Gas Phase Intramolecular Proton Transfer in Cationized Glycine and Chlorine Substituted Derivatives (M – Gly, M = Na^+, Mg^{2+}, Cu^+, Ni^+, and Cu^{2+}): Existence of Zwitterionic Structures?

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Abstract: The intramolecular proton transfer in cationized glycine and chlorine substituted derivatives with M = Na^+, Mg^{2+}, Ni^+, Cu^+, and Cu^{2+} has been studied with the three parameter B3LYP density functional method. The coordination of metal cations to the oxygens of the carboxylic group of glycine stabilizes the zwitterionic structure. For all monocations the intramolecular proton transfer occurs readily with small energy barriers (1 – 2 kcal mol^{-1}). For the dication Mg^{2+} and Cu^{2+} systems, the zwitterionic structure becomes very stable. However, whereas for Mg^{2+}, the proton transfer process takes place spontaneously, for Cu^{2+} the reaction occurs with an important energy barrier. The substitution of the hydrogens of the amino group by chlorine atoms decreases the basicity of nitrogen, which destabilizes the zwitterionic structure. For monosubstituted glycine complexed with Na^+, the zwitterionic structure still exists as a minimum, but for disubstituted glycine no minimum appears for this structure. In contrast, for Mg^{2+} complexed to mono- and disubstituted glycine, the zwitterionic structure remains the only minimum, since the enhanced electrostatic interaction with the dication overcomes the destabilizing effect of the chlorine atoms.

Keywords: density functional calculations · electrostatic interactions · gas-phase chemistry · glycine · zwitterions

Introduction

As the simplest amino acid, glycine, is a very good biochemical model compound. In the gas phase, glycine is known to exist in the neutral form ($H_2N\text{-}CH_2\text{-}COOH$),[1–6] with the zwitterionic ($H_3{}^+N\text{-}CH_2\text{-}COO^-$) structure not even being a minimum on the potential energy surface.[7–9] In contrast, the zwitterionic form is the dominant structure in solution[10] and crystalline state.[11] Theoretical studies have shown that the glycine zwitterion may appear as a minimum in the presence of two water molecules.[12] Similarly, the interaction of metal cations with glycine can stabilize the zwitterionic structure in such a way that in some cases it can become the absolute minimum.[13–15]

Previous theoretical studies have analyzed the interaction of alkali metal cations,[14] Cu^+,[13, 15] and Cu^{2+}[15] with glycine. These studies focus mainly on the bonding and relative energies of the different chelating structures. In all cases the interaction of the zwitterionic structure of glycine with the cation is found as a minimum of the potential energy surface. Moreover, for Cu^{2+}, this structure was found to be the absolute minimum.[15]

The intramolecular proton transfer reaction is a very important process since it relates the neutral and zwitterionic structures of the amino acid, which show different behavior in many biochemical processes. Moreover, such information can be very useful in interpreting the mass spectrometry experiments used for the elucidation of the sequence of peptides cationized by different metals. To our knowledge this process has only been studied for alkaline$^+$ – glycine.[14a,c] The results show that the process is slightly exothermic with a very small barrier. The goal of the present paper is to study the intramolecular proton transfer process, from neutral to zwitterionic species, in cationized glycine with different mono- and dipositive cations, as it is shown in Scheme 1. We will thus focus on the stationary points involved in this reaction and not on the determination of the absolute minimum of each potential energy surface. We have chosen the simple Na^+ and Mg^{2+} metals and the Cu^+, Cu^{2+}, and Ni^+ transition metal cations. This would allow us to analyze the effect of both the charge (mono- or dipositive) and the electronic structure of the metal cation in the reaction; that is,

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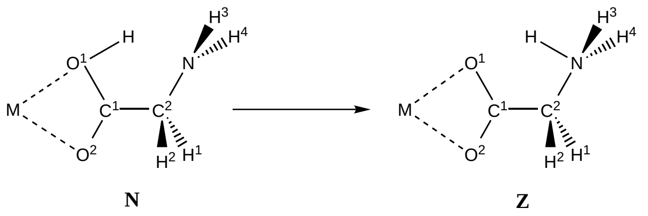

Scheme 1.

whereas Na^+ and Mg^{2+} do not present occupied d orbitals, the electronic ground state of Cu^+ is a d^{10} (^1S) and that of Cu^{2+} and Ni^+ is a d^9 (^2D) one.

On the other hand, it has been shown that the behavior of glycine is different from that of the substituted (*N*-Cl)-glycine, since the chlorine substituent changes the basicity of the amino group.[16] Moreover, *N*-chloro-α-amino acids are formed readily in aqueous solution from the reaction of amino acids with chlorinating agents and thus, they are important from an environmental and synthetic point of view.[17–19] Because of that, we have also studied the intramolecular proton transfer in Cl-HN-CH_2-COOH and Cl_2N-CH_2-COOH cationized by Na^+ and Mg^{2+}. It will be shown that the presence of chlorine atoms in the amino group destabilizes the zwitterionic structure, whereas the interaction of metal cations stabilizes this structure. These two opposite effects can be used to modify the intramolecular proton transfer reaction; that is, to control the process.

Methods of calculation

Molecular geometries and harmonic vibrational frequencies of the considered structures have been obtained using the non-local hybrid three-parameter B3LYP density functional method.[20] The adequacy of density functional methods for the study of the conformational behavior of glycine and other amino acids has been the subject of several studies.[21–23] The results obtained have shown that the hybrid methods, in particular the B3LYP method,[21, 23] provide very similar structural parameters compared with MP2, and that the density functional vibrational frequencies and intensities are in excellent agreement with the experimental data. However, in order to confirm the reliability of B3LYP, we have performed single point calculations for the Na^+–glycine system using the single and double excitation coupled cluster method[24] with a perturbational estimate of the triple excitations CCSD(T).[25] All electrons except the ones similar to 1s have been correlated. On the other hand, our previous study[15] for Cu^+ and Cu^{2+} interacting with glycine showed that B3LYP method provided good relative energies between the different complexed structures compared with the highly correlated modified coupled pair functional (MCPF) method.

Geometry optimizations and frequency calculations have been performed using the following basis sets. For C, N, and O we used the (9s5p)/[4s2p] set developed by Dunning[26] from the primitive set of Huzinaga,[27] supplemented with a set of diffuse sp functions ($\alpha = 0.0438$ for carbon, $\alpha = 0.0639$ for nitrogen and $\alpha = 0.0845$ for oxygen) and one 3d polarization function ($\alpha = 0.75$ for carbon, $\alpha = 0.80$ for nitrogen, and $\alpha = 0.85$ for oxygen). For hydrogen the basis set used is the (4s)/[2s] set of Dunning[26] supplemented with a diffuse function ($\alpha = 0.036$) and a p polarization function ($\alpha = 1.00$). For Na, Mg, and Cl we have used the McLean Chandler (12s9p)/[6s5p] basis sets[28] supplemented with a d polarization function ($\alpha = 0.175$ for Na and Mg, and $\alpha = 0.75$ for Cl). The Cu and Ni basis sets are the [8s4p3d] contractions of the (14s9p5d) primitive set of Wachters[29] supplemented with two diffuse p and one diffuse d functions.[30] The final basis sets are of the form (14s11p6d)/[8s6p4d].

Net atomic charges and spin densities have been obtained using the natural population analysis of Weinhold et al.[31] All calculations have been performed with Gaussian 94 package.[32] Open shell calculations have been carried out using a spin unrestricted formalism.

Results and Discussion

In this work we study the proton transfer process in cationized glycine and derivatives shown in Scheme 1. It should be mentioned that this conformer of glycine, in which the hydroxylic group is acting as proton donor and the amino group as proton acceptor is not the ground state structure of free glycine.[33–37] In fact, this conformer is the second most stable and lies 1.4 $kcal\,mol^{-1}$[4] above the absolute minimum, which shows a bifurcated hydrogen bond between the NH_2 group and the carbonylic oxygen. However, the coordination of metal cations to the carboxylic group of the second conformer shows a more favorable interaction than the one that takes place at the amino group of the ground state structure of glycine.[14] Moreover, the structures shown in Scheme 1 are the ones involved in the proton transfer process that relates the neutral and zwitterionic structures of glycine, which is the process we are interested in.

We will first present the results obtained for Na^+, Mg^{2+}, Cu^+, Cu^{2+}, and Ni^+ interacting with glycine. This would allow us to analyze the effect of the charge, mono- or dipositive, of the metal cation in the proton transfer process. Moreover, the behavior between simple and transition metal cations will be compared. Second, we will present the results of Na^+ and Mg^{2+} interacting with chlorine substituted glycine.

M–glycine (M = Na^+, Mg^{2+}, Cu^+, Ni^+, Cu^{2+})

Figure 1 shows the B3LYP optimized geometry parameters of the initial M–(HOOC-CH_2-NH_2), final M–($^-$OOC-CH_2-NH_3^+) and transition state structures of the proton transfer reaction shown in Scheme 1. The absolute and relative energies of the stationary points found on each potential energy surface are given in Table 1 and the charges in Table 2. Although our interest is obviously in the relative energies, absolute energies have also been included just to emphasize that for some cases only one of the two minima involved in the process is found.

As it has been mentioned, the zwitterionic form of glycine does not exist in gas phase.[7–9] Upon complexation with metal cations, however, such a structure is stabilized and appears as a minimum of the potential energy surface. As expected, this stabilization is larger for the dipositive cations Mg^{2+} and Cu^{2+}.

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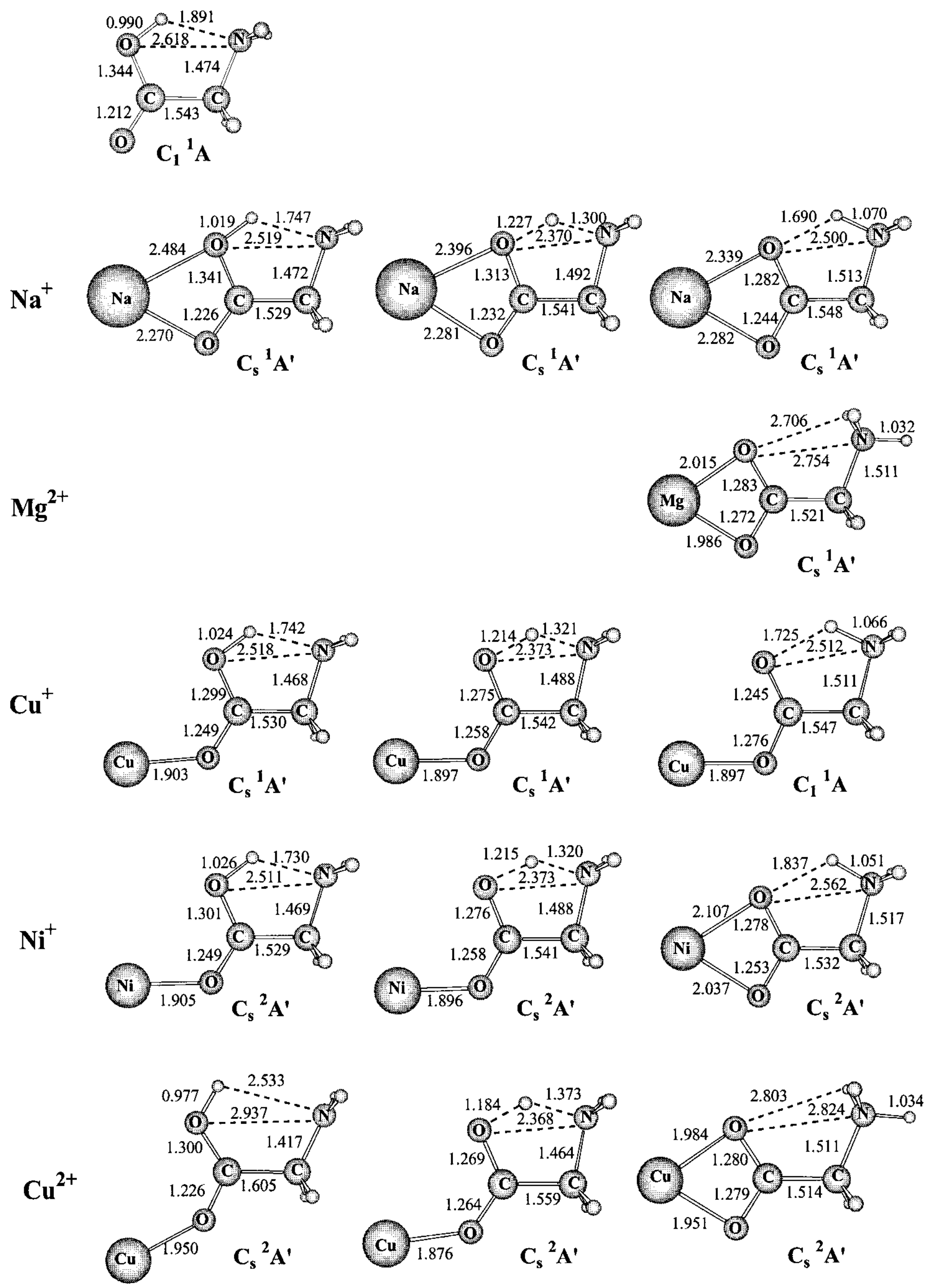

Figure 1. B3LYP-optimized geometries for neutral, transition state and zwitterionic structures involved in the proton transfer process of glycine interacting with different metal cations. Distances are in Å and angles are in degrees.

Table 1. B3LYP absolute (in a.u.) and relative energies (in kcal mol^{-1}) for neutral (N), zwitterionic (Z), and transition state (TS) structures of glycine and substituted derivatives interacting with metal cations.

System	N	TS	Z
Na^+–HOOC-CH_2-NH_2	– 446.6571807 (0.0)	– 446.6538358 (2.1)	– 446.6578500 (– 0.4)
Mg^{2+}–HOOC-CH_2-NH_2			– 484.0195702
Cu^+–HOOC-CH_2-NH_2	– 1924.7498340 (0.0)	– 1924.7470458 (1.7)	– 1924.7523078 (– 1.5)
Ni^+–HOOC-CH_2-NH_2	– 1792.5317925 (0.0)	– 1792.5290474 (1.7)	– 1792.5382064 (– 4.0)
Cu^{2+}–HOOC-CH_2-NH_2	– 1924.2480295 (0.0)	– 1924.2213833 (16.7)	– 1924.2712459 (– 14.6)
Na^+–HOOC-CH_2-NHCl	– 906.2289713 (0.0)	– 906.2200199 (5.6)	– 906.2208453 (5.1)
Na^+–HOOC-CH_2-NCl_2	– 1365.8009248		
Mg^{2+}–HOOC-CH_2-NHCl			– 943.578123452
Mg^{2+}-HOOC-CH_2-NCl_2			– 1403.1391612

For free glycine the process is highly endothermic, that is, assuming a fixed N–H distance of 1.05 Å for the zwitterionic form, the energy difference between the neutral and zwitterionic structures is about 22 kcal mol^{-1}. For the monocations the process is slightly exothermic and for the dications the reaction is very exothermic. For Mg^{2+}, if we assume a fixed O–H distance of 1.0 Å for the neutral form, the reaction energy is computed to be about – 25 kcal mol^{-1}. Given the high exothermicity for Mg^{2+}, it is not surprising that the neutral form of glycine complexed through the two oxygens η^2-*O,O*-(COOH) does not exist as a minimum.

For the two-metal dications, the η^2-*O,O*-(CO_2^-) coordination, that is the structure that arises from the coordination of the metal cation to the negative part of the zwitterionic structure of glycine, is the absolute minimum of the potential energy surface. For the monocation metals Na^+,[14] Ni^+,[38] Cu^+,[13, 15] however, the ground state structure is found to have a bidentate η^2-*N,O*-coordination in which the metal interacts with the nitrogen of the amino group and the carbonyl oxygen.

For all metals, except Mg^{2+}, we have located the minima corresponding to the complexed neutral and zwitterionic forms of glycine and the transition state of the intramolecular proton transfer that connects the two minima. It can be observed in Figure 1 that the interaction of Na^+, Cu^+, and Ni^+ to the neutral form of glycine strengthens the intramolecular hydrogen bond. That is, the H–N and N–O distances decrease whereas the O–H distance increases, which favors the intramolecular proton transfer process that is being studied. In all cases, the obtained structure shows C_s symmetry. A different behavior,

Table 2. Charges from natural population analysis.

	Na^+			Mg^{2+}			Cu^+			Ni^+			Cu^{2+}		
	N	TS	Z	N	TS	Z	N	TS	Z	N	TS	Z	N	TS	Z
M	0.97	0.97	0.96	–	–	1.83	0.90	0.89	0.87	0.89	0.89	0.84	1.06	1.27	1.34
H^+	0.54	0.49	0.48	–	–	0.49	0.54	0.48	0.48	0.54	0.49	0.49	0.56	0.50	0.50
COO	−0.62	−0.69	−0.78	–	–	−0.82	−0.57	−0.61	−0.70	−0.56	−0.61	−0.71	−0.38	−0.28	−0.36
CH_2	0.20	0.21	0.22	–	–	0.30	0.21	0.22	0.22	0.21	0.22	0.24	0.29	0.31	0.31
NH_2	−0.09	0.02	0.12	–	–	0.20	−0.08	0.02	0.13	−0.08	0.02	0.15	0.48	0.20	0.20

however, is observed for the kind of coordination of the metal ion. For Na^+, the two metal–O distances are more similar than for Ni^+ or Cu^+, so that in the first case glycine is acting as a bidentate ligand, whereas Ni^+ and Cu^+ show a monodentate coordination. This is attributed to the fact that the transition metals prefer an unsymmetrical interaction to minimize repulsion between the occupied d shell of the metal and the lone pairs of oxygens.

As mentioned, the η^2-*O,O* interaction of Mg^{2+} to neutral glycine is not found as a minimum, since in the optimization process the proton is transferred spontaneously. However, if the O–H distance is fixed to 1.0 Å, the obtained structure shows the same trends as observed for Na^+, Cu^+ and, Ni^+; that is, the intramolecular hydrogen bond is significantly strengthened. In contrast, Cu^{2+} shows a very different behavior. It can be observed in Figure 1 that when Cu^{2+} interacts with neutral glycine the intramolecular hydrogen bond almost disappears. The H–N distance becomes 2.533 Å whereas that of free glycine is 1.891 Å. Moreover, the O–H distance in Cu^{2+}–glycine is 0.977 Å whereas for glycine is 0.990 Å. On the other hand, the metal–ligand distance is larger for Cu^{2+} than for Cu^+. The lowest electronic state of $[glycine-Cu]^{2+}$ is a $^2A'$ state, the open-shell orbital lying in the symmetry plane. The population analysis given in Table 3 shows that the spin density mainly lies on glycine and thus, the system behaves more as Cu^+–glycine$^+$. This description is confirmed by the atomic charge on Cu^+, which is close to 1 (Table 2). Moreover, the population analysis shows that the spin density mainly lies on the nitrogen atom. The amino group becomes less basic and, thus, it is not surprising that the hydrogen bond is weakened.

Let us now discuss the M–glycine zwitterionic structures. For the monocation Na^+, Cu^+, and Ni^+ metals, the obtained structures show a clear intramolecular hydrogen bond similar to that observed for the M–glycine neutral structures. For Na^+ and Ni^+, the optimized structures have C_s symmetry. For Cu^+, the symmetry is C_1, although the distortion form C_s symmetry is very small. In all cases, the metal–O distances become more similar in the zwitterionic structures than for the initial structures, which is in agreement with the fact that after the proton is transferred the nature of the two oxygens becomes more similar. However, whereas for Cu^+ the obtained structure is monodentate for Ni^+ the coordination is bidentate, in contrast to the neutral form for which both metals ions interact mainly with one oxygen. It must be noted that Cu^+ has a d^{10} electronic configuration whereas Ni^+ has a d^9 configuration. The ground electronic state of Ni^+–glycine is a $^2A'$ state, the open shell lying on the symmetry plane and so, metal–ligand repulsion is smaller for Ni^+ than for Cu^+. Thus, for Ni^+, the enhanced electrostatic interaction in the zwitterionic form overcomes the metal–ligand repulsion favoring the symmetrical position of the metal.

Table 3. Spin densities for neutral (N), zwitterionic (Z), and transition state (TS) structures of glycine interacting with Ni^+ and Cu^{2+}.

	Ni^+			Cu^{2+}		
	N	TS	Z	N	TS	Z
M	0.97	0.97	0.93	0.10	0.34	0.47
H^+	0.0	0.0	0.0	0.0	−0.02	0.0
C^1	0.0	0.0	0.0	0.07	0.01	−0.03
C^2	0.0	0.0	0.0	−0.02	−0.01	0.0
O^1	0.0	0.0	0.03	0.02	0.11	0.25
O^2	0.03	0.03	0.04	0.10	0.36	0.30
N	0.0	0.0	0.0	0.72	0.20	0.0
H^1	0.0	0.0	0.0	0.02	0.0	0.0
H^2	0.0	0.0	0.0	0.02	0.0	0.0
H^3	0.0	0.0	0.0	−0.02	0.0	0.0
H^4	0.0	0.0	0.0	−0.02	0.0	0.0

For the dication Mg^{2+} and Cu^{2+} metals, the intramolecular hydrogen bond disappears and the NH_3^+ rotates in such a way that there is a bifurcated interaction between two hydrogens of the amino group and the oxygen atom. This can be explained in part by the fact that this reduces the repulsive interaction between the metal dication and the NH_3^+ group of zwitterionic glycine. In both cases the metal–oxygen distances are very similar. As for Ni^+, the coordination of Cu^{2+} to glycine changes from monodentate in the neutral structure to bidentate in the zwitterionic form. Note that both metals have a d^9 electronic configuration.

In all transition state structures the two heavy atoms O and N involved in the hydrogen bond are closer than in the reactant or the product. The proton lies in between the two heavy atoms. For the dication Cu^{2+} system the transition state is more reactant-like in good agreement with Hammond's postulate. The main component of the transition vector corresponds to the movement of the proton.

It can be observed in Table 1 that the energy barriers of the proton transfer process are small for all the monocation systems, the smallest one being that obtained for Cu^+ and Ni^+. For Na^+, our computed B3LYP energy barrier of 2.0 $kcal\,mol^{-1}$ is very similar to that obtained at the MP2 level (1.9 $kcal\,mol^{-1}$) by Ohanessian et al.[14a] The reaction energy, however, is slightly more exothermic at the MP2 level (−2.4 $kcal\,mol^{-1}$) than at the B3LYP level (−0.4 $kcal\,mol^{-1}$). At the CCSD(T) level, using the B3LYP optimized geometries, we obtain a value of 3.3 $kcal\,mol^{-1}$ for the energy barrier and a value of −0.4 $kcal\,mol^{-1}$ for the reaction energy.

For the dications Mg^{2+} and Cu^{2+}, the difference is spectacular. That is, for Mg^{2+} the process is spontaneous, as one would expect due to the increase of exothermicity, whereas for Cu^{2+} we obtain a large energy barrier (16.7 kcal mol^{-1}), in spite of the high exothermicity of the process. In this case, the process is much more complex since as it has been mentioned, for $[Cu\text{-}HOOC\text{-}CH_2\text{-}NH_2]^{2+}$ the system behaves more as Cu^+–glycine$^+$, whereas for $[Cu\text{-}^-OOC\text{-}CH_2\text{-}NH_3{}^+]^{2+}$ the metal charge lies in between Cu^+ and Cu^{2+}. These differences can be observed in Table 3; that is, whereas for the neutral form the spin density mainly lies on the nitrogen atom, for the zwitterionic structure the spin density lies on the metal ion and on the two oxygens of glycine. This electronic reorganization that accompanies the proton transfer process implies the appearance of a significant energy barrier. In order to confirm this result, which is very different from that obtained for the other metal cations, we have performed single point calculations using the highly correlated modified coupled pair functional method used in our previous study of Cu^+ and Cu^{2+} interacting with glycine.[15] At this level of theory, the energy barrier is computed to be about 4 kcal mol^{-1} smaller than at the B3LYP level. This is similar to what was observed for glycine radical cation[36] in the $^2A'$ state, for which the process showed an important energy barrier. It is worth noting that, that although Ni^+ and Cu^{2+} have the same electronic configuration (d^9) and show similar coordination patterns for the neutral and zwitterionic structures, their behavior on the proton transfer process is very different. For Ni^+ the spin density mainly remains on the metal ion during the process and thus, the effect of the metal ion is mainly electrostatic. Because of that, the energy barrier is small and similar to that of Na^+ and Cu^+.

As general trends, Table 2 shows that all monocation systems behave similarly, the fundamental effect of the cation on the proton transfer process being mainly electrostatic. The only differences observed is that the charge transfer between glycine and the metal ion is somewhat larger for the transition metal systems. On the other hand, for the dications Mg^{2+} and Cu^{2+} the charge transfer is much more important, specially for Cu^{2+}, for which in the reactant the charge transfer is of about one electron. Thus, glycine acquires an important radical character, which leads to the presence of a considerable energy barrier for the proton transfer process.

M–glycine(*N*-Cl) and M–glycine(*N*-Cl_2) (M = Na^+, Mg^{2+})

In this section we will study the effect of substituting the hydrogens of the amino group by one or two chlorine atoms in the proton transfer process of cationized glycine. We have chosen the simplest mono- and dication metals, Na^+ and Mg^{2+}, since the nature of their effect is mainly electrostatic.

Figure 2 shows the reactant, product, and transition state structures located for single and double substituted Na^+–glycine and Mg^{2+}–glycine. The absolute and relative energies are given in Table 1. First, it can be observed in Figure 2 that the substitution of the hydrogens of the amino group by one or two chlorine atoms weakens the intramolecular hydrogen bond compared with the unsubstituted glycine (see Figure 1). Thus, the proton transfer process that leads to the zwitterionic form is even more unfavorable than for glycine. This is not surprising since the presence of the chlorine reduces the negative charge of the nitrogen atom and thus, due to the decrease of its basicity, it becomes a worse proton acceptor. Populations analysis shows that the net atomic charge at the nitrogen atom is −0.94, −0.72, and −0.57 for glycine, mono- and disubstituted glycine, respectively.

As for unsubstituted glycine, complexation of monosubstituted glycine with Na^+ metal cation leads to the three stationary points on the potential energy surface of the proton transfer process, two minima and the transition state.

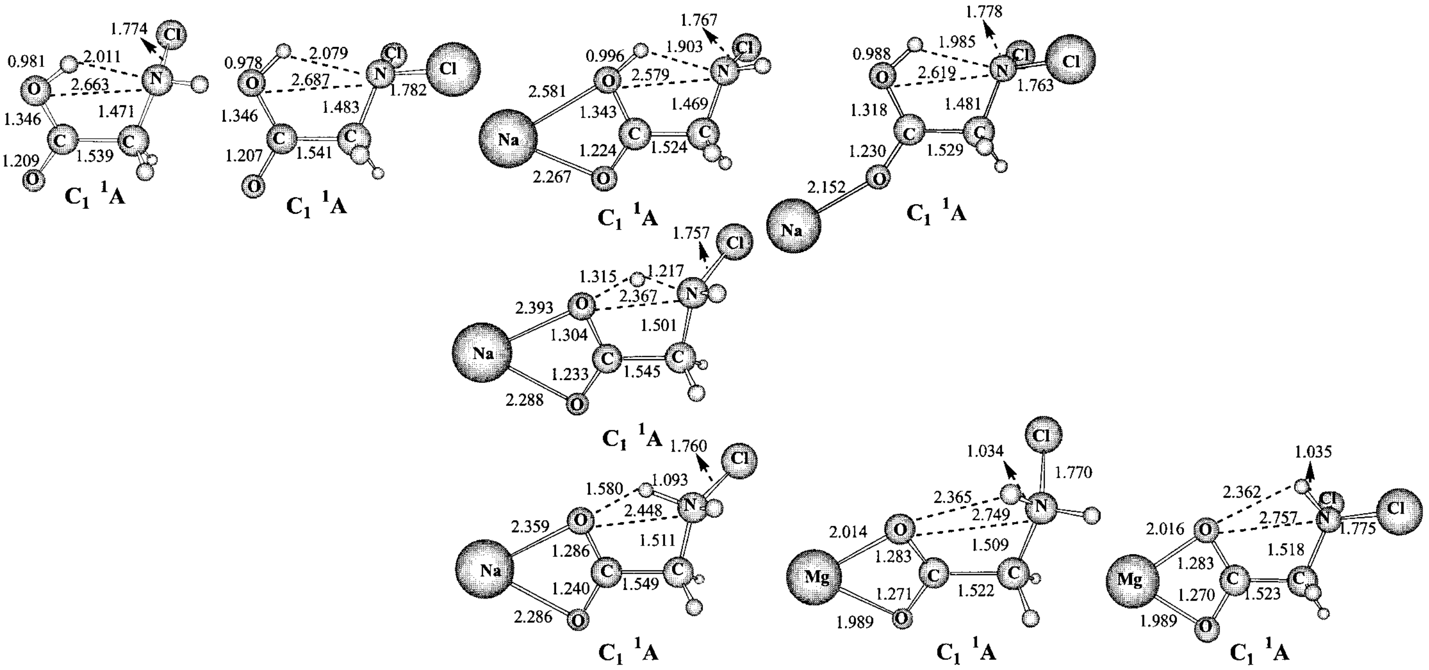

Figure 2. B3LYP-optimized geometries for neutral (top), transition state (middle), and zwitterionic (bottom) structures of chlorine mono- and disubstituted glycine interacting with Na^+ and Mg^{2+}. Distances are in Å and angles are in degrees.

As expected, the presence of the chlorine weakens the intramolecular hydrogen bond of the reactant compared with the unsubstituted glycine complexed by Na^+. This is in agreement with the decrease of the net atomic charge on the nitrogen atom, which is similar to that found for uncomplexed glycine. Because of that, the reaction energy of the proton transfer process becomes now endothermic (5.1 $kcal\,mol^{-1}$) and the energy barrier increases to 5.6 $kcal\,mol^{-1}$. It can be observed in Figure 2 that the transition state geometry is now more similar to the zwitterionic structure, in agreement with the endothermicity of the reaction. Moreover, since the protonated amino group in the product is more acidic than in unsubstituted glycine, the energy barrier of the reverse proton transfer reaction is small (0.5 $kcal\,mol^{-1}$). This barrier disappears when the zero point correction is taken into account.

For disubstituted glycine interacting with Na^+ we have only found the reactant, as a minimum of the potential energy surface. In this case the hydrogen bond is weaker than for mono- or unsubstituted cases and Na^+ adopts a monodentate coordination. The decrease of the proton affinity of the amino group is consistent with the decrease of the negative charge on the nitrogen atom. Thus, the stabilization of the zwitterionic form by complexation with Na^+ is not enough to compensate for the destabilization due to the presence of the two chlorine atoms.

For Mg^{2+} interacting with monosubstituted and disubstituted glycine we have only found the zwitterionic form as a minimum of the potential energy surface. That is, although the presence of one and two chlorine atoms decrease the proton affinity of the amino group, this decrease does not stabilize the reactant enough, compared with the product, to obtain it as a minimum. The fact that Mg^{2+} supports a two positive charge determines the great stability of the zwitterionic structure. The only difference between un-, mono-, and disubstituted glycine is that, whereas in the first two cases, we obtain a bifurcated interaction, in disubstituted glycine the structure shows a weak hydrogen bond.

Conclusion

The coordination of metal cations to the oxygens of glycine stabilizes the zwitterionic form. For Na^+, Cu^+, and Ni^+, the obtained zwitterionic minimum complexed through the COO^- group is slightly more stable than the neutral form complexed at the COOH group. In all cases, the energy barrier of the proton transfer process that connects the two structures is small (1–2 $kcal\,mol^{-1}$).

For the dications Mg^{2+} and Cu^{2+}, the complexed zwitterionic structure is much more stable than for the monocations, in such a way that it becomes the absolute minimum of the potential energy surface. However, there are important differences between Mg^{2+} and Cu^{2+}. That is, whereas for Mg^{2+}, the proton transfer process from neutral to zwitterionic form occurs spontaneously, for Cu^{2+} both minima are separated by an important energy barrier (16.7 $kcal\,mol^{-1}$). This has been attributed to the large electronic reorganization that takes place in the proton transfer process, due to the oxidant character of Cu^{2+}.

The substitution of one or two hydrogens of the amino group by one chlorine atom decreases the basicity of nitrogen atom so that the zwitterionic structure is destabilized. For monosubstituted glycine complexed with Na^+ the zwitterionic structure still exists, although the reaction is endothermic and the energy barrier in excess to endothermicity is small. For disubstituted glycine interacting with Na^+, the zwitterionic minimum disappears in such a way that only the neutral structure is located. For Mg^{2+} complexed to mono- and disubstituted glycine, the high stability of the zwitterionic form due to the enhanced electrostatic interaction with the dication overcomes the destabilizing effect of the chlorine atoms. Thus, in all cases with Mg^{2+}, the only minimum that is localized for the proton transfer process is the zwitterionic structure.

The results obtained in the present paper show that using different metal cations and N-substituents, the intramolecular proton transfer process can be modified in such a way that only the neutral or the zwitterionic forms are stable or both of them. That is, electron acceptor substituents that decrease the basicity of the nitrogen atom will destabilize the zwitterionic form, whereas electon donor substituents will produce the contrary effect.[39] The results obtained for glycine can be extrapolated to other amino acids, since they arise from substitution at the central carbon and thus, the changes in the nitrogen basicity are expected to be smaller.

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