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Aromaticity gain increases the inherent association strengths of multipoint hydrogen-bonded arrays†

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Textbook explanations for the associations of multipoint hydrogen-bonded arrays have long hinged on the secondary electrostatic interaction (SEI) model, which suggests that array association strengths depend on the proton donor (D) and acceptor (A) patterns of the interacting units. Here, computational results based on the block-localized wavefunction (BLW) method reveal limitations of the SEI model, demonstrating instead that, in the gas-phase (and in implicit chloroform solvation), the inherent free-energies of associations of multipoint hydrogen-bonded arrays correlate with the degree of "aromaticity gain" (*i.e.*, the amount of increased cyclic π-electron delocalization) in arrays upon complexation. Excellent correlations for 46 triply (r = 0.940) and quadruply (r = 0.959) hydrogen-bonded arrays are presented.

Multipoint hydrogen-bonded arrays are increasingly featured in the designs of supramolecular polymers, due to their rigid structures and high recognition specificity.[1–4] It is well-known that the stability of the hydrogen bonded array complexes depend on the numbers, types, and patterns[5] of the hydrogen bond donor/acceptor pairs present. What is less clear, however, is whether or not other molecular features might significantly influence the hydrogen bonding interactions of arrays so that their association trends might be predicted more reliably *a priori*. In this paper, we report computational results documenting excellent linear correlation between the inherent association strengths of arrays and the amount of "aromaticity gain" in arrays upon complexation.

Although aromaticity and hydrogen bonding have long been considered as separate concepts in organic chemistry, we recently showed that changes in the aromatic character of heterocycles can significantly influence their hydrogen bonding capabilities through a reciprocal aromaticity-modulated hydrogen bonding (AMHB) relationship.[6–9] Results based on computations[6–8] and high-field NMR spectroscopy[9] revealed that hydrogen bonding interactions that increase cyclic $4n + 2$ π-electron delocalizations in heterocycles are strengthened as a result of enhanced aromatic character in the resulting hydrogen-bonded complex. Conversely, hydrogen bonding interactions that decrease cyclic $4n + 2$ π-electron delocalizations in heterocycles are weakened due to reduced aromatic character in the hydrogen-bonded complex. According to the AMHB relationship, we showed that heterocycles with the same numbers, types, and patterns of hydrogen bond donors/acceptors moieties can exhibit surprisingly different hydrogen bond strengths depending on their π-conjugation patterns.

Here, we report the implication of AMHB as a model to understand and predict the inherent association trends of multipoint hydrogen-bonded arrays. Two examples, the guanine–cytosine (G–C) nucleobase pair **1**·**2** and the ureidopyrimidone (UPy) dimer **3**·**3**, are illustrated in Fig. 1.

Based on the Hückel definition of π-aromaticity for closed-shell planar rings, none of the six membered rings in G, C, and Upy are formally "aromatic" due to lack of a cyclic delocalization of $4n + 2$ π-electrons. However, in their hydrogen-bonded forms, the π-electrons of G, C, and Upy are polarized, resulting

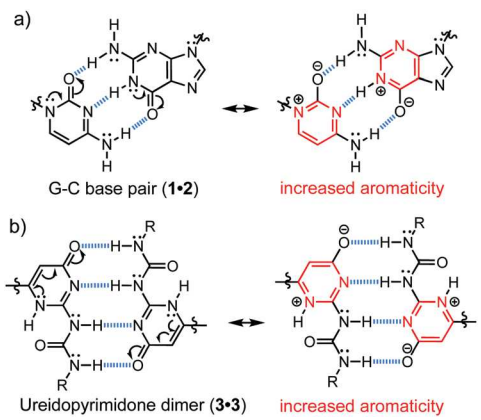

Fig. 1 Schematic illustration of aromaticity-modulated hydrogen bonding (AMHB) in (a) the guanine–cytosine (G–C) base pair, **1**·**2**, and (b) ureidopyrimidone (UPy) dimer, **3**·**3**.

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in increased cyclic $4n + 2$ π-electron delocalization in the six membered rings (see Fig. 1a and b, resonance structures in red), which in turn strengthens the corresponding hydrogen bonding interactions. This "extra" aromaticity gain stabilizes the G–C pair and in the Upy dimer, providing a possible explanation for their stronger than expected association strengths compared to analogous arrays with the same numbers, types, and patterns of hydrogen bonding interactions.[10–13]

Since aromaticity is associated with the cyclic delocalization of π-electrons, aromaticity gain in arrays can be evaluated by the amount of increased π-electron delocalization energy (ΔDE_π) as two array monomers come together to form a hydrogen-bonded complex; $\Delta DE_\pi = DE_{\pi(A-B)} - [DE_{\pi(A)} + DE_{\pi(B)}]$. Here, the block-localized wavefunction (BLW) method,[14–16] an *ab initio* valence bond approach, is applied to measure the π-electron delocalization energies (DE_π) of the monomers and complexes. DE_π is evaluated by the energy difference between that of the fully electron delocalized wavefunction (Ψ_{deloc}) of the monomer or complex considered and that of the π-electron localized wavefunction (Ψ_{loc}), in which all π-electron delocalization effects are disabled; $DE_\pi = \Psi_{loc} - \Psi_{deloc}$. Because of its computational efficiency and documented reliability in reproducing experimental trends, the BLW method has been widely applied to quantify and interpret the effects of π-electron delocalization in many chemical systems.[16] All BLW computations were performed at the B3LYP/6-31G(d) level using the GAMESS-2013-R1 program.[17] Geometries for all monomers and complexes were optimized at the ωB97X-D/6-311+G(d,p) level with an ultrafine grid employing the Gaussian09 program.[18] See computational details in the ESI.†

Following the BLW procedure described above, large positive ΔDE_π values indicate substantial aromaticity gain in arrays upon hydrogen bonding. For example, in the 2-pyridone dimer (see Fig. 2a), two hydrogen bonding interactions polarize the N π-lone pairs and C=O π-bonds to increase cyclic six π-electron delocalization (see resonance form on right), giving rise to considerable aromaticity gain in the six membered rings and a large $\Delta DE_\pi = 26.1$ kcal mol^{-1} value. Small positive ΔDE_π values indicate little to no aromaticity gain (or a decreased aromatic character) in arrays upon hydrogen bonding. For example, in the 2-hydroxypyridine dimer (see Fig. 2b), two hydrogen bonding interactions polarize the N π-lone pairs and C=N π-bonds to decrease cyclic six π-electron delocalization (see resonance form on right), resulting in reduced aromatic character in the six membered rings and a small $\Delta DE_\pi = 5.7$ kcal mol^{-1} value. The effects of aromaticity gain (or loss) upon array complexation also may be considered as a manifestation of non-additivity in resonance-assisted hydrogen bonding.[19]

Based on a survey of 46 hydrogen-bonded arrays, an excellent linear relationship was found between the computed gas-phase association free energies ($-\Delta G_{assoc}$, at 298 K) and ΔDE_π values of 26 triply ($r = 0.940$) and 20 quadruply ($r = 0.959$) hydrogen-bonded arrays (see Fig. 3), suggesting that the inherent association strengths of multipoint hydrogen-bonded arrays correlate with the amount of aromaticity gain in arrays upon complexation. Depending on the π-conjugation pattern of the array monomers considered, hydrogen bonding interactions that increase cyclic $4n + 2$ π electron delocalizations in arrays (as indicated by a large ΔDE_π value) are strengthened, while hydrogen bonding interactions that decrease cyclic $4n + 2$ π-electron delocalizations (as indicated by a small ΔDE_π value) are weakened. Computations in implicit chloroform solvation and analyses based on the natural bond orbital (NBO) deletion method[20] show the same excellent correlation are presented in the ESI.†

This finding points to important limitations of the secondary electrostatic interaction (SEI) model of Jorgensen and Pranata,[5] which has long guided the understanding of multipoint hydrogen bonded arrays and their associations in supramolecular chemistry.

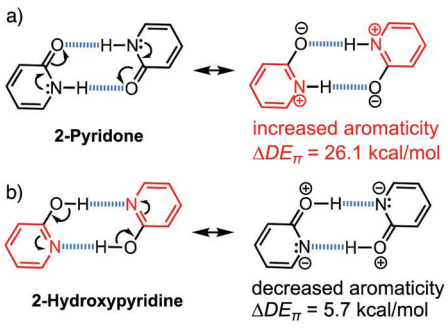

Fig. 2 AMHB in (a) the 2-pyridone dimer (note large ΔDE_π value due to aromaticity gain in the six membered rings) and (b) the 2-hydroxypyridine dimer (note small ΔDE_π value, due to reduced aromatic character in the six membered rings).

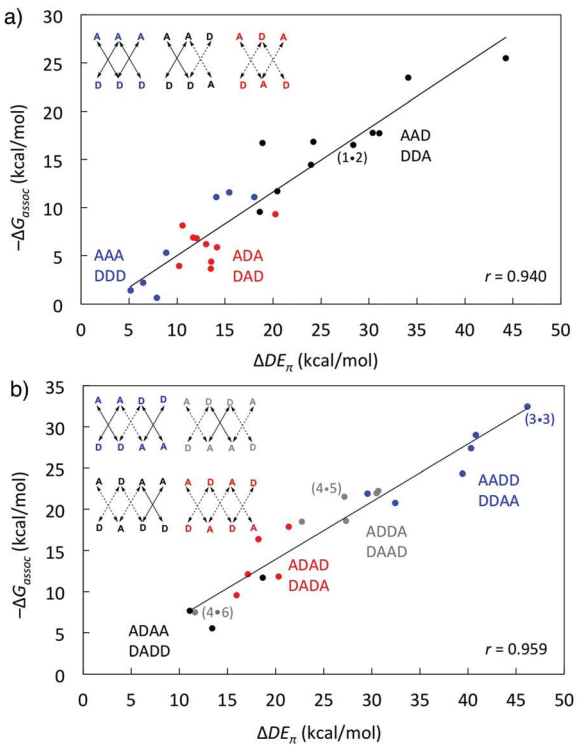

Fig. 3 Plot of $-\Delta G_{assoc}$ *vs.* ΔDE_π for (a) triply and (b) quadruply hydrogen-bonded arrays. The secondary electrostatic interaction (SEI) patterns for each array are color coded; see top left corner of each plot (— lines indicate attractive interactions, --- lines indicate repulsive interactions).

According to the SEI model, it was suggested that for a given number of hydrogen bonds in an array, those with all hydrogen bond donors (D) on one fragment and all acceptors (A) on the other are the most robust, since this arrangement maximizes attractive electrostatic interactions. Thus, the association strengths of triply hydrogen-bonded array are expected to follow the order: AAA–DDD > AAD–DDA > ADA–DAD (Fig. 3a), while those of quadruply hydrogen-bonded arrays are expected to follow the order: AADD–DDAA > ADDA–DAAD ≈ ADAA–DADD > ADAD–DADA (Fig. 3b).

Past studies both supporting and refuting the SEI model have appeared in the literature. Schneider *et al.*,[21] and later Zimmerman and coworkers,[22] have shown that empirical increments taking into account primary and secondary electrostatic interactions (as well as secondary CH···O interactions)[13] can be used to predict the experimental associations of hydrogen-bonded arrays satisfactorily. Based on a survey of more than 60 arrays, Vanka *et al.*[23] found excellent correlation between the computed array association energies and calculated electrostatic forces between the arrays. Popelier and Joubert showed, based on a study of 28 base pairs, that electrostatic interactions between many remote atom pairs also contribute importantly to array binding.[24] However, Lukin and Leszynski argued that the incremental approaches of Scheider and Zimmerman can be deceptive;[25] based on extensive quantum chemical calculations, these authors demonstrated that some ADD–DAA arrays appear to have weaker experimentally observed associations than their analogous AAA–DDD arrays only because of a more solvated ADD and DAA monomer in wet polar solvent. Guerra *et al.* noted that effects other than electrostatic interactions play important roles in the hydrogen bonds of DNA base pairs.[26] Mo commented that changes in the electrostatic components of computed array association energies could arise from changes in the π-electron delocalization energies of monomers upon hydrogen bonding.[27,28] Although the SEI model has been criticized on the basis of both quantum chemical calculations and experimental evidence, it remains the most widely applied concept for the design and synthesis of hydrogen-bonded molecular recognition units.

In sharp contrast to the SEI model, our computations show that arrays with the "best" electrostatic interaction patterns do not necessarily exhibit the strongest inherent association strengths. Surprisingly, the AAA–DDD complexes (in blue), despite having all hydrogen bond donors (D) on one fragment and all acceptors (A) on the other, exhibit lower $-\Delta G_{assoc}$ values compared to those of the AAD–DDA (in black) and ADA–DAD (in red) complexes (Fig. 3a). Even arrays with the same SEI patterns can exhibit a wide range of $-\Delta G_{assoc}$ values. Notably, the computed $-\Delta G_{assoc}$ values for the AAA–DDD, AAD–DDA, AADD–DDAA, and ADDA–DAAD sets vary over a range of *ca.* 10 kcal mol^{-1}, corresponding to a $K_{assoc} \approx 10^7$ difference! These trends violate the SEI model and illustrate the importance of considering aromaticity gain in arrays as a relevant factor for determining the stability of multipoint hydrogen-bonded complexes.

Clear exceptions to the SEI model may be explained when the effects of aromaticity gain in arrays are considered. For example,

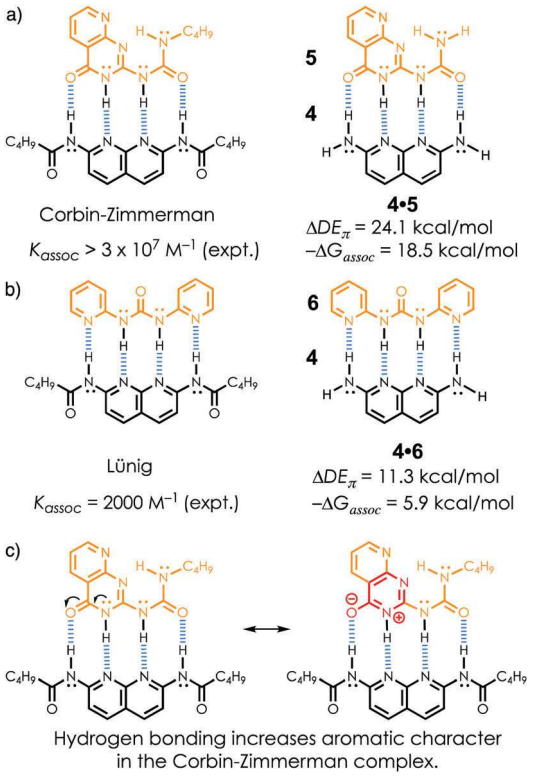

Fig. 4 Experimental K_{assoc} values (in chloroform) for the ADDA–DAAD modules of (a) Corbin–Zimmerman and (b) Lünig; see also model arrays, **4·5** and **4·6**, on right. Note π-conjugation pattern difference highlighted in orange. (c) Resonance form showing increased aromatic character in the Corbin–Zimmerman module upon hydrogen bonding.

the quadruply hydrogen-bonded modules of Corbin–Zimmerman[22] ($K_{assoc} \geq 3 \times 10^7$ M^{-1} in chloroform, Fig. 4a) and Lünig[29] ($K_{assoc} \cong$ 2000 M^{-1} in chloroform, Fig. 4b), exhibit the same ADDA–DAAD pattern, but display drastically different experimental K_{assoc} values. This disparity (a near 10^4 times difference) has been attributed to variances in the preorganization energies of the monomers,[1] but can arise in part due to the different π-conjugation patterns of the monomers (note orange highlight in Fig. 4).

In the Corbin–Zimmerman module, hydrogen bonding interactions can polarize the π-electrons to increase cyclic six π-aromatic character in the 4-pyridone moiety (see Fig. 4c, note resonance form in red), but such aromatization effects are absent in the Lünig complex. Indeed, BLW computations for models of the two ADDA–DAAD arrays, **4·5** and **4·6** (–COC$_4$H$_9$ groups replaced by H atom), show much greater π-conjugation gain for **4·5** (ΔDE_π = 24.1 kcal mol^{-1}, Fig. 4a) than for **4·6** (ΔDE_π = 11.3 kcal mol^{-1}, Fig. 4b) (*cf.* Fig. 2, BLW analysis for 2-pyridone *vs.* 2-hydroxypyridine; fully aromatic rings exhibit less aromaticity gain upon hydrogen bond complexation).

With its near 150 year old history, the term "aromatic rings" has evolved to adopt various shades of meanings in the chemical literature. Very often, rigid unsaturated rings are generally called aromatic rings, even if they do not follow the more stringent Hückel definition – a closed-shell π-conjugated ring having a cyclic delocalization of $4n + 2$ π-electrons. We show here that the traditional Hückel definition of aromaticity has chemical value

for interpreting the inherent association trends of triply and quadruply hydrogen-bonded arrays. Of course blends of factors (*e.g.*, entropy, solvation, conformational and protomeric equilibria of the array monomers) can all influence the experimental associations of arrays. Nevertheless, our findings highlight the surprising impact of aromaticity gain on the association strengths of multipoint hydrogen-bonded arrays, suggesting that the potential for aromaticity gain in arrays should be considered in addition to the often used check-list (*i.e.*, numbers, types, and SEI patterns) for designing hydrogen-bonded molecular-recognition units.

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Conflicts of interest

There are no conflicts to declare.

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