Study of the kinetics of the formation of EuDOTA−

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ABSTRACT. – The formation of EuDOTA− was studied by the radiotracer technique. The reaction takes place through a fast, almost complete formation of an intermediate in which the metal ion is bonded to the carboxylate groups of the macrocyclic ligand. This intermediate converts in a fast deprotonation equilibrium into a second intermediate complex that rearranges in the rate determining step corresponding to the entrance of the metal ion into the cavity of the macrocycle and its linkage to the nitrogen ring atoms.

INTRODUCTION

The chemistry of the complexes of paramagnetic lanthanide ions with macrocyclic ligands has arisen great interest in the last few years, due to their possible use as contrast agents in medical NMR imaging [1,2]. The combined effect of the dimension of the internal cavity of the ring and the nature of the donor atoms and the pH dependent binding groups, turns these macrocyclic molecules into highly selective ligands for metallic cations. Few studies have reported on the formation and/or dissociation kinetics of lanthanide complexes with polyaza–polycarboxylate macrocyclic ligands [3,4].

1,4,7,10–tetraazacyclododecane–N,N',N″,N‴–tetraacetate (DOTA) forms very stable chelates with Ln3+ ions [5]; this paper reports a study of the formation kinetics of EuDOTA−, and proposes a mechanism for the process.

EXPERIMENTAL

All chemicals used are of analytical grade. The macrocyclic ligand DOTA
was provided by Guerbet, Paris. The concentrations of the ligand and of the
Eu\(^{3+}\) solutions were determined by complexometric titrations. The cation
exchange resin, (Dowex 50X8, 100–200 mesh) was converted to the potassium
form. Acetate buffers were prepared by adding the appropriate amount of
potassium hydroxide to acetic acid solutions to the required pH value, and
diluting them to get 0.2 M acetate stock solutions.

The pH was measured with a Beckman digital pH-meter, model 4500. Since
concentrations are used in the kinetic equations, the electrodes were
calibrated with HCl/KCl solutions of known proton concentration, at
the same ionic strength. All pH readings were taken in the potential (mV) scale,
getting the corresponding p\(_{e}\)H values from the calibration equation.

The radiotracer (\(^{152,154}\)Eu, Amersham Radiochemical Centre, Belgium)
was obtained as chloride in dilute hydrochloric acid solution.

All experiments were carried out at 20 °C and at constant ionic strength
(0.1 M KCl), in 0.02 M acetate buffer. The reaction mixtures were prepared
by mixing the appropriate amount of an europium chloride solution and 50 µl
of Eu–tracer with 5 ml of 0.2 M acetate buffer of the desired pH and enough
KCl solution to keep the ionic strength at 0.1 M. The experiment was started
by adding the required volume of the ligand solution and shaking the mixture
vigorously. Samples were collected at fixed time intervals, and the EuDOTA\(^-\)
complex was separated from free Eu\(^{3+}\) ions by running these solutions through
cation exchange columns (0.8x1 cm), pre-equilibrated with buffer solution of
the same acidity. The samples were eluted by rinsing the columns with three
1 ml aliquots of buffer. An equilibrium sample was taken as well as an total
\(^{152,154}\)Eu activity sample.

The activity of \(^{152,154}\)EuDOTA\(^-\) in the eluate samples was measured with
a NaI(Tl) scintillation counter (Packard Cobra 5003); samples were counted
three times, each one until the standard error reached a value of 1%.

RESULTS AND DISCUSSION

The first step in the formation of complexes Ln\(^{3+}\) ions with polycyclic
ligands is the formation of an external sphere species, coupled to the loss of
solvent molecules from the solvation shell of the anion. The next step is the
leaving of water from the internal coordination sphere of the cation [6].
TABLE I – First order rate constants \( (k_{\text{exp}}) \) for the formation of \( \text{EuDOTA}^- \) as function of the metal:ligand ratio \( (r) \) and of the proton concentration. 

\[
[\text{Eu}^{3+}] = 2.54 \times 10^{-5} \text{ M}, \quad [\text{buffer}] = 0.02 \text{ M}, \quad 0.1 \text{ M ionic strength}, \quad T = 20^\circ \text{C}.
\]

* values for ten times lower concentration of \( \text{Eu}^{3+} \) and DOTA.

<table>
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<th>( r )</th>
<th>( 10^5 [H^+] ), M</th>
<th>( 10^2 k_{\text{exp}}, \text{ min}^{-1} )</th>
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The formation of \( \text{EuDOTA}^- \) was shown to obey first order kinetics law, as well under conditions of excess of either one of the reagents as with equimolar concentrations of \( \text{Eu}^{3+} \) and DOTA. The value of the first order rate constant (Table I) is independent of the concentration of either the metal ion or the ligand, but decrease with increasing acidity at higher \( p_cH \) values and tend to become independent of it at lower \( p_cH \). A plot of \( k_{\text{exp}}^{-1} \) vs. \( [H^+] \) shows that the data at different ligand:metal ratio fit a single straight line with an intercept equal to \( -0.021 ± 0.024 \) and a slope equal to \( 0.0455 ± 0.0015 \text{ min} \cdot \text{M}^{-1} \).
A mechanism that is consistent with these observations is given by eq.1–3. The first step is the formation (fast and almost complete reaction) of a protonated complex that is in equilibrium with a deprotonated intermediate in which the Ln\(^{3+}\) ion is bonded to the carboxylate groups of the ligand. The rate determining step consists in a rearrangement of this deprotonated intermediate, where the metal ion fits in the cavity of the macrocycle and binds to the nitrogen atoms of the ligand.

\[
\begin{align*}
\text{Eu}^{3+} + H_{2+x}^{x-}\text{DOTA}^{(2-x)^-} & \xrightarrow{\text{fast}} \text{EuHDOTA} + (1+x)H^+ \quad (1) \\
\text{EuHDOTA} & \xrightarrow{k} \text{EuDOTA}^{x^-} + H^+ \quad (2) \\
\text{EuDOTA}^{x^-} & \xrightarrow{k} \text{EuDOTA}^- \quad (3)
\end{align*}
\]

According to the rate equation derived for the proposed mechanism:

\[
V = k \frac{[\text{EuHDOTA}]}{K \cdot [H^+]}
\]

the plot of \(k_{\text{exp}}^{-1}\) vs. \([H^+]\) is a straight line with zero intercept and with slope \(K/k\), in agreement with the experimental observations.

In their study of the reaction of DOTA with excess Ce\(^{5+}\) ions, Brücher et al. [3] also found the first order rate constant to be inversely proportional to the proton concentration; however, the value of \(k\) increases somewhat with increasing concentration of the metal ion, exhibiting a saturation effect. That would indicate that the formation of the first, protonated intermediate is not yet complete for the smaller concentrations of Ce\(^{3+}\), and may be due to the very high ionic strength used in their study (3 M NaClO\(_4\)).

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REFERENCES