Int. J. Mol. Sci. **2002**, *3*, 907-913

International Journal of
Molecular Sciences
ISSN 1422-0067

www.mdpi.org/ijms/

Proton NMR Chemical Shift Behavior of Hydrogen-Bonded Amide Proton of Glycine-Containing Peptides and Polypeptides as Studied by *ab initio* MO Calculation

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Received: 8 February 2002 / Accepted: 20 February 2002 / Published: 31 August 2002

Abstract: NMR chemical shifts of the amide proton of a supermolecule, an N-methylacetamide hydrogen-bonded with a formamide, were calculated as functions of hydrogen-bond length $R_{N...O}$ and hydrogen-bond angles by FPT-GIAO method within the framework of HF/STO 6-31^{++}G(d,p) *ab initio* MO method. The calculations explained reasonably the experimental data reported previously that the isotropic proton chemical shifts move downfield with a decrease in $R_{N...O}$. Further, the behavior of proton chemical shift tensor components depending on the hydrogen-bond length and hydrogen-bond angle was discussed.
Keywords: NMR chemical shift/ *ab initio* MO/ hydrogen bond/ peptides/ polypeptides/ glycine residue/

Introduction

In solid peptides and polypeptides the hydrogen bond plays an important role for forming the second-order structures such as the α-helix, β-sheet, *etc.* and higher-order structures [1-3]. For this reason, we have studied NMR methodologies for obtaining information about the hydrogen-bonded structure of peptides and polypeptides in the solid state through the observation of solid state NMR chemical shifts. Then, we have elucidated the relationship between the hydrogen-bond lengths and solid state NMR chemical shifts of ^{13}C [4-8], ^{15}N [9,10] and ^{17}O [11-13] nuclei from the experimental

and theoretical aspects. From these systematic works, it has been obtained that the observation of the main-chain chemical shifts leads to the determination of the hydrogen-bond length in solid peptides and polypeptides including proteins.

Most recently, the amide proton NMR spectra of glycine-containing peptides and polypeptides in the solid state, of which the hydrogen-bond lengths are distributed in the wide range, have been successfully measured by high frequency 800 MHz NMR [14] and 300 MHz NMR with the frequency-switched Lee-Goldburg (FSLG) homo-nuclear dipolar decoupling method [15]. These experimental results have showed that the amide proton chemical shifts move downfield with a decrease in $R_{N...O}$ (hydrogen-bond length between the amide nitrogen atom and amide carbonyl oxygen atom) or $R_{H...O}$ (hydrogen-bond length between the amide hydrogen atom and amide carbonyl oxygen atom). It has been preliminarily explained by *ab initio* 6-31G**basis set using a GlyGly supermolecule.

In this work we aim to calculate more sophisticatedly isotropic ^{1}H chemical shifts and ^{1}H chemical shift tensor components of the amide proton in a supermolecule, an N-methylacetamide hydrogen-bonded with a formamide, as functions of hydrogen-bond length $R_{N...O}$ and hydrogen-bond angles θ with the FPT-GIAO method within the HF/STO 6-31^{++}G(d,p) *ab initio* MO framework [16-18] in the Gaussian 98 program [19], in order to understand deeply behavior for the experimental isotropic ^{1}H chemical shifts of Gly-containing peptides and polypeptides associated with hydrogen bonding.

Theoretical Calculations

The 1H chemical shift calculations were made with the FPT-GIAO method within the STO 6-31^{++}G(d,p) *ab initio* MO framework [16-18] in the Gaussian 98 program [19] using the optimized geometries of a supermolecule, an N-methylacetamide hydrogen-bonded with a formamide. In the calculations, the hydrogen-bond length $R_{N...O}$ between the amide nitrogen atom and amide carbonyl oxygen atom and the hydrogen-bond angle θ were changed as shown in Fig. 1. The calculated chemical shifts are converted in ppm relative to tetramethylsilane(TMS).

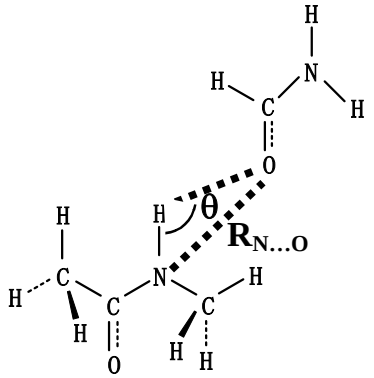

Figure 1. A diagram of an N-methylacetamide hydrogen-bonded with a formamide with the hydrogen-bond length $R_{N...O}$ between the amide hydrogen and amide carbonyl oxygen atoms, and the hydrogen-bond angle θ which is defined to be 180^o for the linear hydrogen bond(N-H…O=C).

Results and Discussion

For understanding a feature of the directions of the ^{1}H chemical shift tensor components of the amide proton, the calculated ^{1}H chemical shifts of an N-methylacetamide molecule are listed in Table 1 and the directions of the chemical shift tensor components are shown together with chemical structure of the molecule in Fig. 2. The chemical shift tensor components are asymmetric, and the anisotropy(= $\sigma_{11} - \sigma_{33}$) is about 11.3 ppm. The σ_{33} is almost directed to the amide N-H bond with the small deviation of 7.6^o from the linear hydrogen-bond (N-H…O=C) for which the hydrogen-bond angle θ is defined to be 0^o, the σ_{11} is perpendicular to the amide plane and the σ_{22} is perpendicular to the amide N-H bond. At this stage, according to our best knowledge there are no experimental data on ^{1}H chemical shift tensor components of peptides and polypeptides in spite of its importance.

The calculated isotropic ^{1}H chemical shifts of the amide proton of the supermolecule as function of $R_{N...O}$ and hydrogen-bond angle θ together with the experimental data on various Gly-containing peptides and polypeptides reported previously [14,15] are listed in Table 2. In the calculations the hydrogen-bond lengths and hydrogen-bond angles for various Gly-containing peptides and polypeptides as determined by X-ray diffraction are used. Fig. 3 shows the plots of the calculated and experimental amide ^{1}H chemical shifts against $R_{N...O}$. For convenience, the calculated chemical shielding value corresponding to GlyGly.HNO_3 was adjusted to that of the experimental chemical shift value of peptide with the maximum hydrogen-bond length in order to convert from the chemical shielding value to the chemical shift value. The isotropic ^{1}H chemical shifts move downfield with a

Table 1. ^{1}H chemical shieldings (ppm) of the amide proton of N-methyl-acetamide calculated by HF/STO STO 6-31^{++}G(d,p) *ab initio* MO method

σ_{iso}	σ_{11}	σ_{22}	σ_{33}
28.1	21.1	29.8	33.4

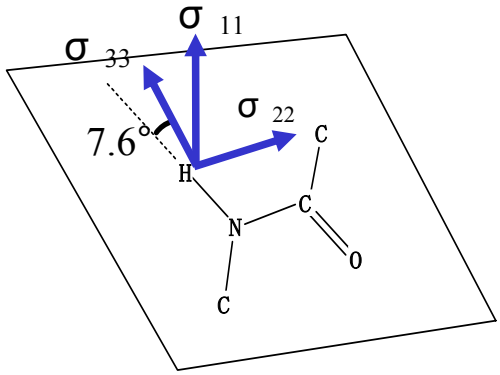

Figure 2. The directions of the chemical shift tensor components σ_{11}, σ_{22} and σ_{33} of the hydrogen-bonded amide proton are shown together with chemical structure of an N-methylacetamide molecule.

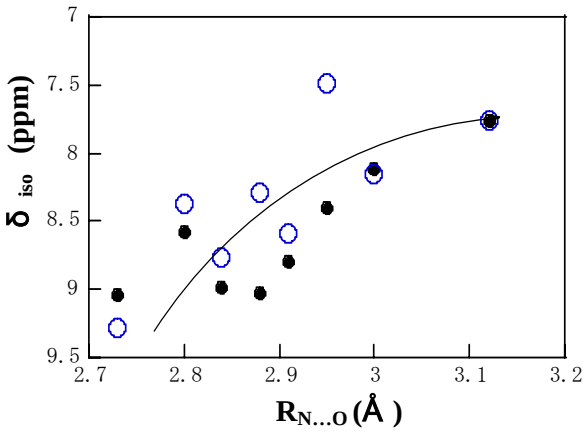

Figure 3. The plots of the calculated and experimental isotropic ^{1}H chemical shifts δ_{iso} of the amide proton as a function of $R_{N...O}$, where the calculated chemical shielding value corresponding to GlyGly.HNO_3 was adjusted to that of the experimental chemical shift value of peptide with the maximum hydrogen-bond length in order to convert from the chemical shift shielding value to the chemical shift value. The open circular symbol is for the calculation and the closed circular symbol for the experiment. The data points for peptide and polypeptide samples can be recognized by seeing the hydrogen-bond lengths in Table 2

Table 2. Calculated ^{1}H chemical shifts of the amide proton of a supermolecule, an N-methylacetamide hydrogen-bonded with a formamide, as functions of hydrogen-bond length $R_{N...O}$ and hydrogen-bond angles by FPT-GIAO method within the framework of HF/STO 6-31^{++}G(d,p) *ab initio* MO method together with the experimental data reported previously [14,15].

Sample	Experimental hydrogen-bonded glycine amide proton chemical shift[a] δ_{iso} (ppm)	Calculated hydrogen-bonded glycine amide proton chemical shift[b] δ_{iso} (ppm)	Hydrogen-bond length $R_{N...O}$ (Å)	Hydrogen-bond angle θ (degree)
Poly glycine (form II)	9.04	9.29	2.73	146.2
Tyr - Gly – Gly	9.03	8.29	2.88	144.0
Pro - Gly – Gly	8.99	8.77	2.84	151.9
Gly – Gly	8.59	—	2.94	—
Poly glycine (form I)	8.40	7.49	2.95	132.8
Ala - Gly – Gly	8.12	8.15	3.00	160.2
Val - Gly – Gly	8.80	8.59	2.91	163.1
Sar - Gly –Gly	8.57	8.37	2.80	137.5
Gly - Gly · HNO_3	7.76	7.76	3.12	164.6

a) From ref. 14

b)The calculated chemical shielding value corresponding to GlyGly.HNO_3 was adjusted to that of the experimental chemical shift value of peptide with the maximum hydrogen-bond length in order to convert from the chemical shift shielding value to the chemical shift value.

decrease in $R_{N...O}$ in the calculations and experiments. From this figure, it is shown that the slope of the curve becomes gradually small with an increase in $R_{N...O}$. This means that the effect of the hydrogen bonding on the chemical shift is asymptotically decreased with an increase in $R_{N...O}$. The calculations reproduce well the experiments.

The calculated ^{1}H chemical shielding tensor components of the amide proton are shown as a function of $R_{N...O}$ in Fig. 4 together with the isotropic ^{1}H chemical shielding, where the hydrogen-bond angle is fixed to be 180°. The isotropic chemical shielding moves downfield with a decrease in $R_{N...O}$. The σ_{11} and σ_{22} components move largely downfield with a decrease in $R_{N...O}$, but the σ_{33} component moves slightly upfield with a decrease in $R_{N...O}$. As mentioned above, the σ_{33} is almost directed to the amide N-H bond. It can be said that the σ_{11} and σ_{22} components govern predominantly the downfield shift in isotropic chemical shift. On the other hand, as shown in Fig. 5 the angle Ψ between the amide N-H bond and the direction of the σ_{33} component approaches 0° with a decrease in $R_{N...O}$ until $R_{N...O}$ = 1.5 A. This shows that the direction of distortion of electronic distribution on the amide proton approaches the N-H bond with a decrease in $R_{N...O}$. If $R_{N...O}$ is further decreased, the angle Ψ deviates with the positive sign from the amide N-H bond again. In the shorter $R_{N...O}$ range, the direction of the distortion electronic distribution on the amide proton is strongly affected by interactions with neighboring atoms and so the angle Ψ deviates with the positive sign from the amide N-H bond again. As reported previously [9,10], the direction of the σ_{33} component for the amide nitrogen is along the N-H bond. This direction is the same as the case of the amide proton σ_{33} component.

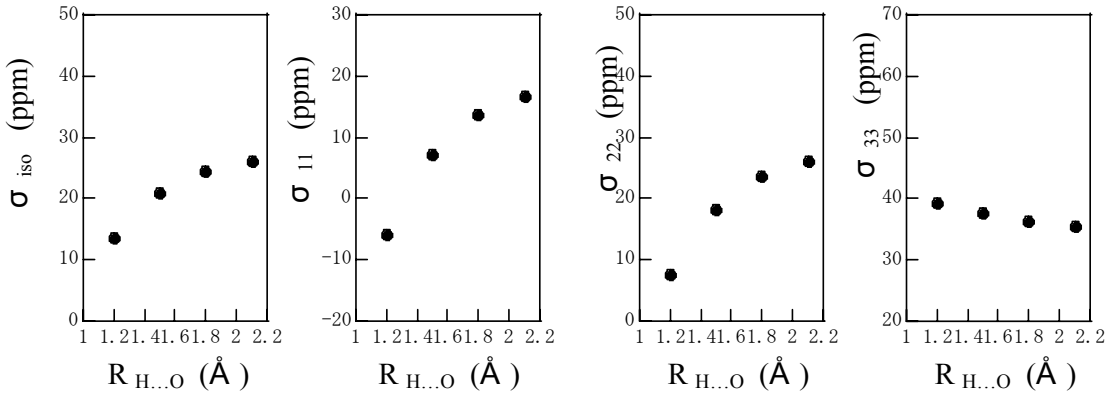

Figure 4. The plots of the calculated isotropic ^{1}H chemical shielding σ_{iso} and ^{1}H chemical shielding tensor components σ_{11}, σ_{22} and σ_{33} of the amide proton of an N-methylacetamide hydrogen-bonded with a formamide against $R_{N...O}$, where the hydrogen-bond angle is fixed to be 180°.

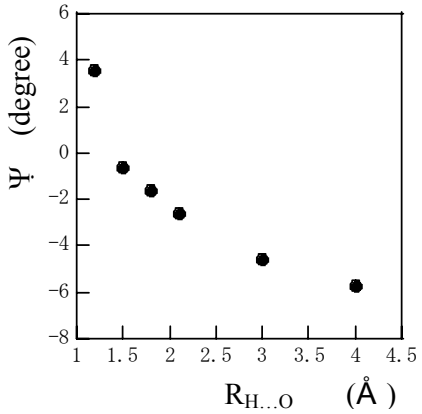

Figure 5. The plots of the angle Ψ between the amide N-H bond and the direction of the calculated ^{1}H chemical shielding tensor component σ_{33} of the amide proton of an N-methylacetamide hydrogen-bonded with a formamide against $R_{H...O}$.

Fig. 6 shows the plots of the calculated isotropic chemical shielding and chemical shielding tensor components against the hydrogen-bond angle θ. The deviation of the linear hydrogen-bond leads to downfield shift for the isotropic chemical shielding. The σ_{11} and σ_{22} components move largely downfield with a decrease in θ, but the σ_{33} component moves slightly upfield with a decrease in $R_{N...O}$. It can be said that the σ_{11} and σ_{22} components govern predominantly the downfield shift in isotropic chemical shift.

At present, there are no experimental data of the amide proton chemical shift tensor components. If these data are obtained, we will be able to obtain deeper insight of hydrogen bonding by comparing the calculations and experiments.

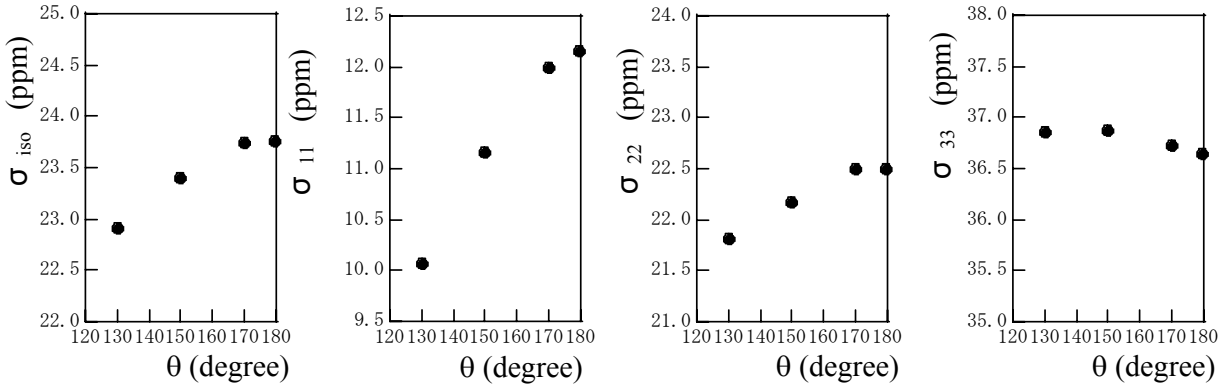

Figure 6. The plots of the calculated isotropic chemical shielding σ_{iso} and chemical shielding tensor components σ_{11}, σ_{22} and σ_{33} of the amide proton of an N-methylacetamide hydrogen-bonded with a formamide against the hydrogen-bond angle θ.

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