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A Self-Associating ADADA Hydrogen-Bonded Double Helix

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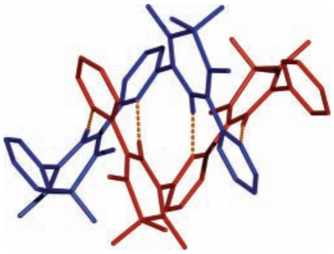
ABSTRACT



We report the design, synthesis, and characterization of an oligomer which incorporates a non-coplanar ADADA (hydrogen bond donor/acceptor) array within its structure. The molecule associates through self-complementary hydrogen bonding to form a dimeric double-helical complex.

The design of wholly synthetic molecules which self-assemble into double helical structures from single molecular strands has been a goal of chemists since the inspirational discovery of the DNA double helix by Watson and Crick.[1] A large number of such systems have been realized using metal−ligand coordination as the driving force for their formation.[2] Much less common are schemes which utilize solely noncovalent interactions to stabilize a discrete double helical complex in solution and solid states. These approaches have previously been based on the hybridization of oligoresorcinols,[3] oligopyridinedicarboxamides,[4] complementary association of amidinium/carboxylate functionalized oligomers,[5] or anion-templated self-assembly.[6] As part of a wider program to design information-containing molecules, we report here the synthesis and characterization of an oligomer which incorporates a non-coplanar ADADA (hydrogen bond donor/acceptor) array within its structure and its self-complementary dimerization to form a double helix.

The design of a double-helical complex was approached by basing the intermolecular recognition motif on the hydrogen-bonding interaction between planar six-membered heterocycles which contain nitrogen-based donor or acceptor groups and are connected sequentially in a 1,3-manner. The obvious choice for the acceptor is pyridine owing to the expansive synthetic repertoire developed over the last century. Less obvious is the selection of the heterocycle containing a donor group. 4-Pyridone itself is unsuitable, as it exists primarily as the hydroxypyridine tautomer. However, simple isosteric replacement of the pyridone carbonyl group for sulfone results in 1,4-thiazine-1,1-dioxide.[7] As a further design element, the thiazine dioxide heterocycles of the final

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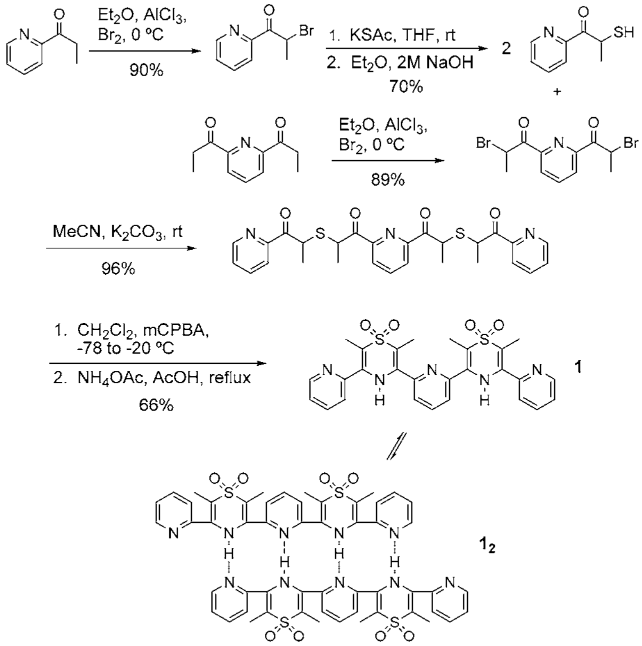
product are substituted with methyl groups at the 2,6-positions to bias adjacent rings in the system out of coplanarity, a requirement for double helix formation in this context. To test the efficacy of this strategy, a simple ADADA pentamer **1** was chosen as an initial target and synthesized (Scheme 1). The synthesis employs readily available starting materials and proceeds in reasonable overall yield (40% from 2-propionylpyridine).

Scheme 1. Synthesis of ADADA Pentamer



A dilution study of **1** monitored by ^{1}H NMR was undertaken to evaluate whether any dimerization is occurring in CDCl$_3$ solution. Spectra were recorded at 298 K and a series of concentrations ranging from 224 to 4.2 mM. A comparison of the proton chemical shifts of **1** in concentrated and dilute solutions displays changes which are consistent with formation of the anticipated double helix under fast exchange conditions (Figure 1). The N−H protons of the thiazine dioxide rings shift downfield at higher concentrations which may be attributed to the hydrogen-bonding interactions predicted in the double-helical geometry. Conversely, all of the pyridyl protons shift upfield to varying degrees likely as a consequence of $\pi-\pi$ interactions between opposing strands of the double helix. UV−vis spectra of the solutions used to acquire the NMR spectra (Supporting Information) support this conclusion. As the concentration of **1** increases, a charge-transfer band appears at approximately 490 nm turning the solution a burnt orange color which is reversible upon dilution. ^{1}H NMR shift data obtained from the N−H protons of the thiazine dioxide rings were fit to a simple dimerization model,[8] and a dimerization constant (K_d) was calculated to be 4.5 M^{-1}, which corresponds to a ΔG of -3.7 kJ mol^{-1} (estimated error $\leq$20%). The weak nature of the dimerization equilibrium at room-temperature could be expected owing to the entirely negative secondary hydrogen-bonding interactions[9] present in the alternating sequence of donors/acceptors and is similar to an analogous ladderlike system previously reported.[10]

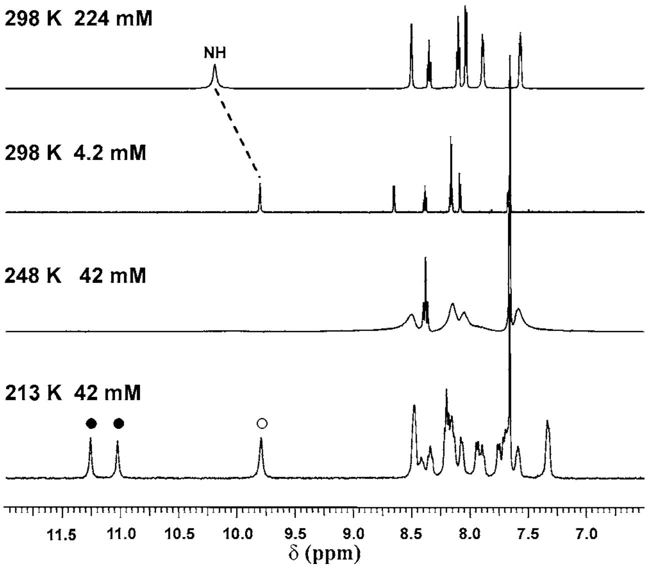


Figure 1. 400 MHz ^{1}H NMR spectra of aromatic region of **1** in CDCl$_3$ at three different concentrations and temperatures. NH protons corresponding to **1** (○) and $\mathbf{1}_2$ (●) at 213 K undergoing slow exchange are indicated.

Assuming the equilibrium observed at room temperature was a result of double-helix formation, a series of ^{1}H NMR spectra of **1** in CDCl$_3$ were recorded at lower temperatures (298−213 K) in an effort to observe the complexation/decomplexation process under slow exchange conditions. The resonances corresponding to **1** broaden as the temperature decreases and coalesce at 248 K. At lower temperatures the spectrum resolves into two separate sets of resonances (Figure 1 and Supporting Information) which may be attributed to monomeric **1** (symmetry related protons are isochronous) and double-helical dimer $\mathbf{1}_2$ (all protons of a given strand have a unique environment). COSY and ROESY spectra performed at 213 K supported the assignment of each set of protons. Notably, the relative integrals of **1** and $\mathbf{1}_2$ change as a function of decreasing temperature, with those corresponding to $\mathbf{1}_2$ becoming more intense as the temperature lowers. Knowledge of the starting concentration of **1** and the integrals of each species yields K_d values for dimer formation in the range of temperatures where slow exchange conditions prevail (213−243 K). Given this information, a

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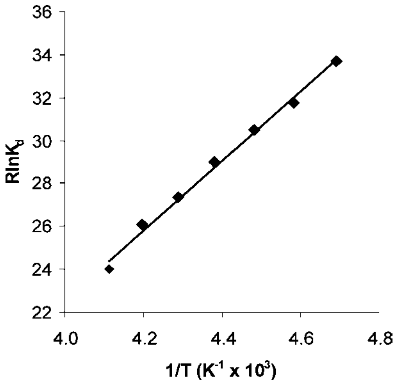

Figure 2. van't Hoff plot of the dimerization equilibrium between **1** and $\mathbf{1}_2$ in $CDCl_3$ from 213 to 243 K including the line of best fit ($R = 0.9942$).

van't Hoff plot was constructed (Figure 2) which yielded thermodynamic parameters of -16 kJ mol^{-1} for ΔH and -42 J mol^{-1} K^{-1} for ΔS, indicating complex formation is a result of molecular recognition rather than solvophobic in nature. Extrapolation of ΔG to 298 K using these parameters results in a free energy at that temperature of -3.5 kJ mol^{-1} which corresponds to a K_d of 4.3 M^{-1}. The result is within error of the equilibrium measured by dilution at room temperature and engenders the conclusion that the two processes are one and the same.

Confirmation of the complex geometry in the solid state was obtained by single-crystal X-ray diffraction. Slow diffusion of isopropyl ether into a concentrated solution of **1** in dichloroethane yielded pale yellow crystals which were suitable for crystallographic analysis. Pentamer **1** crystallizes in orthorhombic space group *Fdd*2 and contains eight symmetry-related dimers per unit cell. The structures of these discrete complexes manifest the double-helical geometry of the intended design (Figure 3). The two molecules of **1** which compose each dimer are related by a C_2 axis and wrap around each other such that four contiguous donors/acceptors (ADAD) on either strand are hydrogen-bonded to the other in register ($(N\cdots N)_{inner} = 3.11$ Å, $(N\cdots N)_{outer} = 2.98$ Å, $(N{-}H\cdots N)_{inner} = 175°$, and $(N{-}H\cdots N)_{outer} = 166°$). None of the adjacent heterocyclic rings in each molecule are coplanar with dihedral angles between those rings participating in the hydrogen-bond array varying from 36 to 53°.

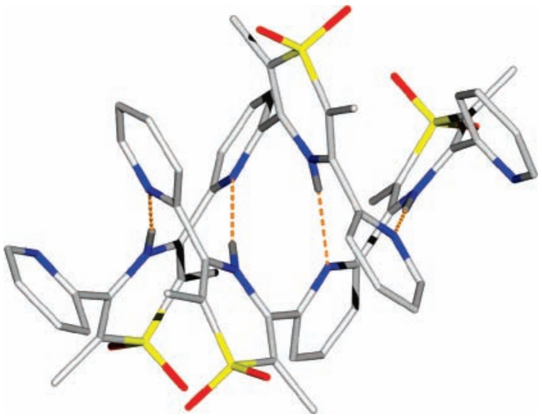

Figure 3. Stick representation of the solid-state structure of $\mathbf{1}_2$. All C−H hydrogen atoms have been removed for clarity. NH···N hydrogen bonds are indicated by dashed orange lines.

In conclusion, we have demonstrated the design, synthesis, and self-assembly of a molecular strand which forms a dimeric double-helical complex using a self-complementary ADADA array of hydrogen bonds. We are currently investigating the synthesis of analogous molecules which have different lengths and hydrogen-bond sequences to fully delineate the parameters of this system.

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Supporting Information Available: Syntheses, characterization, and experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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