Interlocked Molecules using Olefin Metathesis

Thesis by

Erin Nicole Guidry

In Partial Fulfillment of the Requirements for the

Degree of

Doctor of Philosophy

California Institute of Technology

Pasadena, California

2008

(Defended June 19, 2007)

For Ian and M-Wad

Acknowledgements

First, I would like to thank my best friend and future husband Ian Mangion, whose love and support have sustained me these past years. Ian has enriched my graduate school experience in countless ways, and I feel so privileged to begin this new stage of my life with him by my side.

I owe my largest debt of gratitude to my parents, especially my mom who taught me the value and joy of learning. I would also like to thank the rest of my family for their unwavering support and for helping me keep graduate school in perspective.

I would like to thank Bob for being a wonderful research advisor, for allowing me space to explore projects that I find interesting, for his enthusiasm, and especially for providing such a wonderful research environment for me to work in. It has been a pleasure to get to know Bob as both a scientist and a person and he has been a role model for me both inside and outside the lab. I would also like to thank Bob for the annual Grubbs' group camping trip. These trips were some of my favorite times in graduate school, and I am so glad that this tradition is still going strong. I would like to thank my ever evolving committee of Professor MacMillan, Professor Jim Heath, Professor Peter Dervan and Professor David Tirrell for their advice and comments during my graduate career. I would especially like to thank Professor Tirrell for all his thoughtful advice during the MURI meetings and for his support in finding a job.

In a review article on the topic of supramolecular chemistry written by Stoddart and coworkers, the question is asked, "How can anyone not find these molecules fascinating?" I think this really sums up Fraser's enthusiasm for these molecules, and I appreciate him for sharing his knowledge of all things supramolecular and for being a wonderful collaborator. I would also like to thank Professor Stoddart's and Professor Tirrell's research groups for all their great advice and rousing discussions during our MURI meetings.

I would like to thank the reverend, Dr. Stuart Cantrill (whose name I still do not pronounce correctly) for introducing me to the fun and sometimes mysterious world of ammonium binding. I would also like to thank Stu for teaching me countless chemdraw tips, for his superb editing and for cricket.

I would like to thank Professor Dan O'Leary for being a great coworker and for introducing me to the 21 choices in Claremont (along with Maggie, Francis and Katie).

I would like to thank Professor Wayne Steinmetz for introducing me to 2D-DOSY experiments and patiently pouring over all the confusing data I generated. His encyclopedic knowledge of the outdoors is impressive. I wish him all the best in his upcoming retirement.

I have had numerous baymates while in the Grubbs group. I would like to thank James (King James) and Sebastian for being brave enough to work next to a first year from Texas. I would like to thank Andrew Waltman (Drew) for his fantastic sense of humor and his much needed encouragement, especially in the early years. He was a truly wonderful baymate despite the fact that he never fulfilled his promise to show Donde and me his surgical Elvis impression. I would also like to thank Drew and Bill for all the late night Willie Nelson and Prince music and for introducing me to the best lab game of all time, lab ball. I would like to thank Chris Douglas for being a fantastic baymate, who was always eager to chat about chemistry and whose knowledge and passion for organic chemistry was inspiring. I would also like to thank Chris for introducing me to the music of Necko Case and to a recipe for the best macaroni and cheese I have ever tasted. I am sure Chris is going to make a fantastic research advisor and father, and I wish him luck as he begins these new journeys. Last, but certainly not least, I would like to thank Jean Li for becoming the newest member of the bay. Evidently Jean couldn't resist repeating all the fun times we had together during her days as a SURF. I would like to thank Jean Li for being such a fun SURF to spend the summer with and for her patience as I tried to understand what you really need to do to be a good mentor. I have thoroughly enjoy my last few months in the bay with Jean and am continuously amazed by her energy and enthusiasm and am sure that I will be seeing great things from her in the future.

I would like to thank Cristiane Meyer-Marti for her support during the early years and the great vent hood she bequeathed to me. I would also like to thank Cristiane for being a pioneering female member of the Grubbs group basketball team and for a hilarious story involving a European sports bra. I would like to think Dan Sanders for teaching me about metathesis polymer chemistry and being a wonderful guy to talk to about pretty much anything, especially Minnesota sports. I would like to thank Al Nelson for sharing his vast knowledge in all areas supramolecular and for being one of the nicest people I have ever worked with. I would like to thank Connie Hou for joining "team MURI" and being such a pleasure to work with and take road trips to UCLA with. I would also like to thank Connie (along with Donde and Jason) for all their support during the job interviewing process. I would like to thank Lynda Syme for all her help over the years and for the wonderful conversation. I would like to thank Paul Clark for joining the daisy-chain project and bringing such energy and excitement to our work. I would also like to thank Paul for being an absolute angel the past few months helping me with everything from teaching responsibilities to his tireless editing of my thesis. I feel so fortunate to have had the pleasure to work with Paul and am so glad that I get to leave projects in the hands of such a talented chemist and thoughtful individual. I would like to thank Patricio Ramero (Pato), Daryl Allen and Chris Douglas for editing my research proposals and for numerous scientific discussions.

I would like to thank Donde Anderson, my friend and maid of honor for her friendship, for rediscovering the long lost Grubbs group tradition of “Girl Lunch” and introducing me to the best source for recipes and other kitchen advice, Cook’s Illustrated (also known as America’s Test Kitchen). Donde was an almost instant friend and I cannot imagine how I would have survived graduate school without her.

I would like to thank Jacob Berlin (“Coach Cob”) for his friendship, his sense of humor and for convincing me to play on so many intramural sports teams despite my lack of speed and coordination. I hope you really do get your disco ball and dim sum carts. I would also like to thank all the members of Sunday night baseball (Jacob, Nick, Ian, Meghana, Tim, Amy, Andy and Jeff) for all the excellent food and company. I would like to thank Nick Graham for his friendship and helping me not to become homeless. Nick’s sweet tooth is one of the few to surpass my own. I would also like to thank Kate for joining 129 North Craig. It was a pleasure to live with you and get to know you. Take good care of Nick. I would like to thank my nonhusband Andy Hejl for the cookies and cream ring pop, his friendship and being a great camping and drinking buddy. I would also like to thank Tim Funk and Andy Hejl for introducing Ian and me to the joys of homebrewing. I would like to thank Greg Beutner for being a wonderful labmate with an almost encyclopedic knowledge of chemistry and for the country and western dance lessons. I am delighted that I will soon become Greg's coworker again in a few short months. I would like to thank John Matson (Beef) for making my last several years in lab so enjoyable, for attempting to cure cancer and for being a great drinking and dancing buddy (watch out for your toes though). I would also like to thank John for his care and attention of the Grubbs' group mascot "Jedi Olefin Metathesis Barbie." I would like to thank the Ath crew past and present for being such great fun to spend Friday evenings with. I would also like to thank one of the newer members of the Ath crew Ian Stewart for his sharp sense of humor and sharing my love of delicious food from around the world. I would like to thank Eric Ferriera and Kevin Kuhn for their wonderful music recommendations. I would like to thank Katie and Daryl for introducing me to Canadian culture. I would like to thank my classemate Irina for being an excellent outlet shopping companion and teaching me about Russian culture. I would like to thank Paula for adding a little arts and culture to my life. I would like to thank Amy Eastwood for being a great roommate and finding us such a wonderful apartment. I would like to thank the members of the book club (Dave, Jeff, Andy, Wendy, Heather, and Amy) for expanding my reading horizons and giving me yet another excuse to drink wine on a weeknight.

I would like to thank members of the Stoltz, MacMillian, Bercaw and Dervan groups who have taken time to chat about science and have enriched my graduate career (especially, Raissa Trend, Eric Ferriera, Dan Caspi, Nikki Goodwin, Neil Garg, Jeff Byers, Alan Northrup, Ryan Stafford and Katie Saliba).

Finally, I would like to thank the wine of the month club, Babitas, Gales, Lucky Baldwins and the best travel companion a girl could ask for, Meatwad.

Abstract

Olefin metathesis has been employed in the efficient syntheses of a [2]catenane with the templation being provided by the recognition between a secondary ammonium ion and a crown ether. In one approach, a crown ether precursor has been clipped around an NH_2^+ center situated in a macrocyclic ring, yielding the mechanically interlocked compound. In the other approach, the reversible nature of olefin metathesis allows for a magic ring synthesis to occur wherein two free macrocycles can be employed as the stationary materials, leading to the formation of the same [2]catenane.

A strategy for the formation of mechanically interlocked polymers is presented. Ring-closing olefin metathesis has been shown to provide a very high yielding route to [c2]daisy-chains suitably functionalized to allow their one-step conversion to bis-olefins which can be used as monomers in ADMET polymerizations to afford mechanically interlocked polymers. Metathesis, in two different guises is making a hitherto unreachable goal in synthesis a reality.

A method for the production of cyclic polyammonium ions is presented which utilizes a polymer cyclization of azide terminated linear polymer based on the “click” reaction. An azide terminated polymer was prepared using ROMP in the presence of chain transfer agents (CTA). Formation of cyclic polycateanes was explored utilizing the mutual recognition between secondary ammonium ions and crown ether macrocyles. The product of the RCM of linear crown ether dienes around cyclic polyammonium ions was investigated using 2D-DOSY.

The ring-opening metathesis polymerization of a [2]catenane was investigated, using both a cyclic metathesis catalyst and bulky metathesis catalysts for the formation of cyclic polycatenanes and polyrotaxanes respectively. While it was found that the [2]catenane monomer could function as a ROMP monomer, no interlocked polymers were observed as products from the polymerization. Linear impurities present in either or both the [2]catenane monomer and the metathesis catalysts are believed to be responsible for the formation of the non-interlocked polyether and free macrocycle. These results highlight the critical role of purity to the successful formation of cyclic or linear interlocked polymer using a ROMP process.

Table of Contents

List of Schemes

Chapter 2: Magic Ring Catenation via Olefin Metathesis

Chapter 3: [2]Daisy-Chain Dimers and Their Incorporation into Interlocked Polymers

Chapter 4: Cyclic Polycatenanes via Ring-Closing Metathesis

Appendix 1: Studies toward Interlocked Polymers via ROMP of [2]Catenane Monomers

List of Figures

Chapter 1: Introduction

Chapter 2: Magic Ring Catenation via Olefin Metathesis

Chapter 3: [2]Daisy-Chain Dimers and Their Incorporation into Interlocked Polymers

Chapter 4: Cyclic Polycatenanes via Ring-Closing Metathesis

Appendix 1: Studies toward Interlocked Polymers via ROMP of [2]Catenane Monomers

List of Abbreviations

Ac_2O	acetic anhydride
ADMET	acyclic diene metathesis
9-BBN	9-borabicyclo[3.3.1]nonane
Boc	*tert*-butyl carbamate
Boc_2O	di-*tert*-butyl dicarbamate
CAM	citric ammonium molybdate
click	Huisgen dipolar cycloaddition
CM	cross metathesis
COD	cyclooctadiene
COT	cyclooctatetrene
CTA	chain transfer agent
dba	dibenzylammonium ion
DCC	dicyclohexyl carbodiimide
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DNA	deoxyribose nucleic acid
DOSY	diffusion ordered nuclear magnetic resonance
dc	change in concentration
dn	change in refractive index
ESI	electrospray ionization

EtOAc	ethyl acetate
FAB	fast atom bombardment
f_n	average degree of functionality
FTIR	Fourier transform infrared
GPC	gel permeation chromatography
HPLC	high pressure liquid chromatography
K_a	association constant
MALDI	matrix assisted laser desorption ionization
MALLS	multi angle laser light scattering
mCPBA	3-chloroperbenzoic acid
MeCN	acetonitrile
MeOH	methanol
Mn	number average molecular weight
MsCl	methanesulfonyl chloride
NHC	N-heterocyclic carbene
NMR	nuclear magnetic resonance
PCy_3	tricyclohexylphospine
PDI	polydispersity index
PhMe	toluene
PPh_3	triphenylphosphine
RCM	ring closing metathesis
RI	refractive index
ROMP	ring opening metathesis polymerization

SEC	size exclusion chromatography
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TsCl	*para*-toluenesulfonyl chloride

Chapter 1

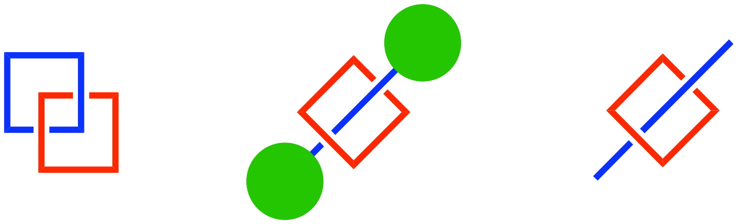
Introduction

Introduction

The Grubbs group has developed functional-group tolerant ruthenium alkylidene catalysts for use in a variety of olefin metathesis reactions. These reactions have impacted numerous and diverse fields of chemistry from complex small molecule synthesis to polymer and material science. One such field that could potentially exploit the advances made in olefin metathesis is supramolecular chemistry, in the synthesis of interlocked molecules. This thesis explores the use of olefin metathesis reactions in the synthesis of small molecule and polymeric interlocked molecules.

Introduction / Historical Perspective

Interlocked molecules are defined as two or more molecules that cannot be separated without covalent bond cleavage, but do not contain covalent bonds between them. The most basic interlocked molecules are the [2]catenane (**1a**) where 'catena' comes from the Latin word meaning chain and the [2]rotaxane (**1b**) where 'rota' comes from the Latin word meaning wheel (Figure 1). A catenane is a compound consisting of two or more rings that are looped through each other and do not contain any covalent bonds between them. Rotaxanes consist of a linear dumbbell-shaped component surrounded by one or more ring-shaped components, which are entrapped on the rod of the rotaxane by large stoppering groups. A common precursor to both catenanes and rotaxanes is a supramolecule, the pseudorotaxane (**1c**), which consists of a rod-like component (with no stoppering groups) surrounded by one or more ring shaped components. Unlike catenanes and rotaxanes, pseudorotaxanes are not permanently interlocked, but instead are in equilibrium with their constituent components. The standard nomenclature of these systems is to place the number of components in brackets before the name of the compound or complex. For example, a [2]catenane consists of two interlocking macrocycles and a [2]rotaxane consists of one dumbbell component and one macrocycle. Interestingly, while both [2]catenanes and [2]rotaxanes are considered interlocked molecules, catenanes are considered topological isomers, which in order to separate into its macrocyclic components cleavage of at least one covalent bond is required. Rotaxanes, by contrast, are considered constitutional isomers because separation into individual components can be accomplished by means other than covalent bond cleavage (such as stretching of the macrocyclic component, shrinkage of the dumbbell component, etc.). On a more practical level, however, most rotaxanes are prepared with sufficiently large blocking groups such that dissociation into the constituent components requires covalent bond cleavage.[1]



[2]Catenane
1a

[2]Rotaxane
1b

[2]Pseudorotaxane
1c

Figure 1: Graphical representation of a [2]catenane (**1a**), [2]rotaxane (**1b**) and [2]pseudorotaxane (**1c**).

Mechanically interlocked molecules have long been of interest to chemists due their unique molecular structures and the synthetic challenge they pose. Furthermore, recent advances in nanotechnology have revealed that these molecules are not only aesthetically pleasing curiosities, but can also function as stimulus responsive switches in both memory and logic circuits (Figure 2). This could potentially allow for the preparation of devices with smaller feature sizes through a "bottom up" approach rather than the traditional microlithography "top down" approach.[2]

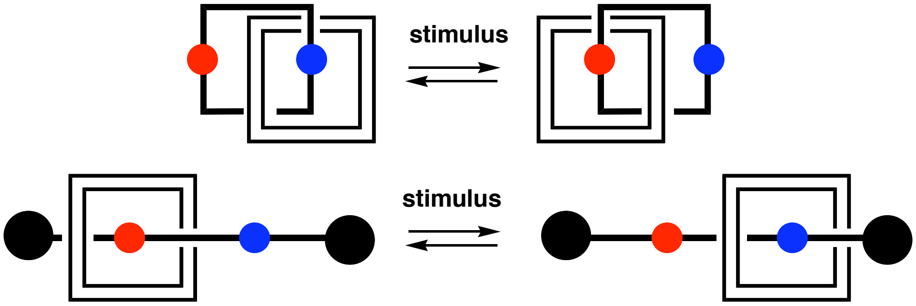
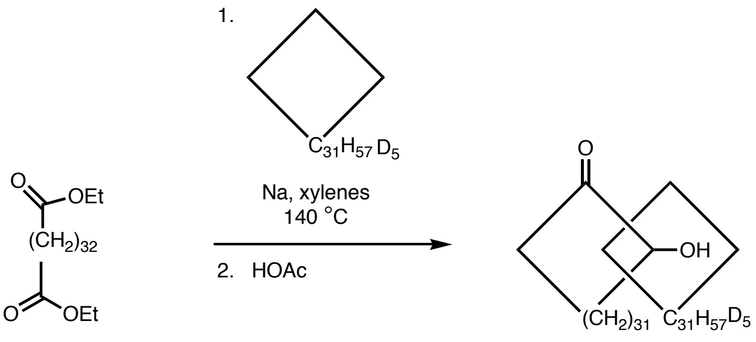


Figure 2: Graphical representation of stimuli-responsive bistable [2]catenanes and [2]rotaxanes that can function as switches in memory and logic circuits.

The first interlocked molecule, [2]catenane **2** was synthesized by Wasserman and coworkers at Bell Laboratories (Figure 3) in 1960.[3] The hydrocarbon-based [2]catenane **2** was formed using a statistical approach, which relies on the chance formation of one macrocycle while threaded through another. An acyloin condensation was used as the final bond forming reaction and [2]catenane **2** was isolated in a 1 percent yield. The yields associated with the statistical approach are quite low, illustrating the disadvantage of relying on chance threading events to form interlocked molecules. Using the statistical method, catenanes, rotaxanes and other interlocked molecules remained rare curiosities.



2

1% yield

Figure 3: Synthesis of a hydrocarbon-based [2]catenane using a statistical approach.

The major breakthrough in the synthesis of interlocked molecules was the use of molecular recognition (or supramolecular chemistry) to make interlocked molecules in a rational and efficient manner. Supramolecular chemistry, meaning "beyond the molecule," also termed host-guest chemistry can be used to template the formation of interlocked molecules, a technique termed directed synthesis. Interactions between host and guest molecules form a supramolecular complex, which after appropriate manipulation can be converted into an interlocked molecule. Typically, non-covalent interactions such as hydrogen bonding, π-π interactions or van der Waals interactions are used to form supramolecular complexes; however, metal coordination interactions have also been exploited. The association constant (K_a), with units of inverse concentration, denotes the amount of host-guest complex relative to its constituents and thus expresses the extent of formation of the subsequent interlocked molecule. Both concentration and temperature impact the K_a such that an increase in concentration favors the association and formation of a supramolecular complex, which is expressed in an increase in the K_a while an increase in temperature favors dissociation of the supramolecular complex into its individual constituents, which is expressed in a decrease in the K_a.[1]

One of the most heavily exploited non-covalent interactions in the formation of supramolecular complexes and interlocked molecules is the hydrogen bond. There are a variety of hydrogen bonding recognition motifs, many of which have been inspired by nature and include systems based on amides,[4] crown ether/ammonium binding[5] and base-pair hydrogen bonding.[6] Throughout this thesis, the molecular recognition between dialkylammonium ions and macrocyclic crown ethers through hydrogen bonding will be exploited in the formation of interlocked molecules (Figure 4).

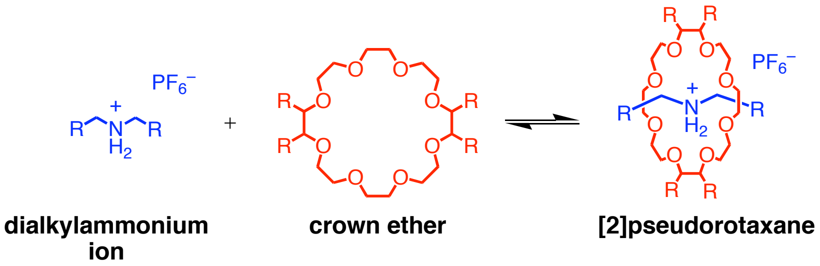


Figure 4: Hydrogen bonding between dialkylammonium ions and crown ethers can be exploited to form [2]pseudorotaxanes.

Crown Ether / Ammonium Binding

Crown ethers are cyclic polyethers with the basic -CH_2CH_2O- repeating structure. These molecules were first discovered by Pedersen[7] at Dupont and subsequently investigated by Cram[8] at UCLA, both of whom later received a Nobel Prize for their work in this area of research. Crown ethers are capable of binding metal cations, such as sodium, potassium, etc. but will also form hydrogen-bonded complexes with primary and secondary ammonium ions.[9] Additionally, ammonium ions may bind in two different modes, either the 'perching structure' where the ammonium ion is binding to the face of the crown ether or the 'nesting structure' where the ammonium ion is binding to the internal cavity of the crown ether (Figure 5). The size of the crown ether dictates which binding mode will operate, and it has been found that [18]crown-6 binds dialkylammonium ions in a perching fashion, while the slightly larger [24]crown-8 binds dialkylammonium ions in a nesting structure.[10]

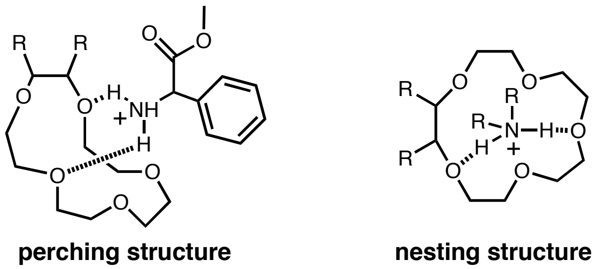


Figure 5: Crown ethers may bind in a facial manner (perching structure) or in a threading manner (nesting structure).

Stoddart and coworkers have exploited the nesting interaction between dialkylammonium ions and crown ether macrocycles in the formation of a variety of interlocked compounds. Through structure-activity studies, they found that both the size and substitution of the crown ether macrocycle play a large role in the K_a of the resulting supramolecule (Figure 6). The association constant between the substituted dibenzylammonium ion (dba) **3** and a range of crown ethers (**4** and **5**) was determined.[11] In the 24-crown-8 series (**4a**, **4b**, **4c**) it was observed that an increase in the number of phenolic oxygen atoms reduced the binding affinity from 4500 M^{-1} for crown ether **4a**, with all dialkyl ether oxygen atoms, to 1000 M^{-1} for crown ether **4c** which contains four phenolic oxygen atoms. Phenolic oxygen atoms have reduced basicity with respect to dialkyl ether oxygen atoms and, as such, their effectiveness as H-bond acceptors is diminished resulting in crown ethers with lower binding affinities. It was also found that the addition of even one extra methylene into the -CH_2CH_2O- structure of crown ethers

(**5a** and **5b**) dramatically decreases the binding affinity. It is thought that the addition of an additional methylene unit disrupts the array of donor atoms directed toward the center of the crown ether cavity. This distortion results in a less favorable geometry for interaction with dialkylammonium ions.

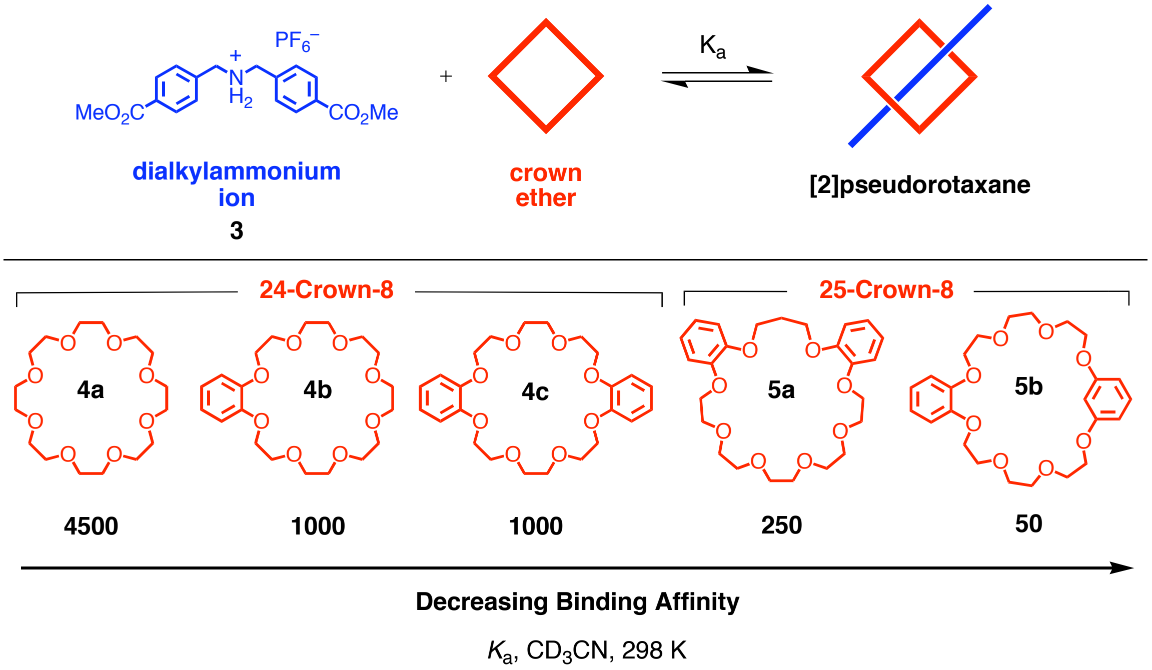


Figure 6: A range of crown ethers will bind dialkylammonium ions. However, both the size and the substituents affect the binding affinity (K_a).

Olefin containing crown ethers (**7a** and **7b**) are also capable of forming [2]pseudorotaxanes with dba **6** (Figure 7), though the association constant is somewhat diminished when compared to crown ether **4c**.[12] The major factor contributing to this decrease in binding affinity is the "loss" of two ether oxygen atoms upon structural modification of crown ether **4c** to olefin containing crowns **7a** and **7b**.

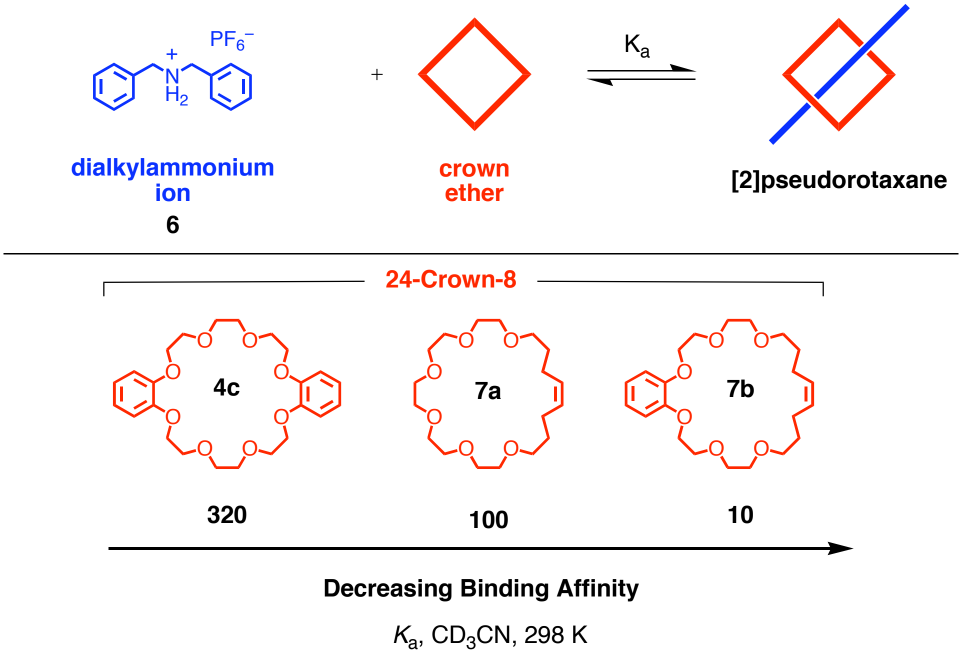


Figure 7: Olefin-containing crown ethers will bind dialkylammonium ions, however, the binding constant is significantly diminished compared to dibenzo-[24]crown-8.

Dynamic Covalent Chemistry

While the association constant between host-guest complexes impacts the product distribution (i.e., yield of interlocked compound), other factors also contribute to the formation of interlocked molecules. The final bond forming step, namely the reaction that transforms a molecule from a supramolecule to an interlocked molecule, is also of great importance due to the impact that it can have on product distribution. Kinetically controlled reactions have been commonly used in the synthesis of interlocked compounds, however, they can suffer from low yields of interlocked compounds due to the irreversible formation of noninterlocked by products.[13] An alternative strategy to this traditional method exploits dynamic covalent chemistry,[14] an approach that utilizes reversible reactions in which the product distribution depends on thermodynamic rather than kinetic control. In this way, the yield of a mechanically interlocked compound reflects its stability relative to those of any other non-interlocked by-products. Examples of equilibrium reactions employed as the final bond-forming step in the synthesis of interlocked molecules include the reversible formation of imines,[15] disulfides[16] and cyclic acetals.[17]

Olefin metathesis is also a dynamic reaction that operates under thermodynamic control. Additionally, ruthenium based metathesis catalysts are functional-group tolerant, which is important due to the many reactive functional groups present in most molecular recognition systems. Olefin functional groups are also orthogonal to most of the molecular recognition systems that are commonly employed in the synthesis of interlocked molecules and a wide variety of olefin metathesis mediated reactions are possible through the variation of the structure or reaction conditions. For these reasons, olefin metathesis is an ideal candidate for use in the formation of interlocked molecules. Throughout this thesis, numerous olefin metathesis reactions will be employed in the synthesis of both small molecule and polymeric interlocked molecules.

Olefin Metathesis

Olefin metathesis is a versatile carbon-carbon bond forming reaction and is mediated by a metal alkylidene, which allows for both the cleavage of carbon-carbon double bonds and their reassembly in new ways. The general mechanism for olefin metathesis was first proposed by Chauvin in 1971. It involves olefin coordination to a metal alkylidene followed by cycloaddition to form a metalocyclobutane intermediate.

This intermediate may then undergo a cycloreversion process in either an unproductive manner to reform the starting olefin and metal alkylidene or in a productive manner to generate a new olefin containing product and regenerate a metal alkylidene species which can re-enter the catalytic cycle (Figure 8). In general, all of these steps are reversible and operate under thermodynamic control.[18]

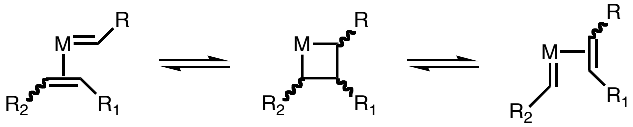
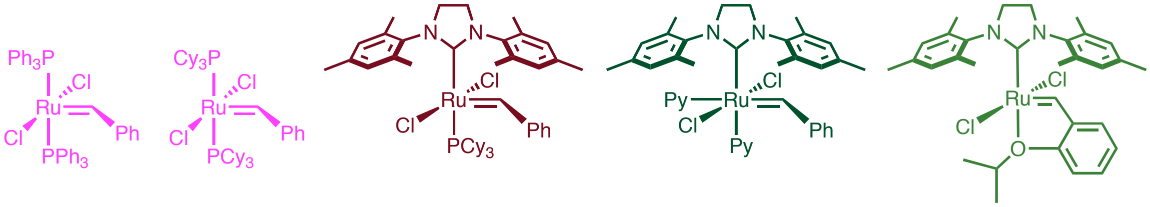


Figure 8: General mechanism of olefin metathesis.

A number of metals are effective at mediating olefin metathesis reactions. The first generation of olefin metathesis catalysts consisted of ill-defined mixtures capable only of polymerizing strained cyclic olefins.[19] More recently, well-defined molybdenum, tungsten and ruthenium catalysts have emerged and greatly expanded the synthetic utility of metathesis reactions. Schrock and coworkers have prepared a number of highly active molybdenum and tungsten based catalysts that have been widely used in olefin metathesis.[20] A general problem with early transition metal catalysts is their extreme air and moisture sensitivity, which frequently requires rigorous solvent and reagent purification. Additionally, substrates with polar functional groups are typically not tolerated by these very electrophillic metals.

Grubbs and coworkers have prepared a number of ruthenium based catalysts which, depending on the ligand subset, also have high activity in olefin metathesis. These late transition metal catalysts are much more tolerant of air and moisture compared with early transition metal catalysts and do not require rigorous solvent or reagent purification. More importantly, they tolerate a wide range of substrates containing polar functional groups, greatly expanding the synthetic utility of the olefin metathesis reaction. The first well-defined ruthenium metathesis catalyst **8a** had low activity and was limited to reactions with highly strained cyclic olefins such as norbornene.[21] Replacement of the triphenylphosphine ligands (PPh_3) with more electron-donating tricyclohexylphosphine ligands (PCy_3), generating catalyst **8b** greatly increased catalyst activity and expanded the substrate scope to include unstrained cyclic olefins and acyclic olefins.[22] The substrate scope was further improved by replacement of one of the tricyclohexylphosphine ligands with a very donating N-heterocyclic carbene (NHC) ligand, generating catalyst **8c**.[23] Increased catalytic activity allowed more electron-deficient olefins (i.e., acrylates) and bulky substrates to undergo olefin metathesis. Additionally ligand modification of catalyst **8c**, including the addition of pyridine ligands, generates catalyst **8d** which has very fast initiation relative to its parent catalyst **8c**.[24] Phosphine ‘free’ systems such as catalyst **8e** have also been developed and are generally more stable than their phosphine analogues, though initiation is typically somewhat slower.[25] Other catalysts based on this general ligand framework have been developed to effect asymmetric,[26] water-soluble[27] and very sterically encumbered transformations.[28]



8a **8b** **8c** **8d** **8e**

Figure 9: Ruthenium-based olefin metathesis catalysts.

As can be seen in Figure 10, olefin metathesis has been applied to the synthesis of small molecule and polymeric architectures. Cyclic olefins can be made from α,ω-dienes through ring closing metathesis (RCM). Acyclic olefins can be made from two chemically distinct olefins through cross metathesis (CM). α,ω-Dienes can also be used to generate polymeric materials through an iterative cross metathesis process termed acyclic diene metathesis (ADMET). Strained cyclic olefins can be polymerized through ring opening metathesis polymerization (ROMP) to form polymeric materials. A driving force is required to generate a single product from these thermodynamic processes. For RCM, CM and ADMET the liberation of volatile small molecules (i.e., ethylene) or the formation of more stable products is a driving force. ROMP is driven by the release of ring strain. Throughout this thesis all four of these major categories of metathesis reactions will be utilized in the construction of interlocked molecules. Factors which affect each of these individual reactions will be discussed.

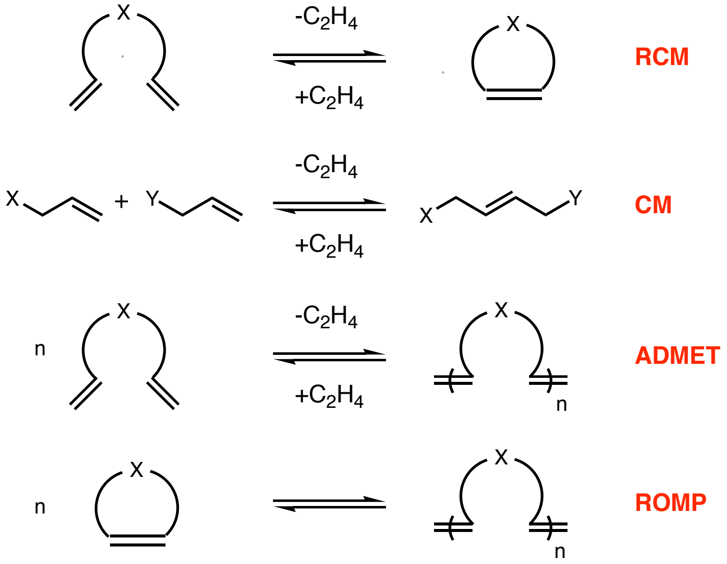


Figure 10: Reactions mediated by olefin metathesis catalysts.

RCM

Ring-closing metathesis converts α,ω-dienes to cyclic olefin-containing products. Both the thermodynamic stability of the product and the expulsion of volatile small molecules (i.e., ethylene) drive product formation. While highly strained cyclic products, such as norbornes, cannot be formed through RCM, a variety of both small and large rings can be prepared. Additionally, low concentration can be important to shift the equilibrium toward the formation of the corresponding cyclic product rather than the formation of various cross metathesis by-products resulting from side reactions of two or more α,ω-diene starting materials.[29]

ADMET

Acyclic diene metathesis polymerization converts α,ω-dienes to polyalkenamers and is driven by the expulsion of volatile small molecules (i.e., ethylene). ADMET is classified as a step growth polymerization where high molecular weight polymer is formed only at very high conversion and somewhat broad polydispersities are typical. At complete conversion, the theoretical polydispersity index (PDI) is 2. In order to push this process to high conversion and obtain large molecular weight polymer, several strategies are utilized. High concentration can be important to shift the equilibrium toward the formation of high molecular weight polymer. Removal of ethylene becomes increasingly difficult as the extent of reaction increases due to the increase in viscosity associated with the formation of higher molecular weight polymers. This issue can be somewhat overcome by the application of vacuum or by increasing the temperature of the reaction, which aid in ethylene removal by improving diffusion.[29]

ROMP

ROMP produces polyalkenamers through the ring opening of strained cyclic olefin monomers and is classified as a chain growth polymerization. Under appropriate conditions with certain metathesis catalysts, ROMP can be controlled to such an extent that it satisfies the criteria of a living polymerization, producing polymers with narrow PDIs. Since all polymer chains are growing at the same rate, molecular weight is directly proportional to monomer conversion. The rate of initiation relative to propagation has an impact on the PDI of the polymer. For active catalysts and very reactive high strain monomers, faster initiating catalysts lead to polymers with narrow polydispersities.[30] Since ROMP operates under thermodynamic control, depolymerization and 'back-biting' (i.e. chain transfer forms cyclic olefins and smaller polymer chains) processes are also possible. These processes are affected by both monomer and catalyst selection. Back-biting processes are more prevalent in the more active catalyst **8c** and can lead to a broadening of the PDI when polymerizing relatively unsubstituted olefin monomers.[31] Substituted norbornene monomers can be polymerized with the fast initiating catalyst **8d** to give very narrow PDI polymer product due to the absence of chain transfer in these more substituted systems. Block copolymers can also be produced through sequential addition of monomer units which do not undergo chain transfer (such as substituted norbornenes) in conjunction with fast initiating catalysts.[32]

The back-biting process is not always undesirable and can be used in the creation of end functionalized (telechelic) polymers. The chain transfer process is typically performed by polymerizing a cyclic olefin in the presence of a linear difunctional olefin which acts as a chain transfer agent (CTA).[33] Catalyst **8c** is typically chosen for this process due to its high reactivity toward chain transfer. The chain transfer agent may react with the metal alkylidene attached to a growing polymer chain, resulting in an end functionalized polymer and a newly functionalized catalyst molecule. This newly functionalized catalyst molecule may then react with a growing polymer chain, transferring the new end group to the polymer and terminating the polymer chain growth or react with a monomer, beginning the growth of a new mono-functionalized polymer chain. The only polymer chains not containing the CTA end group result from the original catalyst alkylidene and terminating species. This process operates under equilibrium and has a theoretical PDI and average degree of functionality (fn) of 2.

References

(1) (a) Schill, G. *Catenanes, Rotaxanes and Knots*; Academic Press: New York, 1971. (b) Amabilino, D. B.; Stoddart, J. F. *Chem. Rev.* **1995**, *95*, 2725–2828. (c) *Molecular Catenanes, Rotaxanes and Knots* Sauvage, J.-P.; Dietrich-Buchecker, C. Eds.; Wiley-VCH: Weinheim, 1999.

(2) (a) Collier, C. P.; Mattersteig, G.; Wong, E. W.; Luo, Y.; Bererly, K.; Samparo, J.; Raymo, F. M.; Stoddart, J. F.; Heath, J. R. *Science* **2000**, *289*, 1172–1175. (b) Pease, A.R.; Jeppesen, J. O.; Stoddart, J. F.; Luo, Y.; Collier, C. P.; Heath, J. R. *Acc. Chem. Res.* **2001**, *34*, 433–444. (c) Luo, Y.; Collier, C. P.; Jeppesen, J. O.; Nielsen, K. A.; DeIonno, E.; Ho, G.; Perkins, J.; Tseng, H.-R.; Yamamoto, T.; Stoddart, J. F.; Heath, J. R. *ChemPhysChem*. **2002**, *3*, 519–525. (d) Diehl, M. R.; Steuerman, D.; Tseng, H.-R.; Vignon, S. A.; Star, A.; Celestine, P. C.; Stoddart, J. F.; Heath, J. R. *ChemPhysChem* **2003**, *4*, 1335–1339. (e) Tseng, H.-R.; Wu, D.; Fang, N. X.; Zhang, X.; Stoddart, J. F. *ChemPhysChem* **2004**, *5*, 111–116. (f) Steuerman, D. W.; Tseng, H.-R.; Peters, A. J.; Flood, A. H.; Jeppesen, J. O.; Nielsen, K. A.; Stoddart, J. F.; Heath, J. R. *Angew. Chem., Int. Ed.* **2004**, *43*, 6486–6491. (g) Flood, A. H.; Ramirez, R. J. A.; Deng, R. P.; Muller, W. P.; Goddard III, W. A.; Stoddart, J. F. *Aust. J. Chem.* **2004**, *57*, 301–322. (h) Flood, A. H.; Peters, A. J.; Vignon, S. A.; Steuerman, D. W.; Tseng, H.-R.; Kang, S.; Heath, J. R.; Stoddart, J. F. *Chem. Eur. J.* **2004**, *10*, 6558–6564. (i) Flood, A. H.; Stoddart, J. F.; Steuerman, D. W.; Heath, J. R. *Science* **2004**, *306*, 2055–2056. (j) Jang, S. S.; Kim, Y. H.; Goddard III, W. A.; Flood, A. H.; Laursen, B. W.; Tseng, H.-R.; Stoddart, J. F.; Jeppesen, J. O.; Choi, J. W.; Steuerman, D. W.; DeIonno, E.; Heath, J. R. *J. Am. Chem. Soc.* **2005**, *127*, 1563–1575.

(3) Wasserman, E., et al. *J. Am. Chem. Soc.* **1960**, *82*, 4433-4434.

(4) (a) Hunter, C. A. *J. Chem. Soc., Chem. Commun.* **1991**, 749. (b) Hunter, C. A. *J. Am. Chem. Soc.* **1992,** *114***,** 5303. (c) Vogtle, F.; Meier, S.; Hoss, R. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1619. (d) Hunter, C. A.; Purvis, D. H. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 792. (e) Carver, F. J.; Hunter, C. A.; Shannon, R. J. *J. Chem. Soc., Chem. Commun.* **1994**, 1277.

(5) Cantrill, S. J.; Fulton, D. A.; Heiss, A. M.; Pease, A. R.; Stoddart, J. F.; White, A. J. P.; Williams, D. J. *Chem. Eur. J.* **2000**, *6*, 2274-2287.

(6) (a) Seeman, N. C. *DNA Cell Biol.* **1991**, *10*, 475. (b) Mueller, J. E.; Du, S. M.; Seeman, N. C. *J. Am. Chem. Soc.* **1991**, *113*, 6306.

(7) (a) Pedersen, C. J. *Prix Nobel* **1988**, 181-197. (b) Pedersen, C. J. *Science* **1988**, *60*, 450-451.

(8) Cram, D. J. *Prix Nobel* **1988**, 105-123.

(9) Pedersen, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 7017-7036.

(10) Cram, D.J., et al. *Acc. Chem. Res.* **1978**, *11*, 8.

(11) Ashton, P. R.; Bartsch, R. A.; Cantrill, S. J.; Hanes, R. E. Jr.; Hickingbottom, S. K.; Lowe, J. N.; Preece, J. A.; Stoddart, J. F.; Talanov, V. S.; Wang, Z. -H. *Tetrahedron Lett.* **1999**, *40*, 3661-3664.

(12) Kilbinger, A. F. M.; Cantrill, S. J.; Waltman, A. W.; Day, M. W.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 3281–3285.

(13) (a) Dietrich-Buchecker, C. O.; Sauvage, J.-P.; Kern, J. M. *J. Am. Chem. Soc.* **1984**, *106*, 3043–3045. (b) Hunter, C. A. *J. Am. Chem. Soc.* **1992**, *114*, 5303–5311. (c) Vögtle, F.; Jager, R.; Handel, M.; Ottens-Hildebrandt, S. *Pure Appl. Chem.* **1996**, *68*, 225–232.

(d) Gong, C. G.; Gibson, H. W. *Angew. Chem., Int. Ed.* **1998**, *37*, 310–314. (e) Kolchinski, A. G.; Busch, D. H.; Alcock, N. W. *J. Chem. Soc., Chem. Commun.* **1995**, 1289–1291. (f) Hansen, J. G.; Feeder, N.; Hamilton, D. G.; Gunter, M. J.; Becher, J.; Sanders, J. K. M. *Org. Lett.* **2000**, *2*, 449–452. (g) Shukla, R.; Deetz, M. J.; Smith, B. D. *Chem. Commun.* **2000**, 2397–2398. (h) Hubbard, A. L.; Davidson, G .J. E.; Patel, R. H.; Wisner, J. A.; Loeb, S. J. *Chem. Commun.* **2004**, *2*, 138–139. (i) Sasabe, H.; Kihara, N.; Furusho, Y.; Mizuno, K.; Ogawa, A.; Takata, T. *Org. Lett.* **2004**, *6*, 3957–3960. (j) Hernandez, J. V.; Kay, E. R.; Leigh, D. A. *Science* **2004**, *306*, 1532–1537.

(14) (a) Rowan, S. J.; Brady, P. A.; Sanders, J. K. M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2143–2145. (b) Lehn, J.-M. *Chem. Eur. J.* **1999**, *5*, 2455–2463. (c) Lehn, J.-M.; Eliseev, A. V. *Science* **2001**, *291*, 2331–2332. (d) Otto, S.; Furlan, R. L. E.; Sanders, J. K. M. *Science* **2002**, *297*, 590–593. (e) Rowan, S. J.; Cantrill, S. J.; Cousins, G. R. L.; Sanders, J. K. M.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **2002**, *41*, 898–952. (f) Corbett, P. T.; Otto, S.; Sanders, J. K. M. *Org. Lett.* **2004**, *6*, 1852–1827.

(15) (a) Cantrill, S. J.; Rowan, S. J.; Stoddart, J. F. *Org. Lett.* **1999**, *1*, 1363–1366. (b) Rowan, S. J.; Stoddart, J. F. *Org. Lett.* **1999**, *1*, 1913–1916. (c) Glink, P. T.; Oliva, A. I.; Stoddart, J. F.; White, A. J. P.; Williams, D. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 1870–1875. (d) Horn, M.; Ihringer, J.; Glink, P. T.; Stoddart, J. F. *Chem. Eur. J.* **2003**, *9*, 4046–4054. (e) Chichak, K. S.; Cantill, S. J.; Pease, A. R.; Chiu, S.-H.; Cave, G. W. V.; Atwood, J. L.; Stoddart, J. F. *Science* **2004**, *304*, 1308–1312. (f) Hogg, L.; Leigh, D. A.; Lusby, P .J.; Morelli, A.; Parsons, S.; Wong, J. K. Y. *Angew. Chem., Int. Ed.* **2004**, *43*, 1218–1221. (g) Schalley, C. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 4399–4401. (h) Cantrill, S. J.; Chichak, K. S.; Peters, A. J.; Stoddart, J. F. *Acc. Chem. Res.* **2005**, *38*, 1–9.

(16) (a) Kolchinski, A. G.; Alcock, N. W.; Roesner, R. A.; Busch, D. H. *Chem. Commun.* **1998**, 1437–1438. (b) Furusho, Y.; Oku, T.; Hasegawa, T.; Tsuboi, A.; Kihara, N.; Takata, T. *Chem. Eur. J.* **2003**, *9*, 2895–2903.

(17) Fuchs, B.; Nelson, A.; Star, A.; Stoddart, J. F.; Vidal, S. B. *Angew. Chem., Int. Ed.* **2003**, *42*, 4220–4224.

(18) Herisson, J. -L.; Chauvin, Y. *Makromol. Chem.* **1971**, *141*, 161-176.

(19) Truett, W. L.; Johnson, D. R.; Robinson, I. M.; Montague, B. A. *J. Am. Chem. Soc.* **1960**, *82*, 2337-2340.

(20) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2003**, *42*, 4592-4633.

(21) Nguyen, S. T.; Johnson, L. K.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3974-3975.

(22) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2039-2041.

(23) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953-956.

(24) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *Organometallics* **2001**, *20*, 5314-5318.

(25) (a) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168-8179. (b) Gessler, S.; Randl, S. *Tetrahedron Lett.* **2000**, *41*, 9973-9976.

(26) Funk, T. W.; Belin, J. M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2006**, *128*, 1840-1846.

(27) Hong, S. H.; Grubbs, R. H. *J. Am. Chem. Soc.* **2006**, *128*, 3508-3509.

(28) Berlin, J. M.; Campbell, K.; Ritter, T.; Funk, T. W.; Chlenov, A.; Grubbs, R. H. Org. Let.

(29) Grubbs, R. H., Ed. *Handbook of Metathesis*; Wiley-VCH: Weinheim, Germany, 2003; Vol. 1.

(30) (a) Sanford, M. S.; Ulman, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 749.

(b) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543.

(31) (a) Bielawski, C. W.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2000**, *39*, 2903.

(b) Bielawski, C. W.; Benitez, D.; Grubbs, R. H. *Macromolecules* **2001**, *34*, 8610.

(c) Scherman, O. A.; Kim, H. M.; Grubbs, R. H. *Macromolecules* **2002**, *35*, 5366.

(32) Choi, T. -L.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2003**, *42*, 1743-1746.

(33) (a) Hillmyer, M. A.; Grubbs, R. H. *Macromolecules* **1993**, *26*, 872-4.

(b) Maughon, B. R.; Morita, T.; Bielawski, C. W.; Grubbs, R. H. *Macromolecules* **2000**, *33*, 1929-1935.

Chapter 2

Magic Ring Catenation via Olefin Metathesis

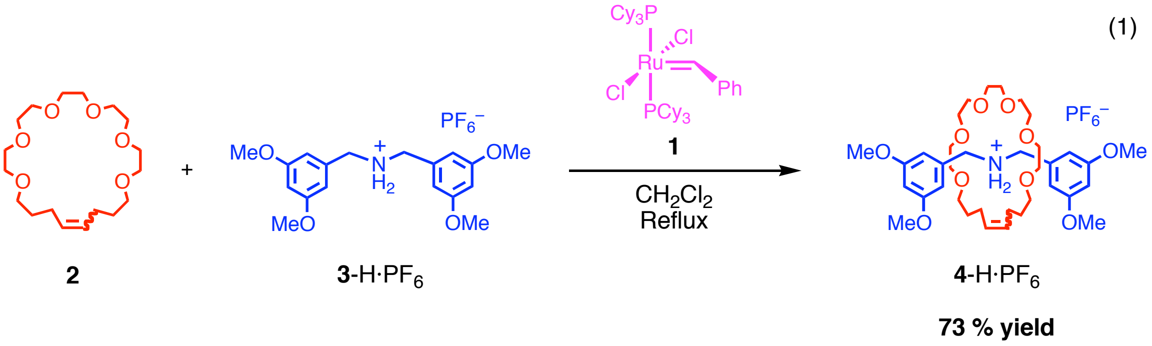
Portions of this chapter have previously appeared as: Guidry, E. N.; Cantrill, S. J.; Stoddart, J. F.; Grubbs, R. H. *Org*. *Lett*. **2005**, *7*, 2129–2132.

Magic Ring Catenation via Olefin Metathesis

Introduction

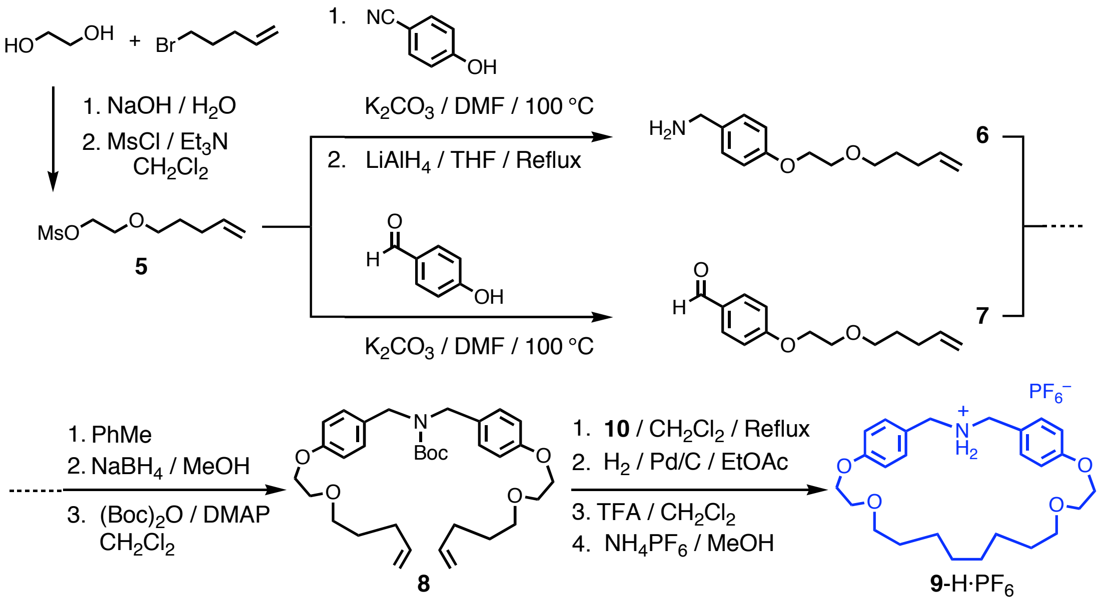
Mechanically interlocked molecules,[1] such as catenanes and rotaxanes, have long been of interest to chemists because of their unique molecular structures. Furthermore, recent advances in the science of nanosystems have revealed that these molecules are not only aesthetically pleasing curiosities, but can also function as the key components in active molecular electronic devices where bistable derivatives, for example, serve as bistable switches in both memory and logic circuits.[2]

Although a vast number of syntheses of catenanes and rotaxanes have appeared in the chemical literature, most of the strategies employ kinetically controlled covalent bond formation as the final interlocking step.[3] This approach does not always result in high yields of mechanically interlocked compounds because of the irreversible formation of unwanted non-interlocked by-products. An alternative strategy, however, exploits dynamic covalent chemistry,[4] an approach that utilizes reversible reactions in which the product distribution depends on thermodynamic rather than kinetic control, i.e., the yield of a mechanically interlocked compound reflects its stability relative to those of any other non-interlocked by-products with proof-reading and error-checking operating up until a final equilibrium state is reached. Examples of equilibrium reactions employed as the final bond-forming step in the synthesis of catenanes and rotaxanes include the reversible formation of imines,[5] disulfides[6] and cyclic acetals,[7] as well as olefin metathesis mediated by functional group tolerant ruthenium alkylidene catalysts.[8] This protocol has been applied successfully in the syntheses of both [2]catenanes[9] and [2]rotaxanes.[10] Recently, coworkers in the Grubbs group have demonstrated[11] that the ring closing of certain olefin-containing polyether substrates around appropriately-substituted secondary dialkylammonium ions results in the reversible formation of [2]rotaxanes (eq 1). For example, by employing the ruthenium catalyst $(PCy_3)_2(Cl)_2Ru{=}CHPh$ (**1**),[12] the macrocyclic polyether **2** containing one olefinic double bond can be induced to undergo a magic ring synthesis in the presence of the dumbbell compound **3**-H·PF_6, wherein the NH_2^+ center acts as the template for the formation of the [2]rotaxane **4**-H·PF_6. Here, we show that two convenient, high yielding methods for constructing [2]rotaxanes can be extended to the template-directed formation of [2]catenanes by (macrocyclic) polyether / secondary ammonium ion recognition[13] by using a cyclic rather than a linear template.



Results and Discussion

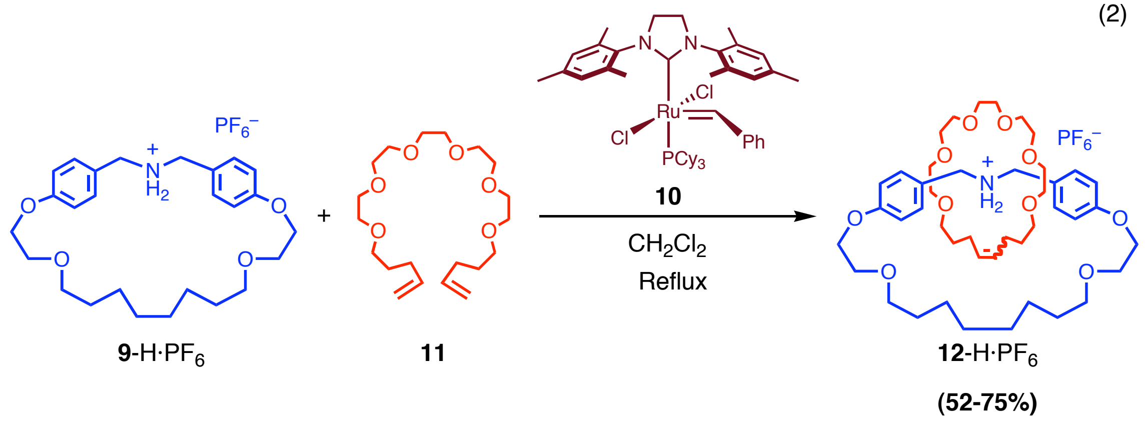
The formation of the [2]catenane requires that the dibenzylammonium-template containing macrocycle is large enough to permit catenation by the polyether macrocycle. The 27-membered macrocyclic template **9**-H·PF_6, shown in Scheme 1, was identified as a suitable target for synthesis. As outlined in this Scheme, 4-hydroxybenzaldehyde and 4-cyanophenol were both alkylated in separate reactions (K_2CO_3/DMF) with the mesylated ether **5**, prepared in two steps from ethylene glycol and 5-bromo-1-pentene. The cyano group in the second alkylation product was reduced to the primary amine **6** using $LiAlH_4$ in THF. Condensation of this amine with the aldehyde **7**, followed by reduction ($NaBH_4$/MeOH) yielded the macrocyclic precursor **8** after protection of the secondary amine function with a Boc group. Ring closing metathesis (RCM) using the ruthenium catalyst $(H_2IMes)(PCy_3)(Cl_2)Ru{=}CHPh$ (**10**)[14] in a CH_2Cl_2 solution of **8** yielded the expected protected macrocycle which was hydrogenated (H_2/Pd/C/EtOAc), deprotected (TFA/CH_2Cl_2), and subjected to counterion exchange (NH_4PF_6/MeOH) to yield the hexafluorophosphate salt **9**-H·PF_6 of the macrocycle.



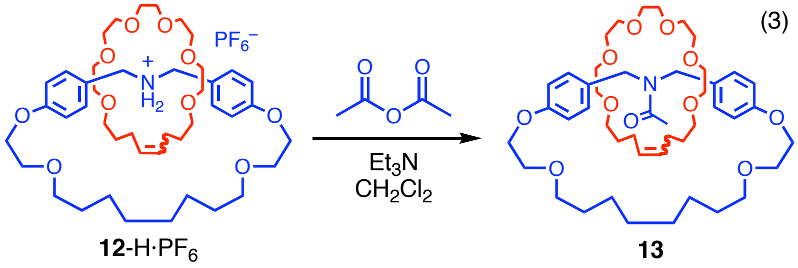
Scheme 1: Synthesis of macrocyclic template **9**-H·PF_6.

Ring-closing of the terminal olefin functions in the acyclic polyether **11** in the presence of the macrocyclic template **9**-H·PF_6 utilizing catalyst **10** afforded (eq 2) the [2]catenane **12**-H·PF_6 in a 75% isolated yield as a mixture of (E) and (Z) isomers, as confirmed by ESI mass spectrometry and both ^1H and ^{13}C NMR spectroscopy. Peaks at *m*/*z* = 774 and *m*/*z* = 760 were observed in the mass spectrum of the [2]catenane **12**-H·PF_6. The lower mass peak arises from an impurity in the dibenzylammonium-based macrocycle **9**-H·PF_6, which is formed during the RCM macrocyclization of the diolefin **8**. Olefin isomerization prior to the RCM reaction affords a macrocycle with one methylene deletion, resulting in a 26-membered ring, rather than the expected 27-membered macrocyclic product.

(2)



Further confirmation of the interlocked nature of the [2]catenane **12**-H·PF_6 was obtained following acylation (Ac_2O/Et_3N) of this compound under basic conditions (eq 3). The acylated product **13**, in which the mutual recognition expressed between the two mechanically interlocked rings has been removed, was proven to be a single non-fragmented species, as evidenced by both NMR spectroscopy and ESI mass spectrometry.



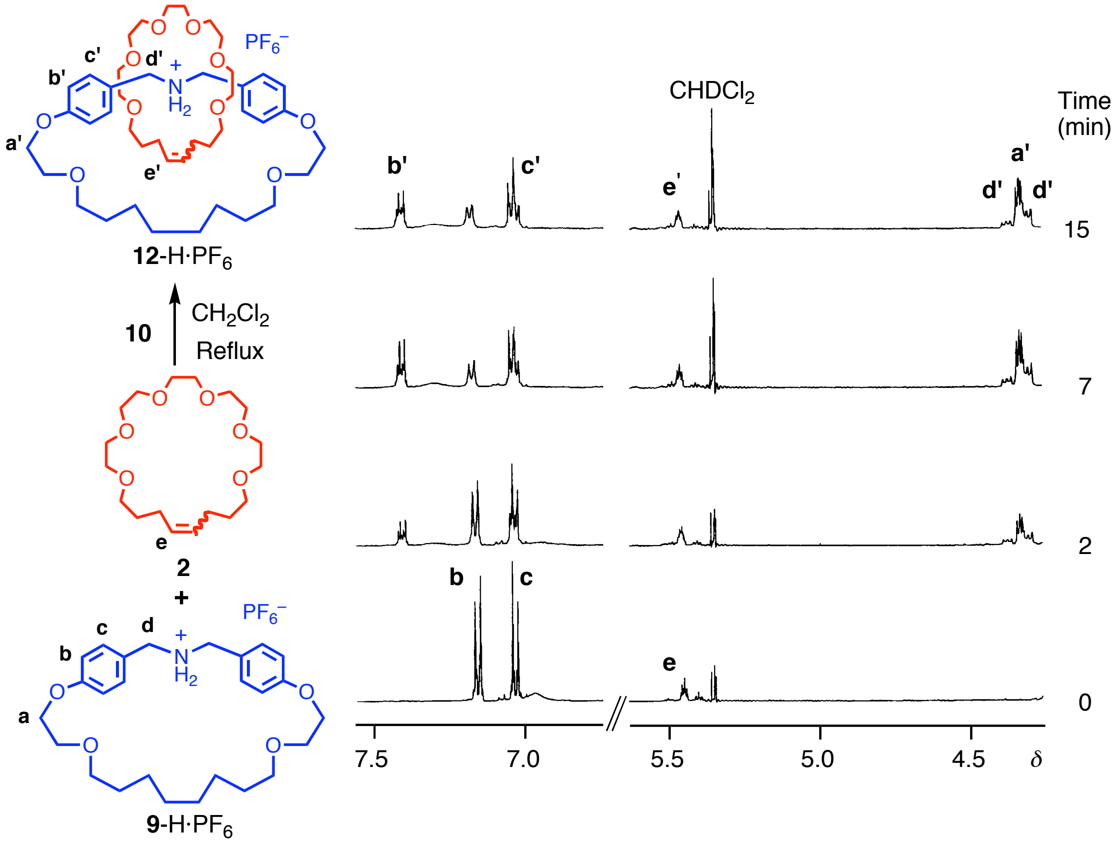
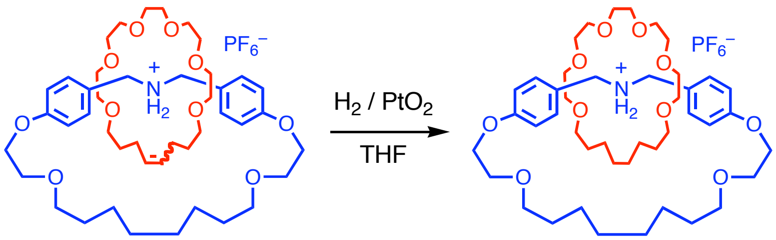


Figure 1: Partial ^{1}H NMR spectra showing the change over time during the magic ring synthesis of the dynamic [2]catenane **12**-H·PF$_6$.

To demonstrate further the reversible nature of the olefin metathesis reaction employed in the synthesis of the dynamic [2]catenane **12**-H·PF$_6$, the preformed macrocycle **2** was employed in the corresponding magic ring synthesis. When the two complementary macrocycles (**9**-H·PF$_6$ and **2**) are dissolved in CH$_2$Cl$_2$, catenation of these separate rings is in the absence of any other species not possible. Upon the addition of a catalytic amount of **10**, however, the formation of **12**-H·PF$_6$ is observed by ^{1}H NMR spectroscopy (Figure 1) to occur within a matter of minutes. After only two minutes, signals are observed in the ^{1}H-NMR spectrum at $\delta \sim 4.3$ ppm, corresponding to the NH$_2^+$-adjacent methylene protons (**d'**) in an environment where they are encircled by a crown ether-like macrocycle – two sets of signals are observed, corresponding to the (*E*) and (*Z*) isomers of the [2]catenane. Furthermore, signals corresponding to 'free' **9**-H·PF_6 (**b** and **c**) are observed to diminish in intensity, as others, corresponding to the [2]catenane **12**-H·PF_6 (**a'**, **b'**, **c'**), increase in intensity over the course of the observation.

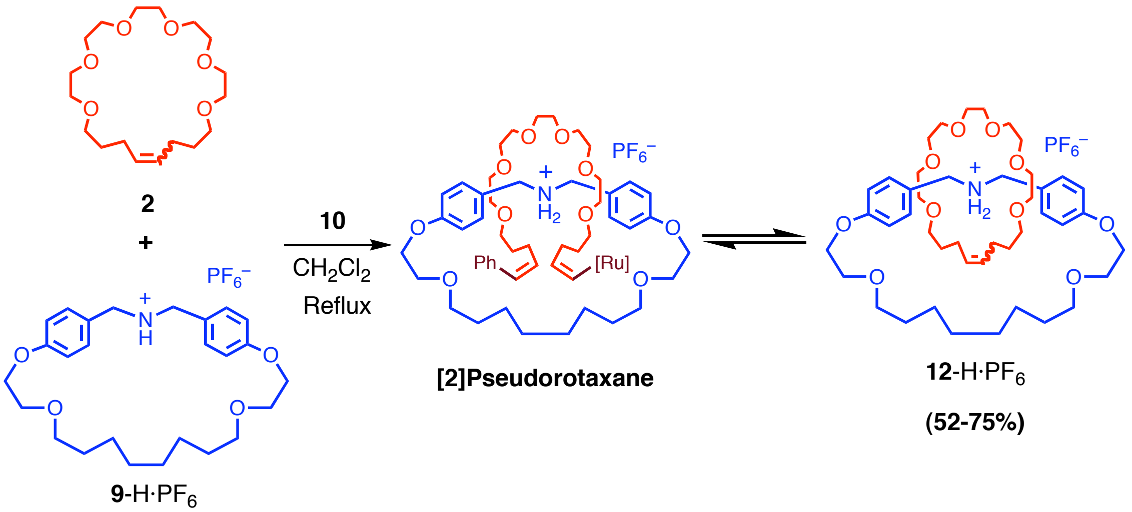
To further simplify the ^{1}H NMR spectrum, the (E) and (Z) isomers of [2]catenane **12**-H·PF_6 were removed by hydrogenation (H_2/PtO_2/THF) of the olefinic double bond which results in the formation of a single species, the [2]catenane **14**-H·PF_6 (eq 4). The signals corresponding to the NH_2^+-adjacent methylene protons (**d'**) in an environment where they are encircle by a crown ether-like macrocycle collapse into a single species due to the removal of the cis/trans isomerization in the crown ether-like macrocycle.



(4)

12-H·PF_6 **14**-H·PF_6

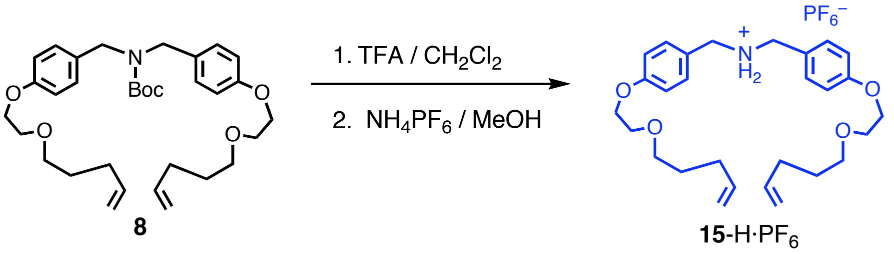
Formation of this interlocked compound presumably occurs via a process in which the olefin **2** undergoes a ring-opening metathesis reaction to form a linear oligoether species, that subsequently threads through the ammonium ion-containing macrocycle **9**-H·PF_6 to form a [2]pseudorotaxane, prior to a ring-closing metathesis reaction that stitches the ends of the linear component back together, to reform a macrocycle with the same constitution as **2**. This macrocycle is now, however, wrapped around the NH_2^+ center of what was previously **9**-H·PF_6, resulting in the formation of a [2]catenane, namely **12**-H·PF_6 (Scheme 2).



Scheme 2: Magic ring synthesis of [2]catenane **12**-H·PF_6 utilizing metathesis catalyst **10**.

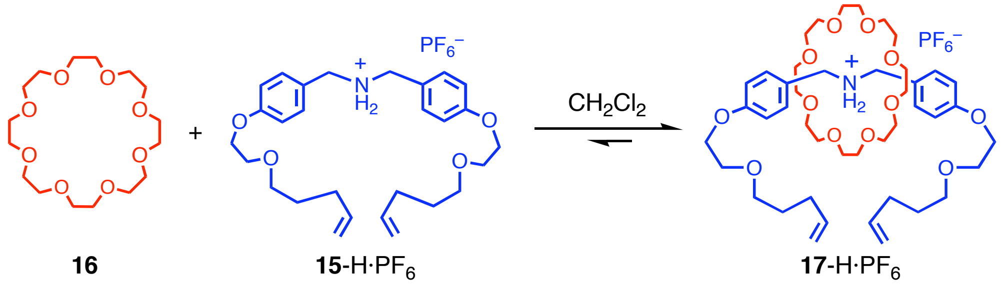
In essence, catalyst **10** enables the topological isomerization of two non-interlocked rings into a catenated architecture, reminiscent of the conjurer's simple parlor trick, or, in a more scientific context, the action of topoisomerases[15] on circular double-stranded DNA.

An alternative approach for the formation of a [2]catenane can be imagined where the dibenzylammonium-containing diene acts as the ring closing substrate around a crown ether macrocycle. Pseudorotaxane formation between diene **15**-H·PF_6 and 24-crown[8] (**16**) followed by RCM would lead to the formation of the [2]catenane **18**-H·PF_6. The linear template **15**-H·PF_6, shown in equation 5 was identified as a suitable target for synthesis. As outlined in this equation, linear template **8** was deprotected (TFA/CH_2Cl_2), and subjected to counterion exchange (NH_4PF_6/MeOH) to yield the hexafluorophosphate salt **15**-H·PF_6 of the linear template.

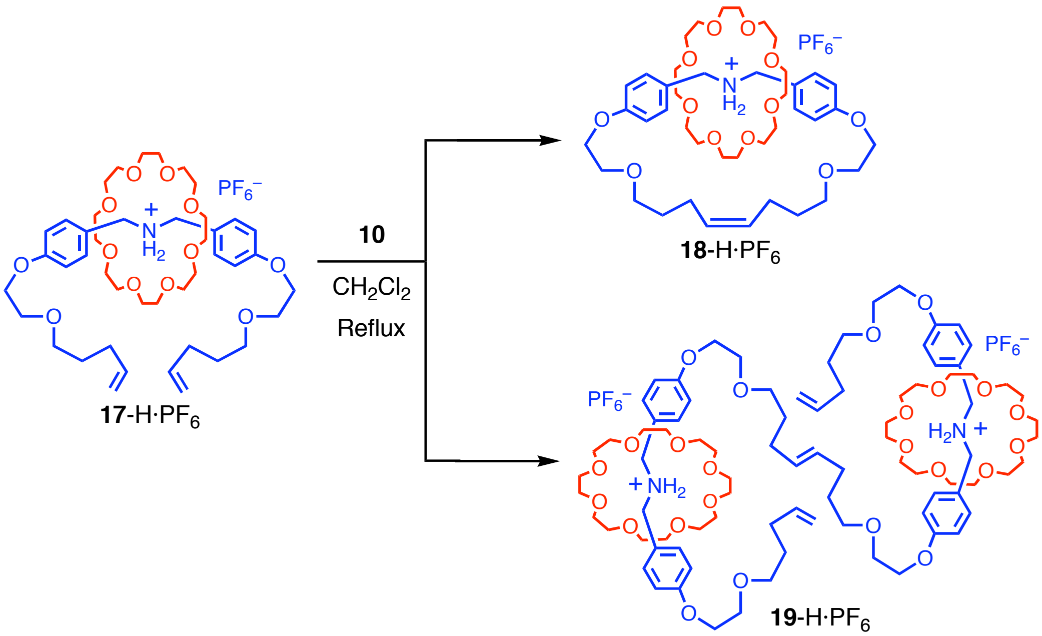


(5)

A mixture of the linear template **15**-H·PF_6 and 24-crown[8] (**16**) does indeed form the desired [2]pseudorotaxane **17**-H·PF_6 (eq 6) as is evident by characteristic changes in chemical shift observed in the ^{1}H NMR spectrum. Ring closing of the terminal olefin functions in the linear template **15**-H·PF_6 in the presence of the macrocyclic 24-crown[8] (**16**) using catalyst **10** afforded (Scheme 3) a product with approximately 50 percent conversion to an internal olefin containing species. However, upon further examination of this compound by ESI mass spectrometry, it was found that the desired [2]catenane **18**-H·PF_6 was not formed. The product of the metathesis reaction was instead [3]pseudorotaxane **19**-H·PF_6 which resulted from the cross metathesis of two molecules of linear [2]pseudorotaxane **17**-H·PF_6.



(6)



Scheme 3: Olefin metathesis mediated reaction of **17**-H·PF_6 does not lead to formation of [2]catenane **18**-H·PF_6 but instead to the formation of [3]pseudorotaxane **19**-H·PF_6.

Conclusion

Olefin metathesis has been employed in the efficient syntheses of a [2]catenane with the templation being provided by the recognition between a secondary ammonium ion and a crown ether. In one approach, a crown ether precursor has been clipped around an NH_2^+ center situated in a macrocyclic ring, yielding the mechanically interlocked compound. In the other approach, the reversible nature of olefin metathesis under the conditions of the reaction allows for a magic ring synthesis to occur wherein two free macrocycles can be employed as the stationary materials, leading to the formation of the same [2]catenane in manner reminiscent of a conjurer's party trick, or, in a more scientific context, the action of topoisomerases on circular double-stranded DNA.

References

(1) (a) Schill, G. *Catenanes, Rotaxanes and Knots*; Academic Press: New York, 1971. (b) Amabilino, D. B.; Stoddart, J. F. *Chem. Rev.* **1995**, *95*, 2725–2828. (c) *Molecular Catenanes, Rotaxanes and Knots* Sauvage, J.-P.; Dietrich-Buchecker, C. Eds.; Wiley-VCH: Weinheim, 1999.

(2) (a) Collier, C. P.; Mattersteig, G.; Wong, E. W.; Luo, Y.; Bererly, K.; Samparo, J.; Raymo, F. M.; Stoddart, J. F.; Heath, J. R. *Science* **2000**, *289*, 1172–1175. (b) Pease, A. R.; Jeppesen, J. O.; Stoddart, J. F.; Luo, Y.; Collier, C. P.; Heath, J. R. *Acc. Chem. Res.* **2001**, *34*, 433–444. (c) Luo, Y.; Collier, C. P.; Jeppesen, J. O.; Nielsen, K. A.; DeIonno, E.; Ho, G.; Perkins, J.; Tseng, H.-R.; Yamamoto, T.; Stoddart, J. F.; Heath, J. R. *ChemPhysChem.* **2002**, *3*, 519–525. (d) Diehl, M. R.; Steuerman, D.; Tseng, H.-R.; Vignon, S. A.; Star, A.; Celestine, P. C.; Stoddart, J. F.; Heath, J. R. *ChemPhysChem* **2003**, *4*, 1335–1339. (e) Tseng, H.-R.; Wu, D.; Fang, N. X.; Zhang, X.; Stoddart, J. F. *ChemPhysChem* **2004**, *5*, 111–116. (f) Steuerman, D. W.; Tseng, H.-R.; Peters, A. J.; Flood, A. H.; Jeppesen, J. O.; Nielsen, K. A.; Stoddart, J. F.; Heath, J. R. *Angew. Chem., Int. Ed.* **2004**, *43*, 6486–6491. (g) Flood, A. H.; Ramirez, R. J. A.; Deng, R. P.; Muller, W. P.; Goddard III, W. A.; Stoddart, J. F. *Aust. J. Chem.* **2004**, *57*, 301–322. (h) Flood, A. H.; Peters, A. J.; Vignon, S. A.; Steuerman, D. W.; Tseng, H.-R.; Kang, S.; Heath, J. R.; Stoddart, J. F. *Chem. Eur. J.* **2004**, *10*, 6558–6564. (i) Flood, A. H.; Stoddart, J. F.; Steuerman, D. W.; Heath, J. R. *Science* **2004**, *306*, 2055–2056. (j) Jang, S. S.; Kim, Y. H.; Goddard III, W. A.; Flood, A. H.; Laursen, B. W.; Tseng, H.-R.; Stoddart, J. F.; Jeppesen, J. O.; Choi, J. W.; Steuerman, D. W.; DeIonno, E.; Heath, J. R. *J. Am. Chem. Soc.* **2005**, *127*, 1563–1575.

(3) (a) Dietrich-Buchecker, C. O.; Sauvage, J.-P.; Kern, J. M. *J. Am. Chem. Soc.* **1984**, *106*, 3043–3045. (b) Hunter, C. A. *J. Am. Chem. Soc.* **1992**, *114*, 5303–5311. (c) Vögtle, F.; Jager, R.; Handel, M.; Ottens-Hildebrandt, S. *Pure Appl. Chem.* **1996**, *68*, 225–232. (d) Gong, C. G.; Gibson, H. W. *Angew. Chem., Int. Ed.* **1998**, *37*, 310–314. (e) Kolchinski, A. G.; Busch, D. H.; Alcock, N. W. *J. Chem. Soc., Chem. Commun.* **1995**, 1289–1291. (f) Hansen, J. G.; Feeder, N.; Hamilton, D. G.; Gunter, M. J.; Becher, J.; Sanders, J. K. M. *Org. Lett.* **2000**, *2*, 449–452. (g) Shukla, R.; Deetz, M. J.; Smith, B. D. *Chem. Commun.* **2000**, 2397–2398. (h) Hubbard, A. L.; Davidson, G .J. E.; Patel, R. H.; Wisner, J. A.; Loeb, S. J. *Chem. Commun.* **2004**, *2*, 138–139. (i) Sasabe, H.; Kihara, N.; Furusho, Y.; Mizuno, K.; Ogawa, A.; Takata, T. *Org. Lett.* **2004**, *6*, 3957–3960. (j) Hernandez, J. V.; Kay, E. R.; Leigh, D. A. *Science* **2004**, *306*, 1532–1537.

(4) (a) Rowan, S. J.; Brady, P. A.; Sanders, J. K. M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2143–2145. (b) Lehn, J.-M. *Chem. Eur. J.* **1999**, *5*, 2455–2463. (c) Lehn, J.-M.; Eliseev, A. V. *Science* **2001**, *291*, 2331–2332. (d) Otto, S.; Furlan, R. L. E.; Sanders, J. K. M. *Science* **2002**, *297*, 590–593. (e) Rowan, S. J.; Cantrill, S. J.; Cousins, G. R. L.; Sanders, J. K. M.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **2002**, *41*, 898–952. (f) Corbett, P. T.; Otto, S.; Sanders, J. K. M. *Org. Lett.* **2004**, *6*, 1852–1827.

(5) (a) Cantrill, S. J.; Rowan, S. J.; Stoddart, J. F. *Org. Lett.* **1999**, *1*, 1363–1366. (b) Rowan, S. J.; Stoddart, J. F. *Org. Lett.* **1999**, *1*, 1913–1916. (c) Glink, P. T.; Oliva, A. I.; Stoddart, J. F.; White, A. J. P.; Williams, D. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 1870–1875. (d) Horn, M.; Ihringer, J.; Glink, P. T.; Stoddart, J. F. *Chem. Eur. J.* **2003**, *9*, 4046–4054. (e) Chichak, K. S.; Cantill, S. J.; Pease, A. R.; Chiu, S.-H.; Cave, G. W. V.; Atwood, J. L.; Stoddart, J. F. *Science* **2004**, *304*, 1308–1312. (f) Hogg, L.; Leigh, D. A.;

Lusby, P .J.; Morelli, A.; Parsons, S.; Wong, J. K. Y. *Angew. Chem., Int. Ed.* **2004**, *43*, 1218–1221. (g) Schalley, C. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 4399–4401. (h) Cantrill, S. J.; Chichak, K. S.; Peters, A. J.; Stoddart, J. F. *Acc. Chem. Res.* **2005**, *38*, 1–9.

(6) (a) Kolchinski, A. G.; Alcock, N. W.; Roesner, R. A.; Busch, D. H. *Chem. Commun.* **1998**, 1437–1438. (b) Furusho, Y.; Oku, T.; Hasegawa, T.; Tsuboi, A.; Kihara, N.; Takata, T. *Chem. Eur. J.* **2003**, *9*, 2895–2903.

(7) Fuchs, B.; Nelson, A.; Star, A.; Stoddart, J. F.; Vidal, S. B. *Angew. Chem., Int. Ed.* **2003**, *42*, 4220–4224.

(8) Trnka, T. M; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18–29.

(9) (a) Kidd, T. J.; Leigh, D. A.; Wilson, A. J. *J. Am. Chem. Soc.* **1999**, *121*, 1599–1600. (b) Weck, M.; Mohr, B.; Sauvage, J.-P. Grubbs, R. H. *J. Org. Chem.* **1999**, *64*, 5463–5471. (c) Arico, F.; Mobian, P.; Kern, J. M.; Sauvage, J.-P. *Org. Lett.* **2003**, *5*, 1887–1890. (d) Iwamoto, H.; Itoh, K.; Nagamiya, H.; Fukazawa, Y. *Tetrahedron Lett.* **2003**, *44*, 5773–5776. (e) Wang, L. Y.; Vysotsky, M. O.; Bogdan, A.; Bolte, M. Böhmer, V. *Science* **2004**, *304*, 1312–1314.

(10) (a) Wisner, J. A.; Beer, P. D.; Drew, M. G. B.; Sambrook, M. R. *J. Am. Chem. Soc.* **2002**, *124*, 12469–12476. (b) Hannam, J. S.; Kidd, T. J.; Leigh, D. A.; Wilson, A. J. *Org. Lett.* **2003**, *5*, 1907–1910, (c) Coumans, R. G. E.; Elemans, J. A. A. W.; Thordarson, P.; Nolte, R. J. M.; Rowan, A. E. *Angew. Chem., Int. Ed.* **2003**, *42*, 650–654.

(11) (a) Kilbinger, A. F. M.; Cantrill, S. J.; Waltman, A. W.; Day, M. W.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 3281–3285. (b) Badjic, J. D.; Cantrill, S. J.; Grubbs, R. H.; Guidry, E. N.; Orenes, R.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **2004**, *43*, 3273–3278.

(12) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100-110.

(13) (a) Glink, P. T.; Schiavo, C.; Stoddart, J. F.; Williams, D. J. *Chem. Commun.* **1996**, 1483–1490. (b) Cantrill, S. J.; Pease, A. R.; Stoddart, J. F. *J. Chem. Soc., Dalton Trans.* **2000**, 3715–3734. (c) Clifford, T.; Abushamleh, A.; Busch, D. H. *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 4830–4836.

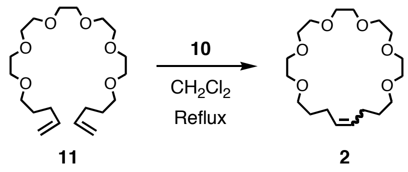
(14) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956.

(15) (a) Champoux, J. J. *Ann. Rev. Biochem.* **2001**, *70*, 369–413. (b) Wang, J. C. *Nat. Rev. Mol. Cell Biol.* **2002**, *3*, 430–440.

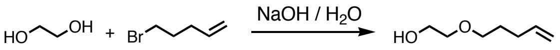
Experimental Information

General Information: NMR spectra were recorded on an Oxford 300 MHz or 500 MHz NMR spectrometer running Varian VNMR software. Chemical shifts are reported in parts per million (ppm) with reference to internal solvent. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), multiplet (m), and broad (br). High-resolution mass spectra (EI, MALDI and FAB) were provided by California Institute of Technology Mass Spectrometry Facility. Molecular mass calculations were performed with ChemDraw Ultra 9 (Cambridge Scientific). Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F254 precoated plates (0.25 mm thickness) with a fluorescent indicator. Visualization was performed using fluorescence quenching or citric ammonium molybdate (CAM), anisaldehyde, potassium permanganate ($KMnO_4$) or iodine stain. Flash column chromatography was performed using silica gel 60 (230-400 mesh) from EM Science. Grubbs metathesis catalysts **1** and **10** were obtained from Materia. All other chemicals were purchased from Aldrich or Acros Chemical Companies and used as obtained unless noted otherwise. Tetrahydrofuran and dichloromethane were purified and dried by passage through a solvent column. Anhydrous dimethyl formamide was purchased in Acros seal bottles from Acros and used as received.

Experimental Section:

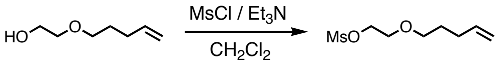


2: Compound **11** (0.5 g, 1.3 mmoles) was dissolved in anhydrous, degassed, CH_2Cl_2 (0.005 M). The catalyst $(H_2IMes)(PCy_3)(Cl)_2Ru$=CHPh **10** (0.06 g, 0.07 mmoles) was added under an Ar atmosphere and the reaction was heated to 40 °C for 12 h. The reaction was cooled to room temperature and quenched by addition of ethyl vinyl ether. The reaction was stirred for an additional 30 minutes at 40 °C. The solvent was removed under reduced pressure and the crude oil was purified by column chromatography (SiO_2: ethyl acetate) to yield **2** as a colorless oil (0.23 g, 50% yield). Characterization for this compound has been reported previously (Kilbinger, A. F. M.; Cantrill, S. J.; Waltman, A. W.; Day, M. W.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 3281–3285.).



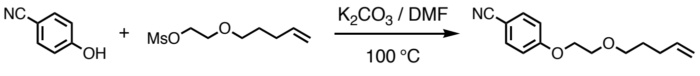
A solution of ethylene glycol (152.1 mL, 2.73 moles), 5-bromo-1-pentene (50 g, 0.335 moles) and H_2O containing NaOH (53.2 g, 1.36 moles, in 53 mL H_2O) was heated at 80 °C for 12 h. The reaction mixture was diluted with water and extracted with ethyl acetate three times to give a crude product, which was purified by column chromatography (SiO_2: hexanes/ethyl acetate 4:1) to yield the monoalkylated product as a colorless oil (33.6 g, 75% yield). ^1H NMR (300 MHz, $CDCl_3$): δ 5.79 (m, center, 1H), 5.03-4.92 (broad m, 2H), 3.75 (t, J = 4.7 Hz, 2H), 3.56 (t, J = 4.8 Hz, 2H), 3.51 (t, J = 6.6 Hz, 2H), 2.12-2.19 (multiplet, 2H), 1.72 (quintet, J = 6.9 Hz, 2H). ^{13}C NMR (75 MHz,

$CDCl_3$): *δ* 138.15, 114.78, 71.81, 70.63, 61.84, 30.28, 28.78. HRMS-EI (*m/z*): [M + e] calcd for $C_7H_{14}O_2$, 130.0994; found, 130.0996.



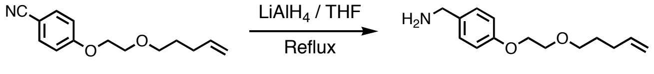
5

5: The monoalkylated product (18 g, 138.5 mmoles) and triethylamine (28.9 ml, 207.7 mmoles) were dissolved in CH_2Cl_2 (500 mL, 0.25 M) and cooled to 0 °C. A solution of mesyl chloride (16.1 mL, 207.68 mmoles) in CH_2Cl_2 (50 mL) was added slowly. The reaction was gradually warmed to room temperature and stirred overnight. The reaction mixture was diluted with water and extracted with methylene chloride 3 times, to give a crude product, which was purified by column chromatography (SiO_2: hexanes/ethyl acetate 3:1) to yield **5** as a colorless oil (23.2 g, 83% yield). ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 5.81 (m, center, 1H), 5.06-4.97 (broad m, 2H), 4.37 (t, *J* = 4.7 Hz, 2H), 3.70 (t, *J* = 4.7 Hz, 2H), 3.50 (t, *J* = 6.6 Hz, 2H), 3.06 (s, 3H), 2.13 (q, *J* = 7.1 Hz, 2H), 1.69 (quintet, *J* = 7.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.97, 115.01, 70.81, 69.25, 68.50, 37.69, 30.14, 28.72. HRMS-FAB (*m/z*): [M + H] calcd for $C_8H_{17}O_4S$, 209.0848; found, 209.0848.



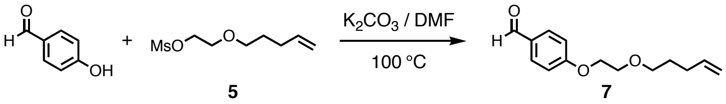
5

Compound **5** (12 g, 57.7 mmoles), 4-cyanophenol (7.56 g, 63.5 mmoles), and potassium carbonate (11.9 g, 86.5 mmoles) were suspended in anhydrous DMF (575 mL, 0.1 M). The reaction mixture was heated to 80 °C with stirring for 3 days. The reaction mixture was diluted with water and washed with ethyl acetate three times to give a crude product, which was purified by column chromatography (SiO_2: hexanes/ethyl acetate 9:1) to yield the alkylated product as an orange oil (13.4 g, 88% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 (d, J = 9.0 Hz, 2H), 6.98 (d, J = 9.0 Hz, 2H), 5.82 (m, center, 1H), 5.06-4.95 (m, broad, 2H), 4.17 (t, J = 4.8 Hz, 2H), 3.80 (t, J = 5.1 Hz, 2H), 3.55 (t, J = 6.6 Hz, 2H), 2.13 (q, J = 7.2 Hz, 2H), 1.71 (quintet, J = 6.9 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.36, 138.27, 134.13, 119.40, 115.54, 115.08, 104.28, 71.12, 69.05, 67.80, 30.34, 28.90. HRMS-EI (*m/z*): [M + e] calcd for $C_{14}H_{17}NO_4$, 231.1259; found, 231.1248.

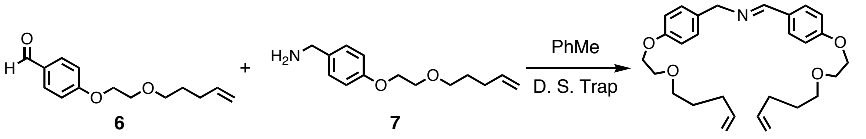


6

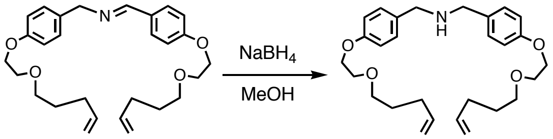
6: The alkylated product (11.3 g, 48.7 mmoles) was dissolved in anhydrous THF (490 mL, 0.1 M) and cooled to 0 °C. Lithium aluminum hydride (5.5 g, 146.0 mmoles) was added slowly, piecewise, to the reaction mixture. The reaction was warmed to 76 °C and refluxed under an argon atmosphere for 12 hours. The reaction was quenched by addition of 5.5 mL of H_2O, followed by addition of 5.5 mL of NaOH(aq) (15 %) followed by addition of 11 mL of H_2O. The reaction mixture was diluted with ethyl ether and washed with water three times to yield compound **6** as a yellow oil (10.9 g, 94% yield). No further purification was necessary. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26 (d, J = 8.7 Hz, 2H), 6.93 (d, J = 8.7 Hz, 2H), 5.86 (m, center, 1H), 5.09-4.98 (m, broad, 2H), 4.15 (t, J = 5.1 Hz, 2H), 3.84 (s, 2H), 3.81 (t, J = 4.8 Hz, 2H), 3.58 (t, J = 6.9 Hz, 2H), 2.17 (q, J = 7.8 Hz, 2H), 1.79-1.70 (m, broad, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.92, 138.38, 135.92, 128.35,114.93, 114.86, 70.99, 69.39, 67.65, 30.35, 28.94. HRMS-EI (*m/z*): [M + e] calcd for $C_{14}H_{21}NO_2$, 235.1572; found, 235.1569.



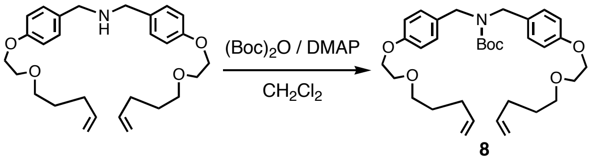
7: Compound **5** (12 g, 57.7 mmoles), 4-hydroxybenzaldehyde (7.7 g, 63.5 mmoles), and potassium carbonate (12.9 g, 86.5 mmoles) were suspended in anhydrous DMF (575 mL, 0.1 M). The reaction mixture was heated to 80 °C and stirred for 3 days. The reaction mixture was diluted with water and extracted with ethyl acetate three times to give a crude product, which was purified by column chromatography (SiO_2: hexanes/ethyl acetate 9:1) to yield **7** as an orange oil (12.4 g, 92% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.88 (s, 1H), 7.82 (d, J = 8.1 Hz, 2H), 7.02 (d, J = 8.7 Hz, 2H), 5.81 (m, center, 1H), 5.05-4.93 (m, broad, 2H), 4.20 (t, J = 4.8 Hz, 2H), 3.80 (t, J = 4.8 Hz, 2H), 3.54 (t, J = 6.6 Hz, 2H), 2.13 (q, J = 6.6 Hz, 2H), 1.70 (quintet, J = 6.9 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.95, 164.07, 138.27, 132.09, 130.20, 115.06, 115.03, 71.07, 69.07, 67.94, 30.32, 28.89. HRMS-EI (m/z): [M + e] calcd for $C_{14}H_{18}O_3$, 234.1256; found, 234.1258.



A mixture of compound **6** (10.7 g, 45.3 mmoles) and compound **7** (10.7 g, 45.3 mmoles) in toluene (450 mL, 0.1 M) was heated under reflux for 12 h using a Dean-Stark apparatus. The solvent was evaporated under reduced pressure to give the imine as a yellow oil (20.5 g). This product was immediately used in the next step without purification.

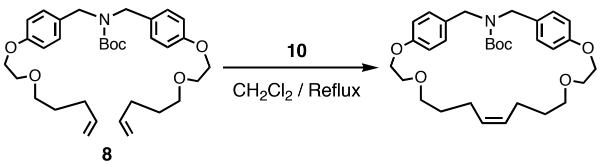


The imine (20.5 g, 45.3 mmoles) was dissolved in MeOH (450 mL, 0.1 M). After portion-wise addition of sodium borohydride (5.2 g, 135.8 mmoles), the reaction mixture was stirred at room temperature for 4 h. The solvent was evaporated under reduced pressure and the crude residue was partitioned between CH_2Cl_2 (400 mL) and 2M NaOH solution (400 mL). The aqueous layer was further extracted with CH_2Cl_2 (400 mL). The organic phases were combined and washed with NaCl (sat.) and dried over $MgSO_4$. Filtration, followed by evaporation gave the crude product, which was purified by column chromatography (SiO_2: hexanes/ethyl acetate 4:1 + 10% Et_3N) to yield the amine as a yellow oil (14.8 g, 72% yield over two steps). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24 (d, J = 8.7 Hz, 4H), 6.89 (d, J = 8.7 Hz, 4H), 5.83 (m, center, 2H), 5.07-4.95 (m, broad, 4H), 4.12 (t, J = 4.8 Hz, 4H), 3.79 (t, J = 5.1 Hz, 4H), 3.73 (s, 4H), 3.55 (t, J = 6.6 Hz, 4H), 2.15 (q, J = 6.9 Hz, 4H), 1.72 (quintet, J = 7.2, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.06, 138.42, 132.83, 129.47, 114.97, 114.75, 71.03, 69.42, 67.65, 52.64, 30.39, 28.98. HRMS-FAB (m/z): [M + H] calcd for $C_{28}H_{40}NO_4$, 454.2957; found, 454.2980.

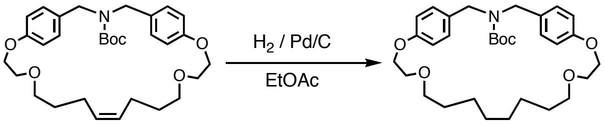


8

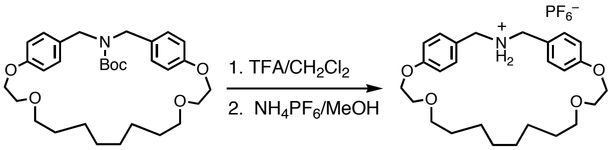
8: The amine (14.8 g, 32.7 mmoles), di-tert-butyl dicarbonate (15.0 mL, 65.4 mmoles) and 4-dimethylaminopyridine (DMAP, cat.) were dissolved in CH_2Cl_2 (350 mL, 0.1 M) and allowed to stir at room temperature overnight. The solvent was evaporated under reduced pressure and the crude residue was purified by column chromatography (SiO_2: hexanes/ethyl acetate 9:1) to yield **8** as a pale yellow oil (15.0 g, 73 % yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.118 (app. s, broad, 4H), 6.88 (d, *J* = 8.7 Hz, 4H), 5.83 (m, center, 2H), 5.08-4.95 (m, broad, 4H), 4.28 (m, broad, center, 4H), 4.12 (t, *J* = 5.1 Hz, 4H), 3.79 (t, *J* = 5.4 Hz, 4H), 3.56 (t, *J* = 6.6 Hz, 4H), 2.15 (q, *J* = 8.1 Hz, 4H), 1.72 (quintet, *J* = 6.9 Hz, 4H), 1.50 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.30, 156.15, 138.42, 130.49, 129.46, 128.93, 114.99, 114.85, 80.08, 71.60, 69.43, 67.68, 48.35, 30.41, 29.00, 28.69. HRMS-FAB (*m/z*): [M + e] calcd for $C_{33}H_{47}NO_6$, 553.3403; found, 553.3394.



9: Compound **8** (3 g, 5.4 mmoles) was dissolved in anhydrous, degassed CH_2Cl_2 (0.005M). The catalyst $(H_2IMes)(PCy_3)(Cl)_2Ru{=}CHPh$ (0.2 g, 0.3 mmoles) was added under a dry Ar atmosphere and the reaction was heated to 40 °C for 12 h. The reaction was allowed to cool to room temperature and quenched by addition of ethyl vinyl ether. The mixture was stirred for an additional 30 min. Solvent was removed under reduced pressure and the crude oil was purified by column chromatography (SiO_2: hexanes/ethyl acetate 9:1) to yield the protected macrocycle as a colorless oil (3g, 52 % yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.96 (m, broad, 4H), 6.70 (m, broad, 4H), 5.42 (m, broad, 2H), 4.34-4.46 (m, broad, 4H), 4.02-4.11 (m, broad, 4H), 3.73 (t, *J* = 4.5 Hz, 4H), 3.52 (t, *J* = 6.3 Hz, 4H), 2.05-2.19 (m, broad, 4H), 1.64 (quintet, *J* = 6.6 Hz, 4H), 1.49 (s, 9H), 1.50 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.18, 130.41, 130.18, 129.22, 114.90, 80.06, 70.81, 69.48, 68.03, 51.46, 29.59, 29.28, 28.68. HRMS-FAB (*m*/*z*): [M + e] calcd for $C_{31}H_{43}NO_6$, 525.3090; found, 525.3085.

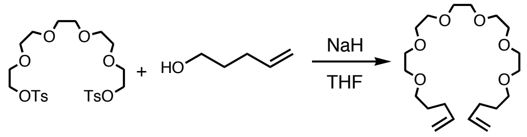


The protected macrocycle (3g, 5.7 mmoles) was added to a suspension of Pd/C (cat.) in EtOAc (0.05 M). The reaction was stirred under an atmosphere of hydrogen for 6 h. The reaction mixture was filtered through celite to remove Pd/C and the solvent was evaporated under reduced pressure. The product required no further purification. The hydrogenated macrocycle was obtained as a colorless oil (2.9 g, 96% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.01 (m, broad, 4H), 6.75 (m, broad, 4H), 4.43 (s, broad, 2H), 4.34 (s, broad, 2H), 4.09 (t, *J* = 4.5 Hz, 4H), 3.74 (t, *J* = 3.9 Hz, 4H), 3.52 (t, *J* = 6.3 Hz, 4H), 1.56 (quintet, *J* = 6.9 Hz, 4H), 1.44-1.32 (m, broad, 8H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.19, 130.11, 129.17, 114.72, 80.06, 71.56, 69.45, 68.08, 51.50, 29.80, 29.30, 28.67, 26.12. HRMS-FAB (*m*/*z*): [M + H] calcd for $C_{31}H_{46}NO_6$, 528.3325; found, 528.3308.



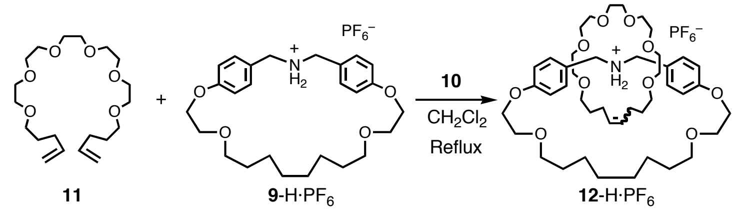
9-H·PF$_6$

9-H·PF$_6$: The hydrogenated macrocycle (2.9 g, 5.5 mmoles) and trifluoroacetic acid (6.3 g, 55.0 mmoles) were dissolved in CH_2Cl_2 (0.05M). The reaction mixture was stirred at room temperature for 3 h. The solvent was evaporated to dryness under reduced pressure. The crude residue was dissolved in MeOH and ammonium hexafluorophosphate (9.0 g, 549 mmoles) was added. The mixture was stirred at room temperature for 3 h to complete the ion exchange. The solvent was removed under reduced pressure and the mixture was portioned between H_2O and CH_2Cl_2. The organic phase was washed with H_2O (2 X 100 mL), and the organic phase was dried over magnesium sulfate, filtered and the solvent was evaporated to dryness under reduced pressure. No further purification was necessary. The dibenzylammonium macrocycle **9** was obtained as an off-white sticky solid (2.9 g, 92% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.10 (d, J = 8.7 Hz, 4H), 6.94 (d, J = 8.7 Hz, 4H), 4.18 (t, J = 4.5 Hz, 4H), 4.16 (t, J = 4.5 Hz, 4H), 3.72 (t, J = 4.5 Hz, 4H), 3.46 (t, J = 6.0 Hz, 4H), 1.90 (s, broad, 2H), 1.47 (q, J = 6.75 Hz, 4H), 1.28 (m, broad, 8H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.37, 130.50, 126.80, 116.51, 71.51, 69.86, 68.30, 50.96, 29.90, 29.62, 26.30. HRMS-FAB (*m/z*): [M + H] calc'd for $C_{26}H_{38}NO_4$, 428.2801; found, 428.2789.

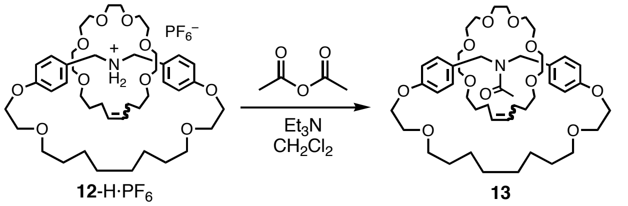


11

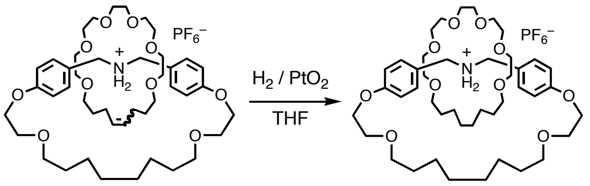
11: Sodium hydride (60% in mineral oil, 7 g, 182.6 mmoles) was suspended in anhydrous THF (183 ml, 0.1 M). 4-pentene-1-ol (4.15 mL, 40.3 mmoles) was added slowly as a solution in THF (20 mL). The mixture was refluxed under a dry Ar atmosphere for 1 h. The reaction was cooled to 0 °C and pentaethylene glycol ditosylate (10 g, 18.3 mmoles) was added slowly as a solution in THF (20 mL). The reaction was warmed to room temperature and stirred under an Ar atmosphere for 5 days. The reaction mixture was quenched by addition of MeOH. The solvent was evaporated under reduced pressure and partitioned between CH_2Cl_2 (200 mL) and brine (200 mL). The aqueous phase was extracted one additional time with CH_2Cl_2 (200 mL). The organic phases were combined, dried over magnesium sulfate, filtered and the solvent was evaporated under reduced pressure. The crude oil was purified by column chromatography (SiO_2:ethyl acetate) to yield **11** as a colorless oil (3.42 g, 50% yield). Characterization for this compound has been reported previously (Kilbinger, A. F. M.; Cantrill, S. J.; Waltman, A. W.; Day, M. W.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 3281–3285.).



12-H·PF_6: Compound **9** (1.5 g, 2.6 mmoles) and compound **11** (0.98 g, 2.6 mmoles) were dissolved in anhydrous, degassed, CH_2Cl_2 (0.005M). The catalyst $(H_2IMes)(PCy_3)(Cl)_2Ru{=}CHPh$ **10** (0.11g, 0.13 mmoles) was added under an Ar atmosphere and the reaction was heated to 40 °C for 12 h. The reaction was cooled to room temperature and quenched by addition of ethyl vinyl ether. The reaction mixture was stirred for an additional 30 min at 40 °C. Solvent was removed under reduced pressure and the crude oil was purified by tritration with ethyl ether (2 X 10 mL), followed by column chromatography (SiO_2:CH_2Cl_2/MeOH 99:1) to yield **11**-H·PF_6 as a light brown sticky solid (1.3 g, 75% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37 (d, J = 8.4 Hz, 4H), 7.04 (d, J = 8.4 Hz, 4H), 5.38 (m, 2H), 4.34 (m, 4H), 4.23 (m, 4H), 3.76 (s, 8H), 3.67 (t, J = 3.9 Hz, 4H), 3.62 (t, J = 6.9 Hz, 4H), 3.52 (m, 4H), 3.30 (t, J = 7.2 Hz, 4H), 3.23 (m, 4H), 2.91 (s, 4H), 2.11 (m, 4H), 1.73 (quintet, J = 6 Hz, 4H), 1.32 (m, 4H), 1.26 (s, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.18, 132.21, 131.07, 123.43, 115.85, 71.90, 71.57, 70.77, 70.47, 69.93, 69.61, 69.32, 67.82, 51.49, 30.43, 30.04, 29.80, 28.60, 28.37, 25.92. HRMS-FAB (*m*/*z*): [M + e] calcd for $C_{44}H_{72}NO_{10}$, 774.5168; found, 774.5156.



13: Compound **12**-H·PF_6 (0.5 g, 0.54 mmoles), acetic anhydride (0.17 g, 1.6 mmoles) and triethyl amine (0.16 g, 1.6 mmoles) were dissolved in CH_2Cl_2 (0.01M). The reaction was stirred at room temperature for 12 hours. Solvent was removed under reduced pressure and the crude oil was purified by column chromatography (SiO_2: EA) to yield the acylated catenane as a clear oil (0.42 g, 95 % yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.316 (d, *J* = 8.4 Hz, 2H), 6.93 (m, 6H), 5.47 (m, 2H), 5.37 (m, 2H), 4.73 (s, 2H), 4.67 (s, 2H), 4.31 (t, *J* = 5.7 Hz, 2H), 4.20 (t, *J* = 4.5 Hz, 2H), 3.86 (m, 4H), 3.58-3.31 (m, 14H), 2.16 (s, 4H), 1.95 (m, 4H), 1.71 (m, 4H), 1.61 (m, 4H), 1.39 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.07, 158.27, 158.19, 130.12, 129.96, 129.74, 129.45, 128.36, 126.70, 115.268, 115.22, 114.52, 71.55, 71.41, 70.86, 70.77, 70.60, 70.52, 70.45, 70.34, 70.23, 70.20, 70.09, 69.72, 69.36, 69.20, 67.03, 66.70, 66.15, 53.74, 52.16, 30.42, 29.90, 29.63, 29.18, 28.85, 28.49, 26.49, 26.08, 24.60, 22.31. HRMS-FAB (*m*/*z*): [M + e] calcd for $C_{46}H_{74}NO_{11}$, 816.5262; found, 816.528.



12-H·PF$_6$ **14**-H·PF$_6$

14-H·PF$_6$: Compound **11**-H·PF$_6$ (0.25 g, 0.27 mmoles) was dissolved in a suspension of THF and PtO$_2$ (Adam's catalyst). The reaction was frozen, evacuated using vacuum, and warmed to room temperature. This process was repeated twice more. An atmosphere of hydrogen was placed over the reaction using a balloon. The reaction was stirred a room temperature for 30 minutes. The reaction was filtered through a pad of celite and solvent removed under reduced pressure to yield **12**-H·PF$_6$ as a light brown sticky solid (0.23 g, 90 % yield). ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.41 (d, *J* = 8.3 Hz, 4H), 7.06 (d, *J* = 8.3 Hz, 4H), 4.36 (m, 4H), 4.25 (m, 4H), 3.85 (s, 8H), 3.67 (t, *J* = 3.9 Hz, 4H), 3.62 (t, *J* = 6.9 Hz, 4H), 3.52 (m, 4H), 3.30 (t, *J* = 7.2 Hz, 4H), 3.23 (m, 4H), 2.91 (s, 4H), 2.11 (m, 4H), 1.73 (quintet, *J* = 6 Hz, 4H), 1.32 (m, 4H), 1.26 (s, 4H).

Chapter 3

[2]Daisy-Chain Dimers and Their Incorporation into Mechanically Interlocked Polymers

Portions of this chapter have previously appeared as: Guidry, E. N.; Li, J.; Stoddart, J. F.; Grubbs, R. H. *J. Am. Chem. Soc.* **2007**, *ASAP*.

[2]Daisy Chain Dimers and Their Incoroporation into Mechanically Interlocked Polymers

Introduction

Much attention has been devoted to the design and synthesis of linear daisy-chain polymers[1], a class of rotaxane-based polymers in which both the host and guest recognition units are coupled covalently together in the same monomer (**1a**). Repetitive self-assembly processes leading to daisy-chain polymers (**1c**) have to compete with the formation of cyclic analogues[2,3] where the thermodynamic driving force lies in the production of small cycles, for example, the [2]daisy-chain dimer (**1b**) shown in Figure 1. In addition to their appeal as challenging targets in polymer synthesis, such macromolecules would also contain mechanical links rather than covalent bonds between the monomer units. It is tempting to speculate that the incorporation of flexible mechanical links, that could also be rendered switchable, would have repercussions for the polymer-chain behavior which is expected to affect both the solid-state and solution properties.[4] Despite the fascination of chemists with these macromolecules, few examples[5] exist on account of the considerable challenge posed by their synthesis. Although numerous attempts have been made at their synthesis, most of them rely on template-directed self-assembly as the polymerization step. More often than not, however, this strategy results[3] in cyclic dimer formation. While higher oligomers have been observed[1a-c,e], the number of repeat units is typically low. Here, we describe a strategy that relies on the polymerization of a bisfunctionalized [c2]daisy-chain monomer.

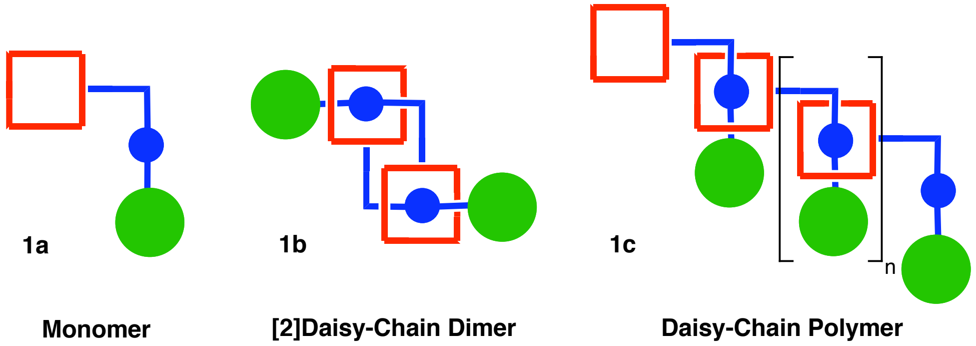


Figure 1: Graphical representation of daisy chain monomer (**1a**), [2]daisy-chain dimer (**1b**) and daisy-chain polymer (**1c**).

Although [2]daisy-chains, based on hydrophobic, hydrogen bond, and metal-coordination templating motifs have been produced, all these approaches involve irreversible stoppering events as the final mechanical bond-forming reactions. On account of the accompanying formation of unwanted byproducts, this strategy does not always result in high yields of mechanically interlocked products. An alternative strategy exploits dynamic covalent chemistry,[6] an approach that relies on reversible reactions in which the product distribution depends on thermodynamic rather than kinetic control. Examples of reversible reactions employed as the final bond-forming steps in the synthesis of catenanes and rotaxanes include the formation of imines,[7] disulfides,[8] and cyclic acetals[9] as well as olefins.[10] The use of functional group tolerant ruthenium alkylidene catalysts has been applied[11] successfully to the synthesis of [2]catenanes[12] and [2]rotaxanes.[13] Previously, we have demonstrated that the ring-closing of appropriate bisolefin-containing polyether substrates around disubstituted dibenzylammonium ions result in the reversible formation of [2]catenanes[14] and [2]rotaxanes.[15] We now describe how we have extended this ring-closing metathesis methodology to the synthesis of [2]daisy-chains.

[2]Daisy-Chain Dimers via Ring-Closing Metathesis

The formation of [2]daisy-chains necessitates that both recognition units reside within the same molecule such that it will not undergo self-complexation to form an intramolecular complex but rather form a [2]daisy-chain dimer (Figure 2). It was imagined that either a short or very rigid linker between the crown ether and ammonium ion recognition units would disfavor the formation of an intramolecular complex. The self-complementary molecule **4**-H·PF_6 was identified as a suitable synthetic target and contains both an ammonium ion and a crown ether recognition unit coupled together within close proximity, making self-complexation very unlikely. As outlined in Scheme 1, 3,4-dihydroxybenzaldehyde was alkylated (K_2CO_3/DMF) with the mesylated ether **2**, prepared in two steps from diethylene glycol and 5-bromo-1-pentene. Condensation of aldehyde **3** with 3,5-dimethoxybenzylamine, followed by reduction ($NaBH_4$/MeOH)

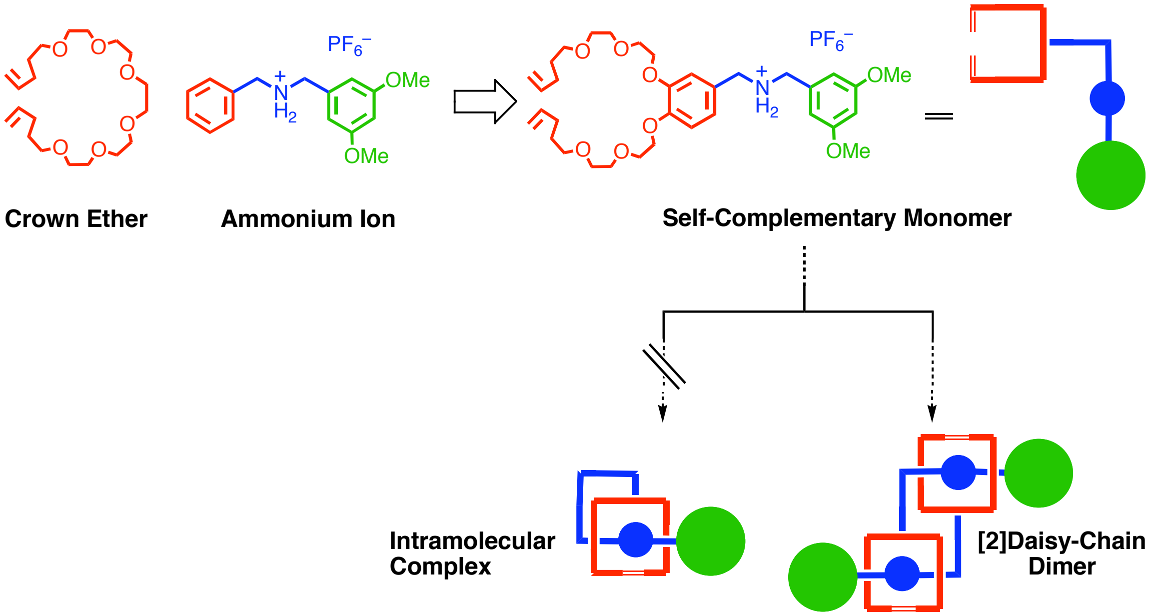
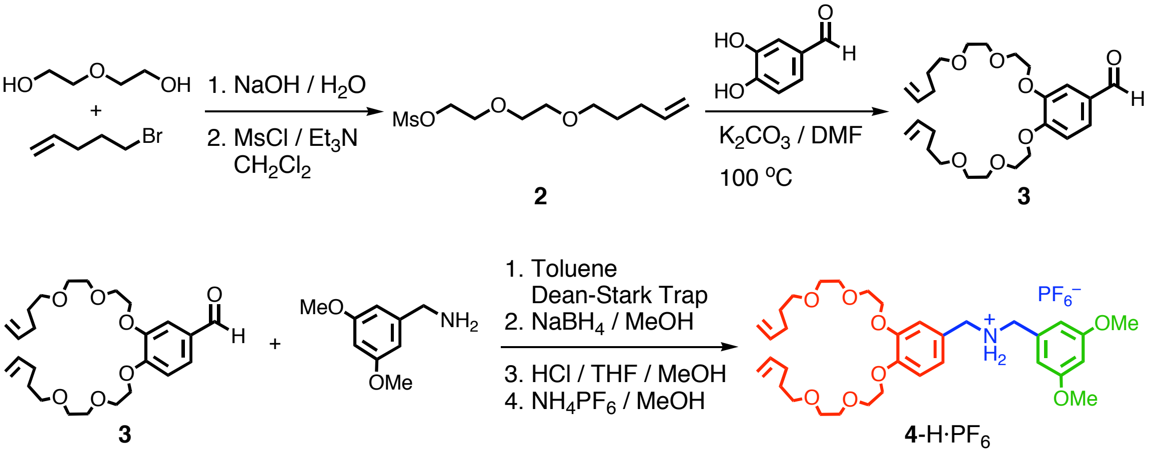


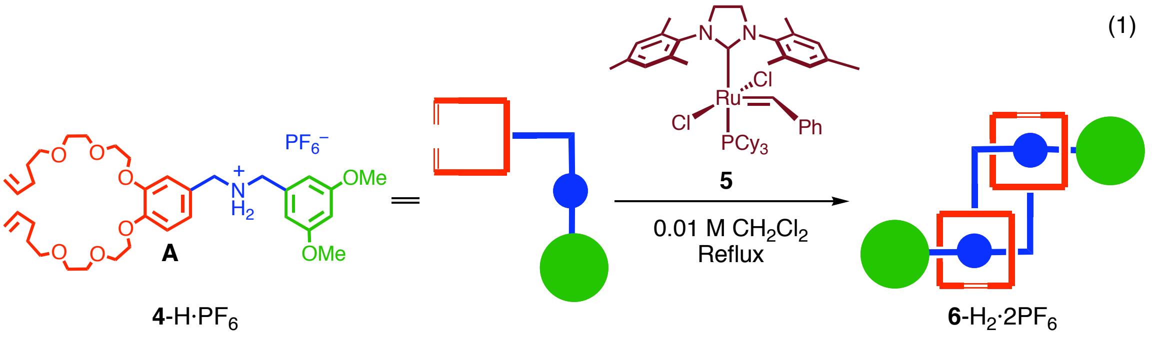
Figure 2: The formation of a [2]daisy-chain dimer requires that both recognition units reside within the same molecule in such a way that dimerization is favored rather than intramolecular complexation.

yielded the secondary amine which was protonated (HCl/Et_2O), and subjected to counterion exchange (NH_4PF_6/MeOH) to yield the hexafluorophosphate salt **4**-H·PF_6 of the self-complementary monomer.



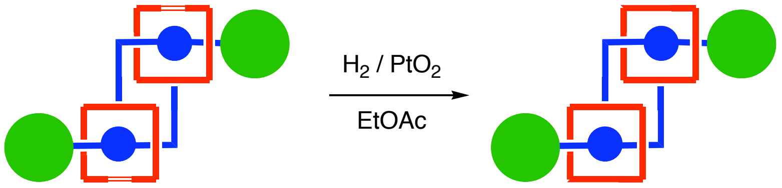
Scheme 1: Synthesis of self-complementary monomer **4**-H·PF_6.

Ring-closing of the terminal olefin functions present in **4**-H·PF_6 using the ruthenium catalyst (H_2IMes)(PCy_3)$(Cl)_2$Ru=CHPh[16] (**5**) afforded (eq 1) the [2]daisy-chain **6**-H_2·2PF_6 in near quantitative conversion and as a 95% yield, isolated as a mixture of (*E*) and (*Z*) isomers, a situation which confers considerable complexity upon the ^{1}H NMR spectrum (Experimental Information).



Hydrogenation of the olefinic bonds in **6**-H_2·2PF_6 to give **7**-H_2·2PF_6 simplifies the spectrum and the characteristic signals for the methylene protons associated with the

–$CH_2NH_2^+CH_2$– units encircled by [24]crown rings, are evident in the range 4.25 – 4.68 ppm.



6-H_2·$2PF_6$ **7**-H_2·$2PF_6$ (2)

Ring-closing of self-complementary monomer **4**-H·PF_6 to form [2]daisy-chain compound **6**-H_2·$2PF_6$ results in the formation of three stereoisomers due to the breaking of constitutional symmetry in the central benzene ring (**A**, equation 1). The three possible stereoisomers include two diastereomers, one of which is a racemic mixture of enantiomers, while the other diastereomer is a non-chiral meso compound. The three stereoisomers are illustrated in Figure 3. The existence of a mixture of diastereomers for daisy-chain compound **6**-H_2·$2PF_6$ results in a ^1H NMR spectrum which is particularly complex in the region where the aromatic protons resonate.

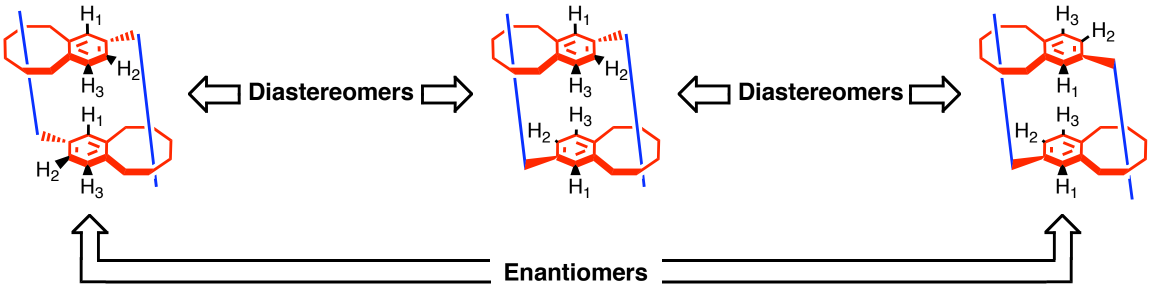


Figure 3: Unsymmetrical substitution of the central aromatic ring of self-complementary monomer **4**-H·PF_6 leads to a mixture of stereoisomers in the [c2]daisy-chain compound **6**-H_2·$2PF_6$.

Crystallization, however, (slow evaporation from EtOAc) leads to the fractional separation of the mesoform, which remains dissolved in the mother liquor, and the racemic mixture, which forms single crystals suitable for X-ray crystallography[17]. The solid-state structure is illustrated in Figure 4 and, in conjunction with ^{1}H NMR spectroscopy and mass spectrometry data, unambiguously confirms the structure of **6**-H_2·2PF_6.

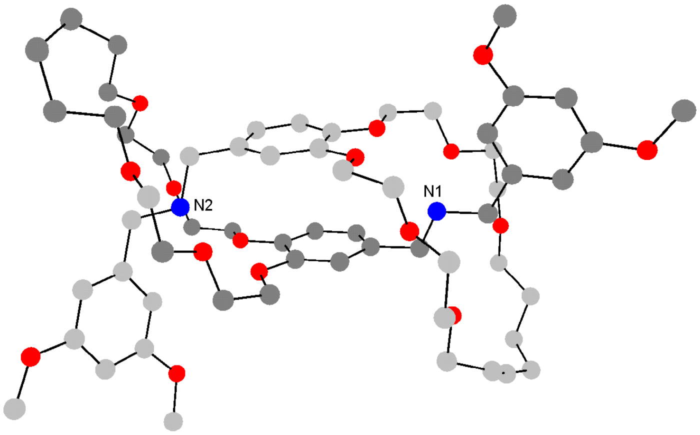
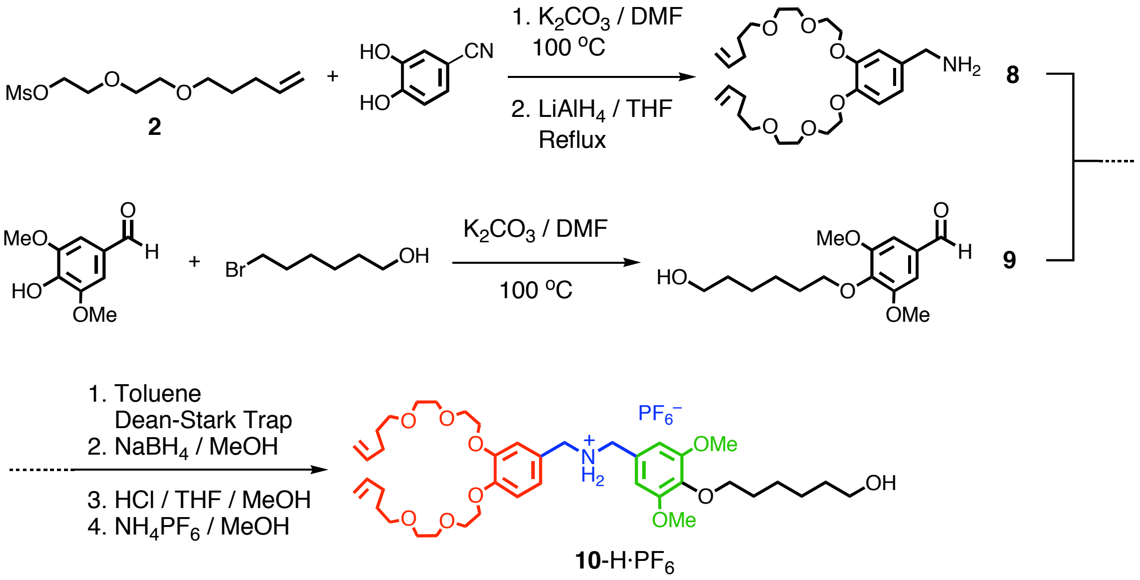


Figure 4: Ball and stick representation of [2]daisy-chain dimer **6**-H_2·2PF_6 generated from a low-resolution X-ray crystal structure. Hydrogen atoms have been omitted for clarity.

Mechanically Interlocked Polymers via Acyclic Diene Metathesis Polymerization

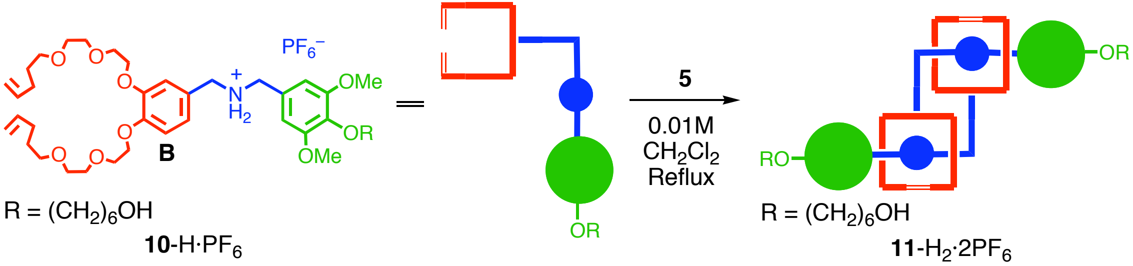
Functionalization of the stoppers in these [2]daisy-chains could provide an alternative means to synthesize mechanically interlocked polymers. Acyclic diene metathesis (ADMET) chemistry looked promising to us since it requires only functionalization of the [2]daisy-chain as a bisolefin that can be polymerized under mild conditions catalytically using **5** and is driven by the removal of ethylene. The synthesis of the self-complementary monomer **10**-H·PF_6, containing functionalizable groups on its stopper is outlined in scheme 2. As is outlined in this scheme 3,4-dihydroxybenzonitrile was alkylated (K_2CO_3/DMF) with the mesylated ether **2** (Scheme 1). The cyano group of the alkylation product was reduced to primary amine **8** ($LiAlH_4$/THF). Syringaldehyde was alkylated (K_2CO_3/DMF) with 5-bromo-1-pentanol. Condensation of amine **8** and aldehyde **9**, followed by reduction ($NaBH_4$/MeOH) yielded the secondary amine, which was protonated (HCl/Et_2O), and subjected to counterion exchange (NH_4PF_6/MeOH) to generate the hexafluorophosphate salt **10**-H·PF_6 of the self-complementary monomer.



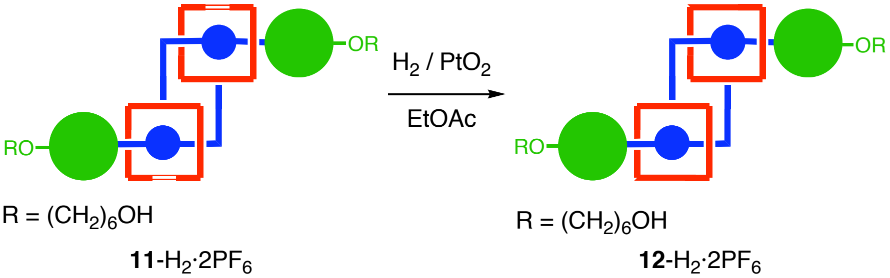
Scheme 2: Synthesis of self-complementary monomer **10**-H·PF_6.

Ring-closing of the terminal olefin functions present in **10**-H·PF_6 using the ruthenium catalyst **5** afforded (eq 3) the [2]daisy-chain **11**-H_2·$2PF_6$ in near quantitative conversion and in 93% yield, isolated as a mixture of (*E*) and (*Z*) isomers, a situation which confers considerable complexity on the ^{1}H NMR spectrum (Experimental Information).

(3)

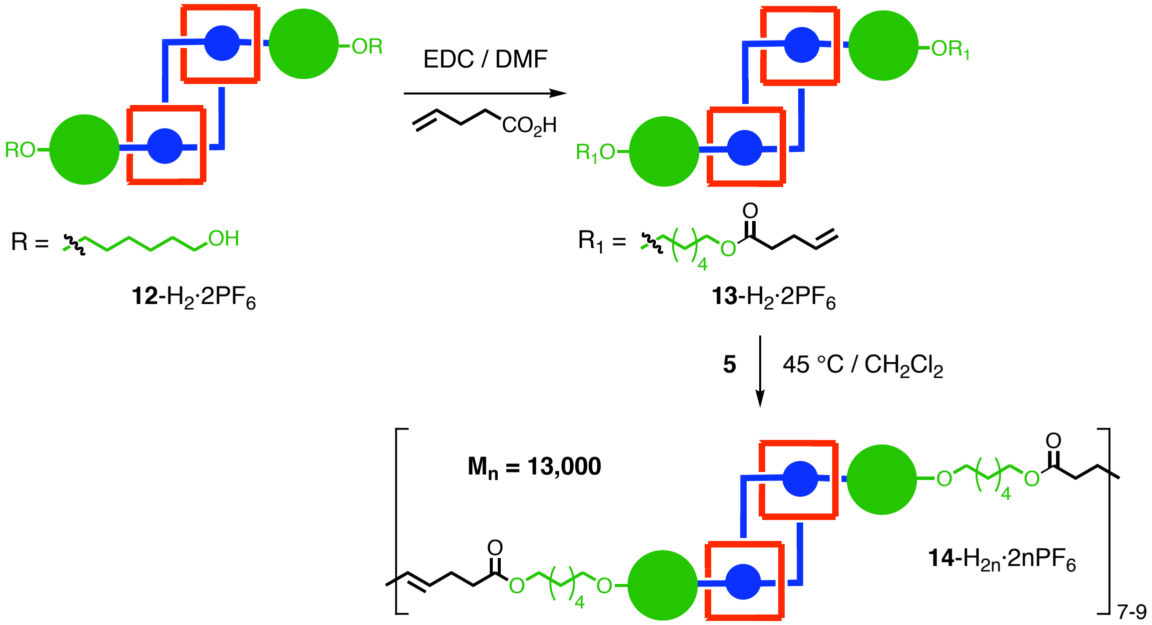


The diol **11-**$H_2·2PF_6$ was hydrogenated using Adams' catalyst (Pt_2O) in EtOAc to afford the saturated derivative **12-**$H_2·2PF_6$ (eq 4), thus simplifying the ^{1}H NMR spectrum and preparing the monomer for polymerization. Characteristic signals for the methylene protons associated with the $–CH_2NH_2^+CH_2–$ units encircled by [24]crown rings, are evident in the range 4.25 – 4.68 ppm. Again, this [2]daisy-chain compound is a mixture of three steroisomers, on account of the breaking of constitutional symmetry in the central benzene ring (**B** in eq 3), the ^{1}H NMR spectrum is particularly complex in the region where these aromatic protons resonate. Unfortunately X-ray quality crystals were not able to be obtained for **11-**$H_2·2PF_6$, however additional structural information was obtained from ESI mass spectrometry. A peak at m/z = 1529.83 was observed in the mass spectrum of **11-**$H_2·2PF_6$. While no X-ray structure was available to unambiguously determine the structural conformation, ^{1}H NMR spectroscopy and mass spectrometry data were in good agreement with **6-**$H_2·2PF_6$, indicating that the proposed structure of **11-**$H_2·2PF_6$ is correct.



(4)

EDC coupling of diol **12-**$H_2 \cdot 2PF_6$ with 4-pentenoic acid gave the [c2]daisy-chain monomer **13**-$H_2 \cdot 2PF_6$ (Scheme 3). Since this monomer is a solid, the polymerization was run in a minimal amount of solvent (CH_2Cl_2) under an Ar purge to aid the removal of the ethylene. When the ADMET polymerization of **13**-$H_2 \cdot 2PF_6$ was performed (monomer:catalyst loadings of 20:1) in CH_2Cl_2 at 45 °C for 24 h, a polymer **14**-$H_{2n} \cdot 2nPF_6$ with a molecular weight of 13,000, determined by ^1H NMR spectroscopy (Experimental Information) using end-group analysis, was isolated (Scheme 3).



Scheme 3: Synthesis of bisolefin functionalized [2]daisy-chain dimer **13**-$H_2 \cdot 2PF_6$ and its subsequent ADMET polymerization to form mechanically interlocked polymer **14**-$H_{2n} \cdot 2nPF_6$.

The number average molecular weight (M_n) was not able to be determined using GPC due to challenges associated with chromatography. Both solvent (THF, DCM, DMF, DMF with 0.1 M LiBr, DMF with 0.1 M NH_4PF_6) and column types (Experimental Section) were varied to try and improve chromatography, but was met with limited success. To further confirm the polymerization results observed in the ^1H NMR and

MALDI spectra, high pressure liquid chromatography (HPLC) was employed. HPLC was used to verify polymerization rather than olefin isomerization (which would have similar olefin region in the ^{1}H NMR). First, the elution time of diene **13**-$H_2 \cdot 2PF_6$ was measured (Experimental Section). Polymer **14**-$H_{2n} \cdot 2nPF_6$ was placed on the HPLC under identical ramp conditions as those for diene **13**-$H_2 \cdot 2PF_6$. The HPLC trace showed that diene **13**-$H_2 \cdot 2PF_6$ had completely disappeared and no new signals were observed over the course of the run, indicating that the internal olefin protons observed in the ^{1}H NMR spectrum of **14**-$H_{2n} \cdot 2nPF_6$ are due to ADMET polymerization rather than olefin isomerization (Experimental Information).

Conclusions

Metathesis, in two different guises is making a hitherto unreachable goal in synthesis a reality. Ring-closing olefin metathesis has been shown to provide a very high yielding route to [2]daisy-chains suitably functionalized to allow their one-step conversion to bis-olefins which can be used as monomers in ADMET polymerizations to afford mechanically interlocked polymers. The properties of these polymers are being investigated and their potential range of applications is also being explored.

References

(1) (a) Hirotsu, K.; Higuchi, T.; Fujita, K.; Ueda, T.; Shinoda, A.; Imoto, T.; Tabushi, I. *J. Org. Chem.* **1982**, *47*, 1143-1144. (b) Mentzafos, D.; Terzis, A.; Coleman, A. W.; de Rango, C. *Carbohydr. Res.* **1996**, *282*, 125-135. (c) Yamaguchi, N.; Nagvekar, D. S.; Gibson, H. W. *Angew. Chem., Int. Ed.* **1998**, *37*, *2361-2364*. (d) Rowan, S. J.; Cantrill, S. J.; Stoddart, J. F.; White, A. J. P.; Williams, D. J. *Org. Lett.* **2000**, *2*, 759–762. (e) Liu, Y.; You, C.-C.; Zhang, M.; Weng, L.-H.; Wada, T.; Inoue, Y. *Org. Lett.* **2000**, *2*, 2761-2763. (f) Stoddart, J. F.; Rowan, S. J.; Chiu, S.-H.; Cantrill, S. J.; Ridvan, L.; Sivakova, S. *Polym. Mater. Sci. Eng.* **2001**, *84*, 148-149. (g) Harada, A. *J. Polym. Sci., Part A: Polym. Chem.* **2005**, 5113-5119.

(2) (a) Ashton, P. R.; Baxter, I.; Cantrill, S. J.; Fyfe, M. C. T.; Glink, F. T.; Stoddart, J. F.; White, A. J. P.; Williams, D. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1294-1297. (b) Ashton, P. R.; Parsons, I. W.; Raymo, F. M.; Stoddart, J. F.; White, A. J. P.; Williams, D. J.; Wolf, R. *Angew. Chem., Int. Ed.* **1998**, *37*, *7*, 1913-1916. (c) Yamaguchi, N.; Nagvekar, D. S.; Gibson, H. W. *Angew. Chem., Int. Ed.* **1998**, *37*, 2361-2364. (d) Mirzoian, A.; Kairfer, A. E. *Chem. Commun.* **1999**, 1603-1604. (e) Bulger, J.; Sommerdijk, N. A. J. M.; Visser, A. J. W. G.; van Hoek, A.; Nolte, R. J. M.; Engbersen, J. F. J.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1999**, *121*, 28-33. (f) Nielson, M. B.; Hansen, J. F.; Becher, *J. Eur. J. Org. Chem.* **1999**, 2807-2815. (g) Jimenez, M. C.; Dietrich-Buchecker, C.; Sauvage, J.-P.; De Cian, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 1295-1298. (h) Hoshino, T.; Miyauchi, M.; Kawaguchi, Y.; Yamaguchi, H.; Harada, A. *J. Am. Chem. Soc.* **2000**, *122*, 9876–9877. (i) Cantrill, S. J.; Youn, G. J.; Stoddart, J. F. *J. Org. Chem.* **2001**, *66*, 6857-6872.

(3) (a) Jimenez, M. C.; Dietrich-Buchecker, C.; Sauvage, J.-P. *Angew. Chem. Int. Ed.* **2000**, *39*, 3284–3287. (b) Fujimoto, T.; Sakata, Y.; Kaneda, T. Chem. Commun. 2000, 2143-2144. (c) Onagi, J.; Easton, C. J.; Lincoln, S. F. *Org. Let.* **2001**, *3*, 1041-1044. (d) Amirsakis, D. G.; Elizarov, A. M.; Garcia-Garibay, M. A.; Glink, P. T.; Stoddart, J. F.; White, A. J. P.; Williams, D. J. *Angew. Chem. Int. Ed.* **2003**, *42*, 1126–1132. (e) Chiu, S.-H.; Rowan, S. J.; Cantrill, S. J.; Stoddart, J. F.; White, A. J. P.; Williams, D. J. *Chem. Commun.* **2002**, 2948–2949.

(4) (a) Fustin, C. A.; Clarkson, G. J.; Leigh, D. A.; Van Hoof, F.; Jonas, A. M.; Bailly, C. *Macromolecules* **2004**, *37*, 7884–7892. (b) Fustin, C.-A.; Bailly, C.; Clarkson, G. J.; Gallow, T. H.; Leigh, D. A. *Macromolecules* **2004**, *37*, 66–70.

(5) (a) Werts, M. P. L.; van den Boogaard, M.; Tsivgoulis, G. M.; Hadziioannou, G. *Macromolecules* **2003**, *36*, 7004–7013. (b) Watanabe, N.; Ikari, Y.; Kihara, N.; Takata, T. *Macromolecules* **2004**, *37*, 6663–6666.

(6) (a) Rowan, S. J.; Cantrill, S. J.; Cousins, G. R. L.; Sanders, J. K. M.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **2002**, *41*, 898–952. (b) Corbett, P. T.; Otto, S.; Sanders, J. K. M. *Org. Lett.* **2004**, *6*, 1852–1827.

(7) (a) Schalley, C. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 4399–4401. (b) Cantrill, S. J.; Chichak, K. S.; Peters, A. J.; Stoddart, J. F. *Acc. Chem. Res.* **2005**, *38*, 1–9.

(8) (a) Kolchinski, A. G.; Alcock, N. W.; Roesner, R. A.; Busch, D. H. *Chem. Commun.* **1998**, 1437–1438. (b) Furusho, Y.; Oku, T.; Hasegawa, T.; Tsuboi, A.; Kihara, N.; Takata, T. *Chem. Eur. J.* **2003**, *9*, 2895–2903.

(9) Fuchs, B.; Nelson, A.; Star, A.; Stoddart, J. F.; Vidal, S. B. *Angew. Chem., Int. Ed.* **2003**, *42*, 4220–4224.

(10) (a) Kidd, T. J.; Leigh, D. A.; Wilson, A. J. *J. Am. Chem. Soc.* **1999**, *121*, 1599–1600. (b) Weck, M.; Mohr, B.; Sauvage, J.-P. Grubbs, R. H. *J. Org. Chem.* **1999**, *64*, 5463–5471. (c) Wisner, J. A.; Beer, P. D.; Drew, M. G. B.; Sambrook, M. R. *J. Am. Chem. Soc.* **2002**, *124*, 12469–12476. (d) Arico, F.; Mobian, P.; Kern, J. M.; Sauvage, J.-P. *Org. Lett.* **2003**, *5*, 1887–1890. (e) Hannam, J. S.; Kidd, T. J.; Leigh, D. A.; Wilson, A. J. *Org. Lett.* **2003**, *5*, 1907–1910, (f) Coumans, R. G. E.; Elemans, J. A. A. W.; Thordarson, P.; Nolte, R. J. M.; Rowan, A. E. *Angew. Chem., Int. Ed.* **2003**, *42*, 650–654. (g) Iwamoto, H.; Itoh, K.; Nagamiya, H.; Fukazawa, Y. *Tetrahedron Lett.* **2003**, *44*, 5773–5776. (h) Wang, L. Y.; Vysotsky, M. O.; Bogdan, A.; Bolte, M. Böhmer, V. *Science* **2004**, *304*, 1312–1314.

(11) Trnka, T. M; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18–29.

(12) (a) Kidd, T. J.; Leigh, D. A.; Wilson, A. J. *J. Am. Chem. Soc.* **1999**, *121*, 1599–1600. (b) Weck, M.; Mohr, B.; Sauvage, J.-P. Grubbs, R. H. *J. Org. Chem.* **1999**, *64*, 5463–5471. (c) Arico, F.; Mobian, P.; Kern, J. M.; Sauvage, J.-P. *Org. Lett.* **2003**, *5*, 1887–1890. (d) Iwamoto, H.; Itoh, K.; Nagamiya, H.; Fukazawa, Y. *Tetrahedron Lett.* **2003**, *44*, 5773–5776. (e) Wang, L. Y.; Vysotsky, M. O.; Bogdan, A.; Bolte, M. Böhmer, V. *Science* **2004**, *304*, 1312–1314.

(13) (a) Wisner, J. A.; Beer, P. D.; Drew, M. G. B.; Sambrook, M. R. *J. Am. Chem. Soc.* **2002**, *124*, 12469–12476. (b) Hannam, J. S.; Kidd, T. J.; Leigh, D. A.; Wilson, A. J. *Org. Lett.* **2003**, *5*, 1907–1910, (c) Coumans, R. G. E.; Elemans, J. A. A. W.; Thordarson, P.; Nolte, R. J. M.; Rowan, A. E. *Angew. Chem., Int. Ed.* **2003**, *42*, 650–654.

(14) Guidry, E. N.; Cantrill, S. J.; Stoddart, J. F.; Grubbs, R. H. *Org. Lett.* **2005**, *7*, 2129–2132.

(15) (a) Kilbinger, A. F. M.; Cantrill, S. J.; Waltman, A. W.; Day, M. W.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 3281–3285. (b) Badjic, J. D.; Cantrill, S. J.; Grubbs, R. H.; Guidry, E. N.; Orenes, R.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **2004**, *43*, 3273–3278.

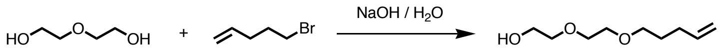
(16) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956.

(17) Crystals of **4**-$H_2 \cdot 2PF_6$ diffract poorly and appear to be twinned. Data used for least-squares refinement was restricted to $2\theta < 40°$ with data between 36-40° being extremely weak. Disorder is observed in the ring-closed portion of the molecules. Restraints were placed on temperature factors, bond distances and bond angles in this portion of the molecules. The structure has been deposited in the CCDC; number 648323. Complete crystallographic details are provided in the supporting information in *J. Am. Chem. Soc.* **2007**, *ASAP*.

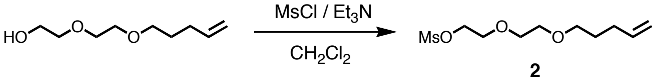
Experimental Information

General Information: NMR spectra were recorded on an Oxford 300 MHz or 500 MHz NMR spectrometer running Varian VNMR software. Chemical shifts are reported in parts per million (ppm) with reference to internal solvent. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), multiplet (m), and broad (br). High-resolution mass spectra (EI, MALDI and FAB) were provided by California Institute of Technology Mass Spectrometry Facility. Molecular mass calculations were performed with ChemDraw Ultra 9 (Cambridge Scientific). Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F254 precoated plates (0.25 mm thickness) with a fluorescent indicator. Visualization was performed using fluorescence quenching or citric ammonium molybdate (CAM), anisaldehyde, potassium permanganate ($KMnO_4$) or iodine stain. Flash column chromatography was performed using silica gel 60 (230-400 mesh) from EM Science. Grubbs metathesis catalysts **5** were obtained from Materia. All other chemicals were purchased from Aldrich or Acros Chemical Companies and used as obtained unless noted otherwise. Tetrahydrofuran and dichloromethane were purified and dried by passage through a solvent column. Anhydrous dimethyl formamide was purchased in Acros seal bottles from Acros and used as received. Reverse-phase high pressure liquid chromatography (HPLC) was conducted using Gemini 5 micron c-18 column under a steady ramp (10% MeCN in 0.1% aqueous trifluoroacetic acid to 100% MeCN) with UV detection at 254 nm using a Beckman System Gold detector. Gel permeation chromatography (GPC) was determined on an HPLC type system, using a Shimadzu LC-10AD pump, a rheodyne model 7125 injector with a 100 uL loop, PLgel 5 um 10E3A size exclusion column and PLgel 5um guard column (purchased from polymer laboratories) connected in series with a Alltech on-line degassing system, a Wyatt Technology optilab DSP differential refractometer and a Wyatt Technology Dawn EOS multi angle laser light scattering (MALLS) detector. Astra V was used to analyze the raw MALLS and RI data. The elutent (DMF with 0.1M NH_4PF_6) was prepated using HPLC grade DMF (purchased from Fischer Scientific) and LiBr (purchased from Aldrich), which was filtered through a 0.45 micron filter before use. The flow rate was set to 0.5 mL/min. Instrument normalization and calibration was performed using a 30K Polystyrene standard with a PDI = 1.06 (purchased from Pressure Chemical Company). No calibration standards were used in determination of molecular weights or polydispersities. The *dn*/*dc* values were obtained for each injection assuming 100% mass elution from the columns. These values were verified by measuring *dn*/*dc* independently using a Wyatt optilab differential refractometer.

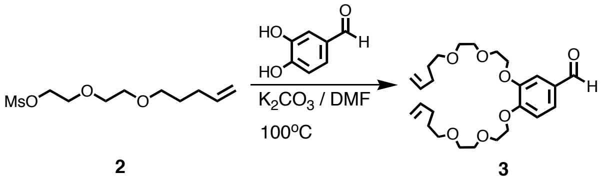
Experimental Procedures:



A solution of diethylene glycol (320 ml, 3.35 moles), 5-bromo-1-pentene (50 g, 0.335 moles) and H_2O containing NaOH (67 g, 1.72 moles, in 67 mL H_2O) was heated at 80 °C for 12 hours. The reaction mixture was diluted with water and washed with methylene chloride three times to give a crude product, which was purified by column chromatography (SiO_2: hexanes/ethyl acetate 4:1) to yield the monoalkylated product as a colorless oil (36 g, 62% yield). Characterization for this compound has been reported previously (Badjic′, J. D., Cantrill, S. J., Grubbs, R. H.; Guidry, E. N.; Orenes, R.; Stoddart, J. F. *Angew. Chem. Int. Ed. 43*, 3273-3278.).

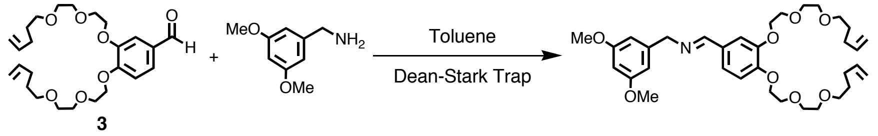


2: The monoalkylated product (36 g, 0.207 moles) and triethylamine (43 ml, 0.306 moles) were dissolved in CH_2Cl_2 (500 mL, 0.4 M) and cooled to 0 °C. A solution of mesyl chloride (24.3 mL, 0.207 moles) in CH_2Cl_2 (50 mL) was added slowly. The reaction was gradually warmed to room temperature and stirred overnight. The reaction mixture was diluted with brine and washed with methylene chloride 3 times, to give a crude product, which was purified by column chromatography (SiO_2:hexanes/ethyl acetate 2:1) to yield **2** as a colorless oil (51 g, 98 % yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.70 (m, center, 1H), 4.95-4.83 (br m, 2H), 4.29-4.26 (m, 2H), 3.68-3.65 (m, 2H), 3.65-3.61 (m, 2H), 3.57-3.53 (m, 2H), 3.49-3.45 (m, 2H), 3.37 (t, J = 10.2 Hz, 2H), 2.99 (s, 3H), 2.04-1.96 (m, 2H), 1.56 (quint, J = 6.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.10, 114.72, 70.55, 69.92, 69.45, 68.90, 52.57, 37.54, 30.11, 28.67. HRMS-FAB (m/z): [M + H] calcd for $C_{10}H_{21}O_5S$, 253.1110; found, 253.1113.

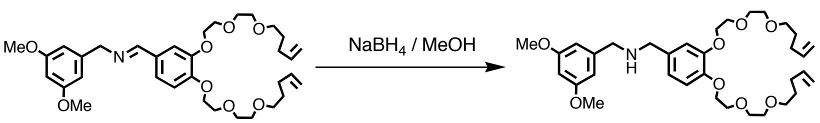


3: Compound **2** (37.1 g, 0.147 moles), 3,4-dihydroxybenzaldehyde (9.67 g, 0.0699 moles), and potassium carbonate (29 g, 0.210 moles) were suspended in anhydrous DMF

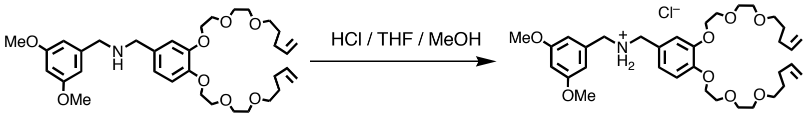
(500 mL, 0.3 M). The reaction mixture was heated to 80 °C and stirred for 3 days. The reaction mixture was diluted with water and washed with ethyl acetate three times to give a crude product, which was purified by column chromatography (SiO_2:hexanes/ethyl acetate 1:1) to yield the alkylated product as an orange oil (28 g, 91 % yield). ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 9.83 (s, 1H), 7.45-7.42 (m, 2H), 7.00 (d, J = 8.7 Hz, 1H), 5.87-5.73 (m, 2H), 5.04-4.92 (m, 4H), 4.23 (quint, J = 4.8 Hz, 4H), 3.90 (q, J = 5.4 Hz, 4H), 3.75-3.72 (m, 4H), 3.61-3.58 (m, 4H), 3.47 (t, J = 6.6 Hz, 4H), 2.10 (q, J = 7.8 Hz, 4H), 1.67 (quint, J = 6.9 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.04, 154.51, 149.34, 138.41, 138.37, 130.39, 126.84, 114.91, 114.88, 112.65, 112.07, 71.18, 71.10, 70.92, 70.34, 69.71, 69.59, 68.90, 68.85, 30.38, 28.91. HRMS-FAB (m/z): [M + H] calcd for $C_{25}H_{39}O_7$,451.2696; found, 451.2713.



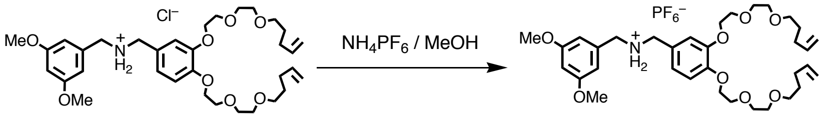
Compound **3** (3 g, 6.66 mmoles) and 3,5-dimethoxybenzylamine (1.11 g, 6.66 mmoles) were dissolved in toluene (70 mL, 0.1 M). The reaction was heated under reflux for 12 hours using a Dean-Stark apparatus. The solvent was evaporated under reduced pressure to give the crude imine as an orange oil (3.99 g). This product was immediately used in the next step without purification.



The imine (3.99 g, 6.66 mmoles) was dissolved in MeOH (67 mL, 0.1 M). After portion-wise addition of sodium borohydride (0.78 g, 19.98 mmoles), the reaction mixture was stirred for 4 h. The solvent was evaporated under reduced pressure and the crude residue was partitioned between CH_2Cl_2 (200 mL) and 2M NaOH solution (200 mL). The aqueous layer was further washed with CH_2Cl_2 (200 mL). The organic phases were combined and washed with NaCl (sat.) and dried over $MgSO_4$. Filtration, followed by evaporation gave the crude product, an orange oil (3.8 g) which was used in the next step without further purification.

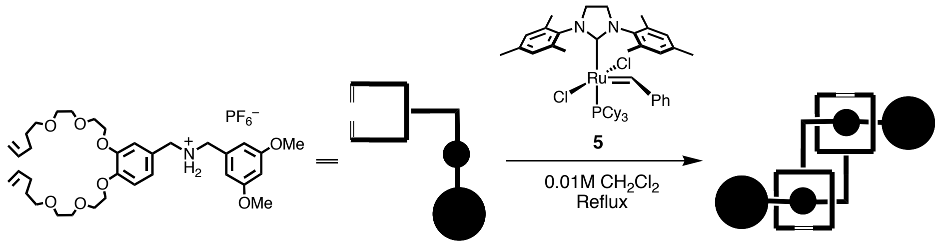


The amine (3.8 g, 6.33 mmoles) was dissolved in a solution of 100 mL of THF, 20 mL of MeOH and 2 mL of 1M HCl. The reaction mixture was stirred for 1 hour. The THF and MeOH were removed under reduced pressure. The crude mixture was partitioned between water and CH_2Cl_2. The organic layer was extracted twice more with water. The organic layer was dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure to yield an orange solid. The solid was purified by washing with cold ether (2X, 20 mL) to yield a white solid (3.74 g). The solid was used in the next step without any further purification.



4-H·PF$_6$

4-H·PF$_6$: The chloride salt (3.74 g, 5.88 mmoles) and ammonium hexafluorophosphate (1.91 g, 11.76 mmoles) were dissolved in MeOH (60 mL, 0.1 M). The reaction was stirred at room temperature for 4 h. The solvent was removed under reduced pressure. The crude mixture was partitioned between CH_2Cl_2 and water. The organic layer was washed two times and dried over magnesium sulfate. The solvent was removed under reduced pressure to yield **4**-H·PF$_6$ as a sticky pale yellow solid (3.69 g, 84 % yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 (broad s, 2H), 6.93 (d, J = 7.8 Hz, 1H), 6.79-6.75 (m, 2H), 6.67 (m, 2H), 6.44 (s, 1H), 5.77-5.64 (m, 2H), 4.95-4.88 (m, 4H), 4.43 (m, 2H), 4.23 (m, 2H), 4.01 (s, 4H), 3.74 (s, 6H), 3.65-3.61 (m, 12H), 3.50-3.42 (m, 4H), 2.07-1.98 (m, 4H), 1.61 (hex, J = 6.9 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.48, 147.35, 146.64, 137.79, 137.72, 133.43, 123.76, 123.43, 115.30, 115.25, 114.86, 114.10, 113.14, 106.49, 100.76, 71.83, 71.59, 71.03, 70.94, 70.84, 70.16, 70.07, 69.79, 69.58, 68.83, 68.12, 55.61, 52.54, 52.31, 30.16, 28.70, 28.66 . HRMS-FAB (m/z): [M + e] calcd for $C_{34}H_{52}NO_8$, 602.3693; found, 602.3690.

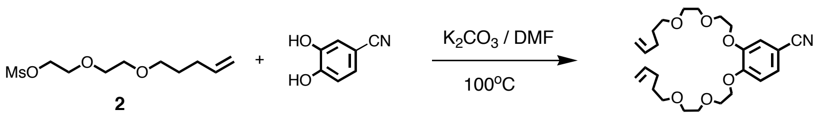


4-H·PF$_6$

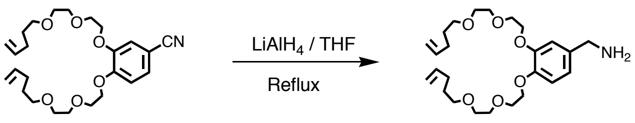
12-H$_2$·2PF$_6$

6-H$_2$·2PF$_6$: Compound **4**-H·PF$_6$ (3 g, 4.02 mmoles) was dissolved in anhydrous, degassed CH$_2$Cl$_2$ (400 mL, 0.01M). The catalyst (H$_2$IMes)(PCy$_3$)(Cl)$_2$Ru=CHPh **5** (0.170 g, 0.201 mmoles) was added under a dry Ar atmosphere and the reaction was heated to 40 °C for 12 h. The reaction quenched by addition of ethyl vinyl ether. The reaction was stirred for an additional 30 min at 40 °C. The reaction mixture was cooled to room temperature. The solvent was removed under reduced pressure and the crude oil was purified by column chromatography (SiO$_2$: methylene chloride/methanol 100:1 gradient to 100:2) to yield **6**-H$_2$·2PF$_6$ as a pale brown foamy solid (2.74 g, 95 % yield). ^{1}H NMR (300 MHz, CDCl$_3$): δ 6.94-6.91 (m, 2H), 6.85-6.80 (m, 2H), 6.72-6.66 (m, 6H), 6.48-6.46 (m, 2H), 5.46-5.32 (m, 4H), 4.68-4.25 (broad m, 16H), 3.85-3.47 (m, 28H), 2.33-2.26 (m, 8H), 2.09-1.96 (m, 4H), 1.78-1.48 (m, 4H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 161.62, 146.94, 146.48, 133.91, 133.74, 131.23, 130.99, 129.95, 129.63, 123.80, 123.65, 113.71, 112.86, 112.62, 106.55, 106.46, 105.64, 100.48, 72.901, 72.45, 72.23, 72.09, 71.81, 71.35, 70.59, 70.13, 69.85, 69.59, 68.75, 68.53, 55.70, 52.69, 52.45, 52.17, 51.94, 30.64, 30.49, 29.04, 28.95, 28.66, 25.40, 25.30. HRMS-FAB (m/z): [M + e] calcd for $C_{64}H_{95}N_2O_{16}$, 1147.668; found, 1147.661.

Crystals suitable for X-ray analysis were grown by slow evaporation from EtOAc. Crystallization lead to fractional separation of the mesoform, which remained dissolved in the mother liquour. The racemic mixture produced crystals suitable for X-ray analysis. Crystals of **6**-H_2·$2PF_6$ diffract poorly and appear to be twinned. Data used for least-squares refinement was restricted to $2\theta < 40°$ with data between 36-40° being extremely weak. Disorder is observed in the ring-closed portion of the molecules. Restraints were placed on temperature factors, bond distances and bond angles in this portion of the molecules. The structure has been deposited in the CCDC; number 648323. See the CIF file for complete details.

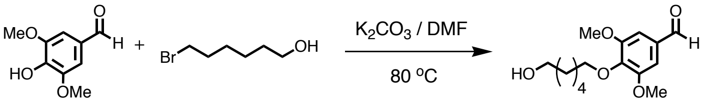


Compound **2** (51 g, 0.202 moles), 3,4-dihydroxybenzonitrile (13 g, 0.963 moles), and potassium carbonate (40 g, 0.289 moles) were suspended in anhydrous DMF (500 ml, 2 M). The reaction mixture was heated to 80 °C and stirred for 3 days. The reaction mixture was diluted with water and washed with ethyl acetate three times to give a crude product, which was purified by column chromatography (SiO_2: hexanes/ethyl acetate 3:1) to yield the alkylated product as an orange oil (23 g, 53 % yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26-7.23 (m, 1H), 7.15-7.14 (m, 1H), 6.92 (d, J = 8.7 Hz, 1H), 5.87-5.73 (m, 2H), 5.04-4.93 (m, 4H), 4.22-4.15 (m, 4H), 3.88 (qt, J = 5.1 Hz, 4H), 3.71 (m, 4H), 3.59 (q, J = 3.3 Hz, 4H), 3.49-3.44 (m, 4H), 2.10 (qt, J = 7.2 Hz, 4H), 1.73-1.63 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.89, 148.86, 138.24, 138.19, 126.77, 119.17, 117.08, 114.76, 114.73, 113.49, 104.10, 70.98, 70.96, 70.79, 70.77, 70.18, 70.16, 69.56, 69.42, 69.15, 68.69, 30.21, 28.74. HRMS-FAB (m/z): [M + H] calcd for $C_{26}H_{40}NO_6$, 462.2856; found, 462.2857.



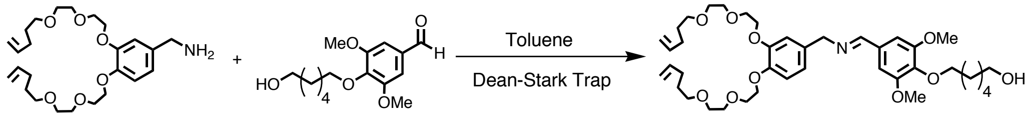
8

8: The alkylated product (23 g, 0.0515 moles) was dissolved in anhydrous THF (250 mL, 0.2 M) and cooled to 0 °C, under an argon atmosphere. Lithium aluminum hydride (5.9 g, 0.155 moles) was added slowly, piecewise, to the reaction mixture. The reaction was warmed to 76 °C and refluxed under an argon atmosphere for 12 h. The reaction was quenched by addition of 6 mL of H_2O, followed by addition of 6 mL of NaOH(aq) (15 %) followed by addition of 18 mL of H_2O. A large excess of celite was added and the mixture was filtered and then the solvent was removed under reduced pressure. The reaction mixture was diluted with methylene chloride and washed with water 3 times with water to yield compound **8** as a yellow oil (18 g, 78 % yield). No further purification was necessary. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.89-6.80 (m, 3H), 5.87-5.73 (m, 2H), 5.04-4.92 (m, 4H), 4.19-4.13 (m, 4H), 3.85 (q, J = 5.4 Hz, 4H), 3.77 (s, 2H), 3.73-3.70 (m, 4H), 3.60-3.57 (m, 4H), 3.46 (t, 6.9 Hz, 4H), 2.10 (q, J = 6.9 Hz, 4H), 1.67 (quint, J = 6.9 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.20, 147.91, 138.40, 120.02, 115.18, 114.85, 114.00, 70.97, 70.87, 70.32, 69.93, 69.24, 69.04, 46.27, 30.37, 28.90.



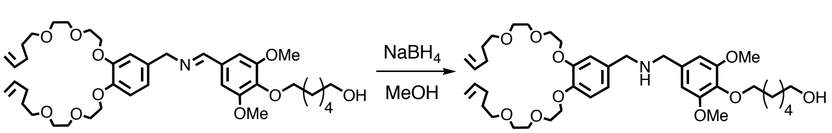
9

9: Syringaldehyde (15 g, 0.0823 moles), 6-bromo-1-hexanol (17.9 g, 0.0989 moles), and potassium carbonate (34 g, 0.247 moles) were suspended in anhydrous DMF (0.2 M, 400 mL). The reaction mixture was heated to 80 °C and stirred for 2 days. The reaction mixture was diluted with water and washed with ethyl acetate 3 times to give a crude product, which was purified by column chromatography (SiO_2: hexanes/ethyl acetate 3:2) to yield the alkylated product **9** as an orange oil (18.6 g, 80 % yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.85 (s, 1H), 7.11 (s, 2H), 4.06 (t, J = 6.6 Hz, 2H), 3.90 (s, 6H), 3.64 (t, J = 6.6 Hz, 4H), 1.77 (quint, 6.6 Hz, 4H), 1.63-1.36 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.36, 154.03, 147.96, 143.11, 131.71, 106.88, 73.67, 62.99, 56.40, 32.84, 30.20, 25.71. HRMS-EI (m/z): [M + e] calcd for $C_{15}H_{22}O_5$, 282.1467; found, 282.1459.

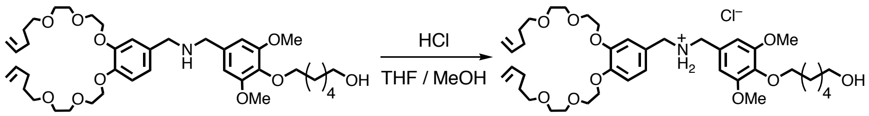


8 **9**

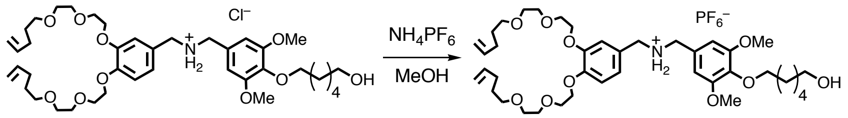
Compound **8** (18 g, 0.0399 moles) and compound **9** (11.25 g, 0.0399 moles) were dissolved in toluene (400 mL, 0.1 M). The reaction was heated under reflux for 12 h using a Dean-Stark apparatus. The solvent was evaporated under reduced pressure to give the crude imine as an orange oil (28.5 g). This product was immediately used in the next step without purification.



The imine (28.5 g, 0.0399 moles) was dissolved in MeOH (400 mL, 0.1 M). After portion-wise addition of sodium borohydride (4.5 g, 0.120 moles), the reaction mixture was stirred for 4 h. The solvent was evaporated under reduced pressure and the crude residue was partitioned between CH_2Cl_2 (400 mL) and 2M NaOH solution (400 mL). The aqueous layer was further washed with CH_2Cl_2 (400 mL). The organic phases were combined and washed with NaCl (sat.) and dried over $MgSO_4$. Filtration, followed by evaporation gave the crude product, an orange oil (28.5 g) which was used in the next step without further purification.

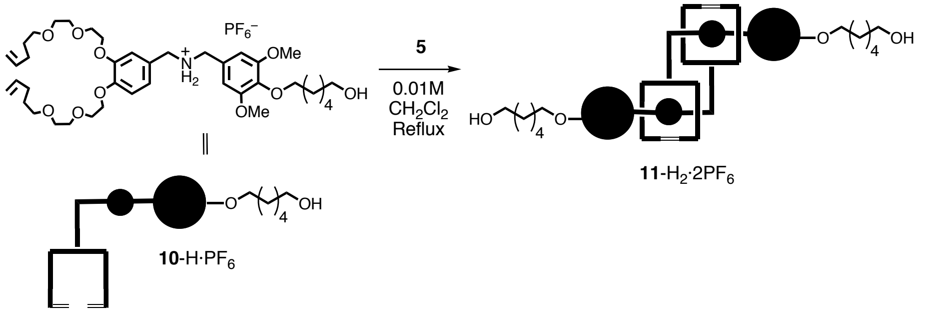


The amine (28.5 g, 0.399 moles) was dissolved in a solution of 200 mL of THF, 40 mL of MeOH and 5 mL of 1M HCl. The reaction mixture was stirred for 1 h. The THF and MeOH were removed under reduced pressure. The crude mixture was partitioned between water and CH_2Cl_2. The organic layer was extracted twice more with water. The organic layer was dried over magnesium sulfate and the solvent was removed under reduced pressure to yield an orange solid. The solid was purified by washing with cold ether (2X, 50 ml) to yield a white solid (27.3 g).



10-H·PF$_6$

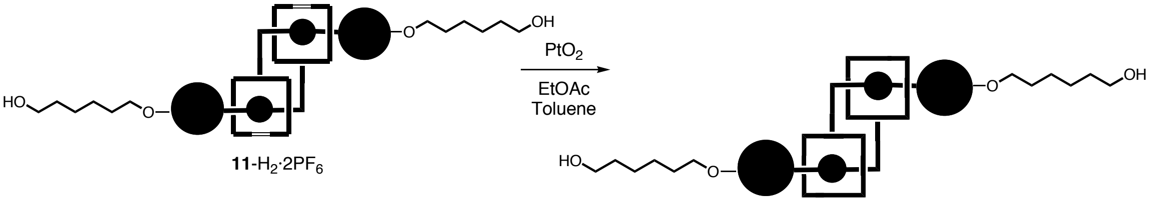
10-H·PF$_6$: The chloride salt (27.3 g, 0.0363 moles) and ammonium hexafluorophosphate (11.8 g, 0.0726 moles) were dissolved in MeOH (360 mL, 0.1 M). The reaction was stirred at room temperature for 4 h. The solvent was removed under reduced pressure. The crude mixture was partitioned between CH_2Cl_2 and water. The organic layer was washed two times and dried over magnesium sulfate. The solvent was removed under reduced pressure to yield **10**-H·PF$_6$ as a sticky pale yellow solid (26.6 g, 85 % yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38 (broad s, 2H), 6.95 (d, J = 8.1 Hz, 1H), 6.83-6.73 (m, 4H), 5.77-5.64 (m, 2H), 4.95-4.88 (m, 4H), 4.37 (s, 2H), 4.24 (s, 2H), 4.02 (s, 4H), 3.87 (t, J = 6.3 Hz, 2H), 3.77 (s, 6H), 3.63-3.42 (m, 16H), 2.01 (m, 4H), 1.62 (quint, J = 6.9 Hz, 6H), 1.55-1.45 (m, 2H), 1.38-1.31 (m, 4H) . ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.94, 147.49, 146.80, 137.79, 137.75, 126.43, 123.73, 123.65, 115.30, 115.26, 114.10, 113.08, 106.14, 73.45, 71.48, 71.20, 71.04, 70.97, 69.96, 69.91, 69.48, 69.36, 68.56, 68.00, 62.81, 65.38, 52.65, 52.40, 32.68, 30.14, 29.96, 28.63, 25.61, 25.53. HRMS-FAB (m/z): [M + H] calcd for $C_{40}H_{64}NO_{10}$, 718.4530; found, 718.4505.



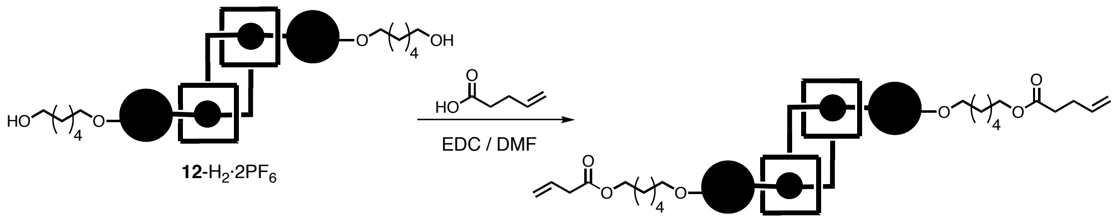
10-H·PF$_6$

11-H$_2$·2PF$_6$

11-H$_2$·2PF$_6$: Compound **10**-H·PF$_6$ (3 g, 0.00359 moles) was dissolved in anhydrous, degassed CH_2Cl_2 (360 mL, 0.01M). The catalyst $(H_2IMes)(PCy_3)(Cl)_2Ru{=}CHPh$ **5** (0.147 g, 0.174 mmoles) was added under a dry Ar atmosphere and the reaction was heated to 40 °C for 12 h. The reaction quenched by addition of ethyl vinyl ether. The reaction was stirred for an additional 30 min at 40 °C. The reaction mixture was cooled to room temperature. The solvent was removed under reduced pressure and the crude oil was purified by column chromatography (SiO_2: methylene chloride/methanol 100:1 gradient to 100:2) to yield **11**-H$_2$·2PF$_6$ as a pale brown foamy solid (2.84 g, 98 % yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75 (br s, 4H), 6.99-6.75 (m, 10H), 5.44 (br m, 4H), 4.63-4.31 (br m, 12H), 4.00 (t, J = 6.9 Hz, 8H), 3.83 (s, 6H), 3.82 (s, 6H), 3.68-3.50 (br m, 36H), 2.32 (m, 2H), 2.12 (m, 8H), 1.79-1.35 (m, 24H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.94, 147.49, 146.80, 137.79, 137.75, 126.43, 123.73, 123.65, 115.30, 115.26, 114.10, 113.08, 73.62, 73.00, 72.69, 72.43, 72.29, 72.01, 71.58, 71.02, 70.50, 69.95, 68.63, 68.39, 63.05, 56.59, 52.69, 52.36, 32.83, 31.12, 30.18, 29.90, 29.78, 29.56, 27.95, 26.04, 25.77, 25.60. HRMS-FAB (m/z): [M + H + PF$_6$] calcd for $C_{76}H_{120}N_2O_{20}F_6P$, 1526.7346; found, 1525.8044.



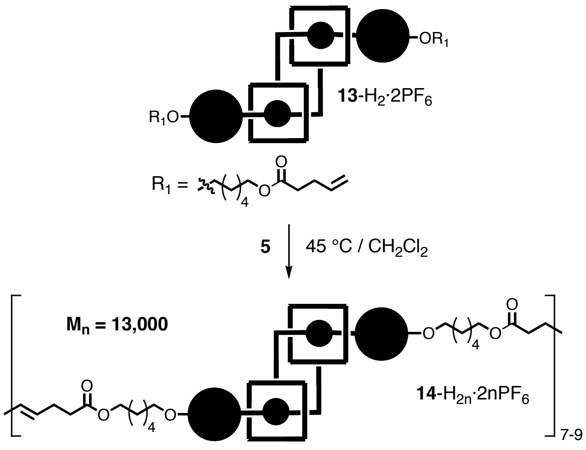
12-H_2·2PF$_6$: Compound **11**-H_2·2PF$_6$ (0.25g, 0.150 mmoles) was dissolved in ethyl acetate (0.001 M, 150 mL). PtO_2 (Adam's catalyst, 1.70 g, 0.0075 mmoles) was added and the reaction atmosphere was flushed with hydrogen for 5 min. An atmosphere of hydrogen was placed over the reaction using a balloon, and it was vigorously stirred a room temperature for 30 min. The reaction was filtered through a pad of celite and solvent removed under reduced pressure to yield **12**-H_2·2PF$_6$ as a light brown sticky solid (0.24 g, 97 % yield). ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.75 (br s, 4H), 7.01-6.77 (m, 10H), 4.63-4.33 (br m, 12H), 4.00 (t, J = 6.6 Hz, 8H), 3.83 (s, 12H), 3.74-3.50 (br m, 36H), 2.20 (m, 8H), 1.79-1.26 (br m, 24H), 0.882-0.83 (m, 8H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 154.23, 154.10, 146.92, 146.43, 138.07, 126.86, 123.90, 123.70, 113.82, 112.54, 105.643, 105.13, 73.68, 73.01, 72.71, 72.45, 72.28, 72.08, 71.53, 71.06, 70.53, 69.97, 68.64, 68.39, 63.05, 56.59, 52.69, 52.36, 32.83, 31.12, 30.18, 29.90, 29.78, 29.56, 27.95, 26.04, 25.77, 25.69, 22.89, 14.33, 1.22. HRMS-FAB (m/z): [M + H + PF$_6$] calcd for $C_{76}H_{124}N_2O_{20}F_6P$, 1529.8389; found, 1529.8329.



12-H_2·$2PF_6$

13-H_2·$2PF_6$

13-H_2·$2PF_6$: EDC (0.64 g, 3.35 mmoles), 4-pentenoic acid (0.34 g, 3.35 mmoles) and DMAP (0.02 g, 0.16 mmoles) were dissolved in anhydrous DMF (9 mL, 0.1M) and stirred at room temperature for 30 min. The diol **12**-H_2·$2PF_6$ (1.40 g, 0.84 mmoles) was dissolved in anhydrous DMF (1 mL) and added via syringe to the EDC mixture. The reaction was stirred under Ar for 24 h. The reaction mixture was diluted with brine and ethyl acetate. The aqueous layer was extracted twice with brine. The organic layer was extracted twice with brine and dried over magnesium sulfate. The solvent was removed under reduced pressure and the crude oil was purified by column chromatography (SiO_2: methylene chloride/methanol 100:1 gradient to 100:2) to yield **13**-H_2·$2PF_6$ as a pale brown foamy solid (1.2 g, 80 % yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74 (br s, 4H), 7.01-6.91 (m, 4H), 6.81-6.76 (m, 6H), 5.89-5.76 (m, 2H), 5.09-4.98 (m, 4H), 4.65-4.33 (m, 12H), 4.09 (t, J = 6.9 Hz, 8H), 3.98 (t, J = 6.6 Hz, 8H), 3.83 (s, 12H), 3.76 (br m, 36H), 2.45-2.34 (m, 8H), 1.83-1.39 (br m, 64H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.39, 173.37, 154.21, 154.08, 146.91, 146.42, 138.14, 136.92, 127.28, 126.89, 123.91, 123.67, 115.65, 113.85, 112.55, 105.09, 73.69, 73.04, 72.71, 72.45, 72.28, 71.55, 71.06, 70.52, 70.02, 68.67, 68.39, 64.61, 56.58, 52.71, 52.36, 37.77, 30.24, 29.94, 29.77, 29.10, 28.81, 27.94, 27.88, 25.91, 25.83, 25.76, 25.70. HRMS-FAB (m/z): [M + H + PF_6] calcd for $C_{86}H_{136}N_2O_{22}F_6P$, 1693.9227; found, 1693.9293.



14-H_{2n}·2nPF_6: The diene **13**-H_2·2PF_6 (20.5 mg, 0.01 mmoles) was dissolved in 1 mL of dry degassed CH_2Cl_2 and placed in a schlenk tube with a teflon stopper. Catalyst (H_2IMes)(PCy_3)$(Cl)_2$Ru=CHPh **5** (0.47 mg, 0.00005 mmoles) was added in 50 uL of CH_2Cl_2. The schlenk tube was heated to 40 °C, with a continuous Ar purge until minimal solvent remained (approximately 25 uL- approximately 30 min). The teflon stopper was closed, and the heating continued for 24 h. The polymerization was quenched by adding ethyl vinyl ether. The solvent was removed under reduced pressure. No further purification was performed. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (br s, 4H), 6.99-6.79 (m, 10H), 5.58-5.31 (br m, 2H), 4.65-4.36 (br m, 12H), 4.14-3.50 (br m, 56H), 2.55-2.21 (br m, 8H), 1.94-1.86 (br m, 64H). M_n was not able to be determined using GPC due to poor chromatography. Both solvent (THF, DCM, DMF, DMF with 0.1 M LiBr, DMF with 0.1 M NH_4PF_6) and column types (PLgel 5 um 10E3A size exclusion column and PLgel 5 um guard column - purchased from polymer laboratories and ViscoGEL I-Series columns, I-MBLMW-3078 and I-MBHMW-3078 - purchased from viscotek) were varied to try and improve chromatography, but with little success. To further confirm the polymerization results observed in the ^{1}H NMR and MALDI, HPLC was employed. HPLC was used to verify polymerization rather than olefin isomerization (which would have similar olefin region in the ^{1}H NMR). Diene **13**-$H_2 \cdot 2PF_6$ has an elution time of 46.876 minutes (steady ramp -10% MeCN in 0.1% aqueous trifluoroacetic acid to 100% MeCN). Polymer **14**-$H_{2n} \cdot 2nPF_6$ was placed on the HPLC under identical ramp conditions. Diene **13**-$H_2 \cdot 2PF_6$ had completely disappeared and no new signals were observed over the course of the 90 minute run, indicating that the internal olefin protons observed in the ^{1}H NMR are due to ADMET polymerization rather than olefin isomerization.

Chapter 4

Cyclic Polycatenanes via Ring-Closing Metathesis

Cyclic Polycatenanes (“Molecular Charm Bracelets”) via Ring-Closing Metathesis

Introduction

Because the properties of polymers are related to their molecular structure, the development of synthetic techniques facilitating precise control over the architecture of polymers such as hyperbranched polymers,[1] block copolymers,[2] dendrimers,[3] and cyclic polymers,[4] is of significant interest. This interest extends into the field of interlocked polymers,[5] which is comprised of polymeric materials such as polycatenanes,[5] polyrotaxanes,[5] and daisy-chain polymers.[5,6] The conceptual transition from a [2]catenane or [2]rotaxane to polycatenanes and polyrotaxanes can be achieved through a number of different design strategies, several of which have been graphically represented in Figures 1 and 2.

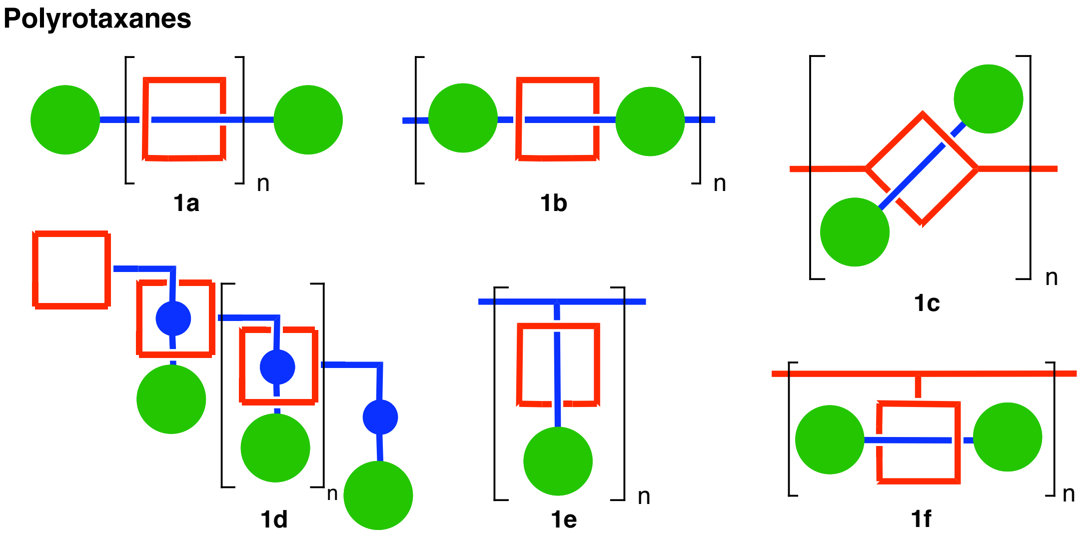


Figure 1: Graphical representation of polyrotaxanes.

Polyrotaxanes can be divided into two categories: main-chain polyrotaxanes, in which the interlocked molecule resides within the polymer chain, and side-chain polyrotaxanes, in which the interlocked molecule is pendant to the polymer chain. Main-chain polyrotaxanes may be formed by encircling a polymeric dumbbell-shaped component with (n) macrocycles (**1a**). Alternatively, a [2]rotaxane can be transformed into a main-chain polyrotaxane by incorporation of its dumbbell (**1b**) or macrocyclic components (**1c**) into the polymer chain. Daisy-chain polymers (**1d**) are another class of main-chain rotaxane-based polymer in which both the host and guest recognition units are covalently bound in the same monomer, and both the macrocycle and dumbbell components are present in the polymer chain. In side-chain polyrotaxanes, either the dumbbell (**1e**) or macrocycle (**1f**) of a rotaxane are covalently attached to a polymer backbone.

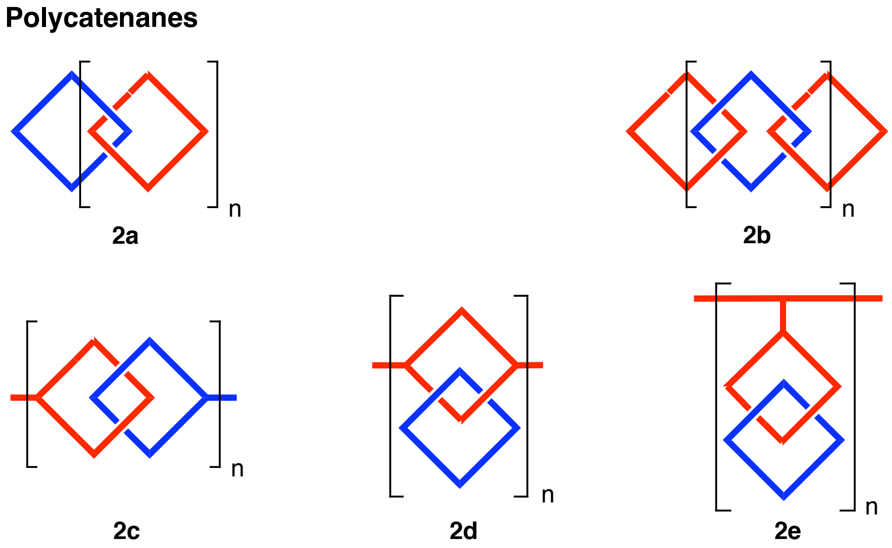


Figure 2: Graphical representation of polycatenanes.

Polycatenanes can be divided into two categories: main-chain and side-chain polycatenanes (Figure 2). Main-chain polycatenanes can be formed by simply enlarging one of the rings so that multiple macrocycles may be accommodated around the enlarged ring (**2a**). The larger ring may also be enlarged in a different manner, thus allowing the interlocking of two or more macrocycles, like links in a chain (**2b**). Introduction of [2]catenanes into the backbone of a polymer chain also generates main-chain polycatenanes (**2c**). Incorporation of a catenated macrocycle into the backbone of a polymer chain (**2d**) produces a main-chain polycatenane. Side-chain polycatenanes may be formed by appending [2]catenane units from a polymer backbone (**2e**).

While many polycatenane architectures can be designed, few have been realized due to the significant synthetic challenge they pose. One such architecture is the cyclic polycatenane (**2a**), for which no syntheses have appeared in the chemical literature. We thought that the key synthetic challenge in the formation of a cyclic polycatenane lay in the production of an appropriate cyclic polymer. Formation of an appropriately-functionalized cyclic polymer, which may function as a multi-site macrocyclic template, followed by ring-closing of corresponding small molecule macrocycles (clipping approach) around a cyclic polymer chain would lead to the formation of a cyclic polycatenane (Figure 3). A clipping approach has been used successfully in the formation of a both rotaxanes and catenanes and involves ring-closing of a macrocycle around a corresponding dumbbell or macrocycle, respectively.[7,8]

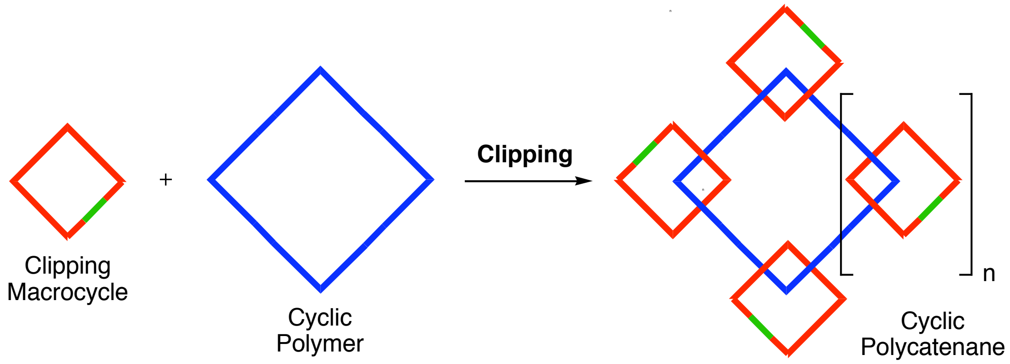


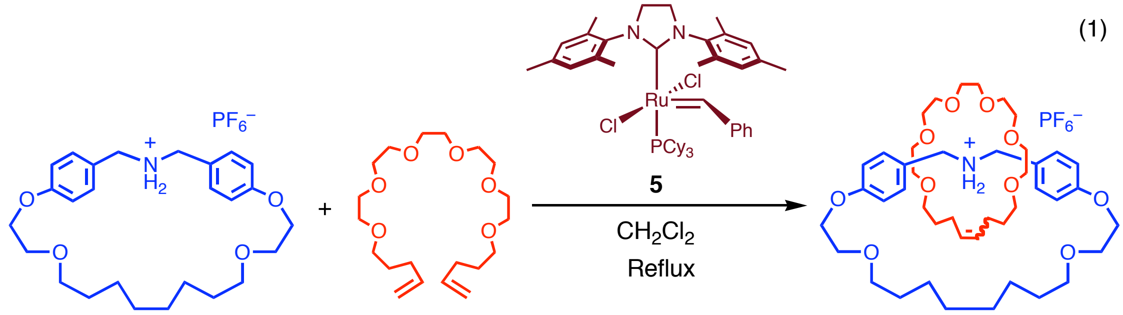
Figure 3: Graphical representation of cyclic polycatenane formation using a clipping approach.

Polycatenane Formation via Clipping

Inspiration for the formation of cyclic polycatenanes can be found in the vast number of syntheses of catenanes and rotaxanes that have appeared in the chemical literature. Most of the strategies employ kinetically-controlled covalent bond formation as the final interlocking step.[9] This strategy does not always result in high yields of mechanically interlocked compounds because of the irreversible formation of unwanted non-interlocked by-products. An alternative strategy, however, exploits dynamic covalent chemistry,[10] an approach that utilizes reversible reactions in which the product distribution depends on thermodynamic rather than kinetic control, i.e., the yield of a mechanically interlocked compound reflects its stability relative to those of any other non-interlocked by-products with proof-reading and error-checking operating up until a final equilibrium state is reached. Examples of equilibrium reactions employed as the final bond-forming step in the synthesis of catenanes and rotaxanes include the reversible formation of imines,[11] disulfides[12] and cyclic acetals,[13] as well as olefin metathesis mediated by functional-group tolerant ruthenium alkylidene catalysts.[14] This protocol has been applied successfully in the syntheses of both [2]catenanes,[15] [2]rotaxanes,[16] rotaxane bundles[17] and [c2]daisy chain compounds.[18]

Previously, we have demonstrated that the ring-closing of certain olefin-containing polyether substrates around appropriately-substituted secondary dialkylammonium results[19] (eq 1) in the reversible formation of [2]rotaxanes,[16a] [2]catenanes,[15a] rotaxane bundles[17] and [c2]daisy-chain compounds.[18] Thus, for example, by employing the ruthenium catalyst $(H_2IMes)(PCy_3)(Cl_2)Ru{=}CHPh$ (**5**),[20] the macrocyclic polyether **4** containing two olefinic double bond can be induced to undergo a ring-closing metathesis reaction in the presence of the macrocyclic compound **3**-H·PF_6, wherein the NH_2^+ center acts as the template for the formation of the [2]catenane **6**-H·PF_6. Utilizing this strategy, we decided to explore the ring-closing metathesis (RCM) of polyether substrates around cyclic, polymeric secondary dialkylammonium ions as a method to synthesize the elusive cyclic polycatenane.

(1)

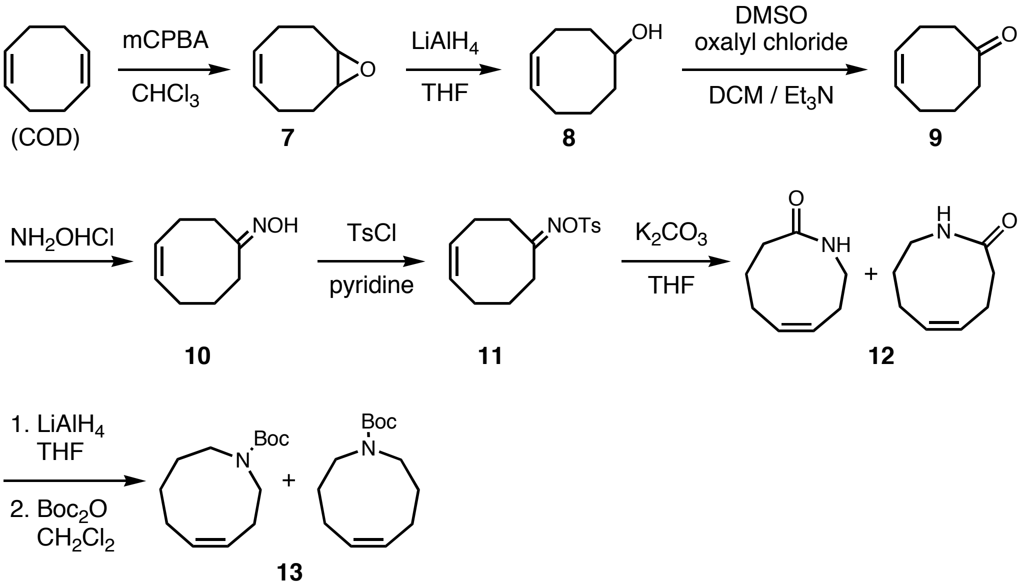


3-H·PF_6 **4** **6**-H·PF_6

(52-75%)

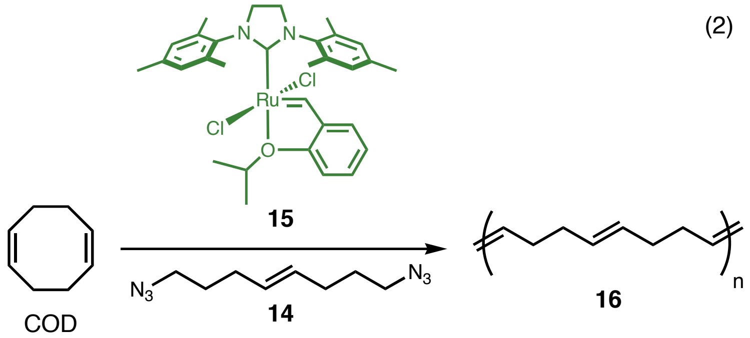
To synthesize the desired cyclic polyammonium ion, we chose a polymer cyclization method based on the copper-catalyzed Huisgen dipolar cycloaddition ("click" reaction) of terminal alkynes and azides to form 1,4-disubstituted 1,2,3-triazoles.[21] This "click" reaction has been used extensively in polymer and materials chemistry due to its high efficiency and operational simplicity, and has more recently been used to synthesize cyclic polystyrene.[22] A challenge in preparing macrocyclic polymers using "click" cyclization is that few polymers can be efficiently synthesized with appropriate end groups. Ring-opening metathesis polymerization (ROMP) in the presence of chain transfer agents (CTA) allows for the preparation of end functionalized (telechelic) polymers with good molecular weight control and relatively narrow polydispersities.[23]

ROMP monomer **13**, was identified as a synthetic target due to the sufficient ring-strain of 9-membered rings[24] and the presence of a protected nitrogen, which, upon further manipulation, could be transformed into a protonated dialkylammonium ion. As outlined in Scheme 1, cyclooctadiene (COD) was monoepoxidated (*m*CPBA/$CHCl_3$) to form **7**. This epoxide was subsequently ring-opened ($LiAlH_4$/THF) to yield alcohol **8**. Standard Swern[25] conditions (DMSO/oxalyl chloride/CH_2Cl_2/Et_3N) oxidized alcohol **8** to ketone **9**. Ketone **9** was then transformed to oxime **10** using $NH_2OH{\cdot}HCl$, and then tosyl-oxime **11** (TsCl/pyridine). A base-catalyzed Beckman rearrangement[26] (K_2CO_3/THF) provided lactam **12,** as a mixture of regioisomers (no attempt was made to separate these regioisomers), which was reduced to the corresponding amine ($LiAlH_4$/THF) and protected with a Boc group (Boc_2O/CH_2Cl_2) to yield ROMP monomer **13**.



Scheme 1: Synthesis of ROMP monomer **13**.

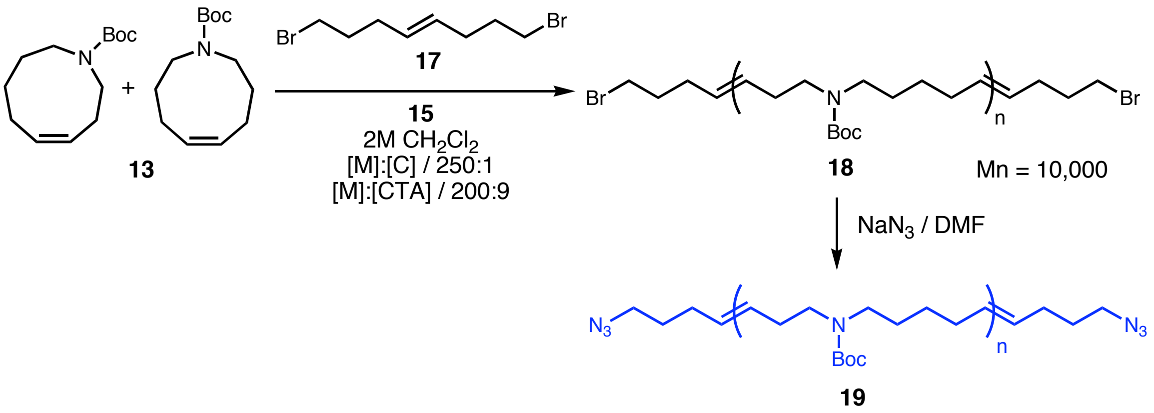
Although CTAs have been utilized in ROMP, no CTAs containing azide functionalities have been previously reported. To test the use of an azide-functionalized CTA in ROMP, COD was polymerized in the presence of azide-terminated CTA **14** (Experimental Information) using metathesis catalyst **15** under standard ROMP conditions (eq 2). Initially green, the reaction color became black after only a few minutes, likely indicating catalyst decomposition. Additionally, the molecular weight of resulting polymer, **16**, was much higher than the theoretical molecular weight (based on the ratio of [monomer]:[CTA]) and contained no CTA incorporation. Based on these observations, it is hypothesized that the azide functionalities caused catalyst decomposition. Due to its large ring-strain energy, the COD monomer polymerized before complete catalyst decomposition; however the chain transfer process, which is much slower, did not take place.



2M CH_2Cl_2
[monomer]:[catalyst] / 250:1
[monomer]:[CTA] / 200:9

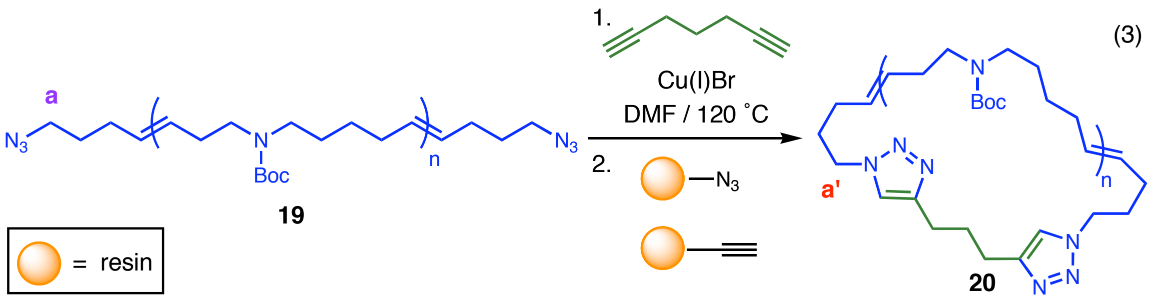
(2)

However, telechelic polymer **19**, containing azide end groups, was prepared from the corresponding dibromide telechelic polymer **18**. ROMP of monomer **13** in the presence of CTA **17** (Experimental Information) and metathesis catalyst **15** yielded polymer **18**. End-group modification of polymer **18** (NaN_3/DMF) afforded the diazide-terminated polymer **19** (Scheme 2).



Scheme 2: Synthesis of azide terminated telechelic polymer **19** via ROMP of monomer **13**.

Cyclization of azide-terminated polymer **19** with 1,6-heptadiyne and CuBr was performed using a syringe pump to simulate ultrahigh dilution conditions. After the click cyclization reaction was complete, alkyne- and azide- terminated scavenging resins were added to remove linear polymer (eq 3).



(3)

*Confirmation of Cyclic Structure of Polymer **20***

^{1}H NMR spectroscopy was used to verify the chemical transformation of the end groups (Figure 4). Resonance observed at 3.25 ppm, corresponding to the azide-adjacent protons (**a**), is clearly observed in the starting polymer **19**. After the cyclization and bead purification, resonances at 3.25 ppm disappear and new resonances at 4.12 ppm corresponding to the triazole-adjacent protons (**a'**) are observed. Further evidence for the formation of triazole was observed in the FTIR spectra by monitoring the disappearance of azide (2090 cm^{-1}) peak (Figure 5). Additionally, MALLS-GPC (multi-angle laser light scattering-gel permeation chromatography) data indicates that no higher molecular weight condensation products, such as dimers or trimers, have formed. As the GPC data (Experimental Information) exclude the possibility of higher oligomer condensation, nearly quantitative formation of the triazole confirms conversion to the cyclic polymer.

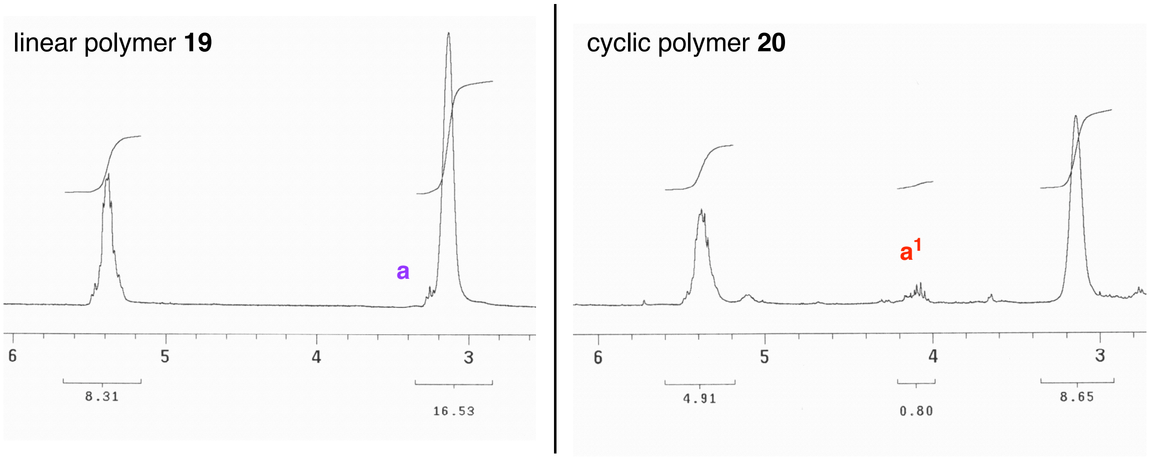


Figure 4: Partial ^{1}H NMR spectra of linear polymer **19** and cyclic polymer **20**. Peak labels are defined in eq. 3.

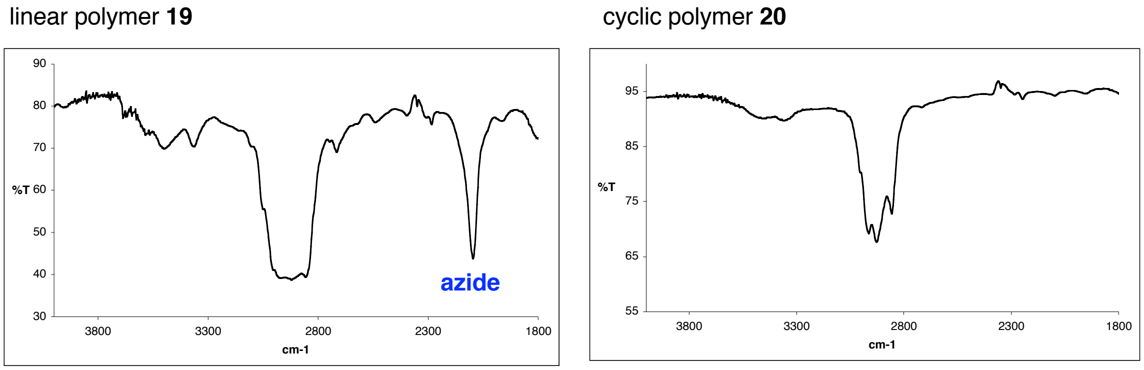


Figure 5: FTIR spectra of linear azide terminated polymer **19** and cyclic polymer **20** after click cyclization.

Additional end-group information was obtained using MALDI-MS (Figure 6). While MALDI-MS can not be used to confirm the molecular weight of the polymer samples, several repeat units were visible and it is possible to obtain the molecular weight of the end group of **20**. The end-group mass (286) may be determined by subtracting the mass of the monomer (225) and the mass of the MALDI_MS matrix (186) from the mass of the lowest visible repeat unit (700). An end-group mass of 286 could correspond to either a cyclized product, or a monoreacted uncyclized product (Figure 6). Due to the absence of appropriate ^{1}H NMR spectroscopy signals and FTIR spectroscopy peaks, it can be concluded that the observed MS peaks correspond to the cyclic polymer **20**.

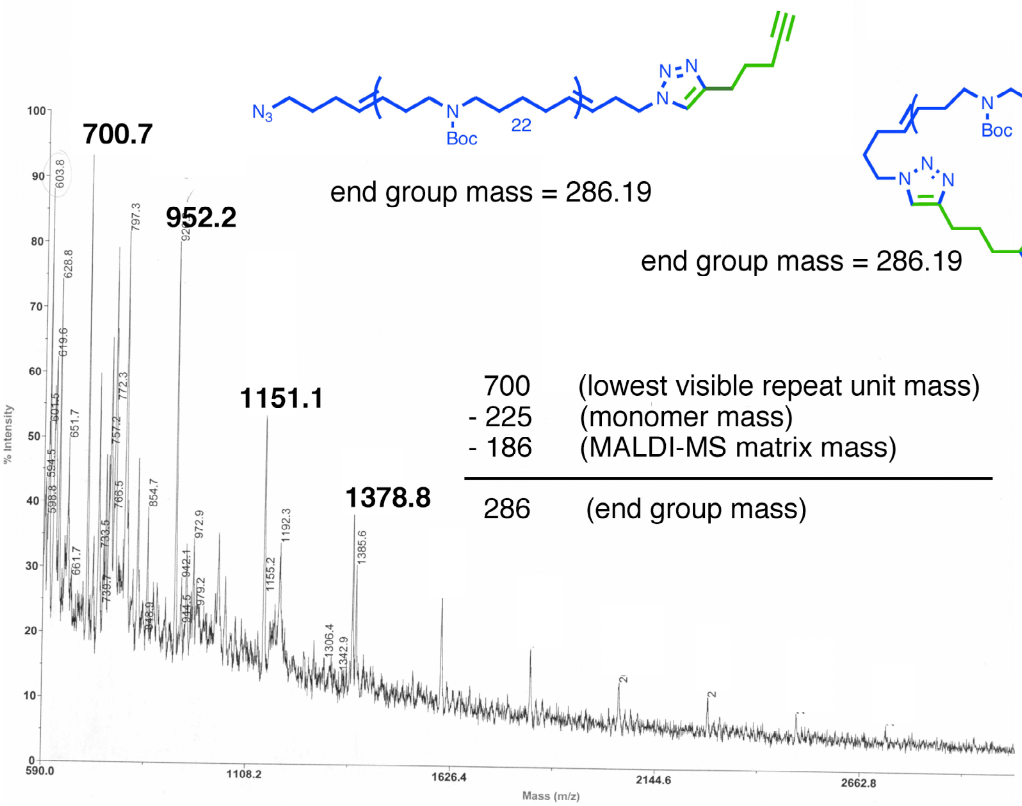


Figure 6: MALDI-MS spectrum of ‘cyclic’ polymer **20** after click cyclization.

Although the experiments described above have shown the absence of any azide end group in the polymer sample, no evidence for the presence or absence of alkyne end groups in the polymer sample has been obtained. Polymer **20** and ^1H NMR spectroscopy labeling agent **21** were reacted under standard click polymer cyclization conditions (CuBr/bipyridine/DMF/120 °C), followed by the addition of alkyne-terminated resin to remove any excess labeling reagent (Figure 7). The ^1H NMR spectrum of cyclic polymer sample **20** after this labeling experiment showed no signals corresponding to labeling agent **21** (Figure 7). A similar experiment using fluorine-containing labeling agent **22** was performed, and no signal corresponding to **22**, was observed in the ^{19}F NMR spectrum. These experiments indicate that there are no alkyne end groups present in cyclic polymer **20**. The end group-analysis experiments indicate that there are neither azide (based on ^1H NMR, FTIR, and MALDI-MS data) nor alkyne (MALDI-MS and labeling experiments) end groups present in polymer sample **20**, supporting the cyclic structure of the polymer.

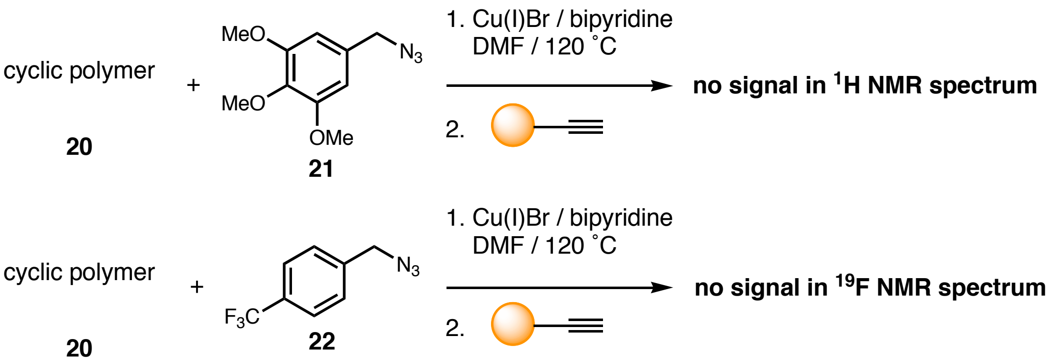
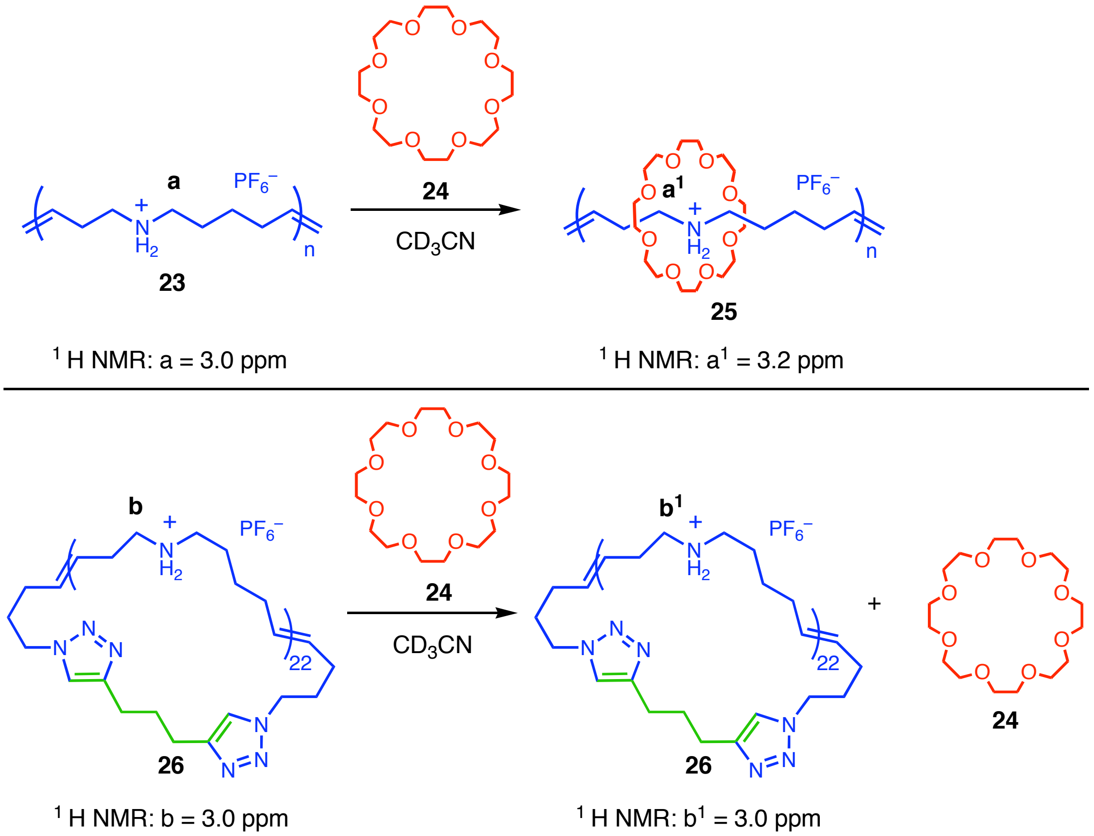


Figure 7: End-group analysis of cyclic polymer sample **20** using labeling experiments.

Perhaps the most informative experiment regarding the structure of polymer **20** exploits the molecular recognition between crown ether macrocycles and appropriately substituted ammonium ions and does not depend on end group identification, but instead relies on the most fundamental difference between linear and cyclic polymers, the presence or absence of chain ends. Linear polyammonium ion **23** (Experimental Information) will thread [24]crown-8 (**24**) nearly quantitatively in CD_3CN after an equilibration period of 24 hours, as confirmed by ^1H NMR spectroscopy. After only a few minutes, resonances are observed in the ^1H-NMR spectrum at $\delta \sim 3.2$ ppm, corresponding to the NH_2^+-adjacent methylene protons (**a'**) in an environment where they are encircled by a crown ether-like macrocycle. Furthermore, resonances at $\delta \sim 3.0$ ppm corresponding to 'free' ammonium sites on the polymer chain (**a**) are observed to diminish in intensity. If [24]crown-8 (**24**) is added to cyclic polyammonium ion **26**, no change in chemical shift is observed in the region between $\delta \sim 3.0$–3.2 ppm, thus unambiguously confirming the 'endless' structure of cyclic sample **20** (Figure 8).



^1H NMR: a = 3.0 ppm

^1H NMR: a^1 = 3.2 ppm

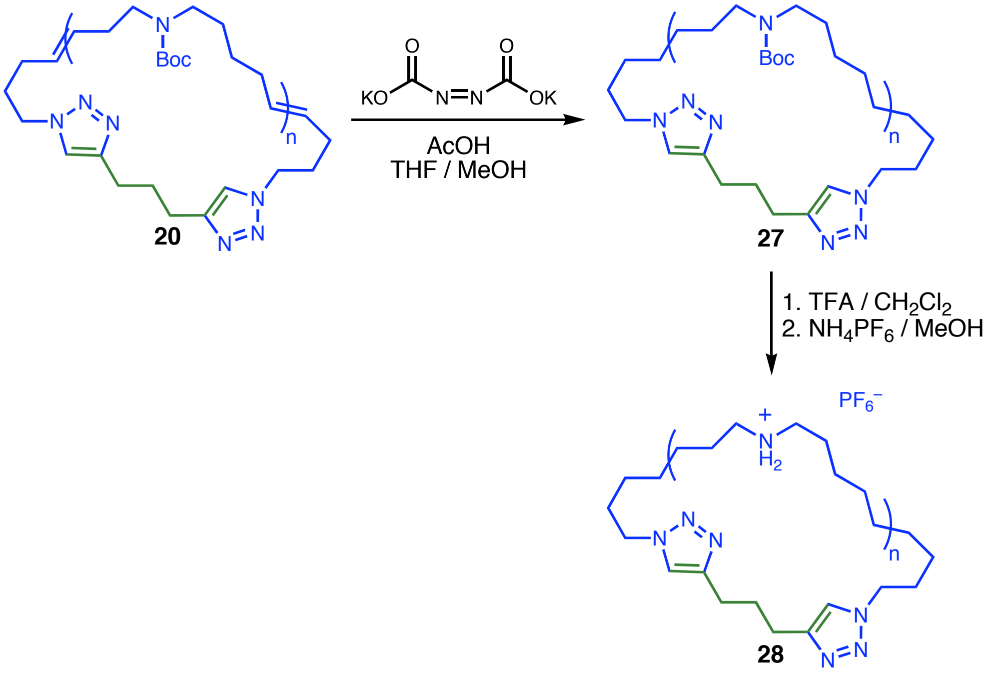
^1H NMR: b = 3.0 ppm

^1H NMR: b^1 = 3.0 ppm

Figure 8: Linear polymer template **23** will thread [24]crown-8 (**24**), forming psuedorotaxane **25**. 'Endless' cyclic polymer template **26** cannot thread [24]crown-8 (**24**) due to its cyclic structure.

Synthesis of Cyclic Polycatenane using RCM

Cyclic polyammonium template **28** was prepared in two steps from cyclic polymer **20** (Scheme 3). First, hydrogenation of **20** using *in situ* generation of diimide ($KO_2CN{=}NCO_2K$/AcOH/THF/MeOH) affords the saturated polymer **27**. Deprotection (TFA/CH_2Cl_2), followed by counterion exchange (NH_4PF_6/MeOH), yielded cyclic polyammonium ion **28**.



Scheme 3: Synthesis of cyclic polymer template **28**.

Ring-closing of the terminal olefin functions in the acyclic polyether **4** in the presence of the cyclic polymer template **28** and metathesis catalyst **5** afforded greater than 95% conversion to the ring-closed polyether. However, no change in chemical shift was observed in the characteristic region ($\delta \sim 3.0$-3.2 ppm) corresponding to the NH_2^+-adjacent methylene protons (**a'**) in an environment where they are encircled by a crown ether-like macrocycle (Figure 9). The polymer template **28** and crown ether **30** have very different solubilities, a property which can be exploited to purify the polymer sample. Repeated precipitation of the reaction mixture (CH_2Cl_2/Et_2O) did not, however, remove the majority of crown ether **30**, as is evident in the ^1H NMR spectrum. Additional purification using size exclusion chromatography (SEC), also failed to remove remaining crown ether **30**. This led us to speculate that crown ether **30** might have an intimate association with the polymer template **28** to form catenation product **29**. MALDI-MS is a useful technique to probe this issue, however using a variety of matrices, the sample proved unsuitable for analysis.

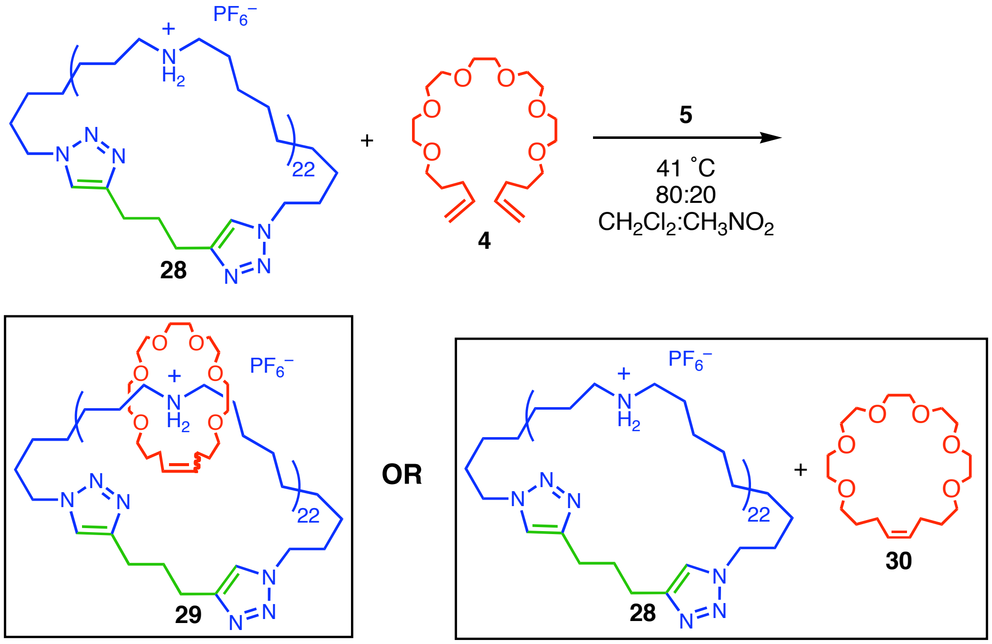


Figure 9: Two possible products of the ring-closing metathesis of diolefin **4** in the presence of cyclic polymer template are presented: (i) the interlocked product, [2]catenane **29** or (ii) a mixture of non-interlocked products crown **30** and cyclic polymer template **28**.

To investigate this hypothesis further, threading experiments between the linear polymer template **23** and crown **30** were performed (Figure 10). Interestingly, upon mixing linear polymer template **23** with the crown ether-like macrocycle **30** in CD_3CN, no change in chemical shift was observed in the characteristic region ($\delta \sim 3.2$ ppm), corresponding to the NH_2^+-adjacent methylene protons (**a'**) encircled by a crown ether-like macrocycle. Two possible explanations for these observations are (i) that crown ether-like macrocycle **30** is threading around polymer template **23** but not causing a detectable change in chemical shift, or (ii) that is there no threading between crown **30** and polymer template **23**.

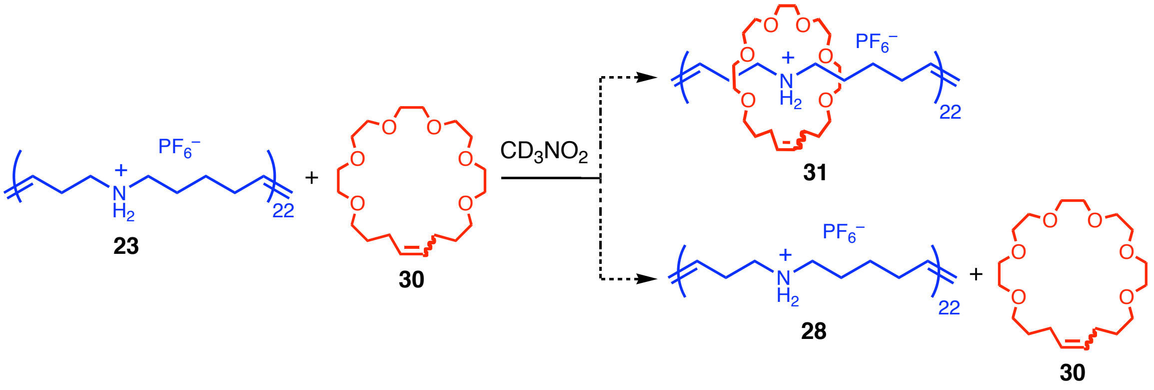


Figure 10: Two possible product mixtures, polypseudorotaxane **31** or a mixture of **23** and **30** may result from the mixing of linear polymer template **23** and crown-like macrocycle **30**.

Two-dimensional diffusion-ordered NMR spectroscopy (2D-DOSY)[27] has been used previously to examine rotaxanated polymers and other host-guest assemblies in which a change in chemical shift upon threading or assembly is not detectable.[28] 2D-DOSY can be used to correlate diffusion coefficients (D) with molecular structure via chemical shifts. Self-diffusion depends on molecular size, with smaller molecules diffusing more quickly than larger molecules. In the case of polyrotaxanes, the threading macrocycles are typically much smaller than the polymeric backbone they encircle, and, therefore, have much faster diffusion raters. However, when the macrocycle is threaded onto the polymeric backbone, the macrocycle self-diffusion is controlled by the polymer self-diffusion.

We first validated the 2D-DOSY method by examining the threading behavior of linear polymer template **23** and [24]crown-8 (**24**). There is an observable change in chemical shift in the ^{1}H NMR spectrum from $\delta \sim 3.0$ to 3.2 ppm corresponding to the NH_2^+-adjacent methylene protons (**a'**) encircled by a crown ether-like macrocycle. Indeed, a distinct change in the self-diffusion coefficient of [24]crown-8 (**24**) is evident in the DOSY spectrum and is similar to the self-diffusion coefficient observed in the polymer sample. A diffusion coefficient (logD) –9.1 m^2s^{-1} (**c**) corresponding to 'free' [24]crown-8 (**24**) is evident in the 2D-DOSY spectrum along with a diffusion coefficient of (logD) –9.9 m^2s^{-1} (**c'**) corresponding to 'threaded' [24]crown-8 (**24**). The threaded crown (**c'**) has a very similar self-diffusion coefficient (**p**) to that of the polymer template **23**, indicating that the diffusion of the threaded crown is governed by that of the polymer template.

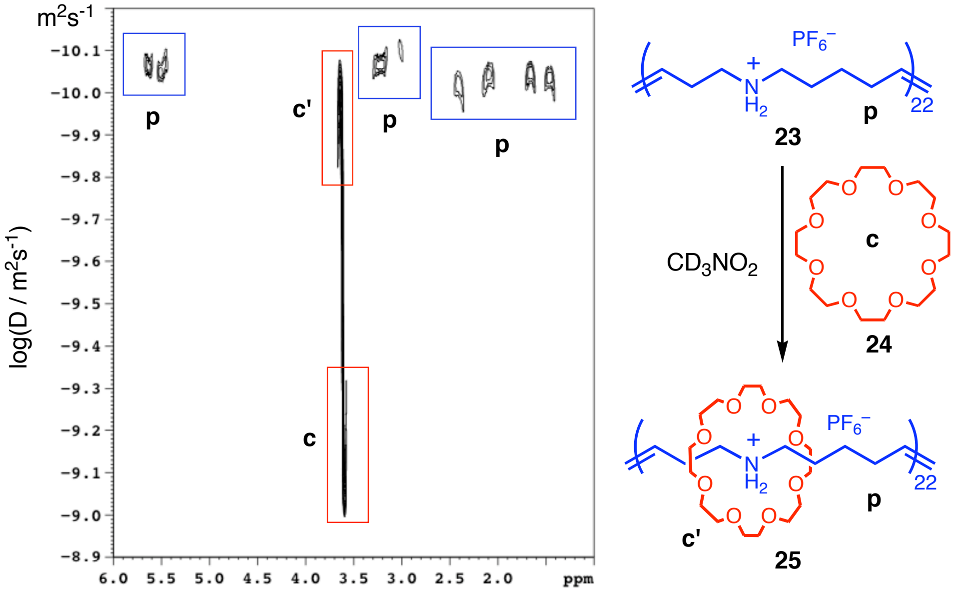


Figure 11: 2D-DOSY spectrum of polypseudorotaxane **25** formed from mixing [24]crown-8 (**24**) and polymer template **23**. A diffusion coefficient (logD) of –9.1 m^2s^{-1} corresponding to unthreaded crown (**c**) is evident along with a diffusion coefficient of –9.9 m^2s^{-1} corresponding to threaded crown (**c'**). Both polymer template **23** and polypseudorotaxane **25** have the same self-diffusion coefficient and are labeled (**p**).

Next, the threading behavior of linear polymer template **23** and crown-like macrocycle **30** was examined. In this sample, no observable change in chemical shift of the NH_2^+-adjacent methylene protons (**a'**) encircled by a crown ether-like macrocycle was observed in the ^1H NMR spectrum ($\delta \sim 3.0$ ppm) upon addition of **30**, thus it was unclear if any polymer threading was occurring. While the spectrum is more complex due to the lower symmetry of crown-like macrocycle **30**, a distinct change in the self-diffusion is evident in the 2D-DOSY spectrum and is similar to the self-diffusion coefficient observed for polymer template **23**. A diffusion coefficient of (logD) –9.1 to –9.5 m^2s^{-1} (**c**) corresponding to 'free' crown-like macrocycle **30** is evident in the 2D-DOSY spectrum, along with diffusion coefficients of (log D) –9.6 to –10.0 m^2s^{-1} (**c'**) corresponding to 'threaded' crown-like macrocycle **30**. The threaded crown (**c'**) has a very similar self-

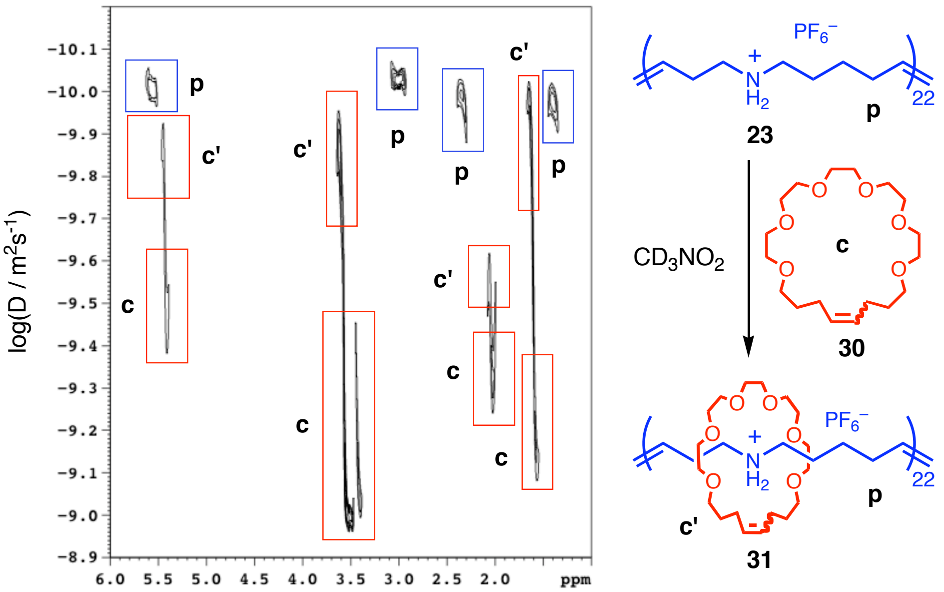


Figure 12: 2D-DOSY spectrum of polypseudorotaxane **31** formed from mixing crown-like macrocycle **30** and polymer template **23**. The diffusion coefficient at –9.2 m^2s^{-1} corresponding to unthreaded crown (**c**) is evident along with diffusion coefficients of –9.5 to –10.0 m^2s^{-1} corresponding to threaded crown (**c'**). Both polymer template **23** and polypseudorotaxane **31** have the same self-diffusion coefficients and are labeled (**p**).

diffusion coefficient (**p**) to that of polymer template **23** indicating that the diffusion coefficient of the threaded crown is governed by that of the polymer template.

Encouraged by the successful application of 2D-DOSY to the threaded system, we attempted to use this technique to investigate the reaction mixture resulting from RCM of **4**, catalyzed by **5**, in the presence of cyclic polymer template **28**. Possible outcomes included formation of cyclic polycatenane **29** or a mixture of non-interlocked crown **30** and polymer **28**. Unfortunately 2D-DOSY experiments did not yield conclusive results. A diffusion coefficient of (logD) –8.6 m^2s^{-1} (**c**) corresponding to a crown-like macrocycle was evident in the 2D-DOSY spectrum along with diffusion coefficients of (logD) –8.6 m^2s^{-1} corresponding to a polyammonium ion. The exact structure, however, could not be determined due to the unusually rapid diffusion exhibited by the polyammonium ion. The diffusion coefficient of the cyclic polyammonium ion in this spectra was much larger (logD = –8.6 m^2s^{-1}) than for linear polyammonium ions **23** or **31** (logD = –10.0 m^2s^{-1}). This result was unexpected, and made precise identification of the polymeric structure using 2D-DOSY impossible.

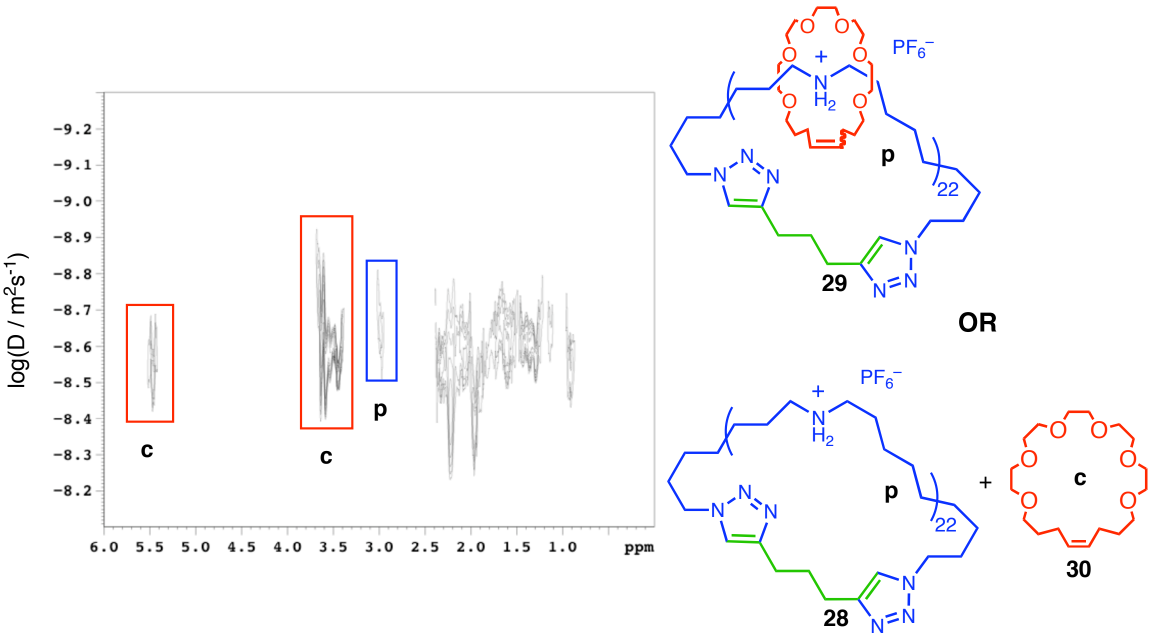


Figure 13: 2D-DOSY spectrum of the reaction mixture resulting from the ring-closing metathesis of the acyclic polyether **4** in the presence of the cyclic polymer template **28** using metathesis catalyst **5**. Possible outcomes include formation of cyclic polycatenane **29** or a mixture of crown **30** and polymer **28.** The diffusion coefficient at –8.6 m^2s^{-1} corresponding to crown (**c**) is evident along with diffusion coefficients of –8.6 m^2s^{-1} corresponding polymer and are labeled (**p**).

Suggested Future Experiments

Identification of the product of the reaction mixture resulting from the RCM of **4** in the presence of the cyclic polymer template **28** using catalyst **5** has proved challenging (Figure 9). Purification using precipitation and SEC was successfully used to remove a portion of crown **30** from the reaction mixture, however, a portion remained after repeated purification (ratio of crown:polymer is 1:6). While the presence of resonances in the ^{1}H NMR spectrum corresponding to a crown ether macrocycle in the reaction mixture after purification was suggestive, it was not possible to confirm the structure of the polymer based on these data alone. Though, ^{1}H NMR and 2D-DOSY spectroscopy have proved inconclusive, other supramolecular techniques could be used to indicate whether the remaining crown is non-interlocked crown **30** or part of interlocked polymer **29**.

The addition of a small molecule ammonium ion, in which a known change in chemical shift occurs upon binding a crown ether macrocycle, might elucidate whether the crown ether macrocycle in the purified reaction mixture is non-interlocked crown **30** or part of an interlocked polymer **29**. One of the most studied supramolecular synthons is the mutual recognition exhibited by the secondary dialkylammonium ion, dibenzylammonium-hexafluorophosphate (**32**) and suitably sized crown ethers.[19] If changes in chemical shift associated with the encirclement of a crown ether type macrocycle around a secondary ammonium ion are observed upon addition of **32** to the reaction mixture, then pseudorotaxane **33** has formed and indicates that non-interlocked crown **30** was present in the sample. If no change in chemical shift is observed in the ^{1}H NMR upon addition of **32** to the reaction mixture, then resonances in the ^{1}H NMR spectrum associated with the crown ether correspond to cyclic polycatenane **29**.

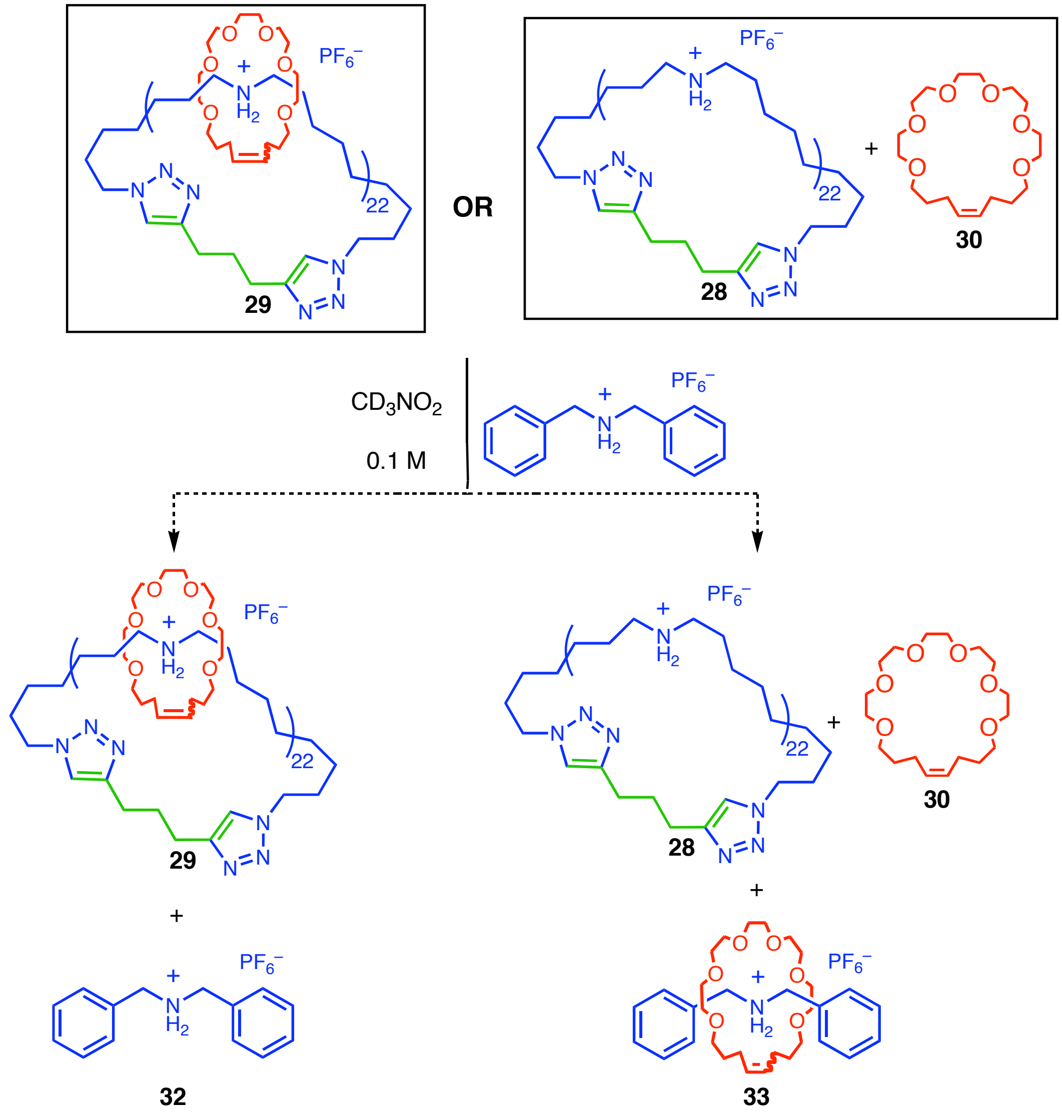


Figure 14: Two possible products can result from the addition of **32** to a purified reaction mixture resulting from the ring-closing metathesis of the terminal olfin functions in the acyclic polyether **4** in the presence of the cyclic polymer template **28** using metathesis catalyst **5**.

Purification Method Using [24]Crown-8

Batch to batch purity issues have been observed for the polymeric product **18** of the chain transfer reaction. Due to the absence of bromide end groups, further functional group modification (NaN_3/DMF) and polymer cyclization (using the "click" reaction) have no effect on the polymeric impurity. More importantly, the resin scavenging technique used to remove linear azide- and alkyne-terminated polymer after the “click” cyclization reaction would also be ineffective due to the lack of reactive end groups on the polymer impurity. We thought a potential solution to this problem was to exploit the differential solubility between unthreaded polyammonium ions, such as **23**, which are insoluble in CH_2Cl_2 and complexed, polypseudorotaxanes, such as **25**, which are soluble in CH_2Cl_2. As examined previously, linear polymer template **23** forms a polypseudorotaxane with [24]crown-8 (**24**), with nearly quantitative threading after an equilibration period of 24 hours. Due to its lack of chain ends, cyclic polymer template **26** does not form a complex when mixed with **24**. The impure polyammonium ion (mixture of cyclic and linear polyammonium ion) and **24** were dissolved in CH_3CN and left standing for 24 hours. CH_3CN was removed by vacuum and the resulting solid was washed with copious amounts of CH_2Cl_2 and Et_2O. The isolated solid was a mixture of cyclic polyammonium ion **26** and **24**. Further washing of the solid removed the remaining [24]crown-8 (**24**), and the remaining solid was pure cyclic polyammonium ion free from any linear polyammonium ion, as determined by ^1H NMR spectroscopy.

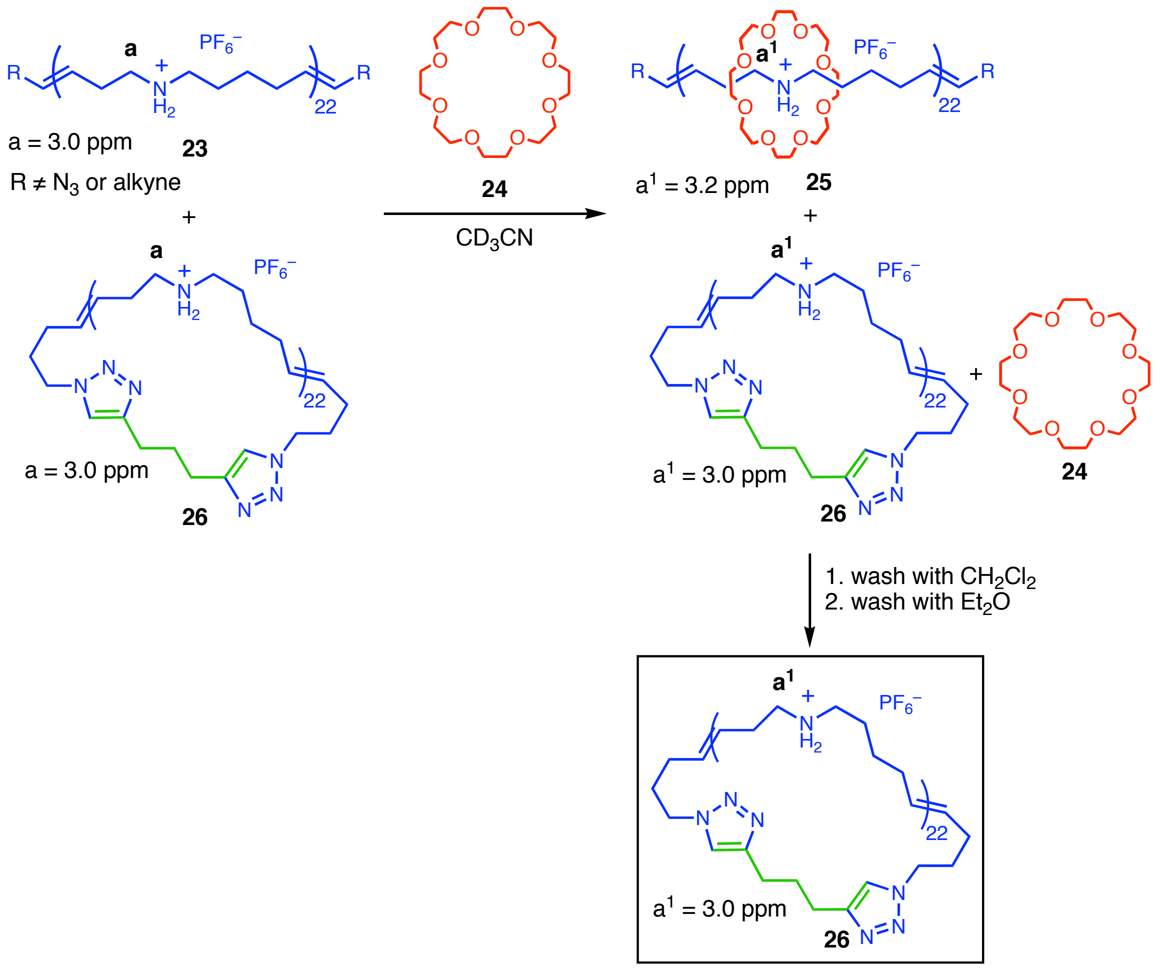


Figure 15: Purification method to remove linear polymer impurities from cyclic polymer samples by exploiting the threading between [24]crown-8 (**24**) and linear polyammonium ions **24**. Polypseudorotaxane **25** has improved solubility in CH_2Cl_2 compared to its unthreaded, cyclic analogue **26**. Washing with CH_2Cl_2 can therefore be used to remove linear polymer.

Conclusions

A method for the production of cyclic polyammonium ions is presented which utilizes a polymer cyclization of azide terminated linear polymer based on the “click” reaction of terminal alkynes and azides to form 1,4-disubstituted 1,2,3-triazoles. An azide terminated polymer was prepared using ROMP in the presence of chain transfer agents (CTA). Formation of cyclic polycateanes was explored utilizing the mutual recognition between secondary ammonium ions and crown ether macrocyles. The product of the RCM of linear crown ether dienes around cyclic polyammonium ions was investigated using 2D-DOSY, however the results were inconclusive. Additional experiments are suggested to determine the product of this metathesis reaction.

References

(1) Mitsutoshi, J.; Masa-aki, K. *Prog. Polym. Sci.* **200**1, *26*, 1233-1285. (b) Gao, C.; Yan, D. *Prog. Polym. Sci.* **2004**, *29*, 183-275.

(2) In *Block Copolymers I*; Abetz, V., Ed.; Adv. Polym. Sci. 189; Springer GmBH: Berlin, 2005; 1-238. (b) In *Block Copolymers II*; Abetz, V., Ed.; Adv. Polym. Sci. 190; Springer GmBH: Berlin, 2005; 1-252.

(3) In *Special Issue: Dendrimers and Dendritic Polymers*; Tomalia, D. A.; Frechet, J. M., Eds.; Prog. Polym. Sci. 30; Elsevier: Amsterdam, 2005; 1-288.

(4) Semlyen, J. A. *Cyclic Polymers*, 2nd ed.; Kluwer Academic: Dordrecht, The Netherlands, 2000.

(5) (a) Gibson, H. W.; Bheda, M. C.; Engen, P. T. *Prog. Polym. Sci.* **1994**, *19*, 843-945. (b) Amabilino, D. B.; Stoddart, J. F. *Chem. Rev.* **1995**, *95*, 2725-2828. (c) Raymo, F. M.; Stoddart, J. F. *Chem. Rev.* **1999**, *99*, 1643-1663. (d) Toshikazu, T.; Nobuhiro, K.; Yoshio, F. *Adv. Polym. Sci.* **2004**, *171*, 1-75.

(6) (a) Hirotsu, K.; Higuchi, T.; Fujita, K.; Ueda, T.; Shinoda, A.; Imoto, T.; Tabushi, I. *J. Org. Chem.* **1982**, *47*, 1143-1144. (b) Mentzafos, D.; Terzis, A.; Coleman, A. W.; de Rango, C. *Carbohydr. Res.* **1996**, *282*, 125-135. (c) Yamaguchi, N.; Nagvekar, D. S.; Gibson, H. W. *Angew. Chem., Int. Ed.* **1998**, *37*, *2361-2364.* (d) Rowan, S. J.; Cantrill, S. J.; Stoddart, J. F.; White, A. J. P.; Williams, D. J. *Org. Lett.* **2000**, *2*, 759–762. (e) Liu, Y.; You, C.-C.; Zhang, M.; Weng, L.-H.; Wada, T.; Inoue, Y. *Org. Lett.* **2000**, *2*, 2761-2763. (f) Stoddart, J. F.; Rowan, S. J.; Chiu, S.-H.; Cantrill, S. J.; Ridvan, L.; Sivakova, S. *Polym. Mater. Sci. Eng.* **2001**, *84*, 148-149. (g) Harada, A. *J. Polym. Sci., Part A: Polym. Chem.* **2005**, 5113-5119.

(7) (a) Amabilino, D. B.; Ashton, P. R.; Perez-Garcia, L.; Stoddart, J. F. *Angew. Chem. Int. Ed., Engl.* **1995**, *34*, 2378-2380. (b) Cardenas, D. J.; Sauvage, J.-P. *Inorg. Chem.* **1997**, *36*, 2777-2738. (c) Hamilton, D. G.; Feeder, N.; Prodi, L.; Teat, S. J.; Clegg, W.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1998**, *120*, 1096-1097. (d) Dietrich-Buchecker, C.; Benoit, C.; Makoto, F.; Akiko, H.; Neri, G.; Shigeru, S.; Kentaro, Y.; Sauvage, J.-P. *J. Am. Chem. Soc.* **2003**, *125*, 5717-5725. (e) Hamann, C.; Kern, J. M.; Sauvage, J.-P. *Inorg. Chem.* **2003**, *42*, 1877-1883. (f) Fuller, A.-M. L.; Leigh, D. A.; Lusby, P. J.; Slawin, A. M.; Walker, D. B. *J. Am. Chem. Soc.* **2005**, *127*, 12612-12619. (g) Ng, K.-Y.; Cowley, A. R.; Beer, P. D. *Chem. Commun.* **2006**, 3676-3678. (h) Miljanic, O. S.; Dichtel, W. R.; Mortezaei, S.; Stoddart, J. F. *Org. Let.* **2006**, *8*, 4835-4838. (i) Bauerle, P.; Ammann, M.; Wilde, M.; Gotz, G.; Mena-Osteritz, E.; Rang, A.; Schalley, C. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 363-368.

(8) see References 11, 12, 13, 14, 15, 16, 17, 18.

(9) (a) Dietrich-Buchecker, C. O.; Sauvage, J.-P.; Kern, J. M. *J. Am. Chem. Soc.* **1984**, *106*, 3043–3045. (b) Hunter, C. A. *J. Am. Chem. Soc.* **1992**, *114*, 5303–5311. (c) Vögtle, F.; Jager, R.; Handel, M.; Ottens-Hildebrandt, S. *Pure Appl. Chem.* **1996**, *68*, 225–232. (d) Gong, C. G.; Gibson, H. W. *Angew. Chem., Int. Ed.* **1998**, *37*, 310–314. (e) Kolchinski, A. G.; Busch, D. H.; Alcock, N. W. *J. Chem. Soc., Chem. Commun.* **1995**, 1289–1291. (f) Hansen, J. G.; Feeder, N.; Hamilton, D. G.; Gunter, M. J.; Becher, J.; Sanders, J. K. M. *Org. Lett.* **2000**, *2*, 449–452. (g) Shukla, R.; Deetz, M. J.; Smith, B. D. *Chem. Commun.* **2000**, 2397–2398. (h) Hubbard, A. L.; Davidson, G .J. E.; Patel, R. H.; Wisner, J. A.; Loeb, S. J. *Chem. Commun.* **2004**, *2*, 138–139. (i) Sasabe, H.; Kihara, N.;

Furusho, Y.; Mizuno, K.; Ogawa, A.; Takata, T. *Org. Lett.* **2004**, *6*, 3957–3960. (j) Hernandez, J. V.; Kay, E. R.; Leigh, D. A. *Science* **2004**, *306*, 1532–1537.

(10) (a) Rowan, S. J.; Brady, P. A.; Sanders, J. K. M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2143–2145. (b) Lehn, J.-M. *Chem. Eur. J.* **1999**, *5*, 2455–2463. (c) Lehn, J.-M.; Eliseev, A. V. *Science* **2001**, *291*, 2331–2332. (d) Otto, S.; Furlan, R. L. E.; Sanders, J. K. M. *Science* **2002**, *297*, 590–593. (e) Rowan, S. J.; Cantrill, S. J.; Cousins, G. R. L.; Sanders, J. K. M.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **2002**, *41*, 898–952. (f) Corbett, P. T.; Otto, S.; Sanders, J. K. M. *Org. Lett.* **2004**, *6*, 1852–1827.

(11) (a) Cantrill, S. J.; Rowan, S. J.; Stoddart, J. F. *Org. Lett.* **1999**, *1*, 1363–1366. (b) Rowan, S. J.; Stoddart, J. F. *Org. Lett.* **1999**, *1*, 1913–1916. (c) Glink, P. T.; Oliva, A. I.; Stoddart, J. F.; White, A. J. P.; Williams, D. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 1870–1875. (d) Horn, M.; Ihringer, J.; Glink, P. T.; Stoddart, J. F. *Chem. Eur. J.* **2003**, *9*, 4046–4054. (e) Chichak, K. S.; Cantill, S. J.; Pease, A. R.; Chiu, S.-H.; Cave, G. W. V.; Atwood, J. L.; Stoddart, J. F. *Science* **2004**, *304*, 1308–1312. (f) Hogg, L.; Leigh, D. A.; Lusby, P .J.; Morelli, A.; Parsons, S.; Wong, J. K. Y. *Angew. Chem., Int. Ed.* **2004**, *43*, 1218–1221. (g) Schalley, C. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 4399–4401. (h) Cantrill, S. J.; Chichak, K. S.; Peters, A. J.; Stoddart, J. F. *Acc. Chem. Res.* **2005**, *38*, 1–9.

(12) (a) Kolchinski, A. G.; Alcock, N. W.; Roesner, R. A.; Busch, D. H. *Chem. Commun.* **1998**, 1437–1438. (b) Furusho, Y.; Oku, T.; Hasegawa, T.; Tsuboi, A.; Kihara, N.; Takata, T. *Chem. Eur. J.* **2003**, *9*, 2895–2903.

(13) Fuchs, B.; Nelson, A.; Star, A.; Stoddart, J. F.; Vidal, S. B. *Angew. Chem., Int. Ed.* **2003**, *42*, 4220–4224.

(14) Trnka, T. M; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18–29.

(15) (a) Kidd, T. J.; Leigh, D. A.; Wilson, A. J. *J. Am. Chem. Soc.* **1999**, *121*, 1599–1600. (b) Weck, M.; Mohr, B.; Sauvage, J.-P. Grubbs, R. H. *J. Org. Chem.* **1999**, *64*, 5463–5471. (c) Arico, F.; Mobian, P.; Kern, J. M.; Sauvage, J.-P. *Org. Lett.* **2003**, *5*, 1887–1890. (d) Iwamoto, H.; Itoh, K.; Nagamiya, H.; Fukazawa, Y. *Tetrahedron Lett.* **2003**, *44*, 5773–5776. (e) Wang, L. Y.; Vysotsky, M. O.; Bogdan, A.; Bolte, M. Böhmer, V. *Science* **2004**, *304*, 1312–1314. (f) Guidry, E. N.; Cantrill, S. J.; Stoddart, J. F.; Grubbs, R. H. *Org. Lett.* **2005**, *7*, 2129–2132.

(16) (a) Wisner, J. A.; Beer, P. D.; Drew, M. G. B.; Sambrook, M. R. *J. Am. Chem. Soc.* **2002**, *124*, 12469–12476. (b) Hannam, J. S.; Kidd, T. J.; Leigh, D. A.; Wilson, A. J. *Org. Lett.* **2003**, *5*, 1907–1910, (c) Coumans, R. G. E.; Elemans, J. A. A. W.; Thordarson, P.; Nolte, R. J. M.; Rowan, A. E. *Angew. Chem., Int. Ed.* **2003**, *42*, 650–654. (d) Kilbinger, A. F. M.; Cantrill, S. J.; Waltman, A. W.; Day, M. W.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 3281–3285.

(17) Badjic, J. D.; Cantrill, S. J.; Grubbs, R. H.; Guidry, E. N.; Orenes, R.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **2004**, *43*, 3273–3278.

(18) Guidry, E. N.; Li, J.; Stoddart, J. F.; Grubbs, R. H. *J. Am. Chem. Soc.* **2007**, *X*, XXX-XXXX.

(19) (a) Glink, P. T.; Schiavo, C.; Stoddart, J. F.; Williams, D. J. *Chem. Commun.* **1996**, 1483–1490. (b) Cantrill, S. J.; Pease, A. R.; Stoddart, J. F. *J. Chem. Soc., Dalton Trans.* **2000**, 3715–3734. (c) Clifford, T.; Abushamleh, A.; Busch, D. H. *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 4830–4836.

(20) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956.

(21) Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984.

(22) Laurent, B. A.; Grayson, S. M. *J. Am. Chem. Soc.* **2006**, *128*, 4238-4239.

(23) (a) Maughon, B. R.; Morita, T.; Bielawski, C. W.; Grubbs, R. H. *Macromolecules* **2000**, *33*, 1929-1935. (b) Morita, T.; Maughon, B. R.; Bielawski, C. W.; Grubbs, R. H. *Macromolecules* **2000**, *33*, 6621-6623. (c) Bielawski, C. W.; Benitez, D.; Morita, T.; Grubbs, R. H. *Macromolecules* **2001**, *24*, 8610-8618. (d) for a general discussion of chain transfer agents see Chapter 1.

(24) Hejl, A.; Scherman, O. A.; Grubbs, R. H. *Macromolecules* **2005**, *38*, 7214-7218.

(25) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.

(26) Gawley, R. E. *Org. React.*, **1988**, *35*, 1.

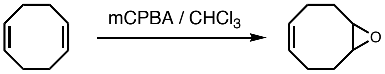
(27) (a) Morris, K. F.; Johnson Jr., C. S. *J. Am. Chem. Soc.* **1993**, *115*, 4291. (b) Schulze, D.; Stilbs, P. *J. Magn. Reson. A* **1993**, *105*, 54. (c) Persson, K.; Griffiths, P. C.; Stilbs, P. *Polymer* **1996**, *37*, 253. (d) Jerschow, A.; Muller, N. *Macromolecules* **1998**, *31*, 6573. (e) Hakansson, B.; Nyden, M.; Soderman, O. *Collid Polym. Sci.* **2000**, *278*, 399.

(28) Zhao, T.; Beckham, H. W.; Gibson, H. W. *Macromolecules* **2003**, *36*, 4833-4837.

Experimental Information

General Information: NMR spectra were recorded on an Oxford 300 MHz or 500 MHz NMR spectrometer running Varian VNMR software. Chemical shifts are reported in parts per million (ppm) with reference to internal solvent. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), multiplet (m), and broad (br). DOSY spectra were recorded on a Bruker spectrometer. High-resolution mass spectra (EI, MALDI and FAB) were provided by California Institute of Technology Mass Spectrometry Facility. Molecular mass calculations were performed with ChemDraw Ultra 9 (Cambridge Scientific). Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F254 precoated plates (0.25 mm thickness) with a fluorescent indicator. Visualization was performed using fluorescence quenching or citric ammonium molybdate (CAM), anisaldehyde, potassium permanganate ($KMnO_4$) or iodine stain. Flash column chromatography was performed using silica gel 60 (230-400 mesh) from EM Science. Grubbs metathesis catalysts **5** and **15** were obtained from Materia. All other chemicals were purchased from Aldrich or Acros Chemical Companies and used as obtained unless noted otherwise. Tetrahydrofuran and dichloromethane were purified and dried by passage through a solvent column.[i] Anhydrous dimethyl formamide was purchased in across seal bottles from Acros and used as received. Gel permeation chromatography (GPC) was determined on an HPLC type system, using a Shimadzu LC-10AD pump, a rheodyne model 7125 injector with a 100 uL loop, PLgel 5 um 10E3A size exclusion column and PLgel 5 um guard column (purchased from polymer laboratories) connected in series with a Alltech on-line degassing system, a Wyatt Technology optilab DSP differential refractometer and a Wyatt Technology Dawn EOS multi angle laser light scattering (MALLS) detector. Astra V was used to analyze the raw MALLS and RI data. The elutent (DMF with 0.1M NH_4PF_6) was prepared using HPLC grade DMF (purchased from Fischer Scientific) and LiBr (purchased from Aldrich), which was filtered through a 0.45 micron filter before use. The flow rate was set to 0.5 mL/min. Instrument normalization and calibration was performed using a 30K Polystyrene standard with a PDI = 1.06 (purchased from Pressure Chemical Company). No calibration standards were used in determination of molecular weights or polydispersities. The *dn/dc* values were obtained for each injection assuming 100% mass elution from the columns. These values were verified by measuring *dn/dc* independently using a Wyatt optilab differential refractometer.

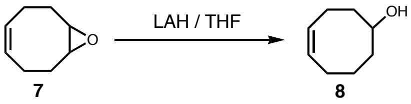
Experimental Section:



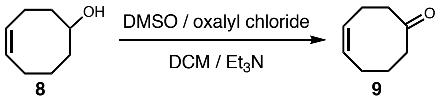
7

7: 3-chloroperbenzoic acid, 77% (124.5 g, 556 mmoles) was dissolved in chloroform (1 L, 0.5 M) and added slowly (2 h) using an addition funnel to neat 1,5-cyclooctadiene (44.1 g, 50 mL, 407 mmoles) with stirring. The mixture was stirred at room temperature for 12 h. The mixture was filtered to remove 3-chloroperbenzoic acid. The organic phase was washed with aqueous sodium bisulfite, followed by washing with aqueous sodium bicarbonate, followed by washing with brine. The chloroform was dried ($MgSO_4$), filtered and concentrated using vacuum. The crude oil was purified by column chromotography (SiO_2: hexanes/ethyl acetate 10:1) to yield **7** as a colorless oil (23.2 g, 46

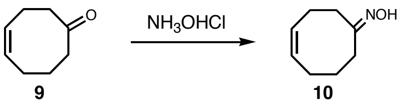
% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.56-5.53 (m, 2H), 3.04-2.98 (m, 2H), 2.46-2.36 (m, 2H), 2.166-1.95 (br m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 128.98, 56.86, 28.25, 23.82. (Hillmyer, M. A.; Laredo, W. R.; Grubbs, R. H. *Macromolecules*, **1995**, *28*, 6311-6316.)



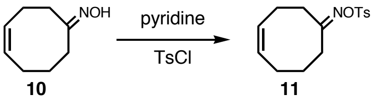
8: Lithium aluminum hydride (21.2 g, 559 mmoles) was added as a solid to a flame-dried flask. Epoxide **7** (23.2 g, 187 mmoles) was added as a solution in dry THF (187 mL, 1 M). The solution was stirred at room temperature, under an argon atmosphere for 12 h. The solution was cooled to 0 °C and Et_2O (200 mL) was added. To quench the reaction, water was added very slowly (21.2 mL), followed by the addition of 15% NaOH (21.2 mL), followed by the addition of H_2O (63.6 mL). The mixture was warmed to room temperature and stirred for 15 min. Celite was added and the mixture was stirred for 15 min. The mixture was filtered and the solid was washed with Et_2O. The organic layers were combined and concentrated using vacuum. The crude oil was purified by column chromotography (SiO_2: hexanes/ethyl acetate 1:1) to yield **8** as a colorless oil (23.1 g, 98 % yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.72-5.52 (br m, 2H), 3.82-3.75 (m, 1H), 2.33-2.21 (m, 1H), 2.16-2.03 (m, 3H), 1.95-1.77 (m, 2H), 1.73-1.42 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.05, 130.35, 129.78, 72.97, 37.94, 36.49, 25.85, 25.07, 22.96. HRMS-EI (m/z): [M + e] calcd for $C_8H_{14}O$, 126.1045; found, 126.1047.



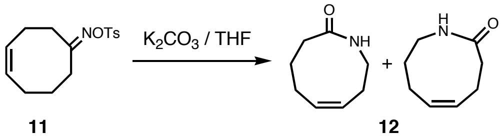
9: Dimethylsulfoxide (24.8 g, 22.5 mL, 317 mmoles) was added as a solution in dry CH_2Cl_2 (350 mL, 0.2 M) to a flame-dried flask. The solution was cooled to -78 °C. Oxalyl chloride (20.1 g, 14.1 mL, 159 mmoles) was added dropwise. The solution was stirred for 20 min. Alcohol **8** (10 g, 79.3 mmoles) was added as a solution in dry CH_2Cl_2 (45 mL). The solution was stirred for 30 min. Triethylamine (80.2 g, 110 mL, 793 mmoles) was added and the solution was stirred for 5 min. The solution was warmed to 0 °C and stirred for 30 min. The solution was warmed to room temperature and stirred for 30 min. The reaction was concentrated under vacuum and purified by column chromotography (SiO_2: hexanes/ethyl acetate 10:1) to yield **9** as a colorless oil (9.15 g, 93 % yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.74-5.60 (m, 2H), 2.49-2.37 (m, 6H), 2.17-2.11 (m, 2H), 1.60-1.52 (m, 2H) . ^{13}C NMR (75 MHz, $CDCl_3$): δ 214.97, 130.95, 130.42, 47.44, 40.53, 26.50, 24.11, 22.01. HRMS-EI (m/z): [M + e] calcd for $C_8H_{14}O$, 126.1045; found, 126.1042.



10: Hydroxylamine hydrochloride (10.3 g, 147 mmoles) and sodium bicarbonate (9.3 g, 110 mmoles) were suspended in methanol (200 mL, 0.3 M). Ketone **9** (9.15 g, 73.7 mmoles) was added as a solution in methanol (45 mL). The mixture was heated to reflux and stirred for 4 h. The mixture was cooled to room temperature and poured into water. The aqueous layer was washed with H_2O (3X). The combined organic washings were dried ($MgSO_4$) and concentrated under vacuum. The crude oil was purified by column chromotography (SiO_2: hexanes/ethyl acetate 3:1) to yield **10** as a yellow oil, which slowly solidifies upon standing (10.0 g, 98 % yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.70-5.59 (br m, 2H), 2.42 (t, J = 6.0 Hz, 2H), 2.31-2.25 (m, 4H), 2.10 (q, J = 7.5 Hz, 2H), 1.74-1.66 (br m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.62, 131.27, 130.54, 130.22, 129.83, 136.23, 32.17, 29.07, 28.26, 27.83, 26.42, 25.79, 23.94, 22.73. HRMS-FAB (m/z): [M + e] calcd for $C_8H_{13}NO$, 139.0997; found, 139.0996.

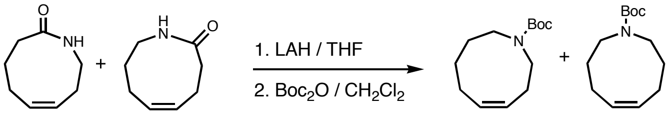


11: Oxime **10** (10.0 g, 71.8 mmoles) was added as a solution in CH_2Cl_2 (650 mL, 0.1 M) to a flask. Pyridine (14.2 g, 14.5 mL, 180 mmoles) was added and the solution was cooled to 0 °C. Tosyl chloride (13.7 g, 79.0 mmoles) was added as a solution in CH_2Cl_2 (70 mL) using an addition funnel over 1 h. The reaction was warmed to room temperature and stirred for 16 h. The organic phase was extracted with 10% aqueous HCl (2X) and extracted with brine. The organic phase was dried ($MgSO_4$) and concentrated using vacuum. The crude product was purified by crystallization from chloroform and pentane to yield **11** as white crystals (10.3 g, 49 % yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ . ^{13}C NMR (75 MHz, $CDCl_3$): δ 182.07, 181.17, 141.33, 140.61, 135.05, 131.72, 129.20, 128.48, 126.01, 124.91, 44.04, 42.06, 32.23, 29.64, 28.90, 27.82, 27.15, 26.90, 25.40, 24.38, 21.53.



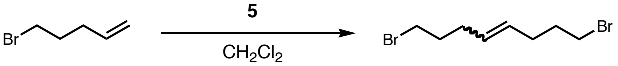
11 **12**

12: Tosyl-oxime **11** (10.3, 35.1 mmoles) was added as a solution in THF (350 mL, 0.1 M) to a flask. Potassium carbonate (3.9 g, 28.1 mmoles) was added to the toxyl-oxime as a solution in water (280 mL, 0.1 M). The mixture was stirred vigorously at room temperature for 12 h. The mixture was diluted with H_2O and washed with CH_2Cl_2 3 times. The combined organic layers were washed with aqueous sodium bicarbonate. The organic phase was dried ($MgSO_4$), filtered, and concentrated using vacuum. The products were purified by crystallization from CH_2Cl_2 and pentane to yield **12** as white crystals (4.7 g, 96% yield). The reaction yields two different lactams **12a** and **12b**. These two lactams were used in subsequent reactions. No attempt was made to separate these two compounds.



12 **13**

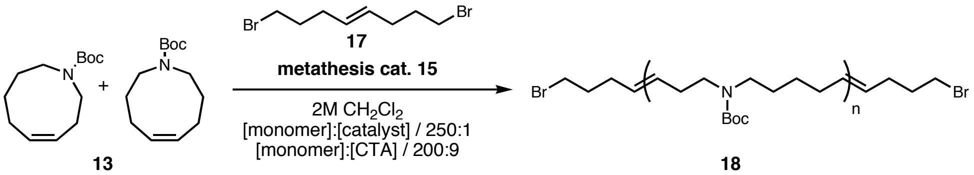
13: Lithium aluminum hydride (3.2 g, 84.5 mmoles) was added as a solid to a flame-dried flask. Lactam **12** (4.7 g, 33.8 mmoles) were added as a solution in dry THF (339 mL, 0.1 M). The solution was stirred at room temperature, under an argon atmosphere for 12 h. The solution was cooled to 0 °C and Et_2O (100 mL) was added. To quench the reaction, water was added very slowly (4.7 mL), followed by the addition of 15% NaOH (4.7 mL), followed by the addition of H_2O (14.1 mL). The mixture was warmed to room temperature and stirred for 15 min. Celite was added and the mixture was stirred for 15 min. The mixture was filtered and the solid was washed with Et_2O. The organic portions were combined and di-*tert*-butyl dicarbonate (22.1 g, 23.3 mL, 253 mmoles), triethylamine (6.8 g, 9.4 ml, 169 mmoles) and 4-di(methylamino)pyridine (0.2 g, 4.3 mmoles) were added to the solution. The solution was stirred at room temperature for 12 h. The reaction was concentrated under vacuum and purified by column chromotography (SiO_2: hexanes/ethyl acetate 15:1) to yield **13** as a colorless oil (7.3 g, 94 % yield). These two compounds (**13a** and **13b**) were used in subsequent reactions. No attempt was made to separate these two compounds. ^1H NMR (300 MHz, $CDCl_3$): *δ* 5.96-5.87 (m, 1H), 5.65-5.55 (m 1H), 3.50 (t, J = 6 Hz, 1H), 3.44 (t, J = 5.7 Hz, 1H), 3.29-3.22 (m, 2H), 2.49-2.39 (m, 2H), 2.31-2.24 (m, 2H), 1.73-1.67 (m, 4H), 1.61 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 132.19, 131.56, 129.35, 128.77, 79.43, 79.33, 48.58, 48.42, 48.04, 47.98, 28.81, 28.75, 27.08, 26.91, 26.84, 25.80, 25.67, 25.53, 24.42, 23.68. HRMS-EI (m/z): [M + e] calcd for $C_{13}H_{23}NO_2$, 225.1729; found, 225.1740.



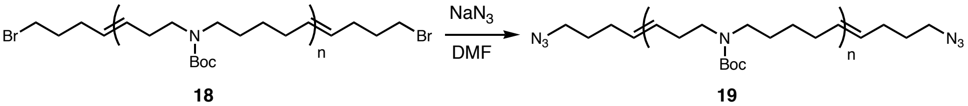
17

17: Metathesis catalyst **5** (0.6 g, 0.7 mmoles) was added as a solid to a flame-dried flask fitted with a condenser. The flask was degassed by bubbling argon gas through the flask for 30 min. Dry, degassed CH_2Cl_2 (67 mL, 0.2 M) was added to **5**. 5-bromo-1-pentene (2.0 g, 13.4 mmoles) was added to the solution of **5**. The solution was heated to 41 °C with stirring for 12 h. The reaction was quenched by the addition of ethyl vinyl ether (0.5 g, 0.7 mL, 7 mmoles). Heating was maintained for 30 min. The reaction was concentrated under vacuum and purified by column chromotography (SiO_2: hexanes) to yield **8** as a colorless oil (1.8 g, 99 % yield). ^1H NMR (300 MHz, $CDCl_3$): *δ* 5.43-5.36 (m, 2H), 3.38 (t, *J* = 9, 4H), 2.13 (m, 4H), 1.89 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ

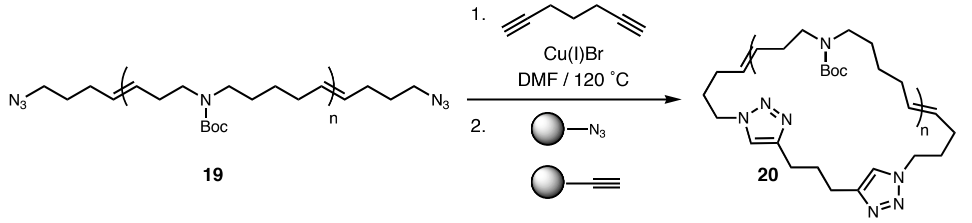
129.98, 33.49, 32.45, 31.03, 29.93. HRMS-EI (m/z): [M + e] calcd for $C_8H_{14}Br$, 269.9442; found, 269.9448.



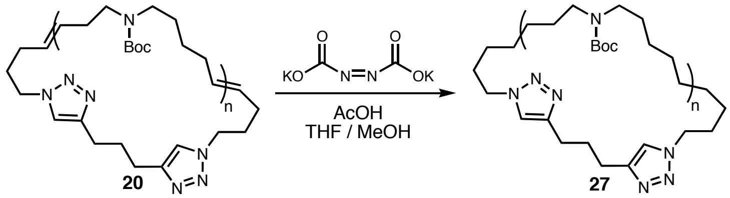
18: Monomer **13** (0.62 g, 2.75 mmoles) was added to a flame-dried, degassed vial, as a solution in CH_2Cl_2 (1 mL, 1.0 M total concentration). Chain-transfer agent **17** (0.03 g, 0.123 mmoles) was added to the vial as a solution in CH_2Cl_2 (1.0 mL, 1.0 M). Metathesis catalyst **5** (0.01 g, 0.014 mmoles) was added to the vial as a solution in CH_2Cl_2 (0.73 mL, 1.0 M). The reaction was heated to 41 °C in a vial sealed with a teflon lined cap, with stirring for 24 h. The reaction was quenched by the addition of ethyl vinyl ether (0.01 g, 0.013 mL, 0.14 mmoles). Heating was maintained for 30 min. The reaction was concentrated under vacuum to yield **18** as a brown, thick oil (0.61 g, 98 % yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.36-5.29 (m, 2H), 3.56 (m, 0.03H), 3.09 (m, 4H), 2.14 (m, 2H), 1.93 (m, 2H), 1.39 (s, 9H), 1.36-1.20 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.73, 132.36, 130.46, 129.18, 127.25, 79.21, 79.17, 47.22, 32.60, 31.77, 28.70, 27.04, 26.90. GPC-MALLS: M_n = 5000 ; PDI = 1.6.



19: Sodium azide (0.18 g, 2.77 mmoles) was added as a solid to a flame-dried flask. Polymer **18** (0.66 g, 2.9 mmoles) was added as a solution in DMF (0.1 M). The solution was stirred at room temperature under an Ar atmosphere for 12 h. The solution was diluted with EtOAc and brine. The organic phase was washed with brine (3X). The organic phases were combined, dried ($MgSO_4$), filtered, and concentrated using vacuum to yield **19** as a red-brown, thick oil (0.66 g, 95 % yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.36-5.29 (m, 2H), **3.56** (m, 0.03H), 3.09 (m, 4H), 2.14 (m, 2H), 1.93 (m, 2H), 1.39 (s, 9H), 1.36-1.20 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.73, 132.36, 130.46, 129.18, 127.25, 79.21, 79.17, 47.22, 32.60, 31.77, 28.70, 27.04, 26.90.

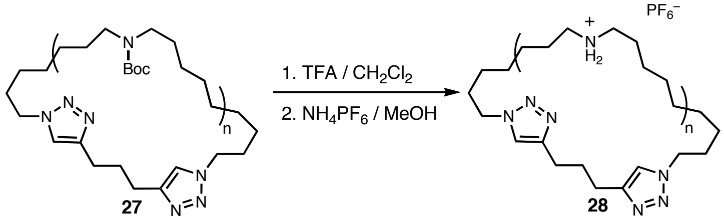


20: DMF (200 mL, 0.0096 mM) was added to a flame-dried flask. The solvent was degassed using 3 freeze/pump/thaw cycles. Copper bromide (61 mg, 0.425 mmoles) was added to the frozen DMF during the final freeze/pump/thaw cycle. The flask was resealed, evacuated with vacuum and refilled with Ar. The flask was warmed to room temperature and then heated to 120 °C. In a separate flask, polymer **19** (0.12 g, 1 eq relative to end group) was added as a solution in DMF (9.90 mL, 2.2 mM) along with 1,6-heptadiyne (2.0 mg, 2.5 uL, 1 eq relative to azide end groups present in polymer). The polymer/alkyne solution was placed in a 10 mL syringe and added to the DMF/Cu solution via syringe pump (0.2 mL/h). 30 min after the polymer/alkyne addition was complete, alkyne terminated resin (0.138 g, 10 eq.) and azide terminated resin (0.054 g, 10 eq.) were added as solids to the reaction mixture. Heating was continued for 1 h. The reaction mixture was cooled to room temperature and diluted with EtOAc and brine. The organic phase was extracted with brine (3X). The organic phases were combined, dried ($MgSO_4$), filtered, and concentrated using vacuum to yield **20** as a red-brown, thick oil (0.096 g, 80 % yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.36-5.29 (m, 2H), **3.56** (m, 0.03H), 3.09 (m, 4H), 2.14 (m, 2H), 1.93 (m, 2H), 1.39 (s, 9H), 1.36-1.20 (m, 4H). IR (cm^{-1}): 3348.83, 2956.07, 2925.06, 2847.54, 1739.11, 1695.20, 1604.79, 1462.73, 1416.23, 1364.57, 1261.25, 1165.68, 1098.52, 1023.61, 966.78, 881.54, 804.05, 770.47, 700.73. MS-MALDI (m/z): [M + H]. GPC-MALLS: M_n = 5000; PDI = 1.6.

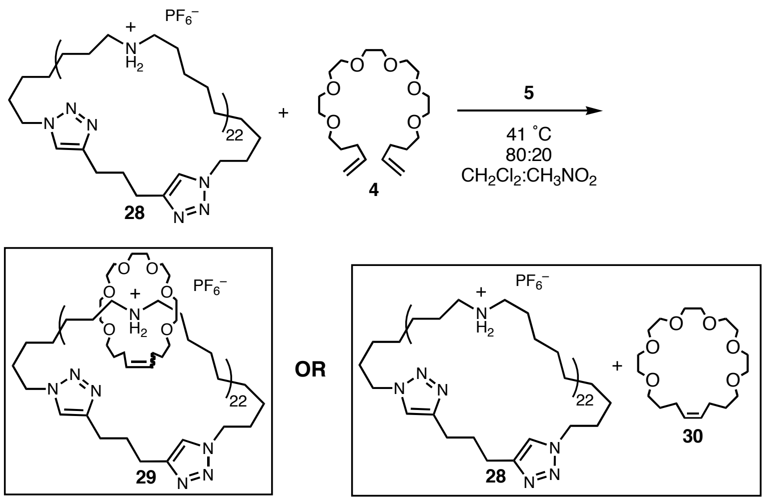


27: Polymer **20** (0.41 g, 1.8 mmol) was dissolved in THF (10 mL). Potassium azodicarboxylate ($KO_2CN{=}NCO_2K$) (3.5 g, 18 mmol) was added as a solid to the solution. Acetic acid (1.97 mL, 36 mmol) was then added slowly using an addition funnel over 1 h at room temperature. After complete addition of acetic acid, the mixture was stirred for 1 h and additional potassium azodicarboxylate (3.5 g, 18 mmol) was added. Again, acetic acid (1.97 mL, 36 mmol) was added slowly using an addition funnel over 1 h at room temperature. After complete addition of acetic acid, the mixture was stirred for 1 h. This process of addition of potassium azodicarboxylate followed by slow addition of acetic acid was repeated 3 more times (or until complete consumption of the starting material). The mixture was poured into a beaker together with Et_2O (100 mL) and brine (100 mL). The aqueous layer was separated and was extracted with Et_2O (100 mL). The combined organic layers were washed with brine (200 mL, 2X), dried

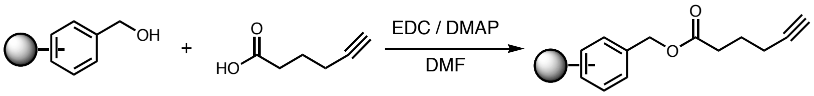
($MgSO_4$) and filtered. The solvent was removed using vacuum. To insure that no olefin functional groups remained, the resulting polymer was dissolved in BH_3THF solution (15 mL, 1M) under an Ar atmosphere. The mixture was stirred at room temperature for 1 hour. The reaction was quenched by slow addition of MeOH. The solvent was removed using vacuum. The crude oil was dissolved in EtOAc (200 mL) and washed with brine (100 mL, 2X), dried ($MgSO_4$) and filtered. The solvent was removed using vacuum to yield polymer **27** as an orange oil (0.32 g, 80 % yield). ^1H NMR (300 MHz, $CDCl_3$): δ 3.09 (m, 4H), 1.39 (s, 9H), 1.36-1.20 (m, 12H).



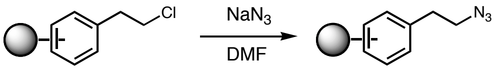
28: Polymer **27** (0.32 g, 1.42 mmol) and trifluoroacetic acid (TFA) (1.05 mL, 14.2 mmol) were dissolved in CH_2Cl_2 (14 mL, 0.1 M). The solution was stirred at room temperature for 12 h. The solvent and excess TFA were removed using vacuum. The resulting oil was dissolved in MeOH (14 mL). NH_4PF_6 (2.32 g, 14.2 mmol) was added and the suspension was stirred at room temperature for 3 h. The solvent was removed using vacuum and the crude product was partitioned between H_2O (100 mL) and n-butanol (100 mL). The organic phase was washed with H_2O (4X, 100 mL). The solvent was removed using vacuum and the resulting solid was washed with Et_2O (3X, 5 mL), followed by washing with CH_2Cl_2 (3X, 5 mL) to yield polymer **28** as a white solid (0.23g, 71 % yield). ^1H NMR (300 MHz, CD_3CN): δ 2.95 (m, 4H), 1.62 (m, 4H), 1.37-1.24 (m, 8H).



29: Polymer **28** (6 mg, 0.02 mmol) and crown ether **30** (8.3 mg, 0.02 mmol) were dissolved in degassed CD_3NO_2 (2.2 mL, 0.01 M) and added to a flamed dried, degassed 2-neck flask containing metathesis catalyst **5** (1 mg, 0.001 mmol). The reaction was heated to 45 °C for 12 hours under an Ar atmosphere. The reaction was quenched by addition of ethyl vinyl ether (1.12 mL, 0.01 mmol). The solvent was removed using vacuum to yield the crude brown oil. Numerous purification procedures are discussed within chapter 4. The solid was washed with ethyl ether to remove any non-interlocked crown ether **30**. Size exclusion chromatography in MeOH was performed, removing additional crown ether **30**. SEC was repeated 3 more times to remove remaining non-interlocked **30**. The identity of the reaction mixture is still unknown. Possible products resulting from the reaction are discussed in chapter 4.



Alkyne resin: Benzyl alcohol, polymer bound (100 - 200 mesh, 1.5 - 2.0 mmol/g loading, 1 % crosslinked with divinylbenzene, 5 g, 7.5 - 10 mmol) was added to a flame-dried flask. Dimethylformamide (20 mL, 0.5 M) was added. 5-hexyonic acid (2.3 g, 2.3 mL, 20 mmol) was added as a solution in DMF (1 mL) along with EDC (3.8 g, 20 mmol) as a solution in DMF (5 mL) along with 4-di(methylamino)pyridine (0.03 g, 0.1 mmol). The mixture was stirred gently under an Ar atmosphere at room temperature for 12 h. The resin was filtered and washed with DMF (20 mL), followed by H_2O (20 mL), followed by Et_2O (20 mL). The resin was dried under vacuum for 12 h. No further characterization of the beads was preformed.



Azide resin: Merrifield resin (2 g, 4.5 mmol/g) and sodium azide (5.8 g, 90 mmol) were added to a flame-dried flask. Dimethylformamide (100 mL) was added. The mixture was stirred gently under an Ar atmosphere at room temperature for 12 h. The resin was filtered and washed with DMF (100 mL), followed by H_2O (100 mL) followed by EtOAc (100 mL). The resin was dried under vacuum for 12 h. No further characterization of the beads was preformed.

Appendix 1

Studies toward Interlocked Polymers via ROMP of [2]Catenane Monomers

Studies Toward Interlocked Polymers via ROMP of [2]Catenane Monomers

Introduction[1]

Because the properties of polymers are related to their molecular structure, the development of synthetic techniques facilitating precise control over the architecture of polymers such as hyperbranched polymers,[2] block copolymers,[3] dendrimers,[4] and cyclic polymers,[5] is of significant interest. This interest extends into the field of interlocked polymers,[6] which is comprised of polymeric materials such as polycatenanes,[6] polyrotaxanes,[6] and daisy-chain polymers.[6,7] The conceptual transition from a [2]catenane or [2]rotaxane to polycatenanes and polyrotaxanes can be achieved through a number of different design strategies, several of which have been graphically represented in Figures 1 and 2.

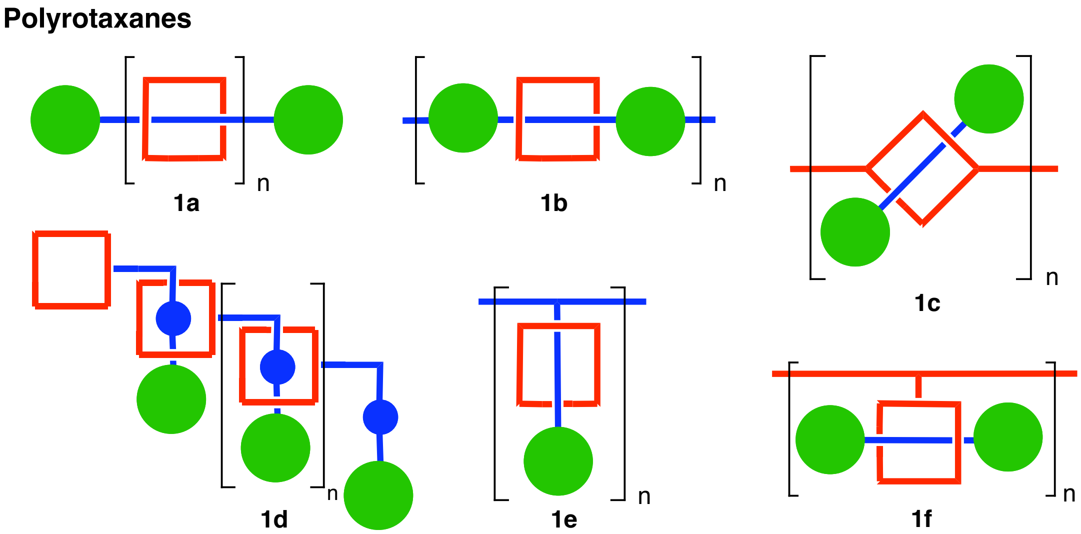


Figure 1: Graphical representation of polyrotaxanes.

Polyrotaxanes can be divided into two categories: main-chain polyrotaxanes, in which the interlocked molecule resides within the polymer chain, and side-chain polyrotaxanes, in which the interlocked molecule is pendant to the polymer chain. Main-chain polyrotaxanes may be formed by encircling a polymeric dumbbell-shaped component with (n) macrocycles (**1a**). Alternatively, a [2]rotaxane can be transformed into a main-chain polyrotaxane by incorporation of its dumbbell (**1b**) or macrocyclic components (**1c**) into the polymer chain. Daisy-chain polymers (**1d**) are another class of main-chain rotaxane-based polymer in which both the host and guest recognition units are covalently bound in the same monomer, and both the macrocycle and dumbbell components are present in the polymer chain. In side-chain polyrotaxanes, either the dumbbell (**1e**) or macrocycle (**1f**) of a rotaxane are covalently attached to a polymer backbone.

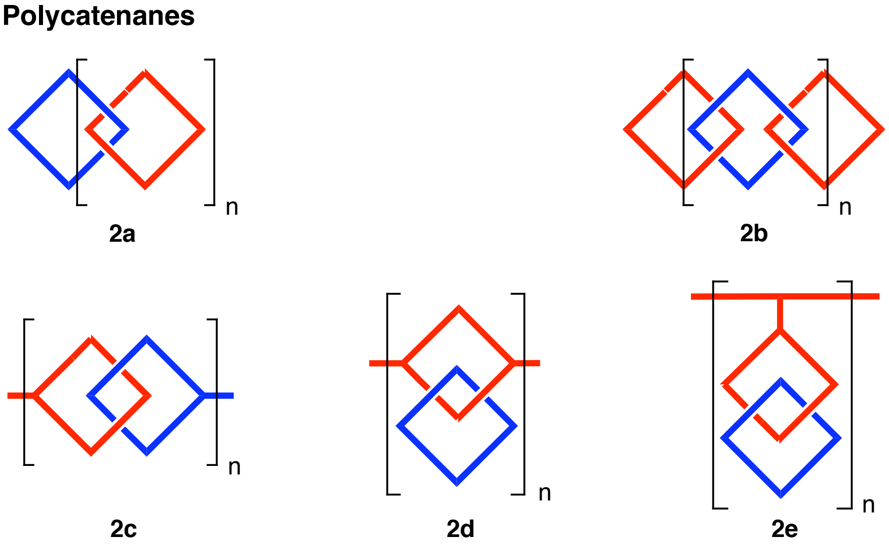


Figure 2: Graphical representation of polycatenanes.

Polycatenanes can be divided into two categories: main-chain and side-chain polycatenanes (Figure 2). Main-chain polycatenanes can be formed by simply enlarging one of the rings so that multiple macrocycles may be accommodated around the enlarged ring (**2a**). The larger ring may also be enlarged in a different manner thus, allowing the interlocking of two or more macrocycles, like links in a chain (**2b**). Introduction of [2]catenanes into the backbone of a polymer chain also generates main-chain polycatenanes (**2c**). Incorporation of a catenated macrocycle into the backbone of a polymer chain (**2d**) produces a main-chain polycatenane. Side-chain polycatenanes may be formed by appending [2]catenane units from a polymer backbone (**2e**).

While there have been many polycatenane and polyrotaxane architectures that have been imagined, many have yet to be realized, due to the significant synthetic challenge they pose. One such architecture is the cyclic polycatenane (**2a**), for which no syntheses appear in the chemical literature. We thought that the key synthetic challenge in the production of a cyclic polycatenane lay in the production of an appropriate cyclic polymer.

Cyclic polymers can be synthesized using a number of methods. The most common route involves an intramolecular macrocyclization of linear polymer precursors at extremely low concentrations.[8] Alternatively, the equilibrium between the formation of cyclic or linear polymer can be shifted to maximize the formation of cyclic polymer for many polymerizations, such as polycondensations, metathesis polymerizations, etc., and again is typically shifted by carefully controlling the reaction or polymerization conditions.[9] While these methods can be used to synthesize a variety of cyclic polymers, incomplete cyclization, large solvent volume and inability to access high molecular weight cyclic polymers are problems that plague these methods.

More recently, coworkers in the Grubbs group have introduced an alternative to the above methods, which does not require a linear polymer precursor. “Cyclic” metathesis catalyst L(PCy$_3$)Cl$_2$Ru=CHR (**4**), is a close structural analogue of the olefin metathesis catalyst $(H_2IMes)(PCy_3)Cl_2Ru{=}CHPh$ (**3**). However, unlike metathesis catalyst **3**, "cyclic" catalyst **4** contains a ruthenium-carbene that is tethered to N-heterocyclic carbene ligand, creating a "cyclic" metathesis catalyst. When used in conjunction with a strained, cyclic olefin monomer, cyclic polymer is produced (Figure 3) through ring-opening metathesis polymerization (ROMP).[10] The polymerization is believed to go through a transient metallocyclobutane, causing an expansion of the ring attached to the catalyst, leaving both ends of the growing polymer chain attached to the catalyst. An intramolecular chain transfer reforms a "cyclic" catalyst, releasing a cyclic polymer chain. This catalyst has been used to synthesize cyclic polyoctenamers,[10] cyclic polyethylene,[10] and cyclic polybutadiene[11] with molecular weights up to 1200 kD while using only very small quantities of solvent.

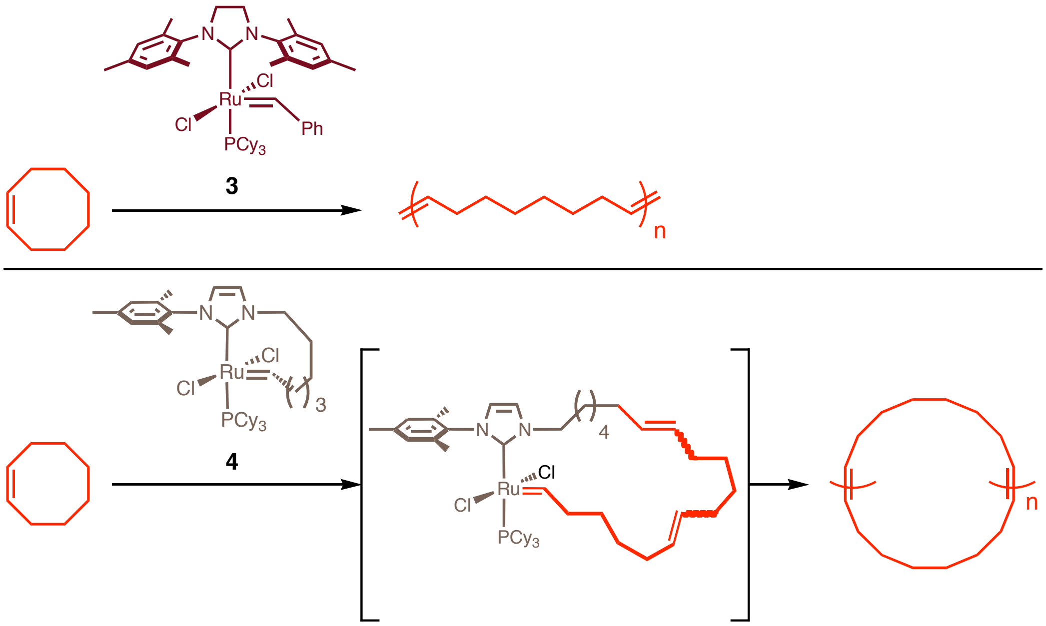


Figure 3: Cyclic polymer formation using a "cyclic" olefin metathesis catalyst and a strained cyclic ROMP monomer.

The use of cyclic olefin metathesis catalyst **4** to form cyclic polymer eliminates the need for linear polymer precursors, uses small quantities of solvent and allows access to a wide range of molecular weights. We envisioned that the use of an olefin-containing [2]catenane as a polymerization monomer in conjunction with a cyclic metathesis catalyst might allow access to the elusive cyclic polycatenane (Figure 4). Additionally, we imagined that the use of an olefin-containing [2]catenane as metathesis polymerization monomer might extend the range of synthetically achievable interlocked polymeric architectures through the use of judicious metathesis catalyst selection (Figure 4). For example, ROMP of a [2]catenane monomer using a metathesis catalyst bearing a bulky carbene initiating group, in conjunction with a chain transfer agent (CTA) bearing bulky end groups, might allow for a one step conversion of [2]catenanes to polyrotaxanes.

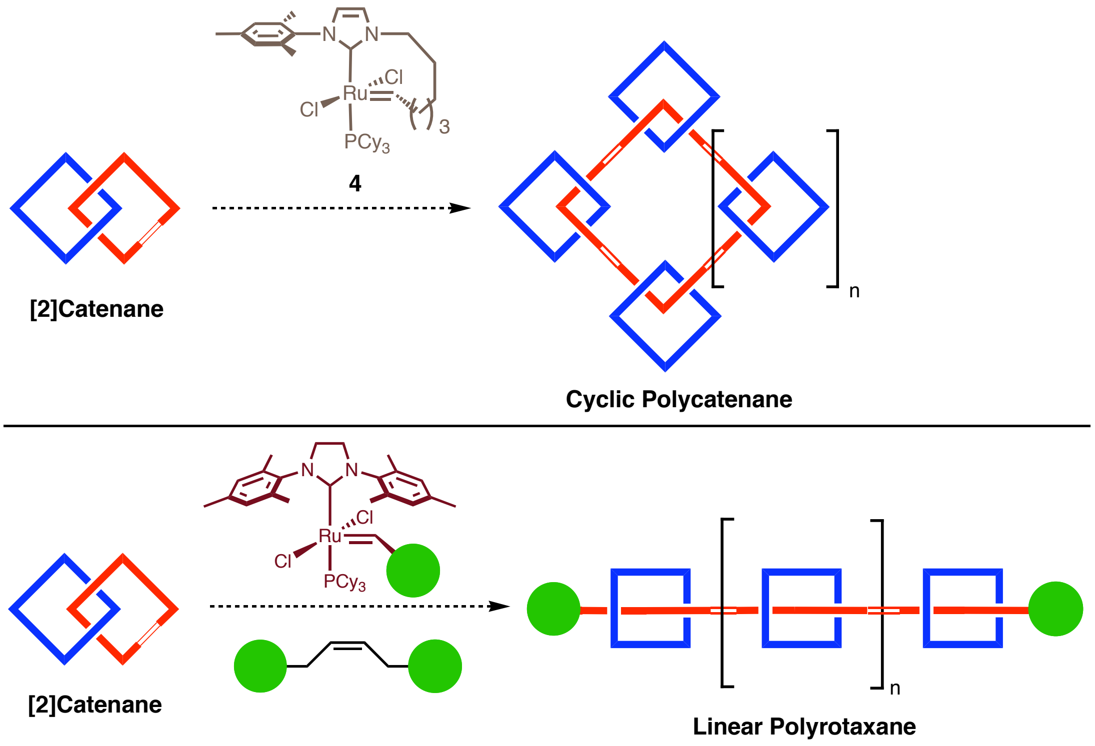


Figure 4: Graphical representation of the formation of interlocked polymers via ring opening metathesis polymerization (ROMP) of an olefin-containing [2]catenane.

Ring Opening Metathesis Polymerization of a [2]Catenane using Grubbs Cyclic Metathesis Catalyst

We sought to design a ring opening metathesis polymerization (ROMP) approach that would utilize an olefin-containing [2]catenane as the polymerization monomer (Figure 5). In this approach, the ring opening of one of the olefin containing macrocycle of the [2]catenane would elongate the polymer chain, while the other macrocycle remain trapped on the "endless" polymer chain. An intramolecular chain transfer reaction should form the cyclic polycatenane and regenerate a new 'cyclic' catalyst molecule.

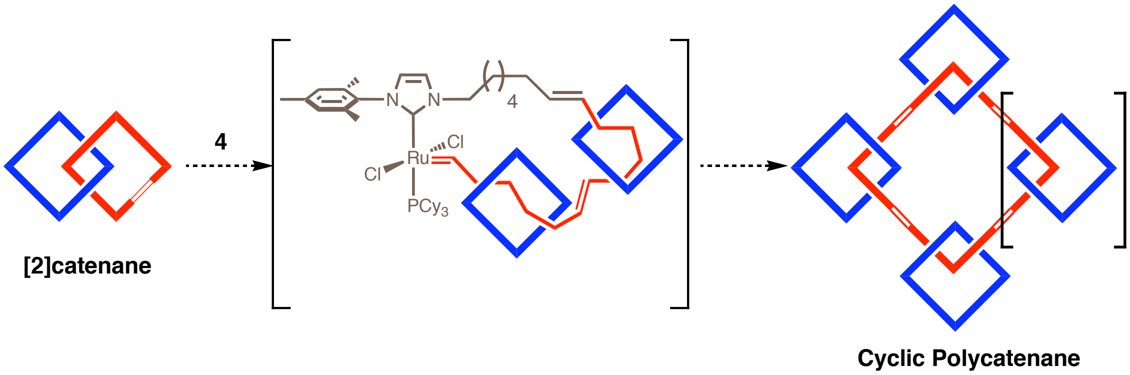
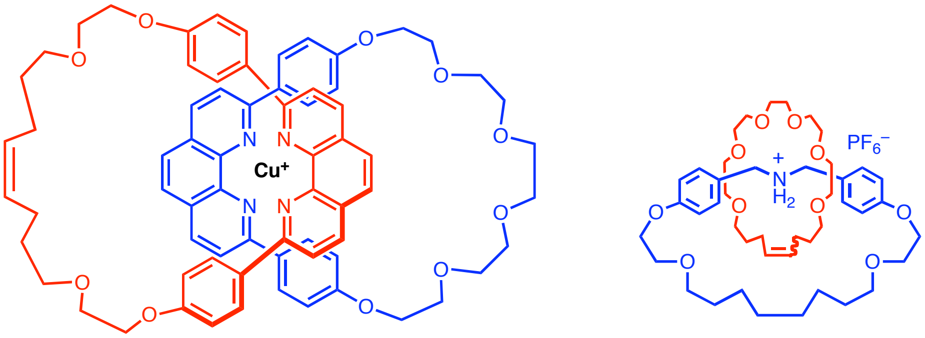


Figure 5: Proposed synthesis of a cyclic polycatenane through the ROMP of a [2]catenane monomer using cyclic metathesis catalyst **4**.

In order to use a [2]catenane as a ROMP monomer, it was first necessary to identify a [2]catenane monomer that (i) contained an olefin functional group in one of the macrocycles, (ii) had adequate ring strain to allow for polymerization and (iii) had good solubility in metathesis-compatible solvents (such as methylene chloride or toluene). The first olefin containing [2]catenane (**5**) was prepared by coworkers in the Grubbs group using ring closing metathesis and is based on the metal coordination between copper and phenanthlalene units (Figure 6).[12] The solubility of this [2]catenane, however was very low in metathesis compatible solvents, making it an unattractive choice as a polymerization monomer. Another olefin containing [2]catenane (**6**) has been prepared by the Grubbs group based on the hydrogen bonding between crown ethers and appropriately substituted ammonium ions (Figure 6).[13] The solubility of this [2]catenane was quite good, and for this reason it was thought that [2]catenane **6** was an ideal candidate for a polymerization monomer.



5

Poor Solubility in CH_2Cl_2

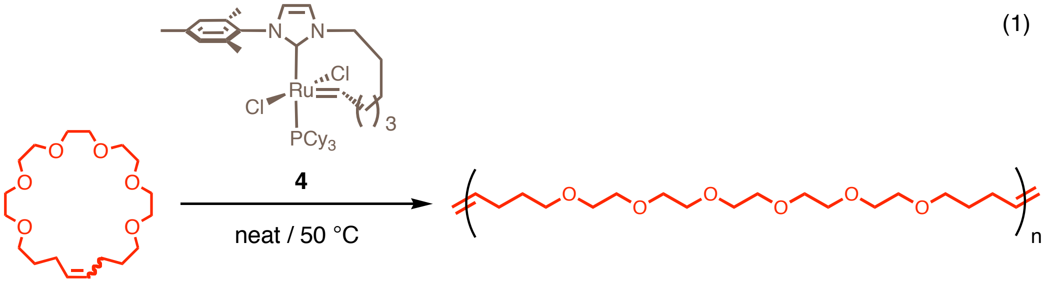
6

Good Solubility in CH_2Cl_2

Figure 6: Olefin containing [2]catenanes for potential use as ROMP monomers.

While the solubility of the [2]catenane monomers could easily be determined, it was not immediately obvious whether the olefin containing 24-membered crown-type macrocycle of [2]catenane **6** had sufficient ring strain to act as a polymerization monomer. To verify this, crown-type macrocycle **7** was independently synthesized and submitted to standard ROMP conditions using cyclic catalyst **4** (eq 1). Gratifyingly, at high monomer concentration, polyether **8** could be formed from monomer **7**.

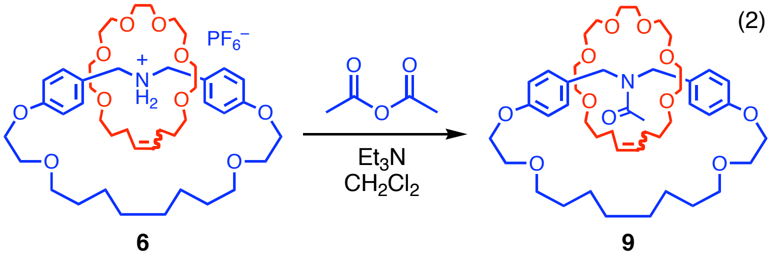
(1)



7

8

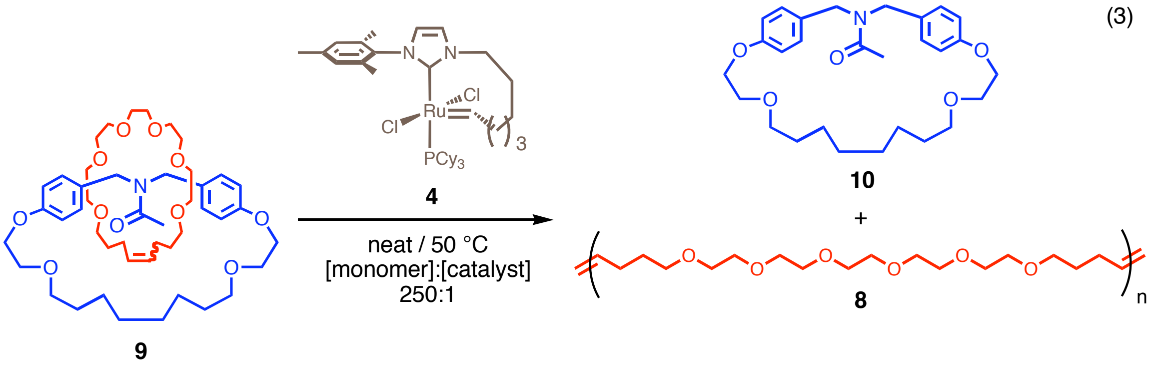
Next we sought to explore the polymerization of the [2]catenane **6** using the cyclic catalyst **4**. However, under identical polymerization conditions as those used in the polymerization of macrocycle **7**, no polymer was obtained, and only starting material was isolated. Our initial speculation was that the need to break additional hydrogen bonds which arises between N^{+}-H···O and C-H···O hydrogen bonds between the crown-type monomer and the -$CH_2NH_2CH_2$- portion of the second macrocycle might be responsible for the poor reactivity of monomer **6**.



6 **9**

To test this hypothesis, the hydrogen bonding interaction between the crown ether and ammonium ion was removed by protection of the nitrogen of the macrocycle of [2]catenane **6** by deprotonation/acylation with triethylamine and acetic anhydride (eq 2). Submission of the acylated [2]catenane **9** to standard ROMP conditions with cyclic catalyst **4** resulted in the formation of polymer. Analysis of the polymeric product, however, revealed that the desired cyclic polycatenane was not formed. Instead, linear polymer **8** resulting from the polymerization of the crown-type macrocycle of [2]catenane **9** was formed along with free, unthreaded acylated macrocycle **10** (eq 3). These products proved challenging to separate by traditional precipitation due to their similar solubility, however, they could be readily separated using preparative scale size exclusion chromatography (SEC) because of their dramatically different molecular weights.

(3)



We began to investigate the formation of linear polymer **8** using cyclic metathesis catalyst **4**. Other reports of linear polymer formation from this process have been reported. Coworkers in the Grubbs group have previously reported the formation of significant linear polymer impurities during the cyclic polymerization of cyclooctadiene (COD) to form polybutadiene.[11] It was observed that linear olefin impurities in the COD monomer of as little as 0.05% led to significant linear polymer contamination. This problem was remedied through the use of a different cyclic olefin, cyclooctatetrene (COT), which does not contain any linear olefin impurities.[11]

The [2]catenane monomer **9** is formed by a ring closing metathesis reaction which could lead to linear olefin impurities in the monomer from (i) unreacted crown precursor **11** or (ii) the products of the cross metathesis of **11** to form **13** (Figure 7). Both of these impurities could be responsible for the formation of linear polymer during the ROMP reaction. The crown-type products **11** and **13** have significantly different solubility than [2]catenane **6** in ethyl ether. As an initial effort at purification, [2]catenane **6** was washed with copious amounts of ethyl ether in an attempt to wash away the various crown-type impurities. After subsequent deprotonation and protection reactions, the newly purified [2]catenane **9** was polymerized. Unfortunately, the same result was observed as in the previous unpurified sample, again generating only linear polyether **8** and free, unthreaded acylated macrocycle **10**.

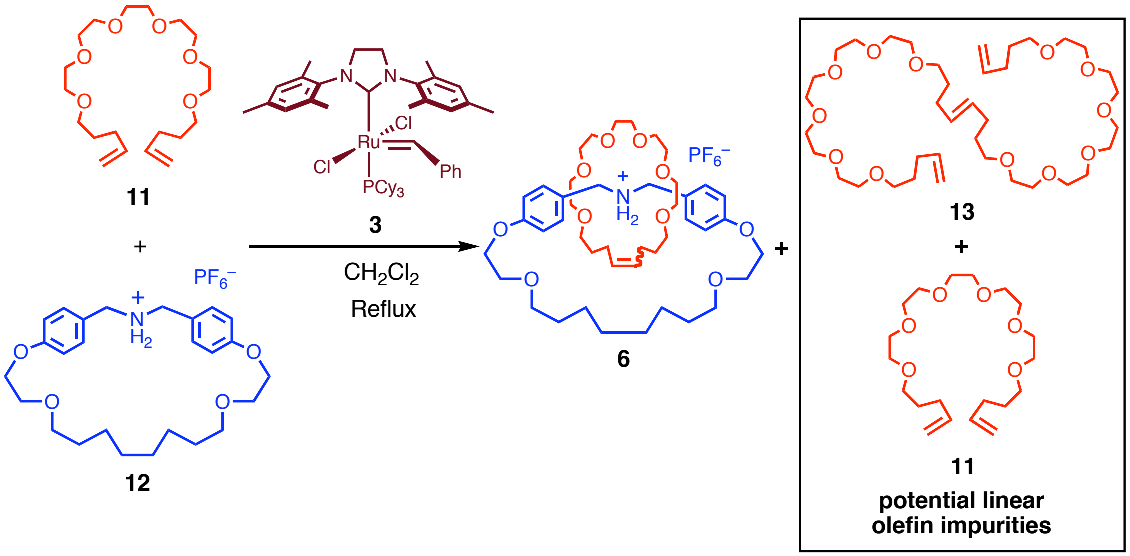
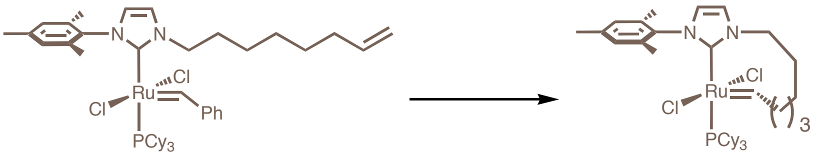


Figure 7: The ring closing metathesis of crown ether macrocycle **11** around dibenzylammonium macrocycle **12** generates [2]catenane **6** but also generates other linear olefin products such as **11** and **13**.

Due to the inability to produce the desired cyclic polymers, a more rigorous monomer purification technique was necessary. Reports have appeared in which COD was purified for use in ROMP through the use of the bulky borane 9-borabicyclo[3.3.1]nonane (9-BBN).[14] This technique proved quite successful at the removal of vinylcyclohexane, the source of linear olefin contamination in COD. The sterically bulky borane is much more reactive towards the mono-substituted 4-vinylcyclohexane as compared to the disubstituted COD. While the exact identity of the linear olefin contaminant present in the [2]catenane monomer **9** is unclear, if the impurity were to contain a terminal olefin, then it would react with the borane and might lead to the elimination of the olefin impurity. The [2]catenane monomer **9** was reacted with an excess of 9-BBN, followed by passage through a small silica plug to eliminate salts generated during the reaction. Despite these efforts, however, polymerization again resulted in the formation of linear polyether **8** and the free acylated macrocycle **10**.

Preparative scale reverse phase HPLC is very useful for the purification of polar organic compounds, after submission of [2]catenane **9** to this technique, a colorless product was obtained (the unpurified [2]catenane is pale brown due to residual ruthenium contamination which persists after standard flash chromatography). This purified monomer was submitted to polymerization with cyclic metathesis catalyst **4**, but unfortunately, only linear polyether **8** and free acylated macrocycle **10** were obtained.

Despite rigorous and varied attempts at purification, only linear polyether **8** and free acylated macrocycle **10** were able to be obtained from any polymerization attempts. While it is possible that the linear olefin impurities were still present in the purified [2]catenane monomer, the cyclic catalyst might also have been a source of contamination. Cyclic catalyst **4** was prepared by a ring-closing process (eq 4).[15] Incomplete cyclization would result in the presence of some residual uncyclized catalyst that would still be catalytically active and that would react to ring-open cyclic monomers, generating linear product. Additionally, the N-heterocyclic carbene would also contain a reactive terminal olefin end-group.



(4)

4

The likely mechanism for linear polymer formation during [2]catenane polymerization using cyclic metathesis catalyst **4** is outlined in Figure 8. Presumably, linear polymer is formed by the ring-opening of growing polymer chains by linear olefin impurities, thus introducing reactive end-groups into the polymerization. These end-groups might react further with other growing polymer chains, leading to significant quantities of linear polymer. Once linear polymer is formed, the acylated macrocycles can unthread from the polymer chain. The issues observed during the polymerization of [2]catenane **9** highlight the issues associated with the use of cyclic metathesis catalysts to form cyclic polymer, specifically, the need for extremely pure cyclic catalyst and cyclic monomers free of any linear olefin impurity.

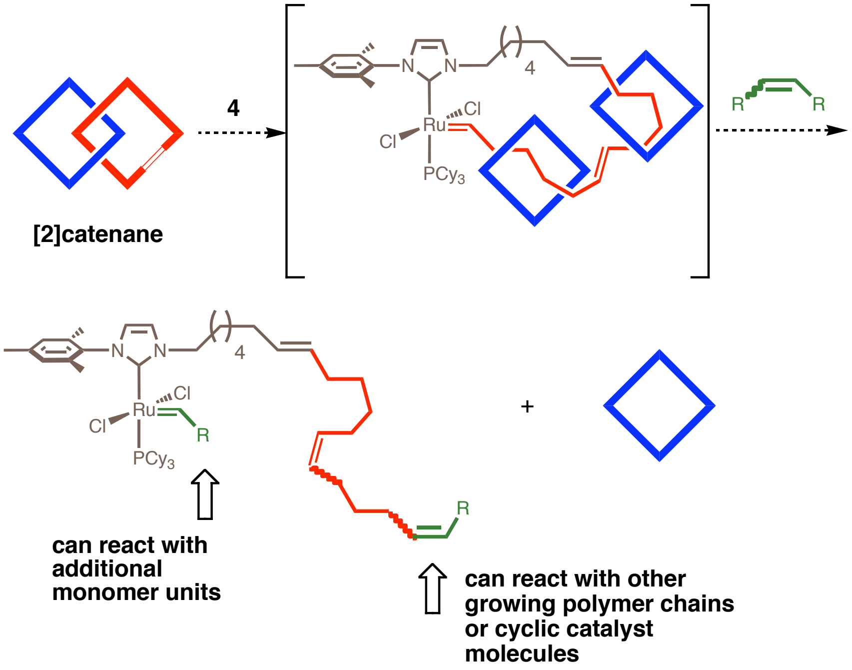


Figure 8: Proposed mechanism of linear polymer formation during the ROMP of a [2]catenane monomer using cyclic metathesis catalyst **4**.

Ring-Opening Metathesis Polymerization of a [2]Catenane using Grubbs Bulky Initiating Metathesis Catalysts

Concurrent with our investigation into [2]catenane polymerization via ROMP with cyclic catalyst **4** were analogous studies toward the preparation of polyrotaxanes using ROMP. We envisioned that the synthesis of a linear catalyst with a bulky initiating group might allow access to polyrotaxanes through ROMP of a [2]catenane monomer (Figure 9). In this approach, the ring-opening of the olefin-containing macrocycle of the [2]catenane extends the polymer chain, while the other macrocycle remains trapped on the growing polymer chain due to the bulk of the groups on the ends of the polymer chain. These groups would initially be the large initiating group and the catalytically active ruthenium carbene species. Chain-transfer reactions with other polymer chains or a bulky chain transfer agents (CTA) is expected to form the polyrotaxane and regenerate a new bulky metathesis catalysts.

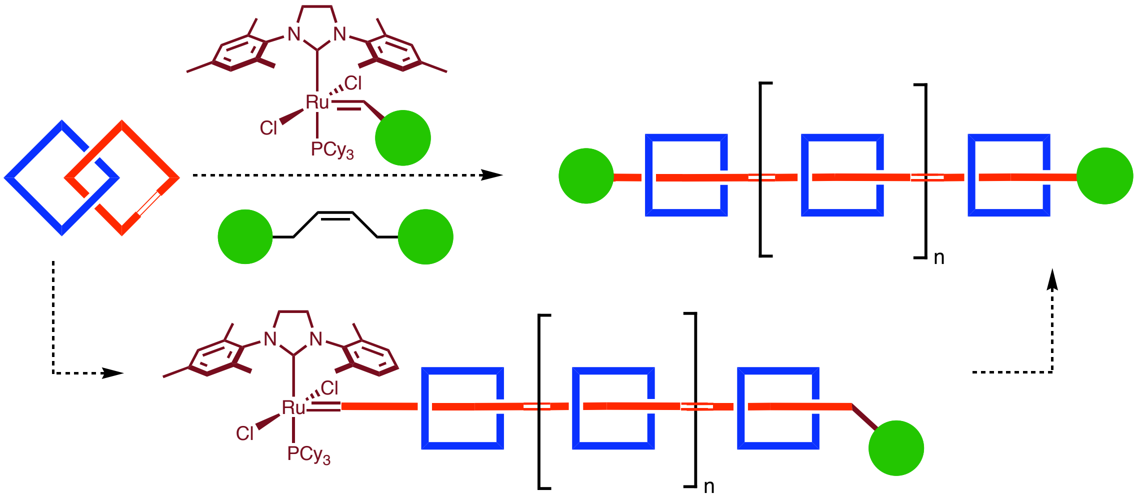


Figure 9: Proposed synthesis of a polyrotaxane via ROMP of a [2]catenane monomer using a bulky metathesis catalyst and chain transfer agent.

Our interest in exploring this polymerization route centered primarily on our interest in this novel method for polyrotaxane formation. Additionally, the bulky initiating catalyst would likely demonstrate improved stability toward typical purification procedures, such as silica gel chromatography, allowing for more rigorous catalyst purification.

Previous work has shown that 3,5-dimethoxybenzyl groups (**14**) are sufficiently large to act as stoppering groups for 24-membered crown-type macrocycle **7**. No such data exists for the 27-membered ammonium macrocycle **12**. Using the correlation between the ring size of macrocycle **7** and the stopper size of 3,5-dimethoxybenzyl group (**14**) as a guide, we speculated that the slightly larger 3,5-di-*t*-butylbenzyl group (**15**) might act as a stoppering group for macrocycle **12** (Figure 10).

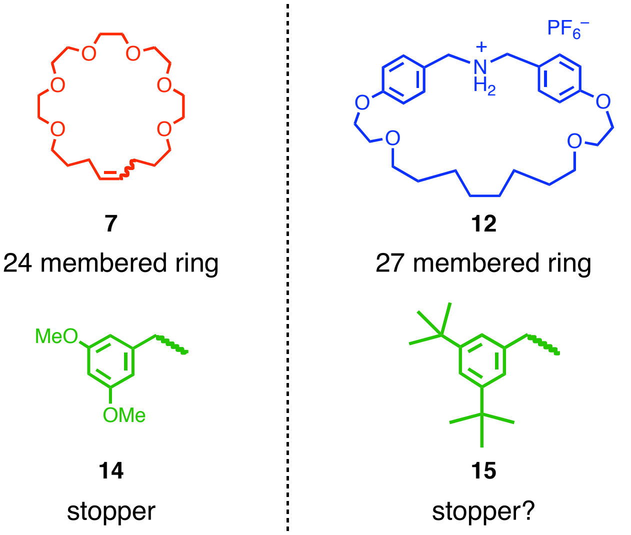
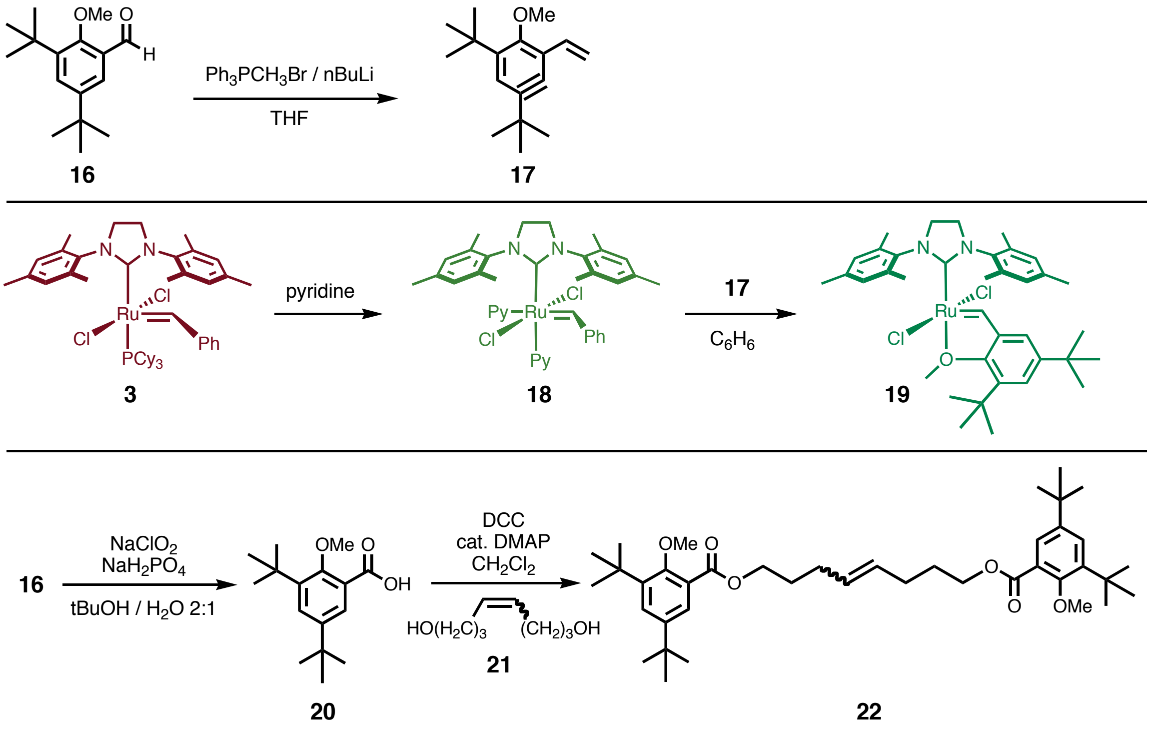


Figure 10: **14** is large enough to act as a stopper for macrocycle **7**. We speculate that stopper **15** will be large enough to act as a stopper for macrocycle **12**.

A "bulky initiator" analogue of the olefin metathesis catalyst **3** $(H_2IMes)Cl_2Ru{=}CHPhR$ (**19**) was prepared. Commercially available aldehyde **16** was converted to styrene **17** using a standard Wittig reaction (Figure 11). The Grubbs second generation catalyst **3** was converted to the bispyridine analogue **18** by reaction with excess pyridine. The bispyridine catalyst **18** was reacted with an excess of styrene **17**. Iterative reaction followed by application of vacuum to remove displaced pyridine aided in driving the reaction to completion (Figure 11). The catalyst was isolated using silica gel chromatography. A bulky chain transfer agent (CTA) was also prepared. Aldehyde **16** was converted to acid **20**, which was coupled to diol **21** using standard DCC (dicyclohexylcarbodiimide) coupling conditions (Scheme 1) to form CTA **22**.

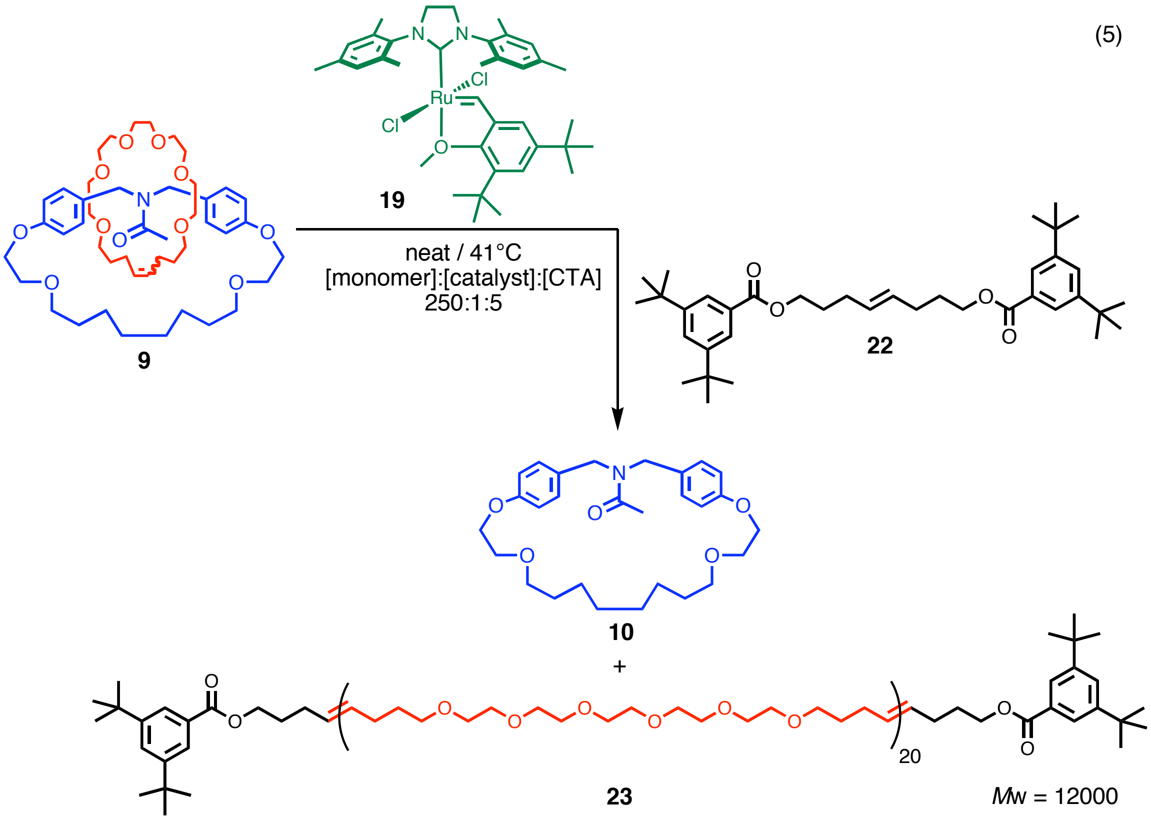


Scheme 1: Synthesis of bulky metathesis catalyst **19** and bulky CTA **22**.

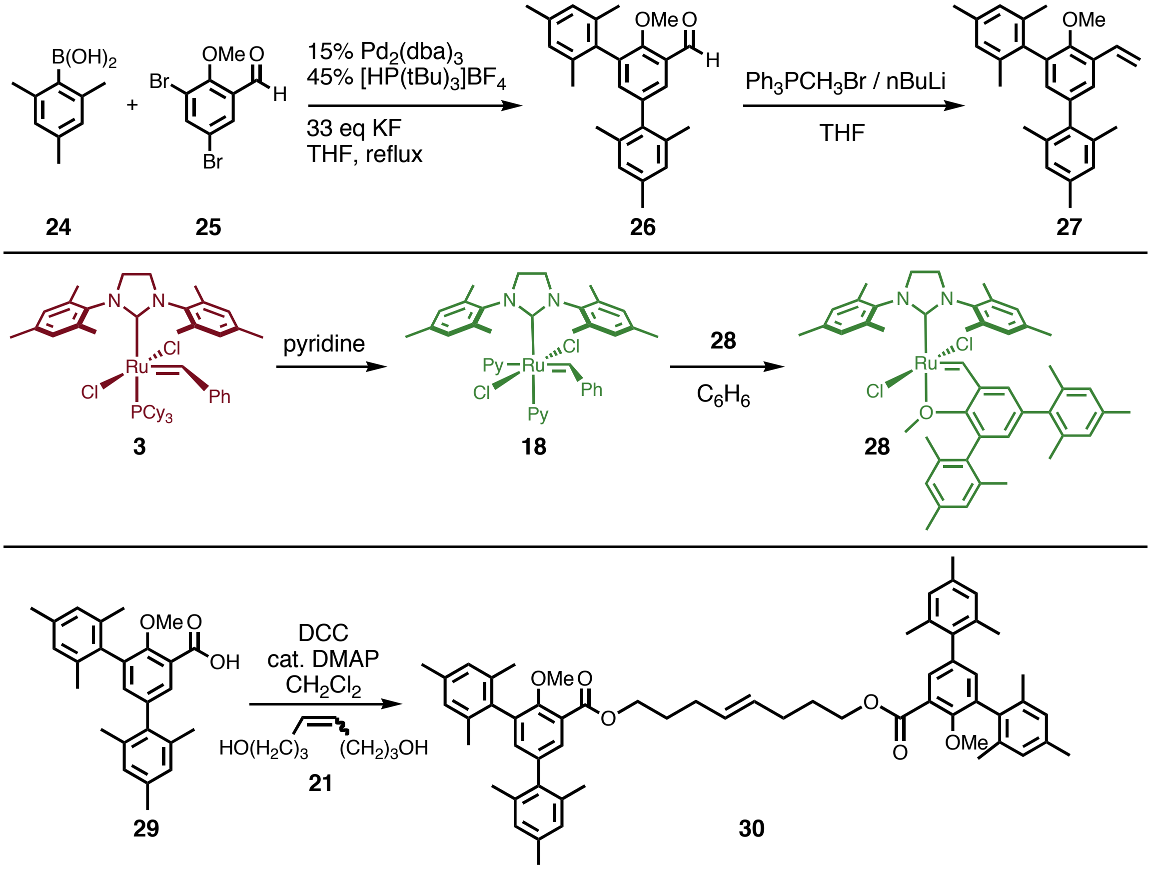
Next, we sought to explore the polymerization of HPLC purified [2]catenane monomer **9** using bulky catalyst **19** and CTA **22** under standard ROMP conditions. Unfortunately, the polymerization using this new bulky catalyst system resulted in a similar result as that observed when using cyclic catalyst **4**: linear polyether **23** and free acylated macrocycle **10** were isolated (eq 5).

Initially, we speculated that the 3,5-di-*t*-butylbenzyl group might not be large enough to prevent dethreading of the macrocycle **10**. To test this hypothesis, an even bulkier initiating catalyst **28** was prepared along with the corresponding bulkier CTA **30** (Scheme 2).

(5)



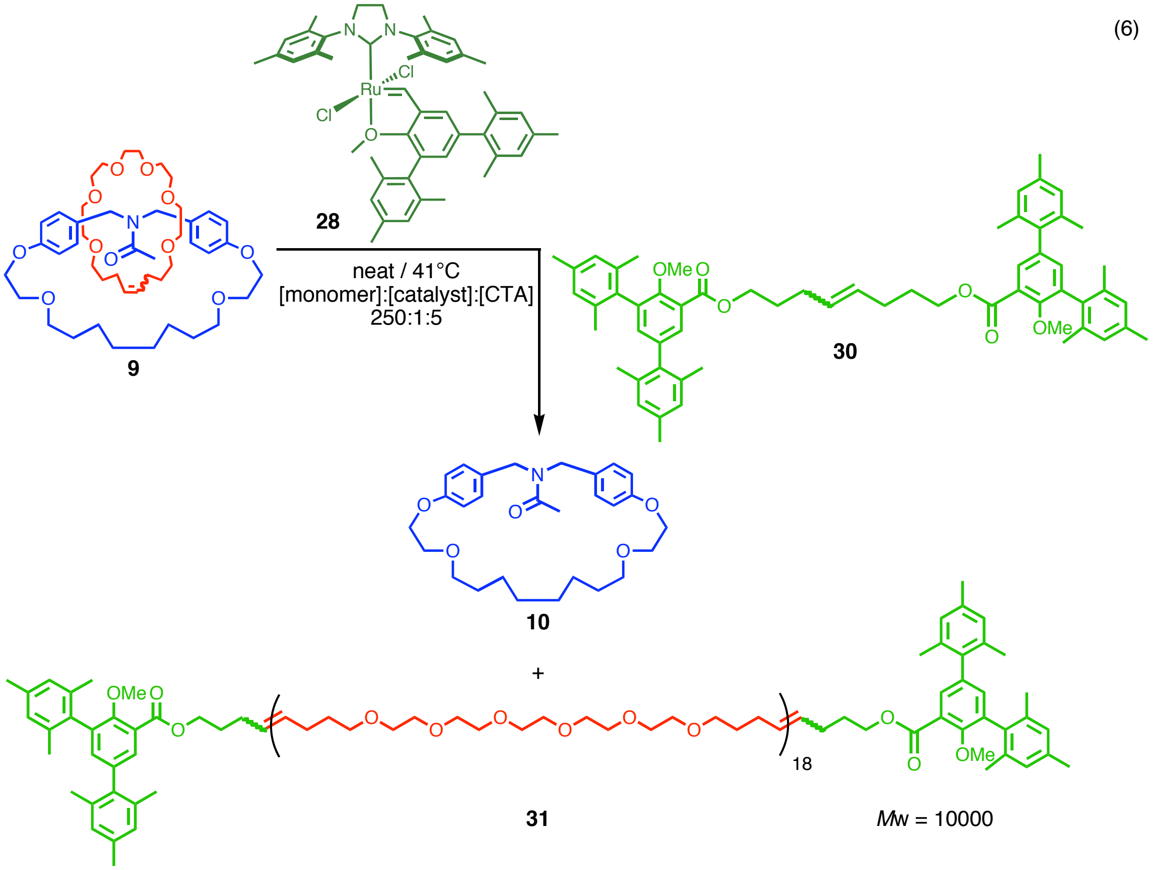
Aldehyde **26** was prepared by a palladium catalyzed Suzuki cross coupling between dibromoaldehyde **25** and boronic acid **24**. Aldehyde **26** was converted to styrene **27** using standard Wittig conditions (Scheme 2). Bulky catalyst **28** was prepared by reaction of catalyst **18** with an excess of styrene **27**. Iterative reaction followed by application of vacuum to remove displaced pyridine aided in driving the reaction to completion. The catalyst was isolated using silica gel chromatography. Bulky CTA **30** was also prepared. Acid **29** was coupled to diol **21** using standard DCC (dicylohexylcarbodiimide) coupling conditions (Scheme 2).



Scheme 2: Synthesis of bulky metathesis catalyst **28** and bulky CTA **30**.

Next, we sought to explore the polymerization of the HPLC purified [2]catenane monomer **9** using bulky metathesis catalyst **28** and CTA **30** under standard ROMP conditions. Unfortunately, polymerization using the new bulky catalyst **28** and CTA **30** generated a similar result as cyclic catalyst **4**, with isolation of only linear polyether **31** and free acylated macrocycle **10** (eq 6).

Polyrotaxane formation by polymerizing [2]catenane monomer **9** using two different catalysts containing bulky initiating groups and the corresponding chain transfer agents was not successful, instead only linear polyether and free macrocycle were isolated. The mechanism of polyether formation for these bulky catalyst systems likely parallels the mechanism proposed for linear polyether generation using cyclic catalyst **4** (Figure 11).



(6)

Bulky catalysts **19** and **28** and chain transfer agents **22** and **30** were prepared by a cross metathesis process (Schemes 1 and 2). Incomplete reaction of the pyridine catalyst **18** with the corresponding styrene (**17** and **27** respectively) would produce an impurity that is still catalytically active and would react to ring-open cyclic monomers to generate linear product. Additionally, incomplete cross metathesis during the synthesis of chain transfer agents **22** and **30** would also leave a reactive terminal olefin end group. The proposed mechanism for linear polymer formation during [2]catenane polymerization using bulky metathesis catalysts **19** or **28** is outlined in Figure 11. Presumably, linear polymer is formed by the ring-opening of growing polymer chains by linear olefin impurities, thus introducing more reactive end groups into the polymerization. These

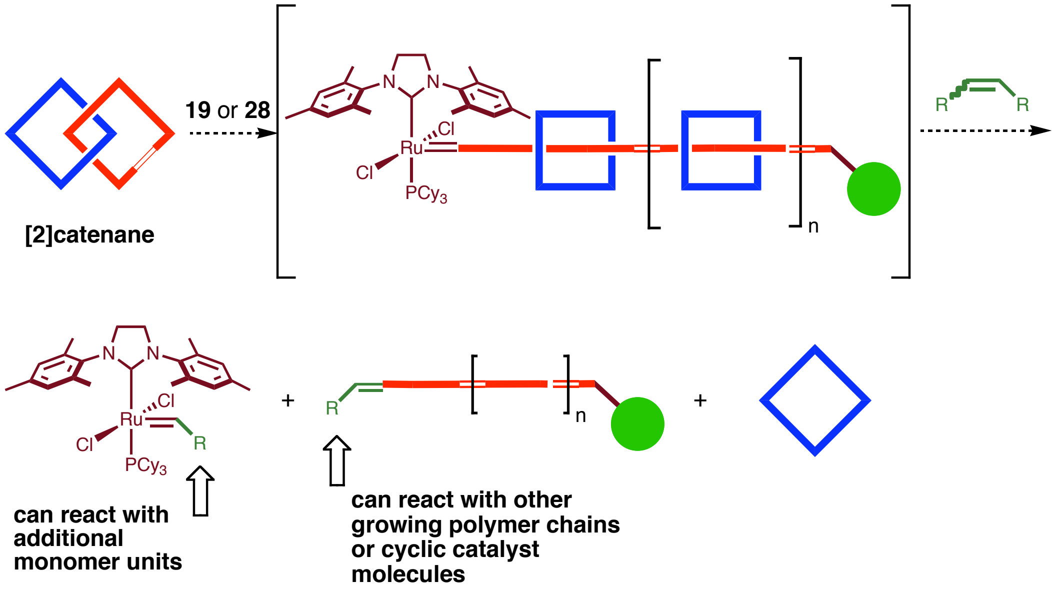


Figure 11: Proposed mechanism of linear polymer formation during ROMP of a [2]catenane monomer using a bulky metathesis catalyst.

endgroups can react further with other growing polymer chains, leading to significant quantities of linear polymer. Once linear polymer is formed, the acylated macrocycles unthread from the polymer chain. The issues observed during the polymerization of [2]catenane **9** highlight the issues associated with the use of these bulky initiating catalysts to synthesize polyrotaxanes, that being the need for extremely pure bulky catalyst, chain transfer agents and cyclic monomers that are free from any linear olefin impurities.

Conclusions

The ring-opening metathesis polymerization of a [2]catenane was investigated, using both a cyclic metathesis catalyst and bulky metathesis catalysts for the formation of cyclic polycatenanes and polyrotaxanes respectively. While it was found that the [2]catenane monomer could function as a ROMP monomer, no interlocked polymers were observed as products from the polymerization. Linear impurities present in either or both the [2]catenane monomer and the metathesis catalysts are believed to be responsible for the formation of the non-interlocked polyether and free macrocycle. Efforts to purify both the [2]catenane monomer and the metathesis catalysts were ineffective, and the desired interlocked polymers were not obtained. These results highlight the critical role of purity to the successful formation of cyclic or linear interlocked polymer using a ROMP process.

References

(1) This introduction has been partially reproduced from Guidry, E. N. Thesis Chapter 3.

(2) Mitsutoshi, J.; Masa-aki, K. Prog. Polym. Sci. 2001, 26, 1233-1285. (b) Gao, C.; Yan, D. Prog. Polym. Sci. 2004, 29, 183-275.

(3) In *Block Copolymers I*; Abetz, V., Ed.; Adv. Polym. Sci. 189; Springer GmBH: Berlin, 2005; 1-238. (b) In *Block Copolymers II*; Abetz, V., Ed.; Adv. Polym. Sci. 190; Springer GmBH: Berlin, 2005; 1-252.

(4) In *Special Issue: Dendrimers and Dendritic Polymers*; Tomalia, D. A.; Frechet, J. M., Eds.; Prog. Polym. Sci. 30; Elsevier: Amsterdam, 2005; 1-288.

(5) Semlyen, J. A. *Cyclic Polymers*, 2nd ed.; Kluwer Academic: Dordrecht, The Netherlands, 2000.

(6) (a) Gibson, H. W.; Bheda, M. C.; Engen, P. T. *Prog. Polym. Sci.* **1994**, *19*, 843-945. (b) Amabilino, D. B.; Stoddart, J. F. *Chem. Rev.* **1995**, *95*, 2725-2828. (c) Raymo, F. M.; Stoddart, J. F. *Chem. Rev.* **1999**, *99*, 1643-1663. (d) Toshikazu, T.; Nobuhiro, K.; Yoshio, F. *Adv. Polym. Sci.* **2004**, *171*, 1-75.

(7) (a) Hirotsu, K.; Higuchi, T.; Fujita, K.; Ueda, T.; Shinoda, A.; Imoto, T.; Tabushi, I. *J. Org. Chem.* **1982**, *47*, 1143-1144. (b) Mentzafos, D.; Terzis, A.; Coleman, A. W.; de Rango, C. *Carbohydr. Res.* **1996**, *282*, 125-135. (c) Yamaguchi, N.; Nagvekar, D. S.; Gibson, H. W. *Angew. Chem., Int. Ed.* **1998**, *37*, *2361-2364*. (d) Rowan, S. J.; Cantrill, S. J.; Stoddart, J. F.; White, A. J. P.; Williams, D. J. *Org. Lett.* **2000**, *2*, 759–762. (e) Liu, Y.; You, C.-C.; Zhang, M.; Weng, L.-H.; Wada, T.; Inoue, Y. *Org. Lett.* **2000**, *2*, 2761-2763. (f) Stoddart, J. F.; Rowan, S. J.; Chiu, S.-H.; Cantrill, S. J.; Ridvan, L.; Sivakova,

S. *Polym. Mater. Sci. Eng.* **2001**, *84*, 148-149. (g) Harada, A. *J. Polym. Sci., Part A: Polym. Chem.* **2005**, 5113-5119.

(8) Laurent, B. A.; Grayson, S. M. *J. Am. Chem. Soc.* **2006**, *128*, 4238-4239. and others

(9) (a) Brown, J. F.; Slusarczuk, G. M. *J. Am. Chem. Soc.* **1965**, *87*, 931-932. (b) Kricheldork, H. R.; Rabenstein, M.; Langanke, D.; Schwarz, G.; Schmidt, M.; Maskos, M.; Kruger, R. -P. *High Perform. Polym.* **2001**, *13*, S123. (c) Scott, K. W.; Calderon, N.; Ofstead, E. A.; Allen, J. W.; Ward, J. P. *Adv. Chem. Series* **1969**, *91*, 399.

(10) Bielawski, C. W.; Benitez, D.; Grubbs, R. H. *Science* **2002**, *297*, 2041.

(11) Bielawski, C. W.; Benitez, D.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 8424.

(12) (a) Mohr, B.; Weck, M.; Sauvage, J. -P.; Grubbs, R. H. *Angew. Chem. Int. Ed., Engl.* **1997**, *36*, 1308. (b) Weck, M.; Mohr, B.; Sauvage, J. -P.; Grubbs, R. H. *J. Org. Chem.* **1999**, *64*, 5463.

(13) Guidry, E. N.; Cantrill, S. J.; Stoddart, J. F.; Grubbs, R. H. *Org. Lett.* **2005**, *7*, 2129.

(14) Ji, S.; Hoye, T. R.; Macosko, C. W. *Macromolecules* **2004**, *37*, 5485-5489.

(15) Fürstner, A.; Ackermann, L.; Gabor, B.; Goddard, R.; Lehmann, C. W.; Mynott, R.; Stelzer, F.; Thiel, O. R. *Chem. Eur. J.* **2001**, *7*, 3236.