On the other hand, the presence of a positive charge outside the first coordination sphere in complex[7] has a profound effect in lowering the proton dissociation energy. This effect is apparently equivalent to the effect of three ammonia ligands, as can be seen by comparing **1** with **7**.

Concluding Remarks

This research has shown that the Zn–OH moiety has a nucleophilicity close to that of the hydroxide group independent of the coordination number and of the nature of the other donor groups. This result is meaningful with respect to the many reactions catalyzed by $Zn–OH_2$ (which then could give rise to a Zn–OH intermediate) and Zn–OH moieties.

The charge of the donor groups (i.e. His, Glu, or Cys) changes the energy of the $Zn–OH_2 \rightleftharpoons Zn–OH + H^+$ reaction. Such energy presumably parallels the pattern of the pK_a values. If for the sake of comparison, one equates the value of 1760 kJ mol^{-1} for the dissociation energy of H_2O into $OH^- + H^+$ (Table I) to 14, the pK_a of water, and scales the other ΔE values in Table I in the same way, a value of 5.7 for the "pK_a" of **1a** is obtained. The pK_a increases to 6.1 and 6.5 for **2a** and **3a**, i.e., with increasing coordination number. As an exmaple, the enzyme carbonic anhydrase with a donor set ZnN_3OH_2 has a pK_a ranging between 5 and 7 depending on the isoenzyme and the nature of the groups inside the cavity.[8] A positive charge inside the cavity lowers the pK_a of coordinated water.[28]

4a and **5a**, with one positive charge less than **1a–3a**, have pK_a's of 8.5 and 8.6. In the enzyme carboxypeptidase there is a Zn-$(His)_2(Glu)OH_2$ moiety, but the coordinated water is hydrogen-bonded to another Glu,[29] which undergoes deprotonation with a pK_a of 5. The enzyme has another pK_a of 9, which has been proposed, among other possibilities, to be due to the coordinated water.[30]

6a, with two sulfurs and no charge, has a pK_a of 11.5. Liver alcohol dehydrogenase has a zinc coordinated to two cysteines and one histidine, besides water.[31] According to the present results, the pK_a should be sizably higher than that in carbonic anhydrase and, indeed, it is 9.2.[32] The presence of a positively charged NAD^+ coenzyme lowers the pK_a down to 7.4,[32] but the presence of a neutral NADH coenzyme molecule raises it to 11.2.[32]

The above comparison is of course artificial, since the energies have been scaled down arbitrarily. Nevertheless, it is also instructive in the sense that the scaled values reproduce not only the experimental trend but also the sizes of the relative variations. This is a further support to the conclusion that the pK_a's of coordinated water in metalloproteins are indeed determined by the electronic properties of the metal complex as a whole, plus the electrostatic contributions from nearby residues, in a predictable way.

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Stabilities of Trivalent Metal Complexes of Phenolic Ligands Related to *N*,*N*′-Bis(2-hydroxybenzyl)ethylenediamine-*N*,*N*′-diacetic Acid (HBED)

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The stability constants and other equilibrium parameters of the trivalent metal ion complexes of three multidentate ligands have been determined: *N*,*N*′-bis(2-hydroxy-3,5-dimethylbenzyl)ethylenediamine-*N*,*N*′-diacetic acid (Me_4HBED); *N*,*N*′-bis(2-hydroxy-3-methyl-5-*tert*-butylbenzyl)ethylenediamine-*N*,*N*′-diacetic acid (*t*-BuHBED); and *N*,*N*′-bis(2-hydroxy-3,5-dimethylbenzyl)-*N*-(2-hydroxyethyl)ethylenediamine-*N*′-acetic acid (HBMA). Alkylation of the aromatic ring significantly increases the basicity of the ligand, as measured by protonation constants, but lowers metal ion affinity, because of steric effects. Replacement of an acetate of Me_4HBED by a hydroxyethyl donor group lowers the protonation constants of the ligand only slightly but lowers affinity for trivalent metal ions by 4–6 orders of magnitude. Stability constants involving trivalent metal ions are compared with those of five other sexadentate ligands, all of which contain two phenolate donor groups. Effectiveness of all eight ligands in binding trivalent metal ions in biological media is assessed by comparing pM values at physiological pH 7.4.

Introduction

Two phenolate-containing sexadentate ligands (Chart I) with an EDTA-type framework, ethylenebis((2-hydroxyphenyl)glycine) (EHPG, **1**) and *N*,*N*′-bis(2-hydroxybenzyl)ethylenediamine-*N*,*N*′-diacetic acid (HBED, **2**) designed to strongly bind Fe(III), have been known for many years.[1,2] Recently a series of analogues of these parent compounds have been developed as ligands having high affinities for Ga(III), In(III), and Gd(III), as well as Fe(III), as radiopharmaceuticals, and as magnetic resonance paramagnetic contrast imaging agents.[3-6] Also recently EHPG has been separated into its *racemic* and *meso* forms, and the stabilities of complexes of each isomer with a wide variety of metal ions have been determined.[7] Two additional new ligands of this general type, with two phenolate donors, a substituted ethylenediamine moiety,

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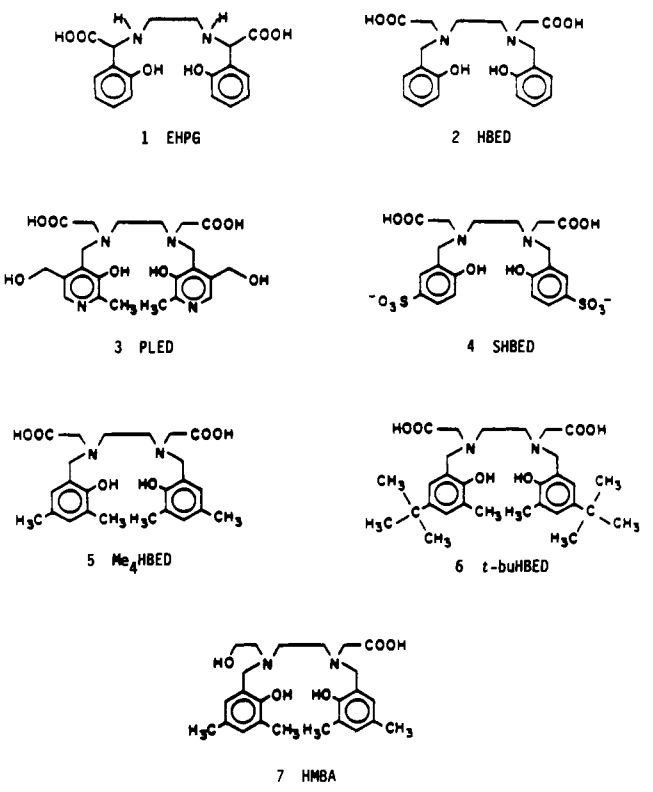
Chart I



and two carboxylate groups, in addition to the parent compounds,[1,2,7] have recently been reported:[8] *N,N'*-dipyridoxylethylenediamine-*N,N'*-diacetic acid (PLED, **3**) and *N,N'*-bis(2-hydroxy-5-sulfonatobenzyl)ethylenediamine-*N,N'*-diacetic acid (SHBED, **4**). This paper adds three new ligands to the series, *N,N'*-bis(2-hydroxy-3,5-dimethylbenzyl)ethylenediamine-*N,N'*-diacetic acid (Me_4HBED, **5**), *N,N'*-bis(2-hydroxy-3-methyl-5-*tert*-butylbenzyl)ethylenediamine-*N,N'*-diacetic acid (*t*-BuHBED, **6**), and *N,N'*-bis(2-hydroxy-3,5-dimethylbenzyl)-*N*-(2-hydroxyethyl)ethylenediamine-*N'*-acetic acid (HBMA), (**7**), thus providing, with the two forms of EHPG, a total of eight ligands containing two amino groups and two phenolate donors for comparison of metal ion affinities and biodistributions of their metal chelates. These new ligands differ from the others by the presence of methyl and/or *tert*-butyl substituents on the aromatic rings, which impart lipophilic character to the complexes formed.

Experimental Section

Ligands. Me_4HBED was prepared by modifying the method of Kroll[9] with improvements described recently;[8] *t*-BuHBED and HBMA were prepared by the method described by Mathias et al.[5]

Potentiometric Methods. The experimental procedure employed for the determination of stability constants by potentiometric measurement of hydrogen ion concentration has been described in detail elsewhere.[10] The experimental solution (50 mL) was contained in a 100-mL thermostated jacketed reaction vessel having an airtight cap fitted with gas inlet and outlet tubes, glass and reference electrodes, a piston buret tip extending below the surface of the solution, and a magnetic stirrer. The Corning Model 150 pH meter employed was calibrated with millimolar concentrations of strong acid (0.10 M HCl) and strong base (0.10 M KOH) at 25.0 °C and 0.100 M ionic strength (KCl) so as to read hydrogen ion concentrations (p[H]) directly. Potentiometric data were processed on the departmental VAX computer with the Fortran program BEST.[11]

Spectrophotometric Methods. UV–vis spectral measurements were made at 25.0 °C with a Perkin-Elmer Model 553 Fast-Scan spectrophotometer equipped with 1.000 ± 0.001 cm matched quartz cells. Stability constants were calculated from spectral data with the help of short Basic programs utilizing mass balance and equilibrium constant equations and by minimizing the least-squares absorbance fit to the observed absorbance curves at a prominent wavelength. Each stability constant determination was based on data from 5 to 15 spectral runs and was generally determined with a Hewlett Packard 150II PC.

Solubilities. In carrying out the potentiometric and spectrophotometric studies described above, it was necessary to overcome difficulties arising from the low solubilities of the ligands. The metal chelates were generally more soluble than the ligands themselves. Me_4HBED is insoluble in the mid-p[H] range but remains in supersaturated solution at millimolar levels. *t*-BuHBED is insoluble below pH 7 and HBMA is insoluble from p[H] 3 to p[H] 8.5. However, all ligands, as well as their metal chelates, form homogeneous supersaturated solutions that remain stable far into the precipitation range when the concentrations are very low (millimolar or less). Insolubility was indicated by a sudden discontinuity in p[H] readings, which could be detected before visual observation of the presence of the insoluble material. Such data were not used in the equilibrium calculations. Instead, the experiments were repeated several times in order to achieve greater supersaturation to the maximum extent possible.

Determination of High Protonation Constants. For each ligand, the two highest protonation constants were determined spectrophotometrically. A series of 5–15 solutions containing appropriate concentrations of KOH and KCl (such that [KOH] + [KCl] = 0.100 M), and with each 0.100 mM in ligand concentration, were measured between 210 and 350 nm, with 1.000-cm quartz cells and a thermostat set at 25.0 °C. In addition, several solutions were prepared with measured higher concentrations of KOH in order to help determine the ultimate molar absorbance of the totally deprotonated ligand. This was necessary because the protonation constants are too high to carry out the extrapolation to complete dissociation with measurements limited to ionic strength 0.100 M. On the other hand, a larger excess of base causes the ligand (most markedly the *t*-BuHBED) to precipitate as a potassium salt. The calculations themselves involved the least-squares minimization of calculated versus observed absorbances through the variation of the first and second protonation constants as well as the second extinction coefficient corresponding to fully protonated phenolic groups.

The absorbance at a given wavelength and p[H] was calculated by means of

$$A = T_L \frac{\epsilon_L + \epsilon_{HL}K_1[H] + \epsilon_{H_2L}K_1K_2[H]^2}{1 + K_1[H] + K_1K_2[H]^2}$$

where ϵ_L, ϵ_{HL}, and ϵ_{H_2L} are the extinction coefficients of L^{n-}, $HL^{(n-1)-}$, and $H_2L^{(n-2)-}$, respectively, and K_1 and K_2 are the stepwise protonation constants leading to the $HL^{(n-1)-}$ and $H_2L^{(n-2)-}$ ions for the ligand H_nL^0. The wavelength chosen is near 300 nm, the characteristic phenolate absorbance maximum.

Protonation Constants Determined Potentiometrically. For HBMA, the third protonation constant was determined from back-titration data (i.e., lowering the p[H] by addition of standard acid) obtained by titration into the supersaturated region near pH 7.0. The fourth and fifth protonation constants were calculated from forward titration data obtained by titrating standard base into the supersaturated region near pH 4.0.

For Me_4HBED the third, fourth, and fifth protonation constants were determined by the direct titration of the (fortunately) supersaturated millimolar solution.

The third, fourth, and fifth constants of *t*-BuHBED were determined by back-titration into the supersaturation region of a 0.0650 mM solution with 0.1000 M HCl delivered from a screw-type microburet with 0.002-mL graduations.

Determination of Stability Constants. The HBMA stability constants with Ga(III), In(III), and Fe(III) were determined by direct titration. The Gd(III) value could not be determined because of the presence of either gadolinium hydroxide or precipitated ligand in the experimental solutions.

All remaining stability constants were determined utilizing dilute (about 10 micromolar) solutions. Absorbances of a series of about six solutions containing appropriate concentrations of HCl and KCl (such that [HCl] + [KCl] = 0.100 M, and each solution was 10.00 micromolar in the ligand) were measured near 240 nm for Ga(III), In(III), and Gd(III) and near 530 nm for Fe(III). The absorbances provide a quantitative measure of the degree of metal chelate formation.

Results and Discussion

Stabilities. In the course of the determination of the protonation constants for HBMA, Me_4HBED, and *t*-BuHBED, the extinction coefficients near 300 nm were determined as described in the

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Table I. Ultraviolet Spectral Characteristics of Ligands[a]

compd	wavelength, nm	ϵ_L, M^{-1} cm^{-1}	ϵ_{HL}, M^{-1} cm^{-1}	ϵ_{H_2L}, M^{-1} cm^{-1}
HBMA	302	9240	2990	800
	283			4170
Me_4HBED	302	9160	4440	650
	285			4140
t-BuHBED	298	8290	4940	1700
	282			3850

[a] 25.0 °C; 0.10 M ionic strength (KCl).

Table II. Ultraviolet Spectral Characteristics of Metal[a] Complexes Formed in This Study

complex	wavelength, nm	ϵ_{ML}, M^{-1} cm^{-1}
$GaMe_4$HBED	240	9860
	291	5430
$InMe_4$HBED	242	9280
	294	5400
$GdMe_4$HBED	243	13200
	298	6400
$FeMe_4$HBED	530	3130
Ga-*t*-BuHBED	242	12300
	289	5140
In-*t*-BuHBED	238	10400
	292	4980
Gd-*t*-BuHBED	243	10200
	295	5700
Fe-*t*-BuHBED	525	3880

[a] 25.0 °C; 0.10 M ionic strength (KCl).

Experimental Section. The values shown in Table I are a result of the iteration process, which simultaneously also produced the two highest protonation constants log K_1^H and log K_2^H. However, the molar absorbances of the trivalent metal ions ϵ_{ML} with the ligand shown in Table II were measured directly since experimental conditions could always be adjusted, usually near pH ~2–3 or higher, where the complex ML is completely formed.

The protonation constants and stability constants for Me_4HBED (**5**), *t*-BuHBED (**6**) and HBMA (**7**) are presented in Table III, along with those of the parent ligand HBED (**2**) and closely related ligands EHPG (**1**), PLED (**3**), and SHBED (**4**). All are sexadentate and have two phenolate donors, two nitrogen donors, and two carboxylate donors, except for HBMA, which has a car-

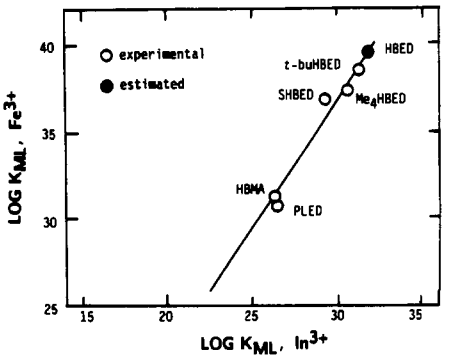

Figure 1. Estimation of In(III) stability constant of HBED: log K_{ML} for Fe(III) chelate of sexadentate diphenolic ligands vs log K_{ML} for the corresponding In(III) chelates.

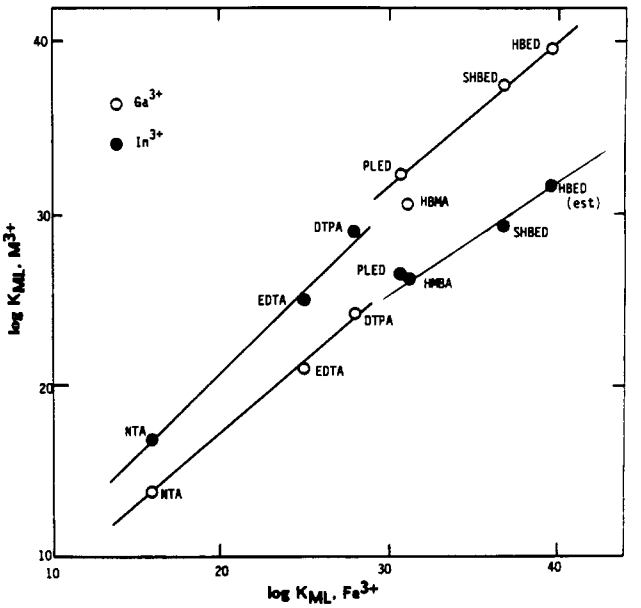

Figure 2. Correlations of stability constants of Ga(III) and In(III) chelates with those of Fe(III), with sexadentate diphenolic ligands (see Table III), and with the amino polycarboxylate ligands nitrilotriacetic acid (NTA), ethylenediaminetetraacetic acid (EDTA), and diethylenetriaminepentaacetic acid (DTPA).

Table III. Logarithms of Protonation Constants and Stability Constants of Trivalent Metal Complexes of Me_4HBED, *t*-BuHBED, HBMA, and Related Ligands[a,b]

	log (quotient)							
quotient	Me_4HBED	*t*-BuHBED	HBMA	*rac*-EHPG[c]	meso-EHPG[c]	HBED	PLED	SHBED
[HL]/[H][L]	13.12	13.21	12.88	12.05	11.90	12.60	10.89	12.91
$[H_2L]/[H][HL]$	12.99	12.95	11.97	10.87	10.85	11.00	10.28	10.42
$[H_3L]/[H][H_2L]$	7.94	7.87	7.55	8.79	8.76	8.44	7.20	7.90
$[H_4L]/[H][H_3L]$	4.09	4.39	4.04	6.33	6.36	4.72	5.73	4.29
$[H_5L]/[H][H_4L]$	1.4	1.7	1.56	...	...	2.53	3.26	1.96
$[H_6L]/[H][H_5L]$	...	...	...	...	...	1.7	2.31	1.2
[FeL]/[Fe][L]	37.41	38.52	31.21	35.54	33.28	39.68	30.78	36.87
[FeHL]/[H][FeL]	...	...	3.43	...	2.72	...	6.93	...
$[FeH_2L]/[H][FeHL]$	...	...	...	...	...	...	6.02	...
[FeL]/[H][FeOHL]	...	...	...	11.78	10.45	...	...	10.57
[GaL]/[Ga][L]	34.19	36.30	30.50	33.89	32.40	39.57	32.31	37.4
[GaHL]/[H][GaL]	...	...	...	2.22	3.44	...	7.10	1.18
$[GaH_2L]/[H][GaHL]$	...	...	...	...	...	...	6.22	...
[GaL]/[H][GaOHL]	...	...	6.71	...	...	...	...	...
[InL]/[In][L]	30.72	31.26	26.30	26.68	25.26	32.2[d]	26.54	29.37
[InHL]/[H][InL]	...	...	...	4.47	6.14	...	7.15	2.82
$[InH_2L]/[H][InHL]$	...	...	...	4.78	3.42	...	6.34	...
[InL]/[H][InOHL]	...	...	8.37	10.57	8.83	...	11.21	10.82
[GdL]/[Gd][L]	20.27	20.38						22.27

[a] 25.0 °C, and 0.10 M ionic strength. [b] The estimated error in the first and second protonation constants is as follows: for values >13, the error is ±0.06; for values >12 but <13, the error is ±0.03; for values >11 but <12, the error is ±0.02. All other protonation values including chelate protonation constants are ±1 in the last digit shown. The errors in the log K_{ML} values parallel directly the errors of the first protonation constants except for gallium log K_{ML}, which is ±0.3. [c] Bannochie, C. J.; Martell, A. E. *J. Am. Chem. Soc.* **1989**, *111*, 4735. [d] Estimated value.

boxylate and a neutral aliphatic hydroxyl donor group. The hard[12] phenolate donors are employed to impart high thermodynamic stability to metal complexes formed with hard metal ions, such as those of Fe(III), Ga(III), and In(III), listed in Table III. This purpose is certainly borne out by the stability constants listed, which for Ga(III) and Fe(III) (which are of comparable ionic radius) are all higher than 10^{30}. It is noted that the stability constants of PLED, which has considerably softer phenolate donors,[8] are many order of magnitude lower than those of the parent ligand (**2**) and its alkyl derivatives **5** and **6**. These considerations do not include other factors that are more difficult or impossible to determine, such as the structures of the complexes formed in solution. The lower metal ion affinity of EHPG (**1**) related to that of HBED (**2**) is due to less favorable steric orientation of donor groups, as is discussed in detail elsewhere.[7] Those steric effects may be seen in the large differences in metal ion affinities of the *racemic* and *meso* forms of EHPG.

The much larger ionic radius (smaller charge/radius ratio) of Gd(III) is reflected in the stability constants, which are 10 orders of magnitude (or more) lower than those of the other trivalent metal ions, indicating that hard phenolate donor groups are not especially suited to effective coordination of large metal ions such as the lanthanides. The lack of stability data for In(III)–HBED is taken care of temporarily by estimating its value with a plot of known constants for Fe(III) and In(III) (Figure 1). The stability constants employed for this correlation did not involve EHPG because the steric effects[7] encountered in the formation of its complexes set it apart from the other ligands. It is seen from the data in Table III that the In(III) stability constants are considerably lower than those of Ga(III) and Fe(III) as might be expected from the effective ionic radii (0.76, 0.78, and 0.94 Å, for Ga(III), Fe(III), and In(III), respectively). Plots of log K_{ML} values for chelates of Ga(III) and In(III) vs those of Fe(III) with phenolate ligands, illustrated in Figure 2, show a fairly uniform difference in stabilities. The graphical comparison reveals that the phenolic complexes of Ga(III) are consistently from 4 to 8 orders of magnitude more stable than their indium counterparts, in agreement with the differences in ionic radii and relative "hardness"[12] of these metal ions. With the amino polycarboxylate ligands, however, the situation is the reverse, with the In(III) chelates considerably more stable than those of Ga(III). This reversal may be rationalized by the fact that the carboxylate donor group is considerably softer than phenolate, as indicated by relative protonation constants (pK values). Part of this effect may also be due to greater steric repulsions between the bulky carboxylate groups in approaching closely and coordinating smaller metal ions. Thus it seems that DTPA is an excellent ligand for In(III) and is superior to several of the phenolic ligands.

The principal rationale for synthesizing and studying the new ligands **5**–**7** was to produce Ga(III) and In(III) complexes with high lipid solubility in order to influence biodistributions of the chelates in vivo. This was accomplished by alkylation, as with Me_4HBED and *t*-BuHBED, and by reducing the overall charge to zero, as with HBMA. Biodistributions were greatly altered by increased lipid solubility, but in the case of HBMA poor clearance from experimental animals was found, probably because of low thermodynamic stabilities of the chelates. These effects are described in detail elsewhere.[5] A striking indication of the effect of alkyl substitution and ionic charge are the octanol/water partition coefficients, which are reported[5] to be 4–5 orders of magnitude higher for the In(III) chelates of *t*-BuHBED and HBMA relative to the In(III) chelates of the hydrophilic ligands PLED and SHBED.

pM Values. The ligands listed in Table III have a wide range of protonation constants. For this reason, the stability constants taken by themselves do not provide a comparable basis or measure of the relative effectiveness of these ligands at physiological p[H]. The different degrees of hydrogen ion competition with the metal ion for the ligands impart varying effective affinities at a given pH value. The high affinities of strongly basic donor groups for metal ions are partially reversed by high affinities for hydrogen ions. A more reliable guide for ligand effectiveness is the pM value (−log [metal ion]), which is similar to the "chemical potential" of the aquo metal ion. These values were computed from the stability constants and protonation constants and are listed in Table IV for p[H] 7.4 (taken as physiological p[H]) and 0.10 M ionic strength. In each case, the total ligand concentration was twice that of the analytical concentration of iron(III). The larger the p[M] values, the more effective is the ligand. It is seen from the pM values listed in Table IV that the parent ligands HBED (**2**), and EHPG (**1**) (*racemic*), together with SHBED, are clearly the most effective ligands for Fe(III) and Ga(III), while they are seemingly only marginally effective for In(III). On the other hand, HBMA is clearly the poorest ligand and cannot compete with transferrin for these metal ions. In fact, the pM values generated by all the phenolic ligands in Table IV except for HBED are comparable in magnitude to those of transferrin and hence would not withstand metal ion exchange with his natural metal ion carrier in the serum over an extended period of time. The large drop in stability (and pM) between Fe(III) and Ga(III) on one hand and In(III) on the other is probably due in part to steric effects, as discussed above. The relative pM values generated by PLED show that the lower log K's corresponding to lower basicities of donor groups are only partially compensated for by lower protonation constants.

The influence of the stabilities of the complexes on the *in vivo* behavior of a series of indium complexes in animals is shown in Figure 3. This figure is adapted from data in ref 5 and shows the rates of clearance of the various complexes with In(III) from the liver. It is seen that the indium following administration of In(III)–EHPG and In(III)–HBMA is trapped in the rat liver. Following the administration of HBED derivatives, the In(III) is cleared. This behavior is not related to lipophilicity because of the two most lipophilic complexes, one (*t*-BuHBED) clears while the other is retained. It appears that the stabilities of the EHPG

Table IV. pM and log K_{ML} Values for Fe(III), Ga(III), and In(III) Chelates Calculated for 100% Excess Free Ligand at pH 7.4

	Fe(III)		Ga(III)		In(III)	
ligand	log K_{ML}	pM	log K_{ML}	pM	log K_{ML}	pM
rac-EHPG	35.54	26.0	33.89	24.3	26.68	17.1
meso-EHPG	33.28	23.9	32.40	23.0	25.26	15.9
HBED	39.68	29.8	39.57	29.7	32.2[a]	22.3
PLED	30.78	24.2	32.31	25.7	26.54	20.0
SHEBED	36.87	27.7	37.4	28.2	29.37	20.2
Me_4HBED	37.41	25.4	34.19	22.2	30.72	18.8
t-BuHBED	38.52	26.6	36.30	24.3	31.26	19.3
HBMA	31.21	20.8	30.50	20.1	26.30	15.9
transferrin[b]	20.67 (K_1)[c] 19.38 (K_2)[c]	20.7	20.3 (K_1)[c] 19.3 (K_2)[c]	20.4	19.2 (KI)[a,c] 18.1 (K_2)[a,c]	18.9

[a] Estimated value. [b] Calculated for 5 mM $NaHCO_3$. [c] K_1 = [MTr]/[M][Tr]; K_2 = [M_2Tr]/[MTr][M].

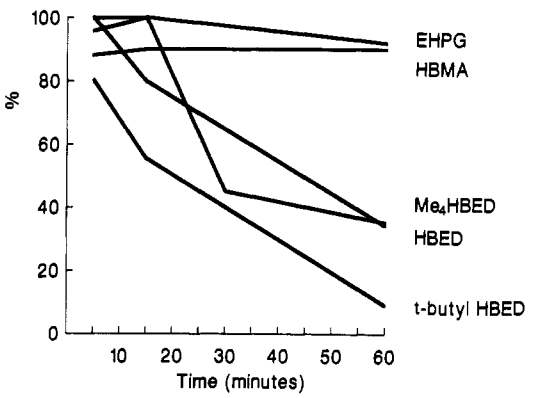

Figure 3. Data adapted from ref 5 showing the retention and/or clearance of indium chelates in rat liver plotted as % indium retained in liver vs time in minutes.

(12) Pearson, R. G. *J. Am. Chem. Soc.* **1963**, *85*, 3533.

and HBMA are low enough for exchange of the In(III) with intracellular binding sites to occur, while for the other ligands this exchange does not occur and so the intact complex is cleared.

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Equilibrium Studies and Molecular Recognition in the Catechol- and TIRON-Bridged Binuclear Cobalt(II) 1,4,7,13,16,19-Hexaaza-10,22-dioxacyclotetracosane Dioxygen Complexes

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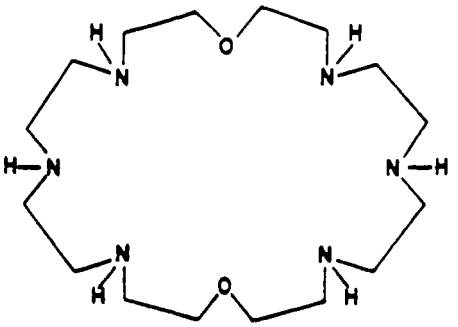
Catechol and TIRON bridge two cobalt centers in the cavity of the macrocyclic 1,4,7,13,16,19-hexaaza-10,22-dioxacyclotetracosane (BISDIEN) dicobalt dioxygen complex, forming five species in each case. In addition to the doubly bridged μ-peroxo, μ-catecholate (or TIRON) complex, mono- and diprotonated forms, as well as monohydroxo and dihydroxo species, have been detected. Under anaerobic conditions catecholate and 3,5-disulfocatecholate anions also bridge the two cobalt(II) centers, stabilizing the binuclear array. Both monobridged complexes add a second, hydroxo, bridge at high pH. The 3,5-disulfocatecholate-bridged complex forms mono- and diprotonated species at low pH. These dinuclear complex systems are characterized by potentiometric titration and UV–vis spectrophotometric measurements. Equilibrium constants for all major complexes formed are reported, and the results are presented in the form of distribution diagrams showing the concentrations of individual complex species as a function of p[H]. Coordinate bonding modes suggested for these complexes show the proposed oxidant (μ-peroxo) and the proposed substrate (μ-catechol or μ-TIRON) in very close proximity, and thus, facile oxidation of the substrates is expected. The dianion of hydroquinone does not bridge the two cobalt centers through its phenolate oxygen donors, apparently reacts with the dinuclear cobalt dioxygen complex through one of its phenolate groups only, and seems to replace the hydroxo bridge in the (μ-peroxo)(μ-hydroxo)dicobalt–BISDIEN dioxygen complex. Reaction with hydroquinone occurs at room temperature to give the inert binuclear cobalt(III)–BISDIEN complex.

Introduction

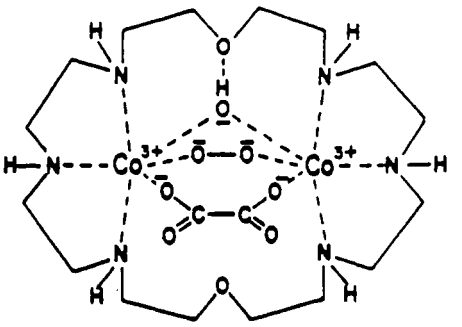
The macrocyclic ligand 1,4,7,13,16,19-hexaaza-10,22-dioxacyclotetracosane (BISDIEN, **1**) has been shown to form binuclear



1 (BISDIEN)

complexes with first-row transition-metal ions, which in turn bind secondary anions as bridging groups.[1-3] In this case, the binuclear metal complexes are themselves the hosts, and the bridging anions are the guests. This secondary bridging type of anion binding has been labeled cascade complex formation by Lehn.[3] Examples of secondary anionic guests in binuclear BISDIEN complexes are hydroxide ion, imidazolate anion, and peroxide, for which quantitative binding constants have been reported.[2] In addition, the crystal structure of an imidazolate-bridged binuclear copper(II)–BISDIEN complex has been reported by Lippard and coworkers.[4,5] Whithout the stabilizing bridging bifunctional anions, the dicobalt–BISDIEN complex is somewhat unstable and decomposes at high pH to form cobalt(II) hydroxide.

Recently, the formation and redox reactions of the oxalato- and peroxo-bridged dicobalt–BISDIEN dioxygen complex (**2**) was



2 ((μ-hydroxo)(μ-peroxo)(μ-oxalato)dicobalt–BISDIEN complex)

reported.[6] This is the first example of oxidation of a substrate coordinated to two metal centers in a macrocycle where the oxidizing agent, dioxygen, is also bound to the two cobalt centers in the same macrocyclic complex. That result suggested the investigation of reactions of other reducing bifunctional substrates capable of acting as bridging donors in the binuclear (μ-peroxo)dicobalt–BISDIEN complex. In this work, equilibrium studies of complexes involving coordinated anions of catechol and TIRON as bridging groups are described and briefly contrasted with the complexes formed by hydroquinone in the same binuclear system.

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