Chain Length-Dependent Affinity of Helical Foldamers for a Rodlike Guest

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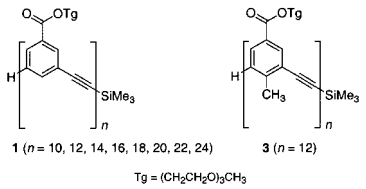
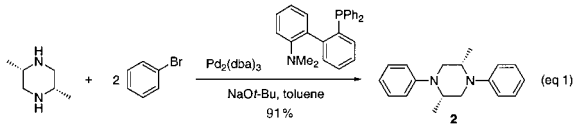
Biology teaches the importance of helical constructs in macromolecular recognition. For example, helical structures play critical roles in DNA−protein and protein−protein binding, as well as regulating various biological events such as the expression of genetic information.[1,2] Although directional interactions such as complementary hydrogen bonds can elicit specificity, shape recognition arising from the morphological features of interacting molecular surfaces significantly contributes to binding affinity.[3] We imagined that the internal cavity of a helix would be complementary in shape to rodlike chain molecules of appropriate diameter. Such a mode of interaction would illustrate an example of recognition based on a helical scaffold unlike those typical of biomacromolecules.[4] We have previously shown that *m*-phenylene ethynylene oligomers **1** exist in a compact helical conformation in polar solvents.[5] The well-ordered conformation of **1** creates a tubular hydrophobic cavity, and certain monoterpenes (i.e., (−)-α-pinene) can bind in the cavity of **1** ($n = 12$).[6] These findings led us to consider rodlike chiral guest molecules whose shape is better matched to the cylindrical cavity of oligomer series **1** (Figure 1a). The strength of complex formation is postulated to depend on the length of the oligomer to its guest. This assumes the affinity depends on the area of contact between the interacting molecular surfaces (Figure 1b).[7] Here we show by systematically varying the size of the host oligomer's cavity that there is length-dependent recognition for a rodlike guest based not on specific interactions, but simply on minimizing the solvent exposed surface of the complex.



1 (n = 10, 12, 14, 16, 18, 20, 22, 24) **3** (n = 12)

Tg = $(CH_2CH_2O)_3CH_3$

Compound **2**, *cis*-(2*S*,5*S*)-2,5-dimethyl-*N*,*N*′-diphenylpiperazine, has a chiral, rodlike structure and its size and shape are complementary to the cavity of **1**, as deduced from molecular modeling studies (Figure 1c).[8] A particularly attractive feature of this molecule (and higher homologues) is that it can be prepared in a straightforward manner (eq 1). Enantiomerically pure *cis*-



(2*S*,5*S*)-2,5-dimethylpiperazine, prepared in three steps from L-alanine derivatives,[9] was coupled with 2 equiv of bromobenzene by Buchwald's amination method[10] using $Pd_2(dba)_3$, 2-diphenylphosphino-2′-dimethylaminobiphenyl, and sodium *tert*-butoxide to afford **2** in 91% yield with no epimerization. Interestingly, amination reactions using other phosphine ligands were unsuccessful. The use of *rac*-BINAP or 2-diphenylphosphinobiphenyl resulted in no reaction or a low chemical yield of **2**, probably due to the steric hindrance of methyl groups. Alternatively, 2-di(cyclohexyl)phosphino-2′-dimethylaminobiphenyl gave a satisfactory yield, but caused a significant amount of epimerization, as observed by ^{1}H NMR.

The binding affinities of **2** for members of oligomer series **1** ($n = 10, 12, 14, 16, 18, 20, 22, 24$)[11] were determined by circular dichroism (CD) measurements. Guest molecule **2** itself exhibits a CD signal at ca. 300 nm. Therefore, induced CD spectra resulting from the interaction of **2** with oligomer series **1** were obtained by subtracting the CD spectrum of **2** from that of the host−guest complex.[12] Figure 2 shows a typical series of spectra resulting from the addition of enantiomerically pure **2** to 22-mer in 40% aqueous acetonitrile. The piperazine guest induces a strong Cotton effect at ca. 315 nm corresponding to the oligomer's diphenylacetylene chromophore. CD spectra recorded over a range of guest concentrations showed saturation behavior with an isodichroic point, which is expected for a single stoichiometry relationship between **2** and **1** (Figure 2). To verify that binding takes place within the helical cavity, we studied solutions of oligomer **3** with guest **2** as a control. Oligomer **3** ($n = 12$) posseses internally situated methyl groups leaving a smaller cavity in the foldamer. No induced Cotton effect was observed when **2** was added to **3** (see Supporting Information). These results indicate that compound **2** binds to the internal cavity of oligomer series **1**, rather than associating by intercalation. The stoichiometry of the complex of **2** and **1** was determined to be 1:1 by the linearity of Benesi−Hildebrand plots.[13] The association constant (K_{11}) calculated by a nonlinear least-squares fitting method was found to be 5600 ± 190 M^{-1} for the 12-mer.[14] In addition, a significant dependence of the binding affinities of **2** on the length of the oligomers was observed (Figure 3). In each case, the stoichiometry

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(8) Molecular modeling was performed with MacroModel 7.0 (OPLS force field). The Monte Carlo search explored the rotation and translation of **2** with respect to **1**. All atoms of **1** and **2** were free to move during the minimization.

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(11) The oligomers were synthesized according to our previously reported methods.[5b] The purity of each oligomer was determined by ^{1}H NMR, MALDI, HPLC, and GPC.

(12) No self-aggregation of **2** (in the absence of **1**) was observed in the experimental concentration range, as deduced from ^{1}H NMR studies.

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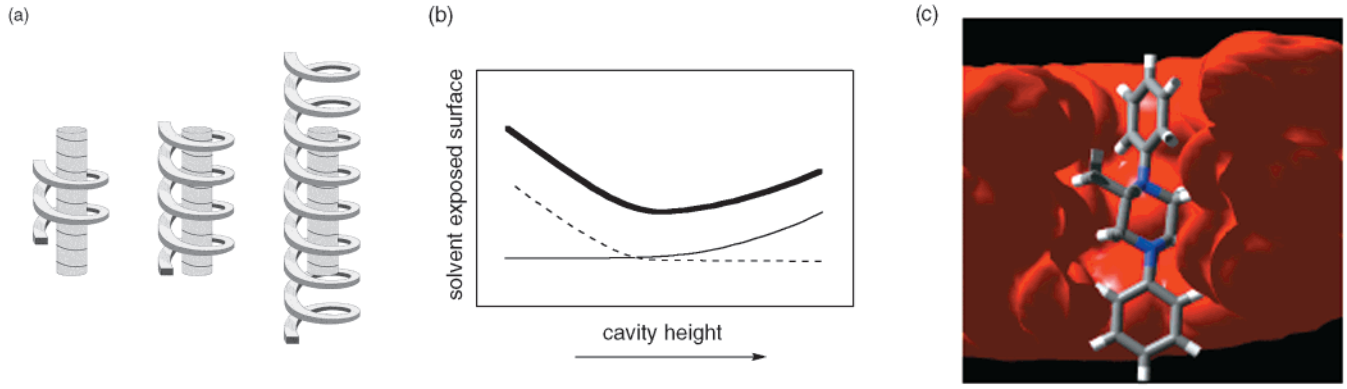

Figure 1. (a) Schematic diagram illustrating the binding of a rodlike guest to helical oligomers of differing lengths. The cavity height is determined by the oligomer length. (b) Solvent exposed surface of the oligomer cavity (—) and the rodlike guest (- - -) in a complexed state as a function of cavity height. The total amount of solvent exposed surface (**—**) shows a minimum that predicts a cavity length with the highest affinity for the rodlike guest. (c) Minimized structure of **1** (n =18) with **2** determined by a Monte Carlo docking algorithm.

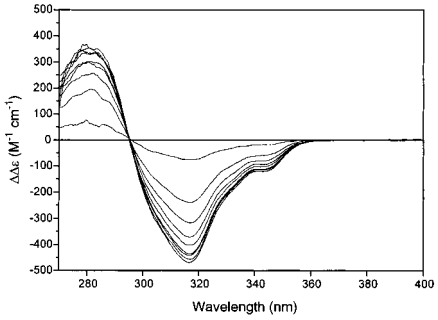

Figure 2. CD spectra of oligomer **1** (n = 22) as a function of the concentration of **2** (range, 4.3−425 μM) in 40% H_2O in CH_3CN (by volume) at 294 ± 1 K. [**1**] = 4.2 μM.

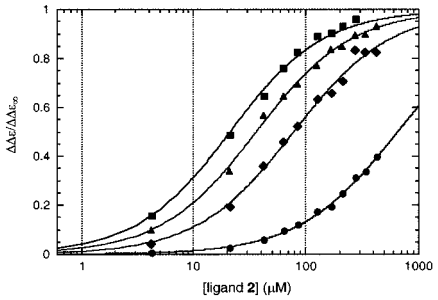

Figure 3. Plot of fractional saturation of the CD signal against the concentration of guest **2** (μM) with various lengths of oligomer series **1**: ■ (n = 22), ▲ (n = 18), ◆ (n = 14), ● (n = 10). 40% H_2O in CH_3CN (by volume) at 294 ± 1 K. [**1**] = 4.2 μM.

of the complex was 1:1. The association constant of the 10-mer is smaller than that of the 12-mer, and the value of K_{11} increased significantly as the length of the oligomer increased up to the 20-mer and 22-mer. The affinity of **2** with the 20-mer and 22-mer of **1** is ca. 30-times larger than that of the 10-mer. Interestingly, the K_{11} value of the 24-mer is smaller than that of the 20-mer and 22-mer by an experimentally significant and reproducible margin. Whether this reduction in affinity is due to destabilization from a cavity-volume/guest-volume mismatch as postulated in Figure 1 or whether this is simply a fluctuation in

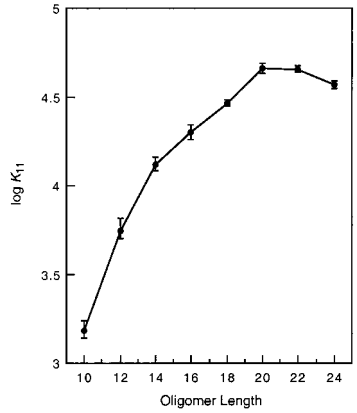

Figure 4. Plot of log K_{11} against oligomer length. The binding affinity of **2** reaches a maximum value with the 20-mer and 22-mer. All measurements were recorded in a mixed solvent of 40% H_2O in CH_3CN (by volume) at 294 ± 1 K. [**1**] = 4.2 μM.

binding strength due to some other effect cannot be established without examining longer oligomeric sequences. Interestingly, models reveal that the fraction of cavity volume occupied by **2** drops as the oligomer becomes longer than the 22-mer (ca. 58% of the volume is occupied for the 22-mer).[15] We plan on investigating these issues in the future.

Our present results support the hypothesis that all members of oligomer series **1** exist in solution as conformationally well-ordered foldamers with chiral cylindrical cavities capable of binding chiral rodlike guest molecules such as **2**. It is presumed that longer rodlike guest molecules will exhibit a maximum affinity to even longer oligomers. Co-modularity of host−guest oligomeric pairs such as the system studied here raises a number of interesting possibilities. For example, the rod lengths of **2** can be easily varied by repeating the aryl−piperazine unit, and may possibly be applied to the selective ligation of oligomer fragments to template the growth of chains of a specific length.

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Supporting Information Available: Synthesis of **1** (n = 20, 22, 24), synthesis of **2**, CD data (binding isotherms, nonlinear least-squares fitting curves, and comparison of hydrogen- and methyl-substituted dodecamers) (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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