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Determination of the most stable structures of selected hydroxypyrones and their cations and anions

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Abstract

Equilibrium geometries of selected hydroxypyrones were determined using quantum-mechanical calculations. Computations were performed for all possible structures of pyromeconic acid, maltol, ethylmaltol and kojic acid. Tautomerism of protonated and deprotonated (kojic acid) forms of the studied compounds were also taken into account. For all neutral tautomers of investigated compounds it was shown that the most stable was enolic form. Cationic species were created by protonation of the keto oxygen atom. In order to form stable kojic acid anion deprotonation of hydroxyl group on the pyran ring is preferred. Obtained results confirm that tautomeric equilibria in a gas phase were only slightly influenced by entropy.
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Keywords: Hydroxypyrones; Ketoenol tautomerism; Equilibrium constants; Quantum chemical calculations

1. Introduction

Compounds studied in this work are commonly used in chemical, pharmaceutical, cosmetic and food industries. Kojic acid (5-hydroxy-2-hydroxymethyl-4H-pyran-4-one, H_2ka) is a fungal metabolite produced by many species of *Aspergillus*, *Acetobacter* and *Penicillium*. It was discovered during investigation of the fermentation of steamed rice ('koji'). It was also found in such food products as *sake*, *miso* (soybean paste), *shoyu* (soy sauce) and many others. Kojic acid is produced on industrial scale and added to food for its antibacterial and fungicidal properties [1]. Additionally, kojic acid is commonly used in cosmetic industry due to its free radicals absorbing properties and inhibition of melatonin production (that effects in skin whitening) [2]. Maltol (3-hydroxy-2-methyl-4H-pyran-4-one, Hma) was for the first time extracted from the larch's bark and later obtained from other plants [3,4]. Similarly to kojic acid, maltol and ethylmalthol (3-hydroxy-2-ethyl-4H-pyran-4-one, Hema) are used as food additives (E363 and E637) and in perfumes production due to their flavour properties. The fourth studied molecule, the pyromeconic acid (3-hydroxy-4H-pyran-4-one, Hpa) has had no commercial application so far but it's the parent molecule of

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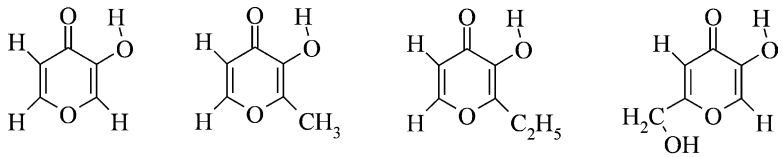

Fig. 1. Structures of investigated compounds.

studied compounds. The structures of all studied compounds are presented in Fig. 1.

The mentioned hydroxypyrones are extensively studied because they form complexes with various metal ions that are potentially useful in medical therapy. So far the most famous are antidiabetic complexes obtained from discussed ligands with vanadium. The oxovanadium(IV) complex with maltol (bis(maltolato)oxovanadium(IV)) is the leading insulin-mimetic agent [5,6]. Bis(kojato)oxovanadium(IV), a close chemical analogue of the maltol complex, was also studied but its therapeutic effect has been shown to be lower then the maltol complex [7]. The ability of the vanadium(III) complexes with kojic acid, maltol and ethylmaltol to normalize glucose level was also recognized [8]. Among others hydroxypyrones complexes, tris(maltolato)iron(III) is a potent drug to be used for the treatment of iron-deficiency anaemia [9]. Aluminium(III) complexes with pyromeconic acid, kojic acid and maltol are investigated because of their neurological properties [10]. Biological activity is also observed in complexes of above mentioned ligands with gallium, zinc, indium, or molybdenum.

Depending on pH discussed ligands form cations and anions in solutions [11]. Their deprotonated molecules exist also in all metal complexes mentioned above. Cations as well as neutral species of interest possess labile hydrogen atom(s) thus they potentially can exist in several tautomeric forms which will be discussed later in this work.

Quantum mechanical calculations are very well establish as tools in determination of physicochemical properties of compounds. Thus far, presented in this work hydroxypyrones have not been objects of systematic theoretical studies. To our best knowledge there is only one work dealing with theoretical study of the O–H stretching vibration in maltol molecule [12]. As it has been discussed above, hydroxypyrones are biologically active compounds, potentially important for pharmaceutical and food industry. Thus, we undertook this study to try to understand structure of these class of ligands that can be very useful in controlling their interaction with metal ions.

2. Computational details

Potential energy surfaces (PES) of investigated compounds, their anions, and cations were examined by relaxed reaction path calculations. The reaction paths involved rotation of hydroxyl, hydroxymethyl or ethyl group. Influence of the pyran ring deformation on energies of investigated compounds was also studied. In the reaction paths computations Hartree–Fock (HF) [13,14] and the density functional theory (DFT) methods with the 6-31G basis set were used. Analysis of the obtained energetic profiles permitted to determine the minima on the PES. For these minima complete geometry optimization calculations were done. Here the HF method and some DFT functionals with the 6-311++G(d,p) basis set were employed. Within DFT methods local (SVWN) [15] and two hybrid (B3LYP [16] and B1LYP [17]) functionals were used. Calculations of the vibrational frequencies were performed to confirm that obtained structures were minima, not saddle points. The zero point energy (ZPE) corrections were also taken into account. Additionally, for each tautomer's global minimum, Gaussian-2 (G2) [18] (pyromeconic acid and maltol) or G2MP2 [19] (kojic acid and ethylmaltol) computations were executed. All theoretical methods mentioned above are embedded in the quantum-mechanical GAUSSIAN 98 set of programs [20].

As it was mentioned, there are tautomeric equilibria among cationic and neutral species of studied hydroxypyrones (and also in kojic acid anion).

Composition of the tautomeric mixture for the one pair of the tautomers (where tautomer A (T_A) can transform in tautomer B (T_B) (Eq. (1))), is defined by the tautomeric equilibrium constant as shown by Eq. (2):

$$T_A \leftrightarrow T_B \tag{1}$$

$$K_T^{AB} = \frac{[T_B]}{[T_A]} \tag{2}$$

where $[T_A]$ and $[T_B]$ are concentrations of tautomers A and B, respectively. The tautomeric equilibrium constants can be estimated from calculated proton affinities and deprotonation enthalpies by general scheme of the acid–base equilibria [21]. The populations of various structures can be also extracted from microcanonical ensemble molecular dynamic simulations [22]. Finally (this approach is used in present work) they can be calculated from Eq. (3) [23]:

$$\Delta G_{AB} = -RT \ln K_T^{AB} \tag{3}$$

where R is the ideal gas constant and T, the absolute temperature. ΔG_{AB} is the free energy variation connected to the enthalpy (ΔH_{AB}) and entropy (ΔS_{AB}) variations by the standard thermodynamic Eq. (4):

$$\Delta G_{AB} = \Delta H_{AB} - T\Delta S_{AB} \tag{4}$$

Sometimes, for tautomeric equilibrium constants estimation, other approximation is used, where variation of the entropy between tautomers is neglected [21,24,25]. Then the Eq. (4) is replaced by Eq. (5):

$$\Delta H_{AB} = -RT \ln K_T^{AB} \tag{5}$$

Truthfulness of this approximation is also examined in this work.

The values of the thermodynamic functions H, S and G are calculated by standard GAUSSIAN 98 procedures [26] during frequency calculations. In all presented computations, pressure is set to 1 atm and temperature is equal 298.15 K.

If one chooses a set of tautomers, to describe the composition of these mixture he has to solve the set of following Eq. (6):

$$\begin{aligned} K_T^{AB} &= \frac{[T_B]}{[T_A]} \\ K_T^{BC} &= \frac{[T_C]}{[T_B]} \\ &\vdots \\ K_T^{YX} &= \frac{[T_X]}{[T_Y]} \\ \sum_{i=1}^{N} [T_i] &= 1 \end{aligned} \tag{6}$$

where $\sum_{i=1}^{N} [T_i] = 1$ is the sum of concentrations of all tautomers. There are few ways to construct the set of Eq. (6). In this work, these equations are set in such way that during transformation the proton covers the shortest distance on going from tautomer A to tautomer B. Additionally, in this work all calculations are performed for the vapour phase.

3. Results and discussion

3.1. Neutral molecules

The structures and abbreviations of possible neutral tautomers of pyromeconic acid, maltol, ethylmaltol and kojic acid are presented in Fig. 2. Performed calculations for all used theoretical methods showed that the Hpa1 tautomer of pyromeconic acid had the lowest energy when it took the strictly planar structure. In this structure the hydroxyl group forms intramolecular hydrogen bond with the oxygen from the keto group. We also showed that tautomer Hpa2 was also planar with the intramolecular hydrogen bond. However, it had slightly higher energy than Hpa1. Hpa1 and Hpa2 tautomers belong to the C_S symmetry point group. Different results were obtained for the SVWN method. When this method was used during geometry optimization the labile proton of Hpa2 tautomer was transferred between oxygen atoms, thus Hpa2 transformed to Hpa1. In other words, tautomer Hpa2 was not a minimum when this method was used. Such effects is always observed in studied compounds (also for cations) for the SVWN method if a proton is bounded to the keto oxygen atom

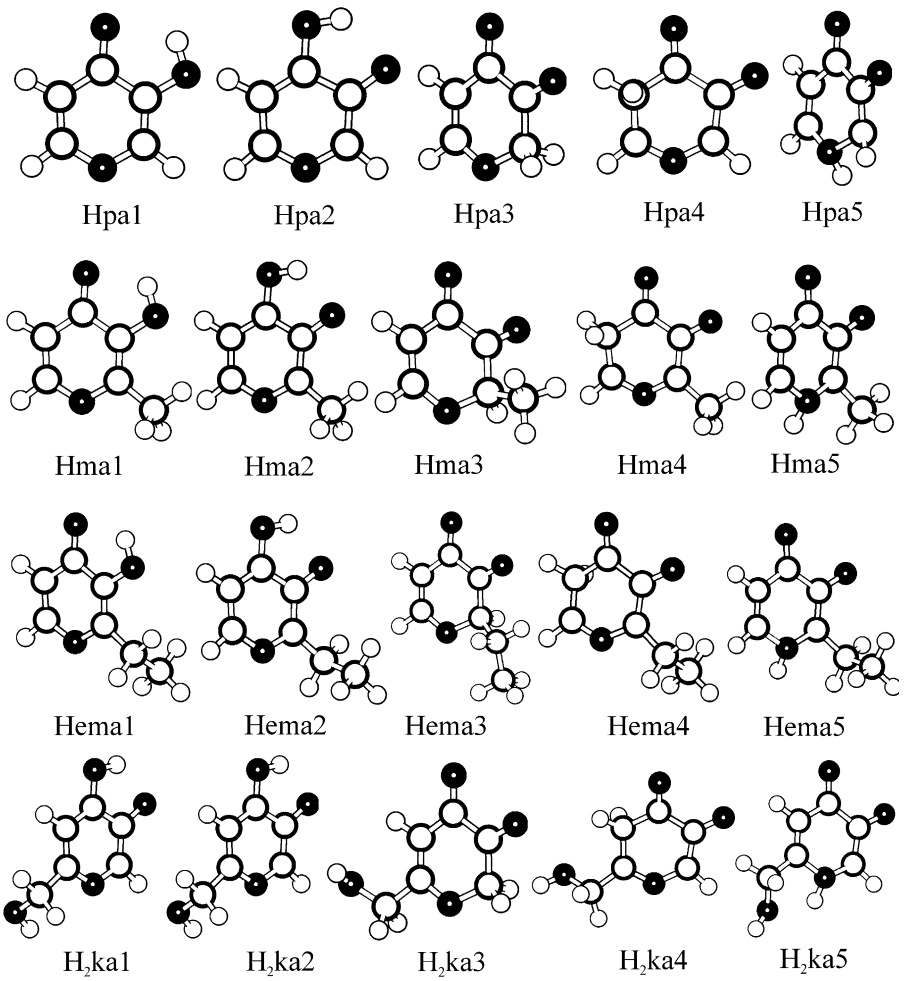

Fig. 2. Configurations of neutral species of studied compounds.

and in the same time oxygen atom from hydroxyl group is deprotonated.

Next tautomer, ketonic form Hpa3, is not a planar structure. Its lowest energy was obtained for a slightly distorted geometry. The torsion angle O=C–C=O between two keto groups varied from 0.9 (SVWN) to 9.9° (HF). Tautomer Hpa4 is also not planar and its pyran ring is much more distorted from planarity than in Hpa3. The lowest energy structure of Hpa5 does not have any plane of symmetry. The most characteristic feature of this structure is that the hydrogen atom connected with intraring oxygen is strongly shifted out of the mean pyran ring plane (see Fig. 2).

Our computations results for the maltol molecule are very similar to these reported above for pyromeconic acid. The equilibrium configurations of Hma1 and Hma2 tautomers has the plane of symmetry and belong to the C_S symmetry point group. The intramolecular hydrogen bonds are observed for these tautomers. Hma3 cannot have a symmetry plane because of the presence of the methyl group. The pyran ring in the Hma3 structure is a bit more distorted than in the Hpa3 structure. The O=C–C=O torsion angle varies between 6.6 and 12.5°, depending on the method used in calculations. Conformation of the heterocyclic ring in Hma4 is very similar to this observed in Hpa4. Also, the lowest energy of structure

Hma5 resembles that of Hpa5 (of course one has to remember that in Hma5 there is the methyl group) with the characteristic out of pyran ring plane location of the hydrogen from the hydroxyl group.

Presence of the ethyl group at the pyran ring causes that none of the ethylmaltol tautomers have symmetry plane. Hema1 and Hema2 are characterized by a planar pyran rings with the intramolecular hydrogen bond. The ethyl group is located nearly perpendicular to the mean plane of the ring. The torsion angle O(ring)–C–C(ethyl)–C(ethyl) depends on theoretical method used in calculations. It varies from 60.1 to 73.0 (Hema1) and from 76.4 to 82.2 (Hema2). In case of Hema3 tautomer, two conformations of the ethyl group with practically the same energy are observed. Fig. 2 shows conformation in which this group is parallel to the ring and has minimally lower energies. In the second conformation of Hema3 the ethyl group takes position similar to that observed for Hema1 and Hema2. The twisting between two keto groups in Hema3 is similar to these reported above for Hpa3 and Hma3. The values of the O=C–C=O torsion angle span the range from 4.1 to 14.3°. The values of the O(ring)–C–C(ethyl)–C(ethyl) angle for Hema4 and Hema5 are about 70°. In these structures the ethyl group is positioned perpendicular to the pyran ring. Other geometrical features for these tautomers are the same as for analogical tautomers of maltol and pyromeconic acid discussed earlier.

Kojic acid has the second hydroxyl moiety that is the part of the hydroxymethyl group. Thus, it can potentially create hydrogen bond with the intraring oxygen atom. However, according to our calculations, the influence of the hydroxymethyl group on the geometry of the rest of H_2ka1 molecule is not significant. As for the corresponding tautomers of the previously discussed compounds, the pyran ring is planar and hydrogen bond is located between keto and hydroxyl groups. The whole molecule has no symmetry plane due to the bulky hydroxymethyl group. The torsion angle between O(ring)–C–C(hydroxymethyl)–O(hydroxymethyl) atoms is about 50°. Thus, as is presented in Fig. 2, the second hydrogen bond that can be formed between hydroxymethyl moiety and intraring oxygen is, if at all, very weak. The H_2ka2 structure is quite similar to H_2ka1. Two conformations of the hydroxymethyl group are possible for H_2ka3. Energetically favourable conformation is presented in the Fig. 2. Here the value of the O(ring)–C–C(hydroxymethyl)–O(hydroxymethyl) angle is nearly 180° thus the intraring oxygen cannot create any hydrogen bond with the hydroxymethyl group. In the higher energy structure this parameter is about 60° and the possibility of creation of the mentioned intramolecular hydrogen bond is still small. The configuration around keto groups is similar to this observed for corresponding structures of other investigated compounds. Possible positions of the hydroxymethyl group in the H_2ka4 structure are analogical to those determined for H_2ka3. Again, the structure with the value of O(ring)–C–C(hydroxymethyl)–O(hydroxymethyl) angle close to 180° is energetically preferred. In H_2ka5 two hydroxyl groups are positioned in the manner that intramolecular hydrogen bond is created between hydroxyl from the ring and the oxygen from the hydroxymethyl group (see Fig. 2).

As mentioned earlier in the text, the obtained relative energies (influence of vibrations on energies is included) for neutral pyromeconic acid, maltol, ethylmaltol and kojic acid are collected in Table 1. It is clearly seen that the most stable are always enolic structures of tautomer 1. For all used theoretical methods ketonic tautomer Hpa3 is the next low energy structure in the case of pyromeconic acid. For this compound energetic gap between Hpa3 and Hpa2 is small (about 4 kJ/mol) when B3LYP or B1LYP functionals are used. But it increases strongly up to 67.1 kJ/mol if the HF method is employed. Calculated energies for Hpa4 are always more than 200 kJ/mol while Hpa5 are more than 300 kJ/mol above energies of the Hpa1 structures for all theoretical methods used. The order from the lowest to the highest energy tautomer (B1LYP, B3LYP, G2 and G2MP2 calculations) for pyromeconic acid is as follow: Hpa1 < Hpa3 < Hpa2 < Hpa4 < Hpa5. This order is modified slightly in the cases of ethylmaltol and maltol. For these ligands the Hma2 and Hema2 tautomers have the second place (except the HF method) in the stability order. The methyl or ethyl groups destabilize the keto structures.

Calculated equilibrium constants between neutral tautomers are given in Table 2. These values show that only enolic tautomers 1 are present in the gas phase of the studied compounds. The concentrations of other expected structures are very low, even for

Table 1
Computed relative energies (in kJ/mol, ZPE included) for the most stable geometries of neutral tautomers of studied compounds. Calculations performed (except G2 and G2MP2) in 6-311++G(d,p) basis set

Relative energy	HF	SVWN	B3LYP	B1LYP	G2	G2MP2
Pyromeconic acid						
Hpa1	0.00	0.00	0.00	0.00	0.00	0.00
Hpa2	95.36		51.17	49.51	55.27	54.33
Hpa3	28.26	86.09	47.63	47.99	49.05	50.52
Hpa4	265.33	206.82	208.01	203.71	212.59	238.75
Hpa5	351.35	365.61	350.01	349.19	376.75	378.72
Maltol						
Hma1	0.00	0.00	0.00	0.00	0.00	0.00
Hma2	95.64		46.22	49.53	54.48	53.58
Hma3	42.36	101.11	64.18	62.23	58.03	59.41
Hma4	280.30	208.58	209.68	214.65	212.34	211.56
Hma5	351.24	363.15	354.28	356.06	354.44	355.01
Ethylmaltol						
Hema1	0.00	0.00	0.00	0.00	0.00	0.00
Hema2	92.25		46.10	49.41	50.01	50.99
Hema3	38.95	96.90	61.67	59.58	60.73	60.02
Hema4	278.52	208.44	208.61	213.51	215.56	214.86
Hema5	350.67	360.26	351.64	353.41	353.63	353.02
Kojic acid						
Hka1	0.00	0.00	0.00	0.00	0.00	0.00
Hka2	96.27		49.02	52.35	52.40	51.45
Hka3	23.61	80.27	46.31	44.35	47.02	45.87
Hka4	252.84	200.78	198.65	202.97	200.01	201.54
Hka5	338.89	332.88	326.58	355.37	357.84	356.78

the second tautomer in the stability order. The obtained results are opposite to these presented for 2-hydroxy-6-methyl-4H-pyran-4-one [24], where the diketo form was the most stable. Data collected in Table 2 confirm that influence of entropy variation on the equilibrium constants values is small.

Data collected in Tables 1 and 2 allow to show few correlations. Applied here theoretical methods give similar results for all studied compounds. The adiabatic connection methods (B1LYP and B3LYP) give very similar results to these obtained by G2 calculations. So, we believe that these methods are reliable and give precise results. The data obtained from G2MP2 method confirm these obtained with G2. Unfortunately, G2 method was not used for ethylmaltol and kojic acid because of the computational cost.

Theoretically determined the lowest energy structures were then compared to available experimental data. The crystal structure of the pyromeconic acid was published [27]. The Hpa molecule exists in the enolic structure of tautomer Hpa1 but it is not exactly planar as in our theoretical calculations. This is especially evident for the hydroxyl group. The torsion angle C(keto)–C–O(hydroxyl)–H(hydroxyl) is 17.8°, not zero as it should be for the exactly planar structure. However, this deviation from the planarity is probably caused by the solid state effects. Two maltol structures, orthorhombic [28] and monoclinic [4,28] were also published. They differ in arrangements of maltol molecules in the crystal unit. However, it has to be emphasized that the single maltol molecule in both structures exists as the Hma1 tautomer with the almost planar pyran ring. Three different polymorphic forms of ethylmaltol: monoclinic, rhombohedral and triclinic were determined in solid state

Table 2
Calculated equilibrium constants K_T between neutral tautomers of studied compounds. K_T values calculated only from enthalpy differences are given in parentheses

K_T	HF	SVWN	B3LYP	B1LYP	G2	G2MP2
Pyromeconic acid						
Hpa1 ↔ Hpa2	1.53×10^{-17} (2.57×10^{-17})		3.80×10^{-10} (4.40×10^{-10})	9.56×10^{-10} (1.23×10^{-9})	1.56×10^{-10} (2.77×10^{-10})	2.28×10^{-10} (4.05×10^{-10})
Hpa1 ↔ Hpa4		1.73×10^{-36} (2.71×10^{-37})				
Hpa1 ↔ Hpa3	3.41×10^{-5} (7.58×10^{-6})	1.10×10^{-14} (3.53×10^{-16})	1.16×10^{-8} (1.15×10^{-9})	2.40×10^{-8} (2.46×10^{-9})	9.64×10^{-9} (1.70×10^{-9})	5.33×10^{-9} (3.31×10^{-9})
Hpa2 ↔ Hpa4	5.83×10^{-30} (7.36×10^{-31})		1.71×10^{-27} (2.52×10^{-28})	1.07×10^{-27} (1.60×10^{-28})	1.25×10^{-27} (1.13×10^{-28})	6.91×10^{-28} (6.26×10^{-29})
Hpa3 ↔ Hpa5	8.94×10^{-57} (7.58×10^{-58})	1.49×10^{-50} (7.47×10^{-50})	2.02×10^{-53} (2.09×10^{-53})	6.65×10^{-54} (6.98×10^{-54})	2.62×10^{-53} (3.06×10^{-54})	2.76×10^{-53} (9.16×10^{-58})
Maltol						
Hma1 ↔ Hma2	1.92×10^{-17} (7.31×10^{-18})		1.21×10^{-8} (7.98×10^{-9})	3.46×10^{-9} (2.09×10^{-9})	2.37×10^{-10} (3.51×10^{-10})	3.94×10^{-10} (5.06×10^{-10})
Hma1 ↔ Hma4		9.40×10^{-37} (1.37×10^{-37})				
Hma1 ↔ Hma3	9.27×10^{-8} (2.61×10^{-11})	5.65×10^{-18} ($5,67 \times 10^{-18}$)	2.27×10^{-9} (4.63×10^{-11})	4.27×10^{-11} (1.04×10^{-11})	1.94×10^{-10} (6.46×10^{-11})	1.11×10^{-10} (3.70×10^{-11})
Hma2 ↔ Hma4	1.43×10^{-32} (2.04×10^{-33})		7.09×10^{-29} (1.15×10^{-29})	3.29×10^{-29} (5.97×10^{-30})	2.89×10^{-29} (2.22×10^{-29})	4.34×10^{-29} (3.21×10^{-29})
Hma3 ↔ Hma5	5.87×10^{-54} (1.42×10^{-55})	1.42×10^{-46} (6.10×10^{-47})	1.49×10^{-51} (6.62×10^{-52})	3.77×10^{-52} (1.46×10^{-52})	1.44×10^{-52} (5.32×10^{-52})	5.28×10^{-52} (3.24×10^{-51})
Ethylmaltol						
Hema1 ↔ Hema2	2.49×10^{-17}		9.90×10^{-9}	2.51×10^{-9}	1.03×10^{-9}	3.28×10^{-9}
Hema1 ↔ Hema4		1.17×10^{-36}				
Hema1 ↔ Hema3	2.79×10^{-7}	3.43×10^{-17}	4.94×10^{-11}	1.02×10^{-10}	3.56×10^{-11}	4.26×10^{-10}
Hema2 ↔ Hema4	2.32×10^{-32}		1.09×10^{-28}	6.10×10^{-29}	3.67×10^{-28}	8.17×10^{-29}
Hema3 ↔ Hema5	1.75×10^{-54}	1.37×10^{-46}	1.96×10^{-51}	4.62×10^{-52}	7.78×10^{-52}	4.22×10^{-52}
Kojic acid						
Hka1 ↔ Hka2	1.47×10^{-17}		3.40×10^{-9}	8.95×10^{-10}	3.84×10^{-10}	4.94×10^{-9}
Hka1 ↔ Hka4		2.28×10^{-35}				
Hka1 ↔ Hka3	1.67×10^{-4}	2.77×10^{-14}	2.10×10^{-8}	4.40×10^{-8}	4.01×10^{-8}	3.76×10^{-8}
Hka2 ↔ Hka4	1.56×10^{-27}		1.74×10^{-26}	1.16×10^{-26}	3.92×10^{-26}	2.95×10^{-27}
Hka3 ↔ Hka5	2.39×10^{-55}	1.12×10^{-43}	4.58×10^{-50}	1.21×10^{-50}	4.93×10^{-51}	4.93×10^{-50}

[29]. All of them are built from units that are almost ideal with Hema1. Thus, their heterocyclic rings are almost planar and the torsion angles O(ring)–C–C(ethyl)–C(ethyl) are 74.8, 70.4 and 84.6° for monoclinic, rhombohedral and triclinic ethylmaltol crystals, respectively. Thus, the closest to the theoretical results is the conformation of the ethyl group in the rhombohedral polymorph. The kojic acid crystal is also built from the enolic tautomer 1 units [30]. The conformation of the hydroxymethyl group is different from this evaluated from the theoretical gas phase calculations. Calculated in this work values of O(ring)–C–C(hydroxymethyl)–O(hydroxymethyl) torsion angle is about 50°. On the other hand, corresponding experimental value is 167.8°. This discrepancy appears as the result of intermolecular hydrogen bond in the kojic acid crystal, in which the hydroxymethyl group is involved. In a gas phase molecules of kojic acid are free from such bonding.

A comparison of selected bond lengths (bond lengths between heavy atoms) and angles (angles in pyran ring) calculated at the B3LYP/6-311++G(d,p) level with proper experimental data is presented in Fig. 3. As one can see this theoretical method used in calculations describes geometry of studied compounds with high quality. A small discrepancies between theoretical and calculated geometries are due to the fact that comparison is made between experimental data obtained for single crystals (where intermolecular hydrogen bonds are created) with calculations of molecules in a gas phase.

3.2. Cations

Similarly to neutral molecules five possible tautomers of cations of investigated compounds have been taken into account (see Fig. 4). In cationic

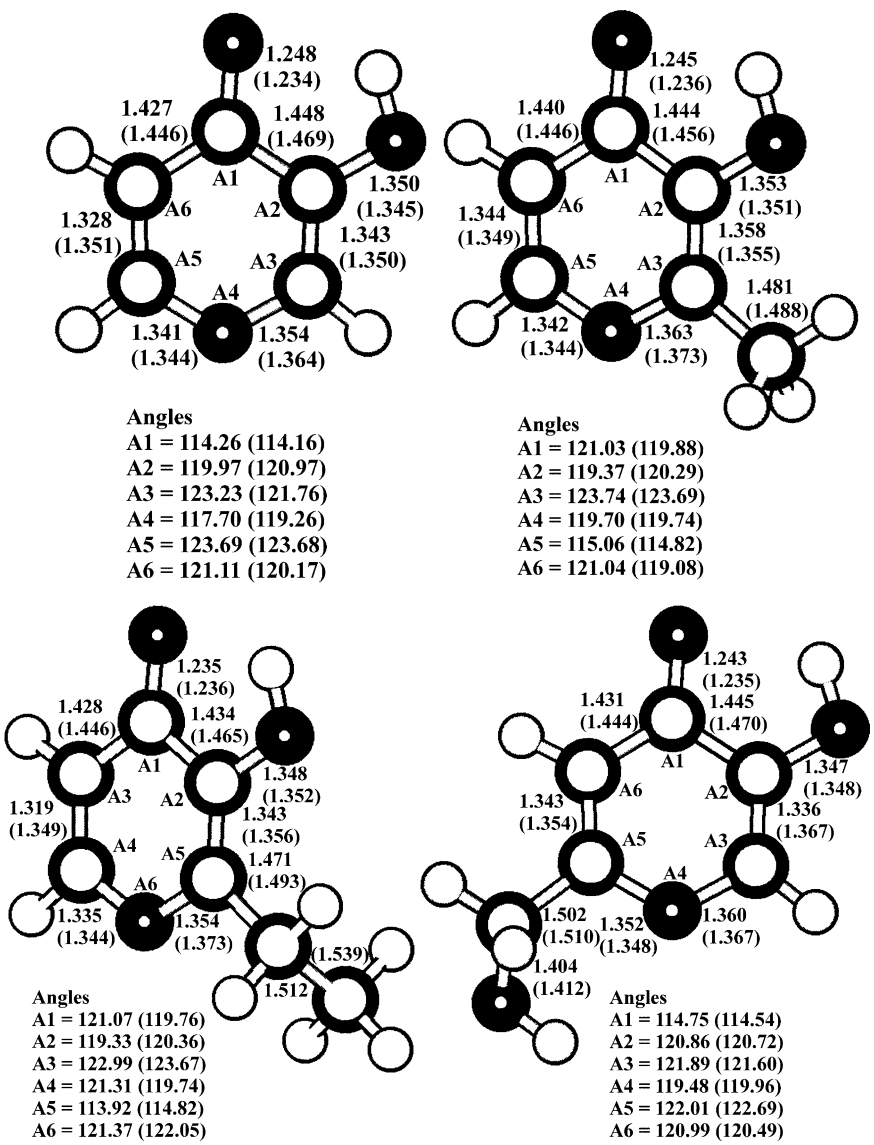

Fig. 3. Selected experimental and theoretical (B3LYP/6-311++G(d,p), in brackets) bond lengths and angles of neutral forms of studied ligands.

tautomer 1 protonation occurs on the oxygen in the keto group. In this tautomer there are two, adjacent hydroxyl groups. We have decided to study this structure in details for the pyromeconic cation, only. Four possible planar conformers, $H_2pa^+1b–e$, are presented in Fig. 4. The potential energy surface shows additional structure with non-planar conformation, H_2pa^+1a. Performed geometry and frequency calculations on H_2pa^+1 conformers show that only H_2pa^+1d is not an energetic minimum. This can be easily explained by the presence of sterical hindrance where hydrogens from both hydroxyl groups are

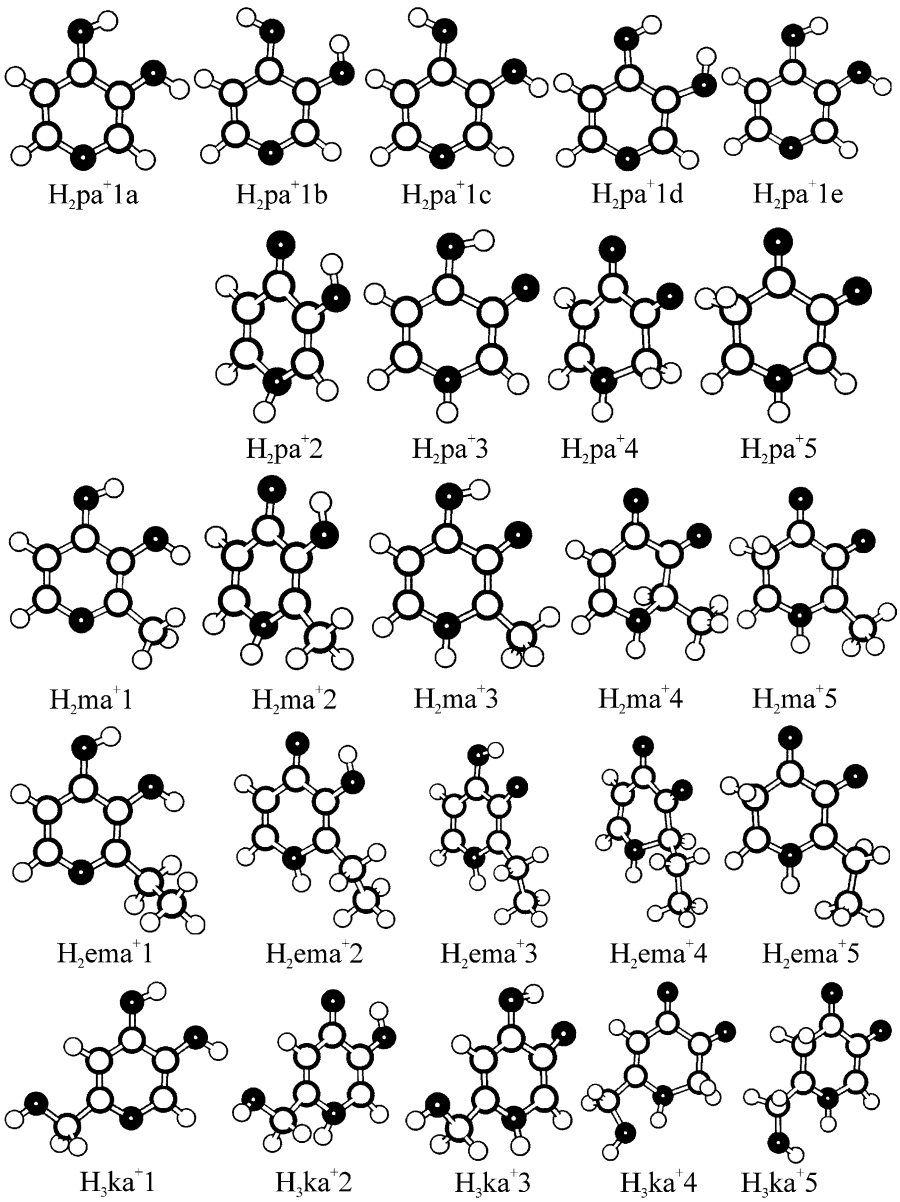

Fig. 4. Configurations of cationic species of studied compounds.

Table 3
Computed relative energies (in kJ/mol, ZPE included) for the most stable geometries of cationic tautomers of studied compounds. Calculations performed (except G2 and G2MP2) in 6-311++G(d,p) basis set

Relative energy	HF	SVWN	B3LYP	B1LYP	G2	G2MP2
Pyromeconic acid						
H_2pa^+1a	0.00	0.00	0.00	0.00	0.00	0.00
H_2pa^+1b	9.12	5.83	5.79	5.97	5.39	5.25
H_2pa^+1c	19.40	18.37	16.43	16.66	15.78	15.81
H_2pa^+1e	0.04	−0.02	−0.04	−0.05	0.06	0.06
H_2pa^+2	234.57	235.21	235.21	235.46	229.83	229.74
H_2pa^+4	244.15	262.30	262.30	264.61	256.42	257.55
Maltol						
H_2ma^+1	0.00	0.00	0.00	0.00	0.00	0.00
H_2ma^+2	234.42	235.21	230.64	230.70	230.82	231.76
H_2ma^+3	370.43		305.60	310.92	311.56	312.01
H_2ma^+4	249.75	316.84	268.99	266.55	265.65	263.56
Ethylmaltol						
H_2ema^+1	0.00	0.00	0.00	0.00	0.00	0.00
H_2ema^+2	233.22	219.98	227.03	227.36	225.84	226.75
H_2ema^+3	368.71		301.65	307.38	310.22	309.65
H_2ema^+4	247.14	302.69	264.38	262.19	260.45	261.93
Kojic acid						
H_3ka^+1	0.00	0.00	0.00	0.00	0.00	0.00
H_3ka^+2	246.61	250.38	244.42	244.40	240.49	242.56
H_3ka^+3	370.97		319.96	324.35	326.64	325.78
H_3ka^+4	218.04	234.06	224.16	223.60	221.55	222.22

located too close to each other. Relative energies of H_2pa^+1 conformers are given in Table 3. H_2pa^+1a structure has been arbitrary chosen as the zero level.

It is seen that the geometries obtained for H_2pa^+1a and H_2pa^+1e are very close to each other. The conformation of hydroxyl groups is similar and the H(hydroxyl)–O(hydroxyl)–O(hydroxyl)–H(hydroxyl) angle for H_2pa^+1e varies from 176.7 to 179.8°, depending on the theoretical method used. The energy gap between H_2pa^+1a and H_2pa^+1e is extremely small (0.04 kJ/mol). The theoretical methods used in these calculations are not able to predict which structure (H_2pa^+1a or H_2pa^+1e) is the global minimum, because the energy difference between these two structures is at the precision limit of calculations. Thus, we conclude that these two structures have the same stability. The energies of the other discussed conformers are about six (H_2pa^+1b) and 17 kJ/mol (H_2pa^+1c) higher. As expected, the highest energy has conformer that does not form any hydrogen bond.

In H_2pa^+2 protonation takes place on the intraring oxygen (see Fig. 4). The lowest energy structure is almost planar, except the hydrogen atom from the just formed hydroxyl group. This proton is strongly out-of-plane deviated. Such effect is also observed in neutral tautomer 5. The H_2pa^+4 structure with the lowest energy does not have a symmetry plane. Its keto groups are twisted about 2° (the effect of keto group twisting was reported earlier for neutral tautomers with two keto groups). This is the reason, why the whole pyran ring of H_2pa^+4 is deformed. No stationary points have been found for the H_2pa^+3 and H_2pa^+5 structures.

The equilibrium geometry for the H_2ma^+1 tautomer does not have a symmetry plane and configuration of two hydroxyl group is the same as that observed for H_2pa^+1a. However, replacing hydrogen atom by the methyl group causes that the structure with the strictly planar pyran group, similar to H_2pa^+1e, is not a minimum in this case. The energetically lowest geometry of H_2ma^+2 is almost

the same as that calculated for H_2pa^+2. Appearance of the methyl group stabilizes the H_2ma^+3 structure. The H_2ma^+3 tautomer has the minimum which does not have the C_S symmetry because of the hydrogen atom from hydroxyl group, which is again deviated out-of-plane (as for H_2ma^+2 and H_2pa^+2).

The conformation of the hydroxyl groups in H_2ema^+1 is close to reported for maltol and pyromeconic acid cations. The pyran ring in H_2ema^+1 is almost planar and the ethyl group is located perpendicularly to the ring. The O(ring)–C–C(ethyl)–C(ethyl) angle varies from 63.7 to 77.0° for various theoretical methods. A value of a torsion angle of the H_2ema^+2 is 50°. All other structural features are similar to that of H_2pa^+2 and H_2ma^+2. The similar structural situation is calculated for H_2ema^+3 where the ethyl group is in the 'perpendicular' position to the ring. On the other hand the ethyl group conformation in H_2ema^+4 is 'parallel' to the ring that causes the ring distortion (see Fig. 4). Additionally, the ethylmaltol cation tautomer 5 seems to have no minimum on the potential energy surface.

In the case of the kojic acid cation, H_3ka^+1, the lowest energy structure, has the plane of symmetry. The conformation of the hydroxyl groups is the same as it was presented earlier for other discussed here structures of the same type. Thus, we conclude that when there is no substituent on the carbon atom located between intraring oxygen and carbon involved in the hydroxyl group binding, the structure of the cationic tautomer 1 possess the plane of symmetry and belongs to the C_S symmetry point group. If the hydrogen bonded to this atom is replaced by 'bulky' substituent ($-CH_3$ in maltol or $-C_2H_5$ in case of ethylmaltol molecule) the plane of symmetry cannot be sustained. The structures calculated for the H_3ka^+2 and H_3ka^+3 tautomers do not have any plane of symmetry due to the hydrogen atom from hydroxyl group formed on the intraring oxygen. The hydroxymethyl group conformation is similar to that observed in H_3ka^+1. For all of these three tautomers, H_3ka^+1–3, the hydrogen bond between the hydroxymethyl group and intraring oxygen is not created. Such, but weak, bonding is observed for the H_3ka^+4, see Fig. 4. As expected in this case, the H_3ka^+5 tautomer has no minimum.

To summarize, the relative energies of studied cations are given in Table 3. The type 1 tautomer is the most energetically favourable. The energies of other tautomers are much higher (more then 200 kJ/mol). Due to such large energy gap between the tautomer with lowest energy and others there is no need to compute the constants of equilibria for cations. Calculated energy values strongly suggest that H_2pa^+1, H_2ma^+1, H_2ema^+1 and H_3ka^+1 exist in gas phase as cations only. The protonation of the 4H-pyran-4-one system has been discussed earlier in the literature [31]. To obtain protonated structures experimentally, the CH_3^+ group was introduced to the 2,5-dimethyl-4H-pyran-4-one molecule. It was observed that this group attached to the keto group, and not to the intraring oxygen [32]. Protonation of the 4H-pyran-4-one molecule and its sulphur derivatives was studied theoretically by semiempirical MNDO method [33]. There was found that exo-heteroatom protonation (oxygen or sulphur) was preferred, by 250–330 kJ/mol, over the attachment of the proton to the intraring heteroatom. It was rationalized by the higher electron density centred on the exo-heteroatom. Our calculations confirm that the keto oxygen is protonated and obtained relative energies correspond well with the above mentioned study.

Among cationic species discussed here ligands the experimental geometry data were published so far only for the maltol cation chloride [34]. Its crystal structure is built from the H_2ma^+1 units but the conformation of the hydroxyl group is different than calculated. Experimentally observed conformation of two hydroxyl groups is the same as for the H_2pa^+1b structure (see Fig. 4). This discrepancy is generated by the chloride anion. In the solid-state chloride anion bind the hydroxyl group created during protonation on the keto atom. Experimental and theoretical geometry parameters are compared in Fig. 5. One can see that, alike as for neutral ligands, B3LYP/6-311++G(d,p) calculations reproduce quite well experimental bond lengths and angles.

3.3. Anions

Deprotonation of the investigated hydroxypyrones leads to creation of corresponding anions. Their structures and abbreviations are shown in Fig. 6. According to obtained theoretical data, pyran group of maltol and pyromeconic acid anions are planar

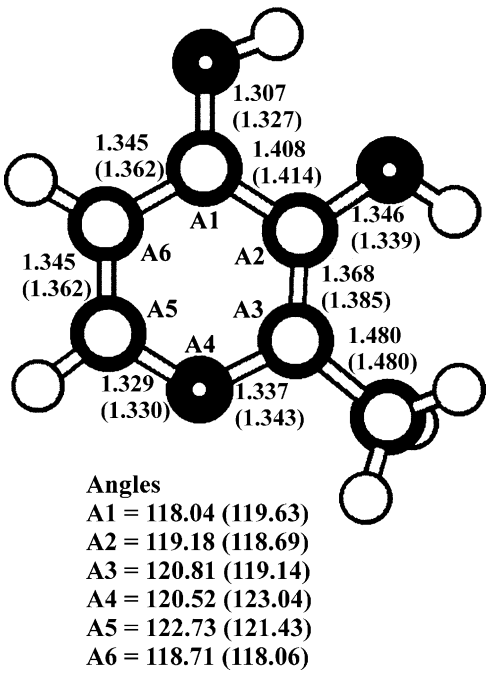

Fig. 5. Selected experimental and theoretical (B3LYP/6-311++G(d,p), in brackets) lengths and angles of neutral forms of maltol cation.

structures and belong to the C_S point symmetry group. The ethylmaltol anion has approximately planar ring. The conformation of the ethyl group is perpendicular to the pyran ring.

From theoretical point of view deprotonation of the kojic acid molecule can occur from both hydroxyl groups. It gives two possible structures of the kojic acid anion; $Hka^{-}1$ and $Hka^{-}2$, see Fig. 6. The pyran ring in the $Hka^{-}1$ molecule is planar. The hydroxymethyl group is conformed here in the way that weak intramolecular hydrogen bond with intraring oxygen is created. The $Hka^{-}2$ structure has the plane of symmetry and the O(intraring)–C–C(hydroxymethyl)–O(hydroxymethyl) torsion angle is equal 180°.

Relative energies of these structures and equilibrium constants between them are depicted in Table 4. All theoretical methods predict that deprotonation from the hydroxyl group attached to the pyran ring is strongly preferable.

In the case of kojic acid the formation of the dianion form by both hydroxyl deprotonation groups is possible. The most stable geometry of such structure is also presented in Fig. 6. The pyran

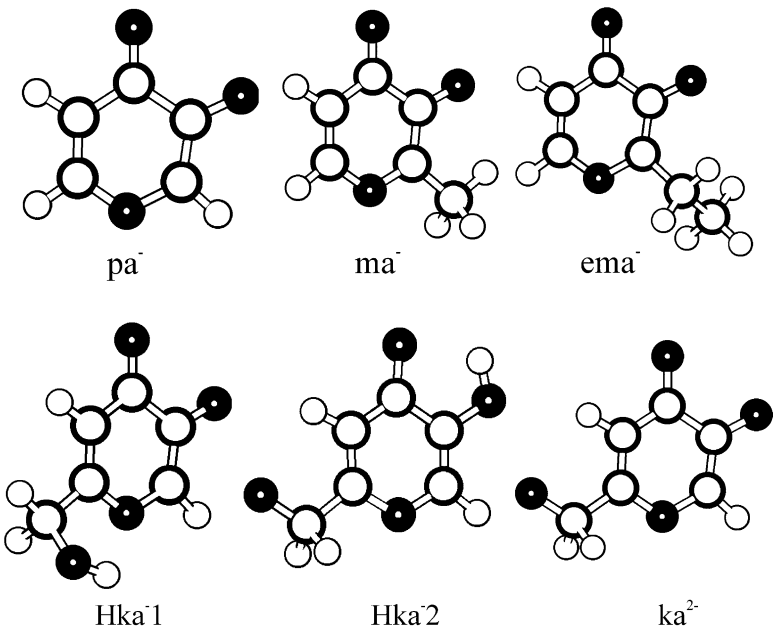

Fig. 6. Configurations of anionic species of studied compounds.

Table 4
Relative energies (in kJ/mol, ZPE included) and equilibrium constants obtained for two forms of the kojic acid anion

K_T	HF	SVWN	B3LYP	B1LYP	G2MP2
Hka^-1	0.00	0.00	0.00	0.00	0.00
Hka^-2	11.41	8.31	13.50	15.87	12.00
$Hka^-1 \leftrightarrow Hka^-2$	7.78×10^{-7}	8.81×10^{-4}	1.24×10^{-7}	1.22×10^{-7}	6.66×10^{-6}

group in ka^{2-} has strictly planar structure and the deprotonated hydroxymethyl group is positioned in such a way that two negatively charged oxygens (intraring oxygen and oxygen from deprotonated hydroxymethyl group) are as far from each other as possible. This is the same conformation as reported for the lowest energy Hka^-2 structure.

Unfortunately to our best knowledge, there are no structural data of the studied anions in the literature. So comparison with the experimental data at this stage of the research is impossible.

All presented in this work geometries, energy values, profiles obtained from PES calculations and thermochemistry parameters can be obtained upon request.

4. Conclusions

Tautomerism phenomena occur in neutral molecules of all studied ligands. Performed theoretical calculations indicate that in the gas phase of investigated hydroxypyrones only enolic forms exist. These structures are stabilized by intramolecular hydrogen bonds. Ketonic forms can exist in the solutions of protic solvents, where interactions with the solvent molecules can make these structures more stable than in the gas phase. It shows how important are calculations involving solvent effects to understand the stability of discussed structures.

According to obtained theoretical results protonation of hydroxypyrones is much more preferable on the oxygen from the keto group than on the oxygen from the ring.

The anions of pyromeconic acid, maltol and ethylmaltol have no labile protons and they cannot form tautomeric structures. In case of kojic acid, which potentially has two dissociable protons, we show that deprotonation is more probable from the hydroxyl group that is directly bound to the pyran ring.

Predicted theoretical geometries of the most stable structures are in a very good agreement with available experimental data.

Obtained results show that entropy has only a small influence on the values of tautomeric equilibrium constants in the gas phase.

The G2 and G2MP2 methods give similar results, thus the G2MP2 calculations seem to be sufficient to obtain precise data. Additionally, we have tested two ACM methods (B1LYP and B3LYP). Obtained results are similar to these evaluated from G2 calculations. This suggests that these methods can be used in the cases where G2 (or G2MP2) calculations are impossible because of required computer resources. Contrary to them, HF and especially SVWN approximations provide results which sometimes differ significantly from ACM and G2 outcomes.

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