Solid and Solution State NMR Spectra and the Structure of the Gallium Citrate Complex $(NH_4)_3[Ga(C_6H_5O_7)_2]\cdot 4H_2O$

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A gallium citrate complex $(NH_4)_3[Ga(C_6H_5O_7)_2]\cdot 4H_2O$ (**1**) has been isolated from an aqueous mixture of gallium nitrate and citric acid at pH = 9. In the solid state **1** is monomeric and includes the near centrosymmetric ion $[Ga(C_6H_5O_7)_2]^{3-}$ in the asymmetric unit, with each tridentate citrate coordinating to gallium through an alkoxide oxygen, an oxygen of the central carboxyl group and an oxygen of a terminal carboxyl group. The second terminal carboxyl group is not bound to the metal centre. The two alkoxide oxygen–gallium distances in the asymmetric unit are significantly shorter than the four carboxyl oxygen–gallium distances, indicating a stronger bond for the former. The number and intensities of the resolved resonances in the solid state ^{13}C MAS/NMR spectrum are consistent with the X-ray structure. In aqueous solution near neutral pH (5.5 to 6.4) the complex partially dissociates to give an equilibrium of the 1:1 and 1:2 gallium/citrate species together with free citrate. Two sets of resonances are observed in both the ^1H and ^{13}C NMR spectra of solutions of the complex and these correspond to bound and free citrate; there is no resolution of resonances for the 1:1 and 1:2 species. The relative strength of the alkoxide oxygen–gallium bond in the metal-bound citrate ligand leads to a slow intermolecular chemical exchange situation (rate < ca. 12 s^{-1}) between the bound and free ligand. The carboxylate oxygen–gallium bonds are quite labile and relatively rapid intramolecular chemical exchange occurs (rate > ca. 700 s^{-1}) between the metal-bound and pendant terminal carboxyl groups, averaging their ^1H and ^{13}C NMR signals. The diffusion coefficients for the free and complexed citrate measured from the ^1H NMR spectra do not appear to be complicated by chemical exchange effects and, as expected, the diffusion coefficient for the complexed ligand is smaller than for the free ligand. In solution in the intermediate pH range (4.8 to 6.4) a new ^{71}Ga signal is observed at ca. δ = 27 ($\Delta\nu_{1/2} \approx 10.6$ kHz) which is assigned to the gallium citrate complexed species.

Introduction

Citrate is a an important endogenous ligand which occurs in blood plasma[1] (ca. 10^{-4} mM) and ca. 0.3% w/w in teeth and bone.[2,3] Metal−citrate complexes are involved or implicated in a wide range of physiological functions; for example, ferrous citrate in the activation of catalytic activity of the enzyme aconitase (citrate isocitrate hydrolyase),[4] zinc citrate in the genetic disorder of zinc metabolism *acrodermatitis enteropathica*,[5,6] and aluminium citrate in neurotoxic conditions.[7] Bismuth−citrate complexes have been used[8,9] in the treatment of peptic ulcers; our interest focuses on gallium citrate complexes. Edwards and Hayes[10] reported that ^{67}Ga citrate accumulates in soft tissue tumours and, subsequently, hot gallium citrate has found wide use in a range of imaging systems for tumour localisation and in identifying inflammatory lesions.[11] In addition, Hart et al.[12] reported the use of cold gallium nitrate for the treatment of solid tumours and, more recently, Jonkhoff et al.[13] studied the therapeutic use of gallium citrate on leukaemic patients. Despite the widespread use of gallium citrate very little structural information is available. Banta et al.[14] reported the X-ray structural analysis of the trimethyl (and triethyl) ester complexes bis[(trimethylcitrato)dimethylgallium(III)] and we recently published the X-ray structure of the gallium(III) citrate complex $(NH_4)_3[Ga(C_6H_5O_7)_2]\cdot 4H_2O$ (**1**).[15] Here we present further discussion on the structure, together with a detailed NMR spectroscopic analysis of the structure both in the solid state and in solution around physiological pH.

Our preliminary report[15] showed that the complex anion is comprised of two tridentate citrate ligands giving rise to approximately octahedral coordination around the gallium. Citrate may act as both a chelating and a bridging ligand, and many X-ray structures have shown the metal complexes to be oligomeric with either the carboxyl groups or the hydroxy oxygens bridging more than one metal centre. However, monomeric 2:1 (citrate/metal) structures have been reported for the complex anions in ammonium bis(citrato)cuprate(II),[16] ammonium bis(citrato)zinc(II),[17] pyridinium bis(citrato)chromium(III),[18] and ammonium bis(monomethylcitrato)germanate(IV).[19] Citrate chelation in relation to enzymatic function has been the subject of an earlier review.[3]

Glickson et al.[20] measured the ^{71}Ga and ^1H NMR spectra of solutions of gallium nitrate with citric acid. They concluded that 1:1 citrate/metal complexes were formed in

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strongly acidic media, whereas in near neutral solutions the stoichiometry of the complexation was more difficult to determine, although polymeric species were indicated. In a subsequent study of the aqueous gallium nitrate/citric acid system, Chang et al.[21] used both ^{1}H and ^{13}C NMR spectroscopy to show the existence of both 1:1 and 2:1 citrate/gallium complexes (Ga_nCit_n and Ga_nCit_{2n}), and for approximately neutral solutions concluded that n is a small integer. Apparent conditional (pH = 5.80) stability constants for the stepwise complexation were estimated as $K_1 = 48 \pm 1$ M^{-1} and $K_2 = 13 \pm 1$ M^{-1}.

Results and Discussion

The X-ray structure determination of (**1**) has been described in a preliminary communication.[15] As shown in Figure 1, two citrate ligands complex with each gallium to yield an approximately centrosymmetric molecule and the asymmetric unit is one molecule. The molecule is achiral with (*R*)-configuration at C3 and (*S*)-configuration at C9.

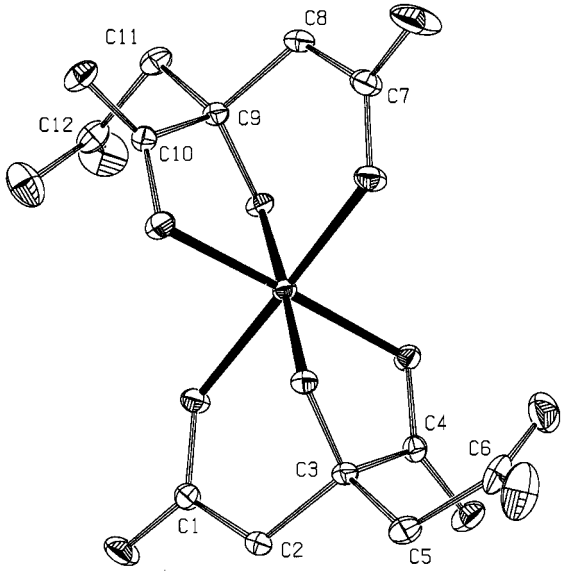

Figure 1. The structure of $[Ga^{III}(citrate)_2]^{3-}$

The high frequency region of the solid state 75.5 MHz ^{13}C magic angle spinning (MAS) NMR spectrum is shown in Figure 2 and summarised in Table 1. There are five well-resolved resonances at δ = 173.9, 179.4, 180.7, 185.6 and 189.9 due to the carboxyl groups, with the resonance at δ = 179.4 being approximately double the intensity of the other four. In addition there are two broader signals to lower frequency at δ = 76.0 due to the nonprotonated carbons C3,9, and at δ ≈ 48 due to the methylene carbons C2,5,8,11. The high frequency region is consistent with the X-ray structure, there being six inequivalent carboxyl groups with the shifts of two being accidentally the same at δ = 179.4. As described below we assign the two highest frequency signals

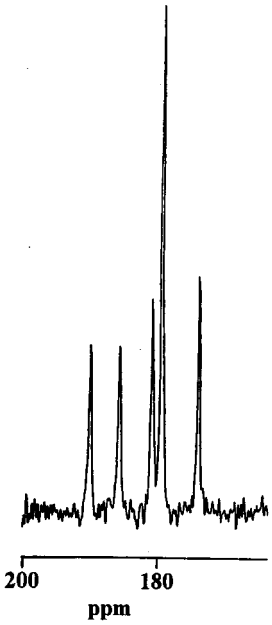

Figure 2. The high frequency region (carbonyl signals) of the 75.5 MHz ^{13}C solid state MAS NMR spectrum of $[Ga^{III}(citrate)_2]^{3-}$

Table 1. ^{13}C Chemical shifts for (**1**) in the solid and in solution

	Solid[a]	Solution[b] pH = 6.4	Solution[b] pH = 1.75
C1,6,7,12	173.9, 179.4,[c] 180.7	179.5	175.5
C4,10	185.6, 189.9	186.5	180.6
C3,9	76.0	74.6	74.7
C2,5,8,10	48	46.5	43.1

[a] Measured at 75.5 MHz. – [b] Measured at 100.6 MHz. – [c] This resonance has double intensity.

(δ = 185.6 and 189.9) to the central carboxyl carbons C4 and C10.

The solution state 122.0 MHz ^{71}Ga spectra of the gallium citrate complex, measured as a function of pH, are shown in Figure 3. The isotope ^{71}Ga has 39.6% natural abundance and the nucleus is quadrupolar with spin $I = {}^3/_2$, and as such it is to be expected that the NMR spectra are dominated by broad signals. The spectrum of the most acidic solution (pH = 1.75) is dominated by a relatively sharp signal at δ ≈ 0 with $\Delta\nu_{1/2}$ < ca. 500 Hz with evidence of a weaker broader ($\Delta\nu_{1/2} \approx$ 12 to 15 kHz) signal to slightly higher frequency (δ ≈ 30 to 40). Similarly, the spectrum of the most basic solution (pH = 9.4) has a sharper signal at δ = 222 with a suggestion of a very weak broad signal at δ ≈ 0. The spectra measured at intermediate pH values showed just a single broad signal: pH = 4.8, at δ ≈ 29 with $\Delta\nu_{1/2} \approx$ 7.7 kHz; pH = 5.5, at δ ≈ 30 with $\Delta\nu_{1/2} \approx$ 11.4 kHz; pH = 6.4, at δ ≈ 27 with $\Delta\nu_{1/2} \approx$ 10.6 kHz.

The ^{1}H and ^{13}C NMR spectra (400 and 100.6 MHz, respectively) show features in common with certain of the ^{1}H spectra reported by Glickson et al.[20] and the ^{13}C spectra reported by Chang et al.,[21] with the expected better resolution here resulting from the use of higher field spectro-

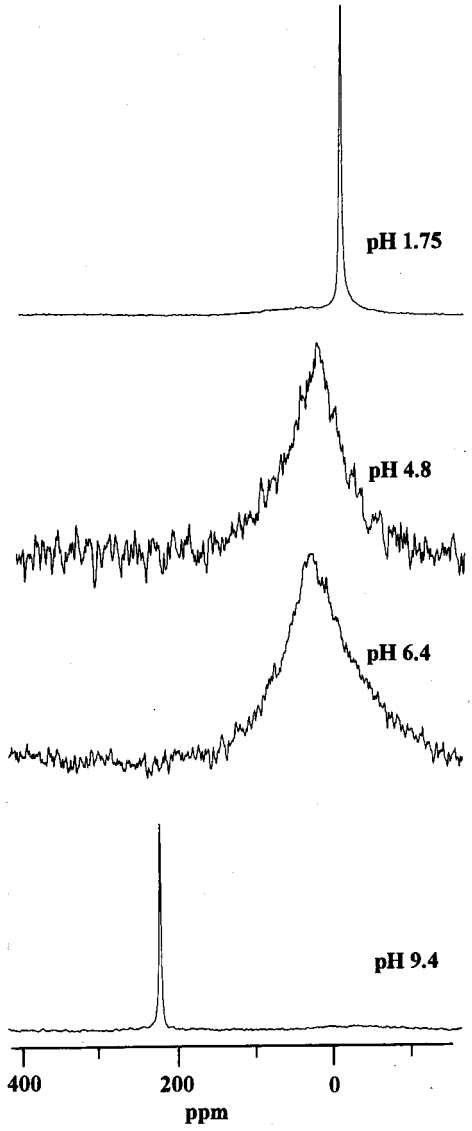

Figure 3. The 122.0 MHz solution state ^{71}Ga spectra of $[Ga^{III}(citrate)_2]^{3-}$ as a function of pH

meters. The ^{13}C spectrum of the complex at pH = 1.75 (Table 1) shows two sets of citrate resonances in an approximate ratio 45:55; the slightly weaker group signals occurring at δ = 43.1 ($-CH_2-$), 74.7 (>C<), 175.5 (terminal $-CH_2CO_2$), and 180.6 (central CO_2) are assigned to citrate in a Ga−citrate complex, whereas the slightly stronger signals at δ = 43.6, 73.7, 173.9 and 177.2 are assigned to free citrate. The assignment between free and complexed citrate for these two groups of signals is confirmed by the ^{13}C shift difference between the two carbonyl signals (3.3 ppm) from a solution of citric acid alone, measured at pH = 1.95. The ^1H spectrum at pH = 1.75 comprises two equally intense multiplets centred at δ = 2.91 and 2.76 due to overlapping signals from the free and complexed citrate methylene protons. At pH = 4.8 the ^{13}C resonances assigned to the complex are more intense than those due to free citrate (in the approximate ratio 65:35), whereas in the range pH = 5.5 to 6.4 the ratio is nearer 80:20. In basic solution at pH = 9.4 only one set of signals is observed due to free citrate. In the intermediate pH range (4.8 to 6.4) the appearance of the ^1H spectra are entirely consistent with the ^{13}C spectra, with two resolved *AB* type splitting patterns (e.g. at pH = 6.4, $\delta_A = 2.58$, $\delta_B = 2.44$, $J_{AB} = 16.9$ Hz for the complex, $\delta_A = 2.54$, $\delta_B = 2.41$, $J_{AB} = 15.2$ Hz for free citrate). The assignment of these *AB* signals between complexed and free citrate is confirmed by the values for J_{AB} across the pH range — Glickson et al.[20] reported J_{AB} values for free citrate in the range 16.2 to 15.4 Hz between pH = 0.75 and 8.71, and for gallium citrate in the range 16.7 (pH = 0.70) to 17.5 Hz (pH = 7.76). In the intermediate pH range many minor signals appeared in both the ^1H and ^{13}C spectra which are probably due to various oligomeric complex species.[20,21] These minor signals were not apparent in either ^1H or ^{13}C spectra measured at extremes of pH (1.75 and 9.4).

The ^{13}C shifts for the complex at pH = 6.4 (Table 1) were δ = 186.5, 179.5, 74.6 and 46.5, with the highest frequency signal due to the central carboxyl carbons C4,10 and the signal at δ = 179.5 due to the carboxyl carbons C1,6,7,12. The average shift for the two highest frequency ^{13}C signals in the solid state (vide supra) is δ = 187.8 and the average for the other carboxyl signals in the solid state is δ = 178.4. These two averages of solid state data compare favourably with the solution state shifts for the carboxyl signals and provide the assignment for the solid state signals.

The diffusion coefficients were measured for 30 mM and 10 mM samples by the ^1H NMR method (see Experimental section). As shown by Stejskal and Tanner,[22] the signal intensities vary according to Equation (1):

$$I_i = I_{0i} \exp(-K^2 \cdot D \cdot \Delta) \quad (1)$$

where $K = \gamma \cdot G_i \cdot \delta$ with γ the nuclear spin gyromagnetic ratio, and G_i and δ are the strength and duration of the field gradient, D is the diffusion coefficient for the molecular species and Δ is the diffusion period. The signal intensities I_i are measured as a function of the gradient strength G_i, and I_{0i} is the signal intensity in the absence of any field gradient. All plots of $\ln(I_i)/K^2$ were linear and the values for the diffusion coefficients obtained are given in Table 2. Deviation from linearity in these plots would have indicated the importance of chemical exchange between the various citrate species, occurring at an intermediate rate on the time-scale of the diffusion period (300 ms). For such complex behaviour a double-exponential dependence of I_i upon K^2 would be expected.[23]

Solid State Structure

Subsequent to our original interpretation[15] of the X-ray crystal structure, we have examined the possibility of alternative distributions of water and ammonium species in the structure refinement.[24] Bearing in mind the relative X-ray scattering of these species with that of the total crystal structure an unambiguous assignment is difficult. A mar-

Table 2. Diffusion coefficients, measured from ^{1}H spectra at 600 MHz, for free and complexed citrate in solutions of (**1**)

Sample[a]	30 mM	10 mM
Free citrate	5.64×10^{-10} m^2 s^{-1}	5.73×10^{-10} m^2 s^{-1}
Complexed citrate	4.34×10^{-10} m^2 s^{-1}	4.24×10^{-10} m^2 s^{-1}

[a] Samples at pH ca. 5.9

ginal improvement in *R* factors is seen with the two half-occupancy water sites changed to ammonium ions. This would suggest a molecular formula of $(NH_4)_4[Ga(C_6H_5O_7)(C_6H_4O_7)]\cdot 3H_2O$, wherein only one of the pendant carboxyl groups is protonated. However, this does not change the coordination geometry at gallium. For what it is worth the elemental analysis (see Experimental Section) supports our original interpretation of three ammonium ions and four water molecules in the molecular formula. An important feature of the previously reported[15] structure are the Ga−O distances. The Ga−O(2) and Ga−O(5) distances are 1.900 and 1.890 Å, and are notably shorter than the Ga−carboxyl oxygen distances which are in the range 1.976−2.054 Å. This feature must reflect the stronger bonding between the gallium and the alkoxide oxygens [O(2) and O(5)] than between gallium and the carboxyl oxygens. The crystal structures of other monomeric 2:1 citrate/metal complexes show the opposite situation, namely the metal−carboxyl bonds are shorter for the bis(citrato)-cuprate(II)[16] and bis(citrato)zinc(II)[17] anions, whereas for the bis(citrato)chromium(III)[18] anion the Cr−O bond lengths are all quite similar. In all three of these latter complexes the integrity of the hydroxyl group is maintained, i.e. it is not deprotonated. On the other hand, in the structure[19] of the bis(citrato)germanate(IV) anion the citrates do coordinate through alkoxide oxygens and the Ge−O(alkoxide) distance is 1.813 Å, with the Ge−O(carboxyl) distances at 1.908 and 1.930 Å. The shortening of the metal−alkoxide oxygen distance relative to the metal−carboxyl oxygen is maintained in other (polymeric) structures where the alkoxide is ligating a single metal, e.g. the complex anions[25] $[Bi_2(citrate)_2]$.

Glusker[3] has reported that the carbon backbone of the citrate ligand (the five carbon fragment including the two terminal carboxyl carbons) typically adopts one of two conformations in metal complexes. These are an extended conformation wherein the two torsion angles about the carbon−carbon bonds are both about 180°, or a folded conformation for which one of the angles is about 180° and the other is about 60°. The two distinct citrate ligands for **1** are both described by extended conformations with the torsion angles[26] for the first ligand C1−C2−C3−C5 and C2−C3−C5−C6 both equal to 176.6°, and for the second ligand C12−C11−C9−C8 equal to 165.2° and C11−C9−C8−C7 equal to −179.5°.

Solution State Structure

The earlier solution-state studies[20,21] used samples prepared by the equilibration of solutions of gallium nitrate and citric acid, in contrast to the samples used here which were prepared by direct dissolution of the crystalline gallium citrate complex **1**. However, it is clear that the main features of the solution structure are similar.

Glickson et al.[20] reported 27.5 MHz ^{71}Ga spectra of gallium nitrate in the presence of citrate in acidic solution. They concluded that the gallium citrate complex partially dissociates in acid medium to give $Ga(D_2O)_6^{3+}$, together with some undissociated complex; however, they did not obtain direct evidence for the presence of the gallium complex since they suggested that the signal due to the complex was broadened beyond detection by quadrupolar relaxation. In highly alkaline aqueous solution a signal due to $Ga(OD)_4^-$ was observed and it was concluded that little of the complex persisted. As indicated below, our analysis of the ^{1}H and ^{13}C NMR spectroscopic data indicate that the gallium citrate complex is the dominant species for a 100 mM solution at about neutral pH, and so our new ^{71}Ga data show the signal due to the complex to occur around $\delta = 27$ with a value for $\Delta\nu_{1/2} \approx 10$ to 12 kHz.

All solution state NMR spectroscopic data on the complex, both from this study and earlier work[20,21] show that in solution the terminal $-CH_2CO_2$ groups in the gallium complex are equivalent. The X-ray structure of the 1:2 complex indicates that in solution there should be at the very least two distinct environments for the $-CH_2CO_2$ groups — two of the groups are bound through oxygen to the gallium, and the other two are not directly bound. However, there are only single ^{13}C signals for the CH_2 and CO_2 groups and only one *AB*-type pattern in the ^{1}H spectrum for the complex. These observations are consistent with rapid intramolecular exchange between the two environments. While we cannot directly quantify the rate of this process, the full spread in ^{13}C shifts from the solid state for the CH_2CO_2 groups is 6.8 ppm (= 680 Hz), and therefore this exchange must occur with a rate greater than ca. 700 s^{-1}. This process cannot be intermolecular since in the intermediate pH range separate ^{13}C and ^{1}H signals are observed for both free and complexed citrate, and so any intermolecular exchange must be relatively very slow — the chemical shift separation for the *B* protons in the two environments is 0.03 ppm (at pH = 6.4), which is 12 Hz, and the rate of intermolecular exchange must be considerably slower than 12 s^{-1}. In solution we cannot specify unequivocally the nature of the gallium citrate complex as a 1:2 or as a 1:1 species. The ^{1}H and ^{13}C shifts for the citrate ligands in the two situations are likely to be very similar and could either be superimposed or coalesced by the intermolecular exchange which, although slow for the free ⇄ complexed citrate process, could be fast with respect to the 1:2 ⇄ 1:1 complexes with the smaller chemical shift difference.

Very slow intermolecular exchange results from the citrate ligands being anchored to the metal by the alkoxide oxygens [O(2) and O(5) in the structure]. The lengths of these metal−oxygen bonds are 1.90 and 1.89 Å, and are significantly shorter than the other four carboxyl oxygen−metal bonds (2.05, 1.98, 2.02 and 1.98 Å); these shorter bonds should also be the least labile.

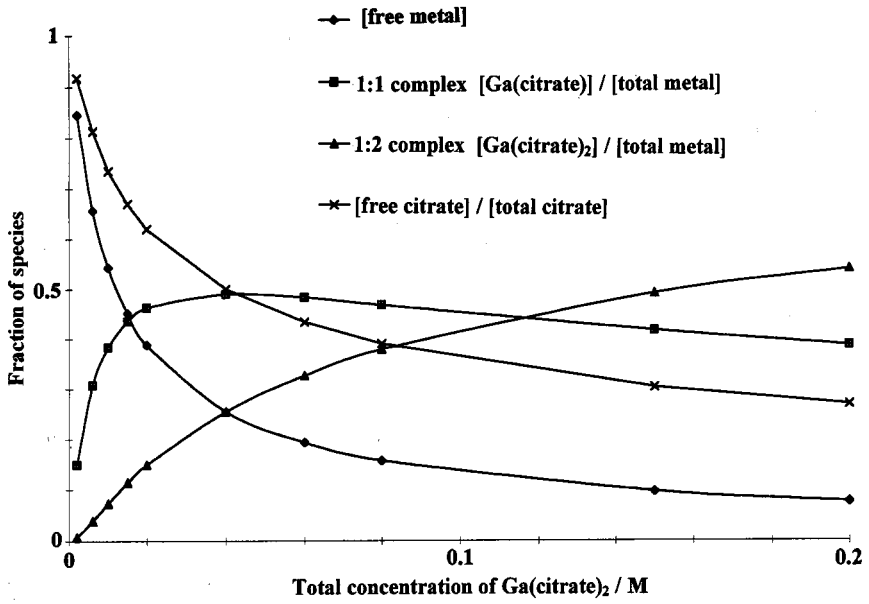

Figure 4. The relative proportions of the species present in a solution of $[Ga^{III}(citrate)_2]^{3-}$, calculated using the stability constants K_1 = 48 ± 1 M^{-1} and K_2 = 13 ± 1 M^{-1}

As indicated above, in the pH range 5.5 to 6.4 the ratio of complexed to free citrate is ca. 4:1, although we are unable to distinguish between complexed citrate in the 1:2 or 1:1 species. Chang et al.[21] were able to estimate conditional stability constants for the stepwise binding of citrate to gallium as K_1 = 48 ± 1 M^{-1} and K_2 = 13 ± 1 M^{-1} at pD = 5.40 (pH = 5.80). With these values we calculate the proportions of the various gallium species present at equilibrium as shown in Figure 4. For a total gallium concentration of 100 mM, as $Ga(citrate)_2$, the proportions of gallium present as the 1:2 complex and the 1:1 complex are 0.41 and 0.45 respectively. This distribution gives a total complexed-to-free citrate ratio as 1.8:1 which is similar to the ratio of 4:1 indicated by the ^{13}C and ^1H NMR spectroscopic data. To further substantiate this suggestion, the 600 MHz ^1H spectrum of a more dilute sample (ca. 30 mM

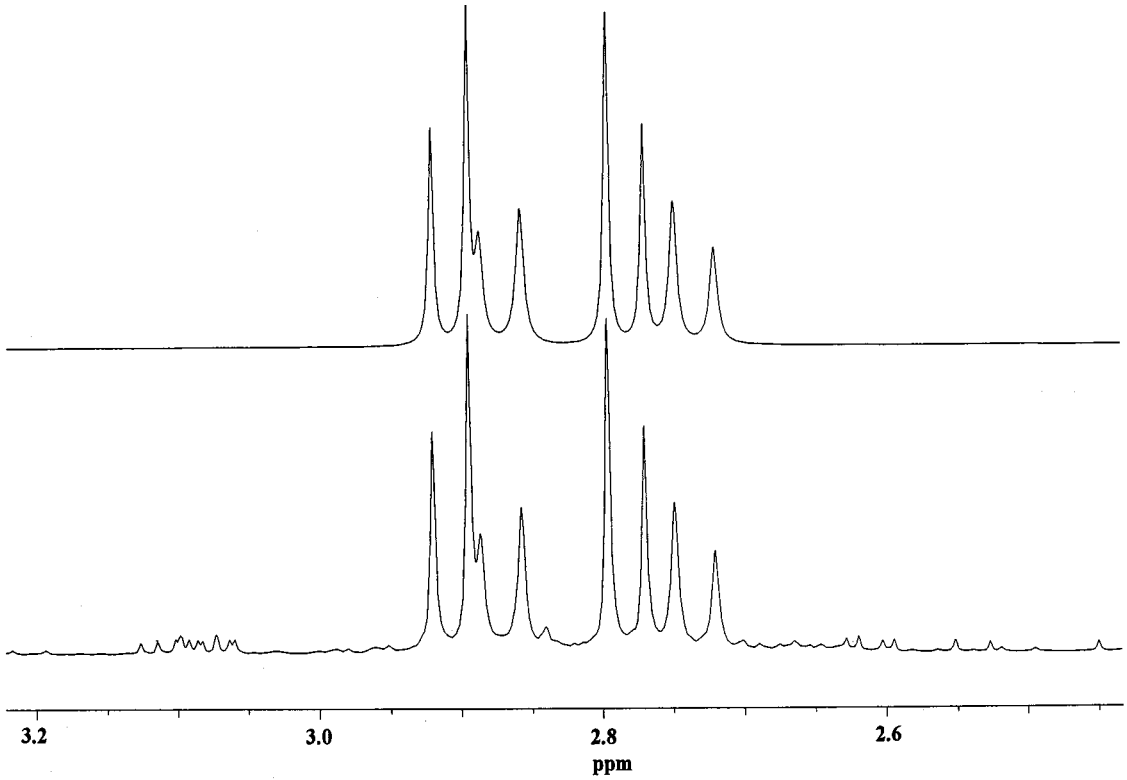

Figure 5. Experimental (lower) and simulated (upper) 600 MHz ^1H NMR spectra of the methylene region of 30 mM $[Ga^{III}(citrate)_2]^{3-}$ at pH 5.9

at pH 5.9) of Ga(citrate)$_2$ was measured (Figure 5) and integration gave a ratio for complexed to free citrate as 1.6:1. Inspection of Figure 5 gives the calculated complexed-to-free citrate ratio 0.8:1 at a total concentration of 30 mM. A third sample of ca. 10 mM gave an experimental ratio for complexed to free citrate as 0.5:1 compared with a calculated ratio (Figure 4) of 0.4:1. In principal our experimental data should allow the calculation of new values for the binding constants K_1 and K_2; however, since our samples were unbuffered solutions, and the concentrations used were approximate, such a calculation was not performed. It is sufficient to note that the complexed-to-free citrate ratios determined here experimentally are in reasonable agreement with those predicted from the conditional stability constant data of Chang et al.[21] in the same pH region.

The calculation for the spectrum shown in Figure 5 employed pure Lorentzian lineshapes and the average linewidth for the four lines of the *AB* pattern due to the complexed citrate was 0.5 greater than the average linewidth for the lines of the free citrate. This observation is fully consistent with the above argument that the ^{1}H NMR signals due to the complexed citrate are a composite of signals from both 1:2 and 1:1 complexes. In the lower field spectra (400 MHz) there was no direct evidence that the signals were due to a superposition of both 1:2 and 1:1 complexes, but at the higher field this additional broadening of the lines could be due to partial resolution of shifts from the two species, or to the higher field pushing the spectrum more towards the coalescence region for intermolecular exchange between the two species.

The diffusion coefficients measured (Table 2) for free citrate average to 5.7×10^{-10} m^2 s^{-1} over the two solutions (10 and 30 mM) and this is to be compared with the value 4.8×10^{-10} m^2 s^{-1} measured[27] for free citrate in human plasma, and 10.2×10^{-10} m^2 s^{-1} measured[28] for free citrate in a ranitidine bismuth citrate solution. It is reasonable that the plasma value should be somewhat lower since plasma is more viscous and contains a multitude of additional endogenous solutes. However, the origin of the larger discrepancy between the value for free citrate found here and that found by Parkinson et al.[28] is not obvious. The pH of the samples may be an important factor and further discussion should await the results of more detailed studies on the effect of the medium on the self diffusion coefficient of citric acid. The average value for the diffusion coefficient of the complexed citrate (Table 2) is 4.3×10^{-10} m^2 s^{-1} and again it is reasonable that this is lower than the free citrate value simply because of the increased molecular weight of the species. These values for the complexed citrate represent a composite of the values for the 1:1 and 1:2 gallium/citrate species which have different relative proportions in the two solutions (10 and 30 mM, vide supra), however the difference in the values for the complexed citrate between the two solutions is not significant (ca. 2%) and should not be interpreted further. The difference in the diffusion coefficients (free − complexed) although not great, is significant; that for the complexed citrate is ca. 25% smaller than that for the free ligand and this similarity helps to reinforce the conclusion that these major complexed species are not oligomeric. Therefore the earlier suggestion by Chang et al.[21] that the major complexed species are Ga_nCit_n and Ga_nCit_{2n} where n is a small integer can be refined to set $n = 1$.

Conclusion

The solid state structure of $(NH_4)_3[Ga(C_6H_5O_7)_2]\cdot 4H_2O$ (**1**) is monomeric and includes the near centrosymmetric ion $[Ga(C_6H_5O_7)_2]^{3-}$ in the asymmetric unit, with each tridentate citrate coordinating to gallium through the alkoxide oxygen, an oxygen of the central carboxyl group and an oxygen of a terminal carboxyl group. The second terminal carboxyl group is protonated and not bound to the metal centre. The two alkoxide oxygen−gallium distances in the asymmetric unit are significantly shorter than the four carboxyl oxygen−gallium distances, indicating a stronger bond for the former case. The number and intensities of resolved resonances in the solid state ^{13}C MAS/NMR spectrum are entirely consistent with the X-ray structure.

The pH-dependent ^{71}Ga NMR spectra of the complex in aqueous solution show a dominant peak due to $Ga(D_2O)_6^{3+}$ at pH = 1.75, and at pH = 9.4 a peak due to $Ga(OD)_4^-$, in agreement with the earlier work of Glickson et al.[20] In the intermediate pH range a new ^{71}Ga signal is observed at $\delta \approx 27$ ($\Delta\nu_{1/2} \approx 10.6$ kHz) which is assigned to the gallium citrate complexed species.

In aqueous solution nearer neutral pH (5.5 to 6.4) the complex partially dissociates to give an equilibrium of the 1:1 and 1:2 gallium/citrate species together with free citrate. For the solution species two sets of resonances are observed in both the ^{1}H and ^{13}C NMR spectra and these correspond to bound and free citrate, with no resolution of resonances for the 1:1 and 1:2 species. The relative strength of the alkoxide oxygen−gallium bond in the metal-bound citrate ligand leads to a slow chemical exchange situation between the metal-bound and free ligand. The carboxylate oxygen−gallium bonds are quite labile and relatively rapid chemical exchange results between the bound and pendant terminal carboxyl groups, thereby averaging their ^{1}H and ^{13}C NMR signals. The diffusion coefficients measured from the ^{1}H NMR spectra do not appear to be complicated by chemical exchange effects and, as expected, that for the complexed ligand is smaller than for the free ligand.

Experimental Section

The preparation of **1** has been previously reported.[15] Typical yields were in the range 60−70%. $C_{12}H_{30}GaN_3O_{18}$: calcd. C 25.11, H 5.27, N 7.32; found C 24.56, H 6.55, N 7.56; {$C_{12}H_{31}GaN_4O_{17}$, i.e. $(NH_4)_4[Ga(C_6H_5O_7)(C_6H_4O_7)]\cdot 3H_2O$: calcd. C 25.15, H 5.45, N 9.78}.

The solid state ^{13}C CP/MAS NMR spectrum was measured at 75.5 MHz using a Bruker MSL-300 spectrometer equipped with a standard Bruker MAS probe with double-bearing rotation mechanism. The sample was studied as a microcrystalline powder in a 4 mm o.d. zirconia rotor at an MAS frequency ca. 8.5 kHz. The spec-

trum was recorded at ambient probe temperature, and the chemical shifts are referenced to external liquid tetramethylsilane. The samples for solution state NMR were prepared by dissolution of the crystalline complex in D_2O at approximate concentrations of 100 mM, 30 mM and 10 mM, and the pH was adjusted by addition of NaOH or HCl solution. pD was measured using a Corning model 7 meter and pH is determined as pD (measured) + 0.40. ^{13}C, ^{71}Ga and ^{1}H solution state NMR spectra were measured at 100.6, 122.0 and 400 MHz, respectively, using a Bruker DRX-400 spectrometer, and additional ^{1}H spectra were obtained with a Bruker AMX-600. Chemical shifts are reported on the high frequency positive scale relative to external TSP (trimethylsilylpropionic acid) (^{1}H and ^{13}C) and a 1.0 M $Ga(NO_3)_3$ solution for ^{71}Ga spectra. The measurements of the diffusion coefficients used the AMX-600 instrument which is equipped with a Bruker B-AFPA30 gradient unit capable of providing gradients up to 2 T m^{-1} along the magnetic field direction (z axis). The diffusion data were acquired using a version of the LED delay pulse sequence[29] with the inclusion of the WATERGATE solvent peak suppression scheme[30] to eliminate the resonance of the water. A series of spectra were measured for values of the gradient strength in the range 1−30% maximum in random order using bipolar sine-shaped gradients (1 ms), a diffusion period of 300 ms and a gradient recovery time of 2 ms. The gradient strength was calibrated in a separate experiment on a water sample assuming a value[31] for the diffusion coefficient of water as 2.37×10^{-9} m^2 s^{-1}. Peak areas were measured by iterative simulation of the spectra using the Bruker WIN-1D and WIN-FIT programs, assuming pure Lorentzian lineshapes, and the intensities for each of the four lines of the *AB* patterns for the free and for the complexed citrate were summed for each value of the gradient strength used.

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