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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 Ce^{3+} and Eu^{3+}. For the other lanthanides log K values were obtained from the study of the competition reaction between the Ln^{3+} ion and the Ce^{3+} or Eu^{3+} ion for DOTA. The stability constants increase with the decrease in the ionic size between La^{3+} and Eu^{3+}, 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 (Ln^{3+}) formed with the macrocyclic ligand 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (H_4DOTA) 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 Ln^{3+} 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.

Cacheris *et al.* [3] determined the stability constants for the whole series of lanthanides by using a competition reaction between DOTA and Arsenaso 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 Ln^{3+} 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 Ce^{3+} and Eu^{3+}, 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 Ce^{3+} or Eu^{3+} and another Ln^{3+} ion for the ligand DOTA.

Experimental

$LnCl_3$ stock solutions were prepared by dissolving lanthanide oxides in HCl. The concentration of the $LnCl_3$ solutions was determined by complexometry using standardized Na_2H_2EDTA solution and xylenol orange as indicator.

The concentration of the H_4DOTA (Schering) solution was determined pH-potentiometrically by titrating the solution with standardized NaOH in the absence and presence of excess $CaCl_2$. The 4f–5d transition bands of Ce^{3+} and the charge transfer band of Eu^{3+} 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 Ln^{3+} ion was varied between 1×10^{-3} and 6×10^{-3} M.

The stability constants of the lanthanides, other than Ce^{3+} and Eu^{3+}, were obtained by investigating the competition reactions in the following systems:

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$$\mathrm{Ce(DOTA)^- + Ln^{3+} \rightleftharpoons Ln(DOTA)^- + Ce^{3+}}$$

$$\mathrm{(Ln^{3+} = La^{3+}, Pr^{3+}, Nd^{3+})}$$

$$\mathrm{Eu(DOTA)^- + Ln^{3+} \rightleftharpoons Ln(DOTA)^- + Eu^{3+}}$$

$$\mathrm{(Ln^{3+} = Nd^{3+}, Sm^{3+}, Gd^{3+}, Tb^{3+}, Dy^{3+}, Ho^{3+}, Er^{3+}, Tm^{3+}, Yb^{3+}, Lu^{3+})}$$

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 ($K_i = [H_iL]/[H_{i-1}L][H^+]$), 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 ($K = [LnL]/[Ln][L]$) 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.

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]

[a] Ref. 2; 20 °C, 1.0 M NaCl. [b] Ref. 9; 25 °C, 1.0 M NaCl.
[c] Ref. 8; 25 °C, 0.1 M KCl.

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 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 Gd^{3+} 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 ($K_{LnHL} = [LnHL]/[LnL][H^+]$) 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 $\log K_{EuHL} = 1.8 \pm 0.2$. This protonation constant is comparable with the value $\log K_{GdHL} = 2.3 \pm 0.2$ calculated by Clarke and Martell [8] from the titration data obtained by the batch method.

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