Proton Affinities of Some Amino Acid Side Chains in a Restricted Environment

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Estimation of proton affinities of amino acid sidechains in finite water clusters

In order to understand the variation of proton affinity in a restricted and fully polar environment, we investigated the dependence of proton affinity values of the side chains of amino acids on confinement in finite water clusters in the gas phase. The proton affinity values of Asp, Glu, Ser, Thr and His are calculated when each of these amino acids is present as a part of a finite water cluster whereby the effect of adding an additional proton to the side chain is probed.

I.   MODEL

We present here of a model of the amino acid side chain in a finite water cluster. A truncated representation of the amino acids is used in this model similar to the one used in recent *ab initio* calculations of energy barriers of proton transfer between amino acid side chain analogs and water molecules [1]. The side chain is shown as $CH_3 - R$ surrounded by a cluster of water molecules in the gas phase.

In order to prepare the finite amino acid-water cluster, we use results of classical constant temperature- constant pressure molecular dynamics (NPT-MD) [2] simulation of the chosen amino acid in water obtained using the parameters of CHARMM force field [3] and the
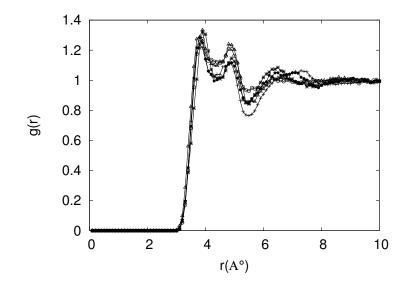
FIG. 1: Radial distribution function, $g_{C-O}(r)$ of Asp (open circle), Glu (solid pentagon), His (+), Ser (triangle) and Thr (*) in water obtained from NPT-MD simulation at 300 K and 1 atm pressure. The radial distance r (in Å) refers to the distance between O atom of water and the C_α atom of the respective amino acid.

simulation package NAMD [4]. Depending on the availability of force field parameters, we have simulated Asp, Glu and His with unprotonated side chains while Ser and Thr were modeled using their protonated side chains. In each simulation, we have used 1296 water molecules to solvate the amino acid at 300 K and 1 atm pressure. The average number of solvent molecules in the solvation shells is then computed from the radial distribution function $g_{C-O}(r)$ as

$$\bar{N} = \rho \int_0^{R_M} dr \ 4\pi r^2 g_{C-O}(r) \tag{1}$$

where ρ is the solvent density and the radial distance r is measured between the C_α-atom of the amino acid and the O-atom of water. The upper limit of integration, R_M is chosen to be the radial distance at which the first minimum appears beyond the first peak of $g_{C-O}(r)$. R_M may correspond to the second or third minimum if a larger water clusters are needed. We then construct the cluster of amino acid and water molecules by the following method. First, the equilibrated trajectories are sampled at a regular interval and the coordinates of the solute amino acid and water molecules within the first solvation shell are collected if

the number of such water molecules are found to be equal to $\bar{N}$. The sets thus collected are further refined by choosing only those characterized by a maximum number of water molecules (N_w) hydrogen bonded to the solute. The water cluster is then constructed by truncating the solute-solvent system at $r = R_M$.

This is followed by a geometry optimization of the solute-solvent cluster using BLYP/dnp basis set [5, 6] method. Once the optimized structure is obtained, single point and zero point energies are calculated using the same method.

It should be noted that the classical simulation methods provide us with a reasonable initial guess of a stable cluster surrounding the amino acid side chain. In those cases, where force field parameters were not available (such as the unprotonated form of Ser and Thr), we have used as input the cluster generated as above as the initial guess by removing the side chain proton and subjecting it to geometry optimization using conjugate energy gradient approaches in *Dmol3* [7].

For the calculation of ΔH_2, the protonated and unprotonated amino acids in their respective optimized clusters were replaced by H_3O^+ and H_2O respectively and the number of surrounding water molecules were kept unchanged. Optmization followed by energy calculation using BLYP/dnp [5, 6] method estimates ΔH_2. All geometry optimizations, energy and frequency calculations were carried out using the software package *Dmol3* [7].

II. RESULTS AND CONCLUSION

The radial distribution function, $g_{C-O}(r)$ obtained from the NPT-MD simulation is shown in Fig. 1 for the five amino acids under investigation. The upper limit of the first solvation shell, R_M was found to be equal to 5.46 Å (Asp), 6.0 Å (Glu), 5.5 Å (His), 5.4 Å (Ser) and 5.5 Å (Thr).

Typical optimized water clusters formed around histidine, with and without an excess proton on its side chain, are shown in Fig. 2.
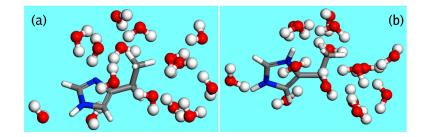
FIG. 2: The cluster constituted by 14 water molecules around histidine with its truncated side chain in (a) unprotonated and (b) protonated forms

TABLE I: Proton affinity (PA) values of Asp, Glu, His, Ser and Thr side chains as part of a finite water cluster in the gas phase. The values are estimated using the BLYP/dnp method for the calculation of ground state electronic and zero point vibrational energies.

System		$-\Delta H_1$	$-\Delta H_2$	PA
		$(kcal\ mol^{-1})$	$(kcal\ mol^{-1})$	$(kcal\ mol^{-1})$
	Asp (17w)	305.19	224.91	80.29
Cluster	Glu (17w)	261.49	224.91	36.58
	His (14w)	154.79	213.67	-58.88
	Ser (17w)	292.68	224.91	67.77
	Thr (17w)	284.20	224.91	59.29

The calculated enthalpies of protonation and overall proton affinity of the five amino acid side chains in finite water clusters with methyl terminated backbones are summarized in Table I. Interestingly, His fails to show any positive proton affinity in the cluster while all other side chains show positive proton affinity values. The results shown for different sizes of the water clusters are those typically obtained from our model construction. The data presented here gives us an idea about how a given side chain may behave in the limiting case of confinement in a finite polar environment and would therefore be useful as the asymptotic limit of possible proton affinity values in the gas phase. However, detection of long-lived water clusters hydrogen bonded to an amino acid side chain having 15 or more water molecules is difficult as such clusters may form only transiently. In those rare cases, these estimates would give us an idea to what extend the proton affinity values may be modified.

4

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