Di- and tetranuclear gadolinium (III) complexes of 2-hydroxypropane-1,2,3-tricarboxylic acid and 1,2,2-trimethylcyclopentane-1,3-dicarboxylic acid: identification and characterization

M. Riri 1*, M. Hor 1, T. Eljaddi 1,2, A. Benajjar 1,3, F. Hadhoudi 1, S. Ezzennouri 1, M. Hlaibi 1,2

1 Laboratory of Material - Material Interaction and Processes Membrane (13MP), Hassan II University, Faculty of Sciences Ain Chock, BP 5366, Maârif, Casablanca, Morocco
2 Laboratoire des Polymères, Biopolymères, Surfaces, UMR 6270 du CNRS, Université de Rouen, Faculté des Sciences, F-76821 Mont-Saint-Aignan, France
3 High Engineering School of Information, Management and Civil Engineering, Casablanca, Morocco
*Corresponding author E-mail: medriri@gmail.com

Abstract

Our studying involved, Identification and characterization of two novel gadolinium complexes with 2-hydroxypropane-1,2,3-tricarboxylic acid (citric acid) noted H2L and 1,2,2-trimethylcyclopentane-1,3-dicarboxylic acid (camphoric acid) noted H2L in aqueous solution and in pH range 5.5–7.5. These acids containing the donor atoms (oxygen of OH and COOH), the formatted complexes are colorless and have no absorption band UV–visible. So, to determine the composition and stabilities of these complexes in solution, we have used an analytical technique called «Indirect Photometry Detection (IPD) » have identified multi-nuclear and multi-dentate complexes studied in this work. Giving for these colorless complexes with a mole ratio (M:L); (4:2) for Gd (III)–Citric acid and (2:2) Gd (III)–Camphoric acid. In addition, we have shown that the compositions and stabilities constant of these complexes are depended on the acidity of the medium.

Keywords: Citric and Camphoric Acid; Colorless Complexes; Indirect Photometry Detection; Gadolinium Complexes; Stability of Contrast Agents.

1. Introduction

The gadolinium ion is highly toxic in its hydrated form [Gd(H2O)4]3+. Its complexation with an organic ligand reduces this toxicity for IRM or other medical using. This complexation should be administered in the form thermodynamically stable (Reimer et al. 1996 p.36). The solution consists of enclosing the gadolinium ion Gd(III) in the organic ligands to form Gd-Ligands complexes non toxic and very stable in the human body (Thunus & L. Lejeune 1999 p.125, Guo-Ping et al. 2005 p 11, Yoshimasa et al. 2016 p. 148, Sofia & Martin 2017 p. 31). The most widely ligands used are polyaminocarboxylates and their derivatives. In this work, we have studied the formation of colorless gadolinium complexes with some linear ligands in dilute solutions (citric and camphoric acid). To study of these colorless complexes, we developed a new analytical technique for determining the compositions and stabilities of some colorless complexes, which have no absorption band UV–visible. This technique is the Indirect Photometry Detection (IPD), based on competitive reactions by ligand–ligand exchange.

\[
\text{Gd}^3+ + n'L' \rightleftharpoons \text{Gd}^3+\text{L}_n'
\]

Color reagent Ligand Colorless Complex Auxiliary Ligand

This method is simple, reproducible, effective and applicable to very dilute solutions. Thus, the importance of IPD technique was also revealed by its adaptation to other techniques of separation, determination and characterization, such as liquid chromatography (Rocklin 1991 p. 175, Verchere & Dona 1992 p. 437), capillary electrophoresis (Morin et al. 1994 p. 178), continuous flow analysis (FIA) (Ramshing et al. 1980 p. 165) and RMN spectroscopies (Hlaibi et al. 2009 p. 310, Riri et al. 2014 p. 130). Some studies show that this technique is very effective for identifying some colorless gadolinium complexes (Riri et al. 2011 p. 303, Riri et al. 2013 p. 49) and tungstate complexes of sugars and organic ligands (Millan et al. 1995 p. 2334, Riri et al. 2014 p. 130). The detection or monitoring of certain diseases sometimes requires injection gadolinium complexes because of the interesting electronic and magnetic properties of this ion (Haruyuki et al. 2002 p. 1119, Nonat et al. 2006 p. 7133). The most contrast agents used in MRI are complexes of amino acids and carboxylic acids with some lanthanides (Anelli et al. 1997 p. 125, Angela & Wing-Tak 2008 p. 1323). Currently, most contrast agents used in MRI are complexes of gadolinium–DTPA, gadolinium–BOPTA, gadolinium–DOTA (Anelli et al. 1997 p. 125, Angela & Wing-Tak 2008 p. 1323, Nwe et al. 2010 p. 5925, Möller & SAsu 2010 p. 125, Jonathan et al. 2010 p. 10056) and its analogs, which are modified to enhance the contrast effect on fabric (Ts’ang-Hwang et al. 2001 p. 3357, Möller et al. 2011 p. 140, Lee et al. 2011 p. 83). Other studies have shown that gadolinium complexes of coumarin-3-
carboxylic acid (2-oxo-2H-chromene-3-carboxylic acid) and its
derivatives have very important pharmaceutical properties (Kos-
tova et al. 2007 p. 8, Yue et al. 2017 p. 5700). In this work, inves-
tigations by indirect photometry detection (IPD) were carried out
to study the interaction of the trivalent gadolinium ions, with con-
jugate base of citric and camphoric acid, detecting the majority of
colorless complexes formed in solution and determining their com-
positions and stabilities constant ($\log K_{\text{st}}$). Other studies are
interested to studying the stabilities of camphoric acid (Huijie et
al. 2015 p. 135, Elisa et al. 2017 p. 147) and citric acid (Xuefei et
al. 2017 p. 103, Soo et al. 2017 in press) complexes with the for-
mation of polymers or organometallic complexes. The acidity
constants and semi developed form of citric and camphoric acid
are noted in the Table 1 (Bjerrum 1958, Serjeant & Dempsey
1979).

2. Experimental section

2.1. Chemicals

Citric acid, Camphoric acid, NaOH, HCl, Chrome Azurol S
($H_{\text{Ch}}$), Gagoliunum nitrate (Gd (NO$_3$)$_3$.6H$_2$O) and other chemi-
cals were commercial products (Aldrich, Prolabo, ...). The purest
available and analytical grade, used as received.

2.2. Indirect photometric detection

Standard Helios $\gamma$ UV–visible spectrometer controlled by Vision
32 software was used for spectrometric measurements, using
quartz cells of optical path length $l = \text{cm}$ . The absorption mea-
surements have been performed at room temperature and at wave-
length $\lambda = 545$nm. Stock solutions of Gd (III) nitrate and
Chrome Azurol S, were prepared with concentrations respectively
10$^{-3}$M and 10$^{-4}$M. In a typical experiment, a solution (v = 50 ml )
of the colored sacrificial complex ($Gd – H_{\text{Ch}}$) was prepared
([Gd$^{3+}$] / [H$_{\text{Ch}}$] = 1.5), using it as a buffer of MESH (0.1 M)
[2-N-morpholino] sulfonic ethane acid]. The initial solution also
contained a calculated amount of 1 M (NaOH) in order to obtain the
desired pH value ($pK_a$ (MESH) = 6.2, experimental pH range
(5.50–7.50). pH values are measured with a microprocessor pH
meter HANNA 210 equipped with a combined electrode glass and
calibrated with commercial buffers (pH 4.00 and 7.00). Then ali-
quots (v = 0.100–0.200 ml) of an aqueous solution of the H$_2$L
and H$_3$L (C$_1$ = 1g/L and C$_2$ = 10g/L, respectively) was added,
using a Gilson micropipet of 0.2 ml. After each addition, the re-
sulting solution was left at least 2 min in order to reach equilibri-
um (and thus a constant absorption value). Addition was repeated
until a maximum volume of 6 ml of the ligand's solution was ad-
ded. The change in the total volume was neglected. For fixed pH
environments, the apparent formation constants $log K_{\text{st}}$ was cal-
culated from the equilibrium of the reaction of formation of these
complexes. The absorption values for the undissociated (A0) and
the totally dissociated (A1), sacrificial complex ($Gd – H_{\text{Ch}}$), are
used as determined in experiments using pure Chrome Azurol S,
and an excess of Gadolinium(III) (performed at pH intervals of
0.25). Assuming various integers for the Gadolinium and organic
acid's stoichiometry, a formation constant is calculated for each
added amount of ligands and corresponding absorption value. The
results are rejected when a systematic variation of $log K_{\text{st}}$ occurs
with increasing added-up amount of ligands or when individual
values of $log K_{\text{st}}$ differed from the mean value by more than 2%.

### Table 1: Some Characteristics of Acids Studied

<table>
<thead>
<tr>
<th>Acid</th>
<th>Chemical formula</th>
<th>$pK_{a1}$</th>
<th>$pK_{a2}$</th>
<th>$pK_{a3}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citric (H$_2$L)</td>
<td>HOOC $\text{CH}_2$ $\text{CHOOCC}_2 \text{OH}$</td>
<td>3.13</td>
<td>4.76</td>
<td>6.50</td>
</tr>
<tr>
<td>Camphoric (H$_3$L)</td>
<td>HOOC $\text{CH}_2$ $\text{COOH}$</td>
<td>4.70</td>
<td>------</td>
<td>------</td>
</tr>
</tbody>
</table>

3. Results and discussion

3.1. Indirect photometric detection study: expression of the
stability constant of complexes Gd–ligands

The complexation reaction of gadolinium ions with acids studied
in this work, given by general reaction (I):

$$x\text{Gd}^{n+} + y\text{L}^- + z\text{H}^+ \rightarrow (x, y, z) \cdot n\text{H}_\text{O}$$

- $L^+$ is ligand (acid) (n=3 for H$_3$L and n=2 for H$_2$L).
- We noted (x, y, z) to simplify the writing of complex formed.
- x, y and z are, respectively, the stoichiometric coefficients re-
  lating to the Gd$^{3+}$ ion, acid studied in its basic form and the
  number of protons $H^+$ involved in complexation reaction.

The formation constant $K_{\text{st}}$ (or stability constant $\beta_{xyz}$) of the
complexes formed defined by equation (1):

$$K_{\text{st}} = [(x, y, z) \cdot (\text{Gd}^{n+}) \cdot (\text{L}^-) \cdot (\text{H}^+)]$$

(1)

Additionally, a conditional constant $K_{\text{st}}$ is defined in case of
constant pH value (buffered solution):

$$K_{\text{st}} = [(x, y, z) \cdot (\text{Gd}^{n+}) \cdot (\text{L}^-)]$$

(2)

3.1.1. Expression of stability constant $\log K_{\text{st}}$ of complex Gd-
H$_2$L

Where C$_L$ represents the analytical concentration of the uncom-
plexed ligand, therefore, we have for H$_3$L $C_L = [\text{L}^-]$ in our pH
range because pH > $pK_a$ of this acid. Using this equality and Eq.
(1) can be written as:

$$K_{\text{st}} = [(x, y, z) \cdot (\text{Gd}^{n+}) \cdot (\text{L}^-)]$$

(3)

$$K_{\text{st}} = K_{\text{st}} \cdot [\text{H}^+]$$

(4)

The formation constant $\beta_{xyz}$ and the apparent constant of this
complex defined by equation (5): $\log K_{\text{st}} = \log K_{\text{st}} + z \cdot pH$

3.1.2. Expression of stability constant $\log K_{\text{st}}$ of complex Gd-
H$_3$L

The chemical equilibrium and acidity constant of citric acid (H$_3$L) are:
The expression of the analytical concentration of citric acid in the solution is given by the formula

\[ C_{\text{L}} = \frac{[\text{HL}^2] + [\text{HL}] + [\text{H}^+] \cdot [\text{L}]^3}{K_{a3}} \]

Therefore, the stability constant expressed by equation (1) takes the following expression:

\[ K_{\text{syz}} = \frac{[\text{HL}]^2 \cdot [\text{HL}] \cdot [\text{H}^+] \cdot [\text{L}]^3}{K_{a3}} \]

And the equation (2) become:

\[ \log K'_{\text{syz}} = \log K_{\text{syz}} - 2 \log K_{3} \]

In the first stage of the characterization of the gadolinium complexes with studied acids, we determined the compositions x, y, z and stability constants of these colorless complexes. The composition of the ligands (acids) can be studied using an spectrophotometric method. Since the reagents (acids) and their gadolinium complexes don’t possess a characteristic UV-visible absorption spectrum, a second ligand (called the sacrificial ligand) is introduced, this ligand must absorb in the UV-visible spectrum and form a colored complex with gadolinium (III). The dissociation of this colored complex has to cause large variations in the UV-visible spectrum which allows for the calculation of the concentration of the sacrificial complex; using the formation constant of this colored complex, the concentration of the unknown complex can be obtained. Therefore, the sacrificial ligand must form a single colored complex of lower stability than the gadolinium complex under study. In this work, Sulfo-3"-dichloro-2"-6"dimethyl-3,3'-hydroxy-4'-fuchson-5,5'-dicarboxylic acid, often called Chrome Azurol S and notable HA, has been used as sacrificial ligand. Chrome Azurol S is a tetraprotic acid with \( pK_{a1} \) values of 2.25 (\( H_2\text{Ch} \), \( \text{HCh} \) and \( \text{HCh}^+ \)) and of \( \text{HCh}^- \) has been neglected. It is an indicator which is generally used for the photometric proportioning of the metal ions in solution (Doná & Verchere 1991 p. 533). In this work the interaction of the \( \text{HCh} \) with gadolinium ions (Gd\(^{3+}\)), gives a colored reagent (\( \lambda_{\max} = 545 \text{ nm} \)) of average stability for values of pH ranging between 5.50 and 7.50. The buffer ‘MESH’ [2-((N-Morpholino) sulfonic ethane acid] was adopted to fix pH in the study of the sacrificial complex (Gadolinium-\( \text{HCh} \) and gadolinium-Ligands (complexes studied in this work). We chose this buffer because it does not present any interaction with Gd\(^{3+}\) ions and so we would be able to work in the range of pH where the stability of the sacrificial complex is maximal.

3.2. Formation of the colored sacrificial complex \( \text{Gd}(\text{HCh}) \)

The majority of organometallic complexes studied are colorless. Thus the study of the formation of the sacrificial complex \( \text{Gd}(\text{HCh}) \) is very important, because this steps decisive parameters (composition and stability) of gadolinic complexes characterized in this work. In this sense, we have demonstrated, experimentally, that the composition and stability of the colored sacrificial complex (Gd–CAS) were determined, we found a complex type (3, 2, 3) and stability constant \( \log K_{\text{as3}} = 16.27 \) in pH range 5.50–7.50 (Ramshing et al. 1980 p. 165, Verchere & Doná 1992 p. 437, Morin et al. 1994 p. 178, Hlaïbi et al. 2009 p. 310), the equilibrium reaction for this complex is

\[ \text{Gd}^{3+} + 2\text{HCh}^- + 3\text{H}^+ \rightarrow (3,2,3) + n\text{H}_2\text{O} \] (III)

We use these results of sacrificial complex formed in solution, to study two colourless complexes Gd–Citrate ions and Gd–camphorate ions.
3.4. Determination of the composition and the stability constant of complexes Gd–Acids

With an aim of determining the composition and the stability constant of the gadolinium–citrate ions and gadolinium–Camphorate ions, we monitoring the evolution of the absorbance during the disappearance of the sacrificial complex by the addition of increasing quantities of ligands. For a given volume (50 mL) of a solution containing sacrificial complex (3, 2, 3) (10^−M), we added increasing quantities of L^3– and L^2– ions with known concentration. The spectrophotometric study carried out with fixed wavelength (λ = 545 nm), showed a reduction in the absorbance of the solution progressively with the addition of acids (figure 1).

The dissociation of the sacrificial complex, relating to the reduction in the absorbance by the addition of ligands, is done in favor of the formation of the colorless complex between Gd^3+ and studied acids. The curves C1 and C2, in figure 1, of complexes formed in solution Gd–H3L and Gd–H2L respectively, clearly show that the absorbance decreases and stabilizes. This stability indicates that all Gd^3+ ions, initially present in the solution have reacted with ligands.

Knowing the concentration of gadolinium ions and the quantity of ligands (added volume Va of acid), necessary to reach this stage of absorption, we could determine the molar ratio \( q = [Gd^{3+}]/[acid] \), involved in the complexation reaction. The preceding experiment was carried out for different values of pH between 5.50 and 7.50, the way in which the absorption decreases, depends on the pH of the medium and on the formation constant of the detected complexes, as well as on the absorption values (A1) and (A0) of the free and totally complexed Chrome Azulor S. Analyzing the experimental data with the computer program written from the balanced reaction (I), the results confirm the reproducibility of the molar ratio \( q = [Gd^{3+}]/[acid] = x/y \) and to determine the composition and the stability constant \( K_{col} \). This program is not a theoretical modeling (but this is a translation of the reaction steps of the balance (I) for ease of calculation). In figure 2 we represent an example of calculating the ratio q at pH 6.46 of complex Gd–H3L, where we inserted the two experimental values: Va and Abs corresponds for each added volume of ligand, to seek the values of X and Y to the value of \( \text{log } K_{col} \) which remains constant.

Fig. 1: Decomposition of Colored Sacrificial Complex by Addition of H3L and H2L Ions.

Fig. 2: Example of Program Used to Calculate the Compositions X, Y and Stability \( \text{log } K_{col} \).

C_m: Mass concentration (1g/L), V_a: volume of acid, A = Abs experimental absorbance, Kc: constant of colored sacrificial complex, \( \text{log } K_{col} \) = 23,54 for \( q = x/y = 4/2 \) and pH = 6.46
The calculations are repeated for different experimental values of pH between 5.50 and 7.50. We obtained a molar ratio $q=x/y$ for Gd–H$_2$L equal 4:2 and 2:2 for H$_2$L. The data-processing treatment of the preceding experimental results, shows that these di and tetra-nuclear complexes are formed between the gadolinium ions and ligands, resulting from the interaction of two Gd (III) ions equivalents with two equivalents of H$_2$L and four Gd (III) ions for H$_2$L, so a molar ratio $q$ and conditional constant $logK_{q}$ remains the same for each fixed value of pH between 5.50 and 7.50 for two complexes formed. The constants and the molar ratio $q$ at different values of pH are given in Table 2.

| Table II: The Conditional Stability of the Two Complexes Detected |
|------------------|------------------|
| Gd–H$_2$L       | $logK_{a}$       |
| pH              | $logK_{a}$       |
| 5.50            | 5.50             |
| 5.63            | 5.63             |
| 5.83            | 5.83             |
| 6.02            | 6.02             |
| 6.24            | 6.24             |
| 6.46            | 6.46             |
| Gd–H$_2$L       | $logK_{a}$       |
| pH              | $logK_{a}$       |
| 5.50            | 5.50             |
| 5.63            | 5.63             |
| 5.83            | 5.83             |
| 6.02            | 6.02             |
| 6.24            | 6.24             |
| 6.46            | 6.46             |

Buffer (MES / MESH), $\lambda = 545$ nm, $l = 1 cm$, $[HCh^{+}] = 10^{-3}M$

Therefore, for the complexation reaction, results of $logK_{syz}$, the reactions (I) and (II) and the equations (1), (2), (5) and (6) allow us to write the following expressions for each complex:

3.4.1. Gd–H$_2$L

$$4Gd^{3+} + 2L^{-} + 2H^{+} \rightarrow (4,2,z) + nH_2O$$

(IV)

$$K_{syz} = [4(2,z)]/(C_{Gd}^{3-}) \cdot [C_L^{4-}]$$

(11)

So, $logK_{syz} = logK_{a} - 2pK_{a} - (z-2)pH$

(12)

3.4.2. Gd–H$_2$L

$$2Gd^{3+} + 2L^{-} + 2H^{+} \rightarrow (2,2,z) + nH_2O$$

(V)

$$K_{syz} = [2(2,z)]/(C_{Gd}^{3-}) \cdot [C_L^{4-}]$$

(13)

And $logK_{syz} = logK_{a} - zpH$

(14)

For two complexes detected, the results in table 2 combined with equations (12) and (14) allow to plot functions $logK_{syz} = f(pH)$ for two complexes formed, hence determine the number $z$ of protons $H^{+}$ involved in the reaction obtained from the straight lines. The evolution of $logK_{syz}$ at different pH values represented in figure 3.

This evolution of $logK_{syz} = f(pH)$ is linear and the slope $p$ of the straight line is equal to $\approx -5/2$ for complex Gd–H$_2$L and $-2$ for complex Gd–H$_2$L. So, the value of $\approx (z-2) = p = -5/2 \approx z = 9/2$ for Gd–H$_2$L and for Gd–H$_2$L, $z = p = -2 \approx z = 2$ represents the number of protons $H^{+}$ involved in the formation of two complexes respectively. The Equations (12) and (14) allowed us to calculate the stability constants $logK_{syz}$ for these two complexes, the experimental results obtained by the IPD are $logK_{syz} = 53.18 \pm 0.01$ with $pK_{a} = 6.50$, so $logK_{syz} = 23.11 \pm 0.01$ ( $K_{syz} = 1,288 \times 10^{10}$ ) for Gd–H$_2$L and Gd–H$_2$L respectively.

Consequently, the spectrophotometric results concerning the interaction of the Gd(III) ion with H$_2$L show that the complexation reaction uses two Gd(III) ions, two carboxylates and fixation of two $H^{+}$ protons, but in the case of complex Gd–H$_2$L, there are four Gd(III) ions interact with two ligands and the intervention of $9/2$ $H^{+}$. So, by comparing with other works on the complexes of the gadolinium ion (Hlaibi et al. 2009 p. 310, Riri et al. 2014 p. 130, Riri et al. 2016 p. 1478), we have given the general formulas of these two complexes Gd-Citrate and Gd-Camphorate, therefore the both formulas are $Gd$Citrate = $4NO_3$H$_2$O and GdCamphorate = $2NO_3$H$_2$O.

Finally, we have obtained one dinuclear complex type (2,2,2) for camporphic acid in pH range 5.50 – 7.50, and one tetranuclear complex type (4,2,9/2) for the complex Gd-Citric acid in 5.50 $<pH <6.50$ but for pH values between 6.50 and 7.50 the study of the formation of complex Gd–Citric acid is not treated in this work.

4. Conclusion

In this work, we have identified and characterized two new polynuclear and polydentate complexes of gadolinium ion in aqueous solutions and in a pH region 5.50 to 7.50, using the indirect photometry detection. This technique was used successfully to determine the composition, and the stability of these major complexes formed in very dilute solution, so we obtained two types of composition (2, 2, 2) for complex Gd–H$_2$L and (4,2,9/2) 2, 9/2 for complex Gd–H$_2$L. The stabilities of these new gadolinium complexes are $logK_{syz} = 53.18 \pm 0.01$ and $logK_{syz} = 23.11 \pm 0.01$ for Gd–H$_2$L and Gd–H$_2$L respectively. We also mentioned that the acidity of the medium has a very important in determining the nature of the chelation site formed: bidentate and tridentate (Hlaibi et al. 2009 p. 310, Riri et al. 2016 p. 1478).

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Synthesis of Gadolinium-based Nanotopic Actinides and Considerations of the Hydrophobicity of Nanoparticles


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