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A Macrocyclic 1,4-Diketone Enables the Synthesis of a *p*-Phenylene Ring That Is More Strained than a Monomer Unit of [4]Cycloparaphenylene

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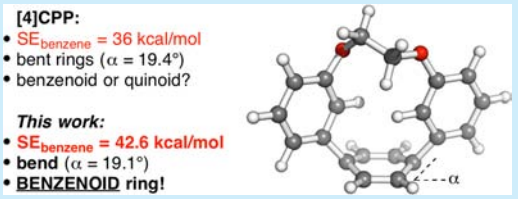
Supporting Information

ABSTRACT: The synthesis of a *p*-terphenyl-based macrocycle, containing a *p*-phenylene unit with 42.6 kcal/mol of strain energy (SE), is reported. The conversion of a macrocyclic 1,4-diketone to a highly strained arene system takes place over five synthetic steps, featuring iterative dehydrative reactions in the aromatization protocol. Spectroscopic data of the deformed benzenoid macrocycle are in excellent agreement with other homologues that have been reported, indicating that the central *p*-phenylene ring of **9** is aromatic.



The synthesis of increasingly strained aromatic systems has required increasingly high levels of synthetic innovation throughout the rich history of nonplanar arene synthesis. For example, the synthesis of the most strained [*n*]paracyclophanes featured the conversion of [*n*.2.2]propelladiene-based (Dewar benzene) precursors to benzenoid systems. In the case of the most strained [*n*]paracyclophane, [4]paracyclophane, strategically placed tetrasubstituted alkenyl groups were incorporated in the bridging unit to prevent *ipso*-protonation, and subsequent strain relief, from occurring at the *para*-carbon atoms.[1] An equally clever molecular design was employed by Tsuji and co-workers in their synthesis of a [1.1]-paracyclophane derivative, which still stands as the most distorted *para*-phenylene ring to be characterized by X-ray crystallography.[2] For nonbenzenoid systems, such as the fullerene allotrope of carbon C_{60}[3] and a short [5,5] armchair carbon nanotube (CNT) end-cap fragment,[4] strategically placed pentagons within polycyclic aromatic hydrocarbon (PAH) frameworks and chlorine atoms at specific arene vertices enabled Scott and co-workers to synthesize both of these molecules. The recent emergence of the [*n*]cycloparaphenylenes ([*n*]CPPs) and their potential application in the controlled bottom-up chemical synthesis of (*n*,*n*) armchair CNTs has renewed interest in the development of synthetic strategies for accessing highly strained benzenoid systems.[5] While several groups have entered this field over the past 8 years, only two have reported on the synthesis of the most strained CPP molecules.

In 2014, Yamago[6] and Jasti[7] individually reported the synthesis of the smallest CPP, [5]CPP. This macrocyclic compound, containing five *para*-linked benzene rings, is predicted to have a strain energy (SE) of 119 kcal/mol (23.8 kcal/mol per benzene ring).[8] Prior to its synthesis and subsequent characterization by X-ray crystallography, the benzenoid nature of its structure was called to question.[9] Indeed, the solid state structure obtained by Jasti and co-workers demonstrated that [5]CPP was in fact benzenoid.[7] The next smallest member of this class of carbon nanohoops is predicted to have 144 kcal/mol of SE (36 kcal/mol per benzene ring) contained within the macrocyclic structure.[8] This high degree of SE has led many to believe that [4]CPP (**1**) may not be composed of benzen(oid)e rings and may possibly prefer a quinoidal-type structure (**2**, Figure 1), which is in part

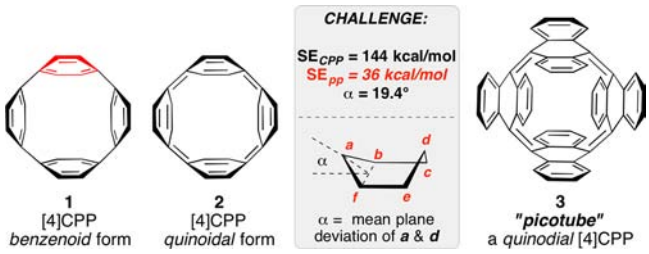


Figure 1. [4]CPP: Benzenoid or quinoid?.

due to the known [4]CPP derivative "picotube" having been shown to be quinoidal. Herges and co-workers reported the synthesis of picotube (**3**) in 1996,[10] which proceeded through a photochemically induced ring expanding metathesis-based strategy. The precursor hydrocarbon of picotube contained C_{sp^2}–C_{sp^2} π-bonds bonds between adjacent "pre-arene" subunits and, therefore, may not represent the best model for **1**. A potentially better suited macrocyclic precursor to [4]CPP is one that contains the requisite C_{sp^2}–C_{sp^2} σ-bonds between adjacent arene and prearene units. However, the synthesis of such a macrocyclic precursor is not trivial (Figure 2).

The synthetic approaches used to construct the macrocyclic precursors of [5] and [6]CPP involved a common intermediate

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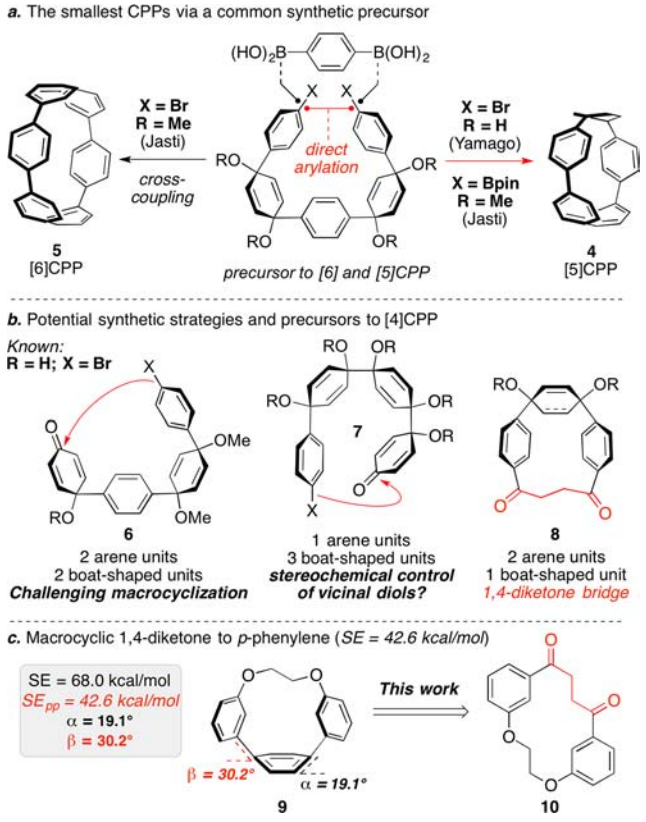
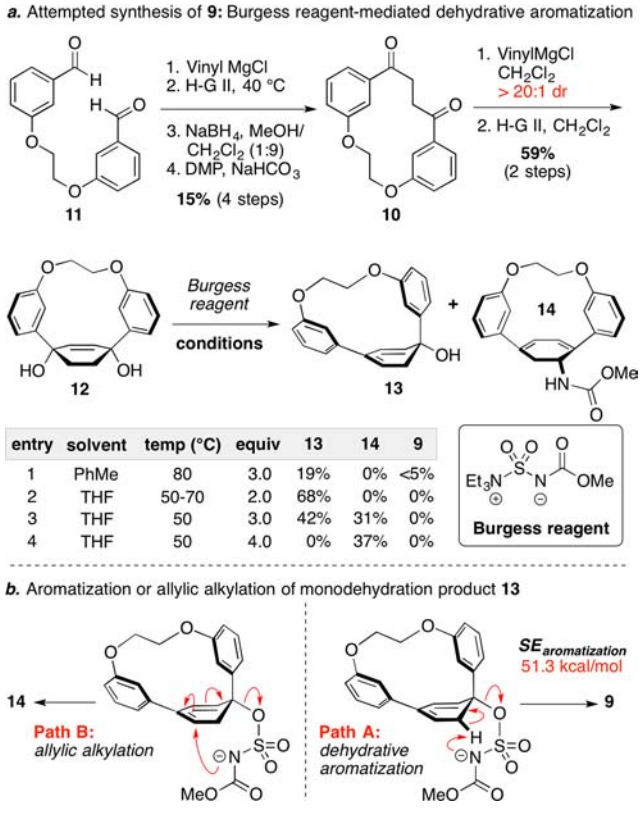


Figure 2. (a) The smallest CPPs via a common precursor, (b) Potential precursors of [4]CPP, (c) A macrocyclic 1,4-diketone-based approach to a *p*-phenylene ring containing 42.6 kcal/mol of SE.

(Figure 2a).[11] Directed arylation startegies, via Ni (Yamago) and Pd-mediated (Jasti) reactions, led to the formation of C_{sp^2}–C_{sp^2} bonds and macrocycle synthesis. Employing the same type of macrocyclization strategy to a smaller precursor molecule poses a significant synthetic challenge. The introduction of boat-shaped, prearene subunits in the common precursor (Figure 2a) and related systems is critical to the success of macrocyclization reactions,[5] as the *syn*-1,4-diol units provide the necessary curvature or kink in the linear acyclic precursors to bring the reacting arene vertices into proximity and facilitate C–C bond formation. The sheer distance between the terminal *para*-vertices of an acyclic precursor containing two arene and two (boat-shaped) prearene units will be difficult to overcome, as will competing intermolecular reactions between an aryllithium or Grignard-type reagent (e.g., **6**, Figure 2b). Introduction of three boat-shaped units into an acyclic precursor (e.g., **7**, Figure 2b) may bring the desired reacting termini closer together; however, controlling the relative stereochemical relationship between vicinal tertiary diol units will be a considerable synthetic challenge. To address both of these (potential) shortcomings, it is proposed that a cyclophane-based approach where a 1,4-diketo-bridging group spanning two arene units, which are further bridged by a single boat-shaped unit, may represent a viable macrocyclic precursor to [4]CPP (e.g., **8**, Scheme 2b). To validate this approach we set our sights on the synthesis of a *p*-terphenyl-based macrocyclic system containing a *p*-phenylene unit that is more strained than a monomer unit of [4]CPP (**9**, Figure 2c). The key feature involves the conversion of a macrocyclic 1,4-diketone unit into a highly strained *p*-phenylene system.[12]

Recently, we reported the synthesis of a homologous series of *p*-terphenyl-based macrocyclic systems, containing highly deformed *p*-phenylene units using a mild dehydrative aromatization reaction that proceeded without rearrangement of the central phenylene ring.[13] Following this strategy, dialdehyde **11** was synthesized using a known procedure.[14] However, the best yield that could be obtained for this reaction, in our hands, was 13%.[15] Nonetheless, gram-scale quantities of **11** could be prepared.[16] Applying a streamlined four-step protocol that has been developed in our laboratory[13] afforded macrocyclic 1,4-diketone **10** in 15% overall yield. Similar to what was observed during the synthesis of a homologous 15-membered 1,4-diketo macrocycle, the ring-closing metathesis (RCM) reaction of the intermediate diene gave a significant amount of a higher molecular weight metathesis byproduct.[13] Treatment of **10** with vinylmagnesium chloride gave the corresponding *syn*-allylic diol (**17**, Scheme SI-1)[17] as a single diastereomer, which was directly subjected to a second RCM reaction to afford macrocycle **12** in 59% yield over two steps. Previously, direct aromatization of cyclohex-2-ene-1,4-diol precursors, such as **12**, was accomplished using a Burgess reagent-mediated dehydrative aromatization reaction to afford the central *p*-phenylene unit. In the case of the most strained system that had been prepared using this strategy, 37.0 kcal/mol of SE was introduced into the macrocyclic benzenoid target upon elimination of two molecules of water, affording a *p*-phenylene ring containing 28.4 kcal/mol of SE.[13] Subjecting diol **12** to the same reaction conditions gave the monodehydration product **13** in 19% yield, with a trace amount (<5%) of the desired 1,4-dioxa[4](3,3″)*p*-terphenylophane (**9**, entry 1, Scheme 1a).[18]

Scheme 1. (a) Synthesis of Macrocycle 13, (b) Proposed Mechanism for the Formation of 13 and 14



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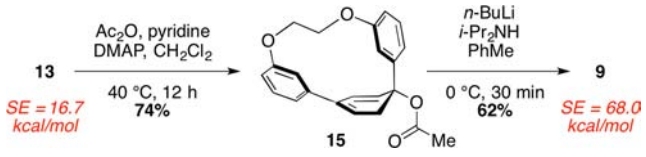
In recent synthetic studies, we have screened different dehydrative aromatization reaction conditions and found that THF can be successfully employed as solvent for this reaction. Moreover, dehydrative aromatization reactions in THF can be run at lower temperatures than the toluene variation, making the reaction conditions potentially better suited for the formation of increasingly strained *p*-phenylene units. Treatment of **12** with 2.0 equiv of the Burgess reagent in THF at 50 °C for 1 h, led to the formation of monodehydration product **13** in 68% yield (entry 2, Scheme 1a). Prolonged heating of this reaction and increasing the temperature to 70 °C did not afford any of the desired aromatized macrocycle **9**. Increasing the number of equivalents (2.0 to 3.0 equiv) of Burgess reagent used led to the formation of **13** (42%) and an allylic alkylation product **14** in 31% yield (entry 3, Scheme 1a). In fact, the addition of 4.0 equiv of Burgess reagent afforded **14** as the sole product of this reaction in 37% yield (entry 4, Scheme 1a). It appears that the second dehydration reaction (Path A, Scheme 1b) under these conditions is less favorable than the corresponding allylic alkylation reaction (Path B, Scheme 1b). However, the observation that the highly strained *p*-phenylene ring was formed, albeit in trace amount, under dehydrative conditions in toluene led us to pursue an alternative aromatization protocol.

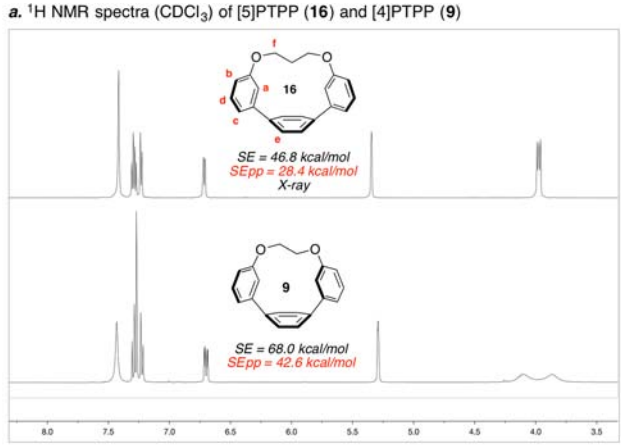
Close monitoring of the dehydration reaction of **12**, to afford a trace amount of **9** (entry 1, Scheme 1a), gave no indication that the desired compound was prone to decomposition or rearrangement reactions. However, the low yield of these two products, when compared to previous results and the THF variation of this reaction, was cause for concern. During the final stages of Jasti and co-workers' synthesis of [5]CPP,[7] it was necessary to modify their aromatization protocol to furnish the remaining two *p*-phenylene rings of the desired nanohoop. In the case of **13**, we envisioned a β-elimination of AcOH could be employed to furnish the highly strained aromatized product **9** (Scheme 2). Thus, **13**, SE = 16.7 kcal/mol, was acetylated to

Scheme 2. Synthesis of 1,4-Dioxa[4](3,3″)*p*-terphenylophane (9)

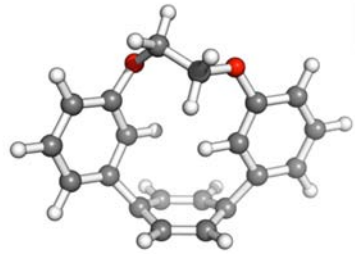


give **15** in 74% yield. In order to introduce the remaining 51.3 kcal/mol of SE, an LDA-mediated elimination of AcOH was designed. Indeed, treatment of acetate **15** with LDA in toluene at 0 °C gave the desired macrocycle **9**. The strain energy induced in this reaction (51.3 kcal/mol) per *p*-phenylene unit generated is greater than that induced during the Jasti synthesis of [5]CPP (cf. 43.5 kcal/mol of SE per *p*-phenylene ring synthesized).[7] Incremental increases in SE induction have been paramount to the successful preparation of increasingly strained arenes. Similarly, this strategy of employing iterative elimination protocols can be tailored to the synthesis of increasingly strained systems such as [4]CPP.

All attempts to grow suitable crystals of **9** for X-ray diffraction studies were unsuccessful. However, the optimized geometry of **9** was obtained from density functional theory (DFT) calculations using the B3LYP functional, in combination with the 6-31G(d) basis set (Figure 3b). Comparing the



b. optimized geometry of **9** with structural and spectral data for **9** and **16**



metric	16 (expt)	16 (DFT)	9 (DFT)
α (°)	**15.7**	**15.4**	19.1
β (°)	**24.6**	**24.5**	30.2
δH_a	5.35		5.29
δH_b	6.72		6.70
δH_c	7.25-7.21		7.24-7.21
δH_d	7.33-7.26		7.31-7.26
δH_e	7.42		7.43
δH_f	4.12-3.81		4.20-3.76

Figure 3. (a) ^{1}H NMR spectra of [4]PTPP (**9**) and [5]PTPP (**16**); (b) optimized geometry of **9**, deformation angles and aromatic proton resonances for **9** and **16**.

deformation angles α and β derived from the X-ray crystal structure of **16** (Figure 3a),[13] with the DFT-derived values for **16**, shows excellent agreement (Figure 3b). In fact, it appears that the computationally derived value of α for **16** is slightly lower than the experimentally determined value. Thus, in the case of **9**, the computational value of α = 19.1° is likely very close to the predicted value of α in [4]CPP (19.4°).[19] The β angle of **9** at 30.2° is considerably larger than the average value of β reported (24.9°) for the most distorted *p*-phenylene ring to be characterized by X-ray crystallography.[2] One of the major questions surrounding the structure of [4]CPP is whether or not the highly strained *p*-phenylene rings will retain their benzenoid form. In the case of **9**, the central arene unit of the *p*-terphenyl system represents a good model for a monomer unit of [4]CPP and can provide valuable insight into addressing this question. Its computed SE of 42.6 kcal/mol is greater than that of a monomer unit of **1**, and the boat deformation angle (α) of 19.1° is in good agreement with the computational predicted value of the bent benzene rings of [4]CPP. Furthermore, the biaryl bonds that connect the central *p*-phenylene ring simulate the structure of a monomer unit of **1** and represent a good model of the arene units contained within the macrocycle.

The overall out-of-plane deformation of the central arene of **16** is nearly identical to the *p*-phenylene units of **4**, as indicated by their α angles of 15.7° and 15.6°, respectively. Despite both of these large deviations from planarity, which impart a great deal of strain on the *p*-phenylene rings (28.4 and 23.8 kcal/mol for **16** and **4**, respectively), the solid state structures of both **16** and **4** revealed that the C−C bond lengths of the strained arene units are between 1.39 and 1.40 Å and 1.38−1.40 Å, respectively. Indicating that both rings are indeed benzenoid. The ^{1}H NMR spectrum of **4** shows one signal at δ = 7.86 ppm,

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which is shifted downfield by 0.22 ppm relative to [6]CPP (**5**). The narrowing of the torsional angle between the adjacent phenyl rings, and not the increase in distortion of the arene(s), is cause for this increase in chemical shift. In the case of the [*n*](3,3″)*p*-terphenylophanes that have been reported, there is very little deviation in the aromatic resonances observed in the ^{1}H NMR spectra due to the larger torsional angles between the arene units. Protons at the 2 and 2″-positions (a, Figure 3a) are generally shifted to higher field as the number of methylene groups in the alkoxy bridging unit decreases.[12] This can be attributed to the increased β angle, which directs these protons toward the shielding cone of the central *p*-phenylene ring. Protons b, c, d, e, and f (Figure 2a) show virtually no deviation in their chemical shift values, and in the case of **9**, its ^{1}H NMR spectrum is nearly identical to that of **16**. Coupled with the X-ray structure of **16** and identical magnetic susceptibility, these data are suggestive that the highly strained *p*-phenylene ring that is part of a teraryl macrocyclic system, containing an SE greater than 36 kcal/mol and an α angle of 19°, is benzenoid. Finally, the computationally derived structure of **9** indicates that the C−C bond lengths of the central arene unit are between 1.40 and 1.41 Å.

In summary, the synthesis of a macrocyclic benzenoid system containing a *p*-phenylene ring that is predicted to be more strained than the *p*-phenylene monomer units of [4]CPP has been developed. The aromatization reaction relies on the application of iterative elimination reactions of two hydroxyl groups present in a precursor macrocycle and is capable of generating 51.3 kcal/mol of SE at 0 °C. The aromatic region of the proton NMR spectrum of **9** is essentially identical to a previously reported homologue, **16**, for which an X-ray crystal structure has been obtained. This provides good evidence that a (teraryl) *p*-phenylene unit containing an α angle comparable to that predicted for [4]CPP and more strain energy than a monomer unit of the yet to be synthesized nanohoop is both benzenoid and within reach synthetically. The utility of this (1,4-diketone) macrocyclic-based approach to strained biaryl *p*-phenylene units continues to be explored, and the synthesis of macrocycles akin to **8** (Figure 2b), for the attempted synthesis of [4]CPP, are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01536.

Experimental procedures, characterization data, including ^{1}H and ^{13}C NMR spectra for all new compounds, and Cartesian coordinates (PDF)

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Notes

The authors declare no competing financial interest.

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(15) See Supporting Information for experimental details.
(16) It should be noted that this compound is available from commercial sources.
(17) This scheme and additional details on compound **17** can be found in the Supporting Information.
(18) HRMS and ^{1}H NMR data were obtained for the trace amount **9** produced in this reaction.
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