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Self-Complementary Quadruply Hydrogen-Bonded Duplexes Based on Imide and Urea Units

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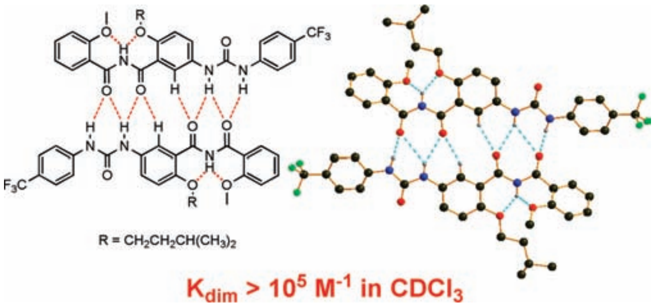
ABSTRACT



The quadruply hydrogen-bonded duplexes based on an imide-urea structure preorganized by three-center hydrogen bonds were found to associate via bifurcated hydrogen bonds. ^{1}H NMR dilution experiments revealed the high stability of the homodimer in apolar solvent ($K_{dim} > 10^5\ M^{-1}$ in $CDCl_3$) and enhancement of association ability due to electron-withdrawing substituent effects. The ready synthetic availability and adjustable association affinity via electronic effects may render these association units potentially applicable in constructing supramolecular architectures.

With their high strength, specificity, directionality and reversibility, multiple hydrogen-bonding modules with arrays of hydrogen-bond donors (D) and acceptors (A),[1] especially quadruple hydrogen-bonding ones, have triggered wide research interest in stimuli-responsive materials, photoelectric materials, surface materials, and molecular recognition.[2] For these applications many artificial hydrogen-bonding modules were designed and tailored to suit a different purpose. Among them, the quadruple ureidopyrimidone derivatives (UPy) by Meijer et al.[3] and deazapterin (DeAP) by Zimmerman et al.[4] are excellent association units to form the stable homodimers in $CDCl_3$ ($K_{dim} > 10^7\ M^{-1}$). These binding units have been successfully applied to construct various supramolecular materials with extraordinary features that fail to display for covalent polymers.[5] An exceptionally stable quadruply hydrogen-bonded heterodimer lately reported by Leigh

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and co-workers is another successful example.[6] Many other heterocycle-based modules were also described.[7] To address the tautomeric problem often associated with the heterocycle modules, different types of the hydrogen-bonding motifs were designed.[8] For example, the aromatic oligoamide duplexes were developed by Gong et al.,[9] which are free of the complication from unfavorable tautomerism. Other duplexes based on amide units were described by Nowick[10] and Hunter.[11] In addition, molecular duplexes based on hydrazide and amidourea motifs were reported by Li et al.[12] and Chen et al.[13] Recently, we reported with collaborators oligoamide hydrogen-bonding duplexes as organogelators and an alternative strategy for tuning the association specificity by varying the spacings between neighboring hydrogens based on incorporation of naphthalene-based residues.[14]

So far the hydrogen-bonded association modules with respect to nonheterocycles include those based on amide, urea, hydrazide, and amidourea moieties. Use of the combination of imide and urea units as building blocks for constructing duplexes has still been unexplored. With increasing interest in supramolecular materials fabricated with multiple hydrogen-bonding modules, the design of molecular hydrogen-bonded duplexes that are structurally simple, synthetically readily accessible, and of high and tunable association ability still represents an urgent need.

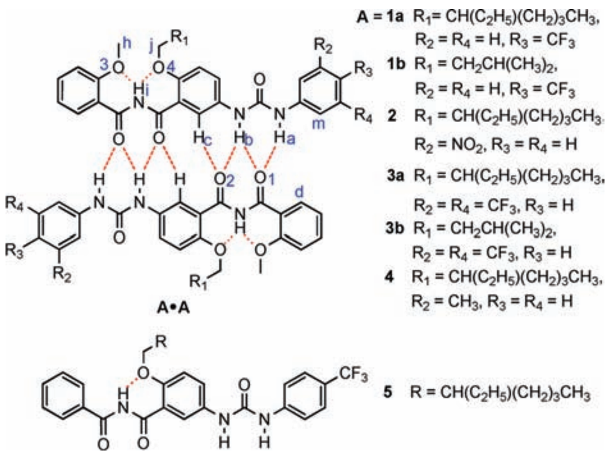

Figure 1. Imide-urea strands **1**–**3** that pair into self-complementary duplexes **A·A** via bifurcated hydrogen bonds. Compounds **4** and **5** are designed for comparison.

Herein we report on a new class of DDAA self-complementary imide-urea modules **1**–**3** that have a high dimerization constant ($K_{\mathrm{dim}} > 10^5\ \mathrm{M}^{-1}$ in $CDCl_3$) via bifurcated hydrogen bonds involving both conventional and weak hydrogen bonding interactions (Figure 1). The high stability is attributed to the preorganization of intramolecular three-center hydrogen bonds and the substituent effect. Compounds **4** and **5** are designed for comparison. This work shown here demonstrated a new type of molecular duplexes based on the combination of imide and urea units that are readily accessible via a simple synthetic strategy.

Since the imide units in our designed molecules serve as hydrogen-bond acceptors it is important to orient its carbonyl oxygens to the same side. Among the three possible conformational isomers, the *trans*–*trans* form is preferred to align the acceptor atoms for hydrogen bonding interactions (Figure 2a). Thus, compound **6** was designed and synthesized first to examine the possibility of preorganizing the imide structure along one edge of the molecule. The presence of an intramolecular three-center hydrogen bond in **6** ensures the rigidification of the backbone and helps circumvent the possible intermolecular hydrogen bonding interactions from the upper edge.

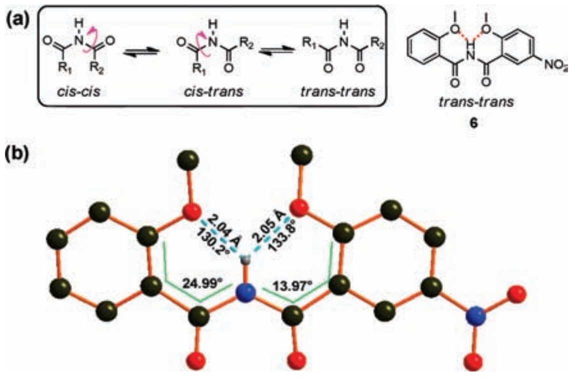

Figure 2. (a) Conformational isomerization and the *trans*–*trans* conformer of imide **6** fixed with a three-center H-bond; (b) X-ray structure of **6** with hydrogen-bond geometry and torsion angles denoted. For clarity, only hydrogen atoms involved in H-bonds are shown.

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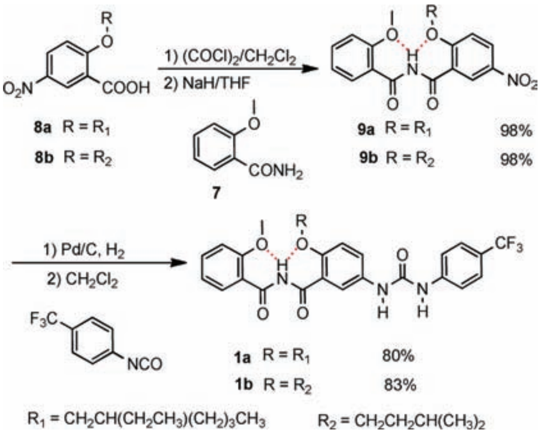
A single crystal of **6** was obtained for X-ray analysis via slow evaporation from CH_2Cl_2/ethyl acetate (Figure 2b). As expected, the imide moiety in the molecule is preorganized in a *trans*–*trans* conformation by virtue of three-center hydrogen bonds consisting of two S(6)-type intramolecular hydrogen bonds. The backbone is a little twisted with the torsion angles of 24.99° and 13.97°, suggesting the nonplanarity of the backbone containing the three-center hydrogen bond that may result from the repulsion of two adjacent carbonyl oxygens.

Scheme 1. Synthesis of Compounds **1a** and **1b**



This preorganized imide structure is more rigid as compared to the one-hydrogen bonded imide[15] and thus should lead to added stability upon incorporating the urea moiety for forming an intermolecular hydrogen bonded dimer. Therefore, following the successful rigidification of the imide backbone in the desired conformation, compounds **1**–**4** were designed by incorporating urea units as hydrogen bonding donors to furnish the complementarity of duplexes in DDAA arrays (Figure 1).

The synthesis of these imide-urea duplexes is simple and straightforward (Scheme 1). For example, compound **1a** (or **1b**) was readily prepared by the reaction of acyl choride of **8a** (or **8b**) and 2-methoxybenzamide (**7**) in the presence of NaH to afford **9a** (or **9b**) in 98% yield, followed by reduction and condensation with commercially available isocyanate in a yield of ca. 80%. Following similar procedures, compounds **2**–**5** were synthesized in 74–83% overall yields.[16]

The formation of the dimer **1a·1a** was evidenced by two-dimensional NOESY in $CDCl_3$. Cross-strand NOEs between protons H^d and H^m were observed. Also, contacts were observed between H^h and H^i, H^j and H^i for **1a**, indicating the presence of the intramolecular three-center hydrogen bond.[16] More direct evidence for the dimerization came from ESI-MS studies. The ESI mass spectrum showed highly intense peaks (*m*/*z*: 1171.49 [**1a·1a** + H]$^+$, calcd 1171.50; 1193.46 [**1a·1a** + Na]$^+$, calcd 1193.48; 1209.42 [**1a·1a** + K]$^+$, calcd 1209.45) corresponding to the presence of the dimeric species.[16]

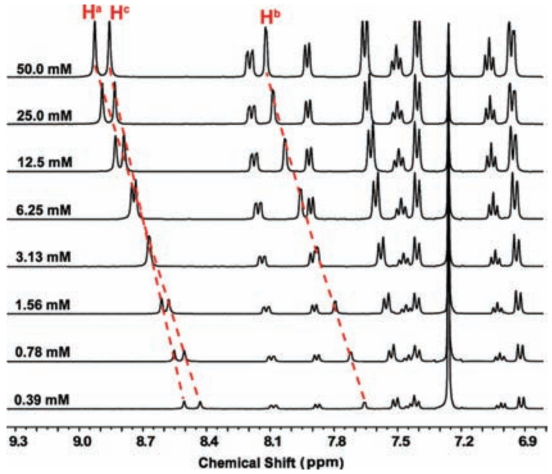


Figure 3. Stacked plots of variable-concentration ^1H NMR spectra of compound **1a** in 5% DMSO-d_6/$CDCl_3$ (v/v) at 298 K.

The binding affinity of **1a** was examined by the ^1H NMR dilution experiment. When a $CDCl_3$ solution of **1a** was diluted from 10.0 to 0.40 mM, no change was found in the chemical shift of urea protons. The K_{dim} of duplex **1a·1a** was estimated to be a lower limit of 1.1×10^5 M^{-1},[16] almost 1 order of magnitude larger than that of oligoamide duplexes in the same DDAA sequence (~10^4 M^{-1}).[9a] More accurate K_{dim} data for dimerization were obtained by increasing the polarity of the solvent. As shown in the ^1H NMR spectra of **1a** in 5% DMSO-d_6/$CDCl_3$ (Figure 3), the protons H^a, H^b of NH both shifted downfield with increasing concentration, indicating these protons were involved in intermolecular hydrogen bonds. Unexpectedly, a pronounced downfield shift of H^c of CH (0.35 ppm) demonstrated the presence of the CH···O interaction as intermolecular hydrogen bonds.[17] Nonlinear regression analysis of the chemical shift data gave the dimerization constant K_{dim} value of 2.8×10^2 M^{-1} in 5% DMSO-d_6/$CDCl_3$ and 1.9×10^3 M^{-1} in 2% DMSO-d_6/$CDCl_3$ (Table 1).

More convincing evidence for the dimerization is from X-ray crystallography. A single crystal of **1b**,[16] differing only in the side chains from **1a**, was obtained for X-ray

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Table 1. Dimerization Constants (K_{dim}) of Compounds **1**–**5** in M^{-1} Based on H^a Proton

compound	solvent[a]	K_{dim} (H^a)
1a	2%	$(1.9 \pm 0.4) \times 10^3$
	5%	$(2.8 \pm 0.2) \times 10^2$
1b	2%	$(1.8 \pm 0.2) \times 10^3$
2	2%	$(2.6 \pm 0.2) \times 10^3$
3a	2%	$(1.2 \pm 0.3) \times 10^4$
4	2%	$(5.6 \pm 0.5) \times 10^2$
5	2%	$(7.9 \pm 0.5) \times 10^2$

[a] Percentage of DMSO-d_6 in the mixed solvent of DMSO-d_6/$CDCl_3$.

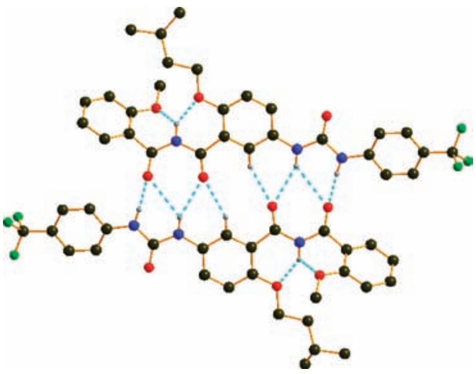

Figure 4. X-ray structure of compound **1b** showing the involvement of CH···O hydrogen bonds in the dimer. For clarity, only hydrogen atoms involved in H-bonds are shown.

analysis via slow evaporation from the mixed solvent of CH_2Cl_2/ethyl acetate (Figure 4).

As expected, in the homodimer arrayed in an AADD sequence, both of the urea hydrogens are involved in hydrogen bond formation with two imide oxygens of another strand. The distance of $NH^a \cdots O^1$ ($H \cdots O$ 1.91 Å, 172.6°) is much shorter than that of $NH^b \cdots O^2$ ($H \cdots O$ 2.41 Å, 154.3°), indicative of the stronger hydrogen bonding for the former. Interestingly, the distance of $CH^c \cdots O^2$ ($H \cdots O$ 2.33 Å, 153.1°) accompanied by a larger angle is even a little shorter than that of both $NH^b \cdots O^1$ ($H \cdots O$ 2.72 Å, 140.2°) and $NH^b \cdots O^2$. This suggests the presence of a bifurcated H-bond consisting of conventional and weak C–H H-bonds. The intramolecular three-center hydrogen bonds consisting of $NH^i \cdots O^3$ ($H \cdots O$ 2.39 Å, 102.2°) and $NH^i \cdots O^4$ ($H \cdots O$ 1.86 Å, 140.4°) were observed in the molecule. Furthermore, in another compound **3b** with two trifluoromethyl groups the crystal structure also revealed the dimeric complex in the solid state.[16]

To evaluate the influence of the intramolecular three-center H-bond in **1a** on a K_{dim} value, compound **5** with only one S(6)-type intramolecular H-bond was prepared. A lower K_{dim} value of 7.9×10^2 M^{-1} for **5·5** was obtained in 2% DMSO-d_6/$CDCl_3$ as compared to that of 1.9×10^3 M^{-1} of **1a·1a,** indicating that the three-center hydrogen bonding favors the formation of a stable dimeric complex.

In addition, electron-withdrawing groups also exerted a marked influence upon the stability of the dimer due to the enhanced acidity of hydrogen-bond donors.[18] As demonstrated in compounds **1a** and **2** with only one electron-withdrawing substituent in the urea moiety, the dimerization constant was determined to be around 2×10^3 M^{-1} in 2% DMSO-d_6/$CDCl_3$; however, introducing two trifluoromethyl groups into the urea unit led to an increase in K_{dim} value to 1.2×10^4 M^{-1} for compound **3a** in the same mixed solvent. In contrast, replacing the nitro group of **2** with an electron-donating methyl group provided compound **4** with a lower K_{dim} of 5.6×10^2 M^{-1} (Table 1). This suggests that the association ability could be tuned by electronic properties of substituents for these imide-urea duplexes.

In conclusion, we have demonstrated a new class of association units based on imide and urea structures that are able to self-associate into stable dimers ($> 10^5$ M^{-1} in $CDCl_3$) via bifurcated hydrogen bonds in the solid state and in solution. The enhanced association capability of these designed duplexes stems mainly from preorganization via intramolecular three-center hydrogen bonding and electron-withdrawing effects. These imide-urea duplexes, which are of high stability and of easy synthetic accessibility, may be used for assembly of supramolecular polymers and other well-defined supramolecular architectures. Detailed studies on the potential application of these association units are currently being investigated in our laboratory.

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Supporting Information Available. Synthesis, analytical data, 2D NMR, the assemblies of the duplexes and X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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