New gadolinium(III) complexes with simple organic acids (Oxalic, Glycolic and Malic Acid)

M. RIRI [a*], M.Hor [a], O. Kamal [a], T. Eljaddi [a], A. Benjjar [a], M. Hlaïbi [a,b,*]

[a] *Laboratoire d'Interface Matériaux et Chimie de l'Environnement LIME, Université Hassan II Faculté des Sciences Aïn Chock, B.P. 5366, Maârif, Casablanca, Maroc.*

[b] *Laboratoire des Polymères, Biopolymères, Surfaces, UMR 6270 du CNRS. Université de Rouen, Faculté des Sciences, F-76821 Mont-Saint-Aignan, France.*

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Corresponding author: E-mail: mohammedriri@yahoo.fr (M. RIRI), Tel:(212)667898763

Abstract

The formation of colorless gadolinium complexes (***x, y, z***), between ***x*** gadolinium ions, ***y*** ligands and ***z*** protons, of some organic acids, has been studied in aqueous solution. In this work we present the results of investigations on the interaction of the gadolinium ion (Gd(III)) with simple carboxylic acids such as oxalic acid, glycolic acid and malic acid, in dilute aqueous solution with pH values between 5.50 and 7.50. The obtained gadolinium complexes with oxalate, glycolate and malate ion are colorless and haven't any absorption band in UV-visible, in this sense, the indirect photometry studies used to identify the major di-nuclear and tri-nuclear complexes. This technique allowed us to calculate the compositions and the stabilities constants of these major complexes in solution and the stability constant depends on acidity, the structures of the final complexes were determined by means of IR and Raman spectroscopies.

Keywords: Gadolinium complexes, oxalate, glycolate, malate, indirect photometry, apparent stability constant, chelation sites.

1- Introduction

Magnetic resonance imaging (MRI) is a medical diagnostic technique for several, recent and powerful diseases. It is based on nuclear magnetic resonance (NMR) of water protons in tissue and organs [1]. The detection or monitoring of certain diseases sometimes requires injection of contrast agent based gadolinium. Most of the contrast agents that used in MRI are complex amino acids and carboxylic acids with lanthanides [2]. Currently, most contrast agents used in MRI are complex types of gadolinium-DTPA, gadolinium-BOPTA, gadolinium-DOTA [3, 4] and its analogs modified to enhance the contrast effect on fabric [5-7]. In solution, some organic acids and acid derivatives of sugars form the colorless complexes with gadolinium ion and not possessing absorption UV-visible band, in this sense we have been able to determine the compositions and the stabilities of some colorless gadolinium complexes with carboxylic acids in dilute solution; using a new technique called Indirect Photometry detection (IPD). This technique is simple, used in

room temperature, reproducible, adaptable to other techniques of separation and determination such as liquid chromatography [8,9], capillary electrophoresis [10] and continuous flow analysis (FIA) [11, 12]. It requires a judicious choice of auxiliary ligand and the metal ion, and based on displacement competitive reactions by ligand-ligand exchange:

$$\mathbf{Gd\text{-}L_n} + \mathbf{n'L'} \longleftrightarrow \mathbf{Gd\text{-}L'_{n'}} + \mathbf{n\,L}$$

Color reagent carboxylic acid Colorless Complex Auxiliary Ligand

2- Experimental methods and chemicals

Oxalic acid, Glycolic acid, Malic acid, Chrome Azurol S (H_4Ch), Gd(III) nitrate and other chemicals were commercial products (Aldrich, Prolabo,….) of the purest available and analytical grade, used as received.

The complexes were synthesized by reaction of gadolinium(III) salts and the Oxalic, Glycolic and Malic acid (ligands), in amounts equal to metal: ligands molar ratio of 2:2, 2:2 and 3:2 respectively. The complexes were prepared by adding water solutions of Gd(III) salts to water solutions of the ligands. The absorption measurements have been performed at room temperature and at wavelength λmax = 545 nm. Stock solutions of Gd(III) nitrate and Chrome Azurol S (H_4Ch), were prepared with concentrations of 10^{-2}M and 10^{-3}M respectively. For fixed pH environments, the apparent formation constants logK'xyz was calculated using a laboratory made computer program. The absorption values for the undissociated (AF) and the totally dissociated (AI), sacrificial complex (Gd(III)-H_4Ch), are used as determined in experiments using pure Chrome Azurol S (H_4Ch), and an excess of Gadolinium(III). The complexes are precipitated at room temperature. The precipitates were filtered, washed several times with water, and dried in a desiccator to constant weight. The complexes were insoluble in water, methanol, and ethanol and well soluble in DMSO.

IR Analyses were performed using an infrared spectrometer, Fourier transform (FT-IR), Perkin Elmer BX, equipped with a DTGS detector, a splitter and a cesium iodide window and the Raman spectra were performed using an Raman spectrometer Fourier transform (FT-Raman) VERTEX 70 with a range of measurement (4000-50) cm^{-1}, laser source NdYag (1.064µm), a nominal power of 500 MW, detecting Ge with high sensitivity and a resolution of $4cm^{-1}$ (64 scan).

3- Results and discussion

3-1. Formation of the colored sacrificial complex:

The complexation reaction of ***x*** gadolinium ions ($\mathbf{Gd^{3+}}$) with ***y*** carboxylate ions and ***z*** protons is given by expression (I):

$$x\mathbf{Gd^{3+}} + y\mathbf{L^{n-}} + z\mathbf{H^{+}} \longleftrightarrow (x\,,y\,,z\,) + n\mathbf{H_2O}\ \mathbf{(I)}$$

Where $\mathbf{L^{n-}}$ represents the ligands (n = 2: Oxalate ions, n = 1: glycolate ions and n = 2: Malate ions). The formation constant K_{xyz} and the apparent constant of these complexes are defined as the equilibrium constant:

$$K_{xyz} = [(x, y, z)].[Gd^{3+}]^{-x}.(C_L)^{-y}.[H^+]^{-z} = K'_{xyz}.[H^+]^{-z}$$

Thus $\mathbf{Log}K_{xyz} = \mathbf{Log}\,K'_{xyz}. + \mathbf{z.pH}$

A series of experiments were conducted to determine, the composition, the stability of the colored sacrificial complex (Gd-HCh^{3-}) and its formation reaction. The evolution of UV-visible spectra for the formation of this sacrificial complex is represented by the diagram in **figure1**. The UV-visible spectra show clearly that the maximum absorbance of the sacrificial complex is located at λ_{max} = 545 nm. So, we have studied the formation of this sacrificial complex at this maximum wavelength, depending on the ratio q=(metal/ ligand) = $[Gd^{3+}]$ / $[HCh^{3-}]_{total}$ as shown in the **figure 2**.

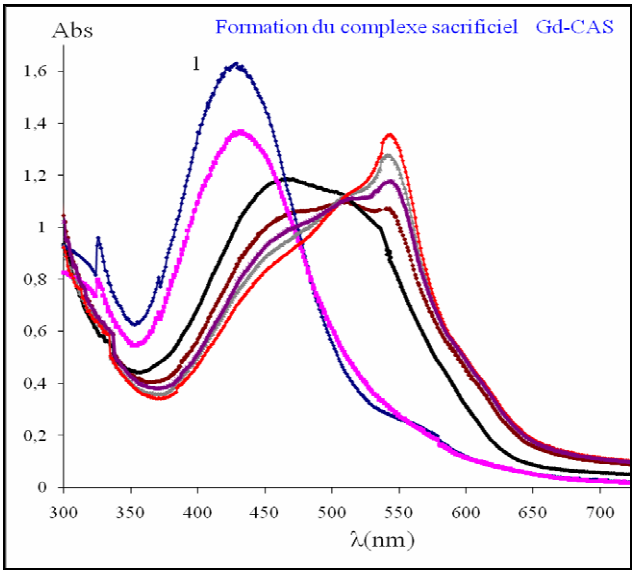

Figure 1: UV-visible spectra for the formation of sacrificial complex (Gd-HCh^{3-}), pH = 5.90

The curve in **figure 2** indicates that the value of the ratio ***q***, relative to the complete formation of this sacrificial complex is the intersection of the linear (positive slope), with the final segment (slope = 0) of the curve, this value of ***q*** is close to **1.50**. For all studied solutions at known values of pH, the apparent constants K'_{32z} were calculated and the obtained results are summarized in the **table 1**. These results show that the stability of the sacrificial complex depends on the acidity of the medium.

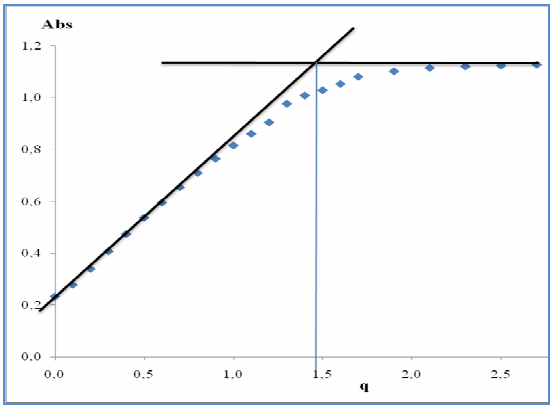

Figure 2: Formation of the sacrificial complex, depending on the ratio $q=[Gd^{3+}]/[HCh^{3-})]_{total}$, λ_{max} = 545nm

Table 1: Evolution of the sacrificial complex stability, depending on the acidity of the medium

pH	**5,50**	**5,70**	**5,90**	**6,12**	**6,30**	**6,50**	**6,70**
Log*K'*$_{32z}$ ±0.05	8,02	7,72	7,40	7,11	6,81	6,53	6,22
A_I	0,358	0,253	0,301	0,225	0,295	0,285	0,265
A_F	1,060	1,178	1,315	1,616	1,665	2,704	2.826

λ_{max} = 545nm, l = 1cm; $[HCh^{3-}]_{total} = 10^{-4}$ M, $[Gd^{3+}]_{init} = 10^{-2}$ M.

For all these solutions, the formation constant K_{32z} on the sacrificial complex is given by the relationship $K_{32z} = K'_{32z} / [H^+]^z$. Hence $\text{Log}K'_{32z} = \text{Log}K_{32z} - z.\text{pH}$, ($K'_{32z}$ conditional constant for a given pH), we plot the curve LogK'_{32z} depending on the medium pH **(figure 3**).

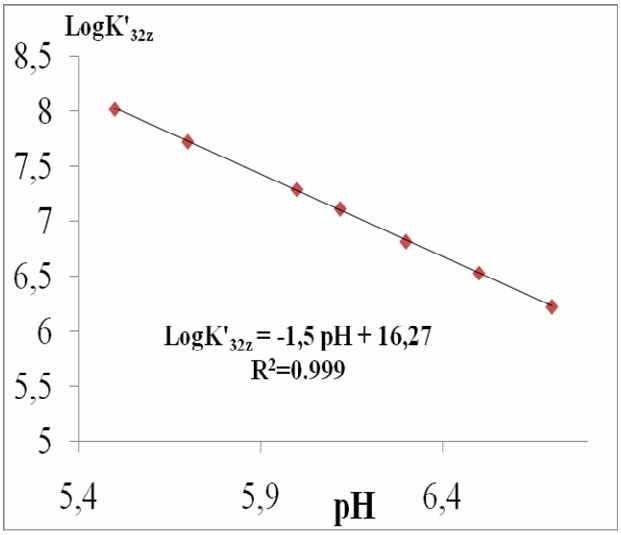

Figure 3: The stability of the tri-nuclear complex $[(Gd)_3(HCh)_2]$ depending on the medium acidity.

3-2. The composition and stability of Gd(III)–Carboxylic acids systems

If the studied ligands (oxalic acid, glycolic acid and malic acid), are added to a colored solution of the sacrificial complex (***3, 2, 3***), this chrome azurol S (**HCh^{3-}**) complex will dissociate. The dissociation of this complex sacrificial by carboxylic acids studied is obtained by reaction (II):

$$x\text{Gd}^{3+} + 2\text{L}^{n-} + z\text{H}^+ \leftrightarrow (x, 2, z) + n\text{H}_2\text{O} \quad \text{(II)}$$

where n=2 : Oxalate ions, n=1: Glycolate ions, n=2: malate ions.

The formation constant K_{x2z} on the complexes are given by the relation (1)

$$K_{x2z}=[(3, 2, z)].[Gd^{3+}]^{-x}.(C_L)^{-2}.[H^+]^{-z}=K'_{x2z}.[H^+]^{-z} \quad (1)$$

$$\text{Thus } \text{Log}K'_{x2z} = \text{Log}K_{x2z} - z.\text{pH} \quad (2)$$

We plot the curves LogK'_{x2z} depending on the medium pH (**figure 4**).

The evolutions of $\text{Log}K'_{x2z}$ of different complexes detected in solution at different pH are linear and the slope of the straight lines are equal to **- *2***. The value (***z* = *2***) represents the number of protons

involved in the formation reaction of these ***new*** nuclear complexes ((***2, 2, 2***), (***2, 2, 2***), (***3, 2, 2***) for Gd(III)-Oxalate, Gd(III)-Glycolate and Gd(III)-Malate respectively). The equation (2) allowed us to calculate the stability constants of complexing reaction of acids studied with gadolinium ion, the experimental results obtained by the IPD are summarized in table 2.

3-3) Vibrational analysis

IR spectroscopic studies are used to identify different groups of oxalic acid, glycolic acid and malic acid (ligands) involved in chelation sites to form gadolinium complexes detected in the solution.

The **table 3** present the bibliographic data [13, 14], theory vibrations value of various groups: -OH, -C=O, -COO^- and –C-C=O, and the experimental vibration value of analyzed spectra of all free carboxylic acids and its complexes studied in this work.

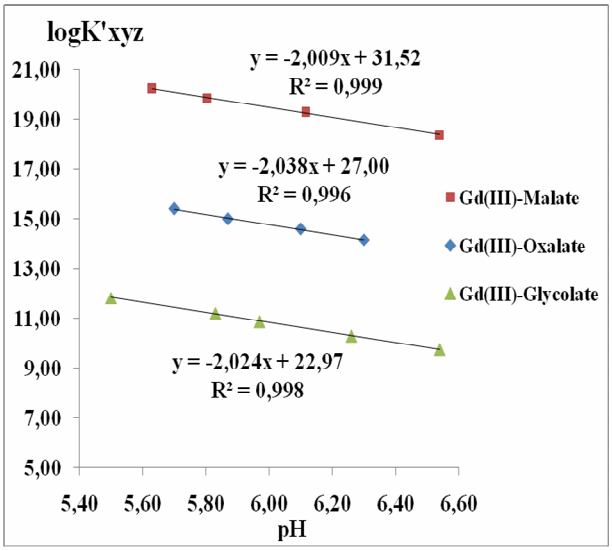

Figure 4: Evolution of $logK'_{x2z}$ for di-nuclear and tri-nuclear Gd(III)-carboxylate complexes detected in solution at different pH values

Table 2: Stability constants of complexing reaction of acids studied with gadolinium ion.

Gd-Oxalate	**Gd-Glycolate**	**Gd-Malate**
$logK_{222}$=26.99	**$logK_{222}$=22.97**	**$logK_{322}$=31.52**
$logK_{xyz}$ ± 0.05		

Table 3: The vibration frequencies for the studied spectra and bibliographic data

Groups	Experimental spectra	Reduction of the free acid bands after complexation %			Réf.[13]	Réf.[14]
	ν(cm^{-1})	Gd-Oxalate	Gd-Glycolate	Gd-Malate	ν (cm^{-1})	ν(cm^{-1})
-O-H	3600–3300	94	91	93	3550–3500	3650–3590
-C = O	1700–1650	89	89	89	1800–1740	1750-1700
-COO^-	1050– 400	98	98	97	700–590	-
-C-C=O		-	-	-	550 – 465	-

The interval experimental measures for the two solutions free acids and complexes acids: [4400 - 400cm^{-1}]

The experimental spectra obtained for the two analyzed samples for each carboxylic acid study, clearly indicate that the groups:-OH,-C=O and -COO^- vibration frequency, have seriously reduced passing the free to complexed ligands (Table 3). So, for each of the two ligands involved in the formation of these detected di-nuclear and tri-nuclear complexes, the four oxygen atoms of the ionized carboxylic groups, participate in chelation sites, and the OH group in α position of the ionized group (-COO^-) of glycolic and malic acid. Moreover, the vibration, Infra red, of Gd(III)-O which is formed in the detectable complexes is located in 150-780cm^{-1} region with weak spectra [15, 16].

A detailed analysis of vibrations in Raman spectroscopy was performed on the basis of comparison of experimental vibrational spectra obtained of oxalic, glycolic and malic acid and its gadolinium complexes. One of these FT-Raman

spectra of free ligands and their complexes with Gd(III) are shown in **Figure 5**. The Raman spectra obtained show that the OH vibrations (3350 ± 100 cm^{-1}) [15, 16] and C=O (1720 ± 90cm^{-1}) [16, 17] of the free acids was not detected in the spectra of the complexes, indicating that the deprotonated ligands form participates in the complexes. The vibration of O-C=O group is reduced from free ligand to complex. So all the oxygen atoms involved in the formation of these new gadolinium complexes.

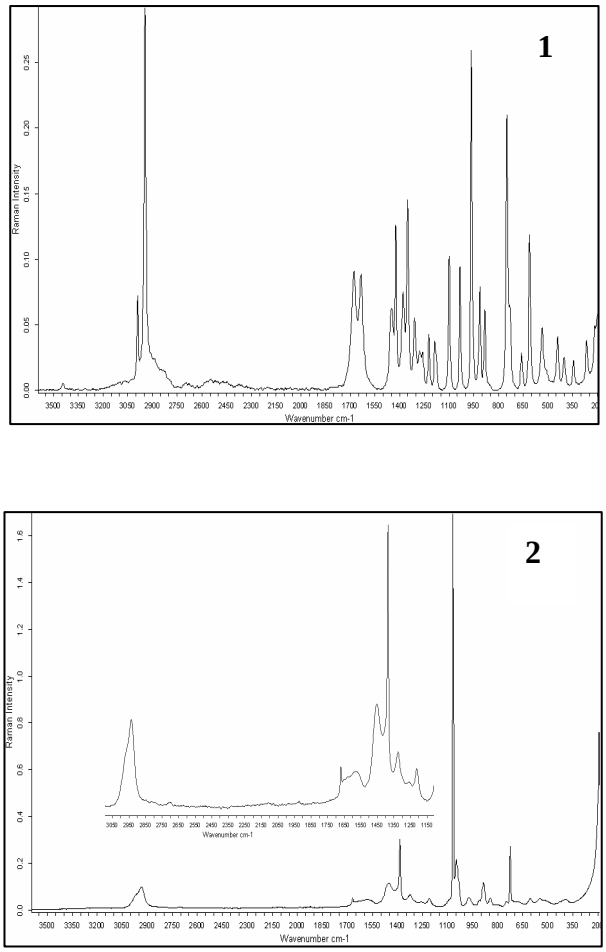

Figure 5: Experimental FT-Raman spectra in the range 3600–200 cm^{-1}: **(1)** free Malic acid **(2)** Gd(III)-Malate complex at pH=5.89, q=[Gd^{3+}] / [malate ions] = 3/2.

There are also vibration spectra (weak broad) of the complexes in (1650 ± 20cm^{-1}) indicate the existence of water molecules [18], intense spectra are observed in the complex near 1050 cm^{-1} indicate the existence the nitrate ion. [15]. Vibrations of the bonds formed Gd(III)-Oxygen carboxylic acids are located in the interval (720-400cm^{-1}) with a weak spectra [18, 19]. And the Gd(III)-oxygen of nitrate are in the vicinity of 190cm^{-1} [20]. Different vibrations of C-C (aliphatic chains) appeared in a long field [(350 ±70 cm^{-1}) and 1220 ± 100cm^{-1})] with intensities medium and intense [18, 21, 22]. Bands in the 2950 ± 80 cm^{-1} region were assigned to the vibrations modes of CH and CH_2 [23, 24].

4- Structures

We, therefore, determined the new complexes containing gadolinium by studies indirect photometry and spectroscopic (IR and Raman). These structures are:

$Gd(III)_2Oxalate_2(NO_3)_2 .nH_2O$
$Gd(III)_2Glycolate_2(NO_3)_2 .nH_2O$
$Gd(III)_3$-$Malate_2(NO_3)_3 .nH_2O$

Conclusion

In this work, we used three techniques to study the interactions of the trivalent Gd(III) ions with different ionic forms of Oxalic, Glycolic and malic acid. The indirect photometry (IPD) was used successfully to determine the composition and the stability of these major gadolinium complexes and the spectroscopy FT-IR and FT-Raman are used for the identification of different chelation sites of the reactions of complexation formed in solution with pH values between 5.50 and 7.50. These techniques allowed us to propose the structures of the major colorless complexes.

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