Molecular Zippers

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Polymeric materials composed of a linear array of recognition sites possess some unique properties, as typified by the nucleic acids. DNA stores genetic information as a sequence of covalently-linked nucleotides, and its ability to reproduce this information is based on the self-assembly of two complementary linear strands into a double-stranded complex via hydrophobic effects, hydrogen-bonds, and π–π interactions.[1,2] Related noncovalent structural motifs are common in biology, for example, β-pleated sheets and leucine zippers in proteins.[3] Recently, synthetic analogues of such structures were reported by Lehn *et al.*[4] Here the coordination chemistry of copper(I) was used to drive the self-assembly of double- and triple-stranded bipyridine oligomers. In this communication, we describe a synthetic system where hydrogen-bonding and π–π interactions direct the assembly of double-stranded complexes of amide oligomers.[5]

We have been working on oligomeric amides composed of the condensation products of isophthalic acid and 1,1-bis(4-amino-3,5-dimethylphenyl)cyclohexane (Figure 1).[6] The concentration-dependent ^{1}H NMR spectra of these compounds indicate that the oligoamides dimerize in chloroform solution. The longer oligomers interact more strongly, which suggests that the compounds form double-stranded complexes with cooperative interactions along the strands. Dimerization induces downfield changes in the chemical shifts of the signals due to the amide protons, indicative of hydrogen-bonding, and upfield changes in the chemcial shifts of the signals due to the isophthaloyl ring protons, indicative of π–π interactions. The double-stranded "zipper" structure shown in Figure 1 is consistent with these observations. However, due to the symmetry of the complexes, it is difficult to prove this structure unambiguously.

On the basis of the proposed noncovalent structural motif in Figure 1, we have developed a system which shows a preference for double-stranded complexes between two *different* but *complementary* amide oligomers (Figure 2). **1** and **2** were synthesized using simple amide coupling reactions and are differentiated by capping groups, benzoic acid or 2,6-diisopropylaniline, which terminate the chains.

1 and **2** both show signs of dimerization at millimolar concentrations in chloroform, which is not surprising given that they can form double-stranded homodimer zipper complexes (Figure 3). However, on mixing the two compounds, large changes in the ^{1}H NMR chemical shifts are observed, indicating the formation of a more stable hetero complex. Job's method of continuous variations was used to determine the 1:1 stoichiometry of this hetero complex.[7] NMR titration and dilution studies in $CDCl_3/CD_3OD$ (95:5) allowed us to determine the stability constants for all of the complexes shown in Figure 3, and the results are summarized in Table 1. The 1:1 hetero complex between **1** and **2** is remarkably stable given the competitive nature of the solvent. It is 1 order of magnitude more stable than the alternative homodimer complexes due to the complementarity of the two strands.

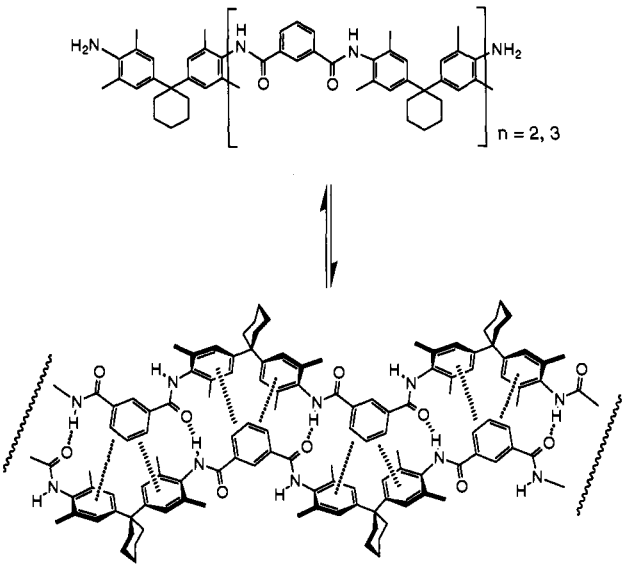

Figure 1. Molecular zippers: proposed structure of the dimeric complexes of the amide oligomers.

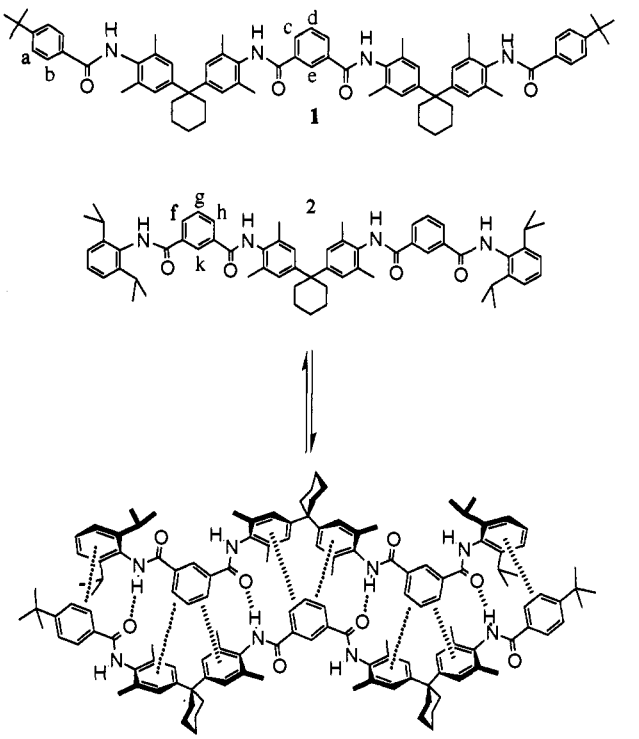

Figure 2. Two different amide oligomers which are perfectly complementary. The proton labeling scheme (a–k) is indicated.

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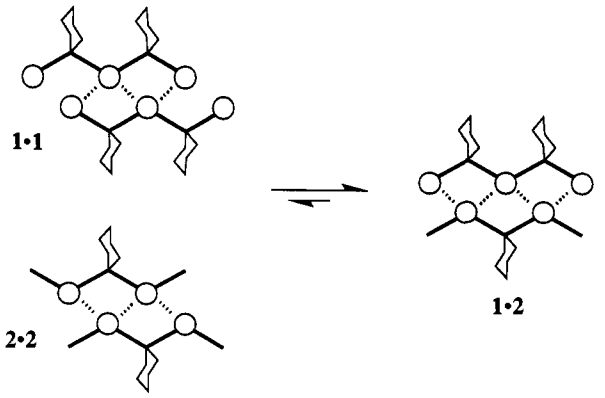

Figure 3. Schematic representations of the complexes present in a solution of **1** and **2**. Hydrogen-bonding interactions are indicated as dashed lines, and π–π interactions are not shown. The **1·2** hetero zipper maximizes the intermolecular interactions and is 1 order of magnitude more stable than the mismatched homodimer complexes, **1·1** and **2·2**.

Table 1. Association Constants Measured in $CDCl_3/CD_3OD$ (95:5)[a]

complex	association constant (M^{-1})
1·1	12
2·2	25
1·2	240

[a] Errors are ±10%.

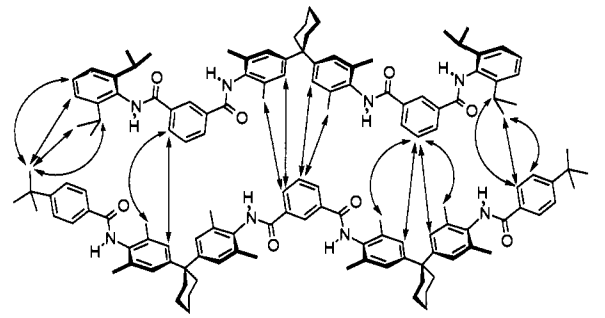

Figure 4. Intermolecular NOEs observed in the two-dimensional ROESY spectrum of the **1·2** complex. The molecules have 2-fold symmetry, but only one set of NOEs is shown.

Two-dimensional ^{1}H NMR was used to determine the structure of the **1·2** complex. A ROESY experiment was carried out in $CDCl_3/CD_3OD$ (95:5) which partially exchanged the amide protons, so no cross peaks were observed for these signals. However, intramolecular NOEs between the other signals allowed complete assignment of the rest of the spectrum. In addition, there were a large number of intermolecular NOEs which are illustrated in Figure 4. These NOEs confirm that the complex does indeed adopt an extended double-stranded structure with intimate contact between the two strands along their entire length. The conformations of the amide groups around the isophthaloyl subunits cannot be determined from this experiment, but the *trans* conformation shown in Figure 2 is more stable than this *cis* alternative,[8] and molecular models of the two strands will only fit together properly for the *all-trans* conformation.

Further evidence for the structure in Figure 2 comes from the complexation-induced changes in ^{1}H NMR chemical shift on formation of the zipper complex relative to monomeric **1** and **2**. The signals due to the amide protons all experience downfield changes, which suggests that they are all involved in hydrogen-bonding in the complex. A *trans* conformation for the isophthaloyl diamide subunits requires that only one-half of the amide protons are hydrogen-bonded at any time (Figure 2), but the complex is in fast exchange with its unbound components which have 2-fold symmetry, so a time average of hydrogen-bonded and free amide signals is observed. The aromatic signals also experience large complexation-induced changes in chemical shift. The signals due to the protons on the capping benzoyl groups (H_a and H_b, see Figure 2) and the isophthaloyl protons on the inside of the zipper (H_c, H_d, H_f, H_g, and H_h) experience upfield shifts of between 0.2 and 1.4 ppm, while the signals due to the aromatic protons on the aniline subunits all experience downfield shifts of *ca.* 0.1 ppm. These ring-current-induced changes in chemical shift provide good evidence for the edge-to-face alignment of the π-systems in the complex. The signals due to the remaining isophthaloyl aromatic protons (H_e and H_k) are not affected by complexation, as they are on the outside of the zipper (Figure 2).

Thus, the complementary covalent structures of the two oligoamide strands are expressed in the formation of a stable double-stranded zipper complex. This complex maximizes the number of hydrogen-bonding and edge-to-face π–π interactions relative to the two competing mismatched homodimer complexes, so that the hetero zipper predominates in solution (Figure 3).

The complexation-induced changes in chemical shift for the **1·2** complex are similar to those observed in the dimerization of the oligomeric amides shown in Figure 1. This suggests that this family of oligoamides all form double-stranded zipper complexes comprised of repeats of the same noncovalent structural motif. The self-assembly properties of the amide oligomers are reminiscent of nucleic acids, and they may therefore be expected to exhibit similar functional properties. This possibility is currently under investigation.

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Supplementary Material Available: Figure showing the complexation-induced changes in chemical shift for the **1·2** complex (1 page). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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