Sequence dependence of methylation rate enhancement in *meta*-phenyleneethynylene foldamers†

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The methylation rates of a *meta*-phenyleneethynylene (*m*PE) oligomer with a terminally-attached 4-dimethylaminopyridine (DMAP) residue are reported for a series of linear and branched methyl sulfonates; these data show that selective methylation is enhanced by locating the DMAP unit at the midpoint of the sequence, allowing the foldamer cavity to function as a reactive sieve.

The use of supramolecular architectures to mimic the catalytic and molecular recognition behavior of biological systems has been extensively researched over the past several decades.[1–4] The realization of enhanced reaction rates through molecular recognition within purely synthetic systems could potentially help to provide an understanding of the fundamental concepts of bioreactivity. Investigations of *m*PE foldamers have recently begun to address the relationship between enhanced reaction rates and molecular recognition in abiological oligomers.[5–12]

*m*PE foldamers can adopt a solvophobically-driven helical conformation, which forms a well-defined cavity known to have molecular recognition capability.[5,13–15] Our group has previously demonstrated that *m*PE foldamers modified with a 4-dimethylaminopyridine (DMAP) unit can enhance the rate of methylation of the DMAP nitrogen by iodomethane up to 400-fold.[7] In a recent publication, we demonstrated that these foldamers were not only capable of accelerating the rate of methylation, but also of differentiating between reactive guests based on their size and shape, a behavior we described as "reactive sieving".[16] In our previous studies, the reactive DMAP unit was positioned at the midpoint of the foldamer backbone (**1**). A testable consequence of the reactive sieving hypothesis is that substrate discrimination will diminish as the reactive group is moved away from the center of the helical cavity. End-functionalized oligomer **2** was thus synthesized (Fig. 1) and subjected to the series of linear (**3a–h**) and branched (**4a–e**) methylating agents used in our initial study. Here, we report the rates of methylation, determined by UV/vis spectroscopy, and compare the results to oligomers having DMAP at their center.[16]

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In addition to the ability of **1** to differentiate between the substrates, it also was observed to enhance the methylation rate compared to the background rate. The relative rate is defined as the rate of methylation of the foldamer (k_{oligomer}) divided by the rate of methylation of the appropriate control ($k_{\text{background}}$). To determine the relative rate enhancement, the methylation of control molecules **5** and **6** were measured. Since the DMAP unit of **2** is attached to the foldamer at only the 2-position (compared to the 2,6-disubstituted DMAP of **1**), a new control was synthesized (**6**) to provide a more accurate background rate approximation (Fig. 1).[17] Oligomers **5** and **6** are too short to fold, and thus their rates can be taken as an approximation of the rate in the absence of binding.

In our previous work, the methylation of oligomer **1** by a series of linear methylating agents showed an increase in rate

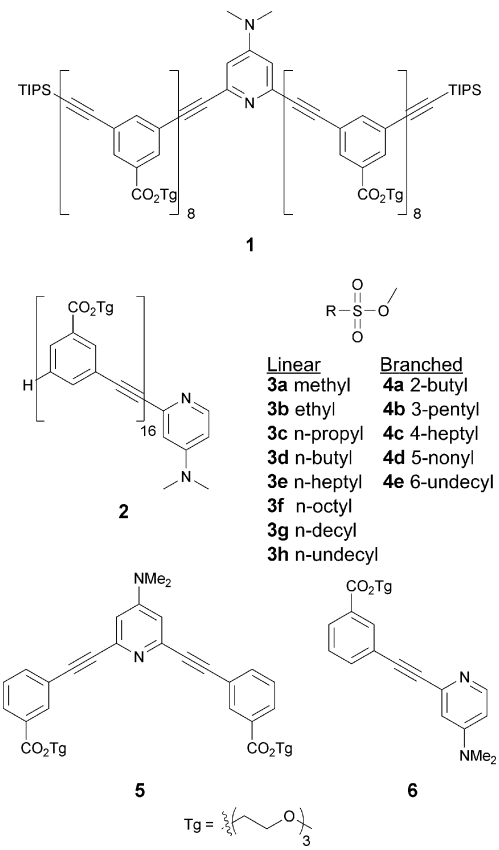

Fig. 1 Center-functionalized oligomer **1**, end-functionalized oligomer **2**, control molecules (**5** and **6**) and all the methylating agents used in this study (**3a–h** and **4a–e**).

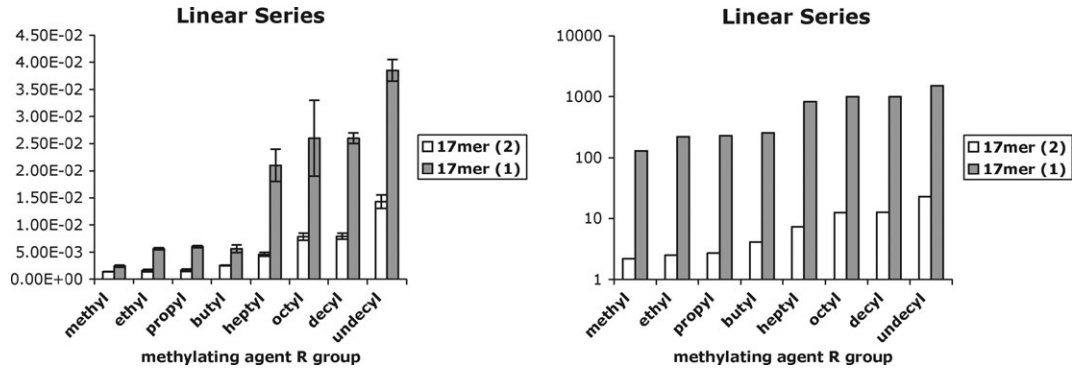

Fig. 2 Left: Comparison of the second order rate coefficients (k_2) between oligomers **1** and **2** for linear methylating agents **3a–h**. Right: Plot of $k_{oligomer}/k_{background}$ for **3a–h** on a logarithmic scale. Kinetic data were measured by UV/vis spectroscopy at 25 °C in acetonitrile, with oligomers in the concentration range 3–4 μM and 5000 equiv. of methyl sulfonate. For more details see the ESI.†

Table 1 $k_{oligomer}/k_{background}$ values for oligomers **1** and **2**

Linear	17mer (**2**)	17mer (**1**)
Methyl (**3a**)	2.2	130
Ethyl (**3b**)	2.5	220
Propyl (**3c**)	2.7	230
Butyl (**3d**)	4.1	255
Heptyl (**3e**)	7.3	830
Octyl (**3f**)	12.5	1000
Decyl (**3g**)	12.6	1000
Undecyl (**3h**)	22.8	1500
Branched	**17mer (2)**	**17mer (1)**
2-Butyl (**4a**)	3.3	870
3-Pentyl (**4b**)	5.5	1600
4-Heptyl (**4c**)	4.2	730
5-Nonyl (**4d**)	3.8	110
6-Undecyl (**4e**)	4.6	150

in correspondence with an increase in the R-group chain length (Fig. 2). When the second order rate coefficients (k_2) of **2** are plotted in comparison with the rates of **1**, it can be seen that for substrates **3a–h**, the trend of increasing rate with increasing length of the alkyl chain is still evident, although diminished. When the relative rates of reaction are calculated for the methylation of **2**, it is revealed that the rate enhancements of the end-functionalized foldamer are also significantly diminished with respect to center-functionalized oligomer **1** (Table 1). To illustrate the vast disparity in the ability of **2** to enhance the rate of reaction in comparison to oligomer **1**, these values are plotted in Fig. 2 on a log scale.

Center-functionalized oligomer **1** exhibited reactive sieving behavior when subjected to branched methylating agents **4a–e**.[16] However, placement of the DMAP group at the end of the chain greatly reduced the ability of the *m*PE foldamer to differentiate between the substrates, leading to nearly identical rate coefficients for **4a–e** (Fig. 3). As seen with the linear substrates, the relative rates of methylation of the branched substrates with **2** are uniformly diminished in comparison to **1**. In this case, however, all of the relative rates are very similar (Table 1).

It is possible that the flexibility of the oligomer backbone is responsible for the observed change in reactive sieving behavior. One rationale, proposed by Menger, posits that holding reactive groups in proximity to one another could result in the large rate enhancements seen in enzymes and intramolecular reactions.[18] Molecular dynamics simulations of the *m*PE foldamer system have indicated that residues at the end of the chain exhibit larger fluctuations than those at the center of the backbone when folded.[19] Since the DMAP group of **1** is at the center of the backbone, it may be held more rigidly in place near bound substrates by the folded structure than the DMAP of end-functionalized oligomer **2**. Although oligomer **2** maintains some of the ability displayed

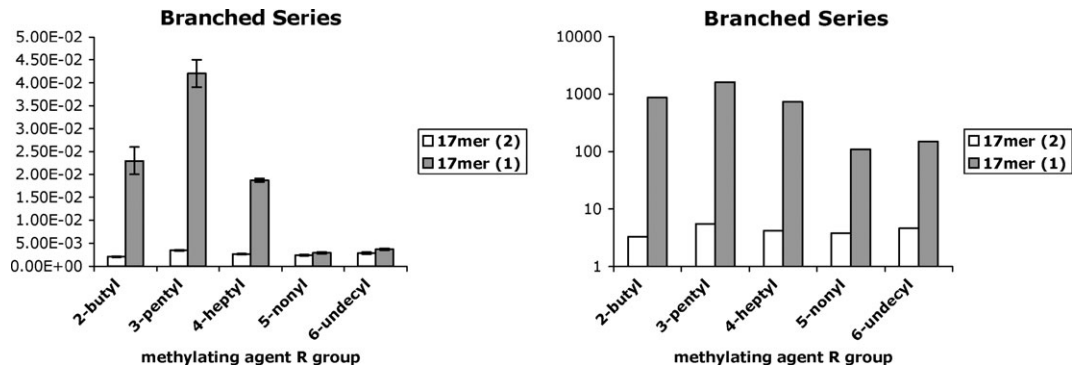

Fig. 3 Left: Comparison of second order rate coefficients (k_2) between oligomers **1** and **2** for linear methylating agents **4a–e**. Right: Plot of $k_{oligomer}/k_{background}$ for **4a–e** on a logarithmic scale. The conditions for the measuring kinetics are the same as those in Fig. 2.

by its center-functionalized analog to differentiate linear substrates, the reaction rates of the branched methylating substrates are essentially identical to one another. This may indicate the presence of an alternate reactive backbone conformation that is not capable of reactive sieving, but can still bind the methylating substrate, thereby leading to a small rate acceleration.

In conclusion, we have shown that the reactive sieving ability of *m*PE foldamers is dependent on the oligomer sequence. End-functionalized oligomer **2** was much less efficient at differentiating linear substrates **3a–h** in comparison with oligomer **1**. In the case of branched substrates **4a–e**, no significant selectivity was observed, and in both cases, the reaction rate enhancements were substantially lower than those observed with **1**. The decrease of the methylation rate enhancement and loss of selectivity observed with oligomer **2** may indicate that the foldamer backbone is sufficiently flexible at the ends of chain, requiring its reactive group to be placed in a structurally-stable position (*i.e.*, the midpoint of the backbone) in order to achieve sieving. Since sequence determines the position of the reactive unit in the folded cavity, we conclude that reactive sieving is most effective for midpoint placement. Future investigations of reactive *m*PE foldamers will attempt to modulate oligomer flexibility and rule out alternate conformations through systematic restriction of the backbone's ability to unfold by using the precise placement of chemical cross-linkers.

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