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A Study on the Intermolecular Hydrogen Bonds of α-Glycylglycine in Its Actual Crystalline Phase Using ab Initio Calculated ^{14}N and ^{2}H Nuclear Quadrupole Coupling Constants

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α-Glycylglycine in its actual crystalline phase is studied by ab initio calculated nuclear quadrupole coupling constants. These physical quantities are computed for ^{2}H and ^{14}N in the hydrogen bonds. The type of hydrogen bond is the N−H···O type. The computations are performed with the RHF and B3LYP methods and 6-31++G** and 6-311++G** basis sets using the *Gaussian 98* program. Values of the calculated nuclear quadrupole coupling constants are shown in Tables 1−3. The aim of this work is the study of ^{2}H and ^{14}N quadrupole coupling constants which contribute in the CON^{2}H···O═CN^{2}H type of hydrogen bond. The computed nuclear quadrupole coupling constants of ^{2}H nuclei meet the related experimental values. In addition, the computed χ value of ^{14}N belonging to the −CO−^{14}NH− group agrees well with values obtained experimentally. However, there are some discrepancies between calculated ^{14}N χ values of the N^{+}H$_3$ residue and experiments. Also, the values of these physical parameters are calculated for >C^{2}H$_2$ of α-glycylglycine in its crystalline phase. Calculations for these parameters are carried out in a single molecule using X-ray diffraction coordinates, too.

Introduction

Hydrogen bonds (HBs) play a vital role in the natural phenomena, especially in the biological systems. Stabilization of polypeptides, for example, is due to the formation of intermolecular HBs. The type of these HBs is N−H···O which, like any other hydrogen bond, is an electrostatic phenomenon.[1]

Accurate structure determination of polypeptide chains in protein molecules is a rather formidable task. However, study of the crystal structure of amino acids and small peptides is feasible, which leads us to a relatively clear understanding of the protein structures.[2,3] α-Glycylglycine (α-glygly) is one of the smallest peptides. Its crystalline phase shows that, like other peptides, it is able to construct intermolecular hydrogen bonds with its nearest-neighbor molecules.

These HBs are very sensitive to the secondary structures of proteins and polypeptides. They are used as critical indicators of the existing α-helices or β-sheets. A variety of theoretical[4−8] and experimental methods have been employed to obtain information about the properties of HBs. The prime tool for this purpose is X-ray crystallography.[9] However, X-ray diffraction is not able to determine the accurate location of hydrogen atoms in the molecules. In addition to this deficiency, diffraction techniques require long-range positionally ordered materials.[10] Because most of the biological systems do not have such a property, nuclear magnetic resonance (NMR) spectroscopy including static and magic angle spinning (MAS) is used to determine the nature of hydrogen bonds.[11−16]

A better technique is nuclear quadrupole resonance (NQR).[17] It is an insightful method for the study of different HB types in the crystalline phase.[18−20] The electric quadrupole moment, eQ, is a characteristic of a particular nucleus with spin angular momentum, I, greater than one-half ($I > {}^{1}/_{2}$), which is a measure of the nuclear charge distortion from the spherical shape. The electric quadrupole moment interacts with the electric field gradient (EFG), which originates from the internal electrostatic charges at the site of the nucleus.[21]

As a result of the formation of an HB in a complex, the resonating quadrupolar nuclei of the complex feel the changes in the EFG, which is reflected in the observed shift of the NQR spectrum. Calculation of nuclear quadrupolar parameters (χ, η) is done by extracting the NQR frequencies,ν_Q, from the NQR spectrum. Nowadays, a highly precise measurement of ν_Q is carried out by low-field-energy-level crossing technique.[22]

Theoretical methods are often used to calculate the NQR parameters. These may be done for ^{2}H and ^{14}N of HBs. However, calculations of χ and η for model compounds such as *N*-methylacetamide hydrogen bonded with a formamide have been also performed.[23−25] Of course, the results drawn from the study of model compounds do not exactly represent the actual systems.

So far, the real systems have not yet been theoretically studied. The present research for the first time used the actual crystalline phase instead of model compounds to directly study the properties of intermolecular HBs. Surely, the results obtained using this technique would be more reliable. As Figure 1 shows, a molecule of α-glygly made hydrogen bonds with its nearest neighbors. Because the hydrogen bond between the amide hydrogen atom and amide carbonyl oxygen atom is essential in biology, we tried to focus more on this hydrogen bond. X-ray diffraction data at 298 K is employed as in a real crystalline structure.[26]

As already mentioned, the important physical parameters that can be determined both theoretically and experimentally are the

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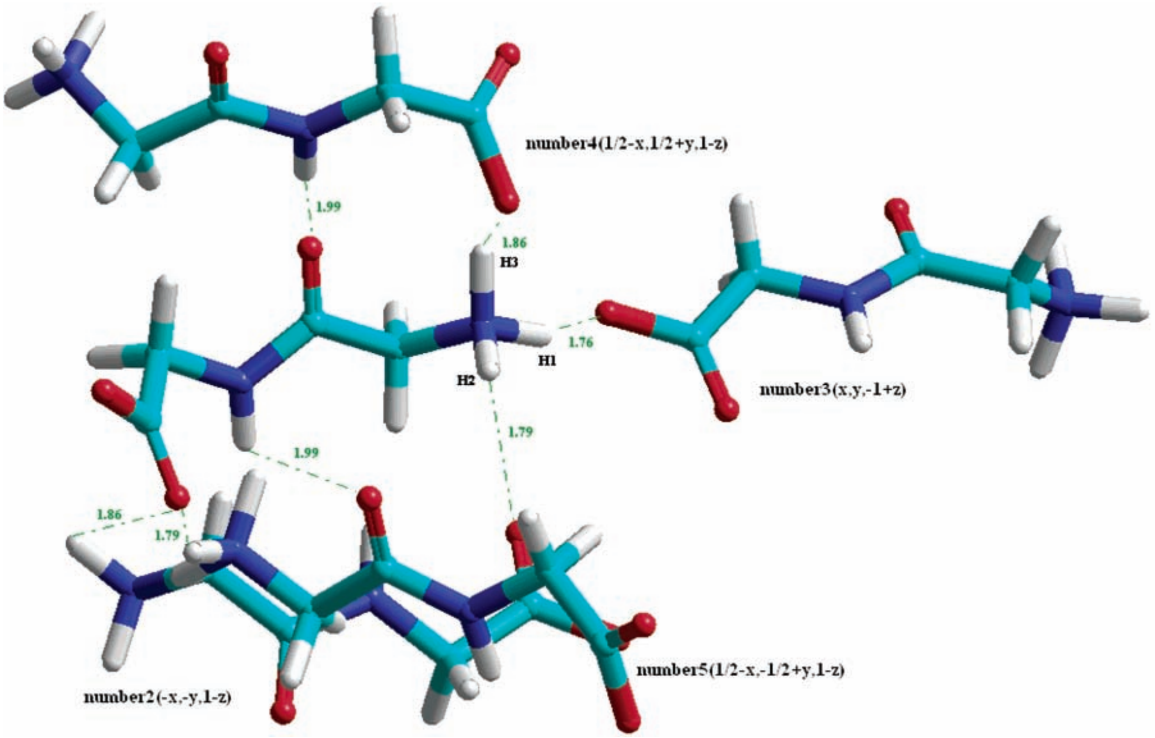

Figure 1. Molecular structure of α-glygly in its solid phase.

nuclear quadrupole coupling constant, χ, and the asymmetry parameter, η. The values of the EFG tensor in its principal axes system (PAS) were used to calculate the nuclear quadrupole coupling constant, χ.[27] The results of our calculations are summarized in Tables 1−3.

Theory

The quadrupolar Hamiltonian, $\hat{H}_Q$, describes the interaction of the quadrupole moment, eQ, of a nucleus with the spin greater than $^1/_2$ with the electric field gradient (EFG) at the nuclear site

$$\hat{H}_Q = \frac{eQ}{6I(2I-1)} \sum_{\alpha\beta} \hat{V}_{\alpha\beta} \left[\frac{3}{2} (\hat{I}_\alpha \hat{I}_\beta + \hat{I}_\beta \hat{I}_\alpha - \delta_{\alpha\beta} \hat{I}^2) \right] \quad (1)$$

where eQ is the nuclear electric quadrupole moment, I is the nuclear spin, the $\hat{V}_{\alpha\beta}$ values are the elements of the electric field gradient tensor, and the Kronecker symbol $\delta_{\alpha\beta} = 1$, or if $\alpha = \beta$, it is equal to zero. This Hamiltonian in the PAS may be written as

$$\hat{H}_Q = \frac{e^2 Q q_{ZZ}}{4I(2I-1)} [(3\hat{I}_Z{}^2 - \hat{I}^2) + \eta(\hat{I}_X{}^2 - \hat{I}_Y{}^2)] \quad (2)$$

where $eq_{ZZ} = V_{ZZ}$, and the asymmetry parameter

$$\eta = \left| \frac{(V_{XX} - V_{YY})}{V_{ZZ}} \right|$$

It is straightforward to use the raising and lowering operators, $\hat{I}_\pm$, to derive the following equation:[28]

$$\hat{H}_Q = \frac{e^2 q_{ZZ} Q}{4I(2I-1)} \left[3\hat{I}_Z{}^2 - \hat{I}^2 + \frac{\eta}{2} (\hat{I}_+{}^2 + \hat{I}_-{}^2) \right] \quad (3)$$

The computed EFGs are used to compute the χ values in kilohertz using the following formula:

$$\chi = \frac{e^2 q_{ZZ} Q}{h} \quad (4)$$

Computational Details

I. Levels of Theory. Ab initio calculations for α-glygly (*NH_3^+ $CH_2CONHCH_2COO^-$*) were performed using *Gaussian 98*.[29] This is done to calculate the components of EFG tensors in the PAS for ^{14}N and ^{2}H nuclei. They are involved in making the hydrogen bond network. These EFGs are calculated at the RHF and B3LYP levels of theory. For DFT calculations, the Becke's nonlocal three-parameter exchange and correlation functional[30] with the Lee et al. correlation functional,[31] designated B3LYP, is used. For the cluster, the 6-31++G** basis set is used, and for the single molecule, calculations are performed with the 6-311++G** basis set. Various combinations of diffuse and polarization functions are incorporated in the basis set that are necessary for computation of the EFGs of nitrogens and hydrogens involved in hydrogen bonds.[32−34] Nuclear quadrupole coupling constants of ^{2}H in $>C^2H_2$ were calculated with the same level of theory. However, a lighter basis set may be sufficient for the EFG calculation of ^{2}H in $>C^2H_2$. The actual crystalline coordinates were applied in order to calculate the electric field gradients.

The electric quadrupole moments of ^{2}H and ^{14}N are taken as $Q = 2.86 \times 10^{-27}$ and 20.44×10^{-27} cm^2, respectively.[35]

II. Inclusion of Correlation Effect. Certainly in general, DFT is more reliable. This depends on the sort of system one is dealing with. The clue of this reliability is that DFT globally minimized structure should have less energy than that obtained from RHF. In this work, both methods support each other by producing similar results.

In the α-glygly cluster, at intermediate distances between molecular electron densities of two α-glygly molecules (e.g., central molecule and one of the neighboring molecules), the

TABLE 1: Nuclear Quadrupole Coupling Constants[a] of ^{2}H (KHz) and ^{14}N (MHz) in Single α-Glygly for X-ray Structure at 298 K

atom	χ/I[a]	χ/II[b]
$N^{+}-{}^{2}H(1)$	267.10	265.98
$N^{+}-{}^{2}H(2)$	240.32	240.44
$N^{+}-{}^{2}H(3)$	267.20	266.54
$CON-{}^{2}H$	247.60	243.57
$>C^{2}H^{av}$	192.74	188.87
$^{14}N^{+}H_3$	0.625	0.158
$CO^{14}NH$	3.342	2.964

[a] I: Results obtained at B3LYP/6-311++G** level. [b] II: Results obtained at RHF/6-311++G** level.

TABLE 2: Nuclear Quadrupole Coupling Constants[a] of ^{2}H of α-Glygly at 298 K

hydrogen bond type	donor−acceptor	χ/KHz
$N^{+}-{}^{2}H(2)\cdots{}^{-}OCOR$	central−number 2 $(-x, -y, 1-z)$	224.62 (224.47)
$N^{+}-{}^{2}H(3)\cdots{}^{-}OCOR$	central−number 4 $(^{1}/_{2}-x, ^{1}/_{2}+y, 1-z)$	239.37 (242.05)
$N^{+}-{}^{2}H(2)\cdots{}^{-}OCOR$	number 2 $(-x, -y, 1-z)$−central	196.35 (196.90)
$N^{+}-{}^{2}H(3)\cdots{}^{-}OCOR$	number 5 $(^{1}/_{2}-x, -^{1}/_{2}+y, 1-z)$−central	232.50 (233.89)
$N^{+}-{}^{2}H(1)\cdots O{=}COR$	central−number 3 $(x, y, -1+z)$	202.68 (203.63)
$CON-{}^{2}H\cdots O{=}CN^{2}H$	number 4 $(^{1}/_{2}-x, ^{1}/_{2}+y, 1-z)$−central	215.21 (219.19)
$CON-{}^{2}H\cdots O{=}CN^{2}H$	central−number 5 $(^{1}/_{2}-x, -^{1}/_{2}+y, 1-z)$	217.51 (222.13)

[a] Results obtained at B3LYP/6-31++G** level. (···) Results obtained at RHF/6-31++G** level.

TABLE 3: Nuclear Quadrupole Coupling Constants[a] of ^{14}N of α-Glygly at 298 K

hydrogen bond type	donor−acceptor	χ/MHz	χ/MHz (exptl)
$^{14}N^{+}H_3\cdots{}^{-}OCOR$	central−number 2 $(-x, -y, 1-z)$	1.955 (2.001)	1.280 (ref 48) 1.247 (ref 49) 1.273 (ref 49)
$^{14}N^{+}H_3\cdots{}^{-}OCOR$	number 2 $(-x, -y, 1-z)$−central	1.016 (1.017)	1.280 (ref 48) 1.247 (ref 49) 1.273 (ref 49)
$^{14}N^{+}H_3\cdots{}^{-}OCOR$	number 5 $(^{1}/_{2}-x, -^{1}/_{2}+y, 1-z)$−central	1.231 (1.251)	1.280 (ref 48) 1.247 (ref 49) 1.273 (ref 49)
$CO^{14}NH\cdots O{=}C^{14}NH$	central−number 5 $(^{1}/_{2}-x, -^{1}/_{2}+y, 1-z)$	3.178 (4.116)	3.030 (ref 48) (3.040) (ref 49)

[a] Results obtained by B3LYP/6-31++G** level. (···) Results obtained by RHF/6-31++G** level. The experimental ^{14}N NQR quadrupole coupling constants are measured at 77 K.

electron motions in a neighboring molecule induce a temporary dipole moment in the central molecule, which in turn induces a charge polarization in the first molecule. This induced dipole moment creates an attractive force between the two molecules. This effect is entirely due to electron correlation, which is not covered with the Hartree−Fock model. Thus, the results of DFT are more reliable to investigate the properties of hydrogen-bonded complexes.[36−40]

Results and Discussion

In this work, we calculated the ^{2}H and ^{14}N nuclear quadrupole coupling constants of α-glygly in the solid phase. Because a cluster made of α-glylgly is considered, it is expected that the calculated χ values will be very close to those quantities measured by the appropriate experimental devices. Of course, they should be less similar to those obtained from the coupling of two isolated molecules, as a dipeptide model.[41,42] Therefore, the ab initio method is used. All calculations are carried out at the RHF and B3LYP methods using 6-311++G** and 6-31++G** basis sets. The results are summarized in Tables 1−3.

To have a base for comparison, a single molecule of α-glycylglycine was studied. The EFG values of all ^{2}H and ^{14}N were computed using X-ray diffraction coordinates. The corresponding ^{2}H and ^{14}N nuclear quadrupole coupling constants were calculated employing these EFG values. The results were summarized in Table 1.

Figure 1, which is constructed using X-ray diffraction atomic coordinates, shows that α-glygly makes intermolecular HBs in the solid phase, and then a cluster is created. To compare the χ values with their given experimental values, one should consider the whole molecules involved in producing this cluster. Therefore, the computations are performed for the cluster accordingly, and the results are summarized in Tables 1−3.

I. ^{2}H Quadrupole Coupling Constants. Table 2 shows the effect of HBs on ^{2}H nuclear quadrupole coupling constants. As previously mentioned, HB formation significantly reduces the χ values of ^{2}H.[43] The central α-glygly molecule makes a short HB with the acceptor molecule at $(x, y, -1+z)$, therefore the reduction of χ of this HB is relatively large.

As Figure 1 illustrates, the central molecule makes intermolecular HBs via an N terminus with molecule numbers 2−4. The hydrogen bond, which is of great importance in biological systems, is formed through the electrostatic interaction of the amide hydrogen atom of the central molecule and the amide carbonyl oxygen atom of molecule number 5. And also, the central molecule makes HBs by its carboxylic group with the other molecules.

The main concern of this work is to calculate the χ's of ^{2}H and ^{14}N, which contribute in the formation of hydrogen bond type $CON^{2}H\cdots O{=}CN^{2}H$, known as peptide HBs. As Table 2 indicates, the value of computed χ for this hydrogen peptide bond is 217.51 kHz. This value, which is obtained by taking the whole cluster into consideration, is expected to be close to the experimental value. However, the nuclear quadrupole coupling constant of the amide deuterium of α-glygly determined by static ^{2}H NMR has been reported as 174 kHz.[43]

In constructing the cluster, acceptors 2−4 are taking part. They are located at the same and also the adjacent layers of the central molecule.[26] These HBs, which make clusters, are of two kinds: $>N^{+}-{}^{2}H\cdots{}^{-}OCOR$ and $>N^{+}-{}^{2}H\cdots O{=}COR$. A typical value for the deuterium quadrupole coupling constant, which was deduced from the static NMR for $N-{}^{2}H$ bonds in amino acids, is 240 kHz.[44−46] Table 2 shows that the nuclear quadrupole coupling constants, χ's, of these hydrogen bonds have different values. As expected, the χ values of the $>N^{+2}H\cdots{}^{-}OCOR$ type are greater than the χ values of $>N^{+2}H\cdots O{=}COR$. Comparison between the data of Table 2 and the experimental findings indicates an agreement.

The carboxylic group of the central molecule forms HBs with molecules number 2 and 5, which are located at different crystallographic sites (Figure 1). These HBs are similar to those produced by their N-terminus. However, the χ values at the sites of ^{2}H are not the same as those computed for the central molecule. This discrepancy is due to the different chemical environments that they have in this cluster.

Finally, the nuclear quadrupole coupling constants at the sites of ^{2}H in $>C^2H_2$ groups of α-glygly are calculated (average value of $\chi = 188.87$ kHz). The computed values of these physical quantities are very close to those observed experimentally.[47] This is due to limited involvement of these $>C^2H_2$ groups in the interactions of the α-glygly in its solid phase.

Comparison of the results of RHF and DFT methods for χ's of ^{2}H reveals that the results are close together when the intermolecular hydrogen bonds are made across a layer. It seems that correlation effect decays with the inverse sixth power of the intermolecular distance, reduces more rapidly than when the intermolecular hydrogen bonds are built within the same layer.

II. ^{14}N Quadrupole Coupling Constants. The hydrogen bonds at the N^+H_3 site of the central molecule involve oxygen atoms of the CO_2^- residues of three neighboring molecules. X-ray crystallography data reveals that α-glygly has a layerlike structure. A quick look at an entire unit cell shows that two hydrogen bonds from the N^+H_3 residue of the central molecule are used to join molecules in the same layer (molecules number 3 and 4). The third hydrogen bond from the terminal nitrogen atom is formed by the interaction between molecules of two layers. One of the oxygen atoms is an acceptor of two hydrogen bonds, one being in the same layer (molecule number 5) and the other being from the adjacent layer (molecule number 2).[26]

Comparison of Tables 1 and 3 reveals the significance of hydrogen bonding in the crystal in determining the electric field gradient. The calculated χ value of N^+H_3 is 1.955 MHz. This shows some discrepancies from experiments (ref 48, $\chi = 1.280$ MHz; and ref 49, $\chi = 1.273, 1.247$ MHz). However, the χ's of the N^+H_3 residue of two adjacent molecules (number 2, $\chi = 1.016$ MHz; number 5, $\chi = 1.231$ MHz) have closer values to the experimental data.[48,49]

Figure 1 shows that the N^+H_3 group of the central molecule joins to two oxygen atoms in neighboring molecules, which participate in one hydrogen bond instead of two. When comparing χ's of the N^+H_3 site of the central molecule, molecule number 2 (across layer) and molecule number 5 (same layer) indicate the significance of the $^-$OCOR donor with respect to O═COR in electric charge distribution around terminal N. Table 3 shows that the χ value of the N^+H_3 residue of molecule number 5 is closer to the experimental one. Consequently, the $^-$OCOR donor of the molecule from the same layer has a greater effect in the electric field gradient of the ^{14}N atom.

The internal $-CO-^{14}NH$ groups are also hydrogen bonded to similar groups in neighboring molecules. Table 3 shows that the calculated χ value of the $CO^{14}NH$ group of the central molecule ($\chi = 3.178$ MHz) is very close to experiments (ref 48, $\chi = 3.03$ MHz; ref 49, $\chi = 3.04$ MHz). This illustrates that the $CO^{14}NH$ site of the central molecule approximately feels the same chemical environment as in the actual solid phase. In addition, the experimental studies are done at 77 K. Therefore, a portion of variation between calculated and experimental data is due to temperature difference.

Table 3 shows that the results of RHF and DFT methods for χ's of ^{14}N are close together when the intermolecular hydrogen bonds are made across a layer. These results for χ's of ^{14}N and ^{2}H are similar. However, most of the difference between the DFT and RHF χ value of $^{14}N^+H_3$ is for the central molecule. As expected, the $^{14}N^+H_3$ sites of the central molecule participate in three intermolecular hydrogen bonds. Then, the perturbation in the distributed electron density of the $^{14}N^+H_3$ site of the central molecule is the strongest. This creates more correlation effects which the Hartree−Fock method is not capable to sense.

Conclusion

On the basis of the findings of present research, it is concluded that the nuclear quadrupole coupling constants, χ's, of ^{2}H and ^{14}N in the hydrogen bond are appropriate parameters to characterize the properties of this bond. Ab initio calculations using RHF and B3LYP methods with 6-311++G** and 6-31++G** basis sets were employed to compute the χ's for a cluster in the solid phase of α-glygly. Nuclear quadrupole coupling constants of ^{2}H for the amide hydrogen bond were determined to be 217.51 kHz. This hydrogen belongs to the central molecule of the cluster. Also, χ values of the HBs produced by $N^{+2}H_3$ and the carboxylic group of the central molecule are computed and are in accord with those obtained experimentally.

The computed ^{14}N χ of $CO^{14}NH$ for the central molecule agrees well with experimental values. However, some discrepancies between calculated ^{14}N NQCC and experimental values of the $^{14}N^+H_3$ residue of the central molecule are obvious. This is due to the deficiency of the selected cluster in not including other molecules which participate in intermolecular hydrogen bonds with the $^-$OCOR donor of adjacent molecules.

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