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Binding Properties of Octaaminocryptands

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Complexation and protonation equilibria were studied in aqueous solution for a new range of aminocryptand ligands, $N(CH_2CH_2NHCH_2RCH_2NHCH_2CH_2)_3N$, (R = *m*-xylyl, *p*-xylyl, 2,5-furan, 2,6-pyridine) and demonstrate that stability constants for first transition series ions Co^{2+} to Zn^{2+} are relatively high. X-ray crystallography shows that the cryptands are reasonably well preorganized for complexation. The furan-spaced cryptand $L^6{\cdot}H_2O$ crystallizes in the rhomobohedral space group $R\bar{3}$ (no. 148) with $a = 14.645(1)$, $b = 14.645(1)$, and $c = 25.530(4)$ Å, whereas the *m*-xylyl-spaced cryptand L^4 crystallizes in the triclinic space group $P\bar{1}$ (no. 2) with $a = 9.517(1)$, $b = 15.584(2)$, and $c = 23.617(4)$ Å. The highest formation constant ($\log \beta_{21} = 33.07$) is observed for the dicopper cryptate of a pyridine-spaced cryptand, suggesting involvement in complexation of donors from the spacer link. This pyridine-spaced host also shows good selectivity for copper(II) over zinc(II), making it a possible candidate for treatment of copper-excess pathology.

Introduction

There is a need for water-soluble, lipophilic receptors for transition and heavier main group cations for a range of applications, the specific usage depending on the relevant thermodynamic and kinetic complexation parameters. Some of these applications require high thermodynamic and/or kinetic stability, whereas others demand only moderate thermodynamic stability combined with kinetic lability. Accurate knowledge of thermodynamic stability constants is thus critical to effective design of receptors for each specific application. Cryptands are attractive candidates for host molecules for many purposes, given the relatively high thermodynamic and kinetic stability (Cryptate effect)[1] which normally characterizes their complexes. Polyether cryptands[2] have limited affinity for transition and heavy main group 3−15 cations; however, as nitrogen donors are substituted for ether-O donors, progressive increase of this affinity is noted. Complexation studies with the series Co(II)−Zn(II)[3−5] using the all N donor *O-bistren* and with Cu(II) alone using the pentamethylene-bridged analogue *C5-bistren*[6] have been reported; speciation plots show the existence of both mono- and dinuclear cryptates of these ligands. In addition, because of the basicity of N-donor cryptands, they frequently reveal[2,5] the presence, in aqueous solution, of cryptates of protonated as well as neutral ligands, in some systems even at near-neutral pH.

Some years ago we generated a new series of azacryptand hosts using a facile Schiff-base [2+3] condensation route to hexaimine macrobicycles[7] and reported the complexation properties of $\mathbf{L^1}$ [*m-xylimBT*], L^2 [*pyimBT*], and $\mathbf{L^3}$ [*furimBT*] in acetonitrile.[8] These hosts show the expected preference for the softer transition and main group cations over the harder group I and II cations; formation constants with Ag^+ and Cu^+ are relatively large, especially for the 2:1 cryptates. As a consequence of a notable entropy/enthalpy compensation effect,[8] no strong selectivity is exhibited, either within the M^{2+} transition series or between toxic cations such as Cd^{2+} and their potential biological competitors Zn^{2+} and Ca^{2+}. The pyridine-spaced cryptand [*pyimBT*] shows the strongest complexation, although it is restricted to 1:1 stoichiometry with cations other than magnesium and copper. There are stability problems with these hexaimine systems; where strongly Lewis-acidic cations are encapsulated, metal-assisted hydrolysis may result in ring-opening on the time scale necessary for achievement of equilibrium.[8]

To avoid such problems with host stability, we generated the octaamino derivatives by borohydride reduction of the hexaimine cryptands.[9−11] Given the basicity of aminocryptands, competition between protons and cations for coordination sites in the host is to be expected; occasionally protonated salts of the ligands[10,11] or mononuclear cryptates of the singly protonated[12] ligand have been isolated instead of the anticipated mono- or ditransition

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ion cryptate. Quantitative complexation studies are needed to predict the outcome of such competition.

In the imine series of ligands, free cryptands and cryptates adopt distinct conformations[13] with, respectively, divergent or convergent disposition of donor lone pairs. This explains the entropy/enthalpy compensation[8] evident in this series; in effect, the hexaimine Schiff-base cryptands are not preorganized for complexation and a considerable entropic cost accompanies their reorganization. A better degree of preorganization is likely for aminocryptands $\mathbf{L}^{4}-\mathbf{L}^{7}$, but up until now no free ligand structures have been determined to test this expectation. Many structures, however, exist [8−12,14−21] for protonated or cation-coordinated aminocryptates.

We here report the potentiometric investigation of protonation and complexation equilibria of octaaminocryptands $\mathbf{L}^{4}-\mathbf{L}^{7}$, in aqueous solution, with a range of target cations from the first transition series, Co(II)−Zn(II). We also describe the crystal structures of two of the free aminocryptands, $\mathbf{L}^{4}$ and $\mathbf{L}^{6}$ (Scheme 1).

Experimental Section

Materials. The ligands studied were synthesized as previously reported.[7−11,18,20] Their solutions were prepared by dissolution of a weighed amount in slightly more than 8 equivalents of $HClO_4$. Argon was bubbled through the solution before dilution with doubly distilled water. A potentiometric titration was used to determine exact ligand concentration. The ionic strength was held constant at 0.1 mol L^{-1} by addition of tetraethylammonium perchlorate (Fluka, purum), recrystallized twice in water, rinsed with ethanol, and dried overnight under vacuum. The titrant base used was a tetraethylammonium hydroxide solution made by dilution of the commercial solution (Fluka, purum, 40% aqueous solution) previously standardized against potassium hydrogen phthalate.

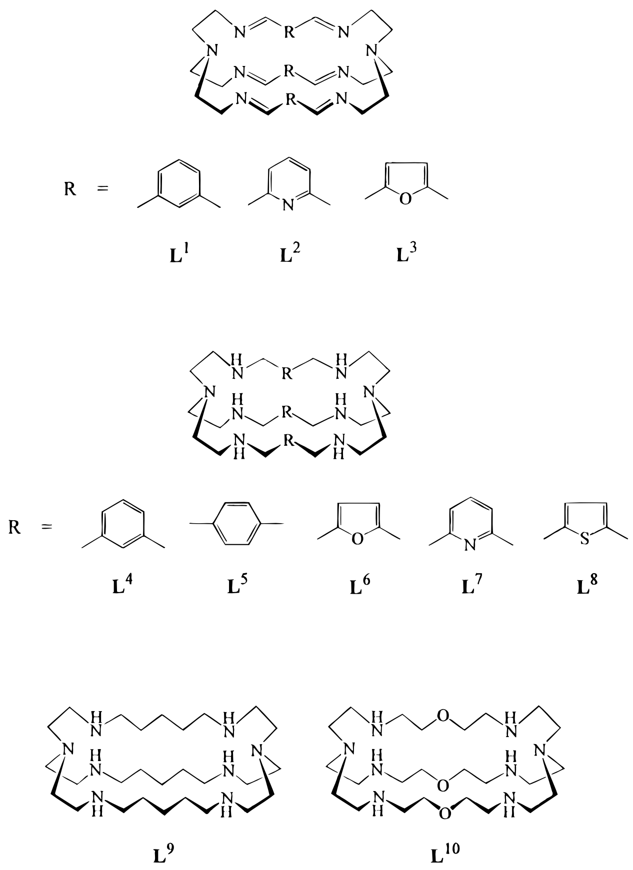
Stock solutions (0.0250 mol L^{-1}) of reagent grade transition metal perchlorates [$Co(ClO_4)_2{\cdot}6H_2O$, $Cu(ClO_4)_2{\cdot}6H_2O$, and $Ni(ClO_4)_2{\cdot}6H_2O$] (Fluka, purum) and $Zn(ClO_4)_2{\cdot}6H_2O$ (Alfa) in doubly distilled water were standardized complexometrically with ethylenediaminetetraacetic acid (EDTA) in the presence of the appropriate indicator.[22]

CAUTION: Perchlorates are known to be potentially explosive and must be handled only in small quantities.

Stability Constant Determination. The stability constants of the complexes were determined potentiometrically using the method of competition with the proton.[6] The titrations were carried out at 25.0 ± 0.1 °C under argon atmosphere using a Mettler DL21 titrator connected to a Mettler TS[2] titration software operating system on a 386-sx computer.

The standard external reference solution (saturated aqueous KCl solution) of the combination glass electrode (Ingold ELE O3c-CH) was replaced by a solution of 0.01 mol L^{-1} Et_4NCl in 0.09 mol L^{-1} Et_4NClO_4 saturated with AgCl(s). The electrode was calibrated with a solution of 10^{-2} mol L^{-1} $HClO_4$ in 9×10^{-2} mol L^{-1} Et_4NClO_4 to read the free hydrogen ion concentration directly. Because the junction electrode potential varies exponentially with $-\log [H^+]$,[23] the relation $-\log [H^+]_{real} = -\log [H]_{read} + a + b{\cdot}[H^+]$ was applied. For reasons of convenience, $-\log [H^+]$ will be replaced by pH throughout the text. The parameters a and b were respectively found to be 0.15 and −14.97 by measuring the pH of a solution of 10^{-3} mol L^{-1} $HClO_4$ in the presence of 9.9×10^{-2} mol L^{-1} Et_4NClO_4.

Scheme 1. Ligand Codes



Experimental solutions were prepared in 25 mL volumetric flasks from 20 mL of stock ligand solution mixed with a precise volume of stock metal ion solution and then adjusted in volume by the supporting electrolyte solution. Typical ligand concentrations were approximately 8×10^{-4} mol L^{-1} and the metal-to-ligand ratios, R, were 1 and 2. Initial volumes of 10 mL were titrated against ca. 8×10^{-2} mol L^{-1} Et_4NOH. The protonation constants of the ligands had been previously determined from titrations in the absence of metal ions. The experimental data corresponding to a minimum of four different titrations (ca. 240 experimental points) were interpreted using the program SIRKO[24] and the strategy described in detail previously.[6] The autoprotolysis constant of water at the ionic strength employed, $pK_w = 13.78$,[25] was held constant during refinements. In most cases, stability constants of metal hydroxo species were omitted during the refinements, as their presence did not improve the fit significantly. For each interpretation, the goodness of the fit was estimated from the value of Hamilton's factor, R_f, given by the program, which was usually <1%.

The distribution curves were calculated using the program HALTAFALL.[26]

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Table 1. Crystallographic Data for $\mathbf{L^4}$ and $\mathbf{L^6}\cdot H_2O$

	$\mathbf{L^6}\cdot H_2O$	$\mathbf{L^4}$
empirical formula	$C_{30}H_{50}N_8O_4$	$C_{36}H_{54}N_8$
formula weight	586.78	598.87
crystal description	colorless block	colorless block
temperature (K)	153(2)	153(2) K
wavelength (Å)	0.71073	0.71073
crystal system	rhombohedral	Triclinic
space group	$R\bar{3}$	$P\bar{1}$
a (Å)	14.645(1)	9.517(1)
b (Å)	14.645(1)	15.584(2)
c (Å)	25.530(4)	23.617(4)
α (°)	90	90.73(1)
β (°)	90	90.94(1)
γ (°)	120	90.746(7)
V (Å^3)	4742.0(9)	3501.6(1)
Z	6	4
density (calculated, mg/m^3)	1.233	1.136
μ (mm^{-1})	0.084	0.069
F(000)	1908	1304
crystal size (mm)	0.93 × 0.54 × 0.33	0.80 × 0.63 × 0.45
θ range for data collection (°)	2.26 to 25.00	2.19 to 24.00
index ranges	$-1 < h < 16$ $-17 < k < 1$ $-1 < l < 30$	$-1 < h < 10$ $-17 < k < 17$ $-27 < l < 27$
reflections collected	2374	11887
independent reflections	1859 ($R_{int} = 0.0214$)	10970 ($R_{int} = 0.0414$)
absorption correction	none	none
refinement method	full-matrix least-squares on F^2	full-matrix least-squares on F^2
data/restraints/parameters	1859/0/141	10970/0/829
goodness-of-fit on F^2	1.050	1.013
final R indices [$I > 2\sigma(I)$]	R1 = 0.0371 wR2 = 0.0884	R1 = 0.0506 wR2 = 0.0997
R indices (all data)	R1 = 0.0471 wR2 = 0.0947	R1 = 0.0965 wR2 = 0.1169
largest diff. peak and hole (e Å^{-3})	0.26 and −0.21	0.17 and −0.17

X-ray Experimental. Crystal data are summarized in Table 1. Both data sets were collected at low temperature on a Siemens P4 diffractometer using graphite-monochromated Mo $K\alpha$ radiation and corrected for Lorentz and polarization effects but not for absorption. The structures were solved by direct methods[27] and refined by full-matrix least-squares on F^2, using all of the reflections. All non-hydrogen atoms were refined with anisotropic atomic displacement parameters and hydrogen atoms bonded to the carbon atoms were inserted at calculated positions with isotropic displacement parameters. In $\mathbf{L^4}$ the amine protons were located from difference maps and were not further refined; in the $\mathbf{L^6}\cdot H_2O$ structure the amine protons were located and allowed to refine; the one-third occupancy protons of the encapsulated water molecule were not included. The unusual cell for $\mathbf{L^4}$ was checked using the IUCr checkcif procedure and no extra symmetry was detected. All programs used in the structure refinement are contained in the SHELXL-93 package.[28]

Results and Discussion

Free Cryptand Structures. Crystals of $\mathbf{L^6}$ suitable for X-ray crystallography were obtained by recrystallization from 1:4 $CHCl_3$−hexane solvent. The molecule (Figure 1) lies on a 3-fold axis, which runs through N1 and N2. A single water molecule is encapsulated within the cryptand, disordered over equivalent positions about the 3-fold axis and moderately strongly hydrogen-bonded to the bridgehead nitrogen atoms. The $N_{bridgehead}$−$N_{bridgehead}$ distance is correspondingly short, at 5.407(3) Å, the shortest so far observed in any of these azacryptand structures. The planes of the furan rings are directed tangentially to the 3-fold axis of the molecule. The protons on the secondary amines are directed into the clefts between the strands of the cryptand and are not involved in any hydrogen bonding. Edge-to-face interactions exist between the furan rings; one of the aromatic protons in each ring lies 2.81 Å above the centroid of a neighboring furan from another molecule.

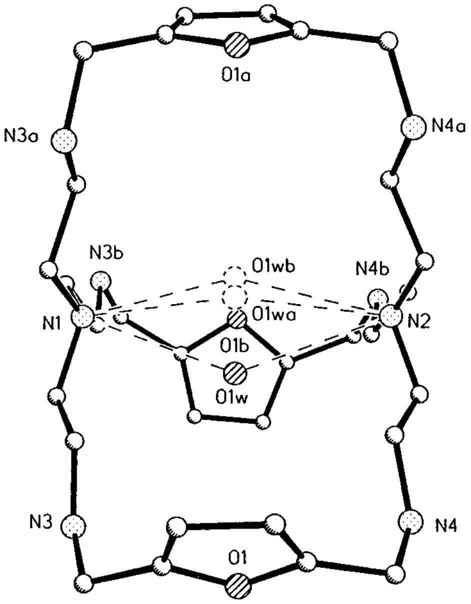

Figure 1. Structure of $\mathbf{L^6}\cdot H_2O$; Ow−H−N hydrogen bond distances: O1W−N1 = 2.876(4) Å, O1W−N2 = 2.941(4) Å; N1−O1W−N2 = 137.7(1)°; $N_{bridgehead}$−$N_{bridgehead}$ = 5.407(3) Å.

Suitable crystals of $\mathbf{L^4}$ were obtained by recrystallization from 1:1 hexane−ether.

The asymmetric unit (Figure 2) contains two independent, but very similar molecules oriented not quite parallel to each other (the N1−N2 and N3−N4 vectors intersect at an angle of 10.1°). Each cryptand has pseudo-3-fold symmetry with the phenyl groups arranged tangentially to the main axis of the

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Table 2. Stepwise Protonation Constants (log $K_i \pm \sigma_{n-1}$)[a] of the Cryptands Studied in Aqueous Solution at 25 °C, $I = 0.1$ (Et_4NClO_4)

log K_i	**L^4**	**L^4**[b]	**L^5**	**L^6**	**L^7**	**L9**[c]	**L10**[d]
log K_1	9.8 ± 0.3	9.92[b]	9.6 ± 0.1	9.2 ± 0.3	9.4 ± 0.4	10.35	9.89
log K_2	9.17 ± 0.06	9.26[b]	9.00 ± 0.04	8.7 ± 0.2	8.8 ± 0.1	9.88	9.23
log K_3	8.5 ± 0.2	8.75[b]	8.62 ± 0.08	8.0 ± 0.2	7.8 ± 0.2	8.87	8.29
log K_4	7.21 ± 0.04	7.67[b]	7.4 ± 0.1	6.6 ± 0.1	7.10 ± 0.09	8.38	7.65
log K_5	6.9 ± 0.1	7.16[b]	6.7 ± 0.1	5.93 ± 0.03	6.2 ± 0.1	8.14	6.64
log K_6	6.70 ± 0.05	6.59[b]	6.52 ± 0.09	5.76 ± 0.06	5.4 ± 0.1	7.72	6.01
Σ log K_i	48.3 ± 0.8	49.35	47.8 ± 0.5	44.2 ± 0.9	45 ± 1	53.34	47.71

[a] Average values of $n \geq 4$ independent experiments; precision: ± the standard deviation σ_{n-1}. [b] Ref 31 ($I = 0.1$ M KNO_3). [c] Ref 6 ($I = 0.1$ M $NaClO_4$). [d] Ref 5 ($I = 0.1$ M $NaClO_4$).

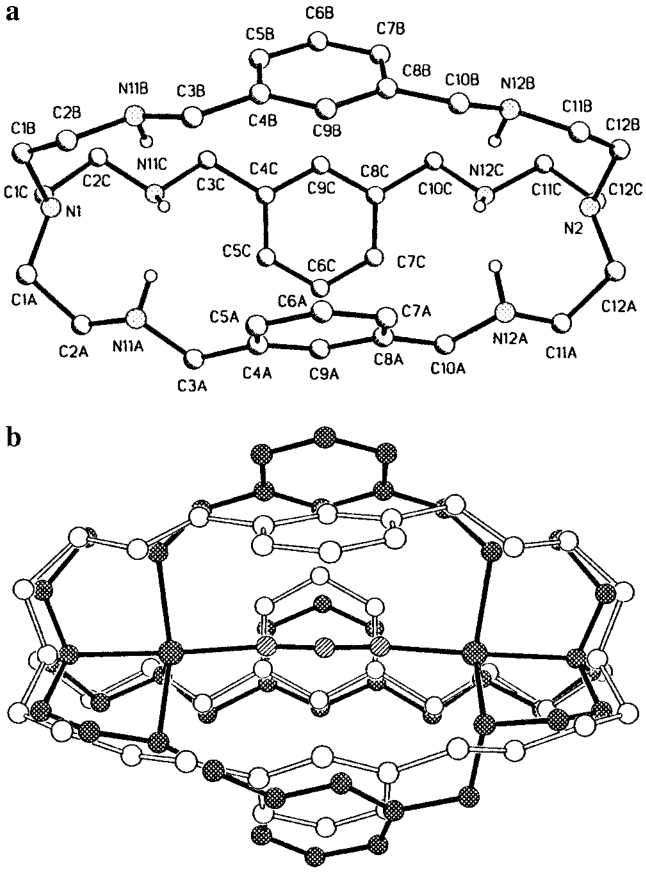

Figure 2. (a) Structure of **L^4**; average $N_{bridgehead}-N_{bridgehead}$ distance = 10.95 Å. Hydrogens, except for NH, omitted. (b) Comparison of conformations in **L^4** and $[Cu_2(N_3)L^4](CF_3SO_3)_3$.

molecule and the amine protons directed into the cavity. The cavity is long and narrow but there is no indication of any intramolecular interactions across it. There are few clear-cut intermolecular interactions; a proton bound to C6 in one cryptand lies 2.89 Å above the centroid of a phenyl group on a neighboring (independent) cryptand (C4C−C9C), but these interactions are not general for all of the aromatic rings as was observed in **L^6**.

In comparison with the analogous iminocryptands **L^1** and **L^3**, the main difference in conformation relates to the disposition of the nitrogen donors. In both iminocryptands these point out of the cavity, whereas in the free aminocryptands the N-donors adopt a position intermediate between that in the iminocryptands and any aminocryptates structurally characterized to date.[29] The structures of **L^4** and **L^6** show that while the conformation adopted is not fully preorganized for complexation, relatively minor alterations of torsion angles will convert it to a conformation capable of complexation. The comparison of the structure of **L^4** with its μ−1,3 azido dicopper(II) cryptate $[Cu_2L^4(N_3)]$ in Figure 2b illustrates this point.

In neither of the cryptands are there any interactions, either $\pi-\pi$, H$-\pi$, or H-bonding, operating intramolecularly, nor, despite the presence of many NH entities, are any intermolecular NH−N H-bond interactions observed, because the NH groups which are included in the cryptand clefts are not appropriately placed for efficient intermolecular H-bonding. The network of edge-to-face intermolecular H$-\pi$ interactions, involving one ring of L^4 and all three rings of L^6, do not appear to persist in solution, as there is no evidence in the ^{1}H NMR spectrum for anomalous shielding in any aromatic resonance such as derives in **L^1** from an intramolecular edge-to-face H$-\pi$ contact of similar length.[9,30]

Acid−Base Properties of the Ligands. Despite the presence of eight potential protonation sites on ligands **L^4**−**L^6**, only six protonation constants could be determined in the pH range studied (2.3−11). The logarithms of the corresponding stepwise values, $K_i = [LH_i]/([LH_{i-1}][H])$, are listed in Table 2, together with data for **L^4**[31] and the related cryptands *C5-bistren* (**L^9**)[6] and *O-bistren* (**L^{10}**)[5] studied by Martell. These values range between 9.4 and 5.4 for **L^7**, 9.2 and 5.76 for **L^6**, 9.6 and 6.52 for **L^5**, and 9.8 and 6.70 for **L^4**. They correspond to the protonation of the six secondary amines, that of the tertiary bridgehead amines being undetectable, as found earlier[5] for **L^{10}**. Protonation constants of **L^4** determined in this work are, with the exception of log K_6, lower than those calculated by Martell in the presence of KNO_3.[31] It has only recently been recognized that anion cryptates are formed by nitrate[32,33] and perchlorate[32] anions with protonated **L^4**, and that for this pair of anions they are of different stoichiometry, 2:1 versus 1:1, respectively. This situation can be expected to generate different log K values in these different media.

If we take into account the confidence intervals, log K_1 values obtained for the four ligands in the present work cannot be said to be significantly different. However, in some of the subsequent protonations, particularly K_5 and K_6, **L^4** is seen to be slightly more basic than the other ligands. It is possible to appreciate the overall basicity of these ligands by comparing the sum Σ log K_i of the protonation constants, which indicates the following sequence of decreasing basicity:

$$\mathbf{L^9 > L^4 > L^5 \approx L^{10} > L^7 \approx L^6}$$

None of these ligands is as basic as **L^9** or the constitutive subunit **Tren** for which log K_1 = 10.12, log K_2 = 9.41, and log

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Table 3. Overall Stability Constants (log β_{xyz})^{a,e} of Transition Metal Ion Complexes in Aqueous Solution (I = 0.1 M Et_4NClO_4, T = 25 °C)

		ligands				
cations	complexes	**L**^{4}	**L**^{4}	**L**^{5}	**L**^{6}	**L**^{7}
Ni^{2+}	ML	5.50 ± 0.06		4.3 ± 0.2	6.4 ± 0.1	9.54 ± 0.03
	MLH	−		12.7 ± 0.1	14.3 ± 0.2	17.61 ± 0.03
	MLH_2	−	24.53^{b}	20.4 ± 0.1	21.35 ± 0.07	24.48 ± 0.01
	MLH_3	−		27.68 ± 0.04	28.7 ± 0.1	31.44 ± 0.08
	MLOH	−4.6 ± 0.1		−	−3.8 ± 0.4	−0.52 ± 0.04
	M_2L	−	10.15^{b}	−	9.75 ± 0.06	15.2 ± 0.2
	M_2LH	−		−	−	22.10 ± 0.02
	M_2LOH	−	1.43	−	1.5 ± 0.2	6.9 ± 0.1
	$M_2L(OH)_2$	−		−	−	−3.56 ± 0.06
Co^{2+}	ML	7.53 ± 0.03	9.81^{c}	6.9 ± 0.4	7.8 ± 0.1	12.02 ± 0.01
	MLH	16.41 ± 0.03	18.91^{c}	15.8 ± 0.2	15.81 ± 0.07	20.63 ± 0.01
	MLH_2	−	26.98^{c}	24.1 ± 0.2	−	27.89 ± 0.01
	MLH_3	−	33.36^{c}	31.60 ± 0.04	−	33.94 ± 0.01
	MLOH	−	−1.20^{c}	−		
	M_2L	−	13.56^{c}	−	−	17.70 ± 0.02
	M_2LH	−	−	−	−	24.0 ± 0.1
	M_2LOH	−	5.75^{c}	−	4.2 ± 0.3	9.70 ± 0.03
	$M_2L(OH)_2$	−	−	−	−5.8 ± 0.4	−
Cu^{2+}	ML	−	16.79^{c}	^{d}	17.20 ± 0.03	20.93 ± 0.07
	MLH	−	25.44^{c}	−	24.98 ± 0.02	29.70 ± 0.05
	MLH_2	31.97 ± 0.03	32.73^{c}	−	30.64 ± 0.02	36.54 ± 0.02
	MLH_3		38.96^{c}			
	MLOH	−	7.09^{c}	−	7.26 ± 0.02	−
	M_2L	25.86 ± 0.05	26.20^{c}	−	25.38 ± 0.08	33.07 ± 0.01
	M_2LH	−		−	−	37.71 ± 0.01
	M_2LOH	−	21.62^{c}	−	19.72 ± 0.03	26.24 ± 0.01
	$M_2L(OH)_2$	−		−	12.08 ± 0.01	18.19 ± 0.01
Zn^{2+}	ML	−		−	8.92 ± 0.04	12.8 ± 0.1
	MLH	18.87 ± 0.07		−	17.74 ± 0.07	21.89 ± 0.05
	MLH_2	−		25.3 ± 0.1	−	29.72 ± 0.04
	MLH_3	32.62 ± 0.02		32.67 ± 0.05	−	35.08 ± 0.01
	M_2L	−		−	16.10 ± 0.05	21.21 ± 0.04
	M_2LH	−		−	−	27.40 ± 0.02
	M_2LOH	−		−	9.23 ± 0.01	13.3 ± 0.1
	M_2LOH_2	−		−	−	2.8 ± 0.4

[a] Corresponding to the general equilibrium: $xM^{n+} + yL + zH^{+} \rightleftharpoons M_xL_yH_z{}^{(xn+z)+}$; precision: standard deviation σ_{n-1} on the mean of n experiments ($n \geq 4$). [b] Ref 35 (I = 0.1 mol L^{-1} in $NaNO_3$). [c] Ref 31 (I = 0.1 mol L^{-1} in KNO_3). [d] No interpretation possible due to precipitation. [e] The stability constants β^{*}_{x1-k} for the hydroxo complexes correspond to the equilibrium: $xM^{n}+ + L + k\ H_2O \rightleftharpoons M_xL(OH)_z{}^{(xn-k)+} + kH^{+}$.

$K_3 = 8.42$.[5] These results are consistent with a previous study of related macrocycles which showed that the proximity of aromatic rings leads to decrease in the basicity of the amino groups (compare **L**^{4} and **L**^{5} to **L**^{9}).[34] The incorporation of oxygen or nitrogen heteroatoms in the aromatic rings by further increasing their withdrawing character, contributes to a significant decrease in the basicity of the neighboring amines (compare **L**^{6} and **L**^{7} to **L**^{4} or **L**^{5}).

The pattern of decreasing sequential log K_i values varies over the series of ligands; for **L**^{4}−**L**^{6} Δlog K is largest between the third and fourth, and smallest between the fifth and sixth protonations. For L^{7} as for L^{10} there is a much more even pattern of decrease. The existence of inclusive anion complexation in the protonated ligands, for which we are currently acquiring increasing evidence,[32] presumably explains the variable behavior of K_5 and K_6 with different anion/ligand systems, as inclusive anion complexation becomes important with relatively highly protonated forms of the cryptands.

Complexing Properties. (a) Nature of the Complexes. Generally, there is no evidence for complex formation before $a = -6$, where a is [(moles base − moles strong acid added)/mole ligand]. The only exception concerns the system Cu^{2+}/**L**^{7}, for which a significant decrease in pH in relatively acid solution (pH 2.5) for R = 1 and 2 indicates the formation of very stable complexes. In some cases, color changes were observed: for instance the Cu^{2+}/**L**^{7} and Cu^{2+}/**L**^{6} solutions turned from blue to blue-green and green, respectively, upon complexation, while the Co^{2+}/**L**^{7} and Co^{2+}/**L**^{6} solutions turned from a very pale pink to orange and green, respectively. With **L**^{4} and **L**^{5}, precipitation was observed at higher pH for almost all cations. With Ni^{2+} and the ligands **L**^{7} and **L**^{6}, the pH fluctuations visible in the titration curves between $a = -6$ and $a = -3$ may be due to microprecipitation. Data corresponding to these regions were not included in the calculations. Analysis of the titration curves allowed us to propose different models for each system studied. Those corresponding to the best fit to the experimental data are given in Table 3 together with the logarithms of the corresponding overall stability constants.

L^{6} and **L**^{7} generally form both mononuclear and binuclear complexes with the transition metal ions studied, as well as some of the corresponding protonated species. There is evidence for the formation of hydroxo complexes, in general of monohydroxo binuclear complexes, in solution. Similar solution complexation of the hydroxo anion was proposed previously with ligands **L**^{10} and **L**^{9}. In contrast, there is no evidence for formation, in aqueous solution, of binuclear **L**^{5} complexes. With **L**^{4}, binuclear complexation has been found only with Cu^{2+}. This contrasts with results previously obtained[31,35] in nitrate medium

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which indicate the formation of binuclear complexes; it seems likely that the reason for stabilization of dinuclear cryptates in nitrate medium is coordination of this anion in bridging mode between the pair of metal ions, as we have demonstrated in the solid state for a mixed nitrate/triflate salt of **L^4**.[21] In general, wherever the appropriate experiments have been attempted, the stoichiometries of the species we find in solution are in agreement with those found for the complexes isolated in the solid state.

(b) Stability of the Complexes. The stability of the mononuclear complexes of the four ligands **L^4**−**L^7** and of the binuclear complexes of **L^6** and **L^7** follows the sequence

$$Ni^{2+} < Co^{2+} \ll Cu^{2+} \gg Zn^{2+}$$

The inversion observed between Co^{2+} and Ni^{2+} with respect to the Irving-Williams[36] series is presumably related to the different geometric preferences of the two cations; simple crystal field stabilization energy (CFSE) considerations predict a reversal of stability of this pair of ions in tetrahedral compared to octahedral fields, and the effect evidently extends to the distorted tetrahedral site furnished by the cryptand host. The same effect has been observed with the related Schiff base cryptands[8] and with carboxylic acid derivatives of polyoxapolyaza macrocycles.[37,38]

Despite its lower basicity, **L^7** forms the most stable complexes. The mononuclear complex of Cu^{2+} with **L^7** is remarkably stable with log β_{110} = 20.93, i.e., higher than its counterpart with the **Tren** (tris(2-aminoethyl)amine) constitutive subunit (log β_{110} = 19.58).[39] This suggests that pyridine nitrogens must be involved in the complexation of the metal ion. **L^4** and **L^5** complexes are the least stable. To compare the complexing ability of the different ligands toward a particular cation, independently of the type of complexes formed, we prepared plots (Figure 3) which reveal the calculated fraction of free cation for one particular case, Cu^{2+}. The observed sequence is **L^7** > **L^{10}** > **L^6** > **L^4**, thus confirming that **L^7** has the highest complexation efficiency for copper of any cryptand so far studied.

With all cation systems except Cu^{2+}, **L^6** complexes are less stable than those of **L^{10}**, a ligand which likewise has oxygen heteroatoms. This reduction of stability may be due to the lower basicity of the former ligand and its greater rigidity. The furan oxygen does not appear to directly influence the equilibrium through involvement in coordination; in no existing dinuclear **L^6** cryptate structure[17,18,21] is close approach of metal ion to the furano-oxygen demonstrated.

Values of the stepwise stability constants corresponding to the formation of the binuclear complexes [M_2L], which can be calculated from the values (log β_{210} − log β_{110}) in Table 3, are lower than those of the 1:1 complexes (log β_{110}). For example, for Cu^{2+} with **L^7**, log β_{110} = 20.93 while log $K_{(CuL\ +\ Cu\ =\ Cu2L)}$ = 12.14, and for Co^{2+} with **L^7**, log β_{110} = 17.70 while log $K_{(CoL\ +\ Co\ =\ Co2L)}$ = 5.66. The complexation of a second cation is less favorable than that of the first one. Therefore, there is no positive cooperative effect for the formation of binuclear complexes, except presumably in the case of Cu^{2+}/**L^4** where the monocopper complex is not observed at all.

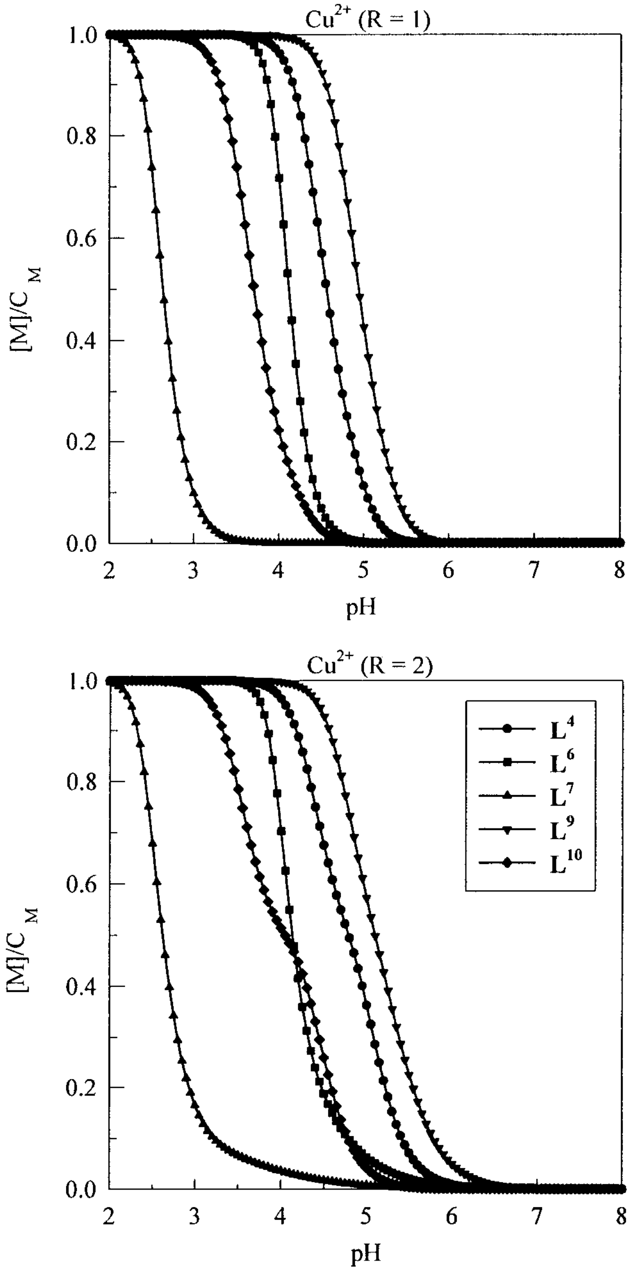

Figure 3. Calculated fraction of free copper concentration vs pH for the ligands studied ($C_L = 10^{-3}$ mol L^{-1}; $R = C_M/C_L$; ▼: **L^9**; ▲: **L^7**; ●: **L^4**; ■: **L^6**; ◆: **L^{10}**).

Hydroxo species are frequently found; the affinities for hydroxide ions are higher in the binuclear complexes than in the mononuclear complexes. This suggests that hydroxide ion bridges the pair of metal cations. The high stability of the monohydroxo binuclear complex of Cu^{2+} with **L^6** (log K_{21-1} = 8.12 instead of 5.53 for the Ni^{2+} complex)[40] suggests the existence of one or several hydrogen bonds between the bridged hydroxide and the oxygen atom of one furan unit in solution, as demonstrated in the solid state.[17] The addition of a second hydroxide bridge is observed in some binuclear species, resulting in dihydroxo complexes; the greatest tendency to form both mono- and dihydroxo species is found in general with Cu^{2+}. It is not surprising that the affinities for the second hydroxide ion

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(40) K_{21-k} is the stability constant corresponding to the stepwise equilibrium: $M_2L(OH)_{k-1}^{(2n+1-k)+} + OH^- \rightleftharpoons M_2L(OH)_k^{(2n-k)+}$. These values can be derived from the expression $K_{21-k} = \beta^*_{21-k}/(\beta^*_{21(-k-1)} \times K_w)$; β^*_{21-k} and $\beta^*_{21(-k-1)}$ values are taken from Table 3.

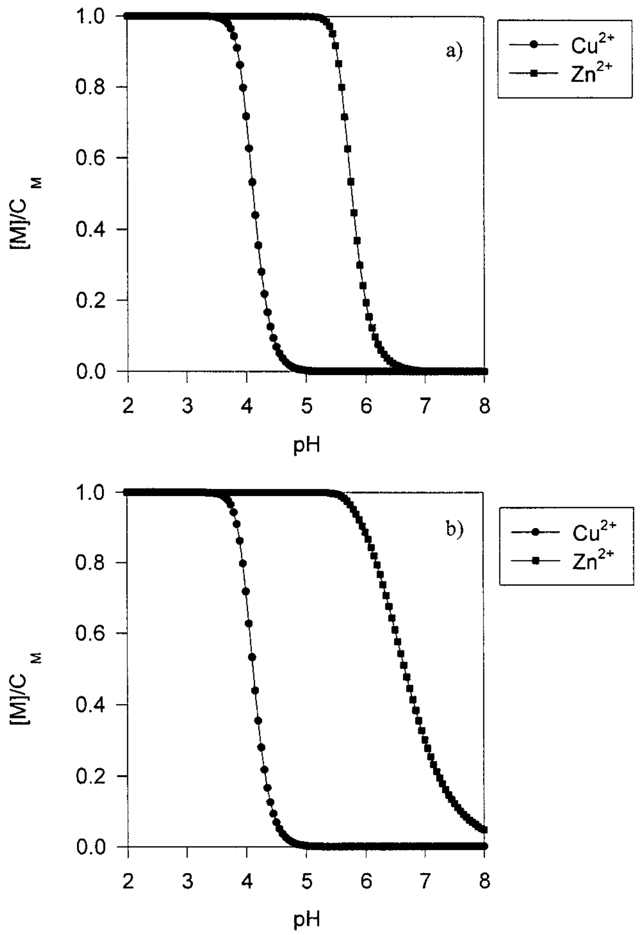

Figure 4. Fraction of free Cu^{2+} and Zn^{2+} vs pH for ligand $\mathbf{L^6}$. (a) The two cations are considered separately in the presence of 1 equivalent of ligand ($C_{Cu} = C_{Zn} = C_L = 10^{-3}$ mol L^{-1}). (b) Equimolar mixture of the two cations in the presence of the ligand ($C_{Cu} + C_{Zn} = C_L = 2 \times 10^{-3}$ mol L^{-1}).

are always lower than for the first (eg. for $\mathbf{L^7}$ and Cu^{2+} log K_{21-1} and log K_{21-2} are 6.95 and 5.73, respectively) because the addition of a second hydroxo bridge will inevitably disrupt any H-bonding contacts.

The complexity of the different systems studied is illustrated by the distribution curves (see Supporting Information) for $Cu^{2+}/\mathbf{L^7}$. For $R = 1$, even though mononuclear species are predominant, binuclear complexes are present in significant amounts. For instance, a maximum of 30% of M_2LH is formed at pH 3 with $\mathbf{L^7}$. For $R = 2$, binuclear species are the major component. The monohydroxo species is present at only 10% with $\mathbf{L^7}$ at pH 6 (in contrast to $\mathbf{L^6}$ where the same species forms at 65% at the same pH), explaining our failure[20] to isolate $[Cu_2(OH)\mathbf{L^7}]$ salts in the solid state at near neutral pH. However, in both systems, the mononuclear complex MLH_2 is present in significant amounts below pH 7.

(c) Complexation Selectivities. Data in Table 3 demonstrate the very high selectivities of these cryptands for Cu^{2+} over the other transition metal ions studied. For mononuclear complexes, these selectivities can be expressed by the ratio of the stability constants $S(Cu/M) = \beta_{110}(Cu)/\beta_{110}(M)$. For instance, the selectivity for Cu^{2+} over Zn^2 shown by the two ligands $\mathbf{L^6}$ and $\mathbf{L^7}$ is higher than 10^8, and thus of the same order of magnitude as that of **Trien** (triethylenetetraamine), a more basic chelating agent used for the treatment of the copper-excess metabolic disorder, Wilsons disease.[41] In addition, our cryptates can be expected to exhibit good kinetic stabilization against decomplexation, which for many biomedical purposes (e.g., copper sequestration or radiocopper delivery) represents a significant advantage over simple chelating ligands. Comparison of the formation constants for dinuclear complexes would suggest an even higher thermodynamic selectivity. Following the plots of Figure 3, the best way to illustrate the selectivity of these compounds is to compare the calculated fraction of free Cu^{2+} and Zn^{2+} left in solution, versus pH, independently of the type of complexes formed. Figure 4a, representing the fraction of each cation considered separately in the presence of $\mathbf{L^6}$ ($C_{Cu} = C_{Zn} = C_L = 10^{-3}$ mol L^{-1}), confirms the high selectivity for copper; it can be seen that at pH 5 all Cu^{2+} is engaged in the complexes, whereas there is still 100% free Zn^{2+}. When a mixture of the two cations ($C_{Cu} = C_{Zn} = 10^{-3}$ mol L^{-1}) in the presence of two equivalents of the ligand ($C_L = 2 \times 10^{-3}$ mol L^{-1}) is examined, it was seen that copper complexes over a much lower pH range (Figure 4b), so there is still excellent selectivity for copper(II) over zinc. Under these conditions, at pH 7, there is still 32% free Zn^{2+}.

Conclusion

The aminocryptands $\mathbf{L^4}$−$\mathbf{L^7}$ exhibit effective complexation of transition ions in aqueous solution, due to good preorganization revealed by comparison of X-ray structures of free ligands and cryptates.

With the furan- and pyridine-spaced hosts, both mono- and binuclear cryptates exist in aqueous solution, whereas the *m*- and *p*-xylyl-spaced analogues generally restrict themselves to monocoordination of cationic guests.

The best complexation properties are seen with the pyridine-spaced ligand $\mathbf{L^7}$, whose stability constants for copper complexation are the highest of any cryptand so far examined. Both $\mathbf{L^6}$ and $\mathbf{L^7}$ show useful selectivity. Studies with the furan-spaced cryptand $\mathbf{L^6}$ show that at pH 5 all Cu^{2+} is coordinated while there is still 100% free Zn^{2+}. Together with the good kinetic stability expected of cryptates, the high thermodynamic stability and selectivity of these systems make the cryptand hosts attractive candidates for sequestration agents in copper-excess pathology, or for radiocopper delivery for imaging and/or therapeutic purposes.

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Supporting Information Available: Two X-ray crystallographic files in CIF format. The species distribution plot for L^7 with coppper-(II) has been deposited. This information is available free of charge via the Internet at http://pubs.acs.org.

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