A Computational Study of N–H…O Hydrogen Bonding to Investigate Cooperative Effects

Setareh Shekarsaraei, Marjan Moridi, Nasser L. Hadipour

Abstract—In this study, nuclear magnetic resonance spectroscopy and nuclear quadrupole resonance spectroscopy parameters of [14]N (Nitrogen in imidazole ring) in N–H…O hydrogen bonding for Histidine hydrochloride monohydrate were calculated via density functional theory. We considered a five-molecule model system of Histidine hydrochloride monohydrate. Also we examined the trends of environmental effect on hydrogen bonds as well as cooperativity. The functional used in this research is M06-2X which is a good functional and the obtained results has shown good agreement with experimental data. This functional was applied to calculate the NMR and NQR parameters. Some correlations among NBO parameters, NMR and NQR parameters have been studied which have shown the existence of strong correlations among them. Furthermore, the geometry optimization has been performed using M062X/6-31++G(d,p) method. In addition, in order to study cooperativity and changes in structural parameters, along with increase in cluster size, natural bond orbitals have been employed.

Keywords—Hydrogen bonding, Density Functional Theory (DFT), Natural bond Orbitals (NBO), cooperativity effects.

I. INTRODUCTION

HYDROGEN bonds play significant roles in intermolecular interactions in terms of structural determination. Hence they are studied many times. It should be mentioned intermolecular forces stabilize important compounds like DNA and RNA [1]. Furthermore hydrogen bond interactions have important roles in biological systems. Two main forces participating in hydrogen bond formation are electrostatic and charge transfer (delocalization) forces and it is believed that hydrogen bonds are the best characterized type of non-covalent interaction [2]-[13].

Ion channels, located in cell membranes, direct electrical current through the cell membrane and defects in them cause some diseases. These ion channels consist of amino acids [14].

Hence, the structural environments of inorganic atoms within biochemical systems such as ion channels ought to studied and investigation of hydrogen bonds can be helpful to determine the structure of these channels. Density functional theory (DFT) methods are appropriate in order to compute non-covalently interactions [15], [16].

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In the past two decades, a large amount of ion channels structural information has been extracted by X-ray crystallography; but the aim of this study is to assess the structure of these channels using solid-state nuclear magnetic resonance (SSNMR) and nuclear quadrupole resonance (NQR), a sensitive technique [17]. In general, NMR spectroscopy technique is very fruitful to study biological molecules such as proteins and structural determining in both the solution [18]-[22] and solid states [23], [34].

Changes in NMR and NQR parameters demonstrate changes in nuclear environment and it can be understood that the structure of amino acids has changed. In this work NMR and NQR parameters calculated by M06-2X which is an appropriate functional and the performance of it is good to study non-covalent interactions compared to other popular functionals. Also, it has been much used to study biological systems [35], [36].

In this study, hydrogen complex interaction in an amino acid hydrochloride salt has been investigated by ^{15}N solid-state NMR spectroscopy. Nuclei with nuclear spin quantum number (I) larger than 1/2, are quadrupolar nuclei. For these nuclei, the electric charge is not spherically symmetrical, and they have an electric quadrupole moment, Q. The electrostatic field gradient tensor (EFG) arising from the electron distribution, and it will couple with Q at the nuclear center, so these nuclei can be studied by NQR spectroscopy. Principal components of EFG tensor must be arranged in this way: $q_{ZZ} \geq q_{YY} \geq q_{XX}$. The calculated NQR parameters in this work are the quadrupolar coupling constant (C_Q) and the asymmetry parameter (η_Q) defined as follow, where, e is the charge on an electron, Q is the nuclear electric quadrupole moment and h is Planck's constant:

$$C_Q(MHz) = \frac{e \times q_{ZZ} \times Q}{h} \qquad (1)$$

$$\eta_Q = \frac{q_{XX} - q_{YY}}{q_{ZZ}} \qquad (2)$$

NMR parameters used in this work are the chemical shift isotropy (σ_{iso}) and anisotropy ($\Delta\sigma$) [37]:

$$\sigma_{iso}(ppm) = \frac{\sigma_{11} + \sigma_{22} + \sigma_{33}}{3} \qquad (3)$$

$$\Delta\sigma(ppm) = \sigma_{33} - \frac{\sigma_{11} + \sigma_{22}}{2} \qquad (4)$$

Another aim of this study is to illustrate the correlations between changes in NMR and NQR parameters and changes in structure from monomer to pentamer.

II. RESULTS AND DISCUSSION

A. Molecular Modeling

All density functional theory (DFT) calculations were performed using the GAMESS electronic structure package [38].

Nuclear magnetic shielding and EFG tensors were calculated based on models generated using atomic coordinates of the neutron diffraction structure by Fuess et al. [39]. Five-molecular models have been designed in which Histidine hydrochloride monohydrate makes extensive intermolecular hydrogen bonds with its neighbor molecules in the crystalline phase, which enables us to study the influence of these interactions on nuclear quadrupole coupling tensors of the nitrogen and oxygen nuclei. In addition, charge transferring and cooperativity have been studied in this system (Fig. 1). However, we focused on investigation of the calculated ^{14}N and ^{17}O NMR, NQR and NBO parameters. The cooperativity between different types of the interaction is mainly caused by the electrostatic effects [40].
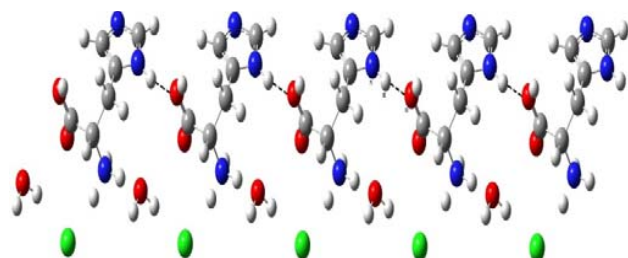

Fig. 1 Hydrogen bonds in Histidine hydrochloride monohydrate clusters optimized with M06-2X/6-31++G (d,p) method

B. Methods of Calculations and Computational Software

Molecular orbital calculations were performed using DFT method. All the computations related to chemical shielding tensors, electric field gradient tensors and population analysis were carried out using GAMESS electronic structure package. The geometry optimization was performed using the M06-2X functional with 6-31++G (d,p) basis sets in order to find the position of hydrogen atoms in the stable state of the system from monomer to pentamer. According to the experimental data, this method provides good results and M06-2X is an appropriate functional in biological systems. Calculations of the nitrogen and oxygen nuclear magnetic shielding, EFG tensors and NBO were done base on designed model along with applying M06-2X and 6-311++G(d,p) basis set.

C. Analysis of Structural Parameters

In this study we have investigated N-H…O hydrogen bond in crystal lattice (related to imidazole ring) for Histidine hydrochloride monohydrate. The A-H…B hydrogen bond is a combination of two effects: rehybridization and hyperconjugation, acting in opposite directions. The observed effect of H-bonding on the bond lengths is a result of a balance of these two intrinsic effects. When hyperconjugation is dominant, the N-H bond lengthens. Similarly, when hyperconjugation is weak and the structure of the H-bond

donor allows changing significantly in N-H bond hybridization, the N-H bond shortens. NBO analysis is used to investigate these trends. Moreover, hyperconjugative is connected with the electron charge transfer (E_{NBO}). This effect is the electron charge transfer from the lone pair of the Lewis base, B, to the antibonding orbital, σ^*, of the A-H bond. This interaction, $n_B \rightarrow \sigma_{AH}^*$, can be calculated as the second-order perturbation theory energy (5) [41]-[43]:

$$E_{NBO} = E^{(2)} = \Delta E(n_B \rightarrow \sigma_{AH}^*) = \frac{-2 < n_B | F | \sigma_{AH}^* >^2}{\varepsilon(\sigma_{AH}^*) - \varepsilon(n_B)} \tag{5}$$

That, $< n_B | F | \sigma_{AH}^* >$, is the Fock matrix element and, $\varepsilon(\sigma_{AH}^*) - \varepsilon(n_B)$, is the energy differences between These two orbitals. Rehybridization effect causes an increase in the s-character of the A-atom hybrid orbital in the A–H bond; as a consequence, A-H bond strengthens and its length decreases.

Calculated structural parameters related to imidazole ring in Histidine hydrochloride monohydrate (N-H…O) from dimer to pentamer are presented in Table I. It is evident that $r_{N–H}$ is increasing from dimer to pentamer and compared to experimental bond length, the percentage of error is 4.42. Furthermore a decrease in $r_{H…O}$ is observed and the computational error is %4.49, illustrating a good agreement between the calculated and experimental data and proving that M06-2X/6-31++G(d,p) has presented a high accuracy level for this system. It is concluded from NBO parameters in Table II, E_{NBO} has increased by 1.72kcal/mol, whereas s-character has increased only slightly. Hence hyperconjugative dominates and the N-H bond lengthenes. There are linear correlations between s-character and N-H as well as H-O bond lengths (Fig. 2). There is a direct correlation between E_{NBO} and bond polarization, shown in Fig. 3.

TABLE I
STRUCTURAL PARAMETERS FOR (HISTIDINE HYDROCHLORIDE MONOHYDRATE)1–5 OPTIMIZED AT M06-2X /6-311++G(D,P) LEVEL

Parameter	n=2	n=3	n=4	n=5	Exp.
r_{N-H}	0.99897	1.00203	1.00239	1.00265	1.047
$r_{H…O}$	1.67635	1.66727	1.66679	1.66611	1.741

TABLE II
NBO ANALYSIS OF N-H…CL INTERACTION FOR (HISTIDINE HYDROCHLORIDE MONOHYDRATE)1–5 OPTIMIZED AT M06-2X /6-311++G(D,P) LEVEL

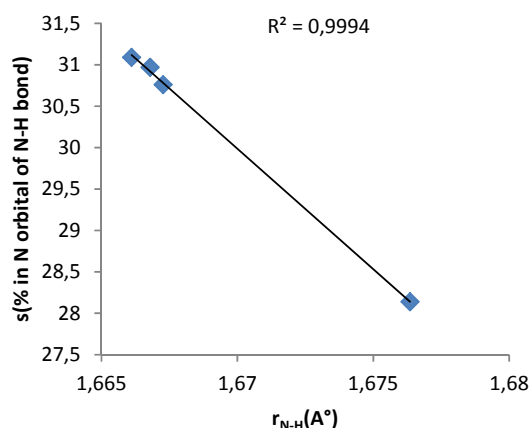| n	E_{NBO} (kCal/mol)	%S Character	% Polarization	Hydrogen charge
2	18.64	28.14	71.71	0.425
3	19.20	30.76	73.99	0.426
4	20.08	30.97	78.29	0.427
5	20.36	31.09	79.25	0.429

Fig. 2 The relationships between the N-H distance and the s-character in the N orbital
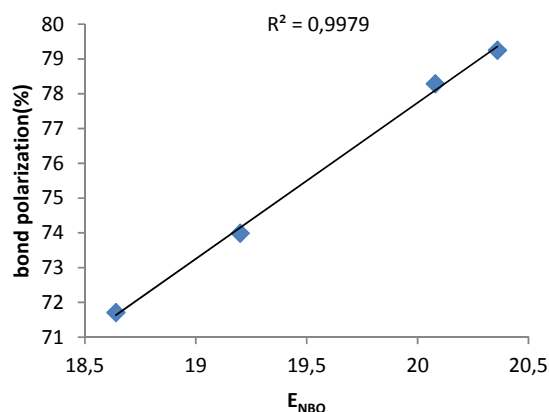

Fig. 3 The relationship between NBO energy and the N-H bond polarization

D.NMR and NQR Calculations and the Correlation between NMR and NBO Parameters

The C_Q, η_Q, σ_{iso} and $\Delta\sigma$ values, shown in Table III, are related to nitrogen nucleus (imidazole ring) in N-H…O. The C_Q decreases from dimer to pentamer whereas η_Q increases. The C_Q has a reduction about 0.544 from dimer to pentamer and the value is 1.325 in pentamer. Furthermore, according to the experimental value which is 1.293, the percentage of computational errors is 2.41. Decline in C_Q value is indicative of an increase in hydrogen bond strength [44]. In addition, the asymmetry parameter (η_Q) which can show the information about the symmetry of nuclear environment increases regularly and the experimental value for η_Q is 0.974; therefore the computational error would be 9.19 [44]. What is more, the σ_{iso} (^{15}N) increases from 57.879 to 60.404 and $\Delta\sigma$ (^{15}N) decreases from dimer to pentamer. As mentioned, NBO analysis can help us explain the reason of these changes. Hybridization of nitrogen atom changed from sp$^{2.25}$ in dimer to sp$^{2.22}$ in pentamer, demonstrating the symmetry of electronic cloud around nitrogen atom is increasing and these changes in trends proves the existence of cooperativity. One additional

reason for cooperativity is hydrogen charge. An increase in hydrogen charge leads to a reduction in H…O bond length. There is a direct correlation between $\Delta\sigma$ and p-character (%p), presented in Fig. 4. Some correlations between σ_{iso}(^{17}O) and hydrogen charge, hydrogen charge and $\Delta\sigma$ as well as hydrogen charge and $r_{H..O}$, are observed and in general these figures proves that there are great correlations among NMR, NQR and NBO parameters (Figs. 4-6).

TABLE III
CALCULATED $^{14/15}$N NMR AND NQR PARAMETERS IN HISTIDINE HYDROCHLORIDE MONOHYDRATE CLUSTERS

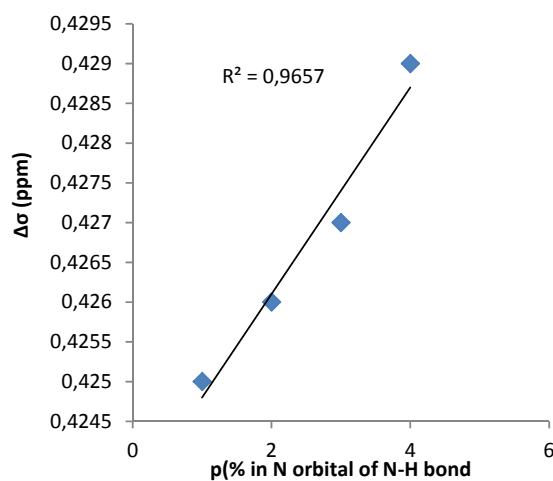| n	Functional	σ_{iso} (ppm)	$\Delta\sigma$ (ppm)	C_Q (MHz)	η_Q
Dimer	M06-2X	57.880	145.616	1.869	0.434
Trimer	M06-2X	57.795	142.204	1.653	0.596
Tetramer	M062X	60.795	141.986	1.417	0.849
Pentamer	M062X	60.404	141.753	1.325	0.892
Exp.		-	-	1.293	0.974

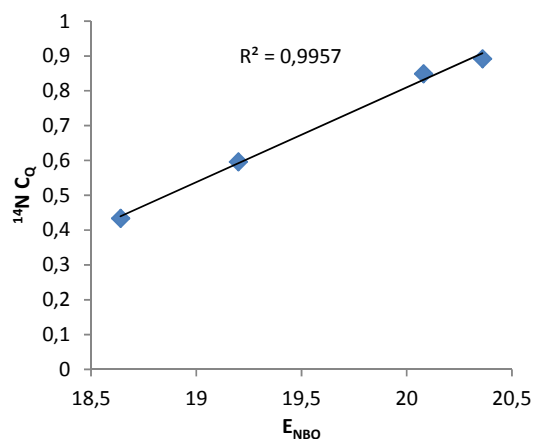Fig. 4 The relationship between p (% in N orbital of N-H bond) and $\Delta\sigma$

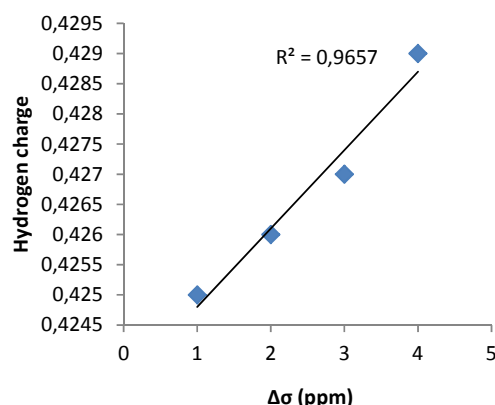Fig. 5 The relationship between NBO energy and the ^{14}N C_Q

Fig. 6 The relationship between hydrogen charge and $\Delta\sigma$ (ppm)

III. CONCLUSION

A computational investigation on the intermolecular hydrogen bonding properties has been done in amnio acids by DFT calculations. The trends of environmental effects on hydrogen bondings as well as cooperativity effects, using obtained results from NMR and NQR have been studied. The effects of neighbor molecules have been illustrated by NMR and NQR detecting slight effects. Furthermore NMR and NQR results as well as NBO methods reveal cooperativity effects, properly. Rehybridization and hyperconjugative have been used to explain the reason of changes and Results reveales that an increase in both hydrogen charge and chemical shift isotropy parameter and a decrease in anisotropy parameter as well as O…H bond length reduction simultaneously lead to strengthening of bond, an obvious proof of cooperative effect. Moreover, a good agreement among the calculated and experimental data shows that M06-2X is an accurate functional for biological molecules such as proteins.

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