Symmetry and ^1H NMR Chemical Shifts of Short Hydrogen Bonds

Shengmin Zhou and Lu Wang

Contact: lwang@chem.rutgers.edu

Department of Chemistry and Chemical Biology, Rutgers University

Introduction

Short hydrogen bonds (SHBs) have the donor and acceptor separations below 2.7 Å, and are observed extensively in small molecules and proteins. For example, we have statistically analyzed 1504 high-resolution structures of proteins, protein-ligand complexes and nucleic acids from the PDB and showed that each biomolecule contains an average of 11 SHBs, with functional implications ranging from enzyme catalysis to cellular signal transduction.¹

Due to their compact structures, SHBs exhibit prominent covalent characters with elongated Donor-H bond and far downfield ^1H NMR chemical shifts. To examine their common features, we carry out first principles simulations on a series of model compounds and elucidate how the interplay of electronic and nuclear quantum effects determines the symmetry and chemical shifts of SHBs.²

First Principles Simulations of Model Molecules

- Systems: 4 model molecules with intramolecular SHBs in organic solvents and aqueous solutions
- *Ab initio* molecular dynamics (AIMD) simulations allow chemical bonds to dynamically form and break.
- *Ab initio* path integral molecular dynamics (AI-PIMD) simulations incorporate the quantum mechanical nature of both the electrons and nuclei.
- BLYP density functional, D3 dispersion correction, GTH pseudopotential, DZVP-GTH plane-wave basis set
- CP2K package³ and i-PI software⁴

Symmetry of the Intramolecular SHBs

- Electronic quantum effects promote proton sharing when R shortens.
- Nuclear quantum effects significantly enhance the symmetry of the SHBs.

- Mismatch of the Donor and Acceptor proton affinity leads to asymmetry of the SHBs.
- Polar solvents can induce transient pK_a mismatch.

^1H NMR Chemical Shifts of the SHBs

- 6012 solute-solvent clusters from the AIMD and AI-PIMD simulations of the model molecules
- Chemical shifts calculated using the B3LYP functional, D3 dispersion correction and the 6-31+G(d,p) basis set
- Decompose the average ^1H NMR chemical shifts:

$$\langle \delta_H \rangle = \int_{-\infty}^{\infty} \delta_H(v) P(v) dv$$

- v is a natural coordinate to represent the electronic state of a hydrogen bond.⁵
- As v approaches 0, δ_H goes up to 22 ppm.
- Universal relation:

$$\delta_H(v) = 21.9 - 16.1v^2$$

^1H NMR Chemical Shifts of the SHBs

- Decompose the isotropic magnetic shielding constant:
 $S_H = S_{N_1H} + S_{N_2H} - S_{HB} = S_{Covalent} - S_{HB}$
- Competition between covalent and hydrogen bonding.

- As $\delta_H(v)$ follows a universal trend, the average ^1H NMR chemical shift is determined by the symmetry of the SHBs.
- Assuming $P(v)$ can be written as a linear combination of two Gaussian functions, the average chemical shift:
 $\langle \delta_H \rangle = 20.5 - 16.1v_0^2$
- Predictions agree very well with the experimental chemical shift or proton position of a SHB.

References

- (1) S. Zhou and L. Wang, *Chem. Sci.*, **10**, 7734 (2019)
- (2) S. Zhou and L. Wang, *Phys. Chem. Chem. Phys.*, **22**, 4884 (2020)
- (3) J. VandeVondele et al., *Comp. Phys. Comm.*, **167**, 103 (2005)
- (4) V. Kapil et al., *Comput. Phys. Commun.*, **236**, 214 (2019)
- (5) M. Ceriotti, J. Cuny, M. Parrinello and D. E. Manolopoulos, *PNAS*, **110**, 15591 (2013)
- (6) R. K. Harris et al., *J. Chem. Soc., Faraday Trans. 1*, **84**, 3649 (1988)
- (7) T. Emmler et al., *J. Mol. Struct.*, **700**, 29 (2004)
- (8) H.-H. Limbach et al., *Isr. J. Chem.*, **49**, 199 (2009)