Structure of N-Methylisatin N(4)-Dimethylthiosemicarbazone and its Electrochemically Synthesized 6-Coordinate Cadmium(II) Complex

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Cadmium, N-Methylisatin N(4)-Dimethylthiosemicarbazone, Electrochemical Synthesis

N-Methylisatin N(4)-dimethylthiosemicarbazone, HMIs4DM, prepared by condensation of N-methylisatin and N(4)-dimethylthiosemicarbazide crystallizes in the orthorhombic space group $Pbc2_1$, with a = 7.539(1), b = 11.566(4), c = 29.320(1) Å, V = 2556.6(9) Å^3 and Z = 8. Cadmium metal was oxidized in the presence of HMIs4DM in an acetonitrile solution, which produced a complex of the formula $[Cd(MIs4DM)_2]$. $[Cd(MIs4DM)_2]$ crystallizes in the orthorhombic space group Pbcn with a = 15.529(5), b = 10.672(4), c = 16.247(3) Å, V = 2692.7(14) Å^3 and Z = 8. $[Cd(MIs4DM)_2]$ is symmetrical with two identical MIs4DM ligands that are at an angle of about 80°.

Introduction

Interest in compounds related to 1-methylisatin thiosemicarbazone, also known as methisazone, is based on its antiviral activity [1–3]. It is thought that thiosemicarbazones inhibit virus growth by binding to copper ions, which are constituents of the virus [4]. In addition to other molecular modifications, substitution at N(4) of the thiosemicarbazone moiety, Fig. 1, has been explored [5]. A single phenyl or methyl group attached to N(4) results in a total loss of anti-smallpox activity, and a propenyl group reduced activity to 4% of that of the unsubstituted thiosemicarbazone. However, substitution of two alkyl groups at N(4) yielded compounds with activity against ectromelia and type 2-polio [6]. Pharmaceutical studies of N(4)-substituted thiosemicarbazones and bis(thiosemicarbazones) derived from a variety of carbonyl (and dicarbonyl) compounds have shown that the N(4)-substituent changes the activity, but as yet, no structure-biological activity relationship has been established [7]. Therefore, structural studies of N(4)-substituted thiosemicarbazones coordinated to different metal centers continue to be of considerable interest. Although there have been a number of structures of 5-coordinate cadmium complexes with one tridentate thiosemicarbazone ligand and two halogen ligands in the coordination sphere [8–13], to our knowledge there have been only a few 6-coordinate CdN_4S_2 complexes of cadmium reported to date [8,14]. Earlier we communicated a structural study of a $CdO_2N_2S_2$ complex of N-methylisatin N(4)-cyclohexylthiosemicarbazone, HMIs4Chex [15]. We report here the structure of N-methylisatin N(4)-dimethylthiosemicarbazone, HMIs4DM, and a second $CdO_2N_2S_2$ complex, $[Cd(MIs4DM)_2]$. A spectral study of HMIs4DM, Fig. 1, and its cobalt(II), nickel(II) and copper(II) complexes was reported several years ago [16].

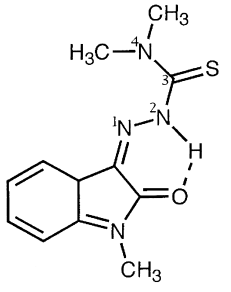

Fig. 1. Drawing of N-methylisatin N(4)-dimethylthiosemicarbazone, HMIs4DM, showing intramolecular hydrogen bonding and the numbering of the thiosemicarbazone moiety.

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Experimental Section

Reagents, materials and syntheses

HMIs4DM was prepared as described previously [16] by condensation of equimolar amounts of 1-methylisatin (Aldrich) and N(4)-dimethylthiosemicarbazide; the latter compound was synthesized by the method of Holmberg and Psilanderhielm [17] and modified by Scovill [18]. $[Cd(MIs4DM)_2]$ was prepared by electrochemical oxidation of cadmium in a solution of HMIs4DM (0.19 mmol, 46.6 mg) in CH_3CN (50 ml) containing 10 mg of tetramethylammonium perchlorate for 1 h at 5 mA. A loss of 10.2 mg from the anode resulted.

X-ray data collection and processing

Yellow, prismatic crystals of HMIs4DM and $[Cd(MIs4DM)_2]$ were mounted on glass fibers and used for data collection. The cell constants and an orientation matrix for data collection were obtained by least-squares refinement of the diffraction data from 25 well-centered reflections for HMIs4DM and 990 reflections for $[Cd(MIs4DM)_2]$. Data were collected at 293(2) K using MoK_α radiation (λ = 0.71073 Å) and the ω-scan technique, and corrected for Lorentz and polarization effects [19]. A semi-empirical absorption correction, ψ-scan (HMIs4DM) or SADABS ($[Cd(MIs4DM)_2]$, was carried out [20]. The structures were solved by direct methods [21] and subsequent difference Fourier maps, and refined on F^2 by a full-matrix least-squares procedure using anisotropic displacement factors [22]. Hydrogen atoms were placed geometrically and refined using a riding model, including free rotation of methyl groups. The remaining hydrogens in HMIs4DM were found on a difference Fourier map and refined isotropically. Atom scattering factors were taken from the International Table for X-ray Crystallography [23] and molecular graphics are from PLATON99 [24] and ORTEP3 for Windows [25]. Table 1 summarizes the crystal data, collection information and refinement data for HMIs4DM and $[Cd(MIs4DM)_2]$.

Results and Discussion

Selected bond distances are presented in Table 2 and bond angles in Table 3. The hydrogen bonding

Table 1. Crystal data and structure refinement for N-methylisatin N(4)-dimethylthiosemicarbazone, HMIs4DM, and $[Cd(MIs4DM)_2]$.

Empirical formula	$C_{12}H_{14}N_4OS$	$C_{24}H_{26}CdN_8O_2S_2$
Color; habit	yellow; prism	yellow, prism
Formula weight	262.33	317.52
Temperature [K]	293(2)	293(2)
Crystal size [mm]	0.30 × 0.25 × 0.22	0.22 × 0.11 × 0.06
Crystal system	orthorhombic	orthorhombic
Space group:	$Pbc2_1$	Pbcn
unit cell dimensions		
a [Å]	7539(1)	15.529(5)
b [Å]	11.566(4)	10.672(4)
c [Å]	29.3200(11)	16.247(3)
Volume [Å^3]	2556.6(9)	2692.7(14)
Z	8	8
Density (mg/m^3)	1.263	1.567
Absorption coeff. [mm^{-1}]	0.247	1.004
Diffractometer	Nonius MACH3	Bruker Smart CCD-1000
Radiation [λ, Å]	Mo-K_α (0.71073)	Mo-K_α (0.71073)
θ Range for data collect. [°]	2.70 to 24.05	2.32 to 26.43
Index ranges	$0 \le h \le 8$	$-15 \le h \le 19$
	$0 \le k \le 13$	$-13 \le k \le 11$
	$0 \le l \le 33$	$-20 \le l \le 16$
Absorption correction	ψ-scan	SADABS
Reflections collected	2091	15232
Independent reflections	2091 R_{int} = 0.0962	2758 R_{int} = 0.1268
Max. & min. transmission	0.9476, 0.9296	0.9422, 0.8094
Data / parameters	2091 / 362	2758 / 168
R Indices [$I > 2\sigma(I)$]	R_1 = 0.0625 wR_2 = 0.0953	R_1 = 0.0526 wR_2 = 0.1209
Final *R* Indices (all data)	R_1 = 0.1711 wR_2 = 0.1377	R_1 = 0.1703 wR_2 = 0.1634
Goodness-of-Fit	1.142	0.863
Largest diff. peak/hole [eÅ^{-3}]	0.315 / −0.338	1.267 / −0.889

parameters for HMIs4DM are listed in Table 4 and the mean plane data for both compounds in Table 5. Perspective views of HMIs4DM and $[Cd(MIs4DM)_2]$ are shown in Fig. 2 and 3, respectively.

Table 2. Selected bond distances (Å) for HMIs4DM and $[Cd(MIs4DM)_2]$.

Bond	HMIs4DM[a]	$[Cd(MIs4DM)_2]$[b]
N1–C12	1.403(13), 1.427(13)	1.381(9)
N1–C13	1.491(13), 1.444(12)	1.468(9)
N1–C2	1.407(12), 1.389(15)	1.354(9)
C2–O1	1.231(11), 1.208(14)	1.238(9)
C2–C3	1.452(14), 1.486(14)	1.472(10)
C3–N2	1.279(14), 1.313(12)	1.301(9)
N2–N3	1.378(10), 1.351(12)	1.331(7)
N3–C4	1.378(12), 1.386(13)	1.353(9)
S1–C4	1.682(10), 1.652(11)	1.716(8)
C4–N4	1.328(11), 1.333(13)	1.329(9)
Cd1–S1		2.569(2)
Cd1–N12		2.313(6)
Cd1–O1		2.582(5)

[a] Listed in the order S1 and S21 molecules throughout; [b] the complex is symmetrical with the bond distances equivalent for the two ligands. Symmetry transformations used to generate equivalent atoms: #1: $-x, y, -z+1/2$.

Table 3. Selected bond angles (°) for HMIs4DM and $[Cd(MIs4DM)_2]$.

Angle	HMIs4DM	$[Cd(MIs4DM)_2]$
C12–N1–C13	126.4(10), 125.4(11)	123.7(7)
C12–N1–C2	111.3(9), 109.3(9)	111.8(7)
C13–N1–C2	122.3(9), 125.3(11)	124.5(7)
N1–C2–O1	125.6(10), 127.2(11)	125.9(7)
N1–C2–C3	105.4(8), 106.1(11)	105.7(7)
O1–C2–C3	129.0(9), 126.7(12)	128.2(8)
C2–C3–N2	128.6(10), 130.3(10)	117.4(7)
C7–C3–N2	124.6(11), 121.8(10)	134.8(7)
C3–N2–N3	115.1(9), 115.1(9)	117.6(6)
N2–N3–C4	121.0(8), 120.8(10)	114.8(6)
N3–C4–N4	113.0(9), 112.3(10)	113.2(7)
N3–C4–S1	122.5(8). 120.8(9)	128.2(6)
N4–C4–S1	124.4(8), 126.8(9)	118.7(7)
S1–Cd1–N2		74.90(16)
S1–Cd1–O1		145.61(13)
S1–Cd1–N2a		125.17(15)
S1–Cd1–O1a		94.79(13)
S1–Cd1–S1a		106.11(11)
N2–Cd1–O1		70.7(2)
N2–Cd1–N2a		149.6(3)
N2–Cd1–O1a		86.16(19)
O1–Cd1–O1a		81.8(2)
Cd1–O1–C2		105.7(5)
Cd1–N2–C3		118.0(5)
Cd1–N2–N3		124.3(5)
Cd1–S1–C4		97.7(3)

[a] Listed in the order S1, S21 molecules.

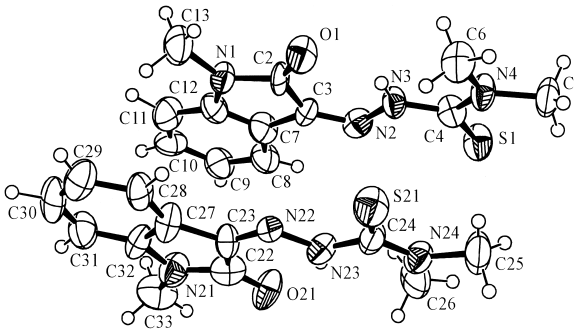

Fig. 2. A perspective view of crystallographically different molecules of HMIs4DM shown at 50% probability.

Structure of HMIs4DM

HMIs4DM has two crystallographically different molecules in the unit cell. Most bonds in the two unique molecules are different, but generally are within the combined esd values. The bond angles of the two molecules show less variation than the bond distances. As is common for organic molecules with significant intermolecular interaction [26], the two unique molecules interact with neighboring molecules differently, Table 4. For example, the most important interaction of C5H5 is with O1 of a neighboring molecule, but the analogous C25H25 interacts with a neighboring S21. Other interactions by hydrogens attached to carbons that have H…X distances of less than 3.0 Å and C-H…X angles > 110° are listed in Table 4. Of note is that the intermolecular interactions in HMIs4DM are between like molecules rather than between crystallographically different molecules. Both molecules have a strong intramolecular hydrogen bond between N3H3 (N23H23) and O1 (O21), but like the rest of the bonds and angles in the crystallographically different molecules, there are small differences in the parameters for this interaction. The unique molecules of HMIs4DM are close to planar with the angle between the mean planes of the isatin moiety and the thiosemicarbazone moiety at *ca.* 5°, and the two molecules are essentially co-planar, Table 5.

The structure of 2-hydroxy-4-methoxyacetophenone N(4)-dimethylthiosemicarbazone, $H_2$4MeOAp4DM was reported recently [27], as was the structure of 2-pyridineformamide N(4)-dimethylthiosemicarbazone, HAm4DM [13], and Table 6

Table 4. Hydrogen bonding interactions for HMIs4DM.

Compound	D	A	d(D–H)	d(H…A)	d(D…A)	< DH…A
HMIs4DM	N3	O1	0.72(10)	2.08(11)	2.738(11)	154(12)
	N23	O21	0.73(9)	2.16(10)	2.792(11)	146(12)
	C5	O1#1	0.96	2.42	3.327(13)	157
	C25	S21#1	0.96	2.96	3.665(12)	131
	C5	N24#2	0.96	2.86	3.677(15)	144
	C9	S1#3	0.84(9)	2.91(10)	3.651(12)	148(9)
	C26	S1#4	0.96	2.97	3.858(14)	154
	C30	S1#5	0.98(9)	2.81(9)	3.733(13)	158(8)
	C31	O21#6	1.06(9)	2.65(9)	3.527(14)	140(6)

Symmetry transformations used to generate equivalent atoms: #1: x, $-0.5+y$, $0.5-z$; #2: $1+x$, y, z; #3: $1-x$, $0.5+y$, z; #4: $-1+x$, y, z; #5: $-1+x$, $1+y$, z; #6: $-x$, $0.5+y$, $-z$.

Table 5. Mean planes, deviations and angles between mean planes for HMIs4DM and $[Cd(MIs4DM)_2]$.

Compound	Plane	rms dev.	largest dev.	Angle with previous plane
HMIs4DM	C3–N2–N3–C4–N4–S1	0.0250	N2, 0.0385(0.0082)	
	N1–C2–C3–C7–C8–C9–C10–C11–C12	0.0144	C12, 0.0265(0.0108)	6.15(0.31)
	N21–C22–C23–C27–C28–C29–C30–C31–C32	0.0211	C32, 0.0382(0.0110)	1.01(0.32)
	C23–N22–N23–C24–N24–S21	0.0227	N23, 0.0399(0.0093)	4.83(0.30)
$[Cd(MIs4DM)_2]$	C3–N2–N3–C4–N4–S1	0.0100	N2, 0.0195(0.0050)	
	N1–C2–C3–C7–C8–C9–C10–C11–C12	0.0097	C2, 0.0181(0.0060)	2.28(0.28)

shows a comparison of bond distances and angles of their thiosemicarbazone moieties along with HMIs4DM. The bond distances of HMIs4DM and $H_2$4MeOAp4DM are similar, but those of HAm4DM show some differences, principally due to the bifurcated structure in which the N3 hydrogen is shifted to N2 [13]. There are greater differences in the bond angles and HAm4DM shows the larger differences from the other two molecules.

Structure of [Cd(MIs4DM)$_2$]

Equivalent atoms in the second ligand are generated by the following symmetry transformations: $-x$, y, $-z+1/2$. The bond distances showing the largest changes from those of HMI4DM on

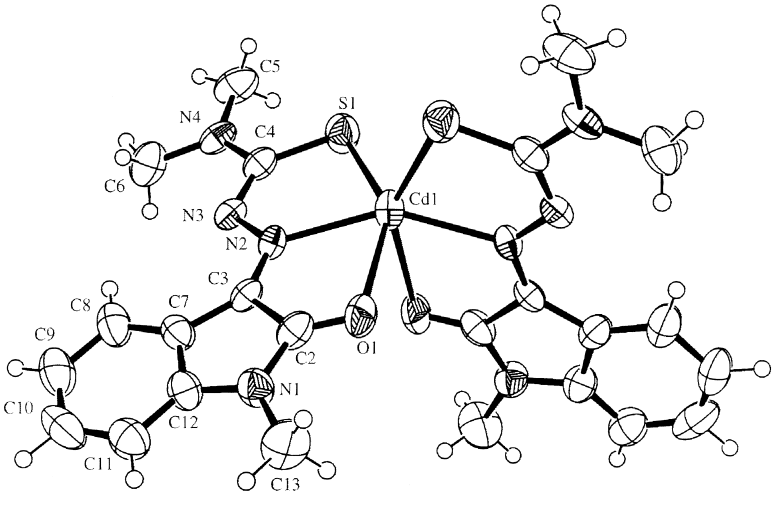

Fig. 3. A perspective view of $[Cd(MIs4DM)_2]$ shown at 50% probability.

Table 6. A comparison bond distances (Å) and angles (°) of three N(4)-dimethylthiosemicarbazones

Bond	HMIs4DM[a]	$H_2$4MeOAp4DM[a,b]	HAm4DM[c]
S1–C4	1.667(11)	1.68(2)	1.723(3)
C3–N2	1.296(14)	1.29(2)	1.302(3)
N2–N3	1.365(14)	1.38(2)	1.378(3)
N3–C4	1.382(13)	1.38(2)	1.337(3)
C4–N4	1.331(13)	1.33(3)	1.352(3)
Angle			
C3–N2–N3	115.1(9)	118.3(13)	121.2(2)
N2–N3–C4	120.9(10)	119.1(13)	111.7(2)
N3–C4–N4	112.6(10)	113.9(14)	114.4(2)
N3–C4–S1	121.7(9)	121.6(12)	124.6(2)
N4–C4–S1	125.6(9)	124.4(12)	121.0(2)

a) Average of two crystallographically unique molecules; b) 4-methoxy-2-hydroxyacetophenone N(4)-dimethylthiosemicarbazone, reference [27]; c) 2-pyridineformamide N(4)-dimethylthiosemicarbazone, reference [13].

anion formation and coordination are the following: S1–C4, which formally changes from a double bond to a single bond, and N3–C4, which formally changes from a single bond to a double bond, and N2–N3. Neither C2–O1 nor C3–N2 is changed significantly on coordination of their donor atoms. Several bond angles are significantly different in $[Cd(MIs4DM)_2]$ compared to HMIs4DM. The coordinated, anionic MIs4DM is even more planar than free HMIs4DM and the angle between the isatin moieties of the two ligands is 78.81(0.14)° indicating a measure of distortion from octahedral symmetry. There are no significant interactions between molecules of $[Cd(MIs4DM)_2]$.

As is usual for coordinated thiosemicarbazones, the Cd1–N12 bond distance is shorter than Cd1–S1, but somewhat surprisingly, the Cd1–O1 bond distance is essentially the same as Cd1–S1. Other indications of distortion from octahedral symmetry are the "trans" angle, N2–Cd1–N2a = 149.6(3)° and the "trans" angle of the tridentate ligand, S1–Cd1–O1 = 145.61(13)°.

In $[Cd(MIs4Chex)_2]$, where MIs4Chex is the anion of N-methylisatin N(4)-cyclohexylthiosemicarbazone [15], the Cd1–N2 and Cd1–S1 distances are the same as those of $[Cd(MIs4DM)_2]$, but Cd–O is shorter, 2.515(9) compared to 2.582(5) Å. The trans angle, N2–Cd1–N2a, is 157.3(3)° indicating that $[Cd(MIs4Chex)_2]$ is marginally closer to octahedral than $[Cd(MIs4DM)_2]$. The Cd1–N2–C3, Cd1–N2–N3 and Cd1–S1–C4 angles of the two complexes are essentially the same, but the Cd1–O1–C2 angle is larger by about 4° in $[Cd(MIs4Chex)_2]$. There are no significant differences in the bond distances and angles in the thiosemicarbazone moieties of the two complexes.

Supplementary material

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no CCDC-179439 for HMIs4DM and CCDC-179440 for $[Cd(MIs4DM)_2]$. Copies of available material can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB21EZ, UK, (Fax: +44-(0)1223-336033 or E-mail: deposit@ccdc.cam.ac.uk).

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