1852 were independent ($R_{int} = 0.033$) and included in the refinement; Lorentzian polarization and absorption corrections (psi scans) performed; min./max. transmission = 0.74/0.90; solution by direct methods(SHELXS-97); refinement by full-matrix least squares based on F^2 (SHELXL-97); 141 parameters, $R = 0.1486$, $wR = 0.2301$ for all data; $R1 = 0.0843$ computed for 1004 observed data ($> 2\sigma(I)$). The fullerene molecule was refined as a rigid group with the use of parameters from a well-determined structure.[18] Twinning is an unlikely explanation for the disorder because there was no evidence of abnormal peak shapes or spurious reflections between layer lines. The space group determination was completely unambiguous; therefore, there was only one minor violation (0, 0, 11) of the conditions for systematic absences. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-102135. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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Controlling the Secondary Structure of Nonbiological Oligomers with Solvophobic and Coordination Interactions**

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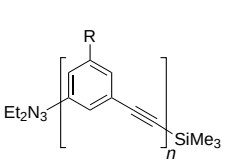
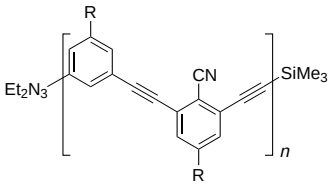
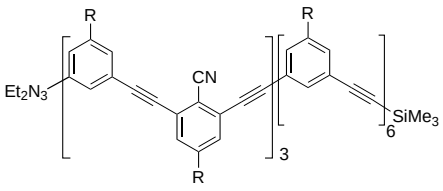
The study of conformationally ordered structures in solution from synthetic chain molecules is an important problem whose ultimate aim is to mimic the properties and functions of natural biopolymers. Well-defined conformations of nonbiological oligomers have been achieved by a variety of strategies including intramolecular hydrogen bonding,[1–3] donor – acceptor complexation,[4] control of monomer torsion through local steric and electrostatic interactions,[1, 5] and metal – ligand interactions.[6–9] Ordered structure in proteins and nucleic acids depends upon a combination of specific and nonspecific noncovalent forces. In general, most evidence supports a picture in which nonspecific hydrophobic interactions provide the energetic driving force for folding, while directional interactions play a structure-defining role. In search of a system that depends on nondirectional forces to drive conformational ordering, we recently reported the solution behavior of a homologous series of *meta*-connected phenylacetylene oligomers **1**.[10] The helical conformation results in a tubular cavity, which upon modification could allow for the creation of novel receptor or catalytic systems.



1, n = 2, 4, 6, 8, 10, 12, 14, 16, 18



2, n = 3
3, n = 6



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R = -$CO_2(CH_2CH_2O)_3CH_3$

We now report one such modification of the tubular cavity that leads to a highly ordered secondary structure controlled

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by a combination of solvophobic and metal-coordination interactions. To the best of our knowledge, this is the first example of a nonbiological oligomer whose solution structure has been designed to involve both nonspecific (solvophobic[11]) and specific (metal-coordination) interactions.[12] These features are present in dodecamer **3**,[13] whose backbone consists of twelve nonpolar phenylacetylene units, each attached to a polar triethyleneglycol monomethyl ether side chain. Six cyano groups that are available for coordination to a metal are located on every other aromatic ring. In the helical conformation, this sequence places the six cyano groups into the interior of the tubular cavity, creating two approximately trigonal planar coordination sites.[14] Molecular models reveal that each nitrogen atom lies about 2.1 Å from the helical axis, a distance consistent with that needed for metal–nitrile ligation (Figure 1).[15, 16]

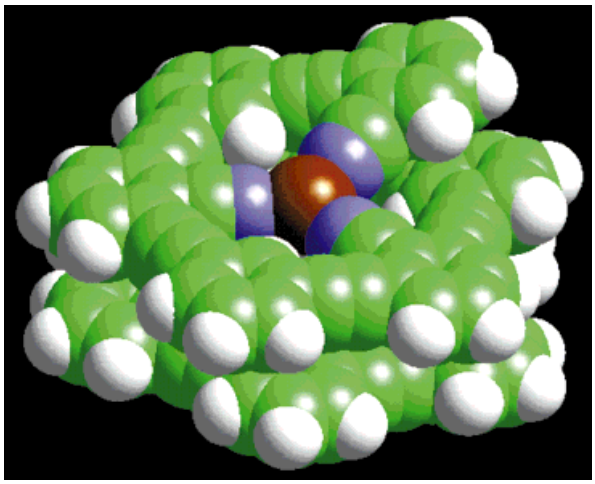


Figure 1. Space-filling model of **3** coordinating to two Ag^+ ions. The triethyleneglycol side chains have been omitted for clarity.

To demonstrate metal-induced formation of the helical structure, there are two important issues that must be addressed. First, a solvent must be used which, on its own, is not capable of causing a solvophobically driven helical structure. Tetrahydrofuran was selected for this reason since **3** displays all of the spectroscopic signatures of the random coil conformation in this solvent.[10] Second, the metal used must prefer to bind in a trigonal-planar coordination environment. Silver triflate (AgO_3SCF_3) was selected since it can adopt such a geometry.[17, 18]

The only difference between the chemical structures of **3** and **1** ($n = 12$) is the presence of six additional cyano groups. This makes **1** ($n = 12$) an ideal control compound since any spectroscopic changes observed for **3** but not for **1** upon addition of metal will indicate interactions between the metal and the cyano groups. Addition of 40 molar equivalents of AgO_3SCF_3 to the oligomers of series **1** resulted in no change in the ^1H NMR or UV/Vis spectra. This shows that silver cations do not interact with the backbone, side chains, or end groups. It also indicates that a solvophobically driven helical conformation is not induced due to the slight increase in the polarity of the solvent upon addition of AgO_3SCF_3.

The structure and stoichiometry of the self-assembled helicate of **3** in solution can be deduced from UV/Vis spectroscopy. Addition of AgO_3SCF_3 to solutions of **3** results in a decrease in the absorption of the band at 306 nm, while the intensity of the band at 288 nm remains relatively constant (Figure 2). These changes are indicative of a cisoid conformation of the diphenylacetylene units, consistent with the

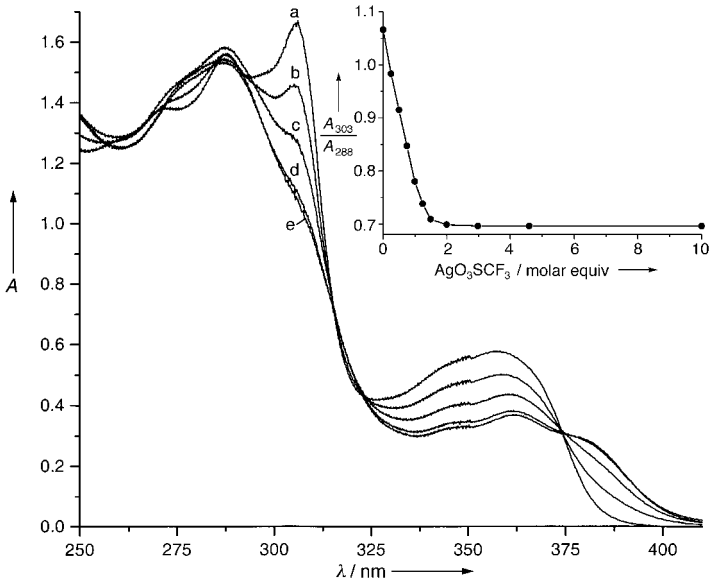
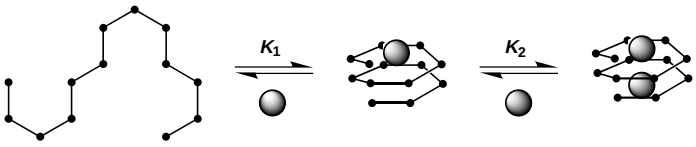


Figure 2. UV absorbance spectra of **3** in THF with increasing amounts of AgO_3SCF_3: a) 0, b) 0.5, c) 1.0, d) 1.5, and e) 2.0 equiv. Inset: Plot of A_{303}/A_{288} versus the number of molar equivalents of AgO_3SCF_3. A = absorbance ($c(\mathbf{3}) = 6.7 \times 10^{-6}$ M).

putative helical conformation.[10] In addition, the presence of a clear isobestic point at 375 nm exhibits that only a single species is formed during the complexation. The inset of Figure 2 shows a Ag^+ titration curve for **3**. It can be seen that the ratio of the two $\pi-\pi^*$ absorbances continues to decrease until two equivalents of $AgCF_3SO_3$ are added. These results as well as those of electrospray ionization mass spectrometry[19] (ESI-MS) are consistent with a single-stranded helicate of **3**. From the titration curve we estimate the product of the two association constants, K_1K_2 (Scheme 1), to be greater than $10^{12}\,M^{-2}$.



Scheme 1. Schematic representation of the metal-induced formation of helical structures. The metal ions (Ag^+) are shown as spheres.

Further evidence for the helical conformation is provided by ^1H NMR spectroscopy (Figure 3). For these studies we synthesized the symmetrical sequence **5** to simplify the spectra.[20] The addition of two molar equivalents of AgO_3SCF_3 to solutions of **5** results in dramatic upfield shifts of all aromatic resonances as well as a significant dispersion of chemical shifts. High dispersion of ^1H NMR signals is typical

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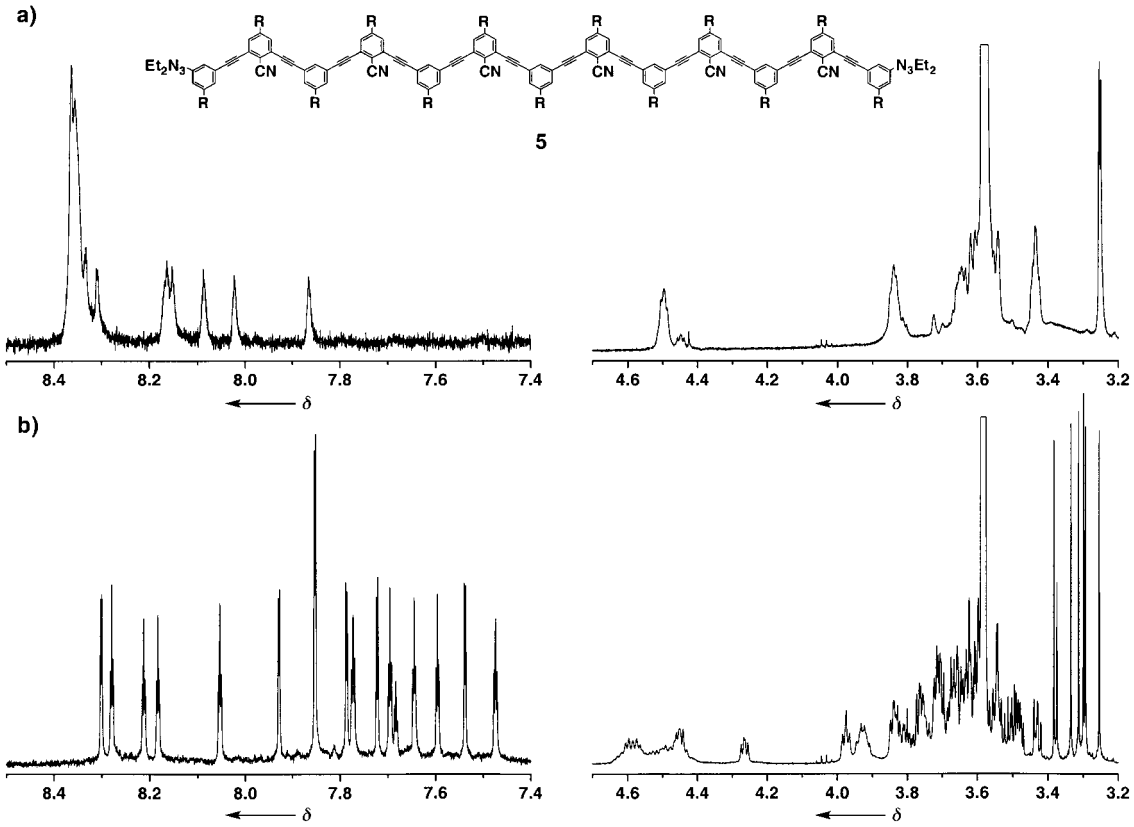

Figure 3. ^{1}H NMR spectra of **5** in [D$_8$]THF upon the addition of AgO_3SCF_3: a) 0 and b) 2.0 equiv (500 MHz, 25 °C, $c = 0.7$ mM); $R = CO_2(CH_2CH_2O)_3CH_3$.

of proteins in a well-ordered solution conformation, and probably indicates the same for $[\mathbf{5}\cdot Ag_2]^{2+}$.[21] The upfield shifts suggest that **5** adopts a π-stacked structure upon the addition of AgO_3SCF_3. These observations are all consistent with the putative helical conformation. Addition of more than two molar equivalents of AgO_3SCF_3 resulted in no change to the ^{1}H NMR spectrum, again showing that **5** binds to only two equivalents of metal.[22]

It was possible to probe the symmetry and dynamics of the metal complex from its ^{1}H NMR spectrum. The NMR resonances from the side-chain methylene protons are split into overlapping AA′BB′ patterns. Thus, the CH_2 protons become diastereotopic, as expected for a slowly exchanging helical conformation. Moreover, signals for only seven aromatic rings and terminal side-chain methyl groups ($\delta =$ 3.2–3.4) are observed upon complexation (Figure 3b). This indicates that on the NMR time scale there is a C_2 axis through the central aromatic ring. This is consistent with **5** coordinating to two molecules of AgO_3SCF_3 in a 6_1 helical conformation.

Not only can solvophobic interactions be used to induce a helical structure,[10] but in the case of **3** they appear to be important to the stability and formation of the metal-induced helicate. Oligomers **2** and **4** differ only by the presence of six additional phenylacetylene units that are not able to coordinate to a metal center. Both oligomers contain three cyano groups on alternating aromatic rings, which should bind one equivalent of AgO_3SCF_3. The addition of up to 40 molar equivalents of AgO_3SCF_3 to solutions of **2** in THF resulted in no change to the UV/Vis, ^{1}H NMR, or ESI-MS spectra, indicating no metal–ligand interactions. However, the addition of AgO_3SCF_3 to solutions of **4** in THF provided a helical conformation, as shown by UV/Vis and ^{1}H NMR spectroscopy. From the UV titration curve the association constant was determined to be 2×10^4 M^{-1}.[23, 24] This result suggests that $K_2 \gg K_1$ and that the binding of two equivalents of AgO_3SCF_3 to **3** is a cooperative process.

To quantify these effects, the binding was studied by isothermal titration microcalorimetry. As shown in Figure 4, the addition of AgO_3SCF_3 to solutions of **2** resulted in no

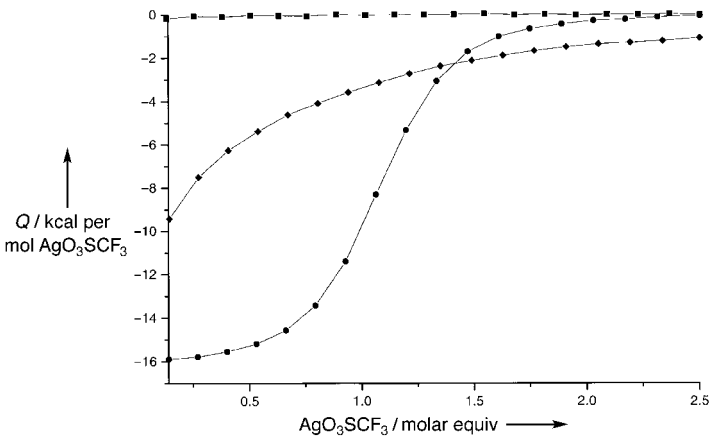

Figure 4. Heat generated Q as a function of the amount of AgO_3SCF_3 added to solutions of **2** (■), **3** (●), and **4** (◆) in THF, as determined by isothermal titration microcalorimetry ($T = 28$ °C, $c = 0.2$ mM).

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generation of heat and no formation of a complex, consistent with the observations noted above. Upon addition of AgO_3SCF_3 to solutions of **3**, heat was evolved (ca. 16 kcal mol^{-1}) until two equivalents of metal were added. This is consistent with the formation of complex $[\mathbf{3}\cdot Ag_2]^{2+}$. The addition of AgO_3SCF_3 to dodecamer **4** also resulted in the generation of heat, but no defined end point was reached due to the lower association constant. These results indicate that the addition of phenylacetylene segments that cannot bind metals to **2** allows for metal–ligand coordination to occur and shows that solvophobic interactions play a role in the metal-induced formation of the helical structure.

In conclusion, our results demonstrate that the oligomer sequence **1** can be modified to tightly and selectively bind metal ions in the internal cavity of a helical structure. The strength of metal ion binding appears to be derived from a combination of solvophobic interactions that favor the helical structure along with the more usual metal–ligand interactions.

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[12] The solvophobically induced helical structure of **3** was characterized by the same methods as oligomers **1**. Solutions of **3** in acetonitrile provided helical structures, as indicated by ^{1}H NMR and UV/Vis spectroscopy. Thus, the secondary structure of **3** can be controlled using a solvophobic driving force, and the cyano groups on the interior of the tubular cavity do not appear to inhibit the formation of helical structures.
[13] Oligomers **2**–**5** were shown to be pure by ^{1}H NMR spectroscopy, size-exclusion chromatography, high-performance liquid chromatography, and matrix-assisted laser desorption ionization mass spectrometry (MALDI-MS). Compounds **2** and **3** gave acceptable elemental analyses. Further details of the preparation and characterization of all compounds will be reported elsewhere.
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[18] Similiar behavior is observed for solutions of **3** with Cu^+ salts, but not with Cu^{2+} salts. This is explained by the ability of Cu^+ ions to adopt trigonal-planar coordination environments, while Cu^{2+} ions prefer a square-planar or octahedral bonding geometry.
[19] Additional evidence for the stoichiometry of metal binding is provided by ESI-MS. The major peak is assigned to a doubly charged species corresponding to $[\mathbf{3}\cdot Ag_2]^{2+}$.
[20] The NMR spectra of **3** are similiar to those of **5**, but there are twice as many resonances.
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[22] The addition of less than two equivalents of AgO_3SCF_3 to a solution in THF results in broad, undefined signals in the aromatic region, characteristic of a system that is fluctional on the NMR time scale.
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[24] The UV/Vis spectra showed a clear isobestic point at 375 nm, indicative of only one species being formed upon complexation.

Peptide Folding: When Simulation Meets Experiment

Xavier Daura, Karl Gademann, Bernhard Jaun, Dieter Seebach, Wilfred F. van Gunsteren,* and Alan E. Mark

The last two decades have seen the horizons of science and engineering being expanded greatly by the use of computer simulation techniques. In particular, computer simulation is the method of choice to study processes that are dangerous, costly, or even impossible to carry out experimentally, or that are of microscopic nature and thereby partially inaccessible to detailed observation. Molecular dynamics (MD) simulations, in which Newton's equations of motion are integrated to reproduce the time evolution (trajectory) of the atoms in a system, are widely used to study dynamic processes in biomolecular systems at atomic resolution.[1]

The ultimate goal of any simulation is to characterize and predict the behavior of real systems. Whether this goal is achieved depends on the quality of the model used and the computational power available. No model is an exact representation of the real system. All models must be verified, normally by comparison to experimental data. In the case of simulations aimed at understanding the mechanism of peptide or protein folding, verification represents a significant challenge. First, the dynamics of individual atoms during the process of folding cannot yet be directly observed experimentally. Experimental data at atomic resolution is only available for equilibrium distributions of conformations under

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