Thermodynamic and kinetic studies of the aqueous complexation of gallium(III) and 5-fluoro-8-hydroxyquinoline by ^{19}F NMR spectroscopy

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Measurement of the ^{19}F NMR signal areas of the appropriate molar ratio of gallium(III) and 5-fluoro-8-hydroxyquinoline (fox) in aqueous solution as a function of pH (NaClO$_4$, $\mu = 0.1$ M) at 25 °C, gave, through predominant species diagrams, the thermodynamic constants of the Ga(fox), Ga(fox)$_2$ and Ga(fox)$_3$ species (log $\beta_{110} = 12.6$, log $\beta_{120} = 24.0_5$, log $\beta_{130} = 34.3$). Only the *mer* stereoisomer of Ga(fox)$_3$ is formed. ^{19}F–^{19}F EXSY measurements on the same type of solutions gave indications on the kinetics of the same equilibria. Comparison of these thermodynamic and kinetic results with literature data for gallium(III) and iron(III) and non-fluorinated 8-hydroxyquinoline is made.

**Etudes thermodynamiques et cinétiques de la complexation dans l'eau du gallium(III) et de la 5-fluoro-8-hydroxyquinoléine par RMN du fluor-19.** L'analyse des aires des signaux de résonance en RMN du fluor, de différents mélanges aqueux de Ga^{III} et de la 5-fluoro-8-hydroxyquinoléine (fox) en fonction du pH (NaClO$_4$, $\mu = 0.1$ M) à 25 °C, permet d'accéder, grâce aux diagrammes de prédominance des espèces, aux constantes de complexation de Ga(fox), Ga(fox)$_2$ et Ga(fox)$_3$ (log $\beta_{110} = 12.6$; log $\beta_{120} = 24.0_5$; log $\beta_{130} = 34.3$). En solution aqueuse, seul l'isomère *mer* est présent. Des expériences 2D de type ^{19}F–^{19}F EXSY sur ces mélanges fournissent des informations d'ordre cinétique. Enfin, des comparaisons entre ces valeurs obtenues et celles données dans la littérature pour les complexes du Ga^{III} et du Fe^{III} avec la 8-hydroxyquinoléine (analogue non fluoré de la fox) sont abordées.

In our recent thermodynamic and kinetic studies of a new tripodal iron chelator O-Trensox, based on 8-hydroxyquinoline, we obtained interesting data from ^{1}H NMR spectra of aqueous solutions of Ga^{III} with this chelator.[1] As no such detailed measurements were done on the corresponding bidentate ligands (the subunit 8-hydroxyquinoline) we studied, using NMR spectroscopy, the coordination chemistry in solution of diamagnetic cations such as Ga^{III} with such bidentate ligands. This cation is used as a diamagnetic analogue of Fe^{III} since they are structurally quite similar: ionic radii are 0.645 Å for Fe^{III}, 0.620 Å for Ga^{III}.[2] Moreover, their thermodynamic hydrolysis constants[3] and their rate constants for exchange of a water molecule from the first coordination shell[4] are close to each other.

In the literature, the complexes of trivalent metal ions of Group 13, namely gallium(III), indium(III) and aluminium(III), have aroused increasing interest in many ways. ^{67}Ga, ^{68}Ga, ^{111}In and ^{113}In can be employed as radioisotopes in standard imaging techniques for the diagnosis and location of tumors and for the imaging of cancerous tissue.[5–7] The presence of Al^{III} may be associated with neurological disorders.[8]

Usually, the stability constants are obtained using spectrophotometric or potentiometric methods. In this paper we illustrate how to use the fluorine atom of a ligand as a probe in order to study, by fluorine NMR spectroscopy, the complexation between a ligand and a diamagnetic cation. Only a few ^{19}F NMR studies of complexes containing fluorine atoms have been described and concern the exchange of ligands around a cation.[9]

In this study, 5-fluoro-8-hydroxyquinoline (fox)[10] was chosen because the parent 8-hydroxyquinoline (oxine or ox) has been used in radiopharmaceutically active complexes of ^{68}Ga and ^{111}In.[11–13] A complete set of equilibrium constants for 8-hydroxyquinoline-5-sulfonic acid (sox) and Fe^{III} was described only recently.[14]
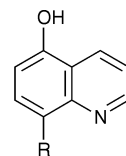
ox (R = H); fox (R = F); sox (R = SO$_3^-$)

The aim of this paper is to measure the three stability constants of the Ga^{III} chelates of fox by ^{19}F NMR, and to show how this technique can contribute in a complexation study. In addition, the stability constants of Ga—fox, Fe—fox and Fe—sox are obtained using the classical spectrophotometric method in order to compare the effect of the fluorine atom on the equilibria of both the Fe and Ga complexes.

Experimental

Materials

5-Fluoro-8-hydroxyquinoline (fox) and 8-hydroxyquinoline-5-

sulfonic acid (sox) were obtained from Fluorochem Limited and Aldrich, respectively, and used without further purification. Gallium nitrate [Ga(NO$_3$)$_3$·9H$_2$O] and iron perchlorate were obtained from Aldrich.

Protonation equilibria were obtained using ligand concentrations equal to 1×10^{-4} M for the spectrophotometric method and 3×10^{-3} M for the NMR technique. Stock solutions of various complexes were prepared by mixing the ligand and the metal salt solutions in the required molar ratio to obtain a ligand concentration $C_L = 3 \times 10^{-3}$ M (i.e. for similar measurement conditions in all ^{19}F NMR spectra) and metal concentrations C_M from 3×10^{-2} to 3×10^{-4} M. All solutions were prepared using distilled deionized water mixed with 20% D$_2$O to provide a deuterium lock. Ionic strength was adjusted to 0.1 M with an adequate amount of NaClO$_4$. Adjustments of the pH were made by adding either 1 M NaOH or 10% HCl. The pH values are measured with a digital Orion 700 pH meter equipped with a 4 mm diameter Ingold microelectrode.

NMR spectroscopy

All the ^{19}F spectra were acquired on a Varian U400 pulsed Fourier transform instrument using 5 mm NMR tubes. Typical conditions were as follows: spectral width 5000 Hz, number of scans 50, relaxation delay 5 s, 32K data points (SI). All the chemical shifts in ppm are relative to an external C$_6$F$_6$ reference in CDCl$_3$ (− 163 ppm relative to CFCl$_3$).

The 2D EXSY spectra were collected by using 1024 data points in t_2 over the desired bandwith (to include all peaks) with 1024 blocks and 4 scans per block. Prior to Fourier transformation and symmetrization, the 2D matrix in each dimension was multiplied with a sine bell squared window function and zero-filled to obtain a 2048 × 2048 ($t_1 \times t_2$) word square matrix. Acquisition and processing parameters were varied to obtain the best resolution and signal-to-noise ratio. Experiments were performed with mixing time delays of 200 and 500 ms.

UV-visible spectroscopy

Variable pH–UV spectra (400–200 nm) of the ligands and the metal complex were recorded on a Pekin–Elmer Lambda-2 spectrophotometer. The concentrations of the ligands in the UV studies were 2.5×10^{-4} and 5×10^{-4} M for complexation with Fe^{III} and Ga^{III}, respectively. Ga and Fe salts were used in tenfold excess.

Results and Discussion

Protonation equilibria

The two protonation constants of fox (abbreviated as LH) were determined by fluorine NMR from the titration curve of δ (fluorine) vs. pH using the same conditions as used in the
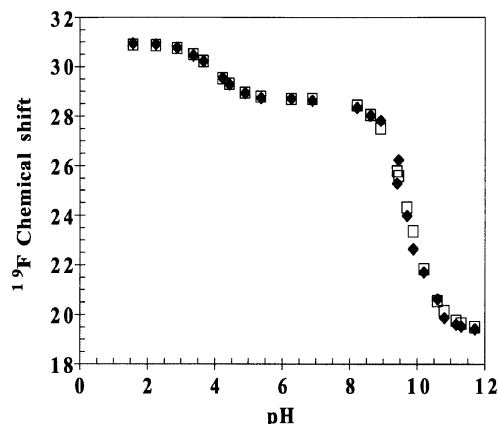

Fig. 1 Dependence of the ^{19}F NMR spectrum of fox (LH$_2^+$ at low pH) on the addition of 1 M NaOH: (◆) measured and (□) calculated chemical shift versus C$_6$F$_6$

complexation study. The data shown in Fig. 1 reveal two important chemical shift jumps (Δδ = 2.3 and 9.3 ppm) as a function of pH. The K_{ai} values were obtained from the observed fluorine chemical shift δ and the following relations:

$$\delta = \delta_{L^-} + [H^+](\delta_{LH} - \delta)/K_{a1}$$

and

$$\delta = \delta_{LH_2^+} + K_{a2}(\delta_{LH} - \delta)/[H^+] \quad (1)$$

where K_{a2} and K_{a1} are the ionization constants of the LH$_2^+$ and LH species; $\delta_{LH_2^+}$, δ_{LH} and δ_{L^-} are the fluorine chemical shifts of the LH$_2^+$, LH and L$^-$ species, respectively, and δ is the observed fluorine chemical shift of the weighted mean of the previous species in fast exchange. The pK_a were measured in two media: in pure D$_2$O and H$_2$O–D$_2$O (8 : 2, v : v). In D$_2$O, the pD was obtained from the measured pH meter readings by adding 0.40 units.[15a] For the dissociation constants in D$_2$O and H$_2$O, the relationship pK_D = 1.018 pK_H + 0.43 was used.[15b] These corrections agree with the recently published IUPAC recommendations.[15c]

The protonation constants were also obtained in H$_2$O using the classical spectrophotometric method.

Values of the constants are listed in Table 1; pK_{a2} and pK_{a1} refer to the pyridinium and OH groups, respectively. The pK_a values obtained with the two methods are in good agreement. The presence of a small amount of D$_2$O does not modify the values.

The deprotonation constant pK_{a2} for fox [3.93 by UV or 3.98 by ^{19}F NMR (Table 1)] is quite close of that for sox [4.18,[11a] 3.95,[3] 4.06[14a] and 3.72 (Table 1)]. On the other hand, the K_{a1} value for fox [9.56 by UV or 9.67 by ^{19}F NMR (Table 1)] is one logarithm unit larger with respect to sox [8.19,[13a]

Table 1 Protonation constants (25 °C, μ = 0.1 M) from ^{19}F NMR and UV-visible spectroscopy of fox and sox with their molecular parameters

Method	Solvent	Ligand	pK_{a2}	pK_{a1}	LH$_2^+$	LH	L$^-$
NMR	D$_2$O	fox	3.93	9.65	30.87[a]	28.53[a]	19.51[a]
NMR	H$_2$O–D$_2$O (8 : 2, v : v)	fox	3.98	9.67	30.93[a]	28.69[a]	19.41[a]
		fox	3.93	9.56	1498[b] (370 nm)	2172[b] (310 nm)	1492[b] (370 nm)
UV/VIS	H$_2$O						
		sox	3.72	8.47	2454[b] (354 nm)	4609[b] (292 nm)	5200[b] (354 nm)

[a] Fluorine chemical shifts in ppm from C$_6$F$_6$ as a reference. [b] Specific absorbance (in M^{-1} cm^{-1}) at the indicated wavelength.
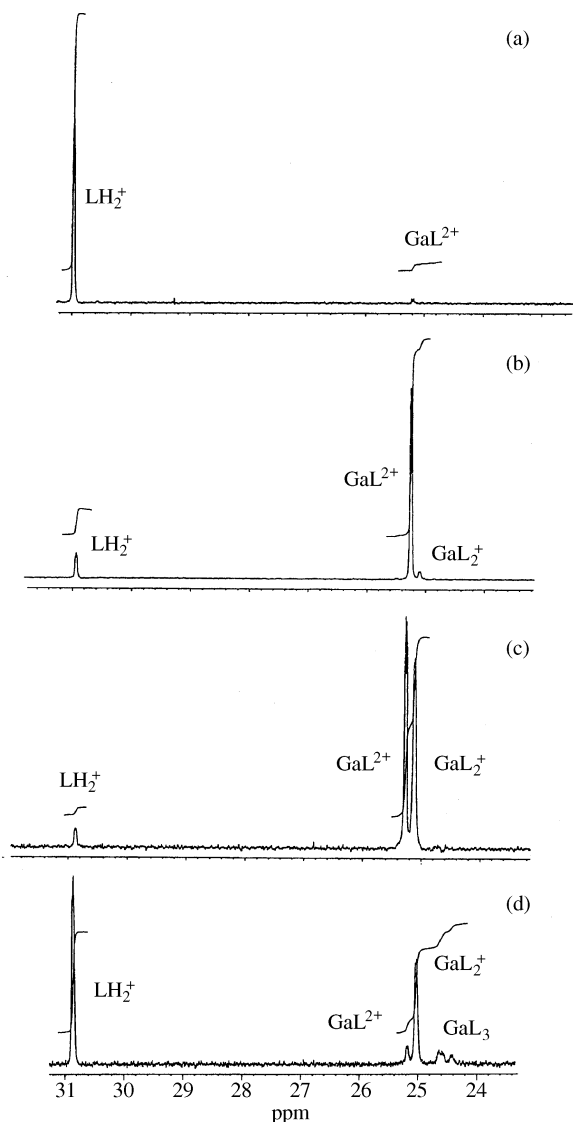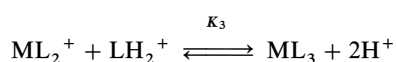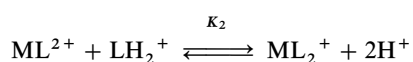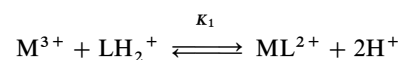
$$K_1 = \frac{[\text{ML}^{2+}][\text{H}^+]^2}{[\text{M}^{3+}][\text{LH}_2^+]}, \quad K_2 = \frac{[\text{ML}_2^+][\text{H}^+]^2}{[\text{ML}^{2+}][\text{LH}_2^+]},$$

$$K_3 = \frac{[\text{ML}_3][\text{H}^+]^2}{[\text{ML}_2^+][\text{LH}_2^+]}$$

and the global constant β_{mlh} of the equilibrium as:

$$m\text{M} + l\text{L} + h\text{H} \overset{\beta_{mlh}}{\rightleftharpoons} \text{M}_m\text{L}_l\text{H}_h$$

where

$$\beta_{mlh} = \frac{[\text{M}_m\text{L}_l\text{H}_h]}{[\text{M}]^m[\text{L}]^l[\text{H}]^h}$$

The complexation of fox with Ga$^{\text{III}}$ was studied using solutions of Ga(NO$_3$)$_3\cdot$9H$_2$O and ligand in H$_2$O–D$_2$O (8 : 2 medium), with various C_M/C_L molar ratios: 10, 3, 1 and 0.3. An initial ligand concentration of $C_\text{L} = 3 \times 10^{-3}$ M was used for pHs ranging from 1 to 3. At higher pH precipitation of the GaL$_3$ species occurs.

The four species have different fluorine chemical shifts: 30.84, 25.25 and 25.11 ppm for LH$_2^+$, GaL^{2+} and GaL$_2^+$, respectively, while three signals were observed for GaL$_3$ at 24.78, 24.73 and 24.57 ppm. Signal separation allows the measurement of the different proportions. Their assignment was made according to the order of appearance with increasing values of pH. Selected spectra for different pHs and C_M/C_L molar ratios are shown in Fig. 2: with a C_M/C_L molar ratio of 10, GaL^{2+} exists in a large excess; with a molar ratio from 3 to 1, both GaL^{2+} and GaL$_2^+$ are observed; the GaL$_3$ species appears only with an excess of ligand ($C_\text{M}/C_\text{L} = 0.3$) and for pH > 2. Each fluorine signal appears as a pair of doublets ($^3J_{\text{FH}} = 8.8$ Hz, $^3J_{\text{FH}} = 4.4$ Hz). For GaL$_3$ one observes three resonances of equal intensity. The arrangement of three asymmetric bidentate ligands around a metal center M(AB)$_3$ may be either facial (fac or OC6-22 in the Chemical Abstracts Service Notation[17]) or meridional (mer or OC6-21).[18] In the facial isomer, where there is a three fold symmetry axis, the three ligands are equivalent, but in the meridional isomer, where there is no element of symmetry, they are all different. So the three resonances observed are solely due to the asymmetric mer isomer in solution.[19]

Evolution of the proportions of the different species vs. pH is obtained directly from the measurement of the areas of the fluorine signals $I_{\text{LH}_2^+}$, $I_{\text{ML}^{2+}}$, $I_{\text{ML}_2^+}$ and I_{ML_3}. Concentrations and percentages are related to these integrals I according to:

$$r_{\text{LH}_2^+} = I_{\text{LH}_2^+}/\textstyle\sum I_\text{L}, \quad r_{\text{ML}^{2+}} = I_{\text{ML}^{2+}}/\textstyle\sum I_\text{L},$$

$$r_{\text{ML}_2^+} = (I_{\text{ML}_2^+}/2)/\textstyle\sum I_\text{L}$$

and

$$r_{\text{ML}_3} = (I_{\text{ML}_3}/3)/\textstyle\sum I_\text{L}$$

with

$$\textstyle\sum I_\text{L} = I_{\text{LH}_2^+} + I_{\text{ML}^{2+}} + I_{\text{ML}_2^+}/2 + I_{\text{ML}_3}/3$$

where r_X is the molar ratio of the species X, and we obtain the concentrations of all the predominant species according to:

$$[\text{LH}_2^+] = r_{\text{LH}_2^+} C_\text{L} \quad [\text{ML}^{2+}] = r_{\text{ML}^{2+}} C_\text{L} \quad [\text{ML}_2^+] = r_{\text{ML}_2^+} C_\text{L}$$

and

$$[\text{ML}_3] = r_{\text{ML}_3} C_\text{L}$$

The complex Ga(OH)$^{2+}$ was included in the refinement using the hydrolysis constant K_h at $\mu = 0.1$ M (log $K_\text{h} = -3.05$[8]); i.e., without correction for the hydrolysis $[\text{M}] = C_\text{M} - [\text{ML}^{2+}] - [\text{ML}_2^+] - [\text{ML}_3]$, and after such a correction, $[\text{M}] = (C_\text{M} - [\text{ML}^{2+}] - [\text{ML}_2^+] - [\text{ML}_3])(1 + K_\text{h}[\text{H}^+]^{-1})^{-1}$.

Distribution curves for the Ga–fox system for different C_M/C_L ratios are given in Fig. 3. The expression of the constant K_1 for the first equilibrium can be written as:

Fig. 2 ^{19}F NMR spectra of Ga–fox species measured in H$_2$O–D$_2$O (80 : 20 medium, NaClO$_4$, $\mu = 0.1$ M) for various pH and C_M/C_L ratios: (a) pH = 1.20 and $C_\text{M}/C_\text{L} = 0.3$; (b) pH = 1.81 and $C_\text{M}/C_\text{L} = 10$; (c) pH = 2.71 and $C_\text{M}/C_\text{L} = 1$; (d) pH = 2.63 and $C_\text{M}/C_\text{L} = 0.3$

8.42,[4] 8.97[16] and 8.47 (Table 1)]. This shows a large electron-withdrawing effect of the sulfonate group as a substituent vs. the effect of the fluorine atom on the phenolic group and a negligible effect on the pyridine nitrogen atom.

Stability constants of gallium(III) complexes with fox using fluorine NMR

M^{3+} cations form three complexes, ML^{2+}, ML$_2^+$ and ML$_3$, with fox as a bidentate ligand (LH$_2^+$) according to the following equilibria:
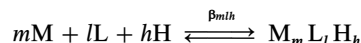
$$\text{M}^{3+} + \text{LH}_2^+ \overset{K_1}{\rightleftharpoons} \text{ML}^{2+} + 2\text{H}^+$$

$$\text{ML}^{2+} + \text{LH}_2^+ \overset{K_2}{\rightleftharpoons} \text{ML}_2^+ + 2\text{H}^+$$

$$\text{ML}_2^+ + \text{LH}_2^+ \overset{K_3}{\rightleftharpoons} \text{ML}_3 + 2\text{H}^+$$

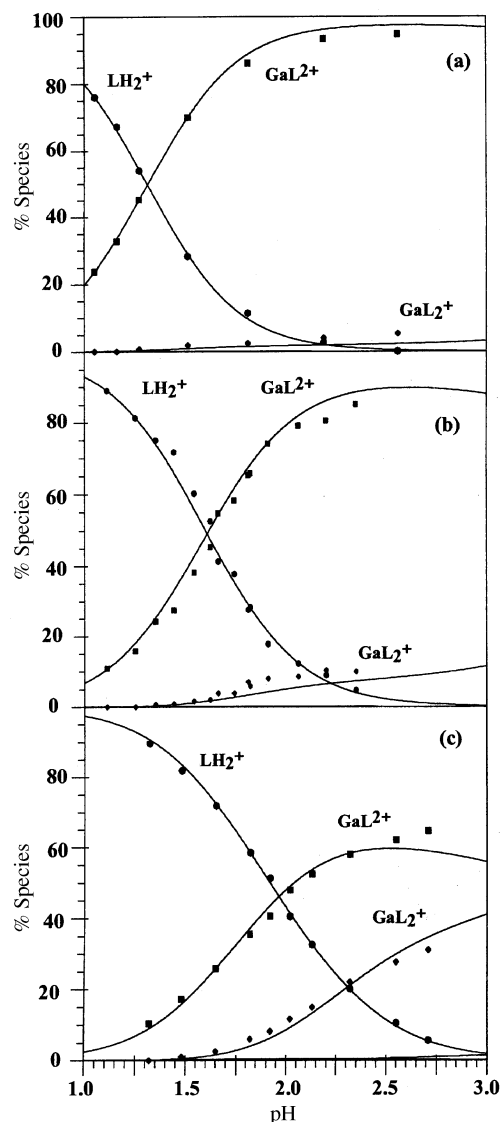The equilibrium constants K_1, K_2 and K_3 are defined as:

Fig. 3 Species distribution diagrams as a function of pH for Ga—fox species at various C_M/C_L ratios equal to (a) 10; (b) 3; (c) 1

$$\log \frac{[ML^{2+}]}{[LH_2^+][M]} = 2pH + \log K_1 \qquad (2)$$

For treatment of the data, concentrations lower than 10% of the initial concentration were not used in the correlation. Relation (2) was plotted *vs.* pH for the three C_M/C_L molar ratios 10, 3 and 1 as shown in Fig. 4 and gave a slope of 1.98 and $K_1 = 0.084$ M (log $K_1 = -1.08$). One can note that the experimental data obtained for the three molar ratios are all aligned and that the slope is very close to 2. This also indicates that two H^+ are released when GaL^{2+} is formed.
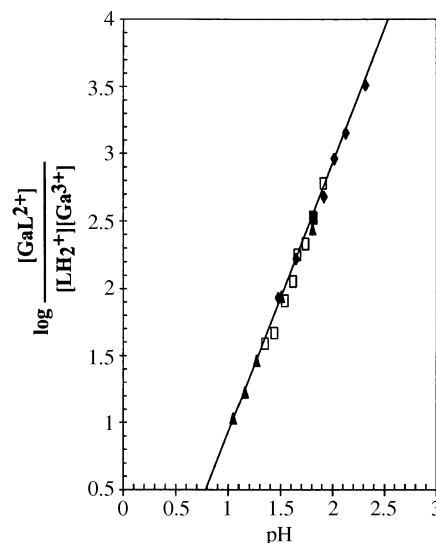

Fig. 4 Log $[GaL^{2+}]/[LH_2^+][Ga^{3+}]$ as a function of pH for various C_M/C_L ratios equal to: (▲) 10; (□) 3; (◆) 1. The straight line corresponds to a slope of 2

Determination of K_2 ($K_2 = 0.0069$ M) is less precise, since the concentrations of GaL^{2+} are often lower than 10%. Instead, K_2 was obtained from a comparison of experimental and calculated species distribution plots by adjustment of all the constants. K_3 ($K_3 = 4.17 \times 10^{-4}$ M) can be evaluated from measurements at 0.3 equivalent. Slow precipitation of GaL_3 under these experimental conditions limits the range of the experimental data. So, values of log β_{mlh} for the complexes between Ga^{3+} and fox, obtained by the NMR method, are 12.6, 24.0$_5$ and 34.3 for β_{110}, β_{120} and β_{130}, respectively [log $\beta_{110} = \log K_1 + pK_{a2} + pK_{a1}$; log $\beta_{120} = \log K_1 K_2 + 2(pK_{a2} + pK_{a1})$; log $\beta_{130} = \log K_1 K_2 K_3 + 3(pK_{a2} + pK_{a1})$].

Comparison of the Ga^{III}—fox stability constants with other measurements and with literature data

Spectrophotometric measurements of the formation of Ga—fox were carried out in aqueous solution (ionic strength $\mu = 0.1$ M with $NaClO_4$, $T = 25\,°C$) with the metal ion in excess with respect to the ligand ($C_M/C_L = 10$) for pH 1–3. The absorbances were measured at 376 nm and the treatment of the data takes into account that GaL and LH_2 absorb at nearly the same wavelength, since GaL species have no metal–ligand charge transfer absorbance. The equilibrium constant of formation of Ga—fox (72 mM) is in agreement with the value obtained by ^{19}F NMR spectroscopy in this study (84 mM).

Data from the literature are shown on Table 2 for K_i and β_{1i0} (with $i = 1, 2, 3$) of ox, fox and sox with Fe^{III} and Ga^{III}. The general tendency is that K_1 increases slightly from ox to fox and from fox to sox, likely in relation with the more accessible pyridinic nitrogen coordinating atom (*cf.* pK_{a1} of ox, fox

Table 2 Values of the pK_{a_i} and the equilibrium constants, K_i/mM and log β_{1i0}, of complexes formed between Fe^{3+} or Ga^{3+} and ox, fox or sox from this work (denoted by a) and literature data

LH	Cation	Ref.	pK_{a2}	pK_{a1}	K_1	β_{110}	K_2	β_{120}	K_3	β_{130}	μ/M	Method
ox	Fe^{III}	20	9.67	5.08	21	13.1					0.1	UV
ox	Fe^{III}	21	9.71	5.00	93	13.7	8	26.3	0.08	36.9	0.1	potent.
fox	Fe^{III}	20	9.49	4.05	107	12.6					0.1	UV
fox	Ga^{III}	a	9.67	3.98	84	12.6	6.9	24.1	0.42	34.3	0.1	^{19}F NMR
fox	Ga^{III}	a	9.56	3.93	72	12.3$_5$					0.1	UV
sox	Fe^{III}	14a	8.19	4.18	500	12.1	63	23.2$_5$	1.1	32.6$_5$	1	UV
sox	Fe^{III}	22	8.35	3.84	260	11.6	102	22.8	—	—	0.1	potent.
sox	Fe^{III}	20	8.45	3.82	180	11.5	40	22.4	1.7	31.9	0.1	potent.
sox	Ga^{III}	14a	8.19	4.18	400	12.0	125	23.4$_5$	3.8	33.4	0.1	potent.

and sox are 5.1, 3.95 and 3.8, respectively). When comparison is possible, K_1 is slightly smaller for Ga^{III} than for Fe^{III}. Some discrepancies, especially for sox, can be related with the taking into account of hydroxo complexes in the treatment.[14a] The same tendency is observed for K_2 and K_3 in the ligand series and when comparing Fe^{III} and Ga^{III}.
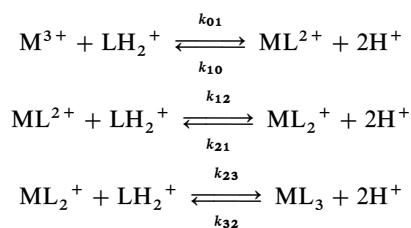
Study of ligand exchange by EXSY NMR

We tried to measure simultaneously, in an aqueous solution of appropriate pH and molar ratio of gallium nitrate and fox, the rate constants of exchange between the four fluorinated chemical species LH_2^+, GaL^{2+}, GaL_2^+ and GaL_3, using the 2D ^{19}F–^{19}F EXSY technique. This three-pulse sequence, described by Jeener et al.,[23] is the same as the conventional NOESY ($90° - t_1 - 90° - \tau_{mix} - 90 -$ acquisition) one, where τ_{mix} is the time of mixing modulating the magnetization transfer. The exchange process can clearly be seen as a two-dimensional exchange diagram that puts the exchange network into clear evidence. Quantitative treatment needs the evaluation of the integrated amplitude of the cross-peak $I_{ij}(\tau_{mix})$ between the two chemical species i and j, the corresponding matrix being denoted $\mathbf{I}_{ij}(\tau_{mix})$. Theory shows that the exchange matrix $\mathbf{L}_{ij}$ can be obtained by:
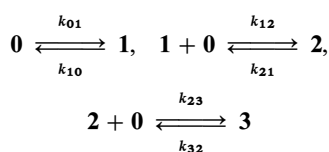
$$I_{ij}(\tau_{mix}) = \exp(\mathbf{L}_{ij}/\tau_{mix})M_j^0$$

where the off-diagonal elements of $\mathbf{L}_{ij}$ are $L_{ij} = -k_{ij}$ (k_{ij} is the first-order rate constant for the exchange from the two chemical species i and j) and M_j^0 is the equilibrium magnetization for species j measured with a very short mixing time and thus with no exchange peaks.[24]

The reactions involved in our system are:

$$M^{3+} + LH_2^+ \underset{k_{10}}{\overset{k_{01}}{\rightleftharpoons}} ML^{2+} + 2H^+$$

$$ML^{2+} + LH_2^+ \underset{k_{21}}{\overset{k_{12}}{\rightleftharpoons}} ML_2^+ + 2H^+$$

$$ML_2^+ + LH_2^+ \underset{k_{32}}{\overset{k_{23}}{\rightleftharpoons}} ML_3 + 2H^+$$

with M for Ga^{III} and L for fully deprotonated fox. For kinetic discussions, a simplification of the notation can be made, with **0** for the free ligand, **1** for the 1 : 1 complex (metal–ligand), **2** for the 1 : 2 complex and **3** for the 1 : 3 complex giving:

$$0 \underset{k_{10}}{\overset{k_{01}}{\rightleftharpoons}} 1, \quad 1 + 0 \underset{k_{21}}{\overset{k_{12}}{\rightleftharpoons}} 2,$$

$$2 + 0 \underset{k_{32}}{\overset{k_{23}}{\rightleftharpoons}} 3$$

It is known that this type of observed reaction rate ($k_{i(i+1)} + k_{(i+1)i}$, i from **0** to **2**) decreases as the stoichiometry of the complex goes from 3 to 1.[25,26] The reaction involving species **3** seems too fast to be observed even with the shortest mixing times. We can predict that: (i) for short mixing times, the I_{02} and I_{12} correlation peaks (between the three species related by the equilibrium between **0**, **1** and **2**) will appear and (ii) for longer mixing times, both the previous peaks and a build-up of the I_{01} correlation peak (between the two species related by the equilibrium between **0** and **1**) will be observed, as both chemical exchange transfers of magnetization are efficient without occurrence of indirect cross-peaks.

Unfortunately, the solubilities of our fluorinated chemical species (fox and the uncharged species GaL_3) are too low and the precipitation of GaL_3 prevented us from getting rate constants with enough precision within a reasonable acquisition time. Nevertheless, interesting qualitative data were obtained: we can see, in Fig. 5(a) and 5(b) the corresponding 2D EXSY spectra with $\tau_{mix} = 200$ and 500 ms, respectively. This con-
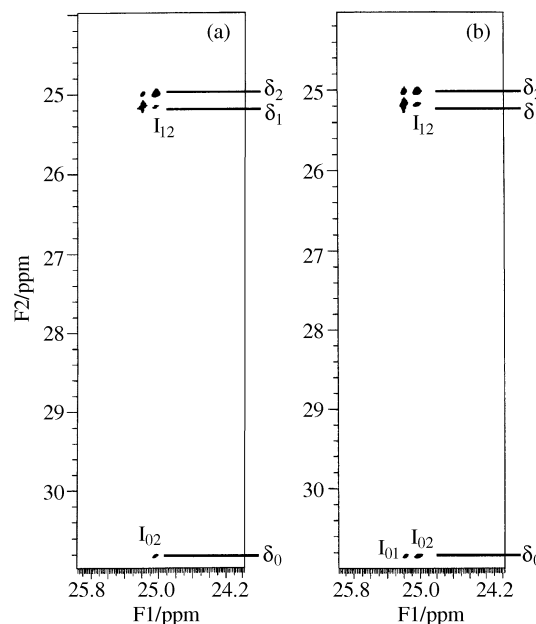

Fig. 5 ^{19}F 2D EXSY NMR spectra for $C_M/C_L = 1$, pH = 2 with a mixing time of: (a) 200 ms; (b) 500 ms

firms our predictions on the reaction rates of hydrolysis and formation of the studied complexes.

We can compare these qualitative data with our stopped-flow studies of a related system, the complexes of iron(III) cation and 8-hydroxyquinoline-5-sulfonic acid (sox) as a ligand. Using the diode array stopped-flow spectrophotometry technique, the values of k_{32}, k_{21} and k_{10} for the Fe—sox system are 800, 150 and 1 M^{-1} s^{-1}, respectively.[20] These rate constants were shown to be first order for both the complex and protonated species. For a solution at a given pH, the lifetime of the three complexes **3**, **2** and **1** are therefore in the ratio 1 : 5.3 : 800. Our qualitative measurements show that the lifetimes of the GaL_3, GaL_2^+ and GaL^{2+} chemical species are of the same order of magnitude as the $Fe(sox)_3$, $Fe(sox)_2^+$ and $Fe(sox)^{2+}$ ones.

Conclusion

Using ^{19}F NMR spectroscopy, we were able to describe the complexation of gallium cations with 5-fluoro-8-hydroxyquinoline (fox) from several points of view: thermodynamically, the values were very precise (especially K_1) as we were able to measure the concentrations of all the fluorinated chemical species; kinetically, we obtained qualitative data giving indications on several reaction rate constants from only one type of measurement. We were able to compare these thermodynamic and kinetic data for the two systems (Ga^{III}—fox and Fe^{III}—sox). The small difference can be interpreted as a slightly higher stability of the iron(III)—pyridinic nitrogen (of the sox) bond in comparison with the gallium(III)—pyridinic nitrogen (of the fox) bond. The same order of magnitude of the data is related with the very similar rate of water exchange for the two cations (Ga^{III} and Fe^{III}).[4] All these experiments also show the usefulness of the fluorine label (with ^{19}F NMR measurements) in ligands or substrates in relation with the small size of the fluorine atoms.[27]

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