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Binding of Heavy Metals at Biologically Important Sites. Synthesis and Molecular Structure of Aquo(bromo)-DL-penicillaminatocadmium(II) Dihydrate

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The reaction of cadmium bromide tetrahydrate with DL-penicillamine in aqueous ethanol gives aquo(bromo)-DL-penicillaminatocadmium(II) dihydrate. Crystals are triclinic, of space group $P\bar{1}$ with $a = 9.050$ (15), $b = 7.795$ (6), $c = 9.464$ (7) Å; $\alpha = 115.72$ (9), $\beta = 88.17$ (4), $\gamma = 96.75$ (4)°. The unit cell contains two molecules. Calculated and measured densities are 2.194 and 2.13 g cm^{-3}. Intensity data were collected by θ–2θ scanning with Mo Kα radiation; 2534 observed intensity data were used in the structure analysis and refinement. The final values of R and R_w were 0.048 and 0.059, respectively. The crystal structure consists of infinite chains of alternating cadmium atoms and bridging tridentate penicillamine molecules linked by asymmetric double bromine bridges. Each penicillamine molecule utilizes a deprotonated sulfhydryl group and two oxygen atoms of the carboxyl group in bonding, the amino group being present as $-NH_3^+$. Principal cadmium–ligand distances are Cd–S = 2.444 (2) Å, Cd–Br = 2.6245 (9) Å (Cd–Br′ = 3.0492 (9) Å), Cd–O(1) = 2.262 (5) Å, and Cd–O(2) = 2.715 (5) Å. The contrasting structures of Hg^{2+} and Cd^{2+} complexes with DL-penicillamine are discussed.

Introduction

In terms of biochemical activity, cadmium occupies an interesting position in the periodic table, being placed in group 2B between zinc which plays an essential role in several biological processes and mercury which is an enzyme and protein inhibitor.[1] Several aspects of cadmium biochemistry suggest a greater similarity to Hg(II) than to Zn(II). Thus Cd^{2+} salts are, like their Hg^{2+} counterparts, exceedingly toxic, with symptoms of Itai-Itai disease appearing in humans exposed to levels in excess of 250 μg/day.[2] The mechanism of poisoning by Cd^{2+} may involve metal–sulfur (cysteine) bonding similar to that postulated to account for protein and enzyme inactivation by Hg^{2+}.[2] The naturally occurring cadmium-containing metalloprotein metallothionein, which has as yet no known biological function, is believed to contain Cd^{2+} bound to three cysteinyl sulfur atoms.[3] Despite the apparent affinity of both Hg^{2+} and Cd^{2+} for sulfur ligands some significant differences between the binding of Cd^{2+} and Hg^{2+} to biological ligands are to be expected since Cd^{2+} should exhibit a much greater tendency to interact with "hard" sites than will Hg^{2+} [4] while in relative terms stability constants decrease in the sense Hg–S(thiol) > Cd–S(thiol).[5] In this context it is significant that D-penicillamine is an effective antidote for inorganic mercury poisoning but has no beneficial effects against cadmium.[6] Also, the biological half-life of cadmium in humans (10–30 years) is much longer than that of mercury.[2]

In an effort to compare and contrast the biological binding preferences of Hg^{2+} and Cd^{2+} we recently undertook a reexamination of the M^{2+}/L-cysteine and M^{2+}/DL-penicillamine systems. In general there is considerable confusion in the literature concerning the stoichiometries and molecular structures of mercury and cadmium complexes of sulfur amino acids, particularly in the solid state.[7] X-ray data are lacking and structural assignments where available are tentative. As a first step in establishing the structural nature of Hg^{2+} and Cd^{2+} complexes in the solid state and in solution, crystalline complexes of various stoichiometries have been synthesized and subjected to x-ray structural studies. A preliminary description of structural data for the Hg^{2+} complexes has been published.[8] In this paper, the characterization of a cadmium bromide complex of DL-penicillamine is described. After completion of our work a communication on the structure of another Cd^{2+} complex $\{Cd[NH_2CH(COO)C(CH_3)_2S]\}\cdot H_2O$ appeared.[9] The mode of bonding of penicillamine to cadmium differs markedly in the two complexes.

Experimental Section

Preparation of $\{CdBr[SC(CH_3)_2CH(NH_3)COO]H_2O\}\cdot 2H_2O$. Cadmium bromide tetrahydrate (1.0 g) dissolved in 50:50 aqueous ethanol was added to DL-penicillamine (0.55 g) in the same solvent. The solution was filtered and allowed to evaporate over a period of several days. Clear irregular prisms of the complex crystallized slowly. Upon removal of the crystals from the solution the compound effloresced, eventually leaving a white powder. Anal. Calcd for $\{CdBr[SC(CH_3)_2CH(NH_3)COO]H_2O\}\cdot 2H_2O$: C, 15.99; H, 3.45; N, 3.73; Br, 21.28. Found: C, 15.71; H, 3.42; N, 3.69; Br, 21.86.

Attempts were also made, under the same conditions to prepare compounds having a higher ratio of penicillamine to cadmium by using excess penicillamine. The only compounds which could be isolated were the bromide complex above and free ligand.

The deuterated complex $\{CdBr[SC(CH_3)_2CH(ND_3)COO]D_2O\}\cdot 2D_2O$ was prepared analogously from 95% D_2O.

Physical Measurements. Microanalysis was performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Infrared spectra were measured as Nujol and Halocarbon mulls on a Perkin-Elmer 180 spectrophotometer. Raman spectra of powders were obtained from a Jarrel-Ash 25-100 spectrophotometer equipped with argon ion laser excitation. Nuclear magnetic resonance spectra were measured on a Perkin-Elmer R-12 instrument operating at 60 MHz. Chemical shifts were as follows for δ (D_2O; downfield from sodium 2,2-dimethyl-2-silapentane-5-sulfonic acid): –CH, 4.18 (3.72 for DL-penicillamine); $-CH_3$, 1.68, 1.58 (1.59, 1.50 for DL-penicillamine).

The NMR spectrum shows the expected nonequivalence of the two methyl groups and the presence of a singlet –CH– resonance somewhat downfield of the free ligand resonance. The latter shift is consistent with carboxylate coordination.

X-Ray Data Collection and Reduction. Since crystals effloresced rapidly in air, an irregular prism was rapidly removed from the solution and sealed in a thin-walled Lindemann glass capillary containing the mother liquor. Preliminary Weissenberg and precession photographs indicated a triclinic system. Successful solution and refinement of the structure confirmed the choice of space group as $P\bar{1}$.

A crystal of dimensions 0.30 × 0.22 × 0.22 mm was mounted in a Lindemann tube with a^* coincident with the ϕ axis of a General Electric XRD-6 Datex automated diffractometer. Accurate unit cell measurements were determined by least-squares refinement of the 2θ setting angles for 22 reflections. Crystal data: $a = 9.050$ (15), $b = 7.795$ (6), $c = 9.464$ (7) Å; $\alpha = 115.72$ (9), $\beta = 88.17$ (4), $\gamma = 96.75$ (4)°; $V = 597.20$ Å^3. For $CdBrSO_5NC_5H_{16}$ of mol wt 394.71 with $Z = 2$, the calculated density is 2.194 g cm^{-3}. The measured density in $CCl_4/C_2H_4Br_2$ is 2.13 g cm^{-3} and is presumably low due to loss of water. Assuming the crystal to be a cylinder, with $\mu = 55.3$ cm^{-1} for Mo Kα radiation, the transmission factors range from 0.55 to 0.85. No absorption correction was deemed necessary.

Intensity data were collected at 24 °C by the θ–2θ scan technique out to a maximum of $2\theta = 55°$. Zirconium-filtered Mo Kα radiation (λ 0.7107 Å) and a takeoff angle of 4° were used. The integrated

Table I. Atomic Positions and Thermal Parameters (Fractional, $\times 10^4$) for $\{CdBr[SC(CH_3)_2CH(NH_3)COO]H_2O\}\cdot 2H_2O$[a]

	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
Cd	1443.8 (6)	168.5 (7)	3266.4 (7)	101.4 (7)	148.2 (11)	159.1 (9)	15.7 (6)	6.0 (6)	92.3 (8)
Br	1297.1 (8)	1400.2 (10)	6792.8 (8)	93.2 (9)	183.2 (16)	108.2 (10)	12.9 (9)	0.2 (7)	56.0 (10)
S	6262 (2)	1312 (2)	7015 (2)	85 (2)	161 (3)	131 (2)	−4 (2)	−3 (2)	94 (2)
O(1)	1094 (5)	3112 (6)	3515 (6)	106 (6)	137 (9)	137 (7)	−10 (6)	−24 (5)	82 (7)
O(2)	3410 (5)	3396 (7)	4309 (6)	99 (6)	175 (10)	153 (8)	20 (6)	−9(5)	104 (8)
O(3)	8493 (6)	3782 (8)	2469 (6)	115 (7)	206 (11)	129 (8)	16 (7)	0 (5)	68 (8)
O(4)	8752 (7)	562 (8)	9561 (7)	162 (8)	245 (13)	126 (8)	61 (9)	3 (6)	87 (9)
O(5)	3895 (11)	146 (15)	9128 (11)	263 (16)	495 (30)	277 (18)	−42 (17)	70 (14)	197 (20)
N	6403 (6)	2701 (7)	4486 (6)	96 (6)	129 (10)	87 (7)	17 (6)	−3 (5)	42 (7)
C(1)	2351 (6)	4046 (8)	3983 (7)	73 (6)	125 (11)	85 (7)	12 (7)	2 (5)	49 (7)
C(2)	7407 (6)	3904 (8)	5888 (6)	67 (6)	113 (10)	76 (7)	11 (6)	−1 (5)	33 (7)
C(3)	6714 (7)	3843 (8)	7396 (7)	87 (7)	130 (11)	83 (7)	27 (7)	4 (6)	54 (8)
C(4)	5252 (8)	4736 (11)	7804 (8)	106 (9)	217 (16)	104 (9)	43 (9)	34 (7)	71 (10)
C(5)	7854 (8)	4844 (10)	8736 (8)	122 (9)	176 (14)	86 (8)	6 (9)	−8 (7)	59 (9)

[a] Anisotropic temperature factors are in the form $\exp[-(h^2\beta_{11} + k_2\beta_{22} + l^2\beta_{33} + 2hk\beta_{12} + 2hl\beta_{13} + 2kl\beta_{23})]$.

Table II. Hydrogen Atom Positions (Fractional, $\times 10^3$) and Isotropic Temperature Factors

	x	y	z	B, Å^2
H(1)	835	330	566	1.2 (21)
H(2)	554	334	458	3.7 (22)
H(3)	689	304	356	7.7 (21)
H(4)	630	128	450	8.3 (21)
H(5)	447	396	683	4.9 (21)
H(6)	470	456	858	5.9 (21)
H(7)	447	391	186	4.4 (21)
H(8)	887	430	859	3.0 (21)
H(9)	203	397	100	3.3 (22)
H(10)	754	454	945	4.9 (22)
H(11)	842	501	300	6.9 (22)
H(12)	917	392	316	7.2 (22)
H(13)	968	32	996	9.1 (22)
H(14)	755	−4	965	9.4 (21)

intensities were measured with a scintillation counter employing a pulse height analyzer. The diffracted x-ray beam passed through a collimator of 1-mm diameter placed 5 cm from the crystal and then to the counter via an aperture of 1-cm diameter, approximately 18 cm from the crystal. The scan width was determined by the equation $\Delta\theta = \pm(0.9 + 0.43 \tan\theta)°$ and the scan rate was constant at 2°/min. Stationary-counter background counts of 10 s were taken before and after each scan. The intensities of three standard reflections were monitored after every 100 reflections measured. These fell by ~11% over the course of data collection and were used to scale the data to a common level. From 3460 independent reflections measured, 2534 had intensities $I > 3\sigma(I)$ and were used in the analysis. Lorentz and polarization corrections were applied to the derivation of structure amplitudes.

Structure Solution and Refinement. An unsharpened Patterson synthesis was readily solved to yield approximate positions for the cadmium, bromine, and sulfur atoms. A structure factor calculation[10] based on the positions of the three heavy atoms led to a residual $R = \sum||F_o| - |F_c||/\sum|F_o|$ of 0.25 and allowed unequivocal identification of all remaining nonhydrogen atoms. A cycle of refinement of positional parameters gave $R = 0.144$. Inclusion of isotropic thermal parameters and two further cycles of refinement reduced R to 0.116. Conversion to anisotropic temperature coefficients for all nonhydrogen atoms led to $R = 0.067$. At this stage, a difference Fourier was calculated revealing reasonable positions for 14 hydrogen atoms. In subsequent least-squares refinement hydrogen atom coordinates were fixed but isotropic temperature coefficients were allowed to vary. A weighting scheme of the type $w^{-1} = 6.7195 - 0.2837|F_o| + 0.0062|F_o|^2$ with coefficients derived from the program RANGER was then introduced. Refinement converged at $R = 0.048$ with $R_w = [\sum w(|F_o| - |F_c|)^2/\sum w|F_o|^2]^{1/2}$ of 0.059. In least-squares refinement the function minimized was $\sum w(|F_o| - |F_c|)^2$. Scattering factors including anomalous scattering corrections for cadmium and bromine were taken from ref 11, with the exception of hydrogen values where the data of ref 12 were used.

A final difference Fourier synthesis showed a general background of approximately 0.5 e Å^{-3} with no peaks greater than 1.5 e Å^{-3}. The observed and final calculated structure factor amplitudes are available.[13] Final positional and thermal parameters for nonhydrogen atoms are listed in Table I, with positions and isotropic temperature factors for hydrogen atoms in Table II. Bond lengths and distances are tabulated in Table III.

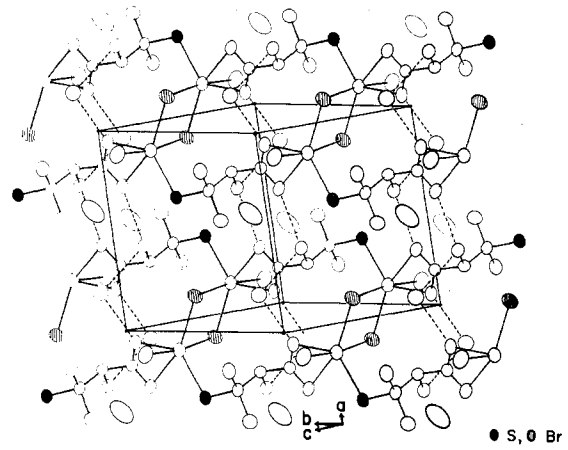

Figure 1. Packing diagram for $\{CdBr[SC(CH_3)_2CH(NH_3)COO]H_2O\}\cdot 2H_2O$ showing the contents of one unit cell.

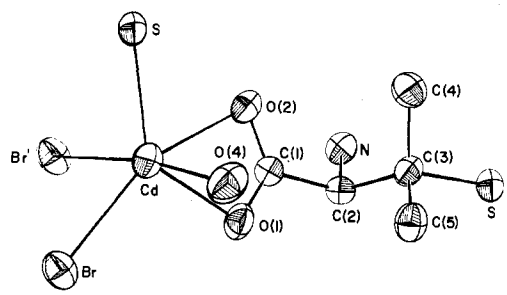

Figure 2. View of the immediate coordination sphere of cadmium in $\{CdBr[SC(CH_3)_2CH(NH_3)COO]H_2O\}\cdot 2H_2O$ showing the mode of bonding of the amino acid. Two water molecules of crystallization have been omitted.

Results and Discussion

Description of the Structure. In the crystal structure (Figure 1) infinite chains of alternating cadmium atoms and bridging, tridentate penicillamine molecules are linked by asymmetric double bromine bridges to give ribbons running parallel to the (100) plane. These ribbons are connected by a system of hydrogen bonds between amino acid moieties and water molecules trapped between the ribbons. Each penicillamine molecule utilizes a deprotonated sulfhydryl group to bind one cadmium atom and two oxygen atoms of the carboxylate group to bond asymmetrically to a second, symmetry-related cadmium atom. The immediate coordination sphere of the cadmium is illustrated in Figure 2 which also gives the atomic numbering scheme used. The cadmium atom is coordinated

Table III. Bond Lengths and Angles

Lengths, Å

Cd–Br	2.6245 (9)	O(3)–H(11)	0.88	Br′–Cd–Br	84.6 (0)	Cd–S–C(3)	109.7 (1)	O(1)–O(3)	2.771 (7)	O(3)–O(4)	3.167 (11)
Cd–Br′	3.0492 (9)	O(3)–H(12)	0.87	Br′–Cd–S	94.0 (0)	Cd–O(1)–C(1)	102.7 (2)	O(1)–O(4)	3.087 (8)	O(3)–N	2.954 (8)
Cd–S	2.444 (2)	O(4)–H(13)	1.00	Br′–Cd–O(1)	92.9 (1)	Cd–O(2)–C(1)	81.7 (2)	O(2)–N	2.848 (7)	O(5)–N	3.167 (11)
Cd–O(1)	2.262 (5)	O(4)–H(14)	1.15	Br′–Cd–O(2)	80.0 (1)	S–C(3)–C(2)	108.1 (2)	O(2)–N	2.733 (8)		
Cd–O(2)	2.715 (5)	C(2)–H(1)	1.00	Br′–Cd–O(4)	171.6 (1)	S–C(3)–C(4)	106.4 (3)				
Cd–O(4)	2.490 (6)	N–H(2)	0.95	Br–Cd–S	127.6 (0)	S–C(3)–C(5)	110.0 (2)				
S–C(3)	1.842 (7)	N–H(3)	1.08	Br–Cd–O(1)	102.1 (1)	C(2)–C(3)–C(4)	112.2 (3)				
C(3)–C(2)	1.557 (8)	N–H(4)	1.10	Br–Cd–O(2)	148.1 (1)	C(2)–C(3)–C(5)	108.5 (3)				
C(3)–C(4)	1.528 (9)	C(4)–H(5)	1.08	Br–Cd–O(4)	91.1 (1)	C(4)–C(3)–C(5)	111.5 (4)				
C(3)–C(5)	1.523 (9)	C(4)–H(6)	0.92	S–Cd–O(1)	130.2 (1)	C(3)–C(2)–C(1)	112.0 (3)				
C(2)–C(1)	1.538 (9)	C(4)–H(7)	0.97	S–Cd–O(2)	81.4 (1)	C(3)–C(2)–N	110.3 (3)				
C(2)–N	1.504 (8)	C(5)–H(8)	1.04	S–Cd–O(4)	94.4 (1)	C(1)–C(2)–N	107.8 (3)				
C(1)–O(1)	1.257 (8)	C(5)–H(9)	0.84	O(1)–Cd–O(2)	51.6 (1)	C(2)–C(1)–O(1)	117.7 (3)				
C(1)–O(2)	1.241 (8)	C(5)–H(10)	0.84	O(1)–Cd–O(4)	80.9 (1)	C(2)–C(1)–O(2)	118.5 (3)				
				O(2)–Cd–O(4)	100.3 (1)	C(1)–C(2)–O(2)	123.8 (3)				
				Cd–Br–Cd	95.4 (0)						

Table IV. Selected Vibrational Frequencies (cm^{-1}) in the Infrared and Raman Spectra of $\{CdBr[SC(CH_3)_2CH(NH_3)COO]H_2O\}\cdot 2H_2O$, the Deuterated Complex, and the Free Ligand

$\{CdBr[Sc(CH_3)_2CH(NH_3)COO]H_2O\}\cdot 2H_2O$		$\{CdBr[SC(CH_3)_2CH(ND_3)COO]D_2O\}\cdot 2D_2O$		$HSC(CH_3)_2CH(NH_3)COO$	$DSC(CH_3)_2CH(ND_3)COO$	
Raman	IR	Raman	IR	IR	IR	Assignments
	~3600 br, sh		~2670 mw			
	~3520 m, br		~2600 m			
	~3400 m, br		~2510 m, br			$\nu(H_2O, D_2O)$ (unbound)
	~3240 m, br		~2450 mw, br	3170 mw, br, sh	2342 m	
~3100–2900 vw,	~3080 m	~2600–2200 vw, vbr	~2310 m	3050 m, br, sh	2244 ms	$\nu_{as}(NH_3, ND_3)$, $\nu_s(NH_3, ND_3)$,
vbr	~3050–2850 m, vbr		~2200 mw	2900 m, vbr	2100 m, br	$\nu(H_2O, D_2O)$ (bound)
				2572 vw[b]	1841 w	ν(S–H, S–D)
1626 vw, br	1625 vs	1197 mw	1197 s	1655 m, sh 1630 s, sh	1194 ms	$\delta_{as}(NH_3, ND_3)$
1596 vw, br	1595 vs	1596 vw, br	1590 s	1614 vs	1617 1605 vs	ν_{as}(COO)
1556 vw, br	1557 vs		1142 s	1571 vs 1537 vs	1144 m	$\delta_s(NH_3, ND_3)$
1417 w	1419 vs	1417 mw	1419 s	1397 vs	1396 vs	ν_s(COO)
1386 w	1391 m	1000 m	1000 w			$\delta(H_2O, D_2O)$
1090 m, br	1098 s	829 m	833 ms	1092 mw 1052 w	785 w 745 w	$\rho_r(NH_3, ND_3)$
698 vw	698 s	536 mw	538 s			
552 m	557 m	346 w, br	350 mw	580 mw	310 w, br	ρ_w or $\rho_r(H_2O, D_2O)$
	525 br, sh		525 br, sh	549 m	550 mw	$\rho_t(NH_3, ND_3)$
380 mw	380 w	378 m	380 vw			ρ_r(COO)
314 w	311 s	313 w	305 m			ν(Cd–O)?
162 vs	160 s, br	163 vs	162 ms, br			ν(Cd–S)[a]
						ν(Cd–Br)[a]

[a] These bands shift to 328 and 150 cm^{-1}, respectively, as the crystal ages (dehydrates). [b] Raman: 2576 (vs) cm^{-1}.

in octahedral fashion by two bromine atoms, a sulfur atom of one amino acid molecule, two oxygen atoms of the carboxylate group of a second amino acid, and the oxygen atom of a water molecule. The Cd–S distance of 2.444 (2) Å appears to be the shortest reported to date even when compared with bond lengths in tetrahedrally coordinated cadmium complexes. For example, in the dialkyldithiocarbamate and *O,O*-diisopropylphosphorodithioates $Cd_2[(C_2H_5)_2CNS_2]_4$[14] and $Cd_2[(i\text{-}C_3H_7O)_2PS_2]_4$[15] where cadmium is tetrahedrally coordinated, Cd–S distances average 2.57 (6) and 2.53 (5) Å. Bond lengths of 2.51 and 2.52 Å have been reported for dichlorobis(imidazoline-2-thione)cadmium[16] while in the $[Cd_{10}(SCH_2CH_2OH)_{16}]^{4+}$ cation[17] where four-, five-, and six-coordinate cadmium atoms are present Cd–S bond lengths of 2.51 Å for trigonal-bipyramidal stereochemistry and 2.56 Å for octahedral were found. The most accurate Cd–S distance reported in the literature is 2.663 (2) Å in cadmium(II) thiodiacetate hydrate[18] where cadmium is octahedrally coordinated by five oxygen atoms and a sulfur atom. The short Cd–S bond in $\{CdBr[SC(CH_3)_2CH(NH_3)COO]H_2O\}\cdot 2H_2O$ also contrasts sharply with the weaker cadmium–sulfur (penicillamine) interaction in $\{Cd[SC(CH_3)_2CH(NH_2)CO-O]\}\cdot H_2O$ (average Cd–S = 2.565 Å)[9] and with the value (2.52 Å) calculated from the sum of cadmium and sulfur tetrahedral covalent radii.[19]

The asymmetric cadmium–bromine double bridge consists of one short metal–bromine interaction (Cd–Br = 2.6245 (9) Å) and one very weak interaction (Cd–Br = 3.0492 (9) Å). The former value is close to the Cd–Br distance expected from sums of covalent radii (2.59 Å) while the latter compares with a limit of 3.332 Å for zero bond formation deduced from the metallic radius of cadmium (1.382 Å) and the van der Waals radius of bromine (1.95 Å).[19] There are three metal–oxygen contacts in the immediate coordination sphere of cadmium. The Cd–O(1) bond to the anisobidentate carboxylate group (2.262 (5) Å) is at the extreme end of the range of cadmium–oxygen distances (2.27–2.52 Å) in non-sulfur-containing amino acid complexes[20] and compares favorably with a range of Cd–O(carboxylate) distances (2.276–2.287 Å) in cadmium(II) thiodiacetate hydrate.[18] By contrast the Cd–O(2)-(carboxylate) bond length (2.715 (5) Å) indicates only a weak interaction. This anisobidentate chelation of the carboxyl group has been noted previously for cadmium maleate dihydrate[21] but appears to be rare for cadmium amino acid complexes.[20] The coordinated water molecule is bound to cadmium in a position which can be loosely described as trans to Br^- in the octahedron with a Cd–O bond length (2.490 (6) Å) considerably longer than corresponding distances in the aquo complexes $Cd(C_4H_4O_4S)H_2O$[18] (2.258 (5) Å) or Cd-(quinoline)$_2(NO_3)_2H_2O$ (2.346 (7) Å).[22]

The most interesting aspect of the present structure is the ligating behavior of the amino acid and the comparison with the recently published structure of D-penicillaminatocadmium(II) hydrate.[9] In $\{CdBr[SC(CH_3)_2CH(NH_3)CO-O]H_2O\}\cdot 2H_2O$ alternate cadmium atoms are strongly bound to sulfhydryl and carboxylate sites of the same amino acid, respectively, with the amino group uncoordinated. The x-ray analysis, a charge balance, and infrared spectra (vide infra) establish that DL-penicillamine is present in the form $^-SC(CH_3)_2CH(N^+H_3)COO^-$. However, for $\{Cd[SC(CH_3)_2C-H(NH_2)COO]\}\cdot H_2O$[9] the amino acid, present in the ionized form $^-SC(CH_3)_2CH(NH_2)COO^-$, utilizes all three types of ligand sites in bonding, albeit rather weakly. Sulfur bridges are present in the latter complex and in the mercury complex $(HgCl_2)_2SC(CH_3)_2CH(NH_3)COOH$[8] but absent in $\{Cd-Br[SC(CH_3)_2CH(NH_3)COO]H_2O\}\cdot 2H_2O$.

Comments on Cadmium–Penicillamine Binding. The present study prompts several observations relevant to the toxicology and general biochemical behavior of Cd^{2+}. First of all, in neutral solution, Cd^{2+} exhibits a strong affinity for bromide ion even in the presence of a fourfold excess of amino acid. We were unable to synthesize bromide-free complexes from $CdBr_2\cdot 4H_2O$ and penicillamine in neutral solution. It appears that Hg^{2+} also binds halide ion in competition with sulfur amino acids.[8] Since chloride ion is an important environmental and biological ligand, it seems likely that mixed Cl^-/amino acid complexes of Hg^{2+} and Cd^{2+} play an important role in biotransport and biotransformation of these heavy metals. In support of this, the stability constants for $CdCl^+$ and $CdBr^+$ in aqueous solution are similar[23] and we have isolated chlorocadmium–L-cysteine complexes from the reaction of cadmium chloride with L-cysteine. A second point concerns the relative affinities of Hg^{2+} (a soft acid) and Cd^{2+} (a borderline acid) toward S, N, and O donor sites. These affinities should be related to cell site specificities. A comparison of binding sites and metal–ligand bond lengths should ideally be made for two complexes of the same stoichiometry but unfortunately the crystalline penicillamine complexes of Hg^{2+} which have been structurally characterized have stoichiometries $[(HgCl_2)_2[SC(CH_3)_2CH(NH_3)COOH]]\cdot 2H_2O$ and $\{Hg[SC-(CH_3)_2CH(NH_3)]COOH]_2Cl\}Cl\cdot H_2O$[8] different from those of the two Cd^{2+} species. Nevertheless the following general points emerge: Cd^{2+} favors weaker binding to a larger number of sites than does Hg^{2+}; cadmium is six-coordinate in $\{CdBr[SC(CH_3)_2CH(NH_3)COO]H_2O\}\cdot 2H_2O$ and $\{Cd[S-C(CH_3)_2CH(NH_2)COO]\}H_2O$ whereas Hg^{2+} is three-coordinate in $\{Hg[SC(CH_3)_2CH(NH_3)COOH]_2Cl\cdot H_2O$[8] and four-coordinate in $\{(HgCl_2)_2[SC(CH_3)_2CH(NH_3)COO-H]\}\cdot 2H_2O$. Direct comparison of metal–ligand bond lengths is often of dubious significance when different coordination numbers are involved. However, it is worth noting here that the primary Hg–S bonds in the penicillamine complexes (average 2.345 Å) are much shorter than in the cadmium compounds (average 2.505 Å), despite the identity of covalent radii (2.48 Å) for mercury and cadmium. Furthermore, neither mercury–carboxylate nor mercury–amine bonding is present in the penicillamine complexes in sharp contrast with the case of the Cd^{2+} species. The present work thus appears to confirm that Cd^{2+} has an affinity for sulfhydryl sites somewhat weaker than Hg^{2+} but that it approaches the behavior of Zn^{2+} in exhibiting a tendency to bind carboxylates. Clearly these facts may contribute substantially to the experimentally observed antagonism of Zn^{2+} and Cd^{2+} in biochemistry.[24]

Finally, structural characterization of $\{CdBr[SC(CH_3)_2-CH(NH_3)COO]H_2O\}\cdot 2H_2O$ and $\{Cd[SC(CH_3)_2CH(NH_2)-COO]\}\cdot H_2O$ allows an assessment of previous literature data for Cd^{2+}/penicillamine complexes. Lenz and Martell[5] suggested tridentate coordination of DL-penicillamine in the 1:1 cadmium complex in solution. In $\{Cd[SC(CH_3)_2CH(N-H_2)COO]\}\cdot H_2O$ the amino acid is tridentate but *not* to one metal ion. A 3:1 penicillamine/Cd^{2+} complex has been briefly mentioned but not isolated.[25] There have been no reports of halide-containing penicillamine complexes of Cd^{2+}. It is of interest that for the related amino acid L-cysteine, Cd^{2+} binds S and N sites in basic solution, but in acid, there is no strong interaction with any of the potential sites.[26] Glutathione binds similarly in alkaline solution.[27] There is as yet no solid-state structural data for the L-cysteine complexes.

In view of the postulated nature of cadmium–protein binding in metallothionein, synthesis and characterization of Cd^{2+}/penicillamine or Cd^{2+}/cysteine complexes rich in amino acid would appear a worthwhile goal. Work on models for metallothionein is currently under way in this laboratory.

Vibrational Spectra. Infrared and Raman spectra of $\{CdBr[SC(CH_3)_2CH(NH_3)COO]H_2O\}\cdot 2H_2O$, the deuterated

complex, and the free ligand (Table IV) were examined in an attempt to provide diagnostic criteria for the bonding mode of penicillamine established by x-ray analysis. In the free amino acid ν(S–H) appears as a very intense Raman band at 2576 cm^{-1}; there is a weak infrared counterpart at 2572 cm^{-1}. The disappearance of these bands on complexation provides an effective criterion for metal–sulfur bonding. The deuteration experiments allow unambiguous assignment of ν(COO) and $\delta(NH_3)$ bands in the 1500–1700-cm^{-1} region (Table IV). The invariant frequencies of strong infrared bands at 1595 and 1419 cm^{-1} in $\{CdBr[SC(CH_3)_2CH(NH_3)COO]H_2O\}\cdot 2H_2O$ (1590 and 1419 cm^{-1} in the deuterated complex) establish these as ν_{as}(COO) and ν_s(COO) respectively. The frequency separation $\sim$176 cm^{-1} is in the middle of the range usually associated with coordinated COO^- groups of amino acids.[28,29] There are two types of water molecule in the crystal, those bonded to cadmium and those "trapped" in the lattice as water of crystallization; only the latter are lost on leaving crystals to effloresce in air (see Figure 1). Bands occurring in the region 3400–3600 cm^{-1} for the cadmium complex fall in the range expected for ν(O–H) of lattice water. There are several isotope-sensitive absorptions within a broad-band envelope stretching from 2800 to 3240 cm^{-1} which are undoubtedly due to ν(O–H) of ligated water and/or $\nu(NH_3)$. It is unrealistic to attempt a detailed assignment for these bands. Finally, in the far-infrared region, strong bands at 160 and 311 cm^{-1} are essentially unchanged on deuteration and we assign these to $\nu(Cd–Br)_{br}$ and ν(Cd–S), respectively. It is of interest that ν(Hg–S) has recently been located in a similar spectral region for a range of sulfur-bound amino acid complexes.[30–34]

Registry No. $\{CdBr[SC(CH_3)_2CH(NH_3)COO]H_2O\}\cdot 2H_2O$, 60873-93-0.

Supplementary Material Available: Listing of structure factor amplitudes (15 pages). Ordering information is given on any current masthead page.

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