Inorganica Chimica Acta, 156 (1989) 149–153

Synthesis and Structure of a 1:2 Addition Compound of Mercuric Chloride with 6-Amino-1,3-dimethyl-5-formyluracil

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(Received June 30, 1988)

Abstract

Crystals of the adduct belong to the monoclinic $P2_1/c$ space group with $a = 10.606(1)$, $b = 14.829(1)$, $c = 13.498(1)$ Å, $\beta = 111.63(1)^\circ$ and $Z = 4$. The structure was refined on 1539 observed Mo K$\bar{\alpha}$ reflections to $R = 0.026$. The unit cell contains ligands and linear $HgCl_2$ molecules packed in an arrangement optimizing interligand van der Waals contacts and Hg–O secondary binding. The $HgCl_2$ molecule deviates slightly from linearity (Cl–Hg–Cl = 175.5°) with a mean bond length of 2.292 Å. Both independent ligands have their formyl oxygen retained on the side of the NH_2 group by hydrogen bonding. Near the plane perpendicular to the Hg–Cl bonds are found, around each Hg, one carbonyl O2 and three formyl oxygens with Hg···O distances ranging from 2.716 to 3.011 Å. The compound dissociates into $HgCl_2$ and free ligand when dissolved in Me_2SO.

Introduction

Structural investigations aimed at determining the binding sites of metal ions in pyrimidine and purine derivatives are a prerequisite step for the understanding of the biological role of such complexes. Over the recent years, much research effort has been devoted to this problem, which has been thoroughly reviewed [1–5]. Pyrimidine and purine derivatives containing exocyclic oxygen and/or nitrogen atoms are of particular interest, since these atoms can participate in selective reactions with metal ions, as evidenced from some of our recent work [6–9].

Uracil or its derivatives are known to bind to metal centres by using various combinations of their available coordination sites. Crystallographic work has shown that the monoanion of uracil can bind via either N1 [10] or N3 [11]. Coordination is cleanly displaced to N3 by N1-methylation [12]. In a series of studies on platinum complexes carried out mainly by Lippert and coworkers, 1-methyluracil was found to act as a bridging ligand for two Pt atoms via N3 and a carbonyl oxygen [13, 14]. In many cases, the other carbonyl group is also used to coordinate extra metal ions, generating mixed-metal species [15]. Interaction via N3, O2 and O4 was also observed for a silver complex [16]. When both N1 and N3 are methylated, reaction can occur through the carbonyl oxygens: for instance, in the $CuCl_2$ adduct, 1,3-dimethyluracil is bonded via O4 [17]. Under conditions that prevent deprotonation, uracil and dihydrouracil were also found to interact with $HgCl_2$ through carbonyl oxygens [18]. Exceptionally, H5 substitution occurred, leading to direct Pt–C5 bonding [19].

Over the last few years, we developed interest in complexes formed by various modified uracil ligands. This paper deals with 6-amino-1,3-dimethyl-5-formyluracil. Methylation of the endocyclic nitrogens renders these two sites inaccessible for the metal, leaving the O2 and O4 carbonyl oxygens and the amino-formyl region as possible targets. It was of interest to determine how these two parts of the ligand would compete for the metal. To this end, the mercuric chloride addition compound obtained in crystalline form was structurally characterized by X-ray diffraction.

Experimental

Preparative Work

The 6-amino-1,3-dimethyl-5-formyluracil ligand (HDFU) was synthesized according to Pfleiderer and Strauss [20] using 6-amino-1,3-dimethyluracil as starting material. It was isolated as colorless crystalline needles. *Anal.* Calc. for $C_7H_9N_3O_3{\cdot}H_2O$: C, 41.79; H, 5.51; N, 20.89. Found: C, 41.80; H, 5.60; N, 20.50%. The compound dehydrates at 99 °C (ΔH

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0020-1693/89/$3.50

dehydration = 61 kJ mol^{-1}) and shows a definite melting point at 196.8 °C (ΔH_f = 20 kJ mol^{-1}).

To prepare $HgCl_2(HDFU)_2$, the ligand (100 mg, 0.48 mmol) was dissolved with stirring in 50 ml ethanol. To this solution was added $HgCl_2$ (135 mg, 0.50 mmol). The resulting solution was heated under stirring for 1 h and allowed to cool to room temperature. The crystals were filtered and air dried. *Anal.* Calc. for $C_{14}H_{18}Cl_2HgN_6O_6$: C, 26.36; H, 2.84; N, 13.18. Found: C, 26.60; H, 2.80; N, 13.10%. $HgCl_2(HDFU)_2$ melts at 230 °C (ΔH_f = 80.5 kJ mol^{-1}). ^{1}H NMR (ppm): 3.14, 3.29 (s, CH_3); 9.72, (s, CH); 8.48, 10.07 (s, br, NH_2).

Instruments and Techniques

The NMR spectra were recorded at ambient probe temperature in a Bruker XH-400 NMR spectrometer using Me_2SO-d_6 as solvent and TMS as internal reference.

The water content of HDFU was determined by thermographic techniques, using a Mettler TG-50 thermobalance, at a heating rate of 10 °C min^{-1} in a dynamic atmosphere of pure air (100 ml min^{-1}). Dehydration and melting enthalpy values for HDFU and $HgCl_2(HDFU)_2$ were obtained from the corresponding DSC curves, recorded on a Mettler DSC-20 differential scanning calorimeter at a heating rate of 5° min^{-1}.

C, H and N microanalyses were performed by the Microanalytical Laboratory of the Bioorganic Institute C.S.I.C., Barcelona.

Crystallographic Work

$C_{14}H_{18}Cl_2HgN_6O_4$, FW = 637.83, monoclinic, $P2_1/c$, $a = 10.606(1)$, $b = 14.829(1)$, $c = 13.498(1)$ Å, $\beta = 111.63(1)°$, $V = 1973.4$ Å^3, $Z = 4$, $D_c = 2.146$ g cm^{-3}, λ(Mo K$\bar{\alpha}$) = 0.71069 Å (graphite monochromator), μ(Mo Kα) = 81.1 cm^{-1}, $T = 293$ K.

A crystal of dimensions 0.05 × 0.10 × 0.20 mm obtained as described above was used for X-ray work. A set of precession photographs revealed $2/m$ Laue symmetry and yielded starting cell parameters. The systematic absences ($h0l$, $l \neq 2n$; $0k0$, $k \neq 2n$) unambiguously determined the $P2_1/c$ space group.

The crystal was mounted on an Enraf-Nonius CAD-4 diffractometer. The cell parameters were accurately determined from 48 centered reflections in the range $20 \leq 2\theta \leq 22.5°$. Intensity data were collected by using the ω scan mode. The scan range (ω) was $(0.80 + 0.35 \tan \theta)°$ extended 25% on either side for background. All reflections were collected at the same rate of 2.5° min^{-1}. Three standard reflections were checked every hour. Their intensity showed only random fluctuations within ±0.8%. Orientation control was done every 400 reflections. A total of 2546 independent hkl and $\bar{h}kl$ reflections ($2\theta \leq 45°$) were measured, of which 1539 were retained for structure determination ($I > 3.0\sigma(I)$). An absorption correction was applied (Gaussian integration, grid 10 × 10 × 10): the transmission factor ranged from 0.45 to 0.70. The data were finally corrected for the Lorentz and polarization effects.

The structure was solved by the heavy-atom method and refined on $|F_o|$ by full-matrix least-squares. Positions for the Hg and Cl atoms were obtained from a Patterson synthesis and the remaining non-hydrogen atoms were located in the subsequent difference Fourier map. Isotropic refinement using individual weights based on counting statistics ($w = 1/\sigma^2(F_o)$) converged to $R = \Sigma||F_o| - |F_c||/\Sigma|F_o| = 0.184$ and $R_w = [\Sigma w(|F_o| - |F_c|)^2/\Sigma w|F_o|^2]^{1/2} = 0.182$. Anisotropic refinement of the Hg and Cl atoms and isotropic refinement of all other non-hydrogen atoms converged to $R = 0.037$ and $R_w = 0.039$. All methyl hydrogens were visible in the subsequent ΔF map. The positions obtained were used to calculate coordinates for idealized methyl groups (C–H = 0.95 Å, sp^3 hybridization, $B = 4.0$ Å^2). The hydrogen atoms of the formyl and amino groups, whose positions were known from those of the non-hydrogen atoms, were fixed at ideal positions (sp^2 hybridization). The hydrogen coordinates were recalculated after each least-squares cycle. Anisotropic refinement of all non-hydrogen atoms with fixed hydrogen parameters converged to $R = 0.026$ and $R_w = 0.028$. The goodness-of-fit ratio was 1.43. The final ΔF map showed maximum residual electron densities of $\pm|0.46\text{–}0.59|$ e Å^{-3} within 1.5 Å from Hg atom, and a general background ±0.42 e Å^{-3}. The refined coordinates are listed in Table 1. See also 'Supplementary Material'. The scattering curves were taken from Cromer and Waber [21], except for hydrogen [22]. Anomalous dispersion corrections were applied to the scattering curves of Hg and Cl [23].

Description of the Structure

The crystal does not contain individual mercury complex molecules. It consists of essentially unperturbed ligands and linear $HgCl_2$ molecules packed in a pattern optimizing interligand van der Waals contacts and secondary binding between mercury and ligand oxygens. Interatomic distances and bond angles are listed in Table 2.

The ligand geometry (Fig. 1) does not greatly differ from those of other uracil derivatives [24]. The amino and formyl substituents are found to be coplanar with the ring. In this orientation, their π electrons can participate in the ring π system. For the two crystallographically independent ligands, the formyl oxygen is on the side of the amino group. This is likely due to intramolecular N(6)–H···O(7) bonding. Although the N–H···O angles (131°) do not define linear hydrogen bonds, this may be balanced by the short H···O distances (1.91 Å).

Four parallel ligands of types 1 and 2, stacked following a 1-2-2-1 sequence, define a 'quartet' roughly oriented in the *c* direction (Fig. 2). Between such quartets repeated by the lattice *a* translation are found pairs of $HgCl_2$ molecules parallel to the *b* axis and lying near the *bc* face. Two $HgCl_2$ molecules with their environment are shown in

TABLE 1. Refined Coordinates ($\times 10^4$, Hg $\times 10^5$) and Equivalent Temperature Factors ($\times 10^3$)

Atom	*x*	*y*	*z*	U_{eq}
Hg(1)	4882(4)	418(4)	17538(3)	41
Cl(1)	305(4)	1578(2)	1666(4)	73
Cl(2)	787(4)	−1496(2)	1814(4)	68
O(21)	9308(6)	151(8)	5839(5)	77
O(22)	8044(6)	187(6)	2374(6)	72
O(41)	5967(7)	−1780(5)	3952(6)	62
O(42)	4606(7)	−1780(4)	899(6)	58
O(71)	3144(6)	218(4)	3020(6)	53
O(72)	1745(6)	175(5)	104(5)	53
N(11)	7272(12)	754(6)	4793(11)	40
N(12)	5908(11)	763(6)	1638(11)	37
N(31)	7663(12)	−825(6)	4883(11)	40
N(32)	6342(12)	−793(6)	1687(11)	36
N(61)	5155(8)	1360(5)	3926(7)	42
N(62)	3733(8)	1333(5)	960(7)	45
C(11)	7840(11)	1661(8)	5153(11)	60
C(12)	6490(12)	1673(8)	1880(11)	58
C(21)	8156(9)	13(13)	5224(7)	50
C(22)	6843(10)	72(11)	1933(7)	46
C(31)	8623(12)	−1574(8)	5263(11)	62
C(32)	7317(12)	−1552(8)	1982(10)	60
C(41)	6345(14)	−987(7)	4224(12)	42
C(42)	4968(14)	−983(7)	1138(11)	36
C(51)	5448(10)	−229(5)	3895(8)	28
C(52)	4053(10)	−253(5)	905(9)	26
C(61)	5952(12)	643(7)	4212(10)	30
C(62)	4579(13)	625(7)	1175(11)	36
C(71)	4026(10)	−375(7)	3304(9)	43
C(72)	2649(10)	−419(6)	365(8)	43

TABLE 2. Environment of Mercury

Distances (Å)			
Hg–Cl(1)	2.286(3)	Hg–O(72)	2.994(7)
Hg–Cl(2)	2.300(3)	Hg–O(72)^c	2.761(7)
Hg–O(21)^a	3.189(7)	Hg–O(22)^b	3.011(7)
Hg–O(71)	2.716(7)		
Angles (°)			
Cl(1)–Hg–Cl(2)	176.5(2)	Cl(2)–Hg–O(22)^b	100.5(2)
Cl(1)–Hg–O(71)	89.2(2)	Cl(2)–Hg–O(72)^c	88.7(2)
Cl(1)–Hg–O(72)	87.0(2)	O(71)–Hg–O(72)^c	79.6(2)
Cl(1)–Hg–O(21)^a	96.6(2)	O(71)–Hg–O(21)^a	72.7(2)
Cl(1)–Hg–O(22)^b	83.0(2)	O(71)–Hg–O(22)^b	128.1(2)
Cl(1)–Hg–O(72)^c	92.3(2)	O(72)–Hg–O(22)^b	150.1(2)
Cl(2)–Hg–O(71)	88.6(2)	O(72)–Hg–O(21)^a	151.9(2)
Cl(2)–Hg–O(72)	89.9(2)	O(71)–Hg–O(72)^c	157.9(2)
Cl(2)–Hg–O(21)^a	85.3(2)	O(21)^a–Hg–O(72)^c	128.9(2)
		O(72)–Hg–O(72)^c	78.5(2)

$^a1-x, -y, 1-z$. $^b-1+x, y, z$. $^c-x, -y, -z$.

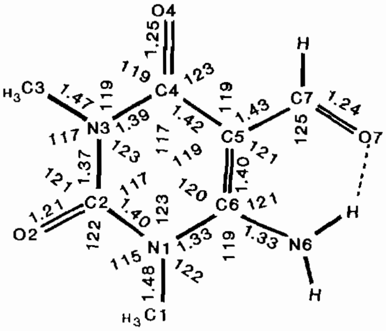

Fig. 1. Schematic diagram of the ligand, with atom numbering, interatomic distances and bond angles (σ = 0.015 Å and 1°). Average values for the two crystallographically independent ligands are given. (For individual values see 'Supplementary Material'.) The first digit in the symbols corresponds to the position in the ring. A second digit is added, when needed, to differentiate between corresponding atoms in the two independent molecules: for instance, O(21) and O(22) represent oxygen O(2) in ligands 1 and 2, respectively.

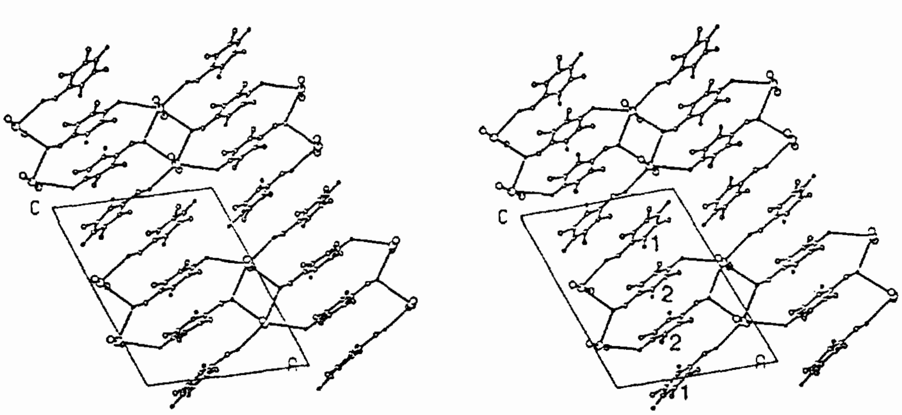

Fig. 2. Stereo view of the unit cell down the *b* axis. This view shows one layer parallel to the *ac* plane, consisting of saw-toothed ribbons running along the *a* direction.

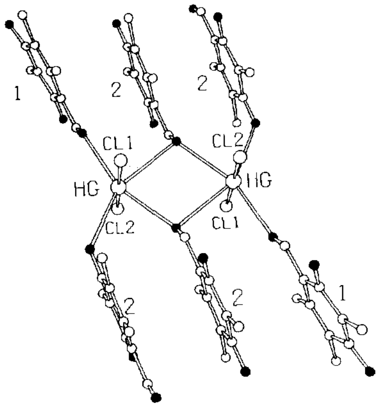

Fig. 3. Surrounding of the pairs of $HgCl_2$ molecules in the unit cell.

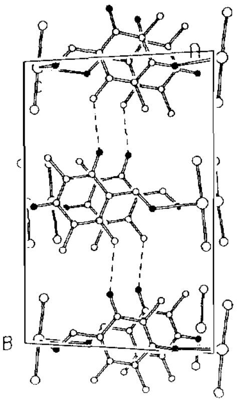

Fig. 4. View of the unit cell down the *c* axis, showing the hydrogen bonds (dotted lines) between the layers seen in Fig. 2.

Fig. 3. The Cl–Hg–Cl unit is nearly linear (176.5(2)°) and the Hg–Cl bonds (2.286(3), 2.300(3) Å) are similar to those found in various mixed compounds of the same type as ours [18, 25]. In the equatorial plane of the $HgCl_2$ unit (whose Hg–Cl bonds are regarded as axial) are found four secondary Hg···O bonds. This is apparently the only known $HgCl_2$ adduct in which no Hg···Cl secondary bonds are established with adjacent $HgCl_2$ units. The donors in these secondary bonds are two bridging O(72) formyl atoms, one monodentate O(71) formyl oxygen and the O(22) ·ring carbonyl oxygen. Although much longer than Hg–O bonds filling primary coordination sites of mercury [26], two of these Hg···O interactions, those with O(71) at 2.716(7) Å and with O(72) at 2.761(7) Å, are very strong for this type of interaction [18, 25]. The other two donors, that is O(72) at 3.011(7) Å and O(22) at 2.994(7) Å, lie at the upper limit of the range for significant secondary coordinative interaction. The angles between the Hg···O bonds and the Hg–Cl bonds vary between 81 and 100°, a feature commonly noted for this type of system. There are no strict rules in mercury compounds as to the number and arrangement of secondary bonds in the equatorial plane. The angles in Table 2 (72.7–128.9°) show large deviations from 90°. The overall geometry of Hg could be described as octahedral, but distortion would be very large. The very wide O(71)–Hg–O(22) angle of 128.1(2)° leaves room for a remote O(21) oxygen to feel the presence of mercury at 3.189(7) Å, but this is not considered here as significant coordinative interaction.

Quartets of ligands and pairs of $HgCl_2$ molecules are repeated in alternance in the *a* direction, thereby defining an infinite 'saw-toothed' ribbon (Fig. 2). The irregular interface originates from the ligands in the quartets not being parallel to propagation direction of the ribbon. Adjacent ribbons with their 'saw-toothed' surface interlocked interact mainly by inter-ring van der Waals contacts. Some contribution to cohesion may also result from the long Hg··· O(21) contact of 3.189 Å mentioned earlier. The infinite layers parallel to the *ac* plane are seen edgewise in Fig. 4. Cohesion between the layers is achieved through hydrogen bonding between the second amino hydrogen and the O(4) carbonyl group, which does not interact with mercury. These hydrogen bonds are strong (N(61)···O(42) = 2.772(10) Å, N(62)···O(41) = 2.814(10) Å) and hydrogen lies close to the N···O direction (Table 5, Supplementary Material).

Discussion

The crystal structure shows that the 6-amino nitrogen is sp^2 hybridized as in cytosine, adenine or guanine. The participation of the lone pair in the ring π system makes it unavailable for metal coordination. The *syn* orientation of the formyl oxygen with respect to C(5)=C(6) is stabilized by a N(6)–H···O(7) hydrogen bond, strong enough to slow down the rotation about the C(6)–N(6) bond and produce distinct ^1H signals for the $-NH_2$ protons (see 'Experimental') having become inequivalent on the NMR time scale. Although this strong intramolecular hydrogen bond may decrease the nucleophilicity of the formyl oxygen to some extent, it does not create serious steric hindrance and O(7) remains accessible.

With only the three hard oxygens available as donors for binding to mercury, it is not surprising that the soft chlorine atoms are not displaced from the $HgCl_2$ molecule. However, optimum use is made of all three oxygens of both independent types of ligands in forming either secondary coordination bonds with mercury or intermolecular hydrogen bonds. The formyl oxygen in both independent ligands forms relatively strong secondary Hg–O bonds, shorter than 2.8 Å. The overall coordination of mercury also includes carbonyl oxygens O(2) of both ligands, but the Hg···O contacts are above 3.0 Å. There is no obvious reason for O(2) being preferred to O(4): efficiency in space filling in the crystal undoubtedly plays a role in this respect. The O(4) carbonyl groups participate only in intermolecular hydrogen bonding.

The Hg···O interactions are not strong enough to be retained when the compound is dissolved in the good donor solvent DMSO. Complete dissociation is indicated by all ^{1}H NMR resonances appearing at the same place as in the free ligand.

Supplementary Material

The following supplementary material can be obtained from A.L.B.: anisotropic temperature factors, hydrogen coordinates, geometry of hydrogen bonds, least-squares planes, ligand geometry and structure factor amplitudes.

Acknowledgements

We wish to thank E. Gabe and Y. Lepage who gave us access to their CAD-4 diffractometer and J. P. Charland for collecting the X-ray data. The financial support of the Natural Sciences and Engineering Research Council of Canada is gratefully acknowledged.

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