Theoretical Studies on the Effect of N-Substitution on the Hydrogen Bonds of Metal Ion/Water/Amide Complexes

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The effect of N-substitution on the hydrogen bonds of metal ion/water/amide complexes is studied on Li^+/N-methylformamide-water as an example. Using the energies and Mulliken atomic populations derived from ab initio calculations with minimal GLO basis set, the Li^+/N-methyl formamide-water and Li^+/formamide-water complexes are compared. The transference of the effect of metal ions along the molecular structure seems to have a profound relationship to the bond polarizabilities of the backbone atoms. This can be discussed qualitatively in terms of changes in the Mulliken atomic publications.

Introduction

The interaction of metal ions with proteins in aqueous solution is subject of great interest since it has been found that various kinds of metal ions are involved in most biological processes [1, 2].

The chemistry and experimental findings of the effect of metal ions on structures and reactivities of proteins have been discussed elsewhere [3, 4].

There is only a limited amount of direct experimental investigations on the effect of metal ions on biological hydrogen-bonded systems, since the behavior of these macromolecules containing various kinds of ions in aqueous solution is too complicate to be studied by usually available experimental techniques [5, 6].

Some theoretical studies on the interaction of metal ion with hydrogen-bonded complexes have been carried out ranging from small systems such as Li^+/water-ammonia [7] to rather large-sized molecular structures like the base pairs of DNA, adenine-thymine and guanine-cytosine [8, 9]. Metal ions seem to be able to transport their effects passing through backbone atoms to various parts of the molecular structures. Hydrogen bonds neighbouring to metal ion binding positions are also affected either by stabilization or destabilization [9], depending on the nature and structure of the molecular backbone. These theoretical results lead to a possible reason for "mispairing" of polynucleotides at rather high metal ion concentration conditions [8].

In continuation of our previous studies, the N-substitution of the peptide backbone is considered in this work. The Li^+/N-methylformamide-water complex was selected as a model for ab initio calculations with minimal basis set. The results of this study are discussed and compared with those of the Li^+/formamide-water complex [10].

Computational Details

The chemical systems as considered in this study are considerably large in the view of ab initio calculations. Therefore, a minimal GLO basis set had to be used. Although the absolute energies are not very accurate in this framework, the relative changes have been proved to reflect correctly the energy effects of cations on hydrogen-bonded systems [7–10]. The exponents of the basis set used were taken from [11], and have been used successfully in several calculations on similar systems [7, 10].

The geometries of N-methylformamide (NMF) and water were taken from [12] and kept constant throughout the calculations since it has been shown in our previous work [7] that the intermolecular geometrical parameters and relative energy changes calculated with the minimal GLO basis set are not

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very sensitive to the monomer geometry optimizations [7].

The geometries of NMF and water are shown in Figure 1. The CH_3 group of NMF was selected cis to the O(8) atom so that the N(9)−H(1) ... O(10) hydrogen bond formation in our model corresponds to that between N−H groups of an amino acid residue in a polypeptide chain and surrounding water molecules. The water molecule, the O=C−N−C backbone and Li^+ ion are located in the same plane.

The Li^+−O(8)−C(6) and N(9)−H(1) ... O(10) angles were fixed at 180° according to the previous results on similar chemical systems [10, 11]. The Li^+−O(8) and N(9)−H(1) ... O(10) distances were optimized.

In order to express systematically the energy effect of metal ions on hydrogen-bonded systems the Net Stabilization Energy (NSE), which is defined as the difference between hydrogen bond energies after and before complexing of a metal ion, is used as a criterion. A positive NSE value corresponds to a more stabilized hydrogen bond, due to metal ion complexing.

The electronic distributions on the molecular structures were studied using the Mulliken population analysis [13]. Although this method is basis set dependent it can, however, be used as a tool to study the relative changes in atomic populations or, in other words, electron densities at atoms due to either metal ion binding or hydrogen bond formation [14]. The changes in the Mulliken atomic populations in this study are represented by Δ_{pop}, which denotes the difference between the Mulliken atomic population after and before metal ion complexing or hydrogen bond formation. Therefore, positive or negative values of Δ_{pop} indicate a gain or loss of atomic populations, respectively.

In order to investigate systematically the substitution effect on the electron distributions over the molecular structure, $\Delta_i^{M}{}_{\rightarrow j}$ is defined as the amount of electrons transfering from an atom or group of atoms i to the group of atoms j in the molecule or complex M.

All calculations were performed at the CDC Cyber 74 computer of the University of Innsbruck.

Results and Discussion

The energy optimized intermolecular geometrical parameters are listed in Table 1. The total, binding and hydrogen bond energies are reported in Table 2, the Mulliken atomic populations of the molecular systems considered here are given in Table 3.

The changes in the atomic populations (Δ_{pop}) are illustrated in Fig. 2, together with the values of $\Delta_i^{M}{}_{\rightarrow j}$.

The N-methylformamide molecule

The total energy of N-methylformamide is −176.4416 hartree. The substitution of CH_3 for H(7) (see Fig. 1) in the N−C=O backbone of formamide (FA) induces the atomic population on H(1) to decrease by about 0.0746. This can be interpreted as an increase in the proton donor ability of the N(9) atom due to the N-methyl substitution. The reason for this will be discussed in details in connection with the NMF-water hydrogen bond formation.

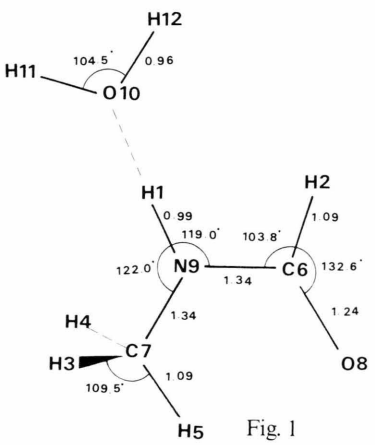


Fig. 1

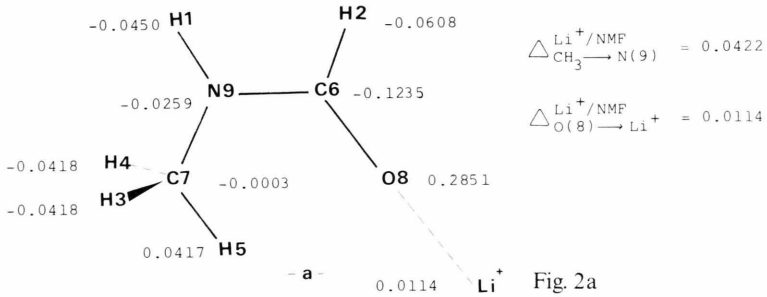
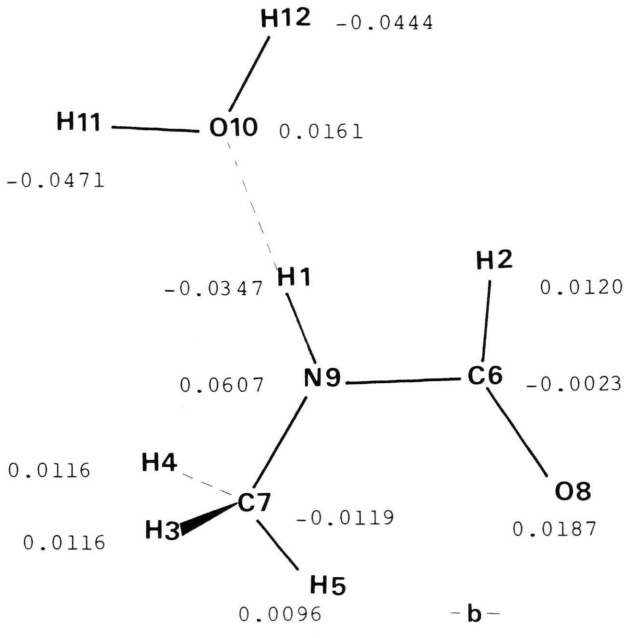


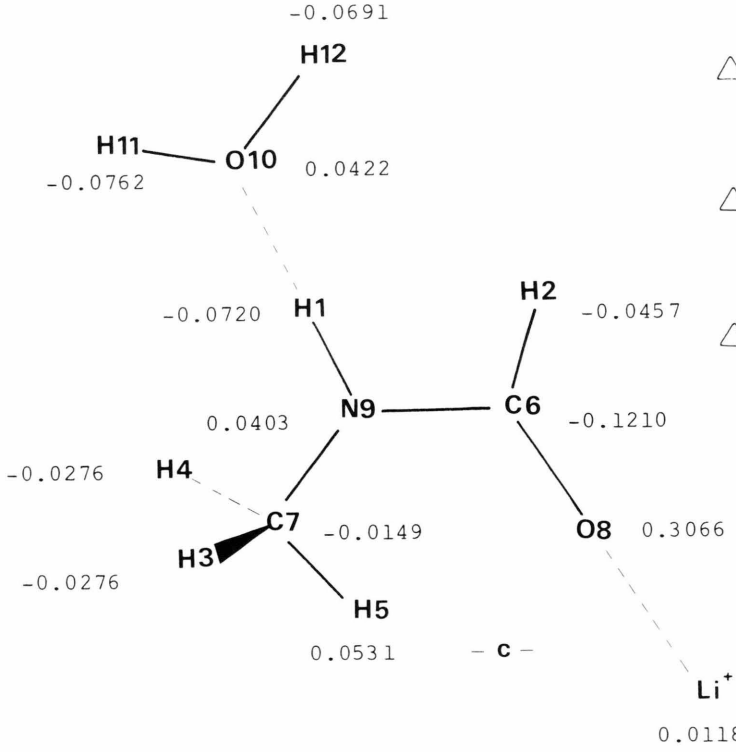
Fig. 2a



$\Delta^{NMF-H_2O}_{O(10)\longrightarrow H(1)} = 0.0754$

$\Delta^{NMF-H_2O}_{N(9)\longrightarrow CH_3} = 0.0209$

Fig. 2b



$\Delta^{Li^+/NMF-H_2O}_{CH_3\longrightarrow N(9)} = 0.0170$

$\Delta^{Li^+/NMF-H_2O}_{O(10)\longrightarrow H(1)} = 0.1031$

$\Delta^{Li^+/NMF-H_2O}_{O(8)\longrightarrow Li} = 0.0118$

Fig. 2c

Fig. 1. Geometries of N-methylformamide and water. (Bond lengths in Å, bond angles in degrees.)

Fig. 2. Changes in atomic populations (Δ_{pop}) due to complex formations. a) Li^+/NMF; b) NMF–H_2O; c) Li^+/NMF–H_2O. Positive or negative values of Δ_{pop} denote gain or loss of atomic population.

$\Delta^{NMF}_{CH3 \rightarrow N(9)}$ is 0.4226, compared to $\Delta^{FA}_{H \rightarrow N(9)}$, 0.3936. This indicates the well known fact that the CH_3 group is a better electron donor than the H atom.

The Li^+/N-methylformamide complex

The total energy of the Li^+/NMF complex at equilibrium geometry is −182.9107 hartree. The optimized Li^+−O(8) distance is 1.77 Å with a binding energy of −37.1 kcal/mole. The binding of the Li^+ ion to the O(8) atom of NMF leads to significant changes in the Mulliken atomic populations as shown in Figure 2.

$\Delta^{Li^+/NMF}_{CH_3 \rightarrow N(9)}$ is 0.0422 whereas $\Delta^{Li^+/FA}_{H(7) \rightarrow N(9)}$ is only 0.0248. This could be interpreted in terms of the higher polarizability of the C−N bond compared to N−H. This has been found already in the studies of the effect of metal ions on the hydrogen bonds of DNA base pairs, but the evidence from the Mulliken population analysis was not so clear according to the complexity of the purine and pyrimidine structures.

The Li^+/NMF complex formation leads to a decrease of the atomic population at the H(1) atom by about 0.045 whereas that of Li^+/FA is about 0.052. This small difference seems to indicate that the inductive effect on H(1) caused by the Li^+ ion is less pronounced when H(7) is substituted by the

Table 1. Optimized geometrical parameters.

System	O(10) ... N(9) (Å)	Li^+−O(8) (Å)
Li^+/NMF	–	1.77
NMF−H_2O	2.70	–
Li^+/NMF−H_2O	2.60	1.77

NMF = N-methylformamide.

Table 2. Total, binding and hydrogen bond energies.

System	Total energy (hartree)	Binding energy (kcal/mole)	H-bond energy (kcal/mole)
Li^+	−6.4100 [a]	–	–
H_2O	−64.5189 [a]	–	–
NMF	−176.4416	–	–
Li^+/NMF	−182.9107	−37.1	–
NMF−H_2O	−240.9867	–	16.4
Li^+/NMF−H_2O	−247.4690	−45.4	24.7

[a] value taken from [7]. NMF = N-methylformamide.

Table 3. Atomic populations calculated at equilibrium geometries.

System	H(1)	H(2)	H(3)	H(4)	H(5)	C(6)	C(7)	O(8)	N(9)	Li^+	O(10)	H(11)	H(12)	H(7)
H_2O	–	–	–	–	–	–	–	–	–	–	8.3776	0.8112	0.8112	–
NMF	0.5439	0.9364	0.8369	0.8369	0.7948	5.4845	6.1088	8.2095	8.2095	–	–	–	–	–
Li^+/NMF	0.4989	0.8756	0.7951	0.7951	0.8365	5.3620	6.1085	8.5333	8.1836	2.0114	–	–	–	–
NMF−H_2O	0.5092	0.9484	0.8485	0.8485	0.8044	5.4822	6.0969	8.2669	8.2702	–	8.3937	0.7641	0.7668	–
Li^+/NMF−H_2O	0.4719	0.8907	0.8093	0.8093	0.8479	5.3935	6.0939	8.5548	8.2498	2.0118	8.4198	0.7350	0.7421	–
FA [a]	0.6185	0.9633	–	–	–	5.5525	–	8.2550	8.0043	–	–	–	–	0.6064
Li^+/FA [a]	0.5664	0.8997	–	–	–	5.4320	–	8.5383	7.9706	2.0114	–	–	–	0.5816
FA−H_2O [a]	0.5807	0.9724	–	–	–	5.5538	–	8.2769	8.0651	–	8.3890	0.7711	0.7723	0.6186
Li^+/FA−H_2O [a]	0.5353	0.9111	–	–	–	5.4366	–	8.5670	8.0371	2.0116	8.4161	0.7417	0.7460	0.5975

[a] Values taken from [10]. NMF = N-methylformamide, FA = formamide. H(7) = The hydrogen atom substituted by the CH_3 group.

CH_3 group. Using the aforementioned concept of bond polarizability one can conclude that within the same molecule the inductive effect can be conducted better through the O=C−N−C backbone than through O=C−N−H.

The N-methylformamide-water adduct

The total energy of NMF-water at equilibrium geometry is −240.9867 hartree. The optimized N(9)−H(1) ... O(10) distance is 2.70 Å, with a hydrogen bond energy of 16.4 kcal/mole. The order of the hydrogen bond energies resulting from this and our previous work is

$$H_2O-NH_3 < FA-H_2O < NMF-H_2O\,.$$

Substitution of H(7) by CH_3 at N(9) makes the N(9)−H(1) ... O(10) hydrogen bond stronger by about 2.0 kcal/mole. This can be understood using the results previously discussed for the NMF and FA molecules, namely the decrease of the H(1) population due to N-methyl substitution. This brings about an increase in the electrostatic interaction between the N(9)−H(1) proton donor and the O(10) proton acceptor resulting in a stabilization of the hydrogen bond.

According to qualitative chemical models, N-methyl substitution should lead to an increase of the N(9) atomic population and the C(6)−N(9) π-bond character, since the CH_3 group is an electron donating group.

The substitution should, therefore, lead to a higher electron density at N(9) inducing less acidity for the H(1) proton and a decrease in the hydrogen bond interaction. Del Bene [15] and Morokuma [16] have independently studied the N-substitution effects in hydrogen bonding of R−O−H ... NH_3. The strength of hydrogen bonds increases as R varies from H to CH_3, NH_2, OH and F. It has been concluded by Del Bene, using the results of the Mulliken population analysis, that the order found follows the order of increasing σ-electron withdrawing ability of the substituent R in the ROH molecule. In our study we found an overall electron shift from CH_3 to N(9). One can explain the decreasing atomic population at the H(1) atom due to the N-methyl substitution considering the delocalization of electrons into the N−C−O backbone. The N-methyl substitution apparently increases the N−C-π-bond character and as a consequence, electrons from H(1) migrate into the N−C−O backbone of the molecule.

The Li^+/N-methylformamide-water complex

The optimized Li^+−O(8) distance remains the same as in the Li^+/NMF complex. The complex formation energy in Li^+/NMF-water is considerably higher than that in Li^+/NMF (by about 8.3 kcal/mole stronger). This may be attributed to both stabilization of the Li^+−O(8) bond and the N(9)−H(1) ... O(10) hydrogen bond. This stabilization was also reflected by the results of the Mulliken population analysis calculated at the equilibrium geometries of the NMF-water and Li^+/NMF complexes as discussed in the previous sections.

The N(9)−H(1) ... O(10) hydrogen bond distance is 2.60 Å, that is about 0.1 Å shorter than in NMF-water. The hydrogen bond energy in this case amounts to 24.7 kcal/mole, which corresponds to an NSE value of 8.3 kcal/mole. This value is 0.5 kcal/mole lower than that of the Li^+/FA-water complex. A lower NSE value due to the N-methyl substitution was expected due to the difference in the H(1) atomic population as discussed previously in the comparison of Li^+/FA with Li^+/NMF.

The order of the Li^+ induced NSE values obtained from this and previous works is, therefore:

$$\begin{aligned}&NSE(H_2O/NH_3) > NSE(H_2O)_2 > \\ &\quad NSE(FA/H_2O) > NSE(NMF/H_2O)\,.\end{aligned}$$

This series indicates that, besides larger distances of the metal ion to the hydrogen bond, also the existence of double bonds (bonds with π-character) in the complex reduces the ion effect on the stabilization of the hydrogen bond, the more, the higher the double bond character is.

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