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Thermodynamic and Kinetic Studies of Lanthanide Complexes of 1,4,7,10,13-Pentaazacyclopentadecane-*N*,*N*′,*N*″,*N*‴,*N*⁗-pentaacetic Acid and 1,4,7,10,13,16-Hexaazacyclooctadecane-*N*,*N*′,*N*″,*N*‴,*N*⁗,*N*⁗′-hexaacetic Acid

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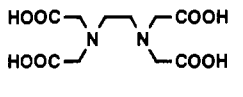
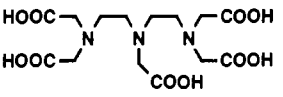
The macrocyclic pentaamino pentacarboxylate ligand PEPA (**5**) and the hexaamino hexacarboxylate HEHA (**6**) were synthesized, and their complexation with lanthanides was investigated. pH-Metric titrations were used for the equilibrium study, and the ligand-exchange reactions of M(III)–Arsenazo III with macrocyclic ligands were employed for the kinetic study. The results are compared with those for known lanthanide chelating agents, namely, linear DTPA (**2**) and macrocyclic DOTA (**3**) and TETA (**4**). The stability trends of PEPA (**5**) and HEHA (**6**) complexes relative to the lanthanide +3 ion size are almost parallel to those of **2** and **4**. Measurements of the thermodynamic parameters ΔH and ΔS show that ΔS is the major contributor to the complex stability as expected. **6** yields with few exceptions more stable 1:1 complexes than **2** at pH ~7. The relative complexation rates of **6** are 10 times slower than those of **2** but 100 times faster than those of **3**.

Introduction

The lanthanide (Ln) complexes with macrocyclic tetraamino tetracarboxylates such as DOTA (**3**) and TETA (**4**) are currently



1 EDTA (H_4L)



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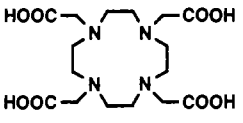
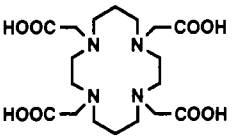


3 DOTA (H_4L)



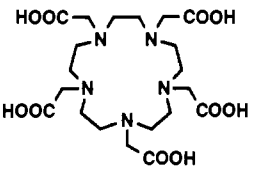
4 TETA (H_4L)

attracting much attention in separation of lanthanides,[1] magnetic resonance imaging (MRI) contrast-enhancing agents,[2] and radiopharmaceuticals.[3] In comparison with the linear analogues EDTA (**1**) and DTPA (**2**), these macrocyclic ligands have a great advantage in forming more stable complexes.[4,5] DOTA (**3**) forms more stable complexes with lanthanides than the larger homologue **4**.[4a] An X-ray crystal structure of Eu(III)–**3**[6] shows a rigid nine-coordinate structure with an additional coordination of H_2O. However, one of the common drawbacks with these macrocyclic ligands is in their slow complexation rates; the tighter the ring size, the slower the encapsulation rate.[4,7] This may pose a serious setback in their practical use.[2]

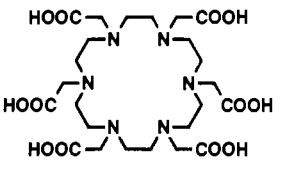
In our current efforts in searching for new chelating agents, we have synthesized the macrocyclic pentaamine PEPA (**5**) and the hexaamine homologue HEHA (**6**) and studied their complexation with Ln(III) and Y(III). Until now, there has been no report on these ligands. In a preliminary experiment, it was found that the complexation of these new macrocycles seemed much more rapid, while maintaining extraordinary thermodynamic stabilities. We now report the syntheses of the ligands and the thermodynamic stabilities and kinetic data for the complex formation reactions.

Experimental Section

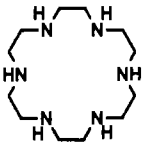
Ligand Synthesis. The macrocyclic pentaamine [15]aneN$_5$ (1,4,7,10,13-pentaazacyclopentadecane) was synthesized by Richman's method.[8] A solution of [15]aneN$_5$ (4.0 g, 19 mmol) in 25 mL of H_2O was added dropwise to chloroacetic acid (18 g, 190 mmol) in 25 mL of



5 PEPA (H_5L)



6 HEHA (H_6L)



7 [18]aneN$_6$ (L)

ice-cooled H_2O. The pH of the reaction mixture was adjusted between 9 and 10 at 50 °C with 1 M NaOH for 5 days. After evaporation of the solvent, the residue was redissolved in H_2O and the mixture was acidified with 6 M HCl solution. The resulting mixture was washed with CH_2Cl_2 to remove the excess chloroacetic acid. After evaporation of the water, the residue was recrystallized from 6 M HCl to give 5.2 g of 1,4,7,10,13-pentaazacyclopentadecane-*N*,*N*′,*N*″,*N*‴,*N*⁗-pentaacetic acid (**5**) (39% yield) as a pentahydrochloride salt (colorless needles). ^{1}H NMR (400 MHz, in D_2O, DSS reference): δ 3.48 (20 H, NCH_2CH_2N), 3.92 (10 H, NCH_2CO). Anal. Calcd (found) for $C_{20}H_{35}N_5O_{10}\cdot 5HCl\cdot 1.5H_2O$: C, 33.60 (33.46); H, 6.06 (6.20); N, 9.80 (9.82). Nearly the same procedure was previously reported for the preparation of **3**,[9,10] **4**,[9] and **6**·6HCl.[11] All other chemicals used were of analytical grade (Aldrich or Dojin).

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(1) Hagan, J. J.; Taylor, S. C.; Tweedle, M. F. *Anal. Chem.* **1988**, *60*, 514. Spirlet, M. R.; Rebizant, J.; Loncin, M. F.; Desreux, J. F. *Inorg. Chem.* **1984**, *23*, 4278.
(2) Lauffer, R. B. *Chem. Rev.* **1987**, *87*, 901.
(3) Cox, J. P. L.; Jankowski, K. J.; Kataky, R.; Parker, D.; Beeley, N. R. A.; Boyce, B. A.; Eaton, M. A. W.; Millar, K.; Millican, A. T.; Harrison, A.; Walker, C. *J. Chem. Soc., Chem. Commun.* **1989**, 797. Wedeking, P.; Tweedle, M. *Nucl. Med. Biol.* **1988**, *15*, 395.
(4) (a) Loncin, M. F.; Desreux, J. F.; Merciny, E. *Inorg. Chem.* **1986**, *25*, 2646. (b) Brücher, E.; Laurenczy, G.; Makra, Z. *Inorg. Chim. Acta* **1987**, *139*, 141.
(5) Cacheris, W. P.; Nickle, S. K.; Sherry, A. D. *Inorg. Chem.* **1987**, *26*, 958.
(6) Spirlet, M.; Rebizant, J.; Desreux, J. F.; Loncin, M. F. *Inorg. Chem.* **1984**, *23*, 359.
(7) Sherry, A. D.; Brown, R. D., III; Geraldes, C. F. G. C.; Koenig, S. H.; Kuan, K.; Spiller, M. *Inorg. Chem.* **1989**, *28*, 620.
(8) Richmann, J. E.; Atkins, T. J. *J. Am. Chem. Soc.* **1974**, *96*, 2269.
(9) Stetter, H.; Frank, W. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 686. Delgado, R.; Silva, J. J. R. F. *Talanta* **1982**, *29*, 815.
(10) Desreux, J. F. *Inorg. Chem.* **1980**, *19*, 1319.
(11) Kimura, E.; Fujioka, H.; Yatsunami, A.; Nihira, H.; Kodama, M. *Chem. Pharm. Bull.* **1985**, *33*, 655.

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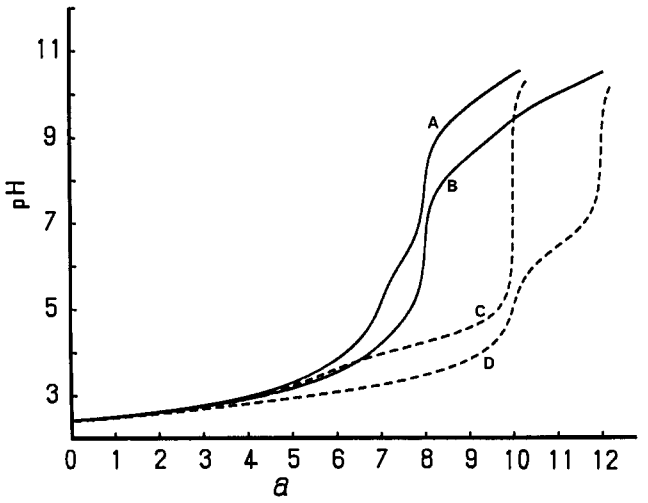


Figure 1. Titration curves for PEPA (**5**) and HEHA (**6**) at 25 °C: A, 1 mM **5** in the presence of 5 equiv of $HClO_4$; B, 1 mM **6** in the presence of 6 equiv of $HClO_4$; C, A + 1 mM Lu(III); D, B + 1 mM Lu(III). *a* is the number of equivalents of base added.

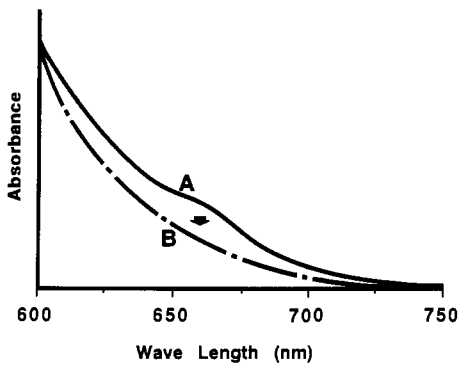
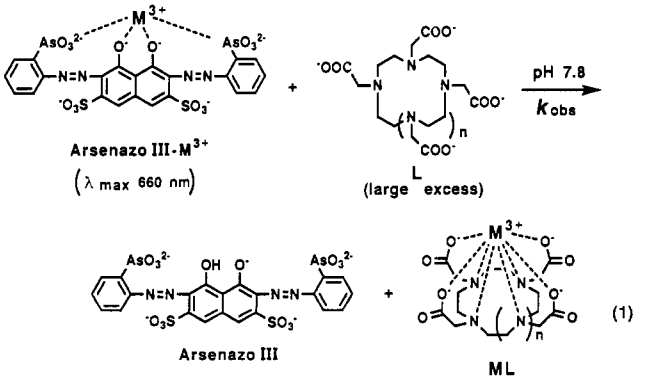


Figure 2. Visible absorption spectra at pH 7.8 (25 mM HEPES buffer) at I = 0.1 ($NaClO_4$) and 25 °C: A, 2.5 × 10^{-4} M Arsenazo III in the presence of 2.5 × 10^{-5} M Lu(III); B, A + 1 mM **6**.

Equilibrium Constant Determinations. Potentiometric titrations and data analysis for the lanthanide and other metal complexes were carried out in the same manner as described in previous papers.[11,12] The test solution temperature was kept within ±0.1 °C, and the ionic strength (I) was adjusted to 0.2 with $NaNO_3$. Figure 1 shows typical titration curves for **5**·5HCl and **6**·6HCl with 0.2 M NaOH in the presence of equimolar Lu(III).

Kinetic Measurements. The time scan measurements were carried out on a Hitachi U-3200 spectrophotometer equipped with a stopped-flow injection attachment. The kinetics of complexation for **2**, **3**, **5**, and **6** were compared on the basis of the reaction 1 under the same conditions (i.e.,



the same reactant concentrations, the same pH 7.8 buffer, 25 °C). Reaction 1 is identical with the reaction reported earlier for a modified **3**–Gd(III) complex at 60 °C.[7] The ligand displacement rates of M(III)

Table I. Protonation Constants of Macrocyclic Polyamine Polyacetates **4**–**6** at I = 0.20 ($NaNO_3$)

ligand	temp, °C	log K_n[a]
4	15	11.24 ± 0.03, 9.86 ± 0.03, 4.40 ± 0.02, 3.27 ± 0.03
	25	11.04 ± 0.03, 9.68 ± 0.03, 4.30 ± 0.02, 3.17 ± 0.03
	35	10.84 ± 0.03, 9.50 ± 0.03, 4.20 ± 0.02, 3.07 ± 0.03
5	15	10.28 ± 0.03, 9.55 ± 0.03, 6.29 ± 0.02, 4.23 ± 0.02, 3.33 ± 0.03
	25	10.15 ± 0.03, 9.41 ± 0.02, 6.14 ± 0.02, 4.11 ± 0.02, 3.19 ± 0.03
	35	10.02 ± 0.03, 9.27 ± 0.02, 5.99 ± 0.02, 4.00 ± 0.02, 3.05 ± 0.03
6	15	10.30 ± 0.03, 10.21 ± 0.03, 9.16 ± 0.02, 8.45 ± 0.02, 4.74 ± 0.02, 3.65 ± 0.03
	25	10.10 ± 0.03 (10.10), 10.01 ± 0.03 (10.01), 8.92 ± 0.02 (8.96), 8.20 ± 0.02 (8.20), 4.64 ± 0.02, 3.53 ± 0.03
	35	9.90 ± 0.03, 9.81 ± 0.03, 8.68 ± 0.02, 7.95 ± 0.02, 4.54 ± 0.02, 3.41 ± 0.03

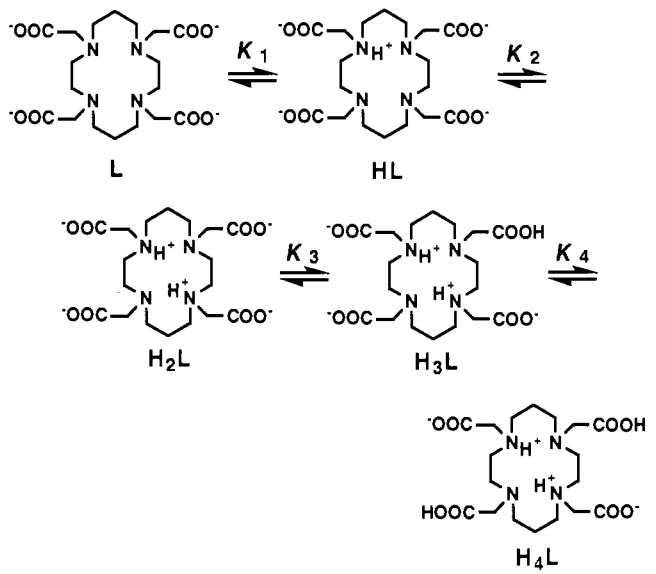
[a] log K_n values in parentheses were taken from ref 11 (I = 0.20 ($NaClO_4$)).

(2.5 × 10^{-5} M)/Arsenazo III (2.5 × 10^{-4} M) with **3**, **5**, and **6** (all in 1.0 × 10^{-3} M) were followed by the decrease in absorbance at 660 nm (A_{660}). Figure 2 shows the visible absorption spectrum for Lu(III)–Arsenazo III in the absence (the starting condition) and in the presence of a large excess of **6** (the final condition) at I = 0.1 ($NaClO_4$), pH 7.8 (25 mM HEPES buffer), and 25 °C. This process followed pseudo-first-order kinetics with rate constants, k_{obs}, as indicated by the good exponential decays with time in all cases.

Results and Discussion

Protonation Constants. The protonation constants of completely deprotonated ligands (polycarboxylate form) TETA (**4**), PEPA (**5**), and HEHA (**6**) were determined at 15, 25, and 35 °C (see Table I). The log K_n values for **6** (at 25 °C) agree well with previous values.[11]

For **4**, the two stronger basic sites with log K of 11.0 and 9.7 (25 °C) are assigned to the macrocyclic nitrogen atoms and the two weaker bases to carboxylate groups, depicted as follows:



This assignment comes from the fact that, with the skeleton cyclam, two amines are very basic with log K of 11.5 and 10.3, while the remaining two are almost nonbasic (log K < 2).[13] From the ^{1}H NMR study of 13–15-membered macrocyclic polyamino polycarboxylates containing **4**, Silva et al. drew the same conclusion that the two amino groups are first protonated above pH 6 and further protonations occur to the carboxylate groups.[14]

(12) Kodama, M.; Kimura, E.; Yamaguchi, S. *J. Chem. Soc., Dalton Trans.* **1980**, 2536.

(13) Kodama, M.; Kimura, E. *J. Chem. Soc., Dalton Trans.* **1980**, 2447.

(14) Ascenso, J. R.; Delgado, R.; Silva, J. J. R. F. *J. Chem. Soc., Perkin Trans. 2* **1985**, 781.

Table II. Stability Constants of Lanthanide Complexes and Their Diprotonated Forms at 25 °C and I = 0.20 ($NaNO_3$)[a]

	TETA (**4**)	PEPA (**5**)	HEHA (**6**)		[18]aneN$_6$ (**7**)	DTPA[d] (**2**)
	log K(ML)	log K(ML)	log K(ML)	log K(MH$_2$L)	log K(ML)	log K(ML)
La^{3+}	12.74	13.57	19.11	15.82	5.70	19.5
Ce^{3+}	13.12	14.16	19.59	15.60	7.51	20.3
Nd^{3+}	13.76 (14.5)[b]	14.85	20.36	16.21	8.03	21.6
Sm^{3+}	14.47 (15.5)[b]	15.35	21.24	16.41	8.14	22.3
Eu^{3+}	14.66 (15.5)[b]	15.59	22.68	17.17	8.27	22.4
Gd^{3+}	14.73 (15.8)[b]	15.88	22.95	17.26	8.40	22.5
Tb^{3+}	14.81	15.91	23.15	17.30	8.50	22.7
Ho^{3+}	14.95	16.48	23.88	16.58	8.62	22.8
Tm^{3+}	15.15	16.61	24.09	16.82	8.95	22.7
Lu^{3+}	15.31	16.71	24.26	17.03	9.15	22.4
Y^{3+}	14.77	16.07	24.04	15.93	8.52	22.1
Hg^{2+}	25.71	27.76	25.27	21.26	29.7[e]	20.4
Pb^{2+}	15.00 (14.7)[c]	18.26	...	17.83	14.1[e]	18.9
Sr^{2+}	5.32 (6.2)[c]	7.31	...	5.85	3.2[e]	9.7

[a] ... Means negligible species under the experimental conditions. K(ML) = [ML]/[M][L] (M^{-1}). K(MH$_2$L) = [MH$_2$L]/[M][H$_2$L] (M^{-1}). Three titrations were conducted for each system. The standard deviations at the 95% confidence level for the complexation constants are ±0.05 unless otherwise noted. [b] Reference 4a. At 80 °C and I = 1.0 (NaCl). [c] Reference 9. At 20 °C and I = 0.1 (KCl). [d] Reference 16. At 25 °C and I = 0.1. [e] The standard deviations at the 95% confidence level are ±0.1.

Table III. Thermodynamic Parameters for La^{3+}, Tb^{3+}, and Lu^{3+} Complexes at I = 0.20 ($NaNO_3$)[a]

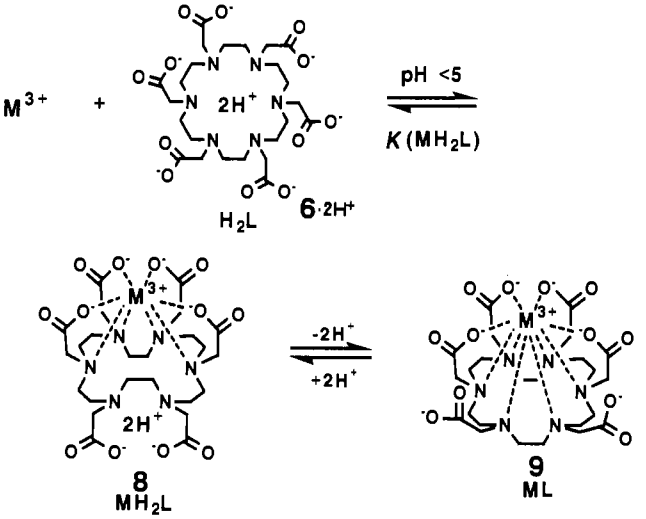
	log K(ML)			ΔH,	ΔS,
ML	15 °C	25 °C	35 °C	kcal/mol	eu
La^{3+}-**4**	12.60	12.74	12.87	5.4 ± 0.4	76 ± 2
Tb^{3+}-**4**	14.68	14.81	14.94	5.3 ± 0.5	86 ± 2
Lu^{3+}-**4**	15.20	15.31	15.40	4.1 ± 0.5	84 ± 2
La^{3+}-**5**	13.55	13.57	13.59	0.7 ± 0.4	65 ± 2
Lu^{3+}-**5**	16.67	16.71	16.74	1.4 ± 0.5	85 ± 2
La^{3+}-**6**	19.21	19.11	19.01	−4.1 ± 0.5	74 ± 2
Lu^{3+}-**6**	24.27	24.26	24.25	−0.3 ± 0.5	110 ± 2
La^{3+}-**7**	5.61	5.70	5.78	3.6 ± 0.3	37 ± 2
Lu^{3+}-**7**	8.96	9.15	9.32	7.1 ± 0.4	66 ± 2
La^{3+}-**1**[b]		15.46		−2.9	61
Lu^{3+}-**1**[b]		19.80		−2.5	82

[a] Three titrations were conducted for each system. The standard deviations at the 95% confidence level for log K(ML) values are ±0.05. The standard deviations at the 95% confidence level for ΔH and ΔS are calculated from the three log K values in each case. [b] From ref 16.

By drawing an analogy and in the light of the known log K_n values of the macrocyclic polyamines [15]aneN$_5$ (10.9, 9.7, 6.0, 1.7, and 1.2) and [18]aneN$_6$ (**7**) (10.2, 9.2, 8.7, 4.1, 2, and 1),[15] we conclude that the three most basic sites in **5** (log K_n = 10.2, 9.4, and 6.1) and the four most basic sites in **6** (log K_n = 10.1, 10.0, 8.9, and 8.2) are all nitrogen atoms and that the remaining weaker basic sites are carboxylate groups. It is to be noted that the six-nitrogen ring attached to six carboxylate anions (**6**) accommodates four protons, while the skeleton ring **7** includes three protons.

Complexation Constants. In contrast to the 12-membered macrocyclic tetraamine **3** and the 14-membered tetraamine **4**, the present 15-membered pentaamine **5** and the 18-membered hexaamine **6** interact with lanthanide ions much faster (even at low pH); hence, the usual pH-metric titration methods could be employed to determine the thermodynamic parameters. We have allowed equilibration times of 30 and 10 min after each addition of 0.2 M NaOH titrant in the case of **5** and of **6**, respectively, in the presence of 1 equiv of metal ion at 15, 25, and 35 °C. For **4**, the equilibration in the lower pH region took as long as 1 h and we barely made reproducible titrations. For **3**, however, the equilibration time was too long (more than several days) to permit us reliable measurements, as observed earlier.[10] The complexation of all the metal ions with **4** and **5** seemed complete below pH 6 (see Figure 1C).

For **6**, the diprotonated-ligand complexes MH$_2$L are formed below pH 5 until a = 10, where the first inflection occurs (see Figure 1D). We postulate that, in these species, two protons are bound to two amine groups in the macrocycle, as depicted by **8**,



since these sites are the most basic. The M(III) ions would stay near anionic donors rather than neutral amine donors. Finally, two more protons are lost at pH ~7 ($10 < a < 12$) to complete the ML (**9**) formation.

The calculated stability constants log K(ML) (25 °C, I = 0.2 ($NaNO_3$)) for the **4**–**6** (diprotonated complexes **8** (MH$_2$L) are also included) with eight +3 lanthanide ions, Y(III), and other +2 metal ions are summarized in Table II, along with some reported values.[16] The linear plots of log K(ML) for **4**–**6** with La(III) and Lu(III) against temperature permit us to estimate the thermodynamic parameters ΔH and ΔS for the 1:1 complexation for the first time in macrocyclic polyamino polycarboxylate systems (Table III). Desreux et al.[4a] reported the stability constants log K(ML) = 14.5–16.5 for several Ln(III)–**4**

(15) Kimura, E.; Sakonaka, A.; Yatsunami, T.; Kodama, M. *J. Am. Chem. Soc.* **1981**, *103*, 3041.

(16) Martell, A. E.; Smith, R. M. *Critical Stability Constants*; Plenum: New York, 1989; Vol. 6.

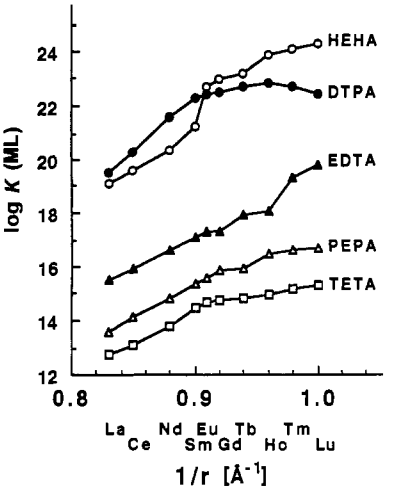


Figure 3. Variation of the stability constants K(ML) of polyaza polycarboxylates with the reciprocal values of the ionic radii of Ln(III) at 25 °C. Literature values for DTPA and EDTA (closed symbols) are shown for comparison with our values for TETA, PEPA, and HEHA (open symbols).

complexes, which were determined potentiometrically at 80 °C. Our calculated log K(ML) value of 15.5 for Tb(III)–**4** at 80 °C (which is extrapolated from ΔH = 5.3 kcal/mol and ΔS = 86 eu) is close to the reported values for Eu(III)–**4** (15.5) and Gd(III)–**4** complexes (15.8)[4a] (see Table II).

As the number of nitrogen atoms in the macrocycle increases, the 1:1 complex becomes more stable, although the macrocyclic N_4 (**4**) and N_5 (**5**) systems are less stable than the linear N_2 (**1**) and N_3 (**2**) systems. Among the macrocyclic ligands **4**–**6**, the hexaamine **6** complexes show the greatest stabilities with any metal ion. The patterns for log K(ML) vs 1/(+3 metal ion radius)[17] for **4**–**6** (Figure 3) are nearly parallel to those for the linear analogues EDTA and DTPA. This fact indicates that the common binding forces, mainly ionic, between M(III) and carboxylate anions govern the complexation. The trends in thermodynamic parameters for the macrocyclic complexes are also analogous to those for the linear ones: the driving force for the complexation is almost exclusively entropic, so that the desolvation from the small +3 lanthanide ions may be an overwhelming factor.

The present stability constants for Ln(III)–**6** complexes do not appear as large as the reported log K(ML) values of 23–30 for Ln(III)–**3** complexes,[4a,5] which, however, are still not free from uncertainty, due to the extremely slow complexation of **3**, as we also experienced (see Experimental Section). We were unable to determine the relative stabilities for **6** vs **3**.

We also have measured the complexation constants and thermodynamic parameters for several lanthanides with the skeleton macrocyclic hexaamine **7**, which are included in Table III. The magnitudes of log K(ML) are considerably smaller than those for the carboxylated **6**. This fact supports the earlier notion that the carboxylate anions are largely responsible for the strong complexation of **6**.

(17) Cotton, F. A.; Wilkinson, G. *Advanced Inorganic Chemistry*; Wiley: New York, 1980; 956.

Table IV. Pseudo-First-Order Rate Constants for M^{3+}–Polyaza Polycarboxylate Complex Formation (Reaction 1) at pH 7.8, 25 °C, and I = 0.1 ($NaClO_4$ + 25 mM HEPES Buffer)[a]

	k_{obs}, min^{-1}			
	DOTA (**3**)	PEPA (**5**)	HEHA (**6**)	DTPA (**2**)
Lu^{3+}	6.3×10^{-3}	9.6×10^{-2}	5.8×10^{-1}	4.6
Y^{3+}	4.6×10^{-3}	2.0×10^{-1}	6.3×10^{-1}	7.3

[a] The standard deviations at the 95% confidence level for k_{obs} values are within 20%. Five measurements were conducted for each system. d[M(III)–polyamino polycarboxylate]/dt = k_{obs}[M(III)–Arsenazo III]. Initial concentrations of Arsenazo III, M(III), and ligand are 2.5 × 10^{-4}, 2.5 × 10^{-5}, and 1.0 × 10^{-3} M, respectively.

Kinetics. Kinetic measurement for the direct reactions of macrocyclic polyamino polycarboxylates **3**, **5**, and **6** with Lu(III) or Y(III) were difficult because of the precipitation of Ln(III) hydroxides at neutral pH. We, therefore, resorted to determination of relative rates using ligand displacement reaction 1 (see Experimental Section), as earlier employed for an analogue of Gd(III)–**3** at 60 °C.[7] For comparison, we also measured the rates for the linear ligand **2**. With any ligand here, reaction 1 went to completion, as judged from the spectroscopic measurements of the solution (see Figure 2).

Pseudo-first-order kinetics were observed in all cases at pH 7.8. Since the protonation constants differ from ligand to ligand, the reactive species of polyamino polycarboxylates have different + charges and available donor numbers.[18] Thus, the calculated k_{obs} values summarized in Table IV are conditional rate constants at the given pH of 7.8. These k_{obs} values are useful only in relative terms for **3**, **5**, **6**, and **2**.

For the macrocycles, k_{obs} increases with an increase in ring size. **6** can form Lu(III) and Y(III) complexes about 100 times faster than **3**. Meanwhile, **6** reacts about 10 times more slowly than the linear analogue **2**. The order of the relative rates, k_{obs}, indicates that the rate-determining step in the Lu(III) and Y(III) complexation is mainly controlled by the ligand flexibility and not by the coordination number.

Conclusions

Although we are unable to directly compare the complex stabilities for **3** (claimed as best) and our new **6**, the latter new macrocyclic ligand seems to be promising as another appropriate lanthanide complexone. The ML complexations are complete at pH ~7. The stability constants K(ML) are very large (greater than those for the currently available linear chelating agent DTPA), and the ML formation rates are only 10 times slower than those for DTPA. The obvious advantage of **6** over **3** is much faster (100 times) complexation rates. On the other hand, macrocyclic N_5 (**5**) seems inferior to the linear DTPA in the ML stabilities as well as in slower ML formation rates.

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(18) The composition for polyaza polycarboxylate solutions at pH 7.8 and 25 °C is as follows: DOTA, H_2L (>99%); PEPA, HL (2%), H_2L (95%), H_3L (2%); HEHA, H_2L (2%), H_3L (28%), H_4L (70%); DTPA, HL (14%), H_2L (86%).