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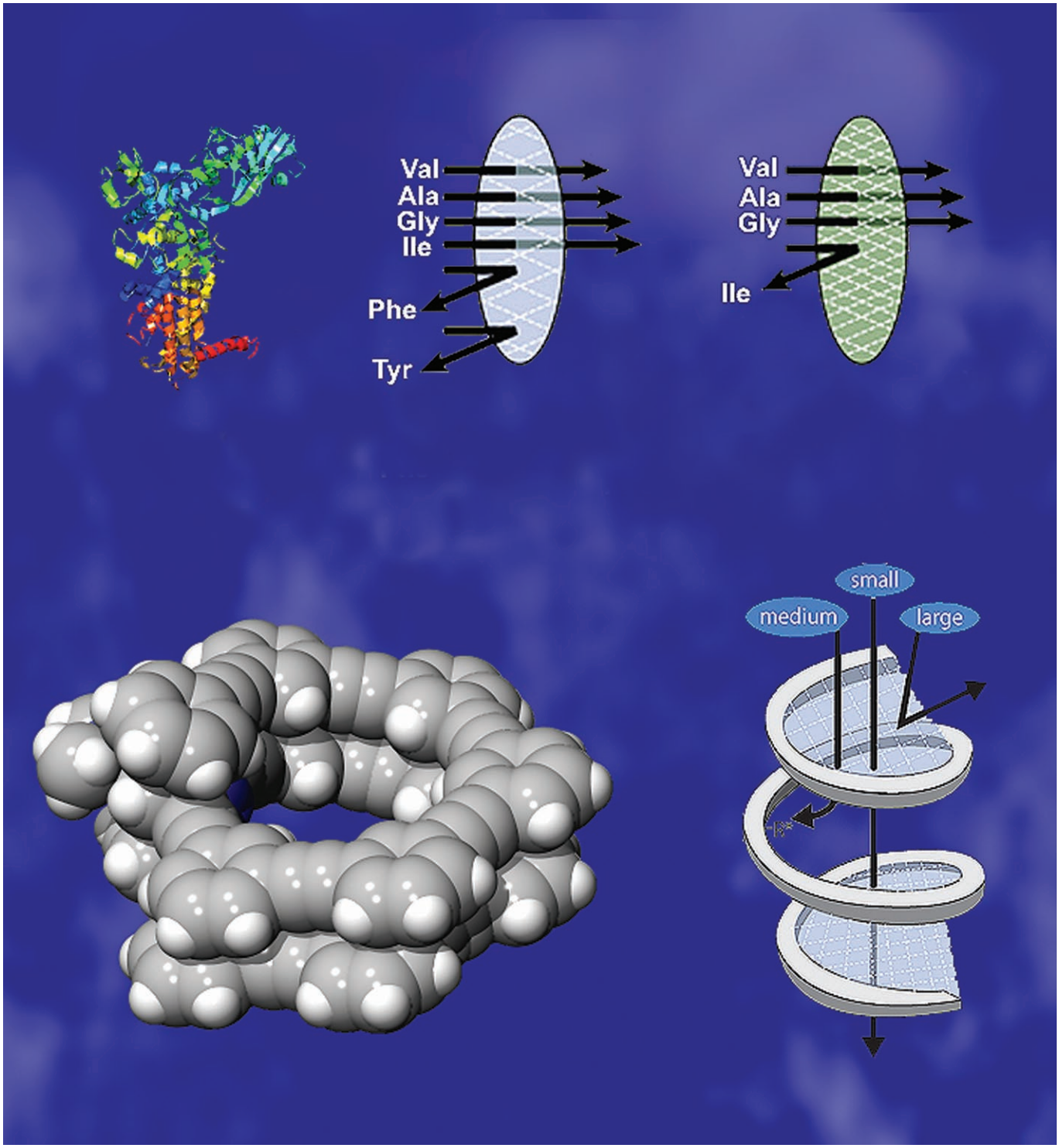
Reactive Sieving with Foldamers: Inspiration from Nature and Directions for the Future

Ronald A. Smaldone and Jeffrey S. Moore*[a]



Abstract: Over the past several decades, chemists have designed a myriad of supramolecular scaffolds for the purpose of mimicking enzyme behavior and creating more advanced catalysts. Foldamers, one class of supramolecular structures that feature rapid, modular synthesis and dynamic structural properties and have been widely investigated for their molecular recognition properties. Specifically, our group has designed a reactive *m*-phenyleneethynylene foldamer, which mimics the selective properties ("reactive sieving") of the isoleucine tRNA synthetase enzyme. In this concept we discuss examples that have inspired our research as well as potential directions for future advancement of this field.

Keywords: cavitands · foldamers · peptide catalysis · supramolecular chemistry · synthetic enzymes

Introduction

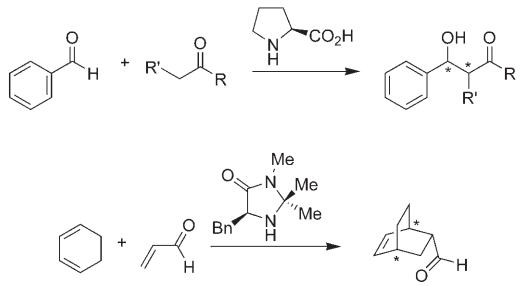
"What I cannot create, I do not understand"
-Richard Feynman

The design of catalysts for use in synthetic chemistry is a major cornerstone of chemical research. The advancement of synthetic methodology has largely centered on the design and development of small-molecule catalysts (both organometallic and organocatalytic) to elicit new types of conversions, or to make existing reactions exquisitely selective. In fact, two of the most recent Nobel Prizes in chemistry have been awarded for small-molecule catalyst development (alkene metathesis 2005, asymmetric catalysis, 2001). When small-molecule catalysts are developed, they are designed to be tolerant of a wide variety of functional group types that are not targeted for conversion (i.e., chemoselectivity provides compatibility). This allows for the catalyst to be applied generally to a wide range of substrates. Although the successes of small molecule catalysts have made their presence ubiquitous in synthetic chemistry, one problem that remains challenging is the ability to transform a single functional group on a molecule in the presence of equally accessible and equally reactive functionality without the use of protecting groups. Biomolecules are the gold standard in selective catalysis because of their ability to produce large rate enhancements relative to the uncatalyzed reaction while maintaining high levels of regio- and enantioselectivity.[1] The ability to re-create all of these desirable characteristics in a synthetic supramolecular system has yet to be achieved. This lack of success in the supramolecular field (in comparison to the widespread success of small-molecule catalysts) might indicate a deficient understanding of the origins of biological catalysis, which is itself actively debated in the literature.[2] To advance our understanding in a systematic way, chemists must have access to diverse molecular scaffolds that can be rapidly synthesized, and are capable of precisely positioning functional moieties in three dimensional space.

Modular construction is a powerful way to achieve diversity and complexity in structure from a simple set of position-interchangeable building blocks. Chain molecules built from a regular repeating unit provide a molecular-level example of this concept. There is no finer demonstration that illustrates the power of modularity than the functional diversity that comes from combinations of the 20 natural amino acids to produce polypeptide heterosequences. Foldamers, a heavily investigated class of synthetic molecules with a diverse membership, meet many of the required criteria and offer the potential for studying the aforementioned recognition and reactivity problems by creating highly controlled molecular compartments. In this concept article, we will discuss the limitations that exist in conventional catalysis and supramolecular chemistry and how advances in foldamer science may provide solutions to these problems.

"Limitations" of Conventional Small-Molecule Catalysis

The design of small-molecule catalysts for organic synthesis has enjoyed great success. To date, a variety of highly efficient, small-molecule catalysts with broad substrate generality have been synthesized and used extensively by chemists.[3–5] Shown in Scheme 1 are two examples of imine-based organocatalysts that have been heavily studied of late.[6] These catalysts react with ketones or aldehydes to form chiral imines which can then undergo other reactions (e.g., aldol, Michael addition, Diels–Alder) to give asymmetric



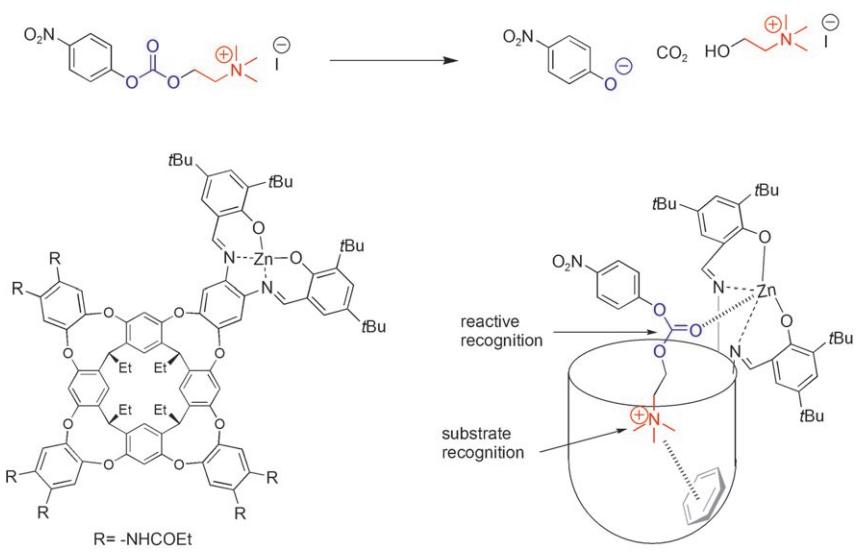
Scheme 1. Examples of imine-based organocatalysts for asymmetric synthesis.

[a] R. A. Smaldone, Prof. Dr. J. S. Moore
Departments of Chemistry
Materials Science and Engineering and
The Beckman Institute for Advanced Science and Technology
University of Illinois, Urbana, IL 61801 (USA)
E-mail: jsmoore@uiuc.edu

products. It can be seen in Scheme 1 that the peripheral groups attached to the reactants (i.e., R groups) are generally uninvolved with the outcome of the conversion. This "limitation" gives small-molecule catalysts their generality, but may limit their ability to select a single functional group out of many nearly identical reactive sites on a polyfunctional molecule (e.g., biomolecules, complex organic molecules). The demand for methodology to perform conversions with this type of selectivity has only increased in recent years with the desire to modify proteins and other biomolecules for the purpose of developing nanoscale devices, therapeutics and more advanced materials using approaches that are free of protecting groups.[7–10]

Cavitand-Based Supramolecular Catalysis

Over the past several decades studies that combine receptor binding and reactivity have attempted to create a "synthetic enzyme". The most common motifs include cyclodextrins, calixarenes, and resorcinarene-based cavitand molecules, all having been modified in various ways in an attempt to achieve this goal.[11–15] One elegant example of traditional supramolecular catalysis involves Rebek's resorcinarene-based cavitand (Scheme 2).[16] This structure is capable of catalytically hydrolyzing *p*-nitrophenylcholine carbonate (PNPCC) using a zinc ion attached to the rim of the cavity, which activates the carbonate for hydrolysis by a solvent water molecule and subsequent decarbonylation. The cavitand is able to recognize PNPCC through a cation–π interaction between the ammonium cation and the aromatic faces of the cavity.[17] There are many other examples of host–guest based catalysis in the literature that perform a variety of reactions including hydrolysis, oxidation, and Diels–Alder cycloadditions.[11,13]



Scheme 2. Example of a resorcinarene-based cavitand that combines host-guest molecular recognition with catalytic reactivity.[16]

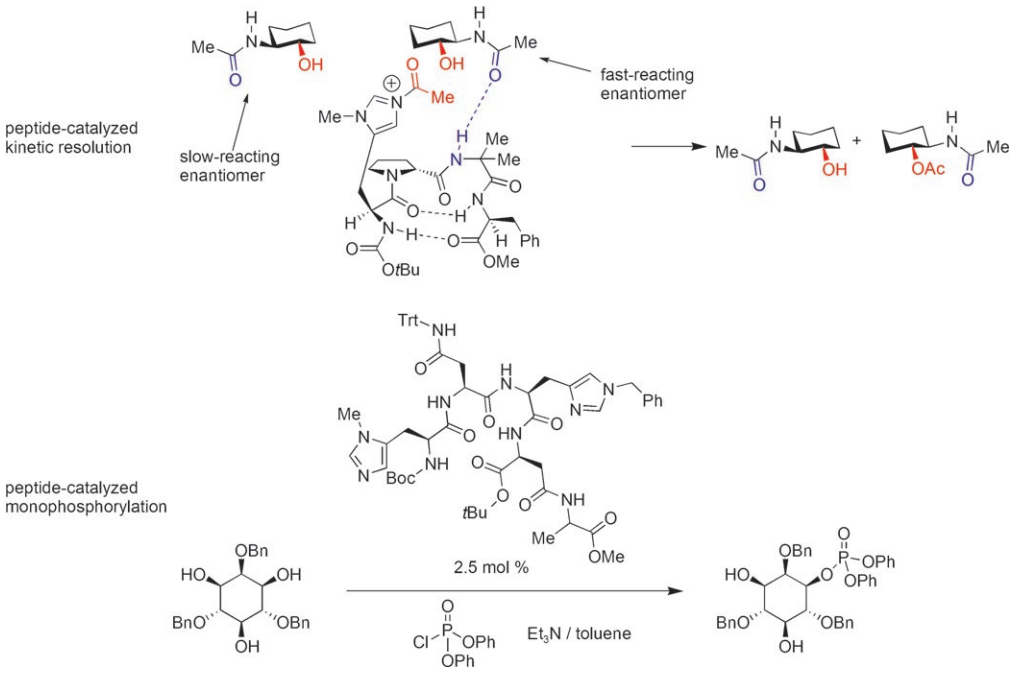
However, most of the systems studied to date have largely been unsuccessful at replicating the rate enhancements or substrate selectivity of enzymes. In addition, since these systems lack the generality of small-molecule catalysts, they have yet to be implemented as a practical technique in synthetic chemistry. The lack of widespread acceptance of these systems as synthetic reagents is probably a consequence of two major factors: the structures are generally rigid and achieve their rate enhancements simply through increases in effective molarity, and the syntheses of these systems can be lengthy, making the construction of a single supramolecular catalyst a project in itself. If synthetic catalysts that utilize sophisticated molecular recognition to enhance the selectivity of chemical reactions are to be created, these problems must be addressed.

Catalytic Peptide Sequences

While cavitand-based systems have contributed to our understanding of supramolecular catalysis, other approaches have made significant advances towards application of these concepts as a practical synthetic technique. Miller and coworkers have developed a number of short, synthetic peptides to perform a variety of reactions including kinetic resolutions of alcohols, aldol reactions, phosphorylation, Michael addition, and Morita–Baylis–Hillman reactions. Some examples of these are illustrated in Scheme 3, and many show significant promise.[18,19] These peptides, although less intensively studied than the previous areas, warrant discussion here. Of special note are Miller's peptides, which incorporate the advantages of the modular chemistry of oligomers. Although some of these catalytic peptides are short sequences (often as few as two amino acids), the most impressive examples are longer chains (between four and eight amino acids), possibly owing to a defined secondary structure. The monophosphorylation reaction shown in Scheme 3 is extremely interesting since the peptide is able to phosphorylate one specific hydroxyl group (98% *ee*) among three, equally reactive hydroxyls. The transformations that catalytic peptides perform are synthetically relevant making this a methodology of great interest.

tRNA Synthetase and Reactive Sieving

In synthesizing complex molecules without the use of protecting groups, enzymes recognize subtle differences in sub-



Scheme 3. Kinetic resolution (top) and phosphorylation (bottom) reactions catalyzed by short, synthetic peptides.

strate structure with high efficiency. One notable example of this behavior is observed in tRNA synthetase enzymes.[20,21] tRNA synthetases are responsible for the aminoacylation of a specific tRNA at the 3′ hydroxyl of the terminal nucleotide with the amino acid for which it is coded. Although amino acids can vary widely in their physical characteristics (shape, size, hydrophilicity), recognition of amino acids with small structural differences is a significant challenge. Residues such as valine and isoleucine differ by only a single methylene group, thus potentially opening the door for errors in protein biosynthesis during the tRNA aminoacylation process. In spite of this challenge, these enzymes operate with an extremely low rate of error (as low as 1 error for every 40000 base pairs).[21] This extraordinary selectivity is achieved using a "double sieve" mechanism (Figure 1), where the enzyme uses multiple binding pockets (sieves) to select the correct amino acid. The first sieve is referred to as the "coarse" sieve, which catalyzes the formation of the amino acid acyladenylate, but only for those substrates that are equal to or smaller in size than the target amino acid. A second "fine" sieve hydrolyzes all the amino acid acyladenylates that are smaller than the intended substrate (Figure 1).[22] This remarkable example of molecular recognition provides an interesting design concept for supramolecular chemists.

Reactive Sieving with Foldamers

Gellman and co-workers first coined the term "foldamer" in 1996 to describe any polymer or oligomer that tends to adopt a specific, compact conformation.[23] Since then there have been several comprehensive reviews on the variety of

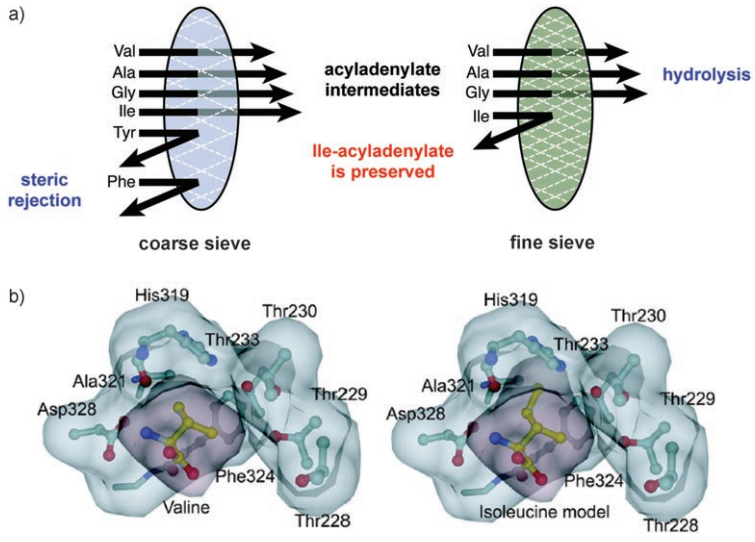
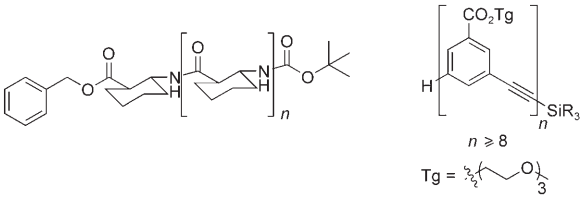


Figure 1. a) Illustration of "double sieve mechanism" proposed by Fersht. b) Binding orientations of valine (left) and isoleucine (right) in the active site of tRNA synthetase. This image is modified from ref. [22].

foldamer structures developed.[23–26] Although there are many types of foldamers, two classes stand out as the most widely investigated: peptide-based foldamers, and aromatic foldamers (e.g. *m*-phenylene ethynylene (mPE) oligomers) (Scheme 4).[23,27,28]



Scheme 4. Two of the most studied foldamer classes: β-peptide foldamer (left) and *m*-phenyleneethynylene foldamer (right).

Among the many kinds of supramolecular hosts that have been reported in the literature over the past three decades, there are several key features that set the foldamer scaffold apart. As mentioned previously, many supramolecular host molecules require lengthy syntheses, and/or are limited in their ability to be unsymmetrically functionalized. For example β-cyclodextrin, although commercially available, requires the use of difficult methodology to site-specifically modify its structure.[29] The iterative sequence-specific synthesis of peptides (both α- and β-) on solid phase has allowed for their construction containing any amino acid (including unnatural variants) at any position in the chain.[30,31] This chemistry is sufficiently facile that it is often carried out using an automated synthesizer. Convenient methodology for the iterative solid phase synthesis of mPE oligomer homo- and heterosequences has also recently been developed.[32] The mPE oligomers are constructed through iterative Sonogashira couplings, using two differentially reactive monomers.

One particularly desirable aspect of mPE foldamers is their capability to direct functional groups to the interior of their helical binding cavity. In the more traditional supramolecular structures, the binding cavity cannot easily be functionalized. For example, the interior cavity of a cyclodextrin cannot be modified, since there are no functional handles (hydroxyl groups line the edges). Similarly, the binding pockets of cavitands such as calixarenes are comprised of the faces of aromatic rings, making it impossible to add functional elements to the interior of the structure (although edge functionalization is possible, analogous to the cyclodextrin systems). mPE foldamers do not have this limitation since the binding cavity is comprised of the edges of the aromatic rings that make up its backbone, rather than the ring faces (Figure 2).

mPE Foldamers and Reactive Sieving

mPE foldamers are particularly attractive as scaffolds for supramolecular catalysis because of their unique structural features. mPE foldamers are solvophobically driven to form helical structures, giving rise to a dynamic, flexible structure which, despite being suggested as a potentially beneficial characteristic in designing supramolecular catalysts nearly a decade ago, has not been a significant area of study.[33] Synthetic oligomers based on the mPE scaffold can have vary-

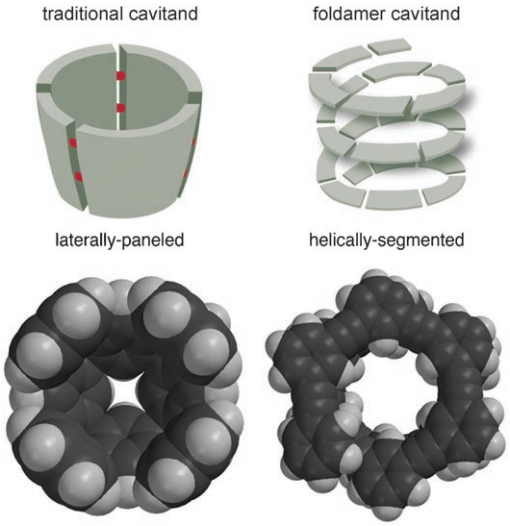
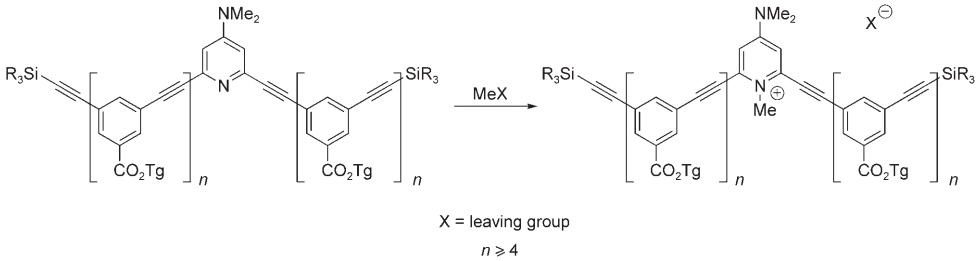


Figure 2. Cartoon illustration contrasting a helical foldamer cavitand (mPE foldamer, right) to a calixarene based cavitand (left). Space-filling models of actual structures are shown below each illustration (structures are not to scale).

ing stability in the folded state depending on solvent composition, temperature, oligomer length, and functional group substitution of the interior cavity.[25,34–37] Consequently, the problem of product inhibition may be less likely for a cavity formed by such a dynamic host. These characteristics make foldamers an ideal target to investigate the effects of structural flexibility on molecular recognition and reactivity.

Numerous studies of the molecular recognition properties of mPE foldamers have been reported in the literature over the last ten years,[38–42] however studies of foldamer reactivity are fewer in number.[43,44] One particular study carried out by our group involved the methylation of a dimethylaminopyridine (DMAP) unit placed in backbone using methyl iodide (Scheme 5).[44] The rate of methylation was increased about 400-fold compared with a control oligomer that cannot bind guests. We were able to conclude from further studies that the rate increase resulted from association of the alkylating agent with the foldamer's interior helical cavity.[45]

Although this is a stoichiometric modification of the foldamer (i.e., not a catalytic reaction) we surmised that the well-defined nature of this cavity may be able to act as a "reactive sieve" similar to the coarse sieve of the tRNA synthetase enzyme. Initially it was thought that the cavity would bind to an ideally sized substrate causing it to react at a higher rate than other similarly reactive guests. Substrates



Scheme 5. Methylation of DMAP-modified foldamers using a methylating agent.

too small in size would insufficiently bind with the foldamer, and react slowly; guests too large would not fit and would react slowly or not at all (Figure 3).

To test this hypothesis, the guest substrate scope was expanded from the initial experiments involving the methylation of DMAP-modified mPE oligomers. A series of methylating agents varying in size and shape were synthesized and used to explore the sieving ability.[46] Alkyl methanesulfonate esters were chosen due to the ability to vary the reactant's size or shape without affecting the reactivity of the active methyl group. It was believed that cavity size, as well as substrate size would be important to the sieving ability; consequently three oligomers of differing lengths were synthesized for the study. These substrates, and foldamers are shown in Scheme 6. Upon subjecting the DMAP modified foldamers to the methylating agents, surprising results were observed. The first was the fact that the reaction rates did not correspond with the expected optimally sized guests. Based on calculation of the cavity volume, we predicted that a sulfonate ester containing a butyl chain would be the ideal substrate.[47] This is not the case, as guest shape appears to influence reaction rate more than size (Figure 4). Secondly, this system is able to differentiate between substrates with only subtle differences in structure, which is demonstrated by the wide range of rate enhancements observed (from 45–1600-fold). Despite our best efforts, we were unable to inhibit the methylation reaction completely by increasing the substrate size or decreasing available cavity volume, possibly indicating that the foldamer backbone is flexible enough to accommodate a variety of guests. Although the exact nature of the origin of selectivity is not yet known, future experiments involving structural restriction (crosslinking) and interior modification will be carried out to explore the similarities to a sieving mechanism. Such perturbations of the foldamer structure are extremely feasible using the solid-phase methodology developed for this system.

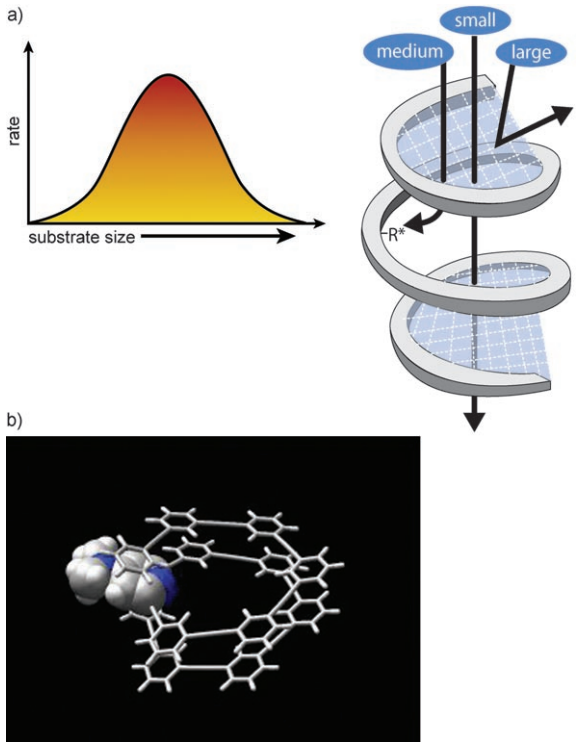
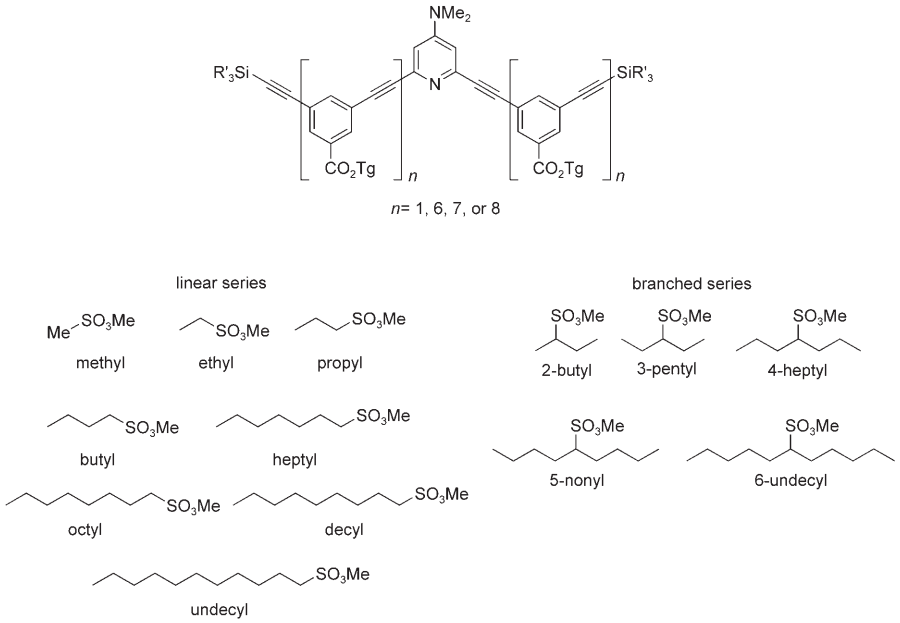


Figure 3. a) Cartoon illustration of expected reactive sieving behavior for a reactive mPE foldamer. b) DMAP-modified foldamer with reactive DMAP unit highlighted in space-filling representation.

Conclusion

In this concept article, we have highlighted some of the attempts by supramolecular chemists to create a "synthetic enzyme". Clearly at this time, nature remains entirely unmatched. This is a similar conclusion to another review of supramolecular catalysis, published in this very journal nearly a decade ago.[33] It is because of this lack of progress that we assert that supramolecular chemistry may not yet be ready to realize the dream of synthetic enzymes. With an ever-increasing demand for more complex molecules and nanoscale devices, the need for precise synthetic techniques will continue to grow. Small-molecule catalysis, by design lacks full-molecule recognition capability. However, combining the diverse synthetic toolbox provided by small-molecule catalysis with precise molecular recognition that may be realized with scaffolds such as foldamers could provide access to precise substrate selectivity, opening the door to new synthetic techniques and increasingly complex synthetic molecules and devices. As more supramolecular scaffolds rapidly become practical, artificial systems may also help to provide insight into more complex aspects of enzymes such as the effect of flexibility and dynamics on catalytic properties. We



Scheme 6. Alkyl methanesulfonate esters used to explore mPE foldamer based reactive sieving.

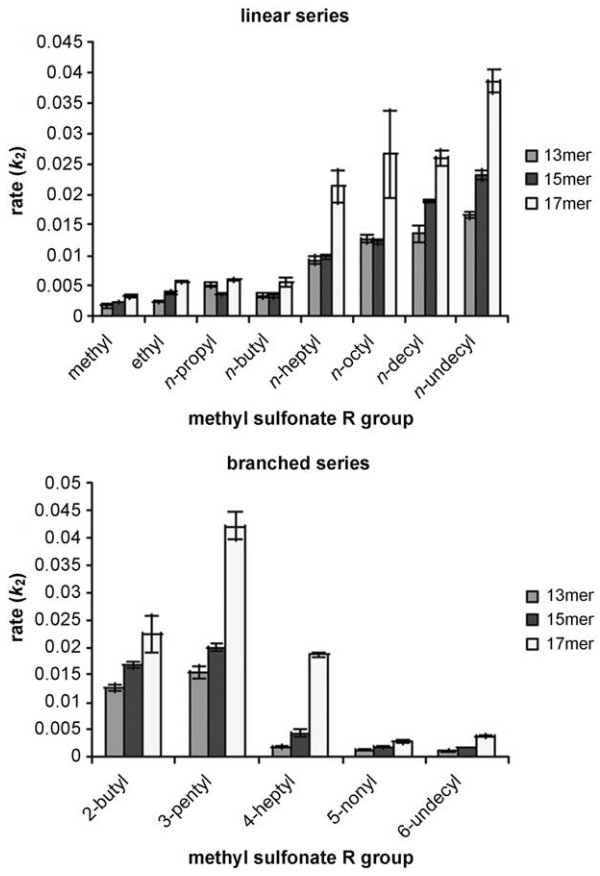


Figure 4. Reaction rates of mPE foldamers with methylating agents differing in size and shape.[46]

believe that foldamer-based scaffolds provide an opportunity to achieve these goals. Their convenient synthesis and modular design invite further development, and their unique properties may enable them to be scaffolds for a new generation of advanced synthetic catalysts custom designed for precise applications.

Acknowledgement

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[1] A. Fersht, *Enzyme Structure and Mechanism*, W. H. Freeman and Company Limited, Reading and San Francisco, **1977**.
[2] F. M. Menger, *Acc. Chem. Res.* **1985**, *18*, 128.
[3] E. Negishi, L. Anastasia, *Chem. Rev.* **2003**, *103*, 1979.
[4] K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem.* **2005**, *117*, 4516; *Angew. Chem. Int. Ed.* **2005**, *44*, 4442.
[5] T. M. Trnka, R. H. Grubbs, *Acc. Chem. Res.* **2001**, *34*, 18.
[6] T. J. Peelen, C. Yonggui, S. H. Gellman, *J. Am. Chem. Soc.* **2005**, *127*, 11598.
[7] J. M. Antos, M. B. Francis, *Curr. Opin. Chem. Biol.* **2006**, *10*, 253.
[8] N. S. Joshi, L. R. Whitaker, M. B. Francis, *J. Am. Chem. Soc.* **2004**, *126*, 15942.
[9] K. S. Raja, Q. Wang, M. J. Gonzalez, M. Manchester, J. E. Johnson, M. G. Finn, *Biomacromolecules* **2003**, *4*, 472.
[10] T. L. Schlick, Z. Ding, E. W. Kovacs, M. B. Francis, *J. Am. Chem. Soc.* **2005**, *127*, 3718.
[11] J. Kang, G. Hilmersson, J. Santamaria, J. Rebek, Jr., *J. Am. Chem. Soc.* **1998**, *120*, 3650.
[12] W. L. Mock, T. A. Irra, J. P. Wepsiec, M. Adhya, *J. Org. Chem.* **1989**, *54*, 5302.
[13] S. Richeter, J. Rebek, Jr., *J. Am. Chem. Soc.* **2004**, *126*, 16280.
[14] D. M. Vriezema, M. C. Aragones, J. A. A. W. Elemans, J. J. L. M. Cornelissen, A. E. Rowan, R. J. M. Nolte, *Chem. Rev.* **2005**, *105*, 1445.
[15] J. Yang, R. Breslow, *Angew. Chem.* **2000**, *112*, 2804; *Angew. Chem. Int. Ed.* **2000**, *39*, 2692.
[16] A. Gissot, J. Rebek, *J. Am. Chem. Soc.* **2005**, *127*, 7424.

[17] J. C. Ma, D. A. Dougherty, *Chem. Rev.* **1997**, *97*, 1303.
[18] S. J. Miller, *Acc. Chem. Res.* **2004**, *37*, 601.
[19] C. A. Lewis, S. J. Miller, *Angew. Chem.* **2006**, *118*, 5744; *Angew. Chem. Int. Ed.* **2006**, *45*, 5616.
[20] A. R. Fersht, *Science* **1998**, *280*, 541.
[21] O. Nureki, D. G. Vassylyev, M. Tateno, A. Shimada, T. Nakama, S. Fukai, M. Konno, T. L. Hendrickson, P. Schimmel, S. Yokoyama, *Science* **1998**, *280*, 578.
[22] R. Fukunaga, S. Fukai, R. Ishitani, O. Nureki, S. Yokoyama, *J. Biol. Chem.* **2004**, *279*, 8396.
[23] S. H. Gellman, *Acc. Chem. Res.* **1998**, *31*, 173.
[24] D. J. Hill, M. J. Mio, R. B. Prince, T. S. Hughes, J. S. Moore, *Chem. Rev.* **2001**, *101*, 3893.
[25] M. T. Stone, J. M. Heemstra, J. S. Moore, *Acc. Chem. Res.* **2006**, *39*, 11.
[26] S. Hecht, I. Huc, *Foldamers*, Wiley-VCH, Weinheim, **2007**.
[27] R. B. Prince, J. G. Saven, P. G. Wolynes, J. S. Moore, *J. Am. Chem. Soc.* **1999**, *121*, 3114.
[28] D. Seebach, T. Kimmerlin, R. Sebesta, M. A. Campo, A. K. Beck, *Tetrahedron* **2004**, *60*, 7455.
[29] I. Tabushi, K. Yamamura, T. Nabeshima, *J. Am. Chem. Soc.* **1984**, *106*, 5267.
[30] E. Atherton, R. C. Sheppard, *Solid Phase Peptide Synthesis: A Practical Approach*, Oxford University Press, Oxford, **1989**.
[31] J. K. Murray, S. H. Gellman, *Org. Lett.* **2005**, *7*, 1517.
[32] E. L. Elliott, C. R. Ray, S. Kraft, J. R. Atkins, J. S. Moore, *J. Org. Chem.* **2006**, *71*, 5282.
[33] J. K. M. Sanders, *Chem. Eur. J.* **1998**, *4*, 1378.
[34] R. B. Prince, J. G. Saven, P. G. Wolynes, J. S. Moore, *J. Am. Chem. Soc.* **1999**, *121*, 3114.
[35] M. T. Stone, J. S. Moore, *Org. Lett.* **2004**, *6*, 469.
[36] H. Goto, J. M. Heemstra, D. J. Hill, J. S. Moore, *Org. Lett.* **2004**, *6*, 889.
[37] J. M. Heemstra, J. S. Moore, *Chem. Commun.* **2004**, 1480.
[38] R. B. Prince, S. A. Barnes, J. S. Moore, *J. Am. Chem. Soc.* **2000**, *122*, 2758.
[39] A. Tanatani, M. J. Mio, J. S. Moore, *J. Am. Chem. Soc.* **2001**, *123*, 1792.
[40] H. Abe, N. Masuda, M. Waki, M. Inouye, *J. Am. Chem. Soc.* **2005**, *127*, 16189.
[41] M. Inouye, M. Waki, H. Abe, *J. Am. Chem. Soc.* **2004**, *126*, 2022.
[42] M. Waki, H. Abe, M. Inouye, *Chem. Eur. J.* **2006**, *12*, 7839.
[43] C. Dolain, C. Zhan, J.-M. Leger, L. Daniels, I. Huc, *J. Am. Chem. Soc.* **2005**, *127*, 2400.
[44] J. M. Heemstra, J. S. Moore, *J. Am. Chem. Soc.* **2004**, *126*, 1648.
[45] J. M. Heemstra, J. S. Moore, *J. Org. Chem.* **2004**, *69*, 9234.
[46] R. A. Smaldone, J. S. Moore, *J. Am. Chem. Soc.* **2007**, *129*, 5444.
[47] S. Mecozzi, J. Rebek, Jr., *Chem. Eur. J.* **1998**, *4*, 1016.

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