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Selectivity of macrocyclic aminocarboxylates for alkaline-earth metal ions and stability of their complexes

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The stability constants of alkaline-earth-metal complexes of several macrocycles derived from 1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid (H_3L^1) were determined by the potentiometric pH-titration method. The derivatives are formed by variation of the substituent R at N^{10}, *i.e.* R = Pr^n (H_3L^2), $CH_2C_6H_4NO_2$-*p* (H_3L^3), $CH_2CH(OH)CH_3$ (H_3L^4), $CH_2CH(OH)CH_2OH$ (H_3L^5), $CH_2CH(OH)CH_2OCH_3$ (H_3L^6) and CH_2CO_2H (H_4L^7). In general, the stabilities of these complexes are greater than those with non-cyclic ligands except in a few cases, *e.g. trans*-1-cyclohexane-1,2-diyldinitrilotetraacetic acid (H_4cdta). For H_3L^1–H_3L^3, the stability trend is CaL > MgL > SrL > BaL; for H_3L^4–H_3L^6 and H_4L^7, CaL > SrL > BaL > MgL. The former trend is similar to those found for smaller, non-cyclic ligands with six or less donor atoms such as H_4cdta. The latter trend is the same as that for the larger, more flexible, and calcium-selective ligand ethylenedioxydiethylenedinitrilotetraacetic acid. The selectivity of H_3L^4–H_3L^6 and H_4L^7 for Ca^{2+}, Sr^{2+} and Ba^{2+} over Mg^{2+} ion is presumably due to their ability to saturate the octahedral co-ordination environment of Mg^{2+} while still allowing the larger Ca^{2+}, Sr^{2+} and Ba^{2+} to be fully eight-co-ordinated.

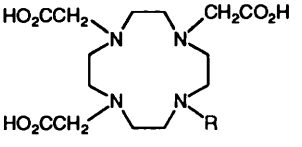
Macrocyclic aminocarboxylate reagents are potentially ion-selective due to their unique structures and conformations. For example, the selectivity of a number of 15- and 18-membered diazaoxacrown diacetic acids toward lighter lanthanide(III) ions is induced by a balance of interactions dominated by the ionic potential and metal-ion size fit.[1,2] The isomeric macrocyclic bis(amide) derivatives 1,4,7-tris(carboxymethyl)-9,14-dioxo-1,4,7,10,13-pentaazacyclodecane and 4,10,13-tris(carboxymethyl)-8,15-dioxo-1,4,7,10,13-pentaazacyclopentadecane show reversed selectivity toward complexation of Gd^{3+} and Zn^{2+}.[3] Another example is the compounds derived from 1,4,7,10-tetraazacyclododecane (cyclen) with a pre-organized complex environment. The metal complexes of 1,4,7,10-tetraazacyclododecanetetraacetic acid (H_4L^7) are usually thermodynamically very stable and kinetically rather inert as compared to those with linear ligand structures.[4–6] They are in general well tolerated *in vivo* and have been tested for use as medical diagnostic agents. One successful clinical application of these potentially selective macrocyclic compounds is to use them as magnetic resonance imaging (MRI) contrast agents and examples include both $Na[GdL^7]$[7] and $[GdL^4]$.[8] Thus, it is very important to understand the structural, stability and selectivity properties of the macrocycles and their metal complexes in order to design compounds for specific applications.

This paper reports the results of a potentiometric determination of the stability constants of alkaline-earth metal complexes of several macrocycles derived from 1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid (H_3L^1) in which the substituent R on one of the macrocycle nitrogen atoms is varied. Studies on H_4L^7 have been reported by at least three groups and different results were obtained.[4,5,9,10]

Experimental

Materials and standard solutions

The salt Na_2H_2edta (H_4edta = ethylenedinitrilotetraacetic acid) was obtained from Fisher. The compounds H_3L^1–H_3L^6 were prepared and purified according to published methods.[11]



R	
H_3L^1	H
H_3L^2	Pr^n
H_3L^3	$CH_2C_6H_4NO_2$
H_3L^4	$CH_2CH(OH)CH_3$
H_3L^5	$CH_2CH(OH)CH_2OH$
H_3L^6	$CH_2CH(OH)CH_2OCH_3$
H_4L^7	CH_2CO_2H

Elemental analysis data (obtained by the Analytical Department of Squibb Institute for Medical Research) are presented in Table 1. The compound H_4L^7 was obtained from Parish Chemical Co. and purified by passing through an ion-exchange column (Dowex 50W-X4, H^+ form)[6] eluted with water followed by 0.5 mol dm^{-3} NH_3. Carbonate-free deionized water was used for all solution preparations.

The concentrations of carboxylate solutions were determined by acid–base titration using a standard tetramethylammonium hydroxide solution (0.1 mol dm^{-3}). They were checked by complexometric back titration. This was performed by adding an excess amount of a standardized $GdCl_3$ solution to a fixed amount of carboxylate solution to allow the formation of [GdL] and titrating the excess of Gd^{3+} by a standardized edta solution. The concentrations of all stock solutions were *ca.* 0.01 mol dm^{-3}. 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.

A 0.1 mol dm^{-3} tetramethylammonium hydroxide solution was prepared by diluting a 20% NMe_4OH–methanol solution obtained from Aldrich. The aqueous NMe_4OH solution was standardized by using reagent grade potassium hydrogenphthalate. A 0.1 mol dm^{-3} HCl solution was prepared by diluting reagent grade HCl to *ca.* 1 mol dm^{-3}, then diluting. This solution was standardized by using the standard NMe_4OH

solution. A 1.0 mol dm^{-3} stock solution of tetramethylammonium chloride (Aldrich) was prepared and diluted to 0.1 mol dm^{-3} for each titration to maintain a constant ionic strength (0.1 mol dm^{-3}, charge units neglected).

Potentiometric titrations

All titrations were carried out at a constant ionic strength of 0.10 mol dm^{-3} NMe_4Cl. A model 670 Metrohm (Brinkmann) Titroprocessor in conjunction with a combination electrode was employed to monitor the pH (±0.001 pH unit, however, for practical calculations, the accuracy was estimated to be ±0.01 pH unit). Before each titration, the pH meter was standardized at pH 4.01, 7.00 and 10.00 with standard buffer solutions from Fisher. A water-jacketed titration vessel of capacity 5 cm^3 (Brinkmann) along with a five-hole cover was used. The electrode and burette were fitted into these holes. The vessel was thermostatted at 25.0 ± 0.1 °C using a Lauda model RM 6 constant-temperature circulating bath.

The sample solution was prepared by pipetting exact amounts of stock solutions into the titration vessel. For the determination of metal complex-formation constants (K_{ML} = [ML]/[M][L]), a 1:1 mole ratio of metal to carboxylate solution was prepared. Generally, the carboxylate concentration was 2.0 mmol dm^{-3} and the metal-ion concentration was in slight excess (≤2%). Under this experimental condition only 1:1 complexes were formed. The ionic strength of the solution was adjusted to 0.1 mol dm^{-3} using 1 mol dm^{-3} NMe_4Cl. The NMe_4OH solution was delivered from an automatic Brinkmann Metrohm model 665 Dosimat burette (10 cm^3) with a reading accuracy of ±0.001 cm^3. The titrations were performed two to four times, and reproducible results were obtained.

All equilibrium calculations were performed using computer programs described elsewhere[1,2,12] and double checked by the computer programs BEST and PKAS[12] and similar results were obtained. The pH-metric titration data were used to calculate the stepwise carboxylate protonation constants defined in equation (1), where n = 1–3. The measured pH values were

$$K_n = [H_nL]/[H_{n-1}L][H^+] \quad (1)$$

converted into $p[H^+]$ values by the activity relationship: $p[H^+] = pH + \log f$, where $[H^+]$ is the hydrogen-ion concentration and f, 0.83, the activity coefficient at 0.1 mol dm^{-3} ionic strength. For calculation of the formation constants, data points in the metal buffer region of 25–75% metal complexation were employed. The average values are presented together with the standard deviations calculated from those valid data points.

Table 1 Elemental analysis data

Compound	Analysis (%)* C	H	N	H_2O
$H_3L^1 \cdot H_2SO_4 \cdot 2.03H_2O$	35.10 (34.95)	6.80 (6.70)	11.60 (11.65)	(7.60)
$H_3L^2 \cdot 0.05H_2O$	51.80 (52.00)	8.45 (8.35)	13.90 (14.25)	(0.25)
$H_3L^3 \cdot 2.53H_2O$	48.10 (47.90)	6.85 (6.90)	13.30 (13.30)	(8.65)
$H_3L^4 \cdot 3.57H_2O$	43.90 (43.75)	8.20 (8.40)	12.10 (12.00)	(13.75)
$H_3L^5 \cdot 2.12H_2O$	44.80 (44.50)	7.75 (7.95)	11.95 (12.20)	(8.30)
$H_3L^6 \cdot 2.46H_2O$	45.05 (45.15)	8.00 (8.20)	11.55 (11.70)	(9.25)

* Calculated values are given in parentheses.

Results and Discussion

Carboxylate protonation constants

The titration curve of H_3L^5 (L of Fig. 1) shows two buffer regions: one from pH 3.8 to 6, which most likely corresponds to the dissociation of the acid proton; another from pH 8 to 11, which corresponds to the simultaneous dissociation of two protons attached to nitrogen atoms. This assignment is consistent with that proposed by an NMR study of the dissociation of the structural analogue, H_4L^7.[5] The titration curves for the other carboxylates are similar to that of H_3L^5. The individual logarithmic protonation constants (log K_n) of all carboxylates and the overall basicities expressed by the sum of the log K_n values of each are listed in Table 2.

The overall basicities for the carboxylates except H_4L^7 are in the range of 24.4–25.0 log K units which are about five units lower than that of H_4L^7. The higher basicity of the latter is mainly due to its higher proton affinity at the two macrocycle nitrogen sites and the additional carboxymethyl functional group which contributes to a fourth protonation constant. The protonation constants of H_4L^7 are very similar to those pub-

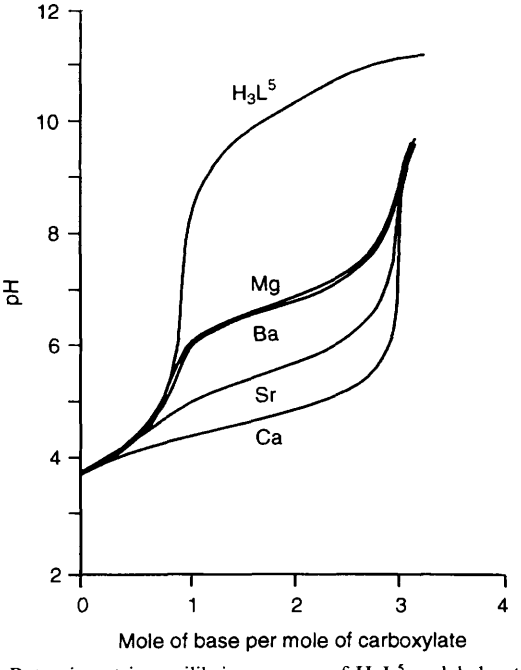


Fig. 1 Potentiometric equilibrium curves of H_3L^5 and 1:1 ratios of H_3L^5 with several metal ions. [M] = $[H_3L^5]$ = 2 × 10^{-3} mol dm^{-3}; 25 ± 0.1 °C

Table 2 Logarithmic protonation constants for the macrocycles[a]

Compound	log K_1	log K_2	log K_3	Σlog K_n
H_3L^1	10.72	9.51	4.40	24.63
H_3L^2	10.69	9.95	4.23	24.87
H_3L^3	10.55	9.62	4.64	24.81
H_3L^4	10.89	9.79	4.29	24.97
H_3L^5	10.63	9.62	4.40	24.65
H_3L^6	10.60	9.62	4.23	24.45
H_4L^7	11.34	9.90	4.60	29.84[b]

[a] For log K_1 and log K_2 the standard deviation ≤ 0.03 log K unit; for log K_3 s.d. ≤ 0.08 log K unit. [b] A fourth protonation constant was determined to be log K_4 = 4.0 and is included in the sum.

lished earlier[4,5] except that the most basic one determined by Delgado and Silva[9] is 0.7 log K unit greater.

Stability of metal chelates

The alkaline-earth-metal complex-formation equilibrium curves with H_3L^5 as the representative ligand are also shown in Fig. 1. All of these curves are lower in pH than that of the carboxylate titration without metal ions, indicating competition between metal ions and protons for binding with the carboxylates.

For all the alkaline-earth-metal ions strong complexation occurs after the carboxymethyl acid protons are neutralized. This is demonstrated in Fig. 1 where the titration curves with or without metal ions overlap with one another between 0 and 1 equivalent of base added. The complexation reactions after removal of carboxymethyl acid protons for the four metal ions are best described by equation (2).

$$M^{2+} + H_2L^- \rightleftharpoons ML^- + 2H^+ \qquad (2)$$

There seems no indication that complexes of the form M(HL) exist within this buffer pH range. Therefore it is assumed that M(HL) is absent in all titrations. If M(HL) is assumed to be present the calculated stability constants all have relatively much larger standard deviations. In addition, crystal structures show that all co-ordination sites are occupied for $Ca[CaL^7]$[13] and $Ca[CaL^4]_2$[14] in the solid state. It is not likely that one of the two macrocycle nitrogen sites is protonated if complexation is to take place. It is possible that carboxylate-protonated species are present as were found for H_4L^7. However, they normally exist at a pH < 4. Table 3 lists the calculated stability constants (log K_{ML}).

In general, if the ligand donor atoms and complex structures are similar, the more basic the ligand the more stable is the complex. Thus, for a given metal ion, the order stability of these complexes is $H_4L^7 > H_3L^4 > H_3L^5 > H_3L^6$ for potentially octadentate ligands. The trend is not obvious for the potentially heptadentate ligands.

For a particular macrocycle, the stability constant is always the greatest for the Ca^{2+} complex. This indicates that the cavity size of these macrocycles seems to fit best metal ions with radii similar to that of Ca^{2+}. When a smaller (Mg^{2+}) or a larger (Sr^{2+} or Ba^{2+}) ion is introduced into the cavity the stereochemical constraints imposed on the ligand can no longer allow it to bind the metal ion at full strength, *i.e.* the metal–donor bond distances are perhaps no longer optimum for a given co-ordination number or the ligand may adopt a less-stable conformation to accommodate the metal ion.

The stability constants (log K_{ML}) of several non-cyclic alkaline-earth-metal complexes are listed in Table 4.[15] When compared to those of non-cyclic ligands with six or more donor atoms, it is found that the potentially eight-co-ordinated macrocyclic complexes usually have greater stability. This is presumably because the macrocyclic ligands adopt a [3333] preorganized conformation[13,16] and, possibly, owing to the resulting higher basicity at the ring nitrogen atoms. The relatively high stability of the six-co-ordinated, non-cyclic $[Mg(cdta)]^{2-}$ complex can be rationalized in a similar way because free *trans*-cdta is preorganized in the skew form for complexation.[17]

Selectivity of ligands

For the non-cyclic polyaminopolycarboxylic acids (L) the observed selectivities or trends (Table 4) in complex stability are: MgL > CaL > SrL > BaL, L = ida; CaL > MgL > SrL > BaL, L = mida, nta, hedta, edta and cdta; CaL > SrL > MgL > BaL, L = eedta, dtpa and ttha; CaL > SrL > BaL > MgL, L = egta. The first two trends are often observed for smaller (*i.e.* the number of donor atoms is six or less such as ida, nta, hedta and edta) and/or more rigid ligands (such as cdta). The other two trends are usually seen for larger and more flexible ligands such as eedta, dtpa, egta and ttha.

Table 3 Stability constants of alkaline-earth-metal complexes of the macrocycles*

	log K_{ML}			
Compound	Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}
H_3L^1	9.79	11.35	8.97	7.39
H_3L^2	9.35	10.65	8.79	7.71
H_3L^3	9.53	11.26	9.23	8.01
H_3L^4	9.70	14.18	12.27	10.03
H_3L^5	9.72	13.96	12.08	10.03
H_3L^6	9.71	13.72	11.92	9.90
H_4L^7	11.79	16.70	14.83	12.31

* At 25 °C, ionic strength = 0.1 mol dm^{-3}; s.d. ≤ 0.10 log K unit.

Table 4 Stability constants (log K_{ML}) of alkaline-earth-metal complexes of open-chain polyaminopolycarboxylic acids* at 25 °C, ionic strength = 0.1 mol dm^{-3}

Compound	Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}
H_2ida	2.98	2.59	2.23	1.67
H_2mida	3.48	3.79	2.90	2.60
H_3nta	5.47	6.39	4.97	4.80
H_3hedta	7.0	8.2	6.8	6.2
H_4edta	8.83	10.61	8.68	7.80
H_4cdta	11.07	13.15	10.58	8.60
H_4eedta	8.36	9.96	9.24	8.07
H_4egta	5.28	10.86	8.43	8.30
H_5dtpa	9.34	10.75	9.68	8.78
H_6ttha	8.43	9.89	9.26	8.22

* Data were obtained from ref. 15. H_2ida = Iminodiacetic acid; H_2mida = *N*-methyliminodiacetic acid; H_3nta = nitrilotriacetic acid; H_3hedta = *N*-(2-hydroxyethyl)ethylenedinitrilo-*N*,*N*′,*N*′-triacetic acid; H_4edta = ethylenedinitrilotetraacetic acid; H_4cdta = *trans*-cyclohexane-1,2-diyldinitrilotetraacetic acid; H_4eedta = oxydiethylenedinitrilotetraacetic acid; H_4egta = ethylenedioxydiethylenedinitrilotetraacetic acid; H_5dtpa = carboxymethyliminobis(ethylenenitrilo)-tetracetic acid; and H_6ttha = ethylenediiminodiethylenedinitrilohexaacetic acid.

For macrocycles such as H_3L^1–H_3L^3 the stability trend of the complexes is CaL > MgL > SrL > BaL. Thus, the macrocyclic ligands with seven donor atoms behave more like the non-cyclic, smaller and/or rigid ligands. For H_3L^4–H_3L^6 and H_4L^7, which all have eight co-ordination sites and one more chelate ring, the trend is CaL > SrL > BaL > MgL. This is the same trend as that observed for egta, a Ca^{2+} ion-selective ligand used preferentially to bind Ca^{2+} against Mg^{2+} because the log K_{ML} value is 10.86 for $[Ca(egta)]^{2-}$ and only 5.28 for $[Mg(egta)]^{2-}$.[15]

The stability constant of $[Mg(egta)]^{2-}$ is between that of mida, log K_{ML} = 3.48, and that of edta, log K_{ML} = 8.83, indicating that approximately half of the egta molecule is used to complex Mg^{2+}. This is consistent with the solid-state structure of $[Mg_2(egta)(OH_2)_6]\cdot 5H_2O$[18,19] in which each end of the $egta^{4-}$ ligand acts as a tridentate aminodicarboxylate ligand and three water molecules complete the octahedral ligand array for Mg^{II}. Thus, the high selectivity of egta for Ca^{2+} is presumably attributed to the two weak backbone ether donors which, with the rest of the ligand donor atoms, afford an eight-co-ordinate environment. The spacial arrangement of the egta donor atoms, however, cannot afford a thermodynamically stable octahedral co-ordination environment for Mg^{2+}. On the other hand, the low selectivity of dtpa (log K_{CaL} − log K_{MgL} = 1.4) for Ca^{2+} may be related to the middle, strongly binding glycinate portion which does not bisect the ligand into two separate Mg^{2+}-binding entities.

The heptadentate macrocycles such as H_3L^1–H_3L^3 can easily fulfil the six-co-ordination requirement of Mg^{II}. Addition of a neutral arm such as the hydroxypropyl group in (H_3L^4) does not improve the magnesium complex stability. This is in contrast to the addition of a carboxymethyl arm as in H_4L^7 which increases the stability by two log K units. This observation is consistent with the ion–ion ($M^{n+} \cdots CO_2^-$) interaction being stronger than the ion–dipole ($M^{n+} \cdots OH$) one and that the $[MgL^7]^{2-}$ complex affords more solution resonance structures than do the other macrocyclic magnesium complexes in this study.

When a neutral or anionic arm is added to H_3L^1 the $\log K_{ML}$ values increase, for example by 2.8, 3.3 and 2.6 units for the respective complexes of Ca^{2+}, Sr^{2+} and Ba^{2+} with H_3L^4, and 5.4, 5.9 and 4.9 units with H_4L^7. The large increases in log K_{ML} indicate that the added arm does participate in complexation in each case. This is corroborated by the crystal structures of $Ca[CaL^4]_2$[14] and $Ca[CaL^7]$.[13] Although the crystal structures may not be the same as those in solution, it has been demonstrated that, for lanthanide–H_4L^7 complexes, the rather rigid solution structures studied by NMR methods are similar to those in the solid state.[6,8] Thus far, most of my studies indicate that calcium and lanthanide complexes are structurally similar. Therefore, the selectivity of H_3L^4–H_3L^6 and H_4L^7 for Ca^{2+}, Sr^{2+} and Ba^{2+} ions over Mg^{2+} is presumably due to their ability to saturate the octahedral co-ordination environment of Mg^{2+} while still allowing the larger Ca^{2+}, Sr^{2+} and Ba^{2+} to be fully eight co-ordinated.

The stability trend observed for the alkaline-earth-metal complexes of H_4L^7 is the same as those reported previously.[9] Minor differences in values result presumably from the different protonation constants used for their calculation.

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