Foldamer-Based Molecular Recognition

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Abstract: The ordered solution conformation of a synthetic chain molecule has been used to create a high-affinity binding site for small-molecule guests. The diastereoselective complexation of chiral monoterpenes with an achiral, amphiphilic *m*-phenylene ethynylene oligomer is demonstrated by induced circular dichroism in polar solvents. The stoichiometry of this solvophobically driven, reversible complex is strictly 1:1. The results are interpreted as a preferential binding of the chiral guest to one of the oligomer's enantiomeric helical conformations. Evidence for binding within the hydrophobic tubular cavity of the helix is provided by studies on modified oligomers.

Introduction

The cornerstone of supramolecular chemistry has rested on the concepts of preorganization and complementarity,[1−3] often manifested as conformationally constrained synthetic receptors and self-assembling building blocks.[4−10] This "lock and key" approach has been a powerful principle for designing molecular complexes of high affinity and specificity. However, recent evidence gathered from both biomolecular[11−13] and synthetic[14,15] fronts has made it increasingly clear that supramolecular catalysts and other functional assemblies fail if they are overconstrained, suggesting the need for molecular reorganization and adaptability. A possible platform on which to develop such an approach is the emerging field of foldamers—oligomers having a strong tendency to adopt specific, compact conformations in solution.[16−18]

We recently described the solvophobically driven, cooperative transition of oligomer **1** from a random coil state in chloroform to a compact helical conformation in acetonitrile.[19,20] Inherent in the folded conformation is the creation of a tubular cavity, into which we reasoned that guest molecules of complementary size and shape could bind. Evidence for an internal cavity was obtained from our recent studies, demonstrating that oligomers modified with inwardly directed ligating groups complex metal ions and subsequently induce the coil-to-helix transition.[21] We now report the reversible 1:1 association of chiral hydrocarbon guests of appropriate size to folded oligomers **1**−**3** driven by solvophobic forces.

Experimental Section

The UV absorption and CD spectra were recorded on an Olis DSM 17 UV/vis CD spectrophotometer using 1-cm rectangular quartz cells (UV) or 1-cm cylindrical quartz cells (CD). CD spectra were recorded as θ in millidegrees and converted to $\Delta\epsilon$ using the equation $\Delta\epsilon = \theta/(33982cl)$, where $\Delta\epsilon$ is the difference in molar absorptivity for oppositely polarized light (in M^{-1} cm^{-1}), c is the concentration of the sample (in mol/L), and l is the path length through the cell (in cm). The absorbance of the solutions for all measurements was approximately 1.0 at 289 nm (absorbance maxima).

For the titration measurements, two stock solutions of the oligomer and guest were prepared in spectrophotometric grade CH_3CN. Solutions of varying guest concentrations were prepared by adding the appropriate volume of water into a volumetric flask, adding oligomer and guest solution, and then diluting to a total volume of 5 mL with CH_3CN. Samples were then shaken vigorously to ensure thorough mixing and allowed to sit for 10 min, after which the appropriate spectra were recorded. In each titration the final concentration of the oligomer solution was 4.2 μM.

Results and Discussions

Induced circular dichroism (CD) spectroscopy is a powerful tool for probing the interaction of a chiral molecule with an achiral molecule.[22] The addition of monoterpenes such as (−)-α-pinene (**4**) to dilute solutions of dodecamer **1** in polar solvents results in only very minor changes to the absorption spectrum of **1** (Figure 1a). This observation provides no significant evidence for intermolecular association, but it does indicate that **1** is in a helically folded conformation[19,20,23] and its concentration

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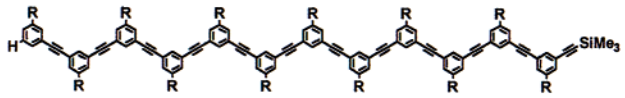

1, R = $CO_2(CH_2CH_2O)_3CH_3$

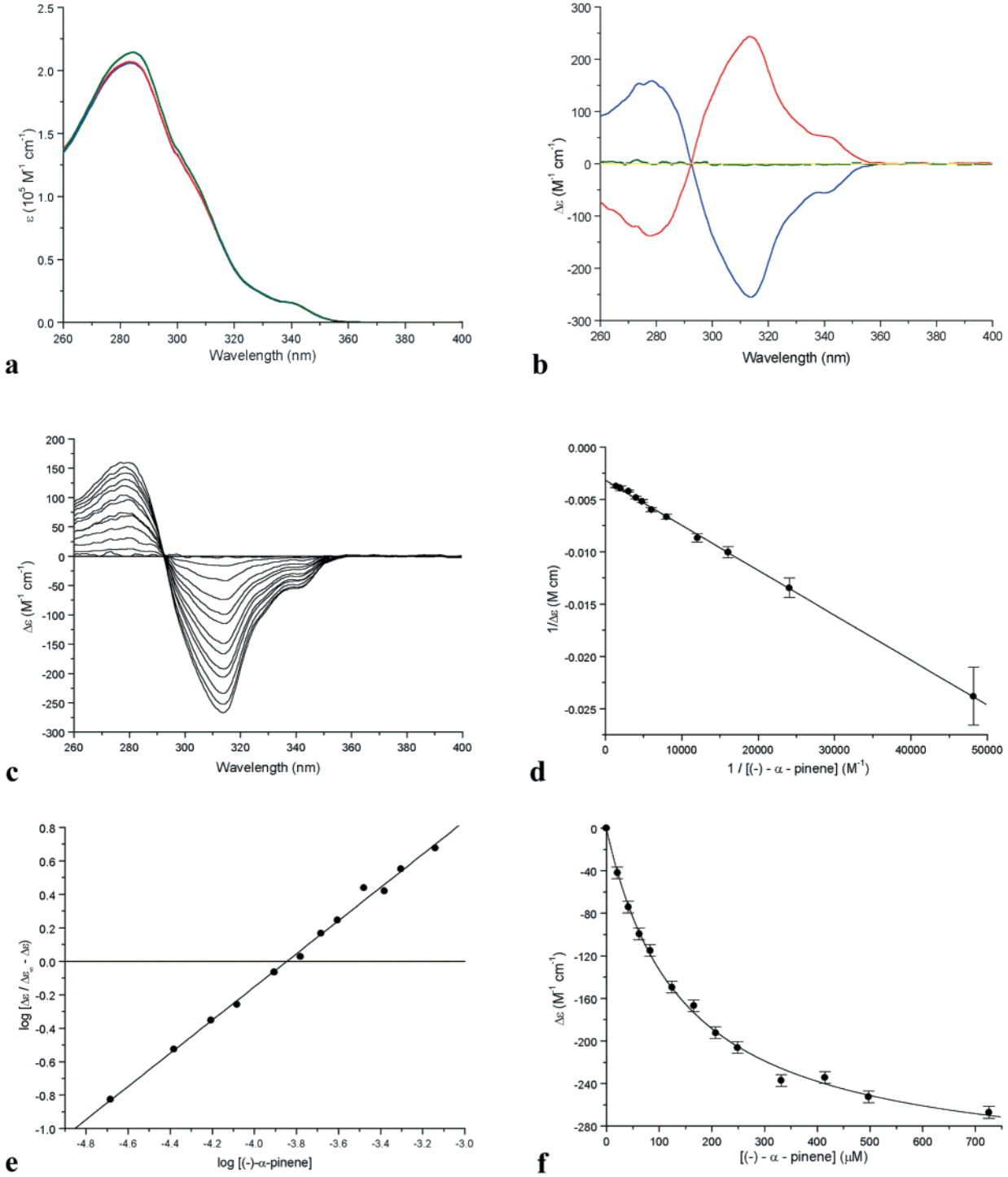

Figure 1. Association of oligomer **1** with (−)-α-pinene (**4**). All measurement were recorded in a mixed solvent of 40% water in acetonitrile (by volume) at 295 K. [**1**] = 4.2 μM. (a) UV spectra. Oligomer **1** (green line) in the presence of 100 equiv of (−)-α-pinene (red line) and 100 equiv of (+)-α-pinene (blue line). (b) CD spectra. (−)-α-Pinene (yellow line, 420 μM), oligomer **1** (green line) in the presence of 100 equiv of (−)-α-pinene (blue line) and 100 equiv of (+)-α-pinene (red line). (c) CD spectra of oligomer **1** as a function of the (−)-α-pinene concentration (concentration range, 0−726 μM). (d) Benesi−Hildebrand double-reciprocal plot of the CD intensity at 314 nm against the (−)-α-pinene concentration. The data are linear (correlation coefficient = 0.9996) and span ca. 5−97% saturation, indicating a 1:1 stoichiometry. (e) Hill plot of the log [$\Delta\epsilon_{314}/\Delta\epsilon_\infty - \Delta\epsilon_{314}$] against log (−)-α-pinene concentration. The data are linear (correlation coeffecient = 0.9978) with a slope of 0.991, indicating the binding of only one guest species. (f) Plot of CD intensity at 314 nm against (−)-α-pinene concentration. The line is the nonlinear fit of the data to the 1:1 binding model. Error bars are based on the signal-to-noise ratio of the CD spectra.

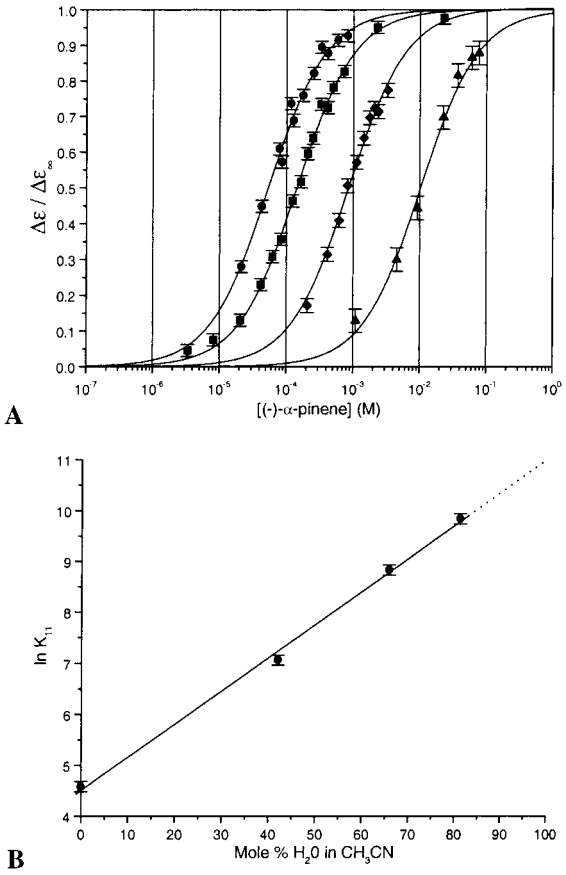

Figure 2. Solvophobically driven binding of (−)-α-pinene to oligomer **1**. All measurements were recorded at 295 K. [**1**] = 4.2 μM. (A) Plot of fractional saturation of the CD signal against (−)-α-pinene concentration for **1** in a mixed solvent of water in acetonitrile (mole percent water): ▲, 0%; ◆, 42%; ■, 66%; ●, 81%. The CD signal at saturation, $\Delta\epsilon_\infty$, was obtained from nonlinear least-squares fitting of $\Delta\epsilon$ vs (−)-α-pinene concentration using the 1:1 binding model. The lines are the nonlinear fits of the data to the 1:1 binding model. Error bars are based on the signal-to-noise ratio of the CD spectra. (B) Plot of ln K_{11} for **1** against the solvent composition. $K_{11}(0\%) = 100 \pm 10$ M^{-1}; $K_{11}(42\%) = 1160 \pm 90$ M^{-1}; $K_{11}(66\%) = 6830 \pm 500$ M^{-1}; $K_{11}(81\%) = 18\,600 \pm 1300$ M^{-1}. The solid line is the least-squares linear fit (correlation coefficient = 0.9987), and the dotted line is the extrapolation to 100% water. Error bars are from the nonlinear fitting of the data in (A).

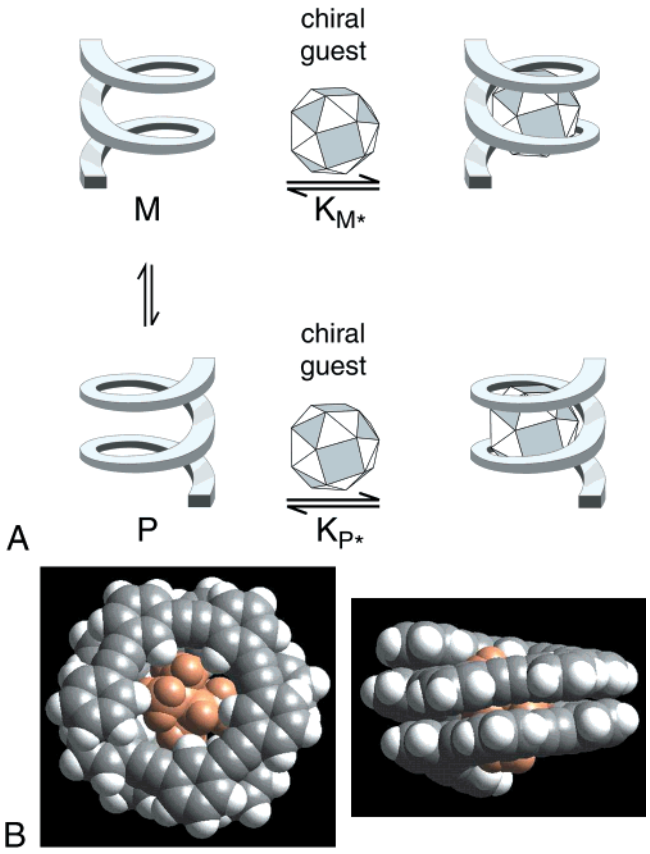

Figure 3. Association models of oligomer **1** and α-pinene. (A) Postulated equilibria. The uncomplexed foldamer exists as a dynamic racemate of enantiomeric *M* and *P* helical conformations. Upon complexation to a chiral guest, a pair of diastereomers is produced. This model predicts that the binding isotherm measured by CD follows the relation $\Delta\epsilon = [\mathbf{1}]K_{11}\Delta\epsilon_\infty[\text{pinene}](1 + K_{11}[\text{pinene}])^{-1}$, where $K_{11} = K_{M*} + K_{P*}$. The molar ellipticity at saturation, $\Delta\epsilon_\infty$, is an equilibrium weighted average of $\Delta\epsilon_{M*}$ and $\Delta\epsilon_{P*}$, the individual diastereomeric ellipticities (i.e., $\Delta\epsilon_\infty = (\Delta\epsilon_{M*}K_{M*} + \Delta\epsilon_{P*}K_{P*})K_{11} - 1$). (B) Space-filling model of the 1:1 complex viewed from the top and side. This is the lowest energy complex determined by a Monte Carlo search in which the position and orientation of α-pinene within the helix cavity were varied.

remains constant upon guest addition. In the absence of **4**, phenylene ethynylene oligomer **1** exhibits no CD, signal as expected for an achiral molecule (Figure 1b, green line). However, as shown in Figure 1b, the addition of enantiomerically pure (−)-α-pinene induces a strong Cotton effect in the wavelength range where the oligomer absorbs.[24] To demonstrate that the induced CD signal is due to α-pinene and not some adventitious impurity, a CD spectrum of **1** and (+)-α-pinene was recorded. The mirror image spectrum was obtained (Figure 1b, red line), indicating that the induced CD signals are the result of an association of the oligomer with α-pinene.[25]

The stoichiometry and binding constant of the complex were determined by CD titration measurements. The incremental addition of (−)-α-pinene (**4**) to a solution of **1** results in the increase and eventual saturation of the CD signal (Figure 1c). The presence of an isodichroic point at 293 nm is an indication that the equilibrium involves a single stoichiometric relationship between (−)-α-pinene and **1**. This stoichiometry was determined to be 1:1 by the linearity of a Benesi−Hildebrand plot (Figure 1d) and the slope of a Hill plot (Figure 1e). The intensity of the CD signal at 314 nm plotted against the concentration of **4** can be fitted to a 1:1 binding model by nonlinear least-squares analysis, yielding an association constant, K_{11}, of 6830 M^{-1} (Figure 1f). The induction of a strong CD signal, the magnitude of the binding constant, and the strict adherence to a 1:1 stoichiometry suggest that complexation between the monoterpene and the oligomer is occurring in a specific manner and is not simply the result of nonspecific associations.

The binding of α-pinene (**4**) to dodecamer **1** was determined to be a solvophobically driven process. Titrations of **1** with **4** were performed in series of mixed solvents of varying mole percent water in acetonitrile (Figure 2A). As shown in Figure 2B, ln K_{11} is linearly correlated to the mole percent water.[26] By extrapolation of the linear fit to pure water,[27] we estimate an association constant of 6×10^4 M^{-1}.

The induced CD and binding analyses described above are consistent with the association model presented in Figure 3A. Dynamic racemization interconverts the enantiomeric *M* and *P*

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(24) All measurements were presumed to be at equilibrium since the observations were independent of time (spectra were measured 10 min after preparation, then again 24 h later).

(25) In the absence of any helical ordering ($CHCl_3$ solvent), no binding of the guests was observed, as evidenced by the absence of a CD signal.

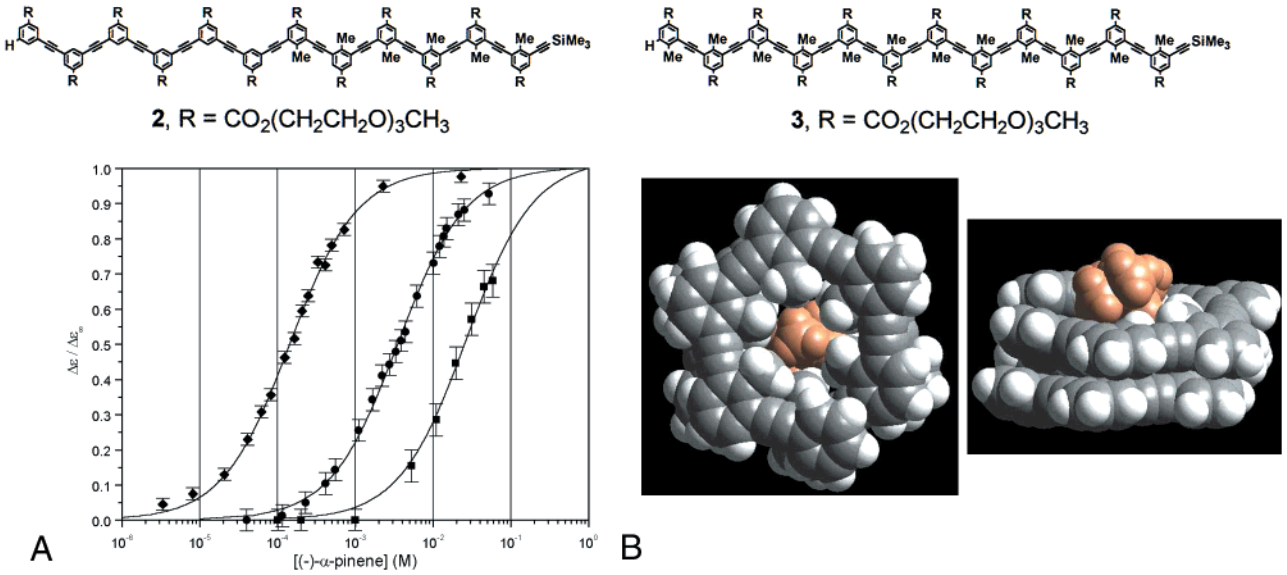
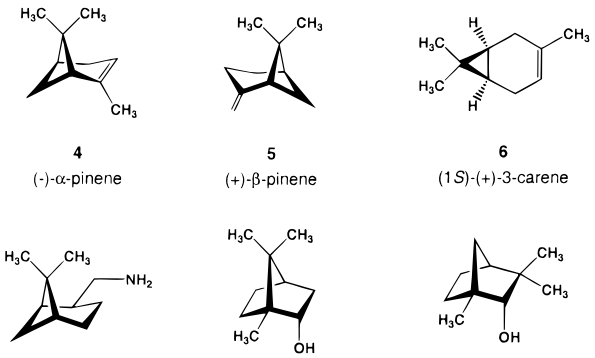


Figure 4. Association of **4** with oligomers **1**−**3**. All measurement were recorded in a mixed solvent of 40% water in acetonitrile (by volume) at 295 K. [Oligomer] = 4.2 μM. (A) Plot of fractional saturation of the CD signal against (−)-α-pinene concentration for the oligomers: ◆, **1**; ●, **2**; ●, **3**. The CD signal at saturation, $\Delta\epsilon_\infty$, was obtained from nonlinear least-squares fitting of $\Delta\epsilon$ vs (−)-α-pinene concentration using the 1:1 binding model. The lines are the nonlinear fits of the data to the 1:1 binding model. Error bars are based on the signal-to-noise ratio of the CD spectra. (B) Space-filling models of the minimum energy complex of oligomer **3** and α-pinene determined by a Monte Carlo search. The guest is positioned on top of the helix since it is larger than the internal cavity. Top and side views are shown.

helical conformations in their uncomplexed state. Upon addition of an enantiomerically pure chiral guest, diastereomeric complexes are formed with association constants K_{P*} and K_{M*}. If these association constants are not equal, an excess of one complex will be formed and an induced CD will be observed.[28] The value of the CD signal at saturation, $\Delta\epsilon_\infty$, is roughly proportional to the diastereoselectivity (i.e., the difference in association constants, $K_{P*} - K_{M*}$).[29] As shown in Figure 3B, molecular models reveal that the size and shape of α-pinene are complementary to the internal space of the hydrophobic cavity of the putative helix. Interestingly, the molecular volume of α-pinene is roughly 55% of the helix cavity volume, thus meeting the criterion established by Mecozzi and Rebek for molecular encapsulation.[30] A Monte Carlo search[31] of the most favorable α-pinene orientation in the *M* and *P* helices suggests that the difference in minimum energy of these diastereomeric complexes is roughly 1 kcal·mol^{-1}.

The binding of other guests was studied to determine the degree of substrate specificity. As summarized in Table 1, dodecamer **1** forms 1:1 complexes with a variety of monoterpenes. Variations in diastereoselectivities are evident as indicated by the $\Delta\epsilon_\infty$ values. Interestingly, α- and β-pinene (**4** and **5**), differing only in the location of the double bond, provide the largest difference in diastereoselectivity. Both have similar association constants, but **4** was ca. 20 times more selective for one helical twist sense. For the entire set of monoterpenes studied, differences in the binding constant, although measurable, are not particularly large (Table 1). However, we have

Table 1. Association of Oligomer **1** with Various Monoterpenes[a]



4 (-)-α-pinene; **5** (+)-β-pinene; **6** (1*S*)-(+)-3-carene; **7** (-)-*cis*-myrtanylamine; **8** [(1*S*)-*endo*]-(+)-borneol; **9** [(1*R*)-*endo*]-(+)-fenchyl alcohol

guest	K_{11} (M^{-1})	$-\Delta G°$ (kcal·mol^{-1})	$\Delta\epsilon_\infty$ (M^{-1}·cm^{-1})[b]
4	6830[c]	5.2	325
5	6000[d]	5.1	15
6	4450[c]	5.0	93
7	2970[c]	4.7	265
8	3920[c]	4.9	124
9	1790[c]	4.4	77

[a] All measurement were recorded in a mixed solvent of 40% water in acetonitrile (by volume) at 295 K. Abbreviations: K_{11}, association constant; M, molarity; $-\Delta G°$, free energy of complex formation; $\Delta\epsilon_\infty$, saturation value of the CD signal from nonlinear fitting of titration data to the 1:1 binding model. [**1**] = 4.2 μM. [b] CD signal at saturation determined from nonlinear least-squares fitting. [c] Determined from nonlinear least-squares fitting to the 1:1 binding model. [d] Calculated by competition experiments with guest **4**.

(26) Although we cannot exclude the formation of aggregates in the high mole percent water solutions (40 and 60 mol %), previous studies have shown that aggregation of dodecamer **1** at a concentration of 4 μm is minimal in low mole percent water solutions (0 and 20 mol %). The linearity in the plot of ln K_{11} vs mol % water over the range of solvent composition indicates that aggregation, if it is occurring, is not affecting the K_{11} or the stoichiometry.

(27) Oligomer **1** is not appreciably soluble in pure water.

(28) Upon addition of (+)-α-pinene (30 equiv) to a solution containing **1** and (−)-α-pinene (30 equiv), no change was observed in the CD signal (θ = 0 mdeg), indicating that the formation of the complexes was a reversible process that reached equilibrium in 15 s.

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(31) Molecular modeling was performed using MacroModel 5.5 (OPLS force field). Complexes of the right-handed helical conformation of **1** and the enantiomers of α-pinene resulted in a more stable complex with (+)-α-pinene. The Monte Carlo search explored the rotation and translation of α-pinene with respect to **1**. All atoms of **1** and α-pinene were free to move during the minimizations. The redundancy of the lowest energy complexes and the independence of the starting point were evidence for converged searches.

Table 2. Association of Oligomers **1**−**3** with (−)-α-Pinene[a]

oligomer	K_{11} (M^{-1})[b]	$-\Delta G°$ (kcal·mol^{-1})	$\Delta\epsilon_\infty$ (M^{-1}·cm^{-1})[c]
1	6830	5.2	325
2	280	3.3	120
3	40	2.1	47

[a] All measurement were recorded in a mixed solvent of 40% water in acetonitrile (by volume) at 295 K. Abbreviations: K_{11}, association constant; M, molarity; $-\Delta G°$, free energy of complex formation; and $\Delta\epsilon_\infty$, saturation value of the CD signal from nonlinear fitting of titration data to the 1:1 binding model. [Oligomer] = 4.2 μM. [b] Determined from nonlinear least-squares fitting to the 1:1 binding model. [c] CD signal at saturation determined from nonlinear least-squares fitting.

made no attempt to optimize the structure of the oligomer to improve specificity. The results provided below clearly demonstrate that the binding strength can be attenuated by modification of the helix cavity.

To test the helical binding model shown in Figure 3B, we synthesized oligomers **2** and **3**, which differ from **1** by the addition of methyl groups to the backbone. In the helical conformation, these methyl groups are placed into the tubular cavity, thus reducing space available for guests. Titration experiments were performed with (−)-α-pinene (**4**) and oligomers **1**−**3** (Figure 4A). Each oligomeric host forms a 1:1 complex with **4**, but the association constant drops by 1 and 2 orders of magnitude for **2** and **3**, respectively (Table 2). From solvent denaturation studies we have previously determined that the helical conformations of **2** and **3** are more stable than **1**. Thus, the reductions in K_{11} cannot be due to a destabilization of the uncomplexed helices **2** and **3**. Moreover, the methyl-lined cavity of **3** is at least as hydrophobic as that of **1**; thus, the reduction in binding cannot be due to decreased hydrophobicity. Rather, the results indicate that by filling the cavity with methyl groups, the space available for guest binding is reduced (Figure 4B). These observations support the idea that the complex formed between **1** and **4** involves binding within the tubular cavity.

Conclusions

The findings presented here show that conformationally ordered oligomers can serve as a platform for the construction of synthetic receptors. The demonstration that a binding site can be created from a folded chain runs parallel to concepts in biopolymer recognition and suggests a new avenue for supramolecular catalysis. For example, it is likely that longer oligomers will bind more than a single substrate and may therefore facilitate bimolecular reactions. The synthetic modularity of sequence-specific oligomers naturally suggests the use of combinatorial methods in refining the active sites. Molecular adaptation, where binding strength is mediated by conformational changes, is easily imagined from the work presented here.

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