Cadmium Coordination Chemistry Related to Chelate Therapy*

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Abstract

Various aspects of the coordination chemistry of cadmium in its dithiocarbamate complexes, which are known to affect the *in vivo* distribution of this toxic metal ion have been examined. Under appropriate conditions, solid complexes of the composition $Cd(DTC)_2$ have been obtained as reaction products with seven dithiocarbamates. The general properties, octanol/water partition coefficients, mass spectra, ^1H, ^{13}C and ^{113}Cd NMR spectra and infrared spectra have been obtained. The molecular structure of the $Cd\{S_2CN(n\text{-}C_4H_9)_2\}_2$ complex has been determined. This compound forms monoclinic crystals $C2/c$, a = 23.577(7), b = 16.877(8), c = 16.209(9) Å, β = 126.93(3)°, V = 5156(8) Å^3, Z = 8, density = 1.343 g cm^{-3}. For the structure determination: λ(Mo Kα) = 0.71073 Å, μ = 1.076 mm^{-1}, $F(000)$ = 2160, T = 296 K and R = 0.064 for 1330 observed reflections. The Cd ion is coordinated to four S atoms at distances ranging from 2.513(5) to 2.601(7) Å and to a fifth one at the much longer distance of 2.888(5) Å. Two of the short metal–sulphur distances are realized by the S atoms of one of the chelate moieties whilst the S atoms of the other moiety realize one short and the longest [2.888(5) Å] metal sulphur distance. The other short bond is subtended to a sulphur atom of an asymmetry-related ligand. The coordination polyhedron can be described as either a very distorted tetragonal pyramid or a very distorted trigonal bipyramid. The shortest Cd–Cd distance is 3.772(6) Å.

Introduction

The development of effective antidotes for cadmium intoxication has proven to be a task of considerable difficulty. The first attempts at this were made over forty years ago [1–4] and there is no clear evidence that the end is in sight, though considerable progress has been made in this area, especially since 1980. The reasons for this difficulty are quite numerous. Firstly, on a molar basis, cadmium is much more toxic than lead, and the normal physiological processes by which it is immobilized involve its bonding to an intracellular protein in the liver and the kidney [5] rather than the semi-permanent deposition of lead in the bone. This metal–intracellular protein complex, cadmium metallothionein (CdMT) does have a reasonably slow rate of transfer from one organ to another, but the long term trend is for the cadmium to be mobilized into the serum in the form of this CdMT complex and ultimately pass to the kidneys, an organ which can be destroyed by CdMT, which is more toxic to it than cadmium bound to high molecular weight serum proteins [5]. Some chelating agents form complexes which are, like CdMT, more toxic to the kidneys than normal cadmium bound to serum proteins [6, 7]. The general goal of chelate therapy is usually the development of chelating agents which will reduce the body burden of a toxic metal by transforming it into a form in which it can be excreted in the urine. The great majority of the chelating agents which form very stable complexes with Cd^{2+} are confined to the extracellular space *in vivo*, a property which renders them unable to effectively mobilize cadmium once it has passed into intracellular sites. Since this passage to intracellular sites occurs quite rapidly [7], these compounds are effective antagonists only while the cadmium is still in the extracellular space [8]. In recent years it has become apparent that two types of chelating agents can mobilize cadmium from its intracellular deposits; uncharged vicinal dithiols (such as BAL or 2,3-dimercapto-1-propanol) [9] and dithiocarbamates [10, 11]. Oddly enough relatively little is known about the behavior of cadmium complexes with either of these types of chelating agents. The

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present study was undertaken to obtain chemical information on various aspects of the coordination chemistry of cadmium with those dithiocarbamates which are known from animal studies to be capable of removing cadmium from intracellular deposits. A more detailed knowledge of these complexes, and the way in which they interact with typical low molecular weight cadmium binding species of the sort found in the serum or the cytosol is expected to assist in the design of molecular structures and procedures which are more effective in counteracting the life-threatening processes which inevitably develop in those individuals with chronic cadmium intoxication.

Experimental

The chelating agents were synthesized using procedures described earlier [11, 12]. The cadmium complexes were prepared by the procedure illustrated for the compound with bis(n-butyl)dithiocarbamate. The chelating agent (7.69×10^{-3} mol) was dissolved in 50 ml of water to which was then added, slowly and with stirring a solution of 3.84×10^{-3} mol of $CdSO_4 \cdot \frac{8}{3}H_2O$ in water. A white precipitate appeared immediately which was allowed to equilibrate with the stirred solution for several hours. It was then collected by suction on a fritted glass filter, washed with water and then dried over P_4O_{10}, to obtain 1.57 g (80% yield). This solid was dissolved in ethyl ether and allowed to evaporate slowly. This resulted in the formation of needle-like crystals which were then used in the crystallographic study.

Infrared spectra were obtained using a Perkin-Elmer 180 instrument; NMR spectra were obtained using the following apparatus: ^1H and ^{13}C in a Brüker WM-250 and Brüker AM-300; ^{113}Cd using a modified Brüker WP-200 [13] and a Brüker WM-250. The mass spectra were obtained using a Nermag-Sidar instrument. The thermogravimetric (TG) curves were obtained on a Regaku Thermoflex balance with a sample size between 9 and 15 mg and heating rate of 3 °C min^{-1} in an air atmosphere.

For the X-ray structural determination, a prismatic, transparent crystal, $0.075 \times 0.200 \times 0.375$ mm, was used in an Enraf Nonius CAD-4 diffractometer, graphite monochromated Mo Kα, cell parameters by least-squares on setting angles from 25 reflections, $7.4° < \theta < 17.4°$, ω–2θ scans, scan width $[0.80 + 0.35 \tan(\theta)]°$, max. scan speed 5.0° min^{-1}, *hkl* range: $-28 < h < 23, k < 18, l < 20, \theta_{max} = 25°$; standard $10\bar{4}1$ varied ±4.2% of mean intensity over data collection; 3765 reflections measured, 3665 unique, $R_{int} = 3.8\%$, 1330 observed above $3\sigma(I)$, L_p and absorption corrections (max. and min. transmission factors 0.9224, 0.7674); structure solved by Patterson and Fourier Methods. In final cycles of blocked full-matrix least-squares refinement only Cd and S atoms were anisotropic. H atoms (except methyl ones) were obtained from difference synthesis, all with fixed isotropic $U = 0.05$ Å^2. Function minimized: $\Sigma w(|F_o| - |F_c|)^2$ with $w = [\sigma^2(F_o) + 0.0015F_o^2]$, 127 parameters refined. Inspection of F_c and F_o values indicated a correction for secondary extinction required $[F_{corr} = F_c/[1.0 - \chi F_c^2/\sin\theta]$, where χ refined to 3.3×10^{-8} in the final run; excluded unobserved reflections $R = 0.064$, $R_w = 0.069$; max. shift/e.s.d. = 0.01; $\Delta\rho$ excursions within 0.53 and −0.38 e Å^{-3}. Refinement of data included scattering factors for non H atoms [14], correction for anomalous dispersion [15], H atoms [16], and the use of the programs SHELX-76 [17] and ORTEP [18]. Calculation were performed on a VAX 11/780 computer.

The partition coefficients were determined by shaking the complexes with a mixture containing equal volumes of water and octanol. The concentration of the complex in each phase was then determined by measurement of the absorption of the solution in the ultraviolet ($\lambda = 206$ and 259 nm) where the absorption was linearly related to the concentration of the complex.

Results and Discussion

The analytical data on the cadmium complexes which were prepared are presented in Table 1 and are

TABLE 1. Elemental Analyses of the Cadmium Complexes $CdL^n{}_2$ Prepared[a]

Complex	% C(?)[b]	% H(?)*	% N(?)*
(1) $CdL^1{}_2 \cdot H_2O$	13.74 (14.02)	2.34 (2.92)	7.93 (8.13)
(2) $CdL^2{}_2$	19.74 (20.43)	3.39 (3.40)	7.72 (7.94)
(3) $CdL^3{}_2$	25.08 (25.25)	4.20 (4.20)	7.08 (7.35)
(4) $CdL^4{}_2$	28.71 (29.40)	5.50 (4.89)	6.36 (6.85)
(5) $CdL^5{}_2$	35.94 (36.16)	6.17 (6.17)	5.85 (6.03)
(6) $CdL^6{}_2$	40.00 (41.50)	6.77 (6.91)	5.11 (5.38)
(7) $CdL^7{}_2$	40.91 (41.50)	6.89 (6.91)	5.11 (5.38)

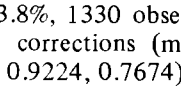
[a] L^n =  ; L^1: $R_1 = H$, $R_2 = Me$; L^2: $R_1 = H$, $R_2 =$ Et; L^3: $R_1 = H$, $R_2 =$ Prop; L^4: $R_1 = H$, $R_2 =$ But; L^5: $R_1 =$ Prop, $R_2 =$ Prop; L^6: $R_1 =$ But, $R_2 =$ But; L^7: $R_1 =$ i-Prop, $R_2 =$ i-Prop. [b] Theoretical analyses.

TABLE 2. Solubilities, Melting Points, Colors and Octanol/Water Partition Coefficients of the Cadmium Complexes

Compound	Melting point[b] (°C)	Color	Solvents	Partition coefficient[a]
$CdL^1_2 \cdot H_2O$	149d	yellow	DMSO	
CdL^2_2	143d	yellow	DMSO	4.4
CdL^3_2	136d	white	DMSO	
CdL^4_2	131d	yellow	DMSO, acetone, ethanol	14.7
CdL^5_2	146	white	DMSO, CCl_4, C_6H_6, $CHCl_3$, ether, acetone	
CdL^6_2	137	white	DMSO, CCl_4, C_6H_6, $CHCl_3$, ether, acetone	10.9
CdL^7_2	172	white	DMSO, CCl_4, C_6H_6, $CHCl_3$, ether, acetone, hot ethanol, hot methanol	68.4

[a]The partition coefficient is the ratio of the concentration of the cadmium complex in n-octanol to its concentration in water when these are equilibrated. [b]d indicates that melting occurs with decomposition.

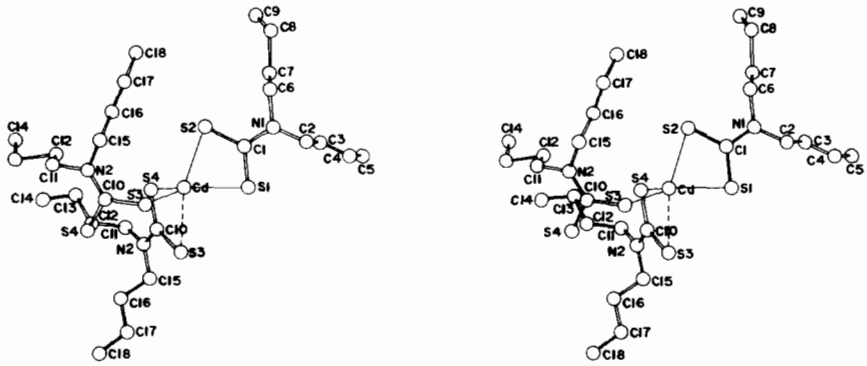


Fig. 1. Ortep stereoview of bis(dibutyldithiocarbamate)cadmium(II) complex showing the atom numbering and the coordination polyhedron surrounding the cadmium(II).

in good agreement with the expected values. The data collected on melting points, solubilities, color and octanol/water partition coefficients are shown in Table 2. The X-ray structure of the cadmium complex of di-n-butyl dithiocarbamate is shown in Fig. 1, for which the atomic coordinates, internuclear distances and bond angles are shown in Tables 3, 4 and 5. The very high temperature factors of some atoms, in particular those of the methyl carbons at the end of the aliphatic chains, are indicative of some positional disorder not uncommon for these types of groups, which is responsible for the rather poor quality of the diffraction data and the consequently high standard deviation in the interatomic bond distances and angles. See also 'Supplementary Material'. The infrared spectra are shown in Table 6 for the sodium salts and cadmium complexes of the chelating agents. The ^{113}Cd, ^1H and ^{13}C NMR spectra of these compounds are shown in Tables 7, 8 and 9.

The data presented in Table 2 shows that the complexes have only a very slight solubility in water and have partition coefficients significantly greater than unity. The solubility in organic solvents of very low dielectric constant is greater for the dialkyl derivatives, information in good accord with the greater ability of the dialkyl derivatives (in comparison to the monoalkyl derivatives) to facilitate the entry of cadmium into the brain in experimental animals [19].

The melting points and behavior on melting suggest a clear difference in the stability of the mono- and the dialkyl derivatives. Thermogravimetric studies (results not shown) confirm this. $Cd(S_2CNRH)_2$ lose mass between 100 and 250 °C. The mass of the residues correspond to the formation of CdS or a mixture of this and CdO. In the thermogravimetric curves there is only a single important mass change, except in compound 4, where an initial inflection corresponds to the formation of $Cd(SCN)_2$ and a second corresponding to the sulfide. The complexes of the type $Cd(S_2CNR_2)_2$ suffer their loss of mass at a level of temperature much higher than is found for the monoalkyl derivatives, *i.e.* 230–320 °C. Compound 7 gives rise to a residue which represents approximately 20% of the original mass, exactly as reported by Riekkola and Mäkitie [20] who found that, in a current of N_2, the final mass was much less than that anticipated on the basis of CdO. This demonstrates that the compound is volatile, whence the utility in chromatographic analysis [20, 21]. The other dialkyl derivatives (including Et_2dtc^-) decompose to a considerable extent to give a mixture of

TABLE 3. Atomic Coordinate Positions for $Cd\{S_2CN(But)_2\}_2$

Atom	x/a	y/b	z/c	B_{eq}
Cd	0.0948(1)	0.4234(1)	0.2956(1)	6.65(5)
S(1)	0.1405(3)	0.2970(3)	0.2684(4)	7.3(2)
S(2)	0.2315(3)	0.4152(4)	0.4311(5)	10.2(2)
C(1)	0.222(1)	0.326(1)	0.371(1)	6.8(4)
N(1)	0.2797(9)	0.280(1)	0.406(1)	8.8(4)
C(2)	0.273(1)	0.207(1)	0.352(2)	8.5(5)
C(3)	0.282(1)	0.221(2)	0.266(2)	11.5(7)
C(4)	0.271(1)	0.159(2)	0.208(2)	13.8(9)
C(5)	0.280(1)	0.172(2)	0.121(2)	13.1(8)
C(6)	0.353(1)	0.299(2)	0.510(2)	11.4(7)
C(7)	0.385(2)	0.346(2)	0.484(2)	13.5(8)
C(8)	0.468(3)	0.352(3)	0.606(4)	25(1)
C(9)	0.486(3)	0.424(4)	0.593(5)	33(1)
S(3)	−0.0442(3)	0.4152(3)	0.0996(3)	6.6(2)
S(4)	0.0552(3)	0.5516(3)	0.1969(4)	7.5(2)
C(10)	−0.0232(9)	0.515(1)	0.099(1)	6.0(4)
N(2)	−0.0697(8)	0.5602(9)	0.018(1)	6.9(3)
C(11)	−0.054(1)	0.644(1)	0.012(1)	8.0(5)
C(12)	−0.068(1)	0.697(1)	0.071(2)	9.0(5)
C(13)	−0.028(2)	0.788(2)	0.080(3)	17(1)
C(14)	−0.060(3)	0.844(3)	0.103(4)	26(1)
C(15)	−0.137(1)	0.533(1)	−0.071(1)	7.8(5)
C(16)	−0.202(1)	0.561(1)	−0.080(1)	7.1(4)
C(17)	−0.270(1)	0.533(2)	−0.176(2)	10.7(7)
C(18)	−0.334(2)	0.559(2)	−0.184(2)	13.1(8)

TABLE 4. Interatomic Distances for $Cd[S_2CN(But)_2]_2$

Cd–S(1)	2.545(6)
Cd–S(2)	2.593(8)
Cd–S(3)	2.888(5)
Cd–S(3)	2.601(7)*
Cd–S(4)	2.513(5)
S(1)–C(1)	1.69(2)
S(2)–C(1)	1.73(2)
C(1)–N(1)	1.36(3)
N(1)–C(2)	1.46(3)
N(1)–C(6)	1.56(3)
C(2)–C(3)	1.55(4)
C(3)–C(4)	1.32(4)
C(4)–C(5)	1.56(5)
C(6)–C(7)	1.33(5)
C(7)–C(8)	1.76(7)
C(8)–C(9)	1.3(1)
S(3)–C(10)	1.76(2)
S(4)–C(10)	1.67(2)
C(10)–N(2)	1.33(2)
N(2)–C(11)	1.48(3)
N(2)–C(15)	1.43(3)
C(11)–C(12)	1.48(3)
C(12)–C(13)	1.76(5)
C(13)–C(14)	1.39(7)
C(15)–C(16)	1.52(4)
C(16)–C(17)	1,49(3)
C(17)–C(18)	1.50(5)

TABLE 5. Bond Angles (°) for $Cd[S_2CN(But)_2]_2$

S(1)–Cd–S(2)	70.2(2)
S(1)–Cd–S(3)	95.0(2)
S(1)–Cd–S(4)	130.2(2)
S(1)–Cd–S(3)	118.5(2)
S(2)–Cd–S(3)	160.1(2)
S(2)–Cd–S(4)	112.5(2)
S(2)–Cd–S(3)	105.6(2)
S(3)–Cd–S(4)	66.4(2)
S(3)–Cd–S(3)	93.1(2)
S(4)–Cd–S(3)	108.7(2)
S(1)–C(1)–S(2)	119(1)
S(1)–C(1)–N(1)	120(1)
S(2)–C(1)–N(1)	120(1)
C(1)–N(1)–C(2)	121(1)
C(1)–N(1)–C(6)	121(1)
C(2)–N(1)–C(6)	118(1)
N(1)–C(2)–C(3)	113(1)
C(2)–C(3)–C(4)	116(1)
C(3)–C(4)–C(5)	117(1)
N(1)–C(6)–C(7)	105(1)
C(6)–C(7)–C(8)	98(1)
C(7)–C(8)–C(9)	97(1)
S(3)–C(10)–S(4)	120(1)
S(3)–C(10)–N(2)	119(1)
S(4)–C(10)–N(2)	121(1)
C(10)–N(2)–C(11)	121(1)
C(10)–N(2)–C(15)	124(1)
C(11)–N(2)–C(15)	114(1)
N(2)–C(11)–C(12)	112(1)
C(11)–C(12)–C(13)	105(1)
C(12)–C(13)–C(14)	105(1)
N(2)–C(15)–C(16)	116(1)
C(15)–C(16)–C(17)	113(1)
C(16)–C(17)–C(18)	113(1)

TABLE 6. Most Significant Infrared Bands

Compound	ν(OH)	ν(NH)	ν(CN)	ν(CS)
$NaL^1 \cdot 2H_2O$	3400sb	3200s	1525	955s
$CdL^1_2 \cdot H_2O$		3260s	1535	960s, 955s
$NaL^2 \cdot 2H_2O$	3400sb	3200s	1520s	955s
CdL^2_2		3240s	1530s	980s
$NaL^3 \cdot 2H_2O$	3400sb, 3300sb	3200s	1510s	950s
CdL^3_2		3200s	1530s	970s
$NaL^4 \cdot 3H_2O$	3400sb	3220s	1500s	920s
CdL^4_2		3190s	1520s	945s, 930s
$NaL^5 \cdot 3H_2O$	3380sh		1470s	970s
CdL^5_2			1495s	970s
$NaL^6 \cdot 2H_2O$	3400sb		1465s	975s
CdL^6_2			1490s	950s, 955sh
$NaL^7 \cdot 4H_2O$	3400sb		1465s	975s
CdL^7_2			1490s	980s

TABLE 7. ^{113}Cd Resonances[a]

Compound	Resonances
$CdL^1_2 \cdot H_2O$	216.94 (DMSO)
CdL^2_2	226.72 (DMSO); 231.28 (Pyr)
CdL^3_2	229.47 (DMSO)
CdL^4_2	227.36 (DMSO)
CdL^5_2	323.96 ($CHCl_3$); 215.81 (DMSO)
CdL^6_2	324.49 ($CHCl_3$); 216.39 (DMSO); 229.72 (Pyr)
CdL^7_2	329.73 ($CHCl_3$); 223.59 (DMSO)

[a]DMSO = dimethylsulfoxide; Pyr = pyridine. In ppm referenced to 0.1 M aqueous $Cd(ClO_4)_2$.

the sulfide and oxide of cadmium(II). The differing stability of $Cd(S_2CNRH)_2$ compared to $Cd(S_2CNR_2)_2$ also shows itself in their mass spectra. For the dialkyl compounds the molecular ion is clearly observable and it undergoes a fragmentation in general accord with the description of Riekkola [22]. Similarly, Bond *et al.* [23] found a very weak signal corresponding to the dimer which has lost a ligand (Cd_2L_3) but no molecular ion corresponding to the dimer itself.

The mass spectra of the monoalkyl derivatives are very different. The signals of high mass species are weak and complex. With CdL^1_2 and CdL^4_2 one observes peaks corresponding to $[M]^+$, though the profile of the signal suggests that it is probably a mixture of $[M]^+$, $[M-H]^+$ and $[M-2H]^+$. It must be noted that the intensity of this signal in the case of CdL^4_2 only amounts to 0.3% of the peak corresponding to $[But\text{-}N{=}C{=}S]^+$, the most intense among the indentifiable ligand signals, while $[M]^+$ in CdL^6_2 is 55% of the peak corresponding to $[L]^+$, the most intense signal of the spectrum. The presence, in all of the spectra of the mono-alkyl derivatives, of weak signals corresponding to masses greater than that of the monomer, suggests that these derivatives are partly associated.

In CdL^6_2 the Cd ion is coordinated, Fig. 1, to four S atoms at distances ranging from 2.513(5) to 2.601(7) Å and to a fifth one at the much longer distance of 2.885(5) Å. Two of the short metal–sulfur distances are realized by the S atoms of one of the chelate moieties (S(1) and S(2)) while the S atoms of the other moiety realize one short [Cd–S(4)] and the longest [Cd–S(3)] metal–sulphur distance. The other short bond is subtended to a sulphur atom S′(3), symmetry-related to S(3) by the two-fold axis transformation $-x$, y, $\frac{1}{2}-z$. This sharing of a sulphur atom gives rise to a dimeric unit in which one of the ligands forms a four-membered chelate ring and the other is coordinated to two different Cd ions while at the same time it completes a chelate ring with a remarkably long approach distance. This situation is similar to that in cadmium

TABLE 8. ^{13}C NMR Spectra[a]

Compound	R_1	R_2	C^1		C^2		C^3		C^4		C^5	
			NaL	CdL_2	NaL	CdL_2	NaL	CdL_2	NaL	CdL_2	NaL	CdL_2
$CdL^1_2 \cdot H_2O$	H	$-C^2H_3$	215.14	206.68	33.69	36.11						
CdL^2_2	H	$-C^2H_2-C^3H_3$	213.91	205.34	41.06	44.61	14.11	13.27				
CdL^3_2	H	$-C^2H_2-C^3H_2-C^4H_3$	214.30	205.75	48.50	51.71	21.80	21.13	11.60	11.27		
CdL^4_2	H	$-C^2H_2-C^3H_2-C^4H_2-C^5H_3$	215.52	205.59	46.51	49.64	30.74	29.81	19.85	19.44	13.88	13.52
CdL^5_2	$-C^2H_2-C^3H_2-C^4H_3$	$-C^2H_2-C^3H_2-C^4H_3$	212.18	204.35	54.17	57.16	20.12	19.78	11.34	10.92		
CdL^6_2	$-C^2H_2-C^3H_2-C^4H_2-C^5H_3$	$-C^2H_2-C^3H_2-C^4H_2-C^5H_3$	212.25	204.08	52.62	55.34	29.37	28.51	20.09	19.45	14.10	13.56
				202.42[b]		55.76[b]		28.19[b]		19.35[b]		12.96[b]
CdL^7_2	$-C^2H_2-C^3H(C^4H_3)_2$	$-C^2H_2C^3H(C^4H_3)_2$	213.75	205.79	60.93	62.97	26.61	26.32	20.33	19.81		

[a]Run in DMSO-d_6, shifts relative to external TMS. [b]In Cl_3CD solution.

TABLE 9. Proton NMR Spectra[a]

Compound	HN		H^2		H^3		H^4		H^5	
	NaL	CdL_2	NaL	CdL_2	NaL	CdL_2	NaL	CdL_2	NaL	CdL_2
$CdL^1_2 \cdot H_2O$	8.18b	9.80q	2.78d	2.85d						
CdL^2_2	8.23t	9.88t	3.37q	3.31q	1.01t	1.10t				
CdL^3_2	8.01t	9.92t	3.18m	3.24m	1.43se	1.53se	0.76t	0.85t		
CdL^4_2	8.01b	9.91t	3.18q	3.27q	1.40qu	1.49qu	1.22se	1.26se	0.84t	0.86t
CdL^5_2			3.84t	3.72t	1.60se	1.71se	0.77t	0.83t		
CdL^6_2			3.89t	3.75t	1.76qu	1.67qu	1.19se	1.26se	0.86t	0.89t
CdL^7_2			3.83d	3.68d	2.40sp	2.38sp	0.82d	0.89d		

[a]Run in DMSO-d_6, shifts relative to external TMS, protons numbered as shown in Table 8; s = singlet; d = doublet; t = triplet; q = quartet; qu = quintet; se = sextet; sp = septet; m = multiplet; b = broad.

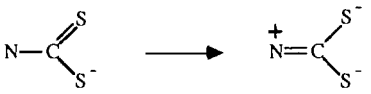
diethyldithiocarbamate [24] in spite of the fact that this compound crystallizes in a different space group. The inter-ion chelate bite is certainly responsible for the rather short Cd–Cd distance of 3.772(6) Å. The coordination polyhedron can be described as either a very distorted tetragonal pyramid or a very distorted trigonal bipyramid. Two points of considerable interest in the structure of cadmium(II) dithiocarbamate complexes, which are seen again here with the dibutyl complex, are the fact that the cadmium exhibits a coordination number of 5, and the abnormally short 'bite' of the dithiocarbamate group when it acts as a chelating agent. Both of these factors may play a role in the ability of dithiocarbamates to remove cadmium from its binding sites in metallothionein [25, 26] in which it exhibits tetrahedral coordination with sulfur atoms from cysteine residues in the protein chain [27, 28]. The ability to form a fifth weak bond with a sulfur donor suggests that this may be the initial step in the overall process in which sulfur containing chelating agents, such as dithiocarbamates or 2,3-dimercapto-1-propanol (BAL), remove cadmium from CdMT *in vivo*. The overall rate of this process would appear to be consistent with the initial formation of a weak Cd–S bond and a subsequent slow-step in which one of the short bonds between cadmium and a sulfhydryl group on MT is replaced to give a cadmium atom which is chelated to both metallothionein and neighboring S atoms on the attacking chelating agent. The subsequent reaction of an additional chelating agent molecule could then occur by a similar process resulting in a further loosening of the bonds between Cd and the MT. An overall process of this sort is consistent with the report third-order dependence on BAL concentration, of hepatic cadmium mobilization [29].

In Table 6 are collected the infrared bands of greatest interest of the compounds which were prepared. The band found at 3200 cm^{-1} in the free ligands and assigned to the ν(N–H) [30] does not undergo any appreciable displacement upon coordination. On the other hand, ν(C–N), which, in the sodium salts is found in a region of the spectrum indicative of the presence of a certain amount of double bond character {ν(C=N) = 1690–1640 cm^{-1}; ν(C–N) = 1350–1250 cm^{-1} [31]}, is displaced towards larger frequencies in the complexes, indicating a reinforcement of this double bond character. A single band assigned to ν(C–N) situated at greater frequencies than in the free ligand in conjunction with a single band or two very close bands around 1000 cm^{-1} associated with ν(C–S), is considered indicative of dithiocarbamate acting as a bidentate ligand [32, 33]. The infrared spectra of the complexes prepared here all show this type of pattern expected for bidentate dithiocarbamate. Nevertheless, it is necessary to note that the spectrum of the compound CdL^6_2, for which the structure has been determined here using X-ray diffraction (see above) and which has bidentate chelate and bidentate bridged ligands, does not show any complexity in the zones of ν(C–N) or ν(C–S). For this reason it does not appear easy to decide from such IR data whether chelate or bridging dithiocarbamates are present.

In the ^{13}C NMR spectra in DMSO-d_6 (Table 8), one does not find different signals for the carbon atoms of the two types of ligands which occur in the structure of CdL^1_2 in the solid state, nor are such different signals found in the spectra of the other complexes. This may be due to a rapid interchange of the ligands in solution (although all of the signals were very sharp) or, as suggested by the shielding of the ^{113}Cd NMR signals when the solvent change from $CHCl_3$ to DMSO (Table 7), the oxygen atom of DMSO molecules may be introduced into the coordination sphere of the cadmium and thus change the structure from that observed in the solid state.

The ^{13}C NMR peaks of the group-CS_2^- are found, in all cases, at around 200 ppm, which indicates that the bidentate character of the ligands is maintained in spite of the possible coordination of the solvent [34]. It is to be noted that this group appears to be more effectively shielded in the complexes of

cadmium than in their sodium salts, as might be expected if the complexation with the cadmium caused a redistribution of charge as



in which the bond order of the C–N bond is increased because this bond is more shielding than the C=S bond [35]. The strong shielding of the C^2 carbon atoms (Table 8) supports such a redistribution of charge.

The behavior of the NH groups in the ^1H NMR spectra (Table 9) which undergo considerable deshielding when the sodium salt reacts to give the cadmium(II) complex, confirms this interpretation. Even though the participation of these groups in a hydrogen bond cannot be eliminated, the position of its peaks (which appear as doublets because of coupling with the H^2 across the N) does not depend on the concentration. On the other hand, the hydrogen atoms H^2 (Table 9), in contrast to the carbon atoms C^2, exhibit slight shielding or deshielding, an effect which may arise from the fact that they are influenced, in different media, by the anisotropic effect of the C=N bond [36].

The bearing of these results on the *in vivo* behavior of cadmium in the presence of dithiocarbamates is quite direct. The variability of the coordination number of cadmium in its dithiocarbamate complexes indicates that mechanisms by which this ligand removes cadmium from *in vivo* sites probably occurs in stages in which the coordination number of the cadmium is expanded, *i.e.*, by an associative process. Such associative processes can be expected to be a common feature of the coordination behavior of Cd^{2+} in the presence of sulfur donors, where a weak bond to an additional sulfur donor is formed readily and without the necessity of invoking an unusual intermediate of high energy. This is presumably the type of process which is responsible for the fact that the removal of cadmium from CdMT is effected much more rapidly by dithiocarbamates [26] than by EDTA [37].

Supplementary Material

H atom coordinates, anisotropic temperature factors and structure factor tables are available from the authors (J.S.C. and M.M.J.) on request.

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