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Directional Cyclooligomers via Alkyne Metathesis

Scott W. Sisco and Jeffrey S. Moore*

Department of Chemistry, University of Illinois at Urbana-Champaign, 600 South Mathews Avenue, Urbana, Illinois 61801, United States

Ⓢ *Supporting Information*

ABSTRACT: Macrocyclic oligomers possessing direction-defining ester linkages were synthesized via metathesis of the nondirectional alkyne functional group. Alkyne metathesis is expected to scramble the relative orientation of adjacent ester groups, potentially leading to a complex mixture of macrocyclic products. We wondered whether a narrow product distribution would be achievable with a proper choice of the building block structure. Here we show that the shape of the building block determines whether the macrocyclic products are directionally uniform or scrambled. Specifically, two isomeric arylene-ethynylene polyesters afforded significantly different product distributions upon being subjected to depolymerization–macrocyclization. These results underscore the importance of learning how the shape and geometry of the building blocks affect the macrocyclization energy landscape.

Dynamic covalent chemistry[1] (DCC) is a powerful tool for the construction of macrocyclic architectures[2] from simple building blocks. Rapid, reversible reactions under thermodynamic control yield product distributions that are determined by the differences in free energy of the possible structures. To realize high yields of a single macrocyclic product, competing structures must possess distinct differences in molecular geometry or conformation, thereby shaping the energy landscape[3] from flat to funnelled. When building blocks with directionality[4] are involved in DCC, achieving such narrow landscapes is especially challenging because "head–tail", "head–head", and "tail–tail" connections are possible.[5] In this communication, we report on the surprising product distributions obtained from the depolymerization of two isomeric polymers consisting of directional ester and nondirectional alkyne bonds (Figure 1).

We recently described a synthetic strategy for preparing shape-persistent arylene-ethynylene macrocycles (AEMs) under thermodynamic control that takes advantage of a highly active molybdenum(VI) propylidyne catalyst[6] and the reversibility of alkyne metathesis.[7] This DCC method yields interesting macrocycles in short synthetic sequences but to date has been tested only on simple geometries and rigid systems.[3,7] Because of the dynamic nature of alkyne metathesis and thermodynamic control of the macrocyclic products, it would be advantageous to generate a set of design principles for the rational synthesis of novel target AEMs. With this goal in mind, the reactivities of two constitutionally isomeric systems under alkyne metathesis conditions provided insight to understand how shape and geometry affect the thermodynamically controlled product distribution (Scheme 1). Specifically, we describe the unexpected yet significant impact the building block shape has on the dynamic depolymerization of these two isomeric arylene-ethynylene polyesters (**MM** and **OP**).

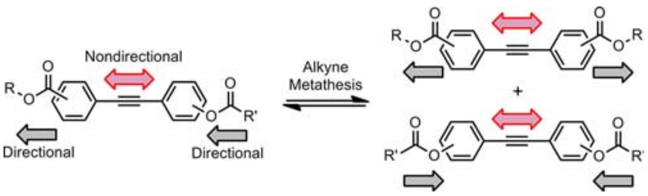

Figure 1. Directionality of functional groups. Here the nondirectional alkyne is utilized in a DCC cyclooligomerization.

Polymerization[8] was achieved by the self-condensation of phenol- and carboxylic acid-functionalized tolane monomers **1** and **2** [see the Supporting Information (SI) for the syntheses of **1** and **2**]. Polymerization with diisopropylcarbodiimide (DIC) and diaminopyridinium *p*-toluenesulfonate (DPTS) in methylene chloride yielded polymers **MM** and **OP**, respectively, after precipitation into methanol. Preparative gel permeation chromatography (GPC) was used to remove low molecular weight oligomers. The corresponding polyesters exhibited good solubility in common organic solvents and moderate molecular weights (MWs) of 18 and 9.6 kDa, respectively. With the polymers in hand, we next explored their behavior under the dynamic conditions of alkyne metathesis (Scheme 1). Specifically, polyester **MM** was subjected to alkyne metathesis using a highly active tris(amido)molybdenum propylidyne complex with triphenylsilanol as the ligand.[9] After 48 h at room temperature, the reaction was analyzed by GPC (Figure 2 top). The trace showed the disappearance of high MW material and a significant increase in lower MW oligomers. Analysis of the crude product mixture by matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS) revealed cyclic macrocycles from trimer to octamer. The crude depolymerization product was purified by silica gel chromatography followed by preparative GPC to obtain **MM-[3]mer** in 17% yield (Figure 2 top). An inseparable mixture of larger cyclic species **MM-[*x*]mer** ($x > 3$) was isolated in 60% yield.

Because of the directional nature of the ester linker, there are $n - 1$ constitutional isomers for each odd-n cyclic [n]mer and m constitutional isomers for each even-m cyclic [m]mer. For example, **MM-[3]mer** has two possible constitutional isomers,

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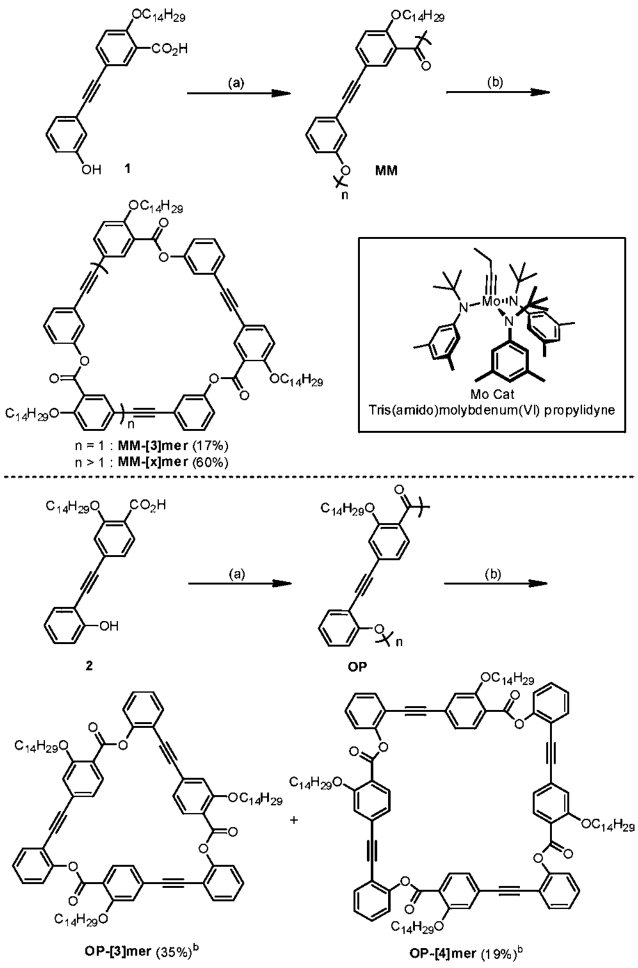
Scheme 1. Synthesis of Macrocyclic Oligomers[a]



[a] Reaction conditions: (a) 1.5 equiv of DIC, 0.5 equiv of DPTS, CH_2Cl_2, 25 °C, 24 h; (b) 10 wt % Mo Cat, 15 wt % Ph_3SiOH, 1,2,4-trichlorobenzene, 25 °C, 48 h. [b] **OP-[3]mer** and **OP-[4]mer** were isolated as a mixture. The yields were determined by ^{1}H NMR spectroscopy.

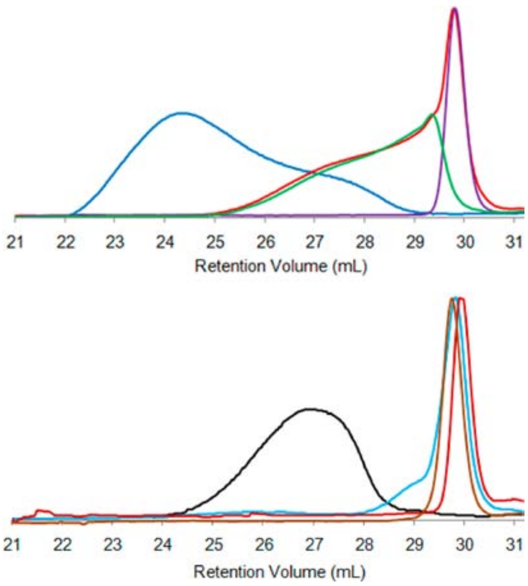


Figure 2. Top: GPC traces of **MM** polymer (blue), the crude metathesis mixture (red), **MM-[3]mer** (purple), and the mixture of macrocycles **MM-[*x*]mer** (green). Bottom: GPC traces of **OP** polymer (black), the crude metathesis mixture (light blue), **OP-[3]mer** (dark red), and **OP-[4]mer** (brown). The intensities have been normalized.

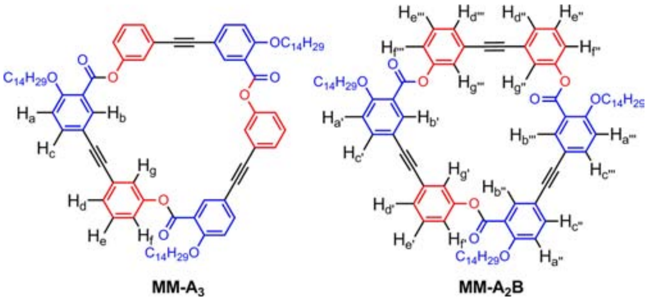


Figure 3. Two constitutional isomers of **MM-[3]mer** and the corresponding aromatic protons.

MM-[4]mer has four possible isomers, and so forth.[10] Further analysis of **MM-[3]mer** predicts a 1:3 statistical mixture of **MM-A$_3$** to **MM-A$_2$B** (Figure 3), assuming no energy difference between the two. The symmetric **MM-A$_3$** isomer is directionally uniform, whereas the unsymmetric **MM-A$_2$B** isomer displays both ester orientations. The ^{1}H NMR spectrum of **MM-[3]mer** in $CDCl_3$ was not well resolved in the aromatic region, but there was considerable shifting and resolution of the peaks when the solvent was switched to C_6D_6 (Figure S1 in the SI). The **MM-A$_3$** isomer has a C_3 rotation axis, so there are 7 unique aromatic protons (a−g). In contrast, **MM-A$_2$B** has 21 unique aromatic protons (a′−g‴) because of the reduction in symmetry (Figure 3). A 1:3 statistical mixture of **MM-A$_3$** to **MM-A$_2$B** will possess a 1:1:1:1 ratio of protons x/x′/x″/x‴ (x = a−g). Comparison of the ^{1}H NMR spectra of the isolated isomeric mixture after metathesis and the pure **MM-A$_3$** isomer isolated after polyesterification (Figure S3), along with COSY analysis (Figure S2), allowed unambiguous assignment of most of the peaks. More specifically, protons g and g′ display the same integrated intensity, consistent with the 1:3 statistical mixture of **MM-A$_3$** to **MM-A$_2$B**.

In great contrast to the depolymerization of **MM**, a completely different result was observed for the depolymerization of **OP**. When polyester **OP** was subjected to metathesis, analysis of the crude product by GPC showed a greater shift toward low MW material (Figure 2 bottom). In fact, only the cyclic trimer and tetramer (**OP-[3]mer** and **OP-[4]mer**, respectively) were observed by MALDI-MS analysis. A mixture of **OP-[3]mer** and **OP-[4]mer** (along with triphenylsilanol) was isolated after silica gel chromatography. Further purification by preparative GPC allowed the isolation of the macrocycles in a combined yield of 54%. A small amount of each macrocycle was separated and used for identification of the macrocycle peaks by ^{1}H NMR analysis. The **OP-[3]mer**/**OP-[4]mer** ratio was determined to be 2.4:1. Interestingly, only the directionally uniform isomers were observed in the ^{1}H NMR spectrum (only seven aromatic protons) for both **OP-[3]mer** and **OP-[4]mer.**[11] This is remarkable, especially for the tetramer, since the same rule applies as for the **MM** system, where two constitutional isomers are possible for the cyclic trimer (Figure 4) and four constitutional isomers are possible for the cyclic tetramer.[10]

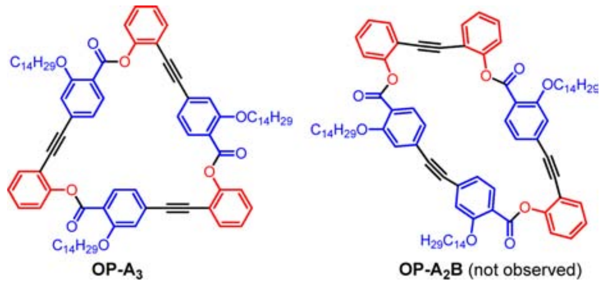


Figure 4. Two constitutional isomers of **OP-**[3]**mer**.

The two polymers **MM** and **OP** contain constitutionally isomeric monomer units, yet their product distributions after metathesis are drastically different. This can be explained by examining how the shape and geometry of the **MM** and **OP** monomer units affect the macrocyclization energy landscape. Both **MM** and **OP** monomer units have the same 60° angle between alkynes (Figure 5), which expectedly favors formation of the [3]mer. However, the two monomers have different shapes because of the positions of the substituents on the phenyl rings. Comparison of the pair of directionally reversed monomers reveals the **MM** monomer to display a congruent shape, whereas the **OP** monomer displays an incongruent shape.

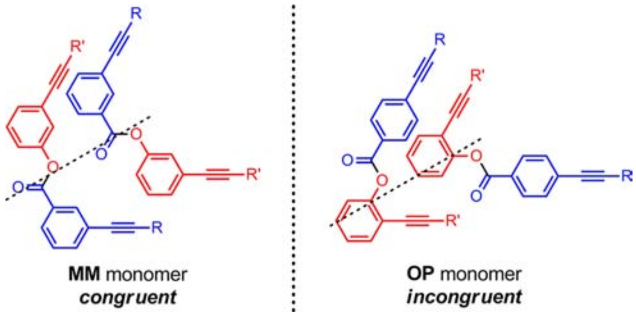


Figure 5. Structural comparisons of directionally reversed monomers (tetradecyl chains removed for clarity).

Because of the congruency of the **MM** monomer, there is no significant thermodynamic preference for one directionality over the other. Therefore, a statistical ratio is observed for the **MM-**[3]**mer** isomers. The three possible diarylacetylenes formed during alkyne metathesis (as shown in **MM-A_2B** in Figure 3) lead to macrocycles with similar energies, since they contain the same substitution pattern (meta,meta). The directionality of the **MM** polymer is scrambled during alkyne metathesis. In contrast, the incongruency of the **OP** system predisposes[4a,b] the product distribution to the directional macrocycles during equilibration. Hence, only the directionally related ortho,para-substituted diarylacetylene leads to isolated product, whereas the other possible diarylacetylenes (ortho,ortho and para,para) lead to macrocycles with higher energy due to greater strain (**OP-A_2B** in Figure 4).

In conclusion, directionally uniform macrocycles have been synthesized via alkyne metathesis mediated depolymerization—macrocyclization of an arylene-ethynylene polyester. The results of this work exemplify the notion that an appropriately designed monomer unit can display a greater tendency to form a narrow macrocyclic product distribution. The profound influence of the building block shape on the reactivities of the **MM** and **OP** systems highlights the need for a better understanding of how different shapes, geometries, and degrees of freedom affect the macrocyclization energy landscape. To accomplish this, the synthesis of a series of structurally unique arylene-ethynylene polymers and an investigation of their corresponding reactivities via alkyne metathesis are currently being pursued.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and NMR, GPC, and MALDI-MS data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

jsmoore@illinois.edu

Notes

The authors declare no competing financial interest.

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(10) See the SI for a more in-depth discussion of macrocyclic isomers.
(11) A mixture of **OP-[3]mer** and **OP-[4]mer** was subjected to basic hydrolysis for unambiguous assignment of the directional isomer. See the SI for more details.