

1,2-Bis(*o*-aminophenoxy)ethane-*N,N,N',N'*-tetra-acetic Acid Derivatives on Complexation with Lanthanoid Metal Ions. Correlation between Size of Trapping Hole and Metal Ion

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ABSTRACT

*Complexation of lanthanoid metal ions with 1,2-bis(*o*-aminophenoxy)-ethane-*N,N,N',N'*-tetraacetic acid and its two derivatives, in which the distance between the chelating functions is changed, has been studied by potentiometric pH titration. There are two complexation modes depending on the size of the metal ion. Structural flexibility of the chelator accounts for the change in the complexation mode.*

Considerable efforts have been devoted to improving the complexing ability and selectivity of a polyamino-poly(*N*-alkanoic acid) such as 3,12-bis(carboxy-methyl)-6,9-dioxo-3,12-diazatetradecanedioic acid (**H₄egta**) with a metal ion by increasing the number of donor groups or by introducing certain rigid aromatic groups such as phenyl,

quinolinyl, or benzofuranyl into the framework [1]. For example, it has been found that 1,2-bis(*o*-aminophenoxy)ethane-*N,N,N',N'*-tetraacetic acid (**H₄bapta**) is an excellent chelator. This chelator is highly selective to Ca²⁺, and its derivatives which have fluorophores in their structure, have been used as versatile Ca²⁺ indicators in the field of medical science [2–11]. In contrast to such a variety of applications, the number of fundamental research studies on complexation from the viewpoints of structure-stability and structure-selectivity relationships are quite limited [12].

In a previous article [12], we reported preparations of two **H₄bapta** derivatives, 1,3-bis(*o*-aminophenoxy)propane-*N,N,N',N'*-tetraacetic acid (**H₄bappta**) and 1,4-bis(*o*-aminophenoxy)butane-*N,N,N',N'*-tetraacetic acid (**H₄bapbta**), and their complexation with alkaline earth metal ions.

In order to elucidate the most suitable ionic size vs. structure relationship for each **H₄bapta** derivative precisely, the series of lanthanoid metal ions is the best because the change in ionic size is delicate within the series. In this article, we wish to report the stability sequences of these chelators for a series of lanthanoid metal ions and to propose two complexing modes contributing to the complexation.

Dedicated to Emeritus Prof. Shigeru Oae on the occasion of his seventy-fifth birthday.

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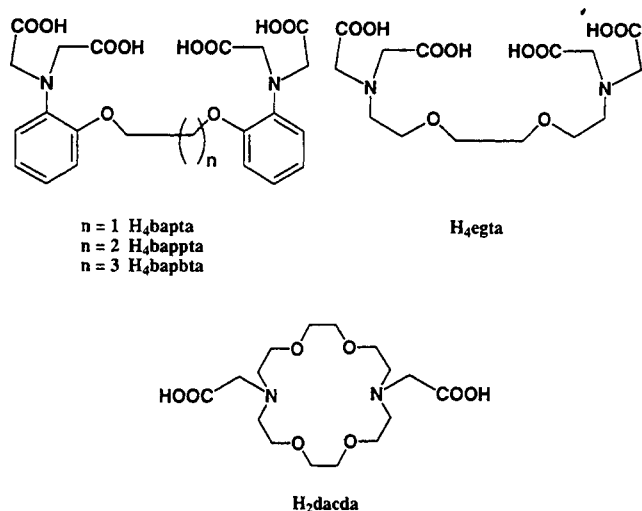


CHART 1

EXPERIMENTAL

Instruments

1H NMR spectra were recorded at 200 MHz on a Varian VXR 200 FT NMR spectrometer. Elemental analyses were performed with a Yanaco MT-5 Elemental Analyzer. All titrations were carried out under argon saturated with aqueous vapor at 298 ± 0.2 K at constant ionic strength of $0.10 \text{ mol} \cdot \text{dm}^{-3}$ KNO_3 . A manual-operating titration system consisted of a Horiba digital ion meter N-8 in conjunction with a Horiba combination pH electrode 6028-10T to monitor the pH (± 0.01 pH unit).

Materials

Chemicals and solvents were used as obtained from commercial sources unless otherwise noted. Water employed for the preparation of stock solutions of chelators was decarbonated by refluxing ion-exchanged and distilled water for 2 hours and storing in a plastic bottle made of polypropylene. Acetonitrile was distilled from calcium hydride immediately before use. All lanthanoid metal ions were provided as hydrous nitrates. They were dried for 2 hours at room temperature under reduced pressure. Standard solutions of aqueous hydrochloric acid were purchased from Nacalai Tesque Co., Ltd., and the ionic strength was adjusted to 0.1 by adding a proper amount of KNO_3 .

Preparation of Chelators

Syntheses of 1,3-bis(*o*-aminophenoxy)propane-*N,N,N',N'*-tetraacetic acid ($H_4bappta$) and 1,4-bis(*o*-aminophenoxy)butane-*N,N,N',N'*-tetraacetic acid ($H_4bapbta$) were described in the previous article [12]. H_4bapta was prepared according to the literature procedure [2].

Potentiometric Titration

A 50 cm^3 three-necked round-bottomed flask was used as a titration vessel with an inlet for argon gas, a glass burette and a temperature probe. The vessel was always kept at 298 ± 0.2 K by using a thermostat. Prior to each titration, the pH meter was standardized at pH 4.01 and 6.86 at 298 K by using standard buffer solutions purchased from Nacalai Tesque Co., Ltd. An HCl solution was delivered from a 10 cm^3 burette with a reading accuracy of $\pm 0.01 \text{ cm}^3$. The measured pH was converted to the concentration of proton ($[H^+]$) according to Eq. [1] with 0.83 for the activity coefficient of proton (f_{H^+}) [13].

$$-\log [H^+] = \text{pH} + \log f_{H^+} \quad (1)$$

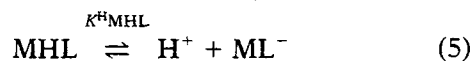
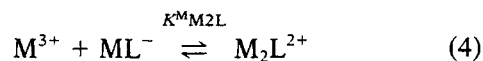
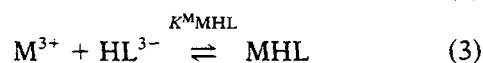
The titrations were performed under two different conditions, (1) $[Ln^{3+}]/[L^{4-}] \approx 10$ and (2) $[Ln^{3+}]/[L^{4-}] = 1$, for determining stability constants and for determining acidity constants of the chelators. The initial concentration of chelators was always kept at $1.00 \times 10^{-3} \text{ mol} \cdot \text{dm}^{-3}$. Stability constants for complexes were determined by the conventional Schwarzenbach's procedure assuming the formation of ML^- , MHL^- , and M_2L -type complexes [14,15].

RESULTS

Determination of Stability Constants

Potentiometric titration was employed for the determination of stability constants. Acidities (pK_a) of chelators have been determined and reported in the previous article [12].

Equilibrium constants for chelation with a lanthanoid metal ion can be defined by Equations 2 through 9.



$$K_{ML}^M = [ML^-]/[M^{3+}][L^{4-}] \quad (6)$$

$$K_{MHL}^M = [MHL]/[M^{3+}][HL^{3-}] \quad (7)$$

$$K_{M_2L}^M = [M_2L^{2+}]/[M^{3+}][ML^-] \quad (8)$$

$$K_{MHL}^H = [H^+][ML^-]/[MHL] \quad (9)$$

where L^{4-} denotes $bapta^{4-}$, $bappta^{4-}$, or $bapbta^{4-}$.

Stability Sequence of Chelation

Some representative titration curves are shown in Figures 1 and 2.

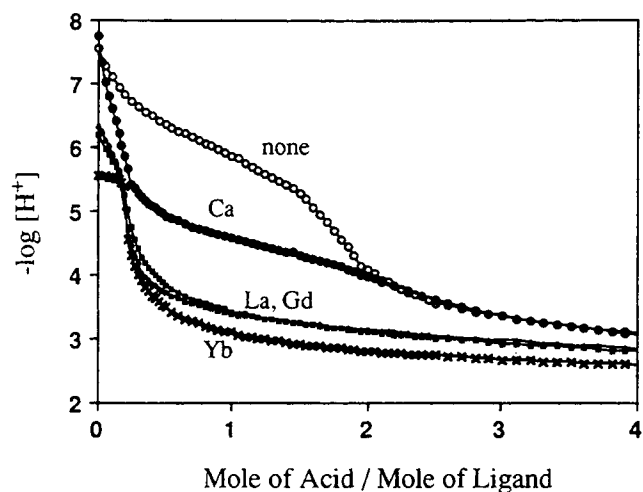


FIGURE 1 Titration curves of $K_4\text{bappta}$ in the absence and presence of the lanthanoid metal ions ($[M^{3+}] > 10[K_4\text{bappta}]$). All titrations were performed at $25.0 \pm 0.2^\circ\text{C}$, $I = 0.1 \text{ mol dm}^{-3}$ (KNO_3).

In the series of complexes of lanthanoid metal ions with **bappta** and **bapbta** [16], no M_2L -type complex was observed: K_{ML}^M calculated by taking into account the formation of an M_2L -type complex affords essentially the same K_{ML}^M obtained by a calculation ignoring the formation of M_2L -type complexes. $K_{M_2L}^M$ appears as a very small positive or negative value. Therefore, we ignored the contribution of $K_{M_2L}^M$ on elucidation of stability constants. Stability constants for lanthanoid metal ion complexes thus obtained by analyzing titration data are summarized in Table 1.

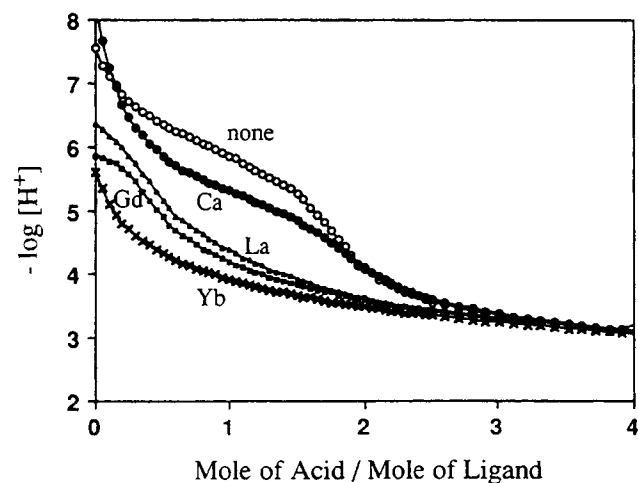


FIGURE 2 Titration curves of $K_4\text{bapbta}$ in the absence and presence of the lanthanoid metal ions ($[M^{3+}] > 10[K_4\text{bapbta}]$). All titrations were performed at $25.0 \pm 0.2^\circ\text{C}$, $I = 0.1 \text{ mol dm}^{-3}$ (KNO_3).

TABLE 1 Logarithmic Stability Constants of **Bapta**-Derivatives^a

Chelator Metal	$H_4\text{bappta}$		
	$\log K_{ML}^M$	$\log K_{MHL}^M$	$-\log K_{MHL}^H$
La	7.76	3.53	2.16
Ce	8.01	3.23	1.60
Pr	7.93	3.11	1.55
Nd	7.80	4.06	2.61
Sm	7.93	4.34	2.77
Eu	8.45	4.42	2.37
Gd	7.67	4.24	2.94
Tb	8.06	4.34	2.65
Dy	8.22	4.63	2.77
Ho	8.22	3.40	1.55
Er	8.56	3.29	1.10
Tm	9.19	3.05	0.27
Yb	9.39	4.40	1.38
Lu	ND ^b	ND ^b	ND ^b

$H_4\text{bapbta}$			
La	6.08	3.76	4.18
Ce	6.45	3.82	3.91
Pr	6.68	4.04	3.89
Nd	6.63	4.06	3.96
Sm	6.76	4.00	3.74
Eu	6.93	4.00	3.58
Gd	6.71	3.82	3.65
Tb	6.81	3.94	3.66
Dy	6.79	3.84	3.66
Ho	6.91	4.07	3.67
Er	6.91	4.09	3.70
Tm	6.72	4.02	3.83
Yb	6.92	4.00	3.58
Lu	6.95	3.91	3.48

^a $K_{ML}^M = [ML]/[M][L]$, $K_{MHL}^M = [MHL]/[HL][M]$, $K_{MHL}^H = [H][ML]/[MHL]$. The ionic strength was adjusted to $0.10 \text{ mol} \cdot \text{dm}^{-3}$ by KNO_3 , and the temperature was $25.0 \pm 0.20^\circ\text{C}$. Standard deviations are all within $\pm 0.10 \log K$ unit.

^bND = not determined.

DISCUSSION

As seen in Figures 1 and 2, the pH values in titration curves are always lower in the presence of a metal ion than in its absence, which indicates that there is significant competition between the metal ion and proton for binding to the chelator. The tendency is larger for lanthanoid metal ions than for Ca^{2+} , simply because the former has a larger charge than the latter.

Figure 3 gives a plot of $\log K_{ML}^M$ against the atomic number of the metal ion. Ionic radius decreases with the increase in atomic number (lanthanoid contraction). Each stability constant in the series of **egta**-complexes [17] increases in a nearly regular manner with the increase in atomic number of the metal ion. On the other hand, the stability sequences with **bappta**, **bapbta**, and **bapbta** appear differently from that of **egta**. The stability sequence with **bappta** has a maximum at Pr^{3+} , whose

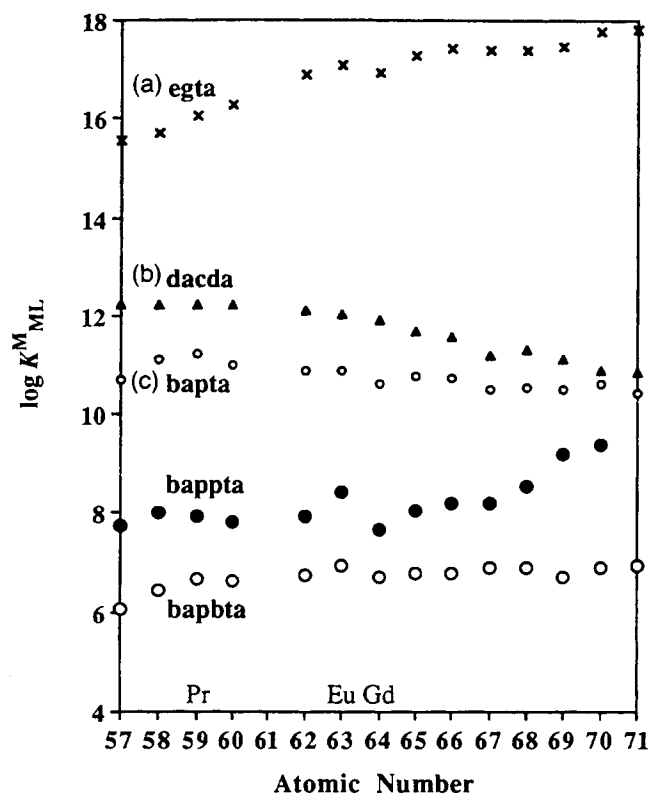


FIGURE 3 Plots of stability constants, $\log K_{ML}^M$, for various chelators against atomic number in the series of lanthanoid metal ions: (a) data from Ref. [17]; (b) data from Ref. [20]; and (c) Data from Refs. [18] and [19].

ionic radius of 1.126 Å is similar to that of Ca^{2+} (ionic radius: 1.12 Å) [18,19]. Although the stability sequence for **bappta** has a local maximum at Eu^{3+} (ionic radius: 1.066 Å), the trend for metal ions lighter than Eu^{3+} resembles that of **bapta**, whereas the trend for metal ions heavier than Eu^{3+} is similar to that of **egta**. The stability of the **bappta**-complex also changes in a nearly regular manner. Although **egta** and **bapbta** afford a similar trend, the increase in stability constants of **bapbta**-complexes with atomic number is slightly smaller than those of the corresponding **egta**-complexes.

In the previous article, we proposed two types of chelating mode, vicinal and geminal types, to explain complexing behavior of **bapta**-derivatives with alkaline earth metal ions based on potentiometric observation (Chart 2) [12].

Namely, in the series of alkaline earth metal ions, the trapping hole of **bapta**-derivatives is too large to form a stable complex with the smallest Mg^{2+} in the vicinal-type chelating mode. Thus, Mg^{2+} is forced to bind to **bapta**-derivatives in the geminal-type chelating mode. On the other hand, the vicinal-type chelation operates mainly for larger metal ions than Mg^{2+} such as Ca^{2+} , Sr^{2+} , and Ba^{2+} . Structures of vicinal-type Ca^{2+} complexes [21,22] and geminal-type Mg^{2+} complexes of **egta** and/or

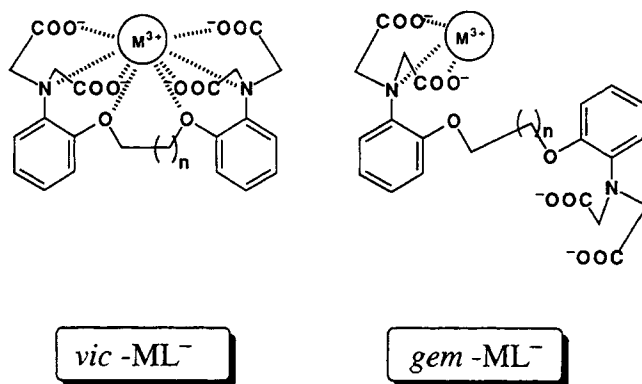


CHART 2

bapta [22,23] have been visualized by X-ray crystallography. Unfortunately, we have not succeeded in obtaining X-ray crystallographic data of **bappta** and **bapbta** complexes.

Increased structural flexibility of chelator molecules will provide adaptability to the chelator for effective complexation at the sacrifice of selectivity toward a particular metal ion. Yuchi *et al.* [18,19] explained a different stability sequence of **bapta** from that of **egta** in terms of an increase in rigidity of **bapta**; that is, introduction of two phenyl rings into the structure of **egta** leads to an increase in structural rigidity. **Egta** is able to adapt its own structure to construct a trapping hole for all lanthanoid metal ions because of its higher flexibility. On the other hand, **bapta** is unable to contract the hole for ions heavier than Pr^{3+} because two phenyl rings in this chelator reduce the structural flexibility. Thus, the structure of **bapta** is too rigid to adapt to the size of a trapping hole for ions of large atomic numbers, and, consequently, the best fit is seen at Pr^{3+} . The idea is supported by the fact that variation of $\log K_{ML}^M$ for **bapta** plotted against atomic number of the metal ion decreases monotonously after the maximum at Pr^{3+} (Figure 3). It is suggested that, from the comparison with 1,10-diaza-4,7,13,16-tetraoxacyclooctadecane-*N,N'*-diacetic acid (**H₂dacda**) which has a ring-type skeleton, this structural rigidity is more serious than that of **bapta**; structural rigidity of chelator molecule is one of the important factors to provide the selectivity in size of metal ions [17,18].

Structural flexibility becomes larger on going from **bapta** to **bappta**, and to **bapbta**. A longer distance between two ethereal oxygen atoms in **bappta** than in **bapta** makes the former easier to adapt to the size of its own trapping hole to the change in size of lanthanoid metal ions in complexation even with smaller metal ion than Pr^{3+} . As shown in Figure 3, the stability sequence of **bappta** is similar to that of **egta**. This means that **bappta** is as flexible to adapt its own structure to all lanthanoid metal ions as is **egta**. The smaller stability con-

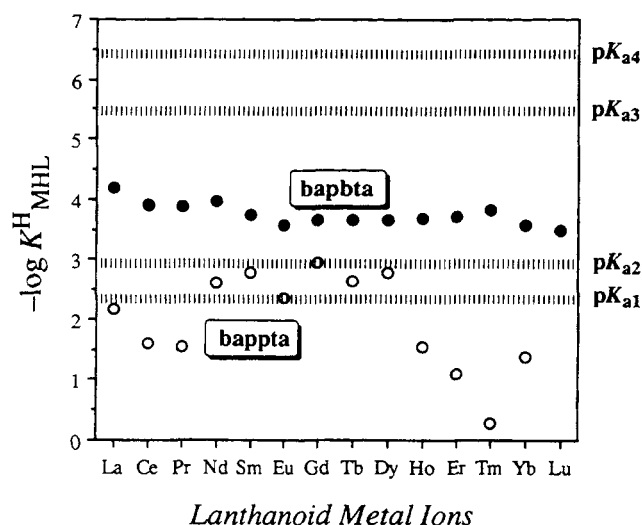


FIGURE 4 Plots of acidity constants, $-\log K_{MHL}^H$, for various chelators against the series of lanthanoid metal ions. pK_{a1} , pK_{a2} , pK_{a3} , and pK_{a4} are averaged acidity constants of **bappta**-derivatives.

stants of **bappta** are mainly attributed to the decrease in basicity of nitrogen atoms by introducing electronegative phenyl rings and the existence of one 6-membered chelate ring (containing two etheral oxygen atoms and a metal ion) in the vicinal-type chelating mode, which is not seen in **bapta**-complexes.

We believe that the local maximum seen at Eu^{3+} in the plot for **bappta** is more or less artificial: for all chelators employed, the points for Gd^{3+} deviate downward from smooth curves. The fact can be interpreted as the gadolinium break arising from the change in hydration number of lanthanoid metal ions [24].

When the spacer distance becomes unnecessarily long to obtain H_4 **bapbta**, the entropic freedom now brings a difficulty in complexing, with the vicinal-type chelating mode providing easiness in complexing with the geminal-type chelating mode.

The predominancy of the geminal-type chelating mode in **bapbta** can also be supported by its acidity, $-\log K_{MHL}^H$. As shown in Table 1 and Figure 4, the values of $-\log K_{MHL}^H$, or pK_a of MHL-complex, for **bapbta** are always higher than the corresponding values for **bappta**. Interestingly, $-\log K_{MHL}^H$ for **bapbta** is larger, and the corresponding values for **bappta** are similar or smaller than pK_{a1} and pK_{a2} , the averaged first and second acidities of the chelates. The evidence reveals that the dissociation of proton from the MHL-complex of **bapbta** takes place easier than that from the corresponding complex of **bappta**. An obvious explanation for this difference is that one of two iminodiacetate moieties is still kept free in the ML-complex of **bapbta** in ac-

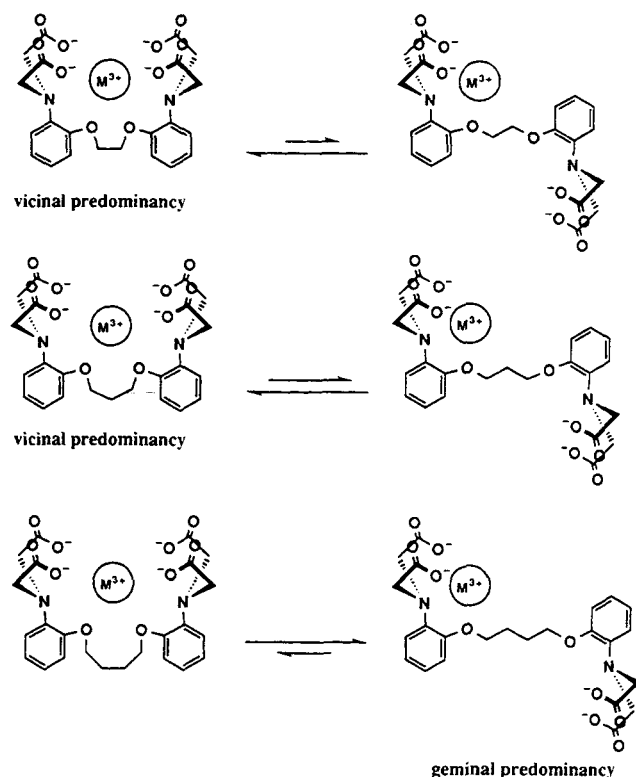


CHART 3

cordance with our proposal that the geminal-type complexation is predominant in **bapbta**.

Comparing the number of chelating interaction between two types of chelating modes, it is predicted that the complex with the vicinal-type mode is more stable than that with the geminal-type mode for a series of lanthanoid metal ions. Thus, the difference in relative stabilities of two complexes in different modes accounts for the fact that the gradient in change of stability constant plotted in Figure 3 for **bapbta** is smaller than that for **egta**.

The values of $\log K_{MHL}^H$ for each chelator, which are listed in Table 1, are quite the same for all the metal ions studied. The MHL-type complex is protonated at a nitrogen atom, as reported in the previous article [12]. Since the protonated nitrogen cannot contribute to the chelation, the complex is inevitably the geminal-type chelating mode regardless of the size of chelator molecule. Since the fourth acidities (pK_{a4}) are quite similar among **bappta**-derivatives, the concentration of HL^{3-} should also be similar at the same pH region.

In conclusion, although flexibility of skeleton is important for exerting a large stability constant for chelation with a metal ion when vicinal-type chelation mode is predominant, this is not always true for highly flexible chelators. Both structural rigidity and skeletal flexibility are required for a

chelator in order to achieve highly stable complexation.

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