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Reciprocal Hydrogen Bonding−Aromaticity Relationships

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Supporting Information

ABSTRACT: Computed association energies and dissected nucleus-independent chemical shifts (NICS) document the mutual enhancement (or reduction) of intermolecular interactions and the aromaticity of H-bonded substrates. H-bonding interactions that increase cyclic $4n + 2$ π-electron delocalization boost aromaticity. Conversely, such interactions are weakened when aromaticity is decreased as a result of more localized quinoidal π character. Representative examples of the tautomeric equilibria of π-conjugated heterocyclic compounds in protic solvents and other H-bonding environments also illustrate such H-bonding/aromaticity interplay.

This communication elucidates the mutual reinforcement (or weakening) of "H-bonding interactions" and the "aromatic character" of representative systems through π-electron polarization effects. Such relationships are based on *changes* in the aromatic character (i.e., the degree of cyclic π-electron delocalization) of π-conjugated heterocycles. Thus, H-bonding interactions that increase cyclic $4n + 2$ π-electron *delocalization* simultaneously enhance both the aromaticity[1,2] of H-bonded substrates and their association energy (Figure 1a).

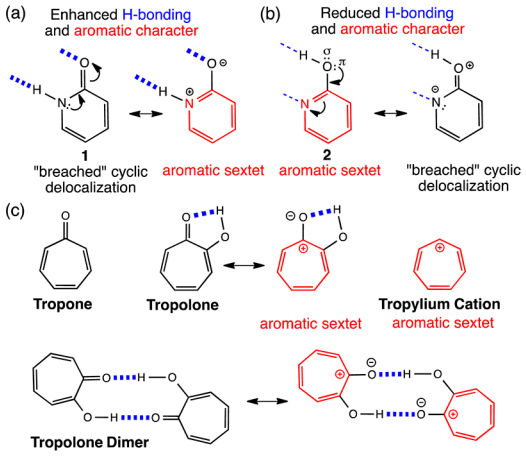

Figure 1. Mutually enhanced (a) and reduced (b) H-bonding interactions and π-aromatic character in H-bonded 2-pyridone (**1**) and 2-hydroxypyridine (**2**), respectively. (c) Tropone, tropolone, the tropylium cation, and the tropolone dimer (note the aromatic resonance contributors). Thick dotted lines (in blue) indicate strong H-bonding interactions; thin dashed lines indicate weak H-bonding interactions. "Aromatic sextets" are highlighted in red.

Conversely, H-bonding that results in greater π-electron *localization* decreases both the aromaticity and association energy (Figure 1b). The ca. 2−4 kcal/mol enhancement or reduction effects per H-bond are substantial; they correspond to changes of 20−60% in the usual H-bond strengths and up to 1000-fold shifts in tautomeric equilibria!

Dewar's 1945 seminal proposals of non-benzenoid aromaticity in stipitatic acid[3] and its parent analogue tropolone[4] (2-hydroxytropone; Figure 1c) were based on his recognition of H-bond-enhanced π aromatization. While the cyclic six-π-electron character of cycloheptatrienone (tropone; Figure 1c) due to the polarization of its exocyclic carbonyl group is quite modest,[5] the aromaticity of tropolone is conspicuous.[6] Intramolecular H-bonding of the exocyclic O−H and C═O groups enhances the aromaticity of the tropolone seven-membered ring. Consequently, tropolone is more aromatic than tropone because of the enhanced cyclic six-π-electron delocalization induced by the O−H···O═C hydrogen bond: the resulting dipolar resonance contributor of tropolone resembles the aromatic tropylium cation[7] more closely (Figure 1c).

In 2,5-dihydroxytropone, the infrared stretching frequency of the H-bonded 2-OH (3170 cm^{-1}) is strongly shifted relative to that of the "free" 5-OH (3660 cm^{-1}) as a result of the strong intramolecular O−H···O═C bonding,[8,9] which enhances the π delocalization. The pronounced ring bond-length equalization of tropolone dimers (Figure 1c) in the solid state[9,10] further illustrates the H-bonding/aromaticity coupling effect.

Other examples of H-bond-induced aromatization[11−29] and the effects of *intramolecular* H-bonding and aromaticity on the tautomeric equilibria of heterocycles have been noted,[11−19] but we emphasize here the general importance of this relationship for *intermolecular* H-bonding interactions. Satsyuk et al. found that intermolecular H-bonding interactions[20] and metal complexation[21] influenced π-electron delocalization in the tautomeric forms of purines. Maksić and co-workers ascribed the high proton affinity of several organic superbases to ring π aromatization.[22−24] Quiñonero and co-workers attributed the superior catalytic H-bond-donor ability of squaramide over urea to the increased aromaticity of the four-membered ring.[25,26] Krygowski and co-workers pointed out that the aromaticity of the purines and pyrimidines constituting DNA and RNA is "sensitive to much weaker perturbations, such as those caused by H-bonding."[27] The effect of intermolecular H-bonding interactions on the geometries of aniline, anilinium, anilide,

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pyridine, and pyridinium derivatives also have been examined.[28,29]

We now present a proof-of-concept for intermolecular H-bonding/aromaticity coupling by emphasizing the remarkable geometric,[30] energetic, and magnetic consequences of this synergistic relationship. H-bonding interaction energies were computed at the PBE0/6-311++G(3df,3pd) level[31,32] without zero-point energy (ZPE) corrections, employing Gaussian 03.[33] Dissected nucleus-independent chemical shifts at 1 Å above the heavy-atom ring centers, NICS(1)$_{zz}$[34−36] (computed at the PW91/Def2-TZVPP level), were used to quantify *changes* in the magnetic aromaticities of the six-membered rings (see ref 37).

Remarkably, 2-pyridone (**1**) (Figure 2a) and 2-hydroxypyridine (**2**) (Figure 2c) dimers, $\mathbf{1}_{dimer}$[38−40] and $\mathbf{2}_{dimer}$, display

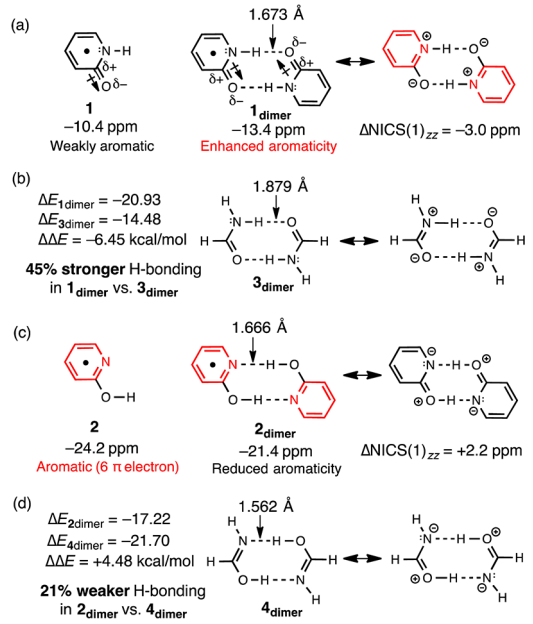

Figure 2. Computed NICS(1)$_{zz}$ (PW91/Def2-TZVPP) and dimerization energies [ΔE_{dimer} in kcal/mol; PBE0/6-311++G(3df/3pd), no ZPE] for (a) $\mathbf{1}_{dimer}$ (H-bond-induced aromaticity enhancement), (b) $\mathbf{3}_{dimer}$, (c) $\mathbf{2}_{dimer}$ (H-bond-induced aromaticity reduction), and (d) $\mathbf{4}_{dimer}$.

opposite *intermolecular* H-bond-induced effects on π aromaticity. Thus, the aromaticity of **1** [NICS(1)$_{zz}$ = −10.6 ppm], due to the polarization of its exocyclic C═O π bond toward the more electronegative O atom (Figure 2a, left), increases in $\mathbf{1}_{dimer}$ [NICS(1)$_{zz}$ = −13.4 ppm (more negative NICS values indicate enhanced π aromaticity); Figure 2a, right] since the two N−H···O═C interactions polarize the benzenoid ring π-electron clouds and enhance their aromatic sextet character (cf. the resonance structure in red at the right of Figure 2a).

As a result of this H-bonding/aromaticity coupling effect, the N−H···O═C interactions in $\mathbf{1}_{dimer}$ are *stronger* than those in formamide dimer ($\mathbf{3}_{dimer}$), where no H-bond-induced π-aromatization results. Thus, the computed dimerization energy (ΔE_{dimer}) of $\mathbf{1}_{dimer}$ (−20.9 kcal/mol) is 45% *larger* than that of $\mathbf{3}_{dimer}$ (−14.5 kcal/mol) (Figure 2b). In accord with its stronger H-bond strength, the intermolecular H···O distances of $\mathbf{1}_{dimer}$ (1.673 Å; Figure 2a) also are noticeably shorter than those of $\mathbf{3}_{dimer}$ (1.879 Å; Figure 2b). The shortened N−CO bond (1.377 Å) and lengthened C═O bond (1.242 Å) of $\mathbf{1}_{dimer}$ (cf. **1**: N−CO, 1.398 Å; C═O, 1.218 Å) also indicate enhanced aromatization in the six-membered rings of $\mathbf{1}_{dimer}$.

Conversely, the computed NICS(1)$_{zz}$ of −24.2 ppm for the six-π-electron compound **2** becomes less negative (diatropic) upon dimerization (−21.4 ppm for $\mathbf{2}_{dimer}$; Figure 2c). The two O−H···N hydrogen-bonding interactions in $\mathbf{2}_{dimer}$ reduce the aromatic sextet character of the six-membered rings (cf. the resonance structure in black in Figure 2c at the right), and are weakened relative to those in the dimer of hydroxyimine (the iminol form of formamide) ($\mathbf{4}_{dimer}$). Hence, the computed ΔE_{dimer} for $\mathbf{2}_{dimer}$ (−17.2 kcal/mol) is decreased by 21% compared with that of $\mathbf{4}_{dimer}$ (−21.7 kcal/mol), which lacks aromatic rings (Figure 2d). The weaker binding of $\mathbf{2}_{dimer}$ compared with $\mathbf{1}_{dimer}$ is especially surprising since phenolic O−H groups generally form stronger H-bonds than amide N−H groups. The computed intermolecular N···H distances of $\mathbf{2}_{dimer}$ (1.666 Å; Figure 2c) also are longer than those of $\mathbf{4}_{dimer}$ (1.562 Å; Figure 2d). Like **2**, 2-aminopyridine[41,42] also displays energetic, magnetic, and geometric features indicative of H-bond-induced aromaticity reduction upon dimerization (for details, see the Supporting Information).

Because of the stabilization afforded by the aromatic sextet (a cyclic array of six π electrons that resists disruption),[1,2] the energy gained by H-bond strengthening due to increased aromaticity (e.g., in $\mathbf{1}_{dimer}$) is greater than the energy lost by weakening an H-bonding interaction by reducing aromaticity (e.g., in $\mathbf{2}_{dimer}$). Compared with aromatic systems, antiaromatic rings are even more susceptible to H-bond-induced π polarization because of their "frustrated" π systems and propensity to relieve antiaromatic destabilization. Such relationships will be explored in a separate publication.

Intermolecular H-bonding interactions between cyclic π-conjugated keto or enol tautomers and protic solvents (or other H-bonding substrates) also perturb aromaticity and can shift tautomeric equilibria in either direction, depending on the situation. The computed PBE0/6-311++G(3df,3pd) keto−enol tautomerization energies for **2** → **1** versus $\mathbf{2}^{w}$ → $\mathbf{1}^{w}$ (complexes with two water molecules) and $\mathbf{2}^{gly}$ → $\mathbf{1}^{gly}$ (complexes with the zwitterionic glycine) in the gas phase (ΔE_T) and in water-solvated models ($\Delta E_{T(PCM)}$) are illustrative (Figure 3). Each model solvated system, $\mathbf{1}^{w}$−$\mathbf{4}^{w}$, was complexed with two explicit water molecules (in their lowest-energy conformation) and in addition with bulk "aqueous solvation" as simulated by the polarizable continuum model (PCM).[43]

Although **1** and **2** are equally stable in the gas phase (tautomerization energy ΔE_T = +0.02 kcal/mol favoring **1**),[44] water solvation "aromatizes" and therefore lowers the energy of the keto form $\mathbf{1}^{w}$ (cf. the enhanced delocalization depicted in Figure 3a, top right) but "dearomatizes" and thereby destabilizes the enol tautomer $\mathbf{2}^{w}$ (Figure 3a, bottom right). Thus, the computed $\Delta E_{T(PCM)}$ for $\mathbf{2}^{w}$ → $\mathbf{1}^{w}$ (−4.4 kcal/mol, with two explicit waters and simulated bulk water solvation; see Figure 3a, center) strongly favors the "aromatized" keto form ($\mathbf{1}^{w}$)! Earlier work attributed such tautomeric shifts to the greater dipolar character of **1**.[45] However, on the basis of the same H-bonding motifs (but lacking H-bonding/aromaticity coupling), the computed ΔE_T values for **4** → **3** (ΔE_T = −12.3 kcal/mol) and for $\mathbf{4}^{w}$ → $\mathbf{3}^{w}$ ($\Delta E_{T(PCM)}$ = −11.2 kcal/mol) differ by only 1.1 kcal/mol (Figure 3b).

Computed NICS(1)$_{zz}$ data reveal that $\mathbf{1}^{w}$ (−13.2 ppm) is more aromatic than **1** (−10.4 ppm), but $\mathbf{2}^{w}$ (−22.0 ppm) is less aromatic than **2** (−24.2 ppm) (Figure 3a). Notably, *changes* in aromaticity, i.e., **1** → $\mathbf{1}^{w}$ (increased aromaticity) versus **2** → $\mathbf{2}^{w}$

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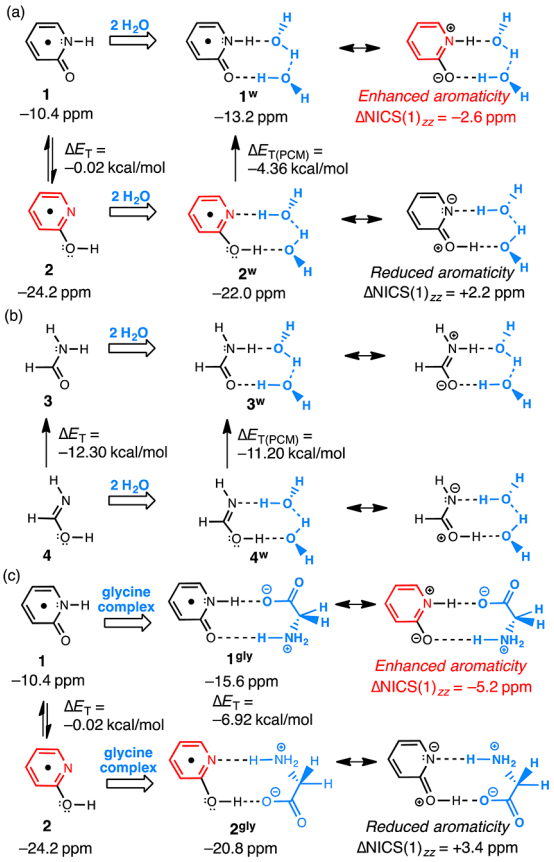

Figure 3. Computed tautomerization energies [PBE0/6-311++G(3df/3pd), no ZPE] and NICS(1)$_{zz}$ (PW91/Def2-TZVPP) for (a) **2** → **1** vs $\mathbf{2}^{w}$ → $\mathbf{1}^{w}$ and (b) **4** → **3** vs $\mathbf{4}^{w}$ → $\mathbf{3}^{w}$ in the gas-phase (ΔE_T) and in implicit water solvent ($\Delta E_{T(PCM)}$). (c) ΔE_T values for **2** → **1** vs $\mathbf{2}^{gly}$ → $\mathbf{1}^{gly}$.

(decreased aromaticity), rather than the inherent relative aromatic character of $\mathbf{1}^{w}$ (less aromatic) and $\mathbf{2}^{w}$ (more aromatic) dictate their tautomeric ratios in water. Accordingly, the N–CO (1.374 Å) and C=O (1.248 Å) bonds of $\mathbf{1}^{w}$ (in water) are shortened (−0.024, enhanced ring bond-length *equalization*) and lengthened (+0.030 Å) substantially compared with those of **1** (N–CO, 1.398 Å; C=O, 1.218 Å) in the gas phase.[45] In contrast, the N=CO (1.329 Å) and C–O (1.328 Å) bonds of $\mathbf{2}^{w}$ (in water) are lengthened (+0.010) and shortened (−0.014) modestly relative to those of **2** (N=CO, 1.319 Å; C–O, 1.342 Å).

H-bonding interactions involving "zwitterions" (e.g., glycine; Figure 3c) can exhibit even more substantial H-bond-induced π-aromatization effects and shifts in tautomeric equilibria. Thus, the computed ΔE_T for $\mathbf{2}^{gly}$ → $\mathbf{1}^{gly}$ (−6.9 kcal/mol) is considerably larger than that for **2** → **1** (−0.02 kcal/mol) (Figure 3c); H-bonding with glycine increases the aromaticity in $\mathbf{1}^{gly}$ and lowers its energy relative to the dearomatized $\mathbf{2}^{gly}$. In the absence of H-bond/aromaticity coupling, the ΔE_T values for $\mathbf{3}^{gly}$ → $\mathbf{4}^{gly}$ (+10.6 kcal/mol) and **3** → **4** (+12.3 kcal/mol) illustrate the opposite effect; glycine complexation reduces the preference for the keto tautomer. The significantly *increased* diatropicity of $\mathbf{1}^{gly}$ [NICS(1)$_{zz}$ = −15.6 ppm vs −10.4 ppm for **1**] and *decreased* diatropicity of $\mathbf{2}^{gly}$ (−20.8 ppm vs −24.2 ppm for **2**) also reveal the difference in H-bond-influenced aromaticity (Figure 3c).

In chemistry, understanding often lags behind observations but then facilitates applications. The synergistic H-bonding/aromaticity coupling effect discussed here provides valuable insights into strategies for tuning H-bond strengths. H-bonding interactions that increase (or decrease) cyclic $4n + 2$ π-electron delocalization are strengthened (or weakened). Such relationships may have considerable implications for molecular design, as the functions of many heterocyclic biomolecules and drugs rely on binding via H-bonds of a dominant keto/imine or enol/amine tautomer.[46−48] Magnifications of H-bonding/aromaticity coupling beyond tuning "H-bond strengths" with "aromaticity" also may be achieved for other types of noncovalent interactions.

■ ASSOCIATED CONTENT

Supporting Information

Cartesian coordinates and total electronic energies for all systems considered, a discussion of H-bond-induced aromaticity reduction in the 2-aminopyridine dimer, and complete ref 33. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(37) Isotropic NICS(1) were computed 1 Å above the heavy-atom centers for all heterocyclic six-membered rings. As the induced π ring currents associated with aromaticity are perpendicular to the applied external magnetic field, the more refined dissected $NICS(1)_{zz}$ index extracts only the out-of-plane *zz* components (perpendicular to the ring plane). Negative $NICS(1)_{zz}$ values denote aromaticity; positive $NICS(1)_{zz}$ values denote antiaromaticity. Negative $\Delta NICS(1)_{zz}$ values indicate enhanced aromatic character upon H-bonding.
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