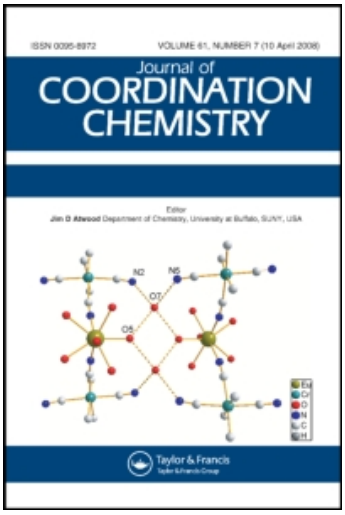

Journal of Coordination Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713455674

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Miwako Sonoda[a]; Isao Yoshida[a]; Ichiro Murase[b]
[a] Department of Applied Chemistry, Kumamoto Institute of Technology, Kumamoto, Japan [b] Dojindo Laboratories Co., Kumamoto, Japan

To cite this Article Sonoda, Miwako , Yoshida, Isao and Murase, Ichiro(2001) 'SYNTHESIS AND DETERMINATION OF METAL CHELATE STABILITIES OF *n*-ALKYLTRIETHYLENETETRA AMINEPENTAACETIC ACID', Journal of Coordination Chemistry, 54: 2, 153 — 165
To link to this Article: DOI: 10.1080/00958970108027151
URL: http://dx.doi.org/10.1080/00958970108027151

J. Coord. Chem., 2001, Vol. 54, pp. 153–165
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SYNTHESIS AND DETERMINATION OF METAL CHELATE STABILITIES OF *n*-ALKYLTRIETHYLENETETRA AMINEPENTAACETIC ACID

MIWAKO SONODA[a], ISAO YOSHIDA[a,*] and ICHIRO MURASE[b]

[a]*Department of Applied Chemistry, Kumamoto Institute of Technology, 4-Ikeda, Kumamoto, 860-0082, Japan;* [b]*Dojindo Laboratories Co., Mashiki-machi, Kumamoto, 861-2202, Japan*

(Received 28 April 2000; In final form 11 October 2000)

n-Alkyl (*n*-$C_{12}H_{25}$- and *n*-$C_{22}H_{45}$-)triethylenetetraaminepentaacetic acids have been prepared by carboxymethylation on N-alkyltriethylenetetraamine. These compounds were originally developed by Miller *et al.*, as useful chelating agents for the removal of actinide ions from the human body. The determination of the chelate stability constants, which was not performed by the original authors, was performed for the C_{12}-derivative with Ca^{2+}, Sr^{2+}, Cu^{2+}, Zn^{2+}, Ni^{2+}, La^{3+}, Sm^{3+}, Er^{3+}, and Th^{4+} including H^+, and the stabilities were evaluated by comparison with those of triethylenetetraaminehexaacetic acid (TTHA).

Keywords: N-alkyltriethylenetetraaminepentaacetic acids synthesis; Lipophilic chelating agents; Metal chelate stability constants; pH titration

INTRODUCTION

Miller *et al.* [1] developed lipophilic triethylenetetraaminepentaacetic acid derivatives, each of which has a long alkyl chain at the terminal nitrogen atoms, namely 1-N-dodecyl- and 1-N-docosyltriethylenetetraamine-N,N′, N″,N‴,N‴-pentaacetic acids, and indicated that these chelating agents, C_{12}-TTPA and C_{22}-TTPA, [2] are excellent agents for efficiently eliminating radioactive Am from the liver, skeleton and carcass of a rat. Their chelate stabilities with Am were also measured quantitatively by gel permeation

*Corresponding author. e-mail: yoshida@chem.sojo-u.ac.jp

chromatography and estimated to be similar to those for ethylenediamine-N,N,N′,N′-tetraaceic acid (EDTA) or diethylenetriamine-N,N,N′,N″,N″-pentaacetic acid (DTPA). These facts indicate that these agents can be useful for chelate therapy to remove radioactive actinide ions from the human body.

From the view point of coordination chemistry, a linear tetraamine as a backbone of the ligand would be excellent, because the coordination ability for metal ions will not be significantly reduced by the presence of a bulky alkyl group at the terminal nitrogen atom. We were also interested in these chelating agents, which would be expected to reveal additional physiological effects.

This paper presents a synthesis of C_{12}-TTPA and C_{22}-TTPA different from the original, as described in the Experimental Section. Since the metal chelate stability will be important for evaluation of the ability of the chelating agents, the determination of stability constants was performed for the C_{12}-derivative with Ca^{2+}, Sr^{2+}, Cu^{2+}, Zn^{2+}, Ni^{2+}, La^{3+}, Sm^{3+}, and Th^{4+}, including H^+, and the stabilities were compared with those of triethylenetetraamine-N,N,N′,N″,N‴,N‴-hexaacetic acid (TTHA).

The C_{12}-derivative is hard to dissolve in water; the potentiometric titration was done in a 50% ethanol-water mixture, so some inaccuracy was inevitable. The solubility of the C_{22}-analogue in the same solvent was much lower, and the titration work was ultimately abandoned.

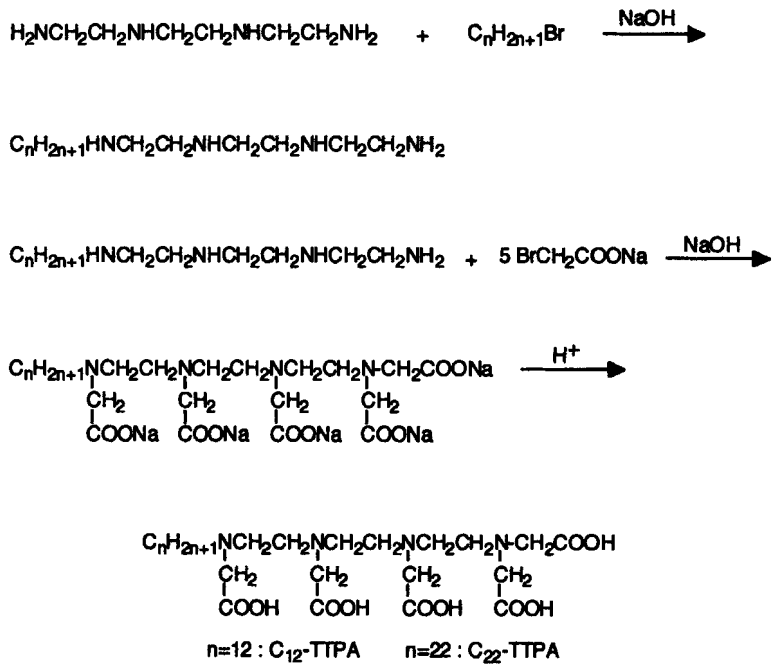
EXPERIMENTAL

Synthesis and Characterization of the Ligands

The ligands were prepared by the procedure shown in Scheme 1. The starting materials, 1-N-dodecyltriethylenetetraamine and 1-N-docosyltriethylenetetraamine were prepared by the method of Miller *et al.* [1] with minor changes. The free amines were obtained as a colorless oil and a fine crystalline powder, respectively.

1-N-Dodecyltriethylenetetraamine

In a 1 liter three-necked flask equipped with a mechanical stirrer, a reflux condenser, and a dropping funnel was placed triethylenetetraamine (146 g, 1.0 mol) in 250 mL of tetrahydrofuran (THF). To this was added dropwise with stirring *n*-dodecyl bromide (56 g, 0.24 mol) in 4 h at room temperature



SCHEME 1 Synthetic process for C_n-TTPA(n = 12 and 22).

and the mixture was heated at reflux overnight. The solvent was removed on a rotary evaporator, 200 mL of water were added to the residue, and the mixture was extracted with 1 L of a 1 : 1 mixture of toluene and *n*-butanol. The organic layer was washed five times with 200 mL of water and dried over anhydrous sodium sulfate. The solvent was removed on a rotary evaporator and 70 g of an oily residue was obtained. This was carefully dissolved in 1 L of 17% hydrochloric acid and the solution was evaporated to dryness on a rotary evaporator. The white solid obtained was heated with 1 L of 50% methanol, insoluble material was filtered off, and the filtrate was allowed to stand overnight at room temperature. The product was obtained as a hydrochloride, which was collected by filtration and recrystallized from 50% methanol. Yield 44 g (40%, based on *n*-dodecyl bromide).

The hydrochloride (40 g) was treated with 40% aqueous sodium hydroxide (75 g) and the oily product was stirred with 500 mL of a toluene and *n*-butanol mixture (1 : 1) on a water bath for 2 h. The organic layer was separated from the aqueous layer at room temperature, the aqueous layer was extracted with 200 mL of a toluene-methanol mixture (1 : 1), and the combined extract was dried over anhydrous sodium sulfate. The free amine

was obtained as a colorless oil by removal of the solvent on a rotary evaporator. Yield 25 g, 89%, TLC Rf: 0.36 (chloroform, methanol, *n*-propanol, ammonia = 5 : 2 : 2 : 1) (Lit.1, Rf: 0.38).

1-N-Dodecyltriethylenetetraaminepentaacetic Acid (C_{12}-TTPA) [2]

In a 1 L three-necked flask equipped with a mechanical stirrer, a dropping funnel, and a thermometer, was placed N-dodecyltriethylenetetraamine(23 g, 0.073 mol) and THF (450 mL). To this was added a sodium bromoacetate solution at 30°C which had been prepared from bromoacetic acid (61 g, 0.44 mol) in 70 ml of water by neutralizing with 30% aqueous sodium hydroxide at a temperature below 5°C. The clear solution obtained was maintained at 50°C by adding 18.5 g (0.44 mol) of sodium hydroxide as a 30% aqueous solution at such a rate as to maintain the pH of the solution corresponding to the pink color of a phenolphthalein indicator. The reaction mixture was then heated at 50°C for 5 h. THF was removed on a rotary evaporator and the pH of the residual solution was brought to about 1 by the addition of concentrated hydrochloric acid. The white precipitates that resulted were separated by means of a centrifuge and washed with water several times (centrifuge). For purification, the white crystalline solid was dissolved in 1 L of water at a pH of 8 by adding aqueous sodium hydroxide. After standing overnight at room temperature, the insoluble precipitate was filtered off and hydrochloric acid was added to the filtrate to bring the pH to about 1. The white precipitate obtained was separated from the supernatant by means of a centrifuge and washed with water several times. Dissolving in alkaline solution and precipitation with hydrochloric acid was repeated again. The crystalline solid obtained (C_{12}-TTPA) was treated with 100 mL of hot methanol and the hot supernatant was removed by decantation. The methanol treatment was repeated and the product was dried over calcium chloride in a vacuum desiccator. Yield 22 g (50%), colorless crystalline powder. Anal. Calcd. for $C_{28}H_{52}N_4O_{10}\cdot H_2O$: C, 53.99; H, 8.76; N, 9.00; H_2O, 2.89. Found: C, 54.27; H, 8.50; N, 8.81; H_2O, 2.21. Mass spectrum (FAB^+): m/z 603 $(M\text{-}H)^+$, ^1H NMR (in $NaOD/D_2O$, pD = 13): 0.62, 1.04 (two s, 25H, $CH_3(CH_2)_{11}$), 2.34, 2.45 (d, 12H, $3(NCH_2CH_2N)$), 2.88 (s, 10H, $5(CH_2COO^-)$) ppm.

1-N-Docosyltriethylenetetraamine

The procedure was almost the same as that of N-dodecyltriethylenetetraamine except for the use of *n*-docosyl bromide instead of *n*-dodecyl bromide. Thus, *n*-docosyl bromide(80 g, 0.205 mol) in 400 mL of THF was added

dropwise to triethylenetetraamine(209 g, 70% purity, *ca.* 1 mol) in 400 mL of THF at room temperature in 4 h and the mixture was refluxed overnight. After evaporating the solvent, dissolving the residue in a toluene-methanol mixture, and washing with water, a sticky residue (83 g) was obtained. This was recrystallized from *n*-hexane to give a nearly pure product (68 g, 74% based on *n*-docosyl bromide) as an amorphous powder. The separation from the solvent was done by means of a centrifuge. TLC Rf: 0.39 (Lit.1, Rf: 0.49).

1-N-Docosyltriethylenetetraaminepentaacetic Acid (C_{22}-TTPA) [2]

The procedure was almost the same as that of C_{12}-TTPA except for using N-docosyltriethylenetetraamine instead of N-dodecyltriethylenetetraamnie. Thus, N-docosyltriethylenetetraamine (4.54 g, 0.01 mol) in 90 mL of THF was mixed with sodium bromoacetate solution which had been prepared from bromoacetic acid (8.34 g, 0.06 mol) in 70 mL of water by neutralizing with 30% aqueous sodium hydroxide at a temperature below 5°C. The clear reaction mixture was heated to 30°C and neutralized with aqueous sodium hydroxide (2.5 g, 0.06 mol NaOH in 6 mL H_2O) so as to keep the pink color of a phenolphthalein indicator in 3 h while the temperature was raised gradually from 30°C to 50°C. After maintenance at 50°C for an additional 1 h, the THF was removed on a rotary evaporator and concentrated hydrochloric acid was added to the residual solution to bring the pH to about 1. The white precipitates that resulted were collected by filtration and washed with methanol. The crude product (7.4 g) was dissolved in 150 mL of boiling acetic acid, filtered hot from an equal mixture of methanol (100 mL) and water (100 mL) which was added to the hot filtrate. The fine crystalline powder that resulted after standing overnight was collected by filtration, washed with methanol, and dried over P_2O_5 at room temperature. An additional amount was obtained from the filtrate by concentration and addition of water. The total yield was 5.8 g, 76%. Anal. Calcd. for $C_{38}H_{72}N_4O_{10}\cdot H_2O$, C, 59.80; H, 9.80; N, 7.34; H_2O, 2.35. Found: C, 59.4; H, 9.75; N, 7.24; H_2O, 2.18. Mass spectrum(FAB^+): m/z 744 $(M\text{-}H)^+$, ^1H NMR(in $NaOD/D_2O$, pD = 13): 1.28 (s, 45H, $(CH_2)_{21}CH_3$), 2.51 (broad s, 12H, $3(NCH_2CH_2N)$), 3.05 (broad s, 10H, $5(CH_2COO^-)$) ppm.

Potentiometric Measurements

Equilibrium potentiometric determinations of the ligand protonation constants and stability constants were carried out in 50% ethanol solutions of various ligand concentrations in the absence and presence of metal ions at

25.0°C, 0.10 M(KNO_3). The constants were calculated from the potentiometric data with the use of the programs PKAS and BEST [3]. Details of the potentiometric method have been described [3]. The potentiometric apparatus consists of a glass jacketed titration vessel, a constant temperature bath, glass and reference(calomel) electrodes, and a 1.0 mL capacity Metrohm piston buret, for which the buret tip was sealed in the cap of the titration cell with a clamp and O-rings. Atmospheric CO_2 was excluded from the titration cell with a purging stream of purified nitrogen gas. Since the ligand C_{12}-TTPA is almost insoluble in most organic solvents as well as in water, the titration was carried out under suspension in a 50%(v/v) ethanol-water mixture. An ultrasonic vibrator was used to make a homogeneous suspension. The solutions of C_{12}-TTPA and metal ions were also in suspension, except for those of Cu^{2+} and Zn^{2+}. The turbidity of these solutions, however, decreased with the addition of KOH and disappeared completely to give clear solutions at pH 3 to 5, respectively. The value of pH where the turbidity disappeared varied with the metal ion. The mixture solutions for Cu^{2+} and Zn^{2+} were clear from the initial stage. The calculation of protonation constants of C_{12}-TTPA and the stability constants of its metal complexes were carried out using the titration data obtained from the clear solutions.

The electrodes were calibrated with standard HCl and KOH in 50% ethanol-water mixture and it was confirmed that the meter p[H] readings were consistent with $-\log[H^+]$ in 50% ethanol in the p[H] range from 2 to 12. The pK_w for 50% ethanol solution was determined to be 14.8 according to the proposed method [3] from the calculated $[OH^-]$ and the pH meter reading standardized using known mineral acid.

RESULTS AND DISCUSSION

Synthesis of the Ligand

Miller and coworkers [1] used ethylbromoacetate for condensation with N-alkyltriethylenetetraamine and obtained the pentaethylester of the desired acid. We followed this procedure and found that an appreciable amount of lactam as an impurity, requiring flash chromatography for purification. In addition, it was necessary to hydrolyze the ester to obtain the free acid. We found that ordinary carboxymethylation with bromoacetic acid could be applied for syntheses by using a tetrahydrofuran-water mixture as the solvent. The free acid could be purified by repeated dissolution in alkaline

and by precipitation by acidification with hydrochloric acid. The compounds we obtained were like powdered soup and separation from solution was best performed by centrifuge rather than by suction filtration.

Protonation Constants

The potentiometric p[H] profile for C_{12}-TTPA is shown in Figure 1. With the addition of alkaline the turbidity gradually diminished and a clear solution was obtained at around pH 5 which corresponded to two moles of alkaline added to one mole of the acid, *i.e.*, $a = 2$. At higher pH, the titration proceeded smoothly and the inflection was found at $a = 3$.

Although C_{12}-TTPA is a five-protonic acid, H_5L, only three protonation constants could be obtained from the titration data in the clear solution region of p[H] = 5 to 12 ($2 < a < 5$). The protonation constants are shown in Table I together with those of TTHA [4]. Assuming $\log K_6 = 2.4$ and

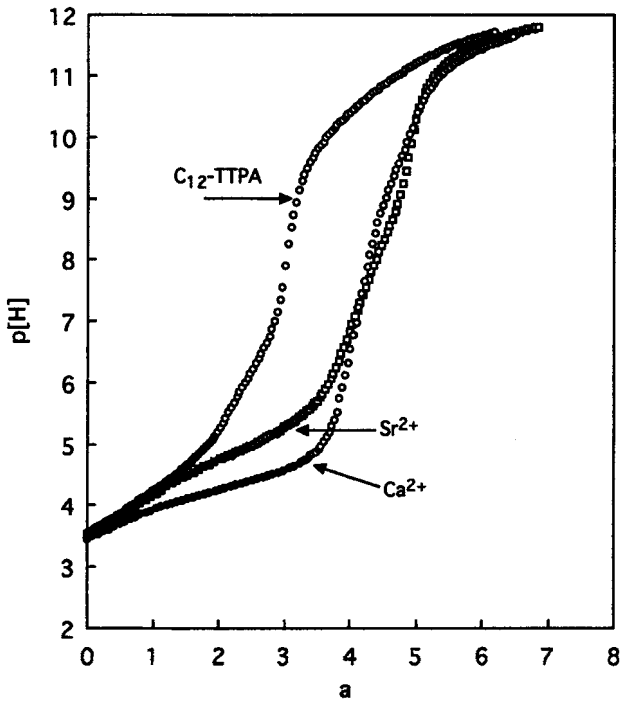


FIGURE 1 p[H] profiles of C_{12}-TTPA and with Ca^{2+} (R = 1.98) and Sr^{2+} (R = 0.989) at 4.94×10^{-4} M in 50% ethanol; a = moles of base added per mole of ligand; $\mu = 0.10$ M(KNO_3), t = 25°C; initial volume = 50.0 mL. Filled marks on the titration curves indicate the sample solutions were turbid at these p[H].

TABLE I Protonation constants of C_{12}-TTPA[a] and TTHA at 25°C and $\mu = 0.10$ M with KNO_3

	$\log K_1$	$\log K_2$	$\log K_3$	$\log K_4$	$\log K_5$	$\log K_6$
C_{12}-TTPA[b]	11.36	9.84	6.21			
C_{12}-TTPA[c]	11.36	9.84	6.17	4.2	2.4	
TTHA[d]	10.19	9.40	6.16	4.16	2.95	2.42

[a] In 50% ethanol solution.
[b] Calcd. by the data obtained in the clear solution region.
[c] Recalcd. by adopting $\log K_4$ and $\log K_6$ values of TTHA. Uncertainties in the constants are estimated as ± 0.23 of the last significant number.
[d] Reference [4].

$\log K_4 = 4.2$ of TTHA were compared to $\log K_5$ and $\log K_4$ values of C_{12}-TTPA, the recalculated $K_1 \sim K_5$ values were almost coincident with the previous values as seen in Table I. Thus these values were considered to be reliable and used for the calculation of the stability constants of the metal chelates.

Stability Constants for Metal Ions

Potentiometric titrations for stability measurements were also performed in 50% ethanol solution. In the presence of a metal ion, the region of solution clarity expanded to lower pH, indicating formation of a metal chelate whose solubility is higher than that of the free ligand. In Figure 1, the titration curves of the ligand in the absence and presence of Ca^{2+} or Sr^{2+} ions are shown at each selected molar ratio, $R = T_M/T_L$ (total metal ion T_M, total ligand, T_L). For Ca^{2+}, the titration curves indicated the presence of a dinuclear chelate (M_2L) in addition to the ML chelate. This is because the curve of $R = 1.49$ differed from that of $R = 0.979$ and that of $R = 1.97$ almost overlapped with that of $R = 1.49$, indicating that the complexes with ratios beyond 2:1 metal to ligand composition (dinuclear chelate M_2L) do not exist.

The distribution curves of the 2:1 Ca^{2+}-C_{12}-TTPA system are shown in Figure 2. The curves indicate that at the pH where the turbidity of the solution becomes clear, the formation of the chelate reaches about 50% for L. In the case of Sr^{2+}, no dinuclear chelate exists, since the titration curves of $R = 0.989$ and $R = 1.49$ overlap each other.

In Figure 3, the titration curves in the presence of Cu^{2+} and Zn^{2+} ions are shown. For the systems, $R = 1.82$ for Cu^{2+} and $R = 1.94$ for Zn^{2+}, the solutions were already clear before addition of alkali. In both systems over $R = 2.0$, the insoluble metal hydroxide appeared around, $pH = 6.0$. This indicates that complexes with compositions over M_2L were not formed. The

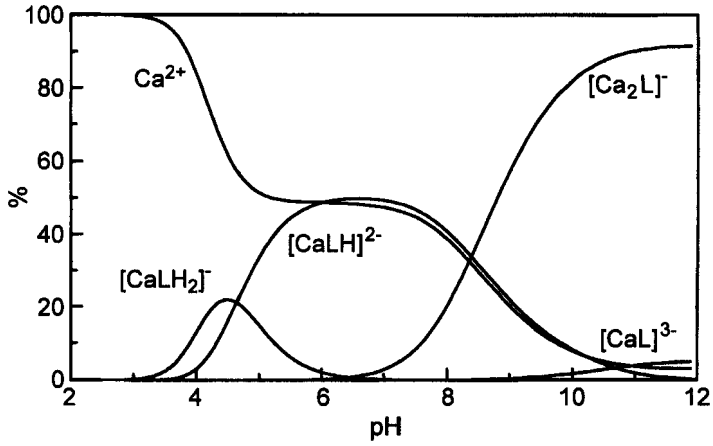


FIGURE 2 Species distribution curves of Ca-C_{12}-TTPA complexes as a function of p[H] in 50% ethanol. $\mu = 0.10\,M(KNO_3)$, t = 25°C; C_{12}-TTPA = 0.0252 mmol, $Ca^{2+} = 0.0493$ mmol, initial volume = 50.0 mL.

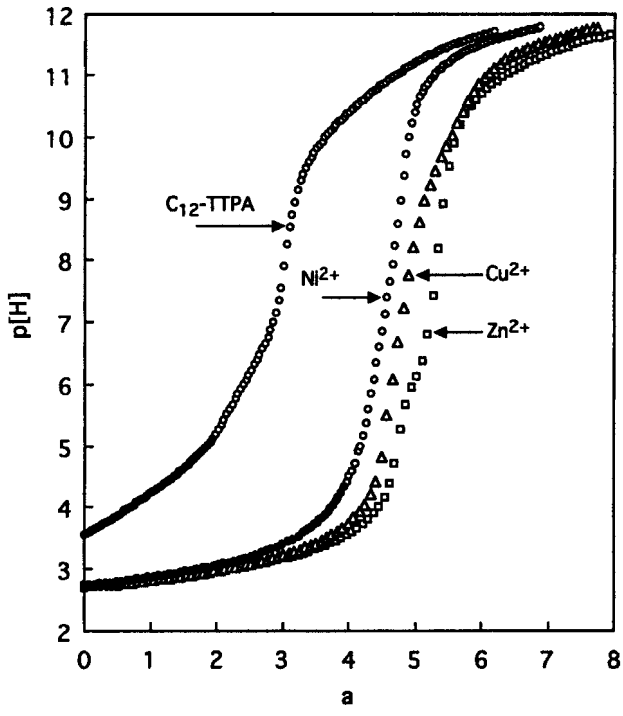


FIGURE 3 p[H] profiles for 4.94×10^{-4} M C_{12}-TTPA in the presence of Cu^{2+} (R = 1.82), Zn^{2+} (R = 1.94) and Ni^{2+} (R = 1.38). a = moles of base added per mole of ligand; μ = 0.10 M(KNO_3), t = 25°C. Filled marks on the titration curves indicate that the sample solutions were turbid.

stability constants, ML and MLH, were determined by analyses of the titration curves of R = 0.521 to 1.95 solutions for Cu^{2+} and R = 0.85 to 1.27 solutions for Zn^{2+}. Those of M_2L and $M_2L(OH)$ were determined from R = 1.82 and R = 1.94 solutions and are shown in Table II.

The titration curves in the presence of Ni^{2+} at R = 1.38 are also shown in Figure 3. The titration profiles are similar to those of Cu^{2+} and Zn^{2+} ions and the stability constants for NiL were calculated from the titration of the solution at R = 0.886 and R = 1.38. The titration curve for R = 1.79 resembled that for strong acids, suggesting the formation of an extremely stable complex having a composition of M_3L_2. A preliminary calculation indicated that there was no free ligand in the solution so the stability constants for 3 : 2 complexes were determined from the titration of the R = 1.38 solution. The stability constants of Ni_3L_2, Ni_3L_2H, and $Ni_3L_2H_2$ are shown in Table II.

When the lanthanide ion Ln^{3+}, at R > 1 was titrated, an insoluble metal hydroxide was formed at around pH 5 ~ 6, indicating that complexes over 1 : 1 composition do not exist. The stability constants of LnL and LnLH were determined from analysis of the titration curves (Fig. 4) in the clear region, R = 0.903 ~ 0.938 solution and are shown in Table II.

The pH of the mixture of the ligand and Th^{4+} ions (Fig. 4) at R = 0.735 was lowest among the solutions in the presence of the metal ions, indicating that Th^{4+} forms a very stable complex with the ligand. Although a slight turbidity remained during the titration, it was considered to be insignificant for analysis of the titration curve and we found formation of ThL, ThLH, and ThL(OH) and their stability constants, as shown in Table II.

TABLE II Log stability constants of metal complexes of C_{12}-TTPA(H_5L) in 50% ethanol at 25°C and $\mu = 0.10$ with KNO_3

	Ca^{2+}	Sr^{2+}	Cu^{2+}	Zn^{2+}	Ni^{2+}	La^{3+}	Sm^{3+}	Er^{3+}	Th^{4+}
[ML]/[M][L]	11.3	12.4	16.9	19.0	18.2	14.4	17.5	22.1	24.5
$[M_2L]$/[ML][M]	5.5	–	12.2	9.7	–	–	–	–	–
[MLH]/[ML][H]	10.7	8.3	7.1	6.1	7.1	5.2	4.4	4.4	4.8
$[MLH_2]$/[MLH][H]	4.6	5.0	–	–	–	–	–	–	–
$[M_3L_2]$/$[ML]_2[M]$	–	–	–	–	10.4	–	–	–	–
$[M_3L_2H]$/$[M_3L_2][H]$	–	–	–	–	11.5	–	–	–	–
[ML(OH)]/[ML][OH]	–	–	–	–	4.3	–	–	–	4.6
$[M_2L(OH)]$/$[M_2L][OH]$	–	–	4.8	5.1	–	–	–	–	–

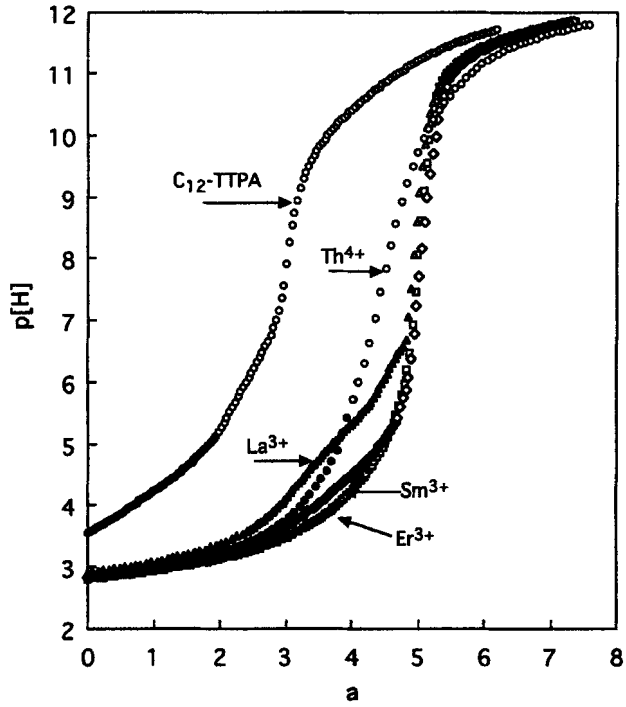


FIGURE 4 p[H] profiles for 4.94×10^{-4} M C_{12}-TTPA in the presence of La^{3+}(R = 0.929), Sm^{3+}(R = 0.938), Er^{3+}(R = 0.903) and Th^{4+}(R = 0.735) in 50% ethanol. a = moles of base added per mole of ligand; μ = 0.10 M(KNO_3), t = 25°C; initial volume = 50.0 mL. Filled marks on the titration curves indicate that the solutions were turbid at the corresponding p[H].

Coordination Mode of C_{12}-TTPA

It is interesting to note that Ca^{2+} forms a dinuclear chelate but Sr^{2+} does not. The difference is due to the difference in ionic radii of these metal ions (Ca^{2+}: 1.12, Sr^{2+}: 1.26 Å). Sr^{2+} ion appears to be too large to be coordinated by half of the ligand molecule. Cu^{2+} and Zn^{2+} do form a dinuclear chelate, while Ni^{2+} does not. This is probably due to the difference in coordination properties of the metal ions. The single ligand has just enough capacity to bind a single hexacoordinated Ni^{2+} ion. Formation of the trinuclear complex, Ni_3L_2 may be explained by considering that the two metal ions require at least six donor sites each, whereas the ligand has nine donor sites and the remaining three donor sites of the two ligands can coordinate to an additional Ni^{2+} ion, although the structure is not known.

The stabilitites of the 1 : 1 metal chelate of C_{12}-TTPA are compared with those of TTHA and EDTA [5] and graphically shown in Figure 5.

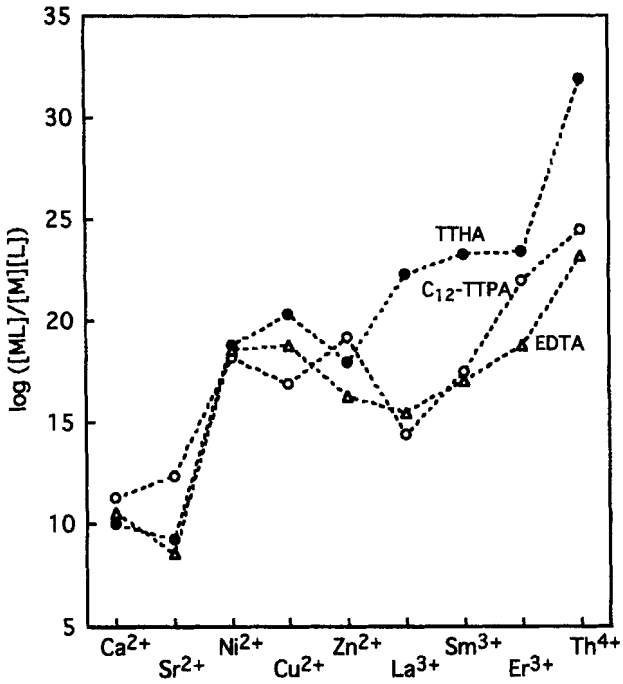


FIGURE 5 Log stability constants, log{[ML]/[M][L]}, of various metal chelates for C_{12}-TTPA, TTHA and EDTA.

Surprisingly, the stabilities of Ca-C_{12}-TTPA and Sr-C_{12}-TTPA ($\log K_{CaL} = 11.3$ and $\log K_{SrL} = 12.4$) are higher than those of TTHA ($\log K_{CaL} = 10.06$ and $\log K_{SrL} = 9.26$) [4]. On the other hand, the stabilities of Ni^{2+}, Cu^{2+}, Zn^{2+} and Ln^{3+} chelates are lower than those of TTHA. The N-dodecyl group of C_{12}-TTPA seems to exert a steric hindrance for the coordination of the metal ions. Since the ligand C_{12}-TTPA has more than enough coordination sites for these metal ions, the terminal N-dodecyl glycyl group probably does not participate in coordination to the alkaline earth metal ions.

As expected from the presence of the bulky alkyl group at the terminal nitrogen atom of the ligand, the stabilities of Ni^{2+}, Cu^{2+}, Zn^{2+} and Ln^{3+} chelates are lower than those of TTHA. On the other hand, however, those of Ca-C_{12}-TTPA and Sr-C_{12}-TTPA are higher than those of TTHA. The reason for this is not clear. The ligand C_{12}-TTPA has more than enough coordination sites for these metal ions, and the terminal N-dodecyl glycyl group may exert some effect other than steric hindrance for the coordination of the metal ion.

It has been reported that the values for stability constants of 1 : 1 chelates of EDTA, DTPA and TTHA with Am^{3+} are 77, 80, and 83% of those for Th^{4+}, and are similar to, or a little higher than, those for Er^{3+} [3]. From these facts it can be estimated that the chelate stability constant of C_{12}-TTPA with Am^{3+} is about $10^{20}\,M^{-1}$, and we concluded that the ligand is a satisfactory agent for chelate therapy.

References

[1] F. W. Bruenger, G. K. Rabiega and S. C. Miller, *J. Med. Chem.* **35**, 112 (1992).
[2] In reference 1, the chelating agents were abbreviated as C_{12}-TT and C_{22}-TT. Instead, we would like to use C_{12}-TTPA and C_{22}-TTPA respectively, because these ligands carry pentaacetic acid groups.
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