Supplementary Information

Unraveling the Structural and Chemical Features of Biological Short Hydrogen Bonds

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1. Computational methods

We chose 101 SHBs and calculated their proton potential energy surfaces using the B3LYP-D3 method[1,2] and the 6-31+G(d), 6-31+G(d,p) and aug-cc-pVDZ basis sets. We then used the equilibrium proton position, v_{eq}, and the barrier for proton sharing, $\Delta E_{v=0}$ to characterize the resulting potential surfaces. These properties are plotted as a function of R in Fig. S1.

The proton potential energy surfaces in the biological SHBs can be divided into three types: single-well potential (SWP), double-well potential (SWP) and SWP with a shoulder. SWP and DWP have one and two minima in the potential energy curves, respectively. If an energy surface has a single minimum and when $\nu > 0$, the energy increase within one scan step ($\Delta\nu$ ~ 0.1 Å) is smaller than 10% of $\Delta E_{\nu=0}$, we call it a SWP with a shoulder. The relative population of the three types at a given R is shown in Fig. S2.

When defining a hybrid hydrogen bond network, we require the network to contain at least one SHB with $2.3\ \text{Å} \leq R \leq 2.7\ \text{Å}$. The rest of the network can be a SHB or a regular hydrogen bond with $2.7\ \text{Å} < R \leq 3.0\ \text{Å}$. For both SHBs and regular hydrogen bonds, the donor and acceptor atoms are N or O, and the Donor-H-Acceptor angle is larger than or equal to 135°.

2. SI figures

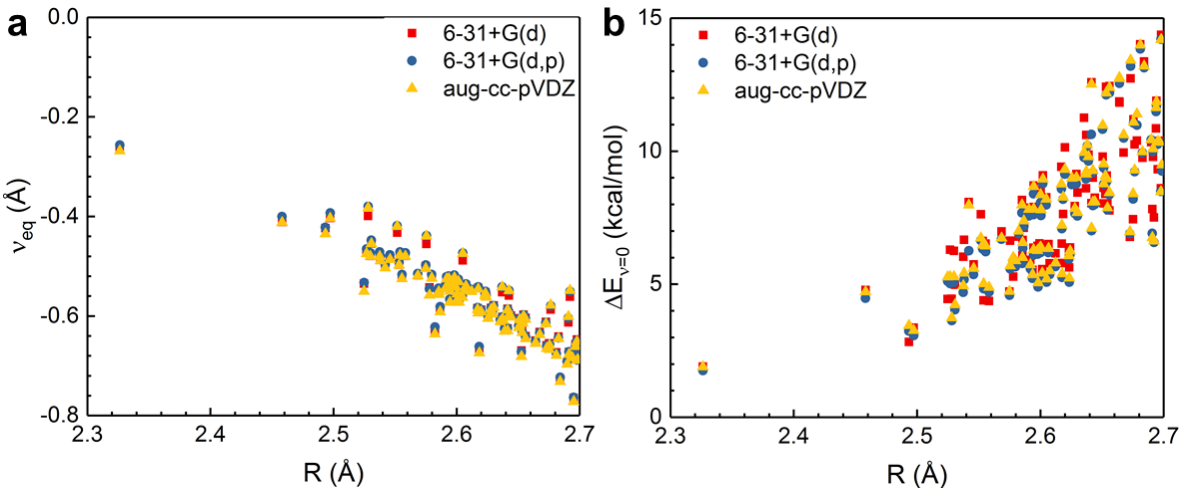

Fig. S1. Properties of the potential energy surfaces predicted using the B3LYP-D3 method and the 6-31+G(d), 6-31+G(d,p) and aug-cc-pVDZ basis sets: (a) v_{eq} and (b) $\Delta E_{v=0}$ as a function of R.

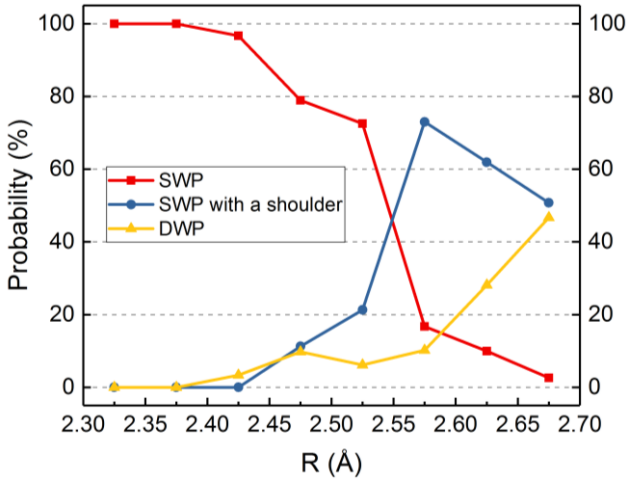

Fig. S2. Probability of different shapes of the potential energy surfaces from analyzing 3665 side chain-side chain short hydrogen bonds. The three types are single-well potential (SWP), single-well potential with a shoulder (SWP with a shoulder) and double-well potential (DWP).

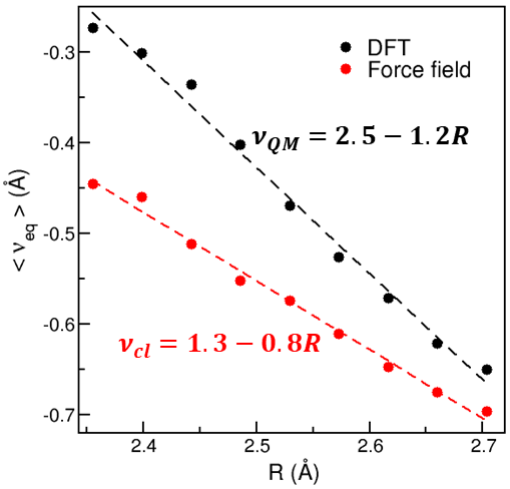

Fig. S3. Average ν_{eq} for each R, calculated from DFT methods (ν_{QM}) and the Amber14SB force field (ν_{cl}). The dotted lines are linear fitting of the data.

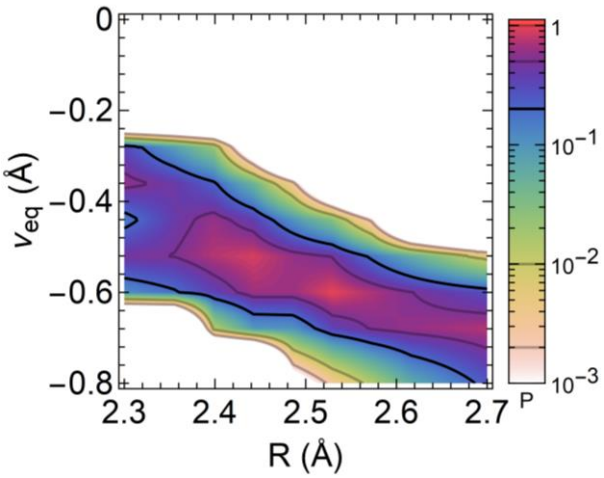

Fig. S4. Conditional probability $P_{cp}(R, v_{eq})$ calculated from geometry optimization using the Amber14SB force field. The probability at each point is normalized by the maximum value.

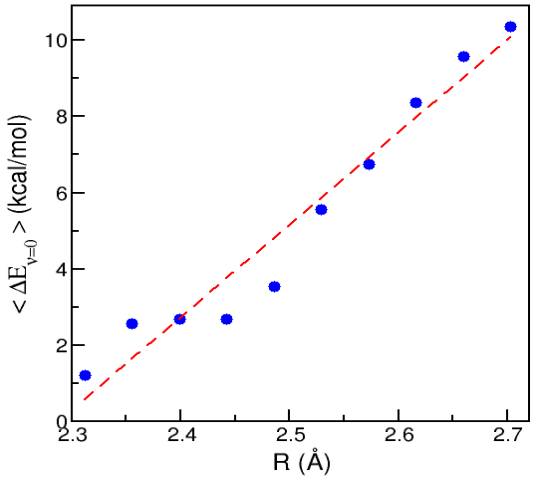

Fig. S5 Average $\Delta E_{v=0}$ for each R, obtained from DFT calculations on the side chain-side chain hydrogen bonds. The dotted line is a linear fitting of the data.

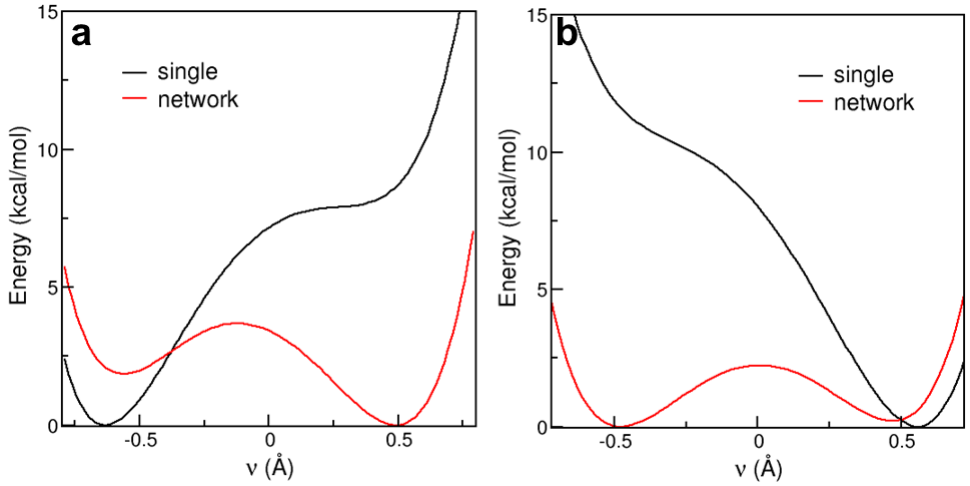

Fig. S6. Example proton potential surfaces of SHBs when they are treated as single hydrogen bonds or in hydrogen bond networks. (a) Potential energy surface for the hydrogen bonded trimer Glu575-Lys366-Gln372, obtained from electronic structure calculations of a pyruvate oxidase (PDB ID 4FEG).[3] The hydrogen bond formed from Glu575 and Lys366 is a SHB with R of 2.69 Å, and ν is calculated as $d_{GluH} - d_{LysH}$. (b) Potential energy surface for the hydrogen bonded trimer Glu128-Tyr195-His310 in a methionine aminopeptidase (PDB ID 2B3H).[4] The hydrogen bond between Glu128 and Tyr195 is a SHB with R of 2.58 Å, and ν is calculated as $d_{GluH} - d_{TyrH}$.

3. References

(1) A. D. Becke, *J. Chem. Phys.*, 1993, **98**, 5648.
(2) S. Grimme, J. Antony, S. Ehrlich and H. Krieg, *J. Chem. Phys.*, 2010, **132**, 154104.
(3) D. Meyer, P. Neumann, E. Koers, H. Sjuts, S. Lüdtke, G. M. Sheldrick, R. Ficner and K. Tittmann, *Proc. Natl. Acad. Sci. USA*, 2012, **109**, 10867-10872.
(4) A. Addlagatta, X. Hu, J. O. Liu and B. W. Matthews, *Biochemistry*, 2005, **44**, 14741-14749.