Hydrogen Bond between Water and the Phenyl Ring in the Structure of a Dipeptide H–Phe–Leu–NH_2 at 90 K and the Structure-based Energy Estimations

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A water molecule forms a hydrogen bond with the aromatic π-electron system within the crystal structure of H–Phe–Leu–NH_2 hydrochloride monosolvate. This water molecule located above the phenyl ring plane, 3.119 Å from the centroid of the ring. Ab initio energy calculations revealed the stabilization energy of the phenyl ring–water hydrogen bond to be 3.26 kcal/mol.

A good deal of circumstantial evidence gathered by using a variety of techniques supports the idea that benzene–water hydrogen bonds should be important molecular interactions with biomolecules.[1] For instance, signs of benzene–water interactions that are consistent with the theoretical in-plane hydration of benzene suggested by ab initio calculations[2] have been observed in ^1H NMR analyses of benzene–water emulsions.[3] Interactions between benzene and water have also been demonstrated using modern infrared spectroscopic techniques.[4] Analysis of the infrared spectrum of benzene–water complexes using the matrix isolation method showed hydrogen bonds between the aromatic π-electron systems and water molecules.[5] In that regard, ground state microwave spectra of jet-cooled benzene–water showed the center-of-mass distance from the water oxygen to the benzene to be 3.32 Å which is similar to the obtained distance with a Gaussian 90-based simulation.[6]

Still, when the existence of benzene–water interactions was surveyed in protein structures using an electrostatic model in which phenylalanine dipeptides served as probes,[7] structures pointing the possibility of their existence were detected, but none could be definitively identified. We think that negative finding is related to the relatively low resolution of the protein structures studied and does not reflect the true importance of benzene–water hydrogen bonds in biological systems.[1] Indeed, the evidences were found in the high resolution X-ray analyses of cycloamanide A,[8] Na_4[calix[4]arene sulfonate][9] and a tripeptide, H–Tyr–Tyr–Phe–OH.[10] By obtaining high-resolution data at low temperature, we were able to clearly define a hydrogen bond between a water molecule and the phenyl ring within the dipeptide H–Phe–Leu–$NH_2 \cdot HCl \cdot H_2O$[11] and its Hartree–Fock energy was estimated from the crystal structure.

The crystal structure of the dipeptide is shown in Figure 1; note the solvated water molecule located above the phenyl ring of the Phe residue. The distance between the water oxygen atom (O1W) and the centroid of the phenyl ring (C_{ph}) is 3.119 Å, which is slightly less than the distances observed in the previous peptide structures (3.26–3.28 Å)[8,10] and rather close to the theoretically predicted distance (3.195 Å).[6] The water hydrogen atoms (H1 and H2) were experimentally determined and refined for the diffraction data measured at 90 K; the geometry was as follows: O1W–H1 = 0.88(3) Å, O1W–H2 = 0.83(4) Å, and $\angle$H1–O1W–H2 = 110(3)°. The O1W–H2 bond was oriented toward the phenyl ring, but was not perpendicular to it. In most spectrum analyses of the benzene–water hydrogen bond, there has been the presumption that the O–H bond is perpendicular to the phenyl ring;[4] however, when the rotation of the water molecule was accounted for in a Gaussian 90-based simulation, the minimum energy was observed when the $\angle C_{ph} \cdots H–O = 135°$,[6] which roughly agrees with the present structure (133.5°). Moreover, our structure is also consistent with those of the previous structures (127–143°), in which an imbedded water molecule interacts with the phenyl rings via O–H bonds that are similarly tilted toward the ring planes.[8–10]

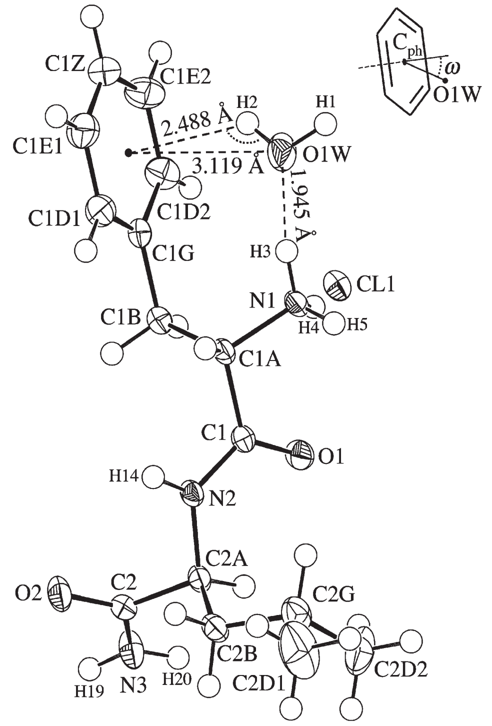

Figure 1. Crystal structure of H–Phe–Leu–$NH_2 \cdot HCl \cdot H_2O$ with the displacement ellipsoids at the 80% probability level. Dotted lines represent the interactions related to the water molecule. An inserted diagram represents the angle ω between the water molecule and the axis perpendicular to C_{ph}.

In earlier theoretical simulations, the position of the water oxygen atom was presumed to be right above the centroid of the benzene ring.[2] In the present structure, the position of O1W was shifted slightly toward C1G from the axis perpendicular to the centroid. The distance from O1W to the least-square plane of the phenyl ring is 3.103(1) Å and the ω angle (Figure 1) is approximately 5.8°. This positional shift appears to be related to the rotation of the water molecule and was also affected by a hydrogen bond with the *N*-terminal cation (N1) (Table 1). O1W was also hydrogen-bonded to the chloride anion (CL1), and it is this connection that mediates the electronstatic interaction between the ions.

Table 1. Geometry of the hydrogen bonds

D	H	A	D···A	H···A	∠D-H···A
O1W	H1	CL1[a]	3.188(1)	2.343	160.9
N1	H3	O1W	2.816(2)	1.945	159.5
N1	H4	CL1	3.270(1)	2.383	164.9
N1	H5	CL1[b]	3.229(1)	2.357	160.4
N1	H5	O1[b]	2.686(2)	2.402	98.2
N2	H14	O2[c]	2.919(2)	2.048	169.9
N3	H19	O2[d]	2.915(2)	2.094	154.9
N3	H20	CL1[e]	3.288(1)	2.440	161.9

Symmetry code: [a] *x*, *y*-1, *z*, [b] 1-*x*, *y*-1/2, 2-*z*, [c] 2-*x*, *y*-1/2, 2-*z*, [d] 2-*x*, *y*+1/2, 2-*z*, [e] 1-*x*, *y*+1/2, 2-*z*.

When the total electron density of the asymmetric content was calculated using the semi-empirical AM1 method implemented in MOPAC 97,[12] the electron cloud of the water molecule was found to extend to the *N*-terminal cloud as well as to the π-electron cloud of the phenyl ring (Figure 2a). To estimate the contribution made by the electron bridge between the water molecule and the phenyl ring, we constructed a model in which the position of the water oxygen was unchanged, but the molecule was rotated so that the H–O–H plane was parallel to the phenyl ring (Figure 2b). In this configuration, the electron cloud of the water molecule still extended to the *N*-terminal cloud, but there was no longer an electron bridge between the phenyl ring and the water molecule at the 0.003 a.u. level.

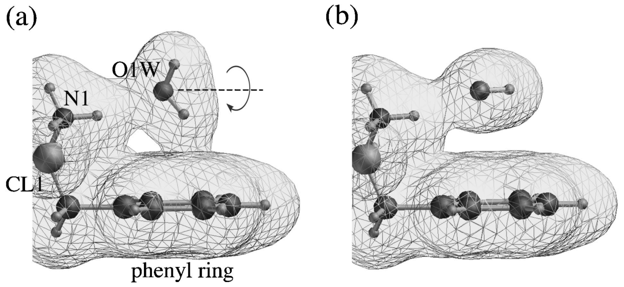

Figure 2. Total electron densities of the (a) crystal and (b) model structures. Contours are drawn at the isocharge 0.003 a.u. level and overlapped on the peptide structure. In the model structure, the water molecule is rotated 90° so that the H–O–H plane is parallel to the ring, but the position of water oxygen atom is unchanged. The axis of rotation is shown as a dotted line.

We then used 6-31++G(d,p) basis sets with Gaussian 98[13] to carry out ab initio Hartree–Fock calculations for both the crystal and model structures to estimate the molecular orbital energy with no optimization of their nuclear positions, the energy difference between the structures (ΔE_{UHF}) was -5.2×10^{-3} hartrees or -3.26 kcal/mol, which is roughly consistent with earlier ab initio calculations reporting stabilization energies of -2.0–-3.8 kcal/mol for benzene–water interactions.[2] Our calculations also show that the difference between the charges of H1 and H2 is less than 0.02 e, indicating that the electron bridge was not caused by the charge localization of the water hydrogens. These molecular orbital simulations thus characterize a hydrogen bond between the phenyl ring of dipeptide and water molecule.

References and Notes

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11 Crystal and experimental data: $C_{15}H_{23}N_3O_2{\cdot}HCl{\cdot}H_2O$, $M = 331.84$, monoclinic, $P2_1$, $a = 11.5471(8)$, $b = 6.9111(5)$, $c = 11.7510(8)$ Å, $\beta = 95.366(1)°$, $V = 933.66(11)$ Å^3, $Z = 2$, $D_x = 1.180\,\mathrm{g\,cm^{-3}}$, $F(000) = 356$, $\mu(\mathrm{Mo}\ K\alpha) = 0.219\,\mathrm{mm^{-1}}$. The data were collected on a Bruker AXS, SMART APEX area detector using graphite-monochromated Mo $K\alpha$ radiation at 90 K. A total of 8470 reflections were measured up to $\theta_{\max} = 28.27°$ (0.75 Å resolution) and merged to 4183 reflections with $R_{\mathrm{int}} = 0.0161$. The structure was solved using SHELXS-97 and refined with SHELXL-97. The water hydrogen atoms were found using a differential Fourier map and included in the refinements. The remaining hydrogen atoms of the peptide were calculated at ideal positions. The structure was converged at goodness of fit = 0.559, Flack parameter = 0.03(4), $(\Delta/\sigma)_{\max} = 0.001$, $\Delta\rho_{\max} = 0.303\,\mathrm{e\,Å^{-3}}$, $\Delta\rho_{\min} = -0.181\,\mathrm{e\,Å^{-3}}$, $R = 0.0299$ and $wR = 0.0796$.

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