Journal of King Saud University – Science 31 (2019) 427–433

Contents lists available at ScienceDirect

Journal of King Saud University – Science

journal homepage: www.sciencedirect.com

Original article

# Study of the structure, the electronic and spectral properties of D-glucaro-dilactones

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## ARTICLE INFO

*Article history:*
Received 8 July 2017
Accepted 10 September 2017
Available online 11 September 2017

*Keywords:*
D-glucaro-dilactones
D-glucaro-1,4:6,3-dilactone
D-glucaro-1,5:6,3-dilactone
Conformations
Relative energies
DFT

## ABSTRACT

The double lactonization of D-glucaric acid can result in two isomeric molecules which are: the D-glucaro-1,4:6,3-dilactone and the D-glucaro-1,5:6,3-dilactone. In the present article we try to understand the differences between these molecules. To this end, all the conformations have been modeled and optimized in order to find the most stable structures. Energies, frontier orbitals (HOMO and LUMO) as well as other electronic and spectral properties have been calculated in vacuum, acidic and aqueous media using the polarizable continuum model (PCM). The calculations were investigated by performing semi-empirical PM6 and density functional theory (DFT) at the B3LYP level of theory. The obtained results do not motivate a possible observation of the two dilactones simultaneously in the same medium, which explains the absence of this coexistence in the scientific works carried out to date.

## 1. Introduction

D-Glucaric acid, formerly known as saccharic acid, is a diacid formed via the oxidation of the aldose sugar D-glucose (1). The common oxidation process utilizes nitric acid as oxidant (Donen et al., 2015).

The transformation of D-glucose (1) begins with a rapid oxidation of the aldehyde function giving D-gluconic acid (2), followed by the oxidation of the primary alcohol function which is slower (Ibert et al., 2002; Solmi et al., 2017). The final product is the D-glucaric acid [(*2R,3S,4S,5S*)-tetrahydroxyhexanedioic acid] ($C_6H_{10}O_8$) (3). The latter can be isolated only in the form of potassium salts, as was already indicated in the work of Sohst and Tollens, as early as 1888 (Sohst and Tollens, 1888).

Otherwise, the crystallization of D-glucaric acid results in a double lactonization and may form, after releasing two water molecules, two different D-glucaro-dilactones : the D-glucaro-1,4:6,3-dilactone (4) or the D-glucaro-1,5:6,3-dilactone (5) (Smith, 1944a; Davey et al., 2006; Amara and Othman, 2016), see Scheme 1.

In 1944, Smith found (Smith, 1944a; Smith, 1944b) that the "saccharolactone" obtained by Sohst and Tollens during the crystallization of a solution of D-glucaric acid was a mixture of two monolactones, namely D-glucaro-1,4-lactone (6) and D-glucaro-6,3-lactone (7), see Fig. 1. Smith indicated as well the existence of the D-glucaro-1,4:6,3-dilactone (4).

In the same year, Smith was able to transform each of the monolactones D-glucaro-1,4-lactone (6) and D-glucaro-6,3-lactone (7) into D-glucaro-1,4:6,3-dilactone (4) and D-glucaro-1,5:6,3-dilactone (5), respectively (Smith, 1944c).

Concerning the D-glucaro-1,5:6,3-dilactone, it should be noted that already in 1936, Rehorst and Scholz carried out a synthesis which had led to the formation of crystallized delta-lactones. This derivative was assigned at that time to the D-glucaro-1,5:6,3-dilactone (5) (Rehorst and Scholz, 1936).

In 2012, Amara and Othman indicated, while synthesizing nucleoside analogues, that D-glucaro-1,5:6,3-dilactone was obtained as a pure substance (Amara and Othman, 2016).

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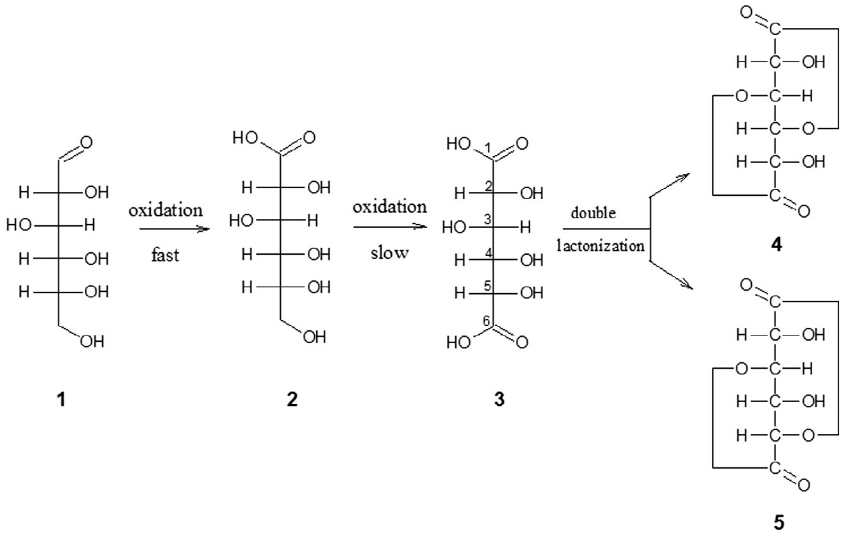
Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.jksus.2017.09.005



**Scheme 1.** From D-glucose (1) to D-glucaro-dilactones (4) and (5).

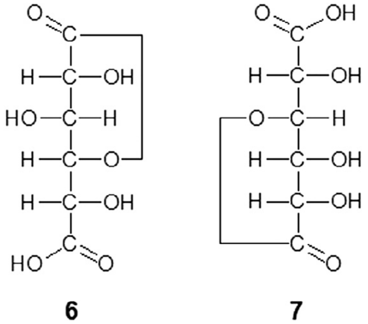


**Fig. 1.** Chemical structures of D-glucaro-1,4-lactone (6) and D-glucaro-6,3-lactone (7).

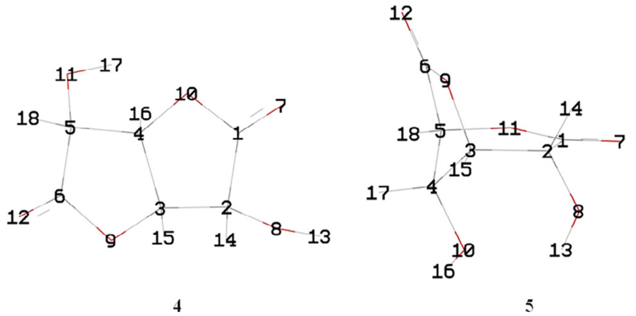


**Fig. 2.** Atom numbering used for the D-glucaro-dilactones (4) and (5).

It is interesting to note, that in the literature, there is an absence of coexistence of the two D-glucaro-dilactones in solutions or in the products of crystallization. In the present article, we make a comparative study of these D-glucaro-dilactones, by looking at the stability of different conformers and the electronic properties of the two dilactones in different solvents.

After a short recall of the employed methodology, we determine, in a first section, the most stable structures of the two dilactones which we compare in a second section, and we look at the electronic and spectral properties, before drawing our conclusions.

## 2. Methodology

After modeling the geometry of the respective D-glucaro-dilactones, the orientations of the free hydroxyl groups and the six-ring conformations were varied by simple « chemical rules » as provided in GaussView 5.0.8 program (Dennington et al., 2009). From the various so-constructed starting points the geometry is rapidly optimized in the semi-empirical PM6 framework and the obtained respective minima taken as starting geometries for a further optimization with B3LYP density-functional calculations (Becke, 1993; Lee et al., 1988). As basis set we chose the 6-31+G (d,p), motivated by the results of Csonka (Csonka, 2002). For the resulting optimum structures, vibrational frequencies, thermochemical and electronic-structure data are extracted.

All calculations have been carried out with the Gaussian 09 software (Frisch et al., 2009). Solvents are implicitly included via the polarizable continuum model (PCM) (Miertus et al., 1981; Cammi and Tomasi, 1995), through a dielectric constant as available in Gaussian 09 (Frisch et al., 2009). As no parameter set is present for concentrated nitric acid, we took the close 2-propen-1-ol (ε of 19.011 instead of 19.000 for concentrated nitric acid).

The numbering of the atoms of the two molecules of D-glucaro-dilactones: D-glucaro-1,4:6,3-dilactone (4) and D-glucaro-1,5:6,3-dilactone (5) is shown in Fig. 2.

## 3. Results and discussion

### 3.1. Equilibrium geometries

#### 3.1.1. D-glucaro-1,4:6,3-dilactone

The frame of the two five-membered rings is almost rigid. The only freedom is the orientation of the two hydroxyl groups. Starting with « chemical rules » using GaussView 5.0.8 we may find nine different starting points which relax by further optimizations with the semi-empirical PM6 to four different structures (see Fig. 3). These we number as A–D, and we display their energies (in Table 1) and relative energies (in Fig. 4), in vacuum and in the two solvents.

The energy ranges are 7.6 mH (milli Hartree) in the vacuum, 6.5 mH in the acid medium and 6.8 mH in the aqueous medium.

From the respective optimum structures (C or D) a DFT geometry optimization is carried out.

The finally obtained structures are numbered as I – III, see Fig. 5.

This optimization does not significantly change the structure but only for the central dihedral angle (C2-C3-C4-C5) which

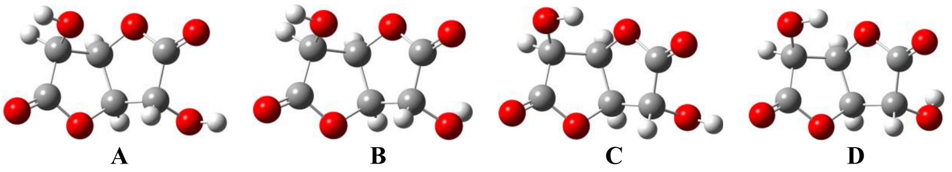


**Fig. 3.** Structures A–D in three dimensions.

**Table 1**
Energies of structures A–D by PM6.

| Molecules | Energy (a.u.) | | |
|---|---|---|---|
| | Vacuum | Nitric acid medium | Aqueous medium |
| A | −0.3662 | −0.3861 | −0.3876 |
| B | −0.3651 | −0.3877 | −0.3895 |
| C | −0.3727 | −0.3910 | −0.3924 |
| D | −0.3719 | −0.3926 | −0.3944 |

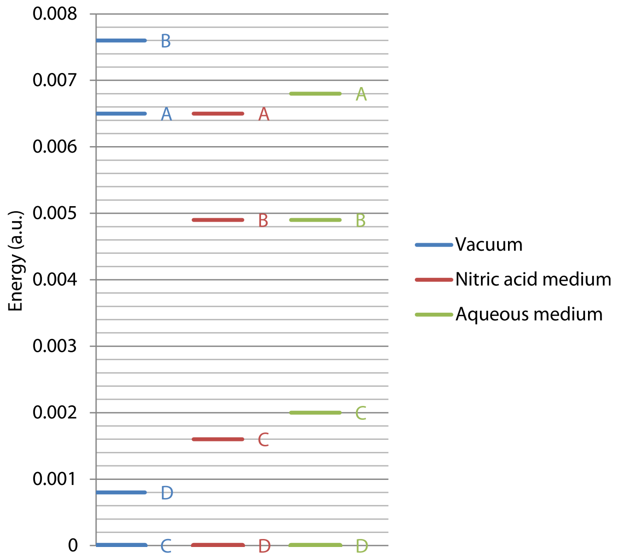


**Fig. 4.** Relative energies of the structures A—D in the three media.

becomes wider by about 20 degrees, in any environment. This seems quite normal, as PM6 takes directly into account only nearest neighbors, whereas DFT considers as well relative orientations of delocalized groups.

#### 3.1.2. D-glucaro-1,5:6,3-dilactone

Beyond the relative orientation of the two hydroxyl groups we have in the six-membered ring the additional freedom of the folding of the ring. From twenty-seven different starting positions we arrive again at different PM6-optimized structures, numbered as E–Q (see Figs. 6–8) whose energies are given in Table 2. The relative energies are displayed in Fig. 9 within ranges of 0.7 (in vacuum) to 7.4 mH (in aqueous medium).

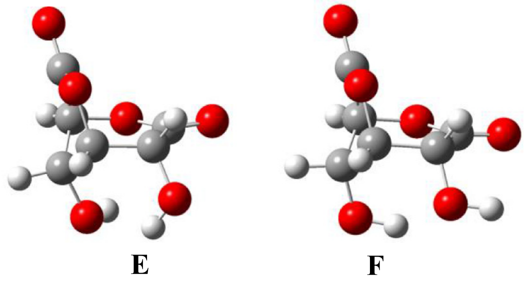


**Fig. 6.** Structures E and F in vacuum.

From the optimal structures in each environment, we arrive at the DFT-optimized structures (IV—VI) displayed in Fig. 10.

In this molecule PM6 and DFT do not result in significant changes of angles as we do not have any more two separated rings with one common edge, but interconnected ones.

### 3.2. Boltzmann populations

The Boltzmann distribution is calculated to determine the percentage of simultaneous existence of the D-glucaro-dilactones at room temperature (27°C). According to the Boltzmann statistic, for a set of equilibrium particles at temperature T, the probability of finding one of these particles in a state of energy E is proportional to the Boltzmann factor: $e^{-E/kT}$ where k is the Boltzmann constant. The values obtained are given in Table 3.

If we compare the differences in total energies of the two most stable structures of the dilactones in their respective environments, we find Boltzmann factors in favor of the D-glucaro-1,4:6,3-dilactone. Thermodynamically speaking, the equilibrium is thus strongly expressed toward this compound, explaining why the simultaneous presence of the two D-glucaro-dilactones has never been observed.

### 3.3. Electronic structure

The electronic structure of the target molecules may lead to a hint why a coexistence of the two molecules is impossible. The calculation furnishes two quantities commonly linked to reactivity,

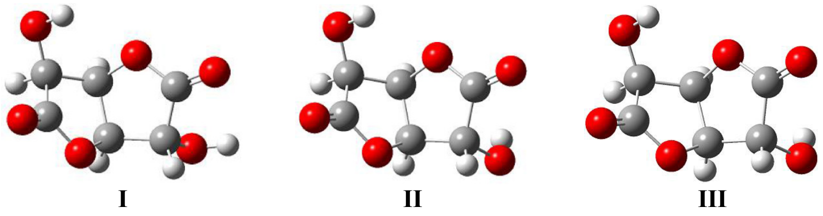


**Fig. 5.** B3LYP-optimized structures for the D-glucaro-1,4:6,3-dilactone in vacuum (I), nitric acid (II) and aqueous (III) media.

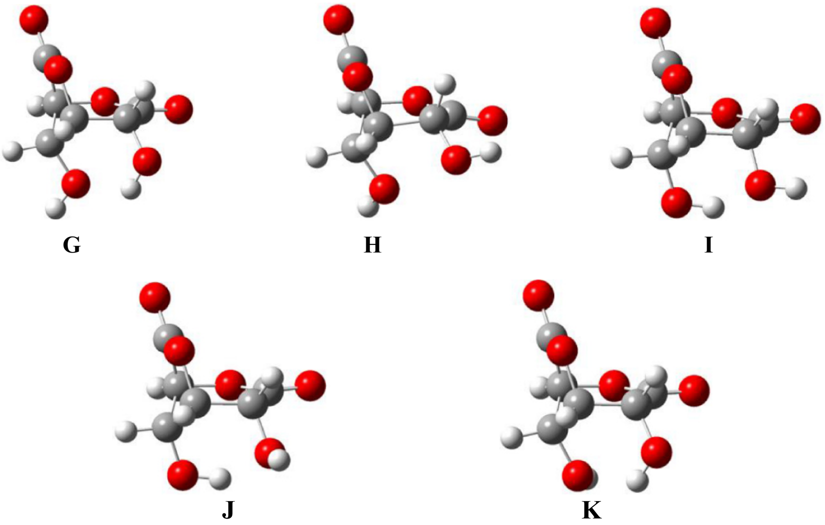


**Fig. 7.** Structures G–K in nitric acid medium.

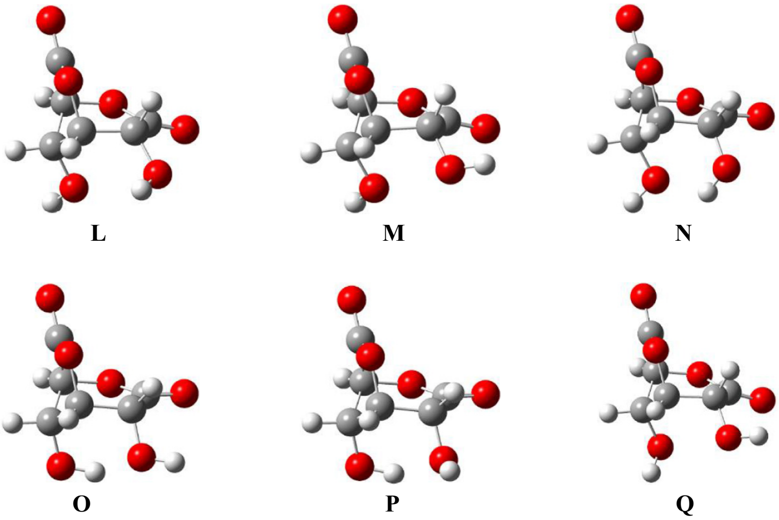


**Fig. 8.** Structures L–Q in aqueous medium.

**Table 2**
Energies of structures E–Q by PM6.

| | Energy (a.u.) | | | | |
|---|---|---|---|---|---|
| Molecules | Vacuum | Molecules | Nitric acid medium | Molecules | Aqueous medium |
| E | −0.3613 | G | −0.3781 | L | −0.3722 |
| F | −0.3606 | H | −0.3724 | M | −0.3740 |
| | | I | −0.3756 | N | −0.3796 |
| | | J | −0.3749 | O | −0.3767 |
| | | K | −0.3776 | P | −0.3762 |
| | | | | Q | −0.3741 |

namely the HOMO–LUMO gap (highest occupied and the lowest unoccupied molecular orbital) and the charges attributed to atoms via a Mulliken analysis.

The HOMO–LUMO gap is, independently of the solvent, and for both molecules in their optimized structures, around 6.5 eV. We may note that when passing from the vacuum to aqueous medium, the gap evolves from 6.48 to 6.50 eV for the D-glucaro-1,4:6,3-dilactone, whereas for the D-glucaro-1,5:6,3-dilactone the range is larger: 6.45 to 6.59 eV. (see Table 4)

Concerning Mulliken charges, the interesting atoms are the bridging oxygens and the carbons joining the two rings. We see from Table 5 that generally the charges are more affected by the solvent for the D-glucaro-1,4:6,3-dilactone than for the other isomer. This is coherent with the previous findings of the

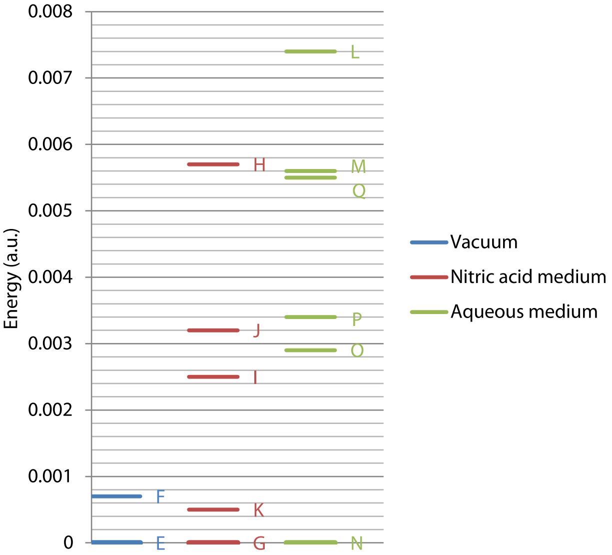


**Fig. 9.** Relative energies of the structures E–Q in the three media.

HOMO–LUMO gap, and may point toward a stronger sensibility of the D-glucaro-1,4:6,3-dilactone to its environment.

We may note that the charge difference between the two carbon atoms of the lactone groups are much closer for the D-glucaro-1,4:6,3-dilactone than for the other one, making the latter more exposed to reactivity than the former.

A look at maps of the electrostatic potential may confirm this charge analysis, see Fig. 11.

The electrostatic potential is evaluated at a constant density of 0.004 e/bohr$^3$ and represented as a coloring of the isodensity surface.

**Table 4**
The HOMO energies ($E_{HOMO}$), LUMO energies ($E_{LUMO}$), HOMO–LUMO energy gap ($E_{gap}$) in eV for the studied molecules by DFT.

| Molecules | $E_{HOMO}$ | $E_{LUMO}$ | $E_{gap}$ |
|---|---|---|---|
| *In vacuum* | | | |
| I | −8.03 | −1.55 | 6.48 |
| IV | −8.00 | −1.55 | 6.45 |
| *In nitric acid medium* | | | |
| II | −7.94 | −1.44 | 6.50 |
| V | −8.00 | −1.41 | 6.59 |
| *In aqueous medium* | | | |
| III | −7.94 | −1.44 | 6.50 |
| VI | −8.00 | −1.41 | 6.59 |

We may recognize that the variation of the potential is indeed slightly different for the two molecules, leaving the carbon atom C4 of the D-glucaro-1,5:6,3-dilactone more exposed to a nucleophilic attack than for the D-glucaro-1,4:6,3-dilactone where the regions of positive potential values are less pronounced.

### 3.4. Vibrational frequencies and thermochemistry

For verifying that indeed minima had been found, all molecular frequencies are calculated. From these we construct the vibrational spectrum, and, assuming a temperature, calculate the contribution to thermochemical data, i.e. ΔG values. The calculated spectra for the two D-glucaro-dilactones in vacuum are given in Fig. 12.

The features in these spectra are not significantly different, C = O, C–H, and OH bands are present in about the same positions.

The values of the calculated frequencies of the two molecules in vacuum and when including the solvents are collected in Table 6.

For the D-glucaro-1,4:6,3-dilactone, the two lactone groups are in a relatively close environment, which explains quite well the

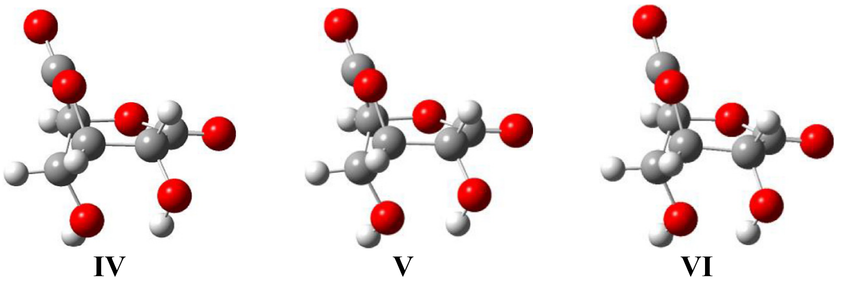


**Fig. 10.** B3LYP-optimized structures for the D-glucaro-1,5:6,3-dilactone in vacuum (IV), nitric acid (V) and aqueous (VI) media.

**Table 3**
Percentage of simultaneous existence of D-glucaro-dilactones according to Boltzmann's statistics by DFT method.

| Molecules | Energy (a.u.) | ΔE (a.u.) | Boltzmann's factor | % |
|---|---|---|---|---|
| *In vacuum* | | | | |
| I | −683.6203 | | 1 | 99.99994 |
| IV | −683.6067 | 0.0136 | 6.14E−07 | 0.00006 |
| *In nitric acid medium* | | | | |
| II | −683.6378 | | 1 | 99.99139 |
| V | −683.6289 | 0.0089 | 8.61E−05 | 0.00861 |
| *In aqueous medium* | | | | |
| III | −683.6398 | | 1 | 99.99372 |
| VI | −683.6306 | 0.0092 | 6.28E−05 | 0.00628 |

ΔE: Energy gap.

**Table 5**
Mulliken charges of the optimum structures for different media by DFT.

| Atoms | Molecules | | | | | |
|---|---|---|---|---|---|---|
| | I | II | III | IV | V | VI |
| *Bridging oxygens* | | | | | | |
| O9 | −0.30 | −0.31 | −0.31 | −0.28 | −0.29 | −0.30 |
| O10 | −0.37 | −0.36 | −0.36 | – | – | – |
| O11 | – | – | – | −0.27 | −0.29 | −0.30 |
| *Link carbons* | | | | | | |
| C3 | −0.13 | −0.09 | −0.09 | −0.16 | −0.15 | −0.15 |
| C4 | 0.05 | 0.07 | 0.07 | – | – | – |
| C5 | – | – | – | −0.05 | 0.00 | 0.00 |
| *Oxygen in —OH* | | | | | | |
| O8 | −0.51 | −0.50 | −0.50 | −0.46 | −0.50 | −0.51 |
| O10 | – | – | – | −0.59 | −0.64 | −0.64 |
| O11 | −0.45 | −0.50 | −0.50 | – | – | – |
| *Oxygen in C=O* | | | | | | |
| O7 | −0.45 | −0.50 | −0.50 | −0.40 | −0.48 | −0.49 |
| O12 | −0.43 | −0.51 | −0.52 | −0.45 | −0.52 | −0.52 |
| *Carbon between two oxygens* | | | | | | |
| C1 | 0.42 | 0.47 | 0.48 | 0.39 | 0.42 | 0.42 |
| C6 | 0.37 | 0.43 | 0.44 | 0.51 | 0.54 | 0.54 |

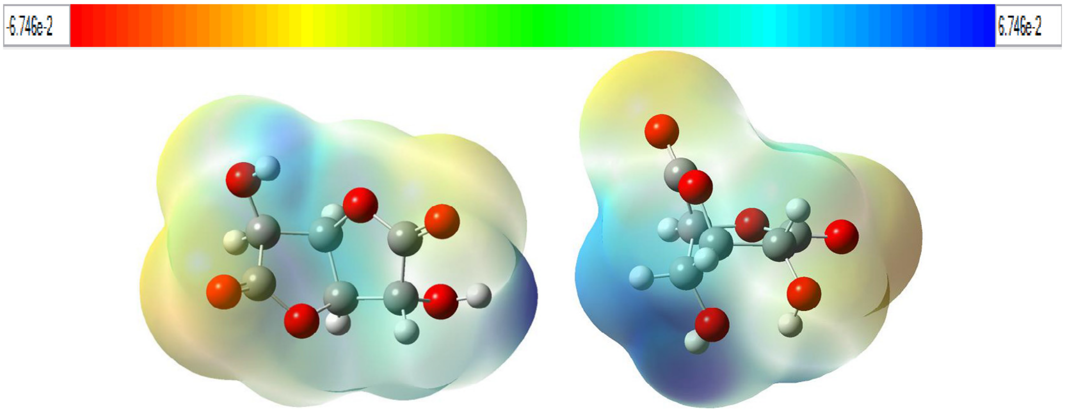


**Fig. 11.** Molecular electrostatic potential maps of (I) and (IV) in vacuum.

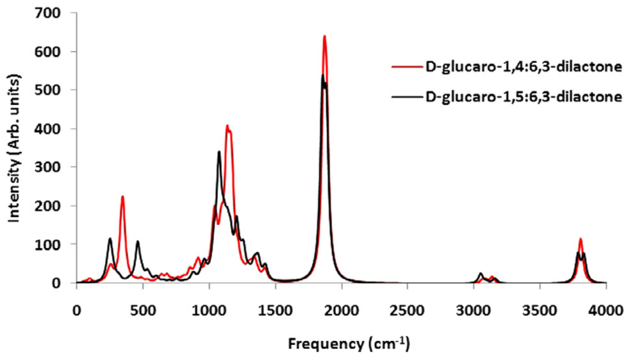


**Fig. 12.** Vibrational spectrum in cm$^{-1}$ in vacuum for the two D-glucaro-dilactones.

fact that the difference of the wave number values is about 21 cm$^{-1}$ in the vacuum and 11 cm$^{-1}$ in the solvents. However, for the D-glucaro-1,5:6,3-dilactone, the presence of a delta-lactone makes the difference more significant with values of 30 cm$^{-1}$ in vacuum, 40 cm$^{-1}$ in nitric acid medium and 42 cm$^{-1}$ in aqueous medium.

In chemical equilibrium, the corresponding constant is determined from $\Delta G$ values, adding to the already cited total energies the impact of entropy terms. We find for the vacuum situation entries for specific heat and entropy of S = 98.915 and 96.507 cal/mol K, and Cv = 37.664 and 37.468 cal/mol K, respectively for D-glucaro-1,4:6,3-dilactone and D-glucaro-1,5:6,3-dilactone. These are, as expected from the spectra already, quite similar and do not allow to modify the conclusions with respect to the previously calculated Boltzmann weights in an equilibrium situation.

**Table 6**
Selected calculated B3LYP/6-31+G(d,p) harmonic frequencies in (cm$^{-1}$) of the compounds I–VI.

| Assignments | In vacuum | | In nitric acid medium | | In aqueous medium | |
|---|---|---|---|---|---|---|
| | I | IV | II | V | III | VI |
| C1=O7 | 1866 | 1855 | 1830 | 1805 | 1825 | 1800 |
| C6=O12 | 1887 | 1885 | 1841 | 1845 | 1836 | 1842 |
| O8—H13 | 3804 | 3782 | 3802 | 3744 | 3796 | 3740 |
| O11—H17 | 3798 | – | 3783 | – | 3783 | – |
| O10—H16 | – | 3862 | – | 3822 | – | 3822 |

## 4. Conclusion

Although the D-glucaro-dilactones derive from D-glucaric acid, each of them is obtained under conditions that are different of its isomer. Well-known works in the chemistry have demonstrated that the formation of a five- or six-membered ring remains closely linked to the reaction conditions. In this study, the conformations of the D-glucaro-dilactones have been modeled and optimized. The structure, electronic and spectral properties have been calculated in vacuum, acidic and aqueous media using the polarizable continuum model (PCM). The analysis of the computational results indicates a pronounced stability for the D-glucaro-1,4: 6,3-dilactone in case of concurrent training between the two molecules.

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