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D-(-)-Quinic acid: an efficient physiological metal ion ligand

Melita Menelaou[1#*], C. Mateescu[2], A. Salifoglou[1]

[1] *Department of Chemical Engineering, Aristotle University of Thessaloniki, Thessaloniki 54124, Greece.*
[2] *Faculty of Food Processing Technology, Banat University of Agricultural Sciences and Veterinary Medicine, Timisoara, Romania*

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Abstract

The in-depth investigation of the pH-dependent synthesis between a (hydroxyl)carboxylate ligand (D-(-)-quinic acid) and transition divalent and/or trivalent metal ions (M(II,III)) led to the isolation and characterization of new binary compounds in the solid state and in solution. The new M(II,III)-(hydroxy)carboxylate species were synthesized in aqueous solution under various molar ratios and different bases. The compounds were characterized by elemental analysis, spectroscopic techniques (FT-IR, UV-Vis, EPR), magnetic studies, and X-ray crystallography. Potentiometric titrations were also carried out in order to investigate the species distribution as a function of pH. Each new species was shown to contain M(II,III) ions in an octahedral environment. The physicochemical profiles of all species, in the solid state and in solution, earmark the importance of aqueous structural speciation, and project a) chemical reactivity pathways in each binary M(II,III)-quinate system, involving various soluble M(II,III) forms, and b) clearly emphasize the versatile nature of quinic acid.

Keywords: D-(-)-Quinic acid, potentiometric titrations, x-ray crystallography, metal ions

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1. Introduction

D(-)-quinic acid, 1α,3α,4α,5β-tetrahydroxy-1-cyclohexane carboxylic acid, is a representative physiological (hydroxy)carboxylate ligand (Figure 1). As a natural low molecular mass binder it can be found in plants, such as cinchona bark, carrots and tobacco leaves [1,2]. Therefore, it is a molecule that is found widely in plants and there it is encountered as a precursor to shikimic acid [3]. The latter molecule is also involved in the synthesis of essential amino acids. Hence, the presence of quinic acid appears to be vital to cellular physiology [4], with the organic acid capable of binding metal ions in biological fluids. Over the last decades, great attention has been paid to the study of the interactions of physiological (hydroxy)carboxylate ligands such as citric acid, malic acid and lactic acid with various metal ions (e.g. transition metal ions) in biological fluids.

Moreover, molecules known as cyclic polyols (such as D(-)-quinic acid) can act as calcium carriers in biological systems while the interest in the employment of quinic acid stems from its use as a versatile chiral starting material in the synthesis of new pharmaceuticals [5]. In this end, D-(-)-quinic acid contains two very important features that render it an efficient molecule and an efficient metal ion binder. It contains: (a) a carboxylate moiety known to promote binding, (b) alcoholic moieties, one of which is in the α- position to the carboxylate group, and (c) three alcoholic groups relevant to polyol functionalities.

Metal ions present in biological systems are mobilized efficiently through interactions with organic molecules-ligands capable of: (a) coordinating them, and (b) solubilizing them in biological fluids.

Corresponding author: *e-mail:* melitacy@yahoo.com

These organic molecules include both low (e.g. (hydroxy)carboxylates and amino acids) and high molecular mass (e.g. proteins) cellular targets. Therefore, metal ions such as Co(II), Mn(II), Fe(III), Ni(II), Zn(II) are aptly coordinated to such ligands and enter further ternary interactions with biological molecules. Therefore, coordination to the aforementioned metal ions promotes: (a) solubilization and (b) contributes to metal bioavailability, leading to metallo(bio)chemical interactions exemplifying in each case the role of the specific metal ion in cellular environments.

Therefore, the exploration of the aqueous chemistry of divalent and/or trivalent transition metal ions with α-(hydroxy)carboxylate binders, like D-(-)-quinic acid, is expected to: (a) shed light into the structural speciation of each aqueous binary system, and (b) provide possible cellular biosynthetic pathways relating the interaction of each metal ion with a biologically important molecule. To this end, the paucity of well-characterised M(II,III)-D-(-)-quinic acid derivative species has prompted us to study in depth the pH-specific synthetic chemistry of several binary systems. To this end, the herein work focuses on: (a) the aqueous solution speciation studies on several binary M(II,III)-quinate systems in order to shed light into the different chemical aspects arising from varying metal-ligand stoichiometries and pH values, and (b) the pH-dependent synthesis, isolation, and structural characterization of M(II,III)-D-(-)-quinate species.

2. Materials and methods

All experiments were carried out in aqueous media under aerobic conditions. Nanopure quality water was used for all reactions. $Co(NO_3)_2 \cdot 6H_2O$ was purchased from BDH Chemicals, Ltd. $Co(CH_3COO)_2 \cdot 4H_2O$ was purchased from RP Carlo Erba, and D-(-)-quinic acid, $FeCl_3 \cdot 6H_2O$, $Fe(NO_3)_3 \cdot 9H_2O$ and $CoCl_2 \cdot 6H_2O$ were purchased from Fluka. Ammonia was purchased from RP Carlo Erba, and ethanol was purchased from PA Panreac. KOH and NaOH were supplied by Fluka. $MnCl_2 \cdot 4H_2O$, $NiCl_2 \cdot 6H_2O$ and $Zn(CH_3COO)_2 \cdot 2H_2O$ were purchased from Merck.

3. Results and Discussion

The aqueous synthetic chemistry of several binary systems M(II,III)-{D-(-)-Quinic acid} were investigated under specific stoichiometric and pH conditions. As a result, new species were isolated in crystalline form suitable for X-ray crystallographic analysis and were further characterized with several physicochemical techniques (elemental analysis, FT-IR spectroscopy, UV-Vis spectroscopy, TGA, cyclic voltammetry, etc). Overall, the quinate ligand plays the role of a physiological ligand acting as an efficient metal ion chelator, since it employs different possible types of anchors available in its structure and effectively formulates the coordination environment around Mn(II), Co(II), Fe(III), Ni(II) and Zn(II).

The syntheses of compounds were carried out in aqueous media and nanopure water was used for all reactions. In each aforementioned binary studied system, the pH value was very crucial for the isolation of the final crystalline materials suitable for further characterization. Moreover, the molecular stoichiometry and the well-defined experimental conditions (method of crystallization, addition of solvent, etc) were also very crucial for the isolation of the final compounds.

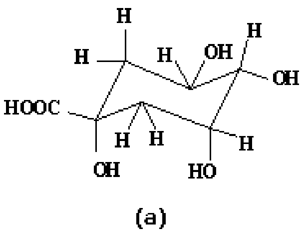
Elemental analysis pointed to the molecular formulation of each compound isolated under different experimental conditions. Further X-ray crystallographic investigations confirmed the analytical formulations. The FT-IR spectra for all isolated compounds in each binary system were recorded in KBr and reflected the presence of vibrationally active carboxylate groups. In all cases, the frequencies of the bands of the antisymmetric $\nu_{as}(COO^-)$ and symmetric $\nu_s(COO^-)$ stretching vibrations were shifted to lower values compared to the corresponding vibrations in free D-(-)-quinic acid, thereby indicating a change in the coordination status of the carboxylates in the quinate ligand. In addition, the frequency difference, $\Delta(\nu_{as}(COO^-)-\nu_s(COO^-))$ [6] was greater than 200 cm^{-1}, indicating the presence of deprotonated carboxylate groups coordinated to the metal ions in a monodentate fashion.

Concurrently, potentiometric titrations of the free ligand D-(-)-quinic acid, as well as M(II,IIII) with D-(-)-quinic acid (M(II,III) = Mn(II), Fe(III), Co(II), Ni(II) and Zn(II)) in various molar ratios were carried out. Some of the derived titration curves, experimental and calculated ones, are shown in Figure 2. The titration curves for each aforementioned binary system were evaluated with different potential speciation models.

Nevertheless, the best fit arising among the experimental and calculated titration curves for the aforementioned binary M(II,III)–quinic acid systems, was obtained by considering various species for each binary system. In addition, various complexes including (oligo)nuclear species, or variably protonated and deprotonated species were rejected or accepted by the computer program (PSEQUAD) during the computational process for each binary system. Therefore, the species emerging from the speciation distribution of each binary system are in line with the species synthesized and isolated in the solid state. Also, ESI-MS spectroscopy was crucial in establishing the presence of various species.

X-Ray crystallography was instrumental in revealing the three dimensional structure of each investigated molecule. In all isolated compounds, D-(-)-quinic acid is deprotonated through the carboxylic acid binding site, while the α-hydroxy group can retains or parts with its proton depending on the different experimental conditions (e.g. temperature). In contrast to that, the employment of the terminal alcoholic moieties in the coordination mode of quinate ligand is again based on various experimental conditions as well as the nature of the metal ions. In addition, in all isolated compounds, quinate binds the aforementioned metal ions through formation of five-membered metallacyclic rings and therefore the arising species are stable. The formation of the five membered metallacyclic rings has already been shown to be present in other M(II,III)-(hydroxyl)carboxylate species. Therefore, the mode of binding of the quinate ligand to the divalent and/or trivalent metal ions is variable.

Beyond analytical, spectroscopic and crystallographic techniques, magnetic susceptibility studies and EPR studies on the various compounds were also carried out to provide valuable information on the nature of each species both in the solid state and in solution.



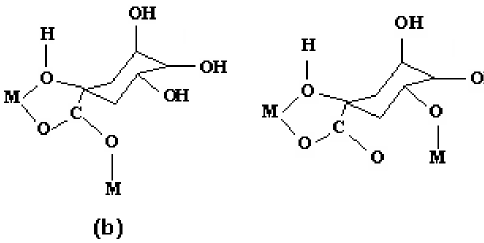


Figure 1. (**a**) The chemical structure of D-(-)-quinic acid, and (**b**) various coordination modes of quinic acid with M(II,III) ions

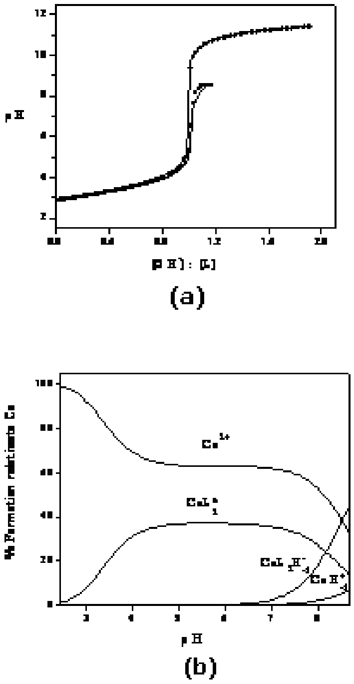


Figure 2. (**a**) Potentiometric titration curves of free quinic acid and Co(II)–quinic acid and (**b**) Speciation curves for species forming in the binary Co(II)–quinic acid system

Conclusions

In the aforementioned work, the aqueous synthetic chemistry of divalent and trivalent transition metal ions toward D-(-)-quinic acid was investigated in-depth, in an effort to delineate the interactions of the transition metal ions with a (hydroxy)carboxylate molecule in aqueous solutions leading to isolable crystalline materials. Therefore, synthetic reactions were carried out between the metal ions and D-(-)-quinic acid in various experimental conditions. The synthetic efforts led to the isolation of discrete soluble and potentially bioavailable species under variable stoichiometries, pH values and different bases.

Concurrently, the aqueous speciation studies in each binary M(II,III)-quinate system contribute to the understanding of the nature of various species forming as a function of pH and molar stoichiometry, and provide a direct correlation of the physicochemical aspects of the proposed species with the structure and properties of the species synthesized and isolated in the solid state. Therefore, the solid-state structures and solution physicochemical properties of the arisen species along with the species suggested in the aqueous speciation models, point out the notion that D-(-)-quinic acid is a molecule capable of coordinating to various divalent and trivalent metal ions entering physiologically important binary and ternary interactions, while concurrently leading to discrete species with well-defined chemical reactivity.

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[#]Current address: *Department of Inorganic Chemistry, Faculty of Chemistry, University of Barcelona, Diagonal 647, E-08028 Barcelona, Spain*

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