

## Communication: Where does the first water molecule go in imidazole?

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Supersonic jet FTIR spectroscopy supplemented by <sup>18</sup>O substitution shows unambiguously that water prefers to act as an O–H···N hydrogen bond donor towards imidazole, instead of acting as a N–H···O acceptor. Previous matrix isolation, helium droplet, and aromatic substitution experiments had remained ambiguous, as are standard quantum chemical calculations. The finding is supported by a study of the analogous methanol complexes and by higher level quantum chemical calculations.

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Imidazole (C<sub>3</sub>N<sub>2</sub>H<sub>4</sub>, *i*) is a well characterized heterocycle<sup>1</sup> that offers a hydrogen bond donor and a hydrogen bond acceptor functionality built on nitrogen. The two are sufficiently far apart not to influence each other directly, in contrast to the related case of pyrazole.<sup>2</sup> Therefore, the binding preference of the bifunctional water molecule (*w*) in a mixed dimer should be determinable in a straightforward way. Either, the water molecule engages one of its O–H bonds in a hydrogen bond towards the heterocyclic N atom lone pair (*wi*) or it engages one of its own lone electron pairs in a hydrogen bond with the N–H group (*iw*, see Fig. S1 (Ref. 3)). Due to the role of neutral imidazole in both biology<sup>4</sup> and materials science,<sup>5</sup> this preference is rather relevant<sup>6</sup> and has been addressed several times.<sup>7–11</sup> In relation to direct methanol fuel cells, comparison to the case of methanol (*m*) solvation is of interest.<sup>5,12</sup> Beyond classical hydrogen bonds, imidazole can also bind water via C–H hydrogen bonds.<sup>13</sup>

Surprisingly, there have been ambiguous spectroscopic answers to the straightforward title question, whereas the protonated imidazole case and the pyrrole case are less controversial.<sup>14,15</sup> An early matrix isolation study found *wi* and *iw* in a more or less equal ratio which could be due to kinetic control or matrix interactions.<sup>8</sup> A He nanodroplet study<sup>10</sup> induces less matrix interaction, but involves more kinetic control.<sup>16</sup> Therefore, the observed 1:1 ratio of both isomers cannot be interpreted in terms of an energy sequence. Rydberg electron transfer spectroscopy suggests imidazole as the hydrogen bond acceptor, but remains ambiguous because of uncertainties in the experimental and calculated excess electron binding energies and dipole moments of the floppy dimers.<sup>9</sup> In contrast, a free jet study of the derivative 4-phenyl imidazole<sup>17,18</sup> only revealed water as a hydrogen bond acceptor, but the influence of the phenyl ring is unclear. Therefore, an independent and unambiguous free jet direct absorption study on the isolated parent compound imidazole appears timely and is provided in this work.

Because of the low volatility of imidazole at room temperature, jet Fourier transform infrared (FTIR) spectra were recorded using a heatable double slit nozzle (0.5 × 10 mm<sup>2</sup>

each). Descriptions of the basic experimental setup may be found in Refs. 19–21. At variance with this earlier work, helium as a carrier gas was first guided through a temperature-controlled saturator containing the volatile liquid (i.e., water, methanol) at a temperature  $\vartheta$  before being admitted into the heated substance chamber containing imidazole-covered molecular sieve at a temperature  $\theta$ . The enclosure of the solid sample between two poppet valves ensured a sufficient substance pick up by the carrier gas. The ternary gas mixture was expanded into an evacuated buffer volume in pulses of 0.3 s duration synchronized to FTIR scans (Bruker IFS 66v/S) and the interferograms were detected by an InSb detector equipped with an appropriate optical bandpass filter. Typical spectra were obtained by coadding 600 FTIR scans collected in 300 gas pulses (1200 scans/600 pulses for some imidazole-water coexpansions). In the case of methanol the helium-solvent mixture was diluted with further helium to reduce the methanol concentration in the jet expansion.

Quantum chemical calculations include standard Pople 6-311G basis sets with diffuse and polarization functions at B3LYP and MP2 levels as well as more elaborate MP2/aug-cc-pV(D,T)Z calculations, together with a comparison to published results.<sup>7,8,11</sup> A basis set superposition error (BSSE) correction was not applied. For the relative energy of *wi* and *iw*, BSSE effects are expected to cancel in part, but a systematic study would be desirable for reliable absolute numbers. This is also the case for reliable anharmonic calculations, whereas our exploratory perturbation treatments (Tab. S4<sup>3</sup>) suffer from a poor description of low frequency modes.

Since spectra containing water aggregates are often ambiguous in their structural assignment, coexpansions of imidazole (*i*) with methanol (*m*) were used to generate benchmark values for the observable vibrational bands. Figure 1(a) shows the original jet FTIR coexpansion spectra and the mixed cluster contributions after subtraction of the pure *i* and *m* spectra. Further original spectra are shown in the supplementary material (Fig. S2 (Ref. 3)). Four bands at 3439, 3377, 3337, and 3227 cm<sup>-1</sup> appear at high methanol concentration. The two highest-wavenumber bands persist with less methanol, suggesting a mixed dimer assignment rather than larger clusters. The more strongly redshifted bands are likely to belong to mixed aggregates containing at least two methanol molecules.

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A mixed dimer with an O–H···N hydrogen bond (*mi*) involves a stronger red-shift for the corresponding stretching vibration than a N–H···O hydrogen bond (*im*) (see Tab. S4<sup>3</sup>). However, this does not fully compensate for the fact that the isolated N–H stretching mode is lower in wavenumber than the O–H stretching mode. The wavenumber sequence  $im < mi$  is thus predicted consistently at all investigated levels. Therefore, the band at  $3439\text{ cm}^{-1}$  can be assigned to dimer *mi*, whereas the weaker band at  $3377\text{ cm}^{-1}$  is ascribed to dimer *im*. MP2/aug-cc-pVDZ calculations suggest the assignment of the two bands at  $3337$  and  $3227\text{ cm}^{-1}$ , which only occur at higher methanol concentration, to the *mmi* structure shown in Fig. S1.<sup>3</sup> Bands due to free O–H or N–H stretching modes in the dimers are too weak to be observed in our spectra due to the dominance of monomer absorptions.

Altogether, both mixed dimers are probably observed in the free jet expansion. Under full kinetic control, the peaks of the two dimers should have similar intensities. Comparison of calculated and observed band intensities (see Fig. 1) suggests that the dimer containing an O–H···N hydrogen bond is more stable than the one with a N–H···O interaction. This is supported by quantum chemical calculations on the MP2/aug-cc-pVTZ level which predict a  $2\text{ kJ mol}^{-1}$  higher binding energy for the O–H···N connection. As shown in Table S2,<sup>3</sup> even the sign of this energy difference is basis set dependent.

Jet FTIR spectra of imidazole-water coexpansions were recorded under similar conditions as with methanol, only changing the solvent temperature to  $2^\circ\text{C}$ , still avoiding a significant water dimer signal (see Fig. S3 (Ref. 3)). Figure 1(b) shows the jet FTIR coexpansion spectrum before and after subtraction of the pure *i* spectra. Three bands assignable to N–H or O–H stretching vibrations of mixed imidazole-water clusters at  $3458$ ,  $3334$ , and  $3280\text{ cm}^{-1}$  can be observed. Comparison with the methanol coexpansion results and quantum chemical calculations (Figs. 1(b) and 2 and Table S4 (Ref. 3)) suggests an assignment of the intense band at  $3458\text{ cm}^{-1}$  to a mixed dimer structure with water as the hydrogen bond donor (*wi*). This is in good agreement with vibrational data in helium nanodroplet experiments,<sup>10</sup> where the band assignment could be carried out unequivocally via vibrational transition moment analysis and isotope substitution. Due to a helium solvent shift in the nanodroplets the observed band position at  $3448\text{ cm}^{-1}$  has to be corrected<sup>16</sup> by about  $+10\text{ cm}^{-1}$ , leading to a perfect match with our isolated mixed dimer band position. Comparison with the nanodroplet experiments<sup>10,16</sup> further shows that we do not observe the *iw* dimer which should have an intense band around  $(3412+5)\text{ cm}^{-1}$ . Postulating that the *iw* dimer overlaps with the *wi* dimer band would require a helium droplet red shift of at least  $40\text{ cm}^{-1}$ . This is unreasonably large, even allowing for the *wi* dimer band width of  $\approx 7\text{ cm}^{-1}$ . It would contradict the experience of more than a decade of He droplet spectroscopy.<sup>16</sup> Nevertheless, we provide independent free jet evidence for the absence of *iw* based on isotope substitution.  $^{16}\text{O}/^{18}\text{O}$  substitution is predicted to shift the O–H stretch absorption of *wi* by about  $-10\text{ cm}^{-1}$ , whereas it leaves the *iw* N–H stretching band unaffected. As shown in Fig. 1,  $\text{H}_2^{18}\text{O}$  shifts the band by  $-8\text{ cm}^{-1}$  without any residue at  $3458\text{ cm}^{-1}$ . This proves that only *wi*, and no *iw* dimer is present.

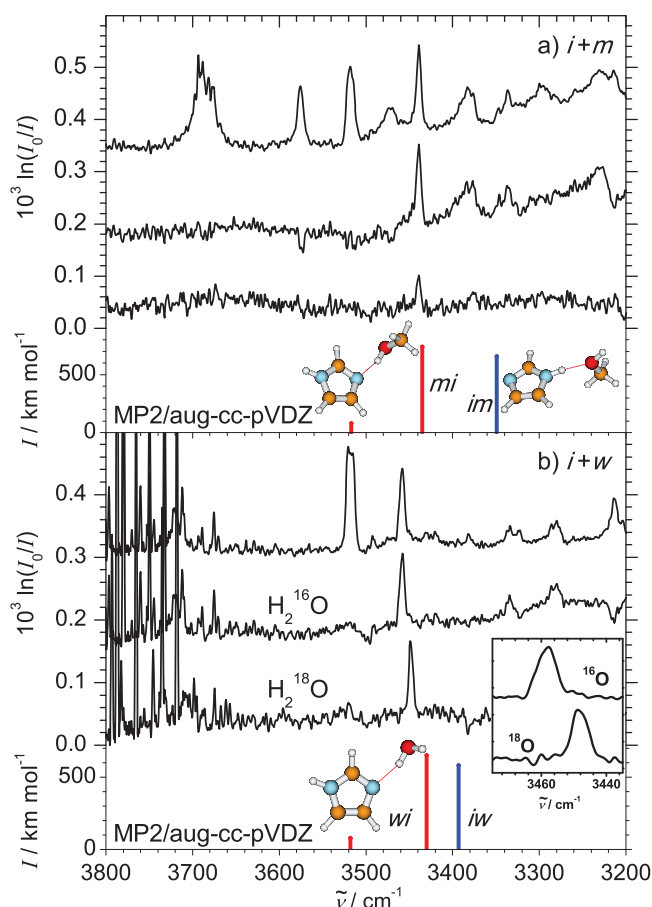


FIG. 1. Original and difference spectra of imidazole solvent coexpansions and corresponding harmonic stick spectra at the MP2/aug-cc-pVDZ level. (a) imidazole ( $\theta = 110^\circ\text{C}$ ) and methanol ( $\vartheta = -28^\circ\text{C}$ ); upper trace: original spectrum, middle trace: after subtraction of pure imidazole and methanol spectra, bottom trace: difference spectrum with lower methanol concentration, (b) imidazole ( $\theta = 100\text{--}110^\circ\text{C}$ ) and water ( $\vartheta = 2^\circ\text{C}$ ); upper trace: original spectrum, middle trace: after subtraction of pure imidazole spectra, bottom trace: difference spectrum using  $^{18}\text{O}$  isotopically labelled water. Calculated wavenumbers are shifted by  $-144\text{ cm}^{-1}$  to match the experimental N–H stretching vibration of the imidazole monomer. Red bars: *mi*, *wi*, O–H stretch, and weak N–H stretch; blue bars: *im*, *iw*, N–H stretch. The first letter in the dimer notation refers to the donor and the second to the acceptor molecule.

Clearly, free jet expansions lead to O–H···N binding but no N–H···O hydrogen bonded dimers when the influence of entropy is ruled out by low temperature. This is remarkable since both forms appear in an  $\sim 1 : 1$  ratio in low temperature helium nanodroplet<sup>10</sup> and matrix isolation<sup>8</sup> setups. However, these results are influenced by strong kinetic control and matrix effects, respectively. Although some degree of kinetic control may occur in supersonic jet expansions as well, the complete absence of a second dimer peak shows that this is not the case. We postulate that initial N–H bound water is efficiently eliminated by water complexation at the free N, carrying away the binding energy excess.<sup>22</sup> This would be an intermolecular variant of solvent-assisted conformational isomerization,<sup>23</sup> in which the incoming solvent molecule displaces the bonded one, which is identical in composition, but inferior in its binding strength. It is noteworthy that the intermediate *wiw* complex has a much higher energy than the *wwi* isomer, making it less sticky for the second water molecule.

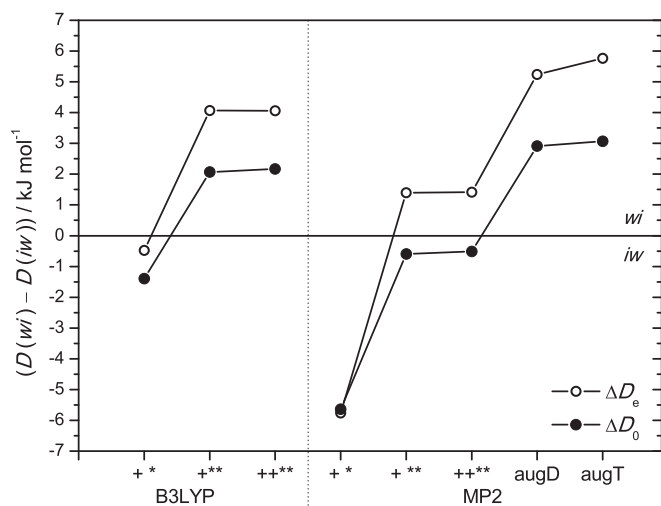


FIG. 2. Basis set dependence of the imidazole hydrogen bond preference towards water in terms of complex dissociation energies  $D_0$  ( $D_e$ ). The Pople 6-311G basis set was augmented by the indicated diffuse and polarization functions, but only the aug-cc-pV(D,T)Z basis sets lead to the correct MP2 prediction.

Such solvent exchange collisions are improbable in cryogenic matrices or solvents, but quite likely in a dense slit jet expansion.

Size-selected experiments with 4-phenyl imidazole<sup>17,18</sup> suggest an opposing strong preference for N-H...O bonded mixed dimers, which is intriguing. Normally, one would expect these experiments to be at least as conclusive for the specific system, but such a dramatic preference switch by the phenyl substitution appears unlikely. We have therefore carried out preliminary FTIR jet measurements on 4-phenyl imidazole, which confirm the presence of the water acceptor complex in the position found by ion dip spectroscopy (3409  $\text{cm}^{-1}$ ). However, it is a minor contribution, and much stronger mixed dimer peaks appear at higher wavenumber, where one would expect the water donor complex. Therefore, it is likely that the double resonance study<sup>17,18</sup> has missed out the electronic transitions of the water donor complex. Our conclusion is that water prefers to act as a hydrogen bond donor towards both imidazole and 4-phenyl imidazole.

Figure 2 and Table S3 (Ref. 3) underline how uncertain the theoretical isomer preference is, when standard Pople basis sets are employed.<sup>7-11</sup> Using correlation consistent basis sets, the prediction becomes robust already at the double-zeta level. It is fully in line with our experimental finding of an enhanced stability for the water donor complex and is confirmed by coupled cluster corrections including single, double and perturbative triple excitations (see Tab. S3 (Ref. 3)). The donor preference of water in the mixed complex appears to exceed the donor preference of methanol. Zero point energy corrections are sizeable and change with the inclusion of anharmonicity because the solvent molecule is bound in a floppy manner. Therefore, the present experiments together with the previous investigations in He droplets<sup>10</sup> and molecular beams<sup>9</sup> are crucial in determining the preference.

How does the dominant interaction in mixed imidazole-water dimers in the gas phase compare to the condensed

phase? For an imidazole molecule embedded in liquid water at room temperature, the acid-base preference is clear. Imidazole is known to be a much better base ( $\text{p}K_a(\text{iH}^+) = 6.95$ ) than acid ( $\text{p}K_a(\text{i}) = 14.20$ ) (Ref. 24) towards water. Our work shows that this strong free energy preference on the order of 40  $\text{kJ mol}^{-1}$  develops from a rather subtle hydrogen bond strength imbalance towards the first water molecule in the gas phase on the order of 4  $\text{kJ mol}^{-1}$ , presumably via cooperative effects. Because the methanol case is less pronounced, it is conceivable that higher alcohols can switch the preference to a hydrogen bond donating imidazole.<sup>25</sup>

For vibrational analysis, harmonic MP2/aug-cc-pVDZ calculations provide satisfactory results and also predict the higher stability of *mi* and *wi* compared to *im* and *iw*. The resulting complexes model the first step in the serine protease mechanism,<sup>26</sup> namely, activation of an O-H bond by histidine, in a most elementary way. Our spectroscopic results thus supply important energy sequence benchmarks for the testing and improvement of intermolecular imidazole and histidine force fields.<sup>27</sup>

Imidazole-water turns out to be a clear-cut case where direct absorption spectroscopy in a free jet provides thermodynamic control, whereas matrix and helium droplet isolation offer kinetic control, and phenyl substitution to enable UV/IR double resonance may lead to an incomplete picture.

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<sup>3</sup>See supplementary material at <http://dx.doi.org/10.1063/1.3624841> for cluster structures, original spectra, quantum chemical calculations, and details on chemicals.

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