Inorg. Chem. **2003**, *42*, 2531–2537

Synthesis and Spectroscopic and Structural Studies of a New Cadmium(II)–Citrate Aqueous Complex. Potential Relevance to Cadmium(II)–Citrate Speciation and Links to Cadmium Toxicity

M. Dakanali,[†] E. T. Kefalas,[†] C. P. Raptopoulou,[‡] A. Terzis,[‡] T. Mavromoustakos,[§] and A. Salifoglou*[,†]

Department of Chemistry, University of Crete, Heraklion 71409, Greece, Institute of Materials Science, NCSR "Demokritos", 15310 Aghia Paraskevi, Attiki, Greece, and National Hellenic Research Foundation, Institute of Organic and Pharmaceutical Chemistry, Athens 11635, Greece

Received August 6, 2002

The presence of cadmium in the environment undoubtedly contributes to an increased risk of exposure and ultimate toxic influence on humans. In an effort to comprehend the chemical and biological interactions of Cd(II) with physiological ligands, like citric acid, we explored the requisite aqueous chemistry, which afforded the first aqueous Cd(II)–citrate complex $[Cd(C_6H_6O_7)(H_2O)]_n$ (**1**). Compound **1** was characterized by elemental analysis, and spectroscopically by FT-IR and ^{113}Cd MAS NMR. Compound **1** crystallizes in the orthorhombic space group $P2_12_12_1$, with $a = 6.166(2)$ Å, $b = 10.508(3)$ Å, $c = 13.599(5)$ Å, $V = 881.2(5)$ Å^3, and $Z = 4$. The X-ray structure of **1** reveals the presence of octahedral Cd(II) ions bound to citrate ligands in a molecular crystal lattice. Citrate acts as a tridentate binder promoting coordination to one Cd(II) through the central alcoholic moiety, one terminal carboxylate group, and the central carboxylate group. In addition, the central carboxylate binds to three Cd(II) ions. Specifically, one of the oxygens of the central carboxylate serves as a bridge to two neighboring Cd(II) ions, while the other oxygen binds to a third Cd(II). A bound water molecule completes the coordination requirements of Cd(II). ^{113}Cd MAS NMR studies project the spectroscopic signature of the nature of the coordination environment around Cd(II) in **1**, thus corroborating the X-ray findings. Collectively, the data at hand are in line with past solution studies. The latter predict that other similar low molecular mass Cd(II)–citrate complexes may exist in the acidic pH region, thus influencing the uptake of cadmium by living (micro)organisms, their ability to metabolize organic substrates, and possibly Cd(II) toxicity.

Introduction

Cadmium belongs to a category of heavy metal ions (cadmium, mercury, lead) that have increasingly attracted research attention over the years, due to their toxic manifestations in the environment and the various organisms living in it, including plants[1] and humans.[2] Cd(II) is found predominantly in minerals and soils in the earth's lithosphere.[2,3] Albeit nonessential in the human physiology, Cd(II) is largely associated with Zn(II), in competition with which a number of its toxic effects are believed to arise.[4] As a toxic metal, Cd(II) is absorbed by the liver, ultimately finding its way to the kidney, the critical organ from the toxicity point of view.[5] Among some of the diseases attributed to Cd(II) toxicity are proteinuria, aminoaciduria, cadmium-induced renal tubular dysfunction, and cadmium-induced creatinuria.[6] The exact mechanism(s) by which cadmium toxicity arises, however multifaceted, remain(s) unknown.

* To whom correspondence should be addressed. E-mail: salif@chemistry.uoc.gr. Phone: +30-2810-393-652. Fax: +30-2810-393-601.
[†] University of Crete.
[‡] NCSR "Demokritos". E-mail: craptop@ims.demokritos.gr (C.P.R.).
[§] Institute of Organic and Pharmaceutical Chemistry. E-mail: tmavro@eie.gr.

(1) Bingham, F. T.; Peryea, F. J.; Jarrell, W. M. In *Metal Ions in Biology*; Siegel, H., Ed.; Marcel Dekker: New York, 1986; Vol. 20, pp 119−134.
(2) (a) Fergusson, J. E. In *The Heavy Elements: Chemistry, Environmental Impact and Health Effects*; Pergamon Press: Oxford, 1990. (b) Hammond, P. B.; Foulkes, E. C. In *Metal Ions in Biology*; Siegel, H., Ed.; Marcel Dekker: New York, 1986; Vol. 20, pp 177−182.
(3) (a) Page, A. L.; Bingham, F. T.; Chang, A. C. In *Effect of Heavy Metal Pollution on Plants*; Lepp, N. W., Ed.; Applied Science Publishers: London, 1981; pp 77−109. (b) Page, A. L.; Bingham, F. T. *Residue Rev.* **1973**, *48*, 1.
(4) Martin, R. B. In *Metal Ions in Biology*; Siegel, H., Ed.; Marcel Dekker: New York, 1986; Vol. 20, pp 21−65.
(5) Bevan, C.; Kinne-Saffran, E.; Foulkes, E. C.; Kinne, R. K. H. *Toxicol. Appl. Pharmacol.* **1989**, *101*, 461−469.

10.1021/ic0205029 CCC: $25.00
Published on Web 03/27/2003

In recent decades, anthropogenic activities have contributed significantly to increasing quantities of Cd(II) in the atmosphere, hydrosphere, and lithosphere of the planet,[7] further raising the stakes of increasing Cd(II) solubility and mobility in the environment. With the latter property being essential in eliciting (bio)chemical interactions from living beings, Cd(II) has invaded soils, plants, and, eventually through the food chain, humans themselves. Direct human contact through professional exposure (e.g., mining, work in battery manufacturing plants) and Cd(II)-laden water drinking has also been shown to impart severe pathophysiological aberrations, like itai-itai disease intimately associated with osteomalacia and bone decalcification.[8]

Of the physiological metal ion binders capable of promoting aqueous interactions with Cd(II), the tricarboxylic citric acid appears to be a very prevalent ligand.[9] It exists in human plasma at a concentration of ~0.1 mM, it is part of the citric acid cycle (Krebs cycle),[10] and it is involved in metalloenzyme systems such as aconitase and NifV$^-$ nitrogenase.[11] It has been elaborated frequently that citrate binding to transition metal ions increases their solubility and ultimate bioavailability. In a number of reports, on the other hand, it has been suggested that complexed forms of Cd(II) with citrate are not transported into the bacterial cells and are consequently not degraded by bacteria.[12] Therefore, citric acid appears to be a very good target for Cd(II), and their interactions are of genuine chemical interest with potential biological ramifications. Solution studies carried out in the past on the Cd(II)−citrate system had proposed various species of 1:1 (Cd(II)/citrate) stoichiometry, with no further insight on their nature and properties.[13] To date, no information exists on structurally characterized low molecular mass cadmium−citrate complexes in aqueous solutions. To that end, we have initiated efforts targeting the aqueous synthetic chemistry between citrate and Cd(II). Herein, we report on the synthesis, isolation, and X-ray structural and ^{113}Cd MAS NMR spectroscopic characterization of the first aqueous cadmium−citrate complex that, under the experimental conditions employed, might bear relevance to biologically relevant Cd(II) and its role in toxicity.

Experimental Section

Materials and Methods. All manipulations were carried out in the open air. $Cd(NO_3)_2 \cdot 4H_2O$ and ammonia (25% solution) were purchased from Fluka. $Cd(ClO_4)_2 \cdot xH_2O$ was purchased from Aldrich. Nano-pure quality water was used for all reactions run.

Physical Measurements. FT-IR measurements were taken on a 1760X FT-IR spectrometer from Perkin-Elmer, using KBr pellets. Chemical elemental analyses were performed by Quantitative Technologies, Inc.

The high-resolution solid-state ^{113}Cd magic angle spinning (MAS) NMR spectra were measured at 88.741 MHz on a Bruker MSL 400 NMR spectrometer, capable of high power decoupling. The experiments were carried out at different spinning rates in order to (a) set the ^{113}Cd chemical shift for the reference sample ($Cd(ClO_4)_2 \cdot xH_2O$) and (b) observe the ^{113}Cd chemical shift for **1** in comparison to that of the reference. High power decoupling was used with a 90° pulse of 5 μs at ambient temperature (25 °C). Each solid-state spectrum was a result of the accumulation of 400 scans. Decoupling and triggering of 20 μs was used. The acquisition time was 40 ms and the relaxation delay 8 s.

Synthesis of $[Cd(C_6H_6O_7)(H_2O)]_n$ (1). Quantities of cadmium nitrate, $Cd(NO_3)_2 \cdot 4H_2O$, (0.30 g, 1.0 mmol) and citric acid (0.37 g, 2.0 mmol) were placed in a 25 mL round-bottom flask and dissolved in 2 mL of water. The reaction mixture was then stirred under heating at 50 °C for 2 days. Subsequently, the clear solution was taken to dryness with a rotary evaporator. The derived residue was redissolved in 2 mL of H_2O. The pH was adjusted to ~2 with an aqueous solution of ammonia (1:1 dilution of 25% ammonia in water). The resulting solution was placed in the refrigerator (4 °C). On the following days, ethanol was added periodically (total volume ~2 mL) and led to the formation of a colorless crystalline material a week later. The crystalline product was isolated by filtration and dried in vacuo. Yield 0.12 g (40%). Anal. Calcd for **1**, $[Cd(C_6H_6O_7)(H_2O)]_n$ ($CdC_6H_8O_8$, MW = 320.52): C, 22.46; H, 2.49. Found: C, 22.51; H, 2.54.

X-ray Crystallography

Crystal Structure Determination. X-ray quality crystals of compound **1** were grown from water−ethanol mixtures. A single crystal with dimensions 0.30 × 0.35 × 0.40 mm^3 was mounted on a Crystal Logic dual-goniometer diffractometer using graphite monochromated Mo Kα radiation. Unit cell dimensions were determined and refined by using the angular settings of 25 automatically centered reflections in the range $11° < 2\theta < 23°$. Relevant crystallographic data appear in Table 1. Intensity data were measured by using a $\theta-2\theta$ scan. Three standard reflections were monitored every 97 reflections, over the course of data collection. They showed less than 3% variation and no decay. Lorentz, polarization, and ψ-scan absorption corrections were applied using Crystal Logic software. Further crystallographic details for **1**: $2\theta_{max} = 50°$; scan speed 4.5°/min; scan range 2.3 + $\alpha_1\alpha_2$ separation; $[\Delta/\sigma]_{max} = 0.254$; $[\Delta\rho]_{max}/[\Delta\rho]_{min} = 0.488/-1.037$ e/Å^3; R/R_w (for all data), 0.0286/0.0727.

The structure of complex **1** was solved by direct methods using SHELXS-86[14] and refined by full-matrix least-squares techniques

(6) Sato, K.; Kusaka, Y.; Okada, K. *Toxicol. Lett.* **1995**, *80*, 161−165.
(7) Sposito, G. In *Metal Ions in Biology*; Siegel, H., Ed.; Marcel Dekker: New York, 1986; Vol. 20, pp 1−20.
(8) (a) Kobayashi, J. In *Toxicity of Heavy Metals in The Environment, Part 1*; Oeme, F. W., Ed.; Marcel Dekker: New York, 1978; pp 199−260. (b) Friberg, L.; Piscator, M.; Nordberg, G. F.; Kjellstträm, T. In *Cadmium in the Environment*, 2nd ed.; CRC Press: Cleveland, OH, 1974; pp 101−114.
(9) (a) Martin, R. B. *Inorg. Biochem.* **1986**, *28*, 181−187. (b) Glusker, J. P. *Acc. Chem. Res.* **1980**, *13*, 345−352.
(10) (a) Hamilton, E. M. N.; Gropper, S. A. S. In *The Biochemistry of Human Nutrition*; West Publishing Company: St. Paul, MN, 1987; p 117. (b) Lippard, S. J.; Berg, J. M. In *Principles of Bioinorganic Chemistry*; University Science Books: Mill Valley, CA, 1994; pp 349−378.
(11) (a) Liang, J.; Madden, M.; Shah, V. K.; Burris, R. H. *Biochemistry* **1990**, *29*, 8577−8581. (b) Beinert, H. *FASEB J.* **1990**, *4*, 2483−2491. (c) Beinert, H.; Kennedy, M. C. *Eur. J. Biochem.* **1989**, *186*, 5−15.
(12) (a) Joshi-Toppe, G.; Francis, A. J. *J. Bacteriol.* **1995**, *177*, 1989−1993. (b) Brynhildsen, L.; Rosswall, T. *Appl. Environ. Microbiol.* **1989**, *55*, 1375−1379.
(13) (a) Bottari, E. *Ann. Chim.* **1975**, *65*, 593−607. (b) Campi, E.; Ostacoli, G.; Meirone, M.; Saini, G. *J. Inorg. Nucl. Chem.* **1964**, *26*, 553−564. (c) Li, N. C.; Lindenbaum, A.; White, J. M. *J. Inorg. Nucl. Chem.* **1959**, *12*, 122−128. (d) Treumann, W. B.; Ferris, L. M. *J. Am. Chem. Soc.* **1958**, *80*, 5050−5052.
(14) Sheldrick, G. M. *SHELXS-86: Structure Solving Program*; University of Göttingen: Göttingen, Germany, 1986.

Table 1. Summary of Crystal, Intensity Collection, and Refinement Data for $[Cd(C_6H_6O_7)(H_2O)]_n$ (**1**)

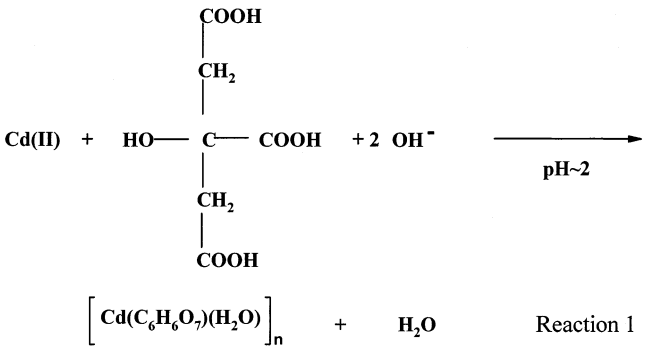
empirical formula	$C_6H_8O_8Cd$
fw	320.52
T	298 K
wavelength	Mo K_α 0.71073 Å
space group	$P2_12_12_1$
a	6.166(2) Å
b	10.508(3) Å
c	13.599(5) Å
V	881.2(5) Å^3
Z	4
D_{calcd}/D_{obsd}	2.416/2.42 Mg m^{-3}
abs coeff (μ)	2.503 mm^{-1}
reflns collected	3397
indept reflns	1556 [R(int) = 0.0605]
range of *h*, *k*, *l*	−7 to 0 −12 to 12 −16 to 16
data/restraints/ params	1556/0/168
GOF on F^2	1.134
obsd reflns [$I > 2\sigma(I)$]	1554
R^a	0.0286^b
$R_w{}^a$	0.0727^b

[a] R values are based on F; R_w values are based on F^2. $R = \sum||F_o| - |F_c||/\sum(|F_o|)$, $R_w = \sqrt{\sum[w(F_o{}^2-F_c{}^2)^2]/\sum[w(F_o{}^2)^2]}$. [b] For 1554 reflections with $I > 2\sigma(I)$.

on F^2 by using SHELXL-93.[15] All non-H atoms were refined anisotropically. All H atoms were located by difference maps and were refined isotropically.

Synthesis

The synthesis of complex **1** was expediently carried out in aqueous solutions. The ratio of cadmium to citrate was essential in driving the reaction to completion and aiding in the retrieval of the product from the reaction mixture. Thus, initially, a 1:2 metal-to-ligand molar stoichiometry was employed, which successfully led to the isolation of complex **1**. Attempts to run the reaction with a metal-to-ligand ratio of 1:1 were equally successful (reaction 1), yet the yield of the reaction was lower than that of the 1:2 ratio.



Elemental analysis of the crystalline material recovered from the reaction mixture suggested the formulation $Cd(C_6H_6O_7)(H_2O)$. The absence of any ammonium cation was also suggested by elemental analysis, lending credence to the fact that pH might have played a key role in establishing conditions of lowest solubility for the species to be isolated from solution upon addition of ethanol. The isolated crystalline complex **1** is not soluble either in water or organic solvents such as dimethylformamide (DMF), dimethyl sulfoxide (DMSO), chloroform, acetonitrile, and methanol, even after strong heating.

(15) Sheldrick, G. M. *SHELXL-93: Structure Refinement Program*; University of Göttingen: Göttingen, Germany, 1993.

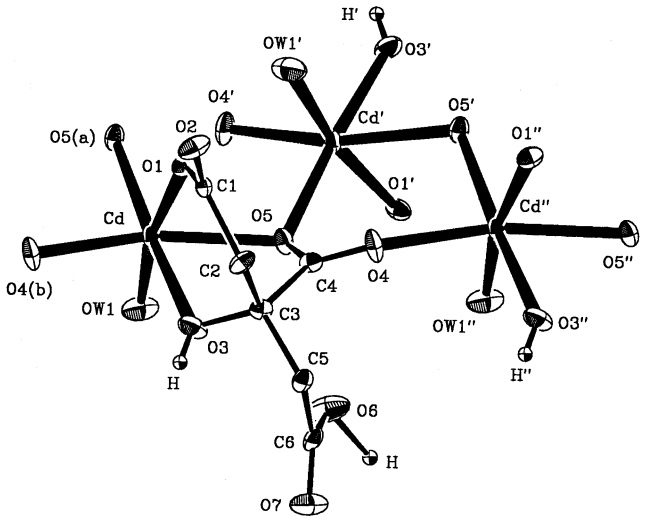


Figure 1. Structure of **1** with the atom-labeling scheme. Thermal ellipsoids are drawn by ORTEP and represent 40% probability surfaces. Symmetry operations: primed atoms (′), 0.5 + *x*, 0.5 − *y*, −*z*; double primed atoms (″), 1 + *x*, *y*, *z*; (a), −0.5 + *x*, 0.5 − *y*, −*z*; (b), −1 + *x*, *y*, *z*.

Table 2. Bond Lengths [Å] and Angles [deg] for $[Cd(C_6H_6O_7)(H_2O)]_n$ (**1**)[a]

Cd−O(1)	2.318(3)	O(5)′−Cd−O(3)	175.5(1)
Cd−O(3)	2.231(3)	O(5)′−Cd−OW1	89.0(1)
Cd−O(5)	2.354(3)	O(3)−Cd−OW1	95.1(1)
Cd−O(5)′	2.225(3)	O(5)′−Cd−O(4)″	89.2(1)
Cd−OW1	2.261(4)	O(3)−Cd−O(4)″	92.5(1)
Cd−O(4)″	2.262(3)	OW1−Cd−O(4)″	93.0(2)
Cd‴−O(4)	2.262(3)	O(5)′−Cd−O(1)	95.1(1)
Cd‴−O(5)	2.225(3)	O(3)−Cd−O(1)	80.6(1)
O(1)−C(1)	1.272(5)	OW1−Cd−O(1)	170.0(1)
O(3)−C(3)	1.425(5)	O(4)″−Cd−O(1)	96.2(1)
O(4)−C(4)	1.233(6)	O(5)′−Cd−O(5)	107.9(1)
O(5)−C(4)	1.288(5)	O(3)−Cd−O(5)	70.1(1)
C(1)−O(2)	1.243(5)	OW1−Cd−O(5)	92.3(1)
C(1)−C(2)	1.520(6)	O(4)″−Cd−O(5)	162.3(1)
C(2)−C(3)	1.528(6)	O(1)−Cd−O(5)	77.8(1)
C(3)−C(5)	1.527(6)		
C(3)−C(4)	1.544(5)		
C(5)−C(6)	1.503(6)		
C(6)−O(7)	1.191(6)		
C(6)−O(6)	1.319(7)		

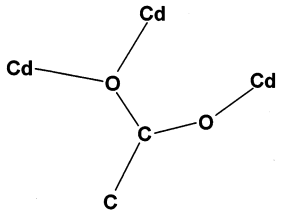
[a] Symmetry transformations used to generate equivalent atoms: (′) $x - 1/2, -y + 1/2, -z$; (″) $x - 1, y, z$; (‴) $x + 1, y, z$; (⁗) $x + 1/2, -y + 1/2, -z$.

X-ray Crystallographic Structure

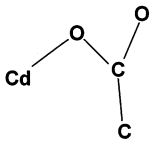
The structure of complex **1** emerges from a molecular type of crystal lattice. The ORTEP diagram for complex **1** is shown in Figure 1. A list of selected bond distances and angles in **1** are given in Table 2. Each Cd(II) exists in an octahedral environment, surrounded by citrate ligands and a water molecule. Specifically, the six apices of the oxygen coordination octahedron are occupied as follows: One citrate ligand employs both the central alcoholic and carboxylate oxygen atoms as well as one of its terminal carboxylate oxygens to bind Cd(II), thus occupying three coordination

positions. Two additional citrate ligands from two adjacently located octahedral Cd(II) ions are reaching out and coordinate to cadmium through the oxygen atoms of their respective central carboxylate groups, thus occupying two coordination positions. The remaining coordination site is occupied by a water molecule. The second terminal carboxylate group of the citrate ligand is protonated and does not participate in any coordination. It remains free, moving away from the Cd(II) sites.

A structural feature worth paying attention to is the mode of citrate coordination to Cd(II). In particular, the citrate central carboxylate group uses one of its oxygen atoms to bind to two Cd(II) ions in an η^1:μ_2 fashion, thus acting as a bridge. Concurrently, the second oxygen atom of the central carboxylate group binds to a third Cd(II) in an η^1 fashion (mode I). This mode of binding has been previously observed in $Cu^I(OOCCH_3)$[16] and differs from that encountered in complex $[Pb(C_6H_6O_7)]_n \cdot nH_2O$,[17] where one of the central carboxylate oxygen atoms binds to two Pb(II) ions in an η^1:μ_2 fashion, while the second carboxylate oxygen stands 3.271(1) Å away from another Pb(II) ion, essentially noncoordinated. In the same molecule, the citrate terminal carboxylate group binds in a bidentate fashion to yet another Pb(II) ion, thus differing from the monodentate binding of the corresponding terminal carboxylate group in **1** (mode II). Consequently, two different carboxylate binding modes for citrate exist within the same molecule in **1**. The central alcoholic group binding is the only common point in the binding mode of the citrate ligand in **1** and $[Pb(C_6H_6O_7)]_n \cdot nH_2O$. Interestingly, the citrate ligand is doubly deprotonated in both cases of the aforementioned complexes. The protonated sites are the central alcoholic group and one of the terminal carboxylates.



mode I



mode II

The Cd−O bond distances are in the range from 2.225(3) to 2.354(3) Å, very similar to corresponding distances in other cadmium octahedral complexes including $\{Cd_2(C_4H_4O_6)_2(H_2O)] \cdot 3H_2O\}_n$ (2.188(3)−2.425(3) Å),[18] the octahedral sites in $Cd_2(C_3H_2O_4)_2(H_2O)_4$ (2.225(4)−2.296(4) Å),[19] $[Cd(C_3H_6NO_2)_2] \cdot 3H_2O$ (2.296(4)−2.326(5) Å),[20] $Cd(C_4H_2O_4) \cdot 2H_2O$ (2.224(5)−2.521(5) Å),[21] and the octahedral site in cadmium maleate (2.226(5)−2.317(5) Å).[22] Overall, the citrate ligand plays the role of a tridentate metal chelator, participating in the octahedral environment around Cd(II) and joining abutting Cd(II) ions in the lattice.

Table 3. Hydrogen Bonds in $[Cd(C_6H_6O_7)(H_2O)]_n$ (**1**)

interaction	D···A (Å)	H···A (Å)	D−H···A (deg)	symmetry operation
O3−HO3···O2	2.589	1.912	174.8	$2 - x, -0.5 + y, 0.5 - z$
O6−HO6···O2	2.645	1.458	129.9	$2.5 - x, -y, -0.5 + z$
Ow1−Hw1A···O1	2.807	1.777	170.5	$-0.5 + x, 0.5 - y, -z$
Ow1−Hw1B−O7	2.712	1.879	166.6	$-0.5 + x, -0.5 - y, -z$

The angles around Cd(II) within the tetragonal plane of the octahedron range from 80.6(1)° to 95.1(1)°, whereas those involving the apical oxygen atoms range from 70.1(1)° to 107.9(1)°. The angle variability observed here appears to be similar to that seen in the case of other metal ion citrate complexes containing Cu(II) (89.7(1)−90.3(1)° and 73.8(1)−106.2(1)°),[23] Zn(II) (88.7(1)−91.3(1)° and 75.1(1)−104.9(1)°),[24] and Mn(II) (87.01(6)−92.99(6)° and 72.47(5)−107.53(5)°).[25] Considering the citrate moiety bound to the metal ion, the carbon atoms C(1), C(2), C(3), C(5), and C(6) of the citrate backbone are coplanar with the largest standard deviation 0.075 Å for C(5). The O(3)−C(3)−C(4) plane of the central carboxylate group is rotated 5.4° out of the O(4)−C(4)−O(5) plane. The terminal carboxylate planes O(1)−C(1)−O(2) and O(6)−C(6)−O(7) are rotated 2.9° and 34.8°, respectively, from the C(1), C(2), C(3), C(5), C(6) plane. The angle between the terminal carboxylate planes O(1)−C(1)−O(2) and O(6)−C(6)−O(7) is 32.1°. The torsion angle H−O(3)−C(3)−C(4) for the hydrogen of the alcoholic group is 144.3°. The aforementioned values are similar to those observed in other metal citrate complexes such as Co(II).[26]

Hydrogen bonding interactions are a dominant feature of the crystal structure of **1**. Specifically, the coordinated water molecule and the protonated central alcoholic and the terminal carboxylate groups of citrate participate in the formation of hydrogen bonds (Table 3). The resulting extensive hydrogen bonding network very likely contributes to the stability of the crystal lattice in **1**.

FT-IR Spectroscopy

The FT-IR spectrum of **1** exhibits strong absorptions for the carbonyls of the carboxylate groups in both the antisymmetric and symmetric vibration regions. The antisymmetric stretching vibrations $\nu_{as}(COO^-)$ extend in the range from 1620 to 1540 cm^{-1}, whereas the corresponding symmetric stretches $\nu_s(COO^-)$ appear in the range from 1430 to 1380

(16) (a) Mounts, R. D.; Ogura, T.; Fernando, Q. *Inorg. Chem.* **1974**, *13*, 802−805. (b) Deacon, G. B.; Philips, R. J. *Coord. Chem. Rev.* **1980**, *33*, 227−250.
(17) Kourgiantakis, M.; Matzapetakis, M.; Raptopoulou, C. P.; Terzis, A.; Salifoglou, A. *Inorg. Chim. Acta* **2000**, *297*, 134−138.
(18) Gonzalez-Silgo, C.; Gonzalez-Platas, J.; Rutz-Perez, C.; Lopez, T.; Torres, M. E. *Acta Crystallogr.* **1999**, *C55*, 710−712.
(19) Chung, K. H.; Hong, E.; Do, Y.; Moon, C. H. *J. Chem. Soc., Chem. Commun.* **1995**, 2333−2334.
(20) Demaret, P. A.; Abraham, E. F. *Acta Crystallogr.* **1987**, *C43*, 2067−2069.
(21) Hempel, A.; Hull, S. E. *Acta Crystallogr.* **1979**, *B35*, 2215−2216.
(22) Post, M. L.; Trotter, J. *J. Chem. Soc., Dalton Trans.* **1974**, 674−678.
(23) Bott, S. C.; Sagatys, D. S.; Lynch, D. E.; Smith, G.; Kennard, C. H. L.; Mak, T. C. W. *Aust. J. Chem.* **1991**, *44*, 1495−1498.
(24) Swanson, R.; Ilsley, W. H.; Stanislowski, A. G. *J. Inorg. Biochem.* **1983**, *18*, 187−194.
(25) Matzapetakis, M.; Karligiano, N.; Bino, A.; Dakanali, M.; Raptopoulou, C. P.; Tangoulis, V.; Terzis, A.; Giapintzakis, J.; Salifoglou, A. *Inorg. Chem.* **2000**, *39*, 4044−4051.
(26) Matzapetakis, M.; Dakanali, M.; Raptopoulou, C. P.; Tangoulis, V.; Terzis, A.; Moon, N.; Giapintzakis, J.; Salifoglou, A. *JBIC, J. Biol. Inorg. Chem.* **2000**, *5*, 469−474.

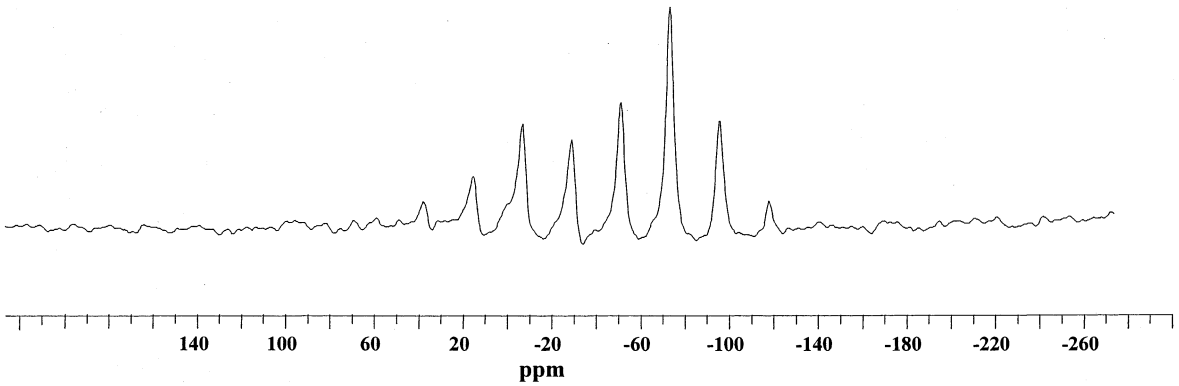


Figure 2. ^{113}Cd MAS NMR spectrum of complex **1** in the solid state.

cm^{-1}. The frequencies for the carbonyl stretches in **1** are shifted to lower values in comparison to those of the free citric acid. From that point of view, they indicate a change in the vibrational status of the citrate anion upon coordination to the metal ion. Similar trends in the frequencies of the carboxylate carbonyls have also been observed in the FT-IR spectra of citrate complexes with other metal ions.[27]

NMR Spectroscopy

The ^{113}Cd metal nuclide has a spin of $^1/_2$. Its employment as a probe of structural features in Cd(II) compounds, through solid-state MAS NMR spectroscopy, has been quite useful.[28] On the basis of such information, a reasonable interpretation of chemical shifts of Cd(II)-containing species in biological media can be projected. In this context, the ^{113}Cd MAS NMR spectrum of **1** was obtained, with $Cd(ClO_4)_2 \cdot xH_2O$ as the reference (0.0 ppm). Positive chemical shift values (δ) are taken to correspond to lower shielding in comparison to the reference. The spectrum of **1** exhibits a main resonance around −73.8 ppm with a number of sidebands (Figure 2). The identity of the main band was confirmed by running experiments with a variable spinning frequency. The resonance, the chemical shift of which did not change with frequency, was the one attributed to the main band. On the basis of literature reports, several patterns have emerged defining distinct regions in the ^{113}Cd spectrum for six-, seven-, and eight-coordinated Cd(II) ions.[29,19] Consistent with the aforementioned information, oxygen-rich octahedral Cd(II) species exhibit ^{113}Cd resonances in the fairly wide range from δ 140 to −70 ppm. The resonance observed at $\delta \sim$ −73.8 ppm for **1** certainly falls close to this range and indicates the presence of octahedral Cd(II) sites surrounded by oxygen-containing ligands. The picture presented by ^{113}Cd NMR corroborates further the X-ray structural data for an octahedral Cd(II) site, with oxygens (citrate, H_2O) bound to it, as in complex **1**.

Discussion

Aqueous Chemistry of Cd(II) in the Presence of the Physiological Ligand Citric Acid. The toxic manifestations arising from the action of heavy metal ions, such as Cd(II), in biological fluids are inexplicably linked with the requisite chemistry that develops as a result of the interactions with both low molecular mass as well as high molecular mass biomolecules. Citrate, a low molecular mass binder, certainly promotes interactions with metal ions including Cd(II), owing to its multidentate binding properties arising from its three carboxylate and one alcoholic moieties. The incipient chemistry between the two partners rests on both the Cd(II)/citrate stoichiometry as well as the pH of the solution at which the chemistry develops. In the present work, Cd(II) exhibited a facile reactivity toward citrate. At the low solution pH 2, citrate was bound to cadmium as a doubly deprotonated tridentate binder, concurrently utilizing one of the terminal carboxylates as well as its central carboxylate and alcoholic groups. Both oxygens of the central carboxylate group participated in coordination, in an $\eta^1{:}\mu^2$ and η^1 fashion, respectively, each promoting bond formation with adjacently located cadmium ions.

Fulfillment of the coordination requirements of Cd(II) by three citrates, which belong to three abutting Cd(II) assemblies projecting their carboxylates into its immediate coordination sphere, establishes a close arrangement between neighboring metal ions. As a result, the latter octahedral ions position themselves in a zigzag fashion (see Supporting Information), extending their array infinitely in one dimension inside the crystal lattice. In the so formed arrays, the distances between the cadmium ions are indicative of the spatial requirements of the citrate ligands which, serving as bridges, essentially dictate the formation of the metal ion arrangement. The Cd···Cd distance in **1** is 3.795(1) Å, much longer than that observed in the metal (2.980 Å). In juxtaposition to the present structure, a similar lead−citrate complex $[Pb(C_6H_6O_7)]_n \cdot nH_2O$, with a molecular type of crystal lattice as well, consists of dinuclear rhombic units of Pb_2O_2 extending to one dimension through interactions promoted by citrate ligands.

Further, it appears that in complex **1**, due to the steric requirements imposed by citrates on the formation of its crystal lattice, one coordination site is not occupied by citrate carboxylates. That allows a solvent molecule of water to enter

(27) (a) Matzapetakis, M.; Raptopoulou, C. P.; Tsohos, A.; Papefthymiou, B.; Moon, N.; Salifoglou, A. *J. Am. Chem. Soc.* **1998**, *120*, 13266−13267. (b) Matzapetakis, M.; Raptopoulou, C. P.; Terzis, A.; Lakatos, A.; Kiss, T.; Salifoglou, A. *Inorg. Chem.* **1999**, *38*, 618−619.

(28) Mennitt, P. G.; Shatlock, M. P.; Bartuska, B. J.; Maciel, G. E. *J. Phys. Chem.* **1981**, *85*, 2087−2091.

(29) (a) Honkonen, R. S.; Ellis, P. D. *J. Am. Chem. Soc.* **1984**, *106*, 5488−5497. (b) Honkonen, R. S.; Doty, F. W.; Ellis, P. D. *J. Am. Chem. Soc.* **1983**, *105*, 4163−4168. (c) Rodesiler, P. F.; Amma, E. L. *J. Chem. Soc., Chem. Commun.* **1982**, 182−184.

the coordination sphere of Cd(II) and ultimately bind to it. That coordinated water along with the central alcoholic and terminal carboxylates of citrate participate in hydrogen bonding interactions most likely enhancing the stability of the arising lattice.

^{113}Cd NMR Spectroscopy and Structural Considerations in 1. The advent of high resolution ^{113}Cd NMR spectroscopy[30] has been of tremendous impact in the study of Cd(II)-containing biomolecules. The ^{113}Cd nucleus has been used successfully in probing the metalloprotein sites containing Cd(II). Among the examples of such molecules are metallothioneins,[31] troponin C,[32] calmodulin,[33] and others.[34] Key to these studies is the chemical shift of ^{113}Cd, which is particularly sensitive to the nature of the donor atom(s) in the ligand(s) bound to the metal ion, and to the resulting coordination number and geometry. In this sense, the successful investigations of the S_2 site in concanavalin A[35] and the EF site of parvalbumin,[36] both of them containing oxygen donors, by ^{113}Cd NMR have been of paramount importance.

The same NMR technique, however, is equally applicable to the investigation of interactions of Cd(II) with physiological substrates (e.g., citrate), especially so when such interactions could be responsible for that metal's interjection in metabolic functions and the manifestation of toxic effects. Given that high-resolution ^{113}Cd NMR spectroscopy could be employed in both the solid state and solution, application of the technique has targeted the potential correlation of the ^{113}Cd chemical shifts in the solid state, and thus the structure of the Cd(II) site investigated, with the chemical shifts of the same species in solution.[37] Highly significant to this approach is the availability of crystalline species, for which X-ray structural data are available. The latter could corroborate the ^{113}Cd MAS NMR spectroscopic data and support further correlation with chemical shift data in solution (although solution and solid-state ^{113}Cd chemical shifts may differ!). To this end, the Cd(II) coordination environment in complex **1** was probed by ^{113}Cd MAS NMR. The data suggest the presence of an octahedral Cd(II) species surrounded by oxygen donor atoms. This conclusion was supported by literature data on ^{113}Cd MAS NMR chemical shifts,[38] accumulated over the years for Cd(II) sites of varying coordination number and type of ligands. Further proof on the aforementioned contention was provided by the available three-dimensional X-ray structure for complex **1**.

The acquired data along with the derived results signify the importance of ^{113}Cd MAS NMR spectroscopy in probing the structural features of Cd(II) species, bearing physiologically important low molecular mass, carboxylate-containing molecules, like citrate. Hence, to the degree that interactions between such partners may lead to isolable species with high solubility in the wide spectrum of pH values, this approach is bound to contribute significantly to the elucidation of the nature of Cd(II) species in aqueous media.[39] The latter conclusion assumes further importance in view of the known toxicity of Cd(II) in biology.

Potential Links to Toxicity and Relevance to Cd(II)−Citrate Speciation. The chemistry developed herein reflects the ability of citric acid to solubilize effectively toxic heavy metal ions through complex formation at very low pH. It is likely, therefore, that conditions in the environment, where acidification promotes toxic metal ion solubilization, may influence Cd(II) complexation chemistry with organic acid ligands, like citrate. As a result, vital functions such as, e.g., plant uptake of organic substrates or metals for key metabolic processes could be affected. In the case of Cd(II), citrate complexation has been invoked to account for the inability of bacterial organisms to (a) internalize and/or (b) metabolize citrate in the presence of Cd(II), thus emphasizing inhibitory effects of Cd(II) on the physiology of organism(s).[40,12]

Solution studies carried out on the cadmium−citrate system, in the pH range from 1 to 9, have suggested the presence of mononuclear species, representing complexes of Cd(II) with citrate bearing a 1:1 stoichiometry.[13] Specifically, complexes of the type $[Cd(C_6H_5O_7)]^-$ and $[Cd(C_6H_6O_7)]^0$ are among those proposed to exist in solution with varying degrees of stability. For the species $[Cd(C_6H_6O_7)]^0$, the aforementioned studies and their results lend credence to the formulation of the cadmium−citrate complex isolated herein. Two main facts appear to be in line with this contention: (a) the 1:1 metal-to-ligand stoichiometry present and (b) the doubly deprotonated citrate anion, which further acts as a ligand to the Cd(II) ion. The second point appears to be the one most relevant to the case of synthetic complex **1**, since the X-ray analysis not only confirms the protonation state of the citrate ligand employed in the potentiometric solution studies but also unravels the mode of coordination of the ligand adopted upon binding to the metal ion. In this respect, the spectroscopic and structural characterizations of complex **1** aid significantly in comprehending the nature of species previously suggested to exist in solution between Cd(II) and citrate. Moreover, it would not be unreasonable to envisage that a pH dependent chemistry directed toward the Cd(II)/

(30) (a) Maciel, G. M. *Science (Washington, D.C.)* **1984**, *226*, 282−288. (b) Yannoni, C. S. *Acc. Chem. Res.* **1982**, *15*, 201−208.
(31) Boulanger, Y.; Armitage, I. M.; Miklossy, K.-A.; Winge, D. R. *J. Biol. Chem.* **1982**, *257*, 13717−13719.
(32) Teleman, O.; Drakenberg, T.; Forsen, S.; Thulin, E. *Eur. J. Biochem.* **1983**, *134*, 453−457.
(33) Andersson, A.; Forsen, S.; Thulin, E.; Vogel, H. J. *Biochemistry* **1983**, *22*, 2309−2313.
(34) (a) Bailey, D. B.; Ellis, P. D.; Fee, J. A. *Biochemistry* **1980**, *19*, 591−596. (b) Evelhoch, J. L.; Bocian, D. F.; Sudmeier, J. L. *Biochemistry* **1981**, *20*, 4951−4954. (c) Uiterkamp, A. J.; Armitage, I. M.; Coleman, J. E. *J. Biol. Chem.* **1980**, *255*, 3911−3917.
(35) Bailey, D. B.; Ellis, P. D.; Cardin, A. D.; Behnke, W. D. *J. Am. Chem. Soc.* **1978**, *100*, 5236−5237.
(36) Cave, A.; Parello, J.; Drakenberg, T.; Thulin, E.; Lindman, B. *FEBS Lett.* **1979**, *100*, 148−152.
(37) (a) Cheung, T. T. P.; Worthington, L. E.; Murphy, L. D.; Murphy, P. D.; Gerstein, B. C. *J. Magn. Reson.* **1980**, *41*, 158−168. (b) Griffith, E. A. H.; Amma, E. L. *J. Chem. Soc., Chem. Commun.* **1979**, 1013−1014. (c) Charles, N. G.; Griffith, E. A. H.; Rodesiler, P. F.; Amma, E. L. *Inorg. Chem.* **1983**, *22*, 2717−2723.
(38) Griffith, E. A. H.; Charles, N. G.; Lewinski, K.; Amma, E. L.; Rodesiler, P. F. *Inorg. Chem.* **1987**, *26*, 3983−3989 and references therein.
(39) Chung, K. H.; Moon, C. H. *J. Chem. Soc., Dalton Trans.* **1996**, 75−78.
(40) Francis, A. J.; Dodge, C. J.; Gillow, J. B. *Nature (London)* **1992**, *356*, 140−142.

citrate synthetic system, under the conditions investigated here, could lead to further deprotonation of the citrate ligand, rendering it triply deprotonated and thus relevant to the formulated complex $[Cd(C_6H_5O_7)]^-$, also proposed to exist in solution. Consequently, other Cd(II)−citrate species may also exist in solution that currently elude isolation and characterization. The synthesis, isolation, and characterization of such species are currently being pursued in our labs.

Acknowledgment. This work was supported with funds provided by the Department of Chemistry, University of Crete, Greece (E.L.K.E. N.1186). We are also grateful to the Agricultural Bank of Greece (ATE) and Mr. John Boutaris for financial support to C.P.R. and A.T.

Supporting Information Available: Tables of X-ray crystal structure refinement data, positional and thermal parameters for $[Cd(C_6H_6O_7)(H_2O)]_n$ (**1**), and ORTEP of the extended structure of **1**. The material is available free of charge via Internet at http://pubs.acs.org.

IC0205029