The biologically ubiquitous OH⋯O and NH⋯O bonds are members of a much larger class of hydrogen-mediated \( \text{AH} \cdots \text{B} \) interactions, all of which may reasonably be called hydrogen bonds. Among the more unusual members of this class is the π-hydrogen bond (πHB) \( \text{AH} \cdots \phi \) where \( \phi \) represents an aromatic ring and \( A \) may be a N, O, or C atom. Such bonds have previously been well characterized in cold (matrix and gas phase) clusters and the interiors of native proteins, but not at protein surfaces in liquid water. Here we report the experimental observation of the quintessential πHB between liquid water and benzene (as well as other aromatics), and quantify the corresponding πHB probability, flexibility, and dynamic equilibrium between the benzene—water πHB and water—water hydrogen bond (wHB). Our results imply that πHB formation is likely to be common at biological interfaces, and thus may well participate in various binding, recognition, and signaling processes.

Early evidence of πHB formation was obtained from vibrational spectroscopic studies of liquid benzene containing a trace amount of dissolved water. These seminal studies were followed by many others, including detailed investigations both under ambient conditions and at high pressure and temperature, as well as in low temperature benzene—water clusters. However, an aqueous solution containing benzene is quite different from any of the above systems, in that liquid water wHB formation provides an energetically and statistically competitive alternative to πHB formation.

Previous experiments have found that πHBs are far more flexible than OH⋯O hydrogen bonds. For example, high-resolution rotational and vibrational spectra of the πHB in benzene—\( \text{H}_2\text{O} \), benzene—HOD, and benzene—\( \text{NH}_3 \) dimers indicate that the formation of a πHB leaves water (or ammonia) remarkably free to rotate. Moreover, recent time-resolved infrared studies of the πHB between phenol and benzene (as well as other aromatics) confirm that the OH group may readily reorient and translate parallel to the aromatic plane even in systems with substantially different πHB strengths. Our results reveal that benzene—water OH⋯\( \phi \) configurations in liquid water are also more flexible (have greater entropy) than water—water OH⋯O structures.

A substantial number of prior theoretical investigations have focused on characterizing the interaction between benzene and water. These include quantum calculations of benzene—(\( \text{H}_2\text{O} \))\(_n\) clusters containing between \( n = 1 \) and \( n = 10 \) water molecules, as well as both classical and quantum mechanical molecular dynamics simulations of benzene in liquid water. Although all of these studies suggest that a πHB may form between water and benzene, detailed predictions obtained using different theoretical methods are not entirely consistent with each other, particularly with regard to πHB strengths, probabilities, and structural distribution functions.

Here we employ a recently developed experimental strategy that combines ultralow-noise Raman scattering measurements and multivariate curve resolution (Raman-MCR) to obtain a solute-correlated (SC) spectrum that reveals OH vibrational features arising from benzene’s hydration-shell. The same Raman-MCR method has previously been used to discover dangling water OH bonds around dissolved saturated hydrocarbon
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The fact that the predicted value of \( n_{\pi HB} \) is larger than the experimental value is consistent with the fact that such classical simulations of benzene in liquid water (with OPLS-AA/TIP4P potentials, and OH vibrational frequency predictions obtained from a semiempirical Stark-shift correlation, as further described in the Supporting Information). The calculated probability of \( \pi HB \)s between benzene and liquid water \( n_{\pi HB} \) is \( \sim 0.64 \pm 0.12 \) at 20 °C, and increases mildly with temperature from \( \sim 0.51 \pm 0.12 \) (at 0 °C) to \( \sim 0.83 \pm 0.12 \) (at 50 °C).

The above experimental results are in reasonable agreement with the predicted value of \( n_{\pi HB} \sim 1.1 \pm 0.03 \), which we have obtained from classical simulations of benzene in liquid water. Extending these results to benzene as well as other aromatic solutes.

Figure 2A shows how the benzene--water \( \pi HB \) peak depends on temperature. The areas of these \( \pi HB \) peaks, combined with those arising from benzene and bulk water, may be used to determine the average number \( n_{\pi HB} \) of \( \pi HBs \) formed between liquid water and a dissolved benzene molecule (as further described below, and in the Supporting Information). In order to improve the accuracy of the resulting \( n_{\pi HB} \) Values, we have made use of the fact that the OH Raman scattering cross section \( \sigma_{OH\cdot\cdot\cdotO} \) is predicted to be \( \sim 1.21 \) times larger than that of \( OH\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\·
both the mean frequency and width of the πHB peak. More specifically, while our experimental results indicate a frequency increase of ~10 cm⁻¹ (from ~3603 ± 1 cm⁻¹ to ~3613 ± 1 cm⁻¹) and a full-width-at-half-maximum (fwhm) increase of ~17 cm⁻¹ (from ~61 ± 4 cm⁻¹ to ~78 ± 4 cm⁻¹) over a 0 to 50 °C temperature range, the simulations predict frequency and width increases of ~25 cm⁻¹ and ~10 cm⁻¹, respectively, over the same temperature range (see Supporting Information for further details).

The temperature dependence of the experimental πHB peak areas may be used to obtain a quantitative estimate of the enthalpy difference ΔH between a benzene—water πHB configuration and an average wHB in liquid water, as shown in Figure 2B. More specifically, the Gibbs–Helmholtz relation implies that ΔH = −R[∂ ln K/∂(1/T)]p where K = [πHB]/[wHB] is the ratio of the πHB and wHB concentration in a benzene—water solution (of fixed benzene concentration), and R ~ 8.3 J/(K mol) is the gas constant. Since [πHB] = nπHB/[H2O] and [wHB] = [H2O], we expect that ln K = ln(nπHB/[H2O]) + C (where C is a temperature-independent constant) and thus ΔH = −R[∂ ln(nπHB/[H2O])/(1/T)]p ~ 7 ± 2 kJ/mol, as shown in Figure 2B. A similar analysis of the temperature-dependent SC spectra of phenol in water yields ΔH = ~3 ± 2 kJ/mol. Although the above ΔH values have significant uncertainty, repeated measurements as well as alternative analysis procedures invariably produce positive experimental ΔH values of similar magnitude, which implies that a πHB is weaker than a wHB in liquid water.

The positive signs of the above ΔH values are consistent with previous experimental and theoretical benzene—water cluster results. For example, fragmentation threshold studies imply that a benzene—water dimer is slightly more weakly bound (by about 10–20%) than a water—water dimer. Moreover, quantum-classical effective fragment potential (QFEP) calculations of benzene—water clusters imply that replacement of one water molecule by benzene in water clusters with 4–8 water molecules leads to an intermolecular binding energy change of +7.5 ± 2.5 kJ/mol. Note that the latter energy difference is remarkably similar to our experimental ΔH result for the enthalpy difference between πHB and wHB configurations in liquid water (see Figure 2B).

Additional information regarding the thermodynamics of πHB formation may be obtained by focusing on a single water molecule situated nearest to the center of the benzene ring. Such a water molecule may be assumed to either form a πHB to benzene HOH···C6H6 (with a probability of p), or not H2O C6H6 (with a probability of 1−p). This simplified two-state description assumes that each of the OH groups on such a nearest neighborhood water molecule either form a πHB to benzene or a wHB to another water. Thus, the transformation of a HOH···C6H6 structure to a H2O C6H6 structure involves exchanging one πHB for one wHB. The ratio of the probabilities of finding the system in the latter two configurations, k = p/(1−p) = nπHB/(2−nπHB), represents the equilibrium constant for the H2O C6H6 ← HOH···C6H6 transformation. Note that the second of the above equalities is obtained by identifying p = nπHB/2 as the probability that a water molecule closest to one side of the benzene ring will form a πHB. The equilibrium constant k may be used to estimate the free energy ΔG and entropy ΔS of the H2O C6H6 ← HOH···C6H6 process. For example, at 20 °C nπHB ~ 0.64, so p ~ 0.32 and k ~ 0.32/(1−0.32) ~ 0.47, which implies that ΔG = −RT ln(0.47) ~ +2 kJ/mol.

This experimental free energy is in remarkably good agreement with value of ΔG ~ +3 kJ/mol inferred from the benzene—water πHB potential of mean force, obtained from our classical molecular dynamics simulations (as further described in the Supporting Information). The experimental ΔG, combined with the fact that ΔH > 2 kJ/mol, clearly implies that ΔS = (ΔH − ΔG)/T > 0. This conclusion is also consistent with the value of ΔS obtained from the temperature derivative of ΔG, ΔS = −(∂ΔG/∂T)T = R[∂ ln(Thv)]/∂T ~ +30 J/(K mol). The positive sign of ΔS indicates that HOH···C6H6 (πHB) configurations have a larger entropy than H2O C6H6 (non-πHB) configurations. In other words, the water molecule nearest to benzene’s center of mass has a greater conformational flexibility when one of its two OH groups forms a πHB than it does when both of its OH groups form a wHB.

Our experimental results imply that the conversion of a wHB to a πHB in liquid water is entropically favored (ΔS > 0) but enthalpically disfavored (ΔH > 0). The observed entropy increase is consistent with previous observations of the remarkably high orientational freedom of a πHB in benzene—water clusters as well as phenol dissolved liquid benzene. We have further found that, in spite of the fact that a πHB is somewhat weaker than a wHB (and the statistically greater number of potential wHB partners), approximately one πHB is formed between liquid water and each dissolved benzene molecule, as well as between water and other aromatic solutes including phenylalanine. The observed ubiquity of πHB formation in liquid water implies that such bonds are undoubtedly common at biological interfaces containing aromatic amino acids, nucleic acids, or metabolites, and thus πHB formation may well prove to play an important role in biological binding, recognition, and signaling processes.

ASSOCIATED CONTENT

6 Supporting Information. Materials and methods, data analysis procedures, and theoretical results. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author
E-mail: bendor@purdue.edu.

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REFERENCES


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