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P. Letkeman^a; A. E. Martell^a; R. J. Motekaitis^a

^a Department of Chemistry, Texas A. & M. University, College Station, Texas

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COMPLEXES OF GALLIUM(III) WITH HYDROXYAROMATIC LIGANDS

P. LETKEMAN, A. E. MARTELL* and R. J. MOTEKAITIS

Department of Chemistry, Texas A. & M. University College Station, Texas 77843

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The equilibria between gallium(III) ion and selected hydroxyaromatic and dihydroxyaromatic ligands at 25°C, $\mu = 0.100$ M (KNO_3) have been determined. Potentiometric measurements on 1:1, 2:1, and 3:1 molar ratios of ligand to Ga(III) have been made as a function of degree of neutralization over the entire accessible $-\log [\text{H}^+]$ scale. Calculations were carried out so as to take account of competing hydrolytic reactions, and formation constants of gallium(III) with chromotropic acid, 8-hydroxyquinoline-5-sulfonic acid, 5-sulfosalicylic acid, and 1,2-dihydroxybenzene-3,5-disulfonic acid were obtained. Stable hydroxo chelates do not form under the reaction conditions employed. The protonation constants of the ligands and the formation constants of the gallium chelates are discussed and compared with previously published work on these gallium chelates and on chelates of "analogous" metal ions such as those of Fe(III) and Al(III).

INTRODUCTION

The development of the aqueous coordination chemistry of gallium(III) has been characterized through the years by the publication of a series of papers from independent investigators often reporting conflicting results and interpretations. Perhaps the single most important reason for these disagreements is derived from the unique hydrolytic and amphoteric properties of the gallium(III) ion itself. Its strong tendency toward hydrolysis is accompanied by considerable polymerization, especially in the intermediate pH range, so that any coordination study made in solutions containing uncomplexed Ga(III) in appreciable concentrations are subject to wide variations in interpretation. When the free Ga(III) concentration at a particular pH exceeds the value allowed by its solubility product, the formation of precipitate may occur very slowly and to an unpredictable extent. Thus experimental observations depended on such factors as duration of the experiment, the difficulty of determining the actual presence of precipitate, the values of Ga(III) hydrolysis constants used, if any, and the values of previously measured equilibrium constants employed. For more concentrated solutions, it has been shown, for example that soluble hydrolytic species containing a molar ratio of 2OH^- to Ga^{3+} gradually disproportionate to form some precipitate in about 400 hours or more.¹ At lower concentrations the extent of hydrolysis and average molecular weights of

hydrolytic aggregates at intermediate pH values is much smaller, but the rates of their formation would also be diminished. Because of the above mentioned problems the complexation chemistry of gallium(III) has probably received comparatively little attention.

Interest in gallium(III) chemistry has been revived recently because of the anticancer activity of its salts and complexes, and its application to the diagnosis of tumors through selective adsorption of radioactive Ga(III). In order to understand and control its transport *in vivo*, it is necessary to obtain quantitative equilibrium data on gallium complexes of natural and synthetic ligands, so that its conversion to active species in mammalian systems can be predicted.

In a definitive paper recently published, Harris and Martell,² provided a reliable consistent quantitative description of gallium(III) equilibrium interaction with seventeen carboxylate, aminocarboxylate, and other amino ligands. Only three of the ligands studied contained aromatic hydroxyl groups. Harris and Martell critically examined older data and revised previous literature interpretations of the complex chemistry of gallium(III) in the presence of aliphatic (saturated) organic ligands. The present work is aimed at accomplishing the same objectives with hydroxyaromatic (phenolate-type) ligands.

The chelating ligands reported in this paper are chromotropic acid (CTA), 8-hydroxyquinoline-5-sulfonic acid (HQSA), 5-sulfosalicylic acid (SSA), and 3,5-disulfocatechol (Tiron). These were chosen

because of their importance in analytical chemistry, the fact that they form stable complexes with certain trivalent metal ions, and that little is known concerning their interaction with gallium(III).

EXPERIMENTAL

With some minor modification, the experimental procedures are identical to those described by Harris and Martell.² Gallium metal (99.99%) was dissolved in concentrated HNO_3 , evaporated to dryness and redissolved in 0.10 M HNO_3 . The exact gallium(III) concentration was determined with excess standard EDTA followed by back titration with standard Cu^{2+} solution to PAN end-point or back titration with Zn^{2+} to a xylene orange end-point. Solutions were warmed to increase the sharpness of the end-point. Chromotropic acid, 8-hydroxyquinoline-5-sulfonic acid, and Tiron were obtained from Aldrich Chemical

Co., while 5-sulfosalicylic acid was obtained from Fischer Scientific Co.

The solution pH (defined in this paper as $-\log [\text{H}^+]$) was monitored with a Corning Digital model 115 pH meter employing a high alkalinity glass extension electrode and a calomel reference electrode.

RESULTS

Protonation Equilibria

The ligand protonation constants for chromotropic acid (CTA), 8-hydroxyquinoline-5-sulfonic acid (HQSA), 5-sulfosalicylic acid (SSA), and Tiron were obtained from potentiometric equilibrium curves shown in Figures 1, 2, 3, and 4 via a computer

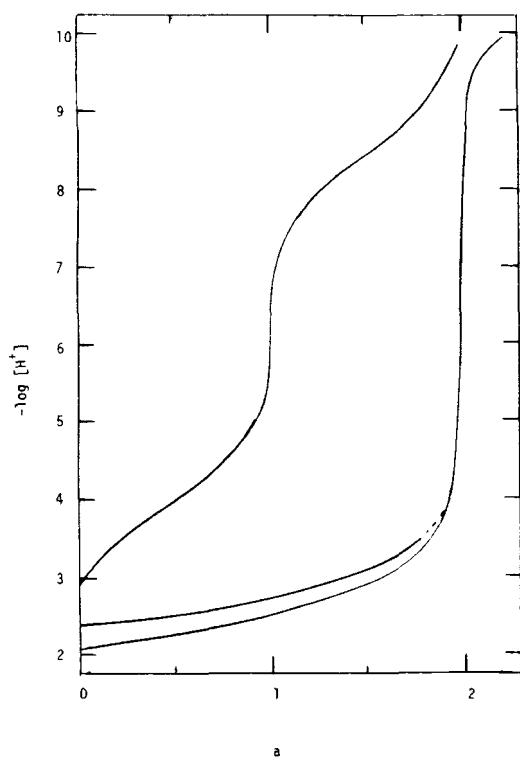


FIGURE 1 Potentiometric equilibrium curves for 8-hydroxy-5-sulfoquinoline H_2L , as a function of a (moles of base per mole of ligand) measured in aqueous solution at 25°C , $\mu = 0.100 \text{ M}$ (KNO_3). Broken line indicates the presence of solid phase. Top curve: $[\text{H}_2\text{L}]_0 = 7.46 \times 10^{-3} \text{ M}$. Middle curve: $[\text{H}_2\text{L}]_0 = [\text{Ga}^{3+}]_0 = 2.40 \times 10^{-3} \text{ M}$. Bottom curve: $[\text{Ga}^{3+}]_0 = 2.20 \times 10^{-3}$, $[\text{H}_2\text{L}]_0 = 6.60 \times 10^{-3} \text{ M}$.

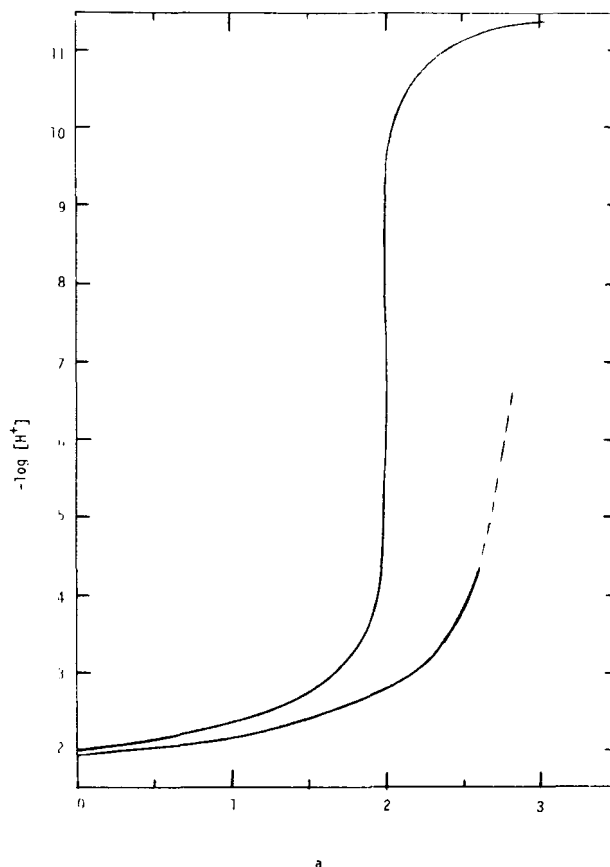


FIGURE 2 Potentiometric equilibrium curves for 5-sulfosalicylic acid H_3L in the absence and presence of metal ion at 25°C , $\mu = 0.100 \text{ M}$ (KNO_3). Broken line indicates presence of precipitate. Top curve: $[\text{H}_3\text{L}]_0 = 7.83 \times 10^{-3} \text{ M}$. Bottom curve: $[\text{Ga}^{3+}]_0 = 2.5 \times 10^{-3} \text{ M}$, $[\text{H}_3\text{L}]_0 = 7.50 \times 10^{-3} \text{ M}$.

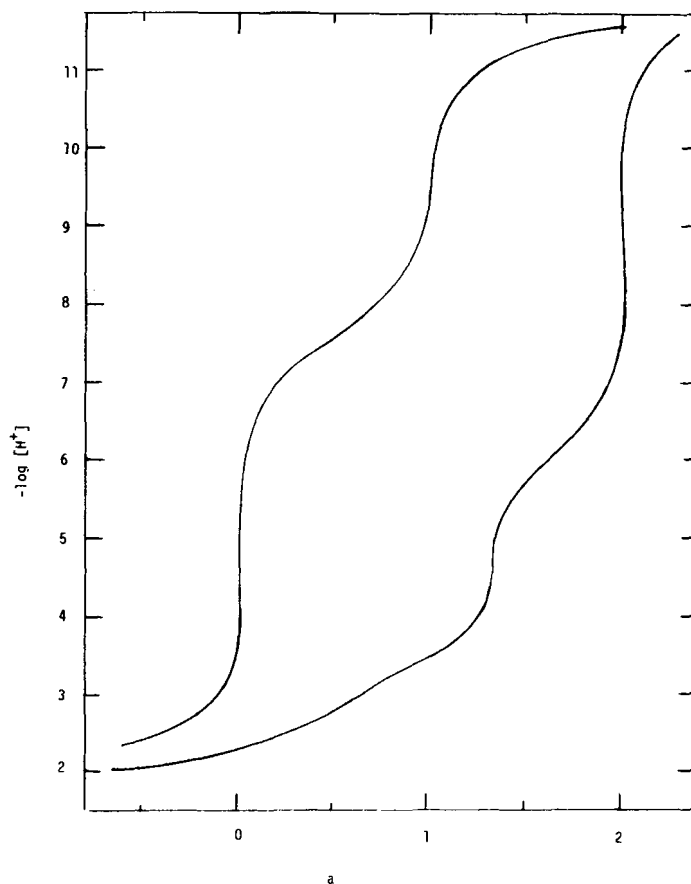


FIGURE 3 Tiron (3,5-disulfocatechol, sodium salt H_2L^{2-}) titration curves at $25.0^\circ C$, $\mu = 0.100 M$ (KNO_3). Top curve: $[Na_2H_2L]_0 = 7.62 \times 10^{-3} M$; Bottom curve: $[Ga^{3+}]_0 = 3.30 \times 10^{-3} M$, $[Na_2H_2L]_0 = 9.90 \times 10^{-3} M$.

refinement technique. The values of these constants are listed in Table I together with those appearing in the open literature, but selected for similarity of test conditions,³ i.e., $\mu = 0.10 M$, $t = 25.0^\circ C$.

For all practical purposes the sulfo groups in these ligands are strong acids. Thus inclusion of these groups in the calculation of $\log K^H$ for the phenolic groups resulted in < 0.001 improvement in calculated pH curves relative to the observed pH profiles. There is only one significant difference in the comparison of the literature values with those of the present work. $\log K_2^H$ for SSA appears to be lower by 0.17 log units. The value of 13.0 of $\log K_1^H$ for CTA is an estimate and no confidence limits can be placed on its magnitude. Because of this uncertainty this protonation constant will not be used in calculating the final value of K_{ML} with gallium for this ligand. Where differences exist, protonation constants determined in this work are believed to describe the LIGAND-PROTON equilibria more accurately than the combined literature values reported previously.³

Gallium(III)-Ligand Equilibrium

Aqueous solutions of the four ligands studied were equilibrated with Ga(III) ion in molar ligand to metal ratios of 3:1, 2:1, and 1:1, and $[H^+]$ was measured as a function of added standard KOH. Selected examples of the resulting potentiometric equilibrium curves illustrating the various similarities and differences in behavior are shown in Figures 1–4.

8-Hydroxyquinoline-5-sulfonic Acid

The presence of an equimolar amount of gallium(III) causes a considerable depression of the HQSA curve resulting in a formation curve for which true equilibrium values are not obtainable beyond $a = 1.8$ ($a =$ moles base added/mole ligand present), because of the formation of a precipitate beyond that point. The 3:1 ligand to gallium curve shown in Figure 1 is continuous and breaks clearly at $a = 2.00$ with no indication of metal ion nor chelate hydrolysis in this

region. Both the potentiometric data shown in Figure 1 and additional equilibrium measurements were analyzed by computer, and were refined by least squares in terms of the equilibrium model given by Eqs. (1), (2), and (3).

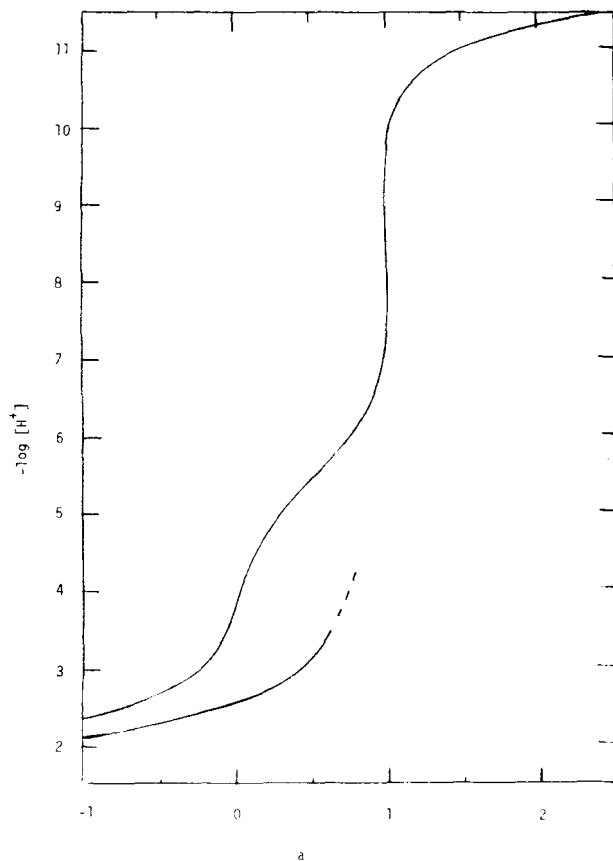
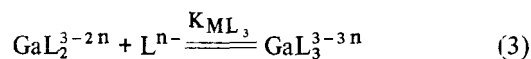
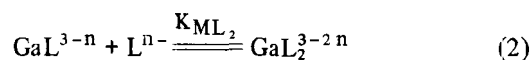
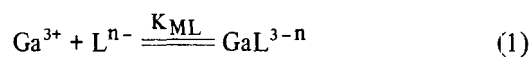


FIGURE 4 Potentiometric equilibrium curves of chromotropic acid, disodium salt, $\text{Na}_2\text{H}_2\text{L}$, alone, and in the presence of gallium(III). Top curve: $[\text{Na}_2\text{H}_2\text{L}]_0 = 4.01 \times 10^{-3}$ M. Bottom curve: $[\text{Ga}^{3+}]_0 = 2.50 \times 10^{-3}$ M, $[\text{Na}_2\text{H}_2\text{L}]_0 = 7.50 \times 10^{-3}$ M; $t = 25.0^\circ\text{C}$; $\mu = 0.100$ M (KNO_3).

TABLE I
Log protonation constants of ligands used in this study. All values listed are for 25.0°C , $\mu = 0.100$ m KNO_3 .^a

Ligand	Log K_1^H	Log K_2^H	Reference
CTA	13.0	5.35 ± 0.01	This work
	—	5.35 ± 0.05	3
HQSA	8.42 ± 0.01	3.95 ± 0.005	This work
	8.42 ± 0.07	3.93 ± 0.05	3
SSA	11.67 ± 0.02	2.32 ± 0.01	This work
	11.72 ± 0.08	2.49 ± 0.02	3
Tiron	12.48 ± 0.05	7.69 ± 0.01	This work
	$12.5 \pm .1$	7.61 ± 0.05	3

^aThe \pm values represent 1σ confidence while no estimate can be placed on 13.0 for CTA.



where H_2L represents HQSA and $n = 2$.

The stepwise formation constants obtained are given in Table II.

5-Sulfosalicylic Acid

The 3:1 SSA to Ga(III) curve shown in Figure 2 has a long formation curve terminating with what would be an inflection point at $a = 2.67$, except that at $\text{pH} \sim 4.4$ hydrolysis of the free Ga(III) ion becomes apparent in the form of incipient precipitation of its hydroxide. The stoichiometry of the protons released from the ligand indicates that at most only a 2:1 ligand to metal complex forms, and this is borne out by the least squares computer fit of the $-\log [\text{H}^+]$ vs. added base curves. The best fit was

TABLE II
Formation constants of gallium(III)-ligand complexes determined at 25.0°C ;
 $\mu = 0.100$ M (KNO_3)

Ligand	Stepwise formation constants		
	Log K_{ML_1}	Log K_{ML_2}	Log K_{ML_3}
8-hydroxyquinoline-5-sulfonic acid	11.97 ± 0.003	11.47 ± 0.03	9.95 ± 0.05
5-sulfosalicylic acid	12.50 ± 0.05	$10.0 \pm .1$	—
3,5-disulfocatechol (Tiron)	19.24 ± 0.01	15.66 ± 0.03	10.70 ± 0.04
1,8-dihydroxynaphthalene-1,6-disulfonic acid	15.62 ± 0.03	$12.5 \pm .1$	—

obtained with the simple model using only Eqs. (1) and (2) where H_3L is sulfosalicylic acid and $n = 3$ indicating that the gallium species formed are GaL and GaL_2^{3-} .

3,5-Disulfocatechol (Tiron)

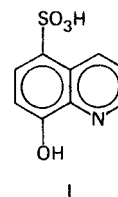
As the pH is increased by the addition of standard alkali to an aqueous solution of Tiron and $Ga(III)$ in a 3:1 molar ratio, three plateaus are observed in the resulting potentiometric equilibrium curve shown in Figure 3. The first region terminates in an inflection at $a = 2/3$, the second at $a = 4/3$ while the third inflection at $a = 2$ is very steep. Thus the shape of the curve indicates that species of the stoichiometry ML , ML_2 , and ML_3 form in succession and that no chelate hydrolysis occurs. Lower ratios of 3,5-disulfocatechol resulted in similar curves, but the solubility product of $Ga(OH)_3$ was exceeded when less ligand was used. The soluble portions of all the potentiometric Tiron curves obtained were analyzed by computer and the three successive formation constants calculated are listed in Table II. These equilibrium constants correspond to Eqs. (1), (2), and (3) where H_4L is 3,5-disulfocatechol and $n = 4$.

1,8-Dihydroxynaphthalene-3,6-disulfonic Acid (Chromotropic Acid, CTA)

As Figure 4 indicates, even a 3:1 ratio of chromotropic acid is not sufficient to keep gallium(III) in solution in competition with hydrolysis. The complexes formed are relatively weak, and the abbreviated formation region in the titration curve can be characterized by equations (1) and (2), where $H_4L = 1,8$ -dihydroxynaphthalene-3,6-disulfonic acid and $n = 4$. The calculated values of the two formation constants are listed in Table II.

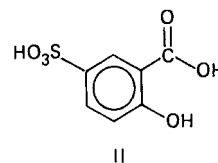
DISCUSSION

The protonation constants and especially the behavior of gallium(III) toward the ligands can best be discussed in terms of structures of the ligands. 8-hydroxyquinoline, I, possesses a neutral aromatic nitrogen donor as well as a phenolic-type hydroxyl group which combine with metal ions to form five membered ring chelates. The electropositive sulfur atom exerts an inductive effect reducing the basicity of both hetero donor groups by about one order of magnitude each compared to the parent ligand, 8-hydroxyquinoline. The strongly acid sulfo group is



also excellent solvating group rendering complexes of the corresponding ligands soluble in water. Hence ligands containing such groups are well suited for the study of aqueous complexes under a variety of solution conditions. Since the deprotonated ligand (HQSA) is dinegatively charged, it is unlikely that an insoluble chelate may be formed, yet since the sulfo group is located *para* to the hydroxy donor, successive degrees of complexation would at most provide a buildup of only a trinegative charge in the immediate coordination sphere around the gallium-(III) ion. This latter point is reflected in the essentially statistical diminution of the successive formation constants, with log values of 12.0, 11.5 and 10.0. The slightly larger separation between the second and third constants may be due to greater steric effects in the 3:1 chelate compound, relative to those in the 1:1 and 2:1 complexes.

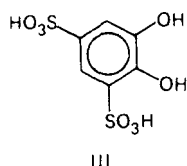
The ligand 5-sulfosalicylic acid, II, has an advantage over the unsulfonated parent compound in its extremely high solubility in water. In metal chelate



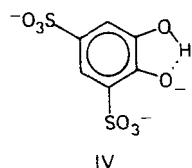
structures, the chelate rings formed are 6-membered with each donor atom providing a negative charge for a total two negative charges per coordinated ligand. The additional negative charge provided by the sulfo group is too peripheral to affect the coordination strength, but it does effectively reduce the basicities of the donor groups, especially the hydroxyl group, compared to the unsulfonated parent compound, salicylic acid. The first formation constant is $10^{12.5}$ which compares well with the first formation constant for 8-hydroxyquinoline indicating large electrostatic as well as group specific contributions. However, the second constant drops to $10^{10.0}$, while the third one could not even be measured. In this case the second formation constant involves the combination of an essentially neutral complex (GaL) with a trinegative ligand to form a trinegative complex. Since further

complexation would require enough energy to overcome the mutual repulsion between two trinegatively charged particles, it is not surprising that the 3:1 complex does not form under the experimental conditions employed.

The ligand commonly known as Tiron, III, is expected to react with Ga(III) because of the *o*-dihydroxybenzene donor groups present. The concerted inductive force of the two sulfo substituents

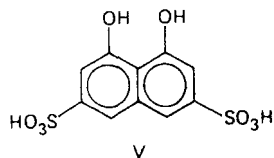


depresses the lower protonation constant by two orders of magnitude (relative to catechol). The magnitude of the first protonation constant is lowered to a considerably lesser extent, probably because of the high affinity of the tetranegative ligand for the proton, which is probably hydrogen bonded between the two phenolate donor groups, as indicated in IV.



The values of the successive formation constants of the Ga(III) complexes listed in Table II are 19.2, 15.7 and 10.7. The decrease in stability that occurs with each step reflects the unfavorable negative charge build-up, around the Ga(III) ion; however the binding of the catecholate donor groups to the metal ion is very high, as indicated by the fact that even the third stepwise formation constant has a value nearly as great as the first formation constant of the two ligands described above.

Chromotropic acid, V, resembles Tiron somewhat with respect to coordination and charge distribution



of donor groups, but its phenolate groups are spaced farther apart, so that only six-membered chelate rings can form with metal ions. The basicity of the

monoprotonated ligand relative to the corresponding 1,8-dihydroxynaphthalene species is lowered by an order of magnitude, down to 5.35 log units. The protonation constant of the tetranegative ligand is probably not lowered extensively since it is very high, with a log K of 13.0 log units. The logarithm of a second protonation constant of 1,8-dihydroxynaphthalene is 6.36, while the first is too high to measure. Since the phenolate donor groups must be oriented differently so that the Ga(III) ion cannot be coordinated as effectively as in the case of Tiron, its first metal formation constant is only $10^{15.6}$, much lower than that reported for Tiron ($10^{19.2}$). The second formation constant is lower than that of the unsulfonated parent ligand by about the same magnitude as described above for Tiron. The lower differences between the first two formation constants in the case of CTA is attributable to the greater volume of negative charge distribution compared to that of the monocyclic Tiron ligand.

Since there has been some previous work on the coordination of gallium(III) by various bidentate phenolate-containing ligand a comparison of the present results with previous reports is in order.

There was an attempt a decade ago by Athavale *et al.*⁴ to determine the stability constants of the chelates formed by Ga(III) and three of the ligands studied in this research. In the case of Tiron, the value reported for K_{ML} was an order of magnitude too low. The stability constant of the 3:1 complex was not calculated. For chromotropic acid, their values for $\log \beta_{ML_2}$ and $\log K_{ML}$ differed by one and two orders of magnitude, respectively, from the values reported here. Sulfosalicylic acid equilibrium was also measured but $\log K_{ML}$ was only estimated while $\log \beta_2$ was listed as 10.15.

Although Richard *et al.*⁵ did not include Ga(III) in their study with 8-hydroxyquinoline-5-sulfonic acid, their values for the analogous Fe(III) chelates are 11.6 and 11.2, which seem reasonable when compared to the stability constants of the corresponding Ga(III) constants listed above.

Guseva and Kumok⁶ reported only the first formation constant for the reaction between Tiron and Ga(III), in good agreement with the present results. However, no higher complexes are reported by these authors.

An appreciation of the high affinities of hydroxy-automatic donor groups for Ga(III) may be obtained through a comparison of Ga(III) chelates of EDTA and NTA with those of ligands in which one or more acetate groups are replaced by *o*-hydroxybenzyl moieties. The log stability constants for the Ga(III)-NTA chelate is 16.20² while the log forma-

TABLE III
Comparison of log formation constants of Ga(III), Fe(III) and Al(III) with hydroxyaromatic ligands

Ligand	Constant	Log formation constants		
		Ga ³⁺	Fe ³⁺	Al ³⁺
8-hydroxyquinoline-5-sulfonic acid	K ₁	11.97	11.6 ^a	N.A.
	K ₂	11.47	11.2 ^a	
	K ₃	9.95		
5-sulfosalicylic acid	K ₁	12.50	14.6 ^b	12.3 ^c
	K ₂	10.0	10.55 ^b	7.7 ^c
	K ₃		5.85 ^b	5.8 ^c
3,5-disulfocatechol	K ₁	19.24	20.4 ^c	16.7 ^c
	K ₂	15.66	15.1 ^c	13.6 ^c
	K ₃	10.70	10.5 ^c	9.7 ^c
Chromotropic acid	K ₁	15.62	23.1	17.2 ^e
	K ₂	12.5	13.76 ^d	13.2 ^e

^aRef. 5; ^bRef. 7; ^cRef. 3; ^dRef. 8; ^eRef. 9.

tion constant for Ga-*o*-hydroxybenzyliminodiacetic acid is 21.55². This difference represents a 33% increase in stabilization energy of the Ga(III) chelate. Perhaps even more dramatic is a similar comparison resulting from the replacing of two acetate groups of EDTA by *o*-hydroxybenzyl groups. In this case an increase of 82% in free energy of formation of the Ga(III) chelate is obtained (log K_{GaEDTA} = 21.7; log K_{GaHBED} = 39.57).²

Trivalent ions closely resembling Ga(III) in properties are those of Fe(III) and Al(III). In Table III a comparison of the stability constants listed for the Fe(III) and Ga(III) complexes provides additional confidence concerning the validity of the values reported. The similarities of the 8-hydroxyquinoline-5-sulfonic acid values and those of Tiron for Fe(III) and Ga(III) in both absolute and relative magnitude indicate that the literature value for log K_{FeL}, where L is 5-sulfosalicylic acid, may be a bit high. The two formation constants of the iron(III) chelates of chromotropic acid listed in Table III are about eight orders of magnitude farther apart than one would estimate on the basis of the magnitudes of the analogous Ga(III) chelates. It is therefore suggested that one of these formation constants is incorrect. Although there are not enough values for Al(III)

stability constants to make meaningful comparisons, it appears that the Al(III) chelates are generally considerably less stable than those of Fe(III) and Ga(III).

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