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Synthesis of Macrocycle Isomers via Metathesis Cyclization and Their Self-Assembly from Aqueous Solutions

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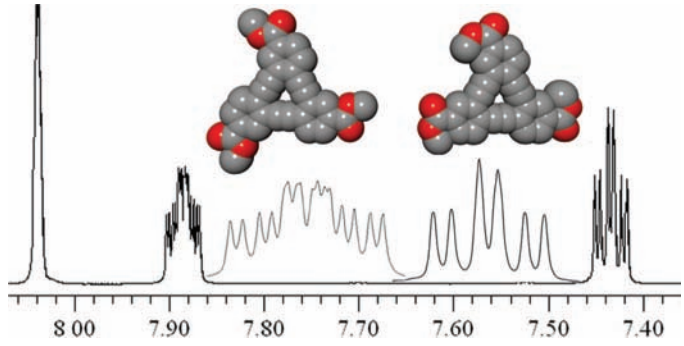
ABSTRACT



Novel triangular macrocycle isomers were synthesized through metathesis cyclization with high yield (77%). HPLC and MALDI-TOF showed that the purity of the macrocycles was higher than 99%, while ^{1}H NMR clearly showed that these macrocycles contain C_2 and C_3 isomers in a ratio of 1:3. AFM and TEM showed that they spontaneously formed vesicular structures in a chloroform/water system with an average diameter of 460 nm, which was corroborated by DLS results.

Carbon-rich macrocycles remain of great interest to both synthetic and theoretical chemists due to their unique structures and interesting properties.[1,2] However, macrocycle synthesis has generally required heroic synthetic efforts including the low-yielding "ultradilution" macrocyclization reaction in the final stages of synthesis. Therefore, reports of metathesis reactions leading to high synthetic yields of macrocycles (up to 85%) were received with great enthusiasm.[3] However, all of these macrocycles were based on symmetrical monomers resulting in a single macrocyclic product. We previously reported a series of novel, singly substituted, ortho-substituted phenylene ethynylene macrocycles (see **M0** in Figure 1) which formed order mesophases and self-assembled into vesicular structures, for the first time.[4,5a] These were prepared by ultradilution methods,[6] and consequently, only very small sample sizes were available. To increase the quantity of available materials, we considered

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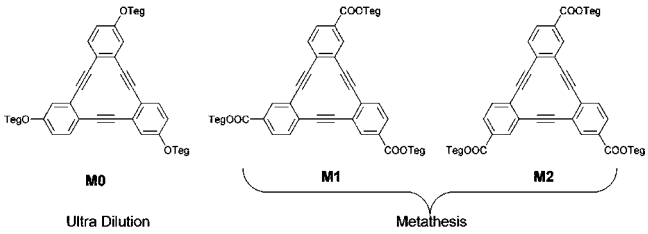
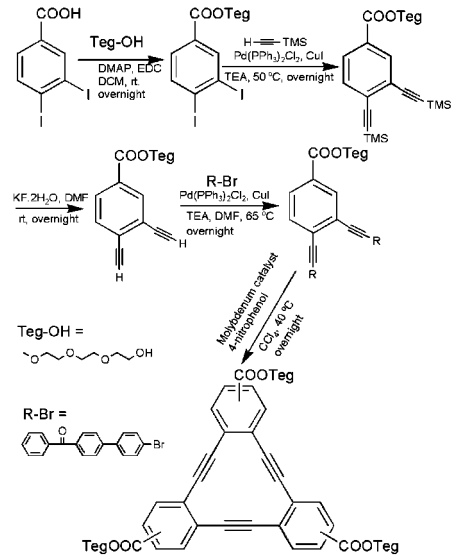


Figure 1. Macrocycles via different cyclization methods.

metathesis macrocyclization;[6] however, due to the unsymmetrical nature of our precursors, a mixture of isomers was expected. The critical question was whether this mixture of macrocycles would assemble into similar vesicular structures previously discovered from the more labor intensive but "pure" macrocycles. In this letter, we demonstrate that metathesis does lead to the expected isomers (see Figure 1 and Scheme 2), and of critical importance, this mixture of isomers readily assembles into vesicles, which appear to be identical to those previously discovered. These findings lead to the conclusion that metathesis produced isomers can still assemble with excellent fidelity yet provide the added advantage of greatly reducing the synthetic effort required to obtain these important building blocks.

We synthesized the TEG substituted *ortho*-phenylene ethynylene triangular macrocycles (**M1** and **M2**) through metathesis cyclization in 77% yield. The final product was isolated as a mixture of two regioisomers that were characterized by HPLC, ^{1}H NMR, and MALDI-TOF. Although these isomers are inseparable using HPLC, ^{1}H NMR signals could be attributed to distinct isomers. Importantly, we found that the mixture displayed self-assembling properties similar to the pure, single isomer samples previously made via ultradilution. For example, AFM and TEM confirmed the self-assembly of this mixture of isomers in a chloroform/water solvent system and showed that they formed vesicular structures with an average diameter of 460 nm, which is similar to that of the macrocycles obtained through the traditional cyclization. Scheme 1 outlines the synthesis of the macrocycle isomers. Starting from 3,4-diiodobenzoic acid,[7] esterification with triethylene glycol monomethyl ether gave TEG ester **2** in 81% yield. This ester was then coupled with (trimethylsilyl)acetylene by Sonogashira conditions[8] to afford **3** in 95% yield. The trimethylsilyl (TMS) protecting groups were removed using potassium fluoride dihydrate in DMF to give diacetylene **4**, which was reacted with 4-benzoyl-4′-bromobiphenyl to afford the metathesis precursor, monomer **5**, as yellow needles. The metathesis cyclization

Scheme 1. Synthetic Route of Macrocycle Isomers



was performed in an argon glovebox due to the sensitivity of the molybdenum catalyst to nitrogen, oxygen, and moisture. Monomer **5**, molybdenum catalyst, ligand, and 4-nitrophenol, were dissolved in carbon tetrachloride and stirred overnight at 40 °C.[3] The mixture was filtered to remove the precipitate, and the solvent was removed using rotary evaporation. The crude product was purified by flash chromatography to give the final product as a viscous yellow oil in 77% total isolated yield.

The formation of regioisomers instead of a single macrocycle is also outlined. Due to the unsymmetric structure of monomer **5**, there are eight possible macrocycles obtained via metathesis cyclization (**M6** to **M13**, Scheme 2). However, careful analysis shows that **M6** and **M7** are identical, related by a C_2 axis as shown. Similarly, **M8** to **M13** are all identical, related by either a C_2 axis or a perpendicular C_3 axis (see Scheme 2). Because each macrocycle should be formed in equal quantities, the expected ratio is 1:3.

The obtained macrocycles were characterized by HPLC, MALDI-TOF, and ^{1}H NMR. The HPLC chromatogram of the isolated isomer mixture showed a single peak indicating the isomers are inseparable and are more than 99% pure (Figure 2a). The MALDI-TOF spectrum shown in Figure 2b has only one main peak at $m/z = 908$ corresponding to $M + K^+$, with no detectable starting materials or oligomers. Both of these methods clearly indicated the purity of the isomers was very high.

The ^{1}H NMR aromatic regions of the precursor and the macrocycle regioisomers are shown in Figure 3a and 3b, respectively. In Figure 3a, the narrow doublet at 8.14 ppm ($J = 1.5$ Hz), the doublet of doublets at 7.92 ppm ($J_{1,2} = 1.5$ Hz, $J_{1,3} = 8.1$ Hz), and the wide doublet at 7.53 ppm ($J = 8.1$ Hz) correspond to Ha_m, Hb_m, and Hc_m of the precursor, respectively, and are characteristic of this substitution pattern.[9] This simple NMR spectrum is contrasted with the one collected from the macrocycles shown in Figure 3b. Initial inspection shows the macrocycle's NMR aromatic

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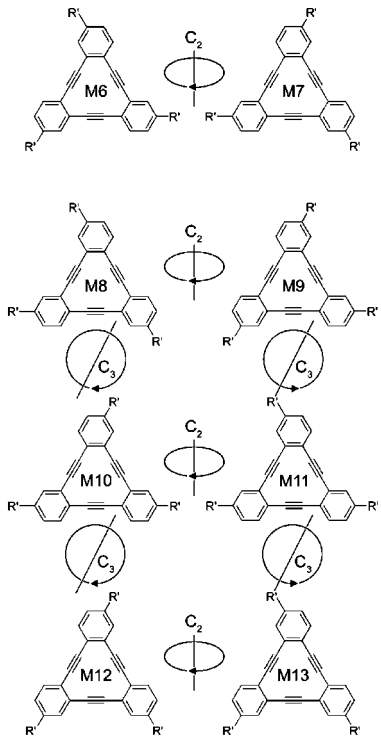
Scheme 2. Possible Macrocycle Isomers Obtained via Cyclization of the Asymmetric Monomer **5**



M6 = **M7** via C_2 rotation; **M8** = **M9** via C_2 rotation;
M10 = **M11** via C_2 rotation; **M12** = **M13** via C_2 rotation;
M8 = **M10** via C_3 rotation; **M9** = **M11** via C_3 rotation;
M10 = **M12** via C_3 rotation; **M11** = **M13** via C_3 rotation.
For another example:
M8 = **M11** via one C_3 rotation plus one C_2.

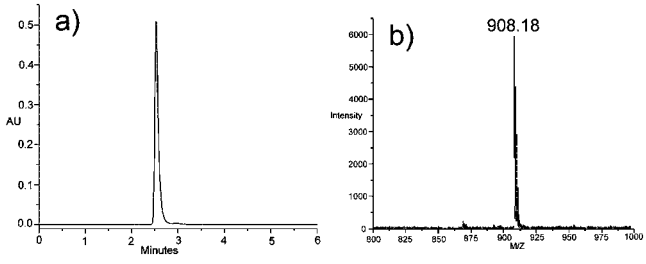


Figure 2. (a) HPLC trace of macrocycle isomers in acetonitrile monitored at 290 nm along with (b) the MALDI-TOF spectrum.

region to be more complicated, although still apparently containing three main sets of signals for the Ha, Hb, and Hc protons. From the expected isomers shown in Figure 1, one would expect **M1** to have three identical Hc_1 protons (3-Hc_1) due to the C3 symmetry. In contrast, **M2** would have three unique Hc protons, Hc_2, Hc_2', and Hc_2'', but because of the expected ratios of each macrocycle (1:3), there should

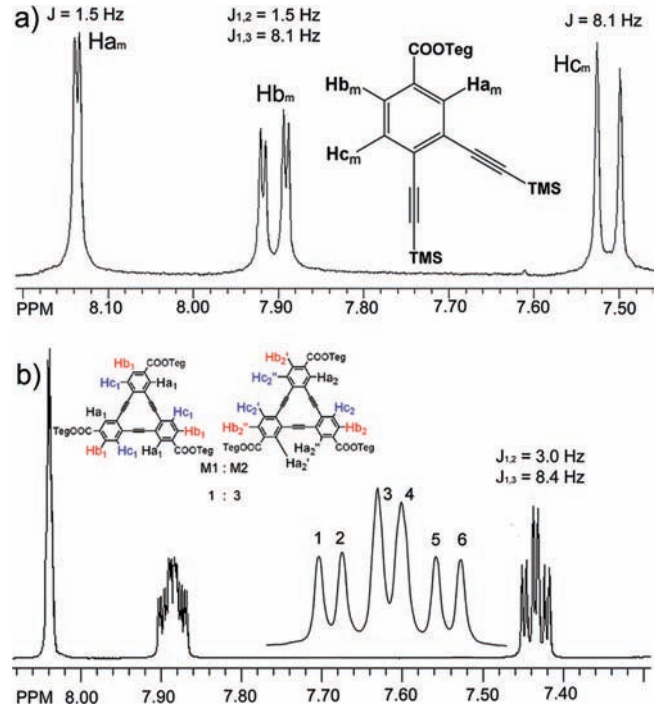


Figure 3. ^{1}H NMR spectrum of precursor and macrocycle isomers. (a) Aromatic region of the ^{1}H NMR spectrum of the precursor. (b) Aromatic region of the ^{1}H NMR spectrum of macrocycle isomers.

be three of each of these protons (3-Hc_2, 3-Hc_2', 3-Hc_2''). Therefore, the expected ratio of Hc protons should be 1:1:1:1. The initial inspection of the NMR aromatic region shows the Hc region between 7.42 and 7.45 ppm to include what appears to be three sets of doublets in a ratio of 1:2:1. However, careful inspection of the coupling constants shows that these are not three doublets, but four. For example, the coupling constant for peaks 1−2, 3−4, and 5−6 is 3.0 Hz which does not agree with any values measured for this spin system.[9a] However, the coupling constants for peaks 1−3, 2−4, 3−5, and 4−6 are 8.4 Hz, in very good agreement with previously measured values for this Hc proton,[4,9a,10] and consistent with four unique, but chemically similar, Hc protons. A similar trend is observed for the Hb protons between 7.90 and 7.87 ppm in which the four doublet of doublets overlap with the highest intensity located in the center. Due to the more complicated splitting, a definite assignment is not possible; nevertheless, the pattern and clearly measurable coupling constants are completely consistent with expectations.

Having confirmed that metathesis generated the expected regioisomers, we wondered if this would impact the spontaneous self-assembly previously observed for the pure macrocycle. The samples for both AFM and TEM were prepared as previously reported.[5a] Briefly, in a small vial, 5 mL of water was added to 5 mL of a 1 mM solution of macrocycles in chloroform. After shaking for a few minutes,

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the mixture was left undisturbed for 2−3 h until it separated into two clear phases. The organic layer was transferred to another small vial, and a carbon-coated copper grid was dipped into this solution. The grid was placed on filter paper and dried under a stream of nitrogen prior to collecting the AFM image shown in Figure 4a. This image shows spherical aggregates on the carbon-coated copper grid with an average diameter of about 460 nm, which is in good agreement with DLS results (440 nm) collected from the organic phase. The combination of DLS and AFM confirms that the AFM images are representative of the bulk structure and that no significant drying artifacts are present. More important, these AFM images support formation of vesicles based on previous literature.[5] However, since AFM cannot determine whether the aggregates are solid or hollow, it is impossible to precisely confirm vesicle formation by AFM, and so TEM experiments were carried out. TEM images (Figure 4b) of the same sample used for AFM confirmed the structures were vesicular by the presence of a dark outer ring and light interior, which is typical for 2D projections of vesicles in TEM. These TEM images show imperfectly circular structures unlike those previously observed from the pure macrocycle; however, this may be a drying artifact, so we prefer not to speculate further. The most important observation in our opinion is vesicle formation despite the presence of isomers.

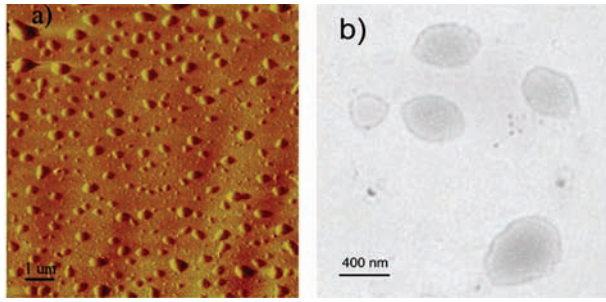

Figure 4. Tapping-mode AFM and TEM images of vesicles formed by macrocycle isomers on carbon-coated copper grid: (a) AFM phase image; (b) TEM images without staining.

Novel *ortho*-phenylene ethynylene triangular macrocycles were successfully synthesized via metathesis cyclization with a high yield of 77% compared to that of the ultradiluted cyclization reaction, which typically yielded 20% of the macrocycle. ^{1}H NMR shows that these macrocycles contain two regioisomers with a ratio of 1:3, while the sample is more than 99% pure as shown by HPLC and MALDI-TOF. DLS, AFM, and TEM were used to characterize the self-assembly of these isomers into vesicles with an average diameter of ∼440 nm. These results indicated that a mixture of isomers obtained through high-yielding metathesis macrocyclization can still be well characterized and behave similarly to other single isomer macrocycles. Understanding the structural limitations of metathesis macrocyclization is important so that one knows when it is necessary to pursue the more time-consuming ultradilution methods.

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Supporting Information Available: Complete synthetic procedures for preparation of monomers **1**−**5** and metathesis cyclization. This material is available free of charge via the Internet at http://pubs.acs.org.

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