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Quantum chemical studies on tautomeric equilibria in chlorokojic and azidokojic acids

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Abstract

Tautomerism of protonated and neutral forms of chlorokojic and azidokojic acids was studied using quantum mechanical calculations. The computations were performed for all possible structures of compounds under investigation. Tautomeric equilibrium constants among the most stable tautomers were then calculated. These values have been determinated by the HF, BLYP and B1LYP methods with the 6-311++G(d,p) basis set. Our calculations clearly show that for neutral molecules, the enolic form is strongly preferred. On the other hand, the cationic species were formed by protonation of the keto oxygen atom. The equilibrium geometries of chlorokojic and azidokojic anions were also determined. The results presented here are compared with the data obtained previously for kojic acid and other hydroxypyrones.

Keywords: Hydroxypyrones; Kojic acid derivatives; Ketoenol tautomerism; Equilibrium constants; Quantum chemical calculations

1. Introduction

Kojic acid (2-hydroxymethyl-5-hydroxy-4H-pyran-4-one), abbreviated as H_2ka, is a biologically important natural product. It is a fungal metabolite produced by many species of *Aspergillus*, *Acetobacter* and *Penicillium*. It was discovered during investigating on the fermentation of steamed rice ('koji') [1]. Kojic acid occurs in such traditional Japanese fermented food products as *sake*(rice wine), *miso* (soybean paste), *shoyu* (soy sauce) and many others. As any fermented food, these products may be contaminated with mycotoxins. However, due to the biochemical properties of kojic acid, they are considered to be one of the safest food products [2]. Thanks to its antibacterial and fungicidal properties, kojic acid is used as a food additive [3]. It is widely used as an antioxidant or antibrowning agent [4] as well. Due to its properties of melatonin production inhibition [5–6], it also plays an important role in the cosmetic industry. Recent research shows that the genotoxicity and toxicity risk of the kojic acid as a skin-lightening agent is negligible [7].

On the other hand, kojic acid and other hydroxypyrones are studied extensively because they form complexes with various metal ions. These complexes have reasonable hydrolytic stability, neutral charge, and significant lipophilicity [8]. They have been tested as new drugs in the therapy of such diseases as diabetes [9] or anaemia [10]. The neurological properties of aluminium(III) complexes with kojic acid and other hydroxypyrones have also been investigated [11].

A number of biologically active derivatives of kojic acid were prepared [12–15]. In this work, we concentrate on two kojic acid derivatives which exhibit herbicidal and growth regulatory activity, namely: chlorokojic acid (2-chloromethyl-5-hydroxy-4H-pyran-4-one, HkaCl) and azidokojic acid (2-azidomethyl-5-hydroxy-4H-pyran-4-one, $HkaN_3$). Chlorokojic acid is a good ligand for the nucleophilic substitution reactions [16,17]. Azidokojic acid is synthesized by the substitution of the chlorine in chlorokojic acid with the azido group [18]. Azidokojic acid has been used as a scavenger of iron(III) ion [19].

To the best of our knowledge, quantum chemical investigations on chlorokojic acid and azidokojic acid

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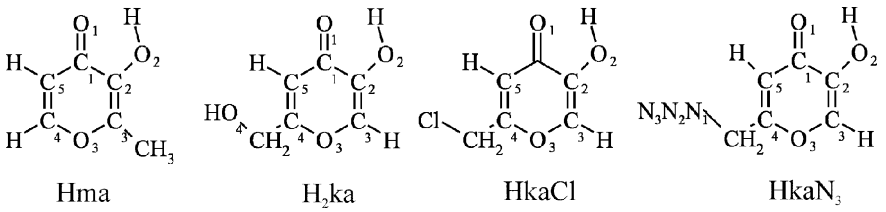

Fig. 1. Structures and atom numbering scheme of compounds investigated.

molecules have not been carried out so far. It is well known that hydroxypyrones [20] can exist in cationic and anionic forms due to the protonation or deprotonation reactions, respectively. Therefore, we have decided to include these species in our work. The results of quantum mechanical investigations on tautomeric equilibria in selected hydroxypyrones (maltol, ethylmaltol and pyromeconic acid) have been published recently [21]. Based on these results, the enolic structures of neutral chlorokojic acid and azidokojic acid molecules are expected to be the most stable ones. They are depicted in Fig. 1. The structures of kojic acid and maltol molecules are also presented in the figure.

The neutral and protonated compounds of interest have a labile proton and they may exist in several tautomeric forms. Investigations on tautomeric equilibria in such compounds are very important for ligands of biological, biochemical, medical and pharmacological interest to understand their biological activity. It is well established that quantum chemical calculations are very useful in the determination of the most stable structures of tautomers and estimation of tautomeric equilibrium constants [22].

2. Computational details

In order to obtain the structures of chlorokojic and azidokojic acids present in equilibria, we performed some theoretical calculations on their isolated tautomers using the GAUSSIAN 98 package [23]. Many tautomeric structures can be proposed for neutral and cationic forms of studied kojic acid derivatives. In order to select the most probable of them, introductory calculations were executed using the Hartree–Fock approximation and a moderate 6-31G basis set. Not all among proposed structures are stable. Potential energy surfaces of the stable tautomers were investigated by the relaxed reaction path calculations. These calculations permitted to select three or four energetically most stable tautomers for further investigations. The most stable conformations of the anions studied were also determined.

The equilibrium structures, energies and free energies of the selected tautomers are required for the determination of the tautomeric mixture composition. The calculations of these properties were executed by the HF and DFT methods with the 6-311++G(d,p) basis set. From various available DFT functionals, we have chosen two namely BLYP [24,25] and B1LYP [26]. We have recently shown [21] that hybrid DFT functionals (B3LYP and B1LYP) constitute the best methods for structural studies of hydroxypyrones. Because both methods gave very similar results, in this work we decided to show results obtained by the B1LYP method, only. On the other hand, we also tested the SVWN method (local DFT functional) that gave the poorest results. Taking this into account instead of the SVWN method, we decided to test the gradient corrected BLYP functional. For the most stable tautomers, the G2 (pyromeconic acid and maltol) or G2MP2 (for ethylmaltol and kojic acid molecules) methods (which calculate molecular energies with higher accuracy) were employed in our previous work [21]. For the same purpose, in the current work, we used G2MP2 method [27] together with one of the complete basis set (CBS-4 parametrization [28]). In the next step, tautomeric equilibrium constants (K_T^{AB}), that give information about particular tautomer concentrations, were obtained according to Eq. (1) [21].

$$\Delta G_{AB} = -RT \ln K_T^{AB} \quad (1)$$

In the above equation, R is the ideal gas constant and T absolute temperature. ΔG_{AB} is the free energy variation describing tautomeric reaction $T_A \leftrightarrow T_B$.

3. Results and discussion

All neutral tautomers of azidokojic and chlorokojic acid have been taken into account. Introductory calculations (see 'Section 2') allowed to select three of these with the lowest energies. These tautomer configurations are depicted in Fig. 2. The lowest energy neutral tautomers of both compounds studied are very similar. Differences occur only for the substituent at the C_4 atom. Tautomer 1 is in enolic form, with a hydroxyl group attached to the C_2 atom. In the second structure, the hydroxyl group is moved to the C_1 atom. Tautomer 3 is a keto structure. In the enolic tautomers, pyran rings are nearly planar with hydroxyl groups forming an intramolecular hydrogen bond. In the case of tautomer 2, the pyran ring is slightly distorted from the planarity. Conformations of the $-CH_2-Cl$ substituent in the neutral chlorokojic acid tautomers are more or less perpendicular to the ring. Orientation of the azido group in the neutral azidokojic acid molecule is perpendicular in the case of $HkaN_3$1 and $HkaN_3$3, but parallel in the case of $HkaN_3$2.

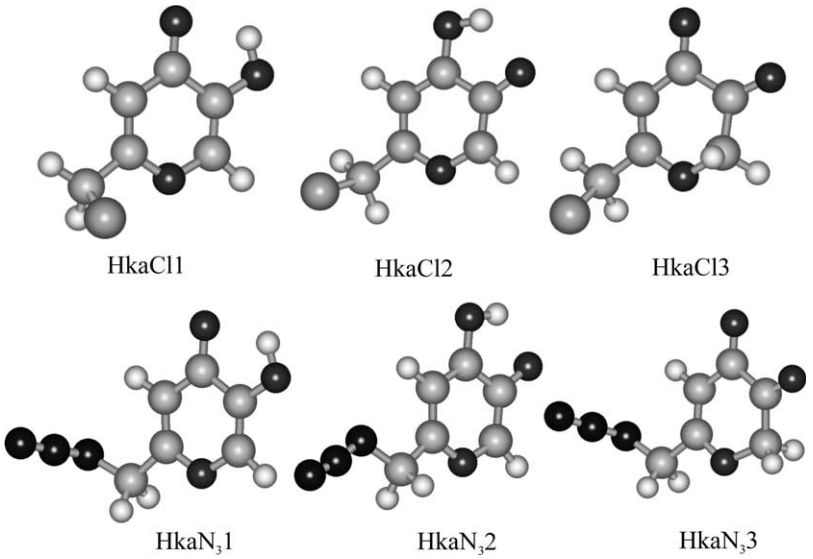

Fig. 2. The most stable conformations of neutral tautomers of compounds studied.

For all of the tautomers presented here, full geometry optimization calculations were performed. Zero point energy (ZPE) corrections and free energy values were also calculated. The obtained results are listed in Table 1. It is evident from these data that in the case of chlorokojic acid, the enolic tautomer (HkaCl1) exhibits the lowest energy value. The energy gaps between the first and the second tautomer are always prominent. However, this difference in energy is relatively low for the HF method (25.77 kJ/mol). The highest barrier is predicted by the G2MP2 method (46.34 kJ/mol) but the differences obtained by B1LYP, CBS-4 and G2MP2 do not seem to be important. The energy gap evaluated from the BLYP functional has a moderate value. Additionally, the used calculation methods differ substantially in their prediction about the second tautomer in the energy order. The Hartree–Fock approach strongly favours keto tautomers. The same result was obtained in the previous work for pyromeconic acid, maltol, ethylmaltol and kojic acid [21]. The gradient corrected DFT BLYP functional also prefers the keto structure. However, the hybrid B1LYP functional and the G2MP2 or CBS-4 computations prefer another enolic tautomer, i.e. HkaCl2. These methods show that the keto tautomer is about 7 kJ/mol less stable than the HkaCl2 structure. Slightly different results were obtained for the azidokojic acid tautomers. The ketoenolic structure of $HkaN_3 1$ is strongly preferred by the calculations. The energy order of the azidokojic acid tautomers is the same as for the chlorokojic acid molecule based on the HF calculations. It is changed when other quantum chemical methods are used. The B1LYP, CBS-4 and G2MP2 data predict that the keto tautomer has the energy lower than the enolic $HkaN_3 2$ structure (see Table 1). It is not clearly understood why the BLYP result is again in disagreement with the G2MP2, CBS-4 or B1LYP data.

The equilibrium tautomeric constants among the energetically lowest neutral tautomers of compounds studied have been calculated and presented in Table 1. As mentioned, the energy gaps between the HkaCl1 or $HkaN_3 1$ tautomers and the other ones are large. Thus, the equilibrium constant

Table 1
Relative energies (kJ/mol, ZPE included) and equilibrium constants for neutral tautomers of chlorokojic and azidokojic acids

Tautomers	HF	BLYP	B1LYP	CBS-4	G2MP2
Chlorokojic acid					
HkaCl1	0.00	0.00	0.00	0.00	0.00
HkaCl2	97.57	47.12	47.01	47.56	46.34
HkaCl3	25.77	35.79	50.34	56.64	55.67
HkaCl1 ↔ HkaCl2	7.74×10^{-5}	2.02×10^{-8}	1.82×10^{-8}	2.12×10^{-8}	7.61×10^{-9}
HkaCl1 ↔ HkaCl3	8.18×10^{-18}	5.37×10^{-7}	1.46×10^{-9}	1.06×10^{-10}	1.77×10^{-10}
Azidokojic acid					
$HkaN_3 1$	0.00	0.00	0.00	0.00	0.00
$HkaN_3 2$	93.28	37.21	50.22	61.62	60.34
$HkaN_3 3$	25.82	44.53	45.35	47.36	45.93
$HkaN_3 1 \leftrightarrow HkaN_3 2$	7.40×10^{-5}	4.79×10^{-7}	2.57×10^{-9}	1.02×10^{-11}	2.68×10^{-11}
$HkaN_3 1 \leftrightarrow HkaN_3 3$	5.26×10^{-17}	5.88×10^{-8}	3.57×10^{-8}	2.91×10^{-8}	8.98×10^{-9}

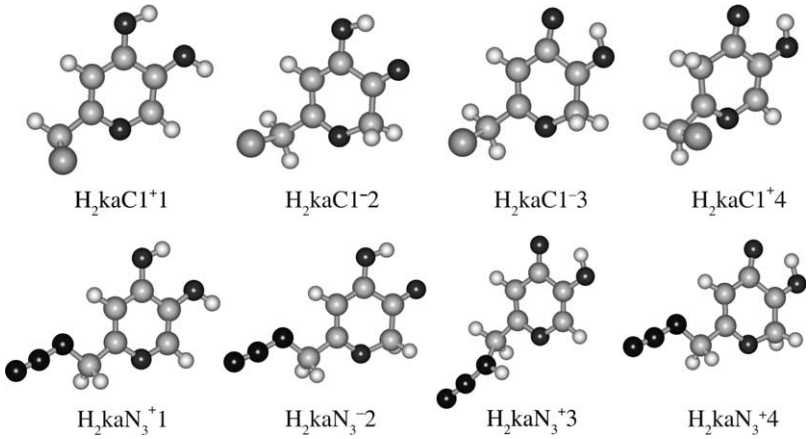

Fig. 3. The most stable conformations of the cationic tautomers of compounds studied.

values show that in the gas phase, only enolic structures, with labile hydrogen connected to the O_2 atom, can really exist. The abundance of the other neutral structures is few orders of lower magnitude. This is consistent with the results published previously for other hydroxypyrones [21].

The same calculation procedure was employed to study cationic tautomers of the kojic acid derivatives. Here, four tautomers were selected for calculations. Their molecular structures are presented in Fig. 3. First of all, the protonation can occur on the keto oxygen, which results in the formation of additional hydroxyl group (structures $H_2kaN_3^+1$ and H_2kaCl^+1). In these tautomers, the pyran ring is flat and the structures are stabilized by an intramolecular hydrogen bond. Tautomers: H_2kaCl^+2, H_2kaCl^+3 and H_2kaCl^+4 have only one hydroxyl group that is always involved in the intramolecular hydrogen bond. In all cases, the intraring methylene group is formed and the pyran rings are distorted from planarity. The conformation of the $-CH_2-Cl$ group is always perpendicular to the pyran ring. Generally, cationic tautomers of the azidokojic and chlorokojic acids are similar, with one exception. It is interesting to note that the N1 atom in the azide group can be also protonated (see structure $H_2kaN_3^+3$). In all cases, the azido group is placed parallelly to the heterocyclic pyran ring. On the other hand, protonation of the intraring oxygen is extremely unfavoured. No such structure is predicted among the lowest energy cationic tautomers for studied ligands.

The relative energies and tautomeric equilibrium constants among cationic tautomers of kojic acid derivatives are listed in Table 2. The results obtained by all computational methods used are similar. In all cases, the most stable tautomer possesses two hydroxyl groups, H_2kaCl^+1 or $H_2kaN_3^+1$. The second tautomer in the energy order is the structure with the hydroxyl group at the C_1 atom and the intraring methylene group bound to the C_3 atom. The mean energy gap between the first and the second tautomer of cations of both acids is about 55 kJ/mol. The energies of other tautomers are usually higher by more than 100 kJ/mol. Due to this energy gap, the calculated tautomeric equilibrium constants strongly

Table 2
Relative energies (kJ/mol, ZPE included) and equilibrium constants for cationic tautomers of chlorokojic and azidokojic acids

Tautomers	HF	BLYP	B1LYP	CBS-4	G2MP2
Chlorokojic acid					
H_2kaCl^+1	0.00	0.00	0.00	0.00	0.00
H_2kaCl^+2	48.05	51.19	59.12	70.26	65.45
H_2kaCl^+3	127.54	110.77	126.65	144.23	140.34
H_2kaCl^+4	129.15	119.30	132.51	137.39	139.54
$H_2kaCl^+1 \leftrightarrow H_2kaCl^+2$	7.24×10^{-9}	2.28×10^{-9}	9.76×10^{-11}	1.24×10^{-12}	3.42×10^{-12}
$H_2kaCl^+1 \leftrightarrow H_2kaCl^+3$	5.31×10^{-23}	6.01×10^{-20}	1.07×10^{-22}	8.35×10^{-26}	2.59×10^{-25}
$H_2kaCl^+1 \leftrightarrow H_2kaCl^+4$	3.44×10^{-23}	1.71×10^{-21}	8.75×10^{-24}	2.83×10^{-24}	3.58×10^{-25}
Azidokojic acid					
$H_2kaN_3^+1$	0.00	0.00	0.00	0.00	0.00
$H_2kaN_3^+2$	43.91	48.63	55.56	66.95	61.59
$H_2kaN_3^+3$	94.32	106.88	114.32	105.32	108.59
$H_2kaN_3^+4$	129.87	109.86	124.56	143.01	133.18
$H_2kaN_3^+1 \leftrightarrow H_2kaN_3^+2$	2.94×10^{-7}	6.23×10^{-9}	3.56×10^{-10}	3.27×10^{-12}	3.34×10^{-11}
$H_2kaN_3^+1 \leftrightarrow H_2kaN_3^+3$	8.41×10^{-17}	3.95×10^{-19}	9.73×10^{-21}	3.33×10^{-19}	6.32×10^{-20}
$H_2kaN_3^+1 \leftrightarrow H_2kaN_3^+4$	8.51×10^{-22}	9.26×10^{-20}	1.51×10^{-22}	1.81×10^{-25}	1.13×10^{-23}

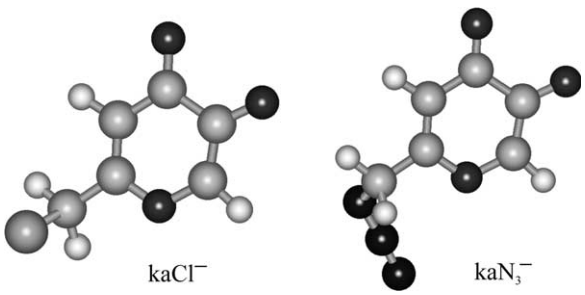

Fig. 4. The most stable conformations of the compound anions studied.

suggest that H_2kaCl^+1 and $H_2kaN_3^+1$ exist in gas phase as cations, only (see Table 2). Our calculations confirm that in hydroxypyrones, the keto oxygen is protonated. The obtained results correspond very well with our previously published data for other studied hydroxypyrones [21].

The anions studied here are formed after deprotonation of the hydroxyl group. However, due to the lack of labile protons, no tautomeric equilibria are possible. Thus, only conformational analysis was performed in this case. Various configurations of the $-CH_2-Cl$ or $-CH_2-N_3$ groups were assumed. The equilibrium structures of the chlorokojic and azidokojic anions are depicted in Fig. 4. The pyran ring in both structures is not much more distorted than in the previously discussed cases. The conformation of the substituents (vide supra) are parallel and perpendicular to the ring for azidokojic acid and chlorokojic acid, respectively.

The geometric parameters computed for the neutral, cationic and anionic structures of chlorokojic and azidokojic acids are gathered in Tables 3 and 4. Unfortunately, to the best of our knowledge, there are no structural available data on the studied compounds. Thus, the comparisons between calculated and experimental results are impossible. In order to test the influence of the theoretical methods on the calculated geometry, we include the results obtained from the HF, BLYP and B1LYP calculations. It has to be emphasized that the same basis set (6-311++G(d,p)) was used for all computations. Nevertheless, some disagreements among the theoretical geometries are observed. Generally, the HF method predicts somewhat different geometry than the DFT methods since it does not take into account the electron exchange correlation function. For example, for the pyran ring the most pronounced structural differences are seen for the O_3-C_4 bond lenghts. This is true for all the studied species. The BLYP method predicts this bond length to be longer by 0.02–0.05 Å than for B1LYP and HF, respectively. Some discrepancies are observed also for O_1-C_1 (neutral chlorokojic and azidokojic acids) and C_2-C_3 (anions of the molecules studied) bonds. The quantum mechanical methods used in these studies also predict a different C–Cl bond length in the chlorokojic acid molecule. On the other hand, predictions by other methods angles do not differ significantly.

The intramolecular hydrogen bond, is present in all cationic and neutral tautomers of the compounds studied except the neutral keto tautomer. The calculated distances between proton and its acceptor in cations and neutral molecules show significant differences only for the BLYP method (2.061 and 2.197 Å for azidokojic acid, and 2.069 and 2.207 Å for chlorokojic acid in neutral molecule

Table 3
Selected bond lengths (in angstroms) and angles (in degrees) of the most stable chlorokojic acid forms

Parameter	Neutral molecule			Cation			Anion		
	HF	BLYP	B1LYP	HF	BLYP	B1LYP	HF	BLYP	B1LYP
O_1-C_1	1.200	1.251	1.232	1.284	1.326	1.308	1.202	1.252	1.234
C_1-C_2	1.470	1.477	1.468	1.425	1.437	1.430	1.516	1.527	1.515
C_2-O_2	1.337	1.356	1.345	1.336	1.358	1.345	1.243	1.266	1.254
C_2-C_3	1.326	1.363	1.348	1.341	1.377	1.363	1.373	1.423	1.405
C_3-O_3	1.350	1.379	1.363	1.323	1.354	1.337	1.391	1.381	1.379
O_3-C_4	1.326	1.366	1.346	1.309	1.358	1.336	1.302	1.366	1.334
C_4-C_5	1.335	1.369	1.354	1.357	1.382	1.370	1.338	1.386	1.365
C_5-C_1	1.454	1.451	1.447	1.397	1.409	1.400	1.466	1.455	1.454
O_1-H				0.951	0.983	0.972			
O_2-H	0.947	0.990	0.974	0.945	0.977	0.965			
$O_1\cdots H$	2.195	2.069	2.099						
$O_2\cdots H$				2.191	2.207	2.187			
$C_4-C(H_2)$	1.494	1.494	1.490	1.496	1.496	1.490	1.494	1.454	1.473
$C(H_2)-Cl$	1.792	1.855	1.822	1.708	1.834	1.806	1.813	2.027	1.885
$O_1-H\cdots O_2$				108.21	109.47	109.05			
$O_2-H\cdots O_1$	112.27	118.30	116.29						
$C_4-C(H_2)-Cl$	111.42	111.83	111.66	109.30	108.67	108.89	112.90	114.72	114.12
$O_1-C_1-C_2-O_2$	0.36	0.32	0.34	−0.05	0.35	0.24	0.47	0.53	0.51
$O_3-C_4-C(H_2)-Cl$	70.91	79.04	75.71	75.57	85.56	82.7	72.75	87.34	83.5

Calculations in 6-311++G(d,p) basis set.

Table 4
Selected bond lengths (in angstroms) and angles (in degrees) of the most stable azidokojic acid forms

Parameter	Neutral molecule			Cation			Anion		
	HF	BLYP	B1LYP	HF	BLYP	B1LYP	HF	BLYP	B1LYP
O_1-C_1	1.201	1.250	1.231	1.285	1.326	1.308	1.201	1.252	1.234
C_1-C_2	1.472	1.479	1.470	1.428	1.438	1.429	1.519	1.530	1.517
C_2-O_2	1.337	1.357	1.345	1.336	1.360	1.346	1.243	1.268	1.256
C_2-C_3	1.325	1.361	1.346	1.339	1.375	1.361	1.371	1.419	1.402
C_3-O_3	1.353	1.384	1.367	1.326	1.358	1.341	1.396	1.397	1.389
O_3-C_4	1.330	1.366	1.347	1.311	1.355	1.335	1.305	1.356	1.331
C_4-C_5	1.334	1.365	1.351	1.359	1.380	1.369	1.337	1.377	1.360
C_5-C_1	1.453	1.452	1.45	1.394	1.408	1.399	1.468	1.461	1.457
O_1-H				0.951	0.983	0.972			
O_2-H	0.947	0.991	0.974	0.944	0.976	0.965			
$O_1\cdots H$	2.184	2.061	2.089						
$O_2\cdots H$				2.183	2.197	2.180			
$C_4-C(H_2)$	1.508	1.552	1.511	1.498	1.508	1.499	1.511	1.495	1.496
$C(H_2)-N_1$	1.457	1.483	1.468	1.448	1.475	1.460	1.467	1.540	1.500
N_1-N_2	1.233	1.247	1.235	1.242	1.252	1.241	1.224	1.236	1.226
N_2-N_3	1.092	1.150	1.129	1.087	1.145	1.125	1.095	1.158	1.135
$O_1-H\cdots O_2$				108.56	109.81	109.41			
$O_2-H\cdots O_1$	112.55	118.52	116.57						
$C_4-C(H_2)-N_1$	114.22	113.66	113.61	107.71	107.84	107.78	115.77	114.88	114.39
$C(H_2)-N_1-N_2$	113.48	116.47	115.72	113.10	115.62	115.12	113.84	116.96	116.64
$N_1-N_2-N_3$	174.51	171.31	172.60	174.70	171.80	173.02	174.58	173.21	172.95
$O_1-C_1-C_2-O_2$	−0.09	0.07	0.03	0.00	0.00	0.00	−0.16	0.34	0.27
$O_3-C_4-C(H_2)-N_1$	175.05	170.09	173.36	180.00	180.00	180.00	168.75	79.42	70.93

Calculations in 6-311++G(d,p) basis set.

and cation, respectively; see Tables 3 and 4). This along with the B1LYP results (where differences are smaller, but bond lengths between proton and its acceptor are also shorter for neutral species), suggest that hydrogen bonding in neutral molecules is slightly stronger than in studied cations. A hydrogen bond is also slightly more linear (from 4 to 9°) in neutral form of chlorokojic and azidokojic acids than in its cationic counterparts.

The changes in bond lengths of the compounds studied here during protonation and deprotonation can be calculated. The theoretical methods used correctly describe structural changes among various species of studied ligands. This is seen for example in elongation of the O(1)–C(1) bond after protonation of the keto oxygen atom in the cation or shortening of the O(2)–C(2) bond after deprotonation of the O(2) atom in the anion.

The most stable structures of the kojic acid are presented in Fig. 5. The lowest energy structures are analogous to those obtained in this work for its derivatives. In order to show the influence of different substituents (–OH, –Cl or N_3) on the geometry of a molecule, we subtracted the respective bond lengths of kojic acid from other ligands (maltol, chlorokojic acid and azidokojic acid). These bond distances were obtained by the B1LYP method (Fig. 6). Calculated differences for all bonds (except $C_4-C(H_2)$ and $C(H_2)-X$, where X denotes –OH, –Cl or $-N_3$ groups) are rather insignificant as those obtained for kojic acid and maltol molecules. Among the kojic acids molecules, the differences are smaller between kojic acid and azidokojic acid than between kojic acid and chlorokojic acid. However, significant differences appear in the $C(H_2)-X$ bond lengths of different compounds. This bond varies strongly because of a different chemical nature of the X substituents, i.e. the hydroxyl group versus the chlorine atom or the azido group. On the other hand, differences in the $C_4-C(H_2)$ bond distance are smaller and the changes in chemical chcaracter of substituents do not affect the geometry of the remaining part of the molecule (i.e. hydroxypyranone unit).

4. Conclusions

The theoretical calculations performed in this work show that in the gas phase, the kojic acid derivatives studied exist

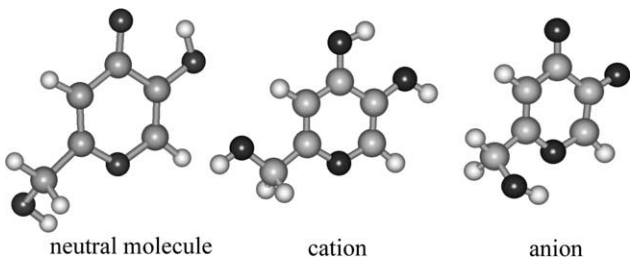

Fig. 5. The most stable structures of kojic acid species.

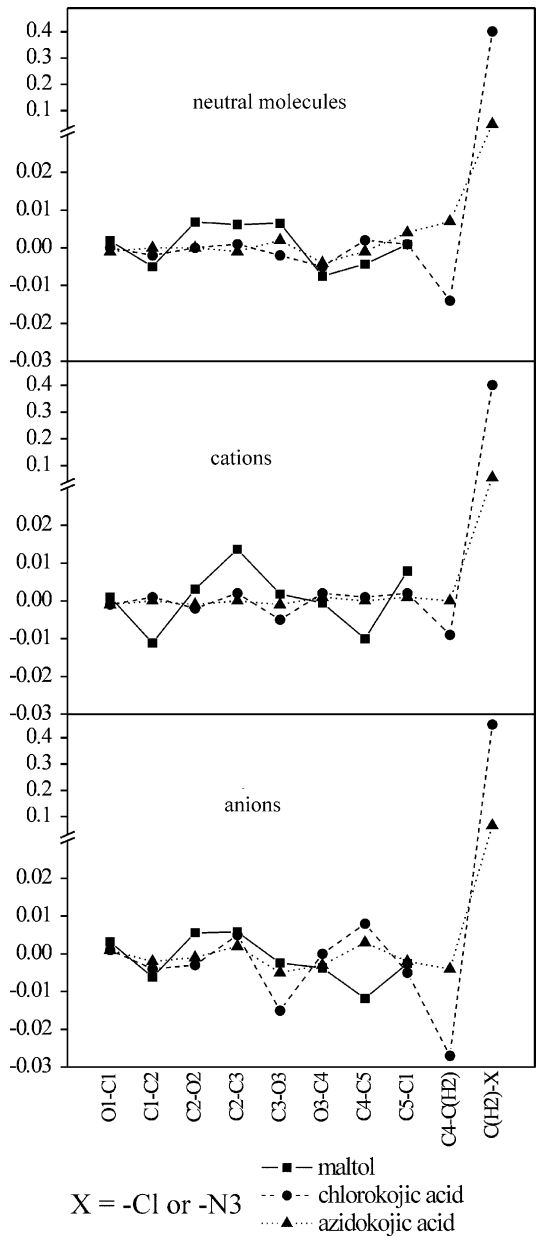

Fig. 6. Differences (Å) in selected bond lengths between kojic acid and other ligands. B1LYP calculations in 6-311++G(d,p) basis set.

in their enolic forms. According to the obtained data, protonation of the oxygen of the keto group is strongly favoured to stabilize the structure. These results are in good agreement with the data obtained previously for kojic acid and other hydroxypyrones. Among all the methods used in the calculations, only B1LYP always correlates well with the precise G2MP2 and CBS-4 calculations. Based on these data, we suggest that B1LYP is the best method for such calculations. In order to avoid the influence of the basis set on the obtained data, the 6-311++G(d,p) set was only used. As expected, the different theoretical methods provide different bond lengths; however, the observed changes are rather not significant. In addition, molecular angles do not depend significantly from the method used in calculations.

Heterocyclic rings in the lowest energy structures of all compounds studied, neutral and cationic species are planar. These structures are stabilized by the intramolecular hydrogen bonding. This bonding is stronger for neutral molecules than for proposed cations. Substitution of the hydroxyl group in kojic acid by the chlorine atom or the azido group does not affect substantially the structure of the hydroxypyranone unit.

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