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REGULAR ARTICLE

Gas-phase proton-transport self-catalysed isomerisation of glutamine radical cation: The important role of the side-chain

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Abstract The gas-phase isomerisation reaction of glutamine radical cation from $[NH_2CH(CH_2CH_2CONH_2)COOH]^{+\bullet}$ to $\left[NH_2C(CH_2CH_2CONH_2)C(OH)_2\right]^{+\bullet}$ has been studied theoretically using the MPWB1K functional approach. The $\left[NH_2C(CH_2CH_2CONH_2)C(OH)_2\right]^{+\bullet}$ diol species has been found to be the most stable isomer for glutamine radical cation. Moreover, it has been observed that glutamine has a long enough side-chain with basic groups that acts as a solvent molecule favouring the proton-transfer from C_α to COOH group. This fact reduces dramatically the isomerisation energy barriers compared to the same process for glycine radical cation in gas phase. Thus, this reaction can be considered as an example of gas-phase proton-transport catalysed reaction in which the proton-transport is carried out by the reactant molecule itself instead of any solvent.

1 Introduction

Amino acid and peptides radicals are of great biological interest. The knowledge of their structure and reactivity is important to understand the role of transient species involved in protein radical catalysis [1] as well as the effects of oxidative damage in proteins [2,3]. Because of that, in the past few years, the properties of different amino acid derived radicals have attracted considerable attention, both from an experimental and theoretical point of views [4–12]. However, most of those studies refer to radicals derived from glycine, the simplest amino acid, and fewer studies exist for other aminoacids [13–18].

Glutamine is the most abundant amino acid in the body. It is a glucogenic amino acid that can be synthesised in the body from glutamic acid, valine or isoleucine by a wide variety of tissues rich in glutamine synthetase. Glutamine may promote muscle protein synthesis in such a way that the quantity of this amino acid in the muscles can be the most important variable for an optimum protein synthesis [19–21]. Moreover, glutamine is the principal carrier of nitrogen in the body, as it comprises approximately 50% of the whole-body pool of free amino acid [22,23] and is considered to be a major fuel for many cells [19,20]. Thus, the study of the conformational properties of glutamine amino acid is of interest. Moreover, it has been observed that glutamine radical cation do not follow the same patterns for fragmentation in mass spectrometry. The mass spectrum for glutamine do not present the peaks corresponding to $COOH^\bullet$, $R^\bullet$, $H^\bullet$ or R^+ cleavages of the α-carbon, which are characteristic of other amino acids [24]. For these reasons, the study of the structure and reactivity of ionised glutamine is important in order to interpret its mass spectrum.

Amino acids usually present intramolecular hydrogen bonds which are crucial to understand their structure and reactivity. These hydrogen bonds, however, can be largely modified upon ionization. Previous studies have shown that removing an electron from such a system modifies both the acidity and basicity of the groups involved in the hydrogen bond, in such a way that it is difficult to establish how this interaction would be affected by oxidation [25]. For glycine the observed changes in intramolecular hydrogen bonds have been related to the nature of the electron hole in different electronic states [26]. On the other hand, oxidised species

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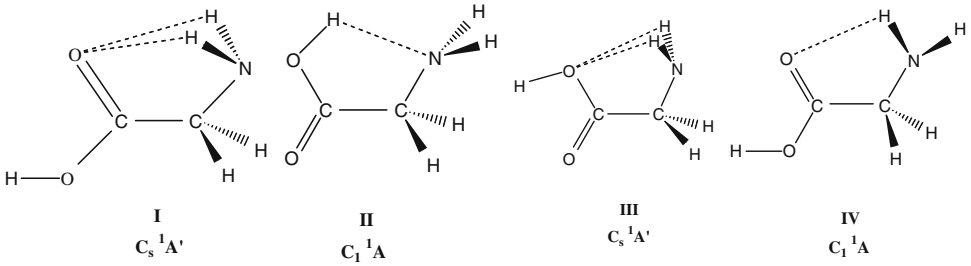
Scheme 1



can also lead to intermolecular spontaneous proton transfer processes in solution. Rega et al. [27,28] observed that the main product after glycine ionisation in solution is the glycyl radical $[NH_2CHCOOH]^{\bullet}$, even at low pH, due to the large acidity of the $-CH_2-$ group [29,30] in the ionised species.

Gas-phase isomerisation reactions has been also studied for glycine radical cation $[NH_2CH_2COOH]^{+\bullet}$ [31]. This study showed that the most stable isomer is a diol like species $\left[NH_2CHC(OH)_2\right]^{+\bullet}$, which is 26.4 kcal/mol more stable than $[NH_2CH_2COOH]^{+\bullet}$. The energy barrier for the isomerisation reaction between these two isomers was found to be very high due to large geometrical distortions at the transition state and important electronic reorganisations. However, the presence of a water molecule reduces drastically the energy barrier [32] because it acts as a proton transport catalyst [33–35]. Several theoretical studies of Radom and coworkers [36–38] have shown that this catalytic effect is especially favourable when the proton affinity of the neutral molecule lies between the proton affinities of the two sites involved in the isomerisation. The catalytic role of solvent molecules in tautomeric processes of neutral molecules has also been observed in different theoretical studies [39–45]. 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.

Glutamine has a quite long side-chain with basic groups such as CO whose proton affinity lies between those of C_α and COOH. Thus, the side-chain may take the role of the solvent and efficiently catalyse the isomerisation reaction. Thus, the purpose of the present paper is to study the role of the side-chain in the isomerisation reaction that leads to the formation of a diol species in glutamine radical cation.

2 Methods

It is well known that amino acids can exist in a large number of conformations due to many single-bond rotamers. Given the conformational complexity introduced by the side chain, the following strategy has been applied to find the lowest energy conformations glutamine amino acid. Starting from the four most stable glycine conformations shown in Scheme 1 (I–V), a Monte Carlo multiple minimum (MCMM) conformational search with the MMFF94s force field has been performed allowing only the internal rotations of the side chain. All plausible structures within an energy window of 50 kJ/mol were selected for subsequent quantum chemical optimisations. All trial structures were used as starting structures for full geometry optimisations using the non-local meta-hybrid MPWB1K density functional approach [46] with the 6-31++G(d, p) basis set [47,48]. Radical cation structures were then obtained after ionisation and reoptimisation of the minima found for each neutral conformation.

The MPWB1K density functional has been shown to perform reasonably well for this kind of systems compared to coupled-cluster single-double and perturbative triple excitation calculations. Moreover, radical cations are open-shell systems, and there are some examples in the bibliography that show that hybrid density functional theory methods with small percentage of exact exchange tend to overstabilise structures with a too delocalised electron hole [49,50]. Recent studies have shown that MPWB1K hybrid meta-GGA functional, which includes 44% of exact exchange, performs well for open-shell species [25,51].

The nature of the stationary points was checked by vibrational frequency calculations. In all cases, intrinsic reaction coordinate (IRC) calculations were carried out to confirm that the located transition states link the proposed reactants, intermediates and products. Thermodynamic corrections were computed assuming an ideal gas, unscaled harmonic vibrational frequencies and the rigid-rotor approximation by standard statistical methods [52]. Net atomic charges and spin densities were obtained using the natural population analysis of Reed et al. [53] All calculations were performed with the Gaussian 03 package [54].

3 Results and discussion

As found for glycine, ionization significantly modifies the relative stability of the I-IV conformers shown in Scheme 1. That is, whereas for the neutral system, the lowest energy structures correspond to conformers I and II, for the ionized system the preferred ones are of type III(+) and IV(+). This is due to the fact that ionization mainly occurs at the

Table 1 Relative energies with respect GlnIV(+)1 conformation at MPWB1K level of calculation

System	Energy		
	ΔE	ΔE_{ZPE}	ΔG^0_{298K}
GlnIV(+)1	0.0	0.0	0.0
GlnIII(+)1	2.9	−0.4	−0.9
GlnIV(+)2	1.6	−0.6	−0.7
GlnIII(+)1-H	1.0	−0.2	0.0
GlnIII(+)1diol	−27.0	−27.6	−27.5

Inclusion of zero point correction and thermal corrections to Gibbs Free energy are also taken into account. Energies in kcal/mol

NH_2 amino group of the backbone, which becomes more planar and increases its acidity. Consequently, the intramolecular hydrogen bonds in which $–NH_2$ acts as proton donor are strengthened and thus, structures III(+) and IV(+) are stabilized. In contrast, structures II(+) in which $–NH_2$ acts as proton acceptor become the most unstable ones due to the decrease of basicity of $–NH_2$ upon ionisation.

Table 1 shows the relative energies of the three most stable conformers obtained for glutamine upon ionisation and Fig. 1 the optimized structures. Each structure has been labelled with a roman number according to Scheme 1 and another natural number according to the relative energy order. As observed in Table 1, these conformations are very close in energy in such a way that the absolute minimum can change if the zero point correction or the entropic terms are included.

Both IV(+)-like structures for glutamine have the $–NH_2$ group interacting as proton donor with the carbonyl oxygen of COOH. In addition the carbonyl oxygen of the side chain interacts with $–NH_2$, either through a 2-centre-3-electron interaction, GlnIV(+)1, or through a NH ··· OC hydrogen bond. As expected, single occupied molecular orbitals (SOMO's) in Fig. 2 show that ionisation in both structures is mainly produced at the NH_2 backbone group. Moreover, the SOMO orbital of GlnIV(+)1 clearly shows the 2-centre-3-electron interaction between the ionised NH_2 backbone group and the CO of the side-chain. Glutamine III(+)-like structure in Fig. 1 is basically obtained by the rotation of the COOH group, in such a way that now the intramolecular hydrogen bonding occurs with the hydroxyl OH basic site. This structure preserves the NH ··· OC hydrogen bond between the amino group and the CO of the side-chain. Since CO is more basic than OH, it is not surprising that the NH ··· OCOH hydrogen bond distance in GlnIV(+)2 (2.137 Å) is shorter than the NH ··· OHCO one (2.273 Å) in GlnIII(+)1. For this reason, the other NH ··· OC hydrogen bond with the side-chain is more strengthened in structure GlnIII(+)1 than in structure GlnIV(+)2.

Figure 1 also includes the optimized structures GlnIII(+)1-H and GlnIII(+)1diol derived from proton transfer reactions. Structure GlnIII(+)1-H results from GlnIII(+)1 after a proton transfer between the backbone NH_2 and the CO of the side chain and can be considered in a fluxional equilibrium with III(+)1 since the energy barrier of the transition state is negligible and the exothermicity is small (−1.9 kcal/mol), (see Fig. 3). The GlnIII(+)1diol species is clearly localised as the most stable structure (see Table 1). In this case, the H of C_α has been transferred to the COOH group, in order

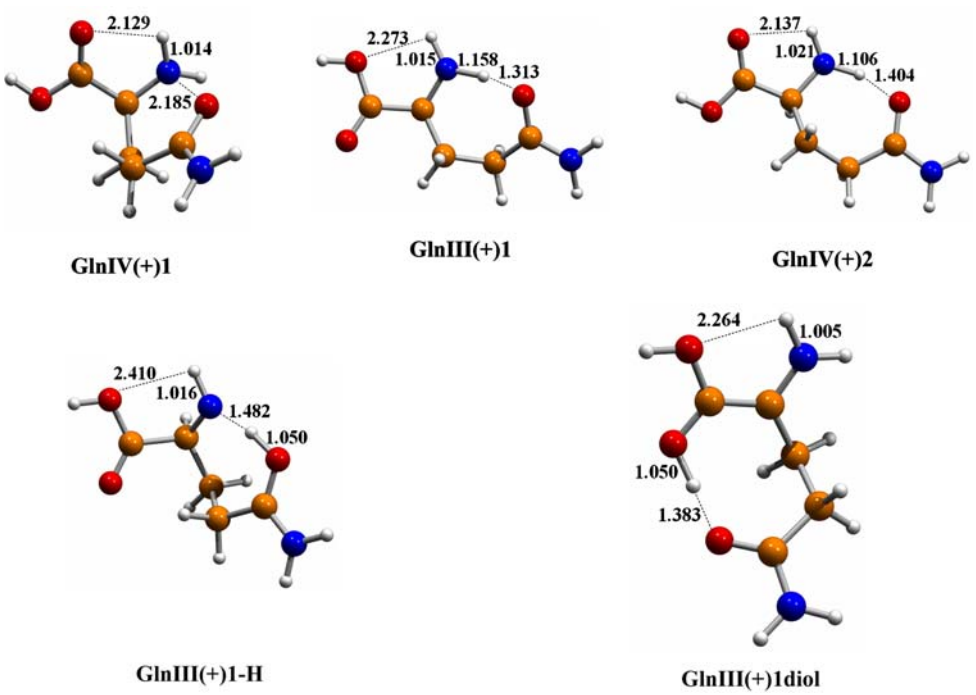


Fig. 1 Optimised geometries of the lowest energy conformers of glutamine radical cations at the MPWB1K/6-31++G(d, p) level of calculation. The proton-trasferred GlnIII(+)1-H and the diol GlnIII(+)1diol structures are also included

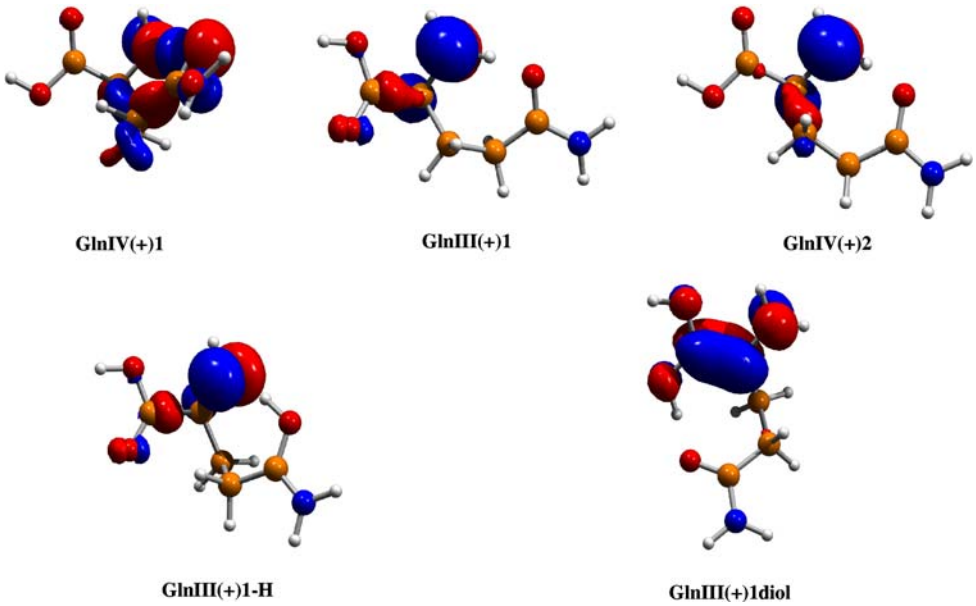


Fig. 2 Single occupied molecular orbital of the most representative structures for glutamine radical cation. SOMO's of the proton-trasferred GlnIII(+)1-H and the diol GlnIII(+)1diol structures are also included

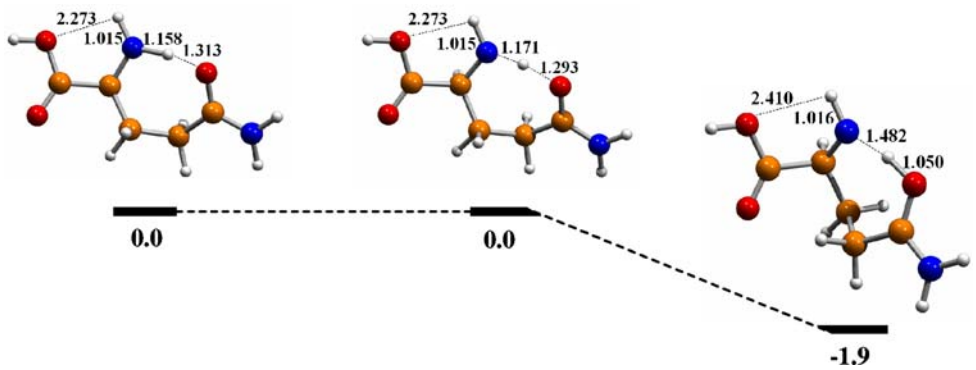


Fig. 3 Fluxional equilibrium between the GlnIII(+)1 conformer of glutamine radical cation and the proton-transferred GlnIII(+)1-H one. Relative energies in kcal/mol taking GlnIII(+)1 conformer as origin of energies. Distances are in Å

to form GlnIII(+)1diol. These diol species were studied for glycine radical cation in gas phase [31] and its formation from $[NH_2CH_2COOH]^{\cdot+}$ was found to require a high energy barrier (∼40 kcal/mol) due to important geometrical distortions and electron reorganisations. However, the presence of a water molecule reduces dramatically this energy barrier owing to a change in the nature of the process [32]. That is, in gas-phase, the isomerisation reaction transforms a nitrogen-centred radical into a carbon-centred radical and the isomerisation process can be viewed as a hydrogen-atom transfer. However, in the water-catalysed system the transition state structure acquires 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. Thus, the presence of a water molecule changes the nature of the isomerisation (from hydrogen atom to proton transfer) and, along with the smaller geometrical distortions in the solvated system, produces an important catalytic effect.

For glutamine, with a long enough side-chain containing a CO basic group, ionisation may cause a proton transfer from the C_α to the CO of the side-chain. Subsequently a proton transfer from the CO to COOH can occur, which would lead to the diol species, similarly to that found for glycine radical cation in the presence of a water molecule. In this case, the side-chain will act as solvent. Because the calculated proton affinity of CO (−213.0 kcal/mol) remains between those for C_α (−198.7 kcal/mol) and COOH (−215.7 kcal/mol) the process is expected to be highly efficient.

As mentioned, the three most stable conformers obtained for glutamine amino acid upon ionisation are close in energy and interconversion among them is easy by rotating the side chain or the COOH group. In order to study the isomerisation mechanism that leads to the diol species it is convenient to start with structure III(+)1 because it is the only one in which the final *O* proton-acceptor to form the diol species is free. Although III(+)1 structure can be considered in a fluxional equilibrium with the proton-transferred III(+)-H isomer (see

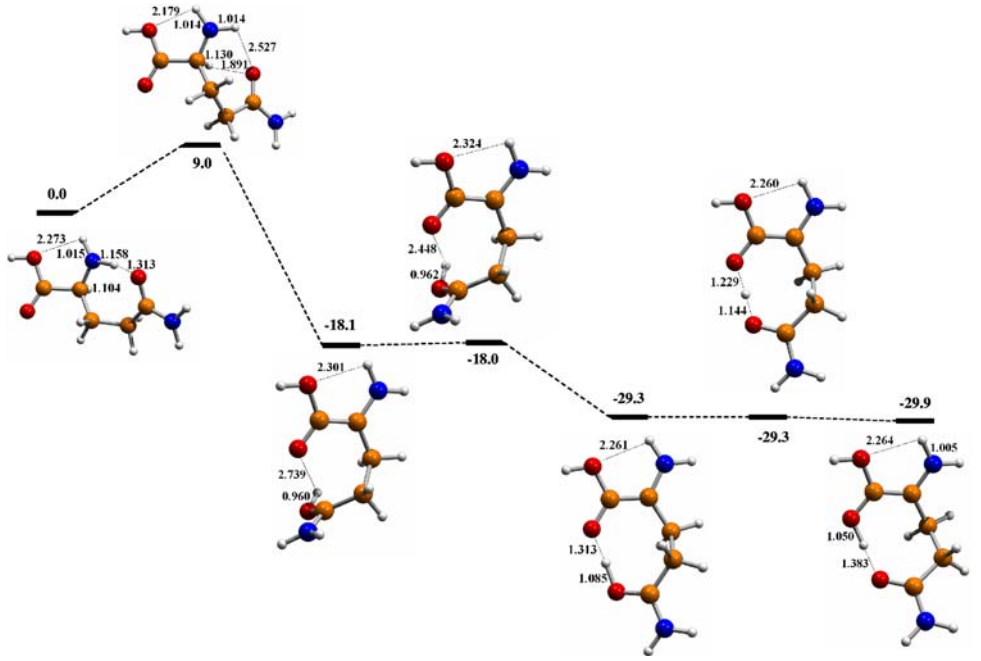


Fig. 4 Gas-phase energy profile for the isomerisation reaction from $[NH_2CH\,(CH_2CH_2CONH_2)\,COOH]^{+\bullet}$ glutamine radical cation to $\left[NH_2C\,(CH_2CH_2CONH_2)\,C\,(OH)_2\right]^{+\bullet}$ diol structure. Relative energies in kcal/mol

Table 2 Relative energies at MPWB1K level of calculation for each stationary point of the isomerisation reaction mechanism considering **GlnIII(+)1** conformation as asymptote

System	Energy		
	ΔE	ΔE_{ZPE}	ΔG^0_{298K}
GlnIII(+)1	0.0	0.0	0.0
TS transfer	9.0	10.2	10.9
GlnIII(+)1transfer	−18.1	−15.2	−15.1
TS rot	−18.0	−15.2	−14.1
GlnIII(+)1rot	−29.3	−27.2	−26.7
TS flux	−29.3	−28.5	−27.4
GlnIII(+)1diol	−29.9	−27.2	−26.7

Inclusion of zero point correction and thermal corrections to Gibbs Free energy are also taken into account. Energies in kcal/mol

above) this process should not be considered to be competitive since the high exothermicity for the diol isomerisation, makes this reaction the most important one for glutamine upon ionisation.

The calculated energy profile for the isomerisation of glutamine radical cation to the diol species is depicted in Fig. 4. Relative energies including the zero point correction and entropic effects are collected in Table 2. The computed mechanism involves three elementary steps. The first one corresponds to the transfer of the proton from C_α to the side-chain CO. In the second step the C–OH bond of the protonated side-chain rotates to establish a OH $\cdots$ OC hydrogen bond with the carbonyl oxygen of COOH. The third and final step involves another proton-transfer from the CO of the side-chain to the COOH in order to form the diol species.

The first step is very favourable from a thermodynamic point of view the exothermicity being −18.1 kcal/mol, (see Table 2 and Fig. 4). Nevertheless, from a kinetic point of view this step has an energy barrier of 9.0 kcal/mol. This energy cost is mainly due to the cleavage of the NH $\cdots$ OC hydrogen bond, which is quite strong as observed in Figs. 1 and 4. The formed transition structure is an early transition state since the C_α proton has not yet been transferred to CO. In this transition state, the $C_\alpha H \cdots OC$ distance is 1.891 Å and has diminished 1.873 Å with respect to the same distance in the initial structure (3.764 Å). Moreover, a rotation of the side-chain to form a $C_\alpha H \cdots OC$ interaction is observed. This rotation increases the NH $\cdots$ OC hydrogen bond distance from 1.313 Å in the initial structure to 2.527 Å in the transition state. The resulting structure of this step can be considered a glycyl-like species, that is, a α-carbon centred radical, which contains both a π-donor (NH_2) and a π-acceptor substituents. Such radicals present an extra stability due to the so-called captodative effects [55], described as the combined resonance effect of the electron-withdrawing (capto) and electron-donating (dative) substituents at the radical centre, which leads to a larger electron delocalisation. Natural population analysis in Table 3 confirms this fact since the computed spin density is delocalised on NH_2 (0.28), COOH (0.26) and C_α (0.45). In this intermediate a side-chain rotation is

Table 3 Charge (spin density) from natural population analysis at MPWB1K level for all stationary points in the energy profile of Fig. 4

System	Fragment			
	NH_2	COOH	R	CH
GlnIII(+)1	0.53(0.89)	0.13(0.07)	0.25(0.00)	0.09(0.04)
TS transfer	0.52(0.74)	0.10(0.01)	0.23(0.12)	0.16(0.12)
GlnIII(+)1transfer[a]	0.13(0.28)	−0.15(0.26)	0.93(0.02)	0.09(0.45)
TS rot [a]	0.14(0.28)	−0.16(0.26)	0.94(0.02)	0.09(0.44)
GlnIII(+)1rot [a]	0.16(0.29)	−0.12(0.31)	0.85(0.01)	0.11(0.40)
TS flux [a]	0.16(0.29)	−0.10(0.32)	0.82(0.01)	0.11(0.38)
GlnIII(+)1diol [b]	0.18(0.29)	0.49(0.37)	0.19(0.01)	0.13(0.33)

[a] *R* includes H from CH whereas H is not included in CH
[b] COOH includes H from CH whereas H is not included in CH

observed so that the protonated CO of the side-chain can interact with the COOH group, the OH ··· OC distance in this structure being 2.739 Å.

The second step involves a C − OH rotation in the side-chain in order to strengthen the OH ··· OC hydrogen bond, in which the recently protonated CO of the side-chain acts as a proton-donor and the COOH as a proton acceptor. This reorientation of the side chain is thermodynamically favourable since the resulting hydrogen-bonded structure causes a stabilisation of the system of 11.2 kcal/mol and has a negligible barrier (0.1 kcal/mol), which denotes the high tendency of the protonated side-chain to form a OH ··· OC hydrogen bond with COOH. Note that for the structures involved in this step this hydrogen bond distance goes from 2.739 to 1.313 Å.

In the third and final step the diol is obtained by transferring the proton from the protonated CO of the side-chain to the COOH group. This diol species is only 0.6 kcal/mol more stable than the intermediate precursor and the transition state is almost degenerate with the reactant. That is, the reaction is barrierless (see Table 2 and Fig. 4). Hydrogen bond distances for these structures are shown in Fig. 4. All the systems involved in this last step can also be considered as glycyl-like species stabilized by captodative effects. Natural population analysis and SOMO (see Table 3; Fig. 2) confirm this fact for the diol $\left[NH_2C\,(CH_2CH_2CONH_2)\,C\,(OH)_2\right]^{+\bullet}$ species since the computed spin densities on the $C\,(OH)_2$, C_α and NH_2 are 0.37, 0.33 and 0.29, respectively and the SOMO orbital is highly delocalized all over the molecule. On the other hand, for the OH ··· OC hydrogen-bonded $[NH_2C\,(CH_2CH_2COHNH_2)\,COOH]^{+\bullet}$ intermediate precursor the computed spin densities are 0.31, 0.40 and 0.29 at the COOH, C_α and NH_2 respectively.

As observed, isomerisation reaction of glutamine radical cation to the diol $\left[NH_2C\,(CH_2CH_2CONH_2)\,C\,(OH)_2\right]^{+\bullet}$ species is a very favourable process both, thermodynamically and kinetically. The reaction energy is −29 kcal/mol and the overall energy barrier 9 kcal/mol. This energy barrier corresponds to the first step and is mainly due to the fact that the initial strong NH ··· OC hydrogen bond between NH_2 and the side-chain CO is disrupted. For glycine radical cation, the energy barrier of the isomerisation reaction in the presence of a water molecule was computed to be 7.4 kcal/mol, which is very similar to the one found for glutamine (9 kcal/mol). That is, for glutamine radical cation, a catalytic effect is observed without any external molecule, being an example of catalysis by the own reactant molecule. This is mainly due to the fact that its long enough side-chain is not affected upon ionisation and takes the role of an external molecule in proton-transport catalysis. These energy values are much smaller than that computed for glycine radical cation in gas phase (about 40 kcal/mol), which points out the importance of assisting this process either by solvent molecules or by the side chain. Nevertheless, compared to the water-catalysed isomerisation of glycine [32], the behaviour of the side chain in glutamine is slightly different from that of the solvent molecule since in the former case the water molecule is oriented in such a way that it accepts a hydrogen atom from the C_α of glycine, but it simultaneously transfers another hydrogen to the oxygen atom; that is to say, the water molecule acts as a bifunctional catalyst and the reaction occurs in one step. However, for glutamine radical cation several intermediates have been located on the potential energy surface. The most important difference for glutamine is that once the side-chain accepts the proton from the C_α, this side-chain needs to be reoriented for transferring it to the oxygen atom of COOH.

4 Conclusions

The gas-phase isomerisation reaction of glutamine radical cation has been studied using the MPWB1K density functional approach. The most stable isomer of glutamine radical cation corresponds to the diol $\left[NH_2C\,(CH_2CH_2CONH_2)\,C\,(OH)_2\right]^{+\bullet}$ structure. The isomerisation reaction from the $[NH_2CHRCOOH]^{+\bullet}$ initial radical cation to the $\left[NH_2CRC\,(OH)_2\right]^{+\bullet}$ diol species is especially favourable for glutamine due to its long side-chain. The computed mechanism consists of three steps: i) a proton-transfer from the C_α to the side-chain CO to form the $[NH_2C\,(CH_2CH_2COHNH_2)\,COOH]^{+\bullet}$

intermediate, ii) a rotation of the protonated side-chain in order to form a OH $\cdots$ OC hydrogen bond with the COOH and iii) a subsequent proton transfer from protonated CO to COOH. Both the first intermediate, $[NH_2C(CH_2CH_2COHNH_2)COOH]^{+\bullet}$, as well as the final diol $[NH_2C(CH_2CH_2CONH_2)C(OH)_2]^{+\bullet}$ species are glycyl like species which are largely stabilised by captodative effects. The overall energy barrier for this isomerisation (9 kcal/mol) is similar to that found for glycine radical cation in the presence of a water molecule (7.4 kcal/mol) which indicates that the side chain takes the role of an external solvent molecule acting as a proton transport catalyst.

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