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Foldamers as Reactive Sieves: Reactivity as a Probe of Conformational Flexibility

Ronald A. Smaldone and Jeffrey S. Moore*

Contribution from the Departments of Chemistry, Materials Science and Engineering and The Beckman Institute for Advanced Science and Technology, University of Illinois, Urbana, Illinois 61801

Received October 26, 2006; E-mail: moore@scs.uiuc.edu

Abstract: A series of *m*-phenyleneethynylene (mPE) oligomers modified with a dimethylaminopyridine (DMAP) unit were treated with methyl sulfonates of varying sizes and shapes, and the relative reactivities were measured by UV spectrophotometry. Using a small-molecule DMAP analogue as a reference, each of the methyl sulfonates was shown to react at nearly identical rate. In great contrast, oligomers that are long enough to fold, and hence capable of binding the methyl sulfonate, experience rate enhancements of 18−1600-fold relative to that of the small-molecule analogue, depending on the type of alkyl chain attached to the guest. Three different oligomer lengths were studied, with the longest oligomers exhibiting the fastest rate and greatest substrate specificity. Even large, bulky guests show slightly enhanced methylation rates compared to that with the reference DMAP, which suggests a dynamic nature to the oligomer's binding cavity. Several mechanistic models to describe this behavior are discussed.

Introduction

The development of synthetic catalysts has resulted in the ability to perform a wide range of reactions under mild conditions with impressive levels of selectivity. The most successful of these have high substrate generality, allowing for widespread application in synthesis.[1−4] While substrate generality is usually desired, a limitation to this approach may be the inability to "choose" a particular reactive site in a polyfunctional substrate, or a specific substrate based on molecular structure distant from the reactive site. This type of selectivity is well-known in biological systems that combine substrate recognition with efficient, catalytic reactivity. Enzymes are able to locate a specific substrate from a myriad of nearly isosteric molecules with very low rates of error (e.g., DNA polymerases, RNA synthetases).[5] Catalytic systems designed to possess recognition-based reactivity are less well developed and have not found widespread use in synthetic applications.[6,7]

There have been many attempts toward artificial "enzymes" that combine molecular recognition properties with catalytic reactivity.[8−14] Over the past several decades numerous host−guest systems have been developed that are capable of reacting catalytically, but these systems typically perform transformations that can be carried out with greater efficiency using small-molecule catalysts (e.g., hydrolysis, Diels−Alder reactions).[8,10] Synthetic systems with a well-defined secondary structure capable of combining molecular recognition along with the ability to perform useful conversions are rare in the literature.[9,11] Rarer still are modular constructs that allow systems to be designed and easily modified to specifically recognize different substrates.[9] Foldamers possess such a modular construction and are candidates for catalysts that combine recognition with reactivity. Our laboratory and others have been interested in pursuing foldamer-based reactivity.[9,15−17] Compared with other supramolecular catalysts or reactors, *m*-phenyleneethynylene (mPE) oligomers are unique in that they combine conformational flexibility in the helical state, along with a modular structure amenable to site-specific functionalization via sequence design. Recent developments in the solid-phase synthesis of these molecules allow for rapid synthesis as well and facile modification of the cavity interior.[18] In moving toward the development of foldamers that operate via covalent catalysis mechanisms, we wanted to understand how reactivity of functionalized mPEs

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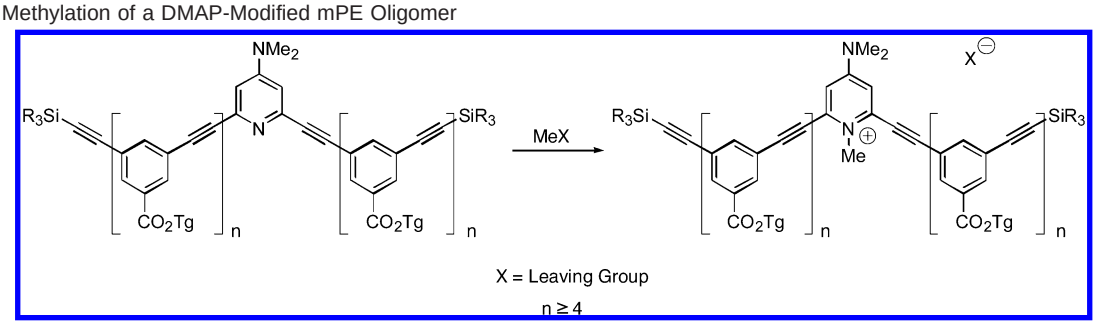
Scheme 1. Methylation of a DMAP-Modified mPE Oligomer



depended on substrate scope. Described herein is a modular oligomeric system with a helical secondary structure that, although exhibiting only simple reactivity, is able to differentiate substrates on the basis of subtle differences in size and shape remote to the reactive group.

Previous studies have demonstrated the ability of mPE oligomers to adopt a solvophobically driven helical conformation that exhibits molecular recognition capabilities.[19−21] When properly functionalized, oligomers of sufficient length display rate enhancements of methylation with iodomethane (Scheme 1).[17] Competitive inhibition studies supported the idea that the methylation reaction occurs within the hydrophobic, helical cavity.[22] This discovery led to the possibility that the oligomer cavity could act as a "reactive sieve", capable of selectively transforming substrates of a certain size or shape. A similar mechanistic concept has been suggested in biological systems where certain synthetase enzymes employ multiple, increasingly selective filters to ensure that the correct amino acid substrate is bound to the active site.[23,24] Here we describe studies aimed at testing the concept of reactive sieving in mPE oligomers.

The simplistic notion of reactive sieving shown in Figure 1 raises two questions that this research attempts to clarify. First, how significant must differences in the substrates be in order for rate differences to be observed? Second, is the helix well defined, or is conformational flexibility a factor, and if so, does the cavity's shape maintain sufficient fidelity to provide substrate discrimination? Conformational flexibility and dynamics are known to be factors in enzyme catalysis, and the extent of the role played by these phenomena has been under intense investigation and debate in recent literature.[25−27] While molecular recognition studies previously performed with mPE oligomers provide insight into the equilibrium binding structure, little information is available about chain dynamics.[19,21] Theoretical simulations have indicated that mPE foldamers are somewhat flexible in the folded state, but no experimental verification of this has been attempted.[28] Monitoring the progress of methylations for different sized methylating reagents and different length oligomers is used here to provide useful, albeit qualitative, information about the range of conformations accessible to the foldamer.

To quantify the reactivity of these oligomers and the various substrates, we employ the general kinetic model shown in eq 1. This model proposes two separate pathways through which an oligomer can be methylated.

$$[\text{Olig-Me}]^{\oplus}[\text{X}]^{\ominus} \xleftarrow{k_{\text{background}}} \text{Olig} + \text{MeX} \rightleftharpoons[K_a] [\text{Olig} \bullet \text{MeX}] \xrightarrow{k} [\text{Olig-Me}]^{\oplus}[\text{X}]^{\ominus} \quad (1)$$

The background reaction is imagined as taking place through an unfolded or partially folded conformation. On the basis of previously reported data,[17] the rate of the background reaction is expected to be significantly smaller than the rate of reaction for the oligomer-MeX complex. This expectation is generally found to hold here. However, a sufficiently large or cumbersome substrate may react slowly with the folded oligomer either because of a low K_a, or because the progression of the complex

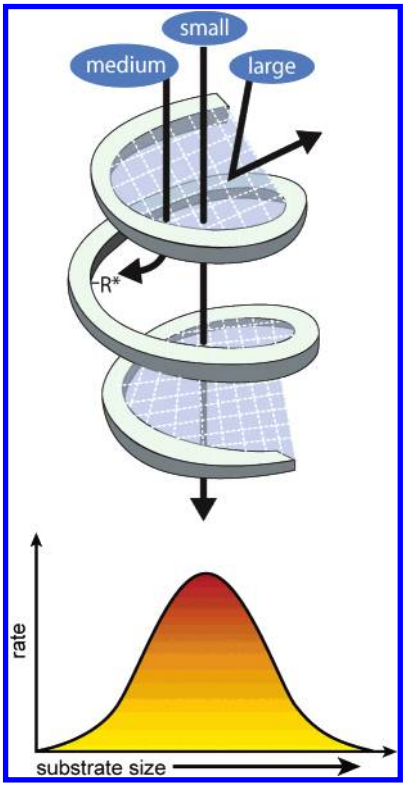


Figure 1. Cartoon illustration of "reactive sieving" along with an expected rate profile for a reaction occurring at active site R*.

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Chart 1. DMAP-modified Trimer **2** and mPE Oligomers **3a**−**d** Used in This Study

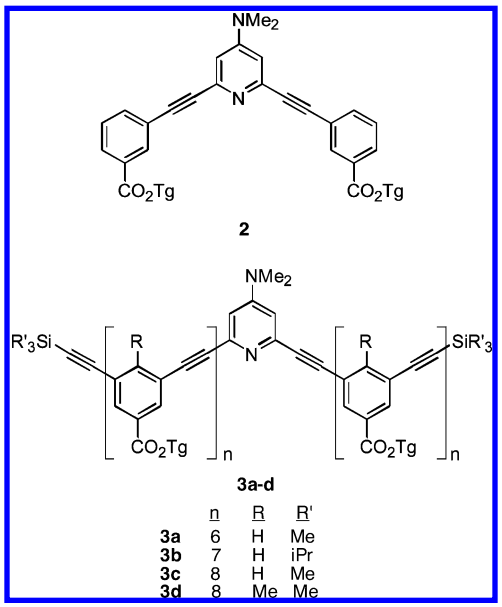
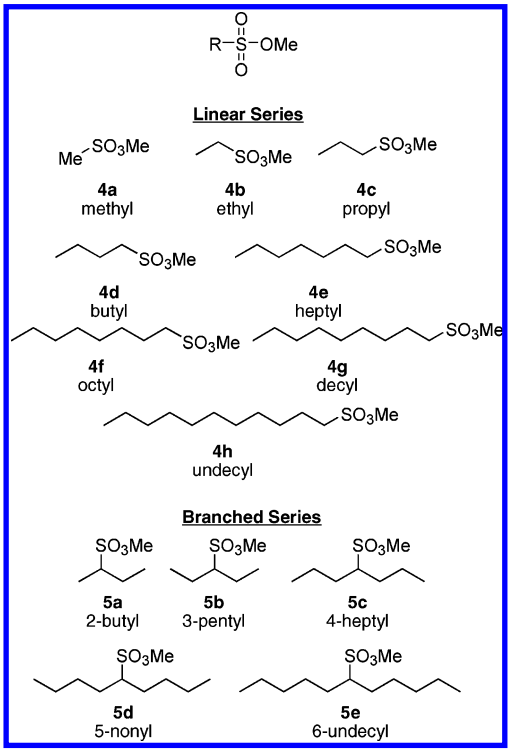


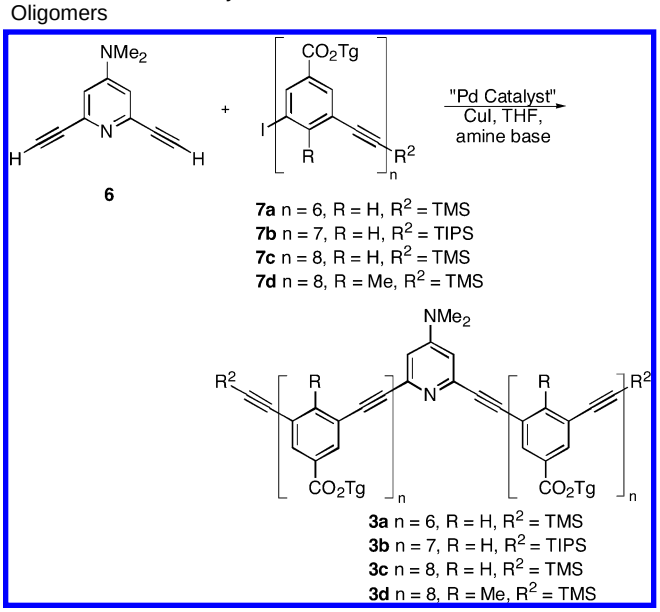
Chart 2. Methyl Sulfonate Esters Used in UV/Vis Kinetics Experiments



to product is inefficient (e.g., the methylating agent may only bind in such a way that the reaction is unfavorable). Attempts to "shut down" the reaction by making the oligomer's cavity congested are also described.

The structures of the oligomers studied are shown in Chart 1. Trimer **2** is a compound that provides a reference reaction rate since it is incapable of adopting the helical conformation. Oligomers **3a**−**c** systematically increase in their length, whereas **3d** has a large fraction of the helix cavity occupied by methyl groups. Chart 2 shows the scope of substrates tested. In particular, a series of linear (**4a**−**h**) and branched methyl

Scheme 2. General Synthetic Method for DMAP-Modified mPE Oligomers



sulfonates (**5a**−**e**) were chosen as methylating agents (**5a** is synthesized as a racemic compound). The ability to systematically vary the alkyl group without affecting the chemical reactivity as determined by reference to compound **2**, along with their UV transparency in the wavelength range monitored for these kinetic studies (360 nm, 340 nm), made this class of molecules ideal for this endeavor.

Synthesis. A general synthetic scheme for preparing the DMAP-modified mPE oligomers is shown in Scheme 2. The synthesis of **6** and the oligomer fragments **7a** and **7c** have been previously reported.[17,22] The synthesis of fragments **7b** and **7d** were carried out using an efficient, iterative solid-phase method that we recently reported.[18] Attachment of **7a**−**d** to **6** was accomplished by a Sonogashira cross-coupling reaction using either $Pd(PPh_3)_4$ or a dimeric Pd(I) precatalyst previously reported by this group.[18] Oligomer fragments and DMAP oligomers were purified by preparative gel permeation chromatography (GPC) and characterized by ^{1}H NMR and MALDI mass spectrometry. Full details are available in the Supporting Information.

Several different pathways were utilized to prepare the various methyl sulfonates.[29−31] A synthetic scheme that shows these methods and the experimental details describing preparations of previously unreported methyl alkylsulfonates can be found in the Supporting Information.

Results

The rate of reaction between methylating agents (**4a**−**h**, **5a**−**e**) and the oligomers (**2, 3a**−**c**) was measured by UV/vis spectrophotometry (Figures 2 and 3).

The reactions were conducted in acetonitrile so as to employ a solvent that is known to promote the helical conformation. Each methylating agent was used in large excess (5000 equiv) in order to simplify the kinetic analysis. The second-order rate coefficients (k_2), obtained by dividing the pseudo-first-order rate

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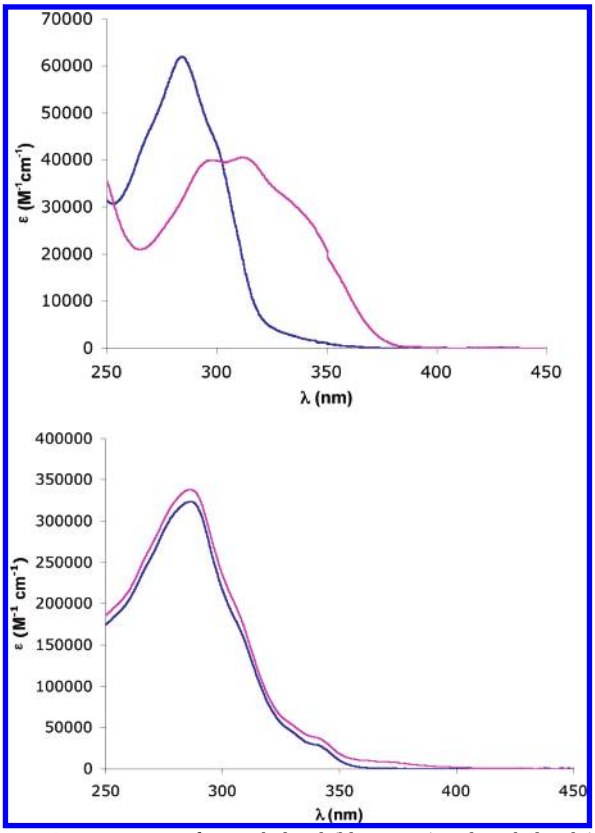


Figure 2. UV spectra of unmethylated (blue curve) and methylated (red curve) DMAP oligomers (**2** top, **3a**, bottom). UV spectra were taken in acetonitrile at 25 °C in the concentration range of 3−4 μM for **3a** and 15−25 μM for **2**. The methylated products for both spectra have methyl sulfonate counterions.

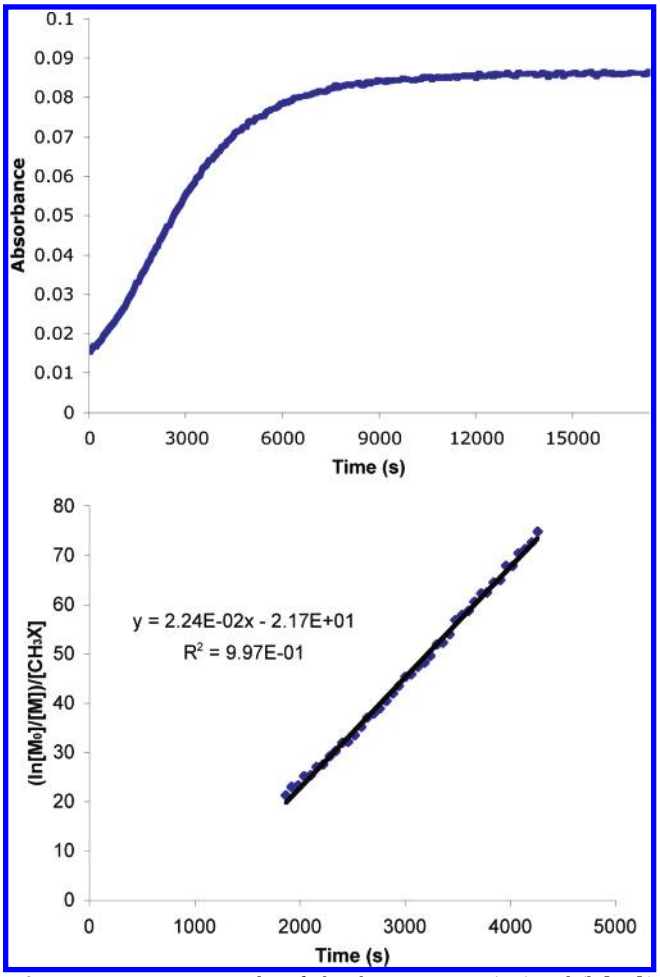


Figure 3. Representative plot of absorbance vs time (top) and (ln[M_0]/[M])/[CH_3X] vs time (bottom) for reaction of oligomer **3c** with substrate **4e** ([M_0] = initial oligomer concentration, [M] = oligomer concentration). Kinetic data were measured by monitoring the absorbance at 360 nm in acetonitrile at 25 °C. Oligomer concentration was 4 μM with excess **4e** (5000 equiv). The second-order rate coefficient (k_2) was obtained by dividing the pseudo-first-order rate coefficient ($k_1 = 0.00042\ s^{-1}$) by the concentration of methylating agent (5000 equiv, ~0.02 M). Additional representative plots are included in the Supporting Information.

by the concentration of methylating agent, are shown in Table 1, and plotted in Figure 4. As can be seen in Table 1, the rate of the background reaction ($k_{background}$), represented by reference compound **2**, is smaller than the experimental error for the rate measurements of the longer oligomers and therefore not significant in the analysis of **3a**−**c**.

The data in Figure 4 indicate that the rate coefficients are highly dependent on the substrate in remarkably subtle ways. To illustrate that these rate differences are significant and that they relate to the structure of the folded oligomer, rate coefficients for each methylating agent were determined using trimer **2** as a reference. These rate coefficients are essentially constant for all substrates, as shown in Figure 5.

Previous studies using methyl iodide as a methylating agent showed that a DMAP-modified 13-mer was capable of enhancing the reaction rate by 400-fold relative to the reference reaction.[17] Shown in Table 2 are the rate enhancements of each methylation reaction by oligomers **3a**−**c** relative to **2**.

As can be seen in Table 2, the smallest rate enhancement observed was in the reaction of **5e** with oligomer **3a**. Despite what appears to be a significant rate reduction in Figure 4, **3a** is still able to enhance the reaction rate by 45-fold compared to the reference reaction with **2**. To test the limits of the mPE helical cavity's ability to enhance the methylation rate, a DMAP-modified 17-mer with methyl groups lining the cavity interior was synthesized (**3d**). Oligomers of this type have been previously shown to fold into a more stable conformation and to more effectively exclude guests due to the decreased cavity space.[19] Additionally, an extremely bulky methylating agent, 1-adamantyl methyl sulfonate (**8**) was used to further reduce the binding affinity (Table 3).[32] The relative rates of these substrates are shown in comparison to relative rates of other branched methylating agents in Figure 6.

Table 1. Second-Order Rate Coefficients (k_2) for Methylations of **3a**−**c**

	2 k_2 ($M^{-1}s^{-1}\times10^{-3}$)	**3a** k_2 ($M^{-1}s^{-1}\times10^{-3}$)	**3b** k_2 ($M^{-1}s^{-1}\times10^{-3}$)	**3c** k_2 ($M^{-1}s^{-1}\times10^{-3}$)
Linear Methyl Alkylsulfonate				
methyl (**4a**)	0.028 ± 0.008	1.8 ± 0.3	2.4 ± 0.1	3.3 ± 0.2
ethyl (**4b**)	0.028 ± 0.003	2.4 ± 0.2	3.9 ± 0.2	5.6 ± 0.2
n-propyl (**4c**)	0.020 ± 0.002	5.1 ± 0.3	3.6 ± 0.1	6.0 ± 0.2
n-butyl (**4d**)	0.022 ± 0.001	3.4 ± 0.3	3.4 ± 0.3	5.6 ± 0.7
n-heptyl (**4e**)	0.023 ± 0.001	9.3 ± 0.7	9.8 ± 0.3	21.2 ± 3
n-octyl (**4f**)	0.026 ± 0.001	12.6 ± 0.7	12.2 ± 0.4	26.7 ± 7
n-decyl (**4g**)	0.027 ± 0.001	13.5 ± 1	18.9 ± 0.2	26 ± 1
n-undecyl (**4h**)	0.025 ± 0.001	16.6 ± 0.5	23.1 ± 0.8	38.5 ± 2
Branched Methyl Alkylsulfonate				
2-butyl (**5a**)	0.023 ± 0.001	12.7 ± 0.6	16.7 ± 0.5	22.5 ± 3
3-pentyl (**5b**)	0.019 ± 0.001	15.4 ± 1	20 ± 0.7	42.1 ± 3
4-heptyl (**5c**)	0.020 ± 0.001	1.9 ± 0.2	4.3 ± 0.7	18.7 ± 0.4
5-nonyl (**5d**)	0.021 ± 0.001	1.3 ± 0.1	1.9 ± 0.1	2.9 ± 0.2
6-undecyl (**5e**)	0.025 ± 0.001	1.2 ± 0.1	1.76 ± 0.03	3.7 ± 0.2

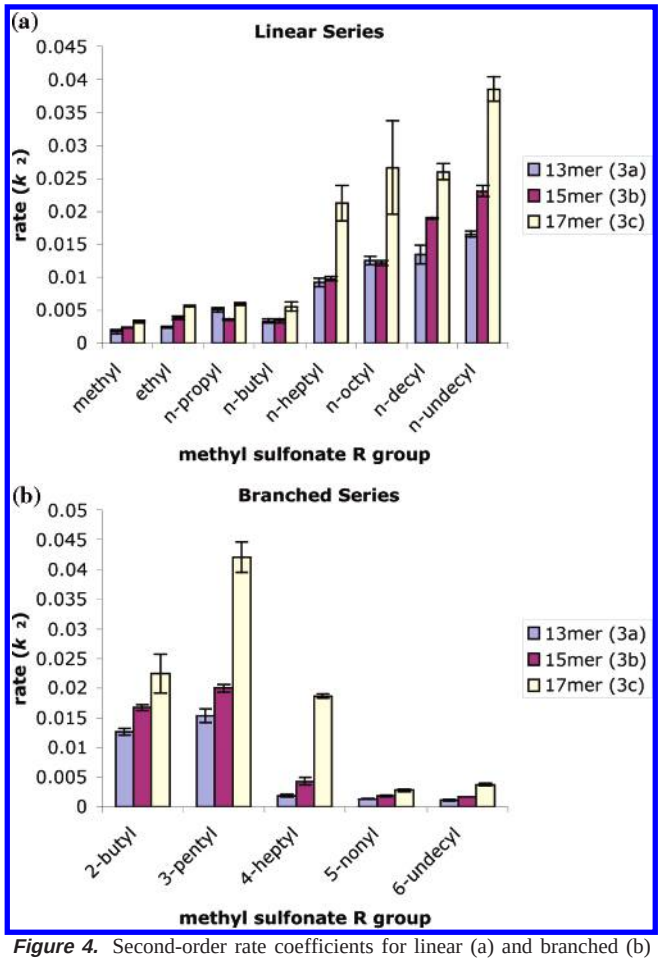


Figure 4. Second-order rate coefficients for linear (a) and branched (b) methyl alkylsulfonates with **3a**−**c**. Kinetic data were measured at 25 °C in acetonitrile with oligomers in the concentration range of 3−4 μM and 5000 equiv of methyl sulfonate.

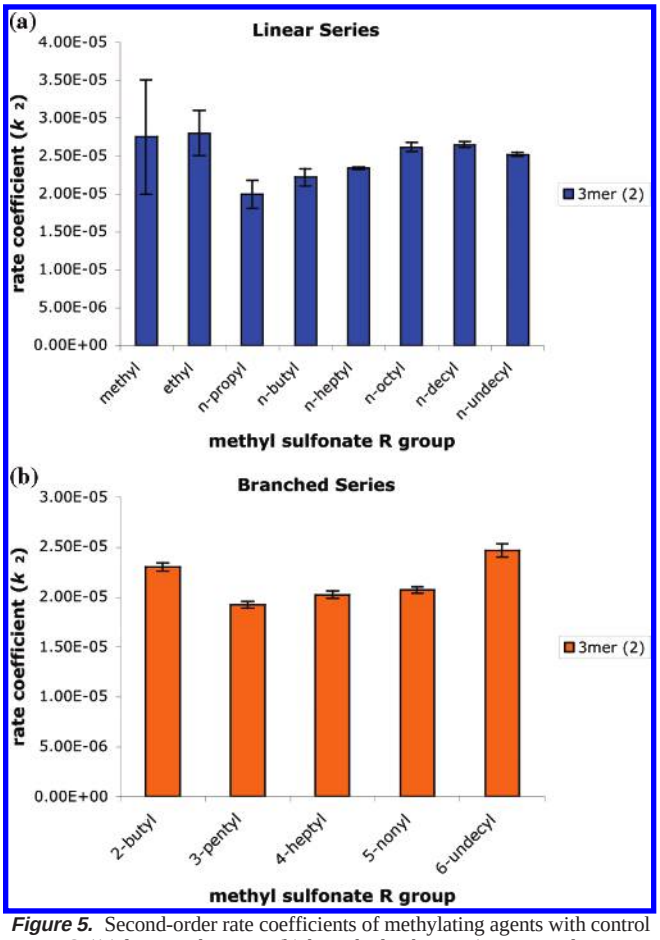


Figure 5. Second-order rate coefficients of methylating agents with control trimer **2** ((a) linear substrates, (b) branched substrates). Kinetic data were measured at 25 °C in acetonitrile. Trimer **2** concentrations ranged from 15 to 25 μM using excess methyl alkylsulfonate (5000 equiv).

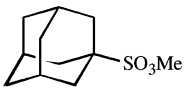
Discussion

There are several general trends observed in Figure 4. All of the oligomers react significantly faster than reference compound **2**. For each member of the linear series, the rate of methylation increases with increasing length of oligomers **3a**−**c**. This difference can be fairly dramatic given that the oligomer length only changes by four monomer units from the shortest oligomer (**3a**) to the longest (**3c**). This trend suggests that the recognition capability of the cavity is a significant factor in determining methylation rate, which is consistent with previous observations involving this system.[17,22] In our communication, relative rate increases of ~400-fold using methyl iodide as a methylating agent were observed.[17] However, in the study reported here, both larger (as high as 1600-fold, **5b**) and smaller (18-fold, **8**) rate increases were observed, depending on the methylating agent used (Table 2). These rate increases are based on the comparison to the rate of reference compound **2**, which is assumed to approximate an upper limit of the background reaction ($k_{background}$). Unlike the behavior with **3a**−**c**, the methyl sulfonates methylate **2** with similar rate coefficients. Referring to the model described in eq 1, the observed rate differences in **3a**−**c** could arise from varied binding affinities of the methylating agents to the oligomer cavity. Typically, in supramolecular systems, molecules that occupy 55% of the host cavity show

Table 2. Relative Methylation Rates (k(**3a**−**c**)/k(**2**))

	13mer (**3a**)	15mer (**3b**)	17mer (**3c**)
	Linear Methyl Alkylsulfonates		
methyl (**4a**)	68 ± 12	93 ± 5	130 ± 10
ethyl (**4b**)	95 ± 10	150 ± 10	220 ± 10
n-propyl (**4c**)	200 ± 20	140 ± 10	230 ± 10
n-butyl (**4d**)	130 ± 20	130 ± 20	255 ± 40
n-heptyl (**4e**)	360 ± 30	380 ± 20	830 ± 110
n-octyl (**4f**)	490 ± 40	470 ± 30	1000 ± 270
n-decyl (**4g**)	520 ± 60	740 ± 40	1000 ± 70
n-undecyl (**4h**)	640 ± 40	900 ± 60	1500 ± 110
	Branched Methyl Alkylsulfonates		
2-butyl (**5a**)	490 ± 34	650 ± 39	870 ± 140
3-pentyl (**5b**)	600 ± 54	780 ± 47	1600 ± 130
4-heptyl (**5c**)	74 ± 10	170 ± 28	730 ± 40
5-nonyl (**5d**)	52 ± 4	75 ± 7	110 ± 10
6-undecyl (**5e**)	45 ± 4	68 ± 4	150 ± 12

Table 3. Adamantyl Sulfonate (**8**) and Rate Coefficient with Oligomer **3d** and Reference Compound **2**



8

oligomer	k_2 ($M^{-1}s^{-1}\times10^{-3}$)	k_2(**2**) ($M^{-1}s^{-1}\times10^{-3}$)	k_2 (oligomer)/k_2(**2**)
3c	200	3.9 ± 0.3	51
3d	70	3.9 ± 0.3	18

(32) It should be noted that the inherent reactivity of **8** is much higher than those of methylating agents **4a**−**h** and **5a**−**e**, making a direct comparison with these substrates difficult. However, since the relative rate enhancement parameter is a ratio of oligomer rate to control rate, these values can be directly compared. The reasons for the inherent rate differences are not intuitive and have yet to be explained.

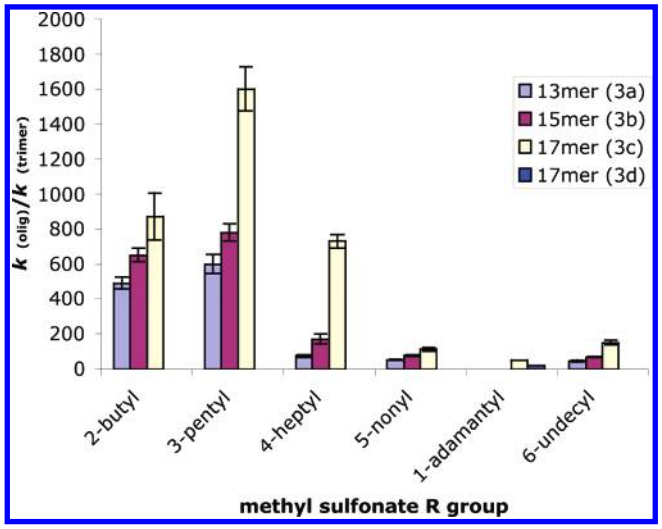


Figure 6. Relative rates of reaction for branched-type methylating agents including **8**. Kinetic data were measured at 25 °C in acetonitrile with oligomers in the concentration range of 3−4 μM and excess methyl alkylsulfonate (5000 equiv).

the highest binding affinity.[33] However, this approximation does not appear to correlate with the methylation data when taken as a whole (see Supporting Information). One possible explanation for this anomaly is the fact that the host molecules used to define the "55% rule" were relatively rigid in structure, whereas oligomers **3a**−**d** contain many degrees of conformational flexibility. The cavity may expand or the chain may unfold to generate a larger cavity volume. This hypothesis is discussed in more detail later in this section.

The reaction rates of linear substrates **4a**−**h** with oligomers **3a**−**c** show a general trend of increasing methylation rate with increasing length of the substrate's alkyl chain even though several of the linear substrates (**4g** and **4h**) occupy more than 70% of the cavity volume.[34] In contrast to the linear substrates, the branched methylating agents **5a**−**e** show a maximum rate with **5b**. The rate of methylation with the branched series for all three oligomers plummets significantly at **5d** and decreases little beyond that (**5e**). Qualitatively, the behavior of the branched substrates is consistent with our expectations of reactive sieving. The reaction of **5e** with all oligomers is much slower than that of **4h** despite the comparable size and volume of these two substrates. This indicates that the reactive group of **5e** may be less favorably positioned for reaction in the bound state compared to that of **4h**. The opposite behavior is seen when **4d** is compared to its branched counterpart **5b**; linear sulfonate **4d** is much slower in comparison to **5b**, despite their similar sizes. The behavior displayed by these examples indicates that shape, rather than size is the most important factor that contributes to the differential reactivity. This may be the result of differing oligomer conformations when a guest is present, or differing substrate orientation with respect to the DMAP unit in the bound state.

As **3a**−**d** all contain the DMAP functional group in the middle of their backbones, it is obvious, but worth noting, that if the reactive conformation of the oligomers is accurately modeled by a helical shape the methyl sulfonate of any

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(34) Cavity volumes were calculated using the program Cerius2, version 4.10; Accelrys Inc. www.accelrys.com. See Supporting Information for a complete table of calculated volumes.

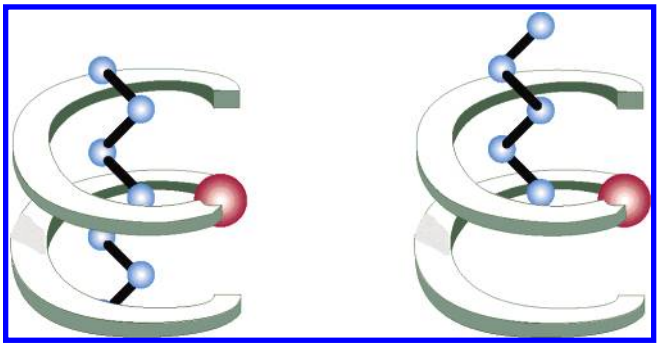

Figure 7. Cartoon representations of possible alkyl chain orientation during methylation for branched (left) and linear (right) series methylating agents. The entire cavity may be utilized during methylation with branched substrates. Red ball = DMAP unit.

methylating agent must be located in the center of the cavity for the reaction to occur (Figure 7). This may be very relevant when considering that **5b** has the fastest rate not only of the branched reagents but also of all methylating agents tested. The location of the methyl sulfonate ester in the middle of substrate **5b** may align the methylating group directly in front of the DMAP nitrogen. The effect of holding reactive species together in close proximity and in proper orientation is known to give substantial rate enhancements and selectivities in biological and physical organic model systems,[35] and supramolecular ones.[11] Assuming this model to be applicable here, one expects the "ideal" R group to match the length of the oligomer's cavity and for the alkyl chain length at which the rate is maximum to increase as the oligomer gets longer. This level of substrate specificity is not observed, although oligomer **3c** appears to have a much larger preference for **5c** than oligomers **3a**,**b** (Figure 6). It is possible that the optimum methylating agent for oligomers longer than 17 units would be a 4-heptyl chain (**5c**) rather than a 3-pentyl (**5b**). However, we did not investigate this possibility.

A much different rate profile is observed for the linear-type methylating agents. One might imagine that the substrate's alkyl group only protrudes from one end of the oligomer cavity (Figure 7), thereby limiting access of the active methyl group to the front of the DMAP nitrogen. Clearly this would impact the rate of reaction for similarly sized, but linear shaped, methylating agents. This explanation does not, however, account for why the largest rate belongs to **4h** whose terminal carbons would seem to be too far away to have such a profound effect on the reaction rate. To explain the differences between the rates of **4h** and **4g**, the oligomer, or substrate must alter its structure in some way such that there is interaction between distant carbons. This could also explain why the addition of only four PE monomer units to the foldamer backbone has statistically significant effects on the methylation rate (**3a** to **3b** to **3c**). Individual monomers lengthen the cavity very little in the canonical, compact, folded structure but increase the fully extended backbone chain length substantially more. Therefore, one possibility is that these seemingly small additions to the oligomer backbone are important because the foldamer exists as an ensemble of conformations, some of which are stretched or partially unfolded from a compact helical structure. However, it is known that longer oligomers give a more stable helix, and therefore they are unlikely to spend more time in an unfolded

(35) Menger, F. M. *Acc. Chem. Res.* **1985**, *18*, 128−134.

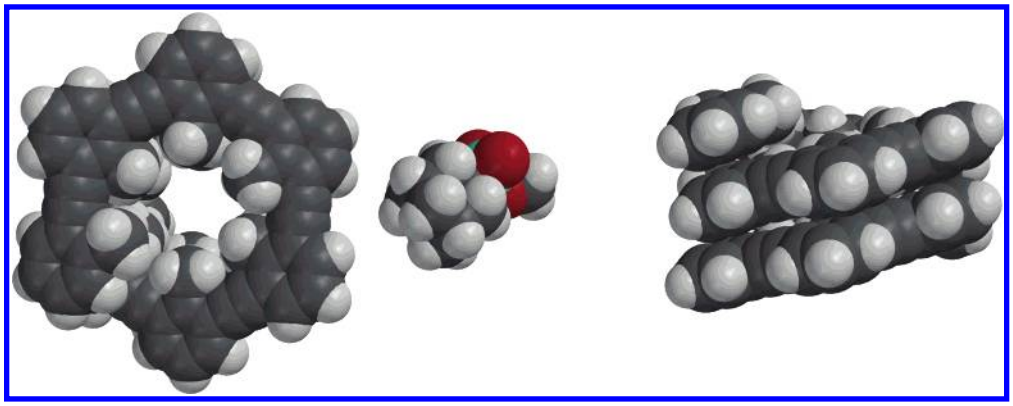

Figure 8. Illustration of generic mPE oligomer (no DMAP unit) with methyl groups lining the interior (left) and **8** (middle). The side view of the oligomer is shown at the right.

conformation.[20] An alternative explanation is that the substrate changes its shape to adjust to the cavity. Rebek[36] and others[37] have explored the conformation and reactivity of alkyl chains in hydrophobic environments. In particular, Rebek and coworkers demonstrated that alkyl chains are capable of adopting a helical conformation where each carbon has gauche, rather than anti conformations, allowing it to pack more efficiently into confined spaces. It is possible that either a long enough alkyl chain has not been used to elicit a decline in reaction rate as was seen with the branched-type agents (methyl alkylsulfonates with carbon chains containing more than 11 carbons are not soluble in acetonitrile) or enough freedom of movement is maintained such that only an asymptotic maximum is reached. Sufficiently long branched-type guests may be bound too restrictively, potentially in a less reactive orientation.

Additional evidence for flexibility of the foldamer is found in Table 3 and Figure 6. A bulky, inflexible substrate such as **8** might be expected to react at equal to, or even more slowly than the rate of the background methylation reaction (i.e., the methylation of reference compound **2)**. However, it is observed that with **3c** the methylation is ~50-fold faster than with **2**. In an attempt to further slow the methylation, **3d** was synthesized. Its interior methyl groups are expected to block the interior cavity for guest molecules. Even in this case, the methylation rates were still ~20 times faster than that of the control. Regardless, the computer models shown in Figure 8 indicate that **8** would be unlikely to fit into the helical cavity formed by **3d** without some kind of conformational rearrangement of the helical structure.[39] The fraction of cavity volume occupied by **8** in **3d** would also appear to be extremely prohibitive in a rigid, collapsed conformation. The volume of **8** is 206 Å^3 which occupies 83% of the cavity of **3d.** Attempts to tune the reactivity by modulating the solvent polarity were also carried out. mPE oligomers are well-known to form more compact helical structures in solvent mixtures more polar than pure acetonitrile[38] (e.g., acetonitrile:water). However, the methyl alkylsulfonate esters tested here were insufficiently soluble in these mixtures to obtain useful data. It may be that the flexibility of the oligomer allows it to adjust its structure to form a host−guest complex that is sufficiently stable such that the reaction rates remain elevated. Such "induced fit"-type behavior has been observed in enzymes.[40]

Additional experiments are in progress to further understand the origin of discrimination for these reactions. Future investigations may include studies of water-soluble guests in more polar solvents to reduce the conformational flexibility of the mPE helix, or the use of modified oligomers that are covalently restricted from unfolding (i.e., chemical cross-linking of the oligomer). The incorporation of catalytic functional moieties into the interior cavity to explore the effect of mPE oligomers on more complex reactions is also a future goal of this research, and results will be reported in due course.

Conclusions

Described in this article is the use of foldamer-based molecular recognition to modulate chemical reactivity. mPE oligomers **3a**−**c** exhibit variable reactivity toward substrates even though the substrates differ minimally in size and shape. In contrast, the reference trimer shows no significant substrate discrimination. Additionally, the flexible nature of the host appears to allow it to accommodate guests of different shape and size, although the rate of methylation for each guest is significantly different. Sieve-like behavior was observed for branched substrates, and our studies have also revealed that the "small, medium, and large" designations are overly simplistic as reactivity is governed by both substrate shape and size. It appears that guest shape is a more relevant factor, possibly in orienting the reactive groups in a certain manner. This system represents a promising foundation for developing foldamers that involve covalent catalysis and that function as reactive sieves.

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Supporting Information Available: Synthetic scheme for the methods of preparation of the various methyl sulfonates and experimental details for preparations of previously unreported methyl alkylsulfonates. This material is available free of charge via the Internet at http://pubs.acs.org.

JA067670A

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