

A New Approach for the Design of Supramolecular Recognition Units: Hydrogen-Bonded Molecular Duplexes

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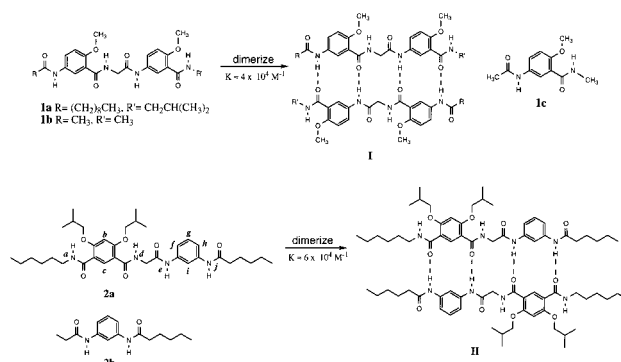
The construction of supramolecular architectures will be greatly facilitated if a diverse set of structural motifs leading to highly specific intermolecular interactions becomes available. Among the noncovalent interactions, hydrogen bonds have attracted the most attention in mediating the self-assembly of supramolecular structures.¹ Hydrogen-bonding motifs, such as amide,² sulfamide,³ carboxylic acid,⁴ cyanuric acid–melamine system,⁵ pyridone dimers,⁶ and 2-aminopyridine–carboxylic acid complexes⁷ have been used for the design of various molecular aggregates. However, the interactions that these relatively simple functional groups bring about are relatively weak. Furthermore, due to the small number of hydrogen bonds associated with each complex, the interaction usually is not very specific. To increase the strength, directionality, and specificity of hydrogen-bonding interactions, there is currently intense interest in designing arrays (sequences) of hydrogen bond donor (D) and acceptor (A) sites. Recent efforts have been focused on quadruply hydrogen-bonded dimers based on derivatives of heterocyclic compounds.⁸ The generality of these systems, however, is sometimes complicated by tautomerism that is often associated with heterocycles. Another disadvantage of previously reported systems is the differences in secondary electrostatic interactions⁹ associated with various arrays of adjacent hydrogen-bonding sites, which result in drastically different stabilities of complexes with the same number of hydrogen-bonding sites. Here we report a new class of hydrogen-bonded duplexes devoid of these problems.

We are interested in developing easily modifiable unnatural molecular systems that self-assemble in a highly predictable fashion. The objective is to develop hydrogen-bonded duplexes with unnatural backbones. Ideally, these duplexes should show predictable stabilities based on their number of hydrogen-bonding sites and, at the same time, should demonstrate high specificity in their formation by including arrays of all possible arrangements of donors and acceptors. Specifically, by combining residues derived from 3-aminobenzoic acid, 1,3-benzenedicarboxylic acid

(isophthalic acid), and 1,3-diaminobenzene (1,3-phenylenediamine), oligoamides with various numbers and sequences of hydrogen-bonding sites should be easily generated. The resulted molecular strands are expected to form duplexes via hydrogen-bonding interactions between the backbone amide O and H atoms. A strand is expected to sequence-specifically pair with another strand of its complementary sequence. Depending on the hydrogen-bonding sequence, either homodimers or heterodimers can be formed. The number of hydrogen-bonding sites can be easily adjusted to afford duplexes of different stabilities.

To test this idea, **1** and **2**, with the self-complementary hydrogen-bonding sequences of DADA and DDAA, respectively, were synthesized and analyzed.¹⁰ Incorporation of alkoxy groups into **1** and **2** should lead to the formation of the highly favorable S(6) type¹¹ intramolecular hydrogen-bonded rings that have been observed in numerous structures.¹² The S(6) systems pre-organize¹³ the benzamide groups in a way that should facilitate the dimerization of these molecules.

¹H NMR studies in chloroform-*d* (Cambridge Isotope Laboratories, 99.8% D content, stored in a desiccator) revealed the significant downfield shifts of the aniline NH signals of **1a** and **2a** (at 10 mM, 10.17 and 9.62 ppm for **1a**; 9.98 and 9.95 ppm for **2a**) compared to those of the one-ring compounds **1c** and **2b** (at 10 mM, 7.91 ppm for **1c** and 7.10 ppm for **2b**), which suggests the formation of duplexes **I** and **II**. ¹H NMR binding studies were



carried out in CDCl₃ by diluting a solution of **1a** or **2a** (from 50 to 0.5 mM). The two aniline NH (carboxamide NH) signals of **1a** showed similar concentration-dependent changes in their chemical shifts, supporting their role in forming intermolecular hydrogen bonds. Nonlinear regression analysis¹⁴ of the NMR data yielded a dimerization constant >4.4 × 10⁴ M⁻¹. Similar analysis on **2a** led to a dimerization constant of ~6.5 × 10⁴. Given the error of the NMR binding experiments (±10%, triplicate runs), the dimers of **1a** and **2a** can be viewed as having similar stabilities. These dimerization constants compare favorably to some of the previously reported triply and quadruply hydrogen-bonded complexes.⁸ The one-ring compound **1c** has a dimerization constant of only 25 M⁻¹ in CDCl₃, indicating that the assembly of **1a** is a cooperative process. Given the considerable degree of rotational freedom, the high stabilities shown by the dimers of **1a** and **2a** are surprising and are worth further investigation. In both **1a** and

(10) See Supporting Information for synthetic procedures.

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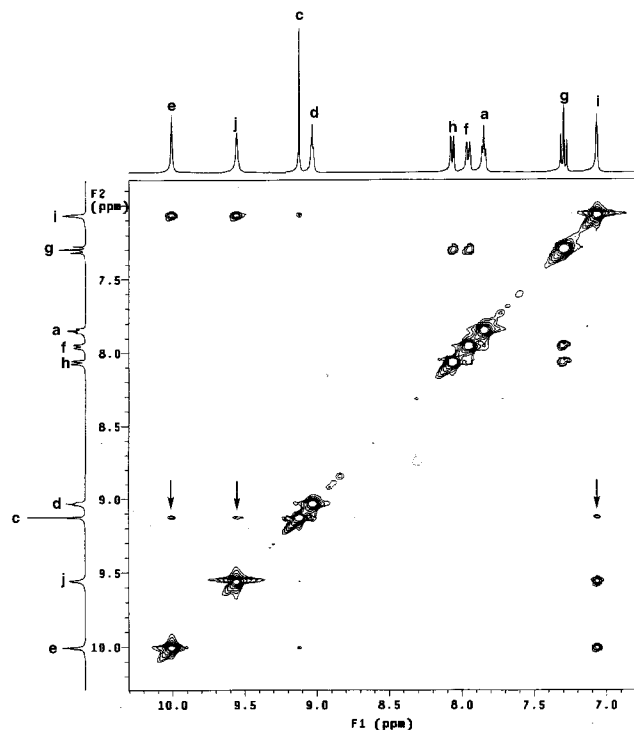


Figure 1. NOESY spectrum of **2a** in CDCl_3 (mixing time: 0.5s). Arrows show contact depicted in text.

2a, the signals of the NH groups that involve in the formation of the intramolecular S(6) rings, showed insignificant concentration-dependent shifts.

Variable temperature measurements of the amide NH signals of **1a** further supported the role of the aniline NH groups in forming intermolecular hydrogen bonds.¹⁵ At a concentration of 15 mM and from 30 to 60 °C in CDCl_3 , the two aniline NH signals of **1a** shifted upfield (3.4×10^{-3} ppm/K, and 6.9×10^{-3} ppm/K). On the other hand, the two glycine NH signals, which formed the S(6) intramolecular hydrogen bonds, showed much smaller changes (1.8×10^{-3} ppm/K, and 2.5×10^{-3} ppm/K) within the same temperature range.

Using sucrose octaacetate and polystyrene as molecular weight standards, vapor pressure osmometry (VPO) studies at 37 °C in CHCl_3 over the concentration range of 5–50 mM consistently gave an apparent molecular weight ($1130 \pm 5\%$) corresponding to the dimer of **1a**. The same VPO analysis gave an apparent molecular weight ($1590 \pm 5\%$) corresponding to the dimer of **2a**. The existence of the dimeric species in solution is also supported by examining the above NMR data, which shows small changes (~ 0.04 ppm for **1a** and ~ 0.03 ppm for **2a**) in the amide-H chemical shifts within this concentration range.

Two-dimensional (2D) NMR (NOESY, CDCl_3 , 400 MHz) studies on **2a** provided the most diagnostic evidence for duplex formation in solution. As shown in Figure 1, contacts were observed between protons *c* and *i*, *c* and *e*, and *c* and *j*. Because within the same molecule of **2a**, distances between *c* and each of the above-mentioned protons are much too long for any cross-peaks to be observed, the signals must correspond to intermolecular contacts between the two molecules constituting the dimer.

Single crystals of **1b** were obtained from a solution in chloroform/methanol at 70 °C. Figure 2a shows the X-ray structure of the centrosymmetric dimer. As expected, the two molecules are held together by four C(4) type¹¹ intermolecular hydrogen bonds ($\text{N}\cdots\text{O}$ distances = 2.938 and 2.882 Å). In each molecule, there are two S(6) type intramolecular hydrogen bonds

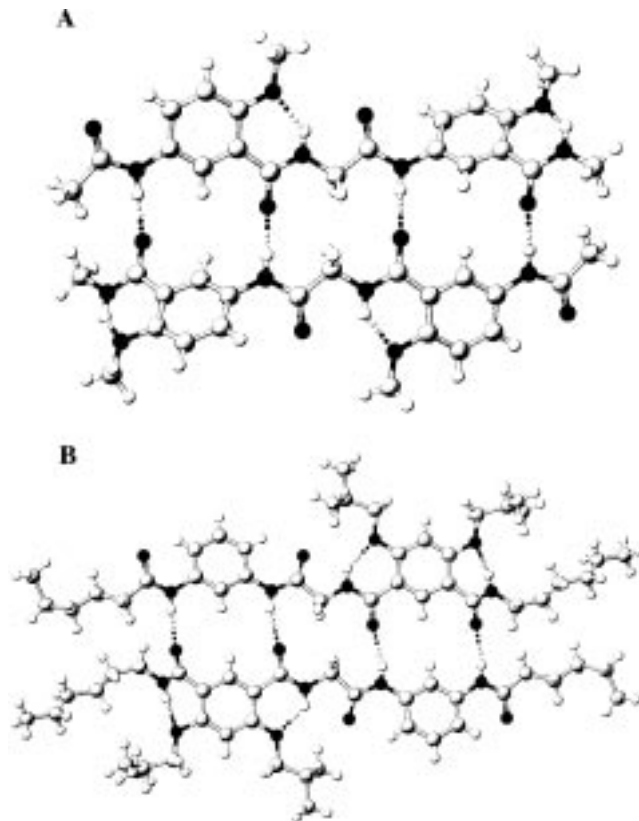


Figure 2. (a) X-ray structure of the dimer **I**. (b) X-ray structure of the dimer **II**.

($\text{N}\cdots\text{O}$ distances = 2.634 and 2.707 Å) that rigidify the backbone. Crystals of **2a** were grown from a solution in methanol at 50 °C. The solid-state structure of **2a** again revealed the structure of a centrosymmetric dimer (Figure 2b). Similar to **1b**, two molecules of **2a** are held together by four C(4) type intermolecular hydrogen bonds ($\text{N}\cdots\text{O}$ distances = 2.857 Å and 2.938 Å). There are two intramolecular S(6) type hydrogen bonds ($\text{N}\cdots\text{O}$ distances = 2.660 and 2.905 Å) in the structure of **2a**.¹⁶

The above results demonstrate that, despite their different hydrogen-bonding sequences, compounds **1** and **2** predictably form stable hydrogen-bonded duplexes. Contrary to previously reported hydrogen-bonded dimers based on heterocycles, the duplexes **I** and **II** exhibit similar stabilities, suggesting that the observed binding strength can be directly related to the number of hydrogen-bonding sites in each duplex.¹⁷ This system thus offers a platform for designing a new generation of supramolecular recognition units with high stability and readily adjustable specificity. For example, the design of higher homologues with six, eight, or more hydrogen-bonding sites is readily achievable by incorporating three, four, or more benzene rings in the oligoamide molecules. Extending this approach to the design of various arrays of multiple hydrogen-bonding sites will also lead to unnatural information-storage duplexes mimicking double-stranded DNA.

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Supporting Information Available: Experimental procedures for the synthesis of **1a**, **1b**, and **2a**, tables of X-ray data collection/refinement parameters, atomic position parameters, and anisotropic displacement parameters for **1b** and **2a** (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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