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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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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.
Thank you very much for your time and consideration.

Yours sincerely,

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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-tetraoxides 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 (TiCl4/AlCl3-MeNO2) 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 (-CH2-) group bridges of different lengths.

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The pioneering work in the cyclophane field was initiated by Cram in 1951,[l] 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[5] and the structures of many different types of cyclophanes have been reported.[5] 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.[6] Due to their flexibility, cyclophanes[5] have significant importance in theoretical studies and there are continuous efforts to synthesize novel cyclophanes of different sizes with numerous modes of ring attachments.[5] 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]MCP.[7] 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 variability-functionalyzed cyclophanes we have been interested in the preparation of various polymethyl-substituted [2.2]MCPs.[8] Recently, syntheses of 8-methyl- and 8-hydroxy[2.2]MCPs via the AlCl3-MeNO2-catalyzed retro-Friedel-Crafts trans-tert-butylation of the corresponding tert-buty1 derivatives in benzene were described by us.[7,9] The research reported herein describes the synthesis and the Lewis acid-induced transannular reactions of 5-tert-buty1-8-methoxy-12,14-dimethyl[2.2]MCP 5b under different conditions, and the...
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. 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. The macrocyclic [2.2]MCP frameworks were synthesized via the cyclocondensation reactions of bis(mercaptomethyl)-thiophenes 1a–b with 1,5-bis(chloromethyl)-2,4-dimethylmethyl-benzene 2 as outlined in Scheme 1.

![Scheme 1. Synthesis of 8-methoxy-12,14-dimethyl[2.2]MCPs 5a–b.](image)

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-isomers of 3a and 3b were obtained, which were assigned by the 1H NMR chemical shifts of the aromatic, methoxy and methyl protons. 1H-NMR spectra (CDCl3, 300 MHz) of 3a and 3b each exhibited singlets in the low field region at δ 7.37 and 3.70 ppm, respectively, for the methoxy protons, which are consistent for syn isomers. 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. The tert-butyl protons were also observed at a higher field, at δ 1.08 ppm, for compound 3b which is also an artifact of the tert-butyl substituent.

![Figure 2. Ortep drawing of 5b with top (left) and side (right) views.](image)

![Table 1. 1H NMR spectroscopic data for the synthesized MCPs in CDCl3.](image)

*Chemical shifts are expressed in ppm (δ) against TMS as internal standard.

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Single crystal of 5b (CCDC 1945511) was grown by diffusing hexane into CH$_2$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$_1$/2 (Table S1) and it adopts an anti-conformation as predicted from the $^1$H-NMR spectrum (CDCl$_3$, 300 MHz) (Fig. 2). The mean distance between the mean geometric centres of the benzene rings of 5b is equal to 3.99 Å, as shown in Fig. 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. 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), 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 (kcal mol$^{-1}$), HOMO–LUMO energies (Eg; 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.

**Iodine and Lewis Acid-Induced Transannular Reactions**

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

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

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

It is presumed that these products were formed via a proposed iodine-aryl $\alpha$-complex intermediate B as shown in Scheme 4, and by analogy with the mechanisms proposed previously for similar transannular cyclizations with other [2.2]MCPs. Here, iodonium ion attacks the $\alpha$-ido-position of 5b to afford B, which produces 6b via C and D and elimination of $^1$ and MeOH from D. Treatment of 5b with 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 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 AlCl₃-MeNO₂ at 50 °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[1] 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 methy cation-Lewis acid complex could also potentially lead to the formation of 6b and intramolecular cyclization (Scheme 5).[2] 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.
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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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