Structure and properties of comenic acid and complex compounds of magnesium, copper (II) and zinc

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Abstract. The paper studies the features of complex formation of comenic acid with Mg²⁺, Cu²⁺ and Zn²⁺ ions. Besides, the paper presents the forms of binding of comenic acid with magnesium, copper (II) and zinc ions as well as the composition of complex compounds formed. Using IR and NMR (¹H, ¹³C) spectroscopy, there was studied the structure of compounds the geometry of which was confirmed by quantum chemical calculations.

1. Introduction

Bioinorganic chemistry is a science covering both inorganic chemistry and biology, which is attracting more and more attention of researchers – theorists and practitioners – since bioinorganic chemistry studies the structure of biological clusters, which include compounds of the so-called metals of life and bioligands, i.e. proteins, nucleic acids, vitamins, hormones and other biologically active compounds [1]. The results of the study in the field of bioinorganic chemistry find their practical application in the following fields: medicine, agriculture, food industry, environmental protection, etc.

Pharmaceutical clusters are being created in our country where the development of biologically active substances and the production of drugs based on them will be carried out. The task of pharmaceutical clusters is to increase the share of Russian drugs in the domestic market, since now the domestic pharmaceutical industry produces only 15–20 % of vital and necessary drugs.

Comenic (CA) (5-hydroxy-4-oxo-4H-pyran-2-carboxylic) acid is C₅H₂O₂(OH)COOH or C₆H₄O₅. There is an opinion [2] that the basis of the manifested biological activity of CA is the ability of the latter to form both simple salts and complex compounds by the metals of life. The goal of the work was to synthesize comenic acid compounds with magnesium, copper (II) and zinc, to study their physical and chemical properties and structural features both in solution and in solid state.

2. Methods and materials

Comenic acid (I) was used in the work (hereinafter, H₂A) obtained by the method of [2], the acid was isolated on an Altex-112 liquid chromatograph with an Ultra-sphere ODS column and an Optilab Multiger 902B differential detector.
Comenic acid at a room temperature is a white crystal, which turns yellow when exposed to air. It is sparingly soluble in water and insoluble in ethanol. Judging by the data of a derivatographic study in an argon atmosphere (Fig. 1), comenic acid does not have a melting point, but sublimes with decomposition at a temperature of 295–297 °C.

Comenic acid was identified by electronic, IR and \(^1\)H and \(^{13}\)C NMR spectra. The dissociation constants (pK\(^i\)) obtained by potentiometric titration of comenic acid against hydrochloric acid were 1.8 and 7.3, respectively.

The salts of magnesium, copper (II) and zinc used in the work, as well as other auxiliary reagents (acids, alkalis, solvents) had qualifications of not less than AR grade. Bidistillate was used to prepare aqueous solutions for spectral and potentiometric studies.

The synthesis of complex compounds of comenic acid was carried out by mixing 0.1 M hot (80 °C) solution of an acid and a metal salt (magnesium chloride, copper (II) chloride, zinc) in an equimolar ratio. The solution was sustained for one day. After that, it had been evaporated until a fine-cristalline precipitate of the obtained compound was formed. The crystals were filtered off, washed with cold alcohol and dried out in a desiccator over calcium chloride.

The isolated compounds were analyzed for the metal content by titration and/or atomic absorption method on ICP-AEC iCAP 6500 Spectrometer, and for the carbon and hydrogen contents on Carlo Erba CHN Elemental Analyzer.

Gross formulas: Mg(HA)\(\cdot\)H\(_2\)O: found %: C – 36.6; Mg – 12.8; [Cu(H\(_2\)O)\(_2\)HA] Cl: found %: C – 22.11; Cu – 20.42. Calculated %: C – 22.64; Cu – 19.9; [Zn (H\(_2\)O)\(_2\)HA]Cl: found %: C – 24.68; Zn – 23.41. Calculated %: C – 25.14, Zn – 22.39.

Thermogravimetric analysis of comenic acid and its compounds was carried out on a NETZSCH STA 409 PC/PG analyzer in argon atmosphere in the temperature range from the room temperature to 400 – 1000 °C with a temperature rise rate of 5–10 K/min.

IR spectra were recorded on a Vertex 70 IR Fourier spectrometer, NMR spectra on a JNM-ECA-400 spectrometer (400 MHz, Japan, JE02)

Quantum and chemical calculations were carried out by the semiempirical method MNDO/PM3 using HyperChem 8.0 software package.

3. Results

Being hydroxy-keto-carboxylic acid, comenic acid in an aqueous solution dissociates in two steps:

\[
\begin{align*}
\text{I} & \quad \text{II} \\
\begin{array}{c}
\text{HA}^+ \\
\text{H}_2\text{A}
\end{array}
\end{align*}
\]

where pK\(_1\) = 1.4 – 2.4 and pK\(_2\) = 7.4 – 7.8 [4-6], respectively.

Thus, the nature of epy interaction of metal ions with comenic acid can depend on the medium pH, which, in turn, is due to the dependence of the concentration of variously protonated forms of comenic acid on the pH of the medium. Although any of such form is capable of coordination with metal, their
different ratio makes it possible to assert different structure of the complexes formed. It should be borne in mind that the formation of a more stable complex compound with a deprotonated form of hydroxy acid (HA\(^-\) and A\(_2\)\(^-\)) shifts the equilibrium of dissociation reactions to the right. This, in turn, leads to the predominance of complexes with a deprotonated ligand at lower pH than it follows from the region where this form predominates in aqueous solution.

It can be assumed that completely deprotonated form of (A\(_2\)\(^-\)) comenic acid during complexation may not be available due to the occurrence of hydrolysis of metal ions at pH>6. However, chelation leads to a shift in equilibrium towards the deprotonated form, and in addition, some metal ions [5] are able to displace hydrogen ions.

Derivatograms of CA in an argon atmosphere (Fig. 1) showed two effects of sample mass change (TG), i.e. the removal of sorption water in the temperature range of 50–80 °C with a weight loss of the order of ≤0.3 % and pyrolysis at a temperature of 292–297 °C. Endo effects in the range of 273–274 °C, indicating the melting of CA were not found.

The pyrolysis of CA compounds is more complicated. According to thermogravimetric measurements in CA compounds with magnesium ion (Fig. 2) at temperatures up to 80–85 °C, sorption moisture evaporates with a mass loss of ≈1.3 %. Then, in the range of 153–193 °C for a monosubstituted and 225–231 °C for a bisubstituted compound, cleavage of the coordination water molecules included in the complex is observed.

The pyrolysis of a monosubstituted complex occurs in two stages in the range of 342–377 °C, and of a bisubstituted complex it occurs in one step at a temperature of 376–384 °C. In this case, the pyrolysis of bisubstituted complex is accompanied by an exo- effect, and for a monosubstituted one, the first stage at a temperature of 342 °C is endothermic, and the second one at a temperature of 377 °C is exothermic. Finally, in the range of 690–790 °C, the final carbonization of the samples occurs with a residual mass of 30.5 % for the monosubstituted and 33.1 % for disubstituted complex.

The data of IR spectra allow us to draw the following conclusions about the structure of CA and its complexes. Comenic acid in solid form is present in the form of dimers (characteristic absorption bands in the range of 3300–2600 (υOH) and 1740 (υC = O carboxyl group) cm\(^{-1}\)); 5-hydroxy group (υOH=3350 cm\(^{-1}\)) is connected by an intramolecular hydrogen bond with the keto group (υC=O=1650 cm\(^{-1}\)).

The monosubstituted complex is formed by the interaction of a metal ion with a carboxyl group (decrease in υC=O to 1620 cm\(^{-1}\)). The presence of υOH absorption bands in the region of 3620–3400 cm\(^{-1}\) suggests the linear structure of the monosubstituted complex.

![Figure 1. Thermal analysis curves of comenic acid with temperature rise rate of 10 K/min](image-url)
The disubstituted complex is formed by the substitution of hydrogen by lithium ion in the 5-hydroxy group and additional coordination with the carbonyl group of the γ-pyron. Consequently, an isle structure with additional coordination of metal ion with water molecules and oxygen atoms of the γ-pyron can be assumed. The absorption bands in the range of 480 and 820 cm\(^{-1}\) can be attributed to the absorption bands of M-O bonds. The isolated complexes of 1:1 composition according to IR spectroscopy probably have a linear structure with additional coordination at the oxygen atom of 5-hydroxy group.

In addition to protolytic equilibrium, CA is capable of forming various tautomeric forms. Therefore, CA in solution and solid form can exist in α-diketone form (III):

![Image of tautomeric forms](image)

Our study of aqueous solutions of CA by \(^1\)H and \(^{13}\)C NMR methods does not confirm the validity of the above diagram in solution. In the \(^1\)H NMR spectrum of an aqueous CA solution, there are only two signals of equal intensity from protons in positions (3) and (6). The Fig. 3 shows the dependence of chemical shifts on the pH value. The equality of the integral intensities of proton signals in positions (3) and (6) makes it possible to conclude that in an aqueous solution in the entire pH range studied, the tautomeric equilibrium is almost completely shifted toward form III.

\(^{13}\)C NMR data for some pH values were compared with data for a solution in DMSO-d6, in which the carboxyl group is slightly ionized. The shift of the signal of the carbon atom in position (7) to a weak field is also observed upon further deprotonation of the carboxyl group (pH 4.11). With a subsequent increase in pH, the deprotonation of hydroxo group of the pyrone ring begins (pH 6.89), which leads to stabilization of the electron system and an increase in the electron density at the carbon atom nucleus (7).
The shift of the signals of carbon atoms in position (4) and (5) corresponds to the deprotonation of hydroxyl group of the pyrone ring. In contrast to proton spectra, there is practically no change in the position of carbon signals in positions (3) and (6) with an increase in pH.

In solid state NMR spectroscopy, $^1$H MAS spectra of organic molecules at moderate rotation frequencies (up to 20 kHz) are usually poorly resolved due to the strong dipole-dipole interaction. Satisfactory resolution was also not obtained for comenic acid in the indicated range. Therefore, several techniques for suppressing the dipole-dipole interaction were tested. The wPMLG3 technique turned out to be optimal for the objects under study. The scaling factor was 0.597.

In the CA spectrum, two proton signals are observed at positions (3) and (6) (7.2 and 8.5 ppm, respectively), a wide signal at ~ 3 ppm (coordination and adsorbed H2O) and a signal of 12.5 ppm of carboxyl group, merging with a wide signal of the OH group of the pyrone ring. The position of the proton signals in positions (3) and (6) in the powder correlates with the values obtained for the aqueous solution at pH<1 (7.27 and 8.19 ppm, respectively). Thus, in the structure in the solid state, comenic acid does not significantly differ from similar derivatives of $\gamma$-pyrons. It consists of dimers formed due to two hydrogen bonds on carbonyl oxygen and hydroxyl of the pyrone ring, which is consistent with the data of IR spectroscopy. In turn, such dimers can crosslink to form sandwich structures in which the ketone groups of one molecule are bonded to the carboxyl group of another molecule, forming structures similar to cinnamic acid.

Theoretical study of the equilibrium geometry and an electronic structure of comenic acid and its compounds

![Chemical structure of comenic acid](image)

**Figure 3.** The dependence of chemical shifts of protons CA on the pH of the aqueous solution
To clarify the features of the geometric and electronic structure, as well as evaluate the enthalpy effects of chelation and the formation of salts and complex compounds of comenic acid, quantum chemical calculations were performed. The data obtained were compared with the results obtained previously [4]. The spatial numbering of atoms in the molecule of comenic acid compounds is shown in Fig. 4.

![Figure 4. Geometrical structure and numbering of atoms in a comenic acid molecule](image)

In the comenic acid compounds, the hydrogen atoms in the positions (14) and (15) are replaced by the corresponding ions of the studied metals.

According to the calculation results, the comenic acid molecule has a flat structure, which is facilitated by the system of conjugated double bonds $C^2-C^3$, $C^4-O^9$, $C^5-C^6$, and $C^7-O^{12}$. In the comenic acid molecule, the $O^{10}-H^{15}-O^9$ hydrogen bond (2.17 Å bond length) is confirmed, as was shown above, by the data of IR spectra. The effect of solvation is manifested in the broadening of the hydrogen bond to 2.21 Å.

In quantum chemical calculations, the molecule was optimized so that only the carboxyl group was assumed to be ionized, that is, the anion of comenic acid was considered singly charged (HA$^-$). This was also due to the main interest in the pH range 3–7, where this form is implemented in solution.

During ionization of the comenic acid molecule, as expected, the charges $q(O^{12})$, $q(O^{13})$ and $q(O^9)$ increase, and the charges $q(C^3)$ and $q(C^5)$ shift to the region of more negative values. In this case, the geometry of the carboxyl group changes, i.e. the conjugation of $C^7-O^{12}$ bond with the system of double bonds disappears, which leads to an extension of $C^2-C^3$ bond; on the contrary, the $C^7-O^{12}$ and $C^7-O^{13}$ bonds come closer together. A change in the bond lengths of the pyrone ring is also observed: lengthening of $O^1-C^2$, $C^2-C^3$ and $C^4-O^7$ bonds, $O^1-C^6$, $C^1-C^5$ bonds are shortened. When passing from a free acid to an anion, the intramolecular hydrogen bond $O^{10}-H^{15}...O^9$ is retained.

The calculation of complexation energies shows that taking into account additional corrections to the energies of solvated molecules is reflected in a 2.4–3.3 kcal/mol decrease in the absolute values of salt and complexation energies and a decrease of $\sim$6 kcal/mol in the absolute values of complex formation energies. As one would expect, upon the transition from the gas phase to the solvated one, the absolute values of the energy effects of complex formation are greatly reduced, nevertheless, these processes remain energetically favorable.

Thus, the authors of this article are in consensus with the work [5], where the results of quantum and chemical calculations illustrate exclusively the fundamental possibility of implementing the proposed mechanism of donor-acceptor binding. Although, based on the results obtained, no conclusions can be drawn about the stability of the resulting complexes in solution.

4. Conclusion

The features of complex formation of comenic acid with Mg$^{2+}$, Cu$^{2+}$, Zn$^{2+}$ ion were studied. The forms of binding of comenic acid and the composition of the resulting complex compounds were determined.

Using the methods of thermogravimetry, IR and NMR spectroscopy, there were studied the structures of CA and their complex compounds. It was shown that complexes of the composition 1:1 have a linear structure. The geometry of the compounds studied was confirmed by theoretical calculation by the semi-empirical method.
According to the IR spectra, the comenic acid in solid form is present in the form of dimers:
\[ \nu_{\text{OH}} = 3300–2600 \text{ cm}^{-1}, \nu_{\text{C}=\text{O}} = 1740 \text{ cm}^{-1}, \nu_{\text{OH}} = 3350 \text{ cm}^{-1}, \]
5-hydroxy group is linked by an intramolecular hydrogen bond to the keto group (\( \nu_{\text{C}=\text{O}} = 1650 \text{ cm}^{-1} \)). Monosubstituted complex compounds are formed due to the interaction of metal ions with the carboxyl and carbonyl groups (\( \nu_{\text{C}=\text{O}} = 1620 \text{ cm}^{-1} \)) and presumably have a linear structure. The disubstituted complexes are formed by the substitution of hydrogen ion in 5-hydroxy group and additional coordination with the carbonyl group of the \( \gamma \)-pyrone and have an isle structure.

According to the NMR spectra of \( ^1\text{H}, ^{13}\text{C} \) in solution and in the solid state, it can be concluded that upon the transition from a solid state to a solution, the geometric structure of comenic acid does not change significantly. The main changes observed in the NMR spectrum are due to the deprotonation of corresponding groups. The ketone group of comenic acid is involved in the structure of complexes in the solid state.

References
[1] Eichhorn G (ed) 1979 Inorganic biochemistry vol 1 (Moscow: Mir) 712 p
[2] Pirogova A N, Bukov N N, Panyushkin V T et al 2009 Complex compounds of lithium with comenic acid Chemistry and Chemical Technol. 52(12) 30–2
[3] Bukov N N, Dzhabrailova L Kh, Shamsutdinova M Kh and Panyushkin V T 2013 Synthesis and structure of complexes with comenic acid J. of General Chem. 85(6) 1053–5
[4] Rogachevsky I. V and Plakheeva I B 2006 Quantum and chemical studies of equilibrium geometry and electronic structure of the genus of derivatives of \( \gamma \)-pyrone J. of General Chem. 76(11) 1904–18
[5] Alekseev Yu T and Zhdanov Yu A 1998 Complexes of natural carbohydrates with metal cations The success of chem. 67(8) 723–44
[6] Derbenev A V, Krylov B V and Shurygin A Ya Effets of neconik and comenic acids on slow solium chennels of secondary nemrons Membr. Cell. Biol. Zoo. 13(3) 379–87
[7] Panova T I 2004 The mechanism of interaction of comenic acid with the opoid receptor 1(1) 128–32
[8] Volynkin V A, Pirogov D I and Panyushkin V T 2011 Study of comenic acid and its salts with Li⁺ and Na⁺ by NMR in solution and solid state J. Struct. Chem. 52(5) 922–5