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Change of the tautomeric preference for radical cation of pyruvic acid. DFT studies in the gas phase

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Abstract

Keto-enol tautomerism was investigated for ionized pyruvic acid using the DFT(B3LYP) method and the larger basis sets [6-31++G(d,p), 6-311++G(3df, 3pd) and aug-cc-pVDZ]. Change of the tautomeric preference was observed when going from the neutral to ionized tautomeric mixture. Ionization favors the enolization process (keto→enol) of pyruvic acid, whereas the ketonization (keto←enol) is preferred for the neutral system. Ionization influences also π-electron delocalization, which increases exceptionally in the enol form, and slightly decreases in the keto form.

Keywords: Pyruvic acid, Keto-enol tautomerism, Ionization effect, DFT

1. Introduction

Among various intramolecular proton-transfers possible for organic and bioorganic molecules, keto-enol interconversion {>HC–C(=O)– ⇌ >C=C(OH)–} is one of the most commonly studied forms of prototropy [1-3]. It takes place for compounds containing at least one C=O group linked to sp^3 carbon(s) bearing one or more H atoms. Generally, the keto form is favored in the gas phase as well as in solution and solid state. Some exceptions are the enol forms stabilized by an intramolecular H-bonding (*e.g.*, enol forms of malondialdehyde and acetylacetone) or by a complete π-electron delocalization (*e.g.*, phenols).

Pyruvic acids (1) - the main natural product of glycolysis, belongs to the family of α-keto acids. Being a C-carbonyl derivative of acetaldehyde (2) containing the electron accepting COOH group, it displays keto-enol tautomerism [1a]. Two tautomeric forms (keto and enol) are possible, for which an intramolecular transfer of the proton accompanied by an intramolecular migration of the π electrons takes place. The structure of neutral pyruvic acid has been extensively studied during the last decade [4, 5]. Its enol form has been signalled in 1981 by Ray et al. as documented for an IR spectrum of the pure liquid phase of pyruvic acid [6] and well proved by IR, NMR and X-ray experiments for solid βC-aryl and βC-heteroaryl derivatives of pyruvic acid [7]. Enolpyruvate has been also found to be a substrate in biosynthesis of aromatic compounds [8]. Computational [HF, MP2 and DFT(B3LYP)] and spectroscopic (FT-IR) investigations performed recently have shown that both tautomers may coexist in the tautomeric mixture with high predominance of the keto form in the gas phase and apolar solvents [5].

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$H_3C–C(=O)–COOH$ (keto) $\rightleftharpoons$ $H_2C=C(OH)–COOH$ (enol) (1)

$H_3C–C(=O)H$ (keto) $\rightleftharpoons$ $H_2C=C(OH)–H$ (enol) (2)

The aim of this paper is to study the keto-enol interconversion for ionized pyruvic acid. Since ionization influences the tautomeric preference for carbonyl compounds [9], one may expect an interesting effect for pyruvic acid. For our investigations, we chose the DFT method [10] and the B3LYP hybrid functional [11], because the DFT(B3LYP) level of theory was successfully applied to study the ketonization and enolization processes for the parent system (acetaldehyde/vinyl alcohol) [12]. To test the effect of enlarging the basis set, calculations were performed using the 6-31++G(d,p), 6-311++G(3df,3pd) and aug-cc-pVDZ basis [13].

2. Computational details

To select all stable tautomers-rotamers of ionized pyruvic acid, geometries of ten starting structures (Fig. 1) were fully optimized without any symmetry constraints at the UHF/6-31++G** level [13a] and harmonic vibrational frequencies calculated.

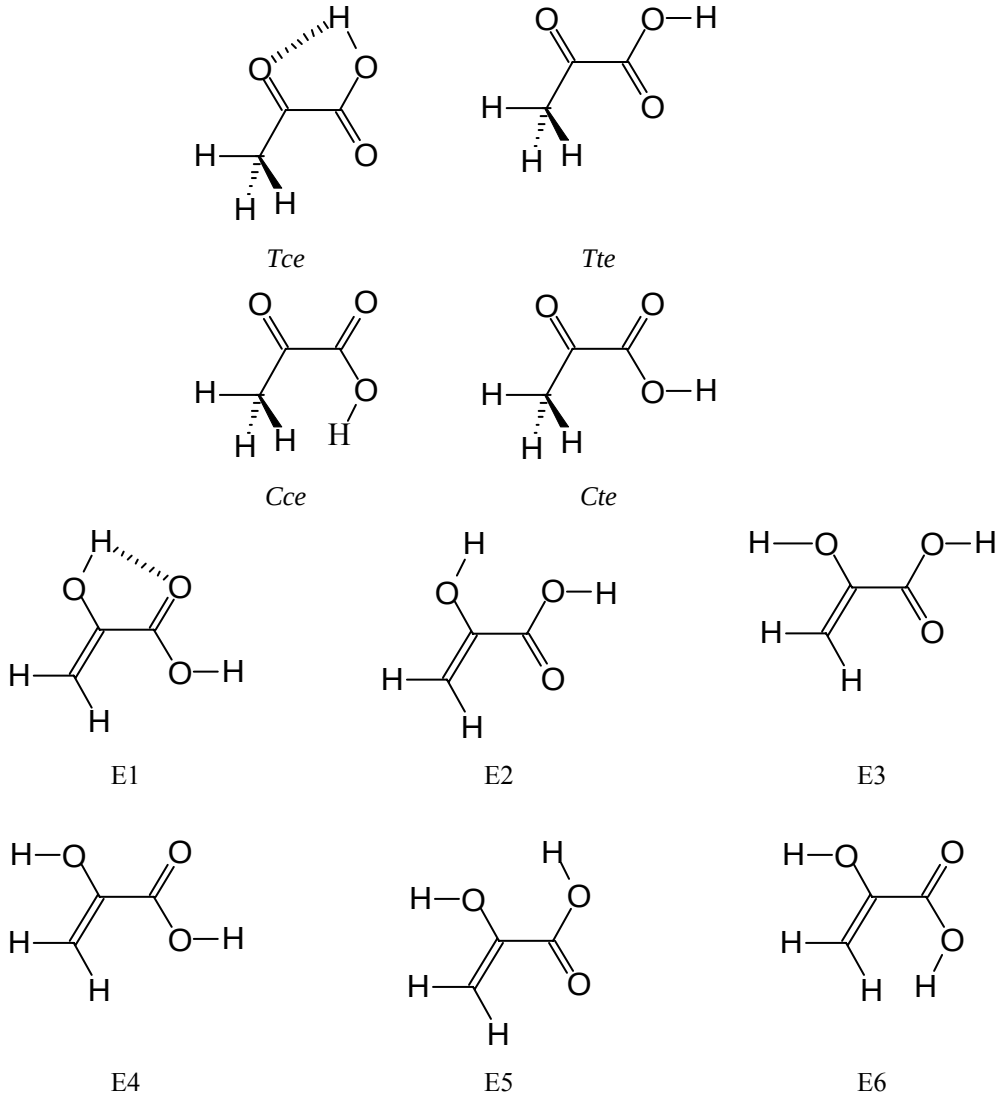


Fig. 1 Possible structures for the keto and enol forms of pyruvic acid

Next, geometries of two selected radical cations (*Tte* and E1) were reoptimized and the Gibbs free energies calculated using the DFT(UB3LYP) method [10, 11] and the 6-31++G**, 6-

311++G (3df, 3pd) and aug-cc-pVDZ basis sets [13]. For all calculations, the GAUSSIAN 98 program [14] runs on Cray super computer at the Interdisciplinary Centre for Mathematical and Computer Modeling (ICM, Warsaw) was applied.

3. Results and discussion

3.1. Thermodynamically stable tautomers

For neutral pyruvic acid (Fig. 1), three keto (*Tce*, *Tte* and *Cte*) and six enol structures (E1-E6) were found to be thermodynamically stable (with real frequencies) in the gas phase [5]. Their stabilities follow the order: *Tce* > *Tte* > *Cte* > E1 > E2 > E3, E4, E5 > E6. The Gibbs free energies relative to that of the most stable *Tce* isomer (ΔG) are equal to 0.0, 1.6, 2.8, 7.4, 9.5, 12.2, 12.5, 12.4, 18.8 kcal mol^{-1}, respectively, at the DFT(B3LYP)/6-31++G(d,p) level [5a].

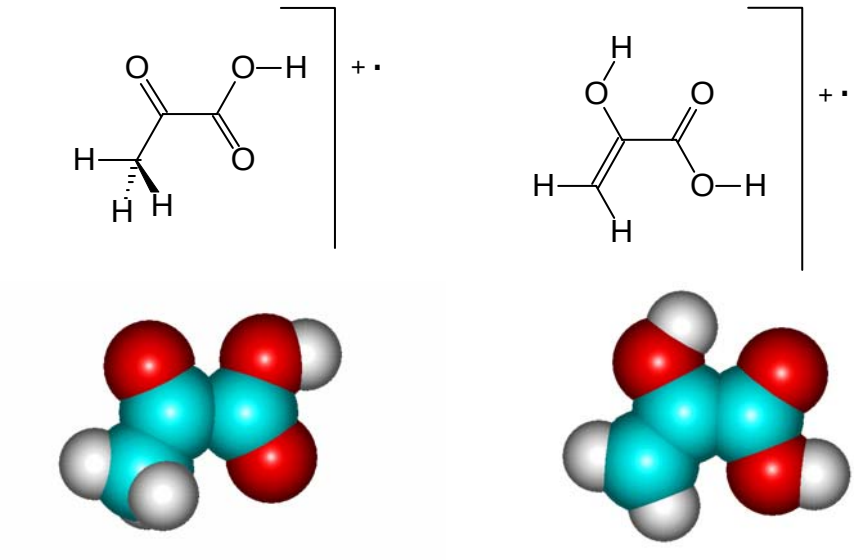
In should be mentioned here that the Gibbs free energy of the most stable enol structure E1 is larger than that of the most stable keto structure *Tce* by *ca.* 7 kcal mol^{-1} [ΔG 6.6 kcal mol^{-1} at the DFT(B3LYP)/aug-cc-pVDZ level]. Due to electron accepting effect of the COOH group, this relative energy is smaller than that calculated by Bertran and co-workers [12] between the neutral enol and keto tautomers of the parent system [ΔE for acetaldehyde 9.4 kcal mol^{-1} at the DFT(B3LYP)/aug-cc-pVDZ level]. Smaller relative energies (by 1-4 kcal mol^{-1} at the same level of theory) than that found for acetaldehyde were also observed for its derivatives containing electron accepting groups (*e.g.*, CN and BH_2) linked directly to the C-carbonyl atom [15].

Higher stability of the *Tce* and E1 structures than the other keto (*Tte* and *Cte*) and enol (E2-E6) structures of neutral pyruvic acid (Fig. 1) has been explained by intramolecular H-bond formations between the αC=O and carboxylic OH groups in *Tce*, and between the enolic OH and carboxylic C=O groups in E1 [4, 5]. These intramolecular interactions possible in the most stable tautomeric forms (*Tce* and E1) increase their Gibbs free energies in comparison to the corresponding non H-bonded forms (*Tte* and E4) by *ca.* 2 and 5 kcal mol^{-1}, respectively at the DFT(B3LYP)/6-31++G(d,p) level. A similar extra stabilization of tautomeric forms was previously observed for other gaseous tautomeric systems, *e.g.*, 4(5)-substituted imidazoles, 4(7)-substituted benzimidazoles, substituted 2-hydroxypyridines, histamine, o-nitrosophenol [16]. Depending on electronic and acid-base properties of the interacting groups and their distances in tautomeric molecules, the stabilizing energetic effects were found to be even higher than 10 kcal mol^{-1}, particularly for the systems where intramolecular H-bond closes six-membered rings.

The keto and enol radical cations of pyruvic acid were obtained by a removal of one electron from the corresponding *ab initio* optimised neutral forms, *i.e.*, by a removal of one electron from the n orbital of the O-carbonyl in the keto tautomer, and by a removal of one electron from the π orbital in the enol tautomer. For calculations, the same starting conformations of the keto (*Tce*, *Tte*, and *Cte*) and enol isomers (E1-E6) were considered for the radical cations as those found for the neutral forms (Fig. 1). The UHF method and the larger 6-31++G(d,p) basis sets were used to select the most stable radical cations. In this way, two stable tautomers-rotamers were found for ionized pyruvic acid: one keto radical cation corresponding to the *Tte* conformation and one enol radical cation corresponding to the E1 conformation (Fig. 2). Other tautomers-rotamers have at least one imaginary vibrational frequency and thus they were neglected in our DFT(UB3LYP) calculations using the larger basis sets: 6-31++G(d,p), 6-311++G(3df, 3pd) and aug-cc-pVDZ.

Generally, effects of enlarging the basis set on selected geometrical parameters are small for the radical cations of pyruvic acid (Table 1 and 2). The E1 radical cation is planar at each level of theory with the dihedral C=αC–C=O angle equal to 0°. This planarity of E1 is a consequence of an intramolecular interaction between the enolic OH and the carboxylic C=O groups. For the

keto *Tte* radical cation, depending on the level of theory, its structure is planar [UB3LYP/aug-cc-pVDZ] or twisted with the dihedral O=$^{\alpha}$C–C=O angle not larger than 25° [15.6° at the UB3LYP/6-31++G(d,p) level, 21.5° at the UHF/6-31++G(d,p) level, and 24.2° at the UB3LYP/6-311++G(3df,3pd) level]. This variation of the dihedral O=$^{\alpha}$C–C=O angle, however, only slightly influences other geometrical parameters (bond lengths and angles). Some differences in geometrical parameters are observed between the UHF and UB3LYP results similarly as it has been found for acetaldehyde/vinyl alcohol system [12, 17].



Tte E1

Fig. 2 Thermodynamically stable keto and enol radical cations of pyruvic acid

Table 1
Selected bond lengths (in Å) for thermodynamically stable keto (*Tte*) and enol (E1) radical cations of pyruvic acid calculated at various levels

Method	*Tte*				
	$^{\alpha}$C–C(H_3)	$^{\alpha}$C=O	$^{\alpha}$C–C(OOH)	C–O(H)	C=O
UB3LYP/6-31++G(d,p)	1.494	1.182	1.715	1.297	1.191
UB3LYP/6-311++G(3df,3pd)	1.487	1.166	1.761	1.288	1.177
UB3LYP/aug-cc-pVDZ	1.486	1.167	1.774	1.289	1.178
	E1				
	$^{\alpha}$C=C(H_2)	$^{\alpha}$C–O(H)	$^{\alpha}$C–C(OOH)	C–O(H)	C=O
UB3LYP/6-31++G(d,p)	1.409	1.288	1.529	1.318	1.208
UB3LYP/6-311++G(3df,3pd)	1.403	1.280	1.528	1.313	1.198
UB3LYP/aug-cc-pVDZ	1.403	1.282	1.528	1.314	1.194

3.2. Comparison of geometrical parameters for neutral and ionized tautomers

The selected DFT geometrical parameters calculated for the thermodynamically stable keto and enol radical cations of pyruvic acid were compared with those previously found at the same level of theory for the corresponding neutral forms (Table 3 and 4). This comparison provides the following informations. Ionization of the *Tte* isomer lengthens only the $^{\alpha}$C–C(OOH) bond. Other bonds [C–O, C=O, $^{\alpha}$C=O and $^{\alpha}$C–C(H_3)] are shortened. It also enlarges the C(H_3)–$^{\alpha}$C=O and O–C=O angles and reduces other angles at the $^{\alpha}$C and C-carboxyl atoms.

Table 2
Selected angles (in degree) for thermodynamically stable keto (*Tte*) and enol (E1) radical cations of pyruvic acid calculated at various levels

Method	*Tte*				
	O=$^{\alpha}$C–C(H_3)	O=$^{\alpha}$C–C(OOH)	O–C–$^{\alpha}$C	O–C=O	Φ[a]
UB3LYP/6-31++G(d,p)	132.4	112.6	108.8	134.7	15.6
UB3LYP/6-311++G(3df,3pd)	134.5	112.0	108.0	136.3	-24.2
UB3LYP/aug-cc-pVDZ	134.6	112.0	107.9	136.3	0.1
	E1				
	O–$^{\alpha}$C=C(H_2)	O–$^{\alpha}$C–C(OOH)	O=C–$^{\alpha}$C	O=C–O	Φ[b]
UB3LYP/6-31++G(d,p)	119.4	114.0	117.3	130.0	0.0
UB3LYP/6-311++G(3df,3pd)	119.7	113.7	117.2	129.9	0.0
UB3LYP/aug-cc-pVDZ	119.7	113.6	117.2	130.0	0.0

[a] Dihedral O=$^{\alpha}$C–C=O angle in the keto *Tte* radical cation of pyruvic acid (Fig. 2).
[b] Dihedral C=$^{\alpha}$C–C=O angle in the enol E1 radical cation of pyruvic acid (Fig. 2).

For the E1 tautomer, ionization lengthens the $^{\alpha}$C=C and $^{\alpha}$C–C(OOH) bonds, and shortens other bonds [C=O, C–O and $^{\alpha}$C–O(H)]. A similar effect, *i.e.*, a lengthening of the C=C bond and a shortening of the C–O(H) bond, has been observed for vinyl alcohol, the enol form of acetaldehyde [12]. Ionization reduces also the O–$^{\alpha}$C=C(H_2) angle, whereas the other angles at the $^{\alpha}$C atom augment. The angles at the C-carboxyl atom vary in a similar way as those for the keto form. The O–C=O angle increases, and the other angles diminish. All these observations indicate that the strongest ionization effects occur for the bond lengths at the $^{\alpha}$C atom and for the O=C–O angle.

3.3. Keto-enol isomerization for ionized pyruvic acid

DFT calculations performed for thermodynamically stable keto (*Tte*) and enol (E1) radical cations clearly show that ionized pyruvic acid prefers the enol E1 structure in the gas phase. Its Gibbs free energy is lower than that of the *Tte* form by 3-5 kcal mol^{-1} at the DFT levels. A different situation has been observed previously for neutral pyruvic acid, which favors the keto form (*Tce*) [5a].

Comparison of the relative Gibbs free energies (ΔG) calculated between the most stable ionized (E1 and *Tte*) and the most stable neutral (E1 and *Tce*) tautomers of pyruvic acid shows evidently a change of the ΔG sign (Table 5). Since the calculated ΔG values are significant, there are no doubts that the tautomeric preference changes upon ionization. Similar behavior has been observed for acetaldehyde and acetone [9, 12] The keto form is favored for the neutral tautomeric mixture, and the enol radical cation becomes more stable for the ionized system.

3.4. π-Electron delocalization

Analysing the variation of π-electron distribution during the keto-enol interconversion in the most stable forms of neutral (*Tce* and E1) and ionized pyruvic acid (*Tte* and E1), the HOMED (Harmonic Oscillator Model of Electron Delocalization) index [18] was applied to the tautomeric moiety (C$^{\alpha}$CO fragment) and geometries optimized at the DFT(B3LYP)/aug-cc-pVDZ level.

Table 3
Comparison of the selected geometrical parameters (bond lengths in Å, and angles in degree) for the neutral and ionized keto (*Tte*) form of pyruvic acid calculated at the B3LYP/6-31++G(d,p) level

Bond length	Neutral form	Radical cation	Δ[a]
αC–C(H_3)	1.505	1.494	0.011
αC=O	1.211	1.182	0.029
αC–C(OOH)	1.551	1.715	-0.164
C–O(H)	1.340	1.297	0.043
C=O	1.213	1.191	0.022
Angle			
O=αC–C(H_3)	124.7	132.4	-7.7
O=αC–C(OOH)	120.2	112.6	7.6
C(H_3)–αC–C(OOH)	115.0	115.0	0.0
O–C–αC	112.7	108.8	3.9
O–C=O	124.5	134.7	-10.2
O=C–αC	122.8	116.5	6.3
O–C–αC=O	0.0	15.6	-15.6

[a] Difference between geometrical parameters of the neutral and ionized forms

Table 4
Comparison of the selected geometrical parameters (bond lengths in Å, and angles in degree) for the neutral and ionized enol (E1) form of pyruvic acid calculated at the B3LYP/6-31++G(d,p) level

Bond length	Neutral form	Radical cation	Δ[a]
αC=C	1.340	1.409	-0.069
αC–O(H)	1.359	1.288	0.071
αC–C(OOH)	1.490	1.529	-0.039
C–O	1.345	1.318	0.027
C=O	1.221	1.208	0.013
Angle			
O–αC=C(H_2)	122.9	119.4	3.5
O–αC–C(OOH)	113.0	114.0	-1.0
C(H_2)=αC–C(OOH)	124.1	126.6	-2.5
O=C–αC	121.5	117.3	4.2
O=C–O	123.2	129.9	-6.7
O–C–αC	115.3	112.7	2.6
O=C–αC–O	0.0	0.0	0.0

[a] Difference between geometrical parameters of the neutral and ionized forms

For the HOMED estimations, we used the equation proposed for the reformulated HOMA (Harmonic Oscillator Model of Aromaticity) index [19]: HOMED=1−[$\alpha_{CX}\cdot\Sigma\{R_{opt}(CX)-$

$R_i(CX)\}^2]/n$, where n is the number of bonds taken into account, α_{CX} is a normalization constant: $\alpha_{CX} = 2\{[R_s(CX) - R_{opt}(CX)]^2 + [R_d(CX) - R_{opt}(CX)]^2\}^{-1}$, $R_s(CX)$ and $R_d(CX)$ are the reference CX (X = C, O) single and double bonds, $R_{opt}(CX)$ is the optimum CX bond length (assumed to be realised when full delocalization of π electrons takes place), and $R_i(CX)$ are the running bond lengths in the system.

The HOMED index is based on the original HOMA idea [20], according to which similar measures of π-electron delocalization were used for different CX bonds, *i.e.*, the simplest molecules of general formulae $H_3C–XH_i$ and $H_2C=XH_{i-1}$ (X = C, O) for the reference single and double CX bonds, respectively. The optimum CX bond lengths and the normalization constants were calculated according to the procedures proposed for the reformulated HOMA index. The following $R_{opt}(CX)$ and α_{CX} values were taken here: 1.397 and 98.89 for CC bond, and 1.273 and 70.80 for CO bond. The HOMED values estimated for the most stable tautomers of pyruvic acid are listed in Table 6. For comparison, the HOMED values estimated for the DFT(B3LYP)/aug-cc-pVDZ structures of acetaldehyde and vinyl alcohol are also given in this Table.

Table 5

Comparison of the relative Gibbs (free) energies (ΔG in kcal mol^{-1}, 1 cal = 4.184 J) between the most stable tautomers of the neutral and ionized pyruvic acid

Method	ΔG	
	Neutral [a]	Ionized [b]
B3LYP/6-31++G**	7.4	-4.7
B3LYP/6-311++G(3df,3pd)	6.7	-3.1
B3LYP/aug-cc-pVDZ	6.6	-2.8

[a] $\Delta G = G(E1) - G(Tce)$; data taken from ref. 5a

[b] $\Delta G = G(E1) - G(Tte)$; this work

Table 6

Comparison of HOMED indices[a] for neutral and ionized tautomers of pyruvic acid and acetaldehyde

Pyruvic acid (1)			Acetaldehyde (2)		
Form	Tautomer	HOMED	Form	Tautomer	HOMED
Neutral [b]	keto (*Tce*)	0.418	Neutral [c]	keto	0.298
	enol (E1)	0.559		enol	0.612
Ionized [d]	keto (*Tte*)	0.211	Ionized [c]	keto	0.178
	enol (E1)	0.995		enol	0.977

[a] DFT(B3LYP)/aug-cc-pVDZ bond lengths

[b] Bond lengths taken from ref. 5a

[c] Bond lengths taken from ref. 12

[d] Bond lengths taken from Table 1

The HOMED index for the neutral keto form of pyruvic acid is slightly smaller than that for the neutral enol form. Both forms are moderately delocalized. However, ionization changes this difference. For the ionized system, the HOMED index decreases for the keto form from 0.418 to 0.211, and it increases for the enol form from 0.559 to 0.995. The π-electrons in the enol radical cation are strongly delocalized (HOMED close to 1). This is consistent with HOMED estimations for the Bertran and co-workers structures of neutral acetaldehyde and vinyl alcohol

and for their radical cations [12]. The ionization process changes the HOMED indices estimated for the DFT(B3LYP)/aug-cc-pVDZ geometries of the two tautomeric forms in the following way: from 0.298 to 0.178 for acetaldehyde (keto form), and from 0.612 to 0.977 for vinyl alcohol (enol form). Removing an electron from the n orbital of the O-carbonyl in the keto tautomer has slight influence on weak delocalization of π-electrons, whereas removing an electron from the π orbital of the enol tautomer causes strong electron delocalization.

4. Conclusion

DFT calculations performed for ionized pyruvic acid show evidently that the keto→enol isomerization in the gas phase is exothermic [by 2.8 kcal mol^{-1} at the DFT(B3LYP)/aug-cc-pVDZ level]. Taking the calculated Δ*G* value for the keto and enol radical cations and the relation between Δ*G* and tautomeric equilibrium constant [$K_T = \exp(-\Delta G/RT)$] into account, the percentage contents of thermodynamically stable tautomers-rotamers E1 and *Tte* are predicted to be 99.1 and 0.9 %, respectively This estimation indicates that modern MS techniques applied to the gas phase may help to investigate experimentally the enolization process for ionized pyruvic acid. The variations of π-electron delocalization during ionization are well described by the HOMED index. This index measures the resonance conjugation in each form, *i.e.*, the σ-π hyperconjugation for the keto form and the n-π conjugation for the enol form.

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