Study of the kinetics of the formation of EuDOTA⁻

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ABSTRACT.— The of kinetics of EuDOTA⁻ was studied by the radiotracer technique. The reaction takes place through a fast, almost complete formation of an intermediate in wich 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 Ln^{3+} 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_cH values from the calibration equation.

The radiotracer ([152-154]Eu, Amersham Radiochemical Centre, Belgium) was obtained as chloride in dilute hydrochloric acid solution.

All expperiments 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 trough 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 polydentate 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_{exp}) for the formation of EuDOTA$^-$ as function of the metal:ligand ratio (r) and of the proton concentration. $[Eu^{3+}] = 2.54 \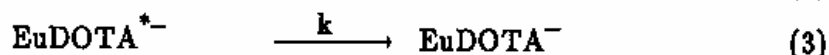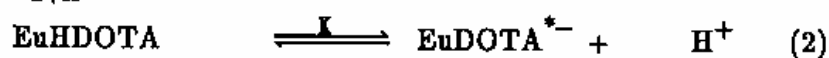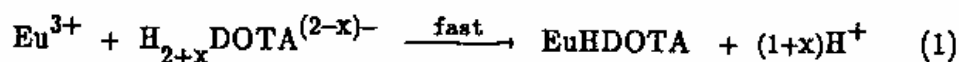cdot 10^{-5}$ M, [buffer] = 0.02 M, 0.1 M ionic strength, T = 20 °C. * values for ten times lower concentration of Eu^{3+} and DOTA.

r	$10^5 \times [H^+]$, M	$10^2 \times k_{exp}$, min^{-1}	r	$10^5 \times [H^+]$, M	$10^2 \times k_{exp}$, min^{-1}
0.5	1.65	15.41 ± 0.35	1.0	1.74	12.98 ± 0.65
	2.50	10.52 ± 0.26		2.67	9.91 ± 0.25
	3.79	7.90 ± 0.09		2.98	7.34 ± 0.11*
	6.14	3.13 ± 0.13		3.82	6.55 ± 0.25
	9.23	2.36 ± 0.02		5.25	4.40 ± 0.01*
	9.26	2.35 ± 0.07			
	9.34	2.24 ± 0.05			
1.5	1.32	15.24 ± 0.45	2.0	1.74	16.31 ± 0.86
	2.60	9.30 ± 0.14		2.54	12.90 ± 0.61
	3.57	7.35 ± 0.57		3.79	8.83 ± 0.15
	5.52	4.93 ± 0.08		6.10	3.67 ± 0.21
	5.87	4.55 ± 0.04		10.40	2.48 ± 0.12
	11.49	2.04 ± 0.05			
10	3.11	8.64 ± 0.16	143	2.69	9.98 ± 0.77
	4.71	5.12 ± 0.06		3.48	6.98 ± 0.27
				5.13	4.58 ± 0.10
				6.17	4.07 ± 0.11
				6.71	3.61 ± 0.08
				9.16	2.23 ± 0.05
				9.33	2.73 ± 0.03
357	2.71	10.06 ± 0.68	714	2.77	10.26 ± 0.53
	3.50	6.99 ± 0.20		3.56	7.12 ± 0.17
	5.13	4.79 ± 0.11		5.17	4.86 ± 0.13
	6.24	4.32 ± 0.12		6.31	4.10 ± 0.14
	6.75	3.98 ± 0.10		6.70	3.79 ± 0.83
	9.12	2.32 ± 0.05		9.16	2.52 ± 0.05
	9.26	2.24 ± 0.03			

The formation of 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 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 al lower p_cH. A plot of k_{exp}^{-1} vs. $[H^+]$ shows that the data at different ligand:metal ratios fit a single straight line with an intercept equal to -0.021 ± 0.024 and a slope equal to 0.0455 ± 0.0015 min·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 wich 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.

$$Eu^{3+} + H_{2+x}DOTA^{(2-x)-} \xrightarrow{\text{fast}} EuHDOTA + (1+x)H^{+} \quad (1)$$

$$EuHDOTA \xrightleftharpoons{K} EuDOTA^{*-} + H^{+} \quad (2)$$

$$EuDOTA^{*-} \xrightarrow{k} EuDOTA^{-} \quad (3)$$

According to the rate equation derived for the proposed mechanism:

$$V = \frac{k \cdot [EuHDOTA]}{K \cdot [H^{+}]} \quad (4)$$

the plot of k_{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^{3+} 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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