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Helix stabilization through pyridinium–π interactions†

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Intramolecular cation–π interactions between a methyl pyridinium ion and a phenyl ring stabilize the folded structure of a phenyleneethynylene oligomer.

The attractive force between a pyridinium ion and an aromatic ring, first studied by Dougherty and coworkers,[1] has been widely used to facilitate reaction catalysis[2] and self-assembly.[3] However, we are unaware of any examples in which pyridinium–π interactions are used to modulate the folding stability of a synthetic chain molecule. Phenyleneethynylene (PE) oligomers previously studied by our group and others,[4] have been found to exhibit a reversible transition from random to helical conformation in response to changes in solvent quality.[5,6] Furthermore, we have demonstrated that a *N*,*N*-dimethylaminopyridine (DMAP) monomer can be incorporated into the backbone sequence of a PE oligomer, such that the pyridine nitrogen is located on the interior of the binding cavity.[7] Here we show how methylation of the pyridine moiety stabilizes the folded conformation of the oligomer through pyridinium–π interactions, and quantify these interactions by systematically varying the oligomer chain length.

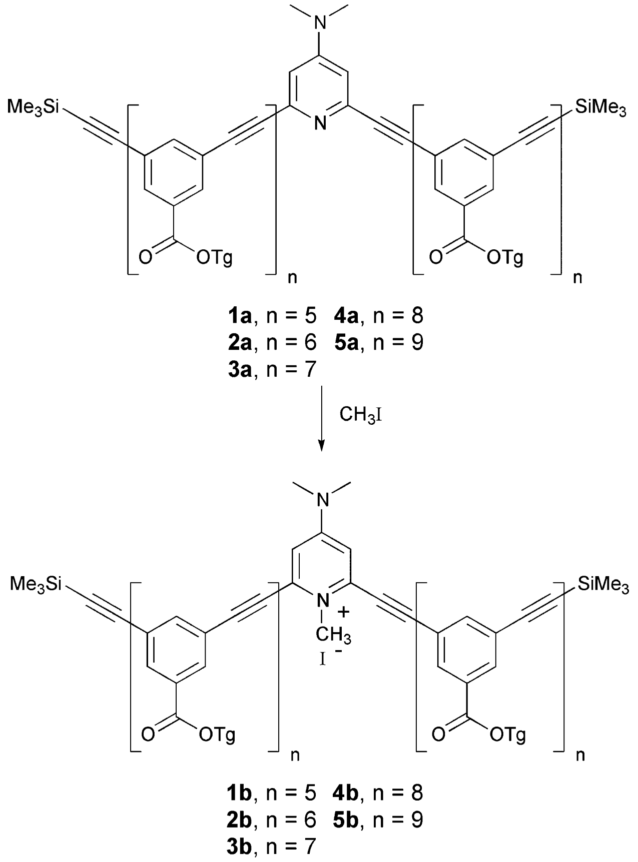
Oligomers **1a–5a** were synthesized each having a DMAP ring at the central position of the chain, varying in length from 11–19 monomer units.[8] Reaction of each of the oligomers in neat methyl iodide yielded the corresponding methyl pyridinium products (Scheme 1).[9] In order to compare the folding properties of **1a–5a** with those of **1b–5b**, UV absorption spectra of each of the oligomers were obtained in a series of solvent mixtures ranging from pure acetonitrile to pure chloroform. In acetonitrile the PE backbone is poorly solvated causing the oligomer to collapse into a helical conformation, whereas in chloroform the PE backbone is better solvated and the oligomer unfolds into a random conformation. The equilibrium constant (K_{eq}) for this folding reaction (eqn (1))

$$\text{random conformation} \xrightleftharpoons{K_{eq}} \text{helix} \qquad (1)$$

represents the ratio between folded and unfolded oligomer. Assuming that the folding reaction follows a two-state model and that all of the oligomers undergo a complete transition between their folded and unfolded states over the observed range of solvent mixtures, the UV absorbance data can be fitted to give the free energy of folding in pure acetonitrile, $\Delta G(\mathrm{CH_3CN})$, for each oligomer.[10]

Table 1 lists $\Delta G(\mathrm{CH_3CN})$ for oligomers **1a–5a** and their corresponding methylated products **1b–5b**. The data reveal that for oligomers having sufficient length to engage in pyridinium–π interactions (**2–5**), methylation increases the folding stability. However, in the case of **1**, which is too short to benefit from pyridinium–π interactions, methylation destabilizes the folded conformation. These observations agree with the representative solvent denaturation curves shown in Fig. 1, where methylation decreases the tendency for oligomer denaturation by $CHCl_3$ for **2**, but increases $CHCl_3$ denaturation for **1**.

It is likely that multiple noncovalent interactions impact the folding stability of the methylated oligomers. Therefore, to measure the precise contribution of pyridinium–π interactions, it is necessary to first determine the relationship between the change in folding stability upon methylation, $\Delta\Delta G(\mathrm{CH_3CN})$, and oligomer length for oligomers capable of pyridinium–π interactions. The relationship between $\Delta\Delta G(\mathrm{CH_3CN})$ and oligomer length is shown in Fig. 2, with the dashed line indicating the approximately linear trend observed for oligomers capable of pyridinium–π interactions.



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

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

Scheme 1 Methylation of pyridine-containing oligomers. Tg = $(\mathrm{CH_2CH_2O})_3\mathrm{CH_3}$.

Table 1 Folding stability of nonmethylated and methylated PE oligomers[a]

Oligomer	Oligomer length ($2n + 1$)	$\Delta G(\mathrm{CH_3CN})$ series **a** ($\mathrm{kcal{\cdot}mol^{-1}}$)	$\Delta G(\mathrm{CH_3CN})$ series **b** ($\mathrm{kcal{\cdot}mol^{-1}}$)	$\Delta\Delta G(\mathrm{CH_3CN})$ ($\mathrm{kcal{\cdot}mol^{-1}}$)
1	11	−2.6 ± 0.1	−2.3 ± 0.1	0.3 ± 0.1
2	13	−3.7 ± 0.1	−5.2 ± 0.1	−1.5 ± 0.1
3	15	−4.7 ± 0.1	−6.5 ± 0.4	−1.8 ± 0.4
4	17	−5.6 ± 0.5	−7.5 ± 0.8	−1.9 ± 0.9
5	19	−6.9 ± 0.7	−8.8 ± 0.9	−1.9 ± 1.1

[a] $T = 25$ °C.

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† Electronic supplementary information (ESI) available: detailed descriptions of all experimental procedures and accompanying analytical data. See http://www.rsc.org/suppdata/cc/b4/b405980h/

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Oligomer **1** deviates from this trend by 1.8 kcal·mol^{-1}, which we attribute to loss of the pyridinium–π interactions. Alternatively, the data in Fig. 2 can be interpreted such that $\Delta\Delta G(CH_3CN)$ is dependent upon oligomer length for **1–3**, but reaches an asymptotic limit of *ca.* 1.9 kcal·mol^{-1} at longer chain lengths. In this case, the contribution of pyridinium–π interactions to stabilizing the folded structure of the oligomer would be slightly more than 2 kcal·mol^{-1}.[11] This latter analysis of the data appears logical, as the strength of the pyridinium–π interactions may be reduced by fraying of the chain ends in the cases of **2** and **3**, and reach maximum strength only at high chain lengths where fraying is less significant. However, the data currently available precludes determination of the precise relationship between oligomer length and $\Delta\Delta G(CH_3CN)$.

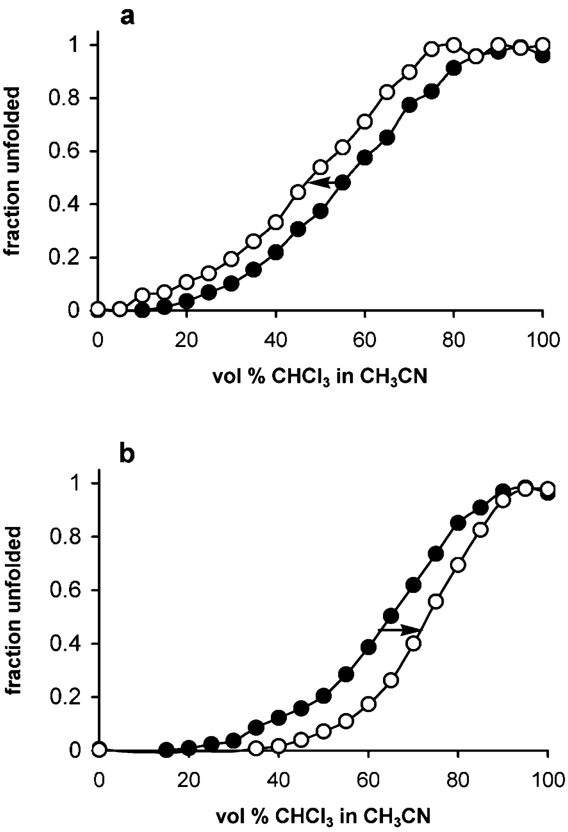

Fig. 1 Representative solvent denaturation curves for (a) **1a** (●) and **1b** (○) and (b) **2a** (●) and **2b** (○). The arrows indicate the midpoint shift of denaturation upon methylation of the pyridine moiety.

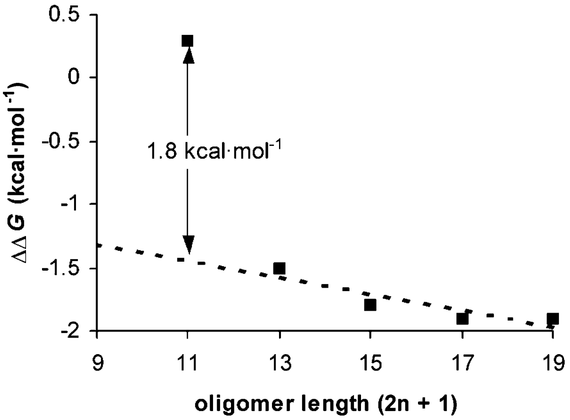

Fig. 2 Effect of methylation on folding stability as a function of oligomer length. The linear equation used to fit the data for oligomers capable of pyridinium–π interactions is given by $\Delta\Delta G = -0.065(2n+1) - 0.735$ ($R^2 = 0.786$).

In conclusion, cation–π interactions between a methyl pyridinium ion and a phenyl ring stabilize the folded conformation of a PE oligomer. Although the precise nature of the relationship between oligomer length and $\Delta\Delta G(CH_3CN)$ remains elusive, the impact of the pyridinium–π interactions is shown to be at least 1.8 kcal·mol^{-1}. This work demonstrates a novel use for pyridinium–π interactions, and shows how the folding reaction can be used to quantify weak supramolecular interactions. Future work will focus on varying the size of the alkylating agent and the nature of the counterion to gain additional control over folding stability.

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