Synthesis, Spectroscopic and Structural Characterization of the First Mononuclear, Water Soluble Iron−Citrate Complex, $(NH_4)_5Fe(C_6H_4O_7)_2 \cdot 2H_2O$

M. Matzapetakis,[†] C. P. Raptopoulou,[‡] A. Tsohos,[‡]
V. Papaefthymiou,[§] N. Moon,[||] and A. Salifoglou*[,†]

Department of Chemistry, University of Crete
Heraklion 71409, Greece
Institute of Materials Science, NRCPS "Demokritos"
Aghia Paraskevi 15310, Attiki, Greece
Department of Physics, University of Ioannina
Ioannina 45110, Greece
Biophysics Research Division, University of Michigan
Ann Arbor, Michigan 48109

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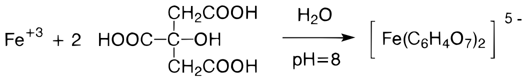
The omnipresence of citric acid, a tricarboxylic acid, in nature has been abundantly established through biological and chemical studies over the years.[1] Its ubiquitous involvement in the active sites of bacterial metalloenzymic systems including aconitase[2] and the *nif*V$^-$ dinitrogenase[3] has been amply demonstrated. Citric acid is also found in human blood plasma[4] at a concentration of ∼0.1 mM and is considered to be a preeminent, small molecular weight binder of a number of metals, including iron. The postulate that, upon binding, citric acid enhances the mobilization and bioavailability[5a,b] and promotes absorption of dietary non-heme iron,[5c,d] has attracted our research interest. Iron−citrate complexes, however, have for a long time eluded crystallization from aqueous solutions due to their high solubility.[6a] To date there exist a limited number of structurally characterized polymeric iron(II)−[6b] and dimeric iron(III)−citrate[7] complexes. The paucity of metabolically relevant, well-characterized, mononuclear iron−citrate complexes, projecting their potential for uptake and release by proteins and enzymes, has prompted us to pursue the aqueous coordination chemistry of iron with citric acid. Herein, we report on the synthesis, isolation, and characterization of the first mononuclear anionic iron(III)−citrate complex.

Reaction between iron(III) nitrate and citric acid with a 1:2 molar ratio in aqueous solution at pH∼8 (eq 1) led to the isolation of yellow crystalline material consistent with the molecular formula $(NH_4)_5Fe(C_6H_4O_7)_2 \cdot 2H_2O$ (**1**).[8] The X-ray structural determination[9] of that material confirmed the above analytical formulation and revealed its three-dimensional structure (Figure 1). In the centrosymmetric structure of **1**, iron(III) is octahedrally coordinated to two citrate ligands. Both citrate ligands are tetraionized, and as such they utilize one terminal as well as the central carboxylate and hydroxyl moieties to bind in a monodentate fashion, thus satisfying the coordination requirements of the octahedral iron(III). A similar type of coordination has also been seen in the mononuclear complexes of $(NH_4)_3[Ga(cit)_2] \cdot 4H_2O$ and $(pyH)_2[Cr(cit)_2] \cdot 4H_2O$.[10] The third, terminal, ionized carboxylate group is not coordinated to the metal and resides away from it (4.342(3) Å for the nearest O(7) atom of the COO$^-$ group). Distortion of the observed geometry around the iron is manifested as elongation of the octahedron along the O(1)−Fe−O(1) direction, rendering in effect the remainder of the ligands equatorial. Thus, the Fe−O(1) distance of 2.068(2) Å is longer than the central carboxylate and central hydroxyl distances of 2.008(2) and 1.958(2) Å, respectively. The Fe(III)−O distances in **1** compare favorably with those in the crystal structure of $[Fe(III)_2(C_6H_4O_7)_2(H_2O)_2]^{2-}$ (**2**) (range:1.987(3)−2.038(3))[7] and are in the range of those observed (2.085−2.178(2) Å) in [Fe-



$$Fe^{+3} + 2\ HOOC{-}\underset{\underset{CH_2COOH}{|}}{\overset{\overset{CH_2COOH}{|}}{C}}{-}OH \xrightarrow[pH=8]{H_2O} \left[Fe(C_6H_4O_7)_2 \right]^{5-} \qquad (1)$$

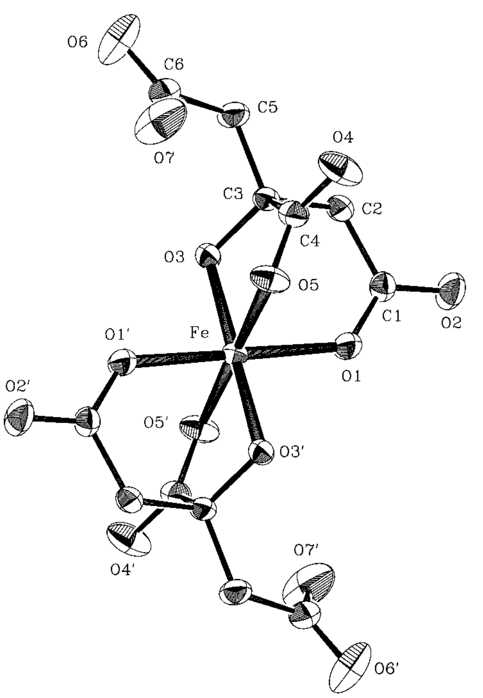


Figure 1. Structure of the $[Fe(C_6H_4O_7)_2]^{5-}$ anion with the atom-labeling scheme in **1**. Thermal ellipsoids are drawn by ORTEP and represent 50% probability surfaces. Selected interatomic distances (Å) and angles (deg): Fe−O(1) 2.068(2) Å, Fe−O(3) 1.953(2) Å, Fe−O(5) 2.008(2) Å, O(3)−Fe−O(5) 81.86(7)°, O(1)−Fe−O(3) 88.17(7)°, O(1)−Fe−O(5) 88.69(7)°.

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* To whom correspondence should be addressed.

[†] University of Crete.

[‡] Institute of Materials Science.

[§] University of Ioannina.

[||] University of Michigan.

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(8) $Fe(NO_3)_3 \cdot 9H_3O$ and citric acid in a 1:2 molar ratio were reacted in an aqueous solution at pH ≈ 8. Precipitation of analytically pure yellow crystalline material was effected with ethanol (yield: 50%). Satisfactory elemental analysis has been obtained for compound **1**.

(9) Crystal Data: Space Group, $P\bar{1}$, $a = 9.669(7)$ Å, $b = 9.714$ Å, $c = 7.265(5)$ Å, $\alpha = 90.93(2)°$, $\beta = 105.69(2)°$, $\gamma = 118.58(2)°$; $Z = 1$; GOF^2 = 1.079, $T = 298$ K; $R(1981$ reflections $I > 2\sigma(I)) = 0.0304$. Single-crystal X-ray diffraction data were collected at room temperature on a Nicolet $P2_1$ four-circle diffractometer using Mo $K\alpha$ radiation. Detailed crystallographic information has been deposited as Supporting Information.

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$(H_2O)_6][Fe(C_6H_5O_7)(H_2O)]_2 \cdot 2H_2O$ (**3**),[6b] $(NH_4)_3[Ga(cit)_2] \cdot 4H_2O$ (1.890(2)−2.054(2) Å) and $(pyH)_2[Cr(cit)_2] \cdot 4H_2O$ (1.965(1)−1.987(2) Å).[10] In the crystal lattice, the penta-anionic complex of **1** is counterbalanced by NH_4^+ cations. Water molecules of crystallization are in contact with both anion and cation of **1** creating an extensive network of hydrogen bonds throughout the lattice, similar to those observed in **3** as well as other metal−citrate complexes isolated from aqueous solutions.[11]

Typical for the FT-infrared spectrum of **1** are the well resolved strong and sharp carbonyl bands for the asymmetric stretching vibrations $\nu_{as}(COO^-)$ between 1626 and 1586 cm^{-1}. The corresponding symmetric stretches $\nu_s(COO^-)$ appear between 1436 and 1372 cm^{-1}. All of the carbonyl absorptions are shifted to lower frequencies with respect to citric acid. The difference between the symmetric and asymmetric stretches, $\Delta(\nu_{as}(COO^-) - \nu_s(COO^-))$[12] is of the order of 200 cm^{-1}, indicating that the carboxylate groups are either free or coordinated to the metal in a monodentate fashion, in agreement with the observed X-ray crystal structure of **1**. The electronic spectrum of **1** (200−800 nm) in aqueous solution at pH = 8.0 shows an ill-defined shoulder around 450 nm ($\epsilon \approx 30$) riding on a continuously rising absorbance into the UV.

The EPR spectrum[13] of the complex in H_2O exhibits a $g = 4.3$ signal consistent with the presence of a high-spin rhombic Fe^{3+} species. The Mössbauer spectrum[14a] displays a broad asymmetric doublet with an isomer shift (δ) of 0.38(3) mm/s and a quadrupole splitting of 1.80 (3) mm/s. These parameters are within the range of those observed for high spin octahedral Fe^{3+}−O (carboxylate/oxygen) containing species.[15] The magnetic susceptibility data[14b] ($\chi_M T = 4.65$ emu mol^{-1} K at 300 K) are consistent with the presence of a spin $S = {}^5/_2$, isotropic $g = 2.02$, and a small zero-field splitting $D = 0.11$ cm^{-1}.

In light of numerous metal ion−citrate solution studies[16] pertaining to charge, nuclearity, stoichiometry, pH dependability, stability, and relative concentration of species in aqueous solutions, **1** or a lower charged analogue (e.g., $Fe(Cit)_2^{3-}$) represents a reasonable structural model for a mononuclear Fe−citrate species with general chemical features not unlike those expected to exist in a biological milieu (e.g., human plasma). It would not be unreasonable for such complexes to affect the mobilization and promote absorption of iron to biological sites (in parallel with transferrin), thus contributing to iron homeostasis. The synthesis and characterization of pertinent soluble forms of iron effected by citrate are currently under way in our lab.

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Supporting Information Available: Tables of X-ray crystal structure refinement data, positional and thermal parameters, magnetics, and EPR for $(NH_4)_5Fe(C_6H_4O_7)_2 \cdot 2H_2O$ (11 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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[13] The EPR spectrum was recorded in a pH ≈ 8.4 solution at 9.174 GHz, 10 mW, 82 K.

[14] (a) The Mössbauer spectrum was recorded at room temperature and parameters are reported vs metallic Fe. (b) Magnetic susceptibility data were collected on powdered samples of **1** with a Quantum Design SQUID susceptometer in the 1.8−300 K temperature range. In $\chi_M T$ vs T, $\chi_M T$ initially falls slightly from 4.65 emu mol^{-1} K ($\mu_{eff} = 6.10\ \mu_B$) at 300 K to 4.40 emu mol^{-1} K ($\mu_{eff} = 5.94\ \mu_B$) at 14 K, then steeply to 3.62 emu mol^{-1} K ($\mu_{eff} = 5.38\ \mu_B$) at 1.8 K.

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