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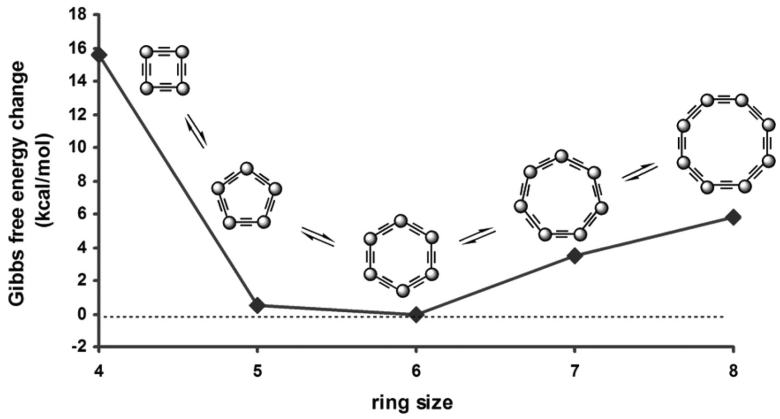

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Reaction Pathways Leading to Arylene Ethynylene Macrocycles via Alkyne Metathesis

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Abstract: Mechanistic studies on the direct formation of arylene ethynylene macrocycles via alkyne metathesis catalyzed by a molybdenum complex are reported. Gel permeation chromatography (GPC) and matrix-assisted laser desorption ionization (MALDI) mass spectrometry on the products from metathesis of monomer **1** show the initial formation of linear oligomers and large macrocycles ($n > 6$), followed by their transformation into the thermodynamically most stable product distribution—mainly the cyclic hexamer. Variable temperature and scrambling experiments reveal the reversibility of macrocycle formation. Nearly identical product distributions are observed from the cross metathesis of hexacycle **2** with diphenylacetylene and from the metathesis of bis(phenylethynyl) substituted monomer **4**, demonstrating that macrocycle formation is thermodynamically rather than kinetically controlled. The metathesis byproduct, 3-hexyne, is shown to inhibit the catalyst. It is suggested that the relative metathesis rates of dialkylalkynes versus diarylalkynes trap the catalyst in a nonproductive manifold, rendering it unavailable for the productive metathesis of aryl alkylalkyne substrates. This finding indicates that dialkyl-substituted alkyne byproducts should be avoided (or efficiently removed) if the metatheses of aryl substrates, especially those with electron-withdrawing groups, are to proceed to high conversion.

Introduction

Shape-persistent arylene ethynylene macrocycles are of interest in the fields of supramolecular chemistry and materials science due to their novel properties and potential applications.[1] A variety of supramolecular assemblies, including porous organic solids, discotic liquid crystals, three-dimensional nanostructures, extended tubular channels, and guest−host complexes have been realized from these building blocks.[1] However, the efficient preparation of functionalized macrocycles has been a challenging task. It is not uncommon for these preparations to involve a large number of synthetic steps, to require dilute conditions (<1 mM), and to afford low overall yields.[2]

The first synthesis of hexakis(arylene ethynylene) macrocycles dates back 30 years, when Staab prepared a hexameric phenylene ethynylene macrocycle in 4.6% isolated yield by the cyclooligomerization of the copper salt of *m*-iodo-phenylacetylene.[3] Since that time, considerable progress has been made to develop efficient synthetic methods that allow not only the preparation of selectively functionalized structures but also their formation in high yields. Current routes favor Sonogashira coupling[4] between aryl iodides and terminal acetylenes and Glaser-type couplings (and their modifications)[5] between terminal acetylenes. These reactions offer high tolerance of functional groups, generally high yields in individual steps, and the ready availability of the required precursors.

The primary disadvantage of coupling-based approaches is that the product distribution is kinetically determined; incorrect bond formation is incapable of being reversed. Oligomer growth that overshoots the target oligomer cannot contribute to the yield of the desired product.[6] To avoid this problem, precursor oligomers must be synthesized in a stepwise fashion, purified by tedious chromatographic methods, and subsequently subjected to cross-coupling reactions under dilute conditions (<1

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(6) Gong recently reported the one-step synthesis of shape-persistent macrocycles via amide bond formation, which surprisingly gives high yields of macrocycles by an approach that is presumably kinetically controlled. The folding and preorganization of the uncyclized precursors through hydrogen bonding are suggested to be responsible for the favored generation of cyclic oligoamides. See Yuan, L.; Feng, W.; Yamato, K.; Sanford, A. R.; Xu, D.; Guo, H.; Gong, B. *J. Am. Chem. Soc.* **2004**, *126*, 11120−11121.

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mM) to form macrocycles via intramolecular cyclization. Although good yields can be achieved when the hexameric precursors are cyclized, the laborious and time-consuming synthesis and purification of the precursors impedes efficient, large-scale preparation of macrocycles via this route. Random cyclization of three or more monomer units has also been applied to prepare target macrocycles, but usually only low yields (1−18% on cyclization step) are obtained.[7]

In contrast to kinetically controlled reactions, approaches based on thermodynamic control are possible. A prerequisite for selective generation of thermodynamically stable products in high yield is an appropriate chemical reaction.[8] As a reversible approach to joining bisfunctionalized monomer units, metathesis reactions ensure nearly equivalent bond energies on both sides of the equilibrium equation. Since the bond energy changes do not significantly bias the reaction equilibrium, the product distribution is determined by the thermodynamic stability of each species.

In the past a few years, alkyne metathesis with either defined carbyne complexes[9,10] or catalysts generated in situ[11,12] has been used to synthesize both saturated and unsaturated ring systems. Analogous to alkene[13] and imine metathesis,[14] alkyne metathesis[15−17] can be a fast, reversible process with equilibrium constant close to unity. The reversibility of the alkyne metathesis reaction attracted our attention as a potentially powerful method for preparing phenylene ethynylene macrocycles.[12] The ready availability of highly active catalyst precursors synthesized by a reductive recycle strategy[17] and the successful examples of dynamic covalent chemistry[8,18−20] in organic synthesis prompted us to investigate an approach to macrocycle preparation directly from monomer via the reversible alkyne metathesis reaction.

In a preliminary communication, we reported a convenient, multigram synthesis of arylene ethynylene macrocycles near room temperature involving precipitation-driven alkyne metathesis.[21] Although this one-step approach greatly facilitates a practical route to macrocycle synthesis, a number of fundamental questions remained unanswered: Are the macrocycle products the result of thermodynamic or kinetic control? How does the growing linear oligomer transform into macrocycle? In this contribution, we track the product distribution as monomer is converted to arylene ethynylene macrocycles. Macrocycle formation is shown to be reversible, and the product distribution is shown to represent thermodynamic equilibrium. The preferential formation of macrocycles via precipitation-driven alkyne metathesis demonstrates how dynamic covalent reactions can be utilized to funnel potentially complex product mixtures to simple desirable outcomes. The method is an example of a supramolecular process (crystallization) driving the formation of a specific covalent product.

Results

During our investigations of precipitation-driven alkyne metathesis, we found that metathesis of bis(benzoylbiphenyl)-substituted monomer **1** in CCl_4[22,23] provided high yields of **2**,

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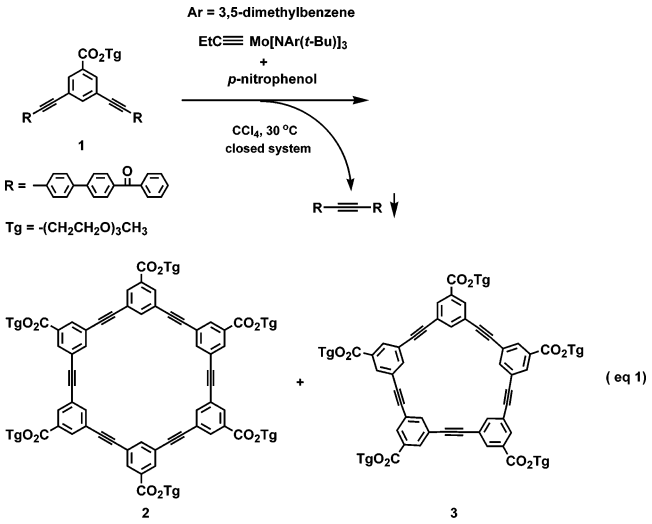
(22) Various arylethynyl-substituted monomers and solvents ($CHCl_3$, CCl_4, ethyl acetate, methyl acetate, 1,2,4-trichlorobenzene) were tested. Metatheses of phenyl-, biphenyl-, or fluorenyl-substituted monomers provided mainly short oligomers with some unreacted monomers. The low efficiency is possibly due to the higher solubility of these diarylacetylene byproducts. However, the diarylacetylene byproduct from metathesis of **1** is insoluble in many solvents. In CCl_4, the UV absorption of the diarylacetylene byproduct is weak, indicating its extremely poor solubility, which strongly shifts the metathesis equilibrium toward high conversion. The solubility of this byproduct in $CHCl_3$ or CCl_4 was measured by UV at 25 °C, and based on the Lambert−Beer law, the K_{sp} in $CHCl_3$ is 5.1×10^{-5} mol/L while the K_{sp} in CCl_4 is only 1.1×10^{-6} mol/L (see Supporting Information for details of byproduct characterization and K_{sp} calculation). The metathesis reactions conducted in methyl acetate or ethyl acetate did not proceed as well as that in CCl_4, likely due to the coordinating effects of the carbonyl group, which decreases the catalytic activity (Freudenberger, J. H.; Schrock, R. R. *Organometallics* **1985**, *4*, 1937−1944). Toluene is also a good solvent for the precipitation strategy with monomer **1**; in this solvent, only a trace of high-molecular weight polymers could be detected as side products.

with pentameric macrocycle **3** being generated to a lesser extent (eq 1).



We thus selected this particular reaction for further investigation. Metathesis of **1** was conducted at various temperatures and the ratio of cyclic hexamer to pentamer was measured using ^{1}H NMR. The study showed that the ratio decreased from 6.5:1.0 at 30 °C to 2.9:1.0 at 95 °C (Figure 1).[24] Experiments were performed to demonstrate that the observed ratios reflect equilibrium product distributions. For example, when the purified macrocyclic mixture from the metathesis reaction at 75 °C (3.3:1.0 hexacycle:pentacycle) was resubjected to alkyne metathesis at 30 °C, after 22 h the ratio of cyclic hexamer to cyclic pentamer increased to 6:1. This is nearly identical to the ratio obtained from the metathesis of monomer **1** at 30 °C.

We monitored the progress of the metathesis reaction starting from monomer **1** in CCl_4 (0.036 M)[26] at 30 °C (eq 1). Aliquots from the reaction were periodically withdrawn and analyzed by ^{1}H NMR and gel permeation chromatography (GPC). The GPC traces of samples removed from the reaction after 1.5 h, 5.5, 21.5, and 66 h are shown in Figure 2. The major signal with a retention time at ca. 26 min corresponds to cyclic

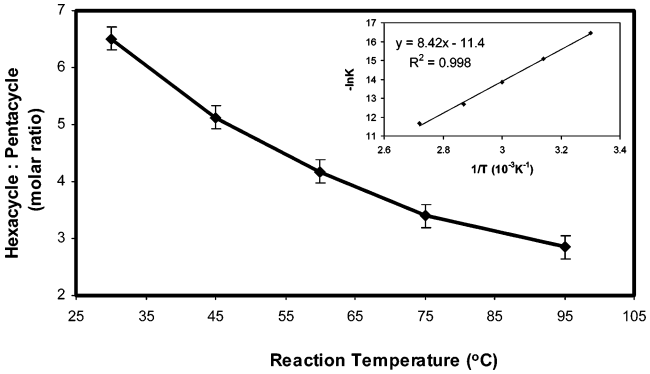


Figure 1. Plot showing how the molar ratio of hexacycle **2** to pentacycle **3** depends on temperature for the metathesis of monomer **1** (36 mM, CCl_4, 22 h). The molar ratio is based on integrated intensities of ^{1}H NMR resonances ($CDCl_3$, 500 MHz, 20 °C). The error bars represent the range observed in duplicate runs. (Inset) van't Hoff plot of these data, where the constant K is for the pentacycle/hexacycle equilibrium.[25]

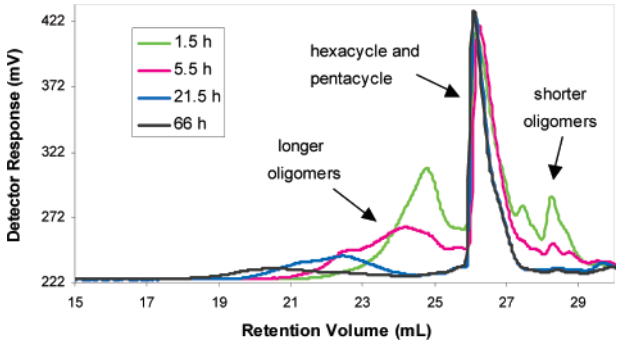


Figure 2. Time course of the metathesis reaction as monitored by GPC (THF, 20 °C). Metathesis conditions: 4.8 mmol monomer, 135 mL CCl_4, 0.24 mmol (5 mol %) EtCMo[NAr(*t*-Bu)]$_3$ + 0.72 mmol *p*-nitrophenol, 30 °C. Additional 3 mol % portions of catalyst were added after 24 h, 48 h.

hexamer and cyclic pentamer. The signals with retention times less than 26 min correspond to higher-molecular weight oligomers, while those with longer retention times (>26 min) correspond to shorter oligomers. In the early stages of the reaction (1.5 h, 5.5 h), high concentrations of short and long oligomers were observed along with the macrocyclic products. However, after 21.5 h, oligomers shorter than hexamer nearly disappeared, and only a small amount of polymer was observed. After 66 h, only a trace of higher-molecular weight oligomers remained, and the macrocycle was the major product.[27] A series of ^{1}H NMR spectra collected over the course of the reaction also shows that the ratio of cyclic hexamer **2** to longer oligomers increases with reaction time (Figure 3).[28] The reaction mixture[29] acquired at 5.5 h (i.e., the GPC trace shown as the purple line in Figure 2) was also analyzed by matrix-assisted laser desorption ionization mass spectrometry (MALDI-MS). As can be seen in Figure 4, two series of high-molecular weight oligomers are observed. One series corresponds to open-chain, linear oligomers, for which chain lengths up to the 20-mer are identified. The other series corresponds to cyclic oligomers, for which chain lengths up to the 22-mer are identified. These longer linear and

(23) A red precipitate was observed upon mixing the molybdenum(VI) propylidyne catalyst precursor and *p*-nitrophenol in CCl_4, which is presumably due to the low solubility of the generated metathesis-active species in this solvent. The same phenomenon was also observed in benzene, toluene, or 1,2,4-trichlorobenzene. In the case of methylene chloride, chloroform, ethyl acetate, or THF as solvent, no precipitation was observed. When other phenols (e.g., 4-trifluoromethyl phenol) were used instead of *p*-nitrophenol to generate the catalytically active species, no precipitation was observed in any solvent mentioned above.

(24) In our previous report on the gram-scale synthesis of macrocycle **2** via precipitation-driven alkyne metathesis at 30 °C, a 9:1 ratio of cyclic hexamer to cyclic pentamer was indicated. In that work, the reaction mixture was passed through a short plug of silica gel to remove the metathesis catalyst (ref 21). However, without silica treatment, a ratio around 6.5:1 is repeatedly observed. Presumably, partial separation of cyclic hexamer from cyclic pentamer occurs during chromatographic treatment. As previously reported, the cyclic pentamer byproduct can be completely removed by using optimized chromatographic purification conditions (ref 21).

(25) On the basis of this van't Hoff plot, the experimental value of ΔH is obtained as 3.4 kcal/mol (per mole hexacycle, theoretical calculation is 4.1 kcal/mol), and ΔS is 0.005 kcal/mol·K (per mole hexacycle, theoretical calculation is 0.012 kcal/mol·K). See Supporting Information for details.

(26) A concentration study was performed to optimize the metathesis conditions. We found that the ratio of cyclic hexamer to high-molecular weight products increased from 0.5 at 0.15 M to a maximum value of 6.5 at 0.036 M, then decreased to 3.9 at a further diluted concentration 0.030 M. When the concentration was below 0.025 M, the metathesis reactions became very slow, and only short oligomers were detected after 22 h at room temperature. Therefore, 0.036 M proves to be the best concentration to perform the macrocycle synthesis.

(27) The molybdenum complex was present at 5 mol % at the start of the reaction. Additional 3 mol % portions were added after 24 and 48 h.

(28) In the ^{1}H NMR spectra of reaction mixtures recorded within the first 12 h, the signals corresponding to cyclic hexamer and oligomer cannot be resolved. Early time data in Figure 3 are thus unavailable.

(29) The "reaction mixture" referred in this article was not subjected to any purification treatment prior to the analysis; thus, the sample is expected to accurately reflect the product distribution.

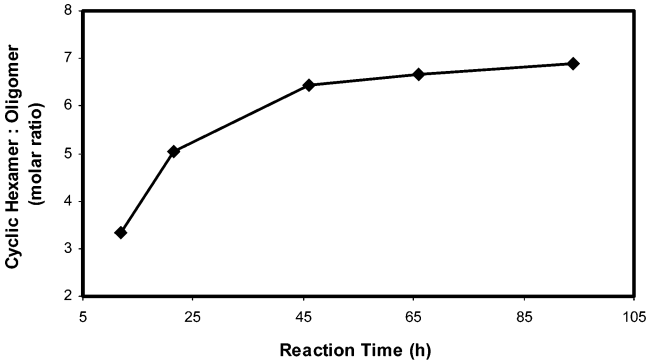
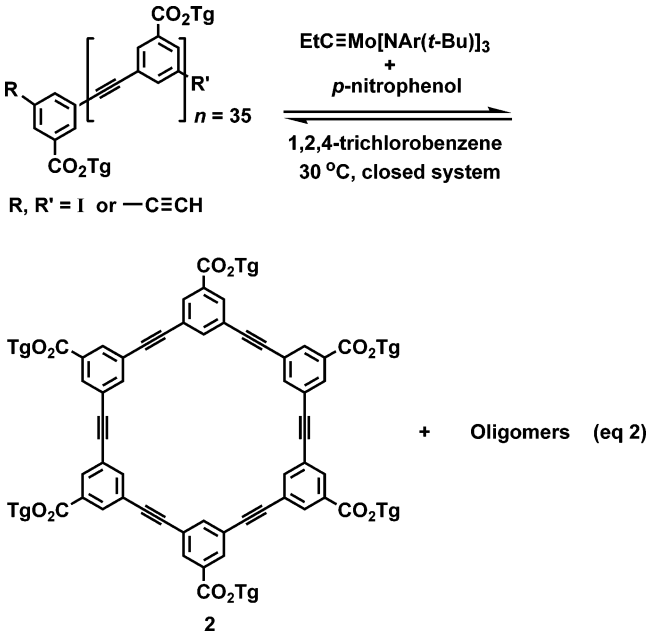


Figure 3. Plot showing how the molar ratio of cyclic hexamer **2** to oligomer changes with reaction time in the metathesis of monomer **1** (36 mM, CCl_4, 30 °C). The molar ratio is based on ^{1}H NMR measurements of integrated intensities ($CDCl_3$, 500 MHz, 20 °C).

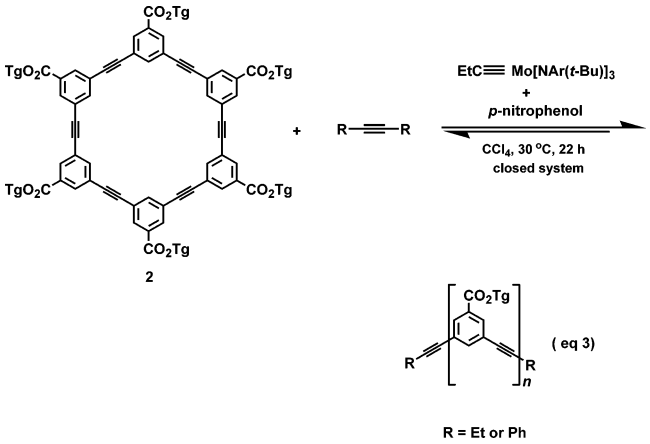
cyclic oligomers were only detected by MALDI-MS in the early stages of the reaction.[30] The combined GPC and MALDI-MS data reveal that open-chain oligomers and large macrocycles are initially formed in the metathesis reaction, but are eventually converted into cyclic hexamer and, to a lesser extent, cyclic pentamer under the reaction conditions described above (eq 1).

Additional evidence supporting the reversibility of all steps is the observation of pathway-independent product distribution. This behavior was determined by subjecting a presynthesized phenylene ethynylene polymer[31] to alkyne metathesis conditions. The reaction was performed in a closed vessel at 30 °C (eq 2). After 22 h, the GPC trace of the reaction mixture showed that the polymer had transformed into shorter oligomers with hexacycle **2** as the major product (Figure 5).[32]

To demonstrate that the cyclic products could be converted back to oligomers, we next conducted a cross metathesis reaction starting from macrocycle **2** and 3-hexyne (eq 3, R = Et). However, in the presence of 12 equiv of 3-hexyne, macrocycle **2** remained nearly unchanged after 22 h based on the GPC trace and MALDI-MS of the reaction mixture.[33] Even in the presence of 200 equiv of 3-hexyne, no open-chain oligomers were detected.[34] Cross metathesis appears not to be a viable process when a large excess of 3-hexyne is present. In great contrast, when diphenylacetylene (12 equiv) was added instead of



3-hexyne (eq 3, R = Ph), the cross metathesis reaction predominantly gave short oligomers within 22 h, which were



characterized by GPC (blue line in Figure 6) and MALDI-MS.

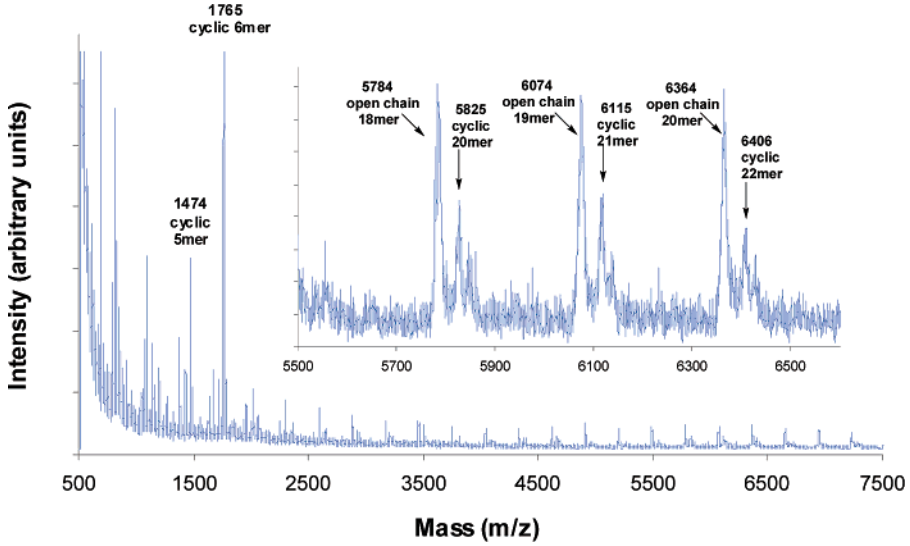


Figure 4. MALDI-MS of the reaction mixture conditions from metathesis of monomer **1** after 5.5 h (HABA matrix). (Inset) Expanded scale in the mass range 5500−6500.

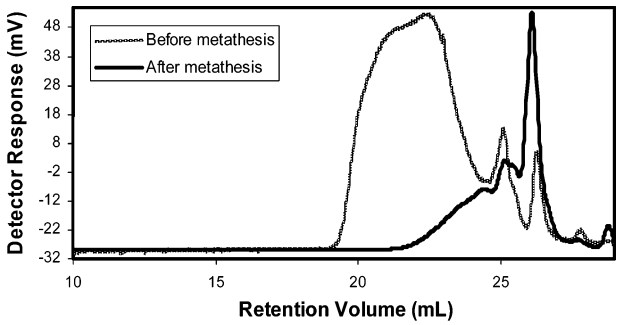


Figure 5. GPC trace of starting phenylene ethynylene polymer and the reaction mixture (after metathesis). Metathesis conditions: 52 mg of polymer, 1.2 mL of 1,2,4-trichlorobenzene, 0.012 mmol EtCMo[NAr(*t*-Bu)]$_3$ + 0.036 mmol *p*-nitrophenol, 30 °C. GPC conditions: THF, 20 °C.

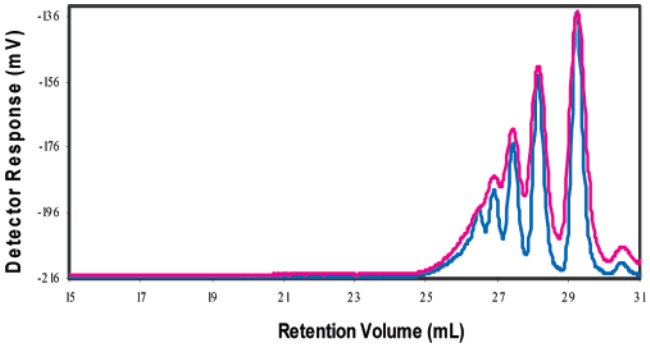
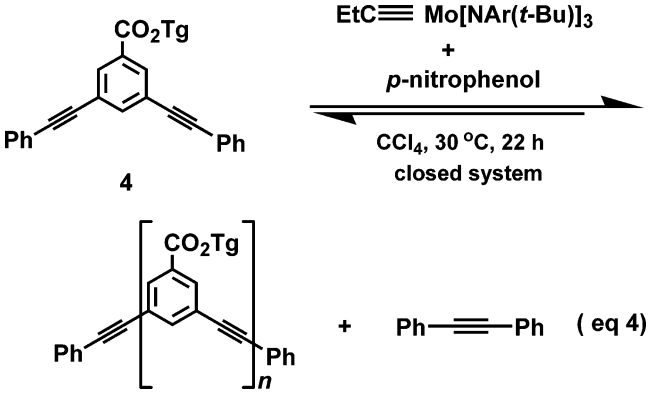


Figure 6. GPC traces from the metathesis reactions in eq 3 (R = Ph) and eq 4 (CCl_4, 30 °C, 22 h). The blue line corresponds to metathesis of hexacycle **2** with diphenylacetylene; the purple line corresponds to metathesis of monomer **4**. GPC conditions: THF, 20 °C.

Moreover, bis(phenylethynyl)-substituted monomer **4** (eq 4) was subjected to the same conditions as those for the cross metathesis



of macrocycle **2** with diphenylacetylene, and the GPC trace of the reaction mixture (purple line in Figure 6) was found to be almost identical to that obtained for the reaction in eq 3 (R = Ph). In both cases, the concentration of macrocycle **2** under these conditions was small relative to that of the open-chain oligomers. These pathway-independent product distributions indicate that

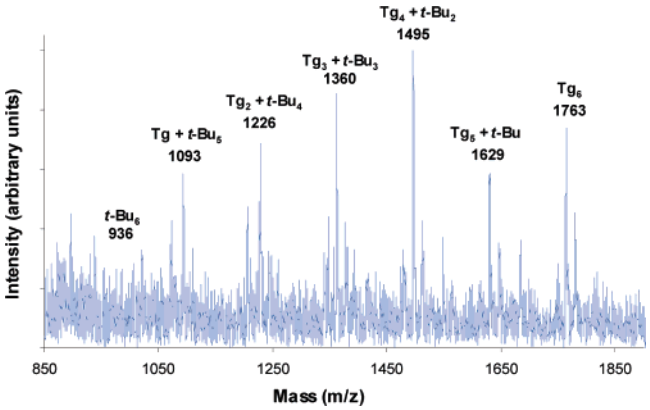
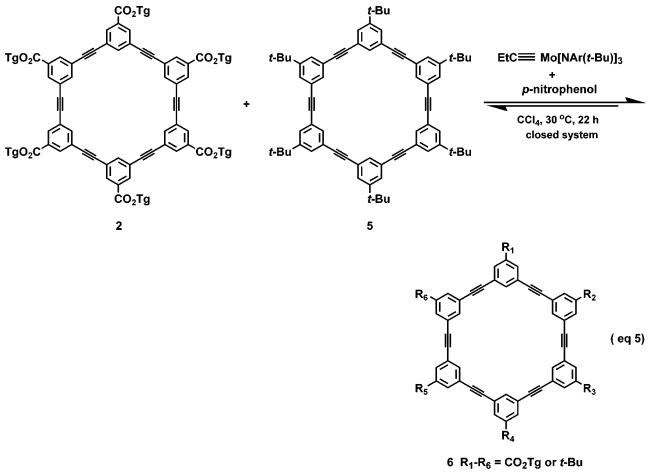


Figure 7. MALDI-MS of the reaction mixture from metathesis of macrocycle **2** and **5** in the presence of EtCMo[NAr(*t*-Bu)]$_3$ and *p*-nitrophenol[initial molar ratio **2**:**5**:Mo = 1:1:1.2, CCl_4, 30 °C, 22h]. *m*/*z* values and assignments are indicated for Na^+ adducts of macrocycles **6**.

equilibrium is attained and that the transformation between open-chain oligomers and macrocycles is a reversible, thermodynamically controlled process.

Further support in favor of reversible macrocycle formation was gained through a scrambling experiment, in which a 1:1 mixture of two different phenylene ethynylene macrocycles (**2** and **5**) was subjected to metathesis (eq 5).



The reaction was conducted in CCl_4 at 30 °C for 22 h followed by MALDI-MS analysis (Figure 7). A series of scrambled macrocyclic products having different combinations of Tg and

(30) After 46 h, the apparent absence of large, open-chain, and cyclic oligomers by MALDI-MS may reflect the poor sensitivity of this technique. As the oligomer grows, the distribution spreads out; thus, there are smaller quantities of oligomer at each length. When the initial loading of molybdenum complex was increased to 10 mol %, after 22 h at 30 °C, no large open-chain and cyclic oligomers were detected by MALDI-MS.

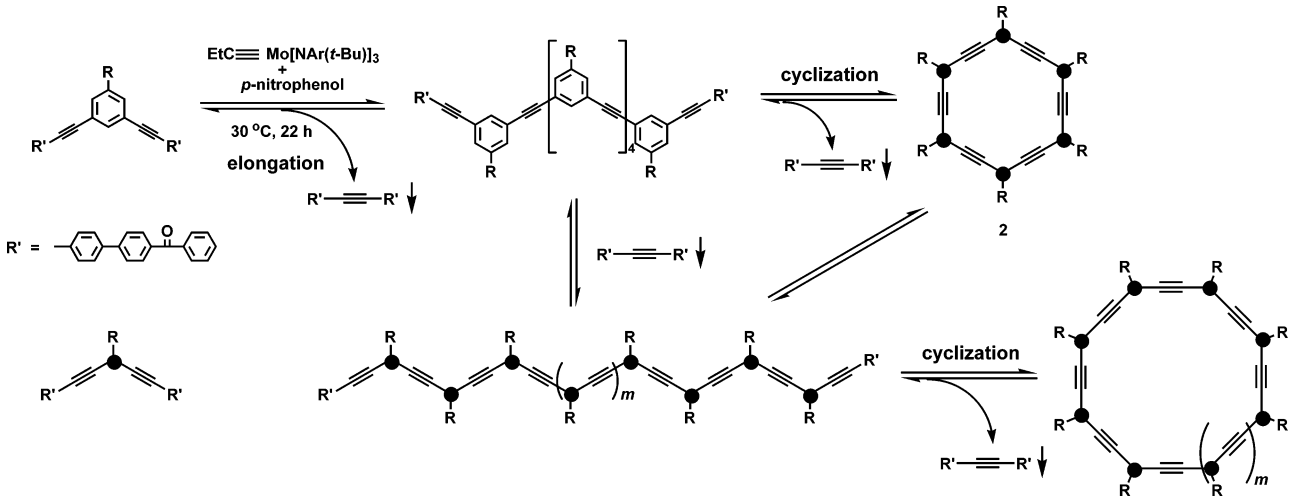
(31) The phenylene ethynylene polymer was synthesized via Sonogashira cross-coupling of 3,5-diiodobenzoate monomer with 3,5-diethynylbenzoate monomer. GPC trace of the polymer showed its molecular weight (M_n) is ca. 10 kDa.

(32) At the end of the reaction, longer oligomers ($n > 6$) can be observed in the GPC trace. From MALDI-MS data, a strong signal corresponding to cyclic hexamer and weaker signals corresponding to other oligomeric species ($n = 8-12$) were also observed. The failed formation of exclusively hexacycle is presumably due to deactivation of the catalyst in the presence of terminal acetylene group, which has been demonstrated to cause catalyst ligand loss during metathesis, see Schrock, R. R. *Polyhedron* **1995**, *14*, 3177−3195. The byproduct ethyne may also poison the catalyst through the ring-expansion mechanism, see ref 17b.

(33) To rule out the possibility that the failed cross metathesis is due to deactivated catalyst, metathesis of butynyl-substituted benzoate ester was performed as a model reaction in the presence of the molybdenum complex (of the same batch as used in eq 3). The observed 42% conversion (based on ^{1}H NMR integration) is consistent with our previous results and indicates the catalyst is still active. Furthermore, the successful cross metathesis between 1,2-dithienylacetylene and 3-hexyne (of the same batch as used in eq 3) (1:1 molar ratio) also rules out the possibility of contamination from impurities in 3-hexyne.

(34) When 12 equiv of 3-hexyne was utilized in cross metathesis, weak signals corresponding to open-chain oligomers (tetramer to dodecamer) could be observed in the MALDI-MS. However, when 200 equiv of 3-hexyne was used, no open-chain oligomers could be detected at all.

Scheme 1. Reaction Pathways Leading to Thermodynamically Favored Macrocycle **2** via Alkyne Metathesis



t-Bu substituted side chains were observed, demonstrating the reversibility of macrocycle formation.

Discussion

On the basis of the results reported above, Scheme 1 compiles the reaction pathways leading to macrocycle formation via precipitation-driven alkyne metathesis. The process can be thought of as involving two stages: a fast monomer-to-oligomer conversion (including the generation of cyclooligomers) followed by slow equilibration[35] of cyclic species leading to the desired hexakis macrocycle. The initial growth of the oligomer is driven by the poor solubility of the diarylacetylene byproduct. Once the chains are sufficiently long, the oligomers can undergo intramolecular metathesis to the corresponding cyclic oligomers ($n \geq 5$) with nearly complete removal of end groups.[36] At this point, open-chain and macrocyclic intermediates can equilibrate, leading predominantly to the pentakis and hexakis cyclic products.

Why is there a strong thermodynamic preference for the hexa- and pentacycles? Enthalpy of the cyclic products is dominated by angle strain, while entropy favors the greatest number of macrocycles (i.e., the macrocycle with the minimum number of monomer units). Intuitively, these conditions are best met by a molecular hexagon, the only cyclic structure whose geometry is commensurate with natural bond angles and planar conformation. The thermodynamic stability of the cyclic hexamer relative to the pentacycle and other possible cyclics is predicted by simple calculations. The entropy change between the various macrocycles in eqs 6−9 can be estimated by a

$$4 \text{ hexacycle} \rightleftharpoons 6 \text{ tetracycle} \quad (6)$$

$$5 \text{ hexacycle} \rightleftharpoons 6 \text{ pentacycle} \quad (7)$$

$$7 \text{ hexacycle} \rightleftharpoons 6 \text{ heptacycle} \quad (8)$$

$$8 \text{ hexacycle} \rightleftharpoons 6 \text{ octacycle} \quad (9)$$

semiquantitative model,[37] and the enthalpy change can reliably be estimated using molecular mechanics models (Table 1, data plotted in Figure 8).[38] These calculations show that the hexacycle is more stable than smaller macrocycles ($n = 4, 5$) because it is enthalpically favored due to less angle strain, while the conversion of hexacycle to large-sized macrocycles ($n = 7, 8$) is largely disfavored entropically. Therefore, the cyclic hexamer is the most favored product among all the macrocycles generated during metathesis. Under the reversible conditions used in the dynamic covalent approach, the transformation of the intermediate macrocyclic compounds into cyclic hexamer and a smaller amount of cyclic pentamer is consistent with thermodynamic equilibrium.

Table 1. Gibbs Free Energy Change (ΔG) in Eqs 6−9[a]

equation	Δ*H* (kcal/mol)	Δ*S* (kcal/mol·K)	Δ*G* (kcal/mol) (303 K)
6	244	0.030	15.6
7	4.1	0.012	0.54
8	0.9	−0.009	3.53
9	1.2	−0.015	5.81

[a] Values are calculated as per mole hexacycle. See Supporting Information for details.

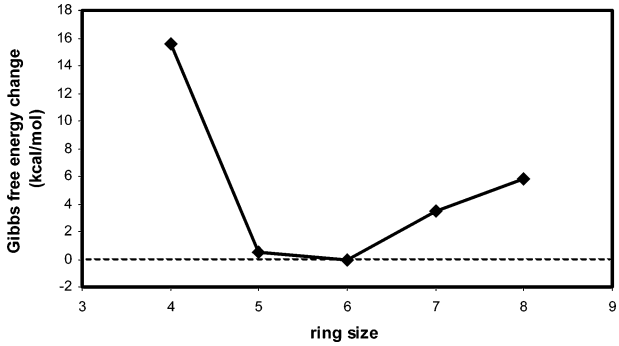


Figure 8. Approximate Gibbs free energy change per mole of cyclic hexamer for tetracycle through octacycle.

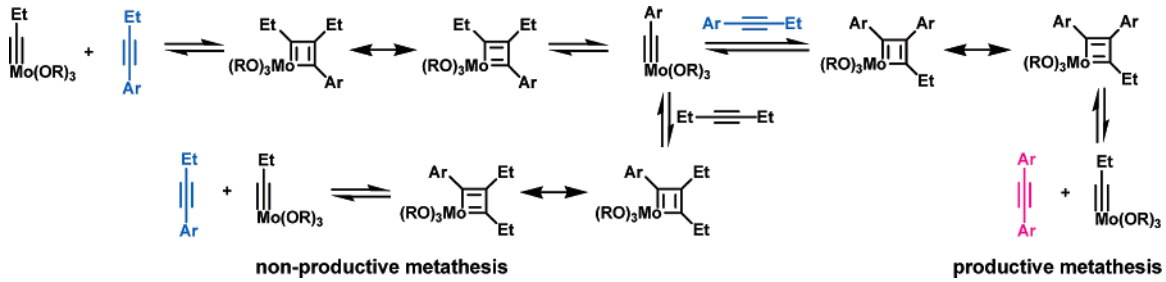
(35) For examples of ring-chain equilibria in macrocyclizations, see: (a) Goodman, I.; Nesbitt, B. F. *Polymer* **1960**, *1*, 384−396. (b) Ercolani, G. *J. Phys. Chem. B* **1998**, *102*, 5699−5703. (c) Ercolani, G.; Mandolini, L.; Mencarelli, P.; Roelens, S. *J. Am. Chem. Soc*. **1993**, *115*, 3901−3908.

(36) Byproduct removal must be highly efficient in these reactions. As demonstrated in eq 3 (R = Ph), the presence of soluble diphenylacetylene (12 equiv, K_{sp} > 5.61 mol/L in CCl_4) shifts the product distribution and predominantly gives short oligomers. Therefore, efficient removal of byproduct is necessary to favor a high yield of arylene ethynylene macrocycles prepared via alkyne metathesis.

(37) Mammen, M.; Shakhnovich, E. I.; Deutch, J. M.; Whitesides, G. M. *J. Org. Chem*. **1998**, *63*, 3821−3830. The entropy values of methyl benzoate macrocycles are estimated.

(38) Spartan software (version 4.0; Wavefunction, Inc.: Irvine, California) at the AM1 level was used to estimate heats of formation for the methyl benzoate macrocycles.

Scheme 2. Productive Metathesis vs Non-Productive Metathesis



Monitoring the progress of the metathesis reaction reveals the presence of open-chain oligomers and large macrocycles (Figures 2 and 4) in the early stages of the reaction. It is evident from the GPC traces that a significant fraction of monomer overshoots the hexamer. However, over time, these longer oligomers transform into the thermodynamically favored cyclic hexamer.

The decrease in the ratio of cyclic hexamer to cyclic pentamer at elevated temperatures reflects the entropically favored formation of smaller macrocycles. At low temperature, the entropy contribution to ΔG is less significant. However, as the temperature increases, the entropy change becomes larger, favoring a higher proportion of the pentacycle. These results demonstrate the importance of conducting the metathesis reaction at low temperatures to favor the formation of cyclic hexamers.[39,40]

The scrambing experiment was performed to rule out the possibility that the cyclic hexamer is formed by a kinetically controlled process. Scrambled products were observed when a 1:1 mixture of macrocycles **2** and **5** were subjected to metathesis, clearly demonstrating the reversibility[41] of macrocycle formation. All evidence indicates that the formation of phenylene ethynylene hexacycles under these conditions is thermodynamically controlled.

Our first attempt at cross metathesis of macrocycle **2** with 3-hexyne was unsuccessful. However, when diphenylacetylene was utilized in the cross metathesis instead of 3-hexyne, the reaction proceeded well, yielding short oligomers as the predominant species. This observation can be explained by considering the substituent differences of the two alkynes.[17b,42] In alkyne metathesis reactions, alkyl-substituted alkynes are more reactive than aryl alkynes, and electron-deficient aryl alkynes react more slowly than electron-rich aryl alkynes.[16c,17b] Since the triple bond in hexyne has two alkyl substituents while the macrocyclic triple bond is connected to two electron-deficient aromatic substituents, metathesis with hexyne is thus expected to be favored over metathesis with the hexacycle. The catalyst is thus kinetically occupied with hexyne rather than the desired cross metathesis reaction, and the nonproductive manifold dominates catalytic activity (Scheme 2). In great contrast, when diphenylacetylene was used, the aromatic substituents on the triple bonds in the hexacycle and diphenylacetylene possess similar reactivities. Hence, the cross metathesis manifold is viable and open-chain oliogmeric products are observed.

These findings have important practical significance. In particular, they reveal that alkyl-substituted alkynes should be avoided (or efficiently removed) to favor the desired metathesis of aryl alkynes. When the two substituents in alkyne substrates are significantly different (e.g., alkyl vs aryl), the generated homodimerized alkyne product will have higher reactivity toward metathesis, which will favor the nonproductive manifold and result in a decrease in the rate of productive metathesis. Therefore, although the alkyl-substituted alkynes do not poison the catalyst in the traditional sense,[43] they do inhibit the catalyst by favoring the nonproductive steps.[17b,21,42,44] This "pseudo-poisoning effect" may help to explain the poor conversion and low yield in our previously reported large-scale synthesis of macrocycle **2** under vacuum-driven conditions.[21] For gram-scale preparation of hexacycle **2** using aryl butynyl groups as the monomer, the byproduct 3-hexyne was more difficult to remove efficiently than in small-scale synthesis. The buildup of 3-hexyne may have led to nonproductive metathesis, preventing macrocycle formation. These results highlight the significant advantages of precipitation-driven alkyne metathesis over the more conventional vacuum-driven approach. For the former case, no extra effort is necessary to ensure efficient removal of the byproduct because, once it is generated, it will precipitate and thus not interfere with the catalyst activity. Therefore, in addition to serving as the initial driving force for the metathesis reaction, byproduct precipitation also prevents catalyst "pseudo-poisoning", which facilitates the one-step, gram-scale synthesis of arylene ethynylene macrocycles in high yields.

Conclusions

The transformation of linear oligomers and large macrocycles into cyclic hexamers is a thermodynamically controlled process.

(39) On the basis of the calculated ΔG value in eq 7, the pentacycle should be favored over hexacycle at reaction temperatures above 75 °C, which was not observed experimentally. This difference presumably results from the error in estimating entropy values. Nonetheless, this model represents a useful tool for estimating the approximate product distribution.

(40) The ratio of hexacycle to pentacycle should rise when the reaction is conducted at temperatures below 30 °C. Therefore, metathesis of monomer **2** or cyclic hexamer at 0 °C was performed. However, the poor solubility of intermediate oligomers and macrocycles in CCl_4 at this temperature made the study impractical.

(41) In this scrambling experiment and also in precipitation-driven alkyne metathesis, the generated macrocycles can be opened by reacting with the metathesis catalyst. However, with limited amount of diarylacetylene byproduct available, this "ring-opening" process does not necessarily lead back to the corresponding open-chain oligomer precursor. Thus, the "reversibility" in this case means that macrocycles can be reopened and reclosed, and it does not necessarily refer to an equilibrium existing between linear oligomers and cyclic species as is the case when a soluble byproduct is present in the system (eqs 3, 4).

(42) (a) Schrock, R. R. *Acc. Chem. Res*. **1986**, *19*, 342−348. (b) Wengrovius, J. H.; Sancho, J.; Schrock, R. R. *J. Am. Chem. Soc*. **1981**, *103*, 3932−3934.

(43) We have shown that catalysts based on Mo(VI) propylidyne precursors can initiate polymerization of 2-butyne byproduct. Once polymerization occurs, the complex is no longer effective for alkyne metathesis. For alkynes with substituents more bulky than methyl groups, the polymerization pathway is retarded, presumably because of steric hindrance. The catalyst remains active significantly longer. However, nonproductive metathesis must also be taken into consideration. Also see ref 17b.

(44) (a) Bly, R. K.; Dyke, K. M.; Bunz, U. H. F. *J. Organomet. Chem*. **2005**, *690*, 825−829. (b) Kloppenburg, L.; Song, D.; Bunz, U. H. F. *J. Am. Chem. Soc*. **1998**, *120*, 7973−7974 and ref 16i.

This conclusion was supported by the reversibility of macrocycle formation as well as pathway-independent product distribution in alkyne metathesis reactions. Precipitation of diarylacetylene byproduct serves as the driving force to favor high conversion of monomers to open-chain and cyclic oligomers, while the thermodynamic stability of hexacycle **2** accounts for its favored production. The "pseudo-poisoning" effect of 3-hexyne on the metathesis catalyst was also discussed, whereby the byproduct traps the catalyst in the nonproductive manifold. This problem is overcome by precipitation-driven alkyne metathesis, in which the diarylacetylene byproduct reactivity is similar to that of the substrate. The successful preparation of macrocycles using the precipitation-driven, reversible alkyne metathesis—a dynamic covalent approach—may enable the expedient synthesis of other two-dimensional or three-dimensional arylene ethynylene structures.

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Supporting Information Available: Summarized mass data (calculated and observed) for the intermediate oligomers shown in Figures 4 and 7, calculation of Gibbs free energy of macrocycles ($n = 4, 5, 7, 8$) relative to cyclic hexamer ($n = 6$), data for van't Hoff plot in Figure 1, characterization and calculation of diarylacetylene byproduct K_{sp} in $CHCl_3$ and CCl_4. This material is available free of charge via the Internet at http://pubs.acs.org.

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