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With Regard to the Hydrogen Bonding in Complexes of Pyridylureas, Less Is More. A Role for Shape Complementarity and CH···O Interactions?

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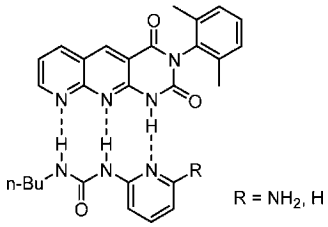
ABSTRACT



A pyridylurea·tetraazaanthracenedione complex with three hydrogen bonds is more stable than an analogous complex with four hydrogen bonds. An X-ray analysis and modeling suggests a steric mismatch destabilizing the latter and a CH···O contact enhancing the stability of the former.

A wide range of hydrogen-bonded complexes have been developed with the result that broad applications to supramolecular science are being realized with significant frequency.[1] At the same time, the increasing database of complex stabilities (mostly multiple hydrogen-bonded, heterocyclic complexes in $CDCl_3$) allows trends to be observed,[2,3] models to be formulated and tested,[2−4] and outliers identified.[5] For example, Lüning and co-workers[6] recently described a quadruply hydrogen-bonded complex **1·2** that was qualitatively less stable than expected, which they attributed to a strong intramolecular hydrogen bond in **2** that must be broken prior to complexation (Figure 1). Even taking into account the intramolecular hydrogen bond, we estimated the K_{assoc} for **1·2** to be ca. 10-fold lower than expected.[7] Herein, we report solution- and solid-state studies on **1**, **2**, and related compounds that provide insight into their unusual complexation chemistry.

Tetraazaanthracenedione **1** was synthesized using the published procedure.[6] To confirm its identity and gain insight into its structure, **1** was crystallized by slow evaporation from tetrahydrofuran (THF) and an X-ray analysis performed. As

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(6) Brammer, S.; Lüning, U.; Kühl, C. *Eur. J. Org. Chem.* **2002**, 4054−4062.

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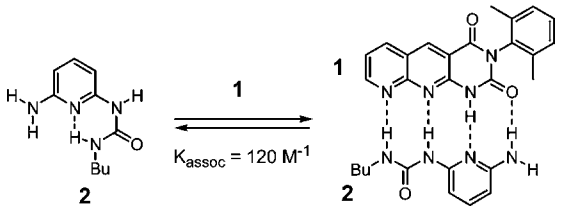

Figure 1. Folded structure of **2** and hydrogen-bonded complex **1·2** with K_{assoc} reported by Lüning.[6] In the present study, the value $K_{assoc} = 180 \pm 25\ M^{-1}$ was determined, which is acceptably close to the reported value.

seen in Figure 2, the assigned structure is correct, and remarkably, it dimerizes in a face-to-face arrangement that places the central nitrogen atoms (N10) in opposing positions.[8] The N10···N10 distance of 3.096 Å is somewhat larger than it might be otherwise as a result of the shorter aromatic C═N bonds causing the hydrogen bonding edge to adopt a slight inward curvature.

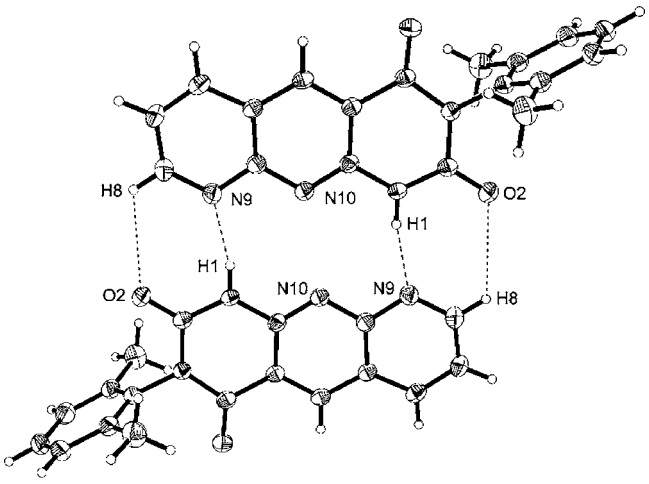

Figure 2. ORTEP representation of **1·1** displaying N···H hydrogen bonds (- - -) and CH···O contacts (···). The intermolecular distances are as follows: O2···H8 (2.941 Å), N1···N9 (3.004 Å), N10···N10 (3.096 Å). Thermal ellipsoids represent 35% probability. Disordered THF has been omitted for clarity and disordered methyl groups are shown in one position.

The O2···H8 distance (2.941 Å) in **1·1** is comparable to the 2CH···O2 distance in the adenine·uracil base-pair[9] and analogous adenine·imide complexes studied by Jorgensen[10] and Rebek.[11] In these systems, it was proposed that a CH···O hydrogen bond stabilizes the complex.[9−11] However, the importance of this unconventional hydrogen bond has been questioned,[12] and it is likely that H8 in **1** is less acidic than the adenine 2CH group. In any event, it was important to establish whether significant dimerization of **1** in solution might explain the low K_{assoc} observed for **1·2**.

Compound **1** may dimerize in solution to form **1·1**, analogous to the solid-state dimer, or as a pyridone-type dimer **1′·1′** (Figure 3). ^{1}H NMR dilution studies in $CDCl_3$ indicated only weak self-association ($K_{dimer} = 10 \pm 5\ M^{-1}$). Indeed, the low solubility of **1** combined with the low K_{dimer} prevented its full dimerization. At 63 mM (ca. 42% dimer), the chemical shift changes for H5, H6, and H7 were small ($\leq \pm 0.015$ ppm), but H8 shifted downfield by 0.096 ppm. A significant shift in H8 relative to the other C−H groups would not be expected in dimer **1′·1′**. This result suggests at least some contribution of **1·1** in solution. Overall, the relatively weak self-association of **1** cannot explain its weak pairing with pyridylurea **2**.

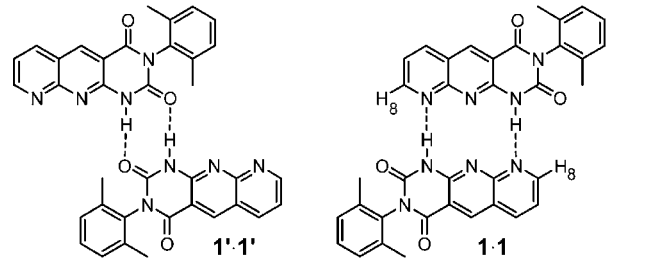

Figure 3.

To gain insight into how subsets of the hydrogen bond acceptor−acceptor−donor−acceptor (AADA) array in **1** pair, its binding of **3**−**5** was studied. Compounds **3** and **4** both present the DDA array whereas **5** contains the DAD motif (Figure 4).

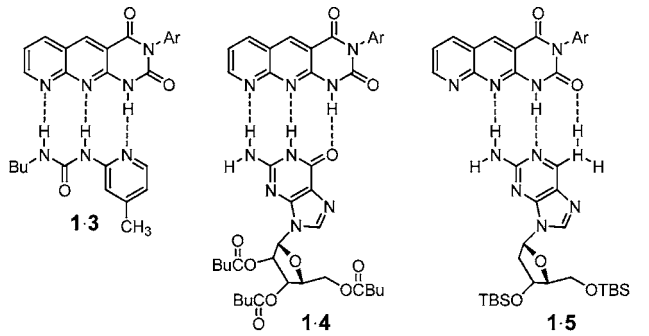

Figure 4.

*Strikingly, **1·3**, which is analogous to **1·2** but lacks the fourth hydrogen bond, is more stable.* The 4-methyl group

(8) See the Supporting Information.

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plays only a minor role as *N*-butyl-*N*′-(pyridin-2-yl)urea (**6**) gave $K_{assoc} = 393\ M^{-1}$ (single determination).

In both **2** and **3** an intramolecular hydrogen bond must be broken prior to complexation.[6,13,14] For **3** this is clearly seen in the chemical shift changes of the NH groups. The **3**−H1 proton, although partially obscured during the titration with **1**, clearly moves downfield considerably (> 1.2 ppm), whereas the **3**−H2 proton moves upfield by ca. 0.5 ppm (Figure 5). This observation is consistent with a free H1

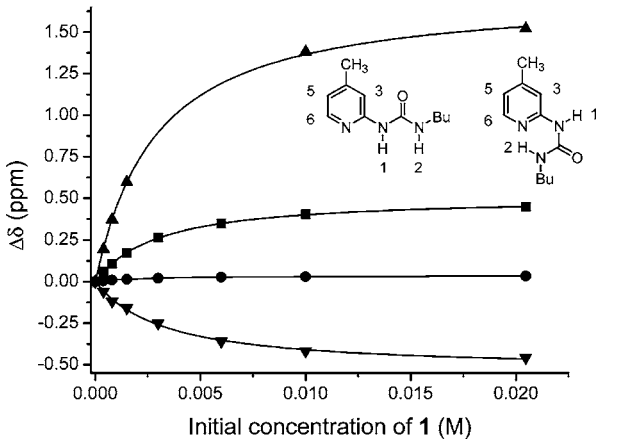

Figure 5. Representative plots of $\Delta\delta$ versus initial concentration of **1** for **3**−H3 (▲), **3**−H6 (■), **3**−H5 (●), and **3**−H2 (▼) at 25 °C using a fixed concentration of **3** (0.4 mM) in $CDCl_3$. $\Delta\delta > 0$ implies a downfield shift.

group in **3** becoming hydrogen-bonded in **1·3** whereas the H2 proton moves from a strong intramolecular hydrogen bond in free **3** to an intermolecular one in **1·3**. Likewise, the >1.5 ppm downfield shift of H3 is consistent with its move into the anisotropic deshielding cone of the urea carbonyl group (see inset to Figure 5). Titration experiments that started with different concentrations of **2** and **3** (0.4 mM or 1.0 mM) gave similar K_{assoc} values, suggesting that self-association of pyridylureas ($K_{assoc} = 5-16\ M^{-1}$)[13] and traces of water do not affect complexation with **1**.

The K_{assoc} values for the **1·4** and **1·5** complexes are in the range expected for complexes with the DDA·AADA and DAD·AADA motifs, respectively.[2a,3,4a,15] These studies suggested that the unexpected stabilities of the **1·2** and **1·3** complexes originate in the pyridylurea components. Molec-

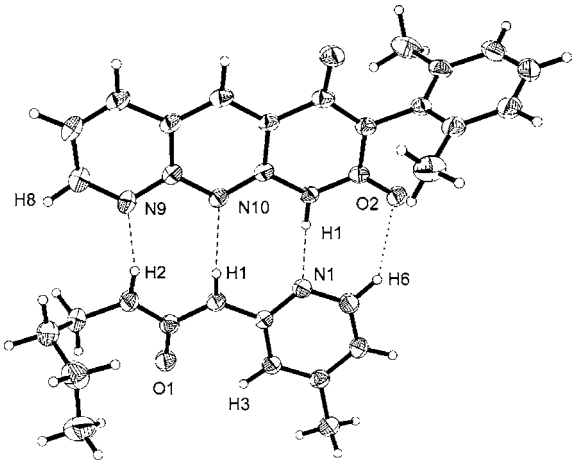

Figure 6. ORTEP view of **1·3** displaying N···H hydrogen bonds (- - -) and CH···O contacts (···). The distances are as follows: N9···H2 (2.052 Å), N10···H1 (2.298 Å), H1···N1 (1.946 Å), O2···H6 (2.520 Å), and O1···H3 (2.197 Å). Thermal ellipsoids represent 35% probability. Disordered methyl groups of **1** are shown in one position.

ular modeling indicated that if the pyridylurea unit in **2** is planar significant steric interactions between the urea carbonyl group and H3 would create a pronounced concave curvature in the DDAD array. To examine this possibility experimentally, a crystal of the **1·3** complex was grown by slow evaporation from ethyl acetate and its structure determined by X-ray analysis.

As seen in Figure 6, the complex shows three N···HN hydrogen bonds. The near coplanarity of the urea carbonyl and pyridyl ring (torsion angle C3−C2−N−CO = 4°) and resultant short H3···O═C contact (2.197 Å) does indeed lead to marked curvature in the DDA hydrogen-bonding motif which in turn gives rise to a short O2···H6 contact (2.520 Å). It is worth noting that in the ^{1}H NMR monitored titration of **3** with **1** the **3**−H6 proton shifts downfield by ∼0.5 ppm whereas an even more dramatic shift ($\Delta\delta_{max} = 1.73$ ppm) is seen in **3**−H3 (Figure 5). Both **3**−H3 and **3**−H6 move into the deshielding cone of carbonyl groups and both have the potential to engage in CH···O hydrogen bonds in **1·3**.

As discussed above, the putative CH···O hydrogen bond between **1**−O2 and **3**−H6 might contribute to the higher stability of the triply hydrogen bonded complex. It is clear from the structure of the **1·3** complex that an amino group at C6 (i.e., **2**) cannot be accommodated readily without additional structural reorganization including an even shorter H3···O═C distance. Thus, the surprising finding that quadruply hydrogen-bonded complex **1·2** is less stable than the analogous complex **1·3** with just three hydrogen bonds can be explained by a combination of this subtle geometrical effect and CH···O hydrogen bonding.

Two additional complexes were considered to test the appropriateness of the model proposed above (Figure 7). The first is **3·7**, which is analogous to **1·3** (DDA·AAD) but lacks the putative CH···O interaction.[16] The reported[13b] K_{assoc} for

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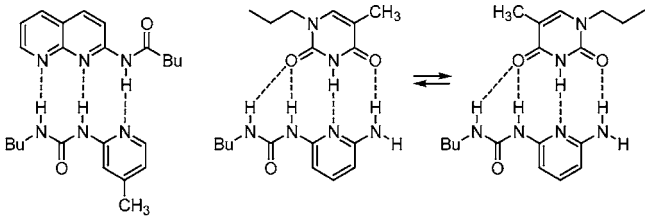

Figure 7.

3·7 is 1 order of magnitude lower than that for **1·3**. Given that **1·3** further contains a repulsive secondary electrostatic interaction not present in **3·7**, it is clear that a CH···O interaction cannot explain the full difference in stability and other factors must play a role.

In the **2·8** complex, the curvature of the DDAD array in **2** is actually advantageous in that it reduces the distance between the **2**−N2H group and the thymine carbonyl group. Thus, its K_{assoc} = 57 M^{-1} reported by Sijbesma and co-workers[17] is high for a DDAD·ADA motif that requires an intramolecular hydrogen bond to break.

In conclusion, pyridylureas **2**, **3**, and **6** were shown to pair complementary heterocyclic units with unexpected stabilities. The complexation strengths can be explained by stabilizing CH···O interactions or a geometric effect wherein the pyridylurea adopts a crescent-shaped structure that may facilitate (shape complementarity) or hinder optimal hydrogen bonding interactions. Whatever the precise origin of the unexpected binding strengths[18] the results clearly illustrate the challenges for a priori determination of association constants involving the pyridylurea unit.

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Supporting Information Available: Crystallographic data (CIFt) for **1** and **1·3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Note that there are three distinct types of CH···O interactions discussed. In the adenine-uracil/thymine base-pair, the **1·1** dimer, and the intramolecularly hydrogen-bonded **2** the CH group is adjacent to two, one, and no nitrogen atoms, respectively. More flanking nitrogen atoms should make for a more acidic C−H group and a correspondingly stronger CH···O hydrogen bond.

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(18) Other plausible explanations exist for the unusual stabilities reported herein. For example, differences in primary hydrogen bonding strengths, differences in the strength of the intramolecular hydrogen bond in **2** and **3**, dipolar interactions, differential solvation, etc. may explain the results. These effects, although potentially quite important, are less readily discernible.