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Aluminum and Gallium Compounds of 3-Hydroxy-4-pyridinones: Synthesis, Characterization, and Crystallography of Biologically Active Complexes with Unusual Hydrogen Bonding

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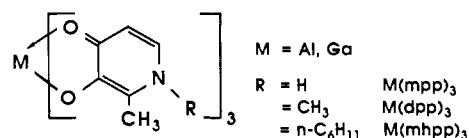
A series of tris(3-hydroxy-2-methyl-4-pyridinonato)aluminum(III) and -gallium(III) complexes have been prepared and characterized wherein the pyridinones have a variety of substituents at the ring nitrogen atom (H, CH₃, *n*-C₆H₁₁). They have been studied by a number of techniques including variable-pH ²⁷Al NMR, variable-temperature ¹H NMR, and single-crystal X-ray diffraction. The complexes M(C₇H₈NO₂)₃·12H₂O (*N*-methyl) are isostructural for M = Al and Ga, crystallizing in the trigonal space group *P* $\bar{3}$ with the following crystal parameters for Al (Ga): *a* = 16.600 (2) (16.6549 (6)) Å, *c* = 6.877 (1) (6.8691 (4)) Å, *Z* = 2. The data were refined by using 1662 (1653) reflections with *I* ≥ 3[σ(*I*)] to *R* and *R*_w values of 0.045 (0.047) and 0.051 (0.055), respectively. They form rigidly *fac* geometries with extensive hydrogen bonding to channels of water molecules, and this involves every available O atom in the unit cell. The resulting structure resembles an exclusion complex; hence, we have termed it an *exoclathrate*. The Al and Ga complexes with N-H and N-CH₃ are water soluble with some lipophilicity and exhibit a wide window of stability to hydrolysis. The dominance of hydrogen bonding is demonstrated in the solid-state structures and is also significant to the solution properties in water. Some of these compounds are being employed in biological studies of Al neurotoxicity and experiments in ⁶⁷Ga localization.

Introduction

As part of a continuing project to detail the coordination chemistry of aluminum and gallium which may pertain to the roles played by these two group 13 metal ions in the genesis and diagnosis of disease, respectively, we have been studying their tris complexes containing certain bidentate monobasic ligands.¹⁻⁴ From our work with the 3-hydroxy-4-pyrones, we discovered the unique combination of properties of tris(maltolato)aluminum(III)^{1,3} that have led to its wide use in the study of aluminum neurotoxicity:⁵ water solubility, hydrolytic stability, and lipophilicity. These properties have opened up an interesting new area of Al chemistry that will hopefully pertain to the relatively mysterious occurrence of the element in certain neurological disorders such as Alzheimer's disease. The chemistry of Al's group 13 congener Ga is somewhat more developed because of the utility of ⁶⁷Ga (*t*_{1/2} = 78.1 h; γ = 93.3, 185, 300 keV) in the field of diagnostic nuclear medicine.⁶⁻⁹ In an effort to extend our results with both these metals to the area of higher dentate ligands, we were struck by the lack of an easily functionalizable site on the ring in the pyrones. This has led us to look at their nitrogen-containing congeners, the 3-hydroxy-4-pyridinones.

Recently, there has been heightened interest in the various isomers (1,2; 3,2; 3,4) of the hydroxypyridinones as binding groups for certain metal ions. This includes the work of Kontoghiorghes and co-workers with Pu and (mostly) Fe,¹⁰ and that of Raymond and coworkers who have been extensively examining the 1-hydroxy-2-pyridinones¹¹⁻¹⁴ and 3-hydroxy-2-pyridinones¹³ as sequestering agents for the actinides and iron. There has also been some attention paid to mimosine (an *N*-alanine-3-hydroxy-4-pyridinone with depilatory properties) and its isomers as chelating agents for various divalent^{15,16} and trivalent metals.¹⁷ In particular, a Chinese group¹⁷ has determined potentiometrically an anomalously high formation constant of 10^{29.2} for the tris(mimosinato)aluminum(III) complex (10^{34.75} for Fe(III)). The *N*-phenyl analogue of the 3,4-complexes that we are reporting has been studied as an extractant for Ga.¹⁸

Herein we report the complete characterization of a series of Al and Ga complexes with the 3-hydroxy-4-pyridinones, including some observations on the great importance of hydrogen bonding in this series, and we comment on the potential utility of these complexes as medical agents based on the results of some preliminary *in vivo* studies.



Experimental Section

Materials and Methods. These were mostly as previously detailed.³ The ligands were prepared by methods in the literature.⁴ A 1.45 M aqueous solution of GaCl₃ was used after preparation and standardization. Only the major ions observed in the fast atom bombardment mass spectra (FABMS) are listed (in decreasing order of intensity) under each compound; the inert matrix was thioglycerol or glycerol. Variable-temperature ¹H and variable-pH ²⁷Al NMR spectra were recorded on a Varian XL-300. The variable-pH spectra of Al(dpp)₃ were recorded on a freshly prepared supersaturated sample before crystallization so as to

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have an adequate concentration.

Tris(3-hydroxy-2-methyl-4-pyridinonato)aluminum(III), Al(mpp)₃. Hmpp (1.25 g, 10.0 mmol) and Al(NO₃)₃·9H₂O (1.24 g, 3.30 mmol) were dissolved in 20 mL of water. The pH was raised to 9 with 2 M NaOH and the volume reduced to 10 mL by heating at 70 °C. While the suspension was still hot, the pink solid was collected by filtration. Drying in vacuo (90 °C, 48 h) gave 1.06 g of product in 83% yield, mp 310 °C dec. Anal. Calcd (found) for C₁₈H₁₈AlN₃O₆: C, 54.13 (53.89); H, 4.55 (4.69); N, 10.52 (10.60). ²⁷Al NMR (H₂O): 37 ppm (*W*_{1/2} = 660 Hz). FABMS *m/e*: 275 ([M - L]⁺ = [ML₂]⁺); 400 ([M + 1]⁺ = [HML₃]⁺). The resistance of a 1.0 mM aqueous solution was 290 kΩ. The water solubility was 0.02 M (22 °C, unbuffered).

Tris(3-hydroxy-2-methyl-4-pyridinonato)gallium(III), Ga(mpp)₃. To Hmpp (1.09 g, 8.70 mmol) in 20 mL of H₂O was added 1.45 M GaCl₃ (2.00 mL, 2.90 mmol). Workup similar to that above for Al(mpp)₃ gave 1.13 g of product in 88% yield, mp 290 °C dec. Anal. Calcd (found) for C₁₈H₁₈GaN₃O₆: C, 48.90 (48.65); H, 4.11 (4.29); N, 9.51 (9.53). FABMS *m/e*: 317, 319 ([M - L]⁺ = [ML₂]⁺); 442, 444 ([M + 1]⁺ = [HML₃]⁺). The resistance of a 1.0 mM aqueous solution was 350 kΩ. The water solubility was 0.008 M (22 °C, unbuffered).

Tris(3-hydroxy-1,2-dimethyl-4-pyridinonato)aluminum(III), Al(dpp)₃. Hdpp (1.69 g, 12.2 mmol) and Al(NO₃)₃·9H₂O (1.52 g, 4.05 mmol) were dissolved in 50 mL of water. The pH was raised to 9 with 12 M NH₄OH and the volume reduced to 20 mL by heating at 70 °C. The pale pink product was collected after overnight cooling at 20 °C. Drying in vacuo (90 °C, 16 h) gave 1.39 g of product in 79% yield, mp 300 °C dec. Pink crystals of the dodecahydrate (-12H₂O) suitable for X-ray diffraction were obtained by recrystallization from hot water. Anal. Calcd (found) for C₂₁H₂₄AlN₃O₆: C, 57.13 (57.40); H, 5.49 (5.54); N, 9.52 (9.67). ²⁷Al NMR (H₂O): 36 ppm (*W*_{1/2} = 680 Hz). FABMS *m/e*: 303 ([M - L]⁺ = [ML₂]⁺); 442 ([M + 1]⁺ = [HML₃]⁺); 744 ([M₂L₅]⁺). The water solubility, while not negligible, was less than 1 mM at room temperature but was significantly higher at elevated temperature.

Tris(3-hydroxy-1,2-dimethyl-4-pyridinonato)gallium(III), Ga(dpp)₃. To Hdpp (1.22 g, 8.80 mmol) in 20 mL of water was added 1.45 M GaCl₃ (2.00 mL, 2.90 mmol). Workup as for Al(dpp)₃ gave 1.10 g of product in 79% yield, mp 280 °C dec. Light orange crystals of the dodecahydrate suitable for X-ray diffraction were obtained by recrystallization from hot water. Anal. Calcd (found) for C₂₁H₂₄GaN₃O₆: C, 52.09 (51.98); H, 5.01 (5.10); N, 8.68 (8.54). FABMS *m/e*: 345, 347 ([M - L]⁺ = [ML₂]⁺); 484, 486 ([M + 1]⁺ = [HML₃]⁺). The water solubility was similar to that of Al(mpp)₃.

Tris(3-hydroxy-2-methyl-1-hexyl-4-pyridinonato)aluminum(III), Al(mhpp)₃. Hmhpp (0.86 g, 4.1 mmol) and AlCl₃·6H₂O (0.33 g, 1.3 mmol) were dissolved in 40 mL (1:1) of methanol/water. Deprotonation by the addition of 12 M NH₄OH (2 mL) was followed by heating at 80 °C for 1 h to remove excess ammonia and methanol. The product was extracted into methylene chloride (2 × 50 mL), and the solution was dried over MgSO₄. Vacuum distillation left a brown oil, which was triturated with hexanes; drying in vacuo (18 h) gave a yellow powder (0.59 g, 67% yield). Sublimation (300 °C at 10⁻² Torr) produced pure compound, mp 305 °C dec. Anal. Calcd (found) for C₃₆H₅₄AlN₃O₆: C, 66.32 (66.50); H, 8.37 (8.19); N, 6.45 (6.34). ²⁷Al NMR (CDCl₃): 38 ppm (*W*_{1/2} = 1100 Hz). FABMS *m/e*: 443 ([M - L]⁺ = [ML₂]⁺); 652 ([M + 1]⁺ = [HML₃]⁺).

Tris(3-hydroxy-2-methyl-1-hexyl-4-pyridinonato)gallium(III), Ga(mhpp)₃. To Hmhpp (0.63 g, 3.0 mmol) in 40 mL (1:1) of methanol/water was added 1.45 M GaCl₃ (0.69 mL, 1.0 mmol). Workup as for Al(mhpp)₃ gave a yellow powder (0.50 g, 71% yield). Sublimation (300 °C at 10⁻² Torr) produced analytically pure compound, mp 285 °C dec. Anal. Calcd (found) for C₃₆H₅₄GaN₃O₆: C, 62.24 (62.42); H, 7.85 (7.94); N, 6.05 (5.93). FABMS *m/e*: 485, 487 ([M - L]⁺ = [ML₂]⁺); 694, 696 ([M + 1]⁺ = [HML₃]⁺); 1180 ([M₂L₅]⁺).

X-ray Crystallographic Analyses. Crystallographic data are given in Table I. Final unit cell parameters were obtained by least-squares refinement on 2 (sin θ)/λ values for 25 reflections with 2θ = 60–90°. In each case the intensities of three standard reflections, measured each hour of X-ray exposure time, showed only small random fluctuations. The data were reduced and corrected for absorption.¹⁹

The structure of the Al complex was solved by direct methods in the centrosymmetric space group *P* $\bar{3}$ which was indicated by the *E* statistics and verified by subsequent analysis. The positions of all non-hydrogen atoms were determined from an *E* map and those of the hydrogen atoms from subsequent difference maps. The hydrogen atoms associated with

Table I. Crystallographic Data^a

	Al(C ₇ H ₈ NO ₂) ₃ ·12H ₂ O	Ga(C ₇ H ₈ NO ₂) ₃ ·12H ₂ O
formula	C ₂₁ H ₂₄ AlN ₃ O ₆	C ₂₁ H ₂₄ GaN ₃ O ₆
fw	657.6	700.3
cryst syst	trigonal	trigonal
space group	<i>P</i> $\bar{3}$	<i>P</i> $\bar{3}$
<i>a</i> , Å	16.600 (2)	16.6549 (6)
<i>c</i> , Å	6.877 (1)	6.8691 (4)
<i>V</i> , Å ³	1641.3 (3)	1650.1 (1)
<i>Z</i>	2	2
<i>D</i> _{calcd} , g/cm ³	1.331	1.470
<i>F</i> (000)	704	740
μ(Cu Kα), cm ⁻¹	11.97	17.89
cryst dimens, mm	0.15 × 0.38 × 0.40	0.11 × 0.16 × 0.50
transmiss factors	0.693–0.837	0.604–0.837
scan type	ω–2θ	ω–2θ
scan range, deg in ω	1.00 + 0.14 tan θ	1.00 + 0.14 tan θ
scan speed, deg/min	1.55–10.06	1.55–10.06
maximum 2θ, deg	150	150
cryst decay	negligible	negligible
no. of unique reflns	2251	2252
no. of reflns with <i>I</i> ≥ 3σ(<i>I</i>)	1662	1653
no. of variables	202	195
<i>R</i>	0.045	0.047
<i>R</i> _w	0.051	0.055
<i>S</i>	1.020	1.023
mean Δ/σ (final cycle)	0.01	0.003
max Δ/σ (final cycle)	0.17	0.023
residual density, e/Å ³	0.23	0.48

^a Temperature 22 °C, Enraf-Nonius CAD4-F diffractometer, Cu Kα radiation (λ_{Kα1} = 1.540562, λ_{Kα2} = 1.544390 Å), nickel filter, 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, σ²(*I*) = *S* + 2*B* + [0.040(*S* - *B*)]² (*S* = scan count, *B* = normalized background count), function minimized Σw(|*F*_o - |*F*_c||²) where *w* = 1/σ²(*F*), *R* = Σ||*F*_o - |*F*_c||/Σ|*F*_o|, *R*_w = (Σw(|*F*_o - |*F*_c||²)/Σw|*F*_o|²)^{1/2}, *S* = (Σw(|*F*_o - |*F*_c||²)/(*m* - *n*))^{1/2}. Values given for *R*, *R*_w, and *S* are based on those reflections with *I* ≥ 3σ(*I*).

the O(5) water molecule were found to be disordered, a twofold model being refined. The refinement of the isomorphous Ga compound was initiated with the final parameters of the Al analogue. The O(5) hydrogen disorder was not resolvable in the Ga structure, an ordered model being used in this case. Non-hydrogen atoms were refined with anisotropic thermal parameters and hydrogen atoms with isotropic thermal parameters. Neutral-atom scattering factors and anomalous scattering corrections for Al and Ga were taken from ref 20. An isotropic type I extinction correction was applied for the Ga compound,^{21–23} the final value of *g* being 0.55 (9) × 10⁴.

Final atomic coordinates and isotropic thermal parameters (*U*_{eq} = 1/3 trace diagonalized *U*) are given in Table II. Bond lengths, bond angles, and hydrogen-bonding data appear in Tables III–V, respectively. Anisotropic thermal parameters, bond lengths and angles involving hydrogen, torsion angles, measured and calculated structure factor amplitudes, and intramolecular torsion angles (Tables S1–S7) are included as supplementary material.

Results and Discussion

The Al and Ga complexes of the series of N-substituted 3-hydroxy-4-pyridinones are easily prepared in high yield from aqueous solution at neutral pH. The M(mpp)₃ complexes (the only ones which are completely water soluble at 1 mM) are uncharged in unbuffered aqueous solution as shown by the resistance values at 1 mM. They are much closer to that of distilled water (350 kΩ) than to that of 1 mM KCl (9.0 kΩ = 124 cm² Ω⁻¹ M⁻¹). All the compounds are very hygroscopic, as were their pyrone analogues.³ This is manifested in the drastic conditions (<0.3 Torr, 90 °C for 16–48 h) required to dehydrate the complexes in order to achieve acceptable elemental analyses. Clearly

(19) 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.

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Table II. Final Positional (Fractional $\times 10^4$, Ga $\times 10^5$, H $\times 10^3$) and Isotropic Thermal Parameters ($U \times 10^3 \text{ \AA}^2$) with Estimated Standard Deviations in Parentheses

atom	x	y	z	U_{eq}/U_{iso}
Al(C₇H₈NO₂)₃·12H₂O				
Al	6667	3333	-849 (2)	27
O(1)	6118 (1)	2250 (1)	717 (2)	32
O(2)	5591 (1)	2640 (1)	-2469 (2)	33
O(3)	7236 (2)	2164 (2)	3786 (3)	57
O(4)	1885 (2)	850 (2)	-305 (3)	50
O(5)	1848 (3)	857 (3)	5622 (4)	67
O(6)	3180 (2)	1441 (2)	2677 (4)	67
N	3852 (1)	193 (1)	206 (3)	34
C(1)	4942 (2)	555 (2)	2947 (4)	46
C(2)	4692 (2)	796 (2)	1033 (3)	32
C(3)	5284 (2)	1618 (1)	75 (3)	28
C(4)	5005 (2)	1841 (2)	-1707 (3)	30
C(5)	4134 (2)	1205 (2)	-2471 (4)	37
C(6)	3583 (2)	398 (2)	-1503 (4)	39
C(7)	3191 (2)	-684 (2)	1182 (5)	51
H(1a)	553 (3)	101 (3)	314 (5)	81 (12)
H(1b)	446 (3)	52 (3)	400 (6)	96 (13)
H(1c)	497 (2)	-2 (3)	290 (5)	88 (12)
H(5)	391 (2)	137 (2)	-367 (4)	50 (8)
H(6)	294 (2)	-12 (2)	-199 (4)	43 (7)
H(7a)	348 (3)	-101 (3)	155 (5)	79 (12)
H(7b)	264 (3)	-99 (3)	35 (5)	88 (12)
H(7c)	293 (3)	-52 (3)	237 (6)	105 (14)
H(O3a)	692 (4)	233 (3)	287 (8)	146 (20)
H(O3b)	724 (3)	245 (3)	471 (6)	70 (12)
H(O4a)	229 (3)	103 (3)	22 (7)	107 (18)
H(O4b)	147 (4)	122 (5)	-20 (8)	189 (24)
H(O5a) ^a	200 (6)	79 (6)	672 (14)	99 (32)
H(O5b) ^a	134 (7)	68 (8)	582 (15)	100 (40)
H(O5c) ^a	136 (6)	-2 (8)	514 (13)	79 (26)
H(O5d) ^a	183 (8)	124 (8)	526 (17)	91 (43)
H(O6a)	383 (3)	196 (3)	302 (5)	78 (11)
H(O6b)	281 (2)	131 (2)	353 (5)	63 (11)
Ga(C₇H₈NO₂)₃·12H₂O				
Ga	66667	33333	-8479 (13)	30
O(1)	6091 (2)	2211 (2)	779 (4)	37
O(2)	5560 (2)	2598 (2)	-2520 (4)	37
O(3)	7235 (3)	2126 (3)	3782 (7)	62
O(4)	1878 (3)	837 (3)	-306 (7)	53
O(5)	1836 (4)	847 (4)	5609 (8)	69
O(6)	3159 (4)	1410 (4)	2682 (7)	69
N	3833 (2)	167 (2)	209 (5)	36
C(1)	4925 (5)	541 (4)	2944 (9)	50
C(2)	4671 (3)	774 (3)	1039 (6)	35
C(3)	5255 (3)	1590 (3)	77 (6)	33
C(4)	4986 (3)	1810 (3)	-1701 (6)	33
C(5)	4116 (3)	1169 (3)	-2465 (7)	41
C(6)	3567 (3)	367 (3)	-1492 (7)	42
C(7)	3179 (4)	-703 (4)	1187 (11)	57
H(1a)	561 (5)	100 (5)	328 (10)	108 (25)
H(1b)	463 (6)	54 (6)	372 (11)	133 (36)
H(1c)	505 (4)	-2 (5)	280 (9)	99 (23)
H(5)	386 (4)	124 (4)	-375 (8)	75 (18)
H(6)	295 (4)	-4 (4)	-204 (8)	69 (17)
H(7a)	341 (4)	-103 (5)	171 (9)	93 (24)
H(7b)	260 (5)	-104 (4)	45 (9)	90 (22)
H(7c)	282 (5)	-63 (4)	234 (9)	92 (22)
H(O3a)	695 (6)	226 (6)	282 (12)	141 (34)
H(O3b)	714 (4)	228 (5)	464 (9)	68 (24)
H(O4a)	218 (5)	104 (5)	27 (10)	71 (29)
H(O4b)	159 (7)	134 (7)	39 (14)	188 (39)
H(O5a)	188 (10)	74 (11)	615 (18)	174 (63)
H(O5b)	129 (11)	-3 (16)	534 (21)	264 (64)
H(O6a)	364 (6)	173 (6)	309 (11)	109 (32)
H(O6b)	275 (5)	129 (5)	359 (10)	91 (25)

^aOccupancy factor 0.5.

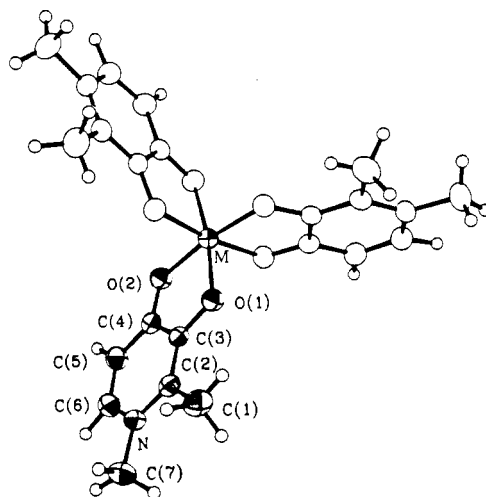
the macroscopic properties of the complexes are quite similar to those of the analogous pyrone compounds.³ However, now the functionalizable ring N in the pyridinones allows tuning of these properties. The N-H derivatives of Al and Ga are both water soluble (>1 mM) while the N-methylated analogues are less water

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

	length		length	
	M = Al	M = Ga	M = Al	M = Ga
M-O(1)	1.893 (2)	1.967 (3)	N-C(7)	1.476 (3)
M-O(2)	1.923 (2)	1.990 (3)	C(1)-C(2)	1.493 (3)
O(1)-C(3)	1.327 (3)	1.342 (5)	C(2)-C(3)	1.385 (3)
O(2)-C(4)	1.299 (3)	1.304 (5)	C(3)-C(4)	1.423 (3)
N-C(2)	1.369 (3)	1.372 (5)	C(4)-C(5)	1.398 (3)
N-C(6)	1.360 (3)	1.349 (6)	C(5)-C(6)	1.359 (6)

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

	angle	
	M = Al	M = Ga
O(1)-M-O(2)	84.23 (6)	83.22 (12)
O(1)-M-O(1')	90.81 (8)	90.90 (12)
O(1)-M-O(2')	95.71 (7)	96.65 (12)
O(2)-M-O(1')	171.85 (7)	170.48 (12)
O(2)-M-O(2')	89.83 (8)	90.01 (12)
M-O(1)-C(3)	112.20 (13)	110.7 (2)
M-O(2)-C(4)	112.00 (14)	110.9 (3)
C(2)-N-C(6)	121.2 (2)	121.1 (4)
C(2)-N-C(7)	121.1 (2)	121.1 (4)
C(6)-N-C(7)	117.7 (2)	117.7 (4)
N-C(2)-C(1)	119.2 (2)	119.4 (4)
N-C(2)-C(3)	119.0 (2)	118.9 (4)
C(1)-C(2)-C(3)	121.9 (2)	121.7 (4)
O(1)-C(3)-C(2)	124.5 (2)	122.4 (4)
O(1)-C(3)-C(4)	115.3 (2)	116.9 (4)
C(2)-C(3)-C(4)	120.2 (2)	120.7 (4)
O(2)-C(4)-C(3)	116.0 (2)	117.9 (4)
O(2)-C(4)-C(5)	125.7 (2)	124.2 (4)
C(3)-C(4)-C(5)	118.4 (2)	117.9 (4)
C(4)-C(5)-C(6)	119.5 (2)	119.7 (4)
N-C(6)-C(5)	121.7 (2)	121.7 (4)

**Figure 1.** ORTEP view of the tris(ligand)metal portion of the Al(dpp)₃ complex (Ga(dpp)₃ is isostructural).

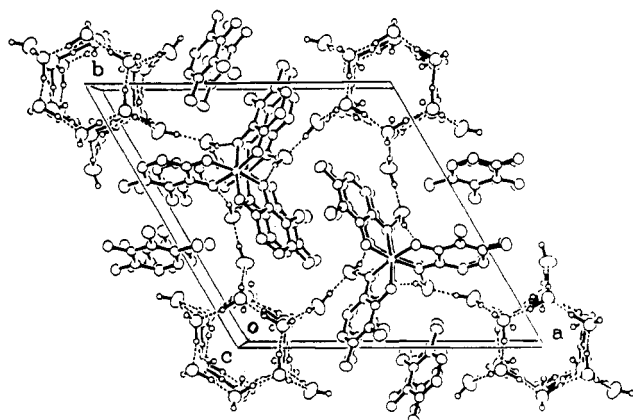
soluble but more lipophilic, and the N-hexylated complexes are negligibly water soluble but highly lipophilic.

The crystal structures of the two dodecahydrate complexes (M(dpp)₃·12H₂O) have been solved, and they are isostructural; the replacement of the Al atom with Ga causes the unit cell volume to increase slightly (see Table I). The complexes each crystallize as the facial isomer (Figure 1). The rigorous threefold symmetry causes the asymmetric unit to consist of one-third of a metal ion, one ligand, and four water molecules. There is a slight compression of the M(dpp)₃ units from ideality along the threefold axis leading to O(1)-M-O(2) angles of 84° for M = Al and 83° for Ga (Table IV). The exocyclic O(1)-M-O(1') (hydroxy O-metal-hydroxy O) angles and the exocyclic O(2)-M-O(2') (keto O-metal-keto O) angles are very close to 90 (±1)°, while the compression is

Table V. Hydrogen-Bonding Distances and Angles in the Complexes $M(dpp)_3 \cdot 12H_2O$

interaction ^a	O—H, Å		H···O, Å		O···O, Å		O—H···O, deg	
	Al	Ga	Al	Ga	Al	Ga	Al	Ga
O(3)—H(O3a)···O(1) ¹	0.94 (5)	0.90 (9)	1.95 (6)	1.98 (9)	2.861 (3)	2.859 (5)	161 (4)	165 (8)
O(3)—H(O3b)···O(2) ²	0.79 (4)	0.69 (6)	2.08 (4)	2.19 (6)	2.849 (3)	2.842 (6)	164 (4)	159 (7)
O(4)—H(O4a)···O(6) ¹	0.68 (5)	0.60 (6)	2.12 (5)	2.19 (6)	2.772 (3)	2.765 (6)	159 (5)	164 (10)
O(4)—H(O4b)···O(4) ³	1.14 (8)	1.24 (12)	1.62 (8)	1.58 (12)	2.747 (3)	2.746 (5)	168 (5)	154 (8)
O(5)—H(O5a)···O(4) ⁴	0.82 (9)	0.44 (13)	2.06 (10)	2.44 (12)	2.802 (4)	2.807 (7)	150 (9)	145 (22)
O(5)—H(O5c)···O(5) ^{5,6}	1.30 (12)	1.29 (23)	1.50 (13)	1.53 (24)	2.793 (4)	2.779 (7)	174 (6)	160 (10)
O(5)—H(O5d)···O(5) ⁶	0.70 (14)		2.17 (13)		2.793 (4)		149 (12)	
O(6)—H(O6a)···O(3) ⁷	1.01 (4)	0.76 (8)	1.72 (4)	1.99 (8)	2.729 (4)	2.734 (7)	174 (3)	167 (8)
O(6)—H(O6b)···O(5) ¹	0.79 (4)	0.87 (7)	2.00 (4)	1.91 (7)	2.791 (4)	2.778 (7)	174 (3)	171 (6)

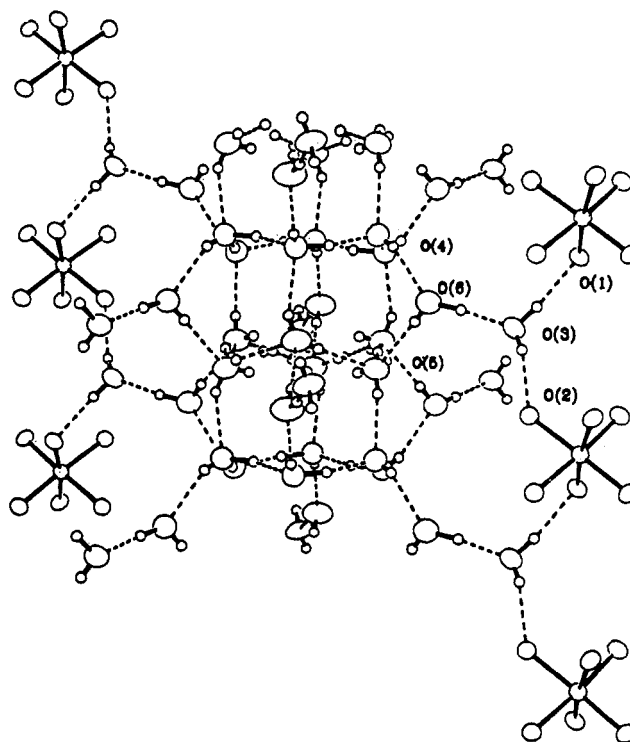
^aSuperscripts refer to symmetry operations: ¹ x, y, z ; ² $1 - y, x - y, 1 + z$; ³ $x - y, x, -z$; ⁴ $x, y, 1 + z$; ⁵ $y, y - x, 1 - z$; ⁶ $x - y, x, 1 - z$; ⁷ $1 - x + y, 1 - x, z$. ^bThis interaction involves H(O5b) for the Ga compound.

**Figure 2.** ORTEP view down the c axis of the unit cell packing of $Ga(dpp)_3$ ($Al(dpp)_3$ is isostructural).

evinced in the exocyclic O(1)—M—O(2') (hydroxy O—metal—keto O) angles, which are around 96° . The two metallacyclic O—C—C bond angles (O(1)—C(3)—C(4) and O(2)—C(4)—C(3)) are slightly decreased (115 – 118°) from the free ligand values (120°)⁴ but much less than in the $(C_6H_5)_2B(dpp)$ complex where they are 114 and 112° , respectively.²⁴ The strain in the dpp anion is clearly less when bound to Ga or Al than to B.

This reduced strain (or better fit) manifests itself in a greater aromaticity for the ligand. The metal—ligand units are planar within 5 or 6° (Table S7 in the supplementary material) and there is evidence for considerable delocalization of the rings when coordinated to Al or Ga. The difference between O(1)—C(3) and O(2)—C(4) decreases from 0.088 Å in $Hdpp^4$ and 0.082 Å in $(C_6H_5)_2B(dpp)^{24}$ to 0.028 Å in $Al(dpp)_3$ and 0.038 Å in $Ga(dpp)_3$ (Table III). This significant bond length averaging indicates some delocalization (toward $C=\bar{O}$), but less than in $Al(acac)_3$, where the six C—O lengths closely average to 1.283 Å with an esd of only 0.01 Å.²⁵ There is also a significant averaging of the ring C—C (C(3)—C(4), C(4)—C(5)) and C=C (C(2)—C(3), C(5)—C(6)) distances upon coordination to Al or Ga (Table III) when compared to the values in the free ligand or $(C_6H_5)_2B(dpp)$. There is greater delocalization in the dpp[−] ligand of these structures than there is in the maltol anion of $Al(ma)_3$ or $(C_6H_5)_2B(ma)$, or in the mpp[−] or dpp[−] ligands of any structure in this category that we have solved to date.^{1,4,24,26}

The most notable feature of these structures is, however, the extensive hydrogen bonding. In the free ligands (which were also crystallized from hot water), head-to-tail dimers are formed with pairs of $C=O\cdots H-O-C$ hydrogen bonds linking the dimers.⁴ In the structure of $Hmpp$, there are also further $C=O\cdots H-N$ bonds tying the dimers into an infinite array. In $Hdpp$ and its complexes, the $N-CH_3$ group renders this latter interaction impossible; however, in the complexes new interactions are discerned

**Figure 3.** ORTEP view of a part of the hydrogen-bonding network of waters in $M(dpp)_3$. The view down the a axis shows all the independent O atoms; all the atoms in the $M(dpp)_3$ units are omitted except MO_6 . Only two of the six columns of $M(dpp)_3$ units are shown.

from the diagram of the unit cell packing (Figure 2). The water molecules of the dodecahydrate form a fascinating and unprecedented three-dimensional array: half (O(3) and O(6)—see Figure 3 for numbering) form a bridge from the *fac*- $M(dpp)_3$ units to the rigidly 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 atoms (O(1) and O(2)) and their nearest water hydrogens (H(O3a) and H(O3b), respectively) are quite strong (Table V), considering that these oxygen atoms are already chelating the metal atoms, an interaction absent in the ligands. All six of the chelating O atoms are hydrogen bonded to $H_2O(3)$ water molecules, and the latter form an infinite chain down the c axis bridging from the hydroxy O(1) in one ligand to the keto O(2) of a ligand rotated by 120° and translated by one unit cell. (This is why Figure 2 shows the contents of two unit cells). In $Hdpp$, the $H\cdots O$ and $O\cdots O$ lengths are 1.94 (5) and 2.692 (3) Å, respectively, while in the complexes for the chelating oxygens these vary from 1.95 (6) to 2.19 (6) Å and from 2.842 (6) to 2.861 (3) Å, respectively. Not surprisingly, the chelating hydroxy O forms shorter $O\cdots H$ bonds than the chelating keto O. This bridging interaction of water molecule O(3) is best seen in Figure 3, which is a view down the a axis, perpendicular to the c axis (which is the sixfold axis in the water channels and the threefold axis in the *fac*- $M(dpp)_3$ units—Figure

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2). There can be no doubt that this interaction enforces the threefold (*fac*) symmetry of the metal-containing portion of the compound.

The hexagonal channels of water molecules in the corners of the unit cell are the most unique feature of the hydrogen bonding in these structures. The water O(5) in the Al complex was found to be twofold disordered and is shown with four half-protons bound to it in Figures 2 and 3. Each of the (H₂O)₆ rings has crystallographically imposed $\bar{3}$ or *S*₆ symmetry. The rings adopt, essentially, the structure of ice in its stable low pressure form ice-*I*_h.²⁷ Each water molecule in the ring is hydrogen bonded to four nearest neighbors with the added distinction that the overall structure is predominantly proton-ordered, unlike ice-*I*_h which is completely disordered, and this is realized in the significant difference between the O-H and the O...H bond lengths (Table V). The O-H...O distances in the channels (only those involving O(4), O(5), and O(6)) vary from 2.75 to 2.81 Å compared with the average value of 2.75 Å for O...O in ice-*I*_h at 100 K.²⁸

Within each water ring the hydrogen bonding is homodromic²⁹⁻³¹ because of the unidirectional circular bonding pattern. All the O-H...O bonds run in a counterclockwise direction when viewed down the hexagonal axis (*c*) as in Figure 2. These circles are well-known in the crystal structures of ice^{27,28} and the clathrate hydrates;^{32,33} however, this is the first example of which we are aware where this arrangement occurs in hydrates containing (relatively) large metal complexes. The arrangement is crystallographically imposed by the space group (*P*3), however, and does not occur independent of symmetry constraints as do the water networks in the structures of some nucleosides³⁴ and β -cyclodextrins.^{35,36} Homodromic hydrogen bonding arrangements are favored (and more frequently observed despite symmetry constraints) over heterodromic or antidromic arrays because of an inherent lower dipole moment.³⁰ There is a considerable cooperative effect that results in increased hydrogen bonding activity for a hydroxyl group when it is already the donor or acceptor in a hydrogen bond. Quantum-mechanical calculations have confirmed that chain structures (particularly cyclic) of hydrogen bonds are energetically favored over individual interactions.³⁷

The above observations suggest that the M(dpp)₃ complexes present (when crystallized from water) appropriate conditions for the formation of the water channels in what is a previously unobserved, but energetically favored, hydrogen bonding arrangement. This probably results by virtue of both the complex size, and the hydrophobic pocket formed in the center of the unit cell (Figure 2). This pocket is formed by the pairs of methyl groups on each of two ligands that point toward each other. There is a clear alternation of hydrophilic and hydrophobic regions along the *ab* diagonals of the unit cell (Figure 2). No doubt this feature also contributes to the unique hydrogen-bonding arrangement. It may be that another driving force for the formation of the unique structures of these dodecahydrates is a variation on hydrophobic clathration^{32,33} as well as the cooperativity³⁸ of hydrogen-bonding networks.

All the individual hydrogen bonds in the water channels are analogous to the type IA donor-acceptor interaction characterized

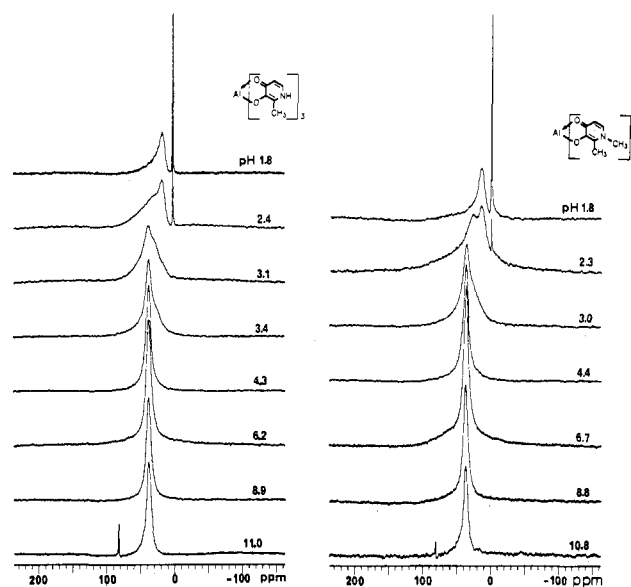


Figure 4. Variable-pH ²⁷Al NMR spectra of Al(mpp)₃ (left, 0.02 M; 0 ppm signal truncated) and of Al(dpp)₃ (right, 0.03 M).

from carbohydrate structures.³⁸ The water molecules may be categorized according to the classification of Falk and Knop³⁹ 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). The water H₂O(3) is a, H₂O(6) is dda, and the two waters in the hexagonal channels (H₂O(4) and H₂O(5)) are ddaa.

We use the term *exoclathrate* to describe these complexes wherein the ML₃ species is contained not within the aquo network as in a standard clathrate hydrate but without it, creating not an inclusion compound, but an exclusion compound. The clathrate hydrates are crystalline compounds that consist of a hydrogen-bonded water host network (often a H₄₀O₂₀ pentagonal dodecahedron) within which a guest is held by an interaction that varies from weakly hydrogen bonding to ionically bonding where one or more ion is associated with, or incorporated in, the water framework.^{32,40} We note similarities here with hexamethylenetetramine hexahydrate ((CH₂)₆N₄·6H₂O), an unusual hydrate in which the latter is not based on a regular polyhedron, so there are no well-defined polyhedral cavities.⁴¹ It shares with the structures reported here the hexagonal (H₂O)₆ units. In the amine, however, the water rings are staggered around the cage-like amine molecules in a spiral (instead of a linear chain) to which the latter are bound. It is not a standard clathrate hydrate, but it is not quite an exoclathrate either despite being the closest analogue that we could find in the literature.

With these extraordinary solid-state properties, one might expect some unusual solution properties for M(dpp)₃. The dpp⁻ anion does appear to have an anomalous affinity for trivalent metal ions. This is concluded from preliminary results of potentiometric titrations⁴² where we have found an overall formation constant for Al(dpp)₃ of 10³², from biodistribution experiments⁴³ with ⁶⁷Ga(dpp)₃, which demonstrate that the complex does not give up ⁶⁷Ga to transferrin, and from the observation of Kontoghiorghes and co-workers that the anion is capable of removing Fe³⁺ from the transferrins^{10a,44} and ferritin.⁴⁵

The variable-pH ²⁷Al NMR spectra for Al(mpp)₃ and Al(dpp)₃ are shown in Figure 4. This technique monitors the hydrolysis

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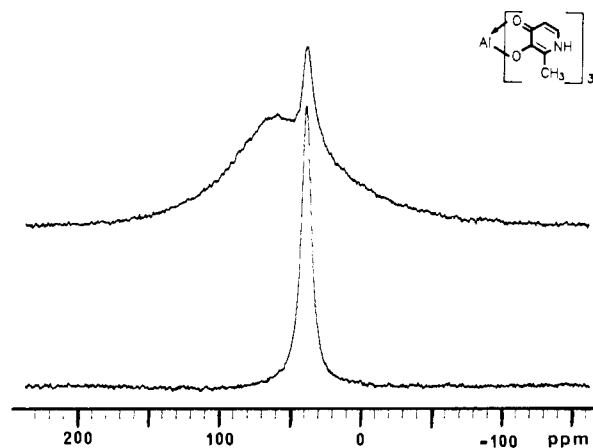


Figure 5. ^{27}Al NMR spectra of $\text{Al}(\text{mpp})_3$ (0.02 M) after 1 day (lower) and 14 days (upper) at pH 9.

behavior of those complexes that are sufficiently water soluble to give good spectra.³ Both these complexes show an even wider pH window of stability to hydrolysis than the aluminum maltol compound.³ In the mpp spectra, acidic hydrolysis is evinced by a shoulder at pH 3.4 on the upfield side of the $\text{Al}(\text{mpp})_3$ peak at 37 ppm ($W_{1/2} = 660$ Hz). This results from the partial protonation of ligands in the coordination sphere of the Al and the replacement of them with waters. At pH 3.1 this shoulder is resolved into two shoulders resulting from the two species $[\text{Al}(\text{mpp})_2(\text{H}_2\text{O})_2]^+$ (28 ppm) and $[\text{Al}(\text{mpp})(\text{H}_2\text{O})_4]^{2+}$ (17 ppm), which are both visible in addition to $\text{Al}(\text{mpp})_3$. As the solution is acidified further the completely hydrolyzed species $[\text{Al}(\text{H}_2\text{O})_6]^{3+}$ is observed; it is the ^{27}Al NMR standard at 0 ppm. As the pH drops, the more highly hydrolyzed species are preferentially observed. The basic hydrolysis proceeds cleanly with evidence for both the intact complex and $[\text{Al}(\text{OH})_4]^-$ (80 ppm) at pH 11. It is concluded by comparison of these variable pH spectra with those for the maltol complex³ that $\text{Al}(\text{mpp})_3$ is more stable to both acidic and basic hydrolysis. The spectrum at pH 1.8 suggests that only the mono(ligand) complex remains (in addition to $[\text{Al}(\text{H}_2\text{O})_6]^{3+}$) whereas peaks for both the mono- and bis(ligand) complexes are clearly resolvable for the maltol complex at pH 1.7. This may be the result of a protonation to $[\text{H}_2\text{mpp}]^+$, which would favor decomplexation at a pH below $-\log K$. (For Hdpp we have determined $-\log K$ of $[\text{H}_2\text{dpp}]^+$ to be 3.72.⁴²) The spectra for $\text{Al}(\text{dpp})_3$ are similar albeit with a slightly wider window of hydrolytic stability. At pH 10.8 there is still mostly intact complex in solution while in the acidic regime the hydrolysis of the ligand complexes is favored by the protonation to $[\text{H}_2\text{dpp}]^+$. The intermediate species occur at 26 ppm ($[\text{Al}(\text{dpp})_2(\text{H}_2\text{O})_2]^+$) and at 14 ppm ($[\text{Al}(\text{dpp})(\text{H}_2\text{O})_4]^{2+}$). At pH 2.3 there appears to be significantly more of the bis(ligand) species as the two peaks 26 and 14 ppm are resolvable, unlike in the $\text{Al}(\text{mpp})_3$ spectra.

The hydrolysis of Al^{3+} is well known to be time- and concentration-dependent.⁴⁶ Figure 5 clearly shows that 0.02 M $\text{Al}(\text{mpp})_3$ undergoes hydrolysis over a 2-week period at pH 9. The ^{27}Al NMR spectrum broadens from the one band characteristic of the tris(ligand) complex (at 37 ppm) to include an additional broad band with a maximum at 61 ppm while the intensity of the former band drops by about one-third. That the broadening appears on the downfield side of the $\text{Al}(\text{mpp})_3$ band suggests that the hydrolyzed species produced are most likely to be four-coordinate mixed aquo/hydroxo/mpp Al complexes, as well as $[\text{Al}(\text{OH})_4]^-$.⁴⁷ The complex is obviously quite robust to basic hydrolysis.

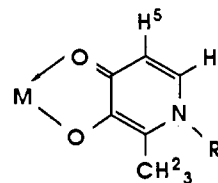
The four-band infrared spectral pattern (1600–1400 cm^{-1}), which is characteristic of the 4-pyridinones,^{4,48} is preserved in the complexes (see Table VI) although, in addition to the expected

Table VI. Characteristic Infrared Absorptions (cm^{-1})^a

assignt	$\text{M}(\text{mpp})_3$		$\text{M}(\text{dpp})_3$		$\text{M}(\text{mhpp})_3$	
	Al	Ga	Al	Ga	Al	Ga
$\nu_{\text{N-H}}$	3280	3280				
$\nu_{\text{C=O}}$	1620	1620	1605	1605	1605	1605
and	1595	1600	1560	1555	1560	1560
ν_{ring}	1535 sh	1530 sh	1520	1510	1520	1520
	1505 b	1500 b	1495	1490	1490	1490
$\nu_{\text{M-O}}$	730	730	635	625	720	720
	640	625	575	575	580	570
	460 b	360 b	440 b	320 b	475 b	340 b

^a All sharp and strong except as noted: b = broad; sh = shoulder.

Table VII. ^1H NMR Data^a



assignt	$\text{M}(\text{mpp})_3$		$\text{M}(\text{dpp})_3$		$\text{M}(\text{mhpp})_3$	
	Al	Ga	Al	Ga ^b	Al ^c	Ga ^c
H^6 (doublet)	7.50	7.48	7.56	7.49	7.02	7.24
H^5 (doublet)	6.56	6.61	6.50	6.47	6.48	6.70
J_{56} (Hz)	6.8	6.7	6.8	6.8	6.8	6.7
H^2 (singlet)	2.31	2.34	2.35	2.43	2.38	2.56
R = H	12.04 ^d					
R = CH_3			3.81	3.80		
R = $n\text{-C}_6\text{H}_{11}$ ^e					3.82 (t)	3.96 (t)
					1.66	1.73
					1.27	1.30
					0.85	0.87

^a All in ppm downfield of Me_4Si except J_{56} in Hz. All recorded at 400 MHz in D_2O except as noted. ^b CD_3OD . ^c CDCl_3 . ^d DMSO-d_6 . ^e All multiplets except t = triplet.

general bathochromic shift, there may be an energy reordering upon complexation such as that which we have already observed in the 4-pyrones.³ In Table VI, the four bands have been listed with the collective assignment $\nu_{\text{C=O}}$ and ν_{ring} since resolving these two modes is extremely difficult because of mixing. Three new bands appear <750 cm^{-1} in the spectrum of each complex ligand and these are probably the $\nu_{\text{M-O}}$ although there may be coupling to ring deformation modes.

Proton NMR data for the complexes are listed in Table VII. These have been collected in D_2O as often as solubilities allow. The same characteristic pair of ring H_5H_6 doublets in the pyrone complexes³ are seen here in the pyridinone complexes, with coupling constants of 6–7 Hz. The complexes of both mpp^- and dpp^- show temperature-dependent NMR spectra, an example of which is displayed in Figure 6 for $\text{Al}(\text{dpp})_3$ in CD_3OD . There appear to be at least two dynamic processes occurring. We have been able to determine ΔG^\ddagger values in some cases for the higher temperature process from the coalescence temperature T_c and the maximum chemical shift difference (the -39 $^\circ\text{C}$ spectrum in this case).⁴⁹ For $\text{Al}(\text{dpp})_3$, $\Delta G^\ddagger = 15.9 \pm 0.1$ kcal/mol with $T_c = 17 \pm 1$ $^\circ\text{C}$. The higher temperature process is probably the *mer-fac* interconversion while the lower T one (which is never resolved in CD_3OD , even at -90 $^\circ\text{C}$) might be the resolution of the Λ and Δ stereoisomers. There is also a marked solvent dependence of the proton NMR spectra of these complexes; for $\text{Al}(\text{dpp})_3$ in D_2O , $\Delta G^\ddagger = 16.50 \pm 0.08$ kcal/mol and $T_c = 30 \pm 1$ $^\circ\text{C}$. The best method to determine the solution processes represented by these spectra is through their simulation, a fairly complicated study that is ongoing and will be the subject of a future communication.⁵⁰ However, it is likely that the solvent

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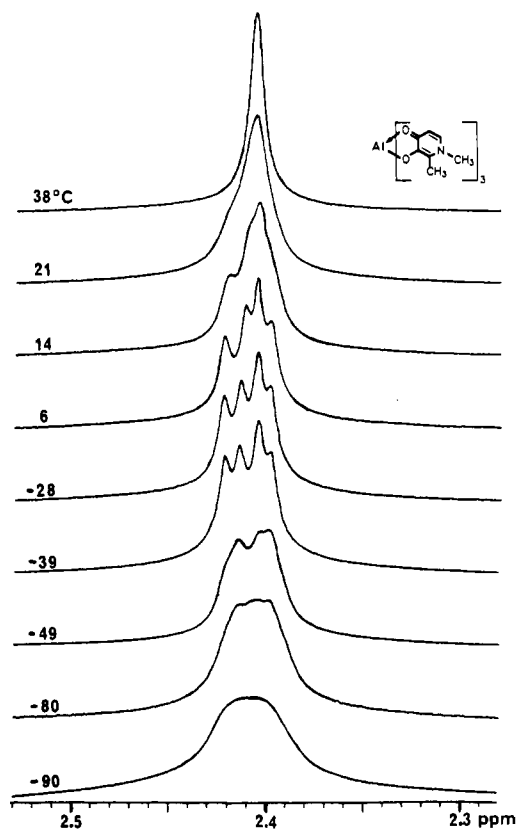


Figure 6. Variable-temperature ^1H NMR spectra of the ring methyl group ($\text{C}-\text{CH}_3$) in $\text{Al}(\text{dpp})_3$ in CD_3OD .

dependence is a result of the hydrogen-bonding potential in these systems.

The central importance of hydrogen bonding in the solid-state properties of these tris(pyridinonato)metal(III) complexes is apparent from cursory inspection of the ORTEP diagrams in Figures 2 and 3. Less directly obvious is the effect that hydrogen bonding has on the solution properties. As noted above, this is manifested in the variable-temperature NMR spectra where we find that the coalescence temperature and thermodynamic parameters are quite solvent dependent. As well, the fact that the ^{27}Al NMR line widths which we see for these species are narrower in water than in, for example, DMSO may be a function of hydrogen bonding to water in the solution. The aluminum maltol complex has $W_{1/2} = 900$ Hz in aqueous solution³ whereas the $\text{Al}(\text{mpp})_3$ and $\text{Al}(\text{dpp})_3$ complex spectra are considerably narrower at 660 and 680 Hz, respectively. This may result from more of the complex in each case being in the *fac* configuration, this arrangement having a lower electric field gradient at the nucleus and consequently a lower $W_{1/2}$.⁵¹ It may be that in any system with hydrogen-bonding donors there will be more complex in the more symmetric *fac* configuration with bonds formed between the chelating O atoms and those donors. We are trying to confirm this by growing crystals of $\text{M}(\text{dpp})_3$ from organic solvents, of $\text{Al}(\text{ma})_3$ from water, and of our other complexes from both aqueous and nonaqueous solvent systems.

Another study that testifies to the importance of hydrogen bonding is our failed attempt to measure 1-octanol/water partition coefficients for comparison with those that we have reported for

the pyrone complexes.³ In all cases, we found these to be highly concentration dependent, ranging in values by an order of magnitude or more when the concentration was changed by 2 orders of magnitude. Using atomic absorption spectrophotometry on samples in the millimolar concentration range, we found values for *p* that were an order of magnitude less for the Al and Ga complexes of maltol than those values previously determined at the 10–100 μM level by using UV-vis spectrophotometry. Presumably, as the starting aqueous concentration of the samples increases, proportionately less complex is extracted into the 1-octanol layer. This may reflect a lower solubility in 1-octanol than in water or it may be connected with the observed large temperature dependence of the water solubilities. Physiological temperature partition coefficients might be significantly larger as formation of the exocathrate structure would be impeded by thermal motion. An anomalously low *p* (0.05 at $\sim 15 \mu\text{M}$) was determined for $\text{Fe}(\text{dpp})_3$ and was noted in the thesis work of Kontoghiorghes.⁵² A greater lipophilicity might be expected for a complex with two methyl groups on each of three ligands.

Both the $\text{M}(\text{dpp})_3$ complexes are several hundred times more water soluble at physiological temperature (37 °C) than room temperature (25 °C). This supersaturation causes the dodecahydrates to crystallize out beautifully as hexagons from hot water as the temperature drops. Higher temperatures disrupt the hydrogen bonding, causing a much greater increase in solubility for $\text{M}(\text{dpp})_3$ than for $\text{M}(\text{ma})_3$ as the temperature is raised from 25 to 37 °C. This could not be observed crystallographically since the $\text{M}(\text{ma})_3$ complexes would not crystallize from water. The hydrogen bonding between $\text{M}(\text{dpp})_3$ and water certainly dictates the *fac* geometry adopted in the solid state. This lends credence to the postulate that the correlation between solution and solid-state structures in high hydrates should be considerable because of the "aqueous-like" crystalline environment contained therein.^{53,54}

In conclusion, a new series of tris(N-substituted 3-hydroxy-4-pyridinone) complexes of Al and Ga show some unusual properties in both the solid and solution states. These complexes are water soluble depending on the N substituent and quite stable to hydrolysis, even more so than their pyrone congeners. Their properties are dominated by their potential to hydrogen bond to solvents, and this is dramatically demonstrated in the formation of exocathrate exclusion complexes when the $\text{N}-\text{CH}_3$ analogues are crystallized from hot water.

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Registry No. $\text{Al}(\text{mpp})_3$, 112506-08-8; $\text{Ga}(\text{mpp})_3$, 112506-09-9; $\text{Al}(\text{dpp})_3 \cdot 12\text{H}_2\text{O}$, 108795-58-0; $\text{Ga}(\text{dpp})_3 \cdot 12\text{H}_2\text{O}$, 112506-10-2; $\text{Al}(\text{mhpp})_3$, 112506-11-3; $\text{Ga}(\text{mhpp})_3$, 112506-12-4.

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 S7) (5 pages); tables of measured and calculated structure factor amplitudes (Tables S5 and S6) (20 pages). Ordering information is given on any current masthead page.

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