In conclusion, complex C formed in the processes of the heme breakdown reaction is a six-coordinate low-spin ferric complex with an anomalously small *g* anisotropy. The coordination structure of complex C is schematically formulated as six-coordinate $Fe^{III}TPP(^{-}OCH_3)(^{-}OOC(CH_3)_3)$ based on the data of ESR and optical spectroscopies. Complex C is a possible model complex for transient intermediate species generated in the reaction processes of heme enzymes such as the monooxygenases, peroxidases, and catalases.

Acknowledgment. We express our sincere thanks to Dr. Masahiro Kohno of JEOL Co. Ltd. for helpful scientific discussions on this work. We also express many thanks to Nippon Oil & Fats Co., Ltd., for supplying *tert*-butyl hydroperoxide. This work was partially supported by a Grant-in-Aid for Scientific Research (No. 62740260) and by a Grant-in-Aid for Scientific Research on the Priority Area of "Macromolecular Complexes" (No. 62612005) from the Ministry of Education, Science and Culture, Japan.

Contribution from the Department of Chemistry,
University of British Columbia, 2036 Main Mall, Vancouver, British Columbia V6T 1Y6, Canada

Metal Chelation with Natural Products: Isomaltol Complexes of Aluminum, Gallium, and Indium

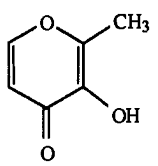
Tammy G. Lutz, David J. Clevette, Steven J. Rettig, and Chris Orvig*

Received August 3, 1988

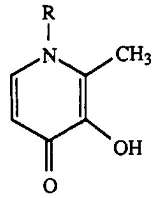
The Al, Ga, and In complexes ($M(ima)_3$) of the naturally occurring starch byproduct isomaltol (Hima) have been prepared in, and isolated from, aqueous solution. They have been characterized by IR and NMR spectroscopy and mass spectrometry; the ^{27}Al NMR spectrum of the Al complex (2.9 ppm, $W_{1/2}$ = 200 Hz) suggested that the three ligands are coordinated in a facial arrangement around the Al center, at least in aqueous solution. Solution equilibrium studies (μ = 0.15 M (NaCl), 25 °C) show that isomaltol is a relatively weak complexing agent for the group 13 (IIIA) metal ions (log β_3 = 14.45 (5) (Al), 16.36 (1) (Ga), 14.80 (2) (In)). The complex $Al(C_6H_5O_3)_3$ has been studied by single-crystal X-ray diffraction. Considerable disorder (two out of three ligands) was found. It crystallized in the monoclinic space group *C*2/*c* with the crystal parameters *a* = 29.215 (2) Å, *b* = 8.2211 (7) Å, *c* = 15.052 (2) Å, β = 98.775 (7)°, and *Z* = 8. The data were refined by using 2091 reflections with $I \geq 3[\sigma(I)]$ to *R* and R_w values of 0.065 and 0.080, respectively.

Introduction

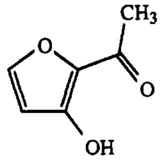
Recently, a number of low molecular weight complexes of aluminum, gallium, and indium have been prepared with properties that have recommended these species to in vivo examination.[1-3] These complexes contained as ligands various pyrones (e.g. maltol (**1**))[1,3] and pyridinones (**2**),[2,3] and the properties of interest were hydrolytic stability, water solubility, neutral charge, and lipophilicity, all occurring simultaneously. Some of these ligands have very high affinities for the group IIIA (or 13) ions,[4] and certain of the complexes have formed unusual solid-state hydrogen-bonding arrays.[2,3,5] The metal complexes are now studied in various laboratories as agents of in vivo ion transport,[6,7] and this work should shed some light on the mechanism of transport of the ions M^{3+} (M = Al, Ga, In) in vivo. This latter interest stems from the involvement of Al in neurological disorders and of Ga and In in diagnostic nuclear medicine procedures.



1



2



3

In efforts to probe further the coexistence of these four properties, to examine closely the aqueous coordination chemistry of these metals, and to search for more extensive hydrogen-bonding arrays, we are examining new binding groups for the Al^{3+}, Ga^{3+}, and In^{3+} ions. We are also interested in ways to incorporate these groups into multidentate ligand systems. Potential ligands that occur in nature and/or that are likely to prevent the hydrolysis characteristic of these metal ions are being examined in our search for candidate binding groups. The hydrolytic instability[8] of aluminum, gallium, and indium is an important factor in the aqueous chemistry of their trivalent ions and must be compensated for in the design of their chelates. In the absence of suitable ligands, the M^{3+} ions rapidly hydrolyze in neutral (or pH 7.4) solutions to form insoluble hydroxides.

This work examines the potential as an M^{3+} binding group of the natural product isomaltol (**3**). Isomaltol (1-(3-hydroxy-2-furanyl)ethanone, abbreviated as Hima), which was first isolated from a bread distillate almost 80 years ago by Backe,[9] was found to be a structural isomer of maltol (**1**) only 20 years ago.[10,11] We were originally attracted to isomaltol because it has a β-hydroxyeneone group (it is a natural product acetylacetone analogue). Because it is well-known that Al^{3+} will displace even aliphatic hydroxyl protons if they are in positions favorable for metal ion coordination,[12] we were sure that **3** would form a stable Al(III) complex.

Isomaltol is found in nature as a byproduct of the enzymatic degradation of starch in breads, and it contributes to the aroma of freshly baked bread. It is a prototype for new ligands that are currently under active investigation in our laboratory: the 2-acyl-3-hydroxyfurans. Isomaltol has been reported cursorily in the literature as iron,[9] copper,[9,10] or sodium salts.[13,14]

---

* To whom correspondence should be addressed.

(1) Finnegan, M. M.; Lutz, T. G.; Nelson, W. O.; Smith, A.; Orvig, C. *Inorg. Chem.* **1987**, *26*, 2171.
(2) Nelson, W. O.; Karpishin, T. B.; Rettig, S. J.; Orvig, C. *Inorg. Chem.* **1988**, *27*, 1045.
(3) Matsuba, C. A.; Nelson, W. O.; Rettig, S. J.; Orvig, C. *Inorg. Chem.* **1988**, *27*, 3935.
(4) Clevette, D. J.; Nelson, W. O.; Nordin, A.; Orvig, C.; Sjöberg, S. Submitted for publication.
(5) Nelson, W. O.; Rettig, S. J.; Orvig, C. *J. Am. Chem. Soc.* **1987**, *109*, 4121.
(6) McLachlan, D. R. *Neurobiol. Aging* **1986**, *7*, 525.
(7) Clevette, D. J.; Lyster, D. M.; Nelson, W. O.; Rihela, T.; Webb, G. A.; Orvig, C. Manuscript in preparation.
(8) Baes, C. F., Jr.; Mesmer, R. E. *The Hydrolysis of Cations*; Wiley: New York, 1976.
(9) Backe, A. *C. R. Hebd. Seances Acad. Sci.* **1910**, *150*, 540; **1910**, *151*, 78.
(10) Hodge, J. E.; Nelson, E. C. *Cereal Chem.* **1961**, *38*, 207.
(11) Fisher, B. E.; Hodge, J. E. *J. Org. Chem.* **1964**, *29*, 776.
(12) Motekaitis, R. J.; Martell, A. E. *Inorg. Chem.* **1984**, *23*, 18.
(13) Goodwin, J. C. *J. Carbohydr. Chem.* **1985**, *4*, 255.
(14) Bartulin, J.; Birke, A.; Gallardo, H.; Leon, G.; Zunza, H. *Bol. Soc. Chil. Quim.* **1982**, *27*, 122.

Since carbohydrates are essential to life, their chelation chemistry with metals is of considerable importance. The alkali metals and alkaline earths form a wide variety of sugar complexes.[15,16] Discrete iron–sugar complexes with reducing sugars have been known for 25 years[17,18] and have been examined from time to time because of their possible role in iron transport across cell membranes.

Experimental Section

Materials and Methods. These were mostly as previously described.[1,2,19] Lactose (Aldrich), $Al(NO_3)_3{\cdot}9H_2O$ (Mallinckrodt), and $In(NO_3)_3{\cdot}5H_2O$ (Alfa) were used as supplied. Ga ingots (Alfa) were dissolved in concentrated HCl, and the solution was standardized. Hima was prepared from lactose in a two-step procedure that involved the dehydration of the glucose moiety of lactose to form *O*-galactosylisomaltol, which was subsequently hydrolyzed to Hima in an overall yield of 15%.[10] The preparations of the complexes were quite similar, and complete details are given for $Al(ima)_3$. The compounds are hygroscopic and are isolated initially as hydrates; accurate anhydrous elemental analyses were obtainable after drying in vacuo at elevated temperature.

Tris(isomaltolato)aluminum(III), $Al(ima)_3$. To isomaltol (1.0 g, 7.9 mmol) in 40 mL of water was added $Al(NO_3)_3{\cdot}9H_2O$ (0.99 g, 2.6 mmol) in 10 mL of water. The pH was adjusted to 6.8 with 2 N NaOH, and an off-white solid precipitated. Recrystallization from methanol gave 0.89 g (86% based on Al), mp 275 °C dec. Anal. Calcd (found) for $C_{18}H_{15}AlO_9$: C, 53.74 (53.70); H, 3.76 (3.73); Al, 6.71 (6.66). ^{27}Al NMR (H_2O): 2.9 ppm ($W_{1/2}$ = 200 Hz). ^1H NMR (δ from TMS in $CDCl_3$): 2.30 (s, 3 H, CH_3), 6.11 (d, 1 H, H(4)), 7.48 (d, 1 H, H(5)). EIMS *m/e*: 152 (ML^+), 277 (ML_2^+), 402 (ML_3^+). IR (cm^{-1}, KBr disk): 1602, 1555, 1515 ($\nu_{C=O}$, $\nu_{C=C}$); 479, 395 (ν_{Al-O}). It is soluble in H_2O (0.62 mM), $CHCl_3$, MeOH, CH_3CN, and acetone and slightly soluble in EtOH.

Tris(isomaltolato)gallium(III), $Ga(ima)_3$. The preparation required isomaltol (1.00 g, 7.6 mmol) and 1.37 M $GaCl_3$ solution (1.92 mL, 2.6 mmol). The yield of the off-white powder was 1.04 g (88% based on Ga), mp 260 °C dec. Anal. Calcd (found) for $C_{18}H_{15}GaO_9$: C, 48.58 (48.31); H, 3.40 (3.37); Ga, 15.67 (15.73). ^1H NMR (δ from TMS in $CDCl_3$): 2.30 (s, 3 H, CH_3), 6.10 (d, 1 H, H(4)), 7.42 (d, 1 H, H(5)). EIMS *m/e*: 194, 196 (ML^+); 319, 321 (ML_2^+); 444, 446 (ML_3^+). IR (cm^{-1}, KBr disk): 1588, 1547, 1514 ($\nu_{C=O}$, $\nu_{C=C}$); 430, 348 (ν_{Ga-O}). Recrystallization from methanol/ether gave crystalline rods. It is soluble in methanol, ethanol and $CHCl_3$ and sparingly soluble in H_2O.

Tris(isomaltolato)indium(III), $In(ima)_3$. The preparation required isomaltol (1.38 g, 10.9 mmol) and $In(NO_3)_3{\cdot}5H_2O$ (1.43 g, 3.7 mmol). The yield of the off-white precipitate was 1.44 g (80% based on In), mp 260 °C dec. Anal. Calcd (found) for $C_{18}H_{15}InO_9$: C, 44.11 (43.84); H, 3.08 (3.39); In, 23.43 (23.59). ^1H NMR (δ from TMS in $CDCl_3$): 2.44 (s, 3 H, CH_3), 6.21 (d, 1 H, H(4)), 7.52 (d, 1 H, H(5)). EIMS *m/e*: 240 (ML^+), 365 (ML_2^+), 490 (ML_3^+). IR (cm^{-1}, KBr disk): 1583, 1538, 1510 ($\nu_{C=O}$, $\nu_{C=C}$); 426 (ν_{In-O}). It was recrystallized from methanol, is soluble in $CHCl_3$, and is slightly soluble in methanol and ethanol.

Potentiometric Equilibrium Measurements. Potentiometric measurements of the ligands in the absence, and presence, of metal ions were performed with an Orion Research EA 920 pH meter equipped with Orion Ross research grade glass and reference electrodes. These were calibrated with standard aqueous HCl and NaOH solutions to read $-\log [H^+]$ directly. A Metrohm automatic buret (Dosimat 665) was used to add the standard NaOH. The temperature was maintained at 25.0 ± 0.1 °C throughout with water-jacketed beakers and a Julabo circulating bath, and the ionic strength was adjusted to 0.15 M (isotonic) by the addition of NaCl.

Isomaltol was twice recrystallized; concentrations were obtained by weighing. All metal-containing solutions were obtained from appropriate dilution of atomic absorption standard solutions of Al, Ga, and In (Sigma or Aldrich). The exact amount of excess acid present in the metal ion solutions was determined by a Gran's plot[20] of $(V_0 + V_t) \times 10^{-pH}$ vs V_t, where V_0 = the initial volume of 1:1 metal–Na_2EDTA solution and V_t is the volume of added standard NaOH. The base consumed is equal to the excess acid plus the Na_2EDTA protons. The total ligand to metal ratio in the titrations was kept at just greater than 3:1 at mM concentrations.

Table I. Crystallographic Data[a]

formula	$C_{18}H_{15}AlO_9$
fw	402.3
cryst syst	monoclinic
space group	*C*2/*c*
a, Å	29.215 (2)
b, Å	8.2211 (7)
c, Å	15.052 (2)
β, deg	98.775 (7)
V, $Å^3$	3572.9 (6)
Z	8
D_c, g/cm^3	1.496
F(000)	1644
μ(Mo Kα), cm^{-1}	1.6
cryst dimens, mm	0.25 × 0.44 × 0.45
scan type	ω–2θ
scan range, deg in ω	1.30 + 0.35 tan θ
scan speed, deg/min	2.0–20.1
data collcd	$+h,+k,\pm l$
$2\theta_{max}$, deg	55
cryst decay	negligible
no. of unique reflcns	4108
no. of reflcns with $I \geq 3\sigma(I)$	2091
no. of variables	261
R	0.065
R_w	0.080
S	3.50
max Δ/σ (final cycle)	0.05
resid dens, e/$Å^3$	−0.31 to 0.37

[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 $I \geq 3\sigma(I)$.

NaOH solutions (0.1 M) were prepared from dilutions of 50% NaOH (less than 0.1% Na_2CO_3) with freshly boiled, distilled, deionized water and standardized potentiometrically against potassium hydrogen phthalate (KHP). Concentration buffers were freshly prepared from standard HCl and NaOH solutions and adjusted to 0.15 M with NaCl. The electrode was calibrated at 5×10^{-3} M $[H^+]$. The range of $-\log [H^+]$ was limited from 2 to 10, in which range the electrode behavior was reversible. All solutions were continuously degassed with prepurified Ar during the course of a titration. Titrations were generally performed in the range $2 \leq -\log [H^+] \leq 4$ or 5 in sets of three or four runs. Above this range, slow hydrolysis was noted.

Computations. The proton dissociation constant of Hima was determined by the half-equivalence method from a Gran's plot. In all M(III) systems, the computations allowed for the presence of $M(OH)^{2+}$, $M(OH)_2^+$, $M(OH)_3$, and $M(OH)_4^-$. In addition, $Al_2(OH)_2^{4+}$, $Al_3(OH)_4^{5+}$, $InCl^{2+}$, $InCl_2^+$, $InCl_3$, and $In(OH)Cl^+$ were included. Formation constants for these various metal species were taken from ref 8. The stability constants for the main species ML^{2+}, ML_2^+, and ML_3 were determined by using the Fortran computer program BEST.[21] This program sets up simultaneous mass-balance equations for all the components present at each addition of base and calculates the pH at each data point according to the current set of stability constants and total concentrations of each component. Stability constants judiciously chosen by the user are automatically adjusted in order to minimize the sum of squares of differences between the calculated and observed values of pH. A standard deviation, σ, is given by the equation

$$\sigma = \sum(pH_{calc} - pH_{obs})^2/(N - 1)$$

where *N* = the number of titration points. This represents the fit in log units for reproducing the calculated titration curve. Adjustment is continued until there is no further improvement in the fit. The constants are reported to the second decimal place, which is representative of the

---

(15) Rendleman, J. A., Jr. *Adv. Carbohydr. Chem.* **1966**, *21*, 209.

(16) Tajmir-Riahi, H.-A. *J. Inorg. Biochem.* **1987**, *31*, 255; **1988**, *32*, 79; see also references therein.

(17) Charley, P. J.; Sarkar, B.; Stitt, C. F.; Saltman, P. *Biochim. Biophys. Acta* **1963**, *69*, 313.

(18) Nagy, L.; Burger, K.; Kurti, J.; Mostafa, M. A.; Korecz, L.; Kiricsi, I. *Inorg. Chim. Acta* **1986**, *124*, 55 and references therein.

(19) Nelson, W. O.; Karpishin, T. B.; Rettig, S. J.; Orvig, C. *Can. J. Chem.* **1988**, *66*, 123.

(20) Gran, G. *Analyst* (*London*) **1952**, *77*, 661; *Anal. Chim. Acta* **1988**, *206*, 111.

(21) Motekaitis, R. J.; Martell, A. E. *Can. J. Chem.* **1982**, *60*, 2403.

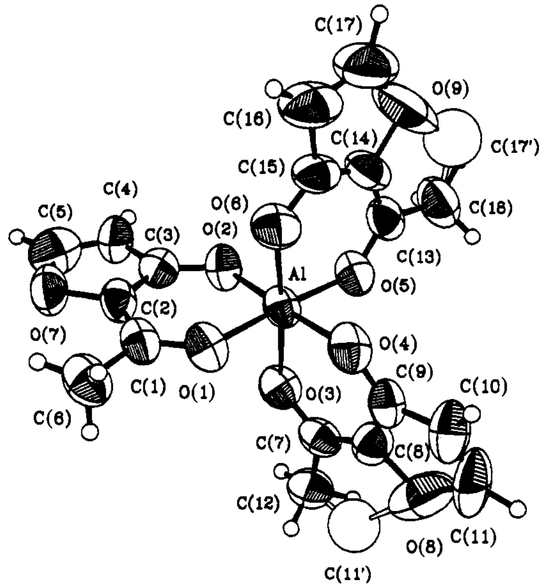


Figure 1. ORTEP view of the Al(ima)$_3$ molecule. Two of the ligands are disordered (see text), and this is represented by the low-occupancy carbon atoms C(11′) and C(17′).

Table II. Final Positional (Fractional ×10^4, Al ×10^5) and Isotropic Thermal Parameters ($U \times 10^3$ Å^2) with Estimated Standard Deviations in Parentheses[a]

atom	x	y	z	U_{eq}/U_{iso}
Al	62258 (4)	32517 (14)	61776 (7)	58
O(1)	6482 (1)	1118 (3)	6306 (2)	69
O(2)	6093 (1)	3132 (3)	4931 (2)	69
O(3)	6829 (1)	4045 (4)	6042 (2)	69
O(4)	6348 (1)	3495 (4)	7437 (2)	73
O(5)	5996 (1)	5400 (3)	6095 (2)	73
O(6)	5654 (1)	2296 (4)	6294 (2)	84
O(7)	6356 (1)	−686 (4)	4124 (3)	94
O(8)	7339 (2)	5808 (5)	8116 (3)	137
O(9)	4803 (2)	5306 (8)	6287 (3)	160
C(1)	6514 (1)	61 (5)	5712 (3)	65
C(2)	6346 (1)	417 (5)	4825 (3)	63
C(3)	6152 (1)	1852 (6)	4477 (3)	62
C(4)	6047 (2)	1671 (6)	3523 (3)	81
C(5)	6164 (2)	201 (8)	3359 (3)	100
C(6)	6733 (2)	−1503 (6)	5979 (3)	89
C(7)	7127 (1)	4730 (5)	6627 (3)	64
C(8)	7040 (2)	4943 (6)	7478 (3)	71
C(9)	6683 (2)	4324 (5)	7867 (3)	65
C(10)	6741 (2)	4727 (7)	8801 (3)	95
C(11)^1	7094 (4)	5645 (11)	8950 (5)	113
C(12)	7571 (2)	5285 (6)	6383 (3)	82
C(13)	5586 (2)	5866 (6)	6141 (3)	74
C(14)	5242 (2)	4710 (8)	6249 (3)	80
C(15)	5279 (2)	3085 (8)	6301 (3)	77
C(16)	4836 (2)	2337 (10)	6357 (4)	114
C(17)^1	4557 (3)	3648 (19)	6373 (6)	138
C(18)	5456 (2)	7589 (7)	6081 (3)	104
C(11′)^2	7740 (8)	5752 (8)	7114 (16)	116 (6)
C(17′)^2	4985 (9)	7307 (35)	6163 (16)	137 (8)

[a] Superscripts refer to occupancy factors 0.705 (1) and 0.295 (2).

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

Al–O(1)	1.905 (3)	O(9)–C(17′)	1.75 (3)
Al–O(2)	1.860 (3)	C(1)–C(2)	1.382 (6)
Al–O(3)	1.919 (3)	C(1)–C(6)	1.465 (6)
Al–O(4)	1.886 (3)	C(2)–C(3)	1.377 (6)
Al–O(5)	1.887 (3)	C(3)–C(4)	1.429 (6)
Al–O(6)	1.878 (3)	C(4)–C(5)	1.289 (7)
O(1)–C(1)	1.261 (5)	C(7)–C(8)	1.354 (6)
O(2)–C(3)	1.281 (5)	C(7)–C(12)	1.472 (6)
O(3)–C(7)	1.271 (5)	C(8)–C(9)	1.372 (6)
O(4)–C(9)	1.283 (5)	C(9)–C(10)	1.429 (6)
O(5)–C(13)	1.271 (5)	C(10)–C(11)	1.27 (1)
O(6)–C(15)	1.275 (5)	C(12)–C(11′)	1.20 (2)
O(7)–C(2)	1.395 (5)	C(13)–C(14)	1.409 (7)
O(7)–C(5)	1.406 (6)	C(13)–C(18)	1.466 (7)
O(8)–C(8)	1.391 (15)	C(14)–C(15)	1.342 (7)
O(8)–C(11)	1.542 (9)	C(15)–C(16)	1.446 (6)
O(8)–C(11′)	2.05 (2)	C(16)–C(17)	1.35 (1)
O(9)–C(14)	1.382 (5)	C(18)–C(17′)	1.42 (3)
O(9)–C(17)	1.55 (1)		

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

O(1)–Al–O(2)	94.1 (1)	C(1)–C(2)–C(3)	127.9 (4)
O(1)–Al–O(3)	88.4 (1)	O(2)–C(3)–C(2)	125.6 (4)
O(1)–Al–O(4)	89.1 (1)	O(2)–C(3)–C(4)	126.6 (4)
O(1)–Al–O(5)	177.2 (1)	C(2)–C(3)–C(4)	107.8 (4)
O(1)–Al–O(6)	86.9 (1)	C(3)–C(4)–C(5)	105.6 (4)
O(2)–Al–O(3)	88.0 (1)	O(7)–C(5)–C(4)	114.4 (5)
O(2)–Al–O(4)	176.8 (1)	O(3)–C(7)–C(8)	120.4 (4)
O(2)–Al–O(5)	88.0 (1)	O(3)–C(7)–C(12)	120.0 (4)
O(2)–Al–O(6)	91.2 (1)	C(8)–C(7)–C(12)	119.6 (5)
O(3)–Al–O(4)	92.0 (1)	O(8)–C(8)–C(7)	122.1 (5)
O(3)–Al–O(5)	89.9 (1)	O(8)–C(8)–C(9)	109.5 (4)
O(3)–Al–O(6)	175.1 (2)	C(7)–C(8)–C(9)	128.4 (4)
O(4)–Al–O(5)	88.8 (1)	O(4)–C(9)–C(8)	123.6 (4)
O(4)–Al–O(6)	89.1 (1)	O(4)–C(9)–C(10)	125.9 (5)
O(5)–Al–O(6)	94.9 (1)	C(8)–C(9)–C(10)	110.5 (5)
Al–O(1)–C(1)	129.3 (3)	C(9)–C(10)–C(11)	106.4 (5)
Al–O(2)–C(3)	123.9 (3)	O(8)–C(11)–C(10)	112.0 (6)
Al–O(3)–C(7)	128.3 (3)	C(7)–C(12)–C(11′)	97 (1)
Al–O(4)–C(9)	125.2 (2)	O(5)–C(13)–C(14)	119.9 (4)
Al–O(5)–C(13)	127.4 (3)	O(5)–C(13)–C(18)	121.7 (5)
Al–O(6)–C(15)	124.4 (3)	C(14)–C(13)–C(18)	118.4 (5)
C(2)–O(7)–C(5)	103.3 (4)	O(9)–C(14)–C(13)	116.6 (6)
C(8)–O(8)–C(11)	101.3 (5)	O(9)–C(14)–C(15)	114.7 (6)
C(8)–O(8)–C(11′)	81.3 (7)	C(13)–C(14)–C(15)	128.7 (4)
C(11)–O(8)–C(11′)	170.6 (8)	O(6)–C(15)–C(14)	124.6 (4)
C(14)–O(9)–C(17)	97.8 (6)	O(6)–C(15)–C(16)	124.2 (6)
C(14)–O(9)–C(17′)	92 (1)	C(14)–C(15)–C(16)	111.2 (6)
C(17)–O(9)–C(17′)	170 (1)	C(15)–C(16)–C(17)	102.0 (7)
O(1)–C(1)–C(2)	119.0 (4)	O(9)–C(17)–C(16)	114.2 (6)
O(1)–C(1)–C(6)	119.2 (4)	C(13)–C(18)–C(17′)	95 (1)
C(2)–C(1)–C(6)	121.8 (4)	O(8)–C(11′)–C(12)	119 (2)
O(7)–C(2)–C(1)	123.2 (4)	O(9)–C(17′)–C(18)	118 (2)
O(7)–C(2)–C(3)	108.9 (4)		

reproducibility of the potentiometric equipment employed.

X-ray Crystallographic Analysis of Al(ima)$_3$. Crystallographic data appear in Table I. The final unit cell parameters were obtained by least squares on $2(\sin\theta)/\lambda$ values for 25 reflections with $2\theta = 37$–$43°$. The intensities of three standard reflections, measured every 4000 s of X-ray exposure time, showed only small random variations. The data were processed and corrected for Lorentz and polarization effects.[22] There was a choice between centrosymmetric and noncentrosymmetric space groups. On the basis of statistical analyses of intensity distributions and the successful solution and refinement of the structure, the space group was determined to be *C*2/*c*.

The structure of Al(ima)$_3$ was solved by direct methods, the positions of 25 of the non-hydrogen atoms being determined from an *E* map. Two of the ligands were disordered (Figure 1), as was also observed for Ga(ima)$_3$.[23] The disorder involves a 180° rotation of the ligands involved about the Al···C(8) and Al···C(14) vectors. A disordered model was refined for Al(ima)$_3$, the only resolvable atoms being C(11) and C(17). Occupancy factors were initially estimated from Fourier peak heights and were subsequently adjusted to result in approximately equal thermal parameters for the resolved atom pairs. Attempts to refine split-atom models for the other atoms affected by the disorder (O(8), O(9), C(10), C(12), C(16), C(18)) were unsuccessful. Since the occupancy factors are substantially different for the two ligand orientations at each site, the structure would still be disordered if refined in *Cc*, therefore no attempt

---

(22) 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; AGNOST, absorption corrections, by J. A. Ibers.

(23) Molecular Structure Corp. Unpublished results.

was made to refine the structure in the lower symmetry space group. All non-hydrogen atoms were refined with anisotropic thermal parameters except for the low-occupancy carbon atoms C(11′) and C(17′). Hydrogen atoms associated with the higher occupancy disordered ligands and the ordered ligand were included as fixed atoms in idealized positions (methyl orientations based on observed peaks; C(sp^2)-H = 0.97 Å, C(sp^3)-H = 0.98 Å, $U_H = 1.3U_{\text{bonded atom}}$ for methyl hydrogens, $U_H = 0.012 \pm U_{\text{bonded atom}}$ for other hydrogens).

Neutral-atom scattering factors and anomalous dispersion corrections were taken from ref 24. Final atomic coordinates, bond lengths, and bond angles appear in Tables II-IV, respectively. Anisotropic thermal parameters, calculated hydrogen coordinates, torsion angles, intraannular torsion angles, and measured and calculated structure factor amplitudes (Tables SI-SV) are included as supplementary material.

Results and Discussion

The three tris(isomaltolato) complexes were easily prepared in high yield from aqueous solution; however, their water solubilities were not as high as expected from those of the maltol complexes that we have previously characterized.[1,3] The Ga complex is only sparingly soluble in water (<0.1 mM), but the other two are at least somewhat soluble (>0.1 mM). All the complexes are quite soluble in most polar organic solvents, especially the lower alcohols.

In the 1600–1500-cm^{-1} region of the infrared spectrum of each complex are bands that are characteristic of combined C=O and ring C=C stretches (as in metal acetylacetonate complexes[25]). Between 500 and 350 cm^{-1}, there are new bands in all the spectra that are most likely the M—O vibrations. Both these infrared spectral patterns are also found in the γ-pyrone and γ-pyridinone complexes[1-3,5] with a general bathochromic shift (and possible energy reordering) upon complexation from those bands observed in the free ligands. In the Experimental Section, the bands have been listed with the collective assignment $\nu_{C=O}$ and $\nu_{C=C}$, since resolving these two highly mixed modes is extremely difficult.

The proton NMR data are also consistent with coordination of the ions by the ligands. The peaks for the bound ligand appear moved from their chemical shifts for Hima (the ring doublets from δ 7.3 and 6.3 to ~7.45 and ~6.1; the methyl from δ 2.4 to 2.3). Mass spectral data (EI) are also consistent, with the appearance of peaks corresponding to $[M(ima)_2]^+$ (the base peak), $[M(ima)_3]^+$ (parent), and $[M(ima)]^+$ (as a weak peak). Isotopic ratios were correct for $Ga(ima)_3$ with the two isotopes ^{69}Ga (60.4%) and ^{71}Ga (39.6%).

The ^{27}Al NMR spectrum of $Al(ima)_3$ has a narrower peak ($W_{1/2}$ = 200 Hz) and lower chemical shift (2.9 ppm referenced to $[Al(H_2O)_6]^{3+}$) than those of the 3-hydroxy-4-pyrone[1] or -pyridinone[2] complexes. Tris(maltolato)aluminum(III) has $W_{1/2}$ = 900 Hz at a shift of 39 ppm.[1] The narrow $W_{1/2}$ in $Al(ima)_3$ can only be ascribed to the binding site of isomaltol being a six-membered metallacycle containing a β-hydroxy ketone functionality rather than a five-membered metallacycle containing an α-hydroxy ketone. The ^{27}Al NMR spectrum of $Al(acac)_3$ has $W_{1/2}$ = 93 Hz at 0 ppm.[26] $Al(acac)_3$ contains an Al coordinated by three completely symmetric β-hydroxy ketones. The arrangement of three unsymmetric bidentate ligands around a metal center may be either *fac*ial or *mer*idional. The ^{27}Al NMR spectrum of $Al(ima)_3$ suggests that, in water, the complex is *fac* because of the high symmetry associated with the spectral findings, which are consistent with arrangements of ligands that give a low electric field gradient (EFG) at the NMR nucleus of interest.[27] A lower EFG (and hence a lower line width) results for a *fac* arrangement. This conclusion is also consonant with the proton NMR spectra, which show only one environment for each type of proton on the ligand (in $CDCl_3$ for Ga and In; in D_2O for Al). The inaccessibility of the low-temperature range in water precludes study of whether the aqueous ^1H and ^{27}Al NMR spectra result from an averaging of environments for a *mer* complex or for a *mer*/*fac* interchange or from the one environment in a *fac* complex.

The Al complex was crystallized from methanol, and structural studies were undertaken. In the solid state, the compound suffers a disorder with two of the ligands in the structure having two orientations (Figure 1). The disorder makes bond angle comparisons difficult; however, comparison of the bond lengths with those in tris(acetylacetonato)aluminum(III)[28] demonstrates a significant delocalization of the double bonds in ima$^-$ when coordinated to Al^{3+}. Looking at the one ordered ligand (comprising the O(1), O(2) donor set), one finds the two carbon–carbon bonds of the metallacycle (C(1)–C(2) = 1.382 (6) Å, C(2)–C(3) = 1.377 (6) Å) to be the same (within experimental error) and to be the

Table V. Logarithms of Metal–Isomaltol Stability Constants (Stepwise = K, Overall = β) Determined by Potentiometric Titration (25 °C, μ = 0.15 M (NaCl))

constant	H	Al	Ga	In
$\log K_1 = \log \beta_1$	5.55 (1)	5.66 (5)	6.63 (2)	7.08 (2)
$\log K_2$		4.76 (5)	5.68 (1)	4.06 (2)
$\log K_3$		4.03 (5)	4.05 (1)	3.66 (3)
$\log \beta_2$		10.42 (1)	12.31 (1)	11.14 (1)
$\log \beta_3$		14.45 (5)	16.36 (1)	14.80 (2)
$\sigma \log [H^+]$		0.011	0.001	0.002

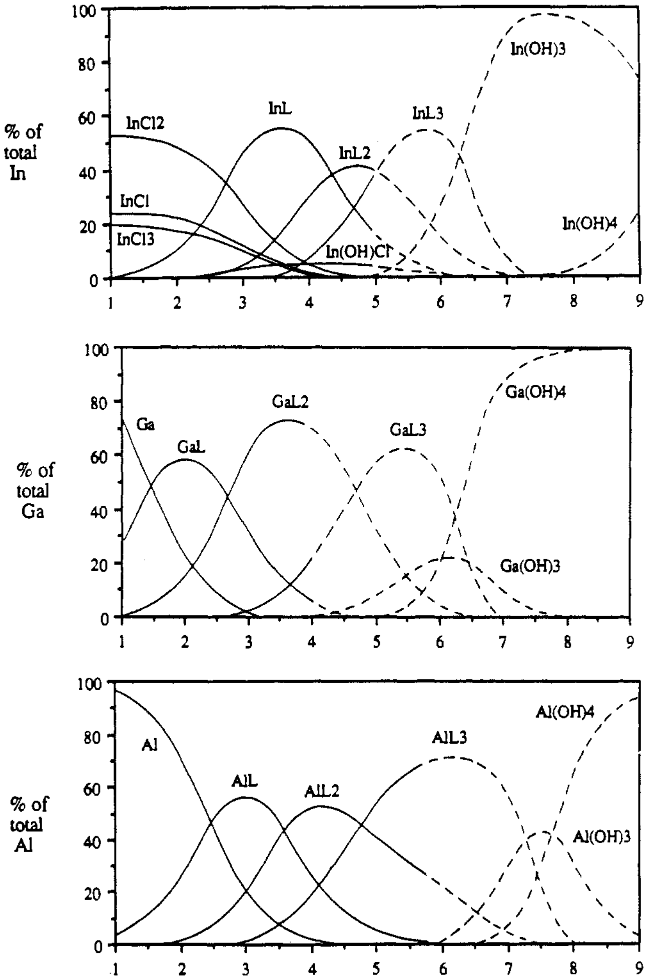


Figure 2. Speciation diagrams for the In, Ga, and Al isomaltol systems (L = ima$^-$). These are based on the experimental conditions of the titrations—1 mM M^{3+}, 3 mM Hima, μ = 0.15 M (NaCl), 25 °C. Dotted lines represent pH regions where there may be two phases.

---

(24) *International Tables for X-Ray Crystallography*; Kynoch Press: Birmingham, U.K. (present distributor D. Reidel: Dordrecht, The Netherlands), 1974; Vol. IV.

(25) Nakamoto, K. *Infrared and Raman Spectra of Inorganic and Coordination Compounds*, 3rd ed.; Wiley: New York, 1978; p 249.

(26) Haraguchi, H.; Fujiwara, S. *J. Phys. Chem.* **1969**, *73*, 3467.

(27) Akitt, J. W.; McDonald, W. S. *J. Magn. Reson.* **1984**, *58*, 401.

(28) Hon, P. K.; Pfluger, C. E. *J. Coord. Chem.* **1973**, *3*, 67.

same as those of $Al(acac)_3$ (average 1.380 (14) Å). C(3)–O(2), the hydroxyl bond length (1.281 (5) Å), is exactly the average for C–O in $Al(acac)_3$ while the ketonic bond is actually shorter (1.261 (5) Å). Overall, the ligand is significantly delocalized on bonding to aluminum, almost as much as is the acac anion.

Solution potentiometry demonstrates that isomaltol is a weak acid and that the isomaltolato anion is not an outstanding binding group for the group IIIA (13) metal ions (Table V). Isomaltol should have potential as the metal-binding component of higher dentate chelating agents, however. Table V lists both the stepwise formation constants K_n and the overall formation constants β_n defined by

$$K_n = \frac{[ML_n^{(3-n)+}]}{[ML_{n-1}^{(4-n)+}][L^-]} \qquad \beta_n = \frac{[ML_n^{(3-n)+}]}{[M^{3+}][L^-]^n}$$

and determined from the potentiometric titration data by the methods outlined in the Experimental Section. The number in parentheses represents the standard deviation between successive runs. The formation constants are less than those for the group IIIA (13) M^{3+} complexes of the 2,4-pentanedionato (acac) anion, where log β_1 is ~8.7, log β_2 ~16.5, and log β_3 ~23.[29] Clearly, the similarity noted above between the ^{27}Al NMR spectral properties of $Al(ima)_3$ and $Al(acac)_3$ does not extend to the thermodynamic binding parameters of the respective complexes.

Speciation diagrams for the $M(ima)_3$ complexes as a function of –log [H^+] are presented in Figure 2, and from these the hydrolysis of the complexes can be easily discerned. The higher second formation constant of ima^- for Ga compared with those for Al and In is demonstrated by the maximum for GaL_2^+ at pH 3.5 rather than 4 or greater. Comparison of the high-pH regions (>6) of the diagrams shows that isomaltol is incapable of preventing the hydrolysis of its simple tris(ligand)metal complexes, at least at the millimolar concentrations studied. As the pH rises, the isomaltolato anion cannot compete with hydroxide for the M^{3+}. With In^{3+} the situation is more complicated by the formation of various chloride species in addition to hydrolysis.[8] Mixed-ligand chloro- or hydroxo–In–ima complexes were not sought. From the high-yield syntheses of the complexes in water, it is obvious that this hydrolysis is minimized by increased concentrations of M^{3+} and isomaltol.

In conclusion, we have shown that the isomaltol moiety is a useful chelating group for some trivalent nontransition-metal ions. Our concern was to find a low molecular weight binding group with a functionalizable site near the metal, and Hima is a successful candidate. We have attempted the synthesis of its methylimine analogue; however, the reaction of isomaltol and methylamine results, through a rearrangement,[30] in a 3-hydroxy-4-pyridinone rather than producing the desired Schiff base condensation at the ketone. Our goal is to prepare tris(2-acyl-3-hydroxyfuran)-based hexadentate chelating agents, and the work reported here suggests that this area will prove fruitful.

Acknowledgments are made to the British Columbia Health Care Research Foundation and the NSERC of Canada for operating grants. We also thank the NSERC for a University Research Fellowship (C.O.), Professor S. Sjöberg for most helpful discussions, and Professor J. Trotter for the generous use of his crystallographic facilities.

Supplementary Material Available: Tables of anisotropic thermal parameters (Table SI), calculated hydrogen coordinates (Table SII), torsion angles (Table SIII), and intraannular torsion angles (Table SIV) (5 pages); a table of measured and calculated structure factor amplitudes (Table SV) (18 pages). Ordering information is given on any current masthead page.

(29) Martell, A. E.; Smith, R. M. *Critical Stability Constants*; Plenum: New York, 1977; Vol. 3, p 246.

(30) Severin, Th.; Loidl, A. *Z. Lebens. Unters. Forsch.* **1976**, *161*, 119.

Contribution from the Departments of Chemistry, The College of William and Mary,
Williamsburg, Virginia 23185, and University of Virginia, Charlottesville, Virginia 22901

Oxoperoxo(citrato)- and Dioxo(citrato)vanadates(V): Synthesis, Spectra, and Structure of a Hydroxyl Oxygen Bridged Dimer, $K_2[VO(O_2)(C_6H_6O_7)]_2{\cdot}2H_2O$

Cirila Djordjevic,*[,1] Myunghi Lee,[1] and Ekk Sinn[2]

Received August 3, 1988

The first citrato complexes of vanadium have been prepared: $M^I[VO(O_2)(C_6H_6O_7)]{\cdot}H_2O$ (M^I = K, NH_4, Cs) and $K[VO_2(C_6H_6O_7)]$. They crystallized from aqueous solution and were characterized by elemental analysis, IR and UV–visible spectroscopy, and X-ray structure analysis. Assignment of the characteristic peroxo IR bands in oxomonoperoxo(citrato)vanadates(V) was done by comparison with the spectrum of potassium dioxo(citrato)vanadate(V). X-ray structure analysis of $K_2[VO(O_2)(C_6H_6O_7)]_2{\cdot}2H_2O$ revealed the presence of a novel stereochemical ligation of the tridentate citrate, involving bridging hydroxyl oxygens to form a dimer and enclosing vanadium in slightly distorted pentagonal bipyramids. A relatively short O–O bond of 1.427 (1) Å was found in symmetrically coordinated peroxo ligands, corresponding well with the observed high ν(O–O) stretching frequency of 933 cm^{-1}. The relationship of these compounds to the biochemistry of vanadium is discussed.

Introduction

Citric acid, the hydroxyl tricarboxylic acid of the formula $HOOCCH_2C(OH)(COOH)CH_2COOH$, and citrate ions are the omnipresent small molecular weight species in most plant and animal tissues. Citrates appear at about 0.1 mM in blood plasma[3] and occur 0.3% by weight in teeth and bone.[4,5] They regulate some fundamental physiological processes and are intermediates in carbohydrate metabolism, e.g. in the "Krebs cycle." The combination of citrato and peroxo ligands on vanadium, a bioessential metal ion of an as yet unknown biological function,[6]

---

(1) The College of William and Mary.

(2) University of Virginia.

(3) Martin, R. B. *J. Inorg. Biochem.* **1986**, *28*, 181.

(4) Glusker, J. P. *Acc. Chem. Res.* **1980**, *13*, 345.

(5) Etcheverry, S. B.; Apella, M. C.; Baran, E. J. *J. Inorg. Biochem.* **1984**, *20*, 269.

(6) (a) Chasteen, N. D. *Struct. Bonding (Berlin)* **1983**, *53*, 105. (b) Boyd, D. W.; Kustin, K. *Adv. Inorg. Biochem.* **1984**, *6*, 312. (c) Erdmann, E.; Werdan, K.; Krawietz, W.; Schmitz, W.; Scholz, H. *Biochem. Pharmacol.* **1984**, *33*, 945. (d) Jandhyala, B. S.; Hom, G. *Life Sci.* **1983**, *33*, 1325.

0020-1669/89/1328-0719$01.50/0 © 1989 American Chemical Society