# Equilibrium and kinetic studies on the formation of the lanthanide(III) complexes, [Ce(dota)]⁻ and [Yb(dota)]⁻ (H₄dota = 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid)

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The protonation constants ($K_i^H$) of 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (H₄dota) were redetermined at 25 °C in 0.1 M NMe₄Cl. The log $K_i^H$ values ($i = 1$–5) are 12.6, 9.70, 4.50, 4.14 and 2.32, respectively. The stability constants of [Ce(dota)]⁻ and [Yb(dota)]⁻ were determined by pH-potentiometry as log $K_{CeL}$ = 24.6 and log $K_{YbL}$ = 26.4. The formation rates of [Ce(dota)]⁻ and [Yb(dota)]⁻ were studied by the stopped-flow method at much higher pH values than before. In the range pH 3.5–9.3 the spectra were interpreted in terms of the formation of diprotonated, [Ce(H₂dota)]⁺, and (at around pH > 8) monoprotonated, [Ce(Hdota)], intermediates. These two species are characterized by the same spectra (and structure). At pH < 7.5 the formation rates of the complexes were directly proportional to the OH⁻ concentration. The rate constants, $k_{OH}$, characterizing the formation of [Ce(dota)]⁻ and [Yb(dota)]⁻ are $2.7 \times 10^5$ and $9.3 \times 10^7$ M⁻¹ s⁻¹, respectively. However, at pH > 7.5 the order of reaction in [OH⁻] is higher than one. The results were interpreted in terms of rate-controlling deprotonation of the monoprotonated intermediate [Ln(Hdota)] followed by rearrangement of the deprotonated intermediate into the product. The deprotonation is a general base-catalysed process, which occurs with the assistance of a H₂O molecule at pH < 7.5. At higher pH values the OH⁻-assisted deprotonation of the intermediate, as another pathway, increases the formation rate of the complexes. By assuming these reaction pathways a general rate expression was deduced and it was shown that $k_{OH} = k_{LnHL}^H/K_{LnHL}^H K_w$, where $K_{LnHL}^H$ is the protonation constant of the monoprotonated intermediates [Ce(Hdota)] and [Yb(Hdota)], $K_{CeHL}^H = 4.4 \times 10^8$, $K_{YbHL}^H = 2.5 \times 10^8$ and $k_{LnHL}$ is the rate constant, characterizing the H₂O-assisted deprotonation of the intermediates, $k_{CeHL}$ = 18.5 and $k_{YbHL}$ = 245 s⁻¹. At pH > 8 the OH⁻-assisted deprotonation of the monoprotonated intermediate needs to be considered in the formation rates of [Ce(dota)]⁻; the rate constant for this pathway is $k_{CeHL}^{OH} = 1.9 \times 10^7$ M⁻¹ s⁻¹.

Complexes of lanthanides with the macrocyclic ligand 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (H₄dota) have been the subject of many investigations in recent years. This interest was aroused by the unusual chemical properties and successful practical applications of the complexes [Ln(dota)]⁻; [Gd(dota)]⁻ is a contrast-enhancement agent used clinically in magnetic resonance imaging[1,2] and [⁹⁰Y(dota)]⁻, attached to monoclonal antibodies, has been suggested for use in the therapy of cancer.[3]

In aqueous solution the complexes [Ln(dota)]⁻ are the most inert lanthanoid(III) chelates known so far. Such kinetic inertness is probably related to the rigid structure of the complexes, which results in the formation of two isomeric forms, as detected by NMR spectroscopy.[4–7] The crystal structure of the complexes has been shown by X-ray diffraction studies to be square antiprismatic.[8–12] The Ln³⁺ is situated in the 'co-ordination cage' determined by the four macrocyclic nitrogen and four carboxylate oxygen atoms, which form two practically parallel planes (a water molecule caps the O₄ face). In solution, ¹H and ¹³C NMR spectroscopic studies indicate the presence of regular square-antiprismatic and 'inverted' square-antiprismatic isomers.[5]

Further unique behaviour of the complexes [Ln(dota)]⁻ is the unusually low formation rate, which can be studied by conventional techniques in the range pH 4–6.[13–17] With regard to the very high characteristic water-exchange rates of Ln³⁺ (aq), it is quite clear that the slow complex formation is related to the properties of the ligand, dota. An unusually stable intermediate has been detected by spectrophotometry,[13,16] ¹H NMR[14] and

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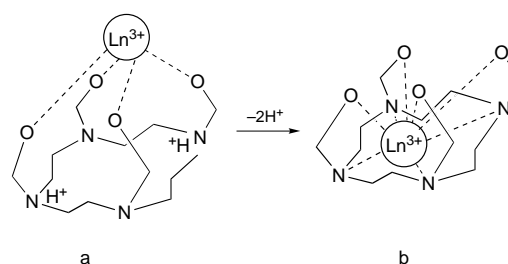


**Scheme 1** The assumed structure of the intermediate **a** which transforms to the complex **b** by deprotonation

luminescence spectroscopy.[17] The formation of an intermediate was also assumed in studies of the formation kinetics of several Ln³⁺ complexes with dota derivatives.[18–21] Its composition and structure have been disputed for some time,[18,19] but it has recently been proposed that it is a diprotonated complex, [Ln(H₂dota)]⁺, in which the Ln³⁺ has an 'out-of-cage' position and only the acetate groups are co-ordinated, while two nitrogen atoms are protonated[16,17] (Scheme 1). A luminescence lifetime study of the intermediate [Eu(H₂dota)]⁺ revealed that the number of H₂O molecules co-ordinated to the Eu³⁺ was between four and five.[17] The stability constant of the intermediate has also been determined from kinetic data,[14] by direct pH-potentiometry and spectrophotometry[16] and by luminescence spectroscopy.[17] The formation rates of the complexes [Ln(dota)]⁻ were found to be directly proportional to the OH⁻ concentration.[13–17]

In order to obtain more direct information on the role of the intermediate in the kinetics and mechanisms of the formation of dota complexes, it would be desirable to study the kinetics of

formation at pH values where the concentration of the species Hdota$^{3-}$ is significant. The values of the protonation constants of dota$^{4-}$ (log $K_1^H$ = 12.09, log $K_2^H$ = 9.76, log $K_3^H$ = 4.56, log $K_4^H$ = 4.09[22]) indicate that the species Hdota$^{3-}$ is present in relatively large amount at around pH > 8.5. It is expected that at such high pH the hydrolysis of Ln$^{3+}$(aq) is significant (in the absence of complex-forming ligands).[23] However, we found that in the presence of a 10–50-fold dota excess the formation of [Ce(dota)]$^-$ could be studied by a stopped-flow method up to around pH 9.3. The formation of [Yb(dota)]$^-$ is faster[16] and its formation rate was studied in the range pH 6–8.

The complexation equilibria formed in the systems Ce$^{3+}$– and Yb$^{3+}$–dota have also been investigated. Since the first protonation constant of the ligand dota ($K_1^H$) is relatively high and the log $K_1^H$ values determined in different laboratories differ considerably, we considered it of interest to redetermine the protonation constants of dota. The new results are also expected to contribute to a better understanding of the kinetic role of the ligand and the intermediate species in the formation of [Ln(dota)]$^-$ complexes.

## Experimental

The ligand dota used for the equilibrium and kinetic studies was synthesized according to a published method.[16] For determination of the protonation constants, another dota sample, kindly provided by Guerbet (Roissy, France), was also used. The purity of the H$_4$dota samples was checked by $^1$H NMR spectroscopy[16] and HPLC, and found to be higher than 99.5%. The sodium and potassium contents of the samples were determined by inductively coupled plasma spectrometry and found to be lower than 0.1%.

The concentration of H$_4$dota solution was determined by pH-potentiometry, on the basis of titration curves obtained in the absence and presence of an excess of CaCl$_2$.

The CeCl$_3$ and YbCl$_3$ solutions were prepared from the oxides; Ln$_2$O$_3$ (99.9%, Fluka) was dissolved in 1:1 HCl and the excess of HCl was evaporated off. The concentrations of these solutions were determined by complexometry with standardized K$_2$H$_2$edta, with xylenol orange as indicator (H$_4$edta = ethylenedinitrilotetraacetic acid).

The protonation constants of dota were determined by pH-potentiometric titration, in vessels thermostatted at 25 °C, with a Radiometer PHM 85 pH-meter, an ABU80 autoburette and G202B glass and K401 calomel electrodes. The titrated solutions (20 cm$^3$) were stirred with a magnetic stirrer and, to avoid the effect of CO$_2$, nitrogen gas was bubbled through the samples. The concentrations of the samples were 0.0062 and 0.0124 M (Guerbet) and 0.0109 M. Two parallel titrations were performed for each sample in the range pH 1.8–12.2. The volumes of the titrated samples increased during the titration, but the ionic strength (0.1 M NMe$_4$Cl) did not because the concentrations of NMe$_4$OH used for the titration were very close to 0.1 M. The protonation constants are defined as $K_i^H$ = [H$_i$L]/[H$_{i-1}$L][H$^+$], where $i$ = 1–5.

For the determination of stability constants an 'out-of-cell' technique was used. In the range pH 2–3.5 ten solution samples (2 cm$^3$) were prepared in duplicate, containing dota and CeCl$_3$ or YbCl$_3$. The concentrations of dota and LnCl$_3$ were 0.005 M.

The equilibrium pH values were measured 4 weeks after the preparation of the samples. The stability constant ($K_{LnL}$) and protonation constant ($K_{HLnL}$) are defined as $K_{LnL}$ = [LnL]/[Ln$^{3+}$][L$^{4-}$] and $K_{LnHL}$ = [HLnL]/[LnL][H$^+$]. The H$^+$ concentration was calculated from the measured pH values. For the calculations a correction term was used, obtained in the titration of 0.01 M HCl with the standardized NMe$_4$OH solution, as the difference between the measured and calculated pH values.[25] The protonation constants and the stability constants of the complexes [Ce(dota)]$^-$ and [Yb(dota)]$^-$ were calculated with the use of the PSEQUAD program.[26] Both the equilibrium and

**Table 1** Protonation constants of dota (25 °C)

|  | 0.1 M NMe$_4$NO$_3$[a] | 0.1 M NMe$_4$Cl[b] | 0.1 M NMe$_4$Cl[c] |
|---|---|---|---|
| log $K_1^H$ | 12.09 | 11.73 | 12.6 (0.01) |
| log $K_2^H$ | 9.673 | 9.40 | 9.70 (0.007) |
| log $K_3^H$ | 4.5556 | 4.50 | 4.50 (0.011) |
| log $K_4^H$ | 4.09 | 4.19 | 4.14 (0.01) |
| log $K_5^H$ | — | — | 2.32 (0.012) |

[a] Ref. 23. [b] Ref. 31. [c] This work.

kinetic studies were carried out at 25 °C. The ionic strength of the solutions was kept constant at $I$ = 0.1 M NMe$_4$Cl.

All kinetic experiments were performed by using an Applied Photophysics SX 17MV stopped-flow apparatus in both single-an multi-wavelength modes. Each trace was obtained as an average of at least three replicate runs. The kinetic curves were fitted with a non-linear least-squares routine provided with the instrument. The rate constants were reproducible within 5%. Time-dependent spectral changes for the system Ce$^{3+}$–dota were constructed from individual kinetic traces recorded at 4 nm intervals in the range 280–340 nm. Detailed kinetic studies on the formation of the complex [Ce(dota)]$^-$ were made at 318 nm by using the following pseudo-first-order conditions: [dota] = 0.004 (pH 5.9–8.3) or 0.01 (pH 8.3–9.3), [Ce$^{3+}$] = 2 × 10$^{-4}$ M. The samples were buffered with 0.05 M 2-morpholinoethanesulfinic acid (mes) (pH 5.9–6.9) or tris(hydroxymethyl)aminomethane (Tris) (pH 7.0–9.3) solution. The formation kinetics of the complex [Yb(dota)]$^-$ was studied by using the indicator method.[22] In slightly buffered reaction mixtures [0.0125 M 3-morpholinopropanesulfonic acid (Mops), pH 6.0–8.0], the approximately 0.1 decrease in pH was monitored at 616 nm by using bromothymol blue as indicator. The concentrations of dota, Yb$^{3+}$ and the indicator were 0.002, 2 × 10$^{-4}$ and 2.5 × 10$^{-5}$ M, respectively.

## Results and Discussion

### Protonation and complexation equilibria

The stability constants of the complexes [Ln(dota)]$^-$ are very high and the log $K_{LnL}$ values reported for some lanthanides differ by several orders of magnitude.[14,27–31] The large differences probably result from the slow formation of the complexes, which does not allow the use of pH-potentiometric titration to determine the stability constants. However, the reported protonation constants of dota, determined in different laboratories, also differ quite considerably.[23,29,31,32] The largest differences are observed in the value of the first protonation constant, which is strongly influenced by the medium, used to maintain constant ionic strength, because of the formation of the complexes [Na(dota)]$^{3-}$ or [K(dota)]$^{3-}$.[23,31] As the most reliable first protonation constant, the value log $K_1^H$ = 12.09 has recently been used.[23,31] It was determined by Delgado and Da Silva[23] in 0.1 M NMe$_4$NO$_3$ by titrating a 0.001 M dota solution. At such low ligand concentrations only a very small part of the added base is neutralized by the ligand protons at around pH 12, and the protonation constant obtained is uncertain.[33] To obtain a more reliable log $K_1^H$ value the use of a much higher ligand concentration is needed. To determine the protonation constants we used approximately 6–10 times higher dota concentrations. The protonation constants determined are presented in Table 1 with standard deviations in parentheses.

For comparison, Table 1 also lists the protonation constants obtained by Delgado and Da Silva[23] and Kumar et al.[31] The values of log $K_2^H$, log $K_3^H$ and log $K_4^H$ determined by the different groups agree very well. However, the first protonation constant, log $K_1^H$, determined by us is larger than those obtained by the other groups. The dota samples we used were synthesized in two independent laboratories and the purity was controlled very

**Table 2** Equilibrium constants ($K_{LnL}$ and $K_{HLnL}$) characterizing the formation of [Ce(dota)]$^-$ and [Yb(dota)]$^-$ at 25 °C

| | 0.1 M KCl[a] | 0.1 M NMe$_4$Cl[b] |
|---|---|---|
| log $K_{CeL}$ | 23.4 | 24.6 (0.06) |
| log $k_{HCeL}$ | — | 1.9 (0.3) |
| log $K_{YbL}$ | 25.0 | 26.4 (0.06) |
| log $k_{HYbL}$ | — | 1.5 (0.2) |

[a] Ref. 28. [b] This work.

carefully. The concentrations of the titrated dota solutions prepared from the two samples were relatively high. Similarly to the values of the other four protonation constants, the values of the first protonation constant calculated from the data of three (duplicate) titration curves (240, 241 and 148 data points) agreed very well (log $K_1^H$ 12.64, 12.64 and 12.60). This agreement indicates the reliability of the log $K_1^H$ value presented in Table 1. However, the uncertainty in it is larger than the obtained standard deviation (it is probably 0.1–0.2 log $K$ unit), because the pH interval in which titration data were obtained was limited up to pH 12.2. The pH measurements were reliable at around pH 12 since the ionic product of water was found to be constant (p$K_w$ = 13.84 ± 0.02) in the range pH 10.91–12.43.

To characterize the protonation equilibria occurring in the interval pH 2–3.5 we determined the value of log $K_5^H$. The fifth proton is probably attached to one of the two unprotonated carboxylate groups or partly to a ring nitrogen.[32] Since the formation equilibria of the complexes [Ln(dota)]$^-$ can be studied in the range pH 2–3.5, use of the log $K_5^H$ value in calculating the stability constants seems to be important.

The stability constants obtained are compared with some other values in Table 2. The log $K_{CeL}$ and log $K_{YbL}$ values found in this work are considerably higher than those reported earlier. These differences resulted in part from the use of log $K_5^H$ (which was not used previously) and of the higher value of the first protonation constant, log $K_1^H$. If we did not use the value of log $K_5^H$ in the calculations, the log $K_{LnL}$ values obtained were smaller by 0.6–0.8 log $K$ unit.

In calculating the equilibrium constants we assumed the formation of the complexes [Ln(dota)]$^-$ and [HLn(dota)].‡ With the assumption of the presence of a diprotonated species [Ln(H$_2$dota)]$^+$ in the equilibria, the fit of the data was worse and we could not obtain a reliable stability constant for the diprotonated complex. On calculation of the species distribution for the system Ce$^{3+}$–dota with the protonation constants and stability constants obtained in this work and with the stability constant obtained for the diprotonated intermediate [Ce(H$_2$dota)]$^+$ in a kinetic study, log $K_{CeH_2L}$ = 4.5,[16] the maximum in the extent of formation of the diprotonated species was below 0.1%.

### Absorption spectra of the intermediates [Ce(H$_2$dota)]$^+$ and [Ce(Hdota)]

The formation of an intermediate in the reaction between the ligand dota and Ln$^{3+}$ was detected first for [Ce(dota)]$^-$.[13] The 4f–5d absorption bands of Ce$^{3+}$(aq), which lie between 210 and 265 nm, are very sensitive to changes in the environment of Ce$^{3+}$. These bands are strongly shifted in the direction of longer wavelengths when the H$_2$O molecules in the inner sphere of the Ce$^{3+}$ are substituted by the charged donor atoms of the ligand. For the reaction mixture of Ce$^{3+}$ and dota at 3.5 < pH < 6 two new absorption bands were observed with maxima at 296 and 318 nm. The intensity of the band at 296 nm decreased with time; this was characteristic for the intermediate [Ce(H$_2$dota)]$^+$.

‡ By using the formula [HLn(dota)] we indicate that in the protonation of the complex [Ln(dota)]$^-$ the proton is probably attached to an acetate group, while in the diprotonated intermediate, [Ln(H$_2$dota)]$^+$, two nitrogen atoms are protonated.
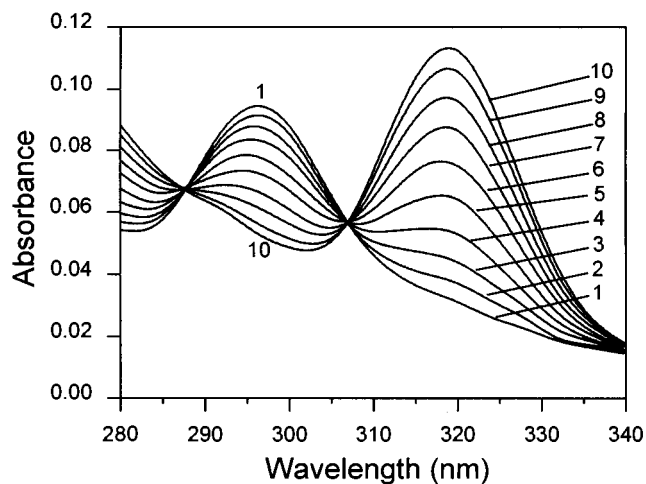


**Fig. 1** Absorption spectra for reacting mixtures Ce$^{3+}$–H$_x$dota. [Ce$^{3+}$]$_t$ = 2 × 10$^{-4}$ M; pH 8.50; [H$_x$dota]$_t$ = 8 × 10$^{-3}$ M. In order of increasing absorbance at 318 nm, the spectra were obtained at 5 (1), 7.5 (2), 11.2 (3), 16.3 (4), 23.8 (5), 33.8 (6), 47.5 (7), 65 (8), 97.5 (9) and 200 (10) ms

The other band, at 318 nm, increased as the reaction proceeded, and proved to be characteristic of the product, [Ce(dota)]$^-$.[13]

At about pH > 6 the formation of [Ce(dota)]$^-$ is faster and could be studied by a stopped-flow method. The stability constant of the intermediate [Ce(H$_2$dota)]$^+$ is relatively high (log $K_{Ce(H_2L)}$ = 4.5[16]), and in the presence of a high dota excess the hydrolysis of Ce$^{3+}$ (aq) does not interfere with formation of the intermediate or product at up to pH ≈ 9.3. Some typical spectra of the reaction mixture are shown in Fig. 1. In the presence of a 40-fold dota excess, the spectrum of the reaction mixture at pH 8.50 indicated fast formation of the intermediate with a band maximum at 296 nm, and its slow transformation to the product [Ce(dota)]$^-$, exhibiting a band maximum at 318 nm (Fig. 1).

The spectra of the Ce$^{3+}$–dota reaction mixtures in the range pH 6–9.3 and in the presence of a 10–50-fold ligand excess are similar to those in Fig. 1. The shapes of the bands and the positions of the band maxima at 296 and 318 nm are identical with those identified in the range pH 3.5—6 as the bands of the intermediate [Ce(H$_2$dota)]$^+$ and the product [Ce(dota)]$^-$.[13,16] The molar absorption coefficients calculated from the spectra obtained at pH 5.96 ([dota]$_t$/[Ce$^{3+}$]$_t$ = 10) are 480 (296) and 494 M$^{-1}$ cm$^{-1}$ (318 nm) for the intermediate and product, respectively. Isosbestic points were observed at 287.4 and 306.6 nm. In the presence of a 40-fold dota excess at pH 8.50 ε = 475 (296) and 495 M$^{-1}$ cm$^{-1}$ (318 nm). The isosbestic points are 287.2 and 307.0 nm. Since the spectrum of the intermediate is identical throughout the whole pH range studied (3.5 < pH < 9.3) it is reasonable to assume that the functional groups co-ordinated to the Ce$^{3+}$ are also identical. Earlier studies supported the assumption that, in the intermediates [Eu(H$_2$dota)]$^+$ and [Gd(H$_2$dota)]$^+$ formed at lower pH values, four carboxylate oxygens are co-ordinated to the Ln$^{3+}$, while two nitrogens are protonated.[16,17] In spite of the fact that the same functional groups are co-ordinated in the intermediates formed at lower or higher pH values, the composition is not necessarily identical. It is expected that the second protonation constant of dota (log $K_2^H$ = 9.70) is significantly reduced on co-ordination to Ce$^{3+}$. It follows that [Ce(H$_2$dota)]$^+$ is in equilibrium with a monoprotonated complex, [Ce(Hdota)], and in the pH > 8.0 region this species needs to be present in significant amounts. As discussed later, kinetic results also suggest the formation of the monoprotonated intermediate. Nevertheless, the spectral changes are not associated with the formation of the new species. This leads to the conclusion that the structures of mono- and di-protonated intermediates are presumably similar. The Ln$^{3+}$ has an 'out-of-

cage' position, the four acetate groups of the ligand are co-ordinated to the $Ln^{3+}$ and one, [Ln(Hdota)], or two nitrogen atoms, [Ln(H$_2$dota)]$^+$, are protonated.

## Formation kinetics of [Ce(dota)]$^-$ and [Yb(dota)]$^-$

Earlier studies on the kinetics of formation of the complexes [Ln(dota)]$^-$ were carried out under pseudo-first-order conditions. Since $Ln^{3+}$ was used in excess in all these studies, the pH in the reacting systems was always lower than 6, in order to avoid hydrolysis of the metal ions. A plot of the pseudo-first-order rate constant against the concentration of $Ln^{3+}$ gave a saturation curve, indicating the formation of a reaction inter-mediate. From the rate data an equilibrium ($K^*$) and a rate constant ($k_r$) were obtained, which characterized the formation and rearrangement rates of the intermediate ($k_r$ is equivalent to the saturation $k_{obs}$ value).[13-17] A previous study of the formation kinetics of the complexes [Ln(nota)] showed that the equilibrium constant $K^*$ was the conditional stability constant of the intermediate (H$_3$nota = 1,4,7-triazacyclononane-1,4,7-triacetic acid).[34] In the formation of the complexes [Ln(dota)]$^-$ the rate constant $k_r$ was found to be directly proportional to the OH$^-$ concentration. This finding permitted the assumption that the rearrangement of the intermediate [Ln(H$_2$dota)]$^+$ was assisted by OH$^-$.

In our study in the range pH 6–9.3 the ligand dota was present in excess and the formation rate of the complex [Ln(dota)]$^-$ can be given as in equation (1) where $k_{obs}$ is the measured

$$\mathrm{d[LnL]}_t/\mathrm{d}t = k_{obs}[Ln^{3+}]_t \qquad (1)$$

first-order rate constant, L = dota and $Ln^{3+} = Ce^{3+}$ or $Yb^{3+}$. Since the stability constant of the intermediate [Ln(H$_2$dota)]$^+$ is relatively high (log $K_{Ce(H_2L)} = 4.5$; log $K_{Yb(H_2L)} = 4.3$[16]) and since in the interval pH 6–9.3 the ligand is present practically in the form of the species H$_2$dota$^{2-}$ and Hdota$^{3-}$, the formation of the intermediate was practically complete and the rate constants $k_{obs}$ were independent of the dota concentration when the ligand to metal concentration ratio was higher than 5:1 {e.g. at pH 7.30 the $k_{obs}$ values obtained for the formation of [Ce(dota)]$^-$ at a 2-, 5-, 10- and 40-fold excess of dota are 0.70, 0.78, 0.77 and 0.80 s$^{-1}$, respectively}. As a consequence of the completeness of the formation of the intermediate at [L]$_t$/[Ln$^{3+}$]$_t$ > 5, the rate constants obtained are the 'saturation' $k_{obs}$ values, which are characteristic for the rate of rearrange-ment of the intermediate to the product at a given pH, i.e. $k_{obs} = k_r$.

The rate data also indicate that intermediates of other than 1:1 metal to ligand ratio (e.g. 1:2) do not form. At around pH 6 several measurements were carried out in the presence of a ten-fold Ce$^{3+}$ ([L]$_t = 2 \times 10^{-4}$ M) or dota ([Ce$^{3+}$] = $2 \times 10^{-4}$ M) excess, and the same $k_{obs}$ values were obtained regardless of the concentration ratio.

The rate constants $k_{obs}$ obtained at a 20-fold excess of dota are shown in Figs. 2 and 3 as a function of pH. In Fig. 2 the data presented were obtained for the formation of [Ce(dota)]$^-$ in 0.1 M NMe$_4$Cl. Fig. 3 shows the $k_{obs}$ values obtained for the formation of [Yb(dota)]$^-$. The rate constants indicate that the formation rates of [Ce(dota)]$^-$ and [Yb(dota)]$^-$ increase with rising pH. In the reaction between Yb$^{3+}$ and dota the rate con-stants $k_r$ are directly proportional to the OH$^-$ concentration, i.e. $k_r = k_{OH}[OH^-]$ and $k_{OH} = (9.3 \pm 1.5) \times 10^7$ M$^{-1}$ s$^{-1}$. In an earlier study of the formation of [Yb(dota)]$^-$ in the range pH 4.4–5.4 (25 °C, 1.0 M NaCl) the value $k_{OH} = (4.1 \pm 0.4) \times 10^7$ M$^{-1}$ s$^{-1}$ was found.[16] When the different conditions are taken into account the agreement between the $k_{OH}$ values is acceptable.

The formation rates of [Eu(dota)]$^-$ and [Gd(dota)]$^-$ were also found to be directly proportional to the OH$^-$ concentra-tion.[15,17] To interpret these experimental findings Wu and Horrocks[17] assumed a fast, OH$^-$-assisted deprotonation of
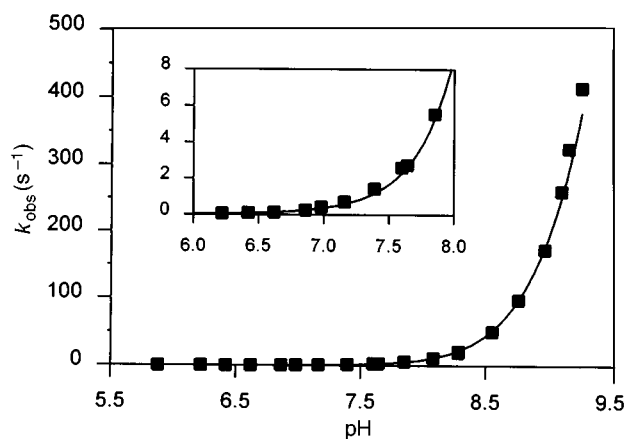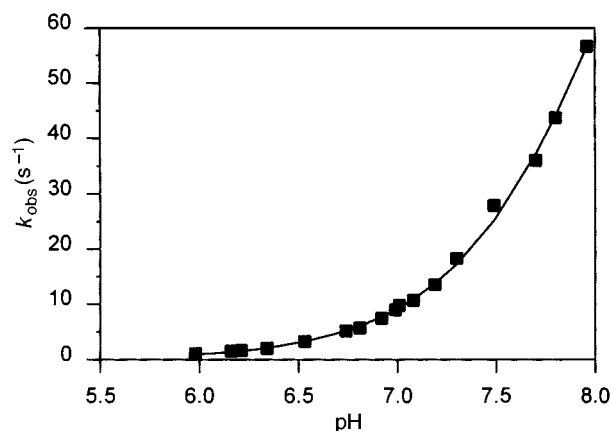


**Fig. 2** First-order rate constants obtained for the formation of [Ce(dota)]$^-$ in 0.1 M NMe$_4$Cl solutions (25 °C)
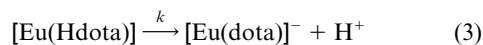


**Fig. 3** First-order rate constants obtained for the formation of [Yb(dota)]$^-$ (0.1 M NMe$_4$Cl, 25 °C)

[Eu(H$_2$dota)]$^+$, which is followed by the rate-determining, OH$^-$-independent deprotonation and rearrangement of the inter-mediate, [Eu(Hdota)], equations (2) and (3). For the calculation

$$[Eu(H_2dota)]^+ + OH^- \underset{}{\overset{K_2}{\rightleftharpoons}} [Eu(Hdota)] + H_2O \quad (2)$$

$$[Eu(Hdota)] \overset{k}{\longrightarrow} [Eu(dota)]^- + H^+ \quad (3)$$
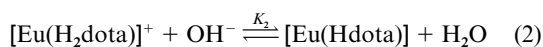
of $K_2$ the second protonation constant of dota ($K_2^H$) was used as an upper limit, instead of the unknown protonation constant of the intermediate [Eu(Hdota)].[17]

For a better understanding of the mechanism of the forma-tion of the complexes [Ln(dota)]$^-$ the knowledge of the proton-exchange rates of the diprotonated intermediate, [Ln(H$_2$-dota)]$^+$, would be very important. In this case it would be easier to decide whether the loss of the first or the second proton, or the structural rearrangement of the deprotonated intermediate, is associated with the rate-controlling step. The kinetic data we obtained are consistent with the assumption that a very fast equilibrium (4) exists between the di- and mono-protonated

$$[Ce(H_2dota)]^+ \rightleftharpoons [Ce(Hdota)] + H^+ \quad (4)$$
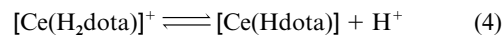
intermediates. This equilibrium is characterized with the proto-nation constant $K_{CeHL}^H = [Ce(H_2L)]/[Ce(HL)][H^+]$.

The linear dependence of the complex-formation rates on the OH$^-$ concentration, observed in the range pH 3.5–7.5, can be interpreted by equilibrium (4) and by assuming the rate-controlling deprotonation and rearrangement of the monopro-tonated intermediate, equation (5). According to equation (4)

$$[Ln(Hdota)] \xrightarrow{k_{LnHL}} [Ln(dota)]^- + H^+ \qquad (5)$$
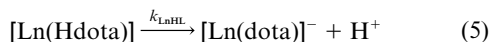
the concentration of the monoprotonated intermediate, [Ce(H-dota)], is directly proportional to $1/[H^+]$ (or to the $OH^-$ concentration), when the equilibrium is shifted to the right. Consequently, the linear relation between the rate constants $k_r$ and $OH^-$ concentration at pH < 7.5 is the result of the dissociation equilibrium (4) and there is no need to assume the participation of the $OH^-$ ion in the equilibrium, as was proposed in equation (2).[17] (The rate of the $OH^-$-assisted proton exchange is in general very slow at pH < 6,[35] where Wu and Horrocks[17] worked.)

The rate constants obtained for the formation of $[Ce(dota)]^-$ at pH > 8 (Fig. 2) increase faster with rising pH than is expected on the basis of the linear dependence observed at pH < 7.5. These experimental data indicate that beside reaction (5) the complex formation can take place *via* another reaction pathway at higher pH values.

Since proton-exchange reactions may occur by $OH^-$ catalysis,[35] we assumed that at about pH > 8 $OH^-$-assisted deprotonation and rearrangement of the intermediate may contribute to complex formation, equation (6). Formation of the product

$$[Ln(Hdota)] + OH^- \xrightarrow{k_{LnHL}^{OH}} [Ln(dota)]^- + H_2O \quad (6)$$
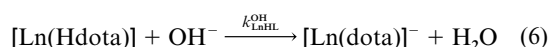
$[Ln(dota)]^-$ occurs *via* reaction pathways (5) and (6), and the rate of formation can be given by equation (7). In the presence

$$d[LnL]_t/dt = k_{LnHL}[Ln(HL)] + k_{LnHL}^{OH}[Ln(HL)][OH^-] \qquad (7)$$

of a ligand excess all the $Ln^{3+}$ forms an intermediate at the start of the reaction, and the total concentration of the complex, $[LnL]_t$, is given by equation (8). In the presence of a ligand

$$[LnL]_t = [Ln(HL)] + [Ln(H_2L)] \qquad (8)$$

excess an intermediate is formed with $Ln^{3+}$ within the deadtime of the stopped-flow instrument. Substitution of the concentration of the intermediate $Ln(H_2L)$ expressed with the protonation constant, $K_{LnHL}^H$, into equation (8) and comparison of equations (1) and (7) leads to equation (9) for the rate

$$k_r = \frac{k_{LnHL}[H^+] + k_{LnHL}^{OH} K_w}{[H^+] + K_{LnHL}^H[H^+]^2} \qquad (9)$$

constant $k_r$ characterizing the formation rate of $[Ce(dota)]^-$. From a fit of equation (9) to the experimental $k_{obs} = k_r$ data shown in Fig. 2, the rate constant $k_{CeHL}$, the protonation constant $k_{CeHL}^H$ and $k_{CeHL}^{OH}$ can be calculated as $18.5 \pm 2.8$ s$^{-1}$, $(4.4 \pm 0.5) \times 10^8$ M$^{-1}$ and $(1.9 \pm 0.1) \times 10^7$ M$^{-1}$ s$^{-1}$ (p$K_w =$ 13.84).

At lower pH values, when $[H^+] > 10^{-7}$ M, equation (9) simplifies to $k_r = (k_{LnHL}/K_{LnHL}^H)[H^+]^{-1}$. This is similar to the expression $k_r = k_{OH}[OH^-]$, found earlier for the formation of dota complexes at pH < 6.[13–17] A comparison of these equations gives the physical meaning of the rate constant $k_{OH}$, *i.e.* $k_{LnHL}/K_{LnHL}^H K_w$. Use of the calculated values of $k_{CeHL}$ and $K_{CeHL}^H$ leads to $k_{OH} = 3.0 \times 10^6$ M$^{-1}$ s$^{-1}$. The linear dependence of $k_{obs}$ on the $OH^-$ concentration in the range pH 6–7.5 furnishes $k_{OH} = (2.7 \pm 0.5) \times 10^6$ M$^{-1}$ s$^{-1}$. A study in the range pH 4.2–5.6 in 1.0 M NaCl revealed that $k_{OH} = 3.5 \times 10^6$ M$^{-1}$ s$^{-1}$.[16] The agreement between the $k_{OH}$ values obtained in this study and in 1.0 M NaCl solution is acceptable.

The formation rate of $[Yb(dota)]^-$ was studied in the interval pH 6–8, where the $OH^-$-assisted deprotonation and rearrangement of the intermediate [Yb(Hdota)] [equation (6)] did not contribute to the overall reaction. In this case from equation (9) we obtain expression (10). By fitting the rate constants $k_{obs} = k_r$ obtained in the range pH 6–7.5 (Fig. 3) using equation (10) the
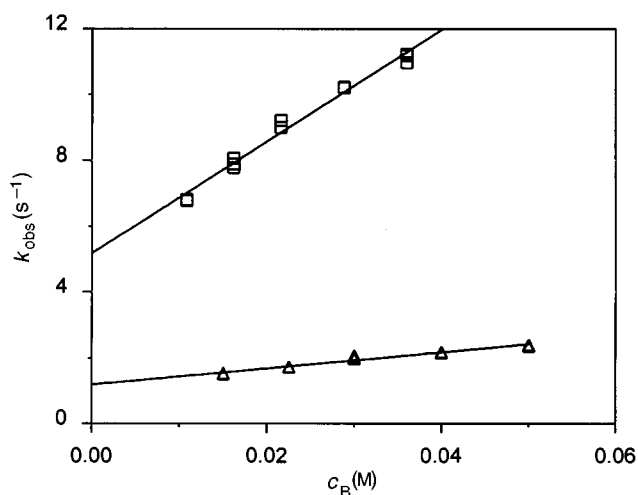


**Fig. 4** First-order rate constants obtained for the formation of $[Ce(dota)]^-$ as a function of the concentration of the basic form of the buffers $N'$-(2-hydroxyethyl)piperazine-$N$-ethane-2-sulfonic acid (hepes) (pH 7.57, $\triangle$) and Tris (pH 8.05, $\square$) at 25 °C, 1.0 M NMe$_4$Cl

$$k_r = \frac{k_{YbHL}}{1 + K_{YbHL}^H[H^+]} \qquad (10)$$

following rate and equilibrium constants were obtained: $k_{YbHL} = 245 \pm 131$ s$^{-1}$ and $K_{YbHL}^H = (2.5 \pm 1.4) \times 10^8$ M$^{-1}$. Unfortunately, the error in these constants is relatively high. At pH < 7.5, $1 \ll K_{YbHL}^H[H^+]$ in the denominator of equation (10), and independent determination of $k_{YbHL}$ and $K_{YbHL}^H$ is rather uncertain. It should be noted that at higher pH the more complete equation (9) may be necessary to interpret the complex-formation kinetics in this system.

The protonation constants ($K_{LnHL}^H$) of the monoprotonated intermediates [Ce(Hdota)] and [Yb(Hdota)], calculated from the rate data, are about 10–20 times lower than that of the ligand Hdota$^{3-}$ ($K_2^H = 5 \times 10^9$ M$^{-1}$). Since the protonation sites are probably quite far from the $Ln^{3+}$ ion in $[Ln(H_2dota)]^+$ (the $Ln^{3+}$ ion has an 'out-of-cage' position in the intermediate), the relatively small difference in the protonation constant of the ligand, Hdota$^{3-}$, and the intermediates, [Ln(Hdota)], seems to be reasonable.

The deprotonation of the monoprotonated intermediate, formed in reaction (4), plays a crucial role in the formation of $[Ce(dota)]^-$. For the deprotonation we proposed reactions (5) and (6). In reaction (5) the proton of [Ce(Hdota)] is transferred to a $H_2O$ molecule which is a relatively weak Brønsted base. The more basic $OH^-$ ion, as is assumed in equation (6), assists the proton transfer more efficiently. Similar effects can be expected for other Brønsted bases, *e.g.* with various buffers. In Fig. 4 the experimentally observed rate constants are shown as a function of the buffer concentration. In these experiments a 10-fold excess of dota was used and constant 1.0 M ionic strength was maintained with NMe$_4$Cl. As shown the rate of complex formation increases with increasing concentration of the basic form of hepes and Tris. This evidence for the existence of general base catalysis indicates that the rate-determining step in the formation of the $[Ln(dota)]^-$ complexes is the deprotonation of the monoprotonated intermediate, which is followed by a fast rearrangement when the $Ln^{3+}$ ion steps into the co-ordination cage, formed by the four nitrogen and acetate oxygen atoms of dota.

## Acknowledgements

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