Regular article

Water-catalyzed isomerization of the glycine radical cation. From hydrogen-atom transfer to proton-transport catalysis

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Abstract. The isomerization reactions of the glycine radical cation, from $[NH_2CH_2COOH]^{\cdot+}$, I, to $[NH_3CHCOOH]^{\cdot+}$, II, or $[NH_2CHC(OH)_2]^{\cdot+}$, III, in the presence of a water molecule have been studied theoretically. The water molecule reduces dramatically the energy barriers of the I → II and I → III tautomerizations owing to a change in the nature of the process. However, the role of the water molecule depends on the kind of isomerization, the catalytic effect being more important for the I → III reaction. As a consequence, the preferred mechanism for the interconversion of glycine radical cation I to the stablest isomer, III, is the direct one-step mechanism instead of the two step (I → II and II → III) process found for isolated $[NH_2CH_2COOH]^{\cdot+}$. When using ammonia as a solvent molecule, a spontaneous proton-transfer process from $[NH_2CH_2COOH]^{\cdot+}$ to NH_3 is observed and so no tautomerization reactions take place. This behavior is the same as that observed in aqueous solution, as has been confirmed by continuum model calculations.

Keywords: Glycine radical cation – Isomerization – Proton-transport catalysis

Introduction

The proton-transport catalysis by a neutral molecule in intramolecular proton-transfer processes is known to occur both in protonated species and in radical cations [1, 2, 3]. Several theoretical studies of Radom and coworkers [4, 5, 6] have shown that the catalytic effect is

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especially favorable when the proton affinity of the neutral molecule lies between the proton affinities of the two sites involved in the isomerization. On the other hand, the catalytic role of solvent molecules in tautomeric processes of neutral molecules has also been observed in different theoretical studies [7, 8, 9, 10, 11, 12, 13]. In these cases, the solvent molecule acts simultaneously as an acceptor and a donor of a hydrogen atom. For this reason these processes are referred to as bifunctional catalysis or as solvent-assisted rearrangements.

A nice example of both, solvent-assisted (in the neutral molecule) and proton-transport (in the radical cation) catalysis, is the enolization of acetaldehyde in the presence of a water or a methanol molecule [14]. For ionized acetaldehyde, the decrease of the potential-energy barrier is much more important in the methanol-solvated system than in the water-solvated one. It must be pointed out that whereas the proton affinity of water is smaller than the proton affinities of $[CH_2-CHO]^{\cdot}$ at the CH_2 site or the oxygen site, the proton affinity of methanol lies between those of the two sites involved in the isomerization. So, in agreement with the studies of Radom and coworkers [4, 5, 6], the catalytic effect is especially favorable in the last case.

In a recent paper, the isomerization and fragmentation reactions of the glycine radical cation $[NH_2CH_2COOH]^{\cdot+}$, I, was studied [15]. Focusing on the isomerization processes, it was shown that the stablest isomer of the glycine radical cation is $[NH_2CHC(OH)_2]^{\cdot+}$, III, the $[NH_3CHCOOH]^{\cdot+}$ one, II, lying between the other two. However, the energy barriers for the isomerizations between the initial radical cation of glycine, I, and the other two isomers, II and III, were found to be very high. This is in agreement with mass spectrometry experiments, which have shown that the spectrum of the glycine radical cation $[NH_2CH_2COOH]^{\cdot+}$ is very different from that of the isomeric enol ion $[NH_2CHC(OH)_2]^{\cdot+}$, thus indicating that ions of high internal energy do not interconvert prior

to dissociation owing to high isomerization energy barriers [16, 17].

On the other hand, the theoretical results [15] showed that the preferred mechanism for the interconversion of the glycine radical cation, I, to the stablest isomer, III, proceeds by means of a two-step mechanism through isomer II and not by a direct I → III one-step process. Moreover, natural population analysis seemed to indicate [15] that the 1,2 hydrogen transfer from the carbon to nitrogen, I → II, corresponds really to a hydrogen-atom transfer since in the reactant the spin is mainly located on the nitrogen, whereas in the product the unpaired electron mainly lies at the carbon atom. In contrast, in the 1,3 hydrogen transfer from the carbon to the oxygen atom, I → III, the nature of the process was found to be very complex since in the reactant the radical character lies on the amino group, which is not involved in the 1,3 transfer, whereas in the product the spin is delocalized all over the molecule, showing an important electronic reorganization.

The purpose of the present paper is to study the role of a water molecule in the two isomerization reactions of the glycine radical cation, I → II and I → III, both on the barrier and on the nature of the process. Furthermore, given that the glycyl radical is the species observed in aqueous solution [18], we try to interpret this result by introducing the rest of the solvent by means of a continuum model.

Methods

Molecular geometries and harmonic vibrational frequencies were obtained using the nonlocal hybrid three-parameter B3LYP density functional approach [19, 20] with the 6-31 + + G(d,p) basis set, the same methodology used for the study of the isomerizations and fragmentations of the glycine radical cation [15]. Such methodology was shown to perform reasonably well for this kind of systems compared to coupled-cluster single–double and perturbative triple excitation calculations [15].

The nature of the stationary points was checked by vibrational frequency calculations. In all cases, intrinsic reaction coordinate (IRC) calculations [21] were carried out to confirm that the located transition states link the proposed reactants and products. Thermodynamic corrections were obtained at the B3LYP level assuming an ideal gas, unscaled harmonic vibrational frequencies and the rigid-rotor approximation by standard statistical methods [22].

The effect of solvation was estimated using the continuum model COSMO algorithm [23], which is based on a conductor-like solvation model, first proposed by Klamt and coworkers for classical calculations [24] and then extended to quantum mechanical systems [25, 26]. This continuum model differs from the polarizable continuum model (PCM), proposed by Tomasi and coworkers [27, 28], in the fact that in the first approach the solvent is treated as a conductor whereas in the model of Tomasi and coworkers the solvent is treated as a dielectric. However, both approaches have many similarities: the cavities are of molecular shape and the reaction field is described through apparent polarization charges included in the solute Hamiltonian. Moreover, the cavitation, dispersion and repulsion terms are computed in the same way as in the PCM.

Net atomic charges and spin densities were obtained using the natural population analysis of Reed et al. [29]. All calculations were performed with the Gaussian 98 package [30].

Results and discussion

First we discuss the isomerization reactions of the glycine radical cation when a water molecule is added in the gas phase. Second, a molecule with higher proton affinity, NH_3, will be considered. Finally, we introduce the solvent effects by means of a continuum model.

The B3LYP-optimized parameters of the stationary point corresponding to the different isomerization processes of the glycine radical cation in the presence of a
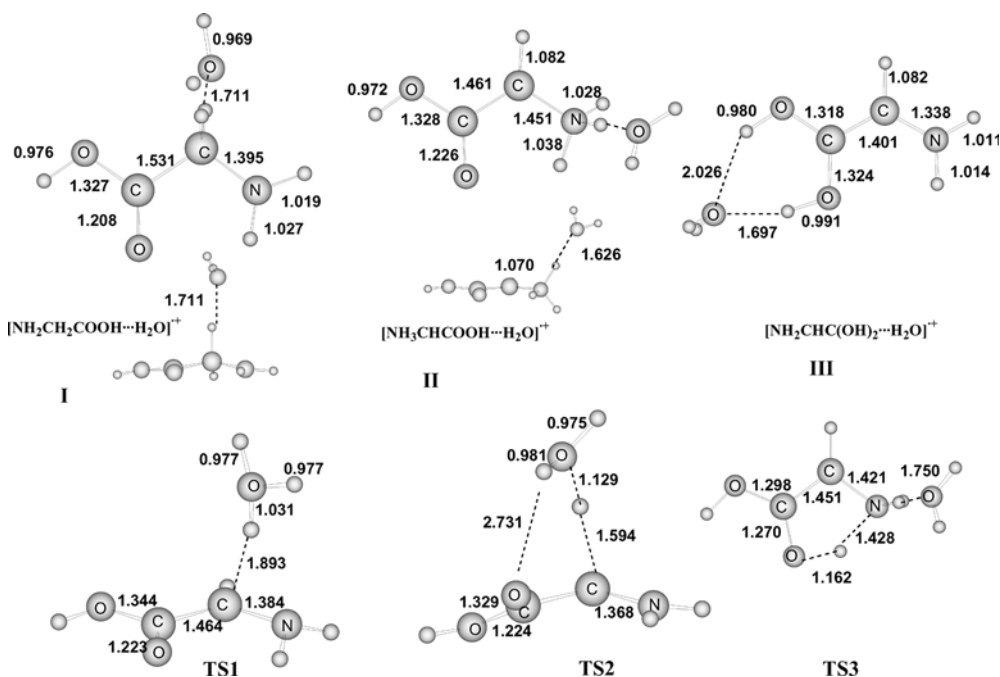

Fig. 1. B3LYP main geometrical parameters of the stationary points corresponding to the isomerization reactions of water–glycine radical cation. Distances in angstroms

water molecule are shown in Fig. 1. The energy diagrams of the reactions considered, in potential energies and in Gibbs free energies, are shown in Figs. 2 and 3, respectively. Both the isolated glycine radical cation [15] and the glycine radical cation plus one water molecule are considered in Figs. 2 and 3.

Although the interaction of water with the lowest-energy conformer of $[NH_2CH_2COOH]^+$, isomer I, may lead to many different conformers we only considered the one involved in the catalysis of the isomerization processes, i.e., the one in which H_2O is interacting with the hydrogens of the CH_2 group. This structure is very stable because removing one electron from glycine produces an important increase of the acidity of the CH_2 group, which leads to the formation of a strong hydrogen bond between the glycine radical cation and water ($E_{int} = -15.5$ kcal/mol). The radical character of $[NH_2CH_2COOH \cdots H_2O]^{+\cdot}$ is mainly located at the amino group, since the spin density at this group is 0.77. Moreover, the population analysis shows that only a slight charge transfer between the glycine radical cation and water has occurred (0.10 au).

It can be observed in Fig. 2 that the complex formed between a water molecule and isomer II of the glycine radical cation, $[NH_3CHCOOH \cdots H_2O]^{+\cdot}$, is stabler than the complex formed with the first isomer, I, $[NH_2CH_2COOH \cdots H_2O]^{+\cdot}$. This was also observed for the isolated glycine radical cation, for which isomer II was found to be 8.7 kcal/mol stabler than isomer I. For the water-solvated system, such a difference increases, isomer II being now 14.3 kcal/mol stabler than isomer I. Thus, isomer II presents a stronger hydrogen bond ($E_{int} = -21.1$ kcal/mol) than I ($E_{int} = -15.5$ kcal/mol). This is not surprising considering that in II water is interacting with the ammonium group (NH_3^+), which has a larger positive charge (0.61) than the $-CH_2$ group in isomer I (0.28). Moreover, this is in agreement with

the optimized geometrical parameters (Fig. 1) which show a shorter hydrogen bond for isomer II. As for the free glycine radical cation, isomer II presents an important distonic character, since the spin density is mainly concentrated on the CH group (0.85), while the charge is on the amino group (0.61).

The third isomer $[NH_2CHC(OH)_2]^+$, III, which was found to be the stablest one (-26.4 kcal/mol with respect to I), owing to the stabilizing captodative effects [31], becomes even stabler when it interacts with the water molecule, the energy difference between III and I being now -33.4 kcal/mol. Therefore, the hydrogen-bond interaction in III ($E_{int} = -22.5$ kcal/mol) is 7 kcal/mol larger than in I ($E_{int} = -15.5$ kcal/mol). This complex presents a double hydrogen bond between the two OH groups and the water molecule (Fig. 1).

Let us now consider the different isomerization processes. First, it can be observed in Fig. 2 that isomerizations I → II and I → III, which were found to have large energy barriers in the gas phase (37.1 and 39.9 kcal/mol, respectively) owing to important geometry distortions and important electronic reorganization [15], have significantly smaller barriers in the presence of a water molecule: 12.0 and 7.4 kcal/mol, respectively. with respect to the initial complex. However, the role of the water molecule in the two isomerization processes is somewhat different.

Isomerization I → II proceeds through the TS1 transition structure. It can be seen from the geometrical parameters represented in Fig. 1 that in this transition structure a hydronium ion has been formed, given that the O–H distance of the transferred hydrogen (1.03 Å) is very similar to the other O–H bonds (0.98 Å). Natural population analysis confirms the proton-transfer nature of the process, given that at TS1 the computed charge density on H_3O^+ is 0.90, while the spin density remains completely on the glycyl fragment (1.00). Thus, this
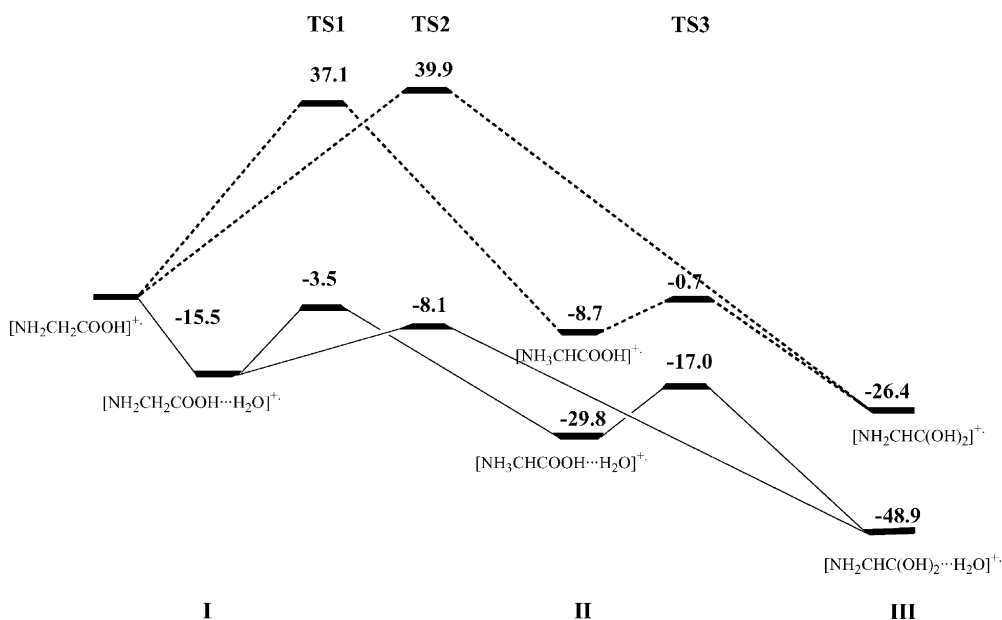

Fig. 2. Potential-energy diagram of the isomerization processes of $[NH_2CH_2COOH]^+$ (*broken line*) and $[NH_2CH_2COOH-H_2O]^+$ (*solid line*). B3LYP energies in kilocalories per mole

transition state presents an important distonic character, since the charge and spin lie on different fragments [32, 33]. Therefore, the present isomerization can be viewed as a process in which a water molecule accepts a proton from the carbon atom of the glycine radical cation, in order to transport and transfer it to the nitrogen atom. Such a process corresponds to the known proton-transport catalysis [1, 2, 3, 4, 5, 6].

Isomerization I → III is also largely catalyzed by a water molecule. From the analysis of the geometrical parameters of the transition state connecting these two minima, TS2, it can be seen that, as in TS1, a proton from the C_α of glycine is transferred to the water molecule. The main difference between TS2 and TS1 is that TS2 is a little more reactant-like than TS1. Note that at TS2 the O–H distance of the transferred hydrogen (1.13 Å) is larger than those of the remaining OH bonds (0.98 Å), and the charge associated with the H_3O^+ fragment is now 0.81. Thus, the glycyl radical (with spin density of 0.90) and the hydronium cation (with charge density of 0.81) are not completely formed. Another important difference that this transition structure, TS2, presents compared with TS1 is that the water molecule accepts a hydrogen atom from the C_α of glycine, but it simultaneously transfers another hydrogen to the oxygen atom, i.e., the water molecule acts as a bifunctional catalyst. During the IRC calculations one can distinguish two stages: a first one in which the water molecule accepts the proton, and a second one in which another hydrogen atom from the hydronium gets closer to the oxygen atom of the carbonyl group.

In contrast to the gas-phase results, the I → III isomerization presents a smaller barrier than the I → II one. This is due to the different catalytic role of the water molecule in the two processes: I → II corresponds to proton-transport catalysis and I → III to proton transport through bifunctional catalysis. Such different behavior is due to the fact that the I → II reaction corresponds to a 1,2 hydrogen transfer, whereas the I → III isomerization corresponds to a 1,3 hydrogen transfer, which favors the bifunctional behavior of the water molecule from a geometrical point of view.

Isomerization I → III can also take place in a two-step process through isomer II. The second step, isomerization II → III, corresponds to a 1,4 hydrogen transfer. All attempts to locate a transition state in which the water molecule was involved in the transfer collapsed to TS3 (Fig. 1), a structure in which the water molecule acts as a spectator of the proton-transfer process. It should be mentioned that the IRC calculations from TS3 do not lead to structure III shown in Figure 1 in which the water molecule is interacting with the two OH groups. Instead, the product obtained is a structure in which the water molecule is forming a hydrogen bond with the NH_2 group. However, because this structure is less stable than III we have not included it in Fig. 1. It can be observed in Fig. 2 that the presence of the water molecule makes the II → III process more difficult, since the computed energy barrier (12.8 kcal/mol) is higher

than the one obtained for the reaction without the water molecule (8.0 kcal/mol). This increase agrees with the fact that the hydrogen-bond distance between water and the glycine radical cation at the transition state, TS3, is larger than at the reactant, II.

The comparison between the results in the gas phase and catalyzed by a water molecule shows that the preferred mechanism for the interconversion of glycine radical cation I to the stablest isomer, III, changes when including the solvent molecule. That is, whereas in the gas phase the preferred mechanism goes through a two-step process (I → II and II → III), in the presence of a water molecule, the direct I → III mechanism becomes the most favorable one.

A rigorous analysis of the catalytic effect must take into account the entropic contributions to the process. Such effects may be especially important for the water-catalyzed system for which the transition-state structures are more ordered than water and glycine separately. The relative Gibbs free energies for the three isomerization reactions in the gas phase and in the gas phase catalyzed by a water molecule are presented in Fig. 3. As expected, entropic effects are not significant for the glycine radical cation since the activation Gibbs free energies of the I → II and I → III isomerizations, (35.8 and 38.8 kcal/mol) are very similar to the energy barriers (37.1 and 39.9 kcal/mol). However, in the presence of a water molecule, the relative Gibbs free energies of TS1 and TS2, computed with respect to the isolated fragments (7.2 and 2.7 kcal/mol, respectively), become positive, whereas they lie below the $NH_2CH_2COOH^{\cdot+} + H_2O$ asymptote (−3.5 and –8.1 kcal/mol) if only potential energies are considered. Similar destabilizations (around 10 kcal/mol) appear for the intermediates, which are also ordered structures. Therefore, the main change observed when including the entropic effects is that the energy diagram is shifted up around 10 kcal/mol with respect to the $NH_2CH_2COOH^{\cdot+} + H_2O$ asymptote. Thus, the energy barriers with respect to the hydrogen-bonded intermediate I are similar both with and without including the entropic effects. In contrast the barriers with respect to isolated reactants change significantly. In spite of that, the catalytic effect of a water molecule is still very important (see Fig. 3).

The calculated proton affinity of water is 165.0 kcal/mol, while the proton affinities of the glycyl radical at the C, N and O atoms are 181.3, 188.2 and 203.9 kcal/mol, respectively. The neutral water molecule has a lower proton affinity than the glycyl radical cation at the three sites and so it is in a good solvent molecule to transport the proton from the carbon to the nitrogen or oxygen atoms [4, 5, 6]. If the solvent molecule had had a proton affinity between the two sites involved in the isomerization, the catalytic effect would have been optimal. However, for molecules with higher proton affinities than the centers involved in the isomerization reaction, one would preferentially expect intermolecular proton transfer from the glycine radical cation to the solvent molecule, rather than an intramolecular
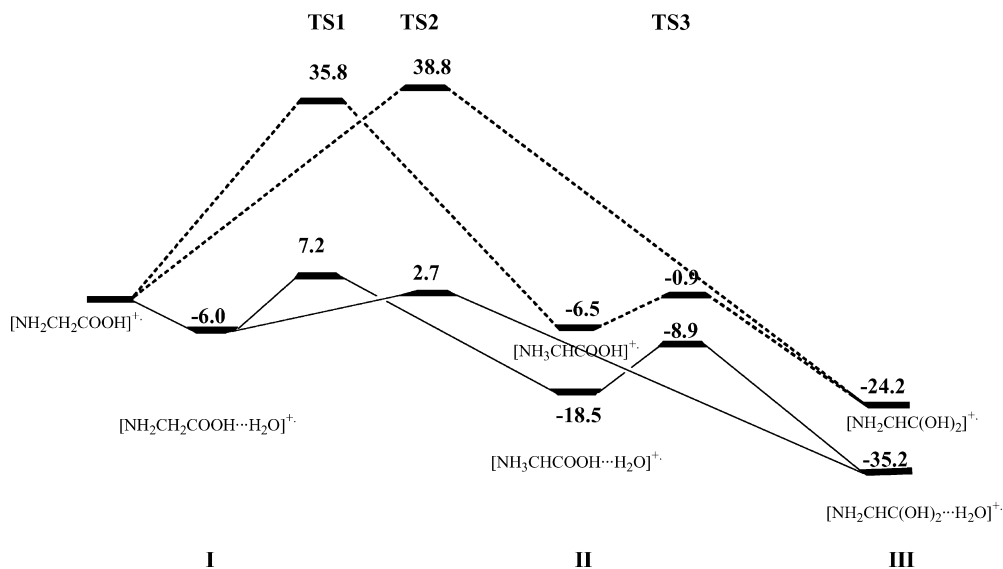
Fig. 3. Relative Gibbs free energies for the isomerization processes of $[NH_2CH_2COOH]^+$ (*broken line*) and $[NH_2CH_2COOH-H_2O]^+$ (*solid line*) B3LYP energies in kilocalories per mole

proton-transfer process [4, 5, 6]. This is the case of the ammonia molecule, NH_3, which presents a computed proton affinity of 204.7 kcal/mol, higher than those of the glycyl radical at the C, N and O centers. Effectively, the results for $[NH_2CH_2COOH^+-NH_3]$ show a spontaneous proton transfer between the glycine radical cation and ammonia to lead to $[NH_2CHCOOH-NH_4^+]$. This complex presents a distonic character [32, 33], since the charge is concentrated at the ammonium cation (0.92), while the spin is on the glycyl radical (1.00).

When a cluster of water molecules is considered instead of a single water molecule, the proton affinity increases, the increase becoming larger with the number of molecules in the cluster. Thus, if the cluster is large enough, its proton affinity can be higher than that of glycyl at the different sites. Consequently, and similarly to ammonia, proton transfer from the glycine radical cation to the water cluster can occur spontaneously, leading to the formation of the glycyl radical and a hydronium cation, as is observed in solution [18]. In order to confirm this, a geometry optimization of $[NH_2CH_2COOH-H_2O]^+$ using the continuum model was carried out. The minimum located is shown in Fig. 4, where it can be observed that in fact an intermolecular proton transfer reaction has occurred, the final complex being formed by the interaction of
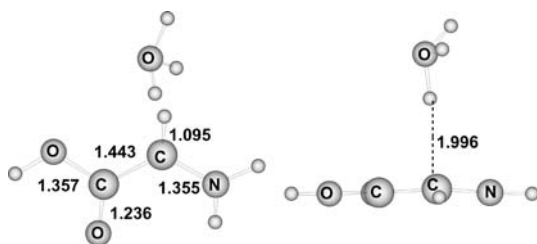

Fig. 4. B3LYP main geometrical parameters of the stationary point located for water–glycine radical cation with the COSMO continuum model. Distances in angstroms

the glycyl radical and the hydronium cation. The deprotonation process from the $-CH_2$ group of the glycine radical cation is preferred over the deprotonation of $-NH_2$ or $-OH$ groups and is consistent with the superacidic nature of hydrocarbon radical cations [34, 35]. Although this is partly due to the large stability of the glycyl radical because of captodative effects [31], recent studies in our laboratory (Gil A, Bertran J, Sodupe M unpublished results) have shown that ionization induces important changes in acidity, in such a way that the CH_4 molecule becomes more acidic than NH_3 or H_2O, in contrast to the relative acidity observed for neutral species.

Conclusions

The gas-phase isomerization reactions of the glycine radical cation, from I to II or III present high-energy barriers owing to important geometrical distortions and electronic reorganizations. The presence of a water molecule reduces dramatically the energy barriers of these tautomerizations owing to a change in the nature of the process. In gas-phase, isomerizations I → II and I → III transform a nitrogen-centered radical into two different carbon-centered radicals. For I → II, the process can be viewed as a hydrogen-atom transfer. However, in the water-catalyzed system both transition states acquire a clear distonic character since a proton from the $-CH_2$ group of the glycine radical cation is almost transferred to the water molecule. These kinds of processes are referred to as proton-transport catalysis. Therefore, the presence of a water molecule changes the nature of these isomerizations (from hydrogen atom to proton transfer), and, along with the smaller geometrical distortions in the solvated system, produces an important catalytic effect. Consequently, the mechanism for the I → III interconversion changes in the presence of a water molecule, the direct mechanism being more favorable than the two-step one.

In aqueous solution these tautomerization reactions do not take place since the distonic transition structure found with one water molecule becomes a stable complex. Thus, spontaneous intermolecular proton transfer to the solvent occurs instead of the tautomeric intramolecular transfer. With this particular example we want to show the importance of the solvent and the potential of continuum models to which Professor Tomasi has made such important contributions. With this work we want to express our affection and admiration to him for his human and scientific qualities.

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