Inorganica Chimica Acta, 139 (1987) 141–142

Studies on the Kinetics of Formation and Dissociation of the Cerium(III)–DOTA Complex*

E. BRÜCHER**, G. LAURENCZY and ZS. MAKRA

Department of Inorganic and Analytical Chemistry, Kossuth University, Debrecen, H-4010, Hungary

The rate of formation of the lanthanide(III) (Ln^{3+}) complexes is in general very high due to the high water exchange rate of the $Ln^{3+}\cdot aq$ ions. The complexes of lanthanides with the multidentate aminopolycarboxylates (e.g. $LnEDTA^-$, $LnDTPA^{2-}$) are also formed very fast as a result of the flexibility of these ligands. Recently it has been observed [1] that the formation of Ln(III) complexes with macrocyclic polyazapolycarboxylates (e.g. $LnDOTA^-$) is very slow due to the rigid structure of the ligands (H_4DOTA = 1,4,7,10-tetraazacyclododecane-*N,N′,N″,N‴*-tetraacetic acid). The dissociation of the Ln(III) aminopolycarboxylates is quite slow [2], but a much lower dissociation rate can be expected for the polyazapolycarboxylate complexes. Knowledge of the kinetic properties of the complexes formed with non-cyclic and cyclic aminopolycarboxylates is very important in their recent application in NMR tomography [3].

Experimental

The chemicals used were of analytical grade. H_4DOTA was prepared and kindly provided by J. F. Desreux [1]. The concentration of the H_4DOTA and $Ce(ClO_4)_3$ solutions was determined by complexometry. The solution of NaCeDOTA was prepared using equivalent amounts of $Ce(ClO_4)_3$ and Na_4DOTA.

The complex $CeDOTA^-$ is thermodynamically unstable at pH < 1.5 but the rate of its dissociation is low and can be studied in the 0.1–2.0 M concentration range of H^+ ions. The ionic strength was kept constant (3 M $NaClO_4$ + $HClO_4$), the temperature was 25 ± 0.1 °C. In the case of the study of formation reactions a 0.05 M sodium acetate buffer was used. The H^+ ion concentration was calculated as before [2].

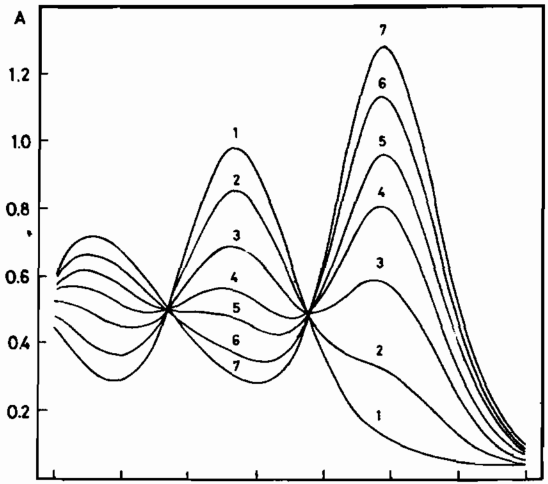

Fig. 1. Absorption spectra of the reacting mixtures recorded (50 nm/min) at 0.5 (1), 6 (2), 15 (3), 25 (4), 35 (5) and 55 min (6) after the reaction was started and at equilibrium (7). [Ce] = 2×10^{-3} M, [DOTA] = 5×10^{-4} M, pH = 4.45.

The UV spectra of $Ce^{3+}\cdot aq$ and $CeDOTA^-$ differ considerably, thus the formation and dissociation of the complex was followed by conventional spectrophotometry, recording the spectra at different times (Fig. 1) or measuring the change in the absorbance at 319 nm after mixing the solutions.

Results and Discussion

Kinetics of Formation of CeDOTA

The spectra of solutions obtained after mixing the reactants (Na_2H_2DOTA and $Ce(ClO_4)_3$) are shown in Fig. 1. After the reaction starts, an absorption band appears with a maximum at 297 nm, the intensity of which decreases with the elapse of time, while another band appears at 319 nm, characteristic of the $CeDOTA^-$ ion. The appearance of the band at 297 nm and the decrease of its intensity during the reaction indicates the fast formation of a relatively stable intermediate, which slowly transforms to $CeDOTA^-$. The concentration of the intermediate can be quite high, particularly at higher pH values and at higher concentrations of the Ce^{3+} ion.

A study of the spectra and the decrease of pH in the absence of buffer, using neutral reactant solutions (pH ≈ 6, when the ligand species H_2DOTA^{2-} predominates) shows that in the first 1–2 min of the reaction the intermediate is formed in a high concentration, while the amount of H^+ ions evolved is very low (about 5% of the total amount of H^+ which forms in the reaction). On the basis of these experiences we assume that the stable intermediate is a diprotonated CeH_2DOTA^+ complex, which slowly deprotonates by the formation of $CeDOTA^-$ ions. It is very probable that in the intermediate CeH_2DOTA^+

---

*Paper presented at the Second International Conference on the Basic and Applied Chemistry of f-Transition (Lanthanide and Actinide) and Related Elements (2nd ICLA), Lisbon, Portugal, April 6–10, 1987.

**Author to whom correspondence should be addressed.

0020-1693/87/$3.50

the protonation sites are the same as in the free ligand. Two nitrogen atoms of the macrocycle are protonated and the four carboxylate groups are coordinated only. The metal ion can enter into the cage of the ligand at the same time as the deprotonation of the intermediate.

The formation of the $CeDOTA^-$ ion can be described as a first-order reaction:

$$\frac{d[CeY]}{dt} = k_p[Y] \qquad (1)$$

where Y = DOTA and [Y] is the ligand concentration ($[Y] = [CeH_2Y] + [CeHY] + [H_2Y] + [H_3Y] + [H_4Y]$). The pseudo-first-order rate constants k_p obtained are shown in Table I.

From the data shown in Table I it could be stated that the rate of the formation of $CeDOTA^-$ is reversely proportional to the H^+ ion concentration ($k_p = k/[H^+]$). However, k_p values increase with increasing Ce^{3+} concentration, exhibiting a 'saturation' behaviour. These results can be explained by the following rate equation:

$$\frac{d[CeY]}{dt} = \frac{k_1K[Ce^{3+}][Y]}{[H^+] + K[H^+][Ce^{3+}]} \qquad (2)$$

where constant K is the stability constant of the intermediate CeH_2Y ($K = [CeH_2Y]/[Ce^3][H_2Y]$) and k_1 is the rate constant characteristic for the rate-controlling step of the reaction. This is probably the loss of the first proton from the intermediate CeH_2Y.

TABLE I. First-order Rate Constants Obtained for the Formation of $CeDOTA^-$

	pH[a]	$[Ce^{3+}]$ (M)	$10^4 \times k_p$ (s^{-1})[b]
1	4.10	1×10^{-2}	1.56
2	4.35	1×10^{-2}	3.15
3	4.61	1×10^{-2}	6.24
4	4.81	1×10^{-2}	10.5
5	5.09	1×10^{-2}	20.9
6	5.34	1×10^{-2}	42.1
7	5.59	1×10^{-2}	73.7
8	5.17	2×10^{-3}	26.6
9	4.70	2×10^{-3}	8.33
10	4.45	2×10^{-3}	5.90
11	5.01	5×10^{-4}	8.82
12	4.98	1×10^{-3}	12.6
13	4.97	2×10^{-3}	13.6
14	4.98	5×10^{-3}	15.1
16	4.96	1×10^{-2}	16.6
17	3.94	5×10^{-4}	0.73
18	3.94	1×10^{-3}	0.91
19	3.92	2×10^{-3}	1.08
20	3.91	5×10^{-3}	1.21
21	3.90	1×10^{-2}	1.28

[a] Corrected pH values from which the H^+ ion concentrations were calculated. [b] The reproducibility of the k_p values is about ±10%.

For the constants in eqn. (1) the following values were obtained: $K = 2.0 \times 10^3$ and $k_1 = 1.7 \times 10^{-8}$ s^{-1}.

Kinetics of Dissociation of CeDOTA

The dissociation of CeDOTA taking place in strongly acidic solutions can be described as a first-order process:

$$-\frac{d[CeY]}{dt} = k_0[CeY] \qquad (3)$$

where k_0 is a pseudo-first-order rate constant.

The k_0 values obtained in $HClO_4$ solutions of various concentration are shown in Fig. 2. The data presented in Fig. 2 indicate that the rate of dissociation increases with increasing H^+ concentration and the k_p values can be expressed by eqn. (4).

$$k_0 = k_1[H^+] + k_2[H^+]^2 \qquad (4)$$

where $k_1 = (8 \pm 2) \times 10^{-4}$ s^{-1} and $k_2 = (2 \pm 0.5) \times 10^{-3}$ M^{-1} s^{-1}. This rate expression is similar to those obtained for the proton-assisted dissociation of the aminopolycarboxylate complexes, but the rate of dissociation of $CeDOTA^-$ is much lower. Equation (4) also indicates that the competition of protons for the ligand DOTA and presumably the protonation of $CeDOTA^-$ plays a predominant role in the dissociation of the complex.

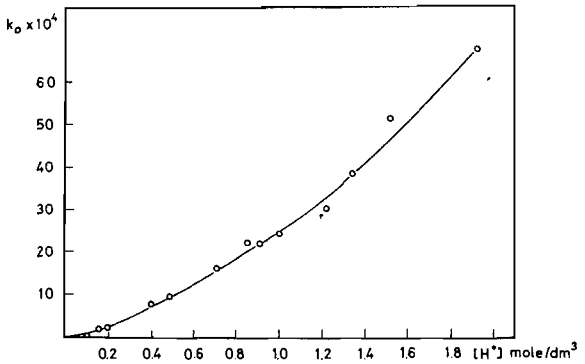

Fig. 2. Dependence of the rate of dissociation of CeDOTA on the H^+ ion concentration.

Acknowledgement

The authors are grateful to J. F. Desreux for providing the sample of DOTA.

References

1 J. F. Desreux, *Inorg. Chem., 19,* 1319 (1980).
2 E. Brücher and G. Laurenczy, *Inorg. Chem., 22,* 338 (1983).
3 C. F. G. C. Geraldes, A. D. Sherry, R. D. Brown and S. H. Koenig, *Magn. Reson. Med., 3,* 42 (1986).