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A Theoretical Charge Density Investigation on Histidine-Histidine Dipeptide in Gas Phase

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Abstract

In the present work, an extensive theoretical calculation study on Histidine-Histidine dipeptide in gas phase is done by using DFT method with Gaussian 98 program. Through investigations on the molecular geometries of this molecule it is found that there is six rings in the molecules not two rings. The presence of four intramolecular hydrogen bonds is responsible for the formation of additional four rings besides two imidazole rings which gives more stability to the molecule. The quantum theory of atoms in molecules (QTAIM) proves these strong intramolecular hydrogen bonds in the title dipeptide.

Keywords: Dipeptides, Histidine, Hydrogen Bonding, DFT, QTAIM.

Introduction

Proteins are essential structural component of living cell. In fact every property that characterizes a living organism is affected by proteins [1]. The keys to realize the function of a given protein is to understand its structure. Proteins and peptides are the polymers of smaller units of amino acids. Two amino acids joined by a peptide bond are called a dipeptide, similarly, when a few amino acids are joined in the same fashion the structure is called oligopeptide. Polypeptides are formed when many amino acids are linked. Peptides are formed by highly controlled polymerization reaction and the polymerization is based on the formation of amino bond, usually called the peptide bond [2-4].

Histidine is one of the 20 most common natural amino acids present in proteins. In the nutritional sense, in humans, histidine is considered as an essential amino acid, but mostly only in children. The imidazole side chains and the relatively neutral pK of histidine mean that relatively small shifts in cellular pH will change its charge. For this reason, this amino acid side chain finds its way into considerable use as a co-ordinating ligand in metalloproteins, and also as a catalytic site in certain enzymes. The imidazole side chain has two nitrogens with different properties: One is bound to hydrogen and donates its lone pair to the aromatic ring and as such is slightly acidic, whereas the other one donates only one electron to the ring so it has a free lone pair and is basic. These properties are exploited in different ways in proteins. In catalytic triads, the basic nitrogen of histidine is used to abstract a proton from serine, threonine or cysteine to activate it as a nucleophile. In a histidine proton shuttle, histidine is used to quickly shuttle protons, it can do this by abstracting a proton with its basic nitrogen to make a positively-charged intermediate and then use another molecule, a buffer, to extract the proton from its acidic nitrogen. In carbonic anhydrases, a histidine proton shuttle

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is utilized to rapidly shuttle protons away from a zinc-bound water molecule to quickly regenerate the active form of the enzyme. The amino acid is a precursor for histamine and carnosine biosynthesis [5].

In this work, it has been studied on Histidine-Histidine dipeptide for importance of this molecule as we explained in the above paragraph. The molecule is optimized with chosen Becks's three-parameter hybrid functional using Lee-Yang-Parr for obtaining geometry. The frequency test has been done for each species to ensure that the obtained wave function and structure are ground state and the analysis of intramolecular interactions has been done.

Computational Details

All calculations were performed with Gaussian 98 [6] quantum chemistry program package in the electronic ground state with density functional theory (DFT) [7,8]. The chemical scheme of the title compound is shown in Scheme 1. The B3LYP method [9], i.e. Becks's three-parameter hybrid functional using Lee-Yang-Parr [10], is chosen because of its satisfactory results for structures and energies for small dipeptides. B3LYP performs best for obtaining geometries and has investigated that mean error for bond lengths for some databases is zero [11]. The many-electron wavefunctions obtained were used to compute the electron density and the critical point features. Bader's *Atoms In Molecules* (AIM) [12,13] has been applied to characterize the hydrogen bond in the investigated molecules. The quantum theory of atoms in molecules (QTAIM) is based on the analysis of electronic density topology and identifies chemical bond as a bond critical point (BCP) and corresponding bond paths (BP). Because of flexibility and reliability of this method, many researches have been devoted to obtain chemical bond strength and nature in both organic and inorganic chemistry, *via* AIM analysis [14-16]. AIM2000 package [17] has been used to obtain bonds properties.

Results and Discussion

An ab initio calculation on the Histidine-Histidine dipeptide structure in gas phase in state of nonpolar has been done. The dipeptide structure was optimized at DFT level of theory individually. The minima of geometry is located using 6-311++G** basis set. The positional parameters are shown in Fig 1. The bond distances (Å) of the intramolecular interactions are shown in Table 1. The Histidine-Histidine molecule is made up of the two imidazole groups, the peptide group and the carboxylic group.

At first, it is assumed that Histidine-Histidine molecule is included two rings concern to two imidazole rings, however, during the conformational study of the stable structure in gas phase, it has been found interestingly that the molecule has six rings. Among them, four rings give the molecule more stability which is due to some intramolecular hydrogen bonding interactions in the dipeptide.

AIM analysis indicates four intramolecular hydrogen bonds in the molecule. The bond critical points of all hydrogen bonds are in Table 1 (a.u.). The presence of four intramolecular hydrogen bonds is responsible for formation of additional four rings besides two imidazole rings and finally gives more stability to this molecule. The rings, bond paths, bond and ring critical points (RCP) are shown in Fig 2.

Now we are in position to introduce some AIM parameters that $\rho(r)$ properly describe bond nature. Laplacian of $\rho(r)$ is related to the bond interaction energy by a local expression of the virial theorem [18,19]:

$$\left(\frac{\hbar^2}{4m}\right)\nabla^2\rho = 2G(r)+V(r) \qquad (1)$$

where $G(r)$ is the electronic kinetic energy density, which is always positive, and $V(r)$ is the electronic potential energy density and must be negative [19]. The sign of $\nabla^2\rho(r)$ at a BCP is determined by which energy is in excess over the virial average of 2:1 of kinetics to potential energy. A negative $\nabla^2\rho(r)$, shows the excess potential energy at BCP. It means that electronic charge is concentrated in the inter-nuclear region, and therefore, shared by two nuclei. This is the case in all shared electron (covalent) interactions. A positive $\nabla^2\rho(r)$ at a BCP

reveals that the kinetic energy contribution is greater than that of potential energy, and shows depletion of charge along the bond path. This is the case in all closed shell (electrostatic) interaction [19, 20].

The electrostatic energy density $H(r)$ at BCP is given by [20]:

$$H(r) = G(r) + V(r) \quad (2)$$

Bonds with covalent character must have a BCP with negative $H(r)$, but the condition in which $|V(r)| < 2G(r)$ and $|V(r)| > 2G(r)$, provides $\nabla^2\rho(r)$ to be positive, while $H(r)$ is negative. Therefore, they must be termed as partially covalent and partially electrostatic. On the other hand, the cases in which the values of $|V(r)|$ is larger than $2G(r)$, and hence larger than $G(r)$, provides negative values for $\nabla^2\rho(r)$ and $H(r)$; a condition which is expected for covalent bonds. But for these cases, another criterion must be taken into account: along the bond path (BP) of covalent bonds, there must be a continuous region of space, including the valence region of the interacting atoms, over which the Laplacian is negative [20].

It has been observed that a very strong hydrogen bond can be occurred between O_{34} and hydrogen of H_7-C_5 bond with the electron density 0.1307 e. Å^{-3}. The intramolecular hydrogen bond has Laplacian $\nabla^2\rho(r)$, 0.0279 e. Å^{-5}, and electronic energy density of 0.3393. A positive $\nabla^2\rho(r)$ and H(r) at BCP reveals that the kinetic energy contribution is greater than that of potential energy, and demonstrates depletion of electronic charge along the bond path. So, it is closed shell interactions. The strength of hydrogen bond represented by E_{HB} can be evaluated by given procedure is,

$$E_{HB} = \frac{1}{2}V(\rho_{BCP}) \quad (3)$$

where *V* is potential energy. Therefore, with having potential energy V = 0.1890 in Table 1, hydrogen bond energy for this hydrogen bond is 59.2987 kcal/mol. Hence, hydrogen bond in O_{34}---H_7 is classified as a very strong bond. The values of $\rho(r), \nabla^2\rho(r)$, $G(r)$, $V(r)$ and $H(r)$ at the BCP of O_{34}---H_7 in the molecule are collected in Table 1. The presence of this interaction makes a six-membered ring (C_{32}, O_{34}, H_7, N_1, C_5 and C_3 atoms) (ring III as shown in Fig 2). The density of ring critical point is 0.0375 e. Å^{-3}. The values of $\rho(r)$, $H(r)$ and other properties at the RCP of the six-membered ring are given in Table 2 (in a.u.).

The second intramolecular hydrogen bond is formed simultaneously as the first one formed during internal rotation of amino acids as shown in Fig 1. It is formed between O_{36} and Hydrogen of H_{16}-C_{12} with $\rho(r)$ equal to 0.0512 e. Å^{-3}. The Laplacian, $\nabla^2\rho(r)$ and H values confirms electrostatic nature of the hydrogen bond. This hydrogen bond is responsible for forming ring II with ring critical point of 0.0140. E_{HB}, which can be evaluated through potential energy $V(r)$ as previously explained, is 21.2095 kcal/mol. Therefore, this hydrogen bond in O_{36}···H_{16} is classified as a very strong hydrogen bond too.

This molecule reveals another intramolecular hydrogen bond, which makes five-membered ring IV. The density of BCP of hydrogen bond O_{10}---H_{21} is 0.0252 e. Å^{-3}, with Laplacian $\nabla^2\rho(r)$ 0.0067 e. Å^{-5}. This hydrogen bond has also normally electrostatic nature and the density of RCP is 0.0181. The strength of this hydrogen bond is 9.0360 kcal/mol that this demonstrates a strong hydrogen bond in this ring.

Finally, the last hydrogen bond is formed with atoms N_1···H_{21} which makes ring V (C_{25}/C_{22}/C_6/C_{18}/H_{21}/N_1/C_{32} atoms) by coming two amino acids near to each other. A hydrogen bond is with electron density of critical point of 0.09230 with Laplacian of 0.0120 and Hamiltonian energy of 1.7865 and with electron density of RCP equal to 0.0127 e. Å^{-3}. This hydrogen bond is also classified as a strong hydrogen bond with E_{HB} equal 36.7401 kcal/mol.

At last, rings I and IV are similar and related to two imidazole rings. Their ring critical point densities are also almost the same. From the calculated results it can be substantiated that ring I including N_{11} and N_{15}, have great ring critical point density of 0.0533 e. Å^{-3} which confirms the existence of

two double bonds in the ring with regarding to linked groups surrounding of the ring. The ring critical point, Laplacian kinetic energy and virial energy is reported in Table 2.

Conclusion

A theoretical analysis of molecular geometry optimizations and their electronic wave function and electron density that have been done with Gaussian 98 program, indicates that the conformational structure of this dipeptide in gas phase has six different rings not expected two rings. Analysis of the molecule shows that forming the rings except for imidazole rings are due to existence of some intramolecular very strong hydrogen bonds. One hydrogen bond is the strongest interaction with hydrogen bond energy of 59.2987 kcal/mol.

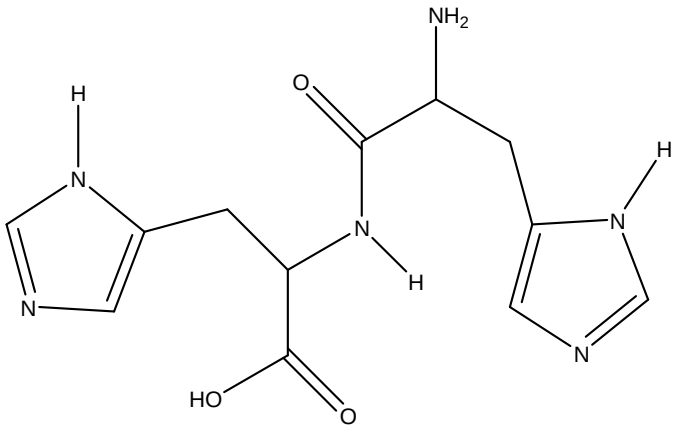
The comparison the rings show that both of imidazole rings have high electron density of ring critical point. Among four other rings, the six-member rings formed C_{33}, O_{34}, N_1, C_3, C_5 and H_7, has the highest electron density related to three other rings and is concerning to hydrogen bond between O_{34} and H_7 in this ring that is strongest interaction with highest electron density of bond critical point. Therefore the presence of strong hydrogen bonds is responsible for observing four rings in addition to imidazole rings that we can see six rings in this dipeptide, interestingly.

Table 1. Density of the bond critical points (e. Å^{-3}), Laplacian (e. Å^{-5}), kinetic, potential and total energies (in a.u.) and bond distances of the intramolecular hydrogen bonds (Å).

Bond	ρ_{cr}	$\nabla^2\rho$	G	V	H	D
N_1---H_{21}	0.0923	0.0120	0.0827	0.1171	0.1998	1.7865
O_{34}---H_7	0.1307	0.0279	0.1503	0.1890	0.3393	1.2830
O_{36}---H_{16}	0.0512	0.0138	0.0616	0.0676	0.1292	2.0338
O_{10}---H_{21}	0.0252	0.0067	0.0278	0.0288	0.0566	2.0103

Table 2. Density (e. Å^{-3}), Laplacian (e. Å^{-3}), kinetic, potential and total energies of the ring critical points (a.u.).

RING	ρ_{cr}	$\nabla^2\rho$	G	V	H
I	0.0533	0.0266	0.0963	0.0860	0.1823
II	0.0140	0.0043	0.0161	0.0149	0.0310
III	0.0375	0.0148	0.0555	0.0516	0.1071
IV	0.0181	0.0069	0.0240	0.0204	0.0444
V	0.0127	0.0036	0.0136	0.0127	0.0263
VI	0.0534	0.0266	0.0923	0.0860	0.1783



Scheme 1. The chemical scheme of Histidine-Histidine dipeptide.

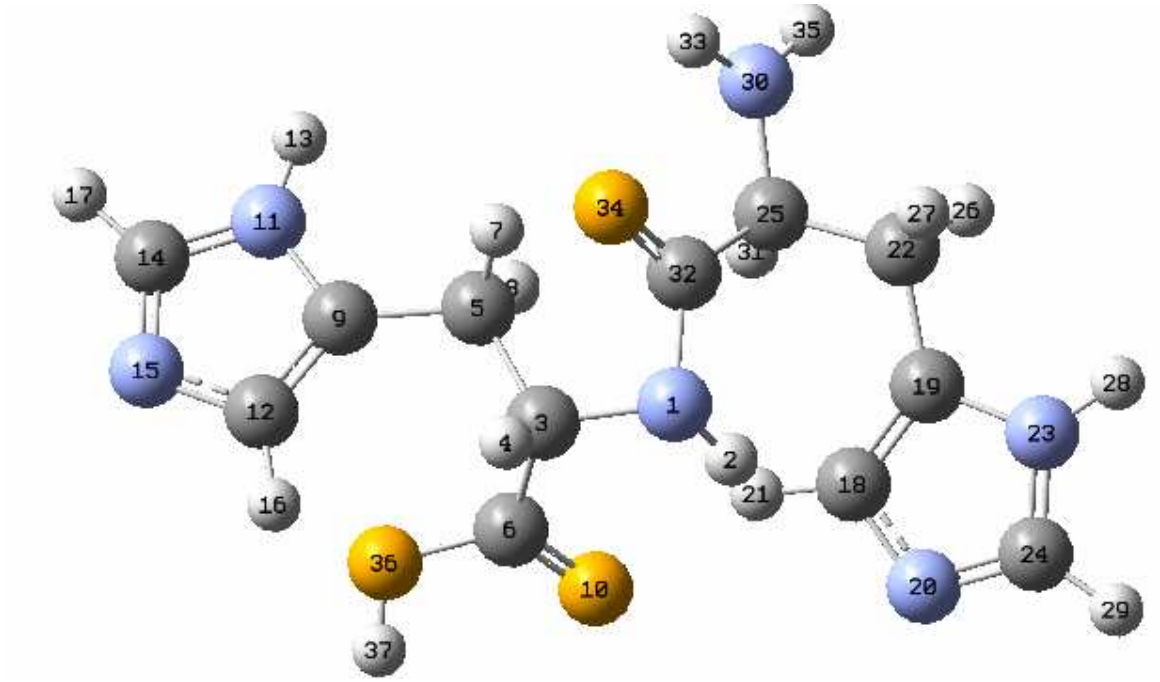


Fig 1. The optimized structure of Histidine-Histidine dipeptide in gas phase by B3LYP/6-31++G** level of theory.

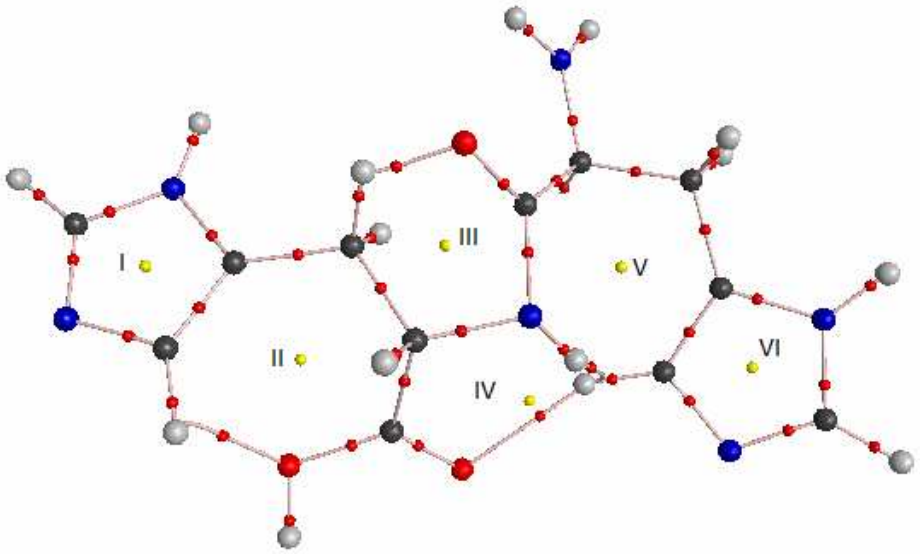


Fig 2. Theoretical molecular graph of the dipeptide in gas phase. Black, blue, red and grey spheres show atomic positions. Small red and yellow spheres (italic numbers) show bond (3,-1) and ring (3,+1) critical points in ρ, respectively.

References

[1] A. Fujihara, H. Matsumoto, Y. Shibata, H. Ishikawa, K. Fuke, *J. Phys. Chem.* A112 (2008) 1457.
[2] S. Mondal, D.S. Chowdhuri, S. Ghosh, A. Misra, S. Dalai, *J. Mol. Struct. (Theochem)*, 810 (2007) 81.
[3] S. Mondal, D.S. Chowdhuri, S. Ghosh, A. Misra, S. Dalai, *J. Mol. Struct. (Theochem)* 805 (2007) 133.
[4] C.P. Chun, A.A. Connov, G.A. Chaas, *J. Mol. Struct. (Theochem)* 729 (2005) 177.
[5] C.D. Keef, J.K. Pearson, *J. Mol. Struct. (Theochem)* 679 (2004) 65.
[6] M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, V.G. Zakrzewski, J.A. Montgomery, Jr., R.E. Stratmann, J.C. Burant, S. Dapprich, J.M. Millam, A.D. Daniels, K.N. Kudin, M.C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G.A. Petersson, P.Y. Ayala, Q. Cui, K. Morokuma, D.K. Malick, A.D. Rabuck, K. Raghavachari, J.B. Foresman, J. Cioslowski, J.V. Ortiz, B.B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R.L. Martin, D.J. Fox, T. Keith, M.A. Al-Laham, C.Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P.M.W. Gill, B. Johnson, W. Chen, M.W. Wong, J.L. Andres, C. Gonzalez, M. Head-Gordon, E.S. Replogle, J.A. Pople, GAUSSIAN 98, Revision A.7, Pittsburgh PA: Gaussian, Inc., (1998).
[7] J. W. Andzelm, in: J.K. Labanowski, and J.W. Andzelm (Ed.), Density Functional Methods in Chemistry (Springer, New York, (1991).
[8] T. Ziegler, *Chem. Rev.* 91 (1991) 651.
[9] C. Lee, W. Yang, R.G. Parr, *Phys. Rev. B*37 (1988) 785.
[10] A. D. Becke, *J. Chem. Phys.* 98 (1993) 5648.
[11] Y. Zhao, D.G. Truhlar, *Theor. Chem. Account.* 120 (2008) 215.
[12] R.F.W. Bader, Atoms in Molecules: A Quantum Theory, (Oxford University Press, Oxford, U.K. 1990).
[13] P.L.A. Popelier, Atoms in Molecules, An Introduction, (Prentice Hall, Pearson Education Limited, 2000).
[14] G.F. Matta, R.F.W. Bader, *PROTEINS: Struct. Funct. Genet.* 40 (2000) 310.
[15] G.F. Matta, R.F.W. Bader, *PROTEINS: Struct. Funct. Genet*. 48 (2002) 519.
[16] G.F. Matta, R.F.W. Bader, *PROTEINS: Struct. Funct. Genet.* 52 (2003) 360.
[17] R.F.W. Bader, F. Biegler-König, J. Schönbohm, AIM2000 Program Package, Ver. 2.0, University of Applied Sciences, Bielefield, Germany, (2002).
[18] R.F.W. Bader, *Phys. Chem. Rev.* B49 (1994) 13348.
[19] R.F.W. Bader, T. Nguyen-Dang, *Adv. Quantum Chem.*14 (1981) 63.
[20] D. Cremer, E. Kraka, *Angew.Chem. Int.* 23, (1984) 627.