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Neutral Water-Soluble Indium Complexes of 3-Hydroxy-4-pyrones and 3-Hydroxy-4-pyridinones

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Several tris(3-hydroxy-4-pyronato)- and tris(3-hydroxy-2-methyl-4-pyridinonato)indium(III) complexes have been prepared and characterized. The pyrones are kojic acid, chlorokojic acid, and pyromeconic acid; the pyridinones have either a proton or a methyl substituent at the ring nitrogen atom. These complexes have been studied by a number of techniques including 1-octanol/water partitioning and single-crystal X-ray diffraction. Several of the complexes have both appreciable water solubility and lipophilicity and are neutral in aqueous solution; tris(maltolato)indium(III) maximizes both these properties. The N-methylated hydroxypyridinone complex $In(C_7H_8NO_2)_3 \cdot 12H_2O$ crystallized in the trigonal space group $P\bar{3}$ with crystal parameters a = 16.842 (1) Å, c = 6.8078 (7) Å, and Z = 2. The data were refined by using 2496 reflections with $I \geq 3[\sigma(I)]$ to R and R_w values of 0.033 and 0.037, respectively. It crystallized as an exoclathrate with a rigidly *fac* geometry incorporating extensive hydrogen bonding to hexagonal channels of water molecules; however, the orientation of the ML_3 units in the unit cell is rotated from the two previous examples of this lattice. The channels and hydrogen bonding involve every oxygen atom in the unit cell.

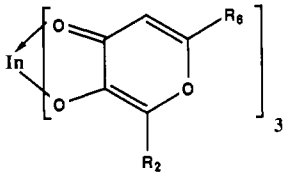
Introduction

We have been exploiting the properties of 3-hydroxy-4-pyrones and their congeners the 3-hydroxy-4-pyridinones to prepare complexes of aluminum and gallium that are neutrally charged and soluble in aqueous solution, as well as of reasonable lipophilicity.[1-4] The 3-hydroxy-4-pyridinones form complexes of considerable thermodynamic stability with Al and Ga,[5] and this has led us to examine these ligands as in vivo directors of ^{67}Ga,[6] as in vivo transport agents for Al,[7] and as possible chelators for aluminum overload.

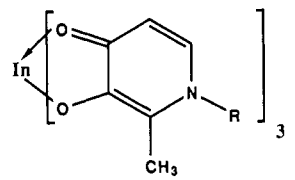
Like Ga, indium, a group 13 congener of Al and Ga, also has isotopes that are compatible with current nuclear medical technology (^{111}In; $t_{1/2}$ = 2.81 days; γ = 172.5, 247 keV; accelerator product. ^{113m}In: $t_{1/2}$ = 100 min; γ = 391.7 keV; generator product). Oxine (8-hydroxyquinoline) has been chelated to ^{111}In (and ^{68}Ga) in radiopharmaceutically active tris(ligand) complexes.[8-10] This simple bidentate ligand has high formation constants for both the ions[11,12] and has been used in the labeling of red blood cells, leukocytes, and blood platelets with these radionuclides.[8-10,13] The tris(oxinato) complexes are neutral and lipophilic, thereby crossing cell membranes easily; however, the complexes are quite insoluble in water and the labeling must be done in vitro (also to avoid transferrin competition). The blood cells are then returned in vivo for the scanning procedure. Tropolone, acetylacetone, and 2-mercaptopyridine *N*-oxide have also been investigated as alternatives in the same transport system.[10,14]

The aqueous coordination chemistry of In^{3+} with multidentate ligands incorporating hydroxy, aminocarboxylato, and catecholato moieties has been scrutinized with nuclear medicine in mind;[15-24] however, there have been few studies of the aqueous chemistry of In with simple bidentate ligands. The great affinity of the ubiquitous iron transport protein transferrin for iron and iron-like ions (Al^{3+}, Ga^{3+}, In^{3+}) dictates that most bidentate ligands will not be able to maintain their chelated In^{3+} when challenged for it by transferrin in vivo.[25] The chemical focus has been on multidentate ligands, where the added entropic contribution of the chelate effect produces a synergistically enhanced binding stability. There have been few attempts to develop a chemistry of the ion with bidentate, but water-soluble, chelating groups.

The great hydrolytic instability[26] of indium is another important factor in its aqueous chemistry. In^{3+} hydrolyzes rapidly in neutral (or pH 7.4) solution to form a highly insoluble hydroxide. Hydrolysis contributes to the paucity of aqueous, simple ligand chemistry of indium.



$R_2 = R_6 = H$ $In(pa)_3$
$R_2 = CH_3$, $R_6 = H$ $In(ma)_3$
$R_2 = H$, $R_6 = CH_2OH$ $In(ka)_3$
$R_2 = H$, $R_6 = CH_2Cl$ $In(ck)_3$



R = H $In(mpp)_3$
R = CH_3 $In(dpp)_3$

The Al^{3+} and Ga^{3+} complexes of 3-hydroxy-1,2-dimethyl-4-pyridinone (Hdpp) form an unusual dodecahydrate structure that

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Table I. Infrared Spectral Data for $In(L)_3$ (cm^{-1})[a]

	L				
	pa	ka	ck	mpp	dpp
ν_{OH}	3420 b	3400 b	3430 b	3420 b	3430 b
ν_{NH}				3260	
ν_{CH}	3095 m	3090	3090 m	3080	3050 m
			3040 m	2940	2960 m
$\nu_{C=O}$ and ν_{ring}	1595	1615	1610	1620 sh	1605
	1550	1560	1565	1600	1550
	1510	1510	1515	1520 sh	1505
	1450	1460	1460	1495	1490
ν_{CCl}			745 m		

[a] All strong or very strong (except m = moderate) intensity. ν = vibration.

Table II. UV Bands,[a] Molar Absorptivities,[a] 1-Octanol/Water Partition Coefficients (p), and Water Solubilities of the Complexes (25 °C)

complex	λ, nm	ε, M^{-1} cm^{-1}	p	solubility, mM
$In(pa)_3$	270	14900	0.24	0.4
	214	26100		
$In(ma)_3$	275	20600	0.98	2.5
	214	41000		
$In(ka)_3$	268	19000	0.12	1.9
	218	40400		
$In(ck)_3$	273	10300		
	227	23200	0.49	0.04
$In(mpp)_3$	288	25800	<0.01	1.0
	227	82700		
$In(dpp)_3$	293	27900	<0.01	1.1
	225	85100		

[a] In H_2O.

we have called an exoclathrate because of its extensively hydrogen-bonded "inside-out" exclusion array.[2,4] We were interested in determining if indium would also form this structure.

In this contribution, we describe complexes of In^{3+} that are designed to be water soluble and hydrolytically stable at physiological pH and have neutral charge. We also report the structure of the dodecahydrate $In(dpp)_3 \cdot 12H_2O$, which is an exoclathrate that is closely related to but different from its group 13 analogues.

Experimental Section

Materials and Methods. These were mostly as previously described.[3,27] Hmpp and Hdpp were prepared by the methods of Nelson,[27] Harris,[28] or Kontoghiorghes and Sheppard.[29] Pyromeconic acid was a gift of Professor J. H. Looker of the University of Nebraska (Lincoln, NE), and indium nitrate pentahydrate ($In(NO_3)_3 \cdot 5H_2O$) was from Alfa. $In(ma)_3$ was prepared in water by the method of Tuck.[30]

The preparations of the complexes were quite similar, and complete details are given only in the first ($In(pa)_3$) case. The complexes are very hygroscopic and are isolated initially as hydrates. Accurate anhydrous elemental analyses were only obtainable after extensive drying in vacuo at elevated temperature. Infrared data for the complexes are displayed in Table I. UV data, water solubilities, and 1-octanol/water partition coefficients of the complexes are given in Table II.

Octanol/Water Partition Coefficients. This procedure for metal complexes has been refined from our previous report[3] and is described in detail. Reagent grade 1-octanol was distilled, and the first and last quarters were discarded. The buffer was Trizma-7.4, hydrogen chloride salt, from Sigma. The buffer solution was 0.05 M Trizma and 0.15 M (isotonic) NaCl; doubly distilled water was used, and the pH was 7.4 at 25 °C. The two solvents were mutually saturated by stirring a 1:1 suspension overnight with a magnetic stirrer and then separating. These saturated solvents were used for all the measurements.

Trial solutions of all the compounds were made to determine the ideal concentrations and wavelengths for measurement on the UV–vis spectrophotometer (Perkin-Elmer Coleman 124). Absorbances between 1 and 1.5 for the buffer solution before extraction were deemed ideal. Extinction coefficients are given in Table II; all the compounds were in the 10–30000 L mol^{-1} cm^{-1} range and their concentrations were approximately 10 μM in order to produce the desired absorbances. Solutions in buffer (25 mL) at these concentrations were made for each of the In compounds. A 10-mL aliquot was removed, placed in a 15 mL centrifuge tube, and labeled as the initial solution. Two 6-mL aliquots were removed and placed in centrifuge tubes along with 6 mL of 1-octanol. Each extraction consisted of a minimum of 100 inversions (>2 min of contact time) followed by >15 min of equilibration time. All of the tubes were then centrifuged for 10 min, and the 1-octanol layer was removed with a Pasteur pipet. The buffer layer was used to rinse the cuvettes and to make one reading per tube; this was repeated three times per compound, thus producing three measurements of the initial concentration and six of the post-extraction value. The reference solution was buffer that had also been centrifuged.

As these were all 1:1 extractions, the values of p were determined as (initial absorbance − postextraction absorbance)/postextraction absorbance. The standard deviations were on the order of ±0.04 and the instrument error (ca. ±0.005 absorbance units) would be ±0.02 at these absorbance readings.

Tris(pyromeconato)indium(III), In(pa)$_3$. $In(NO_3)_3 \cdot 5H_2O$ (0.638 g, 1.63 mmol) and Hpa (0.568 g, 5.07 mmol) were dissolved in 50 mL of water. The pH was adjusted from 2.1 to 9.1 by dropwise addition of 2.0 N NaOH; a white solid precipitated. This was isolated by suction filtration and dried in vacuo for 16 h. The yield was 0.518 g (71%); mp 260 °C dec. Crystallization was accomplished by evaporation of a chloroform solution. Anal. Calcd (found) for $C_{15}H_9InO_9$: C, 40.21 (39.97); H, 2.02 (2.07). Mass spectrum (EI): m/e 226 (ML^+), 337 (100%, ML_2^+), 448 (ML_3^+). NMR (270 MHz, 25 °C, $CDCl_3$): δ 6.74 (d, J_{56} = 5.5 Hz, 1 H, H_5), 7.90 (d, J_{56} = 5.5 Hz, 1 H, H_6), 8.06 (s, 1 H, H_2). Solubility: soluble in chloroform; slightly soluble in water and dichloromethane.

Tris(kojato)indium(III) Hemihydrate, In(ka)$_3$·0.5H$_2$O. A preparation similar to that for $In(pa)_3$ incorporating Hka (1.785 g, 12.56 mmol) and $In(NO_3)_3 \cdot 5H_2O$ (1.624 g, 4.16 mmol) in 25 mL of warm water resulted in a fine white solid (after cooling and the adjustment of the pH to 8.1); this was washed with cold water and dried in vacuo for 16 h. The yield was 1.104 g (50%); mp 240 °C dec. Recrystallization was by slow evaporation of a concentrated aqueous solution. Anal. Calcd (found) for $C_{18}H_{16}InO_{12.5}$: C, 39.51 (39.48); H, 2.95 (3.02). Mass spectrum (FAB–thioglycerol): m/e 397 (ML_2^+), 539 (HML_3^+). NMR (300 MHz, 25 °C, D_2O): δ 4.57 (s, 2 H, CH_2), 6.84 (s, 1 H, H_5); 8.10 (s, 1 H, H_2). Solubility: soluble in water, alcohols, and DMSO; slightly soluble in acetone. The resistance of a 1.0 mM aqueous solution was 235 kΩ.

Tris(chlorokojato)indium(III), In(ck)$_3$. $In(NO_3)_3 \cdot 5H_2O$ (0.391 g, 1.00 mmol) and Hck (0.487 g, 3.03 mmol) were dissolved in 100 mL of 50% aqueous ethanol. After workup the resulting solid was washed several times with water and dried in vacuo overnight. The yield was 0.527 g (90%); mp 300 °C dec. Purification was by Soxhlet extraction with chloroform. Anal. Calcd (found) for $C_{18}H_{12}Cl_3InO_9$: C, 36.43 (36.30); H, 2.04 (2.08); Cl, 17.92 (17.71). Mass spectrum (EI): m/e 275 (MHL^+) 433, 435 (ML_2^+). NMR (270 MHz, 25 °C, $CDCl_3$): δ 4.37 (s, 2 H, CH_2), 6.78 (s, 1 H, H_5), 8.02 (s, 1 H, H_2). Solubility: soluble in DMSO; slightly soluble in chloroform and dichloromethane; scarcely soluble in water.

Tris(3-hydroxy-2-methyl-4-pyridinonato)indium(III) Hemihydrate, In(mpp)$_3$·0.5H$_2$O. This was prepared by using Hmpp (0.405 g, 3.26 mmol) and $In(NO_3)_3 \cdot 5H_2O$ (0.420 g, 1.08 mmol) in 50 mL water. A product was isolated, washed several times with cold water, and dried overnight in vacuo at 80 °C. The yield was 0.291 g (60%); mp 260 °C dec. Crystallization was by slow evaporation of a solution in 5:1 methanol/water. Anal. Calcd (found) for $C_{18}H_{19}InN_3O_{6.5}$: C, 43.57 (43.78); H, 3.86 (3.96); N, 8.47 (8.30). Mass spectrum (FAB–thiogycerol): m/e 363 (ML_2^+), 488 (HML_3^+), 850 ($M_2L_5^+$). NMR (270 MHz, 25 °C, D_2O): δ 2.32 (s, 3 H, CH_3), 6.62 (d, J_{56} = 6.8 Hz, 1 H, H_5), 7.44 (d, J_{56} = 6.8 Hz, 1 H, H_6). Solubility: soluble in water, methanol; slightly soluble in DMSO. The resistance of a 1.0 mM aqueous solution was 290 kΩ.

Tris(3-hydroxy-1,2-dimethyl-4-pyridinonato)indium(III), In(dpp)$_3$. From $In(NO_3)_3 \cdot 5H_2O$ (0.432 g, 1.10 mmol) and Hdpp (0.502 g, 3.61 mmol) in 30 mL of water was isolated an off-white solid after workup and cooling to −15 °C overnight. The solid was isolated and dried overnight in vacuo to give a greater than quantitative yield, indicating

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Table III. Crystallographic Data[a]

compd	$In(dpp)_3 \cdot 12H_2O$
formula	$C_{21}H_{48}InN_3O_{18}$
fw	745.44
cryst syst	trigonal
space group	$P\bar{3}$
a, Å	16.842 (1)
c, Å	6.8078 (7)
V, Å^3	1672.3 (2)
Z	2
D_c, g/cm^3	1.480
$F(000)$	776
μ(Mo Kα), cm^{-1}	7.67
cryst dimens, mm	0.15 × 0.20 × 0.42
transmission factors	0.857–0.899
scan type	ω–2θ
scan range, deg in ω	0.90 + 0.35 tan θ
scan speed, deg/min	1.3–20.1
data collcd	$\pm h, +k, +l(\lvert h\rvert < \lvert k\rvert$ when $h < 0)$
$2\theta_{max}$, deg	60
cryst decay	negligible
no. of unique reflections	3245
no. of reflections with $I \geq 3\sigma(I)$	2496
no. of variables	190
R	0.033
R_w	0.037
S	1.492
mean Δ/σ (final cycle)	0.02
max Δ/σ (final cycle)	0.27 (y of H(1a))
residual densiy, e/Å^3	−0.55 to +0.75 (near In)

[a] Temperature 294 K, Enraf-Nonius CAD4-F diffractometer, Mo Kα radiation ($\lambda_{K\alpha_1}$ = 0.709 30, $\lambda_{K\alpha_2}$ = 0.713 59 Å), graphite monochromator, takeoff angle 2.7°, aperture (2.0 + tan θ) × 4.0 mm at a distance of 173 mm from the crystal, scan range extended by 25% on both sides for background measurement, $\sigma^2(I) = C + 2B + [0.04(C - B)]^2$ (C = scan count, B = normalized background count), function minimized was $\sum w(|F_o| - |F_c|)^2$ where $w = 1/\sigma^2(F)$, $R = \sum||F_o| - |F_c||/\sum|F_o|$, $R_w = (\sum w(|F_o| - |F_c|)^2/\sum w|F_o|^2)^{1/2}$ and $S = (\sum w(|F_o| - |F_c|)^2/(m - n))^{1/2}$. Values given for R, R_w, and S are based on those reflections with $I \geq 3\sigma(I)$.

considerable hydration. The complex was crystallized by evaporation of a concentrated hot ethanolic solution. Some crystals were vigorously dried in vacuo at 80 °C for 16 h to yield the anhydrate, mp 250 °C dec. Anal. Calcd (found) for $C_{21}H_{24}InN_3O_6$: C, 47.66 (47.68); H, 4.57 (4.71); N, 7.94 (7.80). (An analyzable tetrahydrate can also be formed from drying crystals over P_2O_5 overnight.) Mass spectrum (FAB–thioglycerol or DCI): 391 (ML_2^+), 530 (HML_3^+). NMR (270 MHz, 25 °C, D_2O): δ 2.36 (s, 3 H, CCH_3), 3.73 (s, 3 H, NCH_3), 6.55 (d, J_{56} = 6.8 Hz, 1 H, H_5), 7.47 (d, J_{56} = 6.8 Hz, 1 H, H_6). Solubility: soluble in water, methanol, ethanol, and DMSO; slightly soluble in acetone, dichloromethane, and chloroform. The resistance of a 1.0 mM aqueous solution was 190 kΩ.

X-ray Crystallographic Analysis of $In(dpp)_3 \cdot 12H_2O$. Crystallographic data appear in Table III. The final unit cell parameters were obtained by least-squares methods on 2(sin θ)/λ values for 25 reflections with 2θ = 36–49°. The intensities of three standard reflections, measured each 5000 s of X-ray exposure time, showed only small random fluctuations. An extinction correction was not required, and none was applied. The data were processed and corrected for absorption (numerical integration).[31]

Since the structure of $In(dpp)_3 \cdot 12H_2O$ is isomorphous with those of the Al and Ga analogues,[2,4] the structure analysis was initiated by using the coordinates of the non-hydrogen atoms of $Ga(dpp)_3 \cdot 12H_2O$. It was soon apparent that the In compound was not isostructural with the Al and Ga analogues. The indium and all of the oxygen atoms were found to occupy the same positions as the corresponding atoms in the Al and Ga compounds, but the dpp ligands were observed to span a different pair of oxygen atoms about the central indium. The positions of all hydrogen atoms, including a 1:1 proton disorder in one of the two independent $(H_2O)_6$ rings, were determined from a difference Fourier ssynthesis. With the exception of H(O3a) and H(O5a), which would not refine

(31) The computer programs used include locally written programs for data processing and locally modified versions of the following: ORFLS, full-matrix least-squares, and ORFFE, function and errors, by W. R. Busing, K. O. Martin, and H. A. Levy; FORDAP, Patterson and Fourier syntheses, by A. Zalkin, ORTEP II, illustrations, by C. K. Johnson; and AGNOST, absorption corrections, by J. A. Ibers.

Table IV. Final Positional (×10^4; In × 10^5, H × 10^3) and Isotropic Thermal Parameters (U × 10^3 Å^2) with Estimated Standard Deviations in Parentheses

atom	x	y	z	U_{eq}/U_{iso}
In	66667	33333	−9166 (4)	30
O(1)	6088 (1)	2103 (1)	777 (2)	40
O(2)	6996 (1)	2466 (1)	−2674 (3)	43
O(3)	7974 (2)	2790 (2)	3743 (3)	64
O(4)	1862 (2)	1046 (2)	−307 (3)	51
O(5)	1821 (2)	994 (2)	5597 (3)	65
O(6)	3132 (2)	1788 (2)	2654 (4)	65
N	6324 (1)	103 (1)	253 (3)	39
C(1)	5635 (2)	496 (2)	2978 (4)	51
C(2)	6096 (2)	703 (2)	1030 (3)	36
C(3)	6321 (1)	1510 (1)	28 (3)	32
C(4)	6788 (2)	1714 (2)	−1772 (3)	35
C(5)	7014 (2)	1068 (2)	−2500 (4)	43
C(6)	6777 (2)	291 (2)	−1508 (4)	45
C(7)	6119 (2)	−751 (2)	1230 (6)	56
H(1a)	566 (3)	99 (3)	320 (6)	71 (12)
H(1b)	597 (4)	35 (4)	382 (8)	136 (20)
H(1c)	517 (4)	−5 (4)	306 (7)	113 (17)
H(5)	736 (2)	113 (2)	−373 (4)	54 (8)
H(6)	691 (2)	−15 (2)	−202 (5)	66 (10)
H(7a)	617 (3)	−114 (3)	21 (6)	97 (14)
H(7b)	549 (3)	−112 (3)	163 (7)	102 (15)
H(7c)	649 (3)	−60 (3)	236 (7)	94 (14)
H(O3a)	785	318	284	77
H(O3b)	764 (2)	261 (2)	479 (5)	48 (8)
H(O4a)	227 (3)	127 (3)	25 (7)	94 (18)
H(O4b)	148 (5)	124 (5)	−21 (9)	52 (18)
H(O4c)	171 (4)	57 (6)	−14 (9)	37 (18)
H(O5a)	193	105	678	107
H(O5b)	158 (3)	49 (3)	527 (7)	106 (18)
H(O6a)	353 (3)	183 (3)	291 (6)	68 (14)
H(O6b)	286 (3)	162 (3)	358 (6)	80 (15)

Table V. Bond Lengths (Å) with Estimated Standard Deviations in Parentheses

In–O(1)	2.134 (2)	N–C(7)	1.463 (3)
In–O(2)	2.165 (2)	C(1)–C(2)	1.487 (4)
O(1)–C(3)	1.343 (3)	C(2)–C(3)	1.393 (3)
O(2)–C(4)	1.289 (3)	C(3)–C(4)	1.403 (3)
N–C(2)	1.355 (3)	C(4)–C(5)	1.410 (3)
N–C(6)	1.371 (3)	C(5)–C(6)	1.344 (4)

Table VI. Bond Angles (deg) with Estimated Standard Deviations in Parentheses

O(1)–In–O(2)	77.87 (6)	N–C(2)–C(3)	119.7 (2)
O(1)–In–O(1)′	93.58 (6)	C(1)–C(2)–C(3)	121.4 (2)
O(1)–In–O(2)′	166.18 (6)	O(1)–C(3)–C(2)	120.1 (2)
O(2)–In–O(1)′	97.74 (7)	O(1)–C(3)–C(4)	119.1 (2)
O(2)–In–O(2)′	92.40 (6)	C(2)–C(3)–C(4)	120.8 (2)
In–O(1)–C(3)	110.82 (13)	O(2)–C(4)–C(3)	120.0 (2)
In–O(2)–C(4)	111.39 (14)	O(2)–C(4)–C(5)	123.0 (2)
C(2)–N–C(6)	120.2 (2)	C(3)–C(4)–C(5)	116.9 (2)
C(2)–N–C(7)	122.8 (2)	C(4)–C(5)–C(6)	120.8 (2)
C(6)–N–C(7)	117.0 (2)	N–C(6)–C(5)	121.6 (2)
N–C(2)–C(1)	118.8 (2)		

Table VII. Hydrogen-Bonding Distances and Angles in $In(dpp)_3 \cdot 12H_2O$[a]

interaction	O–H, Å	H···O, Å	O···O, Å	O–H···O, deg
O(3)–H(O3a)···O(1)[1]	1.00	1.92	2.900 (3)	165
O(3)–H(O3b)···O(2)[2]	0.87 (3)	1.99 (3)	2.839 (3)	168 (3)
O(4)–H(O4a)···O(6)[3]	0.70 (4)	2.07 (5)	2.744 (4)	160 (5)
O(4)–H(O4b)··O(4)[4]	0.87 (9)	1.90 (9)	2.755 (3)	169 (6)
O(4)–H(O4c)···O(4)[5]	0.72 (8)	2.04 (8)	2.755 (3)	170 (6)
O(5)–H(O5a)···O(4)[2]	0.82	1.99	2.789 (3)	166
O(5)–H(O5b)···O(5)[6]	0.77 (5)	2.01 (5)	2.782 (3)	179 (5)
O(6)–H(O6a)···O(3)[7]	0.66 (4)	2.10 (4)	2.759 (4)	177 (5)
O(6)–H(O6b)···O(5)[3]	0.74 (4)	2.06 (4)	2.780 (4)	164 (4)

[a] H(O3a) and H(O5a) were fixed in observed positions (see text). [b] Superscripts refer to symmetry operations: (1) 1 − y, x − y, z; (2) x, y, 1 + z; (3) x, y, z; (4) x − y, x, −z; (5) y, y − x, −z; (6) y, y − x, 1 − z; (7) 1 − x + y, 1 − x, z.

properly and were fixed in observed positions with thermal parameters proportional to those of O(3) and O(5), respectively, all hydrogen atoms were refined with isotropic thermal partameters. Neutral-atom scattering factors and anomalous dispersion corrections (In) were taken from ref 32.

Final atomic coordinates and isotropic thermal parameters (U_{eq} = one-third of the trace of diagonalized U) are given in Table IV. Bond lengths, bond angles, and hydrogen-bonding data appear in Tables V–VII, respectively. Anisotropic thermal parameters, bond lengths and angles involving hydrogen, torsion angles, and measured and calculated structure factor amplitudes (Tables S1–S6) are included as supplementary material.

Results and Discussion

The In complexes of a series of 3-hydroxy-4-pyrones and N-substituted 3-hydroxy-4-pyridinones are easily prepared in high yield from aqueous solution at neutral pH. We have also prepared the known $In(ma)_3$[30] in aqueous solution in 80% yield as a sesquihydrate by this method. It and the other three complexes which are water soluble at 1 mM (Table II) are uncharged in unbuffered aqueous solution as shown by the resistance values at 1 mM. The values are much closer to that of distilled water (350 kΩ) than to that of 1 mM KCl (a 1:1 electrolyte: 9.0 kΩ = 124 $cm^2\ \Omega^{-1}\ M^{-1}$). All the compounds are very hygroscopic, as were their Al and Ga analogues.[3,4]

The four-band infrared spectral pattern (1620–1400 cm^{-1}), which is characteristic of the γ-pyrones and γ-pyridinones,[33] is preserved in the complexes (Table I) with a general bathochromic shift and possible reordering upon complexation. In Table I, the four bands have been listed with the collective assignment $\nu_{C=O}$ and ν_{ring}, since resolving these two highly mixed modes is extremely difficult. In some of the In complexes, new bands appeared below 450 cm^{-1}, and these are most likely ν_{In-O}, although there may be coupling to ring-deformation modes.

The proton NMR data for the complexes were consistent with the formulation of InL_3 species. The characteristic pair of ring H_5H_6 doublets (J_{56} = 5–6 Hz) was observed in the complexes of pyromeconic acid and maltol and its pyridinone derivatives mpp and dpp. Al and Ga complexes of the latter two ligands show variable-temperature spectra that are most likely due to *fac–mer* interconversion; however, the $In(dpp)_3$ spectrum was unchanged in CD_3OD on cooling from +20 to −50 °C.

The In complexes crystallized much more easily than the Al and Ga analogues. The crystal structure of the dodecahydrate complex ($In(dpp)_3 \cdot 12H_2O$) has been solved; it is isomorphous but not isostructural with its group 13 congeners and, therefore, contributes a new facet to the development of exoclathrates.[4] The complex crystallizes as the *fac* isomer (Figure 1). The rigorous 3-fold symmetry causes the asymmetric unit to consist of one-third of a metal ion, one ligand, and four water molecules. There is a compression of the $In(dpp)_3$ units from O_h down the 3-fold axis leading to an O(1)–M–O(2) angle of 77° (Table VI) compared with 84 for Al and 83° for Ga.[4] This is also manifested in a shorter c and longer $a = b$ in the In complex. The exocyclic O(1)–In–O(1′) (hydroxy O–In–hydroxy O = 93.6°) and O(2)–In–O(2′) (keto O–In–keto O = 92.4°) angles are both greater than 90°, as is the exocyclic O(2)–In–O(1′) (keto O–In–hydroxy O) angle, which is 96°. All three angles are greater than in the Al and Ga analogues. However, the two metallacyclic O–C–C bond angles (O(1)–C(3)–C(4) and O(2)–C(4)–C(3)) are exactly the same as in the free ligand (120°).[27] Every other dpp structure we have solved has had these two angles reduced from 120° because of the smaller size of the metals. The strain in the dpp anion is clearly less than when it is bound to B, Al, or Ga.[2,4,34] We hope to see this manifested in higher formation constants.[5]

The ligand aromaticity is comparable with that in the Al and Ga complexes and more than in $(C_6H_5)_2B(dpp)$. Comparison of

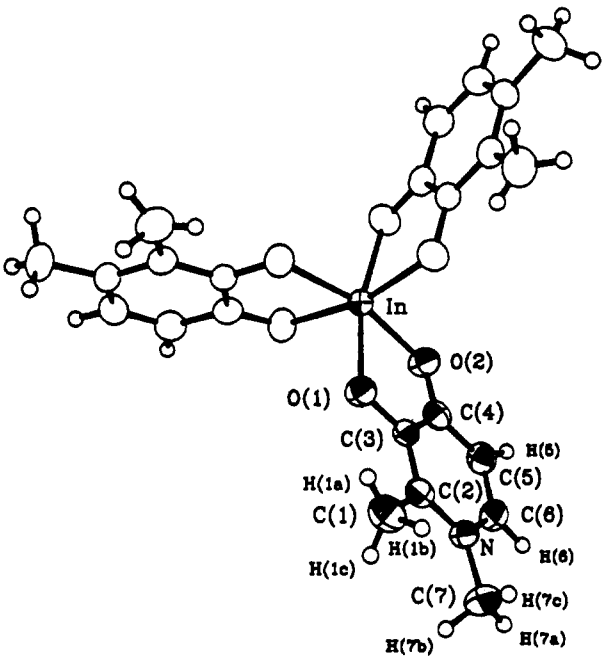

Figure 1. ORTEP view of the tris(ligand)metal portion of the $In(dpp)_3$ complex.

bonds in the ring shows that for the Al and Ga complexes the single bond C(3)–C(4) is longer than C(4)–C(5), and the N–C bond N–C(2) is longer than N–C(6). In the In complex both these comparisons are reversed; however, the double bond C(2)=C(3) remains longer than C(5)=C(6). The ligand is planar within experimental error, but the metal–ligand chelate ring is nonplanar with a flattened In–envelope conformation, In being displaced 0.22 Å from O(1)C(3)C(4)O(2).

The most notable features of this structure are the extensive hydrogen bonding and the hexagonal channels of water molecules. All the ML_3 structures (M = Al, Ga, In; L = dpp), as well as the free ligands Hmpp and Hdpp, have involved hydrogen bonding, which incorporates every possible donor in the respective molecules.[2,4,27] The unbound ligands form head-to-tail dimers with pairs of C=O···H—O—C hydrogen bonds linking the dimers and Hmpp contains further C=O···H—N bonds that tie the dimers into an infinite array.[27] The unit cell packing (Figure 2) clearly shows that the exoclathrate structure is found in $In(dpp)_3$. The water molecules of the dodecahydrate form a three-dimensional array: half (O(3) and O(6)) form a bridge from the *fac*-$In(dpp)_3$ units to the hexagonal channels that are formed by the other half of the water molecules (O(4) and O(5)) in the corners of the unit cell. The hydrogen bonds between the chelating O(1) and O(2) atoms and their nearest water hydrogens (H(O3a) and H(O3b), respectively) are as strong as in the Al and Ga congeners (Table VII).

The major difference in the structure relative to the Al and Ga analogues is a rotation of $M(dpp)_3$ units by about 60° about the 3-fold axis with respect to the H_2O superstructure. Each unit cell contains one Λ and one Δ stereoisomer, and these have changed places in the In cell from their respective locations in the Al and Ga cells. The major features of the exoclathrate structure remain intact. Water bridges from one bound ligand to another, the hexagonal channels consist of homodromic[35–37] circles, and a hydrophobic channel is formed from the four methyl groups down the *c* axis in the center of the unit cell. The $(H_2O)_6$ rings adopt the structure of ice in its stable low pressure form ice-I_h.[38] Each water molecule in the ring is hydrogen bonded to four nearest neighbors.

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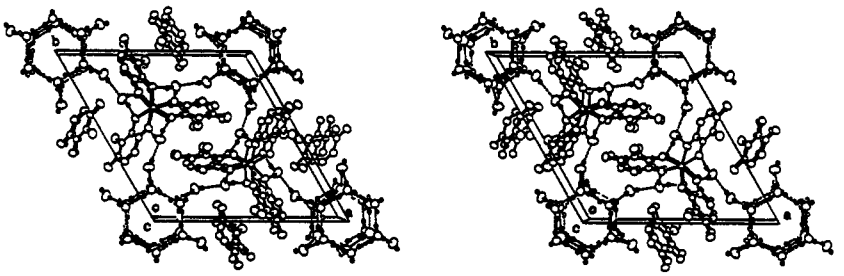

Figure 2. ORTEP stereoview down the *c* axis of the unit cell packing of $In(dpp)_3 \cdot 12H_2O$.

Homodromic circles are known in the crystal structures of ice[38,39] and the clathrate hydrates;[40,41] however, the $M(dpp)_3$ (M = Al, Ga, In) complexes have provided the first examples where this arrangement occures in hydrates containing metal complexes. According to the classification of Falk and Knop[42] (in which they are designated by the number and type of hydrogen-bonding water neighbors—a is a proton acceptor, and d is a proton donor), $H_2O(3)$ is a and $H_2O(6)$ dda, and the two waters in the hexagonal channels ($H_2O(4)$ and $H_2O(5)$) are ddaa.

The three $M(dpp)_3$ complexes present (when crystallized from water) appropriate conditions for the formation of the water channels in a favored, hydrogen-bonding arrangement. There is a clear alternation of hydrophilic and hydrophobic regions along the diagonals of the unit cell when looking down the *c* axis. This feature must contribute to the hydrogen-bonding arrangement.

The hydrolytic stability of the complexes was roughly determined by looking at bound vs unbound ligand from ^1H NMR spectra in D_2O at different pD. This method suffices but does not provide the view of what actually happens at the metal center that we have seen previously with variable-pH ^{27}Al NMR.[3,4] The window of stability to hydrolysis for $In(dpp)_3$ was found to be around 4–9. This can be checked with potentiometric titrations and speciation calculations, work that is under way currently.[5] Several of the compounds were both water soluble and reasonably lipophilic with the best conjunction of these properties occurring in the maltol complex (Table II). Unfortunately this ligand does not have sufficient thermodynamic affinity for trivalent metal ions[43] to be able to maintain them under physiological conditions, except possibly for Al.[44] The hydroxypyridinones are sufficiently good chelators to maintain ^{67}Ga in vivo under appropriate conditions,[6] and this will be tested for In also.[45] The two pyridinones studied here have negligible *p* values; however, should this core prove effective in binding In, it will be modified.[27] The Hansch group report[46] a change in log *p* of 0.01 log unit/deg in the room-temperature region; however, this is not enough to make the values we have determined here viable at 37 °C, as rough experiments have confirmed.

There is a large temperature coefficient to the solubility of $In(dpp)_3$. This complex is 3.5 times more water soluble at 37 °C than at 25 °C. (For comparison, the solubility of $In(ma)_3$ increases by 50%.) Higher temperatures disrupt the hydrogen bonding of the exoclathrate structure, thereby allowing the complex to dissolve because the solvation entropy greatly increases with the much greater disorder provided by the breakup of the exoclathrate. As Pauling has pointed out,[47] the hydrogen bond is not a strong bond (~5 kcal mol^{-1}), but its importance in determining the properties of substances is considerable. The large number of hydrogen bonds in the exoclathrate structure completely dominates crystal packing forces and essentially dictates the array which is found.

We have attempted a solution of the structure of $In(pa)_3$; however, this has proven tortuous because of extensive disorder in the ligands. Pyromeconate, pa^-, a 3-hydroxy-4-pyronate anion with no substituents, is found to have 2-fold symmetry when bound to either Al or In.[48] It is obvious from difficulties with the $M(pa)_3$ and $Al(ma)_3$[1] structures that the hydrogen bonding found in the $M(dpp)_3$ exoclathrates contributes greatly to the highly ordered nature of the crystalline complexes.

The dpp^- anion does have a high affinity for trivalent metal ions. This conclusion is based on results of potentiometric titrations,[5] where we have found an overall formation constant log β_3 for $Al(dpp)_3$ of 32 and for $Ga(dpp)_3$ of 37, and on the observation of Kontoghiorghes that the anion is capable of removing Fe^{3+} from the transferrins[49] and ferritin.[50]

In conclusion, a new and interesting series of 3-hydroxy-4-pyrone and -pyridinone complexes of In have been prepared. They show unusual properties in the solid and solution states, some of which are similar to those of their Al and Ga congeners. These complexes are water soluble, can be lipophilic depending on the ring substituents, and are quite stable to hydrolysis. The exoclathrate exclusion structure is formed when the ligand is the N-methylated pyridinone dpp; however, the lattice is rearranged from the previously characterized examples. We are currently examining In–pyridinone complexes with other N-substituents in order to maximize solubility, lipophilicity, and chelate affinity.

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Registry No. $In(pa)_3$, 116699-24-2; $In(ka)_3$, 116699-28-6; $In(ck)_3$, 116699-25-3; $In(mpp)_3$, 116724-46-0; $In(dpp)_3$, 116699-26-4; $In(dpp)_3 \cdot 12H_2O$, 116699-27-5; $In(ma)_3$, 116781-97-6; octanol, 111-87-5.

Supplementary Material Available: Tables of anisotropic thermal parameters (Table S1), bond lengths and angles involving hydrogen (Tables S2 and S3), torsion angles (Table S4), and intraannular torsion angles (Table S5) (5 pages); table of measured and calculated structure factor amplitudes (Table S6) (7 pages). Ordering information is given on any current masthead page.

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