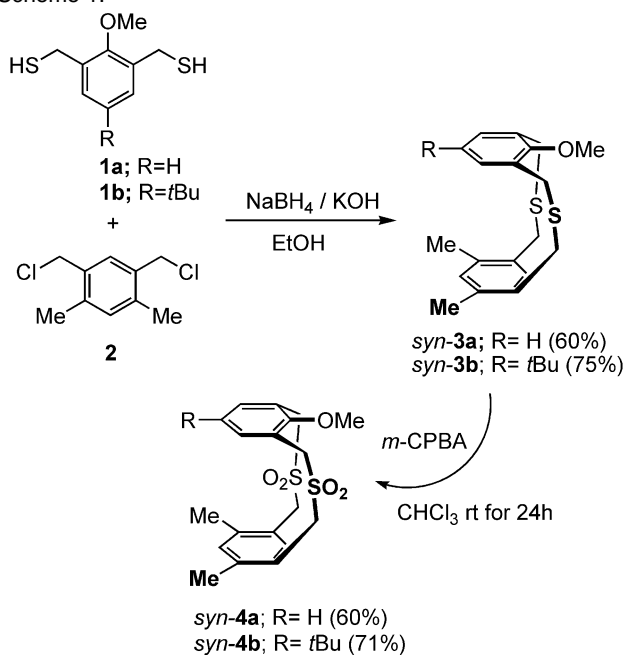
We have previously shown that the introduction of substituents on one of the benzene rings can increase the strain in the cyclophane when compared with a corresponding unsubstituted cyclophane; for example, a deformation of 15° was measured in the *para*-substituted benzene ring of 8-methyl[2.2]MPCP.<sup>[7]</sup> The introduction of a single methyl group at one of the benzene rings of [2.2]cyclophane also increases the strain in the cyclophane. In order to investigate the relationship between strain and the reactivity of variably-functionalized cyclophanes we have been interested in the preparation of various polymethyl-substituted [2.2]MPCPs.<sup>[8]</sup> Recently, syntheses of 8-methyl- and 8-hydroxy[2.2]MPCPs via the AlCl<sub>3</sub>-MeNO<sub>2</sub>-catalyzed *retro*-Friedel-Crafts *trans-tert*-butylation of the corresponding *tert*-butyl derivatives in benzene were described by us.<sup>[7,9]</sup> The research reported herein describes the synthesis and the Lewis acid-induced transannular reactions of 5-*tert*-butyl-8-methoxy-12,14-dimethyl[2.2]MCP **5b** under different conditions, and the

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convenient preparation of the title compounds and their treatment with various Lewis acid catalysts. A proposed mechanism for the Lewis acid-induced reaction of [2.2]MCP **5b** to the corresponding pyrene derivatives is also presented, as well as a DFT and quantum chemical computational study of the possible conformational structures.

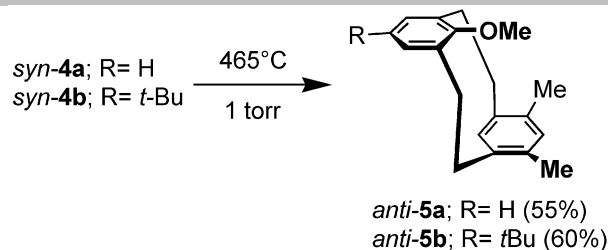
## Results and Discussion

In recent years, pyrene and pyrene derivatives have generated much research interest due to their different photophysical properties such as blue emissive property as well as good hole-transporting ability make them promising candidates for different application possibility.<sup>[10]</sup> As part of our own on-going interest in the synthesis, conformational aspects and studies of Lewis acid-induced transannular reactions of such methyl-substituted cyclophanes to get pyrene derivatives, we conducted a systematic investigation of 8-methoxy-12,14-dimethyl[2.2]MCPs **5a–b**.<sup>[11]</sup> The macrocyclic [2.2]MCP frameworks were synthesized via the cyclocondensation reactions of bis(mercaptomethyl)-anisoles **1a–b** with 1,5-bis(chloromethyl)-2,4-dimethylmethyl-benzene **2** as outlined in Scheme 1.<sup>[8,9,12,13]</sup>



**Scheme 1.** Synthesis of 9-methoxy-14,16-dimethyl[3.3]MCPs **3a–b** and 9-methoxy-14,16-dimethyl[3.3]MCP-2,2,11,11-tetraoxides **4a–b**.

The 2,11-dithia[3.3]MCPs **3a** and **3b** were thus obtained in 60% and 70% yields, respectively. Surprisingly, we found only the *syn* and none of the corresponding *anti*-conformers of **3a** and **3b** were obtained, which were assigned by the <sup>1</sup>H NMR chemical shifts of the aromatic, methoxy and methyl protons. <sup>1</sup>H-NMR spectra (CDCl<sub>3</sub>, 300 MHz) of **3a** and **3b** each exhibited singlets in the low field region at δ 3.73 and 3.70 ppm, respectively, for the methoxy protons, which are consistent for *syn* isomers.<sup>[14]</sup> The aromatic protons, in the region of δ 6.57–6.97 ppm (Table 1) for **3a** and **3b** can clearly be seen to be shielded by the adjacent rings, a consequence of the *face-to-face* benzene-benzene ring interactions, indicative of *syn*-conformers.<sup>[15]</sup> The *tert*-butyl protons were also observed at a higher field, at δ 1.08 ppm, for compound **3b** which is also



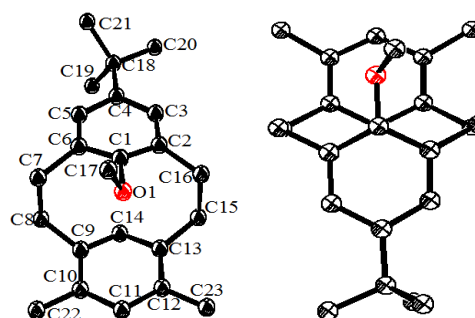
**Scheme 2.** Synthesis of 8-methoxy-12,14-dimethyl[2.2]MCPs **5a–b**.

supportive for the *syn*-conformer. Oxidation of *syn*-**3a** and **3b** with *m*-chloroperbenzoic acid in CHCl<sub>3</sub> afforded the corresponding bis(sulfone)s *syn*-**4a–4b** in 60% and 71% yields, respectively (Scheme 1). Their structures were confirmed by spectral analysis and mass data. Their *syn* conformations were assigned by <sup>1</sup>H-NMR as before deduced for **3a–b** (Table 1). Pyrolyses of bis(sulfone)s *syn*-**4a** and **4b** under reduced pressure (1 torr) at 465°C were conducted using the previously reported method<sup>[12a,14]</sup> to afford exclusively **5a** and **5b** in 55% and 60% yields, respectively (Scheme 2). <sup>1</sup>H-NMR spectra (CDCl<sub>3</sub>, 300 MHz) of **5a** and **5b** exhibit slightly low-field shielded singlets at δ 3.01 and 3.00 ppm respectively, for their methoxy protons at the 8-position, indicating formation of the respective *anti*-conformers (see Fig. 1). The internal aromatic protons at the 16-positions were now shifted to the high field region and were observed at δ 3.98 and 3.90 ppm respectively, indicating that *syn* to *anti* isomerization occurred. The *tert*-butyl protons of **5b** were also shifted to low field at δ 1.35 ppm compared with the corresponding signals for *syn*-**3b** and *syn*-**4b** (Table 1) indicating that in each compound, the two benzene rings are opposite to each other with the methoxy groups being shielded by the benzene rings. Thus, it appears that the *anti*-conformers **5a–b** are more stable than the *syn*-conformers in this [2.2]MCP system.

**Table 1.** <sup>1</sup>H NMR spectroscopic data for the synthesized MCPs in CDCl<sub>3</sub>.<sup>a</sup>

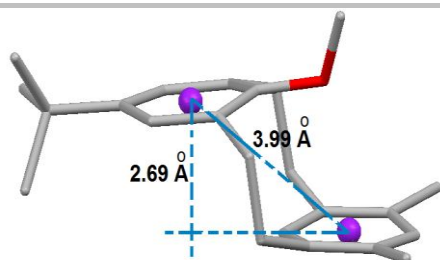
Compd	-Me	-OMe	Benzene protons	<i>tert</i> -Butyl
<i>syn</i> - <b>3a</b>	2.28	3.73	6.57, 6.63, 6.88, 6.96	-----
<i>syn</i> - <b>3b</b>	2.14	3.70	6.80, 6.97	1.08
<i>syn</i> - <b>4a</b>	2.29	3.84	6.78, 6.90, 7.40, 7.44	-----
<i>syn</i> - <b>4b</b>	2.28	3.78	6.71, 7.17, 7.49	1.10
<i>anti</i> - <b>5a</b>	2.29	3.01	3.98, 6.79, 7.05, 7.25	-----
<i>anti</i> - <b>5b</b>	2.28	3.00	3.90, 6.77, 7.04	1.35

<sup>a</sup>Chemical shifts are expressed in ppm (δ) against TMS as internal standard.



**Figure 2.** Ortep drawing of **5b** with top (left) and side (right) views. Thermal ellipsoids are drawn at the 50% probability level. All hydrogen atoms are omitted for clarity.





**Figure 3.** The distance between the geometric centres of the benzene rings of **5b**.

Single crystal of **5b** (CCDC 1945511) was grown by diffusing hexane into  $\text{CH}_2\text{Cl}_2$  at room temperature, and the structures were determined by X-ray crystallography. The crystal structure was found to belong to the monoclinic crystal system with space group  $P2_1$  (Table S1) and it adopts an *anti*-conformation as predicted from the  $^1\text{H-NMR}$  spectrum ( $\text{CDCl}_3$ , 300 MHz) (Figure 2). The mean distance between the mean geometric centres of the benzene rings of **5b** is equal to 3.99 Å, as shown in Figure 3.

### Computational Details

Computational studies were conducted to explore the conformational properties of the conformers of **3–5**. All computations were carried out with the Gaussian 09.e01 package.<sup>[16]</sup> The molecular geometries of the conformers shown were fully optimized in the gas phase, at the DFT level of theory using the B3LYP (Becke, three-parameter, Lee–Yang–Parr),<sup>[16]</sup> exchange–correlation with the 6-31G(d) basis set. The individual geometry-optimized structures and their energies are summarized in Figure 4 and Table 2. The energies of the less energetically-favoured conformers for each compound are presented as  $\Delta E$  values relative to the most energetically-favoured conformer for that compound. The resulting calculations suggest that the relative stabilities of the *syn*-chair-chair shaped structures are the most energetically favoured among the various conformational isomers of compounds **3–4** in the following order: *syn*-chair-chair > *syn*-chair-boat > *syn*-boat-boat. The *anti* conformers of **3a** and **3b** are relatively more stable than their *syn*-boat-boat conformers. Similarly, the *anti* conformers of **4a** and **4b** are relatively more stable than their chair-boat and boat-boat conformers. For **5a** and **5b** the *anti* conformers are relatively more stable than their *syn*-boat-boat conformers which are consistent with the experimental results.

The HOMO and LUMO of conformers **3–5** were also calculated, and are shown in Fig. S1. They reveal that the HOMOs show purely  $\pi$  character and are delocalized over the aryl rings. The relative energies ( $\Delta E$  kJmol<sup>-1</sup>), HOMO–LUMO energies ( $E_g$ ; eV) and HOMO–LUMO energy gaps ( $\Delta E$ ; eV) of the conformers calculated at the B3LYP/6-31G(d) levels of theory are listed in the Supporting Information). The HOMO–LUMO energy gaps of all conformers are relatively large (between 5.111 eV to 5.553 eV) thus confirming the relatively high chemical stability and low chemical reactivity of the respective conformers.<sup>[17,18]</sup>

### Iodine and Lewis Acid-Induced Transannular Reactions

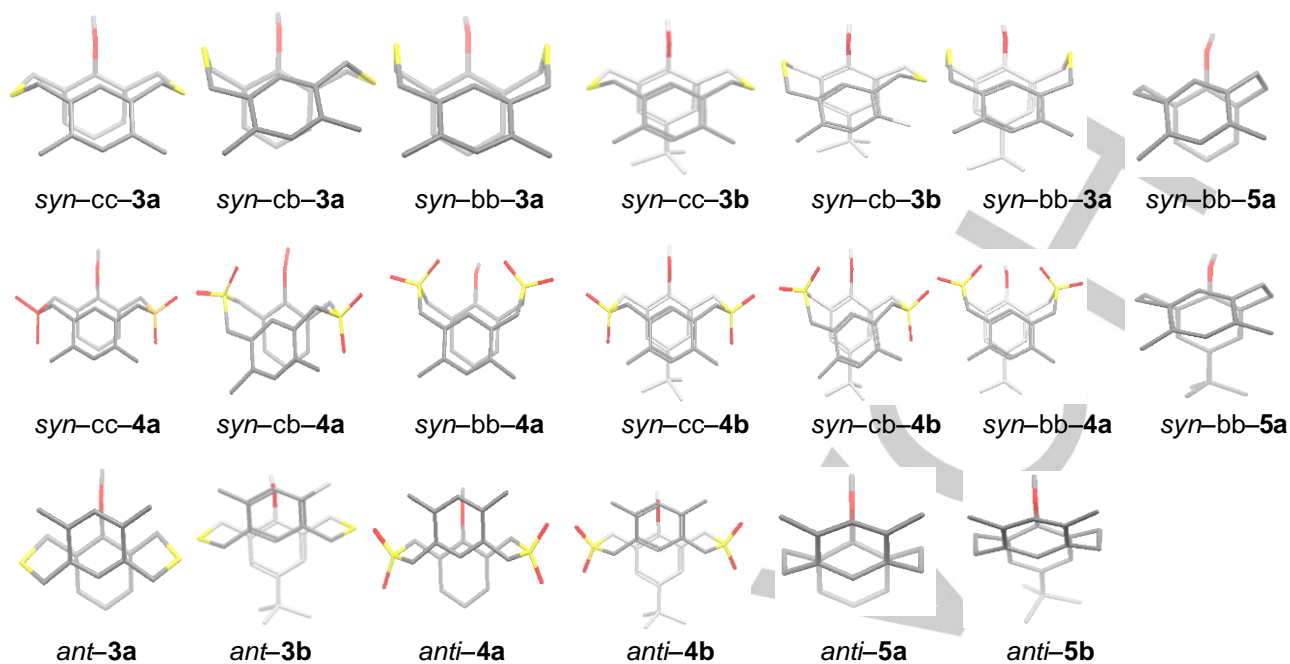
The iodine-catalyzed transannular reactions of **5a** and **5b** in benzene produced 4,5,9,10-tetrahydropyrenes **6a** and **6b** respectively, in 56% and 70% isolated yields (Scheme 3).

**Table 2.** B3LYP/6-31G(d) gas phase calculated optimized energies ( $E$ , kJ mol<sup>-1</sup>); optimized relative energies ( $\Delta E$  kJ mol<sup>-1</sup>) for the conformers of **3–5**.

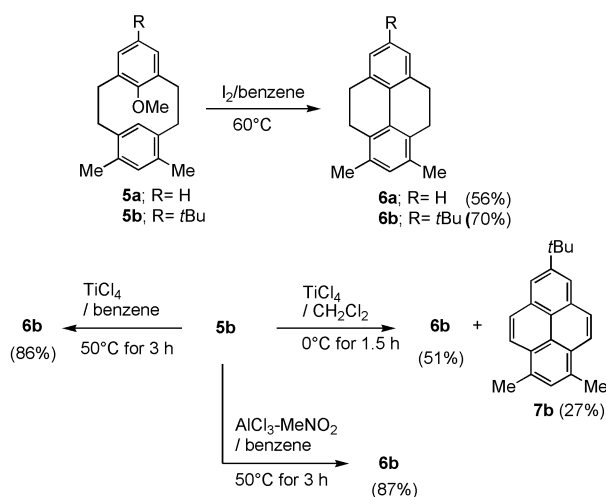
Conformers	Optimized energies $E$ (kJ mol <sup>-1</sup> )	Relative energies ( $\Delta E$ ) kJ mol <sup>-1</sup>
<i>syn</i> -chair-chair- <b>3a</b>	-4224102	0.00
<i>syn</i> -chair-boat- <b>3a</b>	-4224089	13.04
<i>syn</i> -boat-boat- <b>3a</b>	-4224070	31.41
<i>anti</i> - <b>3a</b>	-4224078	24.02
<i>syn</i> -chair-chair- <b>3b</b>	-4636975	0.00
<i>syn</i> -chair-boat- <b>3b</b>	-4636962	12.92
<i>syn</i> -boat-boat- <b>3b</b>	-4636944	31.22
<i>anti</i> - <b>3b</b>	-4636950	25.37
<i>syn</i> -chair-chair- <b>4a</b>	-5013803	0.00
<i>syn</i> -chair-boat- <b>4a</b>	-5013774	28.90
<i>syn</i> -boat-boat- <b>4a</b>	-5013734	68.62
<i>anti</i> - <b>4a</b>	-5013782	20.48
<i>syn</i> -chair-chair <b>4b</b>	-5426679	0.00
<i>syn</i> -chair-boat <b>4b</b>	-5426650	28.82
<i>syn</i> -boat-boat <b>4b</b>	-5426606	72.80
<i>anti</i> - <b>4b</b>	-5426657	21.36
<i>anti</i> - <b>5a</b>	-2133168	0.00
<i>syn</i> -boat-boat- <b>5a</b>	-2133134	34.37
<i>anti</i> - <b>5b</b>	-2546040	0.00
<i>syn</i> -boat-boat- <b>5b</b>	-2546007	33.56

Note: Relative energies ( $\Delta E$ ) =  $E(\text{chair-chair}) - E(\text{chair-chair})$ ;  $E(\text{chair-chair}) - E(\text{chair-boat})$  and  $E(\text{boat-boat}) - E(\text{chair-chair})$ .

It is presumed that these products were formed via a proposed iodine-aryl  $\sigma$ -complex intermediate **B** as shown in Scheme 4, and by analogy with the mechanisms proposed previously<sup>[7,11]</sup> for similar transannular cyclizations with other [2.2]MCPs. Here, iodonium ion attacks the *ipso*-position of **5b** to afford **B**, which produces **6b** via **C** and **D** and elimination of  $\text{I}^+$  and MeOH from **D**. Treatment of **5b** with  $\text{TiCl}_4$  in DCM afforded the transannular cyclization product **6b** and the corresponding pyrene derivative **7b** within 1.5 h in 51% and 27% yields along with unreacted **5b** in 12% yield. Similar treatment of **5b** at 50 °C in benzene for 3 h led to only transannular cyclization reaction to afford **6b** in 81% yield.



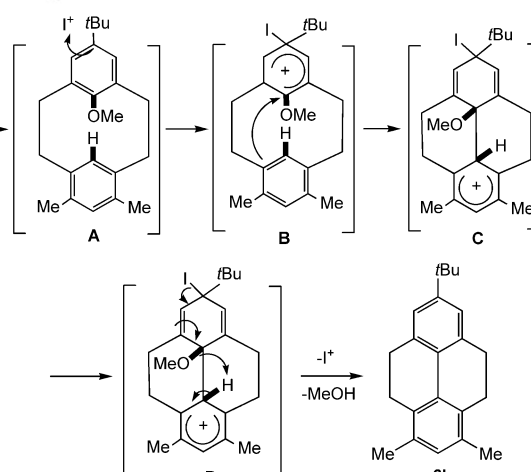
**Figure 4.** The molecular optimized structures of the various conformers of **3–5** MCPs in gas phase. Color code: carbon = grey; oxygen atom = red; sulfur atom = yellow. \*Note: cc = chair–chair, cb = chair–boat, and bb = boat–boat.



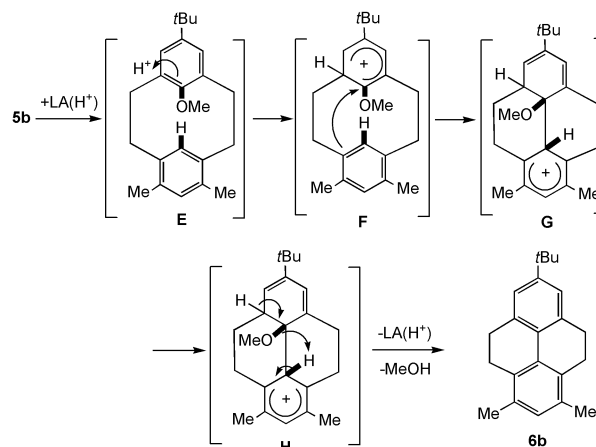
**Scheme 3.** Treatment of **5a** and **5b** with iodine and Lewis acids in benzene.

By contrast, treatment of **5b** with  $\text{AlCl}_3\text{-MeNO}_2$  at  $50^\circ\text{C}$  in benzene for 3 h afforded **6b** in 87% yield along with only very small amounts of **5b** and **7b**.

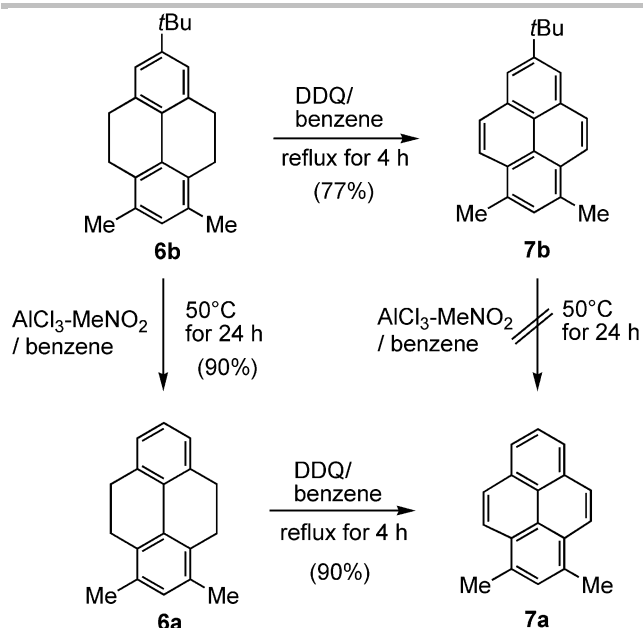
A mechanism for the formation of **6b** from the Lewis acid-catalyzed reactions can only be conjectured upon, as we have previously rationalized<sup>[11]</sup> and summarized in Scheme 5. Thus, protonation (or, as above, Lewis-acid complexation) at the *ortho* (or *para*) position of the methoxy-containing benzene ring of **5** could result in the formation of the stabilized cationic intermediates **E**, **F**, **G** and **H** via stepwise rearrangement and intramolecular cyclization. An alternative mechanism via a stepwise deprotonation-methoxy group elimination to form methanol (or methoxy–Lewis acid complex) followed by a methyl cation–Lewis acid complex could also potentially lead to the formation of **6b** and intramolecular cyclization (Scheme 5).<sup>[11]</sup> Dehydrogenation of **6a** and **6b** with DDQ in benzene afforded the corresponding pyrenes **7a** and **7b** respectively, in good yields.



**Scheme 4.** Reaction mechanism proposed for the formation of **6b** by an iodine-catalyzed transanular reaction.



**Scheme 5.** Reaction mechanism proposed for the formation of **6b** by the Lewis acid (LA)-catalyzed transanular reaction.



**Scheme 6.** Lewis acid ( $\text{AlCl}_3\text{-MeNO}_2$ )-mediated de-*tert*-butylation reaction of **6b** and DDQ dehydrogenation to form 1,3-dimethylpyrene **7a**.

No *trans-tert*-butylation of **7b** to form **7a** occurred under the conditions of  $\text{AlCl}_3\text{-MeNO}_2$  at 50°C in benzene. Only recovery of the starting compound **7b** was observed under the conditions used. However, a similar reaction of **6b** ( $\text{AlCl}_3\text{-MeNO}_2$  at 50°C) led to the effective removal of the *tert*-butyl group to give **7a** together with *tert*-butylbenzene.

The present findings suggest that the reaction pathway **5b**→**6b**→**6a**→**7a** could be exploited for the preparation of pyrene derivatives possessing alkyl groups in a variety of positions.

## Conclusion

Using the sulfur extrusion method, *anti*-8-methoxy[2.2]MCPs **5a** and **5b** were synthesized from *syn*-dithia-9-methoxy[3.3]MCPs **3a** and **3b** via *syn*-[3.3]MCP-2,2,11,11-tetraoxide **4a** and **4b**. Lewis acid-catalyzed reactions of **5b** led to transannular cyclization and de-*tert*-butylation reactions to form considerably less strained pyrene derivatives in good yields. These findings strongly suggest that the 8-methoxy group plays an important role in the transannular cyclization reactions and that the pathways observed in this study could afford alternative routes to new pyrene derivatives. DFT geometry optimized calculations suggest that the relative stability of the *syn*-chair-chair shaped structures are most favored energetically among the various conformational isomers of the [3.3]MCPs precursor compounds **3**–**4** in the following order: *syn*-chair-chair > *syn*-chair-boat > *syn*-boat-boat.

## Supporting Information Summary

Single-crystal X-ray crystallographic data of **5b**; and all DFT computational data and their respective xyz files.

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## Conflict of Interest

The authors declare no conflict of interest.

**Keywords:** DFT computations • Lewis acids • Metacyclophanes • Ring strain • *Syn-anti* conformers • Transannular cyclizations • *Trans-tert*-butylation

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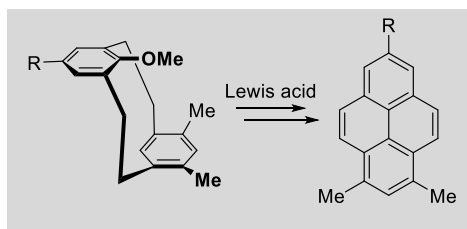


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Layout 1:

## FULL PAPER

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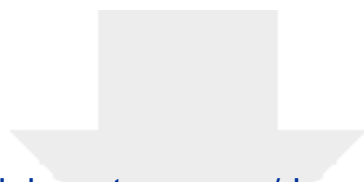


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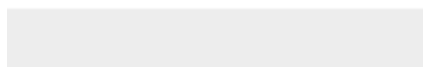
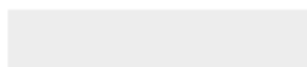
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**Studies on Lewis-Acid Induced Reactions of 8-Methoxy[2.2]metacyclophanes: A New Synthetic Route to Alkylated Pyrenes**

**Keywords:** DFT computations• Lewis acids• Metacyclophanes• Ring strain• *Syn-anti* conformers• Transannular cyclizations• *Trans-tert*-butylation



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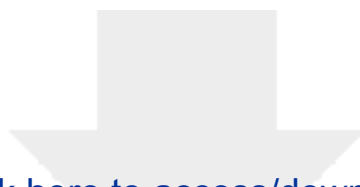




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