Powder X-ray crystallography of gallium 3-hydroxy-4-pyronates

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Two complexes of gallium with 3-hydroxy-4-pyrones were synthesized as potential pharmaceutical compounds for oral administration. These compounds were analyzed by powder X-ray diffraction followed by computer indexing of the data. The first compound, tris(3-hydroxy-2-methyl-4-pyronato)gallium $[Ga(C_6H_5O_3)_3]$, was found to be orthorhombic, $a=18.500(2)$, $b=16.948(2)$, $c=12.012(2)$ Å, $V=3766(1)$ Å^3, $Z=8$, $D_m=1.56(5)$, $D_x=1.570$. The compound appears closely analogous to a similar compound containing Al instead of Ga, which crystallizes in space group *Pbca*. The second compound, tris(3-hydroxy-2-ethyl-4-pyronato)gallium $[Ga(C_7H_7O_3)_3]$, was found to be monoclinic, $a=31.634(2)$, $b=8.7662(5)$, $c=7.8982(5)$ Å, $\beta=103.240(6)°$, $V=2132.0(5)$ Å^3, $Z=4$, $D_m=1.50(5)$, $D_x=1.517$, with a primitive space group.

I. INTRODUCTION

Gallium is used pharmaceutically for both therapeutic and diagnostic purposes. Ionic gallium has therapeutic effects on bone degeneration in diseases such as multiple myeloma and Paget's disease, and it is effective in treating hypercalcemia (elevated calcium levels in the blood) (Warrell and Bockman, 1989; Warrell *et al.*, 1990, 1993; Matkovic *et al.*, 1990). The U.S. Food and Drug Administration in 1991 approved the use of gallium for treating hypercalcemia associated with cancer. Gallium has also been proposed as a treatment for osteoporosis, a very widespread degenerative bone disease, and for some lymphomas (Warrell and Bockman, 1985; Weik *et al.*, 1983). The radioactive gallium isotope ^{67}Ga is in widespread use for the diagnosis of many infectious and inflammatory diseases and several types of cancer. When used for any of these medical purposes, the gallium is administered as a dissolved salt (usually a nitrate or chloride) by injection or intravenously. The gallium salts are not administered orally due to their very low absorption through the gastrointestinal tract. Recent research has found that gallium complexes with some 3-hydroxy-4-pyrones, when protected from stomach acid, have high intestinal absorption and are candidates for orally administrable pharmaceuticals (Bernstein, 1993).

In this paper are presented powder X-ray diffraction data on 1:3 complexes of gallium with 3-hydroxy-2-methyl-4-pyrone (maltol) $[Ga(C_6H_5O_3)_3]$ and 3-hydroxy-2-ethyl-4-pyrone (ethyl maltol) $[Ga(C_7H_7O_3)_3]$.

II. MATERIALS AND METHODS

Maltol ($C_6H_6O_3$) and gallium nitrate nonohydrate $[Ga(NO_3)_3\cdot 9H_2O]$ used in this study were obtained from Aldrich Chemical Company, Milwaukee, WI; ethyl maltol ($C_7H_8O_3$) was obtained from Pfizer Chemical Division, New York, NY. The 1:3 complexes of gallium with the hydroxypyrones were prepared as follows: 20 ml of a 0.75 M chloroform solution of the hydroxypyrone (maltol or ethyl maltol) was slowly added, with continuous stirring, to 10 ml of a 0.5 M ethanol solution of gallium nitrate nonohydrate, and was stirred for an additional 5 min at 23 °C. The resulting solutions were highly acidic; about 5.5 g of powdered Na_2CO_3 were added with stirring to raise the *p*H to close to 7, and stirring was continued for an additional 10 min. The mixtures were then filtered to remove all solids, and the filtrates evaporated in a rotary evaporator. The remaining crystalline solid, which is white to pale beige, is the 1:3 gallium :hydroxypyrone complex. The complex can be recrystallized from alcohol, chloroform, or other solvents, although this was not usually necessary for purification. The solubility in water at 23 °C of the 1:3 gallium:maltol complex was found

TABLE I. Powder X-ray diffraction data for 1:3 gallium:maltol complex [tris(3-hydroxy-2-methyl-4-pyronato)gallium].

h	k	l	$2\theta_{obs}$ (°)	$2\theta_{calc}$ (°)	$\Delta 2\theta$ (°)	d_{obs} (Å)	I/I_0
2	0	0	9.561	9.553	0.008	9.243	100
2	1	0	10.886	10.887	−0.001	8.121	6
0	2	1	12.774	12.774	0.000	6.924	50
0	0	2	14.729	14.737	−0.008	6.009	89
1	0	2	15.514	15.498	0.016	5.707	12
1	1	2	16.355	16.361	−0.006	5.415	5
2	0	2	17.583	17.591	−0.008	5.040	26
2	3	0	18.401	18.387	0.014	4.818	12
4	0	0	19.187	19.174	0.013	4.622	7
2	3	1	19.832	19.826	0.006	4.473	24
0	4	0	20.961	20.949	0.012	4.235	11
1	3	2	22.122	22.111	0.011	4.015	2
3	3	1	22.582	22.573	0.009	3.934	2
4	2	1	23.120	23.107	0.013	3.844	46
2	3	2	23.645	23.644	0.001	3.760	5
0	2	3	24.572	24.569	0.003	3.620	15
0	4	2	25.702	25.710	−0.008	3.463	15
3	3	2	26.007	26.010	−0.003	3.423	7
2	2	3	26.440	26.412	0.028	3.372	5
4	2	2		26.476	−0.036		
2	5	1	29.013	29.000	0.013	3.075	3
6	1	0	29.402	29.419	−0.017	3.035	22
5	2	2	30.253	30.243	0.010	2.952	3
4	2	3	31.343	31.352	−0.009	2.852	2
2	5	2	31.805	31.794	0.011	2.811	5
1	5	3	34.986	34.992	−0.006	2.563	6
1	6	2	35.412	35.422	−0.010	2.533	2
5	3	3	36.673	36.666	0.007	2.448	3
0	6	3	38.991	38.990	0.001	2.308	10
6	3	3	40.183	40.183	0.000	2.242	3
6	7	1	48.354	48.355	−0.001	1.881	4

Unit cell: $a=18.500(2)$ Å; $b=16.948(2)$ Å; $c=12.012(2)$ Å; $V=3766(1)$ Å^3; $Z=8$; $D_m=1.56(5)$; $D_x=1.570$; probable space group *Pbca*

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TABLE II. Powder X-ray diffraction data for 1:3 gallium: ethyl maltol complex [tris(3-hydroxy-2-ethyl-4-pyronato)gallium].

h	k	l	$2\theta_{obs}$ (°)	$2\theta_{calc}$ (°)	$\Delta 2\theta$ (°)	d_{obs} (Å)	I/I_0
0	0	2	5.736	5.735	0.001	15.395	32
0	1	1	10.483	10.484	−0.001	8.432	4
0	0	4	11.490	11.485	0.005	7.695	100
1	0	0		11.500	−0.010		
$\bar{1}$	0	2	11.618	11.618	0.000	7.611	25
0	1	3	13.263	13.271	−0.008	6.670	20
1	0	2	13.992	13.993	−0.001	6.324	4
$\bar{1}$	0	4	14.282	14.284	−0.002	6.196	24
$\bar{1}$	1	1	15.087	15.088	−0.001	5.868	10
1	1	0	15.314	15.316	−0.002	5.781	8
$\bar{1}$	1	2	15.412	15.406	0.006	5.745	8
1	1	1	16.070	16.068	0.002	5.511	4
1	1	2	17.270	17.276	−0.006	5.130	12
$\bar{1}$	1	4	17.514	17.514	0.000	5.060	12
1	0	4	18.063	18.063	0.000	4.907	3
$\bar{1}$	0	6	18.442	18.441	0.001	4.807	4
1	1	3	18.854	18.856	−0.002	4.703	8
0	2	0	20.243	20.243	0.000	4.383	3
0	2	2	21.061	21.057	0.004	4.215	2
$\bar{1}$	1	6		21.060	0.001		
0	2	3	22.034	22.033	0.001	4.031	6
0	1	7	22.608	22.596	0.012	3.932	7
$\bar{2}$	0	1		22.626	−0.018		
1	0	6	22.923	22.913	0.010	3.876	5
$\bar{1}$	2	1	23.195	23.190	0.005	3.832	4
1	2	0	23.350	23.342	0.008	3.807	11
$\bar{2}$	0	4		23.359	−0.009		
1	2	1	23.853	23.850	0.003	3.727	2
$\bar{2}$	1	2	24.714	24.710	0.004	3.599	6
0	2	5	24.917	24.913	0.004	3.571	8
2	0	2	25.105	25.108	−0.003	3.544	4
1	2	3	25.849	25.841	0.008	3.444	1
$\bar{2}$	1	5	26.376	26.372	0.004	3.376	1
2	1	2	27.115	27.118	−0.003	3.286	1
1	2	4	27.257	27.258	−0.001	3.269	1
$\bar{1}$	2	6	27.514	27.516	−0.002	3.239	1
$\bar{2}$	1	6	27.529	27.532	−0.003	3.237	1
1	1	9	27.897	27.898	−0.001	3.196	1
0	1	9	27.969	27.970	−0.001	3.187	1
2	1	3	28.450	28.452	−0.002	3.135	1
$\bar{2}$	2	2	30.448	30.446	0.002	2.933	2
1	3	1	33.130	33.133	−0.003	2.702	1

Unit cell: a=7.8982(5) Å, b=8.7662(5) Å, c=31.634(2) Å, β=103.240(6)°, V=2132.0(5) Å^3; Z=4; D_m=1.50(5); D_x=1.517

to be about 24 millimolar, and of the 1:3 gallium:ethyl maltol complex about 5 millimolar.

For the powder X-ray diffraction analyses, samples of the 1:3 complexes were gently ground by hand for a few seconds with an agate mortar and pestle. Analysis of the 1:3 gallium:maltol complex was performed on a Philips diffractometer equipped with a curved graphite monochromator, a scintillation detector, and fixed slits. The diffractometer was operated using CuKα_1 radiation (λ=1.54056 Å) at 40 kV and 55 mA, using a step scan with a step size of 0.025° 2θ and a dwell time of 10 s/step. The powdered sample was spread on a glass slide. Analysis of the 1:3 gallium:ethyl maltol complex was performed on a Scintag diffractometer equipped with a germanium solid-state detector and fixed slits, using CuKα_1 radiation (λ=1.54056 Å) at 45 kV and 40 mA. The diffractometer was operated using a step scan having a step size of 0.02° 2θ and a dwell time of 24 s/step. The sample was spread on a "zero background plate," which is a plate of single crystal quartz cut and polished on a plane at about a 6° angle from {001}.

The diffraction data for all the studied compounds were initially indexed using the TREOR program of Werner *et al.* (1985). The unit cell parameters were then refined by the method of least squares on all uniquely indexed reflections.

The densities of the samples could not be measured with high precision due to their powdery nature, but an attempt at measuring the densities was made in an effort to ascertain the Z values of the compounds and the reasonableness of the determined unit cells. The densities of the powders were measured with a Jolly balance using toluene.

The two 1:3 gallium:hydroxypyrone complexes were analyzed for gallium using energy dispersive X-ray fluorescence analysis.

III. RESULTS AND DISCUSSION

Powder X-ray diffraction data for the studied compounds are presented together with the derived unit cell parameters in Tables I and II. The density for the 1:3 gallium:maltol complex was measured as 1.56(5) g/cm^3; with Z=8, the calculated density is 1.570. For the 1:3 gallium:ethyl maltol complex, the density was measured as 1.50(5); with Z=4, the calculated density is 1.517. X-ray fluorescence analysis of the 1:3 complexes found the gallium contents to agree with the theoretical contents to within the limits of experimental error.

The diffraction data for the 1:3 gallium:maltol complex strongly suggest that this compound is closely analogous to the 1:3 aluminum:maltol complex that was studied by Finnegan *et al.* (1986) using single crystal x-ray diffraction methods. The aluminum compound is reported to be orthorhombic, space group *Pbca*, a=18.402(1), b=16.964(1), c=11.949(1) Å, Z=8. Based on this close analogy, the likely space group for the gallium compound is also *Pbca*.

The diffraction pattern and unit cell dimensions for the 1:3 gallium:ethyl maltol complex are very different from those of the 1:3 gallium:maltol complex. No analogous compound was found described in the literature. A primitive space group is indicated based on the lack of systematic absences consistent with other lattice types.

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