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Supramolecular Chemistry

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713649759

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To cite this Article Martell, Arthur E. , Motekaitis, Ramunas J. , Clarke, Eric T. , Delgado, Rita , Sun, Yizhen and Rong(1996) 'Stability constants of metal complexes of macrocyclic ligands with pendant donor groups', Supramolecular Chemistry, 6: 3, 353 — 363

To link to this Article: DOI: 10.1080/10610279608032555

URL: http://dx.doi.org/10.1080/10610279608032555

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SUPRAMOLECULAR CHEMISTRY, Vol. 6, pp. 353–363
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Stability constants of metal complexes of macrocyclic ligands with pendant donor groups

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(Received June 13, 1994)

In our studies of the stability constants of metal complexes, we have investigated a number of macrocyclic ligands with pendant donor groups. The ligands are characterized by the fact that they have nitrogen donors in the macrocyclic ring and oxygen or sulfur donors in the pendant arms. These ligands represent seven different macrocycles, and by varying the pendant donor groups, ten different ligands are indicated. The affinities of these ligands for fifteen metal ions will be described. The Fe(III) complex of triazanonane with *o*-hydroxypyridyl or *o*-hydroxybenzyl pendant donor groups are the most stable ferric complexes ever reported. The In(III) complex of triazacyclononane with pendant mercaptoethyl donor groups, is exceptionally stable. Also, the Ca(II) complex of DOTA probably has the highest stability of any calcium(II) complex. These, and other comparisons will be made on the basis of the thermodynamic stability constant data for the ligands described.

INTRODUCTION

From a molecular design point of view ligands with pendant donor groups may be divided into two classifications: 1, ligands with macrocyclic rings which merely provide a framework for attaching the donor groups, which serve as the only groups that complex the metal ion; 2, ligands which serve as a framework for attaching donor groups but which provide some of the functional groups which coordinate the metal ion. Examples of the first class are enterobactin which provides three catechol groups which have a very high affinity for the ferric ion and are attached to the 12-membered macrocycle cycloserine through amide linkages. Several models of enterobactin have been synthesized and studied by Raymond and coworkers[1,2]. Examples of the second class are NOTA (1,4,7-triazacyclononane-N,N',N"-triacetic acid) which has three acetate donor groups attached to cycloazanonane through three coordinating amino groups, and the tetraazamacrocyclictetraacetates, such as the tetraacetate of cyclam. This paper will deal only with the second class of ligand, in which the macrocycle plays an important role in the coordination of various metals while the pendant donor groups offer auxiliary coordinating moieties which generally increase the stability of the complex formed. Thus a metal ion is complexed both by the donors in the macrocyclic ring and by the pendant donor groups.

In this paper a number of macrocyclic ligands with pendant donor groups investigated by the authors will be described. The macrocyclic rings will generally contain nitrogen donors, which allow the attachment of a functional group, and the functional group is also a donor. The pendant functional groups described below include carboxylate, hydroxypyridyl, hydroxyphenyl, and thiolate groups.

Macrocyclic Ligands Containing Pendant Acetate Groups

Macrocyclic ligands containing three coordinating tertiary amino groups and three coordinating acetate groups are indicated and the stability constants of the complexes which they form with divalent transition metal ions, and the zinc(II) ion, are given in Table 1.[3,4] NOTA, **1**, in which three acetate groups are attached to triazacyclononane, is the first member of this series of ligands. The macrocyclic ring may be expanded with oxygen ether functions to give macrocyclic ligands indicated by formulas **2**, **3**, and **4**, containing one, two and three ether oxygens. Each ligand contains only three nitrogens and

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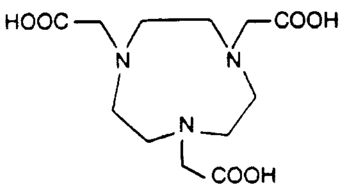
Table 1 Log Stability Constants and pM Values of Macrocyclic Triacetate Complexes of Divalent Transition Metal Ions

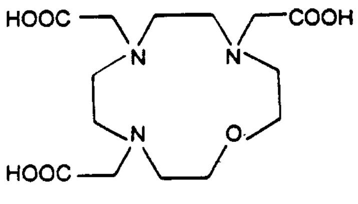
	Log K_{ML}[a] *(pM*[b]*)*			
	Co^{2+}	*Ni^{2+}*	*Cu^{2+}*	*Zn^{2+}*
NOTA, **1**	17.5 (12.9)		19.8 (15.2)	18.3 (13.7)
N3O-Ac, **2**	19.54 (5.1)	18.04 (13.6)	20.17 (15.8)	18.66 (14.3)
N3O2-Ac, **3**	16.38 (12.6)	14.94 (11.2)	17.54 (13.8)	16.38 (12.6)
N3O3-Ac, **4**	9.33 (6.3)	9.84 (6.6)	14.88 (11.4)	9.89 (6.6)

[a] K_{ML} = [ML]/[M][L], μ = 0.10 M (KCl), 25.0°C. [b] pM = -log [M] at p[H] 7.4, 100% excess ligand.

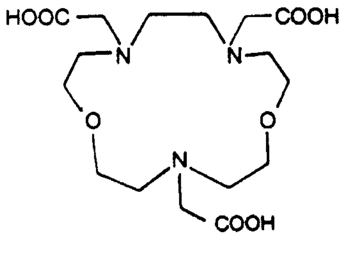
three acetate groups and these may be considered to be the strongest donor groups present. The oxygen ether functions may also be weak donors if their orientation is such that a complex in which they participate as donors can readily be formed, and if the metal can accommodate the additional donors in its coordination sphere. The pM values listed in Table 1 give a good indication of the affinity of a metal ion for the ligand in aqueous solution, because they take into account competition with hydrogen ion at physiological pH. It is seen that the pM values do not increase with the increase in size of the



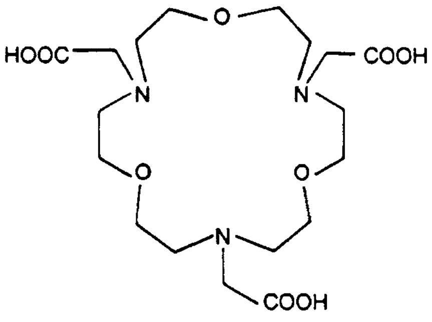
1 NOTA (1,4,7-triazacyclononane-N,N′,N′′-triacetic acid) (N-Ac_3[9]aneN_3)



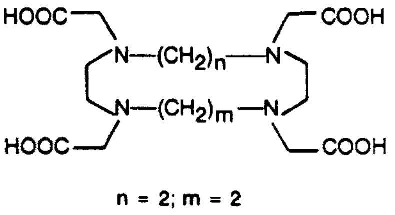
2 N3O-Ac (1,4,7-triaza-10-oxacyclododecane-N,N′,N′′-triacetic acid) (N-ac_3[12]aneN_3O)



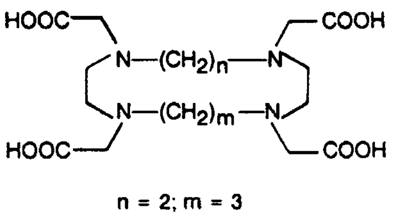
3 N3O2-Ac (1,4,10-triaza-7,13-dioxacyclopentadecane-N,N′,N′′-triacetic acid) (N-ac_3[15]aneN_3O_2)



4 N3O3-Ac (1,7,13-triaza-4,10,16-trioxacyclooctadecane-N,N′,N′′-triacetic acid) (N-ac_3[18]aneN_3O_3)



5 DOTA (1,4,7,10-tetraazacyclododecanetetraacetic acid)



6 TRITA (1,4,7,10-tetraazacyclotridecanetetraacetic acid)

Figure 1

macrocyclic ring, although there is a slight increase in the stability constant in going from a nine-membered to a twelve-membered ring by the addition of an ether oxygen. The slight increase in stability of the resulting complex, however, is overcome by the increased basicity of the ligand and the increased competition with hydrogen ion which results. Further increase of the size of the macrocyclic ring results in general decrease in the stability constant, probably for a steric reasons, since the nitrogen donors cannot as easily coordinate with the metal ion involved. It is noted that the metal ions in Table 1 are generally octahedral, except copper(II) which prefers a square planar or square pyramidal coordination (4 or 5).

The stability constants of the trivalent metal ion complexes of the same series of ligands is shown in Table 2.[3,4] The data show interesting trends in stability as the number of coordinating groups in the ligand is increased by expansion of the macrocyclic ring with ether oxygens. The general trend is toward lower stability but there are considerable differences in how the various metal ions behave in that respect. Metal ions which can expand their coordination shell beyond coordination number of six (octahedral) show less decrease in stability than does gallium(III) which has never been found to form complexes with more than six coordination. Iron(III) and indium(III) are considered borderline in that some of their complexes have been found to seven coordinate. The stabilities of the triazatriacetate complexes do not decrease very much for these metal ions as the number of coordinating groups in the ligand is increased from six to seven (from **NOTA, 1**, to N3O-Ac (1,4,7-triaza-10-oxacycloazadodecane-N,N',N"-triacetic acid, **2**). Beyond this point, however, the decrease in stability constant is quite rapid as the size of the macrocyclic ring increases further. Gadolinium(III) however is a much larger metal ion with longer coordinate bonds and a higher coordination number of about 8 or 9. This metal ion shows the smallest decrease in stability as the size of the macrocyclic ring and the number of coordination sites of the ligand are increased by the addition of ether oxygen donors. In fact the N3O3-Ac (1,7,13-triaza-4,10,16-trioxacyclooctadecane-N,N',N"-triacetic acid), **4**, chelate of Gd(III) has been found to have a coordination number of nine in the solid state.[5] In this case all nine donor atoms of the ligand are coordinated to the metal ion.

Table 2 Log Stability Constants and pM Values of Macrocyclic Triacetate Complexes of Trivalent Metal Ions

	$Log\ K_{ML}{}^{a}(pM^{b})$			
	Fe^{3+}	Ga^{3+}	In^{3+}	Gd^{3+}
NOTA, **1**	28.3 (23.7)	31.0 (26.4)	26.2 (21.6)	
N3O-Ac, **2**	26.8 (22.4)	21.3 (16.9)	25.5 (21.1)	21.6 (17.2)
N3O2-Ac, **3**	19.82 (16.1)	17.1 (13.4)	23.6 (19.9)	17.2 (13.5)
N3O3-Ac, **4**	22.5 (19.0)	19.2 (15.7)	–	18.0 (14.5)

^{a}KML = [ML]/[M][L], $\mu = 0.10$ M (KCl), 25.0°C. ^{b}pM = -log [M] at p[H] 7.4, 100% excess ligand.

Table 3 Log Stability Constants and pM Values of Macrocyclic Tetraacetate Complexes of Alkaline Earth Metal Ions

	$Log\ K_{ML}{}^{a}\ (pM^{b})$			
	Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}
DOTA, **5**	11.15 (6.0)	16.37 (10.2)	14.39 (8.3)	11.75 (6.2)
TRITA, **6**	8.18 (6.0)	11.99 (6.2)	9.64 (6.0)	8.56 (6.0)
TETA, **7**	3.01 (6.0)	8.53 (6.0)	5.91 (6.0)	4.37 (6.0)

$^{a}K_{ML}$ = [ML]/[M][L], $\mu = 0.10$ M (KNO_3), 25.0°C. ^{b}pM = -log [M] at p[H] 7.4, 100% excess ligand.

In Tables 3, 5, and 6 are listed the stability constants of a series of tetraaza macrocyclic tetraacetate complexes of various metal ions.[6,7] These ligands are DOTA (1,4,7,10-tetraazacyclododecanetetraacetic acid), **5**, with a twelve-membered macrocyclic ring, TRITA (1,4,7,10-tetraazacyclotridecanetetraacetic acid), **6**, with a thirteen-membered macrocyclic ring, and TETA (1,4,8,11-tetraazacyclotetradecanetetraacetic acid), **7**, with a fourteen-membered macrocyclic ring. These ligands are potentially octacoordinate and can coordinate effectively with metal ions that can expand their coordination spheres to coordinate as many as eight donor groups. The alkaline earth complexes in Table 3[6] show high stabilities, especially for calcium(II), strontium(II) and barium (II). The magnesium(II) ion does not have a high enough coordination number to fully take advantage of these potentially octadentate ligands. However, for the remaining alkaline earth ions with much higher coordination number the stabilities of complexes formed with these ligands are probably the highest that have been measured thus far, especially for the complexes of DOTA which has a twelve-membered macrocyclic ring. The decrease in stability as the macrocyclic rings are increased in size correlates with the chelate ring size principles established previously,[8] in that six-membered chelate rings favor small metal ions and five-membered chelate rings favor large metal ions. Therefore, as some of the five-membered chelate rings are increased to six, one would expect a decrease in stability for these large metal ions as the trends in Table 3 indicate. In all of these complexes the metal ion is considered to be above the plane established by the four nitrogens of the macrocycle so

Table 4 Stability Constants and pM Values of Ca(II) Complexes of Various Ligands

	Log $K_{ML}{}^a$	pM^b
EDTA, **8**	10.61	7.8
CDTA, **9**	13.15	8.2
EGTA, **10**	10.86	8.3
DOTA, **5**	16.37	10.2

$^a K_{ML}$ = [ML]/[M][L], μ = 0.10 M (KNO_3), 25.0°C. ^{b}pM = -log [M] at pH 7.4, 100% excess ligand.

that the nitrogens are on one side of the metal ion and the negative acetate groups are on the other.

It is interesting to compare the stability constant of the calcium DOTA complex indicated as $10^{16.37}$ in Table 4 with the stabilities of other well-known complexes formed by ligands which have been considered to have a high affinity for the calcium ion. This is indicated in Table 4 in which the stabilities of the calcium complexes of EDTA (ethylenediamine-N,N'-tetraacetic acid), **8**, CDTA (*trans*-1,2-diaminocyclohexane-N,N'-tetraacetic acid), **9**, and EGTA (ethylenebis(oxyethylenenitrilodiacetic acid)), **10**, are compared with the stability constant of the calcium DOTA chelate.[9,10] It is seen that the stability of the calcium DOTA chelate is over three orders of magnitude higher than any of the other calcium chelates. This is partly due to the fact that DOTA provides eight coordinating sites to match the coordination number of the calcium ion, while EDTA and CDTA provide only six. Also the DOTA ligand is more highly preorganized than are any of the other ligands for metal ion binding because of the macrocyclic ring. Thus EGTA, **10**, which has eight donor groups and the same negative charge as DOTA (which also has eight donor groups and a minus four charge) exists in solution in the extended form in which the iminodiacetate groups are as far apart as possible. This lack of preorganization accounts for the lower stability constant of the calcium EGTA chelate.

Table 5 Log Stability Constants and pM Values of Macrocyclic Tetraacetate Complexes of Divalent Transition Metal Ions

	Log $K_{ML}{}^a$ (pM^b)			
	Co^{2+}	Ni^{2+}	Cu^{2+}	Zn^{2+}
DOTA, **5**	19.3 (13.2)	20.5 (14.4)	22.72 (16.6)	18.7 (12.6)
TRITA, **6**	17.5 (11.3)	20.2 (14.0)	22.49 (16.2)	18.04 (11.8)
TETA, **7**	16.7 (11.1)	20.0 (14.4)	21.87 (16.2)	17.6 (12.0)

$^a K_{ML}$ = [ML]/[M][L], μ = 0.10 M (KNO_3), 25.0°C. ^{b}pM = -log [M] at p[H] 7.4, 100% excess ligand.

Table 6 Log Stability Constants and pM Values of Macrocyclic Tetraacetate Complexes of Trivalent Metal Ions

	Log $K_{ML}{}^a$ (pM^b)			
	Fe^{3+}	Ga^{3+}	In^{3+}	Gd^{3+}
DOTA, **5**	29.4 (23.3)	21.3 (15.2)	23.9 (17.8)	24.0 (17.9)
TRITA, **6**	27.5 (21.3)	19.9 (13.7)	23.0 (16.8)	19.2 (13.0)
TETA, **7**	26.5 (20.9)	19.7 (14.1)	21.9 (16.3)	13.8 (8.2)

$^a K_{ML}$ = [ML]/[M][L], μ = 0.10 M (KCl), 25.0°C. ^{b}pM = -log [M] at p[H] 7.4, 100% excess ligand.

In Table 5 are listed the stability constants and pM values of transition metal ions, and the zinc(II) ion with DOTA, TRITA and TETA.[6] The stability constants are rather high, considerably higher than those of EDTA, for example, but not all of the coordinating groups are involved in forming the complexes of these metal ions which for the most part are octahedral, except copper which is tetradentate (square planar) or pentadentate (square pyramidal). It is suggested that the complexes formed involve coordination by all four nitrogens of the macrocycle and one or two of the acetate donor groups. Thus the high stability is mainly accounted for by coordination with the basic nitrogen atoms in the macrocyclic rings.

Comparison of the stability constants in Table 5 with those of the parent tetraazamacrocycles[9,10] shows that for the metal ions with coordination number six that form octahedral complexes, the stability constants are generally increased by 2-4 log units, indicating that the pendant acetate donors participate to some extent in complex formation. The picture that emerges for the probable conformations of the complexes in solution is of equatorial arrangement of the four nitrogen donors and axial coordination of two of the pendant acetate groups. The major part of the energy of coordination must be in the metal-nitrogen bonds, since the stability constants of the tetraazamacrocycles are only a few log K units lower than those of the corresponding acetates. The bond energies are considered to be mainly enthalpic in nature, due to the covalent character of the metal-nitrogen bonds. The major exceptions to this generalization are the copper(II) complexes, for which the stability constants of tetraazacyclic complexes are 2-5 log units higher than the corresponding complexes formed by the ligands with pendant acetate donor groups. This seems to indicate that the complexes formed by Cu(II) are probably four coordinate, involving the amino nitrogens, and any coordination in the axial direction (to form a square-pyramidal complex) is either non-existent or very weak. The small decrease in stability constant observed may be due to steric effects derived from the acetate groups. It should be noted that the nickel(II) complexes derived from cyclam (the 14-membered macrocycle) is also exceptional in that the complex formed by the parent macrocyclic tetramine is 2.2 log K units higher than that of the tetraacetate, indicating that both complexes in solution are probably tetracoordinate square planar complexes of low-spin nickel(II).

It should be pointed out that the formation of 2:1 complexes of these ligands in which two metal ions are coordinated to a single ligand has not be addressed. The possibility that an octadentate ligand will combine with two metal ions in such a way as to provide four donor groups to each metal ion is certainly a possibility. This is especially true with copper(II) which forms very stable complexes with ethylenediaminediacetic acid. Since all three ligands in DOTA, **5**, TRITA, **6**, and TETA, **7**, contains the ethylenediaminediacetate moiety the possibility of forming a very stable 2:1 complex is quite high. The formation and stability of such 2:1 complexes would be a good subject for further investigation.

The stability constants of the complexes formed by the tetraazatetraacetate ligands with trivalent metal ions are listed in Table 6.[7] The constants involved are moderately high but not unusually so when the stability constants are compared with those of other ligands. In all cases there is a decrease in stability constant as the size of the macrocyclic ring increases. The modest decrease in stability constant with increase in ring size is considered due to steric effects; in other words the greater ring size and more flexible the macrocycle the less is the preorganization of the ligand for metal complex formation. The coordination numbers of the ferric gallium, and indium ions are generally six (octahedral) although some Fe(III) and In(III) complexes have been observed with coordination number seven. Obviously in the complexes that are formed with these ligands all of the donor groups cannot be bound to the metal ion. The situation with Gd(III) is quite different, here the higher coordination number of Gd(III) nearly matches the fact that these ligands are all octadentate, so that all of the donor groups of the ligand are expected to be bound to the Gd(III) ion. The considerable decrease in stability of the Gd(III) complexes with increasing size of the macrocyclic ring is considered to be due in part to the greater flexibility and lesser preorganization of the larger rings, and the fact that the metal chelate rings formed with the large Gd(III) ion are more stable for five-membered rings than six-membered rings.[8] Therefore the DOTA complexes with five-membered rings formed with the macrocyclic nitrogen donors would be expected to be more stable than TRITA complexes with one six-membered ring and three five-membered rings, and that should be more stable than the TETA complexes with two six-membered rings and two five-membered rings derived from the macrocycle.

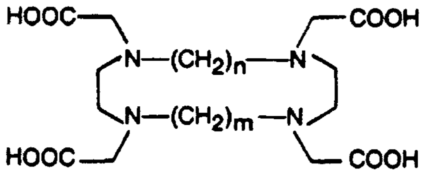
Table 7 Log Stability Constants and pM Values of Trivalent Metal Ion Complexes of Triazacyclononane Ligands Containing Pendant Negative Donor Groups

	Log K[a] (pM)[b]		
	Fe^{3+}	*Ga^{3+}*	*In^{3+}*
NOTA, **5**[c]	28.3 (23.7)	31.0 (26.4)	26.2 (21.6)
TACN-Me2HB, **11**[c,d]	51.3 (32.3)	44.2 (25.2)	34.0 (15.0)
TACN-MeHP, **12**[c]	50.0 (39.3)	45.6 (34.9)	28.0 (17.4)
TACN-TM, **13**[c]		34.2 (23.8)	36.1 (25.2)

[a] K = [ML]/[M][L]. [b] pM = -log [M] at pH 7.4 with 100% excess ligand. [c] μ = 0.10 M KCl, 25.0°C. [d] μ = 0.10 M (KCl), 25.0°C, 75% ethanol, 25% water.

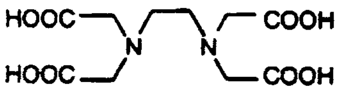
The complexes described in Table 7 involve a single macrocycle triazacyclononane to which are attached as pendant donor groups acetate functions in NOTA, **5**,[3] dimethylbenzyl functions for TACN-Me2HB (N,N',N"-tris(2-hydroxy-3,5-dimethyl-2-hydroxybenzyl)-1,4,7-triazacyclononane), **11**,[11] methylhydroxypyridyl functions for TACN-MeHP (N,N',N"-tris-3-hydroxy-6-methyl-2-pyridylmethyl)-1,4,7-triazacyclononane), **12**,[12,13] and mercaptoethyl groups for TACN-TM (N,N',N"-tris(mercaptoethyl)-1,4,7-triazacyclononane), **13**.[14] The trivalent metal ion complexes of NOTA have already been described (Table 2). The remarkable feature of this table of stability constants are the very high Fe(III) stabilities when the macrocycle is substituted with hydroxybenzyl and hydroxypyridyl groups. The hydroxypyridyl derivative, **12**, has a stability constant of 10^{50} with a pM value of 40.3, probably the highest stability that has ever been reported for the ferric ion.[12] The stability constant in Table 7 for the dimethylhydroxybenzyl derivative, **11**, seems to be somewhat higher, $10^{51.3}$, but this constant was measured in 75% ethanol and 25% water because the ligand is insoluble in pure water. Comparison of relative stabilities in these two solvents of other complexes shows that a stability in water would be somewhat lower that $10^{51.3}$. However, this ligand has much higher pK's than does the hydroxypyridyl derivative, **12**, and therefore the pM is quite a bit lower at pH 7.4 due to hydrogen ion competition.[12] Therefore the hydroxypyridyl derivative is still the most effective ligand for iron that has yet been described. It should be noted that its affinity for the ferric ion is somewhat greater than that of enterobactin, **14**, which is a siderophore that has been considered to be one of the best ligands for the ferric ion.

It is seen that the stability constants of the Ga(III) chelates for the hydroxybenzyl and the hydroxypyridyl

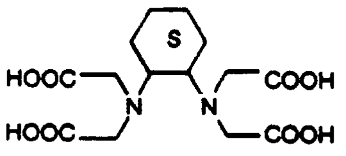


n = 3; m = 3

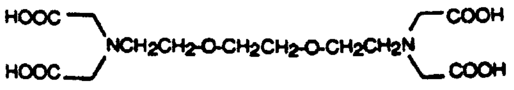
7 TETA (1,4,8,11-tetraazacyclotetradecanetetraacetic acid)



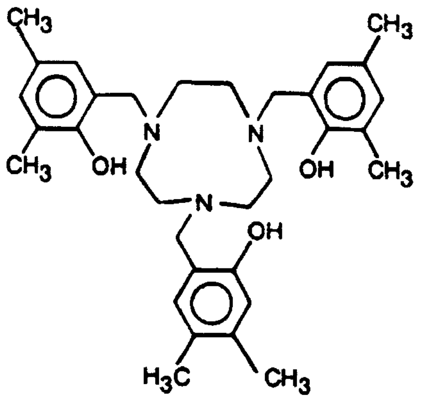
8 EDTA (ethylenediamine-N,N'-tetraacetic acid)



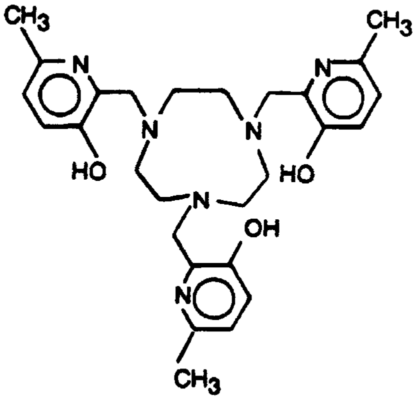
9 CDTA (*trans*-1,2-diaminocyclohexane-N,N'-tetraacetic acid))



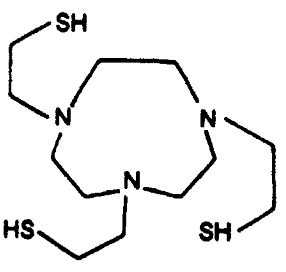
10 EGTA (ethylenebis(oxyethylenenitrilodiacetic acid))



11 TACN-Me2HB (N,N',N''-tris(3,5-dimethyl-2-hydroxybenzyl)-1,4,7-triazacyclononane)



12 TACN-MeHP (N,N'-N''-tris(3-hydroxy-6-methyl-2-pyridylmethyl)-1,4,7-triazacyclononane)



13 TACN-TM (N,N',N''-tris(mercaptoethyl)-1,4,7-triazacyclononane)

Figure 2

Table 8 Stability Constants and pM Values of Fe(III) Complexes Formed by Ligands Having High Ferric Ion Affinity

	Log K_{ML}[a]	*pM*[b]
TACN-MeHP, **12**	50.0	39.3
TACN-Me2HB, **11**	51.3	32.3
Enterobactin, **14**	~49	34.7
MECAM, **15**	46	29.1

[a]K_{ML} = [ML]/[M][L], μ = 0.10 M (KNO_3), 25.0°C. [b]pM = -log [M] at pH 7.4, 100% excess ligand

derivatives of NOTA are somewhat lower than those of Fe(III) but are still very high. Therefore these ligands may be considered quite effective for the Ga(III) ion. On the other hand, the stability constants of these ligands with the In(III) ion are very much lower, about ten or more orders of magnitude, showing that the hydroxypyridyl or hydroxyphenyl donor group is not effective for the larger In(III) ion.

The stability constant of the Fe(III) complex formed with the ligand TACN-TM, **13**, having mercaptoethyl donor groups, is not listed because its measurement is prevented by a redox reaction that occurs between the ferric ion and the ligand. However, this redox reaction does not take place with the Ga(III) and In(III) ions and here it is found that the stability constant of the In(III) complex is quite a bit greater than that of the Ga(III) complex. Therefore, the larger mercapto donor group seems to be more suited to the larger (and softer) In(III) ion. Thus, it seems that to achieve high stability of In(III) complexes, it is desirable to have thiolate donor groups substituted on the ligand.

The stability constants and pM values of four ligands which are recognized as having high affinity for the ferric ion are listed in Table 8. It is seen that because of differences in hydrogen ion competition at physiological pH (7.4) the hydroxypyridyl derivative, **12**, is more effective in complexing the ferric ion than is enterobactin, **14**, even though the stability constants are estimated as fairly close. The differences in pK's result in greater hydrogen ion competition in the case of enterobactin at physiological pH and at other lower pH values.[12,13] It is also seen that the hydroxypyridyl derivative is more effective than the hydroxybenzyl derivative and this is also due to differences in hydrogen ion competition reflected in the pK values of the ligand. MECAM, **15**, is a model ligand which resembles the siderophore enterobactin in having three pendant catechol groups. It is seen that, primarily because of hydrogen ion competition, it is somewhat less effective for complexing the ferric ion.[13]

Table 9 Comparison of Stability Constants and pM Values of Trivalent Metal Ion Complexes of Ligands Having Thiolate Donor Groups

	Log K^a (pM)[b]	
	Ga^{3+}	*In^{3+}*
TACN-TM, **13**	34.2(23.6)	36.1(23.9)
EDDA-SS, **16**	35.6(29.0)	37.0(30.4)
EC, **17**	31.5(24.7)	33.0(26.2)

[a]K_{ML} = [ML]/[M][L], μ = 0.100 M (KNO_3), t = 25.0°C. [b]pM = -log [M] at pH 7.4 with 100% excess ligand.

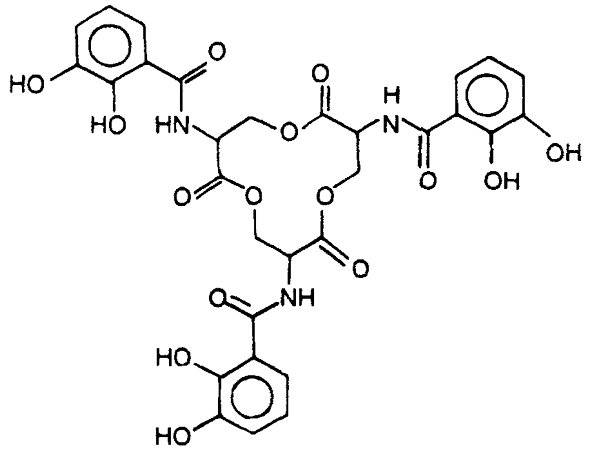
The stability constants for Ga(III) and In(III) of three ligands TACN-TM, **13**,[14] EDDA-SS (N,N'-di(mercaptoethyl)ethylenediamine-N,N'-diacetic acid), **16**,[15] and EC (ethylenebis-(L-cysteine), **17**,[16] having thiolate groups are listed in Table 9, along with the corresponding pM values at physiological pH. It is seen that all the stability constants listed are rather high for both Ga(III) and In(III) and that the In(III) complexes are a little more stable than those of Ga(III). These three ligands, therefore, are considered to be effective complexing agents for both Ga(III) and In(III) ions and the In(III) complexes are probably the more remarkable in that the hydroxypyridyl and hydroxybenzyl containing ligands do not have high affinity for In(III) whereas they do for Ga(III).

Other Variations of Triazacyclononane Ligands with Pendant Donor Groups

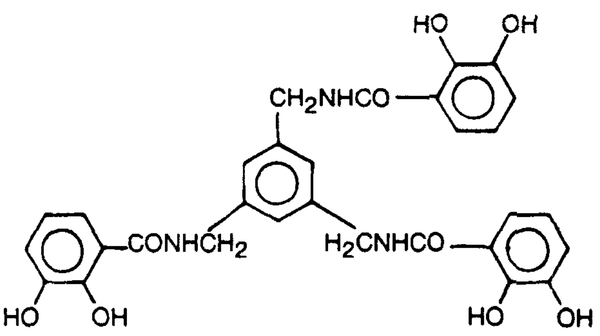
A triazacyclononane derivative with only one pendant acetate donor group, 1,4,7-triazacyclononane-1-acetic acid, and the stability constants of its complexes with various divalent metal ions were reported by Cai and Kaden.[17] The stability constants of complexes formed with this ligand are for the most part considerably lower than the corresponding complexes of NOTA, as expected, in view of the fact that the ligand has only one acetate donor group. The copper(II) complex is only a little less stable, $10^{19.0}$ *vs* $10^{19.8}$, which is reasonable in view of the lower coordination number of copper(II).

The macrocyclic ring of NOTA was expanded by three carbon atoms to form the ligand 1,5,9-triazacyclododecane-N,N',N"-triacetic acid, and the stability constants of some of its divalent metal ion complexes were reported by Sherry and coworkers.[18] Although expansion of the macrocyclic ring increased the basicities of the amino nitrogens (due to lower coulombic repulsion), the stability constants reported were a little lower than those of NOTA. Apparently the greater flexibility and lower preorganization of the larger ring more than counterbalanced the effect of increased basicity.

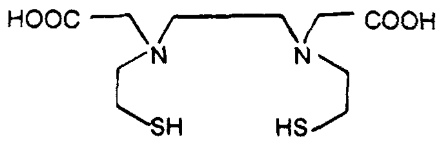
The attachment of a 2-hydroxyphenyl group as a pendant donor group to the 2-carbon atoms of the



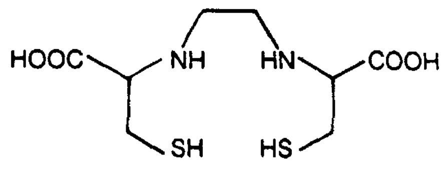
14 Enterobactin



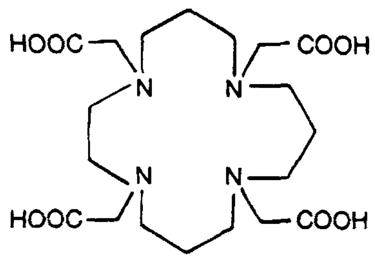
15 MECAM



16 EDDA-SS (N,N′-bis(mercaptoethyl)-ethylenediamine-N,N′-diacetic acid)



17 EC (ethylenebis-(L-cysteine))

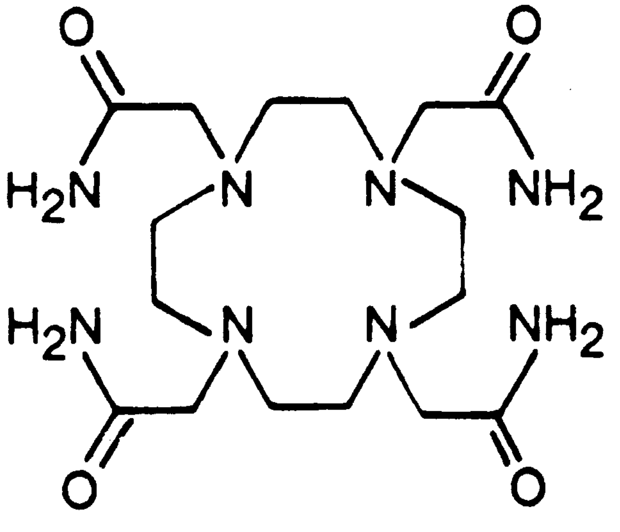


18 PENTA 1,4,8,12-tetraazacyclopentadecane-N,N′,N′′,N′′′-tetraacetic acid

Figure 3

1,5,9-triazacyclododecane has been described by Kimura et al.[19] The stability constants of the complexes were found to be 3-4 log units higher than those of the parent macrocycle for the transition metal ions, except for Cu(II), which showed an increase in stability of over six log units. It is noted that the addition of three acetate groups (in NOTA) increases the stability constants of the transition metal complexes by 7-9 log units.

Other Tetraazamacrocycles with Pendant Groups Tweedle and coworkers[20] investigated Gd(III) and other lanthanide complexes of a seven coordinate ligand, 1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid, and of an eight coordinate ligand (in which the eighth coordinating group is a relatively weak donor) 10-(2-hydroxypropyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid. The purpose was to prepare neutral Gd(III)



19 DOTAM 1,4,7,10-tetrakis(carbamoylmethyl)-1,4,7,10-tetra-azacyclododecane

Figure 4

complexes with a vacant coordination site (probably occupied by a water molecule, or a weakly coordinated group, the 2-hydroxypropyl donor) to promote exchange with the solvent, thus extending the paramagnetism of the metal ion throughout the solvent system. The omission of a pendant acetate donor resulted in the formation of a Gd(III) complex with a surprisingly high stability constant ($10^{21.0}$) which is three log units lower than that of the Gd(III)-DOTA complex, $10^{24.0}$. Replacement of an acetate donor of DOTA by a 2-hydroxypropyl group gave a stability constant of the Gd(III) complex of $10^{23.8}$, only slightly lower than that of the DOTA complex.

Kimura and coworkers[22,23] prepared a number of interesting tetraazamacrocycles in which a single donor group was appended to a carbon atom of the macrocyclic ring. These pendant donors included 2-hydroxyphenyl, substituted 2-hydroxyphenyl, and *o*-hydroxypyridyl donors. The pK's of these ligands were measured potentiometrically and were reported. The stability constants of the Cu(II) complex of cyclam with a pendant *o*-phenolic group was measured polarographically, and seems a little high (1.0×10^{32}) compared to the stability constant of the parent macrocycle ($10^{27.2}$). With the same technique, they found the stability enhancement due to the pendant phenolic group to be about 10^2, which seems quite reasonable. Similar work was carried on a cyclam derivative containing an *o*-hydroxypyridyl pendant group, but no metal ion binding constants were reported. Very interesting, however, is the finding that the nitrogen of the pendant pyridyl group plays an important kinetic role in enhancing the rates of interaction of metal ions with the macrocycle.

The stability constants have been reported[24,25] for the complexes formed by the complexation of some divalent metal ions with the tetraazamacrocycle 1,4,8,12-tetraazacyclopentadecane-N,N',N'',N'''-tetraacetic acid. The stability constants of the Co(II), Ni(II), Cu(II) and Zn(II) complexes of this 15-membered macrocycle with four pendant acetate groups, **18**, essentially represents an extension of the data in Table 5. The stability constants and (pM) values reported (Co^{2+}, $10^{15.93}$ (10.0); Ni^{2+}, $10^{17.19}$ (11.3); Cu^{2+}, $10^{19.85}$ (13.9); and Zn^{2+}, $10^{16.04}$ (10.1) are somewhat lower than the values that would have been predicted from the trends observed in the data listed for the metal complexes in Table 5. These data therefore indicate that as the size of the macrocyclic ring further increases, the stability constants might drop considerably, because of greater flexibility of the macrocyclic ring and consequent poorer preorganization of the ligand.

A recent development is the report by Carlton et al.[25] and by Hancock[26] that attaching four neutral acetamide donor groups to cyclen to give an octadentate ligand, 1,4,7,10-tetrakis(carbamoylmethyl)-1,4,7,10-tetraazacyclododecane, DOTAM, **19**, greatly increases the affinity of the ligand for large metal ions relative to the parent macrocycle. Other weak neutral donors (such as hydroxyethyl groups) increase stability very little when substituted in cyclen as additional pendant donors. The amide group, however, greatly increases the affinity of the ligand for Pb(II) and Cd(II), while apparently having little effect on small metal ions. Thus the log stability constant of Cu(II) complexes decreases from 23.3 to 16.4 on substitution of four acetamido groups, and the log stability constant of the Zn(II) complex decreases from 16.2 to 10.5. This decrease is probably due to steric effects of the substituents, and the fact that these metal ions have relatively low coordination numbers. The log stability constants of the Pb(II) and Cd(II) complexes, however, increase from 14.3 and 15.9, respectively, to very high values (>21) which are too high to be measured potentiometrically. The fact that the Pb(II) and Cd(II) stability constants are over ten orders of magnitude more stable than the Zn(II) complex indicates that pendant neutral amide donor groups may be effective in binding and removing toxic metal ions such as Cd(II) and Pb(II), while not affecting essential metal ions, such as Zn(II).

General Conclusions

In the stability data illustrated above, some general trends are discernable. Several examples show that small metal ions preferentially form complexes with six membered chelate rings and large metal ions prefer five membered rings. Increasing the basicity of a pendant donor group generally increases the stability constants of the metal chelates formed, but may not increase the degree of metal ion binding in solution (measured by pM) because of increased competition with hydrogen ion. Also, decreasing the hardness of the pendant donor group may increase the affinity of the ligand for softer (and larger) metal ions. The macrocyclic ring itself helps to achieve high stabilities through preorganization, high donor basicity, and other aspects of the macrocyclic effect. However, increasing the size of the macrocyclic ring results in a general decrease in stability, because what is gained in donor basicity is more than overbalanced by lower preorganization (due to greater ring flexibility) and the associated steric effects.

The greatest effect on stability is observed when the macrocyclic ring and pendant donor groups work together to closely match the coordination requirements of the metal ion. Thus the exceptionally high stability of the Fe(III) complex of N,N',N"-tris(3-hydroxy-6-methyl-2-pyridylmethyl)-1,4,7-triazanonane is due to an almost perfect octahedral arrangement of the ligand donor groups around the metal ion at angles and distances that its coordination require, and the formation of six chelate rings in the process.

In the case of the high stability of the Ca(II) DOTA complex, the ligand provides eight donor groups arranged favorably for complexing the Ca(II) ion. The metal ion is thus more completely coordinated by DOTA than by ligands that provide fewer donor groups. Also, the macrocyclic ring helps the ligand achieve a high degree of preorganization.

It should also be pointed out that the substitution of certain neutral pendant donor groups, such as acetamido groups, can greatly increase the stabilities of complexes formed with large metal ions while leaving smaller metal ion relatively unaffected. Thus the stability constants of the Cd(II) and Pb(II) complexes of DOTAM are over ten orders of magnitude higher than that of Zn(II). This indicates that amide groups can be used in the design of highly selective ligands for the binding of toxic metal ions.

ACKNOWLEDGEMENT

This work was supported by a research grant, A-259, from The Robert A. Welch Foundation.

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