4070 *Inorg. Chem.* **1994,** *33,* 4070–4076

Kinetics of Formation and Dissociation of Lanthanide(III)–DOTA Complexes

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Received December 8, 1993[⊗]

The formation rates of Ce(DOTA)$^-$, Eu(DOTA)$^-$, and Yb(DOTA)$^-$ have been studied at 25 °C and $I = 1.0$ M (NaCl) by spectrophotometry (Ce^{3+}, Eu^{3+}) and an indicator method (Yb^{3+}). (H_4DOTA = 1,4,7,10-tetraazacyclododecane-*N,N′,N″,N‴*-tetraacetic acid.) In the formation reaction, a diprotonated intermediate, Ln(H_2DOTA)$^+$, is formed very rapidly and slowly rearranges to the product. The intermediates Ce(H_2DOTA)$^+$ and Eu(H_2DOTA)$^+$ have been detected by spectrophotometry. The stability constants of the intermediates were determined by pH-metry and spectrophotometry. ^{1}H-NMR studies indicate that, in the diprotonated intermediates, only the carboxylate groups are coordinated to the metal ions. The rearrangements of the intermediates occurring by the loss of two protons are OH$^-$ ion catalyzed processes. The rate constants, k_{OH}, obtained for Ce^{3+}, Eu^{3+}, and Yb^{3+} are $(3.5 \pm 0.06) \times 10^6$, $(1.1 \pm 0.07) \times 10^7$, and $(4.1 \pm 0.4) \times 10^7$ M^{-1} s^{-1}, respectively. The dissociation of Gd(DOTA)$^-$ and Eu(DOTA)$^-$ is catalyzed by H$^+$ ions. In the pH range of 3.2–5.0 the dissociation of Gd(DOTA)$^-$ occurs via the formation of a monoprotonated complex. The rate constant for the proton-assisted dissociation is $k_1' = (2.0 \pm 0.1) \times 10^{-5}$ M^{-1} s^{-1}. In the interval 0.018 M < [H$^+$] < 2.5 M, the dissociation of Eu(DOTA)$^-$ proceeds through the formation of mono- and diprotonated intermediates. The protonation constants of Gd(DOTA)$^-$ and HGd(DOTA) are $K_1 = 14 \pm 1$ and $K_2 = 0.12 \pm 0.03$, while the rate constants characteristic for their dissociation are $(1.0 \pm 0.5) \times 10^{-6}$ and $(6.2 \pm 0.5) \times 10^{-4}$ s^{-1}, respectively.

Introduction

In recent years there has been growing interest in the synthesis and complexation properties of functionalized 12-membered macrocyclic tetraaza ligands. This has been motivated by both the chemical properties and successful practical application of these ligands. The most important representative of the group is 1,4,7,10-tetraazacyclododecane-*N,N′,N″,N‴*-tetraacetic acid (H_4DOTA). The complexes of DOTA formed with trivalent lanthanides (Ln^{3+}) have the highest stability constants known so far, and both their formation and dissociation rates are much lower than those of acyclic polyamino polycarboxylates, like EDTA.[1-9] The high thermodynamic and kinetic stabilities are of importance in the use of Gd(DOTA)$^-$ as a proton relaxation rate ($1/T_1$) enhancement agent (contrast agent) in magnetic resonance imaging (MRI).[10,11] On the basis of their high stability and slow dissociation, the complexes ^{90}Y(DOTA)$^-$ and ^{212}Pb(DOTA)$^-$ attached to monoclonal antibodies are potential drugs in the therapy of cancer.[12-14] In order to decrease the osmolality of the Gd^{3+}-containing contrast agents in MRI, several new triacetate DOTA analogues have been synthesized.[15-19] The derivatives of H_3DO3A (1,4,7,10-tetraazacyclododecane-*N,N′,N″*-triacetic acid) form neutral complexes with the Gd^{3+} ion. The thermodynamic and kinetic stabilities of these complexes are somewhat lower than the similar properties of Gd(DOTA)$^-$ but sufficiently high to fulfill the requirements of contrast agents.[18]

Most recently, efforts were made to use the complexes of Dy^{3+} in MRI as $1/T_2$ enhancement agents, since the change in susceptibility around water molecules results in an increase in the transverse relaxation rates.[20]

Due to the practical importance of DOTA and its derivatives, some aspects of their complexation properties have been studied in detail. The protonation constants of DOTA were determined in different media.[4,21,22] The structures of NaEu(DOTA) and NaGd(DOTA) have been determined by X-ray diffraction.[23] The structures of the Ln(DOTA)$^-$ complexes in solution were investigated by ^{1}H- and ^{13}C-NMR methods.[1,23b,24] The structures in the solid state and in solution were found to be similar: Ln^{3+} ions are located in a coordination cage determined by the planes of the four nitrogen and four oxygen donor atoms. Above the plane of the oxygens a H_2O molecule is coordinated in the inner sphere of the Ln^{3+} ion.[23,25] This H_2O molecule has a very important role in transfer of the paramagnetic effect of Gd^{3+} to

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[⊗] Abstract published in *Advance ACS Abstracts,* August 1, 1994.

(1) Desreux, J. F. *Inorg. Chem.* **1980,** *19,* 1319.

(2) Loncin, M. F.; Desreux, J. F.; Merciny, E. *Inorg. Chem.* **1986,** *25,* 2646.

(3) Cacheris, W. P.; Nickle, S. K.; Sherry, A. D. *Inorg. Chem.* **1987,** *26,* 958.

(4) Clarke, E. T.; Martell, A. E. *Inorg. Chim. Acta* **1991,** *190,* 37.

(5) Aime, S.; Anelli, P. L.; Botta, M.; Fedeli, F.; Grandi, M.; Paoli, P.; Uggeri, F. *Inorg. Chem.* **1991,** *31,* 2422.

(6) Tóth, E.; Brücher, E. *Inorg. Chim. Acta* **1994,** *221,* 165.

(7) Magerstadt, M.; Gansow, O. A.; Brechbiel, M. W.; Colcher, D.; Baltzer, L.; Knop, R. H.; Girton, M. E.; Naegele, M. *Magn. Reson. Med.* **1986,** *3,* 808.

(8) Brücher, E.; Laurenczy, G.; Makra, Zs. *Inorg. Chim. Acta* **1987,** *139,* 141.

(9) Wang, X.; Jin, T.; Comblin, V.; Lopez-mut, A.; Merciny, E.; Desreux, J. F. *Inorg. Chem.* **1992,** *31,* 1095.

(10) Lauffer, R. B. *Chem. Rev.* **1987,** *87,* 901.

(11) Tweedle, M. F. Lanthanide Probes in Life. In *Chemical and Earth Sciences*; Bunzli, J.-C. G., Choppin, G. R., Eds.; Elsevier: Amsterdam, 1989; p 127.

(12) Moi, M. K.; Meares, C. F.; DeNardo, S. J. *J. Am. Chem. Soc.* **1988,** *110,* 6266.

(13) Brown, C. J.; Cox, J. P. L.; Craig, A. S.; Kataky, R.; Parker, D.; Harrison, A.; Randall, A. M.; Feruson, G. *J. Chem. Soc., Perkin Trans. 2* **1991,** 87.

(14) Kumar, K.; Magerstadt, M.; Gansow, O. A. *J. Chem. Soc., Chem. Commun.* **1989,** 145.

(15) Dischino, D. D.; Delaney, E. J.; Emswiler, J. E.; Gaughan, G. A.; Prasad, J. S.; Srivastava, S. K.; Tweedle, M. F. *Inorg. Chem.* **1991,** *30,* 1265.

(16) Sherry, A. D.; Brown, R. D.; Geraldes, C. F. G. C.; Koenig, S. H.; Kuan, K. T.; Spiller, M. *Inorg. Chem.* **1989,** *28,* 620.

(17) Cox, J. P. L.; Craig, A. S.; Helps, L. M.; Jandowski, K. J.; Parker, D.; Eaton, M. A. W.; Millican, A. T.; Beeley, N. R. A.; Boyce, B. A. *J. Chem. Soc., Perkin Trans. 1* **1990,** 2567.

(18) Kumar, K.; Chang, C. A.; Tweedle, M. F. *Inorg. Chem.* **1993,** *32,* 587.

(19) Lim, M.; Meares, C. F. *Bioconjugate Chem.* **1993,** *4,* 275.

(20) Kennan, R. P.; Zhong, J.; Gore, J. C. *Magn. Reson. Med.* **1991,** *22,* 197.

(21) Desreux, J. F.; Merciny, E.; Loncin, M. F. *Inorg. Chem.* **1981,** *20,* 987.

(22) Delgado, R.; Frausto da Silva, J. J. R. *Talanta* **1982,** *29,* 815.

(23) (a) Chang, C. A.; Francesconi, L. C.; Malley, M. F.; Kumar, K.; Gougoutas, J. Z.; Tweedle, M. F.; Lee, D. W.; Wilson, L. J. *Inorg. Chem.* **1993,** *32,* 3501. (b) Spirlet, M.-R.; Rebizant, J.; Desreux, J. F.; Loncin, M. F. *Inorg. Chem.* **1984,** *23,* 359.

(24) Aime, S.; Botta, M.; Ermondi, G. *Inorg. Chem.* **1992,** *31,* 4291.

(25) Bryden, C. C.; Reilley, C. N. *Anal. Chem.* **1982,** *54,* 610.

0020-1669/94/1333-4070$04.50/0

bulk water through an exchange reaction. This exchange is slower than that taking place between $Gd(OH_2)_8^{3+}$ and bulk water.[26]

While the structures of these complexes are well-known, the stability constants obtained by different authors differ very considerably.[2–6] The main reason for discrepancies is slow complex formation. As a consequence, 2–3 weeks is needed to attain equilibrium and the various indirect "batch" techniques lead to the diverging results. Recently, we reported the stability constants for the whole series of lanthanides obtained by direct (Ce^{3+}, Eu^{3+}) and indirect spectrophotometry (competition reactions).[6]

The rates of dissociation of $Ln(DOTA)^-$ complexes have been studied in relatively strongly acidic solutions.[8,9] Dissociation is catalyzed by H^+ ions, but the contribution of spontaneous dissociation is difficult to estimate because of the acidic solutions used, which are far from physiological conditions.

The results for the formation rates of $Ce(DOTA)^-$ and $Gd(DOTA)^-$ were interpreted by considering the rate-controlling role of different intermediates. In $Ce(DOTA)^-$ formation, a diprotonated $Ce(H_2DOTA)^+$ intermediate has been detected.[8] However, for the formation of $Gd(DOTA)^-$, Marques et al. proposed Gd(HDOTA) as an intermediate,[27] while Wang et al. found $HDOTA^{3-}$ a kinetically active species in the reaction with Gd^{3+}.[9]

Recently, we studied the kinetics of formation of Ce^-, Eu^-, and $Yb(DOTA)^-$ in order to obtain information for the whole series of lanthanides. The dissociation rate of $Gd(DOTA)^-$ was studied at pH 3.2–5.0, which is much closer to physiological conditions than the pH range used earlier. The dissociation of $Eu(DOTA)^-$ was studied in a broad interval of H^+ ion concentrations.

Experimental Section

Synthesis of 1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetrakis(acetic acid ethyl ester) (DOTAE) and $H_4DOTA{\cdot}2HCl$. DOTAE and DOTA were prepared by a procedure similar to that described in the literature.[28] Cyclen (812.9 mg, 4.718 mmol), anhydrous sodium carbonate (4.0 g), and ethyl bromoacetate (3.00 mL, 27.05 mmol) were dissolved in dimethylformamide with vigorous stirring. The mixture was kept at 60 °C for 18 h and at 93–95 °C for 3 h and was then cooled to room temperature. After the mixture was centrifuged, the supernatant was decanted from over a solid, which was then washed with 2 mL of DMF, centrifuged, and decanted. The mother liquor and the washing were combined and evaporated under high vacuum at 90 °C to a solid that was suspended in chloroform, and the mixture was filtered. After evaporation of the filtrate, the residue was redissolved in methylene chloride, the solution was filtered, and the filtrate was evaporated again, yielding a viscous brown oil which proved to be a mixture of DOTAE and sodium carbonate (2.369 g). The oil was dissolved in a mixture of water (3 mL) and hydrochloric acid (38%, 4 mL), and the solution was refluxed for 30 min. After this, the flask was covered with cotton wool and allowed to cool to room temperature. Next day, the crystals formed were filtered off, washed with hydrochloric acid (38%, 2 × 0.4 mL), absolute ethanol (4 × 5 mL), and ether (2 × 5 mL), and dried, giving a snow-white nonhygroscopic solid. From the mother liquor another crop settled out on addition of absolute ethanol. This was filtered off and washed and dried as previously. The first and second crops were combined, resulting in a white solid which was identified as $H_4DOTA{\cdot}2HCl$ (1.442 g, 3.02 mmol, 68%), on the basis of ^1H NMR, chloride analysis, and potentiometric titrations. ^1H NMR (200 MHz, D_2O, pD 7 phosphate buffer, reference TSP): $\delta = 3.61$ (s, 8H, CH_2COO), 3.27 (s, 16H, NCH_2).

The concentration of H_4DOTA was determined pH-potentiometrically by titrating the solution with standard NaOH in the absence and presence of excess $CaCl_2$ or by complexometry determining the excess of Eu^{3+} which did not react with DOTA, using Na_2H_2EDTA solution and xylenol orange as indicator.

$Gd(DOTA)^-$–meglumine (DOTAREM) used in the dissociation studies was a product of Guerbet. Spectrophotometric measurements on the Gd(DOTA) solution in the presence of Ce^{3+} or Eu^{3+} indicated 0.3% free ligand, which was subsequently converted to $Gd(DOTA)^-$ with an equivalent amount of Gd^{3+}.

Stock solutions of Ce^{3+}, Eu^{3+}, and Yb^{3+} were prepared by dissolving lanthanide oxides in HCl, and their concentrations were determined by complexometry using standard Na_2H_2EDTA solution and xylenol orange as indicator.

The ionic strength of the sample solutions was 1 M (NaCl) in the complex formation reactions. The dissociation rate of $Gd(DOTA)^-$ was studied in 0.1 M $Gd(DOTA)^-$–meglumine solution.

For pH measurements a Radiometer pHM-85 pH-meter with a Radiometer combined electrode (GK 2421 C) was used in NaCl solutions. In $NaClO_4$ solutions we used a Radiometer glass electrode (G 202B) and a calomel electrode (K 401; filled with saturated NaCl). The H^+ ion concentration was calculated from the measured pH values using the method suggested by Irving et al.[29] The stability constants of the intermediates were calculated with the program PSEQUAD.[30] The protonation constant of $EuDOTA^-$ was determined at $I = 3$ M ($NaClO_4$), 25 °C. A 3 M $NaClO_4$ solution was titrated with 0.25 M $HClO_4$ (+2.75 M $NaClO_4$) in the absence and presence of $Eu(DOTA)^-$ (0.01 and 0.017 M). In order to determine the stability constant of the $Ln(H_2DOTA)^+$ intermediates ($I = 1.0$ M (NaCl)), samples prepared by mixing H_4-DOTA and $LnCl_3$ solutions were titrated immediately with 0.25 M NaOH (between two doses of NaOH 10–15 s was sufficient to obtain "equilibrium" pH value). Spectrophotometric measurements were carried out on a Varian DMS 100 spectrophotometer, using thermostated cells at 25 °C in the case of formation reactions and the dissociation of $Eu(DOTA)^-$ or at 37 °C in the case of $Gd(DOTA)^-$ dissociation. NMR spectra were recorded on a Bruker WP 200 SY spectrometer.

Formation Kinetics. The formation rates of $Ce(DOTA)^-$ were studied by following the changes in the absorbance of $Ce(DOTA)^-$ at 317 nm or that of the intermediate at 296 nm, where the absorbance of uncomplexed Ce^{3+} is not significant. The formation of $Eu(DOTA)^-$ was studied by following the increase of absorbance of the complex at 253 nm, where Eu^{3+} (aq) does not absorb. In the case of $Yb(DOTA)^-$ the formation was studied in slightly buffered solutions by monitoring the pH decrease (0.05–0.1 pH unit) with bromocresol green (615 nm; pH 4.2–4.7) as indicator.[31] The concentrations of DOTA were 2×10^{-4}, 2×10^{-3}, and 1×10^{-3} M in the reactions of Ce^{3+}, Eu^{3+}, and Yb^{3+}, respectively. The metal concentrations were varied between 2×10^{-4} and 2×10^{-3} M (Ce), 2×10^{-3} and 2×10^{-2} M (Eu), and 1×10^{-3} and 2×10^{-2} M (Yb). The buffer used in all the kinetic measurements was *N*-methylpiperazine, and its suitable concentration was determined experimentally.

Dissociation Kinetics. To elucidate the dissociation of $Gd(DOTA)^-$, the rate of the exchange reaction

$$Gd(DOTA)^- + Eu^{3+} \rightleftharpoons Eu(DOTA)^- + Gd^{3+} \qquad (1)$$

has been studied under nearly physiological conditions (pH 3.2–5.0; 37 °C). The reaction can be readily followed by spectrophotometry, since the formation of $Eu(DOTA)^-$ results in a significant change in the UV spectrum of Eu^{3+}, while neither $Gd(DOTA)^-$ nor Gd^{3+} has any absorption in this range (between 253 and 267 nm). The rate of dissociation at higher pHs was studied at 0.1 M $Gd(DOTA)^-$ and 0.01 or 0.005 M Eu^{3+} (pseudo-first-order conditions). The exchange reactions were followed until $[Eu(DOTA)^-]$ reached 0.001 M, which took about 20–30 days. The samples were kept in closed vessels during this time. Under such conditions, when $[Gd(DOTA)^-]$ is very high and the $Eu(DOTA)^-$ formed can be detected easily (0.0001–0.001 M), the extremely slow dissociation of $Gd(DOTA)^-$ could be studied.

The dissociation of $Eu(DOTA)^-$ was studied in 0.018–2.5 M $HClO_4$ ($NaClO_4$ was added to maintain an ionic strength of 3.0 M). The reaction

$$Eu(DOTA)^- + nH^+ \rightleftharpoons Eu^{3+} + H_nDOTA^{(4-n)-} \qquad (2)$$

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(26) Micskei, K.; Helm, L.; Brücher, E.; Merbach, A. E. *Inorg. Chem.* **1993**, *32*, 3844.

(27) Marques, M. P. M.; Geraldes, C. F. G. C.; D'Olieslager, W. *Eur. J. Solid State Inorg. Chem.* **1991**, *28*, 251.

(28) Craig, A. S.; Helps, I. M.; Jankowski, K. J.; Parker, D.; Beeley, N. R. A.; Boyce, B. A.; Eaton, M. A. W.; Millican, A. T.; Millar, K.; Phipps, A.; Rhind, S. K.; Harrison, A.; Walker, C. *J. Chem. Soc., Chem. Commun.* **1989**, 794.

(29) Irving, H. M.; Miles, M. G.; Pettit, L. *Anal. Chim. Acta* **1967**, *38*, 475.

(30) Zékány, L.; Nagypál, I. In *Computational Methods for Determination of Formation Constants*; Legatt, D. J., Ed.; Plenum Press: New York, 1985; p 291.

(31) Kasprzyk, S. P.; Wilkins, R. G. *Inorg. Chem.* **1982**, *21*, 3349.

was followed by spectrophotometry at 253–262 nm (25 °C). The concentration of $Eu(DOTA)^-$ was 3×10^{-3} M.

Results and Discussion

Kinetics of Formation of Ce-, Eu-, and $Yb(DOTA)^-$. The reaction between the Ln^{3+} ions and DOTA is slow in the pH interval 3–5, and the formation of the $Ln(DOTA)^-$ complexes can be studied by conventional techniques. In this pH range DOTA is present in the forms H_2DOTA^{2-}, H_3DOTA^-, and H_4DOTA (the logarithms of the protonation constants are 11.14, 9.69, 4.85, and 3.95[21]; thus the formation of $Ln(DOTA)^-$ complexes takes place with the release of several protons.

The spectrophotometric data were consistent with a first-order process even at equal metal and ligand concentrations. Similar results were found for the formation of $La(CDTA)^-$, which indicates the formation of a reaction intermediate.[37]

In the formation study of $Ce(DOTA)^-$ a stable intermediate was detected by spectrophotometry.[8] In the UV spectrum of Ce^{3+}(aq) absorption bands due to 4f–5d transitions appear between 210 and 260 nm. In the reaction of Ce^{3+}(aq) and $H_iDOTA^{(4-i)-}$ ($2 < i < 4$) two new bands appear, showing maxima at 296 and 317 nm (Figure 1a). The band at 296 nm appears immediately after mixing the reactants. The intensity of this band decreases in time, which is characteristic of the formation of an intermediate. However, the band at 317 nm increases as the reaction progresses, and it proved to be an absorption band of the product, $Ce(DOTA)^-$. The pH change during the reaction helped to determine the composition of the intermediate. At the start of the reaction there is an abrupt drop in pH in a nonbuffered solution, which is followed by a slow pH decrease. The amount of H^+ ions liberated in the fast and then in the slow processes (calculated from the pH changes) indicates that the intermediate is a diprotonated complex, $Ce(H_2DOTA)^+$. As an example, in the reaction between $H_{2.95}DOTA^-$ (0.001 M) and Ce^{3+} (0.005 M), the pH changes caused by the formation of the intermediate and the product have been determined in a 10-mL weakly buffered solution (0.055 M *N*-methylpiperazine; pH = 4.24; 1 M NaCl). After mixing of the reactants (20–30 s), the pH dropped to 4.14, while 24 h later the equilibrium pH was 3.79. The amount of H^+ ions released in the rapid and slow processes was determined by titrating 10 mL of 0.055 M *N*-methylpiperazine solution (pH = 4.24; 1 M NaCl) with 0.2039 M HCl. The volumes of HCl necessary to decrease the pH to 4.14 and then to 3.79 were found to be 0.045 and 0.090 mL. The amount of H^+ ions released during the first 30 s (when the intermediate is formed) is half of that released in the slow period of the reaction (when the product is formed). This proves that the composition of the intermediate is practically $Ce(H_2DOTA)^+$. The abrupt drop in pH was insignificant when $CeCl_3$ reacted with a solution of $Na_2(H_2DOTA)$ (pH = 6.2), where the species H_2DOTA^{2-} predominates and the formation of $Ce(H_2DOTA)^+$ does not result in the release of any protons. A study of the reaction between Eu^{3+}(aq) and DOTA has led to similar results, indicating that the complexes of other lanthanides are also formed via a diprotonated $Ln(H_2DOTA)^+$ intermediate.

Taking into account the fast formation of the intermediate, it can be inferred that the formation of the product occurs by slow rearrangement of the intermediate taking place with the loss of two protons. The rearrangement proceeds via several consecutive steps, of which the slowest one is the rate-controlling process. The formation of $Ln(DOTA)^-$ can be described by

$$Ln^{3+} + H_iDOTA \rightleftharpoons Ln(H_2DOTA)^+ + (i-2)H^+ \quad (3)$$

$$Ln(H_2DOTA)^+ \xrightarrow[-H^+]{\text{slow}} Ln(HDOTA) \xrightarrow[-H^+]{\text{slow}} Ln(DOTA)^- \quad (4)$$

The formation rate of $Ln(DOTA)^-$ complexes in the presence of excess metal ion can be given as

$$\frac{d[Ln(DOTA)^-]}{dt} = k_f[DOTA] \quad (5)$$

where [DOTA] is the total concentration of the free ligand and k_f is a pseudo-first-order rate constant. The reaction was studied at different metal ion concentrations, and the plot of the k_f values against the lanthanide ion concentration gave a saturation curve, as was found for the formation of $Gd(DOTA)^-$.[9] The relationship between k_f values and the Ln^{3+} concentration can be expressed by the following equation:[32]

$$k_f = \frac{kK^{**}[Ln^{3+}]}{1 + K^{**}[Ln^{3+}]} \quad (6)$$

where K^{**} is the equilibrium constant characterizing the formation of the intermediate[34] (the stability constant of the diprotonated intermediate, $Ln(H_2DOTA)^+$, is $K^* = [Ln(H_2DOTA)^+]/[Ln^{3+}][H_2DOTA^{2-}]$) and k is the rate constant of the deprotonation and rearrangement of the intermediate to product ("saturation" k_f value). Constant K^* can be calculated from k_f values obtained at different $[Ln^{3+}]$ at a given pH. Instead of this procedure, we determined stability constants K^* by direct spectrophotometric measurements in the cases of $Ce(H_2DOTA)^+$ and $Eu(H_2DOTA)^+$ (Figure 1b,d) and by a competition method for $Yb(H_2DOTA)^+$. Parts a and c of Figure 1 show UV spectra of the product and the intermediate. Since the intermediates are sufficiently stable, it is easy to find conditions where $Ce(H_2DOTA)^+$ or $Eu(H_2DOTA)^+$ is formed in practically 100% yield (Figure 1c,d) and the molar absorptivity can be determined. Since rearrangement of the intermediate is slow, the stability constants (log K^*) could be determined by spectrophotometry from absorbance values extrapolated to $t = 0$ time of reaction. The log K^* value for $Yb(H_2DOTA)^+$ was obtained by a reaction study of the competition between the Yb^{3+} and Ce^{3+} ions for $H_nDOTA^{(4-n)-}$.

The rearrangement of the intermediates was sufficiently slow to permit determination of log K^* values by a direct pH-metric titration. The complex $Yb(H_2DOTA)^+$ rearranges faster, and the pH-metric titration data were obtained for separate samples ("out-of-cell" technique). Titration curves for H_4DOTA obtained in (1) the absence and (2) the presence of an equivalent amount of $CeCl_3$ are shown in Figure 2. The abrupt increase of the pH values at $a = 2$ in curve 2 clearly indicates the formation of the intermediate $Ce(H_2DOTA)^+$. At about pH ≥ 4.5 the pH increase slows down, since the rearrangement of the intermediate—taking place by deprotonation—becomes faster. The stability constant calculated from the pH = 3–4 region is well reproducible (fitting parameter is 0.0048). The log K^* values calculated from pH-potentiometric data are listed in Table 1. Stability constants obtained from pH-metric data were calculated by assuming a model where only $Ln(H_2DOTA)^+$ is formed. The good agreement of log K^* values obtained by pH-metry and spectrophotometry also supports reliability of the assumed composition of the intermediate.

Since it was easy to find conditions where the intermediates formed practically in 100% yields, we could directly study the rates of rearrangements of $Ce(H_2DOTA)^+$, $Eu(H_2DOTA)^+$, and $Yb(H_2DOTA)^+$ intermediates, which are first-order processes. The first-order rate constants, k, are proportional to $[H^+]^{-1}$, as shown in Figure 3. The increase of rate constants k with decreasing H^+ ion concentration can be explained by assuming OH^- ion-assisted deprotonation and rearrangement of the intermediates $Ln(H_2DOTA)^+$. (The OH^- ion-catalyzed deprotonation is a well-known pathway in proton exchange reactions

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(32) Wilkins, R. G. *Kinetics and Mechanisms of Reactions of Transition Metal Complexes*; Allyn and Bacon: Boston, MA, 1974; p 26.

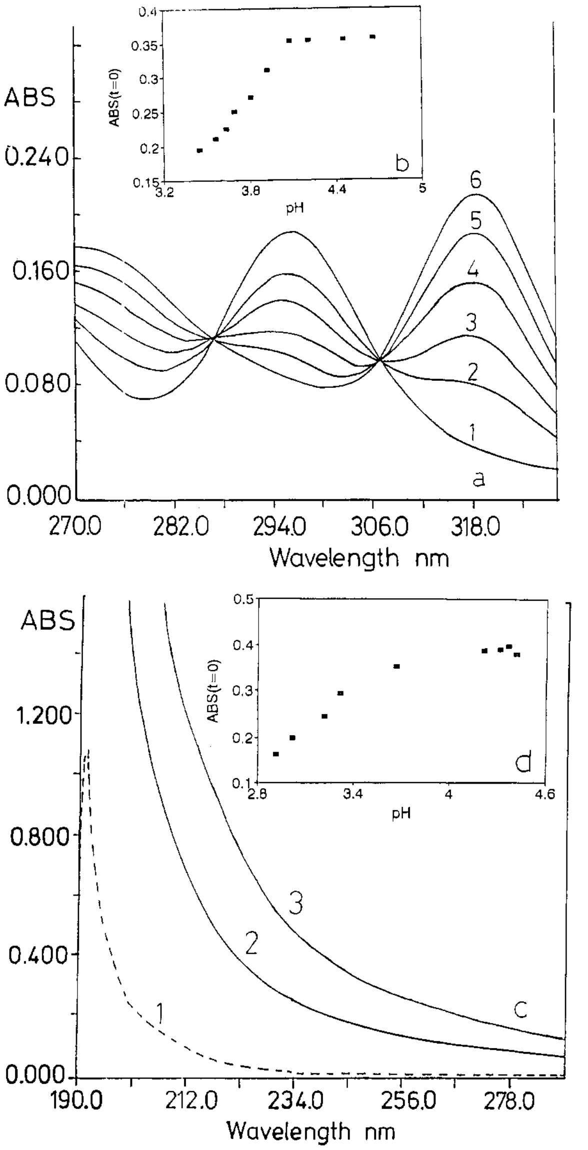

Figure 1. (a) Absorption spectra of $Ce(H_2DOTA)^+$ and $Ce(DOTA)^-$ recorded 0.25 (1), 3 (2), 6 (3), 12 (4), 25 (5), and 70 min (6) after starting the reaction. $c_{Ce} = 4 \times 10^{-4}$ M; $c_{DOTA} = 2 \times 10^{-3}$ M; pH = 4.66. (b) Absorbance of the intermediate $Ce(H_2DOTA)^+$ extrapolated to $t = 0$. $c_{Ce} = 8 \times 10^{-4}$ M; $c_{DOTA} = 2 \times 10^{-3}$ M; 297 nm. (c) Absorption spectra of Eu^{3+}(aq) (1), $Eu(H_2DOTA)^+$ (2), and $Eu(DOTA)^-$ (3). The spectra were recorded 0.25 (2) and 80 min (3) after the reaction started. $c_{Eu} = 1.6 \times 10^{-3}$ M; $c_{DOTA} = 1.6 \times 10^{-3}$ M; pH = 4.80. (d) Absorbance of the intermediate $Eu(H_2DOTA)^+$ extrapolated to $t = 0$. $c_{Eu} = 3 \times 10^{-3}$ M; $c_{DOTA} = 1 \times 10^{-2}$ M; 253 nm.

of amino acids.[33]) Spontaneous rearrangement of $Ln(H_2DOTA)^+$ intermediates is negligible, as the intersection of the straight lines in Figure 3 is zero. Assuming OH^- ion-assisted rearrangement of the intermediate, we obtain

$$k = k'[H^+]^{-1} = k_{OH}[OH^-] \qquad (7)$$

The k_{OH} values calculated from the slopes of the straight lines in Figure 3 ($\log K_w = 13.88$) are presented in Table 1. The values of k_{OH} obtained for the three lanthanides show that, unlike the case of the Ln(NOTA) complexes, where the formation rates were practically independent of the ion size,[34] formation rates of $Ln(DOTA)^-$ complexes increase with decreasing radius of the Ln^{3+} ion. The explanation of the different trends observed in the formation rates of Ln(NOTA) and $Ln(DOTA)^-$ complexes is difficult, since our knowledge of the mechanisms of the reactions is limited. Probably the size of the NOTA ring, which is too small for Ln^{3+} ions, plays a role in the different trends. However, similar to those of $Ln(DOTA)^-$ complexes, formation rates of alkaline earth complexes of DOTA also increase with decreasing ionic size.[31]

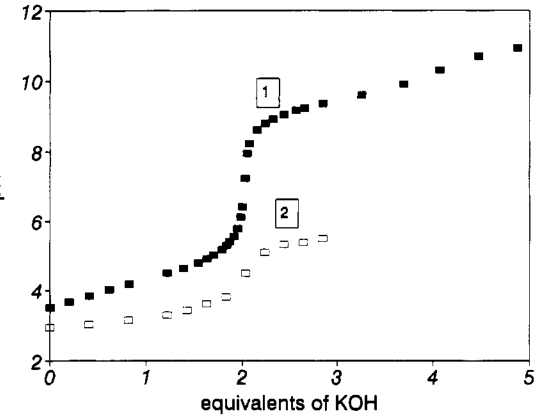

Figure 2. Titration curves of H_4DOTA (1×10^{-3} M) in the absence (1) and presence (2) of $CeCl_3$ (5×10^{-3} M). $T = 25$ °C; $I = 1.0$ M NaCl.

Table 1. Stability Constants (log K^*) and Rate Constants of OH^- Ion-Catalyzed Rearrangements (k_{OH}) of the Diprotonated Intermediates (25 °C, 1 M, NaCl)

	Ce	Eu	Yb
log K^* (spectrophotometry)	4.5 ± 0.1	4.4 ± 0.1	4.3 ± 0.1
log K^* (pH-metry)	4.5 ± 0.05	4.32 ± 0.05	4.2 ± 0.1
k_{OH}, M^{-1} s^{-1}	(3.5 ± 0.06) × 10^6	(1.1 ± 0.07) × 10^7	(4.1 ± 0.4) × 10^7

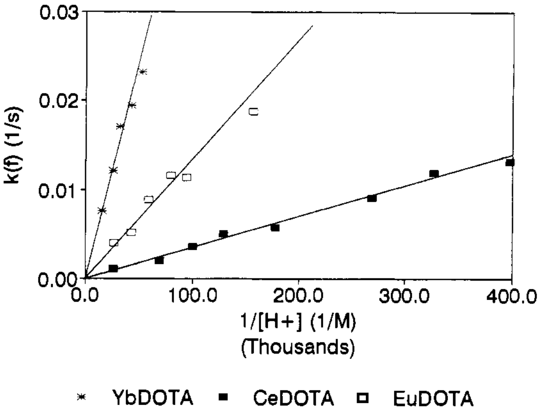

Figure 3. Formation of $Ln(DOTA)^-$ complexes.

In the diprotonated ligand, H_2DOTA^{2-}, protons are attached to two diagonally opposite nitrogen atoms.[2] Probably, in the intermediate these two nitrogens are also protonated, and due to the electrostatic repulsion between the Ln^{3+} ion and protons, only the deprotonated carboxylate groups coordinate to the metal ion. To obtain information on the structure of the intermediate, ^{1}H-NMR spectra of the DOTA ligand were studied in the presence of different amounts of Gd^{3+} (pD = 3.8). The spectra were recorded 1–2 min after mixing the components, when in the presence of excess of DOTA the Gd^{3+} ion was predominantly present in the form of the intermediate, $Gd(H_2DOTA)^+$. The spectra are shown in Figure 4. It can be seen in Figure 4 that at the same Gd^{3+} concentration the broadening of the acetate methylene proton signal is more significant (the relaxation time, T_2, is shorter) than that of the ring protons. The exchange of DOTA between the free and intermediate states is fast.[9] The increase of DOTA concentration at given pH and $[Gd^{3+}]$ values results in a line broadening of the signals, which also indicates a fast ligand exchange and a labile Ln^{3+}–acetate bond. The $Gd(DOTA)^-$ complex has a very small line-broadening effect on

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(33) Pitner, T. P.; Martin, B. *J. Am. Chem. Soc.* **1971**, 4400.
(34) Brücher, E.; Sherry, A. D. *Inorg. Chem.* **1990**, *29*, 1555.

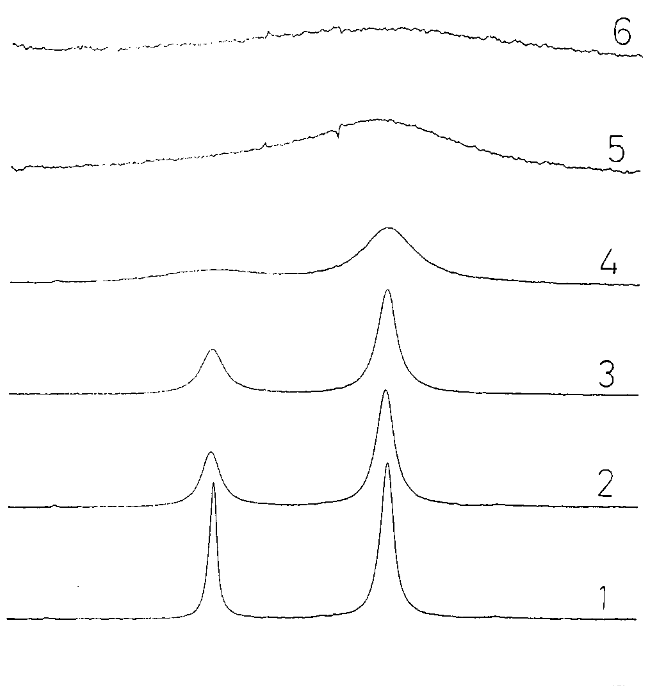

Figure 4. ^{1}H-NMR spectra of DOTA in the presence of Gd^{3+}. c_{DOTA} = 0.02 M; pD = 3.8; c_{Gd} = 0 (1), 5×10^{-5} M (2), 1×10^{-4} M (3), 3×10^{-4} M (4), 1×10^{-3} M (5), and 2×10^{-3} M (6). δ(acetate CH_2) = 4.5 ppm; δ(ring CH_2) = 3.6 ppm.

the ring and acetate methylene protons under the conditions used in these experiments. Since the relaxation rate of the protons ($1/T_2$) is inversely proportional to the sixth power of the Gd^{3+}–proton distance,[35] these observations show that the acetate protons are situated closer to Gd^{3+} in the intermediate than are the ring protons. These findings support the proposed structure of the diprotonated intermediate, where only acetate groups are coordinated to Gd^{3+} outside the coordination cage formed by the four N and O atoms of DOTA, while in $Gd(DOTA)^-$ the Gd^{3+} ion is inside the cage, as was shown by the X-ray diffraction study of $Na[Gd(DOTA)(H_2O)]\cdot 4H_2O$.[23a]

The $Ln(H_2DOTA)^+$ intermediate deprotonates slowly, since the protons are inside the cage. For a spontaneous deprotonation a conformational change of the ring would be necessary, which is hindered by the coordinated acetate groups. The observed catalytic effect of the OH^- ion is probably connected with its small size and high mobility. The OH^--assisted deprotonation of the intermediate, when the Ln^{3+} ion enters the coordination cage, probably proceeds in two consecutive steps. The experimental results do not permit us to differentiate between the two deprotonation steps; that is, we cannot judge whether the release of the first or the second proton is the rate-determining step in the rearrangement of the intermediate.

The "saturation behavior" of k_f values can also be interpreted by treating the formation of the intermediate as a rapid "dead-end" equilibrium and assuming a direct reaction between the Ln^{3+} ion and the $H_nDOTA^{(4-n)-}$ species.[31,32] The slow formation of $Gd(DOTA)^-$ was explained by Wang et al. by assuming a direct reaction between Gd^{3+} and $HDOTA^{3-}$.[9] The concentration of the reactive species $HDOTA^{3-}$ is very small (0.001–0.02% of the total ligand concentration in the pH range studied) but increases with rising pH.

In general, it is difficult to decide between the two interpretations. However, in this case, on the basis of complex formation data for Ce^{3+}, Eu^{3+}, and Yb^{3+}, the explanation we gave before seems to be more probable. Since the water exchange rate for Ln^{3+} ions significantly decreases between Gd^{3+} and Yb^{3+} (by more than 2 orders of magnitude),[26,36] a direct reaction between Yb^{3+} and $HDOTA^{3-}$ would be much slower than that between Eu^{3+} and $HDOTA^{3-}$. In contrast, the formation rate of $Yb(DOTA)^-$ was found to be about 4 times higher than that of $Eu(DOTA)^-$ (Table 1), indicating that the direct formation reaction does not play an important role. It seems more likely that the OH^--catalyzed rearrangement of the diprotonated intermediate may proceed faster for Yb^{3+}, having a smaller size and a higher ionic potential.

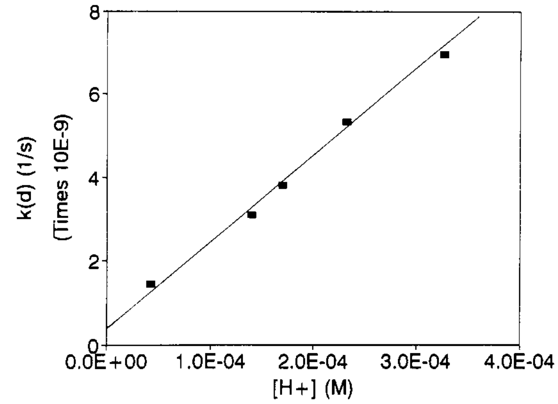

Figure 5. Dependence of k_d on the H^+ ion concentration in the dissociation of $Gd(DOTA)^-$.

For formation of $Ce(DOTA)^-$ we reported kinetic data several years ago.[8] The rate constant calculated from those data, $k_{OH} = 1.07 \times 10^6$ M^{-1} s^{-1}, is significantly lower than the k_{OH} value reported in Table 1. This difference is the consequence of using different buffers. In the earlier study a 0.05 M acetate buffer was used.[8] Later we observed that acetate or other complex-forming ligands significantly decrease the formation rate of $Ln(DOTA)^-$ complexes (e.g., at pH = 5.31 the first-order rate constant, k_f, obtained in 0.02 M acetate buffer is 3.5×10^{-3} s^{-1}, while in *N*-methylpiperazine buffer it is 7.1×10^{-3} s^{-1}). This effect is probably due to competition between acetate and H_2DOTA^{2-} ligands for Ce^{3+}, and as a result, the concentration of the $Ce(H_2DOTA)^+$ intermediate is lower in the presence of acetate buffer. In order to avoid this problem, in recent work *N*-methylpiperazine, which does not form complexes with Ln^{3+} ions, was used as buffer.

Kinetics of Dissociation of $Gd(DOTA)^-$ and $Eu(DOTA)^-$. The rate of the metal exchange reaction between $Gd(DOTA)^-$ and Eu^{3+}(aq) has been studied in the pH range 3.2–5.0. For obtaining measurable rates, the concentration of $Gd(DOTA)^-$ had to be high (0.1 M). Under the conditions used, the exchange could be regarded as a pseudo-first-order reaction, the exchange rate being proportional to the $Gd(DOTA)^-$ concentration:

$$d[Gd(DOTA)^-]/dt = k_d[Gd(DOTA)^-] \qquad (8)$$

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

As can be seen in Figure 5, the rate of the exchange is proportional to the H^+ ion concentration. The k_d values obtained at 0.01 and 0.005 M Eu^{3+} concentrations do not differ, indicating that the exchange rate is independent of Eu^{3+} concentration. The dependence of k_d on the H^+ concentration can be given by

$$k_d = k_0 + k_1'[H^+] \qquad (9)$$

The empirical rate equation obtained by the substitution of eq 9 into eq 8 suggests that the rate-controlling step of exchange reaction 1 is the dissociation of $Gd(DOTA)^-$. The rate constants k_0 and k_1 are characteristic of the spontaneous and proton-assisted dissociation of $Gd(DOTA)^-$. From the data shown in Figure 4, the values $k_0 = (5 \pm 2) \times 10^{-10}$ s^{-1} and $k_1' = (2.0 \pm 0.1) \times 10^{-5}$ M^{-1} s^{-1} were calculated (t = 37 °C).

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(35) Levine, B. A.; Williams, R. J. P. *Proc. R. Soc. London* **1975**, *345*, 5.
(36) Cossy, C.; Helm, L.; Merbach, A. E. *Inorg. Chem.* **1988**, *27*, 1973.
(37) Nyssen, G. A.; Margerum, D. W. *Inorg. Chem.* **1970**, *9*, 1814.

In a study of the dissociation of Gd(DOTA)$^-$ in more acidic solutions (0.02–0.23 M HCl), Wang et al. obtained the values $k_0 < 5 \times 10^{-8}$ s^{-1} and $k_1 = 8.4 \times 10^{-6}$ M^{-1} s^{-1} (t = 25 °C)[9] and proposed neglecting the acid-independent dissociation. Since the value we found for k_0 is 2 orders of magnitude lower than that found by Wang et al., the omission of the contribution of spontaneous dissociation seems to be more reasonable.

Assuming the validity of rate expression 9 at pH = 7, the half-time of dissociation was calculated: $t_{1/2} = 3.9 \times 10^5$ h (37 °C, pH = 7). On the basis of its kinetic inertness, Gd(DOTA)$^-$ can be regarded as a safe contrast agent in MRI.

Since the protonation constant of Gd(DOTA)$^-$ is log K_1 = 2.3 (in 0.1 M KCl),[4] in the pH interval 3.2–5.0, where we studied the rate of exchange reaction, the Gd(DOTA)$^-$ species predominates. The concentration of the monoprotonated complex HGd(DOTA) is not significant (at the lowest pH the amount of the protonated complex HGd(DOTA) is about 10%, but it has no effect on the slope of the straight line in Figure 5). Thus the observed linear dependence of k_d on H$^+$ ion concentration can be explained by proton-catalyzed dissociation of the Gd(DOTA)$^-$ complex. Upon protonation of the complex, the proton is presumably attached to a carboxylate oxygen, producing a free carboxyl group. The thermodynamic and kinetic stability of this protonated complex, H(GdDOTA), is probably lower than that of Gd(DOTA)$^-$, but for a faster dissociation the proton must be transferred to a nitrogen atom of the ligand. This proton transfer, which is probably the rate-controlling step of dissociation, takes place by the intramolecular rearrangement of H(GdDOTA). During the rearrangement, a second proton may be attached to another nitrogen atom. Dissociation occurs due to electrostatic repulsion between the protons and Gd^{3+}: the latter leaves the coordination cage via the formation of a diprotonated intermediate, in which only the carboxylates are coordinated to Gd^{3+}. The rate of dissociation of this Gd(H$_2$DOTA)$^+$ intermediate is very fast.

In a recent study on the dissociation of Gd(HPDO3A) (HPDO3A = 1,4,7,10-tetraazacyclododecane-*N*-(2-hydroxypropyl)-*N′*,*N″*,*N‴*-triacetic acid) in 0.005–1.0 M HCl solutions, where the monoprotonated complexes predominate, the linear dependence of the dissociation rate on the H$^+$ ion concentration was interpreted by proton-assisted dissociation of the monoprotonated species, that is by the dissociation of the diprotonated complexes.[18] In the study of dissociation of Gd(DOTA)$^-$ by Wang et al.,[9] where the concentration of the HGd(DOTA) complex was also significant, the rate of dissociation was also proportional to the H$^+$ ion concentration.

In order to obtain more information on the kinetics of the dissociation of Ln(DOTA)$^-$ complexes and on the role of protonation in it, the dissociation rate of Eu(DOTA)$^-$ was studied in a broad interval of H$^+$ ion concentrations (0.018–2.5 M HClO$_4$). At the lowest [H$^+$] values, where reaction 2 does not go to completion, the first-order rate constants were calculated up to a conversion of about 40%. The k_d values obtained did not show any trend. The dependence of the dissociation rate on H$^+$ ion concentration is shown in Figure 6. As it can be seen, the rate constants, k_d, are linearly proportional to H$^+$ ion concentration up to about 1–1.5 M, but at higher [H$^+$], the increase in k_d values slows down. Similar "saturation curves" were obtained in the study of the dissociation of Gd(HPDO3A) and Gd(DO3A), which was interpreted by assuming the accumulation of diprotonated complexes at high [H$^+$].[18]

On the basis of the data presented in Figure 6, and by taking into account the protonation constant of Eu(DOTA)$^-$, it can be assumed that the dissociation of Eu(DOTA)$^-$ proceeds via the formation of mono- and diprotonated complexes. The complexes HEu(DOTA) and H$_2$Eu(DOTA)$^+$, in which acetate groups are protonated, can be formed in equilibrium reactions. These complexes are not reactive, since the Eu^{3+} ion is inside the "coordination cage". For destruction of this cage structure, the protons must be transferred to nitrogen atoms to form dissociable protonated complexes, Eu(HDOTA) and Eu(H$_2$DOTA)$^+$. The transfer of protons occurs very slowly via the rearrangement of the complex. The position of the rate-controlling step cannot be directly detected. At lower [H$^+$], when the concentration of the monoprotonated complex HEu(DOTA) is also low, the rearrangement of this species can be the slowest process, as it was assumed for the dissociation of Gd(DOTA)$^-$. At higher [H$^+$], when the monoprotonated complex predominates and diprotonated complexes are also formed, the dissociation may take place through the rate-controlling rearrangement of the diprotonated H$_2$Eu(DOTA)$^+$. The rearrangement of the complex H$_2$Eu(DOTA)$^+$ may occur significantly faster than that of HEu(DOTA). The dissociation reaction can be briefly depicted by the following scheme:

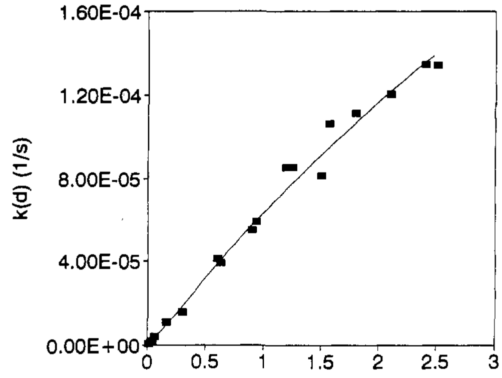
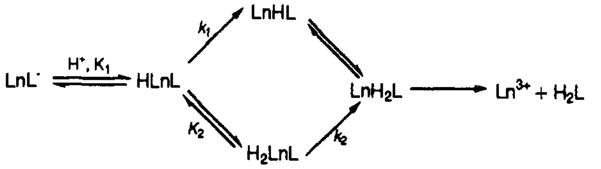


Figure 6. Dependence of k_d on the H$^+$ ion concentration in the dissociation of Eu(DOTA)$^-$.



(10)

A similar reaction scheme was used for describing the dissociation reaction of Ln(NOTA)[34] and Ln(HPDO3A)[18] complexes.

Taking into account reaction scheme 10, the rate of dissociation can be given as

$$-\frac{\mathrm{d[LnL]}}{\mathrm{d}t} = k_1[\mathrm{HLnL}] + k_2[\mathrm{H_2LnL}] = k_d[\mathrm{LnL}]_t \qquad (11)$$

Since

$$[\mathrm{LnL}]_t = [\mathrm{LnL}] + [\mathrm{HLnL}] + [\mathrm{H_2LnL}]$$

$$K_1 = \frac{[\mathrm{HLnL}]}{[\mathrm{LnL}][\mathrm{H^+}]};\quad K_2 = \frac{[\mathrm{H_2LnL}]}{[\mathrm{HLnL}][\mathrm{H^+}]}$$

the pseudo-first-order rate constant, k_d, is expressed by eq 12.

$$k_d = \frac{k_1K_1[\mathrm{H^+}] + k_2K_1K_2[\mathrm{H^+}]^2}{1 + K_1[\mathrm{H^+}] + K_1K_2[\mathrm{H^+}]^2} \qquad (12)$$

From eq 12 rate constants k_1 and k_2 and protonation constants K_1 and K_2 could be calculated, but the errors would be high, because of the inherent difficulties with the independent determination of the corresponding parameters. In order to obtain more reliable data, we determined K_1 by pH-potentiometry. The protonation constant, $K_1 = 14 \pm 1$, was found to be well measurable by titrating 3.0 M NaClO$_4$ solutions in the absence and presence of Eu(DOTA)$^-$ at high concentrations (0.01 and 0.017 M). By fixing the value of K_1 and fitting k_d values to eq 12, we obtained the following k_1, k_2, and K_2 values: $k_1 = (1 \pm 0.5) \times 10^{-6}$ s^{-1}, $k_2 = (6.2 \pm 0.5) \times 10^{-4}$ s^{-1}, and $K_2 = 0.12 \pm 0.03$. The value of the product k_2K_2 was calculated with a low error (about 5%), but the separation of the two constants is difficult because of the low value of K_2. As a consequence, the errors in k_2 and K_2 are relatively high. The contribution of the term $k_1K_1[H^+]$ to k_d (eq 12) is very low at about $[H^+] > 0.3$ M, and therefore the error in k_1 is relatively high. The solid curve in Figure 6 is the calculated curve based on the resolved rate and equilibrium constants.

Equation 12 can be simplified when k_d values are determined in a narrow interval of H$^+$ concentrations. For the interpretation of data obtained for the dissociation of Gd(DOTA)$^-$, we have to take into account that if $[H^+] < 10^{-3}$ M, then $K_1[H^+] \ll 1$ and $K_1K_2[H^+] \ll 1$. Under such conditions, $k_d = k_1K_1[H^+] \approx k_1'[H^+]$ and $k_1' = k_1K_1$. Since the value for k_1' (2×10^{-5} M^{-1} s^{-1}) was obtained at 37 °C and K_1 is known at 25 °C ($K_1 \approx 200$),[4] we can only estimate the order of magnitude of k_1 to be about 10^{-7} s^{-1}.

The form of eq 12 is also simpler at higher $[H^+]$ ($[H^+] > 0.5$ M), when $[HLnL] \gg [LnL]$, and 1 is negligible in the denominator. In this case, k_d is given as

$$k_d = \frac{k_1 + k_2K_2[H^+]}{1 + K_2[H^+]} \approx \frac{k_2K_2[H^+]}{1 + K_2[H^+]} \qquad (13)$$

The rate expression obtained for the dissociation of Ce(DOTA)$^-$ differs from that for Eu(DOTA)$^-$ at about $[H^+] > 1.0$ M. The formation of the diprotonated complex, $H_2Ce(DOTA)^+$, results in a fast increase in k_d and a term in the rate equation which is proportional to the square of $[H^+]$.[8] This phenomenon is probably the consequence of the lower stability constant of Ce(DOTA)$^-$. The dissociation of the complexes proceeds via several consecutive steps. The slow rearrangement of the mono- or diprotonated complex is a complicated process, and the position of the rate-controlling step may depend on the stability of the complex. If the stability is low, it may occur at an earlier stage of rearrangement.

The kinetics of the dissociation of Ce(DO3A) and Ce(HPDO3A) differs also from that of the Gd^{3+} and Lu^{3+} complexes. The plot of k_d vs $[H^+]$ gave a straight line for Ce(DO3A) and Ce(HPDO3A), while for complexes of Gd^{3+} and Lu^{3+} a saturation curve was obtained.[18] In the reaction intermediate formed in the rate-determining process, the extent of interaction between the donor atoms of the ligand and the large Ce^{3+} ion is presumably weaker than that in the intermediates formed with the heavier and lower size Ln^{3+} ions. This difference may result in a shift in the rate controlling step, which leads to a difference in the rate expression for complexes of Ce^{3+} and of heavier lanthanides.

Conclusions

The reaction between Ln^{3+} ions and H_iDOTA species ($4 > i \geq 2$) is unusually slow and occurs via the formation of a well-detectable diprotonated intermediate, Ln(H_2DOTA)$^+$. The stability constants of the intermediate practically do not depend on the size of Ln^{3+} ions.

^{1}H-NMR relaxation data suggest an intermediate structure where a diprotonated ligand is coordinated to the Ln^{3+} ion by acetate groups while two nitrogens are protonated and the Ln^{3+} ion is outside the coordination cage of DOTA. The final product is formed by the rearrangement of the intermediate, which proceeds by the loss of protons. The rearrangement is slow, since the first two protonation constants are high and the protons are hardly accessible in the coordination cage. The deprotonation and rearrangement can take place with the assistance of the very mobile OH$^-$ ions. The rate of the OH$^-$ ion-assisted rearrangement increases with the decrease in the ionic size of the lanthanides.

The dissociation of Ln(DOTA)$^-$ complexes is a proton-assisted process. In slightly acidic solutions ($3.2 < pH < 5$), the rate of dissociation of Gd(DOTA)$^-$ is linearly proportional to the H$^+$ ion concentration, indicating the important role of the monoprotonated complexes in the rate-determining step. In acidic solutions (0.018–2.5 M $HClO_4$), the dissociation of Eu(DOTA)$^-$ is faster and the "saturation behavior" of the pseudo-first-order rate constants indicates the accumulation and kinetic significance of the diprotonated complexes. In the protonated complexes, the protons are attached to carboxylate groups, but for dissociation the protons must be transferred to nitrogen atoms. This proton transfer is very slow due to the rigid structure of Ln(DOTA)$^-$, and as a consequence, the dissociation of these complexes is extremely slow at physiological conditions.

Acknowledgment. We thank the Guerbet, Paris, for kindly providing the complex Gd(DOTA). This work was supported by the Hungarian National Science Foundation (Grant OTKA-1643/91) and by a grant from the COST/ERBIPECT926076/ and Magyar Hitelbank. The authors are grateful to L. Zékány for his help in calculations.