# Folding-Promoted Methylation of a Helical DMAP Analogue

Jennifer M. Heemstra and Jeffrey S. Moore*

*Departments of Chemistry and Materials Science & Engineering, 600 South Mathews Avenue,
The University of Illinois at Urbana–Champaign, Urbana, Illinois 61801*

Received December 19, 2003; E-mail: moore@scs.uiuc.edu

Synthetic molecular containers, or cavitand molecules,[1] represent one class of supramolecular enzyme mimics, as they can be designed to bind guests and provide a microenvironment that lowers the energy barrier for a prescribed chemical reaction.[2] Rebek and co-workers have demonstrated the use of resorcinarene-based cavitand complexes to promote cycloaddition and alkylation reactions.[3] However, the capsular structure of these cavitands makes customization of the binding pocket inherently difficult, limiting the scope of interactions that can be employed to promote chemical transformations. Phenylene ethynylene (PE) oligomers offer a promising alternative framework for the design of cavitand-like molecules having novel capabilities, as they are constructed in a modular fashion from customizable helical segments. Oligomers **1** undergo a solvophobic conformational transition,[4] folding into a
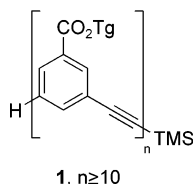
helical structure and generating a hydrophobic cavity that is capable of molecular recognition.[5] The surface of the binding cavity can be easily functionalized by incorporation of a heteroaromatic ring into the oligomer backbone.[6] Here we show how the folded conformation of a pyridine-containing PE oligomer dramatically accelerates methylation of the pyridine moiety, as demonstrated by a kinetic study with systematic variations in oligomer chain length.

Oligomers **2** and **7** were previously synthesized as analogues of (*N*,*N*-dimethylamino)pyridine (DMAP). Oligomer **2** is too short to form a helix, but **7** is of sufficient length to fold, and adopts a helical conformation in acetonitrile.[7] In the helical conformation of **7**, the pyridine nitrogen is located on the interior surface of the cavity, and the pyridine ring is sandwiched between the two terminal phenyl rings of the oligomer.[8] The pK_a values of the oligomers were measured in acetonitrile, and **7** was found to be 0.3 pK_a units higher than **2**, corresponding to a free energy difference of 0.4 kcal·mol⁻¹, attributable to oligomer folding.[6a] This increase in stability for the protonated foldamer may result from pyridinium-π interactions involving the terminal phenyl rings of **7**. We hypothesized that these pyridinium-π interactions could be used to promote chemical transformations in which a positive charge develops on the pyridine ring. To test this hypothesis, the methylation rates of **2** and **7** were measured, employing methyl iodide as the electrophile (Scheme 1).

Using UV spectroscopy, the methylation rates of **2** and **7** were measured in both acetonitrile and chloroform under pseudo-first-order reaction conditions using a large excess of methyl iodide. In acetonitrile, oligomer **7** was found to react over 400 times faster

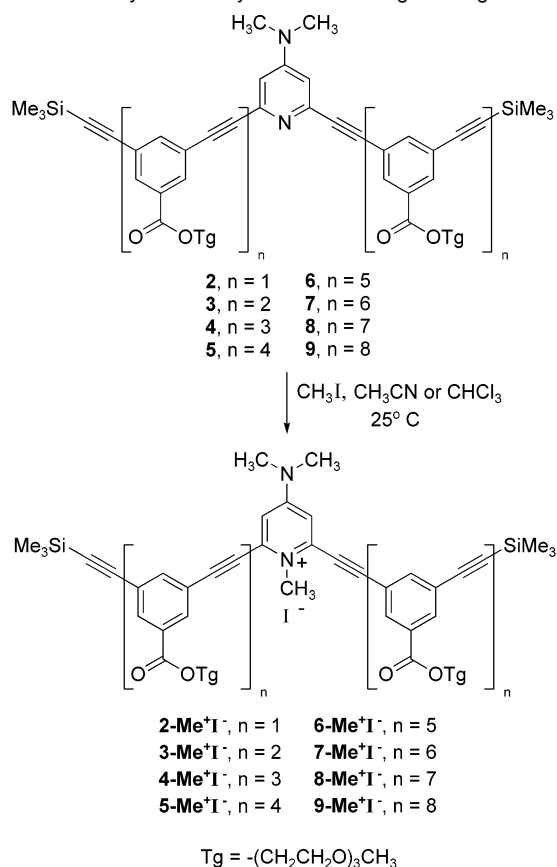**Scheme 1.** Methylation of Pyridine-Containing PE Oligomers

2, n = 1   **6**, n = 5
3, n = 2   **7**, n = 6
4, n = 3   **8**, n = 7
5, n = 4   **9**, n = 8

CH₃I, CH₃CN or CHCl₃
25° C

2-Me⁺I⁻, n = 1   **6-Me⁺I⁻**, n = 5
3-Me⁺I⁻, n = 2   **7-Me⁺I⁻**, n = 6
4-Me⁺I⁻, n = 3   **8-Me⁺I⁻**, n = 7
5-Me⁺I⁻, n = 4   **9-Me⁺I⁻**, n = 8

Tg = -(CH₂CH₂O)₃CH₃

Table 1. Methylation Rates of Oligomers **2** and **7**

oligomer length ($2n+1$)	solvent	k (M⁻¹·s⁻¹)	$\Delta G^{\ddagger}$ (kcal·mol⁻¹)
3	CH₃CN	$3.57 \pm 0.03 \times 10^{-4}$	22.1
13	CH₃CN	$1.59 \pm 0.09 \times 10^{-1}$	18.5
3	CHCl₃	$4.05 \pm 0.17 \times 10^{-5}$	23.4
13	CHCl₃	$8.08 \pm 0.41 \times 10^{-5}$	23.0

than oligomer **2**, with a difference in free energy of activation ($\Delta\Delta G^{\ddagger}$) of 3.6 kcal·mol⁻¹ (see Supporting Information). However, in chloroform only a 2-fold rate enhancement was observed, corresponding to a $\Delta\Delta G^{\ddagger}$ value of 0.4 kcal·mol⁻¹ (Table 1). In chloroform, both **2** and **7** exist in random conformations, but in acetonitrile, **7** adopts a helical conformation, implicating oligomer folding as the key structural change that contributes to the large rate enhancement. Oligomer folding provides multiple noncovalent interactions that may work cooperatively to stabilize the transition-state structure of the methylation reaction. We predicted that the most significant of these factors would be pyridinium-π interactions and preferential solvation of the cavity interior by methyl iodide.
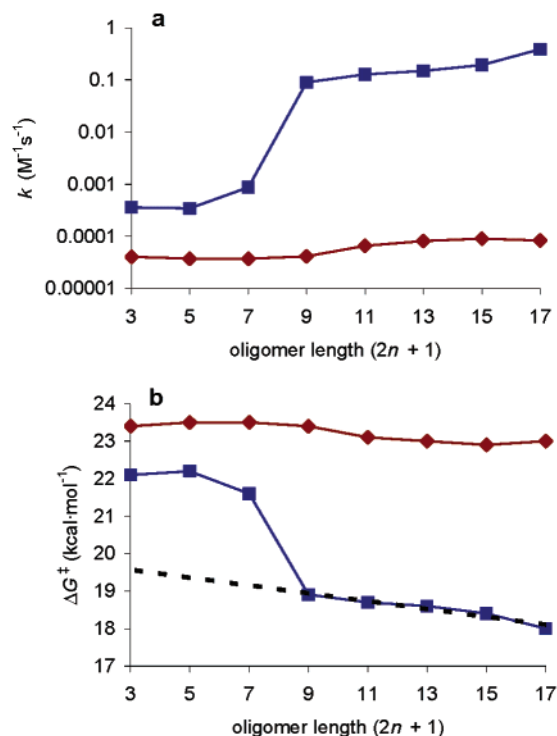
Figure 1. (a) Methylation rate in CH$_3$CN (blue ■) and CHCl$_3$ (red ◆). (b) $\Delta G^{\ddagger}$ in CH$_3$CN (blue ■) and CHCl$_3$ (red ◆).

To gain insight into the nature of the noncovalent interactions responsible for the rate acceleration in acetonitrile, a series of pyridine-containing oligomers was synthesized, varying systematically in length from 5 to 17 monomer units (**3**–**6**, **8**, **9**). The methylation rate was measured as a function of oligomer length in both acetonitrile and chloroform, using the same methods previously described for oligomers **2** and **7** (Figure 1). In chloroform, a slight rate increase is observed with increasing oligomer length, possibly resulting from pyridinium-π interactions between the pyridine ring and the freely rotating PE arms of the oligomer. In acetonitrile, the methylation rate is also dependent upon oligomer length, though not in the linear fashion observed for chloroform. Instead, the addition of only two monomer units from the 7-mer to the 9-mer increases the methylation rate by 2 orders of magnitude. Previous studies have shown that eight monomer units is the minimum length required for PE oligomers to adopt a stable helical conformation at room temperature in acetonitrile,[4] providing additional evidence that oligomer folding is responsible for the methylation rate enhancement.

The contribution of pyridinium-π interactions to stabilization of the transition state structure in acetonitrile can be qualitatively determined by comparing $\Delta G^{\ddagger}$ for oligomers having lengths of 9–17 monomer units. In the folded structure of oligomers having 13 or more monomer units, the pyridine ring is sandwiched between two phenyl rings, enabling pyridinium-π interactions. In contrast, oligomers having 9 or 11 monomer units adopt a folded conformation but do not possess sufficient length to benefit from pyridinium-π interactions. Contrary to our predictions, $\Delta G^{\ddagger}$ follows a linear trend for oligomers having lengths of 9–17 monomer units (Figure 1b, dashed line), likely discounting pyridinium-π interactions as the major contributor to the observed transition-state stabilization. Preferential solvation of the hydrophobic cavity interior by methyl iodide may be the primary reason for the observed rate acceleration, as increasing the oligomer length increases the volume of the binding cavity, allowing a larger number of electrophilic molecules to be bound in close proximity to the pyridine nucleophile and thus accounting for the linear relationship between $\Delta G^{\ddagger}$ and oligomer length.[9]

In conclusion, oligomer folding provides noncovalent hydrophobic interactions that lower the energy barrier for the reaction of methyl iodide with pyridine-containing PE oligomers. The methylation reaction studied in this work excludes the oligomer from acting in a catalytic manner. However, it provides an example showing how the microenvironment created by a foldamer can be used to accelerate reactions involving hydrophobic substrates, and future work will focus on the design of reactions in which the oligomer has potential to act catalytically. Although PE cavitands have yet to attain the same level of functionality as resorcinarene-based cavitands, this work demonstrates their potential to emerge as a new class of functionally diverse synthetic enzyme mimics.

Supporting Information Available: Detailed descriptions of all experimental procedures and accompanying analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) The ratio of absorbance bands at 303 and 289 nm in the UV spectrum is consistent with a predominantly cisoid conformation of the PE backbone, based on the analysis described in ref 4.
(8) Based on a helical model having six PE monomers per turn unit, as described in: Matsuda, K.; Stone, M. T.; Moore, J. S. *J. Am. Chem. Soc.* **2002**, *124*, 11836–11837.
(9) Binding of methyl iodide prior to the reaction implies a kinetic model with higher complexity than the pseudo-first-order model applied in this work. Future studies will explore the reaction mechanism in greater detail, but approximation of pseudo-first-order kinetics is valid for the current work, as k_{obs} was found to be linearly dependent ($R^2 = 0.9993$) on [CH$_3$I] over the concentration range at which k was measured.

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