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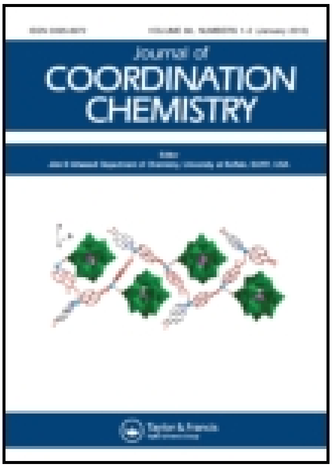

Journal of Coordination Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gcoo20

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Accepted author version posted online: 24 Jul 2014.Published online: 14 Aug 2014.

To cite this article: C. Allen Chang, Chih-Cheng Lin & Chien-Hung Kuo (2014) Dissociation kinetics of macrocyclic trivalent lanthanide complexes of 1-oxa-4,7,10-triazacyclododecane-4,10-diacetic acid (H_2ODO2A), Journal of Coordination Chemistry, 67:13, 2204-2216, DOI: 10.1080/00958972.2014.945923

To link to this article: http://dx.doi.org/10.1080/00958972.2014.945923

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Journal of Coordination Chemistry, 2014
Vol. 67, No. 13, 2204–2216, http://dx.doi.org/10.1080/00958972.2014.945923

Dissociation kinetics of macrocyclic trivalent lanthanide complexes of 1-oxa-4,7,10-triazacyclododecane-4,10-diacetic acid (H_2ODO2A)

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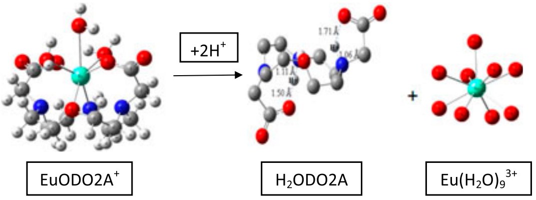
(*Received 20 December 2013; accepted 4 June 2014*)



The dissociation rates of LnODO2A$^+$ complexes (ODO2A^{2-} is the deprotonated dianion of the ligand H_2ODO2A, 1-oxa-4,7,10-triazacyclododecane-4,10-diacetic acid) are all faster than those of the corresponding LnDO2A$^+$ complexes (DO2A^{2-} is the deprotonated dianion of the ligand H_2DO2A, 1,4,7,10-tetraazacyclododecane-1,7- diacetic acid), consistent with the fact that LnODO2A$^+$ complexes are kinetically more labile and thermodynamically less stable than the corresponding LnDO2A$^+$ complexes, and H_2ODO2A is not pre-organized for Ln^{3+} ion complexation but H_2DO2A is.

The dissociation kinetics of selected trivalent lanthanide (Ln^{3+}, Ln=La, Pr, Eu, Er, Lu) complexes of the macrocyclic ligand H_2ODO2A (1-oxa-4,7,10-triazacyclododecane-4,10-diacetic acid), LnODO2A$^+$, were studied in the [H$^+$] range $(0.1–2.4) \times 10^{-4}$ M in the temperature range 15–45 °C. Excess Cu^{2+} ions were used as the scavenger for the ligand in acetate–acetic acid buffer medium. The dissociation reactions are independent of [Cu^{2+}] and follow the rate law $k_{obs} = k_d + k_{AC}[\text{Acetate}] + K'k_{lim}[H^+]/(1 + K'[H^+])$, where k_d, k_{AC}, and k_{lim} are the respective dissociation rate constants for the [H$^+$]-independent, acetate-assisted, and the [H$^+$]-dependent limiting pathways; K′ is the equilibrium constant for the protonation reaction LnODO2A$^+$ + H$^+$ ↔ LnODO2AH^{2+}. The dissociation rates of LnODO2A$^+$ complexes are all faster than those of the corresponding LnDO2A$^+$ complexes (DO2A^{2-} is the fully deprotonated dianion of the ligand H_2DO2A, 1,4,7,10-tetrazacyclo-dodecane-1,7-diacetic acid), consistent with the notion that LnODO2A$^+$ complexes are kinetically more labile and thermodynamically less stable than the corresponding LnDO2A$^+$ complexes, and H_2ODO2A is not pre-organized for Ln^{3+} ion complexation but H_2DO2A is.

Keywords: Lanthanides; Macrocyclic ligands; ODO2A; DO2A; Dissociation kinetics

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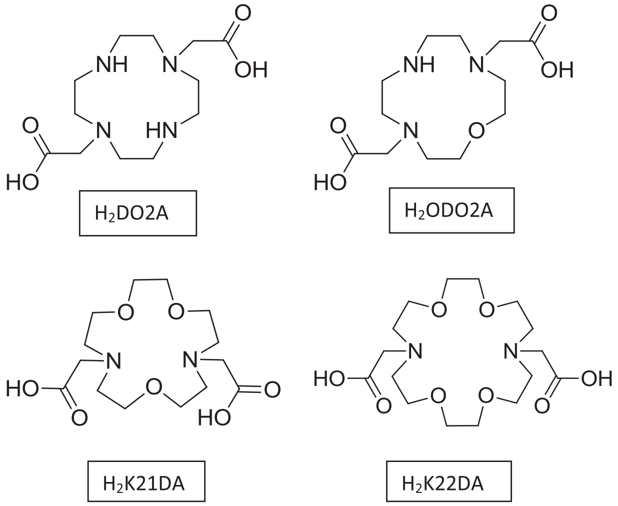
Introduction

Over the last 30 years we have been interested in the study of the coordination chemistry (i.e. thermodynamic stabilities [1], kinetics of complex formation and dissociation reactions [2], solid and solution state structures [3], and spectroscopic properties [4]) of trivalent lanthanide (Ln^{3+}) complexes of macrocyclic ligands and their potential applications as ion selective reagents [1], solvent extraction reagents [5], magnetic resonance imaging contrast enhancement agents [6], nuclear medicine [7], molecular imaging agents [8], luminescent anion sensors [9], and artificial nucleases, peptidases and hydrolases [10]. In a previous paper [11], we reported the trivalent lanthanide complex formation constants (log K_f) of the macrocyclic ligand H_2ODO2A (1-oxa-4,7,10-triazacyclododecane-4,10-diacetic acid, scheme 1) determined by pH titration techniques to be in the range 10.84–12.62 which are smaller than those of the structurally related H_2DO2A (1,4,7,10-tetraazacyclododecane-1,7-diacetic acid, scheme 1) complexes (log K_f range 10.94–13.31). Starting at pH > 7, the equilibrium formation of the dinuclear hydrolysis species, e.g. $Ln_2(ODO2A)_2(\mu\text{-}OH)^+$ and $Ln_2(ODO2A)_2(\mu\text{-}OH)_2$, dominates over the mononuclear species, e.g. LnODO2A(OH) and $LnODO2A(OH)_2^-$. Mass spectrometry confirmed the presence of both the mononuclear and dinuclear species at pH > 7. Density function theory (DFT)-calculated structures of the $EuODO2A(H_2O)_3^+$ and $EuDO2A(H_2O)_3^+$ complexes indicate that three inner-sphere coordinated water molecules are arranged in a *meridional* configuration, i.e. the three water molecules are on the same plane perpendicular to that of the basal N_3O or N_4 atoms of the macrocyclic ligand. However, luminescence lifetime studies reveal that the $EuODO2A^+$ and $TbODO2A^+$ complexes have 4.1 and 2.9 inner-sphere coordinated water molecules, respectively, indicating that other equilibrium species are also present for the $EuODO2A^+$ complex. Additional DFT calculations by using Y(III) ion to substitute Eu(III) ion show that each Y(III) ion is eight-coordinated in the two lowest energy possible *cis*-$[Y_2(ODO2A)_2(\mu\text{-}OH)(H_2O)_2]^+$ and $[Y_2(ODO2A)_2(\mu\text{-}OH)_2]$ dinuclear complex structures. The former includes six-coordination by the ligand $ODO2A^{2-}$, one by the bridged μ-OH ion and one by a water molecule. The second includes six-coordination by the ligand $ODO2A^{2-}$ and two by the bridged μ-OH ions. However, to confine the length of the paper, the studies of the dissociation kinetics of these Ln complexes were excluded from that publication.

Previously, we have also reported the results of our studies on the formation stability, dissociation kinetics, and structures of a number of Ln(III) complexes of macrocyclic ligands, including H_2K21DA (dapda, 1,7-diaza-4,10,13-trioxacyclopenta-decane-N,N′-diacetic acid [1(b), 2(a) and (b)], scheme 1), H_2K22DA (dacda, 1,10-diaza-4,7,13,16-tetraoxacyclo-octadecane-N,N′-diacetic acid [1(a), 2(c)], scheme 1), H_3DO3A (1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid [2(d), 3(c)]), H_4DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid [2(e)]), and their structural analogs [3(e), 12]. The cavity sizes, basicities, steric factors, and conformations of the macrocyclic ligands all affect the physicochemical properties of their Ln(III) complexes, in particular, the formation stabilities and dissociation rates. In this paper, we report the results of the studies of dissociation kinetics of selected $LnODO2A^+$ complexes. These kinetic data fill in the gap of those of two sets of trivalent lanthanide macrocyclic complexes, namely the $LnK21DA^+$/$LnK22DA^+$ complexes and the $LnDO2A^+$/LnDO3A/$LnDOTA^-$ complexes, and would be useful for future quantitative comparisons.



Scheme 1. Structural formulas of H_2DO2A, H_2ODO2A, H_2K21DA, and H_2K22DA.

Results and discussion

Dissociation kinetics of LnODO2A$^+$

Lanthanide complex solutions were carefully prepared at pH range of 6.3–6.7 to ensure complete complex formation before dissociation studies. As the lanthanide complexes do not show appreciable absorption in the near-ultraviolet region, Cu(II) ion was used as the scavenger of free ligand and the reaction kinetics were followed by monitoring the growth in absorbance due to the CuODO2A complex formation at 264 nm. Since the stability of CuODO2A [13] ($\log K_f = 17.85$) is much greater than those of all LnODO2A$^+$ complexes ($\log K_f = 10.84$–12.62) [11], the following exchange reaction (1) will be complete under the experimental conditions (20-fold excess of Cu^{2+}):

$$\mathrm{LnODO2A^+ + Cu^{2+} \rightarrow CuODO2A + Ln^{3+}} \tag{1}$$

Independence of k_{obs} on [Cu^{2+}]

The rates of the exchange reactions are zero order in copper(II) concentration at both pH 4.50 and 3.80 (table S1, see online supplementary material at http://dx.doi.org/10.1080/00958972.2014.945923), suggesting no copper attack on the LnODO2A$^+$ complex to form a rate-determining intermediate due to the steric constraint of the macrocyclic complex. This has been seen for a number of linear and macrocyclic lanthanide complexes with steric constraints, i.e. LnDO2A$^+$ [11], LnK21DA$^+$ [2(b)], LnK22DA$^+$ [2(c)], LnCyDTA$^-$ [14], and LnMEDTA [15], and the obtained rate data can be regarded as those of the dissociation reactions of the LnODO2A$^+$ complexes. For a given lanthanide ion in the solution pH studied, the rate constants and the kinetic labilities are in the order LnK21DA$^+$ > LnK22DA$^+$ > LnODO2A$^+$ > LnDO2A$^+$, even though the thermodynamic stability is not the same trend. For example, the thermodynamic stability trend for the Nd^{3+} complexes is NdDO2A$^+$ >

$NdK22DA^+ > NdODO2A^+ > NdK21DA^+$ [11]. However, for the $LnODO2A^+$ complexes, the trend of kinetic stability is the same as that of their thermodynamic stabilities, i.e. the thermodynamically more stable dissociates more slowly.

Acetate catalysis

The $LnODO2A^+$ dissociation rates are influenced by the presence of acetate ions. Table 1 lists the k_{obs} data for five selected $LnODO2A^+$ complexes at [Acetate] = 1.0−5.0 mM. Linear least squares regression analyses of the plots of the k_{obs} values *versus* [Acetate] give slope values k_{AC} (acetate-assisted dissociation rate constant) and intercept values k_0 with r^2 values close or equal to 1 at both pH 4.50 and 3.80 (equation (2)).

$$k_{obs} = k_0 + k_{AC}[\text{Acetate}] \tag{2}$$

The effect of acetate ion on k_{obs} could be explained by acetate complexation on the positively charged $LnODO2A^+$, leading to a neutral, more labilized intermediate for hydrogen ion attack and dissociation. Usually, the number of inner-sphere coordinated water molecules, their easiness by acetate displacement, and the thermodynamic stability of the complex may all be important to account for the absolute and relative strength of acetate catalysis. The higher the number of inner-sphere coordinated water molecules, the greater the chance for acetate to replace them. The k_{AC} and k_0 values of the $LnODO2A^+$ complexes are in most cases greater than those of the corresponding ones of the $LnDO2A^+$ complexes except for the k_{AC} value for the $LaODO2A^+$ complex, indicating that the kinetic lability of the $LnODO2A^+$ complex is greater than that of the corresponding $LnDO2A^+$ complex.

Similar to $DO2A^{2-}$, $ODO2A^{2-}$ offers six coordination donor sites, the remaining inner-sphere coordination water molecules on the lanthanide ions are possibly 4 for $LaODO2A^+$, 3–4 for $PrODO2A^+$ and $EuODO2A^+$, 2–3 for $ErODO2A^+$, and 2 for $LuODO2A^+$. Thus, under the experimental conditions, the observed k_{AC} value is the highest for $LaODO2A^+$ and it decreases as the atomic number of Ln^{3+} is increased until Eu^{3+}, the value then increases slightly with increasing atomic number. On the other hand, among the five $LnODO2A^+$ complexes studied, the relative acetate catalysis of the $LnODO2A^+$ complex dissociation is the greatest for Lu^{3+}. At 25 °C, pH 4.61, and [Acetate] = 5.0 mM, acetate catalysis constitutes 20, 41, 30, 43, and 75% for the La, Pr, Eu, Er, and Lu complex dissociation pathways, respectively.

The acetate catalysis is found to be greater at pH 3.80 than at pH 4.61 for the $EuODO2A^+$ complex. Specifically, at pH 3.80, acetate catalysis at 1.0 and 5.0 mM constitutes the respective 71 and 90% of the $EuODO2A^+$ complex dissociation pathway.

Table 1. Effect of acetate concentration on $LnODO2A^+$ dissociation kinetics, k_{obs} (s^{-1}). pH 4.61 and 3.80 (Eu only), $[Cu^{2+}] = 1.0 \times 10^{-3}$ M, $[LnODO2A^+] = 5.0 \times 10^{-5}$ M, T = 25 °C, μ = 0.10.

[Acetate]\Ln^{3+}	La	Pr	Eu	Er	Lu	Eu (pH 3.80)
1.0 mM	1.35×10^{-3}	1.57×10^{-4}	4.59×10^{-5}	4.01×10^{-5}	1.81×10^{-5}	1.17×10^{-4}
2.0 mM	1.39×10^{-3}	1.75×10^{-4}	5.19×10^{-5}	4.92×10^{-5}	2.70×10^{-5}	2.02×10^{-4}
3.0 mM	1.43×10^{-3}	1.97×10^{-4}	5.35×10^{-5}	5.58×10^{-5}	3.33×10^{-5}	2.84×10^{-4}
4.0 mM	1.55×10^{-3}	2.15×10^{-4}	5.71×10^{-5}	5.77×10^{-5}	3.96×10^{-5}	3.50×10^{-4}
5.0 mM	1.59×10^{-3}	2.31×10^{-4}	6.14×10^{-5}	6.28×10^{-5}	4.66×10^{-5}	4.61×10^{-4}
k_{AC} ($M^{-1}s^{-1}$)	6.40×10^{-2}	1.88×10^{-2}	3.62×10^{-3}	5.39×10^{-3}	6.96×10^{-3}	8.34×10^{-2}
k_0 (s^{-1})	1.27×10^{-3}	1.39×10^{-4}	4.31×10^{-5}	3.70×10^{-5}	1.20×10^{-5}	3.26×10^{-5}
r^2	0.9998	1.000	0.9998	0.9989	0.9996	0.9943

Because the buffer solutions were prepared using the acetic acid (pKa 4.76)/acetate ion stock solution, the acetic acid concentration at pH 3.80 is ~9-fold of that of [Acetate] and a general acid catalysis by acetic acid cannot be ruled out. However, it is difficult to completely separate the general acid catalysis from the acetate catalysis at present (*vide infra*).

[H^+]-independent and [H^+]-dependent pathways

The observed rate constants for reaction 1, the temperature at which they were measured, and the concentration of hydrogen ion for selected $LnODO2A^+$ complexes (Ln = La, Pr, Eu, Er and Lu) are given in table S2 (Supplemental data). Selected absorbance *versus* time data plots at 15, 25, and 35 °C are shown in figures S1–S8 (Supplemental data). When the observed rate constants are plotted against [H^+] (e.g. figure 1), all five lanthanide complexes show saturation curves with limiting rate constants at higher [H^+]. And in all plots, appreciable intercepts are obtained that correspond to [H^+]-independent or self-dissociation rate constants (k_d). The simplified proposed dissociation mechanisms are shown in scheme 2, which is similar to that of the $LnDO2A^+$ complexes.

The species [LnL^+]*, [LnL(Ac)], and [$LnLH^{2+}$]* are the respective distorted LnL^+ complex, acetate ternary complex, and distorted protonated complex. The rate law consistent with the proposed mechanisms is:

$$k_{obs} = k_d + k_{AC}[\mathrm{Acetate}] + \mathrm{K}'k_{lim}[\mathrm{H}^+]/(1 + \mathrm{K}'[\mathrm{H}^+]) \qquad (3)$$

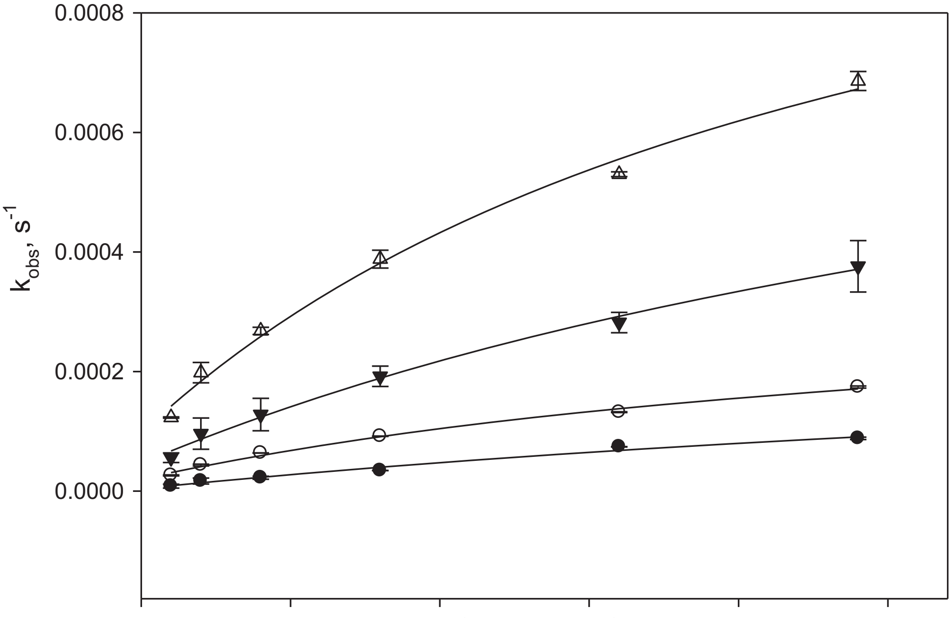


Figure 1. Plots of observed rate constants (k_{obs}) *vs.* [H^+] for the $LuODO2A^+$ complex dissociation reactions at different temperatures 15 ~ 45 °C. ●: 15 °C; ○: 25 °C; ▼: 35 °C; Δ: 45 °C.

I: $[H^+]$-independent direct dissociation pathway

$$\mathrm{LnL^+} \xrightleftharpoons[k_{d'}]{k_d} \left[\mathrm{LnL^+}\right]^* \xrightarrow[\text{fast}]{Cu^{2+}/H^+} \mathrm{Ln^{3+} + CuL + H^+}$$

II: Acetate-dependent dissociation pathway

$$\mathrm{LnL^+ + Ac^-} \xrightleftharpoons[k_{AC}]{k_{AC}} [\mathrm{LnL(Ac)}] \xrightarrow[\text{fast}]{Cu^{2+}} \mathrm{Ln^{3+} + CuL + Ac^-}$$

III: $[H^+]$-dependent, limiting rate dissociation pathway

$$\mathrm{LnL^+ + H^+} \xrightleftharpoons[k_{H'}]{k_H} \left[\mathrm{LnLH^{2+}}\right] \xrightarrow{k_{lim}} \left[\mathrm{LnLH^{2+}}\right]^* \xrightarrow[\text{fast}]{Cu^{2+}} \mathrm{Ln^{3+} + CuL + H^+}$$

Scheme 2. The simplified proposed mechanisms for the dissociation of $LnODO2A^+$ complexes in the $[H^+]$ range $(0.1–2.4) \times 10^{-4}$ M.

where k_d is the $[H^+]$-independent direct dissociation rate constant, K' (= k_H/k_H') is the equilibrium constant for the formation of the monoprotonated complex (equation (4)), and k_{lim} is the limiting rate constant for the protonated lanthanide complex.

$$\mathrm{LnL^+ + H^+ \leftrightarrow LnLH^{2+}} \tag{4}$$

Note that k_0 in equation (2) is equal to $k_d + K'k_{lim}[H^+]/(1 + K'[H^+])$ in equation (3). Strictly speaking, in the pH range 3.6–5.0 studied, there is a small fraction of $LnLH^{2+}$ present for the lighter lanthanide if equilibrium is reached [11], and the acetate anion could form the $LnLH(Ac)^+$ species. However, the amount of the $LnLH(Ac)^+$ species is likely small compared to that of LnL(Ac). Thus, assuming that the term ($k_d + k_{AC}$[Acetate]) does not vary with $[H^+]$ very much, equation (3) can be written as:

$$k_{obs} = k_{d'} + K'k_{lim}[H^+]/(1 + K'[H^+]) \tag{5}$$

Table 2. Resolved rate constants for the dissociation of selected $LnODO2A^+$ complexes.

Ln	T (°C)	$k_{d'}$ (s^{-1})	k_{lim} (s^{-1})	K' (M^{-1} dm^3)
La	15	$(6.37 \pm 0.35) \times 10^{-4}$	$(1.39 \pm 0.05) \times 10^{-3}$	$(1.53 \pm 0.25) \times 10^{4}$
	25	$(1.29 \pm 0.13) \times 10^{-3}$	$(2.58 \pm 0.22) \times 10^{-3}$	$(1.08 \pm 0.39) \times 10^{4}$
	35	$(3.15 \pm 0.23) \times 10^{-3}$	$(7.28 \pm 3.71) \times 10^{-3}$	$(2.93 \pm 2.60) \times 10^{3}$
	45	$(6.33 \pm 0.39) \times 10^{-3}$	$(9.92 \pm 0.56) \times 10^{-3}$	$(1.21 \pm 0.31) \times 10^{4}$
Pr	15	$(8.28 \pm 1.69) \times 10^{-5}$	$(2.89 \pm 0.64) \times 10^{-4}$	$(6.81 \pm 4.33) \times 10^{3}$
	25	$(1.75 \pm 0.23) \times 10^{-4}$	$(6.68 \pm 2.28) \times 10^{-4}$	$(3.88 \pm 2.65) \times 10^{3}$
	35	$(3.91 \pm 0.21) \times 10^{-4}$	$(1.00 \pm 0.07) \times 10^{-3}$	$(7.58 \pm 1.31) \times 10^{3}$
	45	$(8.69 \pm 0.58) \times 10^{-4}$	$(2.33 \pm 0.84) \times 10^{-3}$	$(3.14 \pm 2.03) \times 10^{3}$
Eu	15	$(1.41 \pm 0.49) \times 10^{-5}$	$(7.21 \pm 0.90) \times 10^{-5}$	$(1.04 \pm 0.52) \times 10^{4}$
	25	$(4.58 \pm 0.25) \times 10^{-5}$	$(1.76 \pm 0.31) \times 10^{-4}$	$(3.42 \pm 1.14) \times 10^{3}$
	35	$(1.13 \pm 0.12) \times 10^{-4}$	$(3.61 \pm 0.97) \times 10^{-4}$	$(4.32 \pm 2.46) \times 10^{3}$
	45	$(2.56 \pm 0.21) \times 10^{-4}$	$(5.82 \pm 0.71) \times 10^{-4}$	$(7.34 \pm 2.71) \times 10^{3}$
Er	15	$(1.72 \pm 0.35) \times 10^{-5}$	$(6.48 \pm 5.06) \times 10^{-4}$	$(8.80 \pm 8.35) \times 10^{2}$
	25	$(3.46 \pm 0.60) \times 10^{-5}$	$(1.19 \pm 0.64) \times 10^{-3}$	$(1.03 \pm 0.70) \times 10^{3}$
	35	$(8.22 \pm 1.42) \times 10^{-5}$	$(1.29 \pm 0.29) \times 10^{-3}$	$(2.56 \pm 0.95) \times 10^{3}$
	45	$(1.67 \pm 0.31) \times 10^{-4}$	$(2.76 \pm 1.35) \times 10^{-3}$	$(1.68 \pm 1.16) \times 10^{3}$
Lu	15	$(3.91 \pm 5.07) \times 10^{-6}$	$(2.96 \pm 2.12) \times 10^{-4}$	$(1.73 \pm 1.77) \times 10^{3}$
	25	$(2.01 \pm 0.57) \times 10^{-5}$	$(3.48 \pm 0.80) \times 10^{-4}$	$(3.19 \pm 1.34) \times 10^{3}$
	35	$(4.65 \pm 1.12) \times 10^{-5}$	$(9.03 \pm 2.72) \times 10^{-4}$	$(2.34 \pm 1.12) \times 10^{3}$
	45	$(9.68 \pm 2.49) \times 10^{-5}$	$(1.18 \pm 0.24) \times 10^{-3}$	$(3.97 \pm 1.64) \times 10^{3}$

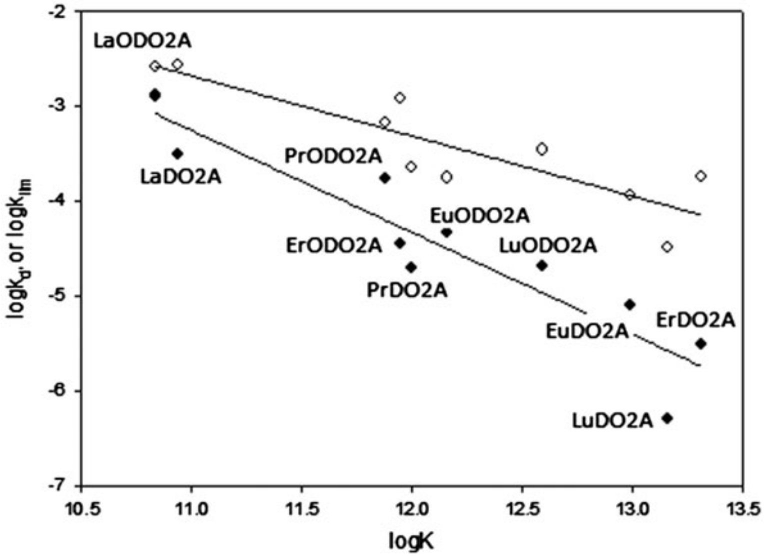


Figure 2. Plots of log $k_{d'}$(◆) and log k_{lim}(◇) values against log K_f values for selected LnODO2A$^+$ and LnDO2A$^+$ [2(f)] complexes at 25 °C (Ln = La, Pr, Eu, Er, Lu).

where $k_{d'} = k_d + k_{AC}$[Acetate]. The values of $k_{d'}$, k_{lim} and K′ are resolved by an unweighted least squares analysis using equation (5) and are listed in table 2.

The values of [H$^+$]-independent rate constants ($k_{d'}$) are in the order La > Pr > Eu > Er > Lu in most temperatures studied, which is in the same trend as the thermodynamic stability (figure 2). This trend is different from that of the limiting rate constants (k_{lim}) which is in the order La > Er > Pr > Eu > Lu. The observation that the ErODO2A$^+$ complex is much more sensitive to proton-assisted dissociation remains to be understood. The fitted log K′ values are in the range 2.94–4.18 which is similar to that determined by pH titration, i.e. 3.28–3.98 [11], and to those of the LnDO2A$^+$ complex, i.e. 3.20–3.98 [2(f)], and the LnK21DA$^+$ complex, i.e. 3.47–4.24 [2(c)].

Effects of temperature

The activation parameters for the [H$^+$]-independent and [H$^+$]-dependent pathways have been obtained from the temperature dependence of rate constants. According to the Eyring equation [16],

$$\mathrm{Ln}(k/T) = \ln(k_B/h) - (\Delta H^*/RT) + (\Delta S^*/R) \tag{6}$$

the activation parameters of these dissociation reactions can be obtained by plotting of ln (k/T) *versus* ($1/T$), where k is the rate constant, R is the gas constant (1.987 cal M^{-1} K^{-1}), k_B is the Boltzmann's constant (1.381×10^{-23} J K^{-1}), h is the Planck's constant (6.626×10^{-34} Js) and T is the absolute temperature, K. The slope and intercept values of these plots yield the activation enthalpy (ΔH^*) and entropy (ΔS^*) data:

$$\mathrm{Slope} = (-\Delta H^*/R) \tag{7}$$

Table 3. Activation parameters for self-and acetate-catalyzed dissociation and proton-catalyzed dissociation reactions of selected $LnODO2A^+$ complexes[a]. ΔG^* values are calculated at 25 °C.

Ln	ΔH^*_d kcal (M)	ΔS^*_d cal/(deg M)	ΔG^*_d kcal (M)	ΔH^*_{lim} kcal (M)	ΔS^*_{lim} cal/(deg M)	ΔG^*_{lim} kcal (M)
$LaODO2A^+$	13.6(0.6)	−26.1(1.9)	21.3	12.1(1.6)	−29.7(5.3)	20.9
$PrODO2A^+$	13.7(0.4)	−29.7(1.5)	22.5	11.5(1.2)	−34.6(3.8)	21.8
$EuODO2A^+$	16.9(0.9)	−21.8(2.4)	23.4	12.2(0.9)	−35.1(3.1)	22.6
$ErODO2A^+$	13.4(0.5)	−33.9(1.7)	23.5	7.4(1.7)	−47.2(5.5)	21.5
$LuODO2A^+$	18.6(2.4)	−18.4(7.9)	24.0	8.7(2.0)	−44.7(6.5)	22.0

[a]Values in parentheses are standard deviations.

$$\text{Intercept} = (\Delta S^*/R) + \ln(k_B/h) \tag{8}$$

The free energy of activation, ΔG^*, can then be calculated according to the following equation:

$$\Delta G^* = \Delta H^* - T\Delta S^* \tag{9}$$

Table 3 lists the values of ΔH^*, ΔS^*, and ΔG^* for the $[H^+]$-independent and $[H^+]$-dependent dissociation reaction pathways of selected $LnODO2A^+$ complexes.

The observed $k_{d'}$ values of the $LuODO2A^+$ and $EuODO2A^+$ complexes have larger temperature variations, leading to the highest and second highest ΔH^*_d values among the five selected $EuODO2A^+$ complexes. On the other hand, the ΔS^*_d values of the two complexes are the least and second least negative (i.e. isokinetic behavior [17]), and the trend of ΔG^*_d values is $LuODO2A^+ > ErODO2A^+ > EuODO2A^+ > PrODO2A^+ > LaODO2A^+$. This trend is similar to that of their complex formation stability and that of the $LnDO2A^+$ complexes. Note that the $k_{d'}$ values have both k_d and k_{AC} components, no attempt was made to separate them for the present temperature variation studies.

For the proton-catalyzed dissociation pathway, the obtained ΔH^*_{lim} values are in the order $EuODO2A^+ \geq LaODO2A^+ \geq PrODO2A^+ > LuODO2A^+ > ErODO2A^+$. With the isokinetic compensation of the ΔS^*_{lim} barriers, the trend for the ΔG^*_{lim} values is $EuODO2A^+ > LuODO2A^+ > PrODO2A^+ > ErODO2A^+ > LaODO2A^+$ which is quite different from that of their complex formation stability and that of the $LnDO2A^+$ complexes.

Comparisons of the dissociation kinetic and thermodynamic data of $LnODO2A^+$ complexes with other Ln(III) macrocyclic complexes

From our current and previously reported data, the thermodynamic formation stability constants for a number of cyclen-based macrocyclic Ln(III) complexes are in the order $LnDOTA^- > LnDO3A > LnDO2A^+ > LnODO2A^+$ [2(f), 11]. For the macrocyclic dicarboxylic acetate ligands with the respective 12, 15, and 18-membered rings, the stability order is $LnDO2A^+ > LnODO2A^+ > LnK22DA^+ > LnK21DA^+$, with a few exceptions. For example, for Ln = La, Ce, and Pr, the stability trend is $LnK22DA^+ > LnDO2A^+ > LnODO2A^+ > LnK21DA^+$, due to better metal ionic radius and macrocycle cavity size fit of the $LnK22DA^+$ complexes. Thus, except for the $LnK22DA^+$ complexes where Ln = La, Ce, and Pr, the other Ln(III) complexes of the macrocyclic K22DA and K21DA ligands with larger cavity sizes are more flexible than those of the smaller 12-membered ring DO2A and ODO2A ligands, and result in faster dissociation rates. At a given pH, the expected ascending

Table 4. Various kinetic rate and equilibrium constants of selected macrocyclic Ln(III) complexes at 25 °C.

	$k_{d'}$, s^{-1}	k_{lim}, s^{-1}	K′, M^{-1} dm^{3}
LaODO2A$^{+,a}$	$(1.29 \pm 0.13) \times 10^{-3}$	$(2.58 \pm 0.22) \times 10^{-3}$	$(1.08 \pm 0.39) \times 10^{4}$
PrODO2A$^{+,a}$	$(1.75 \pm 0.23) \times 10^{-4}$	$(6.68 \pm 2.28) \times 10^{-4}$	$(3.88 \pm 2.65) \times 10^{3}$
EuODO2A$^{+,a}$	$(4.58 \pm 0.25) \times 10^{-5}$	$(1.76 \pm 0.31) \times 10^{-4}$	$(3.42 \pm 1.14) \times 10^{3}$
ErODO2A$^{+,a}$	$(3.46 \pm 0.60) \times 10^{-5}$	$(1.19 \pm 0.64) \times 10^{-3}$	$(1.03 \pm 0.70) \times 10^{3}$
LuODO2A$^{+,a}$	$(2.01 \pm 0.57) \times 10^{-5}$	$(3.48 \pm 0.80) \times 10^{-4}$	$(3.19 \pm 1.34) \times 10^{3}$
LaDO2A$^{+,b}$	$(3.09 \pm 0.79) \times 10^{-4}$	$(2.70 \pm 0.53) \times 10^{-3}$	$(4.91 \pm 2.20) \times 10^{3}$
PrDO2A$^{+,b}$	$(1.94 \pm 0.40) \times 10^{-5}$	$(2.29 \pm 0.11) \times 10^{-4}$	$(8.06 \pm 1.30) \times 10^{3}$
EuDO2A$^{+,b}$	$(7.83 \pm 2.68) \times 10^{-6}$	$(1.14 \pm 0.15) \times 10^{-4}$	$(5.48 \pm 1.76) \times 10^{3}$
ErDO2A$^{+,b}$	$(3.05 \pm 0.94) \times 10^{-6}$	$(1.80 \pm 0.46) \times 10^{-4}$	$(1.58 \pm 0.56) \times 10^{3}$
LuDO2A$^{+,b}$	$(4.99 \pm 1.34) \times 10^{-7}$	$(3.20 \pm 0.33) \times 10^{-5}$	$(2.31 \pm 0.38) \times 10^{3}$
ErK21DA$^{+,c}$	$(3.32 \pm 0.13) \times 10^{-3}$	$(1.04 \pm 0.12) \times 10^{-2}$	$(6.64 \pm 0.85) \times 10^{3}$
LuK21DA$^{+,c}$	$(1.08 \pm 0.06) \times 10^{-2}$	$(4.11 \pm 0.36) \times 10^{-2}$	$(1.22 \pm 0.11) \times 10^{4}$

[a] This work. $k_{d'} = k_d + k_{AC}$[Acetate = 0.005 M dm^{-3}].
[b] Ref. [2(f)].
[c] Ref. [2(c)].

dissociation rate trend would be LnDOTA^{-} < LnDO3A < LnDO2A^{+} < LnODO2A^{+} < LnK22DA^{+} < LnK21DA^{+}.

Table 4 lists various kinetic rate and equilibrium constants of selected macrocyclic Ln(III) complexes of ODO2A^{2-}, DO2A$^{2,-}$ and K21DA^{2-} with similar proposed dissociation mechanisms at 25 °C. In general, the dissociation rate constants $k_{d'}$ and k_{lim} follow the inverse trend of their complex thermodynamic formation stability.

Implications on the effects of ligand structures on Ln(III) complex dissociation and formation reactions

In another paper, we reported the prediction of conformations and protonation sites for the macrocyclic ligands H_2DO2A and H_2ODO2A employing the simulated annealing (SA) method and DFT calculations using the B3LYP/6–31G* method in vacuum and aqueous solution [18]. These SA method/DFT calculations reveal that, in contrast to the H_2ODO2A ligand system, the H_2DO2A ligand system is (1) pre-organized for trivalent lanthanide (Ln) and other metal ion complexation, (2) structurally more symmetrical and slightly more compact in aqueous solution (i.e. more and/or shorter intra-molecular hydrogen bonds), and (3) with greater degree of partial positive charge accumulation on the hydrogen atoms bonded to macrocyclic ring nitrogen atoms when protonated. The H_2ODO2A ligand system is not pre-organized. These observations are in accord with the present experimental findings that the LnODO2A^{+} complexes are less thermodynamically stable and kinetically more labile as compared to the corresponding LnDO2A^{+} complexes.

According to the principle of microscopic reversibility [2(b), 19] (i.e. corresponding to every individual process there is a reverse process, and in a state of equilibrium the average rate of every process is equal to the average rate of its reverse process), the possible dissociation reaction mechanisms are the reverse of the formation reaction mechanisms. Thus, the formation of the LnODO2A^{+} complex is likely going through the following simplified three steps [2(k), 12(i)]: (1) an initial interaction of the aquated Ln(III) ion with one carboxylate group of the non-pre-organized H_2ODO2A, (2) followed by a Ln(III) ion induced ligand reorganization [3(e)] to form an intermediate in which the Ln(III) ion is either coordinated to the two carboxylate groups in a syn-configuration [12(h)] or partially coordinated by

$H_nODO2A^{(2-n)-}$ ($n = 1–2$), and (3) the Ln(III) ion moves into the macrocycle cavity and is fully coordinated by all six donating atoms of $ODO2A^{2-}$ to form the $LnODO2A^+$ complex. Step 3 is most likely the rate-determining step. It has been well documented that the formation reactions are usually catalyzed by OH^- ions [2(d)] and the dissociation reactions by H^+ ions.

If the reactions are slow enough, the formation intermediates in step 2 could be observed by luminescence spectroscopy such as those of the Ln(III)DOTA-like complexes [2(k), 12(h), 12(i)]. Unfortunately, luminescence spectroscopy is not appropriate for our present kinetic studies because the formation and dissociation reactions of $LnODO2A^+$ are much faster than those of the Ln(III)DOTA-like complexes. The lifetime measurements by luminescence spectroscopy could not confirm the presence of the reaction intermediate(s). However, we have used the technique to measure the inner-sphere coordinated number of water molecules ($q = 3–4$) for the respective $TbODO2A^+$ and $EuODO2A^+$ complexes and have reported the results previously [11].

Conclusion

The dissociation kinetics of these $LnODO2A^+$ complexes exhibit certain different features from those of the open chain and macrocyclic polyaminopolycarboxylate complexes reported previously that might be attributed to the replacement of a nitrogen by an oxygen in the rigid macrocyclic ring structure of the ligand. The dissociation rates of $LnODO2A^+$ complexes are all faster than those of the corresponding $LnDO2A^+$ complexes which are consistent with the notion that $LnODO2A^+$ complexes are thermodynamically less stable and kinetically more labile than the corresponding $LnDO2A^+$ complexes, and H_2ODO2A is not pre-organized for Ln^{3+} ion complexation but H_2DO2A is. In particular, the $EuODO2A^+$ and $ErODO2A^+$ complexes have relatively unusual $[H^+]$ and temperature-dependent behaviors and the exact reasons remain to be explored. Overall, the trend of thermodynamic stability is $LnDOTA^- > LnDO3A > LnDO2A^+ > LnK22DA^+ \sim LnODO2A^+ > LnK21DA^+$; the trend of kinetic lability is roughly the reverse of it. These results will be useful for the design of ligands that form mono- and di-nuclear Ln(III) complexes for various analytical and biomedical applications.

Experimental

Materials and standard solutions

Analytical reagent grade chemicals and buffers, unless otherwise stated, were purchased from Sigma (St. Louis, MO, USA), Aldrich (Milwaukee, Wl, USA) or Merck (Darmstadt, Germany) and were used as received without further purification. Disodium ethylenediaminetetraacetic acid (Na_2H_2EDTA) was purchased from Fisher. The ligand ODO2A was prepared and purified as described below. Carbonate-free deionized water was used for all solution preparations.

The concentration of the ODO2A stock solution (ca. 0.01 M) was determined by pH titration using a standard tetramethylammonium hydroxide solution (0.1 M), and was also checked by complexometric back titration. The concentrations of the lanthanide nitrate stock solutions were ca. 0.01 M and were standardized by EDTA titration using xylenol orange as indicator. The EDTA solution was standardized by titrating a calcium carbonate primary standard solution (first dissolved in HCl solution) at pH 10 using calmagite as the indicator.

The 0.1 M tetramethylammonium hydroxide solution was prepared by diluting a 20% $(CH_3)_4NOH$-methanol solution obtained from Aldrich (carbonate-free). The aqueous $(CH_3)_4NOH$ solution was standardized by using reagent grade primary standard potassium hydrogen phthalate. A 0.1 M HCl solution was prepared by diluting a reagent grade HCl solution and standardized by using the standard $(CH_3)_4NOH$ solution. A 1.0 M stock solution of tetramethylammonium chloride (Aldrich) was prepared and diluted to 0.1 M for each titration to maintain a constant ionic strength (0.1 M).

Synthesis of ODO2A

The compound was synthesized according to a published method with minor modification [11, 20]. 4,10-Dicarboxymethyl-1-oxa-4,7,10-triazacyclododecane (H_2ODO2A) in the hydrochloride form was obtained by carboxymethylation of 1-oxa-4,7,10-triazacyclododecane with bromoacetate and recrystallization in ethanolic HCl solution (yield 35%). Anal. Calcd for ODO2A.2.7HCl.H$_2$O ($C_{12}H_{23}N_3O_5.2.7HCl.H_2O$): C, 35.51; H, 6.88; N, 10.36. Found: C, 35.53; H, 6.89; N, 10.12. NMR (D_2O-DSS), ^{13}C: δ42.05, δ50.35, δ52.59, δ55.58, δ66.29, δ170.0 ppm; ^1H: δ3.26, 3.27, 3.28, δ3.34, 3.35, δ3.68, 3.69, 3.70, δ3.89 ppm. ESI (+)-MS, *m/z* 290.1.

Kinetic measurements

All lanthanide complex solutions were freshly prepared by mixing 1.00 : 1.02 metal salts to ligand molar ratio solutions. Stoichiometric amounts of $(CH_3)_4NOH$ solution were slowly added into each metal–ligand mixture to neutralize the protons expelled from the ligand after metal ion complexation. The final pH of each complex solution was carefully adjusted to be in the pH range 6.3–6.7 (i.e. guided from the titration curves of figure S2 in [11]) to ensure complete metal complex formation and the solution was allowed to stand for at least one hour before use. Luminescence spectrum of the EuODO2A$^+$ complex was found to be similar to that previously published at pH 6.0 and 7.0 ([cf 11], figure 7). For kinetic measurements, the pH of each solution was adjusted by using acetic acid/lithium acetate buffer. The final [LnODO2A$^+$] is 5.0×10^{-5} M. The acetate anion concentrations were carefully adjusted to be 1.0–5.0 mM for acetate catalysis studies. As the lanthanide complexes do not show appreciable absorption in the near-ultraviolet region, Cu(II) ion was used as the scavenger of free ligand and the reaction kinetics were followed by monitoring the growth in absorbance due to the CuODO2A complex formation at 264 nm, using a HP 8453 UV–vis diode-array spectrophotometer equipped with a thermostatted cell holder with a constant temperature circulating bath (FIRSTEK SCIENTIFIC B403). The solution temperature was controlled to ±0.1 °C. Although the rates observed are independent of [Cu^{2+}], a pseudo-first-order (20-fold) excess of Cu^{2+} (1.0×10^{-3} M) was used in reaction mixtures. The ionic strength was adjusted to 0.10 M with $LiClO_4$. Pseudo-first order rate constants (k_{obs}) were calculated using the integral rate method by fitting the absorbance *versus* time data to the equation: $A_t = A_0 + A_\infty\ (1-e^{-kobs\cdot t})$. Sigma Plot software was used for curve fitting. Rate constants quoted represent the average values of two to three kinetic runs and were reproducible with 10%.

Funding

The authors wish to thank the National Science Council and the Atomic Energy Council of the Republic of China (Taiwan) for financial support [grant number NSC-98-2113-M-010-001-MY3], [grant number NSC 96-NU-7-009-003], and [grant number NSC-100-2811-M-010-003] of this work.

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