

Note

Stability constants of the lanthanide(III)-1,4,7,10-tetraazacyclododecane-*N,N',N'',N'''*-tetraacetate complexes

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Abstract

The stability constants of the LnDOTA⁻ complexes have been determined by spectrophotometry at 37 °C in 1.0 M NaCl. The log *K* values of CeDOTA⁻ and EuDOTA⁻ were obtained by a direct method using the UV absorption of Ce³⁺ and Eu³⁺. For the other lanthanides log *K* values were obtained from the study of the competition reaction between the Ln³⁺ ion and the Ce³⁺ or Eu³⁺ ion for DOTA. The stability constants increase with the decrease in the ionic size between La³⁺ and Eu³⁺, while for the heavier lanthanides the log *K* values are practically constant.

Key words: Stability constants; Lanthanide complexes; Azamacrocyclic ligand complexes; Contrast agent complexes; Gadolinium complexes

Introduction

The complexes of trivalent lanthanides (Ln³⁺) formed with the macrocyclic ligand 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (H₄DOTA) show very peculiar properties. The formation rate of the complexes is unusually low, and DOTA forms the most stable complexes known to date with the Ln³⁺ ions [1–4]. The structure, equilibrium and kinetic properties of the complexes have been studied by several groups, since besides the interesting chemistry of these compounds, GdDOTA⁻ is used as a relaxation enhancement agent in magnetic resonance imaging to improve image contrast [5–7]. However, despite such interest, the stability constants of the complexes are disputed [8], because the slow formation reactions do not allow the application of the usual experimental methods (e.g. pH-potentiometric titration) for equilibrium studies.

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Cacheris *et al.* [3] determined the stability constants for the whole series of lanthanides by using a competition reaction between DOTA and Arsenazo III. Loncin *et al.* [2] obtained much higher log *K* values for the complexes of Eu, Tb and Lu in a study of the increase of the solubility of the Ln³⁺ oxalates in the presence of DOTA. Most recently the same group reported [9] a much lower log *K* value for GdDOTA⁻, than those known so far. Clarke and Martell [8] described the stability constants of LaDOTA⁻ and GdDOTA⁻ obtained by pH-metry using the batch method.

Since complex formation results in a significant change in the UV absorption bands of Ce³⁺ and Eu³⁺, we have determined the stabilities of CeDOTA⁻ and EuDOTA⁻ by direct spectrophotometry. The stability constants of the complexes of the other lanthanides were obtained from a study of the competition reaction between the Ce³⁺ or Eu³⁺ and another Ln³⁺ ion for the ligand DOTA.

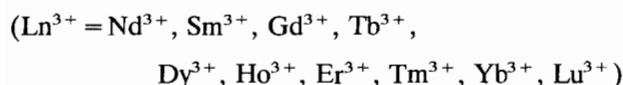
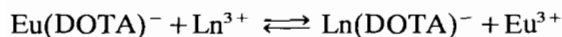
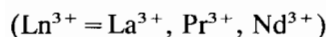
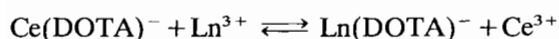
Experimental

LnCl₃ stock solutions were prepared by dissolving lanthanide oxides in HCl. The concentration of the LnCl₃ solutions was determined by complexometry using standardized Na₂H₂EDTA solution and xylenol orange as indicator.

The concentration of the H₄DOTA (Schering) solution was determined pH-potentiometrically by titrating the solution with standardized NaOH in the absence and presence of excess CaCl₂. The 4f–5d transition bands of Ce³⁺ and the charge transfer band of Eu³⁺ are strongly shifted towards the longer wavelengths when the DOTA complexes are formed. The spectra were recorded at six different pH values between pH=1.8 and 3.5, and for the calculations eight absorbance values, measured in the region of 316–330 nm for CeDOTA⁻ and 253–267 nm for EuDOTA⁻, were used. The molar absorbance values were found between 300 and 600 M⁻¹ cm⁻¹ for CeDOTA⁻ and 150 and 200 M⁻¹ cm⁻¹ for EuDOTA⁻. The absorbance of the free ions and of the ligand DOTA is negligible at these wavelengths.

The concentration of DOTA was 1 × 10⁻³ or 2 × 10⁻³ M, while that of the Ln³⁺ ion was varied between 1 × 10⁻³ and 6 × 10⁻³ M.

The stability constants of the lanthanides, other than Ce³⁺ and Eu³⁺, were obtained by investigating the competition reactions in the following systems:



The measurements were carried out in 1.0 M NaCl solutions at 37 °C. In the competition reactions the ligand was added to a solution containing the metal ions. Because of the slow formation reactions of the complexes, the samples were kept in closed vessels for 20 days for attaining equilibrium. After this period of time neither the pH nor the absorbance of the samples changed.

The spectrophotometric measurements were carried out with a Varian DMS 100 spectrophotometer using 1.0 cm cells. For pH measurements a Radiometer PHM-85 pH-meter was used with a Radiometer combined electrode. Hydrogen ion concentrations were calculated from the measured pH values according to the method suggested by Irving *et al.* [10]; the value of pK_w was 13.59. Equilibrium calculations were performed with the computer program PSEQUAD [11].

Results and discussion

The protonation constants of DOTA ($K_i = [\text{H}_i\text{L}]/[\text{H}_{i-1}\text{L}][\text{H}^+]$), used in the calculation of the stability constants at 37 °C ($\log K_1 = 10.80$, $\log K_2 = 9.00$, $\log K_3 = 4.24$, $\log K_4 = 4.05$), were calculated from the $\log K_i$ values determined by Desreux *et al.* [12] at 25 °C ($\log K_1 = 11.08$, $\log K_2 = 9.23$, $\log K_3 = 4.24$, $\log K_4 = 4.18$) and 80 °C ($\log K_1 = 9.95$, $\log K_2 = 8.28$, $\log K_3 = 4.22$, $\log K_4 = 3.65$) in 1.0 M NaCl by assuming a linear relation between $\log K$ values and $1/T$ (1/Kelvin).

The stability constants ($K = [\text{LnL}]/[\text{Ln}][\text{L}]$) of the LnDOTA⁻ complexes, determined by means of both direct and indirect spectrophotometric methods, are shown in Table 1. For comparison, Table 1 contains all the $\log K$ values known so far in the literature.

The reproducibility of the stability constants determined by spectrophotometry was unexpectedly good. The standard deviation of the $\log K$ values was lower than ± 0.1 $\log K$ unit. A more real error could be estimated as the average reproducibility of the $\log K$ values, which was in general ± 0.1 $\log K$, and always lower than ± 0.2 $\log K$ unit.

The stability constants obtained at 37 °C in this work are generally a little lower than those obtained by Cacheris *et al.* [3] and Clarke and Martell [8] at 25 °C. The lower value of the stability constants is partly

TABLE 1. The stability constants ($\log K$) of LnDOTA⁻ complexes

	This work 1 M NaCl 37 °C	Ref. 3 0.1 M KCl 25 °C	Other work
La	20.7	22.9	21.7 ^c
Ce	21.6	23.4	
Pr	22.4	23.0	
Nd	22.5	23.0	
Sm	23.3	23.0	
Eu	23.7	23.5	28.2 ^a
Gd	23.6	24.7	22.1 ^b ; 24.0 ^c
Tb	23.6	24.2	28.6 ^a
Dy	23.5	24.8	
Ho	23.5	24.5	
Er	23.5	24.4	
Tm	23.7	24.4	
Yb	24.0	25.0	
Lu	23.5	25.4	29.2 ^a

^aRef. 2; 20 °C, 1.0 M NaCl. ^bRef. 9; 25 °C, 1.0 M NaCl.

^cRef. 8; 25 °C, 0.1 M KCl.

the consequence of the lower protonation constants and the negative formation enthalpy of the complexes (ΔH values are not known for the DOTA complexes, but presumably they are of negative sign). There are also some differences in the experimental conditions. The $\log K$ values obtained for EuDOTA⁻, TbDOTA⁻ and LuDOTA⁻ by Loncin *et al.* [2] are 4–5 orders of magnitude higher, while that reported for GdDOTA⁻ [9] is about 2 orders of magnitude lower than the other known data. From a comparison of the stability constants presented in Table 1, it can be seen that the $\log K$ values reported here and those of Cacheris *et al.* [3] and Clarke and Martell [8] are more reliable.

Taking into account the very high thermodynamic stability of the complexes, it is surprising to read the statement in the paper of Clarke and Martell [8] about the precipitation of Gd(OH)₃ from a solution of GdDOTA⁻ at a pH about 7. This finding was probably due to the presence of a slight excess of Gd³⁺ in the solution.

The $\log K$ values obtained in this work exhibit a progressive increase from La to Eu–Gd, and remain roughly unchanged for the heavier lanthanides. This trend is slightly different from that of the $\log K$ values published by Cacheris *et al.* [3], who found a sharp increase in the $\log K$ values between Sm and Gd.

At lower pH values protonated complexes, LnHDOTA, are formed, as was shown by Clarke and Martell [8]. Since the spectra of the protonated CeHDOTA or EuHDOTA do not differ from those of the non-protonated complexes, the stability constants of the protonated complexes ($K_{\text{LnHL}} = [\text{LnHL}]/[\text{LnL}][\text{H}^+]$) cannot be determined from spectrophotometric data. (The stability constants obtained for

EuDOTA⁻ and CeDOTA⁻ at different pH values have no dependence on pH). For EuDOTA⁻ a direct pH-metric titration of the complex with HCl at 25 °C resulted in a value of $\log K_{\text{EuHL}} = 1.8 \pm 0.2$. This protonation constant is comparable with the value $\log K_{\text{GdHL}} = 2.3 \pm 0.2$ calculated by Clarke and Martell [8] from the titration data obtained by the batch method.

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