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pH-Specific Aqueous Synthetic Chemistry in the Binary Cadmium(II)–Citrate System. Gaining Insight into Cadmium(II)–Citrate Speciation with Relevance to Cadmium Toxicity

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The involvement of Cd(II) in toxic manifestations and pathological aberrations in lower and higher organisms entails interactions with low and high molecular mass biological targets. To understand the relevant chemistry in aqueous media, we have launched pH-dependent synthetic efforts targeting Cd(II) with the physiological ligand citric acid. Reactions of Cd(II) with citric acid upon the addition of NaOH at pH 2.5 and pyridine at pH 3 and the addition of ammonia at pH ∼7 led to the new complexes $[Cd_3(C_6H_5O_7)_2(H_2O)_5]\cdot H_2O$ (**1**) and $(NH_4)[Cd(C_6H_5O_7)(H_2O)]\cdot H_2O$ (**2**), respectively. Complexes **1** and **2** were characterized by elemental analysis, spectroscopy (FT-IR and NMR), and X-ray crystallography. Complex **1** crystallizes in the monoclinic space group $P2_1/n$, with $a = 18.035(6)$ Å, $b = 10.279(4)$ Å, $c = 12.565(4)$ Å, $\beta = 109.02(1)°$, $V = 2202(2)$ Å^3, and $Z = 4$. Complex **2** crystallizes in the monoclinic space group $P2_1$, with $a = 9.686(4)$ Å, $b = 8.484(4)$ Å, $c = 7.035(3)$ Å, $\beta = 110.28(1)°$, $V = 542.3(4)$ Å^3, and $Z = 2$. Complex **1** is a trinuclear assembly with the citrate ligand securing a stable metallacyclic ring around one Cd(II), with the terminal carboxylates spanning into the coordination sphere of two nearby Cd(II) ions. Complex **2** contains mononuclear units of Cd(II) bound by citrate in an overall coordination number of 8. In both **1** and **2**, the participating citrates exhibit three different modes of coordination, thus projecting a distinct yet variable aqueous structural chemistry of Cd(II) with physiological substrates. The pH-dependent chemistry and its apparent structural diversity validate past solution speciation studies, projecting the existence of mononuclear species such as the one in the anion of **2**. The spectroscopic and structural properties of **2** emphasize the significance of the information emerging from synthetic studies that otherwise would not have been revealed through conventional solution studies, while concurrently shedding light onto the linkage of the requisite chemistry with the potential biological toxicity of Cd(II).

Introduction

Heavy metal ions have long been established as toxic pollutants of the environment, affecting vital processes in the physiology of plants[1] and humans.[2] Their toxic influence throughout the living kingdom has been under extensive scrutiny with the sole purpose of averting catastrophic events at the microscopic level that temporally endanger the integrity

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(1) (a) Fergusson, J. E. In *The Heavy Elements: Chemistry, Environmental Impact and Health Effects*; Pergamon Press: Oxford, U. K., 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.
(2) 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.

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and survival of organisms. Cadmium is one of those heavy metals, for which clear toxicity profiles have been established for a number of biological systems at the cellular level. It is an element found in ample quantities in the form of minerals in the lithosphere of the planet.[2,3] It has been found to be a significant toxicant, which is thought to exert toxic effects on humans in tight competitive association with Zn(II).[4] Cd(II) is not bioessential. It is absorbed by organs such as the liver and ends up being accumulated in the kidneys, with the latter being an important biotarget.[5] It is believed that Cd(II) accumulation in the human body over extended periods of time contributes to the toxic manifestation of the observed physiological aberrations in humans. Among the diseases blamed on Cd(II) toxicity are proteinuria, aminoaciduria, cadmium-induced renal tubular dysfunction, and cadmium-induced creatinuria.[6] Despite the well-established role of Cd(II) in these diseases, the intricate mechanisms by which that metal ion contributes to the disease phenotype is not known.

The presence of Cd(II) in the environment as a result of anthropogenic activities (e.g., battery manufacturing facilities) has increasingly raised global consciousness and awareness, in view of the fact that its pervasive intrusion in plants, animals, and humans is linked to dire toxic symptomatologies. One of the well-known diseases linked to Cd(II) is itai-itai disease, arising from water contaminated with that metal ion and leading to the pathological conditions[7] of osteomalacia and bone decalcification. Key to all of these macroscopic phenomena is the presence of soluble forms of Cd(II) that are easily mobilizable into water aquifers, the food chain, and finally into the cellular fluids of lower and higher organisms.

Mobilization of Cd(II), however, into biological fluids requires the presence of organic ligands, capable of promoting coordination and complex formation, enabling subsequent uptake through biological pathways. Such metal binders exist in biofluids, with outstanding representatives being the α-hydroxycarboxylic acids. Of those, citric acid is a prevalent organic tricarboxylic acid[8] in human plasma (∼0.1 mM) known (a) for its avid chemical propensity to bind metal ions and solubilize them and (b) to participate in key biological processes requiring organic cofactors.[9,10] Characteristic examples are the enzymes aconitase in the Krebs cycle and the $NifV^-$ nitrogenase in nitrogen fixation. It is logical, then, that a suitable target for citric acid is the toxic metal ion Cd(II), the complexed form(s) of which could, upon specific conditions, render the metal cation bioavailable and, thus, capable of interfering with key protein and enzyme functions entailing toxic manifestations at the cellular level. In an effort to comprehend the biological consequences of Cd(II) toxicity, we have launched efforts targeting the structural speciation of the related binary Cd(II)−citrate system. To this end, we report, herein, efforts leading to the pH-dependent synthesis, isolation, and spectroscopic and X-ray structural characterization of two Cd(II)−citrate species arising from aqueous solutions. Their presence in aqueous media and their physicochemical properties are discussed in the context of their potential participation in biological reactivity leading to toxicity.

Experimental Section

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

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

Solid-State NMR. Solid-state NMR experiments were performed on a Bruker MSL400 NMR spectrometer, capable of high-power ^1H decoupling. The high-resolution solid-state cross-polarized ^{13}C magic angle spinning (MAS) NMR spectra were measured at 100.63 MHz. The spinning rate used was 5.5 kHz at ambient temperature (25° C). Each solid-state spectrum was a result of the accumulation of 2000 scans. The recycle delay used was 5s, the 90° pulse was 5 μs, and the contact time was 1 ms. All solid-state spectra were referenced to adamantane, which showed two peaks at 26.5 and 37.6 ppm, and to the external reference of tetramethylsilane (TMS).

The high-resolution solid-state natural abundance ^{113}Cd MAS NMR spectra were measured at 88.741 MHz. 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 24 000 scans. Decoupling and triggering of 20 μs was used. The acquisition time was 40 ms and the relaxation delay 8s.

Solution NMR. The samples for solution NMR studies were prepared by dissolving the crystalline complexes in D_2O. NMR spectra were recorded on a Bruker AM360 (^{13}C) spectrometer. Chemical shifts (δ) are reported in ppm relative to an internal reference of TMS.

Synthesis of $[Cd_3(C_6H_5O_7)_2(H_2O)_5]\cdot H_2O$ (1). Method A. Cadmium nitrate, $Cd(NO_3)_2 \cdot 4H_2O$ (1.5 g, 5.0 mmol), and citric acid (1.0 g, 5.2 mmol) were placed in a 25 mL round-bottom flask and dissolved in 3 mL of water. The reaction mixture was then stirred at room temperature until both reactants were completely dissolved. Subsequently, the clear solution was filtered, and to the filtrate was added pyridine until the pH was 3. The resulting reaction mixture was allowed to stand at room temperature for slow evaporation. Three days later, colorless crystalline material appeared on the bottom of the flask. The crystalline product was isolated by fil-

(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.
(6) Sato, K.; Kusaka, Y.; Okada, K. *Toxicol. Lett.* **1995**, *80*, 161−165.
(7) (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.; Kjellstrőm, T. In *Cadmium in the Environment*, 2nd ed.; CRC Press: Cleveland, OH, 1974; pp 101−114.
(8) (a) Martin, R. B. *Inorg. Biochem.* **1986**, *28*, 181−187. (b) Glusker, J. P. *Acc. Chem. Res.* **1980**, *13*, 345−352.
(9) (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.
(10) (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.

Table 1. Summary of Crystal, Intensity Collection, and Refinement Data for $[Cd_3(C_6H_5O_7)_2(H_2O)_5]\cdot H_2O$ (**1**) and $(NH_4)[Cd(C_6H_5O_7)(H_2O)]\cdot H_2O$ (**2**)

formula	$C_{12}H_{22}O_{20}Cd_3$	$C_6H_{13}NO_9Cd$
fw	823.50	355.57
T, K	298	298
wavelength	Mo Kα 0.71073	Mo Kα 0.71073
space group	$P2_1/n$	$P2_1$
a (Å)	18.035(6)	9.686(4)
b (Å)	10.279(4)	8.484(4)
c (Å)	12.565(4)	7.035(3)
β (deg)	109.02(1)	110.28(1)
V, (Å^3)	2202(2)	542.3(4)
Z	4	2
D_{calcd}/D_{measd} (mg m^{-3})	2.484/2.49	2.178/2.18
abs coeff (μ), mm^{-1}	2.968	2.054
range of h, k, l	−21→20, −12→0, 0→14	−12→12, −11→11, 0→9
GOF on F^2	1.151	1.045
R indices[a]	$R = 0.0191$, $R_w = 0.0589$[b]	$R = 0.0264$, $R_w = 0.0665$[c]

[a] R values are based on F values, 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] [3746 refs $I > 2\sigma(I)$]. [c] [2593 refs $I > 2\sigma(I)$].

tration and dried in vacuo. Yield: 0.76 g (57%). Anal. Calcd for **1**, $[Cd_3(C_6H_5O_7)_2(H_2O)_5]\cdot H_2O$ ($Cd_3C_{12}H_{22}O_{20}$, MW = 823.5): C, 17.49; H, 2.67. Found: C, 17.50; H, 2.70.

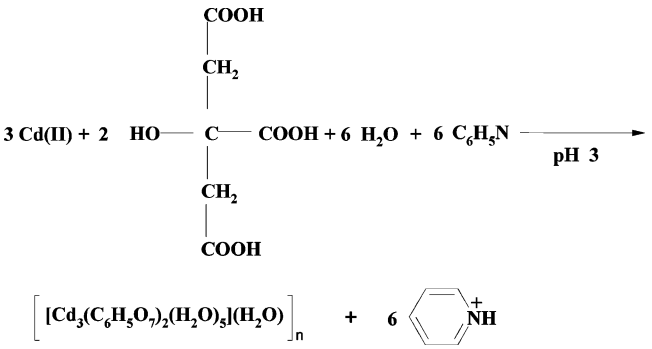
Method B. A quantity of citric acid monohydrate (1.0 g, 4.9 mmol) was placed in a 25 mL round-bottom flask and dissolved in 3 mL of water. To that, cadmium nitrate, $Cd(NO_3)_2\cdot 4H_2O$ (1.5 g, 4.9 mmol), was added slowly and under continuous stirring. The reaction mixture was then stirred at room temperature until both reactants were completely dissolved. Aqueous sodium hydroxide solution (0.1 M) was subsequently added slowly to adjust the pH of the reaction mixture to a final value of ∼2.5. The resulting reaction mixture was clear. It was allowed to stand at room temperature for slow evaporation. A few days later, a colorless crystalline material was deposited on the bottom of the flask. The crystalline product was isolated by filtration and dried in vacuo. Yield: 1.6 g (∼41%). Anal. Calcd for **1**, $[Cd_3(C_6H_5O_7)_2(H_2O)_5]\cdot H_2O$ ($Cd_3C_{12}H_{22}O_{20}$, MW = 823.5): C, 17.49; H, 2.67. Found: C, 17.59; H, 2.68.

Synthesis of $(NH_4)[Cd(C_6H_5O_7)(H_2O)]\cdot H_2O$ (2). 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 water. The reaction mixture was then stirred at room temperature until both reagents had dissolved. Subsequently, the pH of the reaction mixture was adjusted to 7 with an aqueous solution of ammonia. The resulting solution was placed in the refrigerator. On the following day, ethanol was added, which led to the formation of a colorless crystalline material a few weeks later. The crystalline product was isolated by filtration and dried in vacuo. Yield: 0.25 g (∼71%). Anal. Calcd for **2**, (NH_4)-$[Cd(C_6H_5O_7)(H_2O)]\cdot H_2O$ ($CdC_6H_{13}O_9N$, MW = 355.6): C, 20.26; H, 3.66; N, 3.94. Found: C, 20.49; H, 3.68; N, 3.96.

X-ray Crystal Structure Determination. X-ray quality crystals of compound **1** were grown from reaction mixtures upon slow evaporation. Crystallographic quality crystals for **2** were grown from water/ethanol reaction mixtures. A single crystal with dimensions 0.50 × 0.30 × 0.20 mm (**1**) or 0.50 × 0.30 × 0.15 mm (**2**) was mounted on a Crystal Logic dual goniometer diffractometer using graphite monochromated Mo Kα radiation. Unit cell dimensions for both **1** and **2** 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 psi-scan absorption corrections were applied using Crystal Logic software. Further crystallographic details for **1**: $2\theta_{max} = 50°$; scan speed, 4.0°/min; scan range, 2.1 + $\alpha_1\alpha_2$ separation; reflections collected/unique/used, 4058/3870 [$R_{int} = 0.0134$]/3870; 405 parameters refined; $[\Delta/\sigma]_{max} = 0.017$; $[\Delta\rho]_{max}/[\Delta\rho]_{min} = 0.471/-0.733$ e/Å^3; R/R_w (for all data), 0.0201/0.0596. For **2**: $2\theta_{max} = 56°$; scan speed, 4.5°/min; scan range, 2.3 + $\alpha_1\alpha_2$ separation; reflections collected/unique/used, 2808/2608 [$R_{int} = 0.0151$]/2608; 207 parameters refined; $[\Delta/\sigma]_{max} = 0.021$; $[\Delta\rho]_{max}/[\Delta\rho]_{min} = 0.639/-0.557$ e/Å^3; R/R_w (for all data), 0.0264/0.0666.

The structures of compounds **1** and **2** were solved by direct methods using SHELXS-86[11] and refined by full-matrix least-squares techniques on F^2 by using SHELXL-97.[12] In both structures of **1** and **2**, all the non-H atoms were refined anisotropically. All of the H atoms were located by difference maps and were refined isotropically.

Scheme 1. Reaction 1



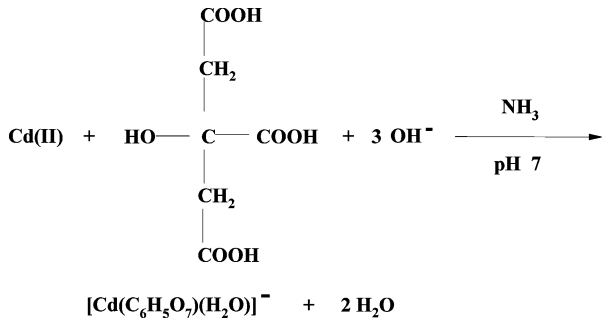
Results

Synthesis. The synthesis of compound **1** was achieved through a facile reaction between Cd(II) and citric acid in aqueous media. The pH, at which the reaction was developed, was 3. The adjustment of the pH was achieved through the addition of pyridine. Pyridine served as a base, replacing the conventional KOH or NaOH often used in adjusting the pH of reaction mixtures in metal citrate chemistry. The stoichiometric reaction leading to the formation of the compound is shown in Scheme 1 (reaction 1).

The compound was easily isolated in pure crystalline form upon standing of the reaction mixture at room temperature and allowing for slow evaporation over a period of a few days. An elemental analysis of the isolated colorless crystalline material suggested the molecular formulation $[Cd_3(C_6H_5O_7)_2(H_2O)_5]\cdot H_2O$ for **1**. Further spectroscopic evaluation of **1** by FT-IR confirmed the presence of citrate bound to Cd(II), thus lending credence to the proposed formulation. In a synthetic approach avoiding the use of pyridine, the same reaction mixture of Cd(II) and citric acid reacted in the presence of NaOH as a base, at a final value of pH 2.5, finally affording a crystalline material. That material proved to be complex **1** by virtue of its identical

(11) Sheldrick, G. M. *SHELXS-86*, structure solving program; University of Göttingen: Göttingen, Germany, 1986.
(12) Sheldrick, G. M. *SHELXL-93*, structure refinement program; University of Göttingen: Göttingen, Germany, 1993.

Scheme 2. Reaction 2



FT-IR spectrum with that of the title compound and the elemental analysis results.

Complex **2** was equally aptly obtained by reaction between Cd(II) and citrate in aqueous solutions. In contrast to the above-mentioned strategy, however, ammonia (1:1 ammonia/water solution) was used here to adjust the pH of the reaction mixture to approximately 7. In fact, ammonia was used as a base, raising the reaction pH and concurrently providing the necessary ammonium cations to counterbalance the charge of the overall complex derived from the attempted reaction. The stoichiometric reaction supporting the synthesis and isolation of complex **2** is shown in Scheme 2 (reaction 2).

The addition of ethanol resulted in the precipitation of crystalline material, which was isolated and subjected to further elemental analysis. The results of the analysis leaned toward the molecular formulation $(NH_4)[Cd(C_6H_5O_7)(H_2O)]\cdot H_2O$ (**2**). FT-IR spectroscopy further revealed the presence of bound citrate ligands around Cd(II), thus supporting the proposed molecular formulation of **2**.

Compound **1** is insoluble in water. Both compounds **1** and **2** were insoluble in organic solvents, like methanol, acetonitrile, chlorinated solvents ($CHCl_3$ and CH_2Cl_2), toluene, and DMF. They were both stable in the air at room temperature for long periods of time.

X-ray Crystallographic Structures. Complex **1** arises into a molecular type of crystal lattice. The ORTEP diagrams for complexes **1** and **2** are shown in Figures 1 and 2, respectively. A list of selected bond distances and angles for **1** and **2** are given in Tables 2 and 3, respectively. Complex **1** crystallizes in $P2_1/n$ with four molecules per unit cell. Complex **2** crystallizes in $P2_1$ with two molecules in the unit cell. In complex **1**, there are two different types of citrates, one per trinuclear assembly comprised of Cd(II) ions, each residing in a variable coordination environment. Specifically, the first citrate ligand is bound to Cd(1) through a terminal carboxylate oxygen O(1) [2.275(2) Å], whereas the second terminal carboxylate oxygen O(2) serves as a $\eta^1{:}\mu_2$ bridging atom between Cd(1) and Cd(2) [at 2.582(2) and 2.415(2) Å, respectively], resulting in a distance of 4.656 Å between the metals (mode II; See Chart 1). The central alcoholic oxygen O(3) is bound to the second Cd(2) ion, with the central carboxylate oxygen O(4) occupying another coordination site around that metal ion. The same oxygen atom serves as a $\eta^1{:}\mu_2$ binding anchor to an adjacently located Cd(1′) ($0.5 - x$, $0.5 + y$, $1.5 - z$) at distances Cd(2)−O(4) = 2.334(2) and Cd(1′)−O(4) = 2.475(2) Å. The resulting

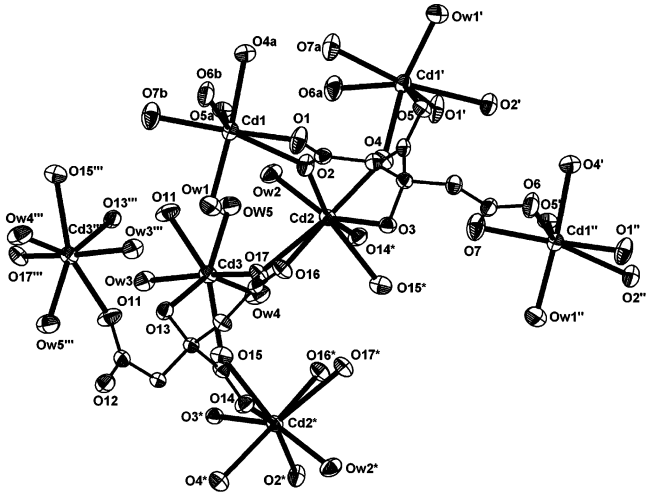


Figure 1. Molecular structure of $[Cd_3(C_6H_5O_7)_2(H_2O)_5]\cdot H_2O$ (**1**) with the atom labeling scheme (50% thermal probability ellipsoids). Symmetry operations shown: (′) $0.5 - x$, $0.5 + y$, $1.5 - z$; (″) x, $1 + y$, z; (‴) $-x$, $-y$, $2 - z$; (*) $-x$, $1 - y$, $2 - z$; (a) $0.5 - x$, $-0.5 + y$, $1.5 - z$; (b) x, $1 - y$, z.

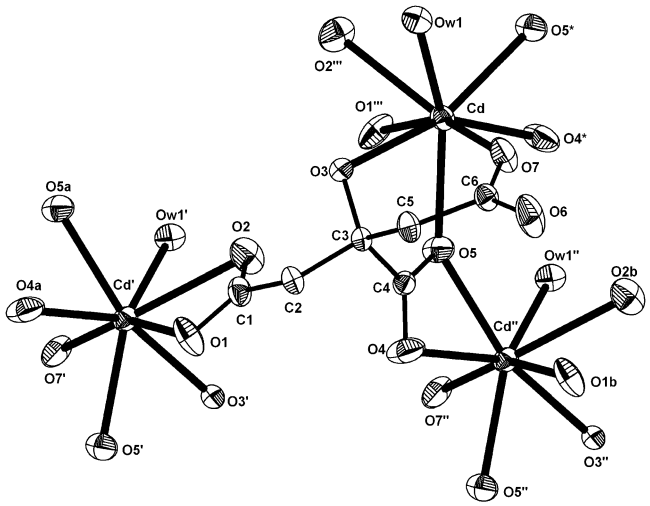


Figure 2. Molecular structure of the $[Cd(C_6H_5O_7)(H_2O)]^-$ anion with the atom labeling scheme in **2** (50% thermal probability ellipsoids). Symmetry operations shown: (′) $-x$, $0.5 + y$, $1 - z$; (″) $-x$, $0.5 + y$, $-z$; (‴) $-x$, $-0.5 + y$, $1 - z$; (*) $-x$, $-0.5 + y$, $1 - z$; (a) x, y, $1 + z$; (b) x, y, $-1 + z$.

Cd(2)···Cd(1′) interatomic distance is 4.601 Å. The second oxygen atom O(5) of the central carboxylate group participates in the η^2 bidentate coordination of that group to Cd(1′) (mode II). The heavy involvement of the central carboxylate and alcoholic groups of the citrate ligand in the coordination around cadmium projects the formation of a stable five-membered metallacyclic ring by that group around the cadmium ion(s). The second terminal carboxylate group O(6)C(6)O(7) of the citrate ligand extends into the coordination sphere of yet a third cadmium ion, Cd(1″) (x, $1 + y$, z), serving as a η^2 bidentate chelator through the two oxygen terminals (mode III). Thus, the first citrate ligand uses its carboxylate and alcoholic oxygen atoms to bind four cadmium ions, namely Cd(1), Cd(1′), Cd(1″), and Cd(2). The remainder of the coordination sites in the three cadmium ions Cd(1), Cd(1′), and Cd(1″) are covered by citrate ligand oxygens from adjacent assemblies of the same type. This

Table 2. Bond Lengths (Å) and Angles (deg) in **1**[a]

		Distances			
Cd(1)−Ow1	2.258(3)	Cd(2)−O(16)	2.276(2)	Cd(3)−Ow3	2.285(2)
Cd(1)−O(1)	2.275(2)	Cd(2)−Ow2	2.286(2)	Cd(3)−Ow4	2.296(3)
Cd(1)−O(6b)	2.334(3)	Cd(2)−O(4)	2.334(2)	Cd(3)−O(17)	2.303(2)
Cd(1)−O(5a)	2.340(2)	Cd(2)−O(14*)	2.355(2)	Cd(3)−Ow5	2.307(3)
Cd(1)−O(7b)	2.408(3)	Cd(2)−O(2)	2.415(2)	Cd(3)−O(13)	2.352(2)
Cd(1)−O(4a)	2.475(2)	Cd(2)−O(3)	2.423(2)	Cd(3)−O(15)	2.394(2)
Cd(1)−O(2)	2.582(2)	Cd(2)−O(15*)	2.553(2)	Cd(3)−O(11‴)	2.507(2)
		Cd(2)−O(17)	2.770(2)		
		Angles			
Ow1−Cd(1)−O(1)	99.5(1)	O(16)−Cd(2)−Ow2	98.97(9)	Ow3−Cd(3)−Ow4	92.2(1)
Ow1−Cd(1)−O(6b)	118.0(1)	O(16)−Cd(2)−O(4)	156.29(7)	Ow3−Cd(3)−O(17)	165.24(8)
O(1)−Cd(1)−O(6b)	85.05(9)	O(4)−Cd(2)−O(14*)	80.82(8)	O(17)−Cd(2)-Ow(2)	70.2(8)
Ow1−Cd(1)−O(5a)	96.2(1)	O(16)−Cd(2)−O(2)	84.80(8)	O(17)−Cd(2)-O(2)	116.5(8)
O(1)−Cd(1)−O(5a)	125.14(8)	Ow2−Cd(2)−O(2)	76.99(9)	Ow4−Cd(3)−O(17)	100.37(9)
O(6b)−Cd(1)−O(5a)	130.87(8)	O(4)−Cd(2)−O(2)	78.26(8)	Ow3−Cd(3)−Ow5	91.6(1)
Ow1−Cd(1)−O(7b)	88.1(1)	O(14*)−Cd(2)−O(2)	155.04(8)	Ow4−Cd(3)−Ow5	74.5(1)
O(1)−Cd(1)−O(7b)	136.87(8)	O(16)−Cd(2)−O(3)	91.31(7)	O(17)−Cd(3)−Ow5	99.15(9)
O(6b)−Cd(1)−O(7b)	54.79(8)	Ow2−Cd(2)−O(3)	148.96(9)	Ow3−Cd(3)−O(13)	87.88(8)
O(5a)−Cd(1)−O(7b)	95.66(8)	O(4)−Cd(2)−O(3)	68.41(7)	Ow4−Cd(3)−O(13)	138.58(9)
Ow1−Cd(1)−O(4a)	150.3(1)	O(14*)−Cd(2)−O(3)	109.65(8)	O(17)−Cd(3)−O(13)	77.59(8)
O(1)−Cd(1)−O(4a)	98.02(9)	O(14*)−Cd(2)−O(15*)	53.10(7)	Ow5−Cd(3)−O(13)	146.89(9)
O(6b)−Cd(1)−O(4a)	87.25(8)	O(16)−Cd(2)−O(15*)	86.73(8)	Ow3−Cd(3)−O(15)	95.13(8)
O(5a)−Cd(1)−O(4a)	54.17(7)	O(2)−Cd(2)−O(3)	74.88(8)	Ow4−Cd(3)−O(15)	72.53(9)
O(7b)−Cd(1)−O(4a)	95.28(8)	Ow2−Cd(2)−O(15*)	139.87(8)	O(17)−Cd(3)−O(15)	81.43(8)
Ow1−Cd(1)−O(2)	78.3(1)	O(4)−Cd(2)−O(15*)	96.89(7)	Ow5−Cd(3)−O(15)	146.57(8)
O(1)−Cd(1)−O(2)	53.03(7)	O(2)−Cd(2)−O(15*)	143.10(7)	O(13)−Cd(3)−O(15)	66.22(8)
O(6b)−Cd(1)−O(2)	137.82(8)	O(3)−Cd(2)−O(15*)	69.48(7)	Ow3−Cd(3)−O(11‴)	89.5(1)
O(5a)−Cd(1)−O(2)	79.90(7)	O(17)−Cd(2)−O(16)	50.6(8)	Ow4−Cd(3)−O(11‴)	148.77(9)
O(7b)−Cd(1)−O(2)	165.07(8)	O(17)−Cd(2)−O15*)	84.1(8)	O(17)−Cd(3)−O(11‴)	83.77(9)
O(4a)−Cd(1)−O(2)	93.59(7)	O(17)−Cd(2)−O(14*)	78.3(8)	Ow5−Cd(3)−O(11‴)	74.26(8)
Ow2−Cd(2)−O(4)	93.29(9)	O(17)−Cd(2)-O(4)	153.0(8)	O(13)−Cd(3)−O(11‴)	72.64(8)
O(16)−Cd(2)−O(14*)	118.96(8)	O(17)−Cd(2)-O(3)	135.3(8)	O(15)−Cd(3)−O(11‴)	138.34(7)
Ow2−Cd(2)−O(14*)	90.85(9)				

[a] Symmetry transformations used to generate equivalent atoms: (a) $0.5 - x, -0.5 + y, 1.5 - z$; (b) $x, 1 - y, z$; (*) $-x, 1 - y, 2 - z$; (‴) $-x, -y, 2 - z$.

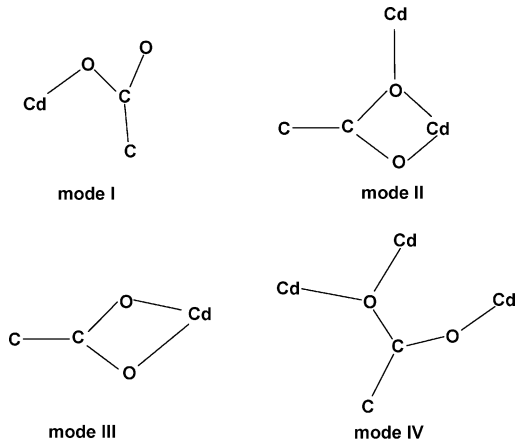
Table 3. Bond Lengths (Å) and Angles (deg) in **2**[a]

	Distances		
Cd−O(7)	2.272(3)	Cd−O(4*)	2.414(2)
Cd−O(1‴)	2.328(3)	Cd−O(5)	2.426(3)
Cd−O(3)	2.386(2)	Cd−O(5*)	2.444(3)
Cd−Ow(1)	2.404(3)	Cd−O(2‴)	2.639(3)
	Angles		
O(7)−Cd−O(1‴)	156.44(11)	O(4*)−Cd−O(5)	78.80(11)
O(7)−Cd−O(3)	82.85(10)	O(7)−Cd−O(5*)	97.05(10)
O(1‴)−Cd−O(3)	87.32(11)	O(1‴)−Cd−O(5*)	99.38(11)
O(7)−Cd−Ow(1)	78.45(11)	O(3)−Cd−O(5*)	160.09(9)
O(1‴)−Cd−Ow(1)	121.03(10)	Ow(1)−Cd−O(5*)	79.83(10)
O(3)−Cd−Ow(1)	80.65(9)	O(4*)−Cd−O(5*)	53.26(10)
O(7)−Cd−O(4*)	95.88(12)	O(5)−Cd−O(5*)	131.38(4)
O(1‴)−Cd−O(4*)	80.77(12)	O(7)−Cd−O(2‴)	145.32(12)
O(3)−Cd−O(4*)	146.65(10)	O(1‴)−Cd−O(2‴)	51.75(10)
Ow(1)−Cd−O(4*)	131.96(11)	O(3)−Cd−O(2‴)	79.75(11)
O(7)−Cd−O(5)	78.49(11)	Ow(1)−Cd−O(2‴)	69.30(10)
O(1‴)−Cd−O(5)	77.98(10)	O(4*)−Cd−O(2‴)	114.93(12)
O(3)−Cd−O(5)	68.26(9)	O(5)−Cd−O(2‴)	121.20(10)
Ow(1)−Cd−O(5)	143.14(10)	O(5*)−Cd−O(2‴)	89.68(12)

[a] Symmetry transformations used to generate equivalent atoms: (‴) $-x, -0.5 + y, 1 - z$; (*) $-x, -0.5 + y, -z$.

unique assembly of ions covered by one citrate ligand leaves one vacant coordination site around each Cd(1) ion. That site is occupied by a bound water molecule [Ow(1)]. The overall coordination number around Cd(1) is 7. The second citrate ligand reflects a slightly differentiated coordination mode. Specifically, one of the terminal carboxylates is coordinated through O(11) to Cd(3‴) ($-x, -y, 2 - z$) [2.507(2) Å], whereas the second carboxylate oxygen O(12)

Chart 1



stands away from coordination (mode I). The central alcoholic oxygen is bound to Cd(3), whereas the central carboxylate oxygen O(14) binds to Cd(2*). The second central carboxylate oxygen O(15) serves as a $\eta^1{:}\mu_2$ bridging atom between Cd(3) and Cd(2*) ($-x, 1 - y, 2 - z$) at distances of 2.394(2) and 2.553(2) Å, respectively. O(13) and O(15) of the central carboxylate promote the formation of a five-membered metallacyclic ring around Cd(3). The resulting Cd(3)···Cd(2*) interatomic distance is 4.747 Å. The second terminal carboxylate group is coordinated to Cd(2) through O(16) [2.276(2) Å] and to Cd(3) through O(17) [2.303(2) Å]. This oxygen atom also coordinates to Cd(2)

at the long distance of 2.770(2) Å, serving as a η^1:μ_2 bridge between Cd(3) and Cd(2) (mode II). The resulting interatomic distance between Cd(3) and Cd(2) is 4.738 Å. Thus, the second citrate ligand is also coordinated to four cadmium ions, namely, Cd(2), Cd(2*), Cd(3), and Cd(3‴). The remainder of the coordination sites in the two Cd(3) and Cd(3‴) ions are covered by citrate ligand oxygens from adjacent assemblies of the same type. This unique assembly of ions covered by one citrate ligand leaves three vacant coordination sites around each Cd(3) ion. These sites are occupied by three bound water molecules [Ow(3), Ow(4), and Ow(5)], leading to an overall coordination number around each Cd(3) ion equal to 7. Apart from the above-described coordination environment around each Cd(2), a water molecule [Ow(2)] is also bound around each Cd(2), leading to an overall coordination number of 8. The multifunctionality of each of the two crystallographically independent citrate ligands and the way they extend into the coordination sphere of four Cd(II) ions, supporting three different coordination modes (I, II, and III), are responsible for the formation of the 3-D polymeric structure of complex **1**. This structure becomes much more complicated if the hydrogen-bonding network is taken into account (see below for details).

In complex **2**, Cd(II) resides in an eight-coordinate environment formulated by citrate ligands as well as bound water molecules. The eight coordination sites are occupied as follows: Three sites are taken up by the central alkoxide oxygen O(3), one of the terminal carboxylate oxygens O(7), and one of the central carboxylate oxygens O(5). Two sites are occupied by the oxygens of the central carboxylate moiety of a citrate ligand associated with a Cd(II) center of an adjacent complex. An additional two sites are occupied by the terminal carboxylate oxygens of yet a third adjacently located Cd(II)−citrate complex. The remaining available site is taken up by a bound water molecule. Therefore, there are three citrate ligands lending their oxygen terminals to the fulfilment of the coordination sphere of cadmium. From the standpoint of the citrate ligand, there are various modes of coordination that its available anchor terminals utilize to satisfy the coordination requirements of Cd(II) in the lattice. Specifically, one of the terminal carboxylates [C(6)O(6)O(7)] binds Cd(II) in a unidentate fashion (mode I). The second terminal carboxylate [C(1)O(1)O(2)] does not participate in the coordination sphere of the same Cd(II). In fact, it spans over to an adjacently located Cd′ ($-x$, $0.5 + y$, $1 - z$) to which it binds in a bidentate fashion (mode III). The central carboxylate group [C(4)O(4)O(5)] binds to a third adjacently located Cd″ ($-x$, $0.5 + y$, $-z$), yet O(5) concurrently participates in the bidentate coordination of the group to Cd(II), serving as a η^1:μ_2 bridging anchor (mode II) between two adjacent Cd(II) ions. The resulting interatomic distance between the two cadmium ions is 4.660 Å. Thus, in the case of complex **2**, the citrate ligand is coordinated to three symmetrically related cadmium ions. A key feature in the structural identity of complexes **1** and **2** is the formation of the stable five-membered metallacyclic ring involving the metal ion and the central alcoholic and carboxylate groups of the bound citrate ligand. The three different coordination modes (I, II, and III) adopted by the citrate ligand in binding three crystallographically equivalent cadmium ions are responsible for the 3-D polymeric structure of complex **2**. The extensive hydrogen-bonding network is further responsible for the complexity of the polymeric structure of **2**.

What is appealing in the structures of **1** and **2** is the distinct mode of citrate coordination to Cd(II) compared to that in complex $[Cd(C_6H_6O_7)(H_2O)]_n$ (**3**).[13] In particular, the citrate central carboxylate group in **2** uses one of its terminal oxygens to bind to two Cd(II) ions in a η^1:μ_2 fashion, whereas the second oxygen terminal participates in the bidentate coordination of that group to the second of the two previously mentioned Cd(II) ions in a η^2 fashion (mode II). In contrast, the citrate central carboxylate group in **3** uses one of its oxygen atoms to bind to two Cd(II) ions in a η^1:μ_2 fashion, thus acting as a bridge (mode IV). 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 in **3** has been previously observed in $Cu^I(OOCCH_3)$[14] and differs from that encountered in complex $[Pb(C_6H_6O_7)]_n \cdot nH_2O$,[15] where one of the central carboxylate oxygen atoms binds to two Pb(II) ions in a η^1:μ_2 fashion, whereas the second carboxylate oxygen stands 3.271(1) Å away from another Pb(II) ion, in essence, noncoordinated. Moreover, the citrate terminal carboxylate group in $[Pb(C_6H_6O_7)]_n \cdot nH_2O$ binds in a bidentate fashion to yet another Pb(II) ion, thus being similar to the binding of the corresponding terminal carboxylate in **2** (mode III) and differing from the monodentate binding of the corresponding terminal carboxylate group in **3**. Consequently, three different carboxylate binding modes for citrate exist within the same molecule in **2**. The central alcoholic group binding is the only common point in the binding mode of the citrate ligand in **2**, **3**, and $[Pb(C_6H_6O_7)]_n \cdot nH_2O$.

The Cd−O bond distances are in the range from 2.258(3) to 2.770(2) Å for **1** and from 2.272(3) to 2.639(3) Å for **2**, very similar to corresponding distances in other cadmium complexes including complex **3** [2.225(3)−2.354(3) Å],[13] $[Cd_3(H_2O)_2(C_6H_5O_7)_2]_n$ [2.255(2)−2.500(2) Å],[16] $\{[Cd_2(C_4H_4O_6)_2(H_2O)] \cdot 3H_2O\}_n$ [2.188(3)−2.425(3) Å],[17] the eight-coordinate sites in $Cd_2(C_3H_2O_4) \cdot 4H_2O$ [2.307(4)−2.775(5) Å],[18] $[Cd(C_3H_6NO_2)_2] \cdot 3H_2O$ [2.296(4)−2.326(5) Å],[19] $Cd(C_4H_2O_4) \cdot 2H_2O$ [2.224(5)−2.521(5) Å],[20] and the eight-

(13) Dakanali, M.; Kefalas, E. T.; Raptopoulou, C. P.; Terzis, A.; Mavromoustakos, T.; Salifoglou, A. *Inorg. Chem.* **2003**, *42*, 2531−2537.
(14) (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.
(15) Kourgiantakis, M.; Matzapetakis, M.; Raptopoulou, C. P.; Terzis, A.; Salifoglou, A. *Inorg. Chim. Acta* **2000**, *297*, 134−138.
(16) Guo, Y.; Lü, J.; Li, Y.; Wang, E.; Lu, Y.; Xu, X.; Xu, L. *J. Mol. Struct.* **2005**, in press.
(17) Gonzalez-Silgo, C.; Gonzalez-Platas, J.; Rutz-Perez, C.; Lopez, T.; Torres, M. E. *Acta Crystallogr., Sect. C* **1999**, *C55*, 710−722.
(18) Chung, K. H.; Hong, E.; Do, Y.; Moon, C. H. *J. Chem. Soc., Chem. Comm.* **1995**, 2333−2334.
(19) Demaret, P. A.; Abraham, E. F. *Acta Crystallogr., Sect. C* **1987**, *C43*, 2067−2069.
(20) Hempel, A.; Hull, S. E. *Acta Crystallogr., Sect. B* **1979**, *B35*, 2215−2216.

coordinate site in cadmium maleate [2.199(5)−2.843(5) Å].[21] Overall, the citrate ligand plays the role of a polydentate metal chelator, effectively formulating the coordination environment around Cd(II).

Considering the citrate moiety bound to the metal ion in compound **1**, 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 0.06 Å for C(3). The O(3)−C(3)−C(4) plane of the central carboxylate group is rotated 9.2° 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 2.5° and 11.2°, 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 13.2°. The torsion angle H−O(3)−C(3)−C(4) for the hydrogen of the alcoholic group is 109.6°. In the second citrate ligand, the carbon atoms of the citrate backbone are not planar. Specifically, atom C(11) is displaced ∼1.3 Å out of the best mean plane defined by C(12), C(13), C(15), and C(16). The O(13)−C(13)−C(14) plane of the central carboxylate group is rotated 5.4° out of the O(14)−C(14)−O(15) plane. The angle between the terminal carboxylate planes O(11)−C(11)−O(12) and O(16)−C(16)−O(17) is 82.8°. The torsion angle H−O(13)−C(13)−C(14) for the hydrogen of the alcoholic group is 107.2°. In compound **2**, the citrate backbone defined by C(1), C(2), C(3), C(5), and C(6) is planar, with the largest deviation being 0.07 Å for C(5). The O(3)−C(3)−C(4) plane of the central carboxylate group is rotated 25.2° 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 18.9° and 25.4°, 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 20.1°. The torsion angle H−O(3)−C(3)−C(4) for the hydrogen of the alcoholic group is 109.8°.

Hydrogen-bonding interactions are a dominant feature of the crystal structures of **1** and **2**. Specifically in **1**, the coordinated water molecule, the protonated central alcoholic and the terminal carboxylate groups of citrate participate in the formation of hydrogen bonds (Table 4, Supporting Information). In compound **2**, the presence of the ammonium counterion, the bound and lattice water molecules, and the protonated central alcoholic and carboxylate groups of citrate participate in the formation of hydrogen bonds (Table 5, Supporting Information). A common feature in both **1** and **2** is the protonated central alcoholic group, which participates in intramolecular hydrogen bonds to carboxylate oxygens of the same citrate. The resulting extensive hydrogen-bonding network very likely contributes to the stability of the crystal lattices in **1** and **2**.

FT-IR Spectroscopy. The FT-IR spectra of **1** and **2** exhibit 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 1606 to 1543 cm^{-1} (**1**) and at around 1587 cm^{-1} (**2**), whereas the corresponding symmetric stretches

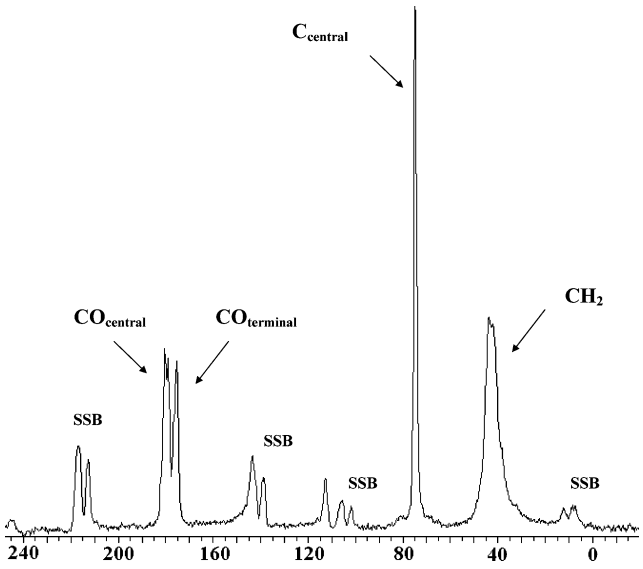


Figure 3. ^{13}C MAS NMR solid-state spectrum of $(NH_4)[Cd(C_6H_5O_7)(H_2O)]\cdot H_2O$ (**2**). SSB signifies the presence of spinning side bands.

$\nu_s(COO^-)$ appear in the range from 1425 to 1351 cm^{-1} (**1**) and from 1412 to 1395 cm^{-1} (**2**). The frequencies for the carbonyl stretches in **1** and **2** 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 for the carboxylate carbonyls have also been observed in the FT-IR spectra of the Cd(II)−citrate complex **3** [$\nu_{as}(COO^-) = 1620-1540$ cm^{-1} and $\nu_s(COO^-) = 1430-1380$ cm^{-1}] as well as in those of citrate complexes with other metal ions.[22]

Solid-State NMR Spectroscopy. The MAS ^{13}C NMR spectra of **1** and **2** (Figure 3) in the solid state reveal the presence of coordinated citrate to Cd(II). Specifically, the spectra show separate peaks for the various carbons of the citrate ligand. Two of those lie in the high field region, whereas the others emerge in the low field region in the spectra of both species. The peak(s) in the high field region could be attributed to the methylene carbon [32.4−42.1 ppm (**1**), 43.6 ppm (**2**)] located adjacent to the coordinated carboxylates of the citrate ligand. The signals at around 72.7 ppm and 74.9 ppm are reasonably attributed to the central carbon atom located adjacent to the bound central carboxylate group in **1** and **2**, respectively. In the low field region, where the carbonyl carbon resonances are expected, there are broad signals at around 179.7 ppm (**1**), attributable to the carboxylate groups (central and terminal), and around 175.4 ppm (**2**), attributable to the terminal carboxylate groups (higher field). Broad signals at around 180.3 ppm (**2**) are tentatively assigned to the bound central carboxylate carbon of the citrate ligand (lower field).

The ^{113}Cd nucleus has a spin of $^1/_2$, a fact that has been reportedly exploited to gain knowledge of structural features

(21) Post, M. L.; Trotter, J. *J. Chem. Soc., Dalton Trans.* **1974**, 674−678.

(22) (a) Matzapetakis, M.; Raptopoulou, C. P.; Tsohos, A.; Papaefthymiou, 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.

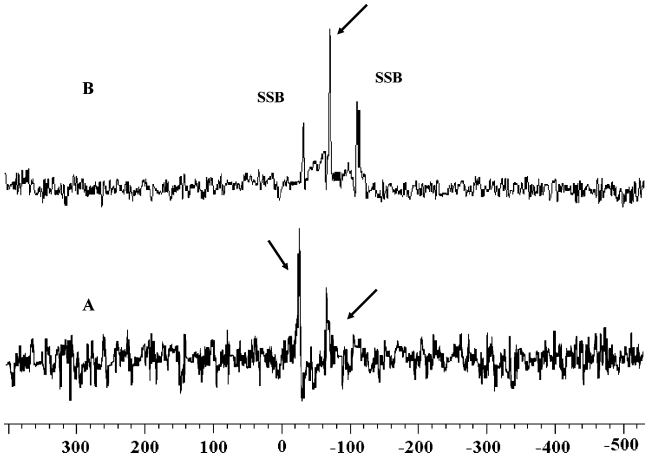


Figure 4. ^{113}Cd MAS NMR spectra of (A) $[Cd_3(C_6H_5O_7)_2(H_2O)_5]\cdot H_2O$ (**1**) and (B) $(NH_4)[Cd(C_6H_5O_7)(H_2O)]\cdot H_2O$ (**2**).

of Cd(II) compounds.[23] To this end, the ^{113}Cd MAS NMR spectra of **1** and **2** were 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 two signals at around −27.1 ppm and −67.0 ppm (**1**), whereas the spectrum of **2** shows a resonance at −72.4 ppm with sidebands (SSB) (Figure 4). On the basis of past reports, various patterns have been observed, earmarking specific regions in the ^{113}Cd spectrum for six-, seven-, and eight-coordinate Cd(II) ions.[24,18] Consistent with the above information, seven-coordinate Cd(II) compounds exhibit ^{113}Cd resonances in the range from δ 0 to −70, whereas eight-coordinate Cd(II) species exhibit ^{113}Cd resonances in the range from δ 0 to −115. The observed resonances fall in this range and indicate the presence of seven- and eight-coordinate Cd(II) sites in **1** and eight-coordinate Cd(II) sites in **2** surrounded by oxygen-containing ligands. The overall picture presented by ^{113}Cd NMR of both compounds is consistent with the X-ray structural depiction of seven- (**1**) and eight-coordinate (**1** and **2**) Cd(II) sites, with oxygens (citrate, H_2O) bound to it.

Solution NMR Spectroscopy. The ^{13}C NMR spectrum of **2** (Figure 5) in solution is consistent with the coordination of citrate around the Cd(II) ion. The spectrum showed separate peak features. Two of those lie in the high field region, whereas the others appear in the low field region. The peak(s) in the high field region could be assigned to the methylene carbon (47.8 ppm) located adjacent to the coordinated carboxylates of the citrate ligand. The signal at around 77.5 ppm is reasonably attributed to the central carbon atom located adjacent to the bound central carboxylate group. In the low field region, where the carbonyl carbon resonances are expected, there are peaks observed at 181.6 and 184.4 ppm attributable to the terminal carboxylate groups (higher field) and the bound central carboxylate carbon of the citrate ligand (lower field), yet they were difficult to discern as

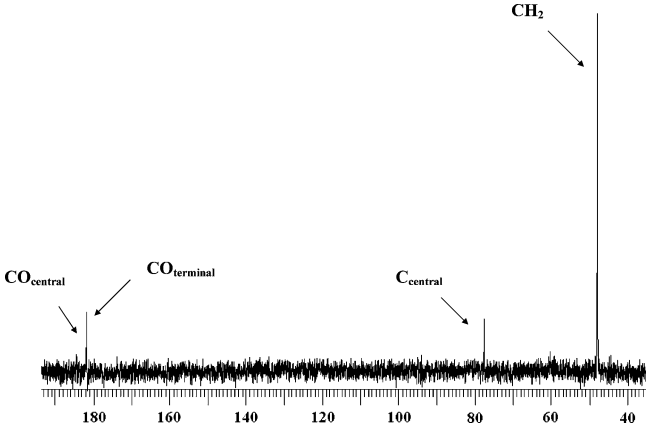


Figure 5. Solution ^{13}C NMR spectrum of $(NH_4)[Cd(C_6H_5O_7)(H_2O)]\cdot H_2O$ (**2**) in D_2O.

discrete signals. A similar pattern of ^{13}C resonances was observed in the case of mononuclear complexes, such as $(NH_4)_5[Al(C_6H_4O_7)_2]\cdot 2H_2O$,[25] and dinuclear complexes, such as $Na_2[Bi_2(C_6H_4O_7)_2]\cdot 7H_2O$.[26] The observed pattern of **2** in solution is consistent with that in the solid state, likely projecting the presence of mononuclear Cd(II)−citrate species.

Discussion

The Binary Cd(II)−Citrate System in Aqueous Media. Comprehending the toxicity of Cd(II) in biological systems entails in-depth understanding of its relevant aqueous chemistry in biological fluids, with partners on both the low as well as the high molecular mass end of the spectrum. In the case of the binary system of Cd(II) with the physiologically relevant ligand citrate, the aqueous chemistry reveals quite interesting results, projecting chemical and structural diversity in the species arising as a result of the investigated reactivity. Initial attempts to delve into the Cd(II)−citrate system had focused on the reactivity of that system at a low pH of ∼2. As a result, compound **3** was isolated and spectroscopically and structurally characterized. In the framework of the present work, the pH dependence of the requisite system was explored, utilizing diverse approaches into the upward adjustment of the pH of the reaction mixtures to different values. Employing 1:1 stoichiometric amounts of the two major reactants, Cd(II) and citric acid, their chemical reactivity was investigated at different pH values, namely, 2.5, 3, and 7. Adjustment of the pH of the reaction mixtures was achieved through the use of variable nature bases covering both organic and inorganic materials. Specifically, facile reactions were developed in which NaOH and pyridine were employed in the first case (**1**), whereas ammonia solutions were used in the second case (**2**). Hoping to involve base-derived cations in the lattice of the arisen chemical species upon crystallization, two different and

(23) Mennitt, P. G.; Shatlock, M. P.; Bartuska, B. J.; Maciel, G. E. *J. Phys. Chem.* **1981**, *85*, 2087−2091.
(24) (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. Comm.* **1982**, 182−184.
(25) Matzapetakis, M.; Kourgiantakis, M.; Dakanali, M.; Raptopoulou, C. P.; Terzis, A.; Lakatos, A.; Kiss, T.; Banyai, I.; Iordanidis, L.; Mavromoustakos, T.; Salifoglou, A. *Inorg. Chem.* **2001**, *40*, 1734−1744.
(26) Barrie, P. J.; Djuran, M. I.; Mazid, M A.; McPartlin, M.; Sadler, P. J.; Scowen, I. J.; Sun, H. *J. Chem. Soc., Dalton Trans.* **1996**, 2417−2422.

distinct chemical entities emerged as a result of this approach, namely, **1** and **2**. In the first case, the produced pyridinium cations (method A) were not involved in the lattice of **1**, nor were sodium cations (method B), in view of the fact that the compound itself was a molecular type of species, not requiring a counterion for balancing negatively charged species. In the second case, the ammonium ion produced at a higher pH participated in the lattice of complex **2** as a counterion, balancing the −1 charge of the derived complex anion.

The advent of the synthetic pH-dependent chemistry present herein showed clearly that at pH values greater or equal to 2.5, the species formed and eventually isolated bear citrate bound to Cd(II) in the triply deprotonated form $(C_6H_5O_7)^{3-}$. That state of (de)protonation persists at near physiological pH values, essentially depicting the chemical behavior of that physiological ligand in the presence of the toxic metal ion Cd(II). In this sense, both complexes **1** and **2** reveal that an increase of pH renders the resulting chemistry totally different from that already encountered in the case of complex $[Cd(C_6H_6O_7)(H_2O)]_n$ (**3**) synthesized and isolated at acidic pH values (pH ∼2). The consequences of this new synthetic chemistry are manifested in (a) the different stoichiometries of Cd(II)/citrate found in the isolated species, (b) the variable nuclearity of the arisen species (trinuclear complex in **1** and mononuclear complex in **2**), (c) the different charges of the arisen species (zero for complex **1** and −1 for complex **2**), (d) the striking structural variability in the coordination modes of citrate bound to the toxic metal ion Cd(II), and (e) the different physicochemical properties of the species isolated at higher-pH-value aqueous media, all compared with the corresponding parameters in complex $[Cd(C_6H_6O_7)(H_2O)]_n$ (**3**).

In all cases, however, of Cd(II)−citrate species structurally characterized thus far, the single most important structural feature standing out is the presence of a protonated alcoholic group of the central carbon in the citrate coordinated to the metal ion Cd(II). This feature is independent of (a) the nature of the Cd(II)−citrate species formed and isolated, (b) the nuclearity of the species isolated, (c) the charge of the overall species, (d) the coordination mode of the citrate ligand bound to Cd(II), and most of all, (e) the state of (de)protonation of the citrate ligand participating in the complex formation. That protonated form of citrate participates in the formation of hydrogen bonds inside the respective lattices of **1**, **2**, and **3**, thus contributing to the overall stability of the investigated species. What would be significant, however, from the biological point of view, is the degree to which the specific protonated form of citrate, that persists in species both at low and high values of the pH spectrum, might contribute to the (bio)chemical reactivity of the solubilized Cd(II), projecting bioavailability and potential toxicity in a biological environment (see below).

The variable state of protonation of the citrate ligand and the involvement of the second terminal carboxylate group in the coordination around the Cd(II) ion are reflected in the polymeric structure of complexes **1**, **2**, and **3**. More specifically, in complex **3**, isolated in the acidic pH region, the protonated terminal carboxylate group is hanging away from the coordination sphere of the cadmium ion. The remaining central and terminal deprotonated carboxylate groups along with the protonated alkoxide fulfill the coordination requirements of the Cd(II) ions, bridging three crystallographically equivalent cadmium ions and establishing a close arrangement between neighboring metal ions. As a result, the latter octahedral ions position themselves in a zigzag fashion, extending their array infinitely in one dimension inside the crystal lattice. In the so-formed arrays, the Cd···Cd distance is 3.795(1) Å. In both **1** and **2**, isolated at low and high pH values, respectively, the deprotonation of the second terminal carboxylate and its involvement in the coordination around the cadmium ions are reflected in the polymeric structures of both complexes. In complex **1**, each citrate ligand participates in the coordination of four cadmium ions, establishing a more open arrangement between neighboring metal ions that extends in three dimensions inside the crystal lattice. The closest Cd···Cd distances in the three-dimensional polymeric structure of **1** range from 4.60 to 4.75 Å. In complex **2**, the citrate ligand participates in the coordination of three crystallographically equivalent Cd(II) ions, adopting three different coordination modes. This results in the formation of a polymeric structure of mononuclear units extending in three dimensions inside the crystal lattice. In that setting, the closest Cd···Cd distance observed is 4.66 Å.

As in the case of complex **3**, the steric requirements in the coordination environment of Cd(II) centers in **1** and **2** impose restrictions on the participation of the citrate terminals in the coordination sphere by citrates only. Thus, solvent water molecules come in and bind to the vacant sites on the available Cd(II) centers. These molecules along with the water molecules of crystallization in **2** participate in the establishment of extensive hydrogen-bonding interactions throughout the lattices of **1** and **2**.

NMR Spectroscopy. ^{113}Cd NMR spectroscopy has been extremely useful in probing biomolecules containing Cd(II). Specifically, the chemical shift of ^{113}Cd is quite sensitive to the type of ligands bound to Cd(II) and the geometry and coordination number generated by the ligands in the coordination sphere of the metal ion. To this end, ^{113}Cd MAS NMR has been used successfully in the case of metallothioneins,[27] troponin C,[28] calmodulin,[29] and others.[30] Quite revealing in this respect were the cases of the S2 site in concanavalin A[31] and the EF site of parvalbumin,[32] both of which contain oxygen donors. Prompted by the potential of

(27) Boulanger, Y.; Armitage, I. M.; Miklossy, K.-A.; Winge, D. R. *J. Biol. Chem.* **1982**, *257*, 13717−13719.
(28) Teleman, O.; Drakenberg, T.; Forsen, S.; Thulin, E. *Eur. J. Biochem.* **1983**, *134*, 453−457.
(29) Andersson, A.; Forsen, S.; Thulin, E.; Vogel, H. J. *Biochemistry* **1983**, *22*, 2309−2313.
(30) (a) Bailey, D. B.; Ellis, P. D.; Fee, J. A. *Biochemistry* **1980**, *19* (9), 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.
(31) Bailey, D. B.; Ellis, P. D.; Cardin, A. D.; Behnke, W. D. *J. Am. Chem. Soc.* **1978**, *100*, 5236−5237.
(32) Cave, A.; Parello, J.; Drakenberg, T.; Thulin, E.; Lindman, B. *FEBS Lett.* **1979**, *100*, 148−152.

gaining such knowledge, ^{113}Cd MAS NMR was used to probe the title compounds **1** and **2**. The data revealed the presence of seven (complex **1**) and eight (complexes **1** and **2**) coordinate Cd(II) species, with the metal ions being surrounded by oxygen donor atoms. This result was (a) in accordance with the chemical shift observed in the case of complex **3** and (b) supported by ^{113}Cd MAS NMR chemical shifts[33] reported in the past for Cd(II) sites bearing various types of ligands, coordination geometries, and coordination numbers. The arising theses were also in line with the available structural data from the crystallographic determinations of **1** and **2**.

Given the importance of gathering information on key structural features of Cd(II) species of varying nature, the employment of ^{113}Cd MAS NMR certainly defines the specific attributes of Cd(II) complexes arising from aqueous solutions of that metal ion in the presence of the physiologically relevant citric acid under pH-variable conditions. That helps clarify the physicochemical details of the speciation of Cd(II) in binary systems with physiological ligands in biologically relevant fluids. To this end, ^{113}Cd MAS NMR is instrumental in extracting information that might be of importance in understanding the toxic manifestations of soluble and bioavailable forms of toxic Cd(II).

Aqueous Speciation and Potential Toxicity. The aqueous chemistry of the binary cadmium−citrate system has revealed a number of discrete species, all of them reflecting the solubilization of cadmium in the presence of the physiological substrate citric acid. In the present work, two more species were established as a result of the pH dependence of the reactivity emerging from the investigated binary system. The two complexes synthesized were isolated at $2.5 < pH < 7$, values that extend from the low to the physiological end of the pH scale. Previous efforts had afforded another cadmium−citrate species at low pH, ∼2. In this sense, it appears that soluble species can exist throughout the pH range and conditions can be formulated that promote the isolation of species of distinct chemical and physical properties. Conceivably, then, such solubilized forms of cadmium can also exist in the environment and potentially reflect bioavailable forms of cadmium, which could elicit interactions with molecular targets at the biological level. In the context of such chemistry, toxic cadmium can be present in biological systems masking itself in complexed forms with organic ligands, like citrate, and consequently could be in a position to be involved, to interfere, and to potentially influence metabolic pathways linked to the integrity of lower and higher organisms, including plants. The ability of the latter to take up organic substrates or metal ions essential to vital functions has been noted before. In particular, cadmium complexation by citrate has been invoked to account for the inability of bacterial organisms to (a) internalize or (b) metabolize citrate in the presence of Cd(II), thus giving way to inhibitory effects of toxic Cd(II) in the physiology of the organisms.[34,35]

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.[36] Specifically, complexes of the types $[Cd(C_6H_5O_7)]^-$ and $[Cd(C_6H_6O_7)]^0$ are among those proposed to exist in solution with varying degrees of stability. Previous synthetic efforts on this binary system had afforded $[Cd(C_6H_6O_7)(H_2O)]_n$ (**3**), a low pH compound, consistent with the formulation of a zerovalent $[Cd(C_6H_6O_7)]^0$ species. The herein reported work has unearthed two more species, one of which has been isolated at near physiological pH and reflects very well the stoichiometry of the species $[Cd(C_6H_5O_7)]^-$. Complex (NH_4)-$[Cd(C_6H_5O_7)(H_2O)]\cdot H_2O$ (**2**) undoubtedly resembles the species projected to exist as a component in the aqueous speciation of cadmium in the presence of citrate.

On the basis of the above facts, it appears that the pH-dependent synthetic chemistry has (a) provided the way to reach soluble species, consistent with the general nature of species proposed by past solution studies of the specific binary system and (b) facilitated the isolation of species, the spectroscopic and structural properties of which were distinct (e.g., **2**) and in line with the corresponding properties of an aqueous complex $[Cd(C_6H_5O_7)]^-$ at near physiological pH value. Such details could not have easily been predicted by solution studies. A direct comparison of **2** with the $[Cd(C_6H_5O_7)]^-$ species arisen from solution studies reveals similarities such as (a) the molecular stoichiometry of Cd(II)/citrate = 1, (b) the coordination of citrate to the Cd(II) ion, (c) the same charge −1, and (d) the triple deprotonation of citrate bound to Cd(II). The major differences between the two species that concurrently denote the detailed description of the anion in **2**, arisen from the structural characterization of the isolated species, are linked to (a) the presence of a bound water molecule to Cd(II) in the anionic complex of **2** and (b) the mode of coordination for the bound citrate ligand. Hence, the significance of the development of a structural speciation in the binary system undoubtedly contributes to the delineation of the nature of species participating in the aqueous distribution of the requisite binary system and offers significant physicochemical information that could help clarify the potential bioavailability of the toxic metal ion in its solubilized form with citrate in biological systems. Given the fact that bioavailability is closely linked to toxicity, the present work supports the idea of discrete soluble chemical species of Cd(II) bound to citrate, participating in the requisite biodistribution in aqueous media and potentially seeking a bioavailability status that could lead to toxicity.

(33) Griffith, E. A. H.; Charles, N. G.; Lewinski, K.; Amma, E. L.; Rodesiler, P. F. *Inorg. Chem.* **1987**, *26*, 3983−3989 and references therein.

(34) Francis, A. J.; Dodge, C. J.; Gillow, J. B. *Nature (London)* **1992**, *356*, 140−142.

(35) (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.

(36) (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.

Collectively, the chemistry developed here shows that under the investigated conditions and likely under similar conditions in the natural fluids, the aqueous chemistry of cadmium with solubilizing metal ion binders can lead to diverse species across the pH range, with distinct chemical and structural properties that might promote ternary interactions at the biological level and concomitant toxicity. Likely, other species could also be present as participants in the aqueous speciation of the binary cadmium−citrate system that currently elude isolation. They, in addition to the ones already discovered, could provide insight into the aqueous chemistry and potentially relate to the toxicity of that metal ion in a biological setting. Efforts to discover such species and their (bio)chemical properties are under way in our laboratories.

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Supporting Information Available: Tables of X-ray crystal structure refinement data and positional and thermal parameters for $[Cd_3(C_6H_5O_7)_2(H_2O)_5]\cdot H_2O$ (**1**) and $(NH_4)[Cd(C_6H_5O_7)(H_2O)]\cdot H_2O$ (**2**). This material is available free of charge via the Internet at http://pubs.acs.org.

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