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Crystal Structure of (Theophyllinato)methylmercury(II) Monohydrate

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The title compound belongs to space group $P2_1/c$, a = 10.884 Å, b = 9.187 Å, c = 14.458 Å, β = 131.02°, Z = 4. The structure was refined on 1355 nonzero reflections to an R factor of 0.059. The crystal contains discrete [CH_3Hg(theophyllinate)] molecules in which the proton initially bound to N7 is replaced by the CH_3Hg^+ ion. The water molecule forms hydrogen bonds with both carbonyl oxygens, whereas an intermolecular contact of 2.98 Å is established between mercury and N9. The intramolecular Hg···O6 distance of 3.18 Å is consistent with the absence of significant Hg···carbonyl bonding interactions in the present structure.

Introduction

The present work was undertaken as part of our continuing study of the stereochemistry of methylmercury complexes with DNA constituents [1]. Although theophylline is not present in nucleic acids, its structural similarity to guanine makes it an interesting ligand to model the interactions of the N7/O6 portion of guanine with heavy metals.

In the solid state, the weakly acidic proton of neutral theophylline (ThH) is bound to N7 [2]. However, the basicities of N7 and N9 do not differ greatly and tautomeric interconversions between the N7–H and N9–H forms in purines have been reported [3]. Both forms have been encountered for neutral theophylline coordinated to a metal. Binding as the N9–H tautomer through N7 has been observed for the $[PtCl_3(ThH)]^-$ ion [4], whereas $[CuCl_2(H_2O)_2(ThH)]$ [5] and $[Rh_2(CH_3CO_2)_4(ThH)_2]\cdot 2H_2O$ [6] contain theophylline bound as the N7–H tautomer through N9. The imidazolic proton dissociates in basic solutions. Complexes formed with the Th^- anion have been consistently found to bind *via* N9 in several cobalt [7] and copper compounds [8, 9].

The crystal structure of the present methylmercury compound was determined, firstly, to ascertain the site of fixation of mercury on the ring. Secondly, the interactions involving O6 were also of interest. Indeed, N7 and O6 have the same relative positions as in guanine and direct chelation of platinum to these sites has been postulated as one of the possible mechanisms of attack of platinum antitumor drugs on the guanine-rich region of DNA [10]. In the above metal complexes, the role of O6 was generally restricted to intramolecular hydrogen bonding with –OH or –NH groups present in other ligands. However, in two copper complexes, some Cu···O6 bonding was detected [9]. Therefore, it was interesting to examine the extent of interaction of O6 with mercury, which does not normally possess tightly-bound ligands in its equatorial plane.

Experimental

Crystal Data

Formula: $C_8H_{12}HgN_4O_3$; fw = 412.80; monoclinic, space group $P2_1/c$, a = 10.884(5), b = 9.187(7), c = 14.458(4) Å, β = 131.02(3)°, V = 1090.7 Å^3, Z = 4 formula units per cell, D_c = 2.513 g cm^{-3}. Crystal dimensions: 0.040 mm (between faces 100 and $\bar{1}00$), 0.06 mm ($0\bar{1}1$ and $01\bar{1}$) and 0.070 mm (101 and $\bar{1}0\bar{1}$), μ(CuKα) = 272.2 cm^{-1}. λ(CuK$\bar{\alpha}$) = 1.54178 Å, t = 20 °C.

Crystallographic Measurements

The sample consisted of a fiber-like microcrystalline material, containing a few crystalline blocks of rather poor quality. Preliminary photographs of one of these blocks revealed, however, that it was suitable for X-ray work. It was transferred to an Enraf-Nonius CAD-4 diffractometer. A list of 25 reflections randomly distributed in the Ewald sphere was produced by the search procedure and subsequently centered in the counter aperture several times. The cell parameters were calculated by the automatic

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indexing program of the CAD-4 software. The Niggli parameters clearly indicated a P-monoclinic Bravais lattice and a fast data collection on the OkO and hOl reflections suggested $P2_1/n$ as the space group. This cell was transformed into the conventional $P2_1/c$ cell. The cell parameters reported above were obtained by least-squares refinement on the setting of the 25 reflections. The cell dimensions and monoclinic symmetry were checked by taking oscillation photographs about each of the three axes. These photographs showed the proper layer-line spacing and the expected symmetry (mirror for oscillation about *b* only). The systematic absences characteristic of space group $P2_1/c$ (OkO, $k \neq 2n$ and hOl, $l \neq 2n$) were subsequently confirmed by inspection of the complete data set.

A second method of preparation of the same compound, as described in [11], eventually yielded diamond-shaped crystals of good quality. A search procedure run on these crystals provided cell parameters in complete agreement with those from the fiber-like monocrystalline material.

The intensity data were collected as described elsewhere [12]. A set of 1614 reflections (octants hkl and $hk\bar{l}$) in a reflection sphere limited by $2\theta \leqslant 120°$ was collected. On the basis of the criterion $I < 2.5\sigma(I)$, 256 measurements were rejected as not significantly above background. The set of 1355 nonzero reflections was used to solve and refine the structure. These data were corrected for the Lorentz effect, polarization and absorption (Gaussian integration, grid 8 × 8 × 8, transmission range: 0.08–0.28).

Resolution of the Structure

The structure was solved by the heavy-atom method and refined by full-matrix least squares. The Hg atom was located from a Patterson synthesis and the light atoms were positioned from subsequent difference Fourier maps. Isotropic refinement of all nonhydrogen atoms using unit weights converged to $R = \Sigma||Fo| - |Fc||/\Sigma|Fo| = 0.096$. These atoms were then refined anisotropically. The hydrogen on C8 was fixed at the calculated position (isotropic $B = 6.0$ Å^2), but those of the methyl groups, which were not unambiguously located, were neglected. In the last cycles, individual weights based on counting statistics were applied to each reflection and a secondary extinction parameter was refined. The anisotropic refinement of all nonhydrogen atoms converged to $R = 0.059$ and $R_w = [\Sigma w(|Fo| - |Fc|)^2/\Sigma w|Fo|^2]^{1/2} = 0.070$. The goodness-of-fit ratio was 1.24. The final difference Fourier map showed three peaks of 1.5–3.2 e/Å^3 within 1.3 Å from Hg, and the general background was $<\pm 1.0$ e/Å^3.

The form factors and the contributions to anomalous dispersion of Hg were from standard sources [13]. The programs used are listed elsewhere [14].

TABLE I. Refined Positional Parameters (10^4, Hg × 10^5).

Atom	*X*	*Y*	*Z*
Hg(7)	19562(6)	16802(6)	13858(5)
N(1)	6374(13)	2098(12)	5822(10)
C(1)	6341(21)	3196(15)	6527(15)
C(2)	7695(15)	1130(16)	6457(13)
O(2)	8775(11)	1183(12)	7571(8)
N(3)	7753(12)	123(13)	5784(9)
C(3)	9157(18)	–868(17)	6420(13)
C(4)	6538(15)	131(16)	4526(11)
C(5)	5243(16)	1069(14)	3935(12)
C(6)	5089(16)	2113(15)	4546(13)
O(6)	3936(13)	2973(11)	4066(10)
N(7)	4230(17)	769(14)	2683(12)
C(7)	–390(24)	2402(21)	217(17)
C(8)	4964(20)	–336(17)	2614(15)
N(9)	6405(14)	–788(13)	3700(10)
W[b]	2181(13)	4528(13)	4615(10)
H(8)[a]	4971	–852	2253

[a] Not refined. [b] Oxygen of the water molecule.

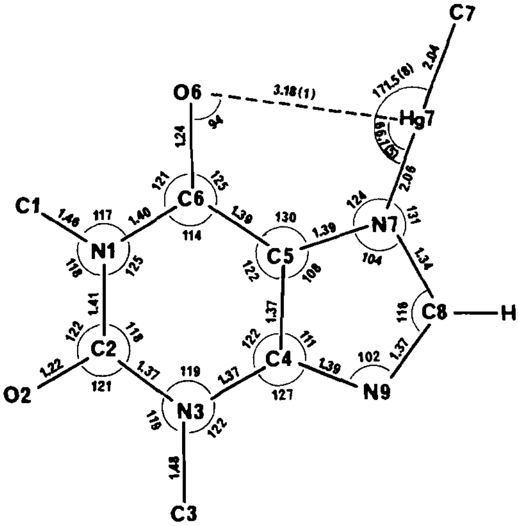

Fig. 1. Interatomic distances and bond angles. Unless otherwise stated, the esds are 0.02 A and 1–2°.

The refined coordinates are listed in Table I. The list of temperature factors and the table of observed and calculated structure factor amplitudes are available upon request.

Description of the Structure and Discussion

The unit cell contains discrete $[(CH_3Hg)C_7H_7N_4O_2]$ molecules in which the proton initially bound to N7 of theophylline [2] has been substituted by the CH_3Hg^+ ion. The interatomic distances and bond angles are schematically represented in Fig. 1. The Hg–N7 and Hg–CH_3 bond lengths (2.06(2) Å and

TABLE II. Environment of Mercury and Hydrogen Bonds.

Distances (Å)			
Hg7–N7	2.06(2)	Hg7–N9^{i}	2.98(1)
Hg7–C7	2.04(3)	Hg7–W^{ii}	2.94(1)
Hg7–O6	3.18(1)		
Angles (deg)			
C7–Hg7–N7	171.5(8)	C7–Hg7–O6	111.5(7)
N7–Hg7–N9^{i}	87.8(5)	N9^{i}–Hg7–W^{ii}	82.2(4)
N7–Hg7–W^{ii}	84.4(5)	N9^{i}–Hg7–O6	79.3(4)
N7–Hg7–O6	66.1(5)	W^{ii}–Hg7–O6	145.5(4)
C7–Hg7–N9^{i}	99.9(7)	Hg7–N9^{i}–C4^{i}	141(1)
C7–Hg7–W^{ii}	100.2(7)	Hg7–N9^{i}–C8^{i}	117(1)
Hydrogen bonds			
	W···O (Å)	Hg–W–O (deg)	W–O–C (deg)
W^{i}–H···O6^{i}	2.88(2)	120.1(5)	140(1)
W^{i}–H···O2^{iii}	2.92(2)	91.2(4)	144(1)

^{i}1 – x, ½ + y, ½ – z; ^{ii}x, ½ – y, –½ + z; ^{iii}–1 + x, y, –1 + z

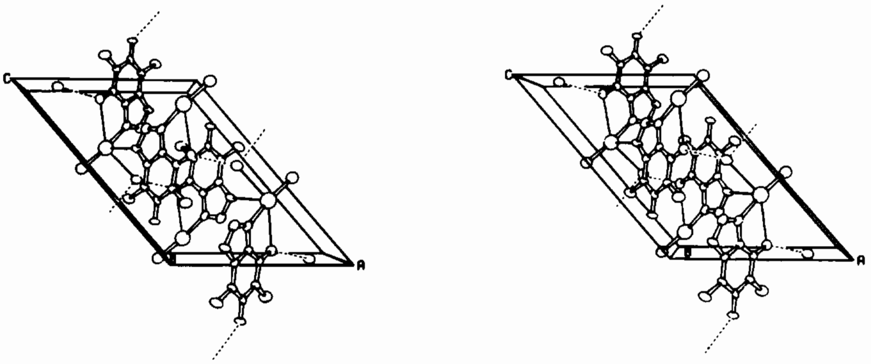

Fig. 2. Stereo view of the unit cell down the *b* axis. The atoms can be identified from Fig. 1. The thermal ellipsoids correspond to 50% probability, except for mercury, where large spheres of arbitrary size were used. The mercury interactions with N9, W and O6 are shown as thin continuous lines. The dashed lines correspond to hydrogen bonds.

2.04(2) Å, respectively) are in the range usually found [15]. The coordination of mercury is roughly linear as expected, but the departure from linearity (N7–Hg7–C7 = 171.5(8)°) is somewhat greater than usual.

The esds on bond lengths and angles involving the light atoms are rather large and no significant differences can be found between our values and those of either free theophylline [2] or its complexes [4–9]. In the first approximation, this ligand possesses a pseudo two-fold axis through C8 and the midpoints of N1–C2 and C4–C5. However, the large difference between the C=O bonds (av. 1.23(2) Å) and the N–CH$_3$ bonds (1.47(2) Å) provides unambiguous proof that the ring atoms have been properly labeled. The ring itself is planar within 2σ (0.02 Å), but two of the exocyclic groups are displaced slightly, although significantly, from the plane: O6, –0.04(1) Å; C1, 0.07(2) Å. The much greater displacement of the CH$_3$Hg group is probably due to packing forces (Hg7, –0.269(1) Å; C7, –0.81(3) Å).

In several copper and cobalt complexes [7, 8], the N7-coordinated theophyllinate ion formed H-bonds with other ligands in the coordination sphere. In the present case, there are no such ligands and direct Hg···O6 interactions could in principle take place. Moreover, the Hg7–N7–C5 angle is 7° smaller than Hg7–N7–C8, as though Hg7 were attracted by O6. This also occurred to different degrees in other N7-bonded complexes of guanosine [16] and 9-methylguanine [17]. Despite this favorable factor, Hg···O6 bonding is probably very weak, the distance (3.18(1) Å) being much above the 3.0 Å limit beyond which bonding effects are believed to be vanishingly small [18].

A stereo view of the unit cell is shown in Fig. 2. The molecules are packed as parallel pairs separated by the usual distance of ~3.5 Å and the amount of van der Waals contact between the rings is large. This particular arrangement hides one side of the equatorial plane of mercury (assuming C7–Hg7–N7 as the axial direction) and prevents the formation of secondary weak bonds with donor atoms in this direction. In addition to the very weak Hg···O6 interaction, two secondary bonds are formed with Hg (Table II). One of them involves the endocyclic N9 atom of an adjacent molecule at 2.98(1) Å. Mercury does not lie exactly along the expected lone pair direction, as is evident from the 24° difference between the Hg7–N9–C angles. This distortion is in a direction consistent with the anticipated steric effect of the N3–CH_3 group. The water molecule (W), forming a moderately strong secondary Hg–O bond of 2.94(1) Å to mercury, is simultaneously hydrogen-bonded with C2–O2 and C6–O6 of two different molecules.

The present structure confirms that the soft CH_3-Hg^+ ion shows a preference for position N7 of deprotonated theophylline, as do the harder Cu^{2+}, Co^{3+} and H^+ cations. Another interesting point is the poor tendency of the carbonyl groups to interact with mercury. Not only is the intramolecular Hg···O6 contact very long, but also none of the carbonyl oxygens form intermolecular contacts in the equatorial plane of mercury. The Hg···N9 interaction is not surprising, since mercury generally shows a preference for the softer N donors over the hard oxygen atoms. Steric hindrance due to the proximity of the molecule providing the Hg···N9 contact could make it more difficult for other molecules to approach their carbonyl groups close enough to mercury. Although this might partly explain the lack of intermolecular Hg···carbonyl contacts, this behavior undoubtedly reflects the poor basicity of these groups for soft metal ions.

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