The Chain-Length Dependence Test

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ABSTRACT

Trends obtained from systematic studies based on chain-length variation have provided valuable insight and understanding into the behavior of *m*-phenylene ethynylene foldamers. The generalization of this experimental approach, the chain-length dependence test, is useful for studying solution conformation, packing in the solid state, specific intrachain interactions, and the contributions of end groups to a particular property.

Introduction

A chain-length dependence test (CLDT) is the measurement of an observable quantity over a series of discrete oligomers that vary systematically in their number of monomer units. While simple in concept, the trends obtained from CLDT studies often provide valuable insight into the behavior of macromolecular systems that would be difficult to obtain from any single measurement. For instance, CLDTs are useful for studying solution conformation, packing in the solid state, specific intrachain interactions, and the contribution of end groups to a particular property. The CLDT is not a new experiment; its origin dates back to 1926 when Staudinger et al. employed this technique to obtain definitive evidence for the macromolecular hypothesis of polymers.[1] Over the years, CLDTs have contributed significantly to our fundamental understanding of biomacromolecules in solution.[2−6] Despite this long history, we hope that the examples highlighted in this Account will stimulate further development of this valuable experimental protocol.

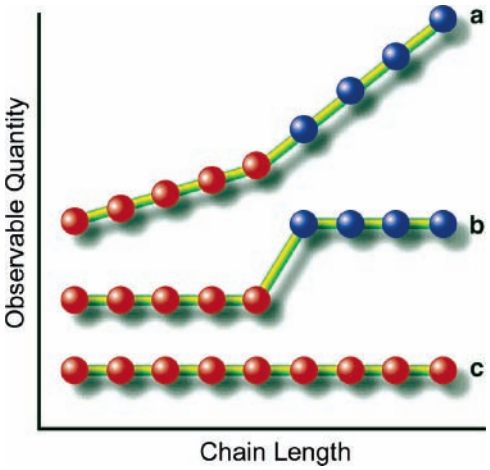

FIGURE 1. Signatures of a critical chain-length phenomenon include (a) a discontinuous change in slope or (b) an abrupt jump in a measured property over a homologous oligomer series. "Reference series" (c) exhibits chain-length independence and is useful as a data set against which a chain-length-dependent series can be compared.

There are many possible outcomes of CLDTs. Chain-length independence is one of the simplest results. This seemingly uninteresting behavior is valuable as a "reference series," against which conditions and structural differences responsible for a chain-length-dependent phenomenon can be compared. A linear result is also common because many properties of chain molecules, such as their molecular weight and molar extinction coefficient, are directly proportional to chain length, while observables dominated by end-group effects often show asymptotic behavior. One of the most intriguing outcomes of the CLDT is the occurrence of a critical chain length. This behavior is marked by an abrupt change in the observable as the length of the chain is increased through a small increment (Figure 1). It is intriguing since incremental changes in chain length generally lead to incremental changes in the observable. Thus, critical chain-length phenomena often mark the onset of cooperativity in a macromolecule.

In 1997, we published an Account describing the structure and properties of shape-persistent molecular objects of nanoscale dimensions derived from *meta*-phenylene ethynylene (*m*PE) building blocks.[7] Among the topics discussed was our discovery that *hexakis*(*m*PE) macrocycles self-associate in solution, apparently stabilized by face-to-face π-stacking interactions. In the concluding paragraphs of the Account, we speculated on the

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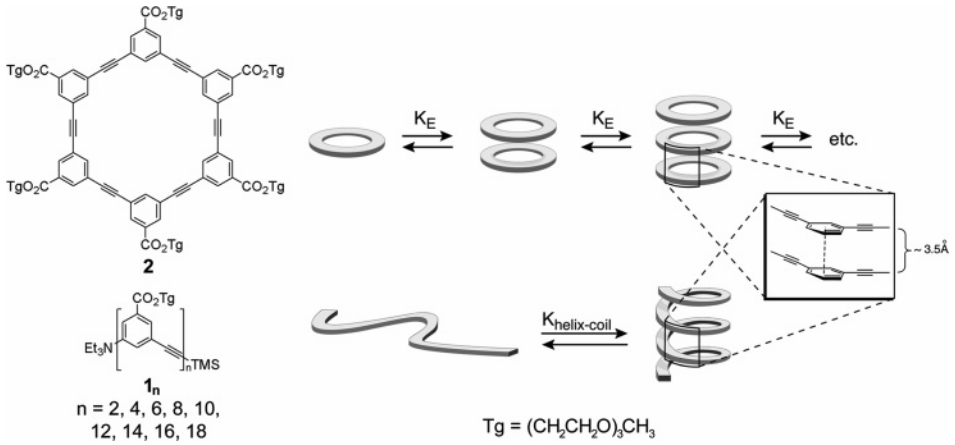


FIGURE 2. Relationship between intermolecular aggregation of *m*PE macrocyles and the intramolecular folding of linear *m*PE oligomers. Reprinted in part from *J. Am. Chem. Soc.* **2000**, *122*, 11315−11319, with permission from the American Chemical Society. Copyright 2000, American Chemical Society, Washington, DC.

possibility of an intramolecular counterpart to this intermolecular self-association. Specifically, we wondered if, in solution, linear oligomers would wrap themselves into a helical conformation, stabilized by π-stacking interactions between nonadjacent monomers (Figure 2). It was about this time that other researchers were independently beginning to envision the concept of foldamers;[8] that is, families of synthetic chain molecules analogous to biomacromolecules in their ability to adopt regular conformations in solution. As we began this work, we wondered how we would determine whether the purported helix was in fact the dominant solution conformation. Obviously, we could not rely on the well-known spectroscopic signatures that had been established for α-helical or β-sheet peptides or double-helical nucleic acids. The compelling evidence that answered our question was found in the CLDT. In the remainder of this Account, we describe how this research story progressed, focusing on those investigations that employed the CLDT.

Employing the CLDT To Establish Structure

In 1995, with the encouragement of colleague Peter Wolynes, the group became motivated to search for new classes of foldable oligomers. Our experience with *m*PE macrocycles had shown that electron-withdrawing substituents on the phenyl ring led to stronger intermolecular self-association, and we speculated that these interactions might be further strengthened by the addition of a solvophobic driving force. However, all of the macrocyles that we had prepared to this point were hindered by limited solubility in polar solvents. Graduate student James Nelson already had experience preparing discrete *m*PE oligomers; therefore, the task fell to him to find a side chain that solubilized these molecules. We settled on oligomer series **1** with its triethylene glycol side chain connected through a benzoate linkage, because ethylene oxide chains are known to have good solubility in a variety of polar solvents. Indeed, when macrocycle **2** was synthesized and studied, it exhibited good solubility in a wide range of solvents. Furthermore, the propensity of this macrocycle to self-associate was strongly solvent-dependent as the self-association constant of **2** in chloroform was only ca. 50 M^{-1}, while in acetone, it was ca. 15 000 M^{-1}. We reasoned that the macrocyles were aggregating to avoid unfavorable solvent interactions with the aromatic rings and that these solvophobic forces would also drive linear *m*PE oligomers to adopt a helical structure under similar conditions.

In the early days of this project, it was unclear what signatures could be found that would be indicative of helical order. Nonetheless, we reasoned that there may be a critical chain length, below which the oligomer would not benefit from a sufficient number of intrachain contacts to overcome the entropic cost of helix formation. A CLDT thus seemed to be a reasonable experimental approach. The first intriguing observation was an abrupt increase in the intermolecular self-association as a function of chain length. From vapor pressure osmometry measurements, the shortest chains were found to be minimally self-associated in acetonitrile. However, the self-association constant of the longer chains increased substantially from 45 M^{-1} for $\mathbf{1_8}$, to 200 M^{-1} for $\mathbf{1_{10}}$, and then to 1200 M^{-1} for $\mathbf{1_{12}}$.[9] What caused this dramatic climb in self-association? We speculated that this behavior represented the onset of a stable, conformationally ordered state, but further evidence was obviously needed.

Characterization of oligomer series **1** by ^{1}H NMR and UV spectroscopy provided more convincing evidence that oligomers having more than eight monomer units exhibit a reversible transition from a random to a helical conformation in response to changes in solvent quality.[10] NMR studies in acetonitrile-d_3 were hampered by the tendency of the presumably folded oligomers to self-associate; however, under dilute conditions where intermolecular association is minimized (e.g., 10 μM), a significant upfield shift was observed for chains longer than eight monomer units. As a set of reference data, spectra recorded in chloroform displayed chemical shifts that were virtually independent of the chain length, strongly suggesting that solvophobic forces were driving folding. Similarly, a set of UV data collected in acetonitrile revealed an abrupt change in the band shape between $\mathbf{1_8}$ and $\mathbf{1_{10}}$, while in

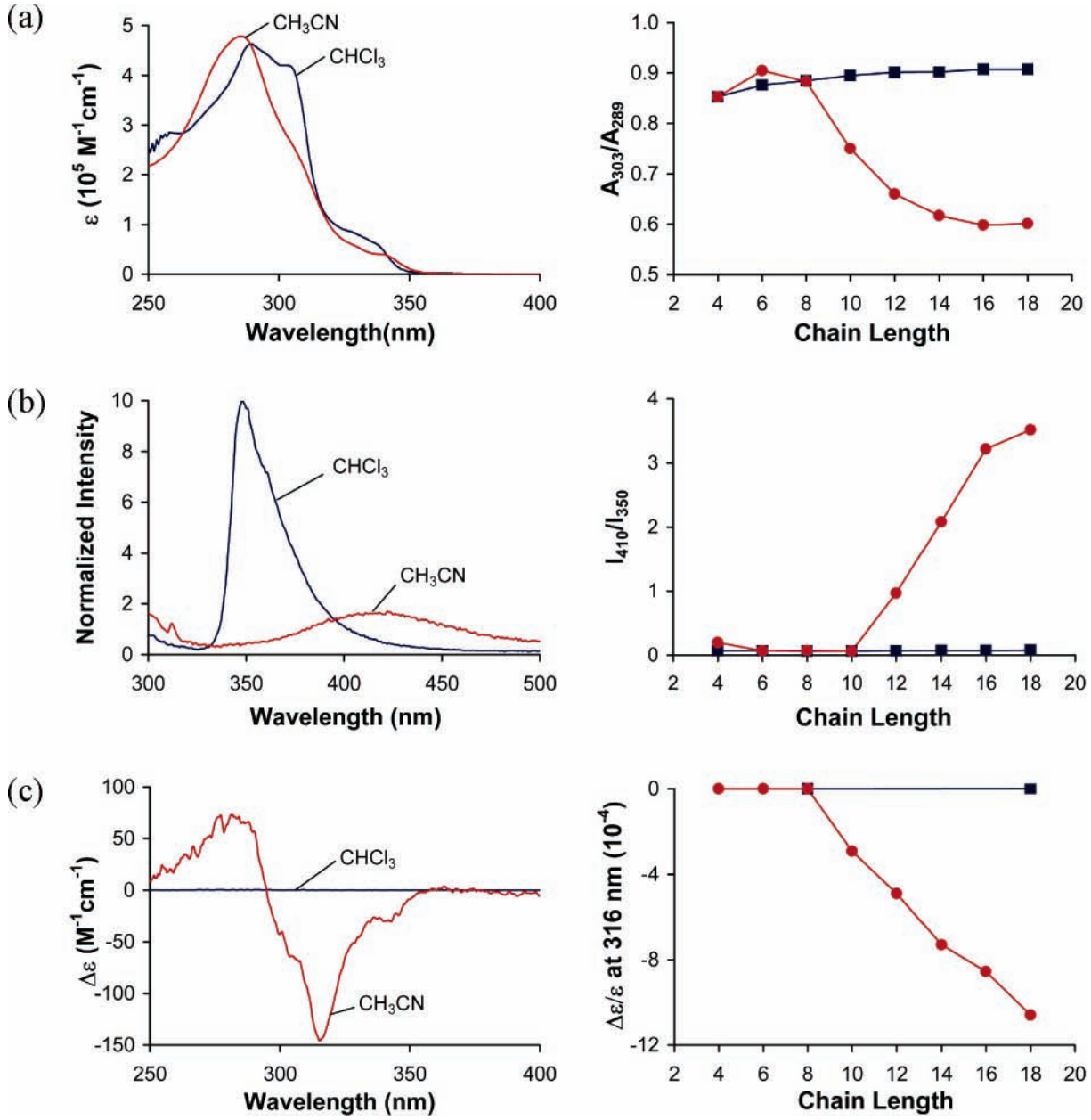
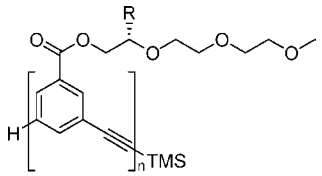


FIGURE 3. (a) UV spectra of $\mathbf{3_{18}}$ (left) and the ratio of absorbances at 303 and 289 nm for $\mathbf{3_4}$–$\mathbf{3_{18}}$ (right). (b) Fluorescence spectra of $\mathbf{3_{18}}$ (left) and the ratio of fluorescence intensities at 410 and 350 nm for $\mathbf{3_4}$–$\mathbf{3_{18}}$ (right). (c) CD spectra of $\mathbf{4_{18}}$ (right) and anisotropy factor ($\Delta\epsilon/\epsilon$) at 315 nm for $\mathbf{4_4}$–$\mathbf{4_{18}}$ (right). Data collected in $CHCl_3$ are indicated by blue ■, and those collected in CH_3CN are indicated by red ●.

chloroform, a consistent band shape was observed over the entire series.



$\mathbf{3_n}$, R = H
$\mathbf{4_n}$, R = CH_3
n = 2, 4, 6, 8, 10, 12, 14, 16, 18

After this initial investigation, graduate student Ryan Prince synthesized oligomer series **3** and acquired UV and fluorescence spectra of these molecules in acetonitrile and chloroform.[11] We interpreted the ratio of absorbance bands at 303 and 289 nm in the UV spectra of $\mathbf{3_{18}}$ to be indicative of the conformation of the oligomer backbone. A high value of $A_{303/289}$ such as that observed in chloroform signified a random mixture of cisoid and transoid conformations, while a low value of $A_{303/289}$ such as that observed in acetonitrile signified a predominantly cisoid or folded conformation (Figure 3a). The fluorescence spectra of $\mathbf{3_{18}}$ also displayed solvent-dependent behavior, as the sharp emission peak centered at 350 nm in chloroform underwent a significant red-shift and peak-broadening in acetonitrile. This behavior is consistent with π-stacking between the aromatic rings as would be anticipated in the helical structure (Figure 3b).[12] In collaboration with Luc Brunsveld from E. W. (Bert) Meijer's

group at the Eindhoven University of Technology, oligomer series **4** having chiral side chains was also synthesized, allowing for characterization of the folding properties by circular dichroism (CD) spectroscopy.[13] Oligomer $\mathbf{4_{18}}$ showed no optical activity in chloroform, consistent with a random conformation. However, a strong Cotton effect with an exciton couplet was observed in acetonitrile, suggesting a highly ordered helical conformation in which the asymmetric side chains bias the handedness of the backbone (Figure 3c).

Although the solvent-dependent spectral properties of *m*PE oligomers were consistent with a random conformation in chloroform and a folded conformation in acetonitrile, the most conclusive support for these hypotheses was achieved by application of the CLDT. In chloroform, the spectral properties were found to be independent of the chain length, in agreement with the hypothesized random conformation. In contrast, the spectral properties in acetonitrile underwent a dramatic change from length-independent to length-dependent behavior when the chain was composed of ca. 10 monomer units. This is consistent with the length-dependent behavior expected from a helical conformation since the intramolecular π-stacking interactions that stabilize the folded structure are not present until the chain length exceeds at least one helical turn.

Subsequent studies of *m*PE oligomers provided a more detailed understanding of the helical conformation and energetics of folding in solution. Spin labeling experiments carried out by visiting scientist Kenji Matsuda and graduate student Matthew Stone found that the helix consisted of ca. six monomers per helical turn.[14] The importance of the electronic properties of the *m*PE backbone to the stability of the folded conformation were examined by graduate students Shreyasi Lahiri and Julie Thompson.[15] Moreover, the role of the solvent in stabilizing the helical conformation was explored by graduate student David Hill.[16]

Having established that *m*PE oligomers can adopt a folded conformation in solution, we wondered if they would maintain this conformation in the solid state. Such tubular structures could function as nanoporous materials with potential applications including semipermeable membranes, catalysts, and sensors.[17,18] The waxy morphology of *m*PE oligomers precluded single-crystal X-ray diffraction studies. However, X-ray powder diffraction experiments in conjunction with the CLDT allowed us to elucidate the supramolecular packing of *m*PE oligomers. We anticipated that two packing modes could accommodate aromatic stacking interactions in the solid state (Figure 4). One packing mode is a lamellar arrangement in which the backbone adopts an extended transoid conformation. The second is a nanoporous columnar arrangement reminiscent of the folded solution structure in which the backbone adopts an all cisoid helical conformation and individual helices are stacked atop one another.

An initial study into the solid-state packing of oligomers $\mathbf{3_8}$–$\mathbf{3_{18}}$ was performed by graduate students Peggy-Jean

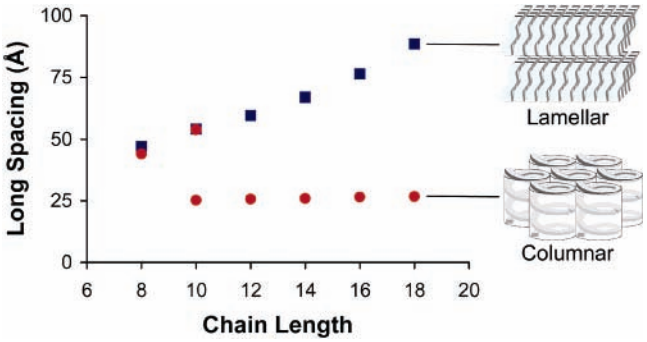
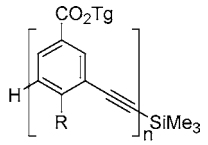


FIGURE 4. Small-angle X-ray diffraction data for oligomers series **3** (blue ■) and **5** (red ●). The d spacings of the 100 diffraction pattern (i.e., the long spacings) are plotted as a function of the chain length. Linear dependence of series **3** is consistent with lamellar packing, while the length-independent behavior of series **5** suggests columnar packing. Reprinted in part from *J. Am. Chem. Soc.* **2000**, *122*, 6134–6135, with permission from the American Chemical Society. Copyright 2000, American Chemical Society, Washington, DC.

Prest and Ryan Prince in which the CLDT was applied to the long spacings observed from small-angle X-ray diffraction (SAXD).[19] The long spacings showed a linear dependence upon the chain length, consistent with lamellar packing as the height of the rows increases linearly with the number of monomer units, giving good agreement with models. Despite our success in the structural assignment of oligomers **3** in the solid state, the nanoporous columnar mode of *m*PE oligomers remained elusive.



$\mathbf{3_n}$, R = H
$\mathbf{5_n}$, R = CH_3
n = 8, 10, 12, 14, 16, 18

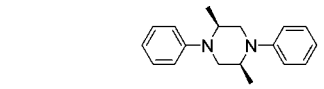
In further studies, graduate student Matthew Mio examined *m*PE oligomers $\mathbf{5_8}$–$\mathbf{5_{18}}$ having a methyl group directed toward the cavity interior. These methyl-substituted oligomers had exhibited higher melting points and increased folding stabilities in solution relative to oligomers **3** of the same length, presumably because of their smaller hydrophobic cavity.[20] On the basis of these observations, we suspected that oligomers of series **5** would have a better chance to pack in the columnar arrangement than **3**. In contrast to series **3**, the CLDT for the long spacings of series **5** showed an abrupt change in packing behavior that correlated with the onset of folding in acetonitrile. Oligomer $\mathbf{5_8}$ is not long enough to fold in solution and was found to have a long spacing that indicated lamellar packing. Oligomer $\mathbf{5_{10}}$ gave a weak signal indicating lamellar packing but also had a second, stronger reflection that was consistent with the centroid–centroid spacing calculated for columnar packing. A mixture of packing modes is reasonable for $\mathbf{5_{10}}$, considering that this length represents the threshold for folding in solution. Longer oligomers $\mathbf{5_{12}}$–$\mathbf{5_{18}}$ have stable folded

conformations in solution and gave length-independent long spacings consistent with columnar packing. Further support for this packing model was provided by the SAXD diffraction patterns that manifested 6-fold symmetry, consistent with a hexagonal arrangement of the helical columns. Our ability to control the structure of *m*PE oligomers both in solution and in the solid state lead us to contemplate how the energy gained through this folded conformation might influence the reactivity of these structures.

Studying Reactivity with the CLDT

An obvious place to begin probing the reactivity of *m*PE oligomers was the presumably hydrophobic interior of the helix, which is the appropriate size and shape to bind small molecule guests. Graduate student Ryan Prince along with undergraduate student Stephanie Barnes found that guest binding could be observed by exploiting the dynamic helical nature of the folded oligomers. In solution, the oligomers exist as a racemic mixture of M and P helices; however, binding with a chiral guest results in diastereomeric complexes that favor one helical twist sense. This shift in the equilibrium of the helical handedness can be detected as an induced circular dichroism (ICD) signal, and monitoring the ICD signal as a function of the guest concentration allows determination of the association constant.[21]

In an initial study of guest binding, we demonstrated that *m*PE dodecamer $\mathbf{3_{12}}$ was capable of forming a 1:1 complex with monoterpene guests by binding them within the helical cavity.[22] We then identified chiral rodlike guest **6** as having a complementary shape to the cylindrical cavity of the helix and hypothesized that the association constant of *m*PE oligomer series **3** with this guest would be dependent upon the length of the oligomer, favoring oligomers having a folded conformation similar in length to the guest (Figure 5a).[23] To this end, visiting scientist Aya Tanatani synthesized rodlike guest **6** and measured its association constant with oligomer series $\mathbf{3_{10}}$–$\mathbf{3_{24}}$ in 40% aqueous acetonitrile using the ICD method (Figure 5b). Application of the CLDT revealed that the association constants of the *m*PE oligomers for rodlike guest **6** increased with the chain length until reaching a plateau for $\mathbf{3_{20}}$ and $\mathbf{3_{22}}$. The plateau occurred at the point where the length of the guest matched the length of the helical cavity.



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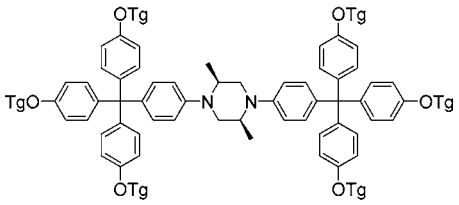

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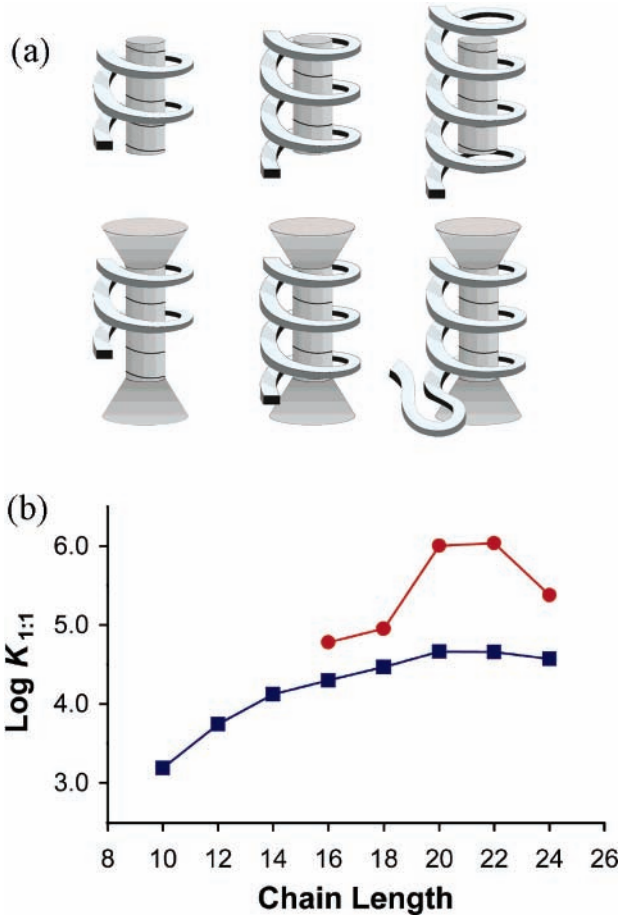


FIGURE 5. (a) Schematic diagram showing increasing lengths of helical *m*PE oligomer complexed with the rodlike guest **6** (top) and capped guest **7** (bottom). (b) Log of the association constant of guests **6** (blue ■) and **7** (red ●) with series **3** oligomers plotted as a function of the length. Values determined in 40% water in CH_3CN.

To increase chain-length specificity, trityl capping groups were added to the ends of rodlike guest **6**. Binding of capped guest **7** with longer oligomers would be sterically disfavored since the caps would distort the folded conformation.[24] Interestingly, a significant overall increase in the association constants was observed for capped guest **7** relative to rodlike guest **6** at corresponding oligomer lengths (Figure 5b). This increased affinity was attributed to aromatic–aromatic interactions between the trityl caps and the end of the folded oligomer. In contrast to rodlike guest **6**, the CLDT revealed a significant specificity for oligomers $\mathbf{3_{20}}$ and $\mathbf{3_{22}}$, as the association constants at these chain lengths were nearly an order of magnitude greater than at the other lengths measured. As predicted, oligomer $\mathbf{3_{24}}$ was found to have a lower association constant relative to $\mathbf{3_{20}}$ and $\mathbf{3_{22}}$ presumably due to the steric hindrance of the capping groups.

Given the capacity of folded *m*PE oligomers to bind guest molecules, we endeavored to probe the reactivity of functional groups within the hydrophobic cavity. To this end, graduate student Jennifer Heemstra synthesized oligomer series **8** incorporating a *N*,*N*-(dimethylamino)-pyridine (DMAP) monomer such that the pyridine nitrogen is located on the interior of the helical cavity (Figure

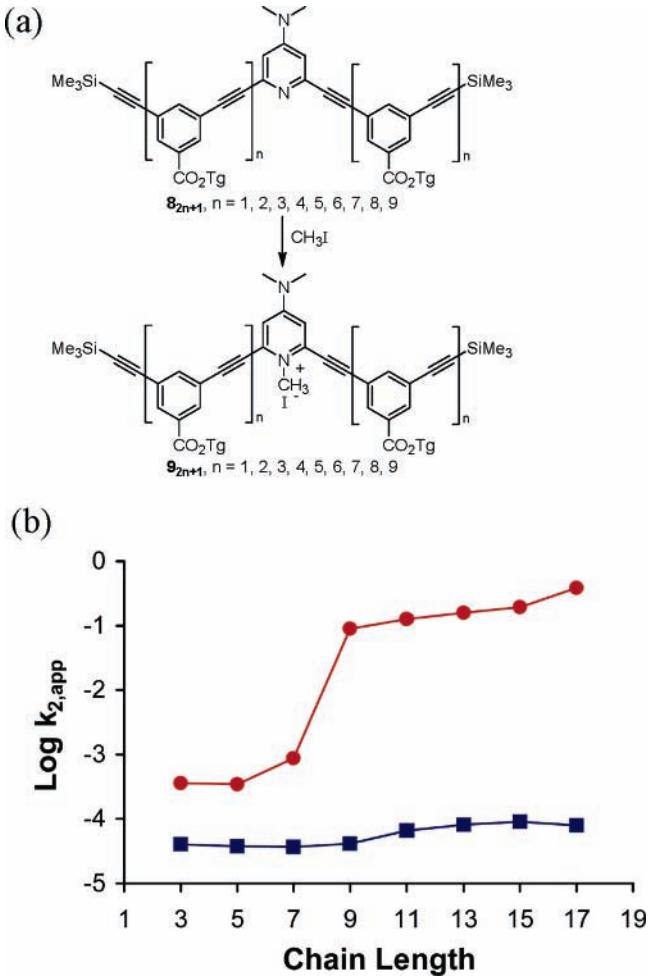


FIGURE 6. (a) Reaction of methyl iodide with DMAP-substituted oligomers **8**. (b) Methylation rate of oligomers **8** in $CHCl_3$ (blue ■) and CH_3CN (red ●).

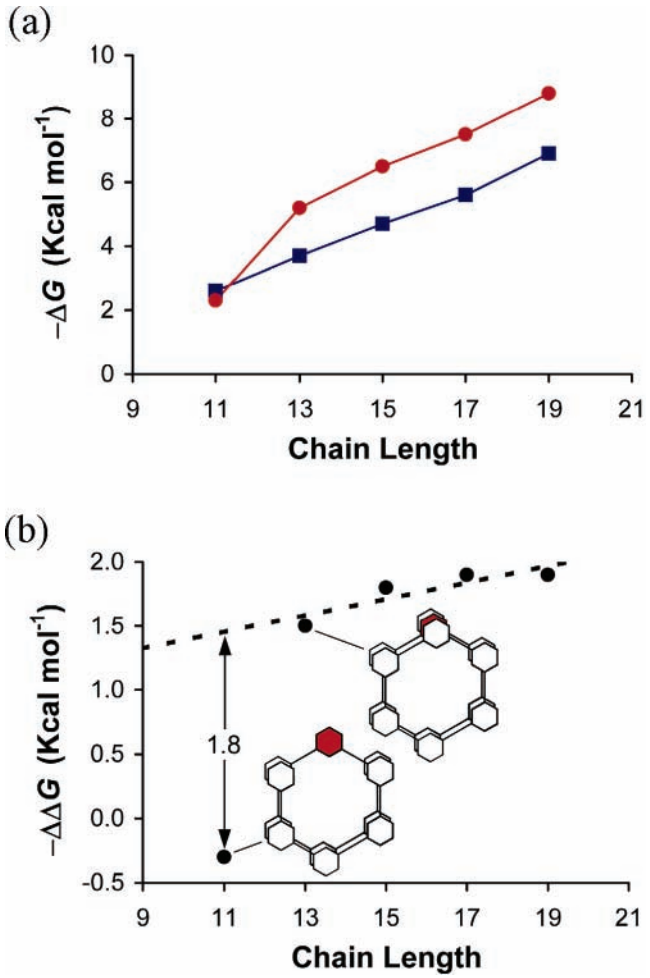


FIGURE 7. (a) Folding stability of oligomers **8** (blue ■) and **9** (red ●). (b) Difference in folding stability between the series attributed to the presence of pyridinium−π interactions. The undecamers (n = 11) deviate from this trend because they are too short to benefit from these interactions. DMAP rings are highlighted in red.

6a). Using UV spectroscopy, the methylation rates of the oligomers were measured in both acetonitrile and chloroform under pseuso-first-order reaction conditions using a large excess of methyl iodide.[25] In chloroform, a slight rate increase was observed with increasing oligomer length, possibly resulting from pyridinium−π interactions between the pyridine ring and the freely rotating *m*PE arms (Figure 6b). In great contrast, the methylation rate in acetonitrile was found to be dependent upon the oligomer length, although not in the linear fashion observed for chloroform. Instead, a critical chain length was observed at ca. eight monomer units as the addition of only two monomer units from $\mathbf{8_7}$ to $\mathbf{8_9}$ increased the methylation rate by 2 orders of magnitude. The correlation between this critical chain length and the minimum length required for *m*PE oligomers to adopt a stable helical conformation in acetonitrile suggested that oligomer folding plays an important role in modulating the rate of the methylation reaction. A subsequent competitive inhibition study demonstrated that the observed rate acceleration results from binding of methyl iodide within the helical cavity of the folded oligomers, where it is constrained in close proximity to the pyridine nucleophile.[26]

We wondered how the introduction of a methyl pyridinium ion would contribute to the conformational stability of the helix through cation−π interactions. The folding stability, $-\Delta G(CH_3CN)$, for oligomers $\mathbf{8_{11}}$−$\mathbf{8_{19}}$ and their corresponding pyridinium products $\mathbf{9_{11}}$−$\mathbf{9_{19}}$ in acetonitrile was determined as a function of the oligomer length (Figure 7a).[27] The difference in folding stability between the two series, $-\Delta\Delta G(CH_3CN)$, revealed a critical chain length. As the oligomer length increased from 11 to 13 monomer units, $-\Delta\Delta G(CH_3CN)$ rose sharply from −0.3 to 1.5 kcal mol^{-1}, while further increases in length showed much smaller differences in stability (Figure 7b). This might be explained by considering that in oligomers having 13 or more monomer units the pyridine ring is sandwiched between two phenyl rings, allowing oligomers $\mathbf{9_{13}}$−$\mathbf{9_{19}}$ to have pyridinium−π interactions.[28] In contrast, oligomers having only 11 monomer units are not of sufficient length to benefit from these interactions (inset of Figure 7b). On the basis of extrapolation of the energy differences from the longer lengths, oligomers composed of only 11 monomer units were found to deviate from this trend by 1.8 kcal mol^{-1}. This deviation was attributed to the absence of pyridinium−π interactions.

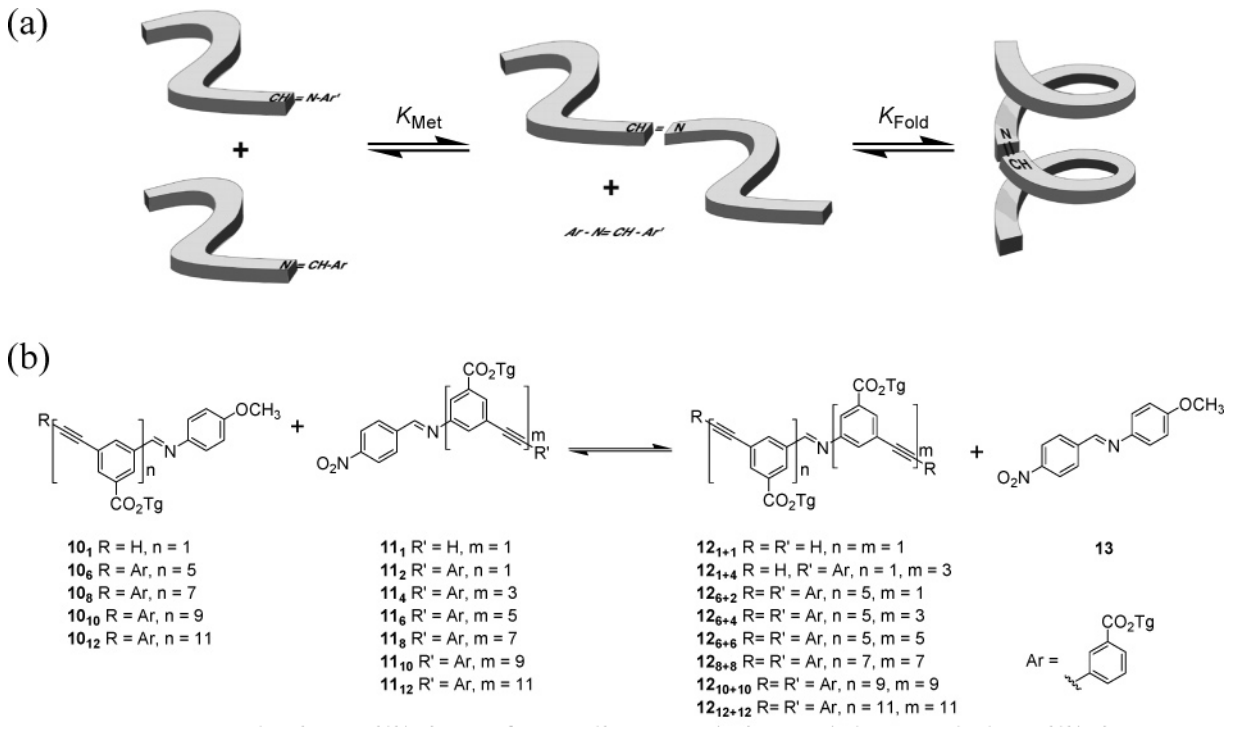


FIGURE 8. (a) Metathesis equilibrium of two oligomer chains and the coupled equilibrium between the denatured and folded conformation of the ligated strand. (b) N- and C-imine-terminated oligomers and products formed by the metathesis reaction.

It was realized that the energy gained through intrachain contacts might be employed to alter the reactivity of the *m*PE oligomer chains beyond what would be predicted by traditional steric and electronic analyses. We decided to test this idea by studying the reaction of oligomer segments joined together by dynamic covalent bonds since equilibrium reactions of these molecules should be influenced by the energy gained through folding interactions. Such oligomers were also intriguing because they could potentially provide dynamic combinatorial libraries.[29] Graduate student Kuenchan Oh and visiting professor Kyu-Sung Jeong found that *m*PE chains joined with an imine linkage had a geometry compatible with the folded helical conformation. Under acidic conditions, the imine-connected oligomers were found to interconvert at a reasonable rate at room temperature via imine metathesis. The equilibrium constant for this metathesis process was known to be close to unity, and therefore, any shifting of the equilibrium distribution of the products could be attributed to supramolecular driving forces, such as folding or guest binding (Figure 8a). An imine-linked oligomer was synthesized and found to have nearly identical folding properties as a *m*PE oligomer of the same length, confirming that the linkage was compatible with the helical conformation.[30] A CLDT was then employed to probe the relationship between conformational stability and the equilibrium distribution of products.

A series of N-terminated imine oligomers **10** and C-terminated imine oligomers **11** of varying lengths were synthesized and reacted under metathesis conditions (Figure 8b).[31] The concentration of components in the metathesis reaction was determined by ^{1}H NMR spectroscopy, allowing the calculation of the equilibrium

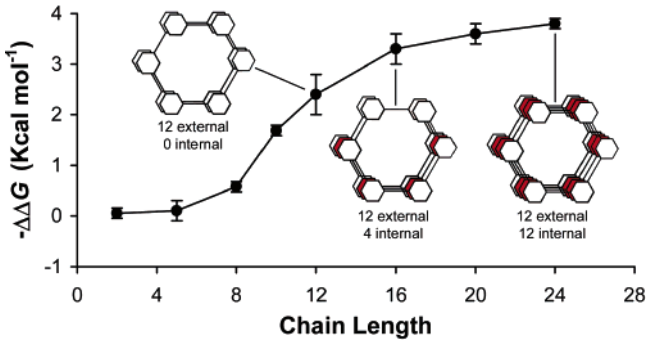


FIGURE 9. Free-energy change for the imine metathesis reaction plotted as a function of the length of product **12**. Asymptotic dependence upon length is explained by the diminishing role that K_{fold} contributes to the coupled equilibrium. For the longest oligomers, the precursor segments are folded prior to metathesis, and stability of products results mainly from contacts between internal segments (colored in red).

constants for reactions involving various combinations of **10** and **11**. The imine linked dimer $\mathbf{12_{1+1}}$, which is unable to fold, was used as a reference to quantify equilibrium shifting. The extent of equilibrium shifting was plotted as a function of the chain length (Figure 9). Imine products composed of less than eight monomer units showed no equilibrium shifting, consistent with the fact that these chains are too short to adopt a folded conformation. In contrast, metathesis reactions forming products composed of eight or more monomer units displayed equilibrium shifting, presumably driven by the coupled folding equilibrium. Our initial investigation of $\mathbf{12_{6+2}}$−$\mathbf{12_{6+6}}$ found that equilibrium shifting was linearly dependent upon the chain length, which is logical because every additional

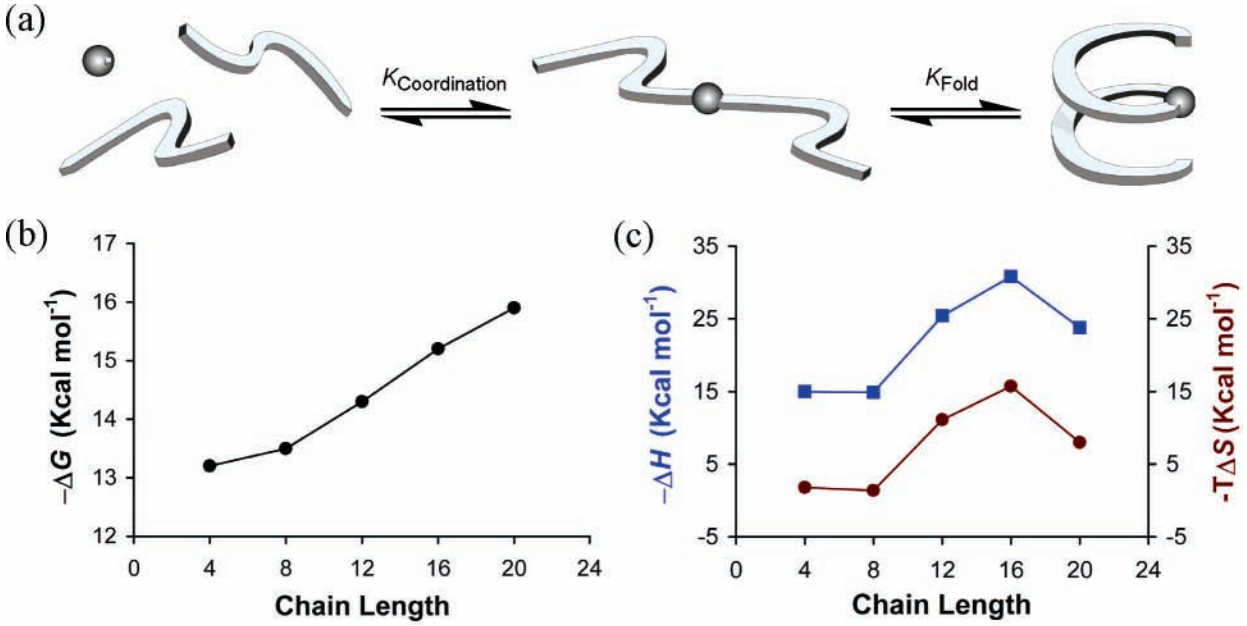


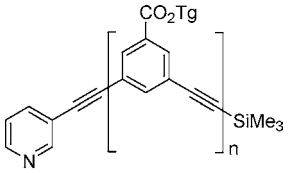
FIGURE 10. (a) Folding-driven coordination of two *m*PE oligomer units to a metal center. (b) Free energy ΔG of complexation for **13** to $PdCl_2(CH_3CN)_2$. (c) Entropy $T\Delta S$ (red ●) and enthalpy ΔH (blue ■) of complexation for **13** to $PdCl_2(CH_3CN)_2$. The oligomer length refers to the total number of aromatic rings in the 2:1 palladium complex.

monomer unit gives one additional intramolecular contact. However, upon extending the study to longer products, we discovered an asymptotic dependence upon the chain length, suggesting that end effects are playing a role in the observed behavior.

Insights gained from CLDTs of imine-linked *m*PE oligomers allowed visiting scientist Tohru Nishinaga to develop a dynamic combinatorial synthesis of an oligomer, whose length was best suited to bind capped guest **7**.[32] Moreover, *m*PE oligomers terminated at both ends with imines allowed graduate student Dahui Zhao to explore reversible polymerizations that proceeded though a nucleation−elongation mechanism. She also showed that the products were driven to high molecular weights by folding.[33−35]

On the basis of the imine metathesis studies, we envisioned that folding energy could also be used to modulate the coordinative ability of functional groups appended to the ends of *m*PE oligomers. Coordination of two oligomer chains to a metal center would result in a complex with twice the number of monomers per strand. If the resulting strand is longer than the critical chain length, additional stability can be gained by adopting a folded helical conformation (Figure 10a). Stabilization of the complex by folding was therefore expected to shift the equilibrium of metal complexation.

To test this idea, graduate student Matthew Stone prepared pyridine-terminated oligomers **13** capable of coordinating a palladium dichloride ion. The resulting geometry around the metal center was determined to be a good match to that of the *m*PE backbone. CLDT studies were conducted with oligomer series **13** using UV absorption and NMR spectroscopy. It was found that the addition of *trans*-dichlorobis(acetonitrile)palladium to $\mathbf{13_6}$ in acetonitrile gave a complex that was effectively 12 monomer units long and adopted a folded conformation.[36] The thermodynamics of complexation with palladium were then investigated by isothermal calorimetry. The CLDT was applied to free energy, enthalpy, and entropy of the complexation (Figure 10b).



$\mathbf{13_{n+1}}$, n = 1, 3, 5, 7, 9

The free energy of complexation increased linearly with the chain length, while enthalpy and entropy gave a more complex behavior. The enthalpy and entropy of complexation for oligomers $\mathbf{13_2}$ and $\mathbf{13_4}$ are equivalent within error, which was anticipated since their palladium complexes are unable to adopt a folded conformation. The increased enthalpy of complexation for $\mathbf{13_6}$ and $\mathbf{13_8}$ is consistent with the formation of ca. six and eight new aromatic−aromatic contacts upon folding of these complexes, respectively (Figure 11). The increase in enthalpy is accompanied by an increase in the entropy that is explained by restricted rotation of 9 bonds for $\mathbf{13_6}$ and 13 bonds for $\mathbf{13_8}$ when complexes of these oligomers adopt a folded conformation. The decrease in enthalpy for $\mathbf{13_{10}}$ can be understood since the oligomer is folded prior to coordination and therefore only six new aromatic−aromatic contacts are formed upon complexation. However, the free energy of complexation for $\mathbf{13_{10}}$ is greater than $\mathbf{13_8}$, owing this additional coordinative ability to its extensive pre-organization. These analyses also provided

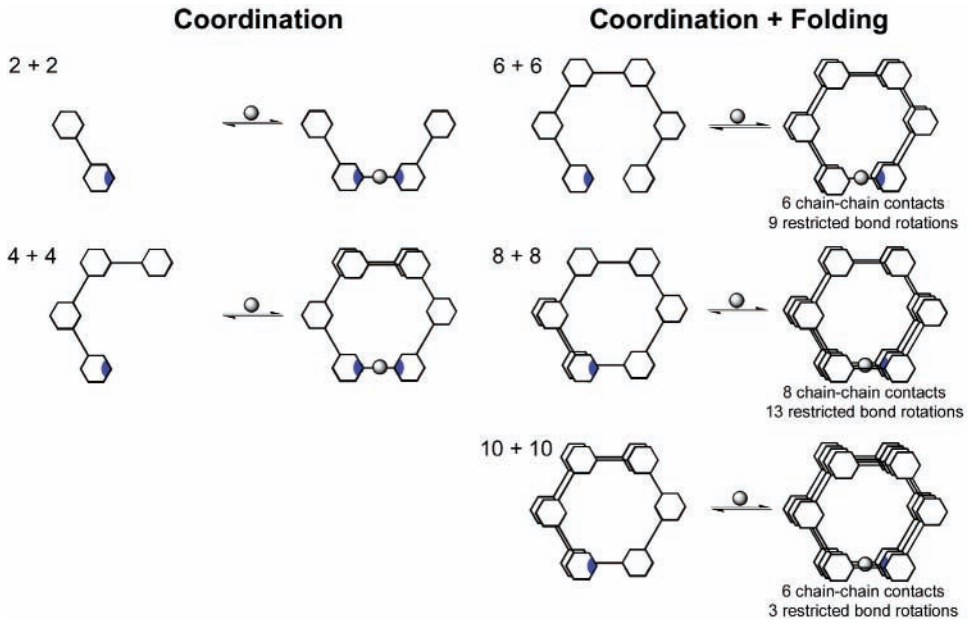


FIGURE 11. Simplified model of complexation thermodynamics of **13** that explains length-dependent behavior. Note that oligomers composed of eight monomer units are incapable of folding.

further thermodynamic insight into the equilibrium shifting observed in the imine oligomers mentioned above.

Future Directions

Having established properties of *m*PE oligomers such as structure, binding, and enhanced reactivity using the CLDT, we have recently begun to customize the interior to develop efficient supramolecular catalysts. Highly symmetric molecular containers, such as cavitands, have previously been demonstrated to function as supramolecular catalysts. However, it is difficult to alter the shape of their cavity or position multiple functional groups at prescribed locations on the interior surface of these molecular containers. Modification of the cavity interior is critical to developing substrate specificity and fine-tuning reactivity. The modular construction of *m*PE oligomers has the advantage that incorporation of functionalized monomers into the chain sequence results in a predictable three-dimensional arrangement within the folded cavity. To exploit *m*PE oligomers as efficient supramolecular catalysts will require the development of facile methods to design, synthesize, and efficiently analyze heterosequences. Understanding the sequence-dependent properties is likely to be as important to the next stage of the project as chain-length dependence was to understanding the basic structure and reactivity of *m*PE foldamers.

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