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Pressure effect on the amide I frequency of the solvated α-helical structure in water

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Abstract

As a model system of the pressure dependence of the amide I mode of the solvated α-helical structure in a helical peptide, we have calculated the frequency shifts of the amide I modes as a function of the distance between *trans-N*-methylacetamide (*t*-NMA) dimer and a water molecule ($d_{C=O\cdots H-O}$) by the density-functional theory (DFT) method at the B3LYP/6 − 31G++(d, p) level. Two amide I frequencies at 1652 and 1700 cm^{-1} were observed under this calculation. The former is ascribed to the amide I mode forming the intermolecular hydrogen bond (H-bond) between *t*-NMA and H_2O in addition to the intermolecular H-bond in the *t*-NMA dimer. The latter is due to the amide I mode forming only the intermolecular H-bond in the *t*-NMA dimer. We have found that the amide I frequency at 1652 cm^{-1} shifts to a lower frequency with decreasing $d_{C=O\cdots H-O}$ (i.e., increasing pressure), whereas that at 1700 cm^{-1} shifts to a higher frequency. The amide I frequency shift of 1652 cm^{-1} is larger than that of 1700 cm^{-1} by the intermolecular H-bond. Thus, our results clearly indicate that the pressure-induced amide I frequency shift of the solvated α-helical structure correlates with the change in $d_{C=O\cdots H-O}$.

(Some figures in this article are in colour only in the electronic version)

1. Introduction

Solvated and buried α-helical structures exist in helical rich proteins because of the difference in the located environment of the α-helix [1] (figure 1). The former is fully exposed to the water molecules and the latter is located in the interior of the protein. Recently we reported that

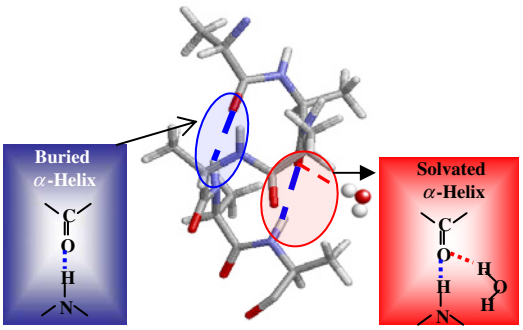

Figure 1. Scheme of the solvated (right) and buried (left) α-helix in a peptide.

the amide I′ frequencies, (N-deuterated), of the solvated α-helical structures ($\sim$1635 cm^{-1}) of *de novo* designed oligopeptides such as AK16(YGAAKAAAAKAAAAKA-NH_2) and the four-helix bundle protein (α-l-α)$_2$ shift to a lower frequency with increasing pressure, while those of the buried α-helical structure ($\sim$1655 cm^{-1}) shift to a higher frequency [2–5]. Then, what contribution causes the amide I frequency shift of the α-helical structures? Here, we have focused on the hydrogen bond (H-bond) between the α-helical structure and solvated water molecules to clarify the pressure-induced lower amide I frequency shift of the solvated α-helical structure.

We selected *N*-methylacetamide (NMA; $CH_3CONHCH_3$) dimer + H_2O as a model system of the solvated α-helical structure. NMA is the simplest model compound for investigating the structural and physical properties of the peptide group [6]. Early x-ray diffraction data suggested that NMA has the *trans* structure in the crystalline phase and takes the coplanar structure (*trans*-NMA and *cis*-NMA refer to the orientation of C=O and N–H with respect to the C–N bond) [7]. Nuclear magnetic resonance (NMR), Raman and UV-Raman experiments, and *ab initio* molecular orbital (MO) calculations indicate that NMA in aqueous solution takes mainly the *trans* conformation, but is in a thermodynamic equilibrium with the *cis* conformation, which is about 10 kJ mol^{-1} higher in free energy [8–10].

In the present study, we have calculated the frequency shift in the amide I mode as a function the molecular distance between the *trans*-NMA (*t*-NMA) dimer and a water molecule ($d_{C=O\cdots H-O}$) by a density-functional theory (DFT) calculation at the B3LYP/6 − 31G++(d, p) level. We discuss the consequence of the hydrogen bond on the amide I frequency shift of the solvated α-helical structure of oligopeptides in water.

2. Methods

All DFT calculations were carried out using the GAUSSIAN03 program [11]. The geometry optimization and the frequency calculation were performed for *t*-NMA dimer + H_2O at the B3LYP/6 − 31G++(d, p) level including the solvent effect, which is the polarized continuum model (PCM) [12]. Ghosh *et al* [13] showed that the average number of water molecules combined with the peptide bond in the α-helical structure of EK peptide (Ac-YA(EAAKAA)$_3$F-NH_2) in water is about one by a molecular dynamics (MD) simulation. Garcia *et al* [14] supported the simulation result of Ghosh *et al* by MD simulation of Ac-A(AARA)$_3$A-NHMe. Therefore, we selected the *t*-NMA dimer and a water molecule to investigate the hydrogen-bond effect on the amide I frequency.

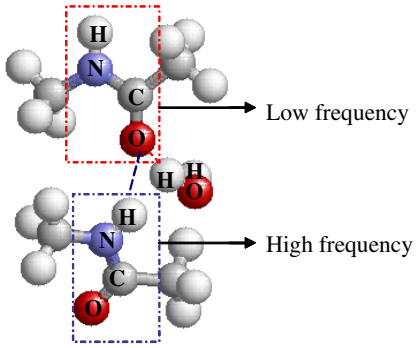

Figure 2. Optimized structure of *t*-NMA dimer + H_2O for the B3LYP/6 − 31G++(d, p) basis set.

Table 1. Optimized structural data of *t*-NMA dimer+H_2O for the B3LYP/6 − 31G++(d, p) basis set.

Structural data	*t*-NMA dimer[a]	*t*-NMA dimer + H_2O	Buried α-helix[b]	Solvated α-helix[c]
$d_{(H\cdots O)}$ (Å)	2.32	2.36	2.30	2.40
$d_{(C{=}O\cdots HOw)}$[d] (Å)	—	1.98	—	2.33
$\angle_{(N-H\cdots O)}$ (deg)	157.7	149.2	139.4	135.0
$\angle_{(C{=}O\cdots O)}$ (deg)	149.8	140.2	130.0	126.5
$\angle_{(C{=}O\cdots Ow)}$ (deg)	—	125.6	—	131.7

[a] B3LYP/6 − 31G++(d, p).
[b] The average value of the H-helix, which is located at the exterior of myoglobin taken from PDB file (2MB5).
[c] The average value of the F-helix, which is located in the interior of myoglobin taken from PDB file (2MB5).
[d] (C=O · · · HOw) shows the distance between the C=O group of NMA and the HO group of a water molecule.

3. Results and discussion

3.1. The optimization of t-NMA dimer + H_2O.

Figure 2 shows the optimized structure of *t*-NMA dimer + H_2O. The optimized structural parameters of *t*-NMA dimer, the solvated (H-helix), and buried (F-helix) α-helical structures of myoglobin are compared with those of *t*-NMA dimer +H_2O in table 1. The H-helix and F-helix structures of myoglobin are located at the exterior and in the interior in myoglobin, respectively. The average values of $d_{O\cdots H}$ in the buried α-helical structure of myoglobin are shorter than those of the solvated α-helical structure. The average values of $\angle_{(N-H\cdots O)}$ and $\angle_{(C=O\cdots H)}$ of the buried α-helical structure are larger than those of the solvated α-helical structure. These differences in the structural parameters between the solvated and buried α-helical structures are mainly due to the intermolecular H-bonds between the peptide groups and water molecules [1]. On the other hand, the value of $d_{O\cdots H}$ of *t*-NMA dimer is shorter than that of *t*-NMA dimer + H_2O. The values of $\angle_{(N-H\cdots O)}$ and $\angle_{(C=O\cdots H)}$ of the *t*-NMA dimer are larger than those of *t*-NMA dimer + H_2O. The difference in the structural parameters between the *t*-NMA dimer and *t*-NMA dimer + H_2O is qualitatively consistent with those between the buried and solvated α-helical structures of myoglobin.

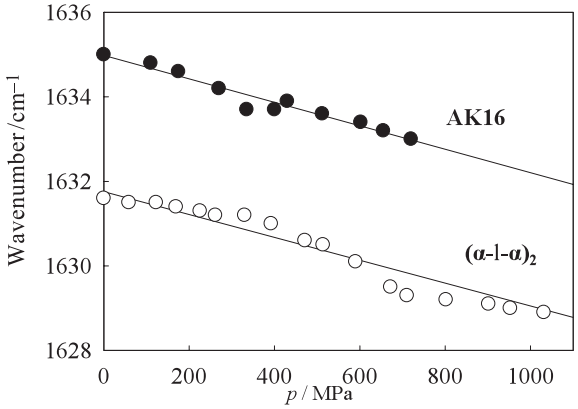

Figure 3. Pressure dependence of the amide I′ frequency shifts of the solvated α-helical structures of AK16 and $(\alpha\text{-l-}\alpha)_2$ in aqueous solution. The representation of the amide I′ frequency obtained by the experiments is due to the deuteration of the backbone amide proton.

Two amide I frequencies of t-NMA dimer + H_2O at 1652 and 1700 cm^{-1} were observed under this calculation, and those of t-NMA dimer at 1684 and 1702 cm^{-1} were observed. The peak at 1684 cm^{-1} of the t-NMA dimer shifts to 1652 cm^{-1} because of the intermolecular H-bond between the t-NMA dimer and a water molecule. Thus, the peak at 1652 cm^{-1} of t-NMA dimer + H_2O is ascribed to the amide I mode forming an intermolecular H-bond between the t-NMA dimer and a water molecule in addition to the intermolecular H-bond in the t-NMA dimer. The peaks at 1700 and 1702 cm^{-1} are due to the amide I mode forming only an intermolecular H-bond in the t-NMA dimer.

Generally, it is known that the amide I frequency of the solvated α-helix appears lower than that of the buried α-helix [1]. The calculated average amide I frequency of t-NMA dimer+H_2O (1676 cm^{-1}) appeared at a lower value than that of the t-NMA dimer (1693 cm^{-1}). The order in the calculated amide I frequencies between t-NMA dimer and t-NMA dimer + H_2O is qualitatively consistent with that between the solvated and buried α-helical structures. According to the results of an *ab initio* MO calculation by Ham *et al* [15, 16], the amide I frequency of t-NMA monomer was found to be linearly proportional to the hydration-induced displacement of the C=O bond length when t-NMA monomer is hydrated by a few water molecules. The intermolecular H-bond formation between the t-NMA dimer and a water molecule induces a lower-frequency shift of the amide I mode of the t-NMA dimer. The difference in the amide I frequency between the solvated and buried α-helix structures of myoglobin [17] is qualitatively consistent with that between t-NMA dimer + H_2O and t-NMA dimer. Therefore, t-NMA dimer + H_2O provides the simplest model system of the solvated α-helical structure.

3.2. Pressure dependence of the amide I mode of the solvated α-helical structure

Generally, it is known that the stretching vibrational frequency shifts to a lower frequency with increasing pressure [18]. Figure 3 shows the pressure dependence of the amide I′ frequencies of the solvated α-helical structures of AK16 and $(\alpha\text{-l-}\alpha)_2$ in water. The amide I′ frequencies of the solvated α-helical structures of AK16 and $(\alpha\text{-l-}\alpha)_2$ shift to a lower frequency with increasing pressure. Because the intermolecular H-bond between the C=O group of the peptide bond and water molecules becomes stronger with increasing pressure, the C=O force constant weakens

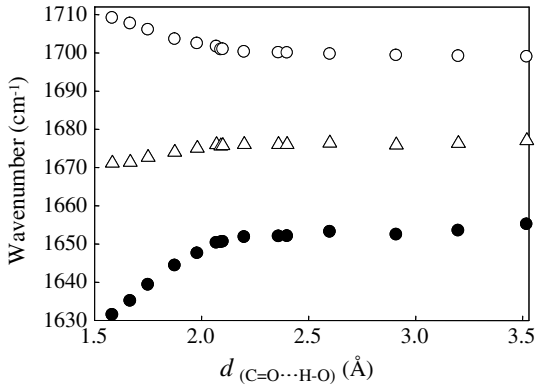

Figure 4. Distance ($d_{(C=O\cdots H-O)}$) dependence of the amide I frequencies of *t*-NMA dimer + H_2O for the B3LYP/6 − 31G++(d, p) basis set. The closed and open circles represent the lower and higher amide I frequencies, respectively. The open triangle represents the average frequency of the two amide I frequencies.

and the contribution of the anharmonicity of the C=O bond is larger. The change in the intermolecular H-bond distance between the C=O group of the *t*-NMA dimer and the O–H group of a water molecule relates to the pressure-induced changes of the intermolecular H-bond distance in the solvated α-helical structure. We calculated the $d_{C=O\cdots H-O}$ dependence of the amide I frequencies of *t*-NMA dimer + H_2O.

Figure 4 shows the $d_{C=O\cdots H-O}$ dependence of the amide I frequency shifts of *t*-NMA dimer + H_2O. The amide I frequency at 1652 cm^{-1}(•) shifts to a lower frequency with decreasing $d_{C=O\cdots H-O}$ (i.e., increasing pressure), whereas that at 1700 cm^{-1} (○) shifts to a higher frequency. The two amide I frequency shifts become much larger below $d_{C=O\cdots H-O}$ = 2.36 Å. These shifts indicate that the intermolecular H-bond between the C=O group of the *t*-NMA dimer and the O–H group of a water molecule becomes stronger with shortening $d_{C=O\cdots H-O}$, whereas the intermolecular H-bond in the *t*-NMA dimer weakens. Because the amide I frequency shift of 1652 cm^{-1} is larger than 1700 cm^{-1}, the average amide I frequency shift of *t*-NMA dimer +H_2O below $d_{C=O\cdots H-O}$ = 2.36 Å is dominated by the frequency change of 1652 cm^{-1}. This lower amide I frequency shift of *t*-NMA dimer + H_2O with shortening $d_{C=O\cdots H-O}$ (below $d_{C=O\cdots H-O}$ = 2.36 Å) is similar to that of the solvated α-helical structure. Hence, our results indicate that pressure-induced shortening of the intermolecular H-bond between the C=O group of the peptide bond and O–H group of water molecules is the cause for the lower-frequency shift of the amide I mode of the solvated α-helical structure. In a recent simulation study of the IR spectrum by Paschek *et al* [19], it was suggested that the pressure-induced lower amide I frequency shift of AK peptide (Ac-AA(AAKAA)$_3$AAY-NHMe) is due to the hydration effects between the peptide and water molecules rather than the structural changes in the peptide. The present results support the simulation results by Paschek *et al*.

In summary, we have investigated the frequency shifts of the amide I mode of *t*-NMA + H_2O as a function of the distance between the *t*-NMA dimer and a water molecule ($d_{C=O\cdots H-O}$) by DFT calculation at the B3LYP/6 − 31G++(d, p) level. Due to the strong intermolecular H-bond formation between the C=O group of the *t*-NMA dimer and the O–H group of a water molecule, the amide I frequency of *t*-NMA dimer + H_2O shifts to a lower frequency with shortening $d_{C=O\cdots H-O}$. The present results are qualitatively consistent with the pressure-induced lower amide I frequency shift of the solvated α-helical structure of oligopeptides. Thus,

the lower amide I frequency shift of the solvated α-helical structure strongly correlates with the change in $d_{C=O\cdots H-O}$.

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