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CHELATING AGENTS FOR METAL BUFFERING AND ANALYSIS IN SOLUTION

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Abstract - The design of chelating ligands that are effective as metal buffers in aqueous solution and are useful in analysis of metal ions requires both high stability and selectivity in their reactions with the metal ions of interest. In addition, highly stable and selective metal buffer systems have important applications in metal cleaning, control of metal-catalyzed degradation and oxidation of foods and other organic compounds, trace metal plant nutrition, and the removal of toxic metals from physiological systems.

High stability in a metal chelate may be achieved by designing the multidentate ligand so that it will have a sufficient number of donor groups to fully satisfy the coordination requirements of the metal ion, by employing a favorable steric orientation of these donor groups to fit the geometric requirements of the metal ion, and by selection of the types of donor groups that have high intrinsic affinities for the metal ion under consideration. The chelate effect, and the a- or b-character requirements of donor and acceptor atoms provide useful guidelines for the design of chelating ligands. Important factors in the formation of highly stable metal chelates in solution are described.

Selectivity in a chelating agent is measured quantitatively by the use of the appropriate stability constants of the metal ions under consideration, together with the equilibrium constants for metal ion hydrolysis and ligand donor group protonation. Examples are also given of the use of qualitative observations on the effectiveness of certain donor groups in cases where stability constant data are not available. Consideration is given to a "treshold" reaction in which a metal ion induces a specific proton dissociation reaction in the ligand, thus increasing selectivity of metal-ligand interaction by many orders of magnitude.

Examples are given of synthetic and natural chelating agents that are effective for the buffering or sequestering of troublesome metal ions, such as Fe(III), the lanthanides, and tetrapositive metal ions. Among the functional groups employed to achieve high affinity and selectivity for higher valent metal ions are phenolate, hydroxamate, amide, catecholate, and phosphonate groups. Suggestions for the development of new and more effective ligands are given.

INTRODUCTION

Scope

Multidentate ligands that have potential applications as metal buffers through the formation of highly stable and soluble metal chelates in aqueous solution may have either an open arrangement of donor groups, as in EDTA, or may have its donor groups enclosed in a macrocyclic ring system, as in the porphyrins, crown ethers, their nitrogen analogs, and the cryptates. This paper is intended to review the progress that has been made with the open structures, and to evaluate the possibilities for the further development of new ligands of this type to achieve greater effectiveness in metal binding and selectivity. Many of the non-cyclic multidentate ligands have been constructed on a polyamine framework and may be considered to be derived from the "complexones" that were first investigated by Schwarzenbach and coworkers. Elaboration of these ligand types by the introduction of special donor groups to achieve higher stability with certain metal ions has been carried out by this investigator and his coworkers over the past twenty years. Since recent studies have indicated the possibilities of developing new, potentially useful ligands, further development of this research area over the next several years may be expected.

Applications

The formation of highly stable and soluble metal chelates in aqueous solution has important applications in analytical chemistry, and in many other fields. In order that a ligand be useful in the titrimetric analysis of a metal ion, the metal complex (chelate) formed should

not be appreciably dissociated in very dilute solution. As is shown below, this requires 1:1 stoichiometry between metal ion and ligand, and achievement of maximum stability by use of a multidentate ligand having the appropriate number and type of donor groups. Chelating ligands having high metal ion affinity and selectivity may be used in metal separations by supressing hydrolytic precipitation or other reactions of certain metal ions while other metals less effectively bound are removed by ion exchange, precipitation, or extraction.

The properties that make chelating agents useful in analytical chemistry also render them potentially effective for various commercial and medicinal applications. Thus resistance to hydrolytic precipitation and to adsorption by mineral ion exchangers makes possible their use in natural and artificial soils, and in nutrient solutions, for the transport of essential metal ions to growing plants. Today large quantities of chelating agents are used for this purpose. Multidentate ligands are also used extensively to condition industrial water, and to remove metal scale from metal equipment such as steam boilers. High stabilities of the chelates are generally needed because of the extreme insolubility of such metal deposits. For other industrial equipment, as in nuclear reactors, chelating agents may be used to prevent the formation of radioactive metal deposits in inaccessible places.

Chelating agents have several current uses, and many potential applications, for the removal of toxic metals from the body. The use of EDTA for the treatment of lead poisoning is now routine and well known. Highly specific chelating agents for iron(III) are now being developed, with NIH support, in several U.S. laboratories. The study of the use of chelating agents for the removal of radioactive metals (including fission products, and the actinides) from the body has been sponsored by the AEC (now ERDA) and many experiments in man, as well as with experimental animals, have been described.

LIGAND DESIGN

Requirement of largest possible number of donor groups per ligand

The need for the maximum number of chelate rings in chelating agents useful in titrimetric analysis is illustrated in Fig. 1 (Ref. 1). Titration of Zn(II) ion by various polyamines

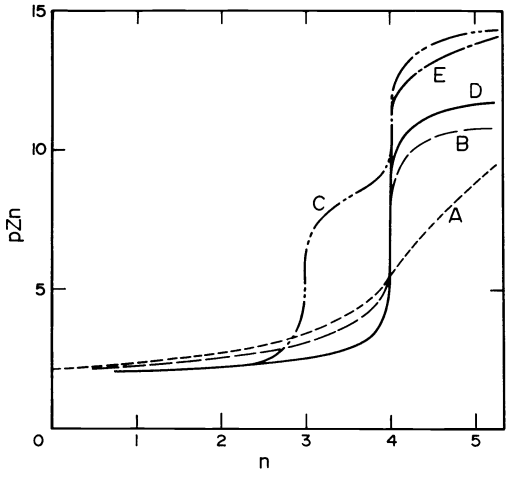


Fig. 1. Complexometric titration of Zn(II) with ammonia and polyamines. A, ammonia; B, En; C, Dien; D, Trien; E, Tren. n = moles of ammonia or amino groups added per mole of metal ion.

and ammonia is seen to produce the sharpest break in pM (and also in other solution properties such as pH and redox poential) when the ligand contains four or more donor groups, even though all systems illustrated contain four or more basic nitrogen atoms coordinated to the metal ion at the end point. Thus it is seen that the chelate effect is necessary to achieve minimum degree of dissociation of the complex in very dilute solution.

For metal ions of coordination number six, the following two reactions involving monodentate and sexadentate ligands may be compared:

$$M + 6A \rightleftharpoons MA_6 \qquad \beta_{MA_6} = [MA_6]/[M][A]^6$$

$$M + L \rightleftharpoons ML \qquad K_{ML} = [ML]/[M][L]$$

For the complex MA_6 the units of β_6 are M^{-6} and the degree of formation of the complex, as

measured by $[MA_6]/[M]$ decreases in dilute solution and is proportional to the sixth power of the free ligand concentration. The degree of formation of the chelate ML of the multidentate ligand, on the other hand, is much less sensitive to concentration, and decreases linearly with the first power of the free ligand concentration.

The fact that chelating agents can accomplish this objective more effectively, with increasing numbers of chelate rings producing the best results, is clearly the result of the relative values of the entropy of dilution of the complexes and chelates relative to the entropies of the dissociated species with which they are in equilibrium. The experimental fact that metal chelates are much less dissociated in dilute solution is illustrated in Table 1 (Ref. 2), which compares degrees of dissociation of complexes containing 2 and 3

Table 1. Degrees of dissociation of complexes and chelates in dilute solution

No. of chelate rings	Formation Constants	Value	1.0 M Complexes		1.0×10^{-3} M Complexes	
			Free [M]	% Dissociation	Free [M]	% Dissociation
0	$\frac{[MA_4]}{[M][A]^4}$	10^{18}	1×10^{-5}	1×10^{-3}	1×10^{-4}	10
2	$\frac{[MB_2]}{[M][B]^2}$	10^{22}	3×10^{-8}	3×10^{-8}	5×10^{-9}	5×10^{-4}
3	$\frac{[ML]}{[M][L]}$	10^{24}	1×10^{-12}	10^{-10}	3×10^{-14}	3×10^{-9}

chelate rings with those containing no chelate rings. A chelate effect of 10^2 per chelate ring is assumed as the basis for the arbitrary stability constants listed. The superior properties of the metal chelate in dilute solution are dramatically illustrated by a simple calculation of the degrees of dissociation in 1.0 molar and 1.0×10^{-3} molar solutions.

It has been pointed out by Adamson (3) that the entropy-related chelate effect, as manifested in the stability constants, disappears when unit mole fraction replaces unit molality as the standard state for solutes in aqueous systems. On this basis the stability constants assumed for the model compounds in Table 1 would have to be equivalent in magnitude regardless of the number of chelate rings formed. On the other hand, the relative degrees of dissociation of the model compounds in Table 1 remains an experimental fact, with the larger concentration unit giving smaller numerical concentrations for the solutions illustrated thus compensating for the disappearance of the chelate effect in the numerical values of the stability constants.

Other factors controlling stabilities of complexes

Table 2 indicates that there are many factors in addition to the entropy-derived chelate effect that must be taken into account in designing ligands with maximum stability and

Table 2. Factors influencing solution stabilities of complexes

Enthalpy effects	Entropy effects
Variation of bond strength with electronegativities of metal ions and ligand donor atoms.	Number of chelate rings
	Size of the chelate ring
Ligand field effects	Arrangement of chelate rings
Enthalphy effects related to the conformation of the uncoordinated ligand	Changes of solvation on complex formation
Steric and electrostatic repulsions between ligand donor groups in the complex	Entropy variations in uncoordinated ligands
Other coulombic forces involved in chelate ring formation	Effects resulting from differences in configurational entropies of the free ligand and the ligand in complex compounds

selectivity. Mutual coulombic repulsions between donor groups in the metal chelate are important, and the extent to which these repulsions are partially overcome in the free chelating ligand relative to analogous unidentate ligands is a manifestation of the enthalpy-based chelate effect. This property, which greatly increases stability constants, is developed

to an even higher degree in macrocyclic and cryptate ligands that hold the donor groups at geometric positions relatively close to the positions that they would assume in the chelate. Thus stability and specificity would be increased in all types of multidentate ligands by synthesizing structures in which the freedom of the donor groups to move away from each other is decreased as much as possible. One of the obvious ways to achieve this objective is to synthesize organic ligands having rigid molecular frameworks, as may be achieved by use of unsaturated linkages and aromatic rings in the bridging groups of the ligands. Increase in rigidity of the ligand would also minimize or remove completely the unfavorable entropy effects related to the decrease of vibrational and rotational freedom of ligand atoms that generally occurs in metal ion coordination.

It is obvious that many of the factors listed in Table 2 (e.g., number of rings, chelate ring shape) are not sensitive to properties of the metal ion and therefore will not provide differences in metal-ligand interaction. Selectivity in metal complex formation, as measured by differences in stability constants, requires the use of factors that are very sensitive to the nature of the metal ion. The most effective way to achieve selectivity in chelate formation with multidentate ligands is to change the nature of the donor group in such a way as to change the degree of covalency of the metal ligand bonds formed. Thus the matching of a and b character of the metal ion and ligand donor atoms would take advantage of differences in electronegativity and polarizability of the metal ions under consideration. Those factors that are sensitive to only size of the metal ion (e.g., size of the chelate rings) would probably be less effective in achieving selectivity for open-structured ligands, but may be much more effective for macrocyclic anc cryptate ligands. For metal ions differing in ionic charge and/or coordination number there is no difficulty in achieving high degrees of selectivity, even with relatively simple chelating ligands.

The application of the principles described above to the design of chelating agents, and the results obtained, will be illustrated below with related series of chelating ligands. The strength and selectivity of metal binding will be measured in so far as possible by the corresponding formation constants of the chelates. In many cases, when quantitative data are not available, qualitative observations will be employed as an indication of the effectiveness of the ligands under consideration.

Donor groups

Examples of donor groups that may be built into chelating ligands are illustrated in Plate 1. This is only a partial listing of the more common donor groups, and many more are possible. For the donor groups involving oxygen atoms, for example, analogous groups containing sulfur atoms are of course possible. In addition to the monodentate groups a number of coordinate bond-coupled, resonance linked bidentate donor groups are also listed. These groups are of interest because a sufficient number of ligands containing them have been investigated to demonstrate their relatively high affinity for certain types of metal ions that would otherwise be relatively difficult to "sequester" in aqueous solution. The bidentate ligands are of interest because they have remarkably high affinity for "troublesome" metal ion such as the ferric ion, other tripositive metal ions, and the tetravalent forms of the actinide metals. Strong metal bonding to these ligands requires symmetric orientation of the bidentate pair to the metal ions. In many multidentate ligands such binding presents steric requirements that are frequently difficult to meet, as discussed below.

In addition to well known combinations of amino and carboxylate groups, special attention will be given to phosphonate, phenolate, hydroxamate, catecholate and peptide donors.

POLYAMINOPOLYCARBOXYLATES

Table 3 presents representative data that are currently available (Ref. 4) on the stabilities of metal chelates of a series of ligands that constitute a linear extension of the NTA and EDTA structures. If one assumes that all of the amino and carboxylate donor groups become coordinated to the metal ion, the complexes formed would contain n-1 five membered chelate rings, where n is the total number of nitrogen and oxygen donors (one oxygen per carboxylate group). This seems to be a reasonable assumption for many metal ions, provided that the coordination number of the metal ion is not exceeded.

The data in Table 3 show that for divalent metal ions continued increase in the number of donor atoms does not result in a continued increase in stability constant. In fact a decrease finally sets in with the maximum value achieved with DTPA for Ca^{2+}, and with TTHA for Cu^{2+}. For metal ions of higher charge the maximum stabilities are not discernable from the data available, but probably occur with TPHA, or the next member of the series, TPOA (not shown). In retrospect, this kind of behavior is understandable in view of the fact that basic metal ions such as Ca^{2+}, La^{3+}, and Th^{4+} depend strongly on the formation of an ionic "cage" for effective chelation in aqueous solution. For moderate to low coordination number ($\sim$6-8) this objective is best achieved in the range EDTA and DTPA. For TTHA some of the carboxylates will not be coordinated, with perhaps an unbound pair at one end of the ligand. On that basis TTHA would present only four negative charges to the calcium ion, whereas DTPA would provide five. Similar effects may be expected for higher members of this series of

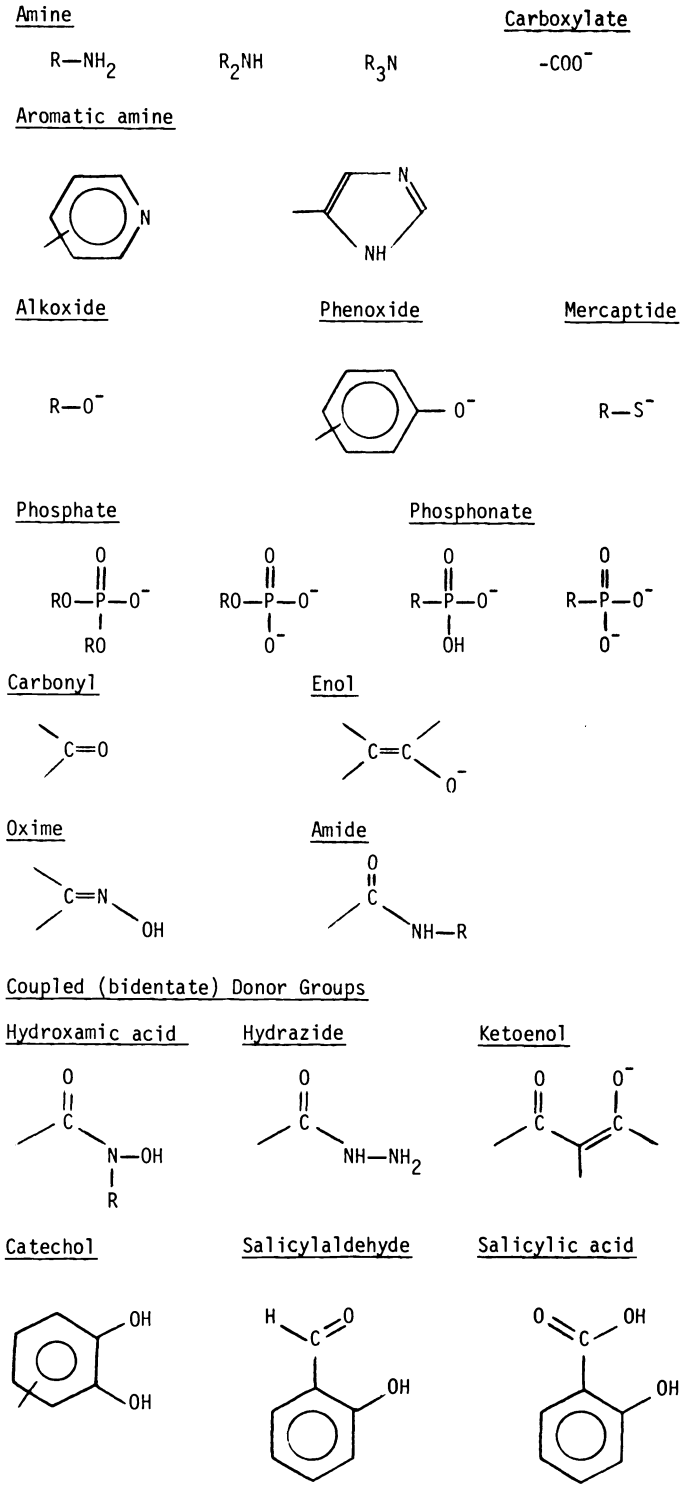
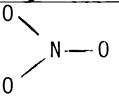
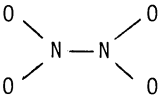
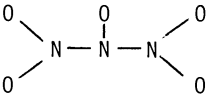
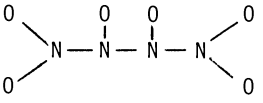
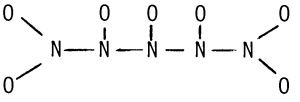


Plate 1. Types of donor groups

ligands in combination with basic metal ions of higher charge and coordination number, such as the tripositive lanthanides and the tetrapositive actinides.

Quantitative studies of the higher members of the series of compounds listed in Table 3 have been hampered by the unavailability of pure samples of the ligands. TTHA has recently become

Table 3. Structural analogs of NTA and EDTA (t = 25°C; μ = 0.10)

Ligand	Log formation constants of 1:1 chelates Ca^{2+}	Cu^{2+}	La^{3+}	Th^{4+}
NTA 	6.57	12.96	10.47	12.4
EDTA 	10.4	18.7	15.2	23.2
DTPA 	10.7	21.1	19.5	28.78
TTHA 	9.9	20.3	23.1	31.9
TPHA 	∿9.0	∿20	>27	≫27

available in pure form and may be purchased from specialty chemical companies (e.g., Dojindo, Kumamoto, Japan). Recently the author and his coworkers have obtained pure experimental samples of TPHA and PHOA, so that more quantitative equilibrium data on these ligands may be expected in the near future.

VARIATION OF FUNCTIONAL GROUPS OF AMINOPOLYCARBOXYLATE LIGANDS

In the design and synthesis of new chelating ligands, the method most frequently employed is the replacement of aminocarboxylate ligands, such as those listed in Table 3, by one or more coordinating groups having special coordinating properties. In many cases greater specificity and stability have been achieved by the introduction of functional groups recognized as having high affinity and specificity for certain metal ions. Significant examples of such structural variations are given below.

Aliphatic hydroxyl

Perhaps the first extensive variation of the aminocarboxylate structure was introduced industrially by the Versenes Company to provide sequestering agents that would have higher affinity for Fe^{3+} than do NTA and EDTA, thus increasing their effectiveness in alkaline aqueous solutions. Five examples of these substances, in which acetate groups are replaced by hydroxyalkyl functions are illustrated in Plate 2. The series HIMDA, DHG, and TEA, derived

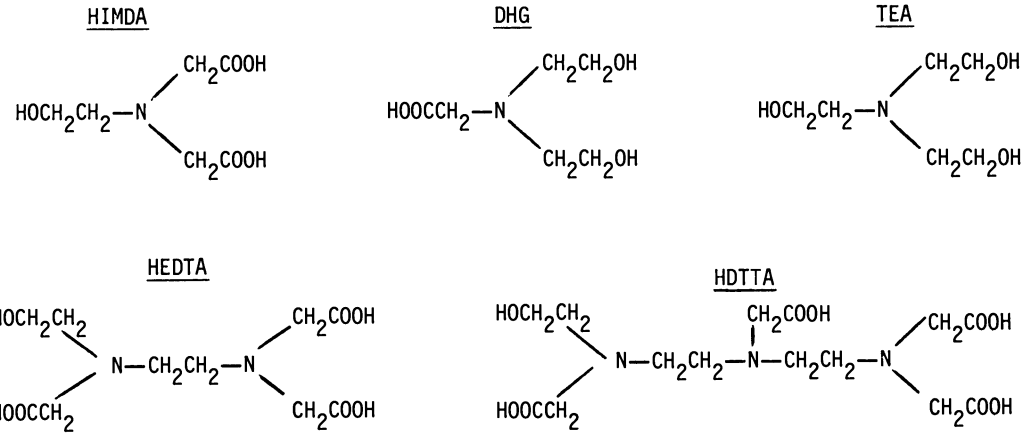


Plate 2. Hydroxyethyl derivatives of NTA and EDTA

from NTA, provides ligands that show increasing ability to sequester Fe^{3+} in alkaline solution. As the number of hydroxyethyl groups increases, the resistance of the Fe(III) complex to disproportionation via ferric hydroxide precipitation extends increasingly into the alkaline region. In the case of the highest member of the series, triethanolamine, soluble, colorless Fe(III) chelates are formed at pH 14 and above, and even in solid alkali hydroxides. Experimental work by this investigator has demonstrated that above pH 13, increasing $[OH^-]$ increases the effectiveness of triethanolamine in the formation of stable complexes having the general formula $Fe_a(OH)_b(H_{-n}L)_c^{3a-b-nc}$, whereby b and the ratio a/c become much greater than unity at very high pH (Ref. 5). While members of this series of compounds become more effective for Fe^{3+} as the pH increases, they become increasingly less effective at low pH, so that mixtures of these ligands are employed in industry to achieve effectiveness of Fe(III) complexing over a broad pH range. Frequently industrial sequestering agent preparations are composed of mixtures of these ligands with EDTA.

The replacement of one acetate function of EDTA by a hydroxyethyl group, to give HEDTA, also results in the formation of a compound which extends the useful Fe(III)-sequestering range of EDTA to higher pH (the EDTA-Fe(III) chelate system decomposes to precipitate $Fe(OH)_3$ around pH 8, depending on conditions and the concentration of excess EDTA). Since similar variation of the NTA structure provides "Fe(III)-specific" complexing agents through dissociation of the hydroxyl group to negative alkoxide donors, it was first thought that HEDTA functions in a similar way, by the formation of chelates such as $FeH_{-1}L^-$ (where H_3L represents HEDTA). While such is certainly the case for Th^{4+}, which forms a unique polynuclear complex with HEDTA (Ref. 6) evidence has been presented (Ref. 7) to show that the hydroxyethyl group remains intact in Fe(III) complexes, even at pH values high enough to produce hydroxo complexes and the corresponding μ-oxo dimer. This conclusion is further supported by the crystal structure of Fe(III)-HEDTA μ-oxo dimer (Ref. 8). If one accepts for aqueous solution structures similar to those found in the solid state in which the hydroxyethyl group is not coordinated, one is still left with the problem of explaining the experimental fact that HEDTA-Fe(III) complexes are more stable than those of EDTA with respect to $Fe(OH)_3$ precipitation, even though the stability constant of the normal chelate (FeL^- for EDTA and FeL for HEDTA) is much greater in magnitude for EDTA. Under these circumstances, and in view of the x-ray data, the only reasonable explanation lies in the greater stabilities of the hydrolytic forms of the iron(III)-HEDTA chelate, for which equilibrium data are available, and which are illustrated schematically in Plate 3. Apparently the species $FeLOH^-$ and $FeL(OH)_2^{2-}$ are relatively resistant to disproportionation to ferric hydroxide, and the hydroxyethyl group must somehow be involved (e.g., through solvation) in the achievement of this effect.

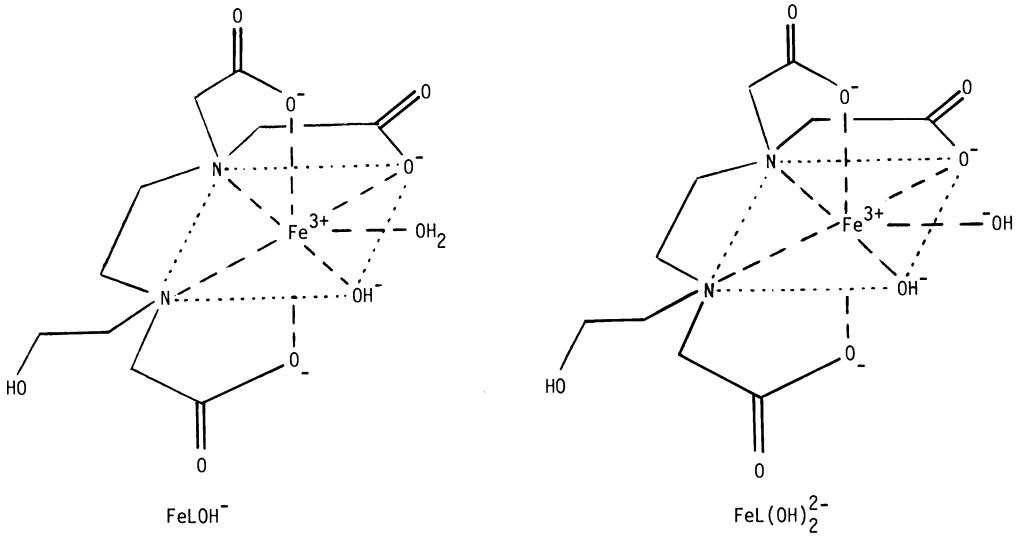


Plate 3. Hydrolyzed forms of HEDTA-Iron(III) chelate

In view of the unique interaction (Ref. 6) of HEDTA with Th^{4+}, it appears that HEDTA and similar ligands offer potentially highly specific reagents for the sequestration of tetravalent metal ions, such as the actinides, in aqueous solution. In this respect multidentate

ligands such as HDTTA, and similar ligands with larger numbers of coordinating groups and hydroxyethyl groups, are especially promising.

Aminophosphonic acids

Although there is considerable interest in amino and polyaminophosphonic acids as chelating ligands, progress in this field is hampered by the lack of reliable equilibrium data on their proton and metal ion affinities (Ref. 9). All three analogs of NTA and EDTA indicated in Plate 4 are available commercially (e.g., from Monsanto Chemical Company) in the form of their sodium salts. Preparation of pure reagent grade samples for experimental studies has presented problems. Very little data on NTP are available, as is seen in Ref. 9. In the

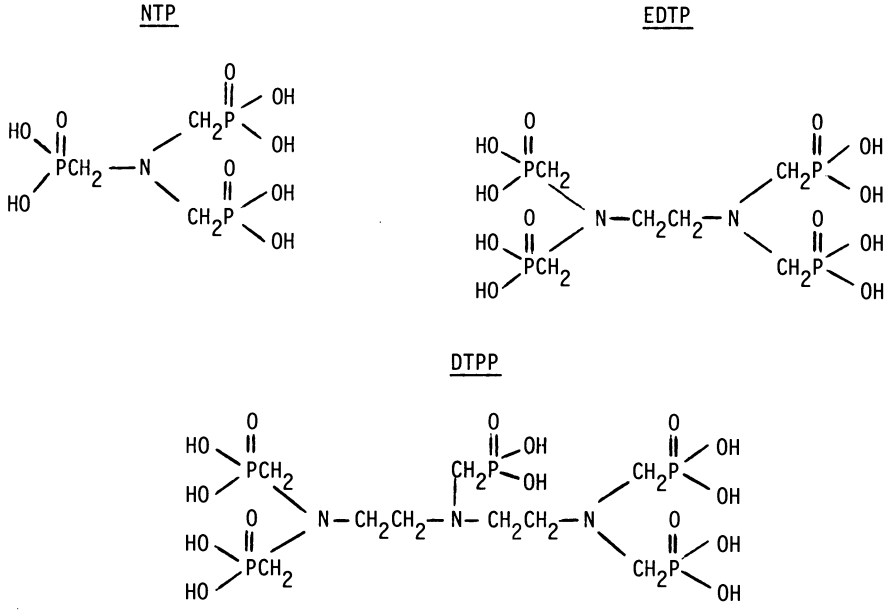


Plate 4. Phosphonate analogs of NTA and EDTA (t = 25°C; μ = 0.100 M)

Table 4. Comparison of chelating tendencies of EDTA and EDTP

Log protonation constants, K_n^H			Log stability constants, K_{ML}			
n	EDTA	EDTP	M^{n+}	EDTA	EDTP	Δ
1	10.17	12.99	Cu^{2+}	18.70	23.21	5.51
2	6.11	9.78	Ni^{2+}	18.52	16.38	-2.14
3	2.68	7.94	Co^{2+}	16.26	17.11	0.85
4	2.0	5.88	Zn^{2+}	16.44	18.76	2.32
5		4.77	Ca^{2+}	10.61	9.36	-1.25
6		2.82	Mg^{2+}	8.83	8.43	-0.40
7		1.24	Fe^{3+}	25.0	>>25	(large)
8		~1.0				

case of the EDTA analog, EDTP, earlier work by several investigators on what proved to be relatively impure samples has finally been followed up by the synthesis of pure material by a special method, and by the determination of reliable pK's and formation constants (Ref.10). Although the next higher analog is available as a commercial grade sodium salt, a sufficiently pure sample for quantitative measurements of solution equilibria apparently has not yet been prepared.

The equilibrium data now available on EDTP are compared with those of EDTA in Table 4. It is interesting to note that with basic metal ions of relatively low coordination number such as Mg^{2+} and Ca^{2+}, the stability constants of the EDTP chelates are lower than those of EDTA. This effect is probably due to the need to invoke all four negative donor groups of the

ligands for effective binding of these ions, resulting in much higher mutual repulsions between the binegative phosphate groups. In the case of Ni^{2+}, with coordination number 6, a similar effect seems to occur. The reason for the observed increase of stabilities of the Zn(II) and Co(II) is not obvious, but there is the possibility that 4- and 5-coordinate complexes are reasonably stable for these metal ions. In the case of Cu^{2+}, with only four strong coordination sites, it is seen that the EDTP chelate is clearly the more stable, in accordance with the fact that only two phosphonate oxygens need to be positioned close to the metal ion. The increase in stability in this case is considerable, and may be due in part at least, to the inductive (electron-release) effects of the negative phosphonate groups on the coordinated nitrogen atoms.

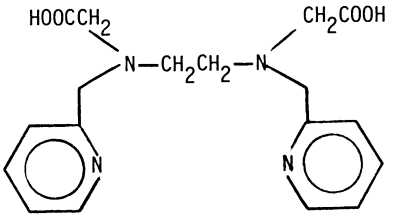
Although it has not yet been reported, the stability constant of the Fe(III) chelate must be very large, and much larger than that of EDTA, since it is stable to $Fe(OH)_3$ precipitation in alkaline solution. This suggests more extensive investigation of phosphonate-containing polydentate ligands for effective coordination of tri- and tetravalent metal ions.

Pyridine analogs

The stability constants of a ligand in which two carboxyl groups of EDTA are replaced by α-pyridyl groups (Ref. 11), indicated in Table 5, show considerable drop in the stabilities of

Table 5. Pyridine analogs of EDTA

Ethylenebis-N,N'-(2-aminomethyl)pyridine-N,N'-diacetic acid (EDAMPDA)



	log K_{ML}			log K_{eff} at pH 4.5		
	EDTA	EDAMPDA	Δ	EDTA	EDAMPA	Δ
Cu^{2+}	18.7	20.4	1.7	11.4	14.9	3.5
Ni^{2+}	18.5	16.6	-1.9	11.2	11.1	-0.1
Co^{2+}	16.3	14.0	-2.3	9.0	8.5	-0.5
Zn^{2+}	16.4	15.2	-1.2	9.1	9.7	0.6
Ca^{2+}	10.6	7.9	-2.7	3.3	2.4	-0.9

$$\log K_{eff}^{4.5} = \log K_{ML} - \log K_1^H - \log K_2^H - 2 \log [H^+]$$

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

chelates of the divalent transition metal ions as well as of the alkaline earth ions, except for copper(II). In the latter case the availability of four nitrogen donors for the four-coordination requirement of the metal ion represents an improvement over the two nitrogens and two acetate oxygens provided by EDTA. While the absolute values of the stability constants are not very high, considerable selectivity in Cu(II) binding over the other transition metal ions listed has been achieved.

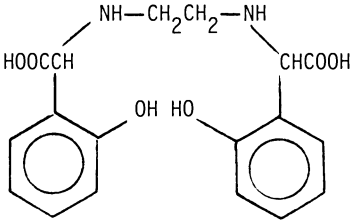
The generally lower binding constants listed in Table 5 for EDAMPDA may be ascribed to lower basicities of the six donor groups compared to those of EDTA. For acid solutions, however, it is seen that these lower basicities result in lower hydrogen ion competition so that formation of the metal chelates of the divalent transition metal ions is about as complete as that of EDTA. While the substitution of pyridine nitrogen donors for acetate oxygen donors in the EDTA structure does not constitute an improvement for most transition metal ions, this is not the case for the polyamines. It has been shown (Ref. 12) that the replacement of some of the basic aliphatic amino groups by less basic aromatic nitrogen donors greatly increases the effective metal binding by the polyamines in acid solution.

Phenolate groups

Although it has been known empirically for a long time that phenolic oxygens exhibit very high affinity for the ferric ion, there are relatively few examples in the literature of the modification of the EDTA structure by the use of phenolic oxygen donors. The sexadentate ligand of EHPG, illustrated in Table 6 and first reported by Martell and coworkers (13) is

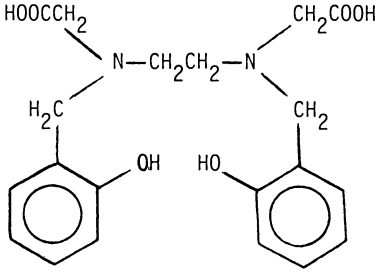
Table 6. Phenolic analogs of EDTA

Ethylenebis-o-hydroxyphenylglycine (EHPG)



	log K_{ML}	Δ log K
Cu^{2+}	23.90	5.20
Ni^{2+}	19.60	1.14
Zn^{2+}	16.80	0.36
Ca^{2+}	7.20	-3.41
Fe^{3+}	33.91	8.91

N,N'-bis(o-hydroxybenzyl)ethylene-diamine-N,N'-diacetic acid (HBED)



	log K_{ML}	Δ log K
Cu^{2+}	21.38	2.68
Ni^{2+}	19.31	0.79
Zn^{2+}	18.37	1.93
Ca^{2+}	9.29	-1.32
Fe^{3+}	39.68	14.68

$$\Delta \log K = \log K_{ML} - \log K_{ML}^{EDTA}$$

unusual in that it has secondary amino groups. The stability constant of the iron(III) chelate, $10^{33.9}$ was unique at that time, and the ligand has since been widely used as an iron(III) carrier for plant nutrition in alkaline soils. A novel medical application for treatment of Cooley's Anemia may result from the recent discovery of the effectiveness of the ligand in removal of ferric ion from experimental animals.

Because of the fact that EHPG has steric restraints for octahedral coordination, it is not surprising that HBED, with a more favorable orientation of its coordinating groups, has a much higher iron(III) chelate stability constant (Ref. 14). The results obtained with HBED suggest that the *o*-hydroxybenzyl group may also be effective for tetravalent metal ions such as the actinides, when built into higher multidentate frameworks such as those of DTPA and TTHA.

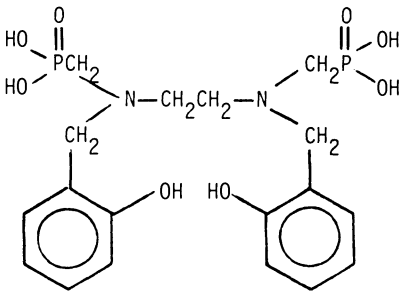
The ligand HBEDPO, (Ref. 15), see Table 7, contains phosphonate and *o*-hydroxybenzyl groups substituted for the acetate groups of EDTA. The results show that while the ligand is probably not significantly different from EDTA for divalent metal ions, it is probably much more effective for the Fe(III) ion. Here also, it appears that the substitution of *o*-hydroxybenzyl and methylenephosphonate groups in place of acetate groups of DTPA and TTHA would offer considerable promise for the formation of effective ligands for trivalent and tetravalent metal ions of high coordination number.

COUPLED BIDENTATE DONOR GROUPS

There are very few examples of the use of coupled bidentate donor groups for the design and synthesis of multidentate ligands exhibiting sexadentate or higher metal ion coordination number. Such functional groups have been known for a long time (e.g., acetylacetone, salicylic acid, salicylaldehyde, 8-hydroxyquinoline, catechol, etc.) but their requirement of symmetrical coordination of both donor groups for effective metal ion coordination has generally restricted their incorporation into large multidentate ligands, although in principle there is no reason why this cannot be done with a sufficiently elaborate organic structure.

Several types of tetradentate ligands containing, in effect, coupled bidentate donor

Table 7. Chelating tendencies of N,N'-bis(o-hydroxybenzyl-N,N'-ethylenediamine-di(methylenephosphonic) acid (HBEDPO)



	Log K_{ML}				
M^{n+}	EDTA	HBED	HBEDPO	Δ	Δ'
Cu^{2+}	18.70	21.38	24.00	5.30	2.62
Ni^{2+}	18.52	19.31	17.91	-0.61	-1.40
Co^{2+}	16.26	19.89	18.02	1.76	-1.87
Ca^{2+}	10.61	9.29	8.36	-2.25	-0.93
Mg^{2+}	8.83	10.51	7.95	-0.88	-2.56
Fe^{3+}	25.0	39.68	>40	>15	(?)

functions, have been synthesized and extensively studied. Common examples are Schiff bases of acetylacetone and salicylaldehyde with diamines, and certain macrocyclic structures derived from these ligands. Porphyrins are of course examples in which resonance coupling is extended symmetrically throughout the tetradentate macrocycle. Consideration of such ligands is beyond the scope of this paper, and attention will be focused on two types of bifunctional donor groups, hydroxamic acids and catechols. These functions are now available in compounds containing two or three such groups forming tetradentate and sexadentate ligands.

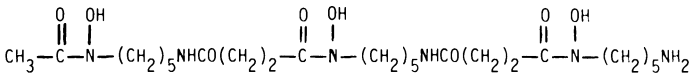
Hydroxamic acids

The role of hydroxamic acids in nature for transport of the ferric ion has been reviewed (Ref. 16); the crystal structure of an iron(III) chelate has been determined (Ref. 17); and acid-base equilibria and metal binding constants have been measured (Refs. 18,19). More recently, geometric and optical isomerism of inert metal complexes of natural hydroxamates have been studied (Refs. 20-22).

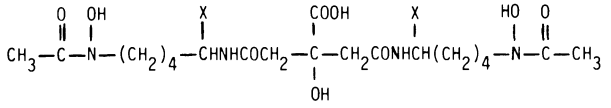
Examples of bidentate, quadridentate and sexadentate natural secondary hydroxamic acid ligands are illustrated in Plate 5. The sexadentate types seem to fall into two classes - the open-chain type such as desferal ferrioxamine-B (DFB, also desferrioxamine) and a number of cyclic compounds such as Ferrichrome A and Fusigen. For all the sexadentate ligands, the bidentate hydroxamic acid groups are far apart in solution in the absence of metal ion, so that the process of coordination to a central metal ion requires extensive changes in orientation of the donor groups, resulting in adverse coulombic enthalpy effects, and restriction of vibrational, translational, and rotational motion of the ligands. Thus it is not surprising that Anderegg et al. (19) found that the sexadentate ligands exhibited little or no chelate effect relative to coordination by three simple bidentate ligands such as acethydroxamic acid.

It should be noted that the donor groups in the sexadentate ligands are part of long open chains or are bound by several carbon atoms to macrocyclic rings, thus allowing them considerable freedom of motion in solution. It is suggested that the way to achieve more favorable entropy effects that would increase the stabilities of the metal complexes of these ligands is to build them into a relatively tight macrocyclic structure in which they would have little freedom of motion, and would be oriented favorably for simultaneous metal ion coordination. Recently, a primary hydroxamate analog of EDTA, ethylenediaminediaceticdihydroxamic acid, illustrated below, has been reported (Ref.23). Although this ligand was found to complex Fe^{3+} very strongly, it is obvious that for steric reasons it cannot promote symmetrical bidentate coordination of Fe(III) by the hydroxamic acid groups as has been found

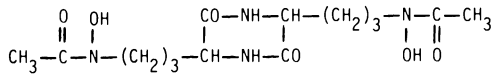
Desferal Ferrioxamine B



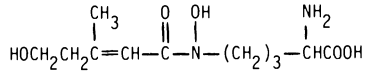
Arthrobactin (X= H); Aerobactin (X = COOH)



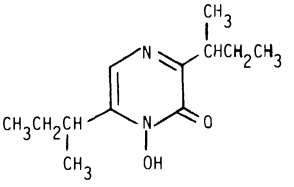
Rhodotorulic Acid

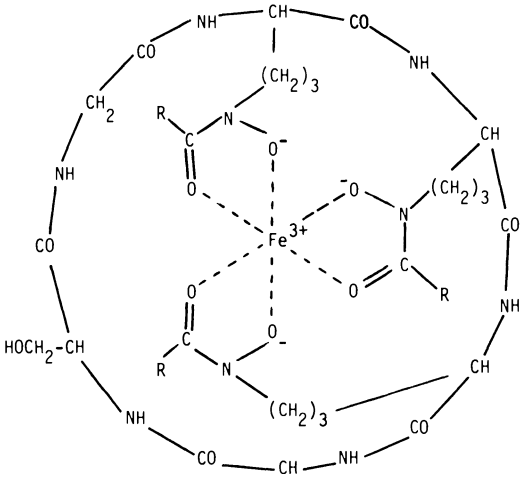


Fusarinine

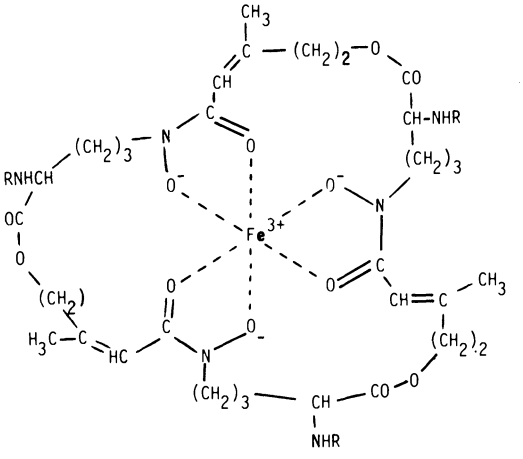


Aspergillic Acid





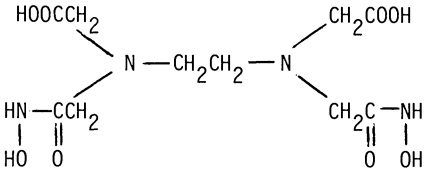
Ferrichrome A (R = CH═C(CH$_3$)CH$_2$COOH)



Fusigen (R = H)

Plate 5. Linear and cyclic microbial secondary hydroxamates

N,N'-Ethylenediaminediacetic-N,N'-diacethydroxamic acid



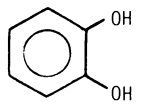
to occur for the natural siderochromes. In fact spectral evidence was found (Ref. 23) for monodentate N-coordination of metal ions by this ligand.

CATECHOLS

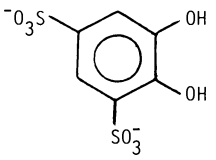
Catechols have long been known to have very high affinity for the Fe^{3+} ion, as indicated by the three examples listed in Table 8 (Ref. 24). While the exceptionally high stability of

Table 8. Stability constants of metal chelates of dihydroxyaromatic compounds

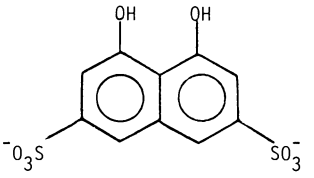
Catechol I



Tiron II



Chromotropic Salt III



	Log Stability Constants (β_2)		
	I	II	III
Cu^{2+}	24.9	25.5	23.8
Ni^{2+}	14.4	14.9	-
Co^{2+}	15.0	14.4	-
Zn^{2+}	17.4	18.5	-
Fe^{3+}	-	35.9 (45.8 β_3)	36.9
Fe^{3+}/Cu^{2+}	-	10.4 (20.3)	13.1

R. M. Smith and A. E. Martell, "Critical Stability Constants" Vol 3, Plenum, 1977

the 3:1 tiron:Fe(III) chelate is very impressive, its proton affinity is also extremely high, so that in mildly alkaline, neutral and acid solutions it binds Fe(III) much les effectively than does HBED, for example. In fact, proton competition with Fe^{3+} for catechol is sufficiently strong that 3:1 chelate solutions stable at high pH disproportionate with the precipitation of $Fe(OH)_3$ as the pH is lowered. It should further be noted that the high affinity of diphenolic ligands for Fe(III) result in the achievement of very high specificity of Fe(III) complexing relative to Cu(II), as indicated in Table 8.

Nature has taken advantage of high iron affinity of catechol groups through the incorporation of such groups in many natural microbial iron(II) carriers. Some typical examples are indicated in Plate 6 (Refs. 16, 25-27). Although stability constants have not yet been measured for the Fe(III) chelates of these phenolic compounds, that of the sexadentate ligand, enterobactin (Ref. 27), should be near 10^{50}, or about three times the log value of the 1:1 catechol-iron(III) complex. For the same reasons as those stated above for the sexadentate trishydroxamates, a favorable chelate effect relative to the analogous bidentate ligands is not expected for these complexes.

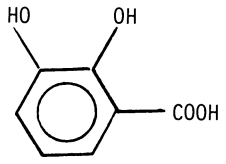
AMIDES AS COORDINATING LIGANDS

Although the coordination of secondary amide linkages by metal ions has been known for some time (Refs. 28,29), its use as an active part of multidentate chelating ligands has generally been neglected. Although amide and peptide carbonyl oxygens are believed to coordinate weakly with transition metal ions when additional, more-strongly coordinating groups are present in the ligand, strong coordination by a negative amide or peptide nitrogen has been observed for only a few metal ions (most notably Co(III), Cu(II), Ni(II), Co(II) and Fe(III)), and these reactions seem to be highly selective. Thus simple dipeptides, HL, generally combine with Cu(II) via strong peptide nitrogen coordination in aqueous solution at intermediate ($\sim$neutral) pH to give complexes of the type $Cu(H\text{-}nL)_x$. The Ni^{2+} ion, on the other hand usually does not form such compounds unless the pH exceeds 9-10, whereas Co^{2+} and other first row transition metal ions do not form complexes of this type at all under an inert atmosphere.

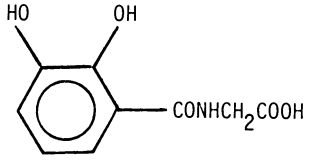
The data in Table 9 (Ref. 30) indicate the effects on amide coordination resulting from substitution of two acetate groups at the N-terminal positions of polyglycine peptides. In general the effect is to suppress the ability of divalent metal ions to displace protons from secondary amide positions. This result is most clearly seen in the case of Ni^{2+}. For Cu^{2+} and Co^{2+} amide proton dissociation occurs completely for the di- and tripeptide derivatives, but fails for the third site of the tripeptides.

For the Fe(III) ion, the presence of the two additional acetate groups greatly increases the tendency toward formation of stable chelates through peptide proton dissociation. The stable

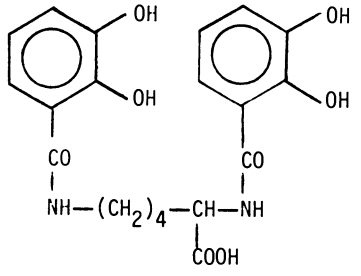
2,3-dihydroxybenzoic acid

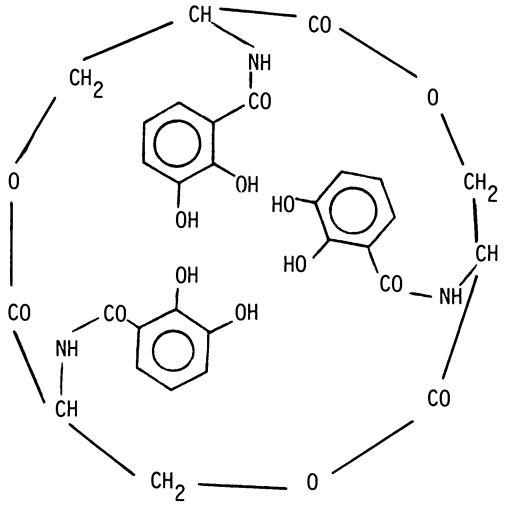


2,3-dihydroxybenzoylglycine



Bis-(2,3-dihydroxybenzoyl)lysine





Cyclic triester of 2,3-dihydroxybenzoyl-L-serine (enterobactin)

Plate 6. Microbial catechol compounds

Table 9. Dissociated amide groups as ligands

Ligand	Complexes Formed			
	Cu^{2+}	Ni^{2+}	Co^{2+}	Fe^{3+}
H_3L $HOOCCH_2NHCOCH_2N(CH_2COOH^a)(CH_2COOH)$	CuL^-	NiL^-	CoL^-	FeL
	$CuH_{-1}L^{2-}$	-	$CoH_{-1}L^{2-}$	$FeH_{-1}L^-$
				$FeH_{-1}LOH^{2-}$
H_3L $HO(OCCH_2NH)_2COCH_2N(CH_2COOH^a)(CH_2COOH)$	CuL^-	NiL^-	CoL^-	FeL
	$CuH_{-2}L^{3-}$	$NiH_{-1}L^{2-}$	$CoH_{-2}L^{3-}$	-
H_3L $HO(OCCH_2NH)_3COCH_2N(CH_2COOH^a)(CH_2COOH)$	CuL^-	NiL^-	CoL^-	FeL
	$CuH_{-2}L^{3-}$	$NiH_{-2}L^{3-}$	$CoH_{-2}L^{3-}$	-
H_4L $(HOOCCH_2)_2NCH_2COHNCH_2CH_2NHCOCH_2N(CH_2COOH^b)(CH_2COOH)$	CuL^{2-}	NiL^{2-}	CoL^{2-}	FeL^-
	$CuH_{-2}L^{4-}$	-	-	-
	$Cu_2H_{-2}L^{2-}$	-	$Co_2H_{-2}L^{2-}$	-
H_4L $HOOCCH_2NHCOCH_2N(CH_2COOH)CH_2CH_2N(CH_2COOH)CH_2CONHCH_2COOH^b$	CuL^{2-}	NiL^{2-}	CoL^{2-}	FeL^-
	$CuH_{-2}L^{4-}$	-	-	$FeH_{-2}L^{3-}$

complexes formed with glycylglycinediacetic acid, $FeH_{-1}L^-$ and $FeH_{-1}LOH^{2-}$ are stable against $Fe(OH)_3$ precipitation at high pH, whereas Fe(III) complexes formed with glycylglycine itself are very unstable and do not involve displacement of peptide protons. With higher members of the polyglycinediacetic acid series, there is insufficient reaction of Fe(III) with the peptide linkages to form stable chelates. This variation in coordination tendency is seen in the two isomeric potentially octadentate EDTA analogs illustrated in Table 9 (Ref. 31). In the case of DGENTA (N,N'-diglycylethylenediamine-N",N",N"',N"'-tetraacetic acid) the Fe^{3+} ion forms relatively unstable chelates at low pH, and is completely converted to a precipitate of $Fe(OH)_3$ as the pH is increased, and no interaction with the peptide groups involving proton dissociation takes place. On the other hand with the isomeric ligand EDDAG-DA (N,N'-ethylenediaminedi(acetylglycine)N,N'-diacetic acid), initial chelation of Fe(III) at low pH by the central ethylenediaminediacetic acid moiety is followed by conversion at higher pH to a metal chelate in which the metal ion is strongly coordinated to two negative (dissociated) amide linkages. Thus the difference in arrangement of the coordinating groups in these two isomeric ligands is very critical in determining whether $Fe(OH)_3$ precipitates at intermediate pH, and whether high pH-stable chelates involving dissociated amide linkages can form at all.

Perhaps some of the most selective reactions involving Cu^{2+}, Co^{2+}, and Ni^{2+} can be achieved through the reactions of these metal ions with the amide linkages of dipeptides and polypeptides. The types of interaction that may take place are illustrated schematically in Plate 7 for the potentially quadridentate ligand glycylhistidine. Formation of very stable, peptide nitrogen-deprotonated complexes of Cu^{2+} and Ni^{2+} occurs in aqueous solution (in the case of Ni^{2+} at high pH) in the presence of an inert atmosphere. Under these conditions peptide proton displacement does not occur in the presence of Co^{2+}, and the metal precipitates as the hydroxide as the pH is raised. In the presence of oxygen (or air) however, the Co^{2+} ion very rapidly forms a dioxygen complex with peptide proton displacement, and is then converted to a very stable complex of Co(III) with the ligand.

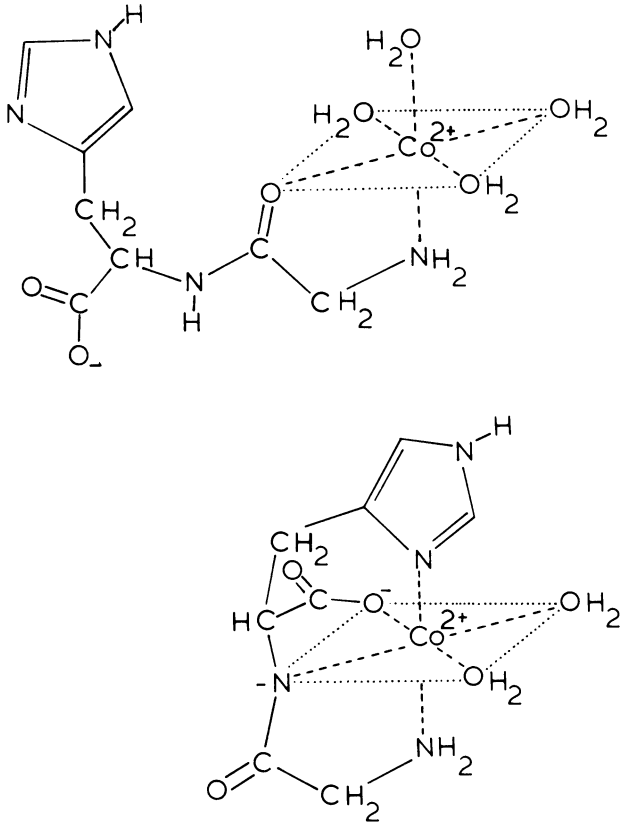


Plate 7. Bonding modes for cobaltous dipeptide complexes

CONCLUSIONS

In this review, use was made of currently available stability constant data for guidance in the design of chelating ligands having high affinities and selectivities for various metal ions, particularly those of high charge and coordination number. It is apparent, however, that such data are lacking for most of the more interesting ligands, since physico-chemical equilibrium studies generally lag far behind the synthesis of new chelating ligands. Therefore qualitative observations (such as precipitation or non-precipitation of metal hydroxides) were employed to evaluate the effectiveness of many of the new ligands. In many cases it was also necessary to employ intuitive concepts for the design of the more elaborate ligands and for the introduction of donor groups, such as the hydroxamic acids, for which the nature of metal ion coordination is still relatively poorly understood.

It is apparent from the examples given that the evolution of synthetic multidentate ligands is still at a relatively rudimentary stage, and that much needs to be done in developing more elaborate molecular structures that involve new combinations of highly specific mono- or bidentate donor groups. An important objective of future work in the field should be the synthesis of more rigid molecular frameworks in which the donor groups are held reasonably close to the positions and orientations necessary to maximize coordination with the metal ions of interest, thus overcoming unfavorable entropy and enthalpy effects associated with coordination. While these objectives have been achieved to some extent in the cryptates, such structures are often associated with slow kinetics of metal chelate formation or exchange, thus presenting difficulties with analytical chemical separations and catalysis, for which reasonable reaction rates are essential. In principle it should be possible to design more open, non-cryptate, multidentate ligands in which the metal ion is cradled by a molecular framework in which one or more faces of the coordination polyhedra are not covered by the bridging atoms of the multidentate ligands, thus allowing more facile dissociation and recombination with metal ions.

ABBREVIATIONS

Chromotropic salt	3,5-disulfo-1,8-dihydroxynaphthalene
DGENTA	N,N'-diglycylethylenediamine-N",N",N"',N"'-tetraacetic acid
DHG	N,N-bis(2-hydroxyethyl)glycine
Dien	diethylenetriamine
DTPA	diethylenetriaminepentaacetic acid
DTPP	diethylenetriaminepenta(methylenephosphonic) acid
EDAMPA	N,N'-bis(2-pyridylmethyl)-ethylenediamine-N,N'-diacetic acid
EDDAG-DA	N,N'-ethylenediaminedi(acetylglycine)-N,N'-diacetic acid
EDTA	ethylenediaminetetraacetic acid
EDTP	ethylenediaminetetra(methylenephosphonic) acid
EHPG	ethylene-2-(*o*-hydroxyphenyl)glycine
En	ethylenediamine
HBED	N,N'-bis(*o*-hydroxybenzyl)ethylenediamine-N,N'-diacetic acid
HBEDPO	N,N'-bis(*o*-hydroxybenzyl)ethylenediamine-N,N'-di(methylenephosphonic) acid
HDTTA	N-(2-hydroxyethyl)N,N',N",N'-diethylenetriaminetetraacetic acid
HEDTA	N-(2-hydroxyethyl)N,N',N'-ethylenediaminetriacetic acid
HIMDA	N-(2-hydroxyethyl)iminodiacetic acid
NTA	nitrilotriacetic acid
NTP	nitrilotri(methylenephosphonic) acid
PHOA	pentaethylenehexamineoctaacetic acid
TEA	triethanolamine
Tiron	3,5-disulfopyrocatechol
Tren	tris(2-aminoethyl)amine
Trien	triethylenetetramine
TPHA	tetraethylenepentamineheptaacetic acid
TTHA	triethylenetetraminehexaacetic acid

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