Towards an Understanding of the Aldo-Enediolate Tautomerism of Glycolaldehyde in Basic Aqueous Solution

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Abstract: The biochemically important interconversion process between aldoses and ketoses is assumed to take place *via* 1,2-enediol or 1,2-enediolate intermediates, but such intermediates have never been isolated. The current work was undertaken in an attempt to detect the presence of the 1,2-enediol structure of glycolaldehyde in alkaline medium, actually a 1,2-enediolate, and to try to clarify the scarce data existing about both the formation of the deprotonated enediol and the aldo-enediolate equilibrium. The Raman spectra of neutral and basic solutions were recorded as a function of time for eleven days. Several bands associated with the presence of the enediolate were observed in alkaline medium. Glycolaldehyde exists as three different structures in aqueous solution at neutral pH, i.e. hydrated aldehydes, aldehydes and dimers, with a respective ratio of approximately 4:0.25:1. Additionally, the formation of *Z*-enediolate forms takes place at basic pH, together with the increase of aldehyde species, as 2-oxoethan-1-olate, and the decrease of hydrated aldehyde and dimeric forms. The theoretical ratio ~1.5:1 aldehyde:*Z*-enediolate reproduces the experimental Raman spectrum in basic medium, with the additional contribution of the previously mentioned ratio between hydrated aldehyde and dimeric forms. Finally, Raman spectroscopy allowed us to monitor the enolization of this carbohydrate model and to conclude that the aldo-enediol tautomerism, formally aldo-enediolate, happens when a suitable amount of basic species is added.

Introduction

Sugars, saccharides or carbohydrates are synonymous terms to refer to a same type of compounds constituted by carbon, oxygen and hydrogen atoms that obey to the general formula $C_nH_{2n}O_n$ where $n \geq 3$. Regarding the functionalization, carbohydrates are generally composed of one aldehyde (aldoses) or ketone (ketoses) group and many hydroxyl groups attached to a carbon skeleton. They are the most abundant organic compounds on Earth by mass, with a string of relevant functions as energy storage, metabolic intermediates, structural building blocks, and bacterial and viral recognition targets, among others. The interest in the study of carbohydrates has increased in recent years due to new insights in their chemistry and biochemistry.[1] Sugars are also components of fundamental molecules for Life, as is the case of D-ribose and its 2-deoxy derivative, constituent parts of the nucleic acids RNA and DNA, respectively.

Carbohydrates experiment many fundamental processes as pseudorotation,[2] mutarotation,[3] and glycosylation,[4] however, literature remains unclear concerning the isomerization process which has its basis in the aldo-enediol tautomerism. Fedoroňko *et al*.[5] studied polarographically the kinetics of enolization of glycolaldehyde and methoxyacetaldehyde in acid (HCl at 30-60 ºC) and alkaline (NaOH at 20-40 ºC) media. In these two media, glycolaldehyde exists in equilibrium with its enediol form, which is quantitatively oxidized to glyoxal by an excess of methylene blue. From the values obtained for the rate constants they observed that the enolization of glycolaldehyde in acid medium is much slower than in basic one. Furthermore, Kobayashi *et al*.[6] analyzed the far IR (FIR), IR and Raman spectra of glycolaldehyde in solid phase, melted and in fresh saturated H_2O, D_2O, DMSO and DMSO-d_6 solutions, observing in the DMSO spectrum that several new bands appeared five days after preparation of the solution. These bands were attributed to the dissociation of dimeric molecules into monomeric ones. However, further spectral changes were not observed after fifteen more days, suggesting that equilibrium in solution was then established among the molecular species, including dimeric and monomeric molecules. They concluded that monomeric molecules predominate over other species in the melt and in water solution. However, Michelsen *et al*.[7] reported, in a study using IR and Raman spectroscopies, that both as a melt and as a supercooled liquid or when dissolved in water or polar organic solvents, glycolaldehyde apparently exists as an equilibrium between monomer and dimer species, the latter predominating. The addition of hydrochloric acid to the aqueous solution did not result in any noticeable change in the carbonyl absorption band. In addition, Collins and George[8] performed studies of glycolaldehyde by NMR technique at room temperature in D_2O solution, concluding to the presence of at least four different molecular species: 70% of hydrated aldehyde, 4% of aldehyde form, and 26% of dimers (9% of 2,5-dihydroxy-1,4-dioxane and 17% of 2-hydroxymethyl-4-hydroxy-1,3-dioxolane). More recently, these results were supported by Yaylayan and co-workers[9] in a study of the mechanism of the dissociation of glycolaldehyde dimer in different solvents and at

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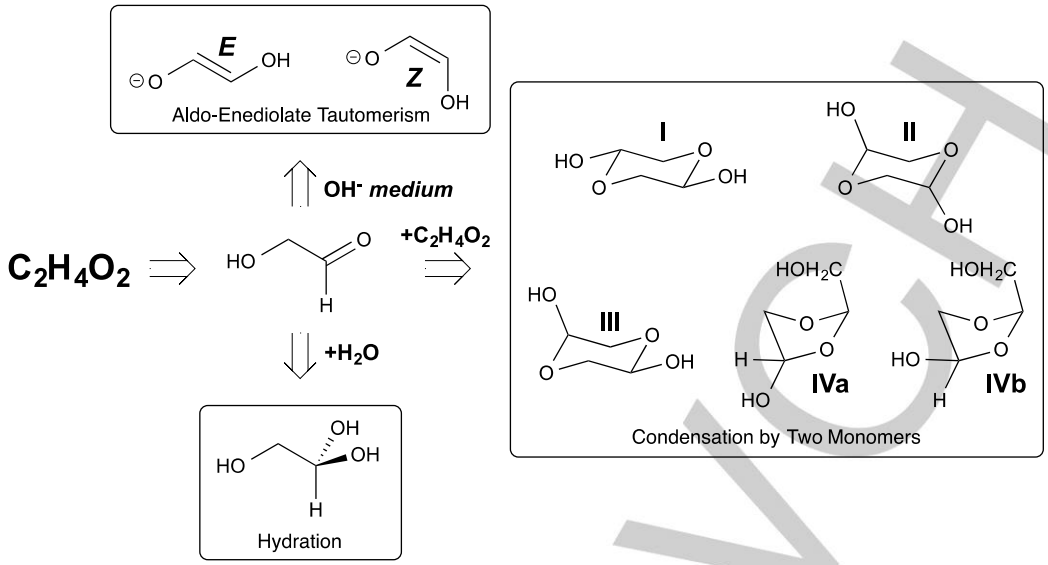

Scheme 1. Glycolaldehyde ($C_2H_4O_2$) species: aldehyde (center), enediolate in its *E* and *Z* isomers (top, basic medium), hydrated aldehyde (bottom) and rings by condensation of two aldehyde monomers (right).

different pH and temperatures by means of the IR spectroscopy. They assigned tentatively a band that appeared at 1703 cm^{-1} to the presence of enediol, which increased during the heating cycle and decreased during the cooling cycle. Finally, Yaylayan *et al*.[10] also confirmed the presence of enediol forms in neutral aqueous solutions of selected reduced sugars by IR spectroscopy. The relative concentration of enediol to that of carbonyl was studied as a function of temperature and concentration. The ratio of intensities of the enediol to carbonyl absorption bands was found to decrease with temperature and increase with concentration.

With regard to the solid phase, Mohaček-Grošev *et al*.[11] reported on the stable crystal structure of the glycolaldehyde dimer characterized by the X-ray powder diffraction method at room temperature. The glycolaldehyde dimer molecules are *trans*-isomers with the electronegative hydroxyl groups in axial positions. They also analyzed the IR and Raman spectra with the help of *ab initio* calculations. Glycolaldehyde has also been studied in the gas phase by different techniques such as MB-MWFT spectroscopy[12] or supersonic jet infrared (IR) and Raman techniques.[13] Specifically, in ref. 13 the authors: a) showed that C_2-symmetric dimers could be formed with intermolecular O-H···O=C bonds, while the corresponding intramolecular H-bonds were broken, b) assigned spectral bands to the vibrational movements of the M4 monomer and of the D8 and D4 dimers, being D8 the most stable dimer; c) suggested a rotational spectroscopic study of the most stable polar dimer, which is probably thermodynamically more stable than the chemically bound dimer; d) reported that the glycolaldehyde shows that cooperative hydrogen-bond patterns can be superseded by isolated bonds if the geometric constraints are favorable for the latter, conclusion obtained from an analysis supported by quantum chemical calculations of the O-H stretching range. It is important to stand out that our most stable aldehyde conformer optimized in PCM-water has a similar structure to the most stable monomer (M4) of the ref. 13 and to that of the ref. 12.

Our objective in the present work consists in the understanding and clarification of the aldo-enediol equilibrium in glycolaldehyde ($C_2H_4O_2$). Glycolaldehyde is formally considered as a sugar, being not only a formal precursor of more complex sugars, but also a model system with many of the features of carbohydrates. Scheme 1 gathers the different chemical forms of glycolaldehyde in aqueous solution: aldehyde, hydrated aldehyde by hydration of its aldehyde group, enediolate (in its *E* and *Z* diastereomers, in basic environment) and its cyclic dimer obtained by condensation of two monomers. The dimer could be a six-membered (1,4-dioxane-2,5-diol) or a five-membered ring [2-(hydroxymethyl)-1,3-dioxan-4-ol], although it is known that the compound is a dioxane.[11,14]

Our experimental and computational results based on Raman spectroscopy and an exhaustive *ab initio* conformational search reveal the existence of enediol species (in their enediolate forms) in basic environment, and they correct much of the literature that provides erroneous results when an enediol structure is assigned in neutral medium.

Computational and Experimental Details

Computational Details

The conformational search of the glycolaldehyde in aqueous solution, in its aldehyde ($HOCH_2CHO$) and enediol (HOCH=CHOH, *E* and *Z* isomers) forms, was conducted following this strategy: i) selection of initial structures by

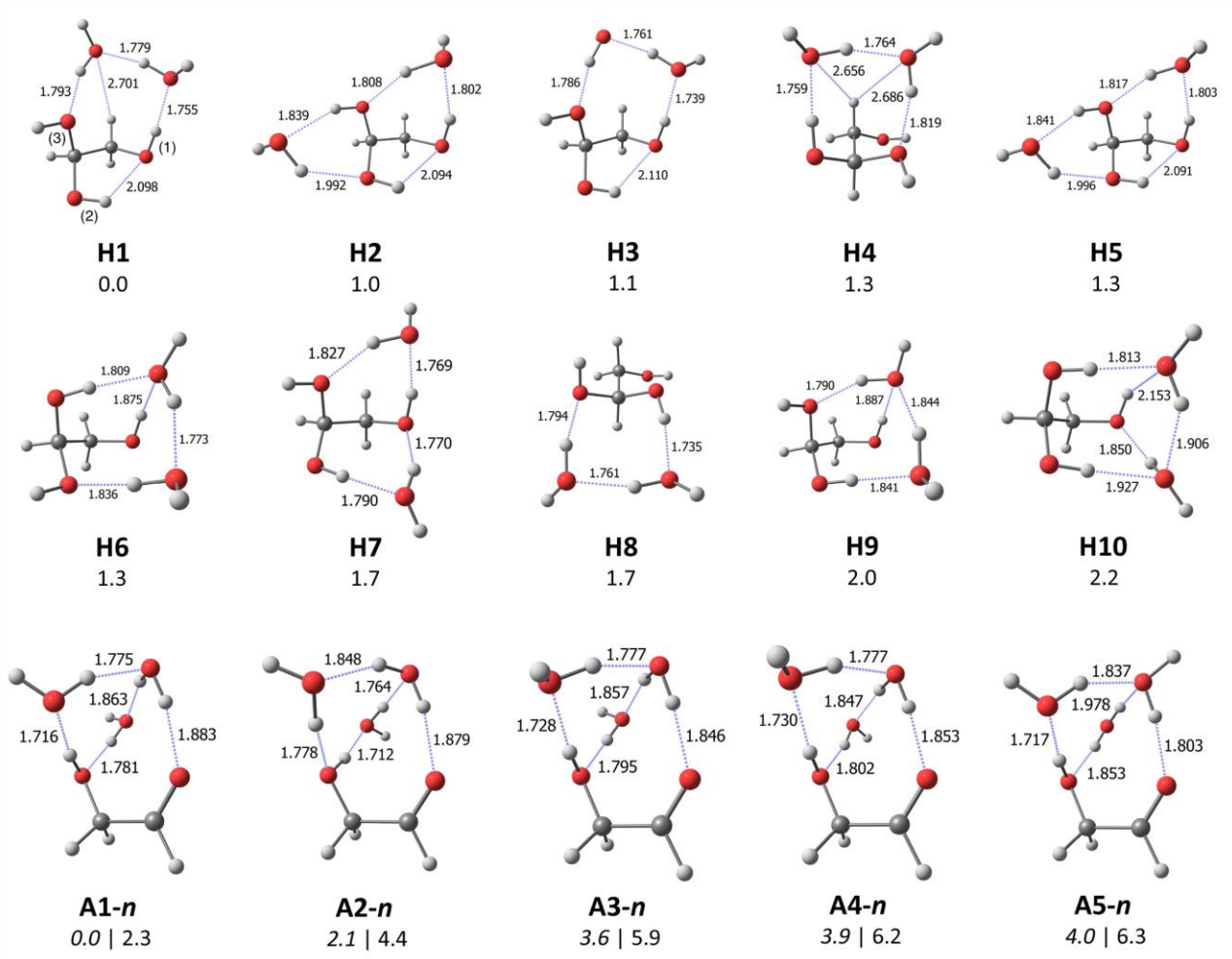

Figure 1. Structures of the most stable hydrated aldehyde (**H**) and aldehyde (**A-*n***) (with relative energies less than 5 kJ·mol^{-1}) complexes ($C_2H_4O_2$ + $3H_2O$). Relative energies (electronic plus ZPE) are in kJ·mol^{-1}. In aldehyde complexes, values with respect to the most stable complex of the aldehyde form and to the most stable complex of the hydrated aldehyde form appear in italic and normal fonts, respectively. Calculations accomplished at MP2/aug-cc-pVDZ computational level in PCM-water and in presence of explicit H_2O molecules.

combination of the rotatable bonds attending to the *gauche'*, *gauche* and *trans* (*g'*, *g* and *t*) conformations and removing those duplicated by symmetry;[2d] ii) for each of the conformations generated in step (i), explicit water molecules have been included using a random method,[15] getting a total of $2{\cdot}3^{(n+1)}$ initial dispositions of the water molecules, where 2 refers to the number of lone pairs and/or π electrons for a given atomic center, 3 refers to the major number of H-bond donor or acceptor binding sites in the monomers, and *n* is the number of explicit water molecules employed, *n* = 3 in our case. This algorithm ensures a representative set of initial structures for the description of the conformational landscape; iii) optimization at M06-2X[16]/6-31+G(d)[17] DFT-level *via* Gaussian09 package,[18] including implicitly the bulk solvent by use of the Polarizable Continuum Model (PCM)[19] with the standard parameters for water; and iv) re-optimization *via* Gaussian09 package[18] by means of *ab initio* second-order Møller-Plesset perturbation theory (MP2)[20] with the aug-cc-pVDZ[21] basis set with the objective to obtain more accurate values and emulating the solvent effect by the PCM-water method,[19] and including, in this case, the solute-solvent dispersion interaction energy, the solute-solvent repulsion interaction energy and the solute cavitation energy.

The numbers of initial structures proposed for the first optimization at DFT-level were 810 (= $5{\cdot}2{\cdot}3^4$) and 648 (= $4{\cdot}2{\cdot}3^4$) for the aldehyde and enediol (*E* and *Z* isomers) forms in each case. Once obtained the set of minima at M06-2X level, they have been compared and the duplicated structures were removed by application of the following screening criterion: two structures are considered identical if their relative energies (ΔE) differ in less than 0.1 kJ·mol^{-1}, and at the same time their geometrical root-mean-square (rms) is less than 0.05 Å.[2d,e,22] The same criterion was also applied for the final set of structures obtained at MP2 level. In the remaining structures, vibrational frequencies were calculated to obtain the IR and RAMAN spectra, the zero point energy (ZPE) and also to corroborate that the final structures correspond to true energetic minima. Subsequently, the wave-functions were analyzed by means of the Atoms in Molecules (AIM)[23] theory *via* the AIMAll program[24]

with the aim of identifying the noncovalent interactions[25] (mainly H-bonds).[26]

These results in neutral environment were used as starting points in basic environment by abstraction of one of the acidic protons each time in the MP2 minima: the six possible H atoms in the three explicit H_2O molecules and the H atoms in the OH functional groups of glycolaldehyde. These structures were re-optimized at MP2/aug-cc-pVDZ level, including the PCM solvent environment as in the neutral systems.

In addition, the energy surface in neutral environment was completed with the hydrated aldehyde [$HOCH_2CH(OH)_2$] plus two explicit H_2O molecules (2286 = $42{\cdot}2{\cdot}3^3$), in order to have isoatomic complexes which allow the energetic comparison and the relative Boltzmann populations of each species. Besides, the dimeric compounds obtained by condensation of two monomers in presence of two explicit H_2O molecules have been considered.

Experimental Details: Raman Spectra

The glycolaldehyde dimer was purchased from Sigma-Aldrich and used without further purification. 25 μL and 10 μL of NaOH solution (4M) were added separately to two different fresh prepared water solutions of glycolaldehyde (3.57 M). The Raman spectra of these two solutions were recorded three times per day for eleven days, allowing us to follow the evolution of the isomerization in basic medium of glycolaldehyde to its enediolate form. The Raman spectra of the solution of glycolaldehyde (3.57 M) at neutral pH (without the addition of NaOH) were also recorded for several days, but no substantial changes were found.

The Raman spectra were recorded using a BRUKER MultiRAM Stand Alone FT-Raman Spectrometer, equipped with a Nd:YAG laser (excitation line at 1064 nm) and a Ge detector cooled at liquid nitrogen temperature. The spectra of the two basic solutions were measured using standard liquid cells, with 300 scans and a resolution of 8 cm^{-1}, whereas the spectra of the neutral solution were recorded with 300-400 scans and 4-8 cm^{-1} of resolution. A resolution of 4 cm^{-1} for basic solutions was not possible in order to get a good signal/noise ratio. All the spectra were recorded in the 2000-650 cm^{-1} spectral region.

Results and Discussion

Potential Energy Surface Analysis and Bounded Properties

The computational results indicate that glycolaldehyde exists as monomers in aqueous solution in two forms: aldehyde and hydrated aldehyde, being the second one the most stable and populated species. Percentages of both of them obtained at MP2/aug-cc-pVDZ level in PCM-water with three explicit H_2O molecules are 9 and 91%, corresponding to a ratio of aldehyde:hydrated aldehyde ~1:9. No significant populations of enediol form, either *E* or *Z* isomers, have been observed in neutral environment. Figure 1 reports the structures for the solvated aldehyde form with relative energies less than 5 $kJ{\cdot}mol^{-1}$ (five minima) and the structures (ten minima) of the solvated hydrated aldehyde form, which are more stable than the most stable minimum of the aldehyde form.

Table 1. Relative energies in $kJ{\cdot}mol^{-1}$ and Boltzmann populations in percentage for the most stable minima of hydrated aldehyde, aldehyde (**H** and **A-*n***, respectively; in both cases restricted for conformers with energies less than 5 $kJ{\cdot}mol^{-1}$) and dimer forms (**D**, restricted for conformers with energies less than 10 $kJ{\cdot}mol^{-1}$) of glycolaldehyde at the MP2/aug-cc-pVDZ computational level (T = 298.16 K) in neutral medium.

Neutral medium

Hydrated Aldehyde and Aldehyde		
Struc.	ΔE_0	Pop.
H1	0.0	10.9
H2	1.0	7.4
H3	1.1	7.0
H4	1.3	6.5
H5	1.3	6.5
H6	1.3	6.4
H7	1.7	5.5
H8	1.7	5.4
H9	2.0	4.8
H10	2.2	4.6
A1-*n*	2.3	4.3
H11	2.3	4.3
H12	2.3	4.3
H13	2.6	3.9
H14	2.9	3.4
H15	3.7	2.4
H16	4.2	2.0
A2-*n*	4.4	1.8
H17	4.5	1.8
H18	4.5	1.8
H19	4.6	1.7
H20	4.6	1.7
H21	4.7	1.6

Aldehyde		
Struc.	ΔE_0	Pop.
A1-*n*	0.0	48.6
A2-*n*	2.1	20.5
A3-*n*	3.7	11.1
A4-*n*	3.9	10.0
A5-*n*	4.0	9.8

Dimer		
Struc.	ΔE_0	Pop.
D1	0.0	75.3
D2	5.4	8.6
D3	5.5	8.3
D4	7.6	3.5
D5	8.1	2.8
D6	9.8	1.4

As commented above, the hydrated aldehyde complexes exhibit ten minima (**H1**-**H10**) between 0.0 and 2.2 $kJ{\cdot}mol^{-1}$, which are more stable than the most stable minimum of the aldehyde complexes. The most stable minimum, **H1**, presents

g'tg conformations for the hydroxyl groups in the substrate (following the numbering of the hydroxyl groups in Figure 1) and the two explicit H_2O molecules interact with the substrate and with each other by H-bonds with similar interatomic distances, ranging between 1.7 and 1.8 Å, which is practically 0.2 Å shorter than for the water dimer (1.949 Å at MP2/aug-cc-pVDZ computational level).[27] Additionally, an intramolecular H-bond between the *g'* and *g* hydroxyl groups is found with a R(O···H) distance of 2.098 Å.[2d] Likewise, there is a secondary noncovalent interaction which consists in a non-classical long H-bond between H_2O···HC with R(O···H) = 2.701 Å.[28] Other minima, as **H2**, **H3**, **H5**, **H7** and **H9**, have similar *g'tg* conformations for the hydroxyl groups than in **H1**. The explicit water molecules in them are placed interacting with different orientations and/or locations. In addition, **H4**, **H6** and **H8** are characterized by *g'g't* conformations (following the numbering of the hydroxyl groups in Figure 1), while **H10** has *g'g'g* conformations. Moreover, although **H1** and **H9** have the glycolaldehyde molecule with the same conformation, a difference of 2 kJ·mol^{-1} and a ratio of 8.2:3.7 in Boltzmann populations is obtained for them (attending to all the conformers derived from the conformational search).

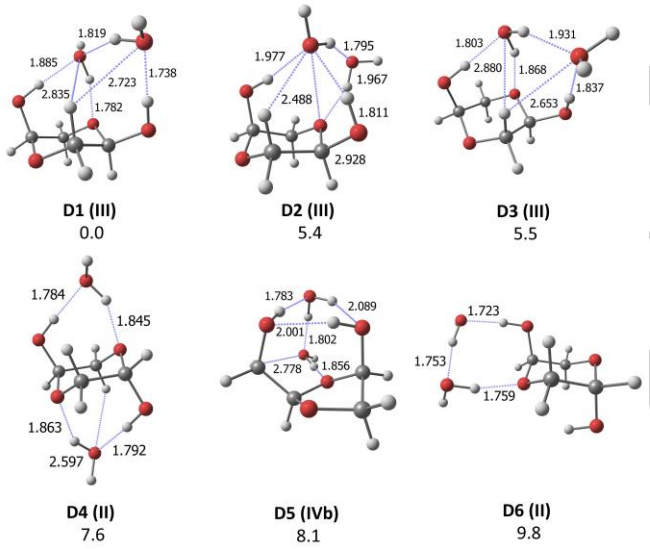

Figure 2. Structures of the most stable glycolaldehyde dimers (**D**) with relative energies less than 10 kJ·mol^{-1}. Relative MP2 energies are in kJ·mol^{-1}. Calculations performed at MP2/aug-cc-pVDZ computational level in PCM-water with the presence of explicit H_2O molecules.

Figure 1 also shows the structures of the minima of the aldehyde form in presence of three explicit H_2O molecules with relative energies (electronic plus ZPE) less than 5 kJ·mol^{-1}: **A1-*n*** to **A5-*n***, up to 4.0 kJ·mol^{-1}. The most stable complex of them is 2.3 kJ·mol^{-1} less stable than the global minimum of the hydrated aldehyde complexes. Always, the substrate has φ_{OCCO} *s-cis* conformation, and the explicit H_2O molecules surrounding the oxygen atoms of glycolaldehyde. With exception of the **A2-*n*** (*g*) complex, all the φ_{CCOH} dihedral angles have *g'* conformation.

As in the previous case of the hydrated aldehyde complexes, explicit H_2O molecules establish primarily H-bonds through the interaction with the hydroxyl and carbonyl groups in the substrate and to each other with similar distance parameters. Only the H-bonds between H_2O and the CHO moiety have longer interatomic distances, around 1.8 and 1.9 Å, than those observed between hydroxyl groups from substrate or solvent.

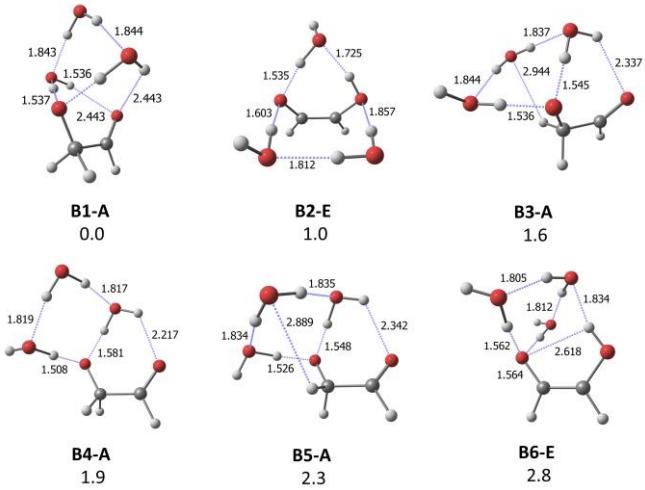

Figure 3. Structures of the most stable aldehyde (**B-A**) and *Z*-enediolate (**B-E**) species with relative energies less than 3 kJ·mol^{-1}. Relative energies (electronic plus ZPE) are in kJ·mol^{-1}. Calculations carried out at MP2/aug-cc-pVDZ computational level in PCM-water with the presence of explicit H_2O molecules.

The energy surface of glycolaldehyde in aqueous solution and neutral environment is completed with the description of the cyclic structures formed by condensation of two monomers. As previously indicated in Scheme 1, four isomers are possible: **I**, **II**, **III** and **IV**, this last one in its subtypes **a** and **b**. Results at MP2/aug-cc-pVDZ level, reported in Figure 2, reveal that up to 10 kJ·mol^{-1} of MP2 relative energies, six minima are found: the three most stables, **D1** (0.0), **D2** (5.4) and **D3** (5.5 kJ·mol^{-1}) are of **III** type, i.e. with one hydroxyl group in *axial* and the other one in *equatorial* dispositions and attached to a chair ring conformation. Moreover, minima **D4** (7.6 kJ·mol^{-1}) and **D6** (9.8 kJ·mol^{-1}) are of type **II**, that is, both hydroxyl groups in *axial* disposition and chair conformation for the cycle. Finally, **D5** (8.1 kJ·mol^{-1}) is of type **IVb**, i.e. both hydroxyl groups with (*R*) stereochemistry and a five-membered ring, in this case, envelope with puckering in the CH_2 moiety. In type **III** compounds, explicit H_2O molecules are placed above the rings as represented in Figure 2, being engaged in a large number of H-bonds. One important characteristic that should be highlighted is the presence of O···H bonds between H_2O (H-bond donor) and one of the endocyclic O atoms (H-bond acceptor). These H-bonds are in a range of distances between 1.759 and 1.868 Å in this set of complexes, shorter than the results obtained in the most stable minimum of *β*-furanose of D-ribose and the *α*- and *β*-furanose of 2-deoxy-D-ribose in presence of one explicit H_2O

molecule, in which these O···H distances are 1.999, 1.885 and 1.943 Å, respectively.[2e] Besides, these noncovalent interactions in such sugars were reported only for furanose rings and never for pyranoses, which are the analogous of the **III** and **II** types discussed here.

As can be seen in Figure 3, aldehyde and enediol species in basic environment are in their deprotonated forms. The effect of the proton abstraction leads to the 2-oxoethan-1-olate and the 2-hydroxyethen-1-olate species, in each case. The ratio of the Boltzmann populations in basic environment is 56:44 aldehyde:*Z*-enediolate with no significant presence of the *E* isomer, in contrast to the results obtained in neutral aqueous solution. Figure 3 shows the structures of the six minima with relative energies less than 3 kJ·mol^{-1}, in which structures **B1-A** (0.0), **B3-A** (1.6), **B4-A** (1.9) and **B5-A** (2.3 kJ·mol^{-1}) correspond to aldehyde species and **B2-E** (1.0) and **B6-E** (2.8 kJ·mol^{-1}) to *Z*-enediolate ones.

Table 2. Relative energies in kJ·mol^{-1} and Boltzmann populations in percentage for the most stable minima (restricted for conformers with energies less than 5 kJ·mol^{-1}) of aldehyde (**B-A**) and deprotonated enediol (**B-E**) forms of glycolaldehyde at the MP2/aug-cc-pVDZ computational level (*T* = 298.16 K) in basic medium.

Basic medium		
Aldehyde and Deprotonated Enediol		
Struc.	ΔE_0	Pop.
B1-A	0.0	18.1
B2-E	1.0	11.9
B3-A	1.6	9.6
B4-A	1.9	8.6
B5-A	2.3	7.0
B6-E	2.8	5.9
B7-A	3.0	5.3
B8-E	3.3	4.9
B9-E	3.3	4.7
B10-A	3.6	4.2
B11-E	3.6	4.2
B12-A	3.7	4.1
B13-E	4.2	3.3
B14-E	4.5	2.9
B15-A	4.6	2.8
B16-E	4.8	2.6

A common characteristic in the most stable complexes is that the hydroxyl groups of glycolaldehyde are the ones deprotonated. Very short distances between the deprotonated hydroxyl groups and the H atoms in explicit H_2O solvent molecules, ~1.55 Å, are found. This fact leads to structures with very similar energy stability and it is the reason why, in basic environment, analogous species that were energetically widely separated in neutral medium are now located very close. Another important characteristic can be seen in the H-bonds in which the aldehyde CHO moiety acts as H-bond acceptor. In these cases, the CHO···H_2O bonds experiment a huge increment of the interatomic O···H distance compared to those results obtained in the neutral aldehyde (2.2-2.4 Å *vs*. 1.8-1.9 Å, respectively).

At this point, it should be mentioned the different results obtained by including explicit H_2O molecules *vs*. only implicit PCM model. In this regard, for example, the conformational search in basic environment of glycolaldehyde in PCM-water reveals the existence of two, two and one minima for aldehyde, *Z*-enediolate and *E*-enediolate species, and a ratio of Boltzmann population percentages of 0.2:99.8:0.0. It shows the large difference between the ~1:1 and 1:499 aldehyde:deprotonated enediol ratios obtained with these two different procedures. The subsequent experimental results will prove that the inclusion of explicit water molecules improve considerably the results obtained by using the PCM-model.

In summary, i) glycolaldehyde in neutral aqueous solution exists as hydrated aldehyde, free aldehyde and cyclic dimer forms; ii) the monomeric Boltzmann population in this case corresponds to a ratio of ~1:9 aldehyde:hydrated aldehyde; and iii) in basic environment, glycolaldehyde experiments aldo-enediolate tautomerism with a ratio ~1:1 aldehyde:enediolate, being the deprotonated enediol form only present in its *Z* isomer.

Study of the Aldo-Enediolate Tautomerism by Raman Spectroscopy

In order to detect and monitor the process of enolization of glycolaldehyde in aqueous medium and thus to increase the understanding of the aldo-enediolate tautomerism of this compound in alkaline medium, and hence of more complex hydroxycarbonyl systems (as sugars), we have recorded its Raman spectra at room temperature, over a period of several days under different pH conditions.

In this way, we added separately different amounts of NaOH solution (4 M) to two different fresh prepared water solutions of glycolaldehyde (3.57 M). The Raman spectra of these solutions were recorded three times per day for eleven days, allowing us to follow the evolution of the enolization reaction of the glycolaldehyde. This evolution can be seen in Figure 4 (with the addition of 25 μL NaOH) and in Figure S1 from the Electronic Supplementary Information (ESI; with the addition of 10 μL NaOH). Figure 4 shows: a) the recorded Raman spectra for the $C_2H_4O_2$ + NaOH system in aqueous solution for seven days; and b) the difference Raman spectrum obtained subtracting the recorded Raman spectrum at neutral pH (before adding NaOH into the system and, thus, prior to the start of the reaction) and the last of the three recorded in the

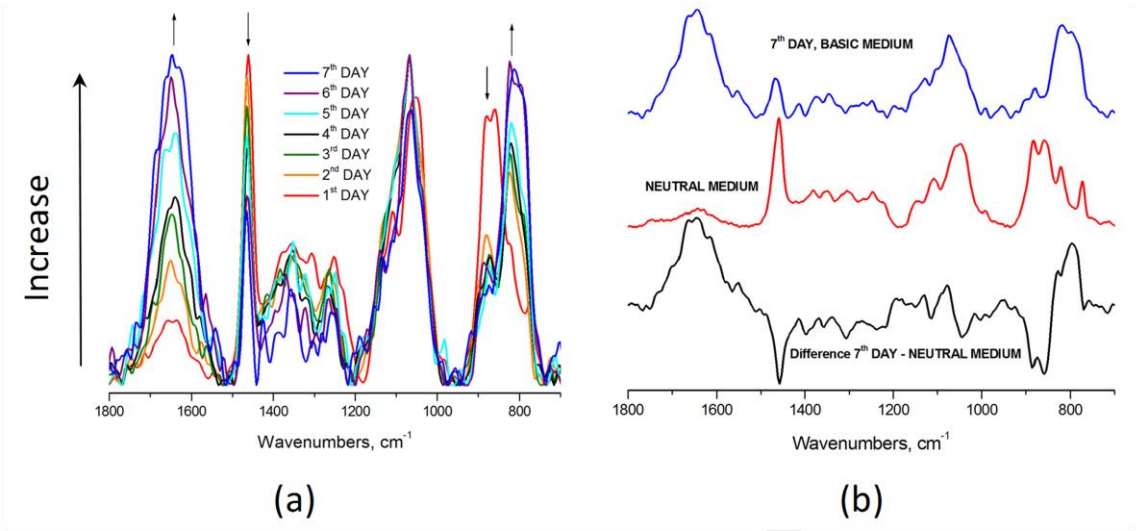

Figure 4. Evolution over time of the Raman spectrum of glycolaldehyde in basic environment (an amount of 25 μL NaOH was added) up to its enediolate form for seven days: a) the first recorded spectrum of each day is shown in the 1800-700 cm^{-1} region. The arrows mark the three most relevant regions that show changes over time (see text for explanation); and b) the difference Raman spectrum between the last spectrum measured the seventh day and that recorded at neutral pH (see text for explanation).

seventh day from the beginning of the process. The main differences observed are pointed out with arrows. This difference spectrum shows clearly how the bands at 1650 cm^{-1} and at 809 cm^{-1} increase and how the bands at 1461 cm^{-1} and at 875 cm^{-1} decrease in intensity with regard to the time. We will analyze these bands in detail below, noticing that the increase of the intensity of the two first bands is due to the formation of aldehyde and *Z*-enediolate forms, while the two second ones decrease because of lower population of hydrates and dimers at basic pH.

In addition to these results, the recorded Raman spectra from the eighth day until the eleventh day (see Figure S2 from ESI) did not show substantial changes, as the equilibrium in the system was practically reached from the eighth day. The Raman spectrum of glycolaldehyde in neutral aqueous solution was also recorded for several days, but there were no significant differences observed among them in relation to the initially measured. On the contrary, Kobayashi *et al*.[6] observed in the IR spectrum of glycolaldehyde in fresh DMSO solution that several new bands appeared five days after preparation of the solution (see Introduction).

To theoretically simulate our experimental findings, a first step was to try to reproduce the recorded Raman spectrum at neutral pH with the help of quantum chemical calculations. Thus, Figure 5 displays both the recorded Raman spectrum of glycolaldehyde at neutral pH and the theoretical spectra of the most stable set of hydrated aldehyde, aldehyde and dimer complexes formed in the system, which are the most populated at MP2/aug-cc-pVDZ level of theory, using an implicit (PCM) plus explicit solvent model, and, as a consequence, expected to be mainly present in aqueous solution at neutral pH. The theoretical spectra have been weighted according to the predicted populations of the most stable conformers (with energy less than 5 $kJ{\cdot}mol^{-1}$ for hydrated aldehyde and aldehyde forms and less than 10 $kJ{\cdot}mol^{-1}$ for the dimer ones, see Table 1). The contribution of aldehyde and hydrated aldehyde complexes is noted in red and green, respectively, for a better visualization of the points in the following discussion. Because Boltzmann populations of dimers around 15-20% seemed to offer the best results when comparing the theoretical spectrum to the recorded one, a 20% of these species was taken into account in our weighted spectrum (in dark yellow, see discussion below). In order to include the presence of 20% of dimers, the populations of hydrated aldehyde and aldehyde (94:6) were multiplied by 0.8 (that is, 75.2:4.8), to attain the 100%.

Thus, the theoretical spectra were taken as reference to interpret the band structure of the recorded spectrum in the 1750-650 cm^{-1} spectral region and some spectral Raman features can be assigned to the presence of the hydrated aldehyde, aldehyde or dimer forms of glycolaldehyde:

(i) Beginning from the high wavenumber range, the weak band at 1744 cm^{-1} in the recorded spectrum can be associated with the C=O stretching normal mode of the aldehyde structure, whereas the band at 1650 cm^{-1} is theoretically identified as arising from H_2O bending modes of the explicit water molecules that surround the different forms of glycolaldehyde.

(ii) Additionally, hydrated aldehyde and dimer forms give the intense band at 1461 cm^{-1}, while the sequence of bands of medium intensity observed at 1384, 1349, 1303, 1268 and 1245 cm^{-1} need the presence of one or two forms to be reproduced. In particular, the band at 1384 cm^{-1} is well predicted by the computations of the hydrated aldehyde and aldehyde forms, those at 1349 and 1303 cm^{-1} by the computations of hydrated aldehyde and dimer forms, while the bands at 1268 cm^{-1} and at 1245 cm^{-1} are well predicted by the only presence of dimers and hydrated aldehydes, respectively. The first mentioned band is attributed mainly to CH_2 scissoring and COH bending normal modes, with the additional contributions of C–C stretching and CH wagging. The rest of the bands can be assigned to COH bending vibrations coupled with CH_2 scissoring (only from

aldehyde forms), CH_2 twisting, and CH and CH_2 wagging normal modes.

(iii) Three further bands at 1149 (shoulder), 1106 (shoulder) and 1052 cm^{-1} (strong) are well accounted by the computations and can be reproduced chiefly by hydrated aldehyde conformers, being assigned to combinations of C–C and C–O stretchings, among other vibrations. However, it is necessary the participation of dimers for the complete prediction of the width of the last band, i.e. ring deformation.

(iv) Finally, it is noteworthy that the band at 875 cm^{-1} is assigned to the O–H torsion normal mode of explicit water molecules coupled with different vibrations of the hydrated aldehyde forms. On the contrary, the band at 775 cm^{-1} corresponds to ring breathing motion of the closed structures formed by condensation of two monomers. These two bands are well predicted by the only presence of hydrated aldehyde or dimer complexes, respectively.

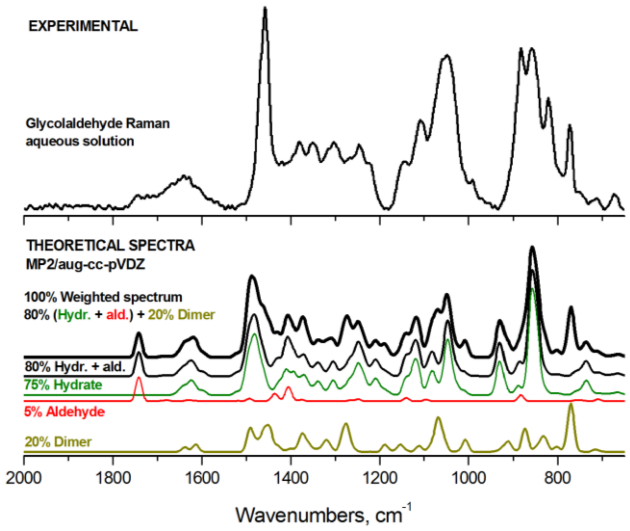

Figure 5. Experimental (top) and predicted (bottom) Raman spectra for glycolaldehyde in aqueous solution in neutral medium in the 2000-650 cm^{-1} spectral region. The solution was prepared with a concentration of 3.57 M. Weighted theoretical spectra (100% bold, 80% black) are obtained with the populations of the most stable hydrated aldehyde (in green), aldehyde (in red) and dimer (in dark yellow, contributing only to the 100% spectrum) species. Gaussian function, pitch = 1 cm^{-1}, FWHM (Full Width Half Minimum) = 16 cm^{-1}.

We can conclude from this analysis that glycolaldehyde molecule exists as three different types of structures in aqueous solution at neutral pH: hydrated aldehydes, aldehydes and dimers. The experimental data are supported by the theoretical ones and the respective ratio 4:0.25:1 (populations around 75, 5 and 20%) seems to be suitable for a correct description of the complex energy surface. Remark the crucial importance of the high-level calculations employed for reaching the previous conclusions. Without an accurate prediction of the most stable conformers of each type of molecular species present and their theoretical spectra, this conclusion could not have been drawn.

Concerning the population of dimers, we can estimate a value between 15 and 20% for this type of species present in the medium by comparing the intensities of some of the theoretical and the experimental Raman bands to which these species contribute partially or totally, i.e. the bands at 1461, 1268 and 994 and 775 cm^{-1}. Thus, if the dimers contributed with a population of 100%, we should have observed an experimental band at 1420 cm^{-1}, with the same intensity that the one at 1461 cm^{-1}. But we do not see this feature so intense. With a 20% of dimers and 75% of hydrated aldehydes, the experimental band at 1461 cm^{-1} is well reproduced. Also, the band at 1268 cm^{-1} is only due to dimer species. It appears with an appropriate intensity using 15-20% of them (see Figure S4 from ESI), having a similar intensity than the band at 1245 cm^{-1}. If we had used percentages higher of this molecular form to weight the spectra, this band would appear with the same intensity that the band at 1461 cm^{-1}. Another fact in favor of the above mentioned contribution of dimers is the adequate theoretical reproduction with this percentage of the weak band observed at 994 cm^{-1}. In addition, the band at 775 cm^{-1} is the most intense one of the weighted theoretical spectrum (dark yellow) of the dimer species; however, the most intense band in the experimental spectrum appears at 1461 cm^{-1}, with a relative intensity ratio of 1:0.4 between this last (taken for it the unit value of relative intensity as reference) and the band at 775 cm^{-1}. This ratio is theoretically 1:0.6 if we chose 20% as population for dimer species, and it changes to 1:0.5 if we use a 15% for it.

Our results are similar to those obtained by Collins and George[8] and Kobayashi *et al*.,[6] who reported that monomeric molecules (in the hydrated form in the case of ref. 8) predominate over other species in D_2O and H_2O solutions, respectively. On the contrary, our results do not agree with those obtained by Michelsen *et al*.,[7] who disclosed that for glycolaldehyde dissolved in water an equilibrium between monomer and dimer species apparently exists, the latter predominating. Finally, Yaylayan *et al*. confirmed the presence of enediol forms in neutral aqueous solutions of selected reduced sugars[10] and, in particular, of glycolaldehyde[9] by FTIR spectroscopy, but we did not find clear evidences of their presence in this medium in the case of glycolaldehyde.

In the same way as for Figure 5, Figure 6 shows for basic medium the last Raman spectrum recorded the seventh day, compared with the weighted theoretical spectrum of the most stable aldehyde, *Z*-enediolate, hydrated and dimer species (less than 5 $kJ \cdot mol^{-1}$, see Table 2). It can be observed in Figures 5 and 6 that the recorded Raman spectra show appreciable differences between them (see also Figure 4) and, therefore, distinct signatures. Hydrates and dimers are also present in basic medium, but in a minor proportion than in neutral pH, while enediol species in their deprotonated forms are present thanks to the addition of basic reagent. Likewise, the proportion of aldehyde complexes with respect to those of hydrated aldehyde and dimer ones has been increased in relation to those present in neutral medium. The ratios ~1.5:1 aldehyde:*Z*-enediolate and ~4:1 hydrated aldehyde:dimers have been conserved in order to weight the theoretical spectra. The ratio of hydrated aldehyde and dimer species is three-fold the ratio of aldehyde and *Z*-

enediolate structures. We deduced this by comparing the intensity of the band at 1461 cm^{-1} in neutral and basic media, which is 1 and 0.35, respectively, after normalizing. Thus, respective populations around 10, 15, 60 and 15% of deprotonated *Z*-enediol, aldehyde, hydrated aldehyde and dimer structures seem to reproduce in a suitable way the recorded spectrum. The bands that are not reproduced with the theoretical spectra of aldehyde and *Z*-enediolate forms are assigned to remains of hydrate and dimer species. There is no information in the literature about the yield of the enolization process of glycolaldehyde, but it can be expected that it is not 100%, because an equilibrium state in the system is reached prior to the enolization process being completed.

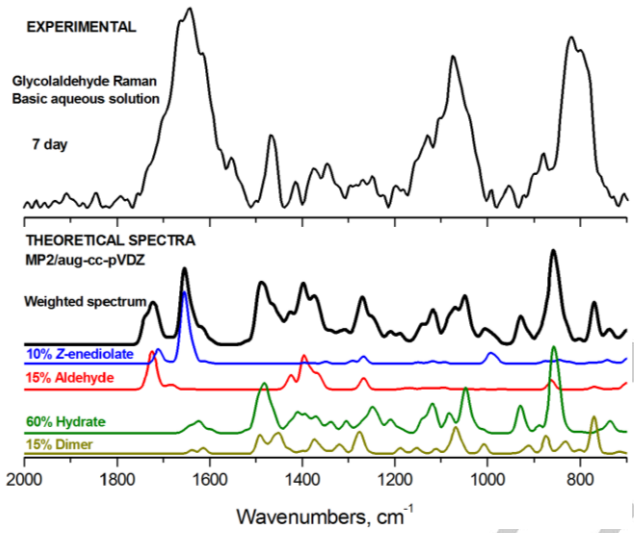

Figure 6. Experimental (top) and predicted (bottom) Raman spectra for the $C_2H_4O_2$ + NaOH system in the 2000-700 cm^{-1} spectral region. The last recorded Raman spectrum in aqueous solution at pH = 14.00 on 7th day is shown (in black) at the top. At the bottom, theoretical spectra are weighted with the population of the most stable *Z*-enediolate (in blue), aldehyde (in red), hydrated aldehyde (in green) and dimer (in dark yellow) species. Gaussian function, pitch = 1 cm^{-1}, FWHM (Full Width Half Minimum) = 16 cm^{-1}.

The main Raman signatures that confirm that the aldo-enediolate tautomerism has taken place are highlighted as follows:

(i) The band at 1650 cm^{-1} appears much more intense than at neutral pH and it was increasing from the first day until the seventh day, as can be observed in Figure 4. At this zone, H_2O bending modes are present; if this band was only due to water, it should not increase over time. *Ab initio* calculations threw light on this fact and they supported the assignment of this band to the C=C stretching normal mode of *Z*-enediolate forms and to the C=O stretching normal mode of aldehyde species, the latter appearing at higher wavenumbers. Experimentally, we see a broad band, which is centered at 1650 cm^{-1}. The width of this band can be justified by the different components that contribute to it, i.e. the above mentioned normal modes of the stretchings of the C=O and C=C bonds of the aldehyde (15% of population) and deprotonated *Z*-enediol (10% of population) forms, respectively, as well as the deformation modes of the H_2O molecules of the solvent. Thus, the increase of intensity of the band in the course of the enolization reaction assisted by NaOH could be supported by the appearance and increase of the enediolate forms in the reaction medium. In addition, it is observed an increment over time of the proportion of aldehyde species relative to those initially present in neutral solution of glycolaldehyde to the expense of a decrease in the populations of the hydrated aldehyde and dimer forms.

(ii) Another change that confirms this fact is the decrease in intensity of the band at 1461 cm^{-1} and that also observed in the bands of the sequence previously mentioned, i.e. 1384, 1349, 1303, 1268 and 1245 cm^{-1}, which also shift due to the higher population of aldehyde forms instead of hydrated aldehyde ones. It is logical because the band at 1461 cm^{-1} was associated with CH_2 scissoring and COH bending modes, and the total population of the forms that could be responsible for these normal modes is lower, i.e. hydrated aldehyde and dimer structures have a total population of 95% and 75% at neutral and basic pH, respectively.

(iii) At lower wavenumbers, the bands at 1149 and 1106 cm^{-1} attributed to the presence of hydrated aldehydes appear weaker and the one at 1052 cm^{-1} owing to the presence of dimers shift to higher frequencies, appearing at 1075 cm^{-1}.

In brief, the bands that could be associated with the appearance and increase of the enediolate and aldehyde species raised their intensities, namely, the bands assigned to the C=O and C=C stretchings and CH_2 scissoring. On the contrary, the bands due to the presence of hydrated aldehyde and dimer forms decreased in intensity, i.e. those bands attributed to CH_2 scissoring, C–C and C–O stretchings and COH bending normal modes. Besides, the recorded Raman spectrum the seventh day at basic pH is well reproduced by the weighted theoretical spectrum considering the ratios ~1.5:1 aldehyde:*Z*-enediolate and ~4:1 hydrated aldehyde:dimer. Once again, the use of high-level calculations was decisive to analyze what species were present in basic environment. This study is complex in view of the multiple reactions that can take place when glycolaldehyde is in aqueous solution under basic conditions. Analyzing the reactive process, it seems to be clear that the sodium hydroxide, acting as a nucleophile, opens the rings of the dimers, dissociating them into hydrate and aldehyde forms, and part of these aldehydes are converted to enediolate species by a migration of a hydrogen atom and the formation of a C=C double bond. Though there are many species present in the medium, the presence of aldehyde, deprotonated *Z*-enediol, hydrated aldehyde and dimer forms here considered seems to reproduce the complex situation in the enolization process from glycolaldehyde to its *Z*-enediolate form. Additionally, it is noteworthy that it is required the combined use of both explicit and implicit solvation models in order to accomplish a correct description of the energy surfaces and to get accurate energies and, consequently, populations. Thus, the Raman technique together with *ab initio* calculations lead us to conclude that the enolization process has taken place and, consequently, aldo-enediolate tautomerism happens when a suitable amount of

basic reagent is added to aqueous solutions of sugars. This result is in concordance with Fedoroňko *et al*.[5] who reported from polarographic measures that glycolaldehyde exists in equilibrium with its enediol forms in alkaline medium; however, the substrate in this second case is not formally an enediol species, but actually the deprotonated one.

Conclusions

We have conducted the first Raman spectroscopic study combined with high-level quantum chemical calculations of the aldo-enediol and aldo-enediolate tautomerisms of glycolaldehyde, the simplest sugar related molecule.

The recorded Raman spectra of aqueous solutions of glycolaldehyde at neutral and basic pH displayed quite distinct features. For this reason, the study was focused on the vibrational modes associated to them, which were closely related to the formation of enediol/enediolate and the increase of aldehyde forms and to the decrease of hydrated aldehyde and dimer structures of glycolaldehyde, namely, the C=C, C=O, C–C and C–O stretchings, CH_2 scissoring and COH bending normal modes, among others. High-level *ab initio* calculations (MP2/aug-cc-pVDZ) allowed us to explain properly the spectral differences, since the theoretical spectra agreed well with the experimental ones. On the one hand, the glycolaldehyde molecule exists as three different structures in aqueous solution at neutral pH, i.e. hydrated aldehydes, aldehydes and dimers, with respective ratio of 4:0.25:1, approximately. On the other hand, together with the previous proportion of hydrates and dimers, a ratio ~1.5:1 aldehyde:*Z*-enediolate was enough to reproduce the experimental Raman spectrum at basic medium. Through this analysis, the complex energy surface of the system under study was described correctly. We conclude that aldo-enediol tautomerism never happens *via* neutral medium, however, the inclusion of basic reagent promotes the existence of aldo-enediolate tautomerism.

In addition, this methodology can also be useful for the study of the enolization of other carbohydrates and for the exploration of their conformational landscapes.

Another general contribution of this work has been the illustration of the potential use of the combination of Raman spectroscopy and computational techniques for the elucidation of the conformational landscapes of the different forms of a flexible molecule in basic and neutral aqueous media. This synergy of experimental and theoretical tools for studying this kind of chemical problems provides the possibility to study the evolution over time of reactions that involve molecules whose natural environment is water, since water itself gives a weak Raman spectrum.

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Keywords: Raman spectroscopy • quantum chemical calculations • aldo-enediol tautomerism • explicit solvent • H-bonds

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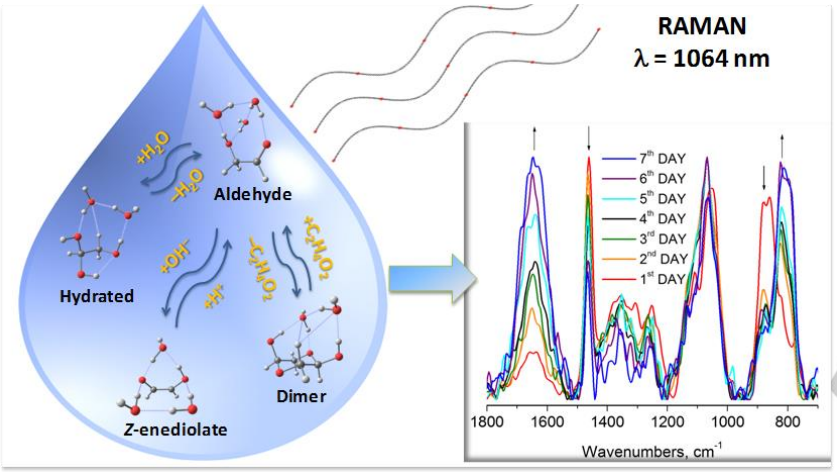

Aldo-Enediolate Tautomerism: The Raman spectra of neutral and basic solutions of glycolaldehyde were recorded as a function of time for eleven days. This carbohydrate model exists as three different structures in aqueous solution at neutral pH, *i.e.* hydrated aldehydes, aldehydes and dimers. The formation of *Z*-enediolate forms takes place at basic pH, together with the increase of aldehyde species, as 2-oxoethan-1-olate, and the decrease of hydrated aldehyde and dimeric forms.

L. M. Azofra, M. M. Quesada-Moreno, I. Alkorta, J. R. Avilés-Moreno, J. Elguero and J. J. López-González**

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Towards an Understanding of the Aldo-Enediolate Tautomerism of Glycolaldehyde in Basic Aqueous Solution

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