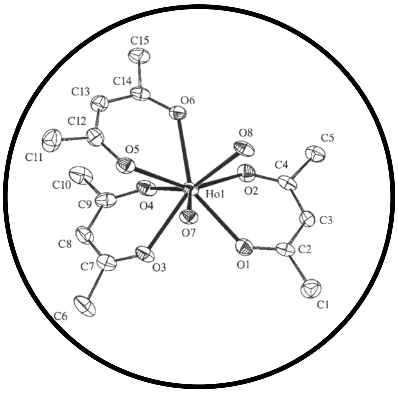
Chapter 3

Diaquatris(pentane-2,4-dionato-O,O')-holmium(III) monohydrate and diaquatris(pentane-2,4-dionato-O,O')-holmium(III) 4-hydroxypentan-2-one solvate dihydrate

Acta Crystallographica Section C 2000;C56:156-158



H. Kooijman[1], J.F.W. Nijsen[2], A.L. Spek[1] and A.D. van het Schip[2]

[1]*Bijvoet Center for Biomolecular Research, Department of Crystal and Structural Chemistry, Utrecht University, Utrecht, The Netherlands*

[2]*Department of Nuclear Medicine, University Medical Center, Utrecht, The Netherlands*

Abstract

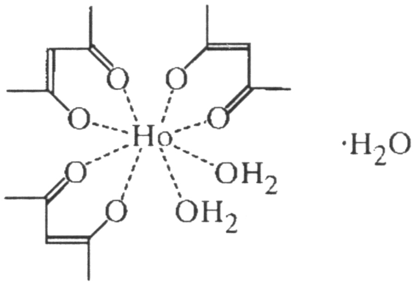
The structures of the title compounds, $[Ho(C_5H_7O_2)_3(H_2O)_2].H_2O$ and $[Ho(C_5H_7O_2)_3(H_2O)_2].C_5H_8O_2.2H_2O$, both show an eight-coordinate holmium(III) ion in a square antiprismatic configuration. The packing of these structures consists of an infinite two-dimensional network of hydrogen-bonded molecules. In both structures, the same hydrogen-bonded chain of Ho^{III} complexes is found.

3.1 Comment

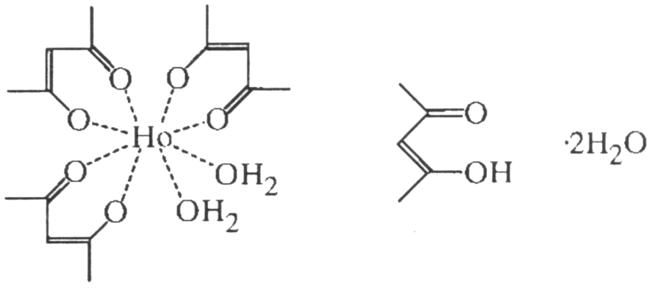
Holmium in the trivalent state, like other rare earths, reacts with acetylacetonate (pentane-2,4-dione) to form a complex coordinated with three acetylacetonate ligands and one or two water molecules [1,2]. The crystal structure of diaquatris(pentane-2,4-dionato-O,O')-holmium(III) monohydrate was reported by Aslanov et al. [3] with R = 0.13, but no further data are available from the Cambridge Structural Database (Version of April 1999; [4]). The pentanedione-Ho complex is essential for the development of a new intra-arterial radionuclide therapy for the treatment of liver metastases [5]. For the preparation of microspheres embedded with holmium we needed a stable hydrophobic holmium complex which can be incorporated easily and in high concentration into poly(L-lactic acid) (PLLA) microspheres. This study reports structural data on the holmium acetylacetonate (HoAcAc) complex, which was chosen for further investigation because it has the above-mentioned properties.

The HoAcAc complex showed a high chemical stability in PLLA microspheres before and after irradiation in a nuclear reactor. Release of neutron-activated holmium from the microspheres is <1.6% after 192h incubation in liver homogenate. As the incorporation of holmium in PLLA microspheres can be as high as 17% w/w, holmium-loaded microspheres are therefore suitable for selective internal radionuclide therapy. Neutron-activated ^{166}Ho is a β-emitter which can be used for treatment of liver metastases. It also emits γ-photons which can be used for imaging the distribution of activity in the patient. Owing to the high selectivity of the technique by which it is administered, the radiation is mainly restricted to the tumour.

Crystals of diaquatris(pentane-2,4-dionato-O,O')holmium(III) were obtained under different experimental conditions, such as pH (see Experimental). The crystal structures were determined to identify unambiguously the composition of the materials obtained. Two of these structures are presented here, namely, diaquatris(pentane-2,4-dionato-O,O')holmium(III) monohydrate, (I), and diaquatris-(pentane-2,4-dionato-O,O')holmium(III) 4-hydroxypentan-2-one solvate dihydrate, (II), obtained at pH 8.5 and 9.0, respectively.



(I)



(II)

In both structures, $\mathrm{Ho}^{\mathrm{III}}$ displays square antiprismatic coordination by eight O atoms. There are no significant differences between the geometric parameters of these complexes.

In structure (II), hydrogen bonds between the complexes join them into a chain running in the [010] direction. A link between two Ho atoms is formed either by a hydrogen-bonded motif with graph set R_2^2 (8) or by two symmetry-related motifs, each with graph set R_2^2 (6) [6]. Two non-coordinating water molecules and a free 4-hydroxypentan-2-one molecule also form a hydrogen-bonded chain in the [010] direction. This solvent chain donates three hydrogen bonds to the O atoms coordinated to Ho and accepts one hydrogen bond from a coordinated water molecule, thus forming a two-dimensional network in the (010) plane (see Fig. 3). The hydroxyl atom of the 4-hydroxypentan-2-one is disordered over two positions. The minor position forms a bifurcated intra/intermolecular hydrogen bond, whereas the major component forms only an intermolecular hydrogen bond.

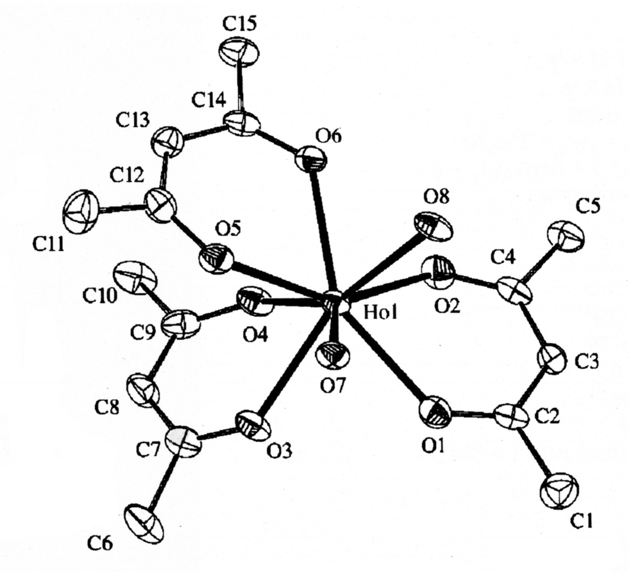


Fig. 1. Displacement ellipsoid plot [7] of (I) showing the atomic labelling scheme and 50% probability displacement ellipsoids. H atoms and the non-coordinating water molecule have been omitted for clarity.

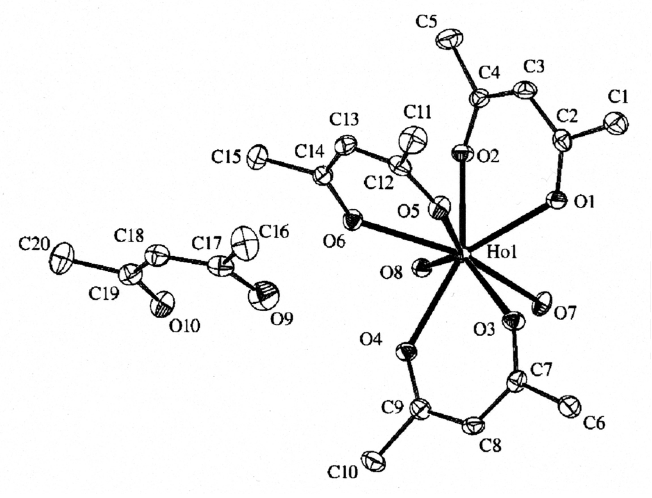


Fig. 2. Displacement ellipsoid plot [7] of (II) showing the atomic labelling scheme and 50% probability displacement ellipsoids. H atoms and the non-coordinating water molecule have been omitted for clarity.

Fig. 3. Crystal packing diagram for (II). The hydrogen-bonded chain of solvent molecules has been accentuated using solid bonds. Methyl groups and H atoms not involved in hydrogen bonding have been omitted for clarity.

In structure (I), the complexes are joined by hydrogen bonds into an infinite one-dimensional chain running in the [101] direction. This chain is identical to that found in structure (II). The non-coordinating water molecule links these chains in a two-dimensional network in the (010) plane. One of the H atoms of this water molecule is disordered over two positions, in both of which it forms hydrogen bonds.

3.2 Experimental

Pentane-2,4-dione (180 g, 1.80 mol) was dissolved in water (1080 g, 59.34 mol), followed by addition of ammonium hydroxide (28% w/w) until a solution of pH 8.5 was obtained. Holmium chloride hexahydrate (10 g, 26.4 mmol) in water (30 g, 1.64 mol) was then added to the solution, yielding yellow crystals (pink under fluorescent lighting) of (I) after 24h at room temperature. Satisfactory spectroscopic data (^{1}H NMR, ^{13}C NMR and IR) were obtained. At pH 9.0, crystals of (II) were obtained, which were also yellow in daylight and pink under fluorescent lighting.

Compound (I)

Crystal data

$[Ho(C_5H_7O_2)_3.(H_2O)_2].H_2O$

M_r = 516.30

Monoclinic, $P2_1/c$

a = 8.242 (2) Å

b = 21.782 (6) Å

c = 12.557 (3) Å

β = 119.292 (14)°

V = 1966.1 (9) Å^3

Z = 4

D_x = 1.744 Mg m^{-3}

Mo $K\alpha$ radiation

Cell parameters from 447 reflections

θ = 2-25°

μ = 4.07 mm^{-1}

T = 150 K

Needle, yellow-pink

0.35 x 0.08 x 0.03 mm

Data collection

Nonius KappaCCD diffractometer

Area-detector φ and ω scans

Absorption correction: multi-scan (Spek, 1990)

T_{min} = 0.614,T_{max} = 0.855

15 088 measured reflections

3548 independent reflections

2947 reflections with $I > 2\sigma(I)$

R_{int} = 0.086

θ_{max} = 25.24°

$h = -9 \rightarrow 9$

$k = -25 \rightarrow 26$

$l = -15 \rightarrow 13$

Refinement

Refinement on F^2

$R(F)$ = 0.042

$wR(F^2)$ = 0.099

S = 1.151

3548 reflections

254 parameters

H atoms: see below

$w = 1/[\sigma^2(F_o^2) + (0.027P)^2 + 9.5P]$ where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{max}$ = 0.002

$\Delta\rho_{max}$ = 1.19 e Å^{-3}

$\Delta\rho_{min}$ = -1.51 e Å^{-3}

Table 1.
Selected geometric parameters (Å, °) for (I).

Ho1 - O1	2.360 (4)	Ho1 - O5	2.306 (5)
Ho1 - O2	2.321 (5)	Ho1 - O6	2.401 (4)
Ho1 - O3	2.374 (5)	Ho1 - O7	2.420 (5)
Ho1 – O4	2.327 (5)	Ho1 - O8	2.364 (5)
O1 - Ho1 - O2	73.15 (16)	O5 - Ho1 - O6	72.84 (16)
O3 - Ho1 - O4	71.05 (17)	O7 - Ho1 - O8	71.49 (16)

Table 2.
Hydrogen-bonding geometry (Å, °) for (I).

D-H…*A*	*D*-H	H…*A*	*D*…*A*	*D*-H…*A*
O7-H74…O3^{i}	0.78 (6)	2.00 (6)	2.771 (7)	168 (6)
O7-H75…O1^{i}	0.79 (5)	2.29 (6)	2.940 (6)	140 (5)
O8-H84…O9	0.78 (7)	1.98 (7)	2.759 (9)	177 (7)
O8-H85…O6^{ii}	0.79 (6)	2.06 (6)	2.841 (6)	174 (8)
O9-H94…O4^{iii}	0.79 (9)	2.01 (9)	2.760 (8)	159 (9)
O9-H95…O2^{iii}	0.79 (16)	2.39 (16)	2.994 (8)	134 (14)
O9-H95…O9^{iv}	0.79 (16)	2.35 (15)	2.785 (8)	115 (13)
O9-H96…O2^{iii}	0.78 (10)	2.42 (15)	2.994 (8)	131 (12)

Symmetry codes: (i) 1 - *x*, -*y*, 2 - *z*; (ii) -*x*, -*y*, 1 - *z*; (iii) 1 + *x*, *y*, *z*; (iv) 1 - *x*, -*y*, 1 - *z*.

Compound (II)

Crystal data

$[Ho(C_5H_7O_2)_3(H_2O)_2].C_5H_8O_2.H_2O$

$M_r = 634.43$

Monoclinic, $P2_1/c$

$a = 11.4903\ (11)$ Å

$b = 11.0242\ (6)$ Å

$c = 20.5442\ (15)$ Å

$\beta = 93.440\ (7)^\circ$

$V = 2597.7\ (3)$ Å^3

$Z = 4$

$D_x = 1.622$ Mg m^{-3}

Mo $K\alpha$ radiation

Cell parameters from 25 reflections

$\theta = 11.49$-18.35°

$\mu = 3.10$ mm^{-1}

$T = 293$ K

Needle, yellow-pink

0.70 x 0.20 x 0.05 mm

Data collection

Enraf-Nonius CAD-4T diffractometer

ω scans

Absorption correction: Gaussian (Spek, 1990)

$T_{min} = 0.517$, $T_{max} = 0.857$

9388 measured reflections

4697 independent reflections

3764 reflections with $I > 2\sigma(I)$

$R_{int} = 0.041$

$\theta_{max} = 25.25^\circ$

$h = -13 \rightarrow 13$

$k = 0 \rightarrow 13$

$l = -24 \rightarrow 24$

3 standard reflections

frequency: 60 min

intensity decay: 1%

Refinement

Refinement on F^2

$R(F) = 0.032$

$wR(F^2) = 0.069$

$S = 1.173$

4697 reflections

338 parameters

H atoms: see below

$w = 1/[\sigma^2(F_o^2) + (0.02P)^2 + 5P]$

where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{max} = 0.002$

$\Delta\rho_{max} = 1.66$ e Å^{-3}

$\Delta\rho_{min} = -1.96$ e Å^{-3}

Table 3.
Selected geometric parameters (Å, °) for (II).

Ho1 - O1	2.387 (3)	Ho1 - O5	2.302 (3)
Ho1 - O2	2.334 (3)	Ho1 - O6	2.383 (3)
Ho1 - O3	2.305 (3)	Ho1 - O7	2.356 (3)
Ho1 – O4	2.342 (3)	Ho1 - O8	2.416 (3)
O1 - Ho1 - O2	71.77 (11)	O5 - Ho1 - O6	71.59 (11)
O3 - Ho1 - O4	73.59 (11)	O7 - Ho1 - O8	71.29 (11)

Table 4.
Hydrogen-bonding geometry (Å, °) for (II).

D-H…*A*	*D*-H	H…*A*	*D*…*A*	*D*-H…*A*
O7-H74…O10^{i}	0.82 (4)	1.92 (4)	2.721 (5)	165 (5)
O7-H75…O1^{ii}	0.81 (4)	2.09 (5)	2.854 (5)	159 (5)
O8-H84…O4^{i}	0.84 (4)	1.99 (3)	2.788 (5)	157 (4)
O8-H85…O6^{i}	0.82 (4)	1.99 (5)	2.765 (5)	157 (5)
O9-H94…O12	0.89 (5)	2.01 (5)	2.887 (7)	173 (12)
O11-H114…O2^{iii}	0.84 (4)	2.07 (4)	2.906 (4)	171 (6)
O11-H115…O10^{iv}	0.83 (4)	2.13 (4)	2.918 (5)	159 (6)
O12-H124…O5	0.84 (5)	2.21 (5)	2.879 (5)	136 (5)
O12-H125…O11	0.85 (6)	1.92 (6)	2.756 (5)	170 (6)
C10-H101…O11^{v}	0.96	2.58	3.375 (7)	141

Symmetry codes: (i) –*x*, 1 – *y*, -*z*; (ii) –*x*, -*y*, -*z*; (iii) *x*, ½ - *y*, ½ + *z*; (iv) –*x*, *y* - ½, ½ -*z*; (v) –*x*, ½ + *y*, ½ - *z*.

For both structures, H atoms bonded to O were located on difference Fourier maps and their coordinates were included as parameters in the refinement. Distance restraints were applied to ensure reasonable intramolecular geometries. Methyl-H atoms were located from difference Fourier syntheses and refined as part of a rigid group allowed to rotate around the C-C bond but not tip or distort. All other H atoms were introduced at calculated positions, riding on their carrier atoms. The high uncertainties shown by some of the data given in Tables 2 and 4 are due to H95 and H96 being disordered components. The occupation ratio of the disordered H atom of (I) was fixed; the occupation ratio of the disordered H atom of (II) was refined. Displacement parameters of all H atoms were related to their carrier atom by a fixed constant. For (I), the highest peak of 1.66 Å^{-3} in the difference Fourier synthesis was located 1.07 Å from Ho1; the deepest trough of -1.96 Å^{-3} was 0.92 Å from the same position.

Data collection: *COLLECT* [8] for (I), locally modified *CAD-4 Software* [9] for (II); cell refinement: *DENZO-SMN* [10] for (I), *SET4* [11] for (II); data reduction: *DENZO-SMN* for (I), *HELENA* [12] or (II); for both compounds, program(s) used to solve structure: *SHELXS86* [13]; program(s) used to refine structure: *SHELXL97* [14]; molecular graphics: *PLATON* [7]; software used to prepare material for publication: *PLATON*.

Acknowledgement

This work was supported in part (ALS) by the Council for Chemical Sciences of the Netherlands Organization for Scientific Research (CW-NWO).

References

1. Stites JG, McCarty CN and Quill LL. The rare earth metals and their compounds VIII. An improved method for the syntheses of some rare earth acetylacetonates. *J. Am. Chem. Soc.* **1948**;70:3142-143.
2. Brown WB, Steinbach JF and Wagner WF. Extraction of the lanthanides with acetylacetone. *J. Inorg. Nucl. Chem.* **1960**;13:119-124.
3. Aslanov LA, Korytnii EF. and Porai-Koshits, M. A. *Zh. Strukt. Khim.* **1971**;12:661-662.
4. Allen FH and Kennard O. *Chem. Des. Autom. News* **1993**;8:31-37.
5. Nijsen JFW, Zonnenberg BA, Woittiez JRW, Rook DW, Swildens-van Woudenberg IA, van Rijk PP and van het Schip AD. Holmium-166 poly lactic acid microspheres applicable for intra-arterial radionuclide therapy of hepatic malignancies: effects of preparation and neutron activation techniques. *Eur. J. Nucl. Med.* **1999**;26:699-704
6. Bernstein J, Davis RE, Shimoni L and Chang N-L. *Angew. Chem. Int. Ed. Engl.* **1995**;34:1555-1573.
7. Spek AL. *Acta Cryst.* **1990**:A46:C-34.
8. Nonius. COLLECT. Nonius BV, Delft, The Netherlands **1997**.
9. Enraf-Nonius. CAD-4 Software. Version 5.0. Enraf-Nonius, Delft, The Netherlands **1989**.
10. Otwinowski Z. and Minor W. Methods Enzymol. **1997**;276:307-326.
11. Boer, de JL and Duisenberg AJM. *Acta Cryst.* **1984**;A40:C-410.
12. Spek AL. HELENA. University of Utrecht, The Netherlands **1997**.
13. Sheldrick GM. SHELXS86. University of Göttingen, Germany **1985**.
14. Sheldrick GM. SHELXL97. University of Göttingen, Germany **1997**.