

The Importance of Properly Modeling the Hydrogen Bond in Histidine

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Abstract

The hydrogen bond plays a vital role in many reactions. This study is to investigate the effect of different hydrogen bonding modes, such as single and double hydrogen bonds, via the quantum mechanic (QM) methods. Four histidine models (A, B, C, and D) with different numbers of intra-molecular hydrogen bonds were studied. The QM model results indicate that the double hydrogen bond is plausible and has a more stable geometry. However, this study suggests that the data from QM methods require further evaluation with solvation models to produce an even better energy profile.

Keywords: hydrogen bond, density functional theory, basis set, electronic structure

Introduction

Hydrogen bonds determine the molecule structure of many proteins and are required for proper function. Tuck introduced the hydrogen bond in 1968 (Emsley, 1980), and since then, it has been investigated by scientists around the world. Its importance is very significant in the fields of physics, chemistry, and biology. The hydrogen bond plays a vital role in protein folding, water molecule interaction, solution structure, nucleic acid base pairing,

etc. (Parthasarathi, Subramanian, & Sathyamurthy, 2006). Also, one of its primary roles is in molecular recognition and chemical and enzymatic reactions (Tamura, Tamura, Takeda, Nakagawa, & Tomishige, 2014).

Intra- or inter-molecular hydrogen bonding is a noncovalent interaction between two different atoms ($X-H \cdots Y$) within the same molecule or between two different molecules. One of the atoms is a proton donor ($X-H$), and the other one is a proton acceptor (Y). As for the proton donor, hydrogen has to be bonded to an electronegative atom (nitrogen [N], oxygen [O] or fluorine [F]). The proton acceptor can be any electronegative atom or a region of the electron. Moreover, within a molecule, it is possible to form a single or double hydrogen bond, which could produce different chiral (Jiang & Fang, 2016) and optical properties (Breuer et al., 2004).

With the ever-increasing power of computer hardware and the complexity of the software, more scientific problems can be modeled and solved. Gaussian 09 (G09) is a quantum mechanics (QM) modeling software (Revision C.01 2010, Gaussian Inc.). We investigated the ability of the different density functional theory (DFT) to use the functional and basis sets implemented in the G09 software package to reasonably reproduce the final geometric and electronic structure of a hydrogen bond. This investigation compared the electronic and geometric structures with the known experimental results. With the emerging DFT functionals, the modeling can provide better guidance and more accurately predict the electronic properties of novel molecules. This work will test the new DFT functionals and compare with the widely used DFT functionals; the results can determine the effectiveness of the new DFT functionals in hydrogen bond modeling. The amino acid's skeletal structure enables the formation of peptide bonds through the C-terminus ($-COOH$ group) and N-terminus ($-NH_2$ group). Complex and rich protein structures arise from the different side chains of twenty amino acids in the human body. Because of the

proximate of C-terminus and N-terminus, neutral amino acids can take on a unique form called a *zwitterion*, also known as inner salt or dipolar ion. This is an ion with a positive and negative electrical charge at different locations within a molecule. The various protonation states of amino acids can provide different inter- and intra-hydrogen bonding. Therefore, the histidine amino acid is used as a model for this study.

General Modeling Procedures

The G09 modeling software arranges valence electron in the molecule. However, because of their speed, electrons are invisible to the human eye; that is why electronic structures are difficult to understand and too abstract for many students. In QM, the fundamental Schrödinger equation, coupled with the Born–Oppenheimer approximation provides a reasonable mathematic solution to understand the electronic movement and electronic structure of interactions in various materials. Based on a QM solution to the Schrödinger equation, there is the Pauli Exclusion Principle, the Aufbau Principle, Hund’s Rule, and the Heisenberg’s uncertainty principle or Heisenberg’s indeterminacy principle. All of these principles govern the movement of electrons in matter and can be used in molecular models. Molecular modeling or computational chemistry does have an advantage over the bench work of mixing chemicals, because modeling does not incur physical safety hazards. In this paper, we will use computational chemistry and visualization modeling tools to design optimized molecule forms under various DFT functional and basis sets to illustrate the impact of different DFT models on the structure and property relationship of the hydrogen bond. We will study and compare the difference between the electronic structure and geometry representation.

Methods

To better explore different bindings, we employed the DFT to compare the different functional sets (B3LYP, M062x, PBE1PBE, B3PW91, TPSSPTSS, X3LYP, and ω B97XD). We used solvation modeling to identify the most effective modeling approach. The different functional sets were set up through a Linux server. Before any actual data could be collected, investigators learned how to model and create the different forms of histidine. This was done via a chemistry modeling software, GaussView (Gaussian, Inc.), which was developed for Linux workstations to create different chemical and biological molecules from scratch. With GaussView, an individual can quickly and efficiently construct different molecular systems and molecules from the input file; the output is compatible with the G09 software. This simple graphic user interface program incorporates a variety of user-friendly features, which enables a user to adapt and begin constructing models.

Results and Discussion

Zwitterion Form of Histidine

Because zwitterions form from compounds that contain both acid and base groups (namely ampholytes), the amino acid will have a negatively charged $-\text{COO}^-$ and a positively charged $-\text{NH}_3^+$. Studies have shown that, depending on the pH value of the histidine solution, amino acids can have four forms of different protonation states: A^- , HA , H_2A , and H_3A^+ where “A” here represents the basic framework of histidine and “H” represents the protons from solution that can be added/attached to the base framework (Titration Curve 2019). This variation of protonation states of histidine earned it the name of *polyprotic acid*. At $\text{pH}=8$, histidine will be at its neutral state and can form a zwitterion form as shown in Figure 1.

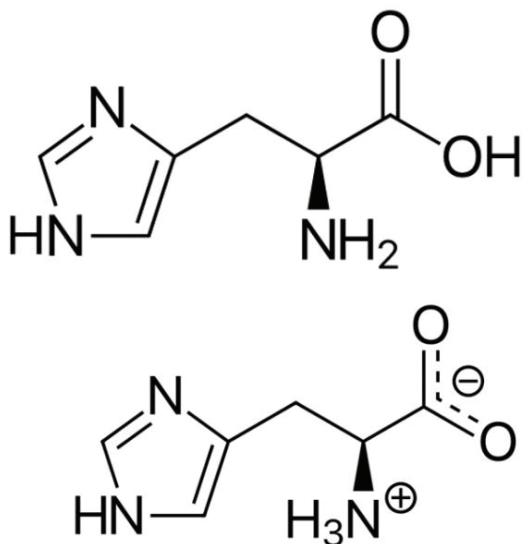


Figure 1. The zwitterion form of neutral histidine

We began our study by modeling the neutral histidine form (HA). We developed models of different hydrogen bond modes including the following: single hydrogen bond mode (models A and B) and double hydrogen bond mode (models C and D).

Single Hydrogen Bond Mode (A & B)

Single hydrogen bonding is when only one intra-hydrogen bond is used. In our case, the obvious hydrogen bond was between the oxygen of the C-terminus and the nitrogen of the N-terminus as shown in Figure 2. Model A creates a single hydrogen bond between N1-H and O2. A hydrogen bond was constructed between N1-H and O2. This hydrogen bond length was measured at 1.17 Å.

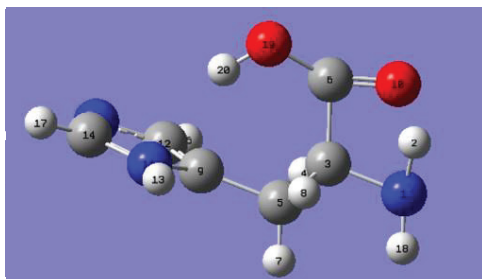


Figure 2. Model A showing the single hydrogen bonding between N1-H and O2. All carbon molecules are dark grey, oxygen molecules are red, hydrogen molecules are white, and nitrogen molecules are blue. The nomenclature is as follows: oxygen 1 (O1, #19); oxygen 2 (O2, #18); carbon 1 (C1, #6); carbon 2 (C2, #3); nitrogen 1 (N1, #1); carbon 3 (C3, #5); carbon 4 (C4, #9); nitrogen 2 (N2, #11); and carbon 5 (C5, #12) is connected to C4 and nitrogen 3 (N3, #16) of the ring. Carbon 6 (C6, #14) is connected to both N2 and N3.

Model B is displayed in Figure 3. A single a hydrogen bond was constructed between N1 and O2-H. This hydrogen bond length was measured at 1.31Å.

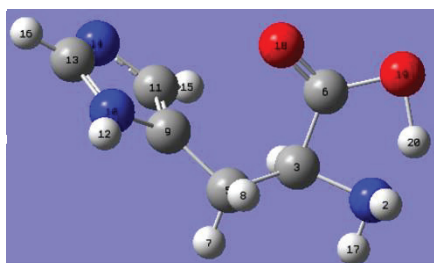


Figure 3. Model B shows the single hydrogen bonding between N1 and O2-H. All carbon molecules are dark grey, oxygen molecules are red, hydrogen molecules are white, and nitrogen molecules are blue. The nomenclature is as follows: oxygen 1 (O1, #19); oxygen 2 (O2, #18); carbon 1 (C1, #6); carbon 2 (C2, #3); nitrogen 1 (N1,

#1); carbon 3 (C3, #5); carbon 4 (C4, #9); nitrogen 2 (N2, #10); carbon 5 (C5, #11); nitrogen 3 (N3, #14); carbon 6 (C6, #13).

It is important to point out that both models A and B were constructed to only have one possible hydrogen bond, because the results of these two models would provide insight as to why models C and D are necessary. In model A, the donor hydrogen atom (#2) was on N-terminus while the donor hydrogen atom (#20) for model B is from C-terminus.

After G09 software was used to optimize model A and model B to their lowest energy forms, model A has only one hydrogen bond, but model B has two hydrogen bonds. Further, the bonds were not constructed in the same places for each model. The Newman Projection was utilized to understand the orientation of the hydrogen bonds better. Model B created two Hydrogen bonds in its lowest energy form. The O₂-H bond is slightly longer in model B (0.9850 Å) than that of model A (0.9678 Å). Since the geometric environments around these hydrogen bonds are different, could it be that the double bond affects the bonding of model B? Or could it be that the O₂ has to retain a hydrogen bonding no matter what? To answer those questions, the third and fourth models (C and D) with two hydrogen bonds were constructed.

Double Hydrogen bonding Model

To create two hydrogen bonds in histidine, one must use the nitrogen atom on the imidazole ring as a hydrogen receptor. As Figure 4 shows model C and has the double hydrogen bond formed between O1 and N2-H, which is 0.2300 Å and another bond between O2 and N1-H, which is 0.1800 Å. Figure 5 shows model D with a double hydrogen bond as well. One of the Hydrogen bonds is between O1-H and N1, which is 0.2497 Å and the Hydrogen bond is between O2 and N2-H, which is 0.3600 Å. Even though the bonds were initially constructed at different places for the two different models, the bond lengths seem to

be close. It is very important to determinate what happens after geometry optimization to see if there is any differences occur.

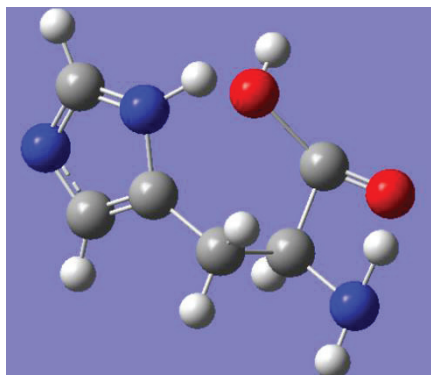


Figure 4. Model C has a double hydrogen bond between O2 and N1-H and O1 and N2-H.

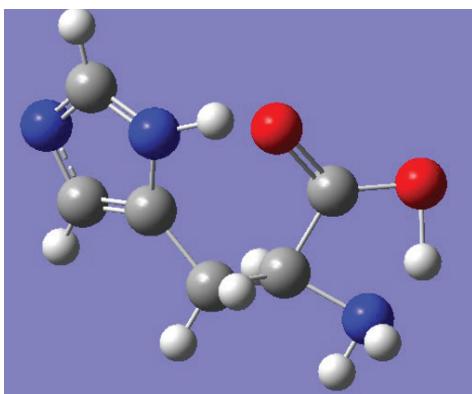


Figure 5. Model D has a double hydrogen bond between O1-H and N1 and O2 and N2-H.

After optimization produced models with the lowest energy forms, the differences can be seen (Figure 6). Even though model C started with a double hydrogen bond, it ends up with only a single hydrogen bond. However, in the model D the double hydrogen bond increased in length, meaning that the molecules

did not get close together but instead retracted from each other while maintaining the hydrogen bond. The model D geometry resembles much of model B. This suggests that regardless of the construction of the initial geometry/conformation, the double hydrogen bond structure formed by models B and D might still be the more stable version.

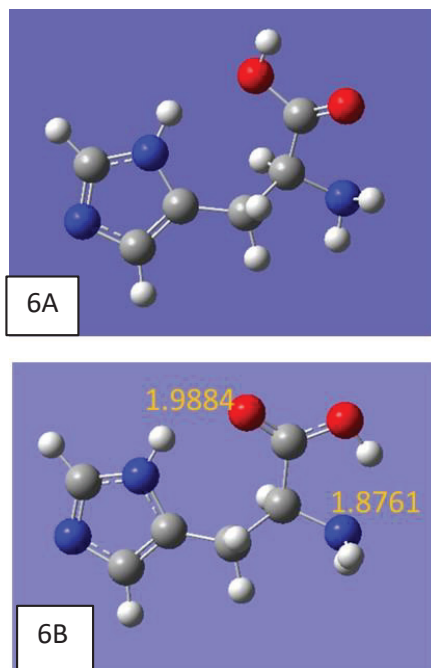


Figure 6. Optimized geometries of double hydrogen bonding in models C (6a) and D (6b)

Conclusions

In this study, we carefully designed four histidine models (A, B, C, and D) that contained different constructions of intra-molecular hydrogen bonds. The QM model results suggest that the double hydrogen bond is plausible and has a more stable geometry. Since the current study did not employ any solvation models such as Polarizable Continuum Model (Tomasi, Mennucci, & Cammi,

2005) or the Solvation Model based on Density (Marenich, Cramer, & Truhlar, 2009), these modeling results do not match published experimental observations where the zwitterion form is the most stable form of amino acid. Furthermore, comparing the bond length differences between each model enable scientist to further understand bonding mechanics and to find the optimized geometry structure.

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