Organic LETTERS

Letter

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A Strain Induced Change of Mechanism from a [2 + 2 + 2] to a [2 + 1 + 2 + 1] Cycloaddition Reaction

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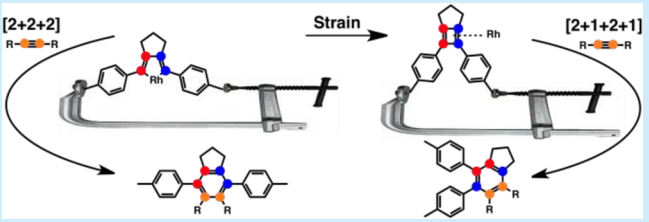
Supporting Information

ABSTRACT: While investigating the [2 + 2 + 2] cycloaddition as a tool to build up strained oligophenyl systems with a diyne-ethylene glycol macrocyle, a surprising change of mechanism was observed. Instead of the expected [2 + 2 + 2] *para*-terphenyl, the *ortho*-terphenyl product explained by a formal [2 + 1 + 2 + 1] cycloaddition was formed. An η^4-coordinated metal-cyclobutadiene is proposed as the key structure in the catalytic cycle, which is formed to release the induced strain. The optical properties of the *ortho*-terphenyl products have been measured as well as the coordination ability of Na^+ and K^+.



The [2 + 2 + 2] cycloaddition has been established as one of the best methods to access substituted benzene rings.[1] The high efficiency, combined with a broad tolerance of functional groups as well as the perfect atom economy, characterizes this useful process. Therefore, this reaction has been applied in a number of syntheses of complex molecules and natural products.[2] In this reaction three alkynes are combined to an aromatic system using a metal catalyst such as Rh, Co, Ru, or Ir. The mechanism has been studied extensively for different metal catalysts.[3] Driving force for the [2 + 2 + 2] cycloaddition is the large amount of energy gained from the aromaticity. Hence, this transformation should be ideal to overcome energetic barriers introduced in the cycloaddition product, e.g., by strain.

With this reasoning we envisioned the synthesis of strained oligophenylenes[4] using the [2 + 2 + 2] cycloaddition as the method of choice, which might serve as a model system for the assembly of cycloparaphenylenes.[5,6] King and co-workers showed the feasibility of introducing strain via the [2 + 2 + 2] cycloaddition in the synthesis of a highly strained quadranulene.[2c]

In order to bend the oligophenylene, a suitable tether was attached in the terminal *para*-positions (Figure 1). Thus, the strain introduced could be conveniently adjusted by the tether length. Because the preparation of such macrocyclic precursors is notoriously difficult, both tethers had to be carefully chosen. The two alkynes were joined by a $CH_2C(CH_2OCH_3)_2CH_2$ fragment. The quaternary carbon center will force the two alkyne moieties into closer proximity due to a Thorpe−Ingold effect. The second tether between the two phenyl rings consists of an oligoethylene glycol chain. The O atoms in the tether increase the flexibility dramatically compared to their carbon analogue. Additionally, the possibility to add a templating metal further increased its attractiveness.

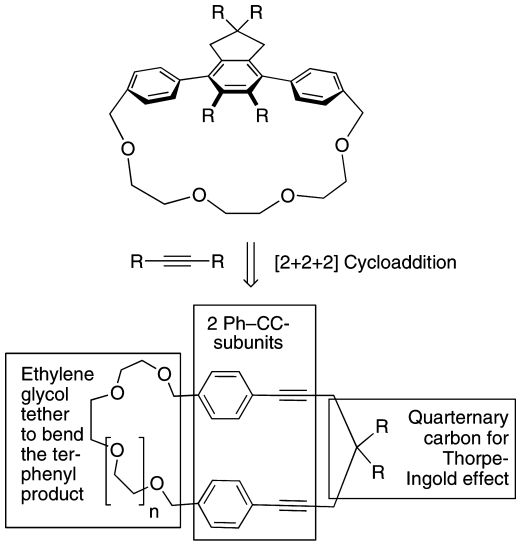


Figure 1. Design of a macrocyclic precursor for the synthesis of strained oligophenylenes.

The synthesis commences with the Sonogashira coupling of bisalkyne **1** with the iodobenzene derivative **2** to yield the desired bisbenzylalcohol **3** (Scheme 1). The strategy chosen for the macrocyclization relied on an ether formation by a substitution reaction between ditosylated triethylene glycol **4** and the benzylic alcohols of the dialkyne building block **3** using NaH as the base.[7] By taking advantage of the template effect of the sodium cation, the desired macrocycle could be isolated in 33% yield. A crystal structure of the macrocycle is shown in

Received: March 14, 2014
Published: April 23, 2014

   dx.doi.org/10.1021/ol5007604 | *Org. Lett.* 2014, 16, 2410−2413

Scheme 1. Synthesis of the Macrocyclic Precursor 5

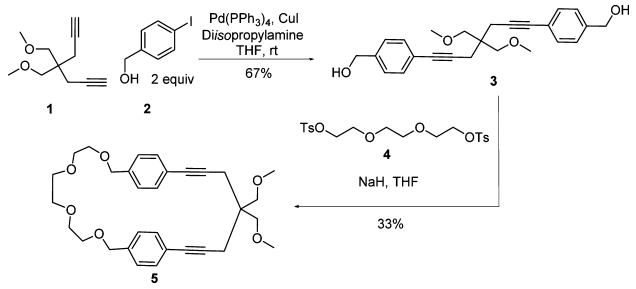


Figure 2. The attempt to close the ring via alkene metathesis was not successful. Also, changing the order in the reaction sequence, building up first the bisaryl ethylene glycol chain and then closing the macrocycle via Sonogashira coupling, did not lead to the desired product.

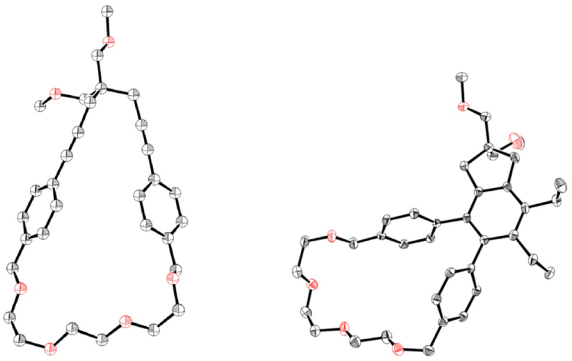


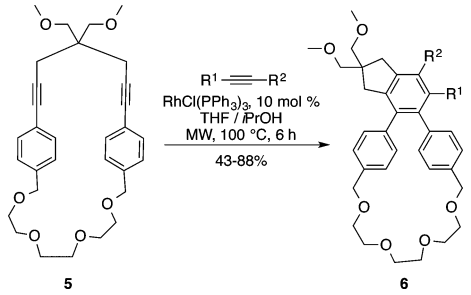
Figure 2. Crystal structure of the macrocyclic precursor **5** (left) and the [2 + 1 + 2 + 1] product **6a** (ORTEP drawing, hydrogens, solvent, and disorder are omitted for clarity).

With precursor **5** in hand the [2 + 2 + 2] cycloaddition reaction was tested. The procedure reported in the literature[8] was modified using microwave irradiation to reduce reaction times. Without microwave irradiation, the reaction required 40 h and the addition of a second batch of catalyst to achieve completion. Under microwave irradiation, reaction times could be reduced to 6 h and the catalyst loading down to 10 mol %.

Surprisingly, when 3-hexyne was used as a reaction partner, an *ortho*-terphenylene was observed instead of the expected *para*-terphenylene product. The structure of the product was unambiguously proven by NMR experiments as well as by X-ray analysis (Figure 2). To test the generality of this unexpected outcome, the reaction was performed with various monoynes (Table 1). In all cases tested the *ortho*-terphenyl product was obtained in moderate to good yield. Besides aromatic and alkyl substituents, free hydroxyl groups were also well tolerated. Only ester and TMS substituted alkynes did not give the desired product. Instead the trimerization of these alkynes was observed. In the case of dimethyl acetylenedicarboxylate no reaction was observed (Table 1, entry 9). Unsymmetric substituted alkynes preferentially gave one regioisomer with the larger R-group next to the phenyl.

Different solvent systems and concentrations were tested in order to provoke the formation of the *para*-terphenylene [2 + 2 + 2] cycloaddition product initially expected. However, the *ortho*-terphenyl product was always favored. Traditional heating led to the same results. The influence of different catalysts (such as $Pd(PPh_3)_4$, Grubbs I, $NiBr_2(dppe)/Zn$, CoI_2/Zn) was

Table 1. [2 + 1 + 2 + 1] Cycloaddition on Strained Precursor



	alkyne			
entry	R^1	R^2	product	yield
1	Et	Et	**6a**	88%
2	Ph	Ph	**6b**	64%
3	CH_2OH	CH_2OH	**6c**	59%
4	Ph	H	**6d**	67%
5	$C(CH_3)_2(OH)$	H	**6e**	62%
6	$CH_2CH_2CH_3$	H	**6f**	64%
7	CH_2CH_2OH	H	**6g**	43%
8	Me	CH_2OH	**6h**	64%
9	COOMe	COOMe	**6i**	–
10	TMS	TMS	**6j**	–

also investigated, but no reaction was observed with any of the other catalytic systems screened.

To explain the formation of the unexpected product, we propose the mechanism shown in Figure 3. The first step involves ligand dissociation and coordination of the two alkyne moieties of the macrocycle **5** to rhodium. Next, the well accepted rhodacyclopentadiene **B** is formed. However, already at this stage intermediate **B** experiences the strain induced by the tether. Therefore, instead of the expected coordination compound **G** followed by insertion of the alkyne to the rhodacycloheptatriene **H**, the η^4 complex **C** is proposed, which is formed via reductive elimination.

This deviation from the standard [2 + 2 + 2] catalytic cycle allows reduction of the strain induced by the tether compensating for the ring strain of the cyclobutadiene, which is additionally stabilized by the coordination with the metal.

The η^4 complex can be represented by two resonance structures **C** and **D**. Insertion of the metal delivers the less strained complex **E** which then follows the classical mechanism. Coordination of the monoalkyne, followed by its insertion, formed metallacycloheptatriene **F**. Finally, reductive elimination leads to the product **6**. *Hence, the strain induces a change of the mechanism from the [2 + 2 + 2] mechanism to a formal [2 + 1 + 2 + 1] cycloaddition.* The curvature of the *para*-terphenyl product **I** corresponds roughly to an [8]CPP, for which the ring strain was calculated to ~70 kcal/mol,[6] translating into a strain energy of ~26 kcal/mol for **I**. Similar reactivity has been observed as a side reaction by Tanaka and co-workers during the synthesis of a helicene.[9] The usual cycloaddition mechanism does not involve cyclobutadiene intermediates **C** and **D** and is considered to be nonprogressive for the catalytic cycle. Numerous cyclobutadiene complexes of cobalt and rhodium have already been isolated.[10] If the strain was the cause for the observed change in mechanism, increasing the tether length should influence this parameter and restore the [2 + 2 + 2] reactivity. Indeed, increasing the number of ethylene glycol units from three to six lead to the isolation of the [2 + 2 + 2] cycloadduct as the sole product allowing a straight

dx.doi.org/10.1021/ol5007604 | *Org. Lett.* 2014, 16, 2410–2413

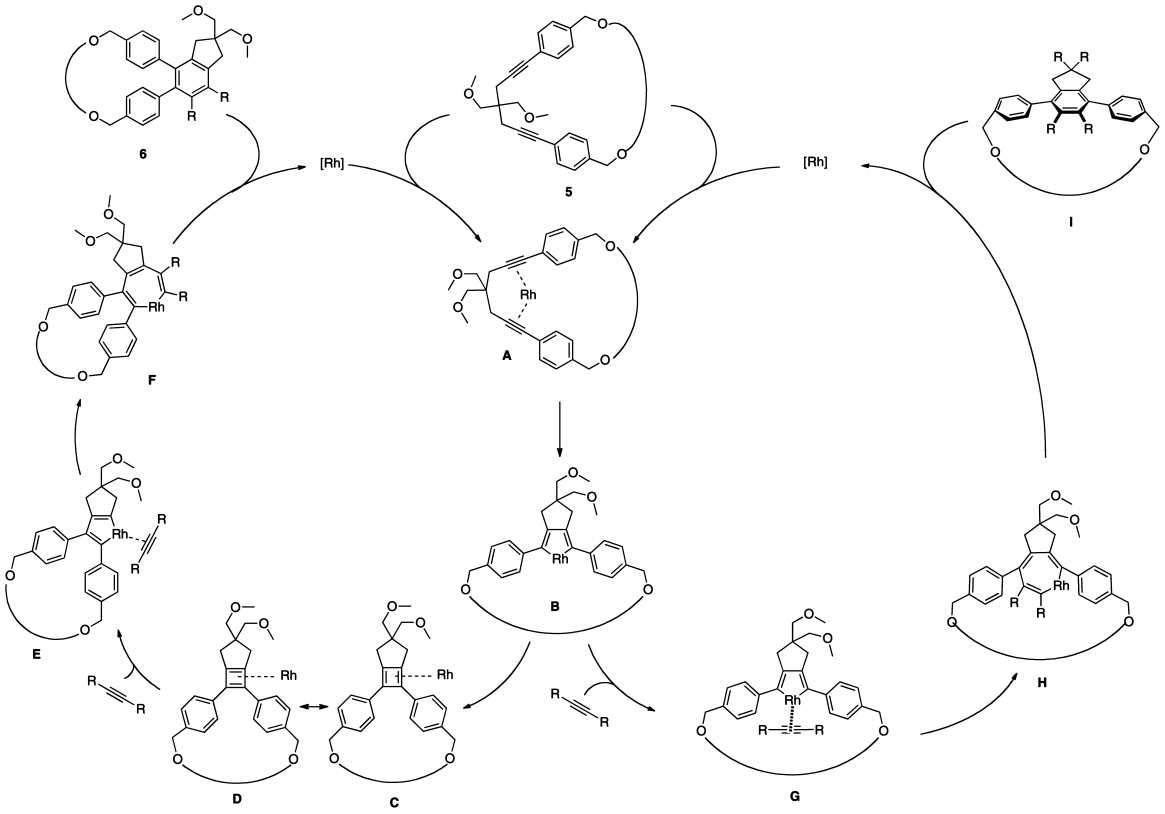


Figure 3. Proposed mechanism for the [2 + 1 + 2 + 1] cycloaddition reaction of strained system (left) and the standard [2 + 2 + 2] cycloaddition reaction (right) (ligands are omitted for clarity).

arrangement of the *para*-terphenyl moiety. Not surprisingly, if no tether was present, only the [2 + 2 + 2] product was observed.

Photooptical properties were measured for the macrocyclic molecules. The absorption maximum was observed at 245 nm, and emission occurred around 350−375 nm. Unsubstituted linear *ortho*-terphenyl in contrast absorbs at 260 nm and presents emission maxima at 450 and 478 nm.[11] The tethered macrocyclic *ortho*-terphenyls have smaller Stokes shifts. Notably, the diphenyl substituted molecule showed an even shorter Stokes shift with absorption at 250 nm and emission at 350 nm (Figure 4).

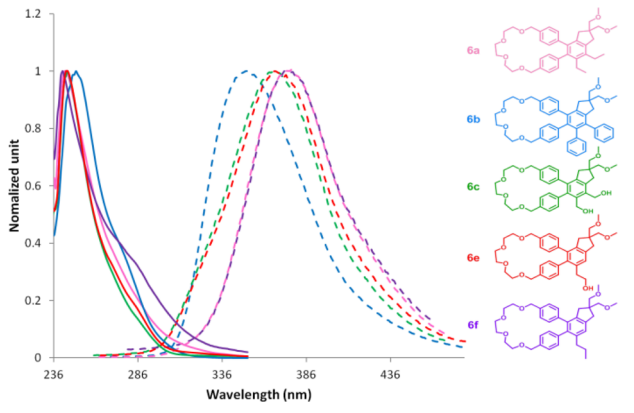


Figure 4. UV−vis absorption (solid line) and fluorescence spectra (dashed lines) of [2 + 1 + 2 + 1] cycloaddition products (normalized spectra, measured in chloroform).

Noncovalent cation−π interactions are playing an important role in stabilizing biological and chemical assemblies.[12] Therefore, polyaromatic systems combined with a crown ether cavity could function as electrochemical sensors for sodium or potassium cations. Such molecules hold potential application for functional extractants or conductive electrolytes. As the [2 + 1 + 2 + 1] cycloadducts **6** ideally suit such criteria the ability to bind cations such as Na^+ and K^+ was investigated. The binding of the Na/K cation to the macrocycle was monitored by ^{1}H NMR spectroscopy in deuterated acetone (0.02 M) with the incremental addition of a solution of $NaPF_6$ and KPF_6 respectively (0.008 M in acetone d6) analogously to the procedure reported by Rathore and co-workers.[7] The addition of potassium resulted in a dramatic shift of the signals of both the aromatic and the ethylene glycol protons (by up to 0.1 ppm) indicating a strong coordination of the potassium cation to both the crown ether part of the molecule and the phenyl rings. The addition of sodium cations led, however, only to a shifting of the ethylene glycol protons signals (0.05 ppm), while the aromatic signals remained unchanged (see SI). The sodium cation is smaller than the potassium cation and can be fully accommodated by the triethylene glycol crown ether part of the molecule further away from the phenyl moieties, as can be seen in modeled structures (Figure 5). Similar to Rathore, it was not possible to calculate binding constants based on the NMR-titration, as the values were too high.[7]

In conclusion, an unexpected change of reactivity was observed in the [2 + 2 + 2] cycloaddition when a strained precursor was subjected to the Rh-catalyzed reaction conditions. Instead of observing [2 + 2 + 2] cycloaddition, a [2 + 1 + 2 + 1] cycloaddition took place leading to an *ortho*-terphenylene macrocyclic product. This outcome offers new

dx.doi.org/10.1021/ol5007604 | *Org. Lett.* 2014, 16, 2410−2413

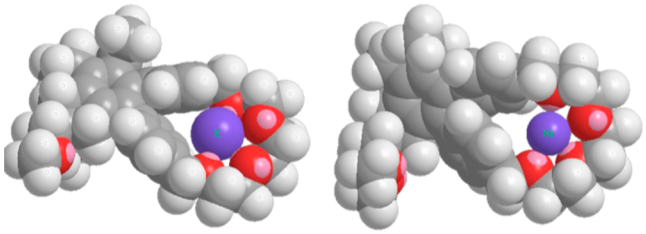


Figure 5. Space-filling model (MM2 optimization) of the complex between the macrocycle **6** and potassium (left) or sodium (right).

insight into the reaction mechanism involved in the [2 + 2 + 2] cycloadditions and increases the applicability and predictability of this useful synthetic tool. Finally, the optical properties and the complexation with alkali metals were studied identifying different binding modes for K^+ and Na^+, rationalized by the different sizes.

■ ASSOCIATED CONTENT

Supporting Information

Syntheses and characterization of all new compounds, crystallographic data of **5** and **6a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Dedicated to Prof. Dr. Armin de Meijere, Georg-August-Universität, Göttingen, on the occasion of his 75th birthday. This work was financially supported by the university of Basel, Staatssekreteriat für Bildung and Forschung SBF and the COST action MP0901 NanoTP.

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