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HYDROGEN BONDED COMPLEXES WITH THE AA•DD, AA•DDD, AND AAA•DD MOTIFS: THE ROLE OF THREE CENTERED (BIFURCATED) HYDROGEN BONDING

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Abstract: The stabilities of hydrogen bonded complexes containing the AA·DD, AA·DDD, and AAA·DD motifs were measured in chloroform. X-ray analysis of the **1·6** and **1·7** complex and solution studies support the formation of an unsymmetrical bifurcated hydrogen bonding motif.

Many factors affect the stability of multiply hydrogen bonded complexes,[1] including the number,[2] strength, and geometry of the individual hydrogen bonds, and the extent of solvent competition for the donor and acceptor sites. Recent attention was focussed on the importance of the arrangement of the hydrogen bonds. In the context of base-pairing, it was suggested that both A-T and G-C base-pairs benefit from "π-cooperativity" wherein the cyclic arrangement of hydrogen bonds allows each to strengthen the other (Figure 1A).[3] π-Cooperativity favors the alternating arrangement of hydrogen bonds found in AD·DA and DAD·ADA complexes. Another type of polarization, shown in Figure 1B, would disfavor AA·DD and AAA·DDD complexes. Recently, Jorgensen noted that ADA·DAD complexes contain four repulsive secondary electrostatic interactions, whereas AAD·DDA and AAA·DDD complexes contain zero and four attractive secondary electrostatic interactions, respectively (Figure 1C).[4] We reported several new multiply hydrogen bonded complexes, including the first example of a AAA·DDD complex, whose K_{assoc} were consistent with the secondary electrostatic interaction model.[5] Herein we report on the role of extra "over-hanging" donor and acceptor groups[4b] in hydrogen bonded complexes with the AA·DDD and AAA·DD motifs (i.e., **1·3** and **5·2**).

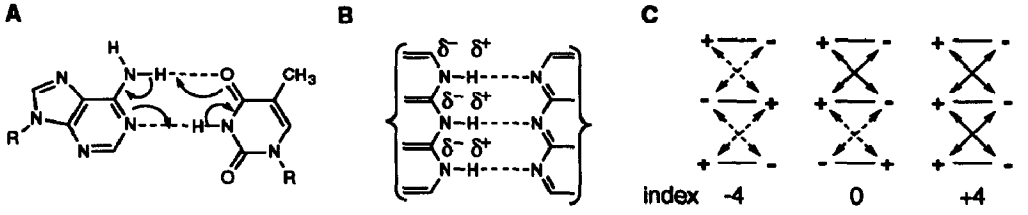

Figure 1. A. π-cooperativity. B. Polarization of hydrogen bonds in a DDD·AAA complex. C. Jorgensen's secondary electrostatic interaction model. ——, primary hydrogen bond, ←——→, attractive, and ←·····→, repulsive secondary electrostatic interaction.

With the exception of **5**,[7] the compounds used in this study (**1-4**, Chart) were prepared by known methods.[8] All compounds gave a correct elemental analysis, and had spectral data

consistent with the assigned structures. Dihydropyridines **2** and **3** can exist in 1,4- and 3,4-tautomeric forms. By ^{1}H NMR ($CDCl_3$), **2** exhibited a >20:1 preference for the 1,4-dihydro form, while **3** was a 2:1 mixture of 1,4- to 3,4-dihydro forms. ^{1}H NMR binding studies were performed in $CDCl_3$ by titrating **2** or **3** with **1**, **4**, or **5** and monitoring the downfield shift of an NH group, or by diluting a 1:1 complex and monitoring the upfield shift of an NH group.

Chart

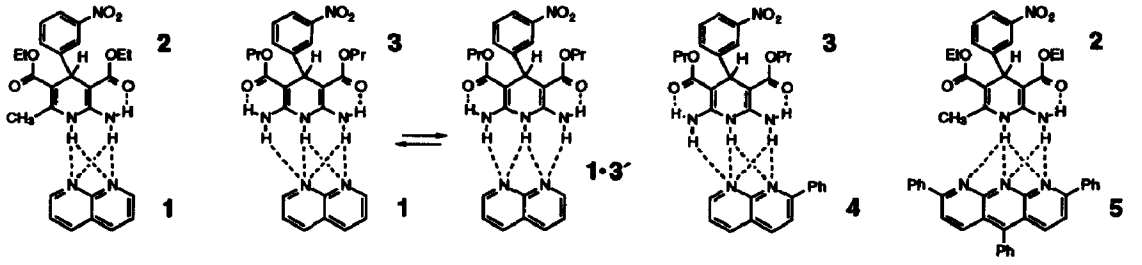

Table. Association Constants and Complexation Data for Various Complexes in Chloroform-*d*.[a]

complex	motif	method used	proton monitored	$\Delta\delta_{max}$ (ppm)	K_{assoc} (M^{-1})	$-\Delta G°_{298}$ (kcal mol^{-1})
1·2	AA·DD	A	2-NH_2	2.01	260	3.3
1·3	AA·DDD	A	2-NH_2	1.05	3×10^3	4.7
4·3	AA·DDD	A,B	2-NH_2	0.83	2×10^3	4.4
5·2	AAA·DD	A,B	1-NH	4.80	848	4.0

[a]At 298 K. Duplicate runs agreed within 7%. Method A: titration, method B: dilution of 1:1 complex.

The association constants and complexation shifts are compiled in the Table. The **1·2** complex is quite stable (K_{assoc} = 260 M^{-1}). For comparison, 2-pentanoylaminopyridine dimerizes with K_{dimer} = 2 M^{-1} (AD·DA motif), and many triply hydrogen bonded complexes with the ADA·DAD motif exhibit $K_{assoc} \leq 200$ M^{-1}.[5] These results are consistent with the secondary electrostatic interaction model.[4]

The **1·3** complex is very stable ($K_{assoc} = 3 \times 10^3$ M^{-1}). The additional amino group in this complex raises its association constant more than 10-fold. Even with the statistical correction for the increased number of contact sites, the extra hydrogen bond donor (NH_2 group) contributes over 1 kcal mol^{-1}. The additional amino group in **3** may provide an additional, "over-hanging" attractive secondary electrostatic interaction.[4b] Alternatively, it may increase the strength of the primary hydrogen bonds. The latter possibility is less likely because the N-H groups in **3** are expected to be less acidic than those in **2**.

The **5·2** complex is noticeably more stable than the **1·2** complex. However, after applying the necessary statistical correction for the additional contact sites, the increase in stability is modest. Although this result may reflect the inherent importance of an "over-hanging" acceptor group, the anthyridine acceptor sites are expected to be less basic than those in naphthyridine,[9] and the weaker primary hydrogen bonding strengths complicate the analysis.

What is the structure of the 1·3 complex? Two limiting geometries are represented by 1·3 and 1·3′. In the former, two N-H groups are each involved in unsymmetrical three centered (bifurcated) hydrogen bonds,[10] and the third engages in a nonlinear two centered hydrogen bond (secondary electrostatic interaction). In complex 1·3′, the central N-H group makes a symmetrical three centered (bifurcated) hydrogen bond to the naphthyridine, while the flanking N-H groups form bent two centered hydrogen bonds. To distinguish between these possibilities, 2-phenyl-naphthyridine (4) was synthesized. Molecular modeling indicated that the phenyl group in 4 could be accommodated in complex 1·3, if the phenyl group were rotated slightly from its preferred dihedral angle of ca. 20°, but would suffer a steric interaction with the amino group of 3 in symmetrical complex 1·3′, even if the naphthyridine and phenyl groups were perpendicular. The similar K_{assoc} values for the 1·3 and 4·3 complexes is more consistent with complex structure 1·3.

Attempts were made to co-crystallize 1 with 2 and 1 with 3 to gain additional structural information about the complexes. Although complexes 1·2 and 1·3 did not readily crystallize, analogs 1·6 and 1·7 formed X-ray quality crystals by slow evaporation from 1:1 solutions in acetonitrile-tetrahydrofuran. The results of the X-ray analyses are shown in Figure 2. Isotropic thermal coefficients were refined for the amine hydrogens and an empirical isotropic extinction parameter was refined.[11] The geometry of the hydrogen bonding motif is very similar in the two structures (Figure 2). Both contain two nearly linear hydrogen bonds (N—H—N angles >170°),

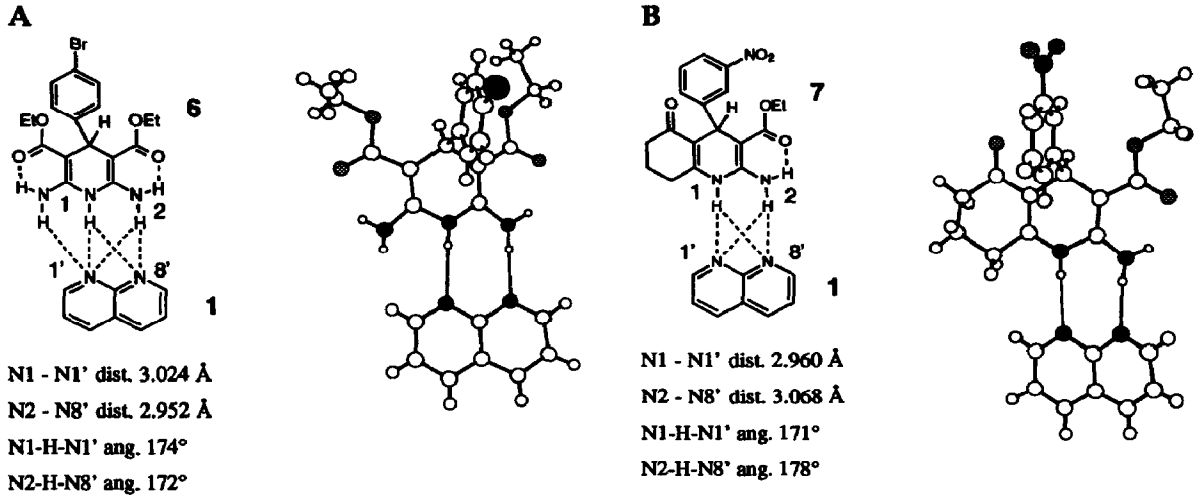

Figure 2. Kekulé and X-ray structures of 1·6 (A) and 1·7 (B) and selected distances and angles.

the average length of which is very similar in the two complexes. The latter finding suggests similar hydrogen bonding strengths for the two complexes. Although the additional hydrogen bond donor group in 1·6 is only 2.96 Å from N1′, the 6-amino group has pyramidalized so the unpaired hydrogen favorably contacts an N2 of a neighboring molecule 6. It is not known what effect this close contact has on the overall crystal structure.

The data described herein indicate that complexes such as **1·2**, containing the AA·DD hydrogen bonding motif, are quite stable as expected from the additional secondary electrostatic interactions[4] present in the three centered hydrogen bonds. The overhanging amino group in **1·3** raises its stability over complex **1·2** by an additional 1.4 kcal mol^{-1}. This added stability may arise from the additional nonlinear two-centered hydrogen bond (secondary electrostatic interaction). The X-ray data and binding results with **4** suggest that unsymmetrical complex **1·3** is favored over symmetrical complex **1·3'**. The former complex is favored because it contains 5 hydrogen bonds, two of which are linear. The latter complex contains 4 bent hydrogen bonds.

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