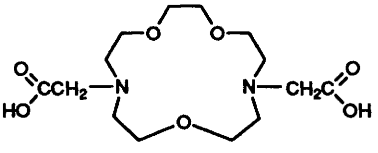
Thermodynamics of the Complexation of Cerium-, Europium- and Erbium-(III) with 1,4,10-Trioxa-7,13-diazapentadecane-*N*,*N*′-diacetic Acid and 1,4,10,13-Tetraoxa-7,16-diazaoxacyclooctadecane-*N*,*N*′-diacetic Acid†

Vijay K. Manchanda,*[a] Prasanta K. Mohapatra,[a] Chengyue Zhu[b] and Reed M. Izatt[b]
[a] *Radiochemistry Division, B.A.R.C., Bombay, 400085, India*
[b] *Department of Chemistry, Brigham Young University, Provo, Utah 84602, USA*

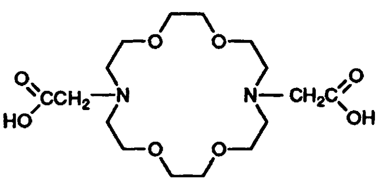
Enthalpy changes for the complexation of Ce^{3+}, Eu^{3+} and Er^{3+} with two cyclic diaza diacetates 1,4,10-trioxa-7,13-diazacyclopentadecane-*N*,*N*′-diacetic acid (H$_2$L^1) and 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-*N*,*N*′-diacetic acid (H$_2$L^2) have been obtained by isoperibol titration calorimetry. From these values and corresponding Gibbs energy data, the entropy changes for these reactions were derived. The results show that complex formation is stabilized in each case by entropy changes. There is a favourable enthalpy contribution for interactions of Ce^{3+} and Eu^{3+} with H$_2$L^2. There is a direct correlation between the entropy contributions and enthalpy terms for the complexes of both the ligands. The results are consistent with an encapsulated model for complexes of H$_2$L^2 and a *cis*-carboxylate model for complexes of H$_2$L^1.

Lanthanide(III) ions (Ln^{3+}) form unusually strong complexes with ionisable macrocyclic ligands as compared to those with their corresponding acyclic analogues.[1–4] As a consequence of their kinetically inert nature, gadolinium- and yttrium-(III) complexes of 1,4,7,10-tetraazacyclododecane-*N*,*N*′,*N*″,*N*‴-tetraacetic acid (H$_4$dota) and related ligands have been found useful as contrast agents in magnetic resonance imaging[5] and as radiopharmaceuticals in tumour targeting[6] respectively. Similarly, a europium(III) complex of 1,4,10-trioxa-7,13-diazacyclopentadecane-*N*,*N*′-diacetic acid (H$_2$L^1) has been found to be a promising candidate for fluoroimmunoassay of antibodies in biological samples.[7] Chang *et al.*[8,9] have demonstrated the possibility of employing H$_2$L^1 and 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-*N*,*N*′-diacetic acid (H$_2$L^2) for the kinetic control of group separation of lighter Ln^{3+} ions from the heavier ones.

The radius of the cavity of 12-membered H$_4$dota (0.68 ± 0.08 Å)[10] is too small to accommodate a gadolinium(III) ion (crystal ionic radius, 1.247 Å, co-ordination number nine)[11] and the unusual stability of the complex is attributed to the rigid capped-square-antiprism conformation rather than to any macrocyclic effect.[2] On the other hand, the crystal structures of the Ln^{3+} ion complexes of 15-membered H$_2$L^1 and 18-membered H$_2$L^2 have not been reported. Contradictory reports have appeared from various laboratories about the possible solution structures of these complexes. Chang and his co-workers,[3,4] on the basis of equilibrium and kinetic data proposed an encapsulated arrangement of donor atoms for complexes of H$_2$L^2. They have also suggested that in complexes of H$_2$L^1, the Ln^{3+} ion is outside the macrocyclic ring. On the other hand, Holz *et al.*[12] suggested on the basis of laser induced Eu^{3+} luminescence and Y^{3+} NMR spectroscopic studies that H$_2$L^1 rather than H$_2$L^2 effectively accommodates Ln^{3+} ions in its cavity. Similar contradictory conclusions have also been drawn for the Ln^{3+} complexes of analogous crown ethers, *viz.* 1,4,7,10,13-pentaoxacyclopentadecane (15-crown-5) and 1,4,7,10,13,16-hexaoxacyclooctadecane (18-crown-6), by Bünzli and Pilloud[13] on the basis of potentiometric studies and Mei Tsay *et al.*[14] on the basis of solvent extraction studies.



H$_2$L^1



H$_2$L^2

In the present work, heats of complex formation in aqueous solution of H$_2$L^1 and H$_2$L^2 with some typical Ln^{3+} ions were determined using an isoperibol titration calorimeter. Thermodynamic data thus obtained may be helpful in understanding the structure of these complex species in solution and rationalising the trends observed in the equilibrium constant data.

Experimental

Reagents.—The compounds H$_2$L^1 and H$_2$L^2 were prepared according to the method of Kulstad and Malmsten[15] with minor modifications. Recrystallised H$_2$L^1 conformed to the stoichiometry $C_{14}H_{26}N_2O_7{\cdot}2HCl$ [Found (calc.) C, 40.97 (41.28); H, 6.78 (6.93); N, 6.80 (6.88%)]; it undergoes decomposition at 235 °C. Recrystallised H$_2$L^2 had the stoichiometry $C_{16}H_{30}N_2O_8{\cdot}2HCl{\cdot}3H_2O$ [Found (calc.) C, 38.13 (38.02); H, 7.60 (7.52); N, 5.93 (5.54%)]; m.p. 121.4 °C.

---

† *Non-SI unit employed:* cal ≈ 4.184 J.

Table 1 Thermodynamic data for the complexation of lanthanides with H_2L^1 and H_2L^2 in water at 25 °C

Reaction	Cation radius[11]/Å	H_2L^2			H_2L^1		
		log *K**	ΔH/kcal mol^{-1}	ΔS/cal K^{-1} mol^{-1}	log *K**	ΔH/kcal mol^{-1}	ΔS/cal K^{-1} mol^{-1}
$L^{2-} + H^+ \rightleftharpoons HL^-$	—	8.45	−7.16	14.6	9.02	−4.92	24.8
$HL^- + H^+ \rightleftharpoons H_2L$	—	7.80	−5.23	18.1	8.79	−6.73	17.6
$L^{2-} + Ce^{3+} \rightleftharpoons [CeL]^+$	1.336	12.23	−7.79	29.8	10.89	3.02	60.0
$L^{2-} + Eu^{3+} \rightleftharpoons [EuL]^+$	1.260	12.02	−3.08	44.7	11.85	1.32	58.6
$L^{2-} + Er^{3+} \rightleftharpoons [ErL]^+$	1.202	11.30	0.73	54.1	11.15	3.69	63.4

* Ref. 4.

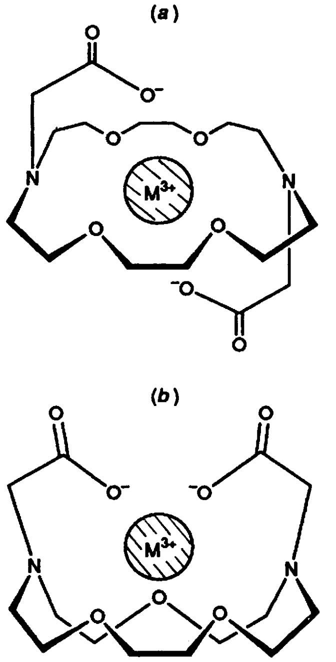


Fig. 1 Stereographic diagrams for the (*a*) encapsulated *trans*-carboxylate and (*b*) *cis*-carboxylate models of metal complexes with $[L^2]^{2-}$ and $[L^1]^{2-}$ respectively

Solutions of the ligands (0.01 mol dm^{-3}) were standardised by tetramethylammonium hydroxide solution in the presence of equimolar calcium chloride.

Analytical grade $Eu(NO_3)_3 \cdot 5H_2O$, $Er(NO_3)_3 \cdot 5H_2O$, $NMe_4OH \cdot 5H_2O$ and NMe_4NO_3 from Aldrich and $CeCl_3 \cdot 6H_2O$ from Fisher were used as received. Effective concentrations of different solutions used for experiments were: H_2L^2, 2.547 x 10^{-3} mol dm^{-3}; H_2L^1, 2.731 x 10^{-3} mol dm^{-3}; Ce^{3+}, 2.420 x 10^{-3} mol dm^{-3}; Eu^{3+}, 2.387 x 10^{-3} mol dm^{-3}; Er^{3+}, 2.393 x 10^{-3} mol dm^{-3} and NMe_4OH, 1.0069 x 10^{-3} mol dm^{-3}.

Equipment and Procedure.—The calorimetric determinations were carried out using a TRONAC model 450 isoperibol titration calorimeter, with a 25 cm^3 glass Dewar as the titration vessel, and a 5 cm^3 precision constant-rate burette for titrant delivery. The thermostat was maintained at 298.150 ± 0.003 K with a TRONAC model 40 precision temperature controller. The ligand solution (20 cm^3) was titrated with NMe_4OH solution to determine the heats of protonation of the ligands corresponding to reactions (1) and (2). A solution containing

$$L^{2-} + H^+ \rightleftharpoons HL^- \qquad (1)$$

$$HL^- + H^+ \rightleftharpoons H_2L \qquad (2)$$

equal concentrations of Ln^{3+} ion and the ligand in the neutral form (H_2L) was titrated with NMe_4OH, $I = 0.1$ mol dm^{-3} tetramethylammonium nitrate, to determine the heat of complexation. The computer program CALTIT-OPTDES was developed[16] for the calculation of enthalpy changes associated with ligand protonation and ligand–Ln^{3+} complexation.

Results and Discussion

Table 1 summarises the calorimetric data obtained in the present study, together with the Ln^{3+} ionic radii for Ce^{3+}, Eu^{3+} and Er^{3+} (chosen as representative light, middle and heavy lanthanide ions of the series). Holz *et al.*[12] and Bünzli and Pilloud[13] suggested that the Ln^{3+} ions in their macrocyclic complexes were nine-co-ordinated. The ionic radii for nine-co-ordinate Ce^{3+}, Eu^{3+} and Er^{3+} are in the range 1.202–1.336 Å.[11] The cavity radii of H_2L^2 and H_2L^1 by analogy with the corresponding crown ethers are estimated to be 1.45 ± 0.15 and 0.98 ± 0.12 Å respectively.[10]

Interaction of Ln^{3+} *with* H_2L^2.—In contrast to transition-metal ions, Ln^{3+} ions form complexes mainly by electrostatic interactions and have no strict stereochemical demands for a specific co-ordination geometry. The fluxional character of the metal–ligand bonds allows a closer adjustment of the ligand to match the size of each ion. The ligand H_2L^2 has eight donor atoms to encapsulate the metal ion, allowing it to interact with Ln^{3+} ions more effectively than H_2L^1 which has seven donor atoms and a smaller non-compatible cavity size. The distinctly larger $-\Delta H^\circ$ values for the 1:1 complexes of the three Ln^{3+} ions with H_2L^2 over H_2L^1 provide evidence for the stronger binding of the former by these ions. Kodama *et al.*[1] have also reported favourable enthalpy contributions for the lanthanide(III)-ion complexation of 18-membered 1,4,7,10,13,16-hexaazacyclooctadecane-$N,N',N'',N''',N'''',N'''''$-hexaacetic acid as compared to those for the 15-membered 1,4,7,10,13-pentaazacyclopentadecane-N,N',N'',N''',N''''-pentaacetic acid. According to the ionic radii of Ln^{3+} ions, all the three metal ions are likely to enter the cavity of H_2L^2 and interact with four oxygen and two nitrogen atoms of the ring. Owing to its more favourable metal-ion: ligand-cavity radius Ce^{3+} binds most strongly followed by Eu^{3+} and Er^{3+}. The oxygen atoms of the two carboxylate groups which form two vertices of a hexagonal bipyramid [Fig. 1(*a*)] should also interact relatively more effectively with the larger Ce^{3+} ion than with the other ions. Owing to the increase of desolvation energy of the metal ion with increased cation-charge density, its contribution towards $-\Delta H^\circ$ is expected to decrease in the order $Ce^{3+} > Eu^{3+} > Er^{3+}$ which indeed is the order of metal–ligand interactions as discussed above.

Upon complexation, all but one of the water molecules are released causing an increase in entropy as shown by the positive ΔS° values in Table 1. The loss of entropy due to the reorganisation of the ligand is proportional to the degree of interaction of this ligand with the metal ion, *i.e.* $Ce^{3+} > Eu^3 > Er^{3+}$. The overall ΔS° value is dependant on these two factors. Fig. 2 shows a plot of ΔH° *vs.* ΔS°: the correlation is linear as was also found for alkaline-earth ion–H_2L^2

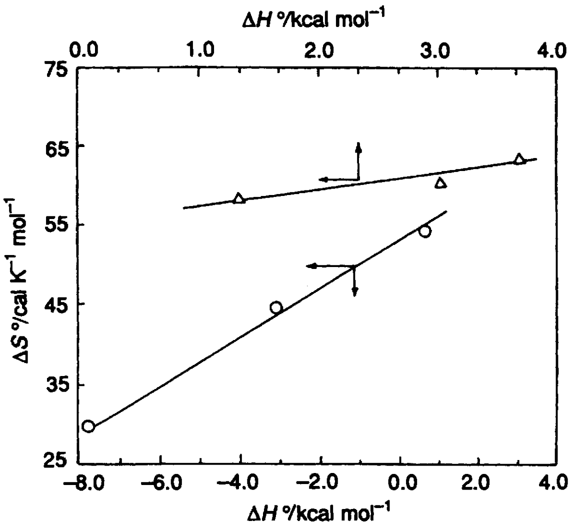


Fig. 2 Plot of $\Delta S°$ *vs.* $\Delta H°$ for the formation of Ln^{3+} complexes of H_2L^1 (Δ) and H_2L^2 (○)

interaction.[17] The effective interaction of metal ions with the donor atoms of the ligands is proportional to the loss of configurational entropy since the number of water molecules released is identical in all the cases. The lack of significant variation in the log K values with the change of compatability ratio from Ce^{3+} to Er^{3+} is a consequence of the large slope of this linear relationship. The strong dependence of the $\Delta H°$ values on the compatability ratios indicates that the metal–ligand interactions are predominantly electrostatic in nature.

Interaction of Ln^{3+} *with* H_2L^1.—The $\Delta H°$ values given in Table 1 show that the Eu^{3+} ion is of optimum size to strike a good balance between the two mutually exclusive types of metal–ligand interactions. The metal ion forms ion–dipole interactions with the cyclic donor atoms whereas it forms ion–ion interactions with the carboxylate oxygens, which may also be affected by the ionic potential of the metal ion. Interestingly, H_2L^1 does not encapsulate Ln^{3+} ions but imparts size selectivity owing to its favourable *cis*-carboxylate configuration. Such unusual behaviour of H_2L^1 is reflected by the largest complexation constant of the three Ln^{3+} ions being for Eu^{3+}. The rigid conformation proposed by Holz *et al.*[12] is also a consequence of this favourable conformation rather than favourable encapsulation. It is noteworthy that no size selectivity is observed[13] in the Ln^{3+} complexes of 15-crown-5 where rigidity on account of ion–ion interactions are absent. As expected in such cases, the stability constants for the heavier Ln^{3+} ions are usually larger than those for their lighter analogues. The formation of 1:2 complexes also suggests the lack of encapsulation in the latter case.[13]

A larger favourable entropy contribution is observed for complexes of H_2L^1 compared to that for complexes with H_2L^2 in spite of the fact that fewer water molecules are released in the former case.[12] This implies that the configurational entropy loss that plays a major role in complexes of H_2L^2 is not as significant for complexes of H_2L^1. Configurational entropy loss is a salient feature of macrocyclic complexes of encapsulated metal ions interacting electrostatically. Relatively weakly interacting H_2L^1 undergoes little distortion upon complexation. Nevertheless as reported by Delgado *et al.*[18] for alkaline-earth metals a linear relation with a slight slope is observed in the enthalpy–entropy plot (Fig. 2). The small variation in the entropy contribution with atomic number also suggests that an identical number of water molecules is released in all three complexes of H_2L^1, and this is an important factor.

The present studies suggest that the Ln^{3+} ions do not enter the cavity of H_2L^1 but are drawn quite close to the five donor atoms of the macrocyclic ring and the two oxygen atoms of the carboxylate groups in a *cis*-carboxylate configuration [Fig. 1(*b*)]. The large Ce^{3+} ion may find it relatively difficult to approach the ring donor atoms but may readily interact with the carboxylate oxygens. However, the Er^{3+} ion interacts with the ring donor atoms more effectively than with the carboxylate oxygens.

Conclusion

The ligand H_2L^2 interacts strongly with Ln^{3+} ions by encapsulation. The degree of interaction decreases with decreasing ionic radius (or atomic number) of the metal ion. The contribution of entropy loss is significant and proportional to the degree of interaction of the ligand-donor atoms with the metal ion. The overall entropy gain is due to the release of a large number of water molecules.

Lanthanide(III) ions are not encapsulated and interact only externally with the *cis*-carboxylate configuration of $[L^1]^{2-}$. The size selectivity observed for Eu–H_2L^1 complexes is enthalpic in origin and emanates principally from its optimum size for better ion–dipole interactions with the donor atoms of the macrocyclic ring together with ion–ion interactions with the carboxylate oxygens. The configurational entropy loss is not significant and the favourable entropy contribution is influenced by the release of the same large number of water molecules for all three metal ions.

The linear correlation of enthalpy–entropy contributions suggests that lanthanide ions, like alkaline-earth metal ions, interact essentially electrostatically with these ligands.

Acknowledgements

The authors thank Dr. R. H. Iyer, Radiochemistry Division for his valuable advice (V. K. M. and P. K. M.) and Department of Energy Basic Energy Sciences for partial financial support (C. Z. and R. M. I.). Appreciation is also extended to Jon Hathaway for his assistance in preparing the manuscript.

References

1 M. Kodama, T. Koike, A. B. Mahatma and E. Kimura, *Inorg. Chem.*, 1991, **30**, 1270.
2 M. F. Loncin, J. F. Desreux and E. Merciny, *Inorg. Chem.*, 1986, **25**, 2646.
3 C. A. Chang and M. E. Rowland, *Inorg. Chem.*, 1983, **22**, 3866.
4 C. A. Chang and V. O. Ochaya, *Inorg. Chem.*, 1986, **25**, 355.
5 P. Wedeking, K. Kumar and M. F. Tweedle, *Magn. Reson. Imaging*, 1992, **10**, 641.
6 O. A. Gansow, M. W. Brechbiel, T. J. McMurry, G. Pippin, C. Wu, K. Garmestani, R. Huneke, P. Squire, M. Strand, J. Carrasquillo and T. A. Waldmann, *Seventh International Symposium on Macrocyclic Chemistry*, Provo, UT, 1992.
7 P. G. Sammes, G. Yahioglu and G. D. Yearwood, *J. Chem. Soc., Chem. Commun.*, 1992, 1282.
8 C. A. Chang, V. K. Manchanda and J. Peng, *Solvent Extr. Ion Exch.*, 1989, 7, 413.
9 C. A. Chang, V. K. Manchanda and J. Peng, *Inorg. Chim. Acta*, 1987, **130**, 117.
10 R. M. Izatt and J. J. Christensen, *Progress in Macrocyclic Chemistry*, Wiley, New York, 1979, vols. 1 and 2.
11 R. D. Shannon, *Acta Crystallogr., Sect. A*, 1976, **32**, 751.
12 R. C. Holz, S. L. Klakamp, C. A. Chang and W. D. Horrocks, jun., *Inorg. Chem.*, 1990, **29**, 2651.
13 J. C. Bünzli and F. Pilloud, *Inorg. Chem.*, 1989, **28**, 2638.
14 L. Mei Tsay, J. S. Shih and S. C. Wu, *Analyst (London)*, 1983, **108**, 1108.
15 S. Kulstad and L. A. Malmsten, *Acta Chem. Scand., Ser. B*, 1979, **33**, 46.
16 C. Zhu and R. M. Izatt, personal communication.
17 M. R. Spirlet, J. Rebizant, M. F. Loncin and J. F. Desreux, *Inorg. Chem.*, 1984, **23**, 4278.
18 R. Delgado, J. J. R. Frausto da Silva, M. C. T. A. Vaz, P. Paoletti and M. Micheloni, *J. Chem. Soc., Dalton Trans.*, 1989, 133.

Received 17th *November* 1994; *Paper* 4/07013E