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Importance of Secondary Interactions in Twisted Doubly Hydrogen Bonded Complexes

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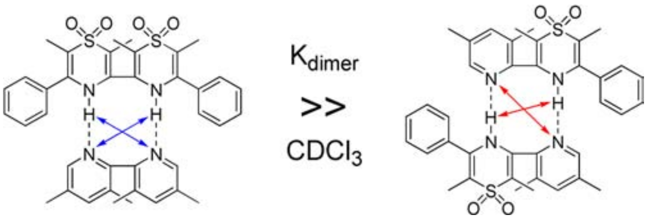
ABSTRACT



Three model hydrogen bond arrays that form complexes with large twist angles between their heterocyclic rings were synthesized differing only in the sequence of their hydrogen bond donors and acceptors. The complementary and self-complementary association of the arrays to form complexes was studied computationally and in solution. The analysis reveals the significant impact secondary interactions have on complex stability in such an arrangement despite the very different topology in comparison to typical planar arrays.

The association of two molecular fragments through hydrogen bonding between multiple donor/acceptor contacts is a ubiquitous feature of molecular recognition and assembly in naturally occurring and artificial systems.[1] Hence, the strength of a binding interaction in this context is very important, and the contribution of individual hydrogen bond donor/acceptor pairs to complex stability can be predicted with reasonable accuracy using both empirical and purely theoretical techniques.[2]

However, in situations where adjacent hydrogen bond donor–acceptor pairs may influence each other through space, the situation is more complex and not a simple function of the number of primary hydrogen bonds present. In particular, hydrogen bonding between nucleobases or similar heterocycles has been studied in detail to understand the relationship between the arrangement of the donor(D)/acceptor(A) pairs that interact to form a complex and the resulting stabilization.[3] The influence of secondary interactions in these cases was first introduced by Jorgensen and Pranata,[4] and empirical methods for evaluating the stabilities of such complexes in nonpolar solutions have been formulated with largely successful results.[5] These methods predict that nucleobase-like complexes incorporating hydrogen bond arrays with favorable

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secondary interactions (e.g contiguous $(AA)_n$ and $(DD)_n$ sequences)[6] will be more stable than those containing the opposite arrangement (e.g., alternating $(AD)_n$ sequences).

Complexes formed from the planar heterocycles described above generally contain an approximately coplanar array of hydrogen bond donor and acceptor groups. We have recently described the formation of double-helical complexes from oligomers of pyridine, thiazine-1,1-dioxide, and indole-based heterocycles that self-assemble through complementary hydrogen bonding arrays.[7] In contrast to planar arrays like the nucleobases, the adjacent hydrogen bond donor−acceptor pairs in our double helical examples are oriented at an approximately 90° angle to one another when viewed down the axis of the double helix (i.e., they have a pitch of approximately 4 heterocycles/helical turn). This lead to an assumption that secondary hydrogen bond interactions would likely be mimimal or nonexistent due to this orthogonality. Much to our surprise, even though the two examples pictured in Figure 1 are both assembled through four primary hydrogen bonds, the overall stabilities of their dimers in solution are remarkably different ($K_{\text{dimer}} = 5$ and $5700\ \text{M}^{-1}$; $\Delta G = -4.0$ and $-21.4\ \text{kJ mol}^{-1}$) and not simply accounted for by the relatively small differences in donor/acceptor character of their hydrogen bonding subunits.[7a,d] However, this disparity could be a result of their different sequences of donors and acceptors (ADADA versus AADD). The accumulation of these and other similar results have led us to postulate that secondary hydrogen bond interactions may have a significant influence on complex stability in this type of twisted arrangement too. Herein, we examine the extent of this putative influence using identical hydrogen bond donor/acceptor heterocycles in the comparator molecules.

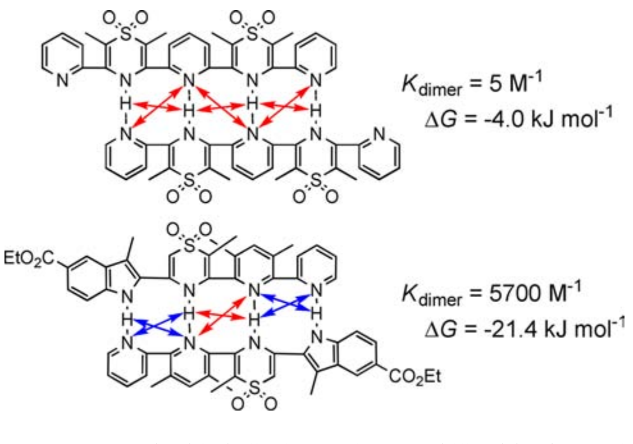
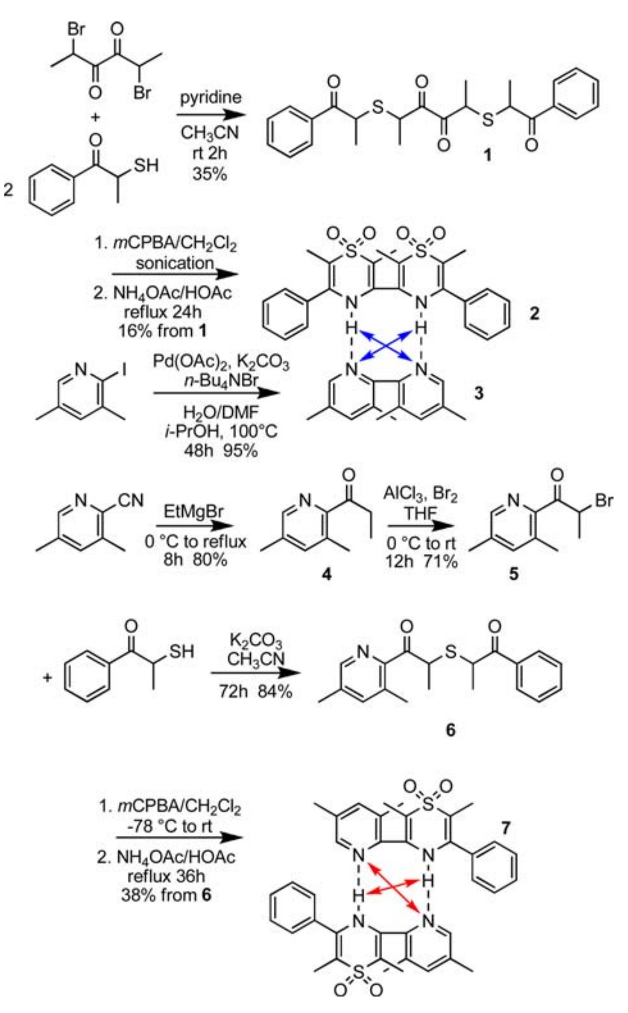


Figure 1. Two double-helical complexes stabilized by four primary hydrogen bonds (K_{dimer} measured in $CDCl_3$ at rt). Arrows indicate potentially attractive (blue) and repulsive (red) secondary interactions.

The simplest approach to establishing the impact of secondary interactions in this system is to examine the stability of minimal doubly hydrogen bonded analogues. We therefore synthesized three model compounds (Scheme 1) that can potentially interact in solution to form a complementary DD/AA complex (**2•3**) and a self-complementary AD/DA dimer (**7•7**). If secondary interactions between adjacent donor−acceptor pairs influence the stability of the resulting duplexes, then complex **2•3** (containing two attractive secondary interactions; blue arrows) should be more stable than **7•7** (containing two repulsive secondary interactions; red arrows).

The model compounds were designed specifically so that a direct comparison could be made between the complex **2•3** and the dimer **7•7**. The structures of **2**, **3**, and **7** are therefore isomeric only in the connectivity between their heterocyclic rings. Methyl groups were installed in positions *ortho*- to the connection between the pyrzidyl and thiazine rings of **7** to strictly prevent any attractive intramolecular interactions via N−H···N hydrogen bonding that might affect the dimerization equilibrium.[7d]

Scheme 1. Synthesis of the DD (**2**), AA (**3**), and AD (**7**) Model Compounds and Their Intended Hydrogen Bonded Complexes



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^{1}H NMR spectroscopy was used to examine both complex and dimer formation in $CDCl_3$ solution at 298 K. The DD array **2** was titrated with AA array **3**, and the changes in the chemical shift of the NH proton resonances were monitored during the addition (Figure 2). The data were fit to a 1:1 binding model[8] using nonlinear least-squares regression to provide an association constant $K_a = 375\ M^{-1}$ ($\Delta G = -3.51$ kcal mol^{-1}). In a similar manner, a solution of **7** was diluted from an initial concentration of 4 M, and the change in the chemical shift of the NH resonance was observed. The data was fit to a 1:1 dimerization model[8] to give a dimerization constant $K_{dimer} = 0.4\ M^{-1}$ ($\Delta G = +0.55$ kcal mol^{-1}). The extreme solubility of **7** in chloroform permits measurements that describe the majority of the complexation isotherm, even at this low value of K_{dimer}, allowing a confident evaluation of the dimerization equilibrium.

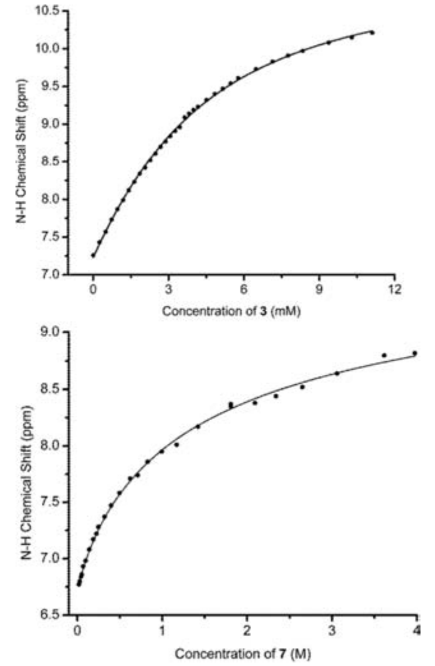

Figure 2. Calculated (curves) and experimental (●) isotherms measured for the complexation of **2** with **3** (top) and the dimerization of **7** (bottom).

The structure of complex **2•3** was confirmed in the solid state using X-ray crystallography (Figure 3). Single crystals were grown by the slow diffusion of isopropyl ether into a chloroform solution of a 1:1 mixture of **2** and **3**. The complex displays C_2 symmetry along an axis bisecting the bonds connecting the heterocycles in both molecules and is stabilized by hydrogen bonds between the two N acceptors of **3** and the NH donors of **2** ($\underline{N}-H\cdots\underline{N}$ = 2.86 Å, $N-H\cdots N$ = 139°). The hydrogen bond geometry is likely distorted away from the linear ideal by the steric influence of the methyl substituents on the two molecules. This inference is supported by the interheterocyclic dihedral angles observed in **2** and **3** (HN−C−C−NH = 103° and N−C−C−N = 79° respectively) that preclude a more linear arrangement of the donor/acceptor groups while maintaining both hydrogen bond interactions.

To investigate the origin of this difference computationally, we constructed dimer and monomer structures of **2•3** and **7•7** based on the crystallographic structure. Dispersion corrected density functional theory (DFT-D3) using the B3LYP functional[9] and the def2-TZVPP basis set[10] was used to calculate the interaction energy of these dimers in their minimum energy geometries (see Supporting Information). The calculated **2•3** dimerization energy was −22.8 kcal mol^{-1} while the **7•7** dimerization energy was −18.5 kcal mol^{-1}. The difference in dimerization energies $\Delta\Delta E$ = 4.34 kcal mol^{-1} is remarkably close to the experimental $\Delta\Delta G$ of 4.06 kcal mol^{-1}. Although solvent, entropic, and zero-point energy corrections are not included in the calculated energies, we would expect these corrections to be similar for the two dimers since they only differ in the connectivity of the heterocyclic rings. Further the dispersion interactions for the two dimers were calculated to be within 0.56 kcal mol^{-1} of one another (−19.35 and −18.79 kcal mol^{-1} for **2•3** and **7•7**, respectivley). Thus, the correlation of this dimerization energy to the relative dimerization free energies supports the hypothesis that the difference in dimerization behavior of these compounds corresponds directly to the molecular interaction energies.

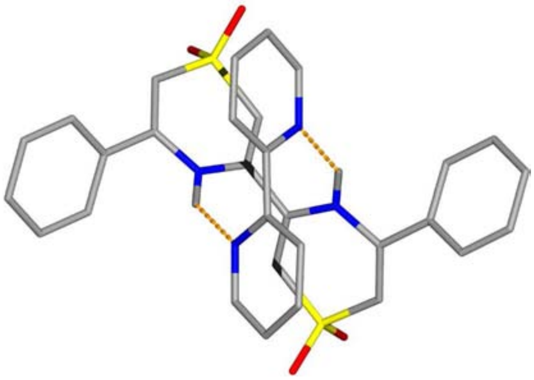

Figure 3. Stick representation of the X-ray crystal structure of complex **2•3** looking down the C_2 axis with intermolecular hydrogen bonds indicated as dashed orange lines. All C−H hydrogen and methyl carbon atoms have been removed for clarity.

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Secondary interactions in hydrogen bonded donar/acceptor systems have primarily been attributed to electrostatic interactions between neighboring hydrogen bond pairs.[4] To analyze the origin of the difference in interaction energies observed between **2•3** and **7•7** we assigned Natural Population Analysis (NPA) charges in structures **2**, **3**, and **7**. The charges of the N and H atoms of the hydrogen bond donor N−H bonds were approximately $-0.52\ e^{-1}$ and $0.42\ e^{-1}$ respectively in **2** and **7**, while the hydrogen bond accepting pyridine nitrogen atoms were approximately $-0.42\ e^{-1}$ for both structures **3** and **7**, indicating that the electronic characteristics of the hydrogen bonding sites of these compounds are constant and differences in bond polarity or anionicity cannot explain the differences in dimerization energy.

We then calculated the Coulombic interaction energy between the fragments in the two dimers using the assigned NPA charges (Table 1). The primary H-bonded interactions, defined as those involving only the N−H bond and the N atom of the acceptor, are similar in the two dimers (−8.31 and −8.00 kcal mol^{-1} in **2•3** and **7•7**, respectively). This reflects that the charges and geometries of the hydrogen bonds in these two dimers are very similar. The secondary H-bonding electrostatic interactions between the atoms of adjacent hydrogen bonding sites show much sharper differences. The secondary interactions of the **7•7** dimer are 10.2 kcal mol^{-1} more repulsive than in the **2•3** dimer. This reflects that there is a strongly replusive interaction between the N−H bonds of the opposing monomer of **7** that is not present in the **2•3** dimer. The sum of the primary and secondary hydrogen bonding interactions shows that the net strength of the electrostatic interactions at the hydrogen bonding centers is much larger in **2•3** than in **7•7**. This difference is partially canceled by electrostatic interactions involving other atoms, as the difference in the total electrostatic interactions of the two dimers is only 4.80 kcal mol^{-1}. This purely electrostatic model of the dimerization overestimates the difference in dimerization energies of **2•3** and **7•7**, although the trend and origin of these differences are apparent through this decomposition.

Table 1. Decomposition of the Interaction Energies of Complexes **2•3** and **7•7** in Terms of Primary, Secondary, Net Hydrogen Bond and Total Electrostatic Energies

complexation energy component (kcal mol^{-1})	**2•3**	**7•7**
primary hydrogen bond interactions	−8.31	−8.00
secondary hydrogen bond interactions	6.00	16.2
net hydrogen bond interactions	−2.31	8.20
total electrostatic interactions	−15.8	−11.0

Our analysis is consistent with the results presented by Jorgensen and Pranata,[4] which attributed the difference in dimerization energies of nucleic acid pairs to secondary interactions between neighboring hydrogen bond acceptor and donor sites of the opposing monomer. The sharp difference observed in the dimerization energies of AA/DD complex **2•3** and the AD/AD complex **7•7** is in accordance with this secondary interaction hypothesis, indicating that this model can be used as a design principle in hydrogen bonded supramolecular dimers with large twist angles, such as these.

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Supporting Information Available. Details of synthetic procedures, characterization, spectroscopic data, theoretical methods, and calculated complex structures. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.